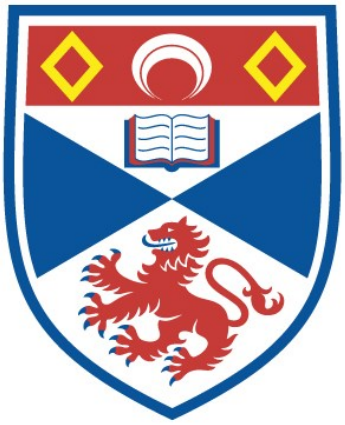
ISOTHIOUREA-CATALYSED ENANTIOSELECTIVE [2,3]-SIGMATROPIC REARRANGEMENTS OF ALLYLIC AMMONIUM YLIDES: SYNTHETIC AND MECHANISTIC STUDIES

Thomas H. West

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



2017

Isothiourea-Catalysed Enantioselective [2,3]-Sigmatropic Rearrangements of Allylic Ammonium Ylides: Synthetic and Mechanistic Studies

Thomas H. West

This thesis is submitted in partial fulfilment for the degree of PhD

at the

University of St Andrews

September 2016

For my Family

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Abstract

The research in this thesis describes the development of an isothiourea-catalysed enantioselective [2,3]-rearrangement of allylic ammonium ylides, subsequent mechanistic and collaborative computational studies and the its application to the enantioselective synthesis of free α-amino esters.

Chapter 1 aims to place this work in the context of the previous literature, highlighting a range of stereoselective [2,3]-rearrangements of allylic ammonium ylides. Examples of catalytic stereoselective [2,3]-rearrangement of allylic ammonium ylides as well as state-of-the-art examples of organocatalytic enantioselective variants of the related [2,3]-Wittig rearrangement are discussed. The aims of this research project are also set out.

Chapter 2 describes the discovery and optimisation of the isothiourea-catalysed [2,3]-rearrangement of 4-nitrophenyl ester quaternary ammonium salts (either isolated or generated *in situ*) to give a range of *syn*-α-amino acid derivatives in excellent yields (33-89%) and stereocontrol (up to >95:5 dr and >99% ee). This represents the first catalytic enantioselective variant of a [2,3]-rearrangement of allylic ammonium ylides.

Chapter 3 describes mechanistic studies. Reaction kinetic analysis by ^{19}F NMR has allowed reaction profiles to be built up, orders of each component to be determined and catalyst resting state to be probed. A catalytic intermediate has been observed; its constitution was proved unambiguously by ^{13}C and ^{15}N isotopic labelling. Isotopic entrainment has proved the observed intermediate to be on-cycle and productive towards catalysis. Competition kinetic isotope effects have provided detailed insight into the [2,3]-rearrangement step of the process. The effect of HOBt upon stereocontrol and the resting state of the catalyst have been probed through *in situ* ^{19}F NMR. Crossover experiments have given detailed insight into the reversibility of each of the proposed catalytic steps. Collaborative computational work has elucidated the origins of stereocontrol and has supported the experimentally proposed mechanism.

Chapter 4 describes the application of this methodology to the enantioselective synthesis of free α-amino esters *via* [2,3]-rearrangement of *N*,*N*-diallyl allylic ammonium ylides. Enantio- and chemoselective [2,3]-rearrangement gave a range of *N*,*N*-diallyl α-amino esters, which could be readily selectively *mono*- or *bis*-*N*-allyl deprotected. *Bis*-*N*-allyl deprotection gave a range of enantioenriched free α-amino esters. Selective *mono*-*N*-allyl deprotection was employed in the synthesis of a functionalised piperidine motif.

Chapter 5 summarises the work outlined in this thesis and draws conclusions, as well as giving insight into potential future projects within the area.

Publications

The work described in this thesis has formed the basis of the following peer reviewed publications:

1) "An Isothiourea-Catalyzed Asymmetric [2,3]-Rearrangement of Allylic Ammonium Ylides"; West, T. H.; Daniels, D. S. B.; Slawin, A. M. Z.; Smith, A. D.; *J. Am. Chem. Soc.* **2014**, *136*, 4476-4479; (Highlighted in *Synfacts* **2014**, *10*, 0536)

2) "Catalytic Stereoselective [2,3]-Rearrangement Reactions"; West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith A. D.; *ACS Catal.* **2015**, *5*, 7446-7479;

3) "Isothiourea-catalysed chemo- and enantioselective [2,3]-sigmatropic rearrangements of *N*,*N*-diallyl allylic ammonium ylides"; West, T. H.6; Spoehrle, S. S. M.; Smith A. D. *Manuscript Submitted*

4) "Catalytic Enantioselective [2,3]-Rearrangement of Allylic Ammonium Ylides: A Mechanistic and Computational Study"; West, T. H.; Walden, D. M.; Taylor, J. E; Brueckner, A. C.; Johnston, R. C; Cheong, P. H. –Y.; Lloyd-Jones, G. C.; Smith, A. D.; *Manuscript Submitted*

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Musolino, Rifahath Mon NP, Danila Gasperini, Jiufeng Wu, Peter Zhang, Liz Munday, Susana Estopina, Patrick Roberts, thank you for all the memories over the years!

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Abbreviations

Ac	Acetyl
ACE-Cl	1-Chloroethyl chloroformate
APCI	Atmospheric pressure chemical ionisation
aq.	Aqueous
Ar	Aryl
atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
BTM	Benzotetramisole
Bu	Butyl
Bz	Benzoyl
C	Celsius
CAN	Ceric ammonium nitrate
CI	Chemical ionisation
cm	Centimetre
d	Doublet
D	Dextro (right)
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DFT	Density functional theory
DIBAL-H	Di-*iso*-butylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppb	1,3-Bis(diphenylphosphino)butane
dr	Diastereomeric ratio
E	Entgegen (opposite)
ee	Enantiomeric excess
EI	Electron Impact
equiv.	Equivalent molar quantity
ESI	Electrospray ionisation
Et	Ethyl
g	Gram(s)

GC	Gas chromatogrpahy
h	Hour(s)
hfacac	hexafluoroacetylacetonato
HOAt	1-Hydro-7-azabenzotriazole
HOBt	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IPA	Isopropanol
i	Iso
ITU	Isothiourea
J	Coupling constant
kcal	Kilocalorie(s)
L	Laevo (left)
LDEA	Lithium diethyl amide
lit.	Literature
M	Molar (mol dm^{-3})
mmol	Millimole
m	Multiplet
Me	Methyl
Mes	Mesityl
MHz	Megahertz
min	Minute(s)
mg	Milligram(s)
mL	Millilitre(s)
mol	Mole(s)
mp	Melting point
M.S.	Molecular Sieves
NFSI	*N*-Fluorobenzenesulfonimide
NHC	N-heterocyclic carbene
NMR	Nuclear magnetic resonance
NSI	Nanospray ionisation
Nuc	Nucleophile
PCC	Pyridinium chlorochromate
Ph	Phenyl
ppm	Parts per million

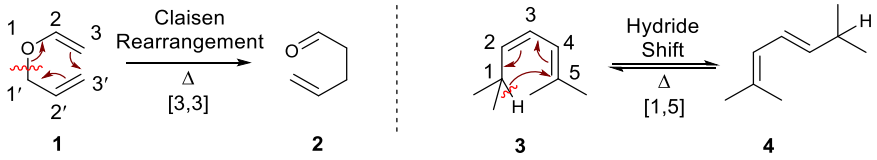
q	Quartet
quant.	Quantitative
R	Rectus (right)
rt	Room temperature
s	Singlet
S	Sinister (left)
sat.	Saturated
t	Tertiary
t	Triplet
T_1	Spin lattice relaxation time
TBAB	Tetra-*n*-butyl ammonium bromide
TBAF	Tetra-*n*-butyl ammonium fluoride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosyl
Z	Zusammen (together)
δ	Chemical Shift

Table of Contents

Chapter 1: Introduction

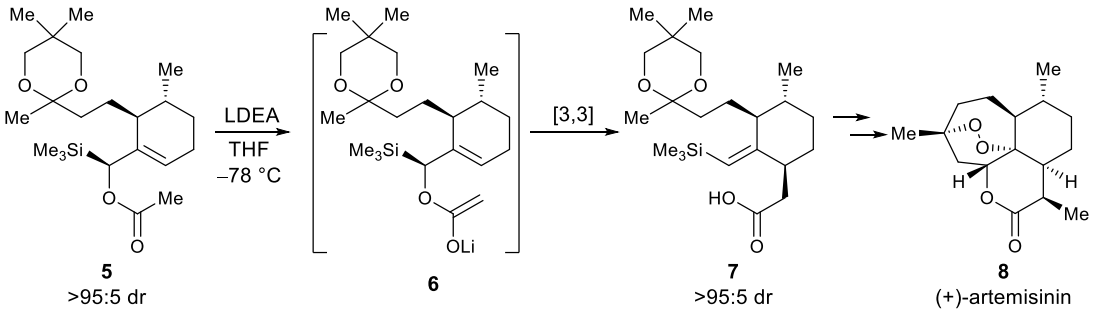
1.1 Sigmatropic Rearrangements

Sigmatropic rearrangements are commonplace within organic synthesis and are routinely utilised in the construction of complex molecular architectures.[1] A sigmatropic rearrangement is defined as the intramolecular migration of σ-bonds adjacent to multiple π-electron systems. These reorganisation processes are a subclass of pericyclic reactions, as they proceed through a transiently conjugated cyclic transition state *via* a concerted reaction mechanism. Sigmatropic rearrangements are classified using the Woodward-Hoffmann nomenclature,[2] of the order of [*n*,*m*]- where atoms are numbered from the bond breaking to the new forming bond (*Scheme 1*).[3]



Scheme 1: Examples of sigmatropic rearrangements highlighting the Woodward-Hoffmann nomenclature.

Sigmatropic rearrangements typically proceed in a stereospecific manner as a result of having a well-defined rigid transition state that proceeds in a concerted fashion. Consequently, sigmatropic rearrangements can be employed when planning multistep synthesis of complex molecules.[1d] For example, the [3,3]-Claisen rearrangement of enolate **6** proceeds with high diastereospecificity (>95:5 dr) to form acid **7**, which is a key intermediate in the total synthesis of the antibiotic (+)-artemisinin **8** (*Scheme 2*).[4]

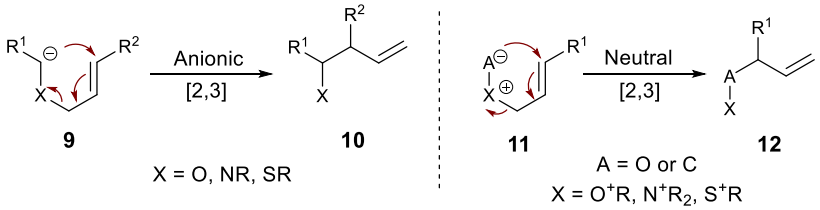


Scheme 2: Example of stereoselective [3,3]-rearrangement employed in total synthesis.[4]

1.2 Stereoselective [2,3]-Rearrangements

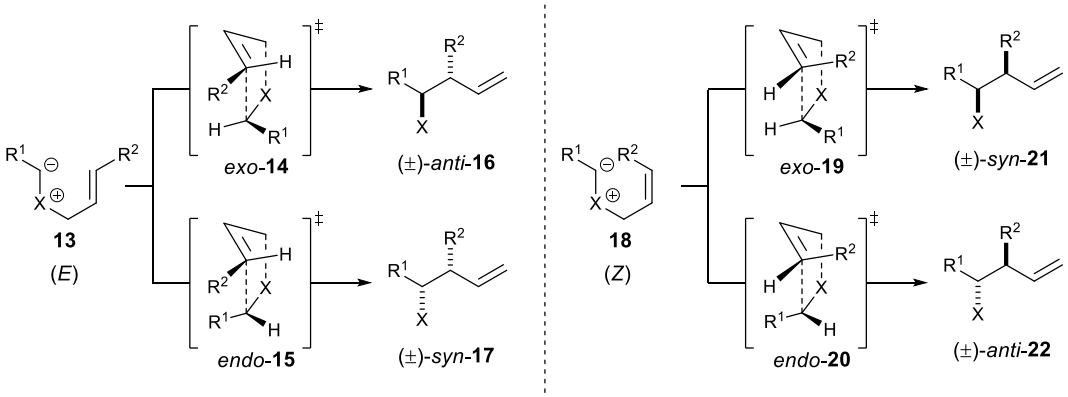
Stereoselective [2,3]-rearrangements have found particular wide-spread use in the synthesis of complex organic molecules. There are two types of [2,3]-rearrangement: anionic and neutral, with neutral [2,3]-rearrangements involving ylide intermediates (*Scheme 3*). [2,3]-Rearrangements differ from many

thermally mediated rearrangements, as they are typically initiated through either a deprotonation or oxidation event to generate the reactive species.



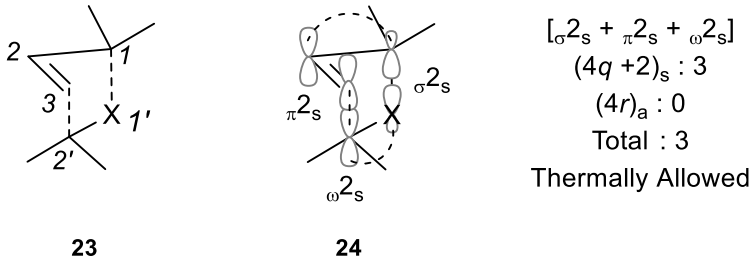
Scheme 3: Classification of neutral and anionic [2,3]-rearrangements.

Stereoselective variants of these processes are of particular interest to synthetic chemists as they allow the construction of up to two stereogenic centres around the newly formed σ-bond as well as (*E*)- or (*Z*)-selectivity on the new π-bond. [2,3]-Rearrangements offer greater conformational flexibility within their five-membered transition state compared with the six-membered transition state of a [3,3]-rearrangement. As a consequence, [2,3]-rearrangements are often more heavily influenced by substituents decorated around the transiently formed five-membered ring, than their [3,3]-rearrangement counterparts, whose conformational flexibility can often make achieving high levels of stereocontrol problematic. The diastereocontrol of many [2,3]-rearrangements is often rationalised by extrapolation of transition states calculated by Houk and Marshall for the [2,3]-Wittig rearrangement (*Scheme 3*, X = O).[5] The stereochemical outcome of a [2,3]-rearrangement is typically dependent upon the substituents adjoined to both the alkene and the anion, as well as the nature of the heteroatom (X) present. The diastereocontrol is dependent upon the relative energies of the *exo* and *endo* transition states. Many [2,3]-rearrangements are stereospecific, with different alkene geometries leading to the opposite relative configurations within the product. For example, (*E*)-**13** leads to the formation of (±)-*anti*-**16** when proceeding through an *exo*-transition state, whereas (*Z*)-**18** leads to the formation of (±)-*syn*-**21** (*Scheme 4*).



Scheme 4: General stereochemical rationale for [2,3]-rearrangements.[5]

[2,3]-Rearrangements are thermally allowed processes under the symmetry guidelines set out by Woodward and Hoffmann. The five-membered envelope transition-state structure of the [2,3]-rearrangement results in direct overlap of the $_{\omega}2_S$ anion component with the $_{\pi}2_S$ alkene component in the formation of the new σ-bond between C(2'), and C(3) in a suprafacial manner, satisfying the Woodward-Hoffman rules for a thermally allowed rearrangement. Breaking the σ-bond between C(1) and C(1') ($_{\sigma}2_S$), and migration of the π-system ($_{\pi}2_S$), both occur in a suprafacial manner. Considering all components this satisfies the Woodward-Hoffman equation, resulting in the process being thermally allowed (*Figure 1*).[6]

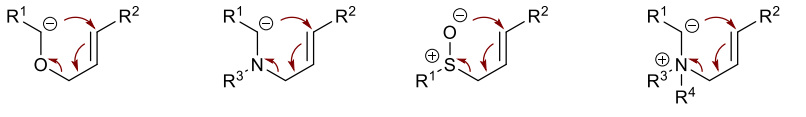


23 **24**

Figure 1: Woodward-Hoffmann analysis of [2,3]-rearrangements.[6]

The mechanism for many [2,3]-rearrangements is thought to proceed through a concerted ionic mechanism, rather than a radical based mechanism. However, as a result of the often complex nature of these reactions making them difficult to study both experimentally and computationally, detailed mechanistic information for many [2,3]-rearrangements is unclear.

Within the area of stereoselective [2,3]-rearrangements there is a wide variety of possible anionic and neutral [2,3]-rearrangements (*Scheme 5*). This thesis focuses on the [2,3]-rearrangement of allylic ammonium ylides, thus the remainder of this introduction focuses on the literature relevant to stereoselective [2,3]-rearrangement of allylic ammonium ylides.

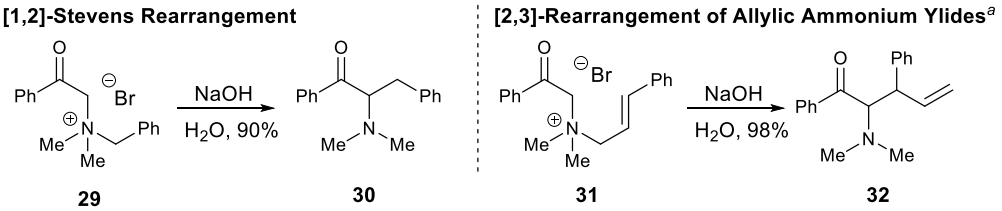


Scheme 5: Examples of [2,3]-rearrangements.

1.3 [2,3]-Rearrangements of Allylic Ammonium Ylides

The [2,3]-rearrangement and competitive [1,2]-rearrangement of allylic ammonium ylides is a powerful route to form α-amino acid derivatives bearing multiple defined stereocentres in a single transformation. The base mediated [1,2]-rearrangement of allylic ammonium ylides was first discovered in 1928 by Stevens.[7] Treatment of isolated *N*-benzyl ammonium salt **29** with NaOH resulted in [1,2]-

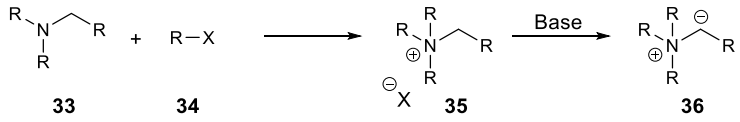
rearrangement of the *N*-benzyl group to *C*(2), which is thought to proceed through homolytic cleavage of the ammonium ylide to form a radical pair, which can readily recombine to form rearrangement product **30**.[7] The competing [2,3]-rearrangement of allylic ammonium ylides was developed in the late 1960's by Ollis.[8] Treatment of isolated *N*-cinnamyl ammonium salt **31** under basic conditions resulted in exclusive [2,3]-rearrangement to form α-amino ketone **32** (*Scheme 6*).[8]



Scheme 6: Competitive [1,2]- and [2,3]-rearrangement of allylic ammonium ylides.[8]
[a]Diastereoselectivity of crude material not reported.

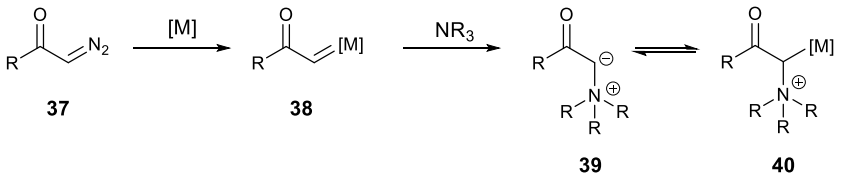
1.3.1 Generation of Ammonium Ylides

The most commonly utilised method for the *in situ* generation of ammonium ylides is through deprotonation of the corresponding quaternary ammonium salt adjacent to the nitrogen atom. Quaternary ammonium salts are themselves prepared through alkylation of the requisite tertiary amine. Whilst this methodology is often employed in the [2,3]-rearrangement of allylic ammonium ylides, there are significant drawbacks with this methodology such as the isolation of reactive ammonium salts. In some cases, isolation can be aided through counterion exchange to non-coordinating counterions, although many quaternary ammonium salts undergo facile *N*-dealkylation to return the corresponding tertiary amine upon attempted ammonium ylide formation.[1f] An example of this methodology is highlighted in *Scheme 6*.



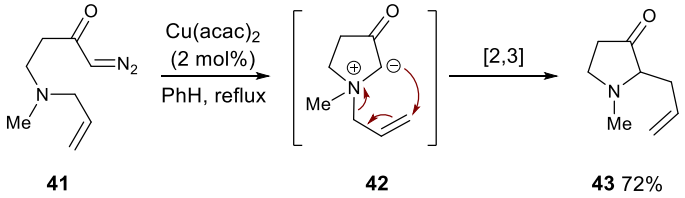
Scheme 7: Generation of ammonium ylides from ammonium salts.

Alternatively, ammonium ylides can be directly generated in a catalytic manner from tertiary amines and diazo compounds in the presence of a copper or rhodium catalyst.[1b] Decomposition of a diazo compound **37** mediated by a transition metal catalyst generates the corresponding metal carbenoid **38**, which can be subsequently intercepted by a Lewis basic tertiary amine to access the desired ammonium ylide **39** or metal bound equivalent **40** (*Scheme 8*).



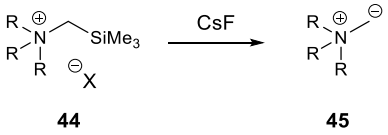
Scheme 8: Generation of ammonium ylides from tertiary amine and diazo compounds.

Clark has extensively examined this type of ammonium ylide generation methodology in an intramolecular manner. This methodology has been employed in the synthesis of a number of cyclic amines, of varying ring size, for example, treatment of *N*-allyl diazoketone **41** with a catalytic amount of $Cu(acac)_2$ (2 mol%), forms ammonium ylide **42**. Subsequent [2,3]-rearrangement of allylic ammonium ylide **42** formed cyclic amine **43** in 72% yield (*Scheme 9*).[9]



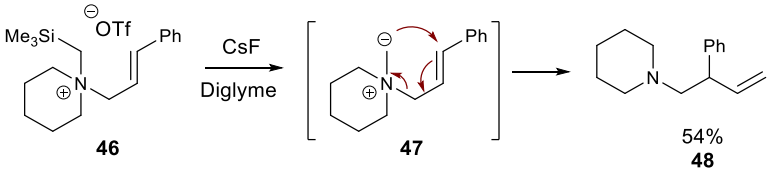
Scheme 9: Copper catalysed ammonium ylide formation and [2,3]-rearrangement.[9]

A less commonly used strategy for the generation of ammonium ylides is the desilylation of ammonium salts bearing a trimethylsilyl substituent. For example, treating β-substituted trimethylsilyl ammonium salt **44** with cesium fluoride results in desilylation to form the corresponding ammonium ylide **45** (*Scheme 10*).[10]



Scheme 10: Ammonium ylide generation through desilylation.

This type of ammonium ylide generation was utilised by Martinez *et. al.* in 1980.[10-11] Treatment of β-trimethylsilyl substituted ammonium salt **46** with cesium fluoride, readily generates the desired ammonium ylide **47**, which can undergo [2,3]-rearrangement to give homoallylic amine **48** in 54% yield (*Scheme 11*).

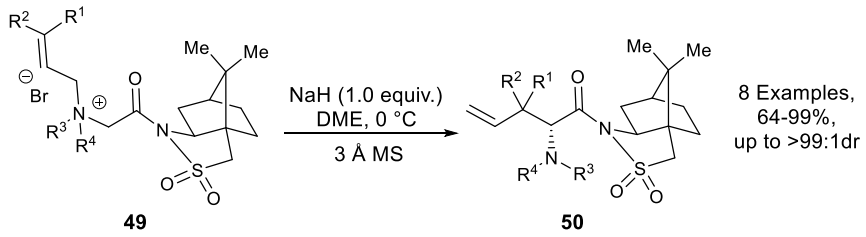


Scheme 11: Utilisation of fluoride mediated ammonium ylide generation.[10-11]

1.3.2 Stereoselective [2,3]-Rearrangements of Allylic Ammonium Ylides

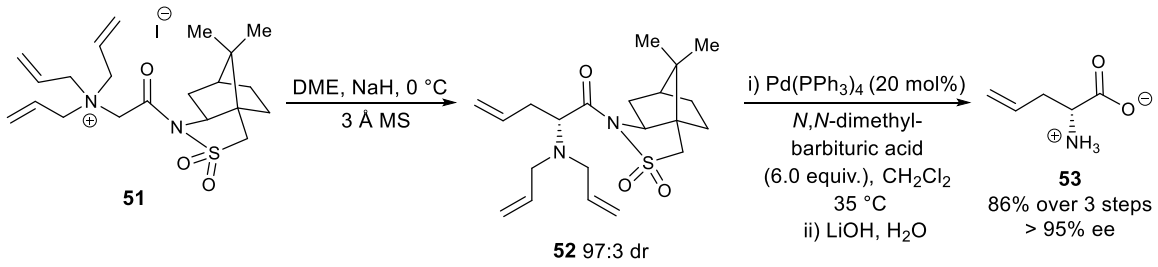
Since the initial work in the area by Ollis and co-workers, a significant body of research has been undertaken to develop stereoselective variants of this reaction. Numerous methods of inducing stereocontrol have been employed in recent years, with the induction of enantiocontrol in these process a particular challenge. A series of key examples of diastereo- and enantioselective [2,3]-rearrangements of allylic ammonium ylides will be highlighted.

In 2005 Sweeney and co-workers[12] reported the asymmetric [2,3]-rearrangement of allylic ammonium ylides utilising Oppolzer's camphorsultam auxiliary[13] to induce diastereo- and enantiocontrol (*Scheme 11*). A range of isolated ammonium salts bearing a camphorsultam auxiliary **49** undergo base-mediated [2,3]-rearrangement when treated with sodium hydride, giving allyl-glycine derivatives **50**, with excellent levels of diastereocontrol (up to >99:1 dr).



Scheme 11: Sweeney's auxiliary approach to stereoselective [2,3]-rearrangements.[12]

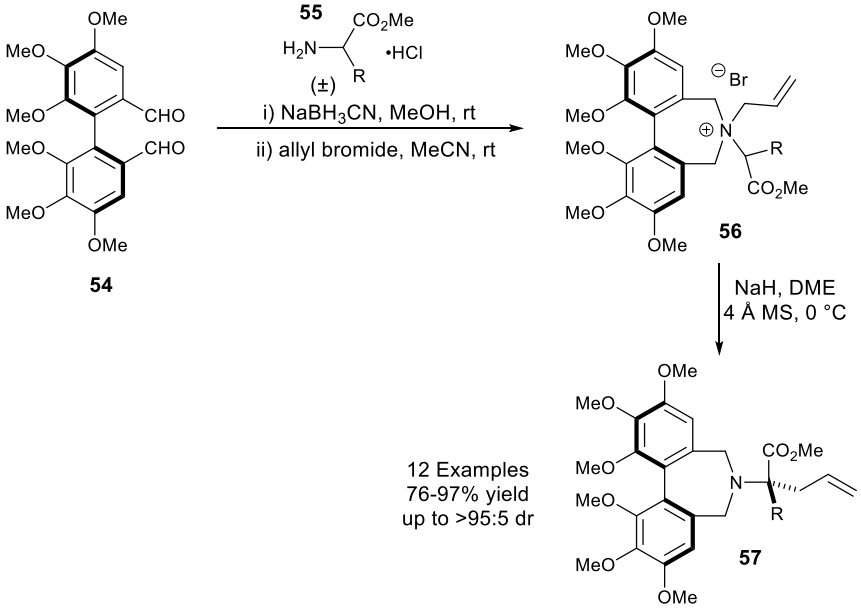
Additionally, the authors demonstrated that this methodology could be applied to the synthesis of (*R*)-allyl glycine **53**. Diastereoselective [2,3]-rearrangement of triallyl ammonium salt **51** gave *N*,*N*-diallyl glycine **52** (97:3 dr). Subsequent Pd-catalysed *N*,*N*-deallylation, followed by hydroxide mediated auxiliary cleavage, gave (*R*)-allyl glycine **53** in 86% yield over the three steps with excellent enantiocontrol (>95% ee) (*Scheme 12*).[12]



Scheme 12: Application of Sweeney's camphorsultam controlled [2,3]-rearrangement to the synthesis of (*R*)-allyl glycine **53**.[12]

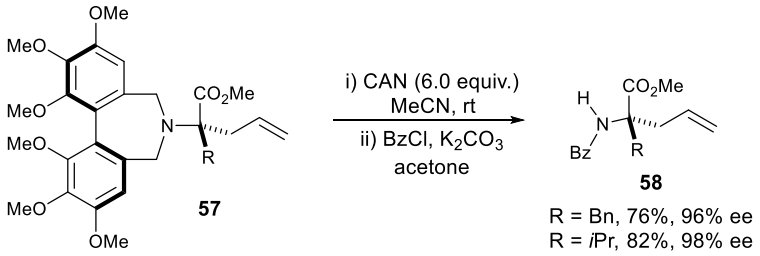
In 2012 Zhu and Xu[14] also employed a chiral auxiliary approach for the synthesis of quaternary α-amino acids through a diastereoselective [2,3]-rearrangement of isolated ammonium salts **56**. Double reductive amination of α-amino ester **55** with axially chiral di-aldehyde **54**, followed by treatment with

allyl bromide gave axially chiral allylic ammonium salt **56**. Treatment of **56** with sodium hydride in DME facilitated diastereoselective [2,3]-rearrangement to give a range of α-aryl and α-alkyl amino esters in excellent yield with excellent levels of diastereocontrol (typically >95:5 dr) (*Scheme 13*).[14]



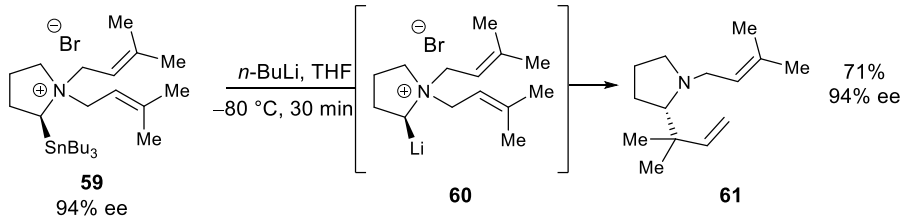
Scheme 13: Zhu and Xu's chiral biaryl auxiliary-controlled [2,3]-rearrangement.[14]

Furthermore, the auxiliary could be readily removed from two α-allyl examples through treatment with CAN, and *N*-benzoyl protection gave α-quaternary amino esters **58** in good yield and with excellent levels of enantiocontrol (96-98% ee) (*Scheme 14*). Notably, chiral dialdehyde **54** could be recovered and recycled once cleaved from the α-amino ester product.[14]



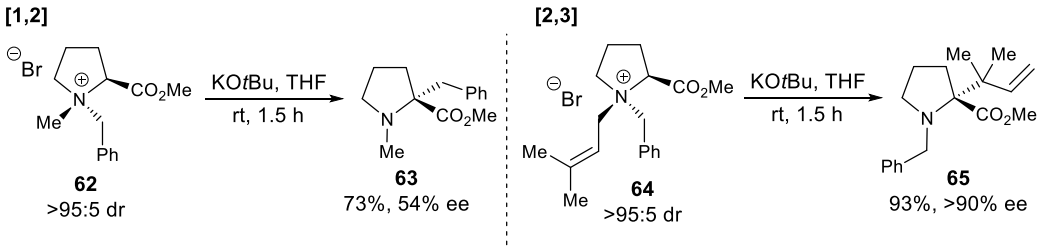
Scheme 14: Removal of biaryl chiral auxiliary.[14]

In 1995, Gawley and co-workers demonstrated that proline-derived enantioenriched organostannane ammonium salts could readily undergo lithium-tin exchange to form the corresponding ammonium ylide, which can undergo [2,3]-rearrangement. For example, treatment of stereodefined *N*,*N*-diprenyl ammonium stannane **59** (94% ee) with *n*-BuLi at −80 °C resulted in smooth lithium-tin exchange followed by enantiospecific [2,3]-rearrangement to give *N*-prenyl proline derivative **61** in good yield with complete retention of enantiopurity (94% ee) (*Scheme 15*).[15]



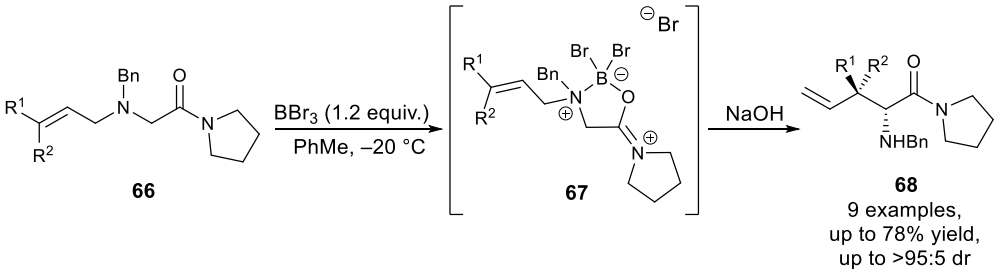
Scheme 15: Chirality transfer through Li-Sn exchange of enantioenriched organostannane ammonium salts.[15]

In 1999, West and co-workers[16] reported the [1,2]- and [2,3]-rearrangements of proline and threonine-derived ammonium ylides with excellent levels of chirality transfer. For example, diastereoselective quarternisation of *N*-benzyl L-proline methyl ester with prenyl bromide gave ammonium salt **64**, which upon treatment with potassium *tert*-butoxide selectively gave [2,3]-rearrangement product **65** in excellent yield (93%) with complete chirality transfer. In contrast the treatment of *N*-methyl,*N*-benzyl ammonium salt **62** under the same rection conditions gave exclusive [1,2]-rearrangement to give *N*-methyl L-proline methyl ester **63** in reduced enantiopurity (54% ee). This methodology was utilised in the rearrangement of *N*-prenyl L-proline and L-threonine derived ammonium salts (*Scheme 16*).[16]



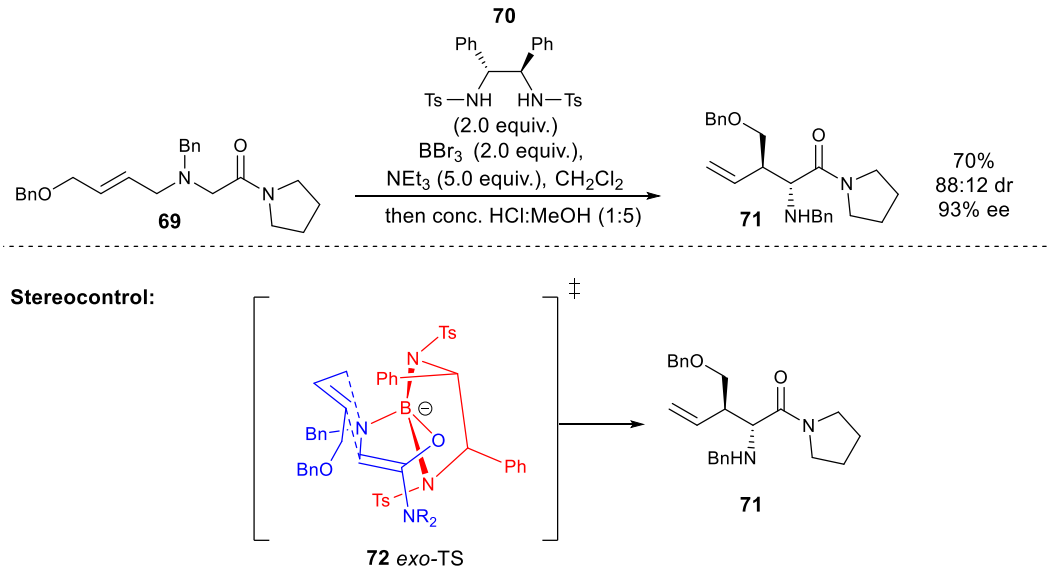
Scheme 16: Chirality transfer in the [2,3]-rearrangement of *N*-prenyl L-proline derived ammonium salts.[16]

Somfai and co-workers[17] reported the use of stoichiometric boron tribromide as a Lewis acid to mediate the [2,3]-rearrangement of allylic α-amino amides **66**. Treatment of **66** with boron tribromide forms ammonium salt **67**, which upon treatment with aq. sodium hydroxide undergoes rapid [2,3]-rearrangement to form α-amino amides **68** in excellent yield with excellent levels of diastereocontrol. This proof of concept methodology was demonstrated to proceed well when *N*-crotyl and *N*-cinnamyl substituents were incorporated into **68** (*Scheme 17*).[17]



Scheme 17: BBr_3 mediated [2,3]-rearrangement of α-amino amides.[17]

In 2005 Somfai and co-workers[18] subsequently reported a highly enantioselective version of this process. Enantiomerically pure diamine **70** and boron tribromide were used in stoichiometric amounts to facilitate the enantioselective [2,3]-rearrangement of α-amino amides to form the corresponding homoallylic amines with excellent levels of stereocontrol (up to 95:5 dr and up to 99% ee). For example, treatment of CH_2OBn substituted *N*-allyl amine **69** with BBr_3 (2.0 equiv.) and **70** (2.0 equiv.) followed by NEt_3 resulted in [2,3]-rearrangement of **69** to form homoallylic amine **71** in 70% yield and 88:12 dr (*anti*:*syn*) and 93% ee (*Scheme 18*). A number of C(3)-substituted alkyl and aryl allylic amines were tolerated within the reaction, and notably chiral amine **70** could be readily recovered in quantitative yield. The observed *anti*-diastereoselectivity can be rationalised by the [2,3]-rearrangement step proceeding through the kinetically preferred *exo*-transition state **72**. The enantiocontrol is a consequence of the allyl group rearranging *anti* to the *N*-Ts group on the chiral diamine ligand.[18-19]



Scheme 18: Enantioselective [2,3]-rearrangement of *N*-allyl amine **69**.[18-19]

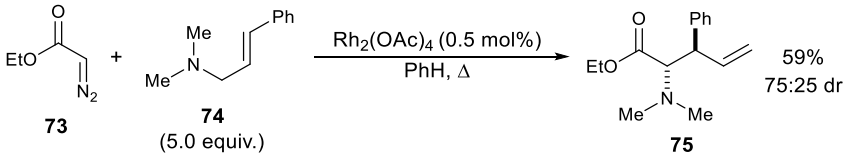
1.3.3 Catalytic Stereoselective [2,3]-rearrangements of allylic ammonium ylides

Previous examples have showcased the use stoichiometric auxiliaries or ligands to effect stereocontrol in the [2,3]-rearrangement of allylic ammonium ylides. This next section will highlight a range of

catalytic stereoselective [2,3]-rearrangements of allylic ammonium ylides. In this context the term "catalytic" is used to refer to the use of a substoichiometric quantity of catalyst either in the generation of ammonium ylide/salt or to facilitate the [2,3]-rearrangement step of the process.

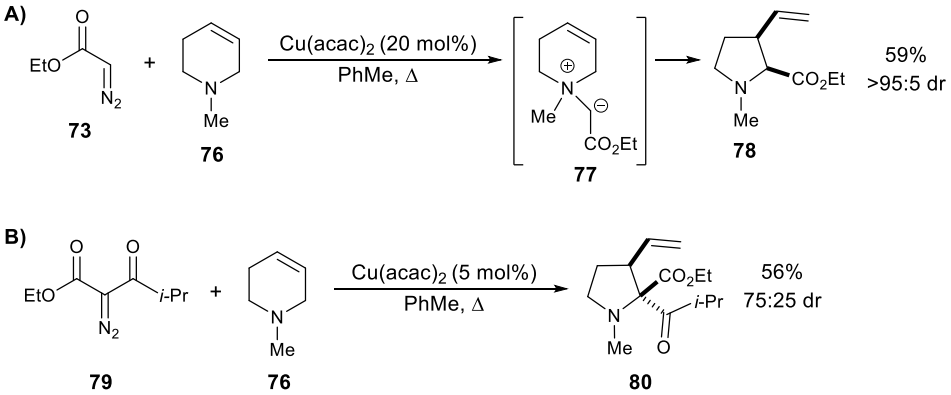
1.3.3.1 Intermolecular Generation of Ammonium Salts/Ylides

In 1981 Doyle and co-workers[20] reported the first diastereoselective intermolecular ammonium ylide formation and [2,3]-rearrangement utilising the catalytic decomposition of a diazo compound. Treatment of ethyl diazoacetate **73** with $Rh_2(OAc)_4$ (0.5 mol%) in the presence of excess *N*,*N*-dimethyl tertiary amine **74** gave α-amino acid derivative **75** in 59% yield and 75:25 dr (*anti*:*syn*) (*Scheme 19*). Che and co-workers have also reported a similar reaction employing a ruthenium-porphyrin catalyst, obtaining **75** with the same level of diastereocontrol.[20]



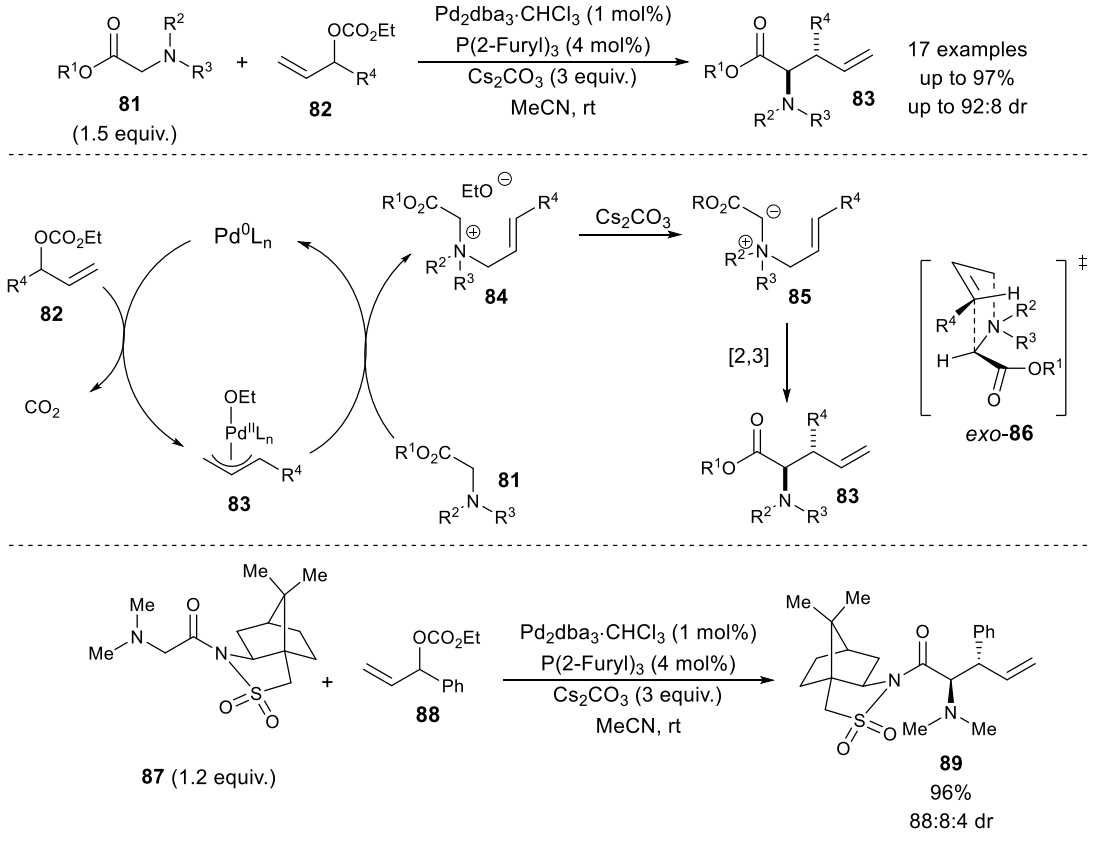
Scheme 19: Doyle's Rh-catalysed ammonium ylide generation and [2,3]-rearrangement.[20]

In 2003 Sweeney and co-workers[21] reported ammonium ylide generation and subsequent [2,3]-rearrangement using *N*-methyl tetrahydropyridine **76**, ethyl diazoacetate **73** and $Cu(acac)_2$ (20 mol%). Notably, the use of $Rh_2(OAc)_4$ resulted in a complex mixture of products, likely due to a competing cyclopropanation reaction on the alkene. The reaction of ethyl diazoacetate **73** with *N*-methyl tetrahydropyridine **76** resulted in the formation of *syn*-pyrrolidine **78** in 59% yield with excellent diastereocontrol (>95:5 *syn*:*anti*). α-Keto diazoacetates could also be used in this process, allowing access to pyrrolidine **80** bearing a quaternary stereocentre in moderate yield (56%) and diastereocontrol (75:25 dr *syn*:*anti*) (*Scheme 20*).[21]



Scheme 20: Copper-catalysed ammonium ylide formation [2,3]-rearrangement using *N*-methyl tetrahydropyridines.[21]

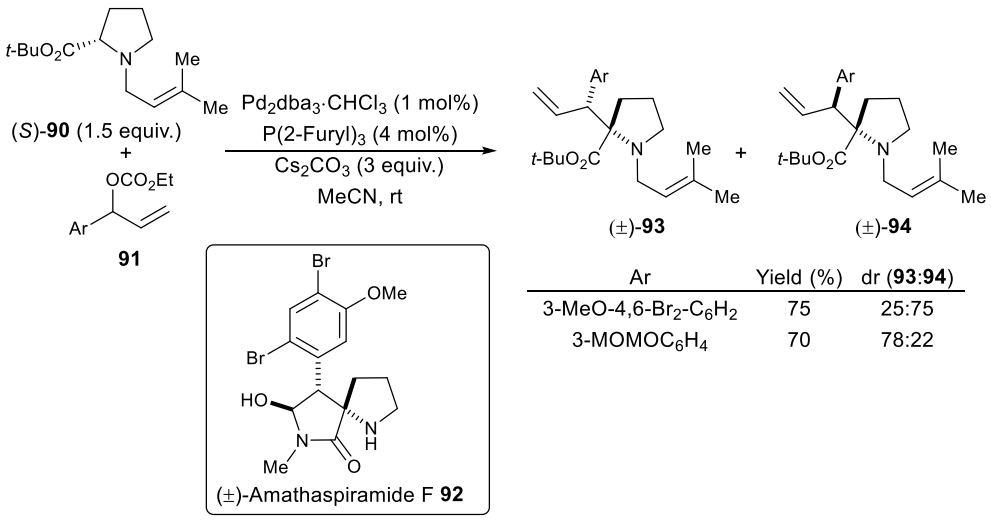
In 2011, Tambar and co-workers[22] reported the catalytic generation of ammonium salts and subsequent stereoselective [2,3]-rearrangement utilising Pd-catalysed allylic substitution chemistry. Reaction of allyl carbonate **82** with Pd^0L_n forms $Pd^{II}L_n$ allyl complex **83**, which upon interception with tertiary amino esters **81** forms the corresponding quaternary ammonium salt **84**. Which undergo rapid deprotonation into ammonium ylides **85**, and subsequent diastereoselective [2,3]-rearrangement forms *anti*-α-amino esters **86** in excellent yield and diastereocontrol. Reaction optimisation found the catalyst ligand combination of $Pd_2dba_3{\cdot}CHCl_3$ and P(2-furyl)$_3$ to be optimal for good yields of the rearranged product. The reaction was general across a range of aryl, heteroaryl, and alkyl substituted allylic carbonates, as well as for a number of substituted α-amino esters and ketones, forming the corresponding *anti*-α-amino acid derivatives. This methodology could be rendered enantioselective through employment of Oppolzer's camphorsultam auxiliary, generating enantiomerically enriched α-amino acid derivatives such as **89** in excellent yield and diastereocontrol. The observed *anti*-diastereocontrol is thought to be a result of an *exo*-transition state **86** during the stereodetermining [2,3]-rearrangement step of the process (*Scheme 21*).[22]



Scheme 21: Pd-catalysed generation of ammonium salts and subsequent diastereoselective [2,3]-rearrangement.[22]

Tambar[23] subsequently applied this methodology to the formal total synthesis of marine alkaloid (±)-amathaspiramide F **92** (*Scheme 22*). Treatment of proline derived α-amino ester **90** with decorated aryl

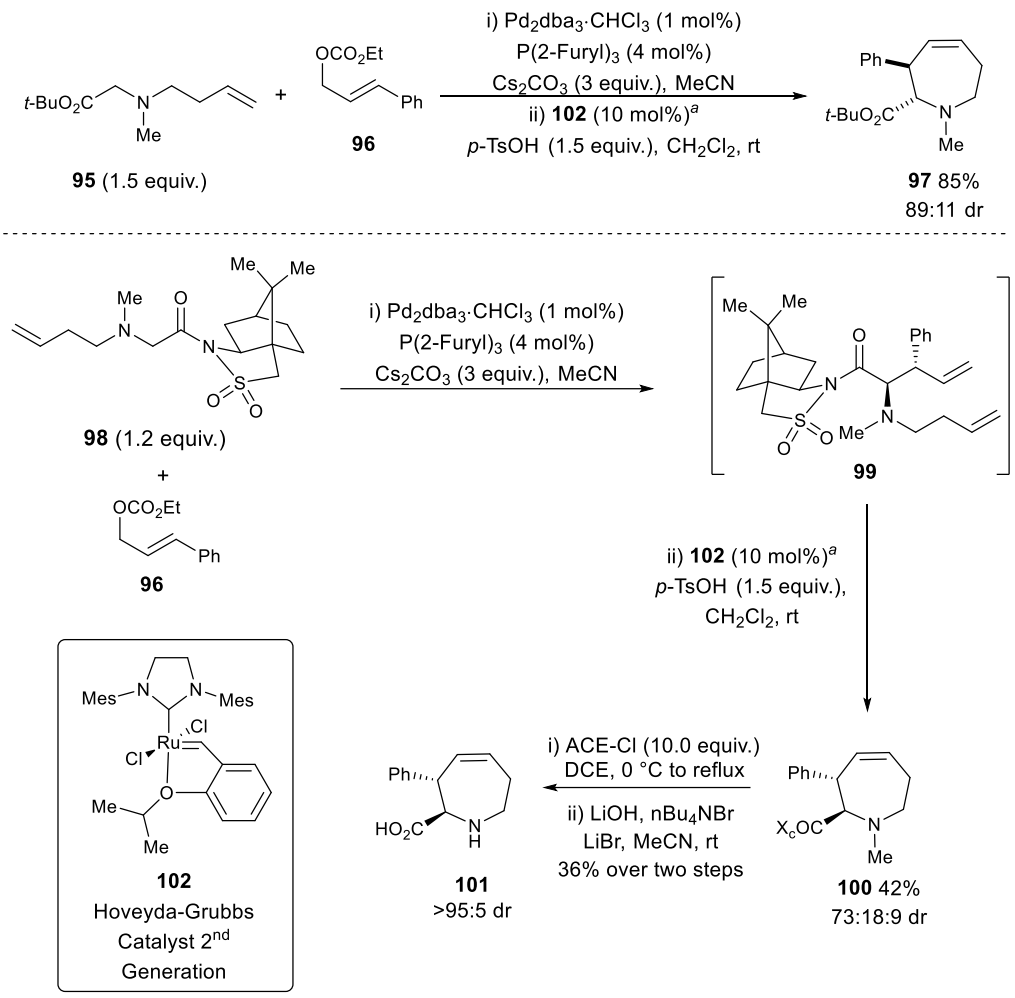
carbonate **91** under the previously optimised reaction conditions resulted in the formation of the corresponding [2,3]-rearrangement product in good yield (75%) albeit with preferential formation of the undesired diastereoisomer **94** (75:25 dr). Examination of a simplified substrate found that the presence of an *ortho*-substituent led to preferential formation of the undesired diastereomer. Adjustment in the synthetic route resulted in the use of 3-OMOM substituted allylic carbonate, giving preferentially the desired diastereoisomer **93** in excellent yield and moderate diastereocontrol (78:22 dr). Subsequent derivatisation of the rearrangement product **93** gave an advanced intermediate in the formal total synthesis of (±)-amathaspiramide F **92** (*Scheme 22*).[23]



Ar	Yield (%)	dr (**93**:**94**)
3-MeO-4,6-Br_2-C_6H_2	75	25:75
3-MOMOC_6H_4	70	78:22

Scheme 22: Pd-catalysed ammonium salt formation-[2,3]-rearrangement of proline derived tertiary amine and formal synthesis of (±)-amathaspiramide F **92**.[23]

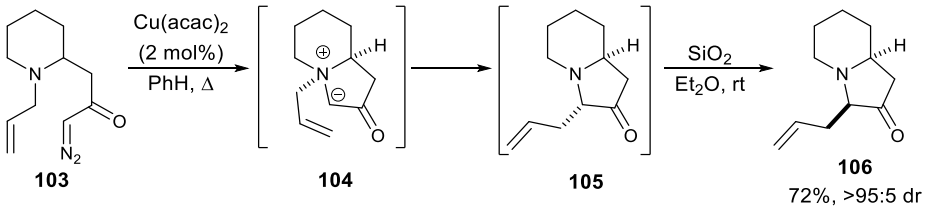
This methodology was further applied to the diastereoselective synthesis of a range of cyclic α-amino acid derivatives through a tandem ammonium salt formation-[2,3]-rearrangement followed by ring-closing metathesis.[24] For example, treatment of *N*-methyl-*N*-homoallyl amino ester **95** with cinnamyl carbonate **96** under the previously optimised conditions, followed by ring-closing metathesis using Hoveyda-Grubbs II catalyst **102** using *p*-TsOH as an additive, gave cyclic α-amino ester **97** in 85% yield with good diastereocontrol (89:11 dr). This methodology could be used to access an enantioenriched α-amino acid **101** using an α-amino ester **98** bearing Oppolzer's camphorsultam as the starting material, followed by subsequent *N*-methyl deprotection and auxiliary cleavage (*Scheme 23*).[24]



Scheme 23: Application of Pd-catalysed ammonium salt formation-[2,3]-rearrangement to the synthesis of cyclic α-amino acids, [a]Hoveyda-Grubbs II **102** added in two portions (2 × 5 mol%).[24]

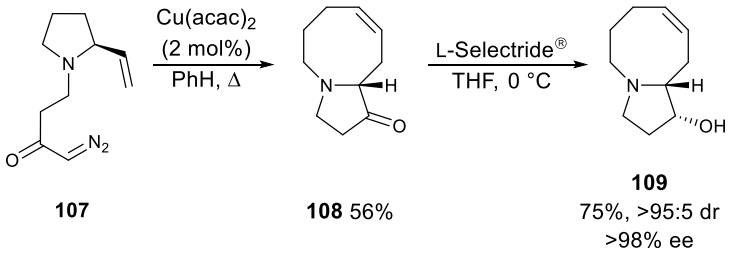
1.3.3.2 Intramolecular Generation of Ammonium Salts/Ylides

In 1994, Clark and co-workers reported the first example of intramolecular ammonium ylide generation-[2,3]-rearrangement.[9] Reaction of diazoketone **103** with $Cu(acac)_2$ (2 mol%) generated ammonium ylide **104** *via* the corresponding metal carbenoid. Subsequent diastereoselective [2,3]-rearrangement gave indolizidine **105** as a single diastereomer, however treatment with silica gel resulted in complete epimerisation into the opposite diastereoisomer **106**, which was isolated in 72% yield. This strategy was applied to the diastereoselective synthesis of a range of pyrrolizidine, indolizidine, and quinolizidine architectures. A range of acyclic substrates containing a stereogenic centre on the alkyl tether connecting the allylic amine and the diazoketone was also examined in this methodology. Ylide-formation and [2,3]-rearrangement gave the corresponding cyclic amines, but with low diastereocontrol (*Scheme 24*).[9]



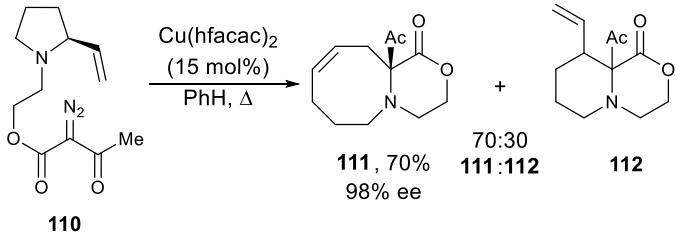
Scheme 24: Intramolecular copper-catalysed ammonium ylide generation-diastereoselective-[2,3]-rearrangement.[9]

Clark and co-workers[25] subsequently applied this methodology to the asymmetric synthesis of the CE ring system of the manzamine and ircinal families of marine alkaloids. Diazoketone **107** was readily prepared from (*S*)-prolinol in four steps. Diazoketone **107** was then reacted with $Cu(acac)_2$ (2 mol%) forming bicycle **108** in 56% yield. Reduction with L-Selectride® gave alcohol **109** as a single diastereoisomer with excellent levels of enantiocontrol (>98% ee), demonstrating full chirality transfer within the copper-catalysed ammonium ylide-[2,3]-rearrangement process (*Scheme 25*).[25]



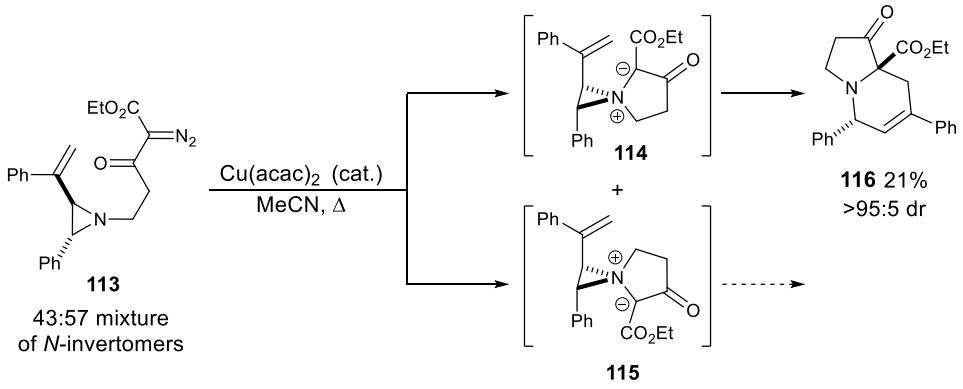
Scheme 25: Asymmetric synthesis of CE ring utilising copper catalysed ammonium ylide generation-[2,3]-rearrangement.[25]

In 1996 McMills and co-workers[26] reported a similar approach to the synthesis of medium-sized azacane rings. (*S*)-Proline derived diazo ketoester **110** was treated with a catalytic amount of $Cu(hfacac)_2$ (15 mol%), to form azacane **111** in excellent yield (70%) with high levels of enantiocontrol (98% ee). The authors also observed competing [1,2]-rearrangement to give **112** (70:30 [2,3]:[1,2]), which is likely due to the increase in tether length relative to **108** (*Scheme 25*), the relative and absolute configurations of [1,2]-product **112** were not reported.[26]



Scheme 26: Asymmetric synthesis of azacane ring **111**, using ammonium ylide generation-[2,3]-rearrangement.[26]

Rowlands and Barnes[27] have reported the copper-catalysed aziridinium ylide generation-[2,3]-rearrangement of diazoketone **113**. The reaction of **113** with a catalytic amount of $Cu(acac)_2$ resulted in the formation of two aziridinium ylides **114** and **115**, due to slow rate of inversion of configuration at nitrogen in the aziridine starting material **113** (43:57 mixture of *N*-invertomers). Selective [2,3]-rearrangement of **114** resulted in the formation of bicyclic amine **116** in modest yield (21%) with excellent levels of diastereocontrol (>95:5 dr). The opposite ammonium ylide invertomer **115** is unable to undergo [2,3]-rearrangement, accounting for the low yield of rearrangement product **116** (*Scheme 27*).[27]



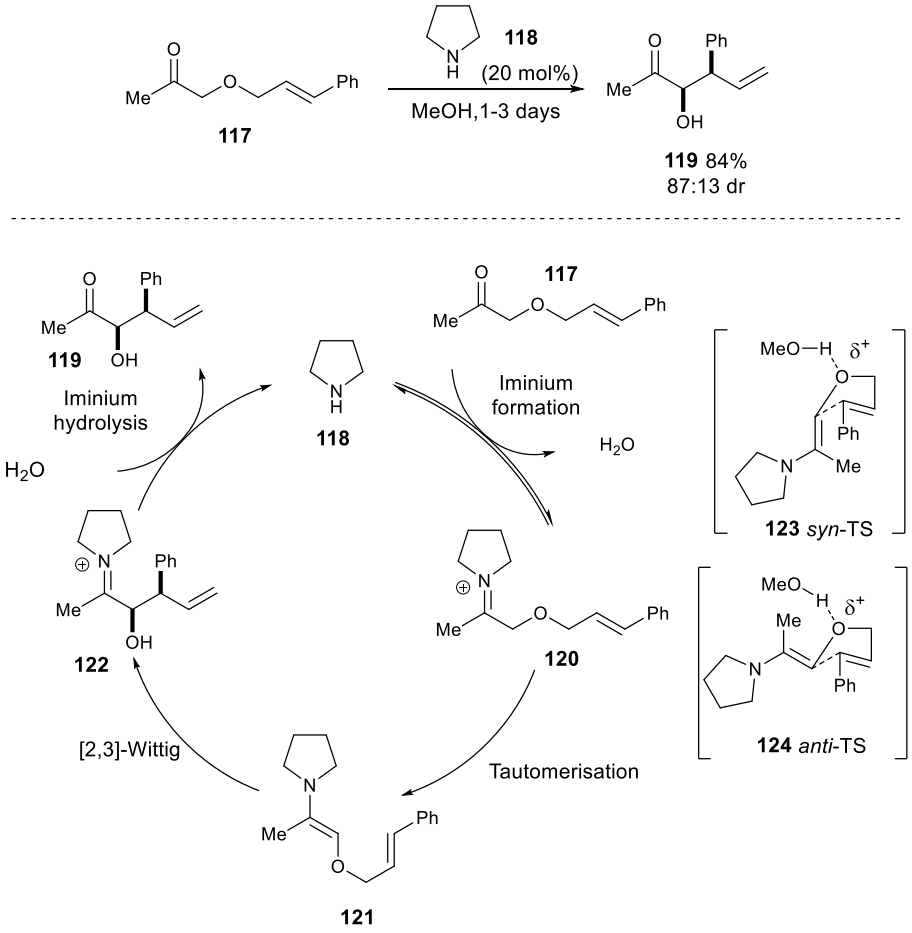
Scheme 27: Copper-catalysed aziridinium ylide formation-[2,3]-rearrangement.[27]

1.4 Conclusions and Aims

Whilst there are a number of elegant methodologies to achieve catalytic stereoselective [2,3]-rearrangements of allylic ammonium ylides, at the onset of this thesis there were no catalytic enantioselective variants of this reaction. It is the aim of this thesis to develop and fully investigate an organocatalytic enantioselective [2,3]-rearrangement of allylic ammonium ylides.

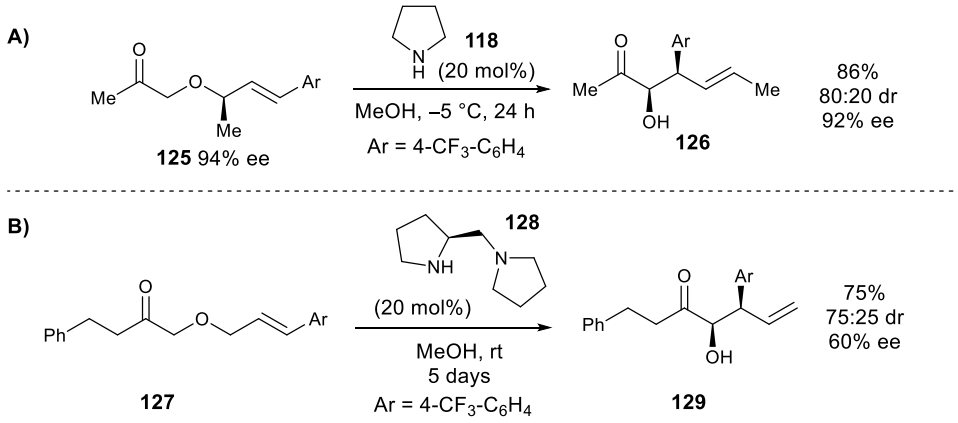
Although there are no organocatalytic enantioselective [2,3]-rearrangements of allylic ammonium ylides, there have been a few reports of related organocatalytic [2,3]-Wittig rearrangements. In 2006 Gaunt and co-workers[28] reported their efforts towards an enantioselective organocatalytic variant of the [2,3]-Wittig rearrangement using secondary-amine catalysis. Initial work in the racemic series showed that employing pyrrolidine **118** as a catalyst, α-allyloxy ketone **117** reacts to form enamine **121**, which can undergo diastereoselective [2,3]-rearrangement into homoallylic alcohol **119** in good yield with excellent levels of diastereocontrol (87:13 dr). The reaction was applied to a wide range of aliphatic ketones, as well as a number of allylic ethers incorporating alkyl, aryl, alkynyl and alkenyl substituents all reacting smoothly to give a suite of homoallylic alcohols in excellent yield with modest to excellent diastereocontrol. The authors noted that the diastereoselectivity of the reaction could be improved through lowering the reaction temperature to −25 °C, however this resulted in significantly longer reaction times to achieve complete substrate conversion. Using methanol as the solvent was essential

to achieve diastereocontrol, suggesting that the protic solvent is intimately involved in hydrogen-bonding to the substrate during the [2,3]-rearrangement step. The observed *syn*-diastereoselectivity was rationalised by *syn*-pre transition state assembly **123**, where the (*E*)-geometry of the enamine dictates the relative configuration of the products (*Scheme 28*).[28]



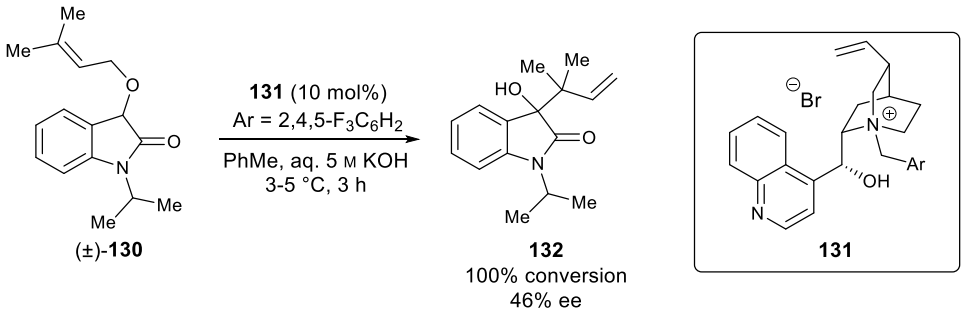
Scheme 28: Pyrrolidine-catalysed [2,3]-Wittig rearrangement.[28]

Notably, the use of enantioenriched allylic ether **125** (94% ee) resulted in good-levels of chirality transfer into rearrangement product **126** (4:1 dr, 92% ee), suggesting that the [2,3]-rearrangement proceeds through a concerted mechanism (*Scheme 28*). In addition, a single example of an enantioselective variant was reported using (*S*)-proline derived diamine **128** (20 mol%) as the catalyst. Treatment of α-allyloxy ketone **127** with **128** in methanol for five days resulted in enantioselective rearrangement, forming **129** in 75% yield with modest diastereocontrol and encouraging enantiocontrol (60% ee) (*Scheme 29*).[28]



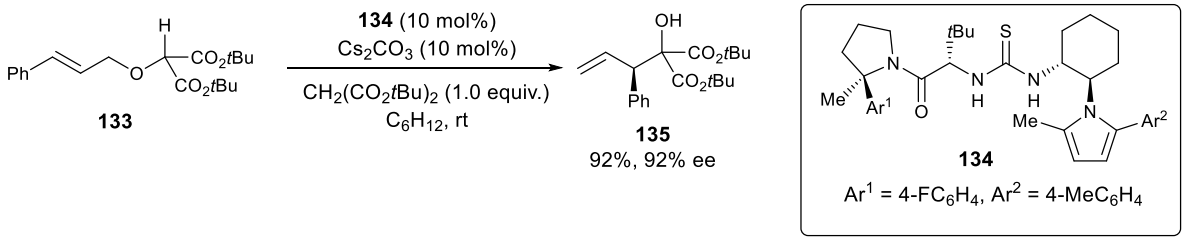
Scheme 29: A) Chirality transfer in pyrrolidine-catalysed [2,3]-Wittig rearrangement **B)** Enantioselective variant of organocatalysed [2,3]-Wittig rearrangement.[28]

In 2015, Denmark and co-workers[29] reported an enantioselective [2,3]-Wittig rearrangement utilising chiral quaternary ammonium salts as phase-transfer catalysts. A range of 3-(alkenyloxy)-1-protected-2-oxindoles was evaluated with various cinchonidine-derived quaternary ammonium salt catalysts. For example, prenyl-ether oxindole **130** was treated with a catalytic amount of **131** (10 mol%) in the presence of aq. 5 M KOH, resulting in full conversion of **130** into rearranged product **132** with modest, albeit encouraging enantiocontrol (46% ee). This methodology was applied to a range of allyl- and prenyl-oxy ether substituted and *N*-protected oxindoles, all proceeding with good conversion into the rearrangement products with modest levels of enantiocontrol (*Scheme 30*).



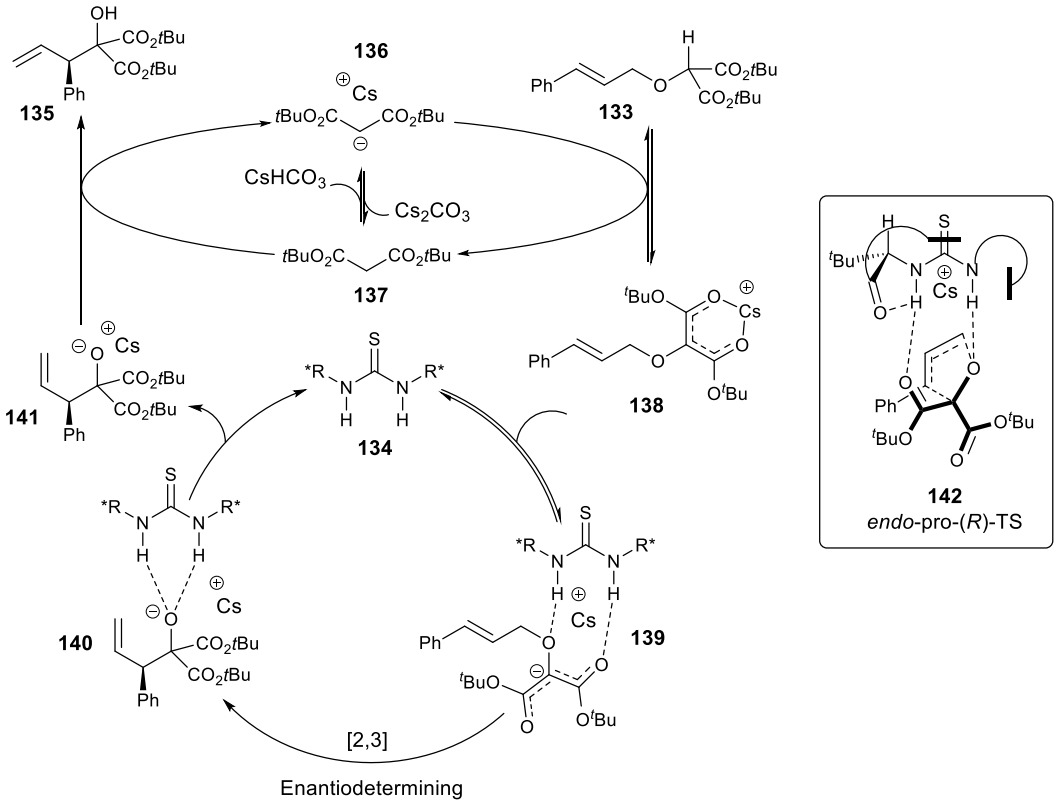
Scheme 30: Enantioselective phase-transfer-catalysed [2,3]-Wittig rearrangement of alkenyloxy oxindoles, absolute configuration of the major enantiomer not determined.[29]

In 2016 Jacobsen and co-workers[30] reported an enantioselective catalytic [2,3]-Wittig rearrangement of α-allyloxy carbonyl compounds using a chiral thiourea catalyst to give a range of homoallylic alcohols with excellent levels of enantiocontrol. For example, reaction of cinnamyl di-*tert* butyl malonate **133** with *in situ* generated cesium di-*tert*-butyl malonate in the presence of chiral thiourea **134** resulted in [2,3]-rearrangement to form homoallylic alcohol **135** in 92% yield and 92% ee (*Scheme 31*). This methodology was applied to a range of aryl, heteroaryl and alkyl substituted allylic ethers giving a suite of homoallylic alcohols in excellent yield and levels of enantiocontrol (72-93% ee).



Scheme 31: Jacobsen's thiourea-catalysed enantioselective [2,3]-Wittig rearrangement.[30]

The authors also conducted rigorous mechanistic and computational studies. Reaction Progress Kinetic Analysis, a series of crossover experiments, and kinetic isotope effects resulted in the following mechanistic proposal (*Scheme 32*). Substrate **133** undergoes reversible deprotonation by $CsCH(CO_2{}^tBu)_2$ **136** to form cesium enolate **138** with thiourea catalyst **134** binding to enolate **139** to facilitate irreversible enantiodetermining and turnover-limiting [2,3]-rearrangement. Release of anion **141** and subsequent protonation by di-*tert* butyl malonate **137** forms product **135** and regenerates thiourea catalyst **134**. DFT calculations have elucidated the origins of stereocontrol, with cation-π interactions between the Cs^+ and both pyrrole and aryl units of the catalyst leading to a favoured *endo*-type transition state **142**.



Scheme 32: Proposed catalytic cycle for thiourea catalysed [2,3]-Wittig rearrangement and cartoon representation of the proposed transition state.

1.4.1 Project Aims

This thesis aims to develop a highly enantioselective catalytic [2,3]-rearrangement of allylic ammonium ylides. It was postulated that a chiral Lewis basic tertiary amine based catalyst, such as an isothiourea, could facilitate such a process. Isothiourea catalysts have been extensively used as effective catalysts for a wide range of enantioselective acylative catalytic processes, including the kinetic resolutions of alcohols, kinetic resolutions of carboxylic acids and Steglich rearrangements.[31] Isothioureas have also been employed in enantioselective silylations and in the activation of α,β-unsaturated substrates, however probably the most prominent use of isothioureas by the Smith group and others, is in the generation of C(1)-ammonium enolates (*Figure 2*).[31]

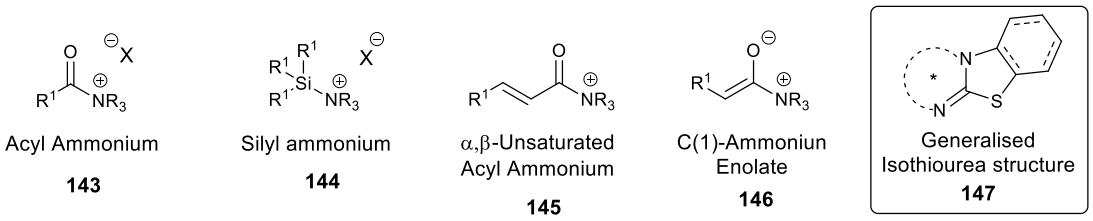
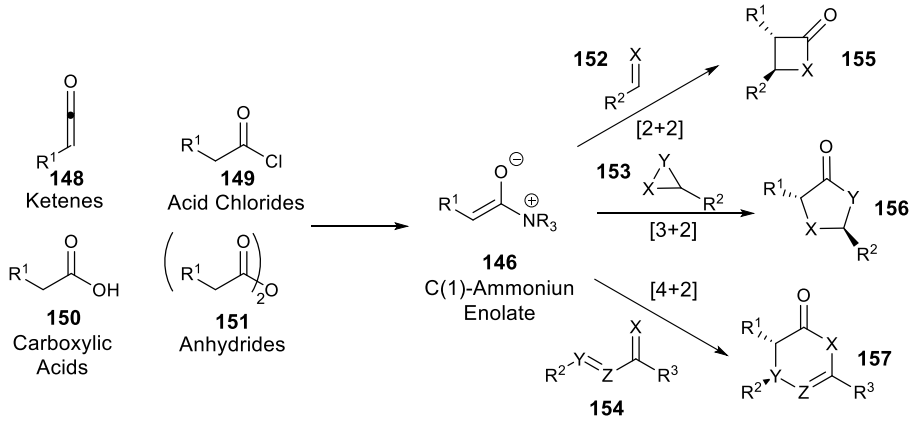


Figure 2: Isothiourea reactive intermediates utilised in catalysis.

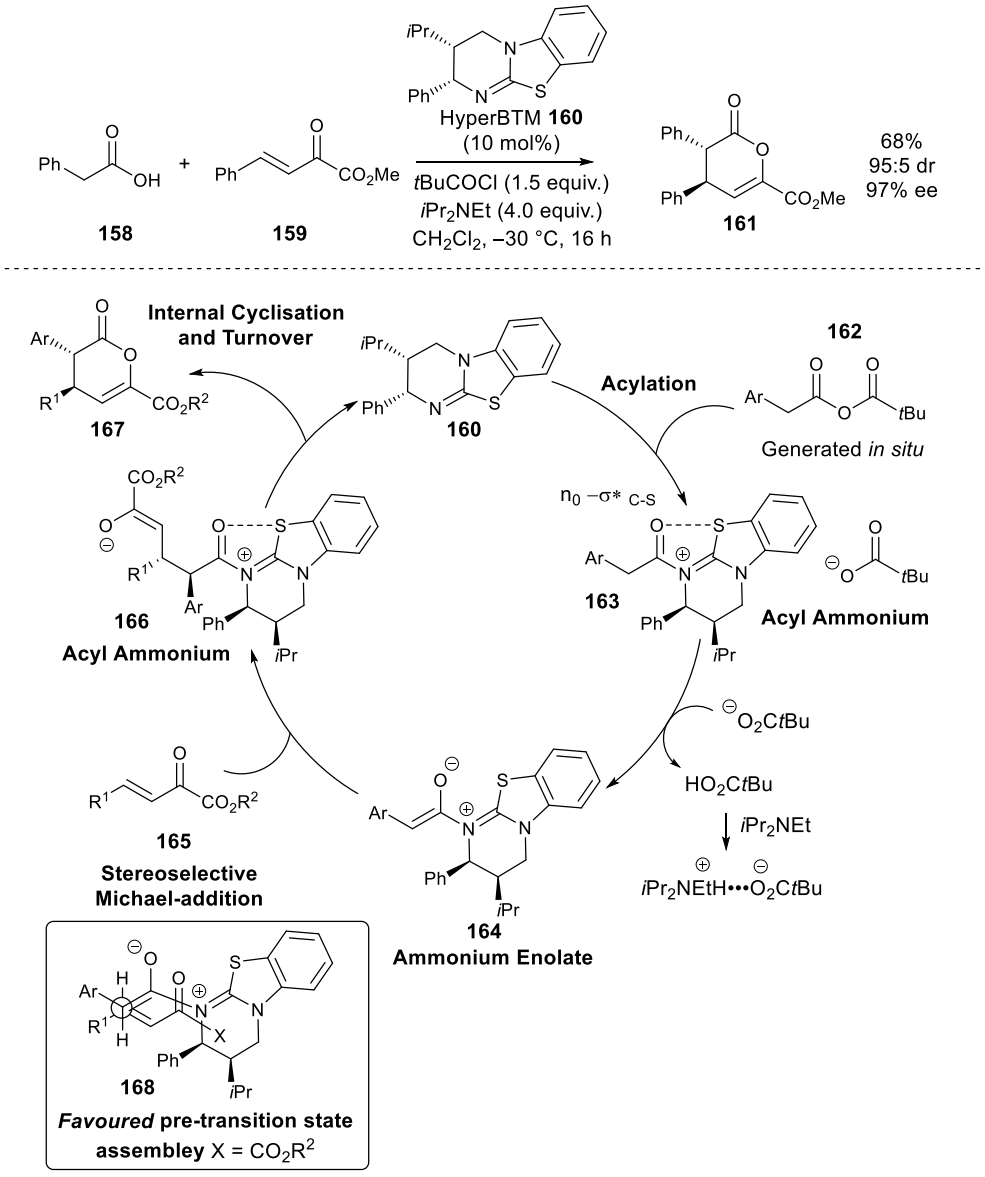
C(1)-Ammonium enolates **146** are typically generated *in situ* from either ketenes, acid chlorides, carboxylic acids or anhydrides and react in inter or intramolecular formal cycloaddition processes with suitable π-systems to form a wide range of stereodefined heterocyclic products (*Scheme 33*).



Scheme 33: Use of C(1)-ammonium enolates in catalysis.[31]

In these processes, intramolecular cyclisation is essential to release the isothiourea catalyst to continue in the catalytic cycle. This internal cyclisation turnover methodology has been extensively explored by the Smith group and others. For example, Smith and co-workers[32] demonstrated that HyperBTM **160** efficiently catalyses the intermolecular Michael addition-cyclisation of arylacetic acid and α-keto-β,γ-

unsaturated esters to give a range of *anti*-dihydropyranones with diastereo- and enantiocontrol (up to 98:2 dr, up to 99% ee). Mechanistically *in situ* activation of the arylacetic with pivaloyl chloride to form the corresponding mixed anhydride, provides a suitable C(1)-ammonium enolate precursor **162**. Acylation of HyperBTM **160** forms acyl ammonium **163**, deprotonation *via* the pivalate counterion forms C(1)-ammonium enolate **164**. Enantioselective Michael addition forms acyl ammonium **166**, internal cyclisation through the generated enolate forms the *anti*-dihydropyranone **167** and releases the isothiourea catalyst. The observed stereocontrol can be rationalised by pre-transition state assembly **168**, with a key non-bonding 1,5 oxygen sulfur interaction stabilising this assembly allowing for high levels of enantiocontrol. This key interaction with be discussed in detail in the context of [2,3]-rearrangements in *chapters 2 & 3*.[32]

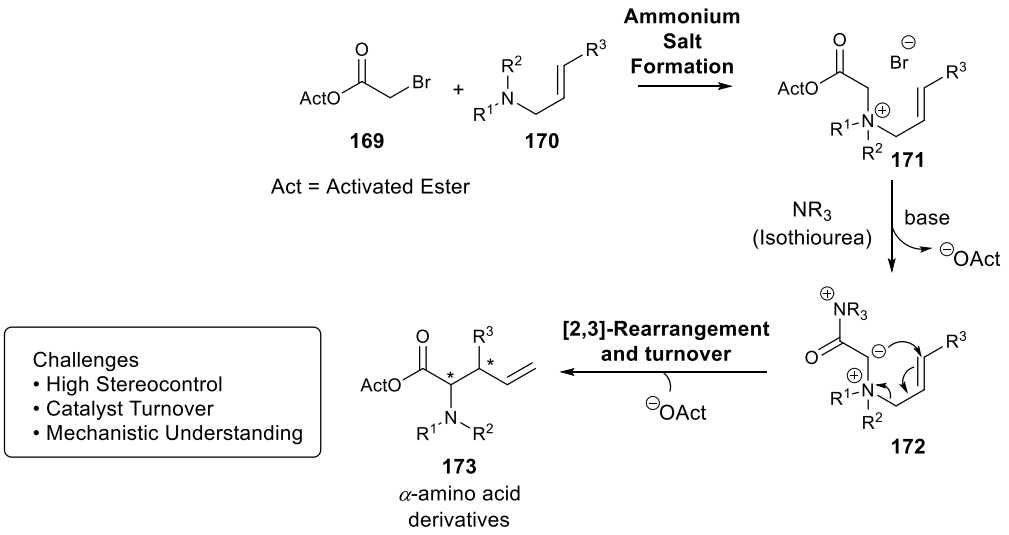


Scheme 34: Example of the use of C(1)-ammonium enolates in an intermolecular Michael addition internal cyclisation process.[32]

At the on-set of this work there were no examples of isothiourea-derived ammonium enolates undergoing catalyst turnover using external nucleophiles, which is a significant challenge within the area of tertiary amine-based Lewis base catalysis.[31]

1.4.2 Concept

As previously noted in this chapter, prior to this work there were no reports of catalytic enantioselective variants of a [2,3]-rearrangement of allylic ammonium ylides. To tackle this problem an enantioselective isothiourea-catalysed strategy was developed. It was thought that a quaternary ammonium salt **171** bearing a suitable activated ester could be generated either *in situ* or isolated from the reaction of the corresponding allylic amine **170** and bromoacetate **169**. Subsequent addition of a chiral isothiourea followed by deprotonation could form isothiourea-bound allylic ammonium ylide **172**, which may undergo stereoselective [2,3]-rearrangement. Subsequent catalyst turnover, ideally by the alkoxide displaced in the initial step, would provide an efficient route to stereodefined α-amino acid derivatives **173** (*Scheme 35*).

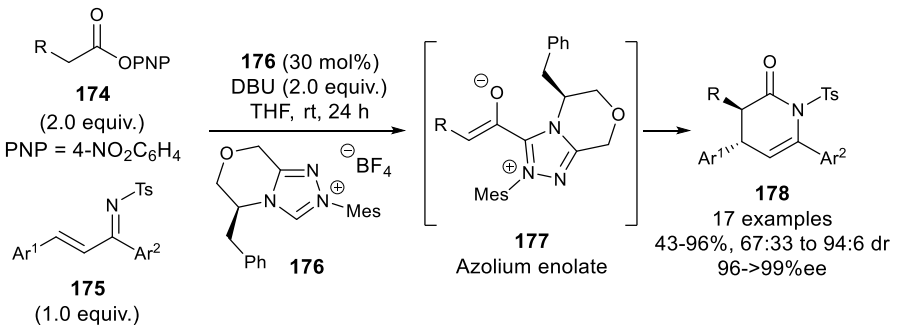


Scheme 35: Isothiourea-catalysed enantioselective [2,3]-rearrangement concept

The aim was to develop a robust methodology applicable to a range of substrates, which could be readily scaled to produce valuable synthetic building blocks. Gaining detailed mechanistic insight into the developed methodology, though experimental and computational analysis is also a key goal of this research program.

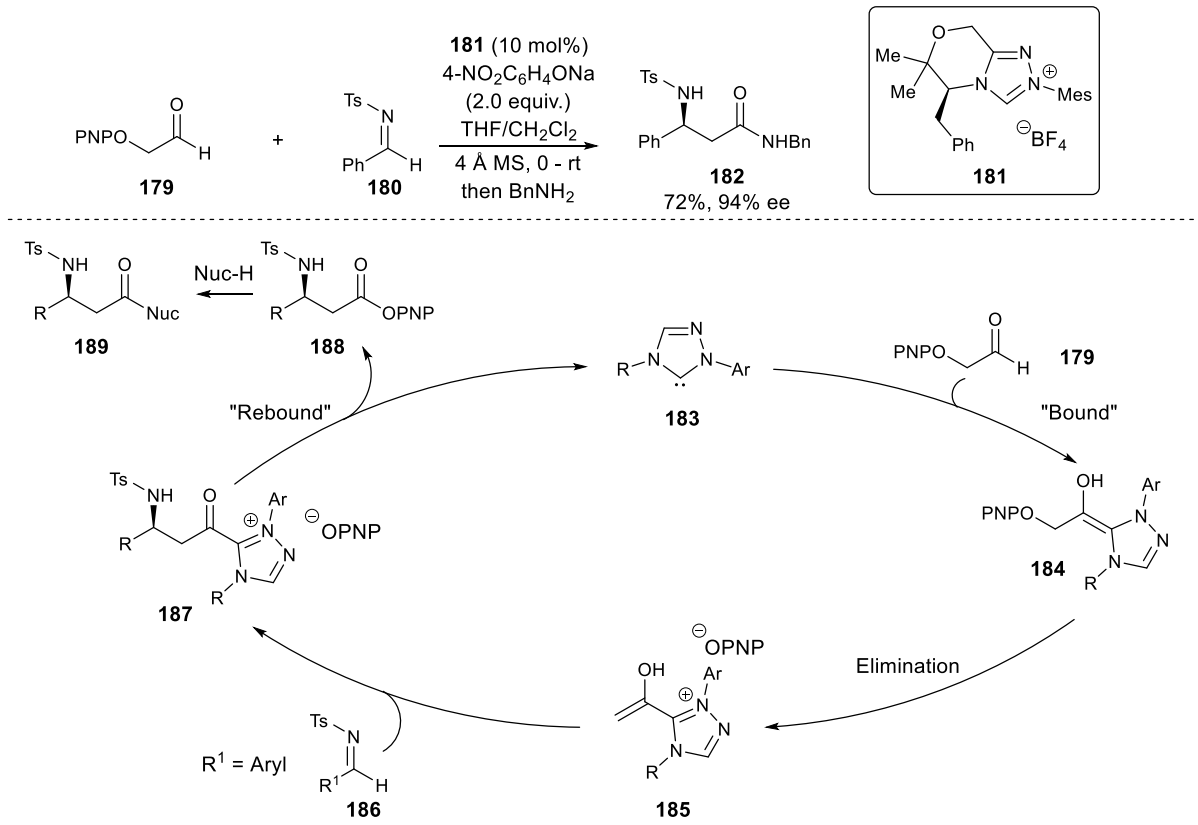
Acyl 4-nitrophenyl (PNP) esters were considered to be suitable substrates for Lewis base activation and catalyst turnover for this process due to considerable literature precedent. Chi and co-workers have previously demonstrated the use of 4-nitrophenyl esters as azolium enolate precursors in a range of stereoselective N-heterocyclic carbene (NHC)-catalysed processes.[33] For example, a range of alkyl substituted acetic activated esters **174** has been used in a NHC-catalysed formal [4+2] cycloaddition

with *N*-tosyl ketimines **175** to form a number of *anti*-dihydropyridinones **178** in excellent yields (43-96%) and stereocontrol (67:33 to 94:6 dr, 96->99% ee) (*Scheme 36*).[33c]



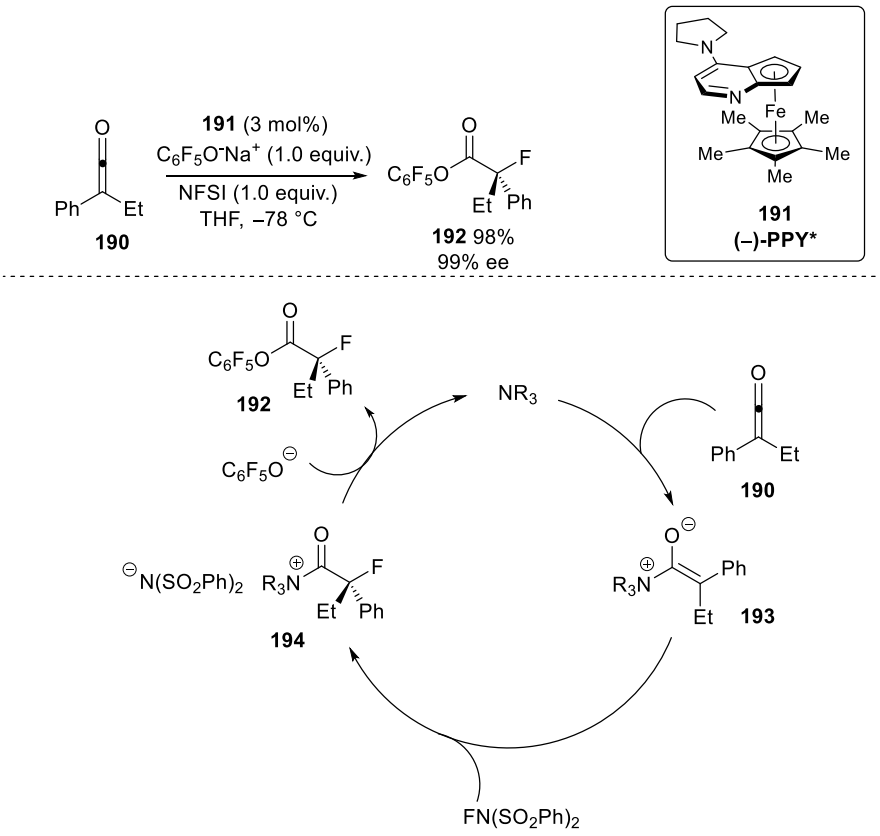
Scheme 36: An example of the use of PNP esters as azolium enolate precrusors.[33c]

Scheidt and co-workers[34] have previously used 4-nitrophenoxide as an effective catalyst-turnover agent in a related NHC-catalysed enantioselective Mannich reaction, utilising a "bound-rebound" strategy. For example, the reaction of 4-nitrophenoxyacetaldehyde **179** with *N*-Ts imine **180** in the presence of a catalytic amount of triazolium salt **181** and stoichiometric sodium 4-nitrophenoxide gave β-amino acid derivative **182**, after addition of benzylamine, in excellent yield (72%) and enantiocontrol (94% ee). Mechanistically it is postulated that treating 4-nitrophenoxyacetaldehyde **179** with a Lewis basic NHC generates Breslow intermediate **184**, with subsequent elimination of 4-nitrophenoxide forming azolium enol **185**. Enantioselective Mannich reaction addition into a range of *N*-tosyl aryl imines **186** forms acyl azolium **187**. The 4-nitrophenoxide eliminated from Breslow intermediate **184** can then turnover acyl azolium **187** to form a number of β-amino 4-nitrophenyl esters **188**, with *in situ* derivatisation giving a range of β-amino acid derivatives **189** (*Scheme 37*).[34]



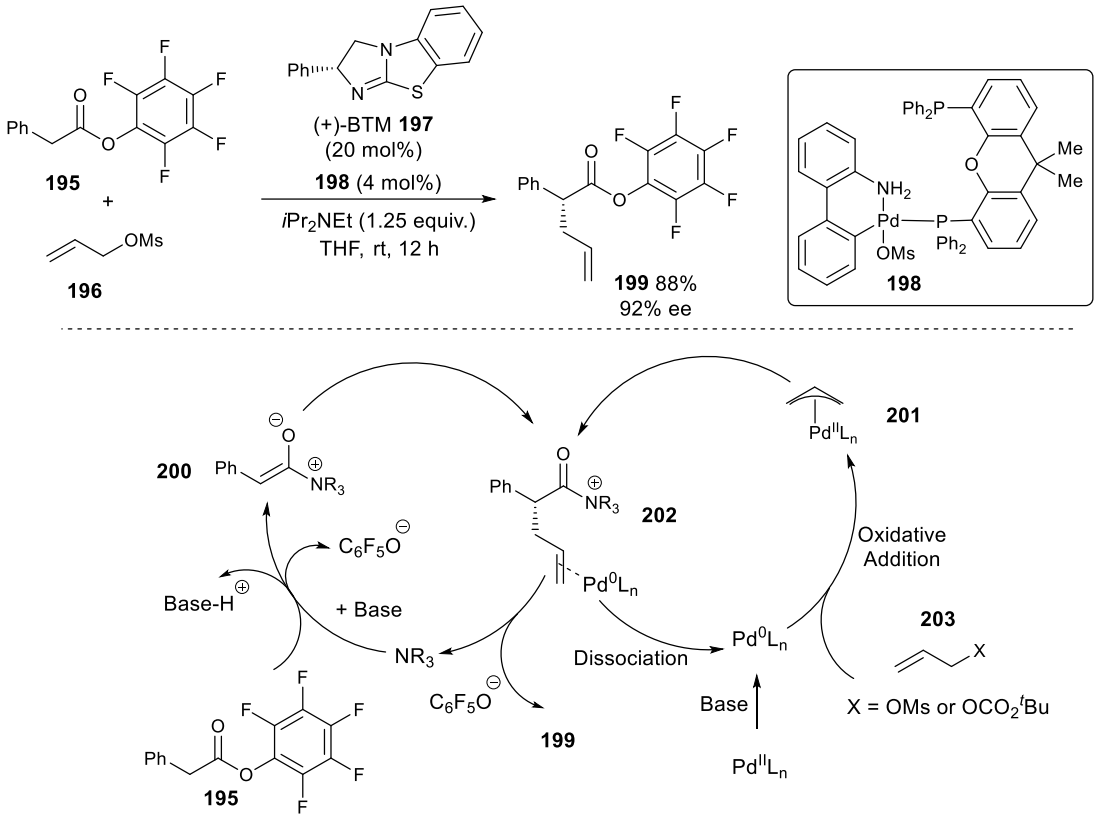
Scheme 37: Scheidt's "Bound-Rebound" strategy for azolium enol generation and external turnover.[34]

After the completion of the work described in this chapter Fu and co-workers[35] reported the use of pentafluorophenoxide ($C_6F_5O^-$) to effect external turnover of acyl ammonium intermediates. For example, reaction of ethyl phenyl ketene **190** with NFSI and sodium pentafluorophenoxide in the presence of chiral DMAP derivative (−)-PPY* **191** (3 mol%) gave tertiary alkyl fluoride **192** in excellent yield and enantiocontrol (*Scheme 38*). This methodology was applied to a range of aryl alkyl substituted ketenes, proceeding with excellent yields (up to 98%) and enantiocontrol (up to 99% ee).[35] Mechanistically, treating isolated ketene **190** with (−)-PPY* **191** generates C(1)-ammonium enolate **193**, with enantioselective fluorination by NFSI forming α-fluoro acyl ammonium **194**. Pentafluorophenoxide is able to intercept acyl ammonium **194** and facilitate catalyst turnover to generate the pentafluorophenyl ester product **192** and release the catalyst.



Scheme 38: (−)-PPY*-catalysed synthesis of tertiary alkyl fluorides from ketenes

In 2016, Snaddon and co-workers[36] reported an enantioselective α-allylation of electron deficient aryl acetic esters, utilising the combination of Pd-catalysed allylic substitution and isothiourea catalysis. Treatment of pentafluorophenyl ester **195** with allyl mesylate **196** and *i*Pr$_2$NEt in the presence of (+)-BTM **197** (20 mol%) and Buchwald Xantphos based Pd^{II} pre-catalyst **198** (4 mol%) resulted in the formation of α-allyl ester **199** in excellent yield (88%) and excellent enantiocontrol (92% ee). Pd^{II} pre-catalyst **198** forms the active Pd^{0}L$_n$ catalyst *via* deprotonation of the palladium-bound amine to give a Pd-amido complex which reductively eliminates to form Pd^{0}L$_n$, carbazole and a methanesulfonate salt.[37] Reaction of allyl mesylate **203** with Pd^{0}L$_n$ catalyst forms Pd^{II} allyl complex **201**, which can be intercepted by C(1)-ammonium enolate **200**, generated from the reaction of pentafluorophenyl ester **195** with (+)-BTM **197** in the presence of *i*Pr$_2$NEt, to give enantioenriched α-allyl acyl ammonium **202**. Acyl ammonium **202** can release the catalyst and form the α-allyl ester product **199**, through displacement with $C_6F_5O^-$. This methodology has been applied to a range of aryl acetic esters and a number of allylic coupling partners (mesylates and carbonates) with excellent yields (up to 91%) and enantioselectivies (up to 98% ee).[36]



Scheme 39: Dual catalytic α-allylation of pentafluorophenyl aryl acetic esters.

This chapter has aimed to place the concepts explored in this thesis within the context of previous literature. *Chapter 2* describes synthetic studies into these concepts, *chapter 3* describes subsequent mechanistic and stereochemical studies and *chapter 4* describes an application of the developed methodology.

1.5 References

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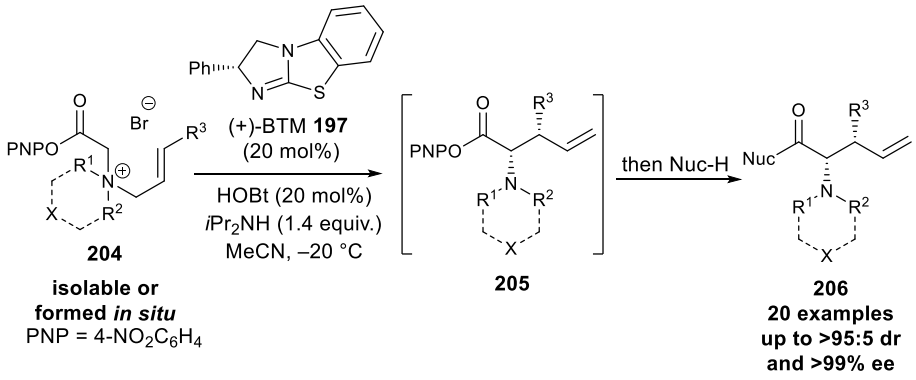
Chapter 2: Synthetic Studies

2.1 Summary

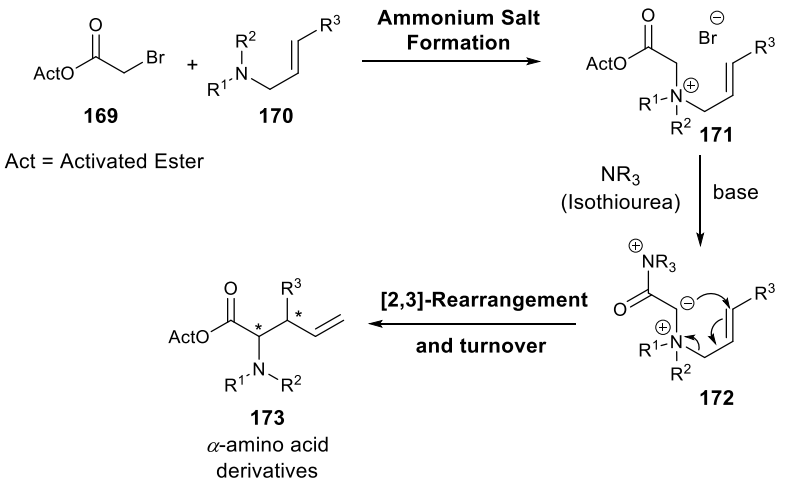
This chapter describes the discovery and reaction development of the isothiourea-catalysed enantioselective [2,3]-rearrangement of 4-nitrophenyl ester quaternary ammonium salts **204** (either isolated or generated *in situ* from 4-nitrophenyl bromoacetate and the corresponding allylic amine) to give a range of *syn*-α-amino acid derivatives **206** in excellent yield and stereocontrol (up to >95:5 dr, >99% ee) (*Scheme 40*). This represents the first catalytic enantioselective variant of a [2,3]-rearrangement of allylic ammonium ylides.



Scheme 40: Catalytic enantioselective [2,3]-rearrangement of allylic ammonium ylides.

2.2 Concept and Aims

As outlined *Chapter 1*, prior to this work there were no reports of catalytic enantioselective variants of a [2,3]-rearrangement of allylic ammonium ylides. To tackle this problem an enantioselective Lewis base-catalysed strategy was developed (*Scheme 41*). It was thought that a quaternary ammonium salt **171** bearing a suitable activated ester could be generated either *in situ* or isolated from the reaction of the corresponding allylic amine **170** and bromoacetate **169**. Subsequent addition of a chiral isothiourea followed by deprotonation could form isothiourea-bound allylic ammonium ylide **172**, which may undergo stereoselective [2,3]-rearrangement. Subsequent catalyst turnover, ideally by the alkoxide displaced in the initial step, would provide an efficient route to α-amino acid derivatives **173**.

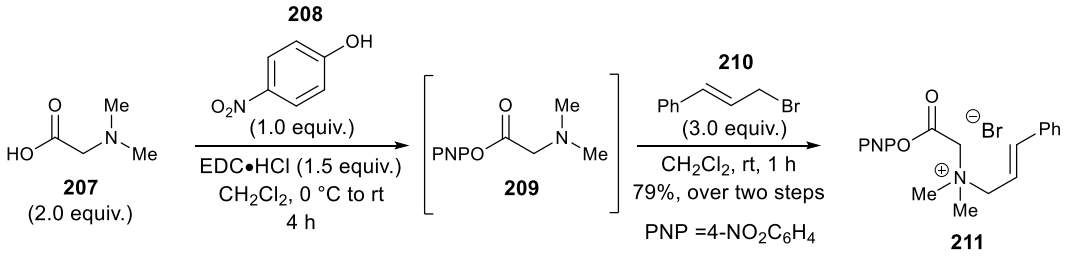


Scheme 41: Isothiourea-catalysed enantioselective [2,3]-rearrangement concept

2.3 Initial Studies

2.3.1 Model Substrate Synthesis

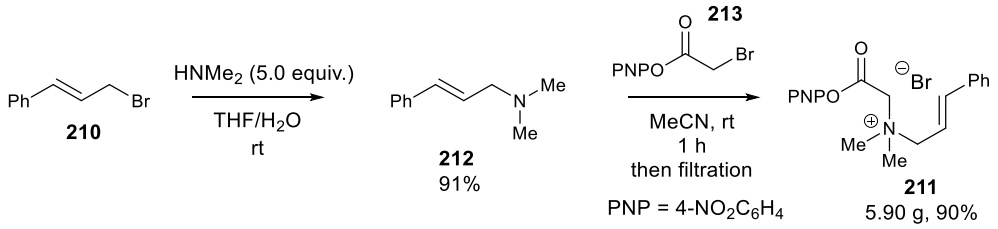
In order to conduct initial proof of concept studies into the catalytic enantioselective [2,3]-rearrangement of allylic ammonium ylides, a model substrate **211** was chosen. This ammonium salt was chosen as it could be readily synthesised from commercially available starting materials. Firstly, an EDC·HCl mediated coupling of *N*,*N*-dimethylglycine **207** with 4-nitrophenol **208** gave 4-nitrophenyl ester **209**. Notably a large excess (2.0 equiv.) of *N*,*N*-dimethylglycine was required to achieve full conversion of 4-nitrophenol **208**. Direct treatment of **209** with excess cinnamyl bromide **210** gave the desired ammonium salt **211** in 79% yield over two steps (*Scheme 42*).



Scheme 42: Initial synthesis of model ammonium salt **211**.

It became apparent that this initial synthesis was not suitable for the synthesis of multi-gram quantities of ammonium salt **211**, due to the need to use large excesses of reagents and the unreliable nature of the EDC·HCl coupling step. Hence, efforts were made to develop an alternative route for the synthesis of ammonim salt **211**, in conjunction with post-doctoral co-worker Dr. David S. B. Daniels. Direct substitution of cinnamyl bromide **210** with aq. dimethylamine provided *N*,*N*-dimethyl cinnamyl amine **212** in 91% yield. Alkylation of **212** with 4-nitrophenyl bromoacetate **213** gave ammonium salt **211** bearing an 4-nitrophenyl ester in 90% yield as a bench stable white solid. The synthesis of **211** could

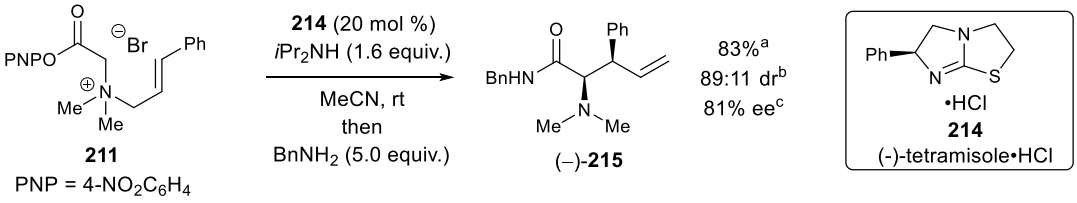
be readily performed on a multi-gram scale, with the ammonium salt isolated by simple filtration (*Scheme 43*).



Scheme 43: 2nd generation synthesis of ammonium salt **211** on multi-gram scale.

2.3.2 Optimisation Studies

Having developed an efficient synthesis of model substrate **211**, the proposed catalytic enantioselective [2,3]-rearrangement could be investigated. Pleasingly, treatment of **211** with commercially available Lewis base isothiourea catalyst (−)-tetramisole·HCl **214** (20 mol %) and *i*Pr$_2$NH (1.6 equiv.) in MeCN at rt led to [2,3]-rearrangement, with subsequent addition of benzylamine giving benzylamide (−)-**215** in 89:11 dr and an encouraging 81% ee (*Scheme 44*).

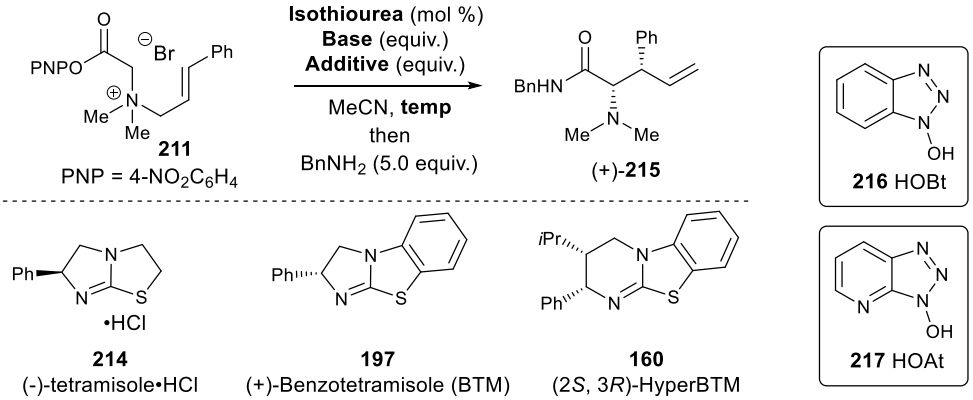


Scheme 44: Initial proof of concept. [a]Determined by ^{1}H NMR in comparison with internal standard, 4-nitrotoluene. [b]Determined by ^{1}H NMR analysis. [c]Determined by chiral HPLC analysis.

The enantiomeric excess of the reaction was determined by chiral phase HPLC, through comparison with the HPLC trace of a genuine sample racemic product, synthesised in analogous route using (±)-tetramisole·HCl **214** as an isothiourea catalyst at rt

With a promising initial hit in hand, the reaction was optimised to improve the stereoselectivity. Addition of co-catalytic hydroxybenzotriazole (HOBt) (20 mol %) led to an improvement in both diastereocontrol and enantiocontrol (*Table 1 entry 2*). Other amine bases such as *i*Pr$_2$NEt or NEt$_3$ could be used without affecting the diastereo- or enantiocontrol. However, the use of *N*-methylmorpholine (*N*MM) resulted in a loss of stereocontrol (*Table 1, entries 3 - 5*). Lowering the reaction temperature to −20 °C led to further improvements in enantiocontrol (*entries 6 & 7*). Variation of the isothiourea catalyst found that (+)-benzotetramisole ((+)-BTM) **197** was optimal, giving **215** in 76% yield, >95:5 dr and 99% ee (*Table 1 entry 9*). HOBt was again essential for maximal stereocontrol at −20 °C, while use of hydroxyazabenzotriazole (HOAt) as an alternative co-catalyst resulted in a loss of diastereocontrol (*Table 1 entry 11*). Notably, the reaction could be performed using lower catalyst

loading of both isothiourea and HOBt with diminished, but still acceptable, stereocontrol (*Table 1 entries 12 & 13*).



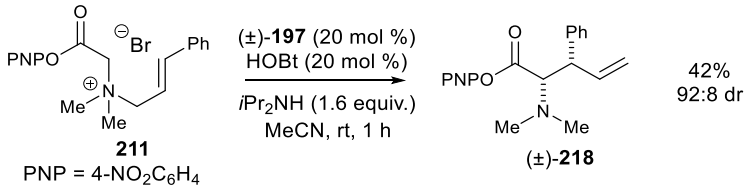
Entry	Isothiourea (mol %)	Additive (mol %)	Base (equiv.)	*T* (°C)	Yield (%)[a,b]	dr[b]	*ee*[c]
1	**214** (20)	-	*i*Pr$_2$NH (1.6)	rt	(83)	89:11	81(*ent*)
2	**214** (20)	**216** (20)	*i*Pr$_2$NH (1.6)	rt	68	93:7	84(*ent*)
3	**214** (20)	**216** (20)	*i*Pr$_2$NEt (1.6)	rt	(76)	89:11	81(*ent*)
4	**214** (20)	**216** (20)	NEt$_3$ (1.6)	rt	(75)	90:10	83(*ent*)
5	**214** (20)	**216** (20)	*N*MM (1.6)	rt	(45)	63:37	ND
6	**214** (20)	**216** (20)	*i*Pr$_2$NH (1.6)	0 to rt	88	92:8	89(*ent*)
7	**214** (20)	**216** (20)	*i*Pr$_2$NH (1.6)	−20	65	91:9	93(*ent*)
8	**197** (20)	-	*i*Pr$_2$NH (1.4)	−20	(61)	92:8	95
9	**197 (20)**	**216 (20)**	***i*Pr$_2$NH (1.4)**	**−20**	**76**	**>95:5**	**99**
10	**160** (20)	**216** (20)	*i*Pr$_2$NH (1.4)	−20	(33)	72:28	ND
11	**197** (20)	**217** (20)	*i*Pr$_2$NH (1.4)	−20	49	90:10	98
12	**197** (10)	**216** (10)	*i*Pr$_2$NH (1.4)	−20	62	88:12	96
13	**197** (5)	**216** (5)	*i*Pr$_2$NH (1.4)	−20	41[d]	79:21	92

[a] Yields in parentheses determined by ^{1}H NMR using 4-nitrotoluene as an internal standard, [b] Isolated yield after flash column chromatography, >95:5 dr. [b] Determined by ^{1}H NMR analysis of crude material. [c] Determined by HPLC analysis. [d] 84:16 mixture of diastereoisomers (isolated).

Table 1: Optimisation of reaction conditions

The optimal conditions for the enantioselective [2,3]-rearrangement of allylic ammonium salt **211** were (+)-BTM **197** (20 mol %), HOBt **216** (20 mol %), *i*Pr$_2$NH (1.4 equiv.) in MeCN at −20 °C, followed by the addition of benzylamine (5.0 equiv.) to give **(+)-215** in 76% yield with excellent stereocontrol (>95:5 dr, 99% ee).

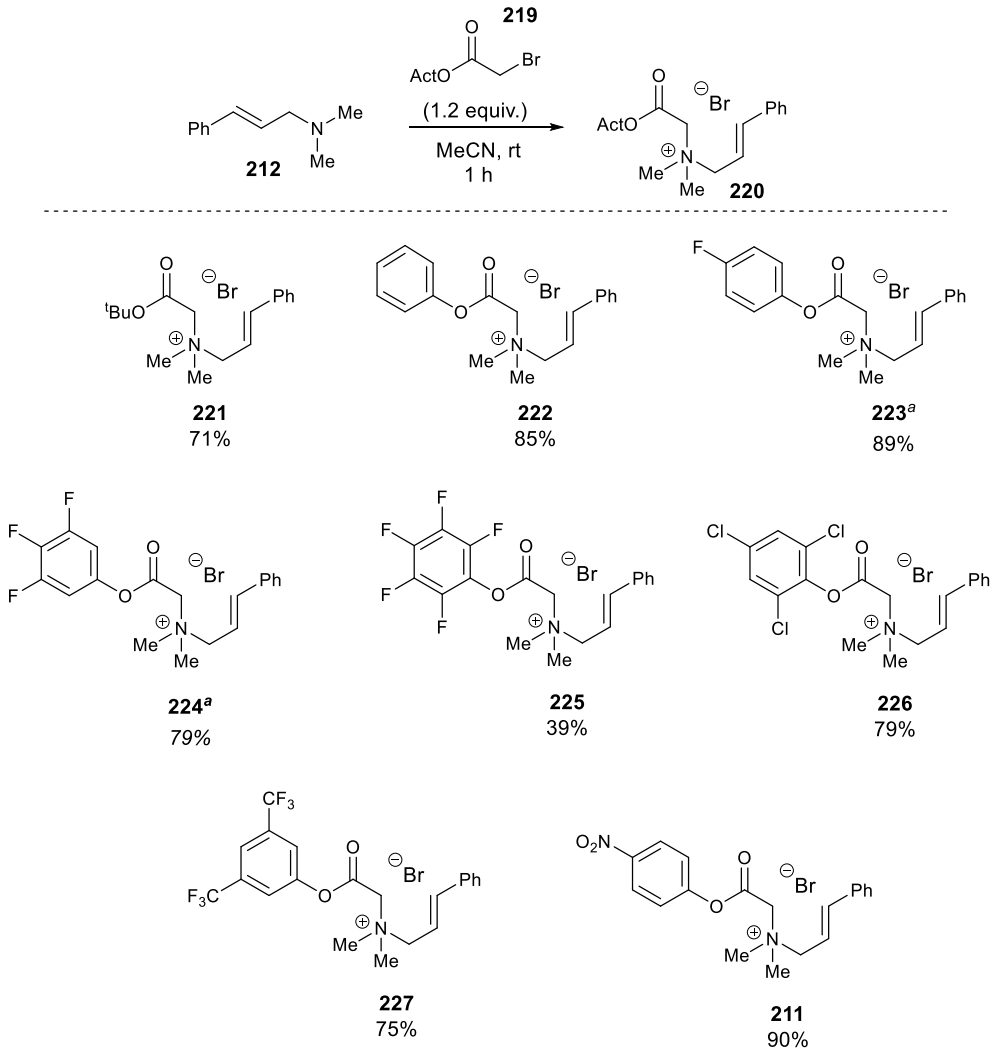
Direct isolation of the rearranged 4-nitrophenyl ester is possible prior to the addition of an external nucleophile. However, diminished yields of ester (±)-**218** were observed, which is likely to be due to partial hydrolysis of the activated ester upon work-up (*Scheme 45*). The enantiopurity of (±)-**218** could not be directly determined due to decomposition upon treatment with *i*PrOH during HPLC analysis.



Scheme 45: Direct isolation of rearranged 4-nitrophenyl ester (±)-**218**.

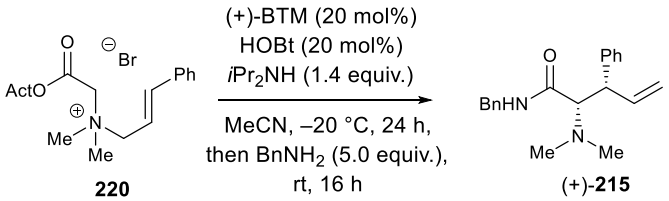
2.3.3 Evaluation of Activated Esters as Ammonium Ylide Precursors

With optimal conditions in hand, alternative activated esters were evaluated to access the electronic requirements for reactivity and to determine if a non-toxic alternative to 4-nitrophenyl ester could be employed. A number of cinnamyl ammonium salts were synthesised using the method developed for the synthesis of model substrate **211**. Treatment of *N*,*N*-dimethyl cinnamyl amine **212** with the requisite bromoacetate **219** gave a number of ammonium salts bearing a range of alternative esters in excellent yields (*Scheme 46*).



Scheme 46: Synthesis of *N*,*N*-dimethyl cinnamyl ammonium salts. [a]Synthesised by Dr David S. B. Daniels.

With a range of alternative ester ammonium salts in hand, the electronic requirements of ester on the ammonium salt were assessed. Under the optimal conditions it was found that *t*-butyl **221**, phenyl **222** and 4-fluoro-phenyl **223** esters were unreactive and returned starting material after exposure to the reaction conditions (*Table 2, entries 1-3*). The use of 3,4,5-F_3CH_2 ester **224** led to formation of rearranged product **(+)-215** with good levels of stereocontrol (>95:5 dr, 91% ee) albeit in poor yield (15%) (*Table 2, entry 4*). The rearrangement of 3,5-$(CF_3)_2C_6H_3$ ester **227** and 2,4,6-$Cl_3C_6H_2$ ester **226** gave **(+)-215** in modest yield and comparable stereocontrol to 4-nitrophenyl ester **211** (*Table 2, entries 5 & 7*). The use of pentafluoro phenyl ester ammonium salt **225** gave the rearrangement product with poor levels of diastereocontrol, likely a result of significant base-mediated background reaction. The 4-nitrophenyl ester was still found to give optimal yield and stereocontrol. From these studies it is clear that a strongly electron-withdrawing aryl ester is a requirement for efficient reactivity within the isothiourea-catalysed [2,3]-rearrangement of allylic ammonium ylides.



Entry	Act	Yield (%)[a]	dr[b]	ee[c]
1	*t*Bu	-	-	-
2[e]	Ph	-	-	-
3[e]	*p*-FC_6H_4	-	-	-
4[e]	3,4,5-$F_3C_6H_2$	15	>95:5	91
5[e]	3,5-$(CF_3)_2C_6H_3$	49	>95:5	93
6	C_6F_5	ND	66:44	ND
7	2,4,6-$Cl_3C_6H_2$	41	>95:5	93
8	4-$NO_2C_6H_4$	76	>95:5	99

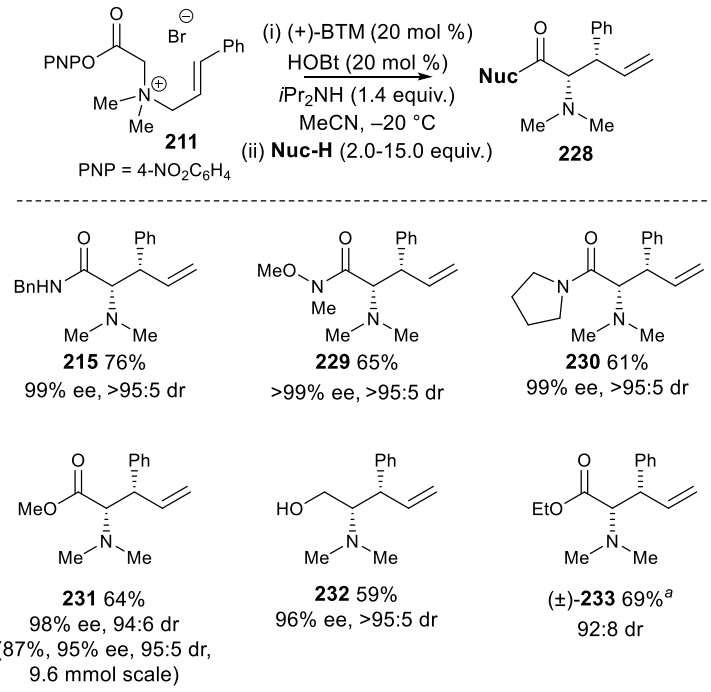
Reactions performed on 0.24 mmol scale [a]Isolated yield after chromatographic purification of >95:5 dr. [b]Determined by ^{1}H NMR analysis of crude material. [c]Determined by Chiral HPLC analysis. [d]ND = Not Determined. [e]Performed by Dr. David S. B. Daniels.

Table 2: Evaluation of alternative activated esters.

2.4 Scope of Nucleophilic Derivatisation and Scale Up

The scope of the reaction under the previously optimised conditions was initially examined through variation of the nucleophile used in the *in situ* derivatisation step. The [2,3]-rearrangement product of cinnamyl ammonium salt **211** could be *in situ* derivatised with sodium methoxide, pyrrolidine, *N*,*O*-dimethylhydroxylamine or $LiAlH_4$ to access a range of α-amino acid derivatives **229**-**232** in good yields and excellent stereocontrol (up to >95:5 dr and >99% ee). This process was readily performed on a multi-gram scale with maintenance of stereocontrol, with 1.95 g (8.3 mmol) of amino ester **231** (86%, 95:5 dr, 95% ee) being generated from 4.0 g (9.6 mmol) of ammonium salt **211** (*Scheme 47*).

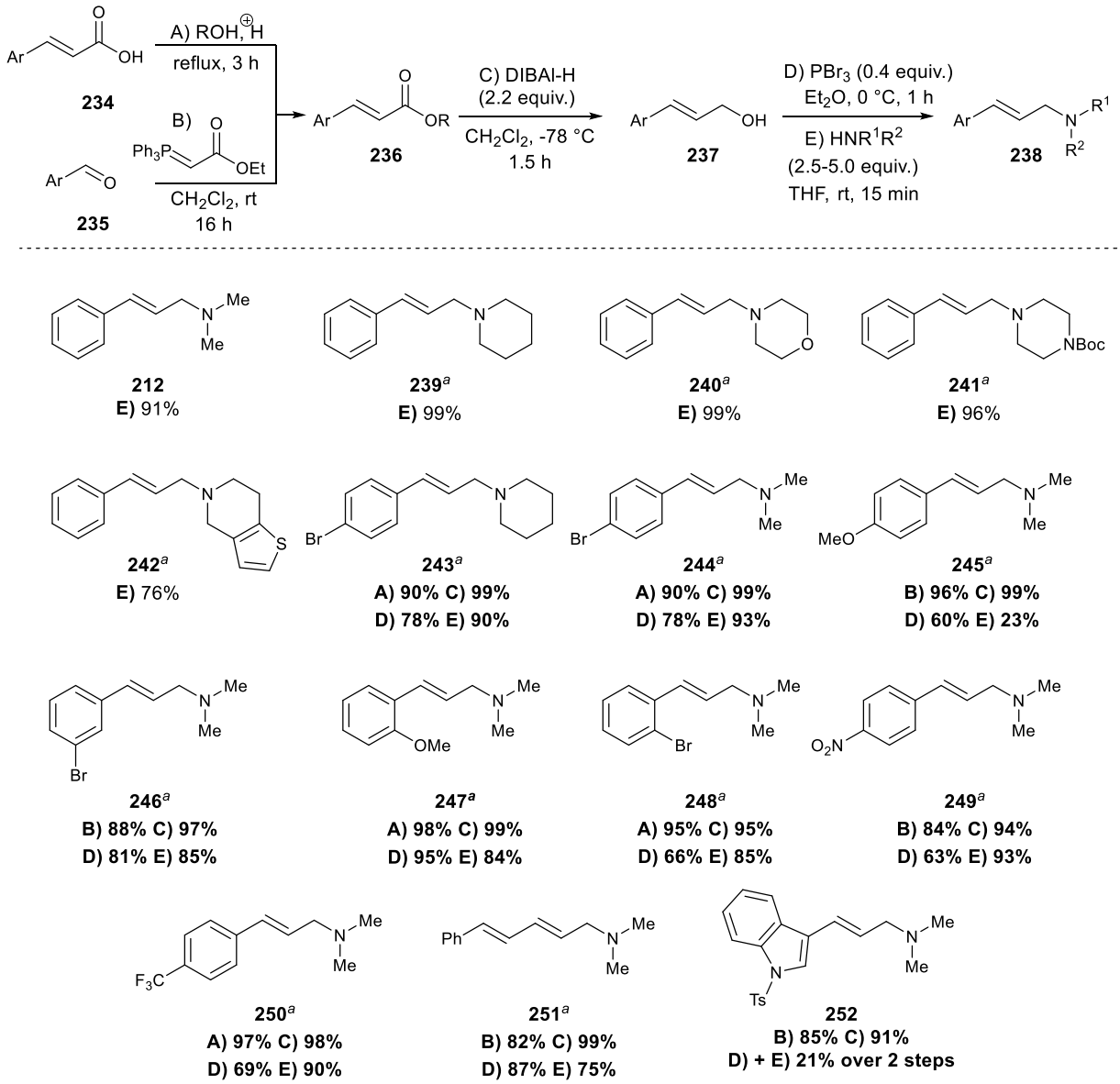
In situ derivatisation with sodium ethoxide after [2,3]-rearrangement using racemic (±)-BTM, gave literature known ethyl ester (±)-**233**. The ^{1}H NMR spectrum is consistent with provided by Doyle and co-workers[38] for the *syn*-diastereoiomser confirming the relative configuration of the rearrangement products.



Scheme 47: Scope of the nucleophilic *in situ* derivatisation, [a]performed at rt using (±)-BTM.

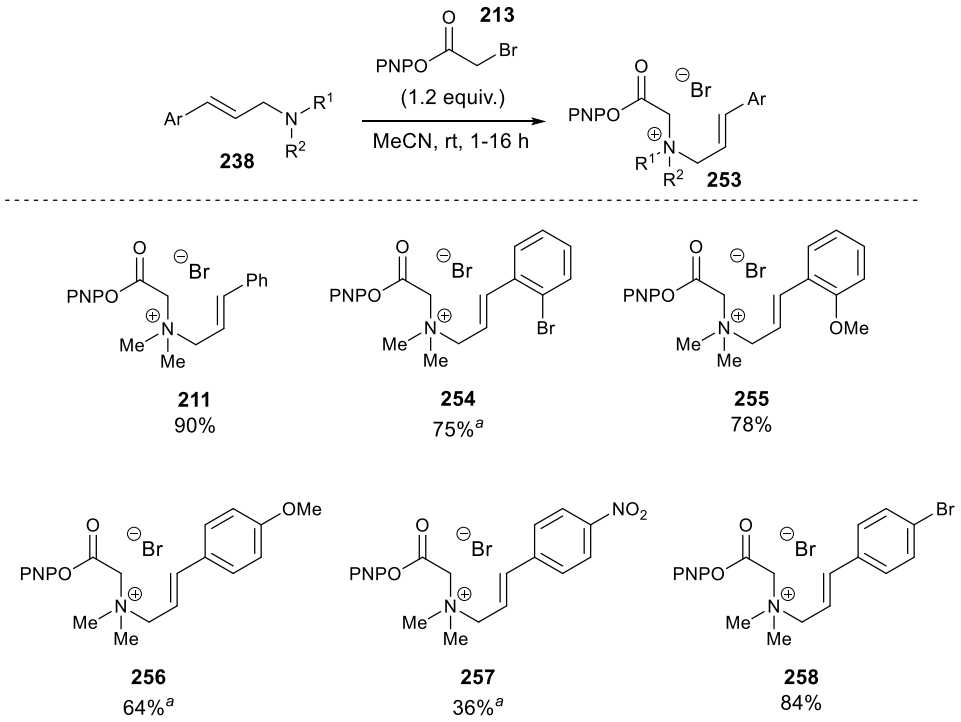
2.5 Synthesis of Allylic Ammonium Salts

To examine the tolerance of the reaction towards a variety of *N*- and aryl substituents, a general route for the synthesis of a range of allylic amines was developed. Substituted allylic amines could be synthesised through a four-step route, from either the requisite cinnamic acid **234** (if readily available) or substituted benzaldehyde **235**. Esterification of the cinnamic acid **234** with either methanol or ethanol gave the corresponding α,β-unsaturated ester **236**. Alternatively, a Wittig olefination between the requisite benzaldehyde and ethyl 2-(triphenylphosphoranylidene)acetate gave **236** in excellent yields. Subsequent reduction with DIBAL-H gave the corresponding allylic alcohol **237**. Bromination of **237** using phosphorus tribromide gave the corresponding allylic bromide, which was subsequently substituted using the corresponding secondary amine. Alternatively, cinnamyl amines **239**-**242** were synthesised in a single step from commercially available cinnamyl bromide **210**.



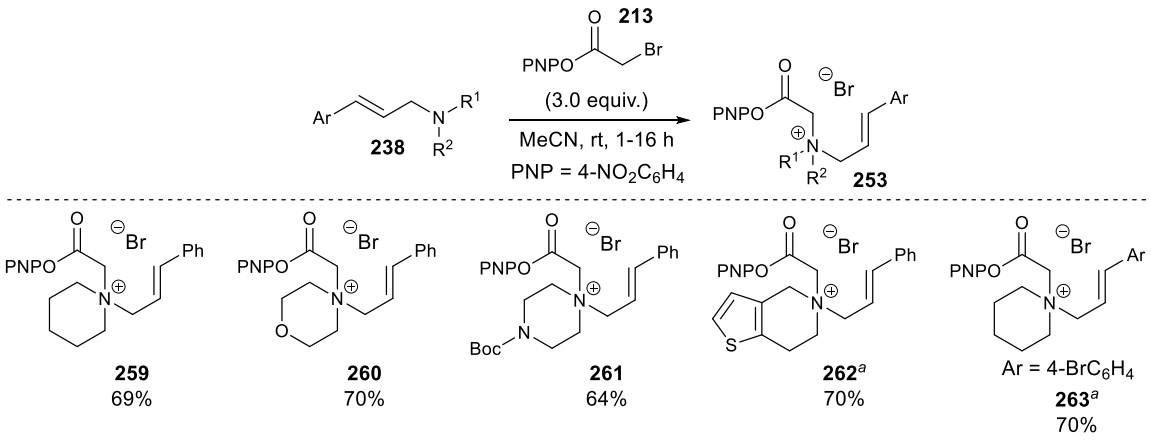
Scheme 48: Synthesis of allylic amines. [a]Synthesised by David S. B. Daniels

With a range of allylic amines in hand the corresponding 4-nitrophenyl ester ammonium salts were synthesised. As noted in *Chapter 1*, a major challenge in the use of allylic ammonium salts in synthesis is their preparation and isolation. Pleasingly, allylic ammonium salts **254**-**258** were directly isolated, and routinely recrystallized where required. A range of *N*,*N*-dimethyl ammonium salts were synthesised bearing both electron-releasing and electron-withdrawing C(3)-aryl substituents, allowing a range of aryl substituents to be evaluated within the isothiourea-catalysed [2,3]-rearrangement. Treatment of the requisite allylic amine **238** with a slight excess (1.2 equiv.) of 4-nitrophenyl bromoacetate **213** gave the desired ammonium salts **253** in modest to excellent yields (*Scheme 49*).



Scheme 49: Synthesis of *N*,*N*-dimethyl ammonium salts, [a]Et_2O/CH_2Cl_2 (4:1v:v) used in place of MeCN.

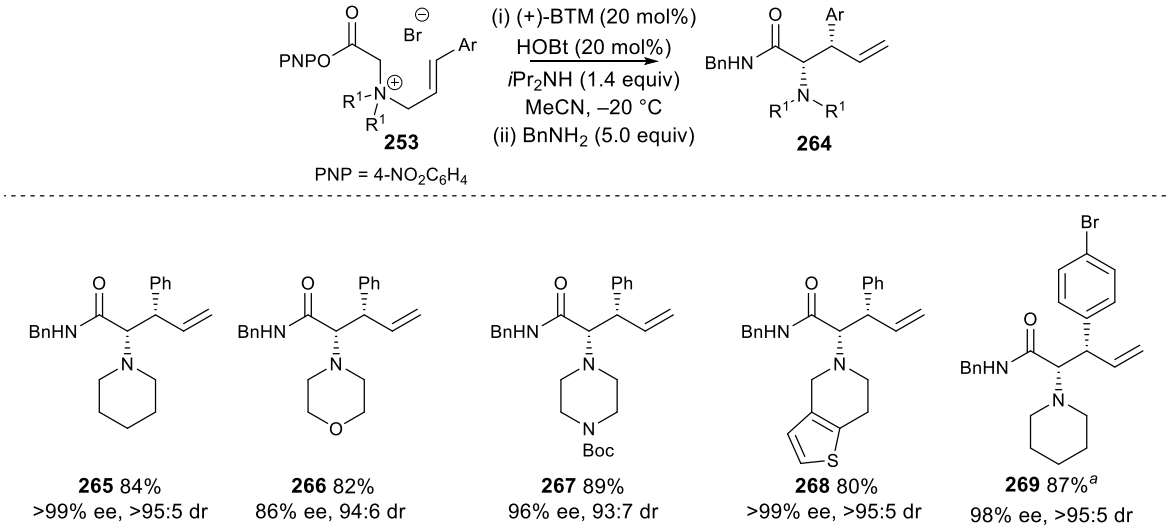
In order to evaluate the substrate of the isothiourea-catalysed [2,3]-rearrangement with respect to the *N*-substituent, a range of ammonium salts bearing cyclic medicinally interesting motifs were synthesised. Allylic amines bearing cyclic *N*-substituents were found to be significantly less nucleophilic than their *N*,*N*-dimethyl counterparts, so a greater excess of 4-nitrophenyl bromoacetate **213** was employed to facilitate ammonium salt formation. This strategy allowed the synthesis of a range of cyclic *N*-substituents ammonium salts **259**-**263** in good yields (64-70%) (*Scheme 50*).



Scheme 50: Synthesis of 4-nitrophenyl ester allylic ammonium salts. [a]Synthesised by David S. B. Daniels.

2.6 Reaction Scope: *N*-Substituent Variation

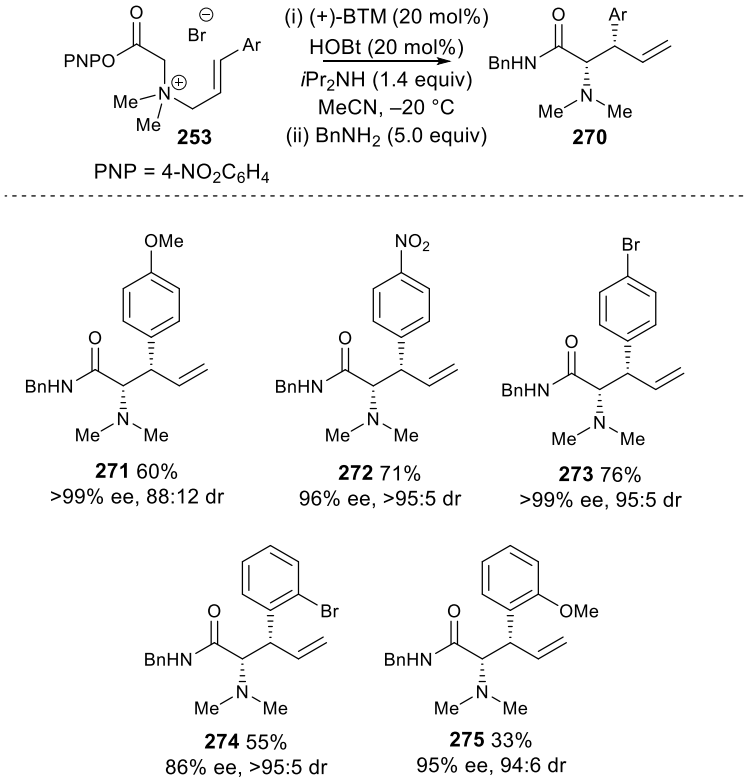
First, the reaction scope with respect to the *N*-substituents was assessed under the previously optimised conditions. A range of simple and medicinally relevant *N*-substituents such as piperidine, morpholine and *N*-Boc piperazines were well accommodated, giving the corresponding α-amino acid derivatives in good yields and outstanding stereocontrol (up to >95:5 dr, >99% ee). Interestingly, unsymmetrical 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine substituent was also well tolerated to give **268** in excellent yield (80%) and stereocontrol (>95:5 dr, >99% ee).



Scheme 51: Reaction substrate scope, *N*-variation. [a]Synthesised by David S. B. Daniels.

2.7 Reaction Scope: Aryl-Substituent Variation

Variation of C(3)-substituent within the allylic ammonium salt demonstrated that both electron-withdrawing and electron-releasing substituents are well tolerated within the C(3)-aryl substituent, giving **271**, **272** and **273** in good yield and excellent stereocontrol (up to >95:5 dr, >99% ee). *Ortho*-substitution of the C(3)-aryl group is also accommodated forming rearrangement products **274** and **275** with excellent stereocontrol, although accompanied by significantly diminished yields (33-55%).



Scheme 52: Reaction scope, C(3)-aryl variation.

The relative and absolute configuration of α-amino amide **274** bearing an *ortho*-bromo aryl substituent was confirmed through X-ray crystallographic analysis. Analysis of the crystalline material confirmed the relative *syn*-configuration between the C(2)-NMe_2 and C(3)-aryl substituents, with a (2*S*,3*S*) absolute configuration. All other rearrangement products were assigned by analogy.

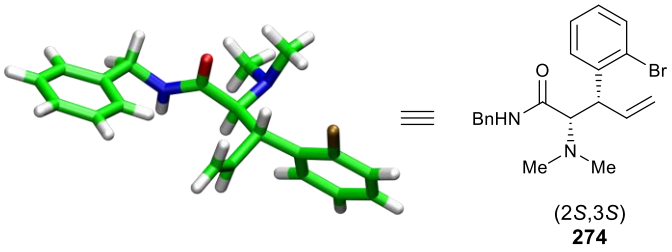
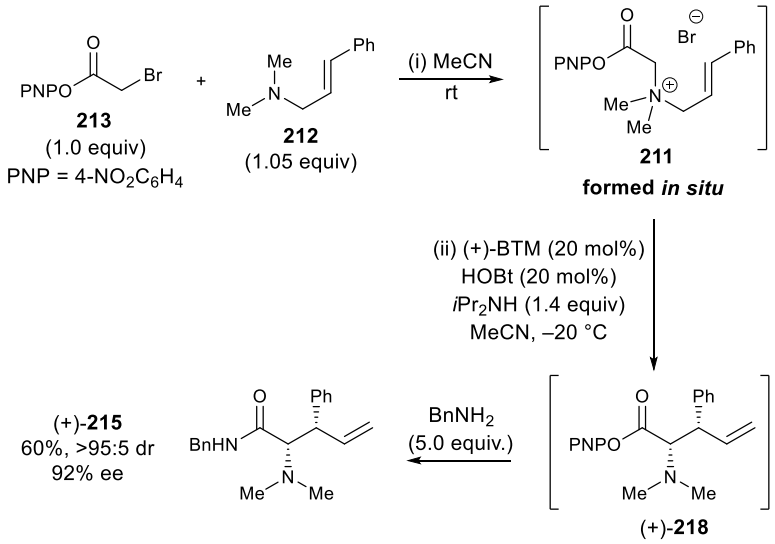


Figure 3: X-ray analysis of **274**, showing the relative (*syn*) and absolute configurations (2*S*,3*S*). X-ray analysis performed by Prof. Alexandra M. Z. Slawin.

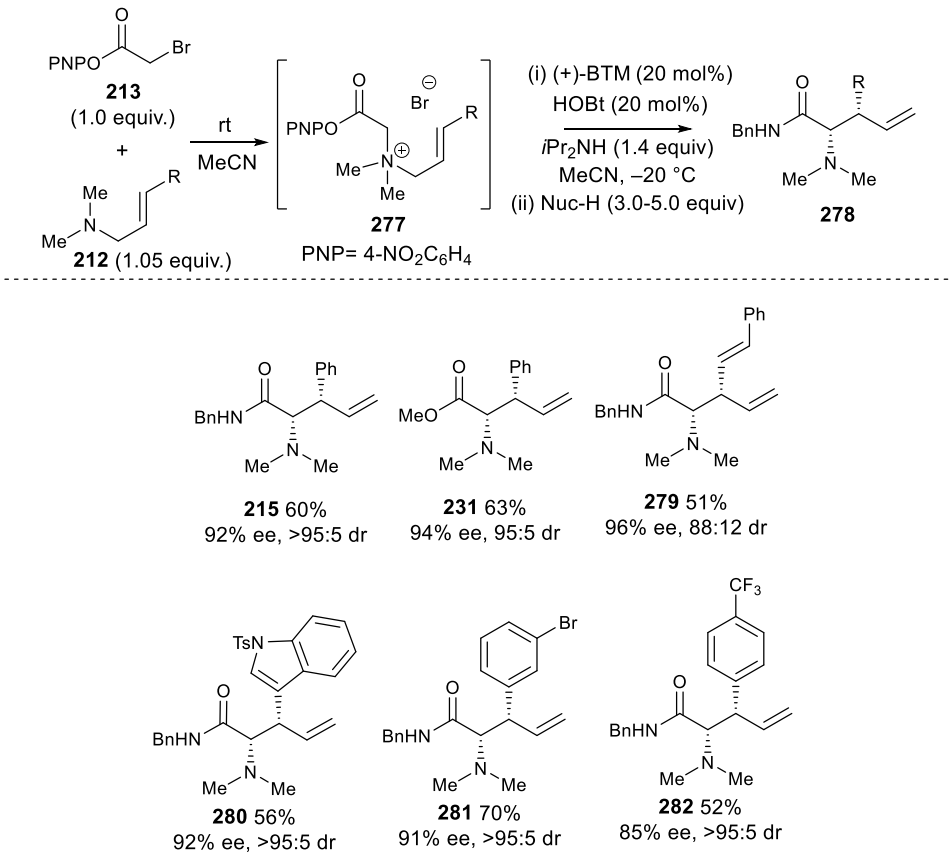
2.8 Catalytic Enantioselective [2,3]-Rearrangement from *in situ* Generated Ammonium Salts

Whilst a number of ammonium salts (*scheme 49*) could be isolated and purified by recrystallization (if required), many of them formed ionic liquids or oily gels which could not be readily isolated or purified. For example, treatment of *meta*-bromo cinnamyl amine **246** with 4-nitrophenyl bromoacetate **213** resulted in formation of a hydroscopic gel which could not be isolated or purified. This meant that full examination of the reaction substrate scope was impeded as many of the desired ammoniums salts could not be isolated. To circumvent this problem a new strategy was required, and *in situ* formation of the ammonium salt, was postulated. Treating 4-nitrophenyl bromoacetate **213** with a slight excess (1.05 equiv.) of allylic amine **212**, formed the desired ammonium salt **211** *in situ*. Cooling the reaction to −20 °C before adding ((+)-BTM (20 mol %), HOBt (20 mol %) and *i*Pr_2NH (1.4 equiv.), in MeCN, resulted in [2,3]-rearrangement and subsequent addition of benzylamine allowed benzylamide **215** to be isolated in 60% yield with excellent stereocontrol (>95:5 dr, 92% ee) (*Scheme 53*). It was also found that methyl ester **231** could be readily synthesised through the *in situ* protocol, with comparable yield and stereocontrol (*Scheme 54*).



Scheme 53: *In situ* ammonium salt formation and subsequent catalytic enantioselective [2,3]-rearrangement.

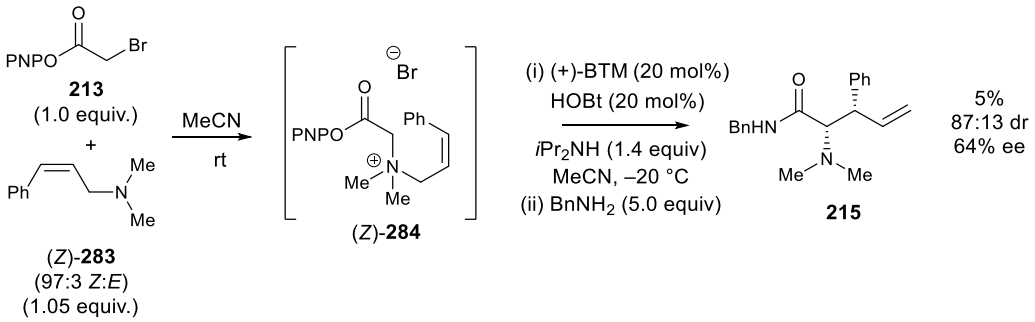
Gratifyingly the *in situ* protocol allowed the incorporation of a wider range of C(3) substituents within the ammonium salt. The substrate scope was extended to include a heteroaromatic substituent, a styryl substituent and other cinnamyl derivatives **279**-**282**, whose ammonium salts could not be isolated, all with excellent stereocontrol (up to >95:5 dr, 96% ee) and good yields (51-70%) (*Scheme 54*).



Scheme 54: Reaction scope of *in situ* generated ammonium salts.

2.9 Reaction Stereospecificity

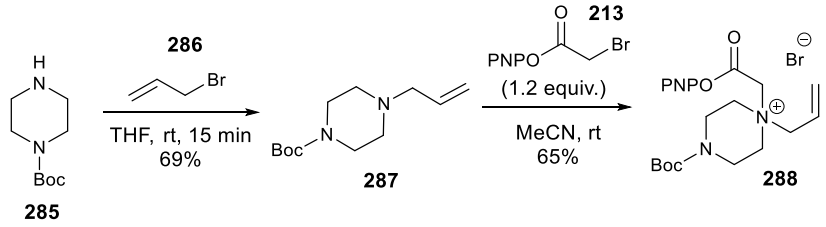
Next, the reaction stereospecificity was assessed by comparing (*E*)- and (*Z*)-allylic ammonium salts to see if the opposite diastereoisomer is obtained. (*Z*)-Cinnamyl ammonium salt (*Z*)-**284** could not be isolated and so the *in situ* protocol was utilised. Treating (*Z*)-**283** under the previously optimised reaction conditions resulted in the same major, *syn*-diastereoisomer of **215** (87:13, *syn*:*anti*) being formed, albeit with reduced enantiocontrol (64% ee) and very poor isolated yield. This indicates a lack of stereospecificity, as both (*E*)- and (*Z*)-ammonium salts result in the same diastereomer of the product. However due to the low yield, isomerisation from (*Z*)-**284** to the (*E*)-**211** under the reaction conditions cannot be ruled out.



Scheme 55: Examination of reaction stereospecificity, study performed by David S. B. Daniels

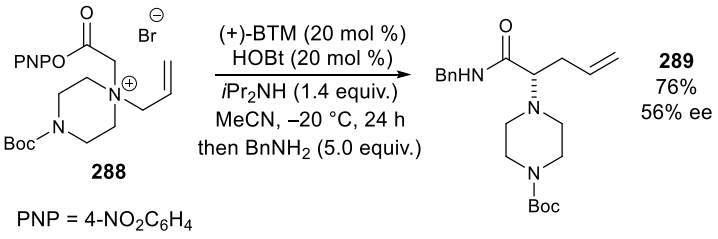
2.10 Requirement of the C(3)-Aryl Substituent

Further evaluation of the substrate scope investigated the requirement of the C(3)-aryl unit within the ammonium salt. Synthesis of substrate **288** required the use of an *N*-Boc piperazyl *N*-substituent to make the resulting allyl ammonium salt **288** sufficiently crystalline to allow for its isolation. Following the previously developed synthetic route ammonium salt **288** was synthesised in good yield across the two steps (*Scheme 56*).



Scheme 56: Synthesis of *N*-allyl ammonium salt.

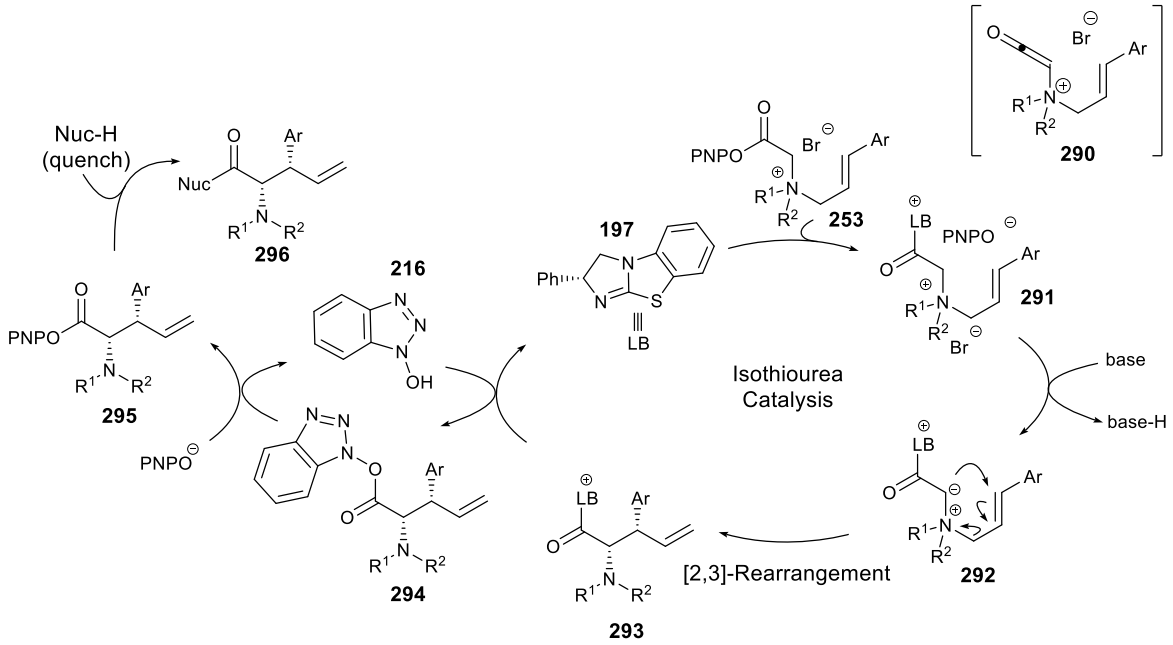
Rearrangement of **288** under previously optimised reaction conditions proceeded smoothly, giving product **289** in good yield, albeit with low enantioselectivity (56% ee) (*scheme 57*). This suggests that the C(3)-π system within the ammonium salt is a key structural requirement to obtain high levels of enantioselectivity (*Scheme 57*).



Scheme 57: Evaluation of the requirement of a C(3)-π system.

2.11 Postulated Mechanism

A number of potential mechanisms for this process proceeding though either Lewis base or Brønsted base catalysis can be postulated. Whilst a Brønsted base mechanism, where the isothiourea directly deprotonates ammonium salt **253** to form a chiral ion-pair, cannot be discounted at this point, a tentative Lewis basic mechanism is proposed (*Scheme 58*). Dicationic acyl ammonium ion **291** can be formed through direct *N*-acylation of (+)-BTM **197** with activated ester ammonium salt **253** before deprotonation of **291** with a suitable base generates ammonium ylide **292**. Alternatively, ylide **292** can be accessed through base-mediated elimination of 4-nitrophenol from **253** to form ammonium ketene **290**, followed by addition of (+)-BTM **197**. Subsequent [2,3]-rearrangement of ylide **292** generates acyl ammonium **293**, which can be intercepted directly by 4-nitrophenoxide to form the isolable PNP ester **295**. Alternatively, **293** can be intercepted by nucleophilic co-catalyst HOBt to form **294**, which can be transesterified to **295** in a secondary catalytic cycle as previously described by Rovis and co-workers.[39] PNP ester **295** can then be derivatised *in situ* to form a range of α-amino acid derivatives **296** in good yields and stereoselectivities.



Scheme 58: Proposed catalytic cycle.

2.12 Stereochemical Rationale

The observed *syn*-diastereoselectivity is thought to arise from the stereodetermining [2,3]-rearrangement step occurring preferentially through *endo*-type pre-transition-state assembly **297**. In this assembly, the carbonyl oxygen preferentially aligns *syn* to the sulfur atom of the acyl ammonium ion, allowing for a stabilising n_0 to $\sigma^*_{C\text{-}S}$ interaction. This n_0 to $\sigma^*_{C\text{-}S}$ interaction is thought to provide the origin of stereocontrol in a range of isothiourea catalysed processes and has been studied extensively

both computationally and crystallographically.[40] The stereocontrolling phenyl substituent on the acyl ammonium, sits in a pseudoaxial orientation to minimise 1,2-steric interactions, with [2,3]-rearrangement occurring *anti* to this unit. A key π-cation interaction between the acyl ammonium ion and the allylic C(3)-aryl or styryl unit is postulated, further stabilising the *endo*-type array **297**, rationalising the key C(3)-aryl structural requirement for stereocontrol. This type of interaction has previously been proposed in other enantioselective isothiourea-catalysed reactions.[41]

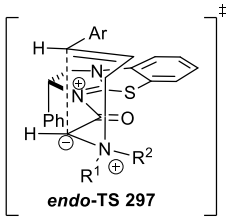


Figure 4: Proposed pre-transition state assembly

2.13 Conclusions

The first catalytic enantioselective variant of the [2,3]-rearrangement of allylic ammonium ylides has been discovered and developed. The isothiourea (+)-benzotetramisole **197** catalyses the [2,3]-rearrangement of quaternary ammonium salts bearing activated 4-nitrophenyl esters to form a range of *syn*-α-amino acid derivatives in good yield and excellent stereoselectivities (up to >95:5 dr, >99% ee). The substrate scope of the reaction has been examined for over 20 examples, including on a multi-gram scale. For ammonium salts which were not isolable an *in situ* formation protocol has been developed to enable further exploration of the substrate scope of the reaction.[42]

2.14 References

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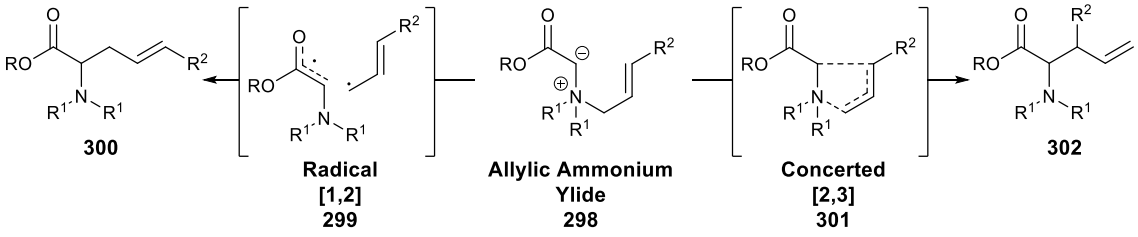
Chapter 3: Mechanistic and Stereochemical Studies

3.1 Summary

This chapter describes mechanistic investigations into the isothiourea-catalysed enantioselective [2,3]-rearrangement developed in *chapter 2*. Reaction kinetic analysis of the process by ^{19}F NMR has allowed a kinetic profile to be built up, and analysed under different conditions. This has allowed the catalyst resting state, the reaction orders with respect to each component, and the effect of various additives, including HOBt, to be studied. Furthermore, a catalyst substrate adduct has been identified and characterised by ^{13}C and ^{15}N isotopic labelling experiments. This adduct is both a genuine intermediate and is on the productive cycle as determined through isotopic entrainment. Kinetic isotope effects and collaborative computational work has provided detailed insight into the stereodetermining [2,3]-rearrangement step, while Hammett analysis has given experimental insight into the susceptibility of the transition state to electronic effects. Collaborative computational studies have probed the origins of stereocontrol, giving insight into key cation-π and 1,5 $n_0 - \sigma^*_{c\text{-}s}$ interactions. Computational reaction coordinate modelling has excluded potential mechanistic possibilities and has provided further support for the experimentally proposed mechanism.

3.2 Introduction and Aims

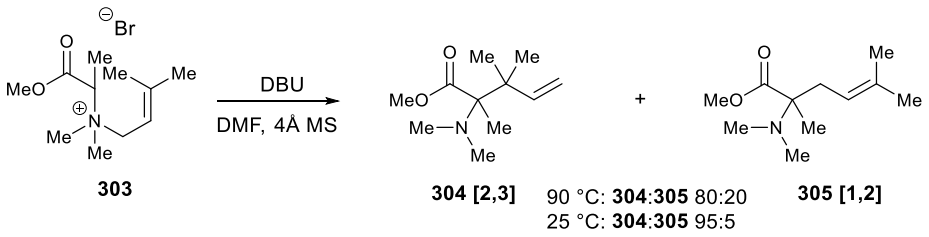
As detailed in *chapter 1*, the [2,3]-rearrangement of allylic ammonium ylides is an elegant method for the synthesis of stereodefined α-amino acid derivatives.[43] The mechanism of such processes and related [1,2]-Stevens rearrangements have been the subject of much discussion in the literature. It is thought that [2,3]-rearrangements proceed through an ionic concerted thermal sigmatropic rearrangement and the competitive [1,2]-rearrangement proceeds *via* radical bond cleavage (*Scheme 59*).[43]



Scheme 59: Competitive [1,2]- and [2,3]-rearrangements of allylic ammonium ylides.

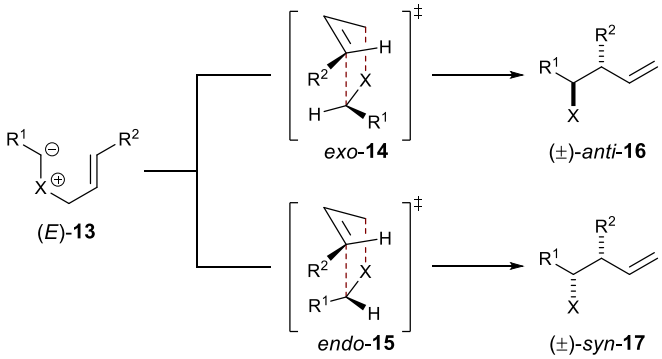
Currently there are surprisingly few detailed mechanistic analyses of [2,3]-rearrangement processes, and there is no mechanistic understanding of enantioselective [2,3]-rearrangements of allylic ammonium ylides. Current state-of-the-art within this area is the elegant studies performed by Singleton and co-workers,[44] focusing on the competition between [2,3]- and [1,2]-rearrangements from allylic ammonium ylides generated using DBU. Through the use of natural abundance ^{13}C kinetic isotope effects, computational modelling, and crossover experiments the authors were able to show that in cases

of competitive [1,2]- and [2,3]-rearrangement that both processes proceed through a common formal [2,3]-transition state such as **301** (*Scheme 59*).[44]



Scheme 60: Singleton's investigation into competing [1,2]- and [2,3]-rearrangements.[44]

Jacobsen and co-workers have recently reported a detailed mechanistic and computational investigation into the related thiourea-catalysed [2,3]-Wittig rearrangement detailed in *chapter 1*.[45] The observed diastereocontrol of general [2,3]-rearrangements is often rationalised by the relative energies of the *exo* and *endo* transition states. These general transition states are typically based upon those calculated by Marshall and Houk[46] for the [2,3]-Wittig rearrangement (*Scheme 61*). The stereochemical outcome of many [2,3]-rearrangement processes is informed by the steric and stereoelectronic properties of the substituents (R^1 and R^2) and also the heteroatom present. Whilst the diastereocontrol of many [2,3]-rearrangements can be rationalised through these transition states, the origins of enantioselectivity of the majority of [2,3]-rearrangements is unclear.



Scheme 61: Generalised diastereoselectivity rationale, based upon Marshall and Houk's calculated transition states.[46]

In *chapter 2* a Lewis base-catalysed mechanism is proposed for the isothiourea-catalysed enantioselective [2,3]-rearrangement of allylic ammonium ylides previously described. However, a number of alternative possibilities cannot be initially excluded, including Lewis or Brønsted base-catalysed pathways that would proceed through a variety of different reactive intermediates. For example, if a Lewis base-catalysed pathway is operative the reaction could pass through ammonium ketene **307** *en route* to the reactive Lewis base-bound ammonium ylide **306**. Alternatively, the

isothiourea catalyst could act as a Brønsted base-catalyst which could directly deprotonate the substrate to form chiral ion pair **308**.

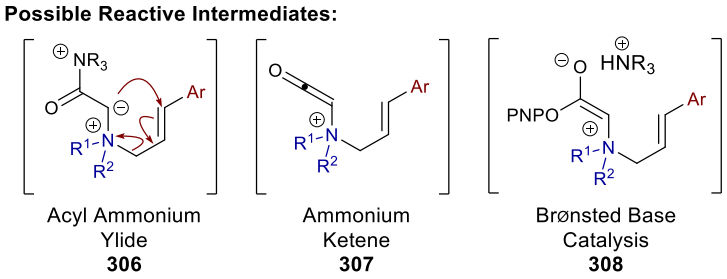
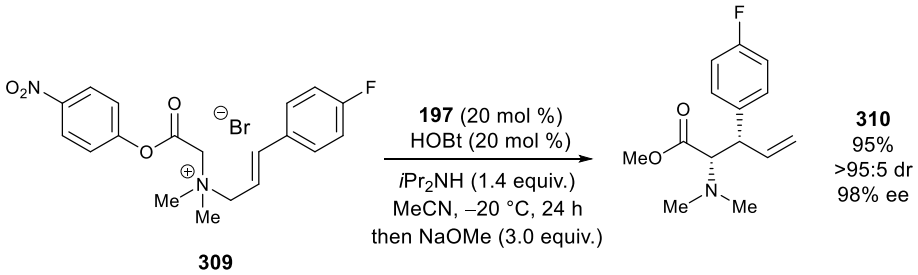


Figure 5: Potential reaction intermediates.

This chapter aims to gain detailed mechanistic and stereochemical insight into the isothiourea -catalysed enantioselective [2,3]-rearrangement developed and described in *chapter 2*. We aimed to gain information regarding the overall process through kinetic and reaction order analysis, to look at the reversibility of each of the key reaction steps, identify any potential catalytic intermediates, probe the turnover-limiting step of the process, and to assess the role of the co-catalyst HOBt. Through collaboration with computational chemists Prof. Paul Ha Yeon-Cheong and Daniel Walden at Oregon State University, we aimed to probe the origins of stereochemical control within the process and validate any experimental mechanistic hypotheses.

3.3 Kinetic Reaction Profiling

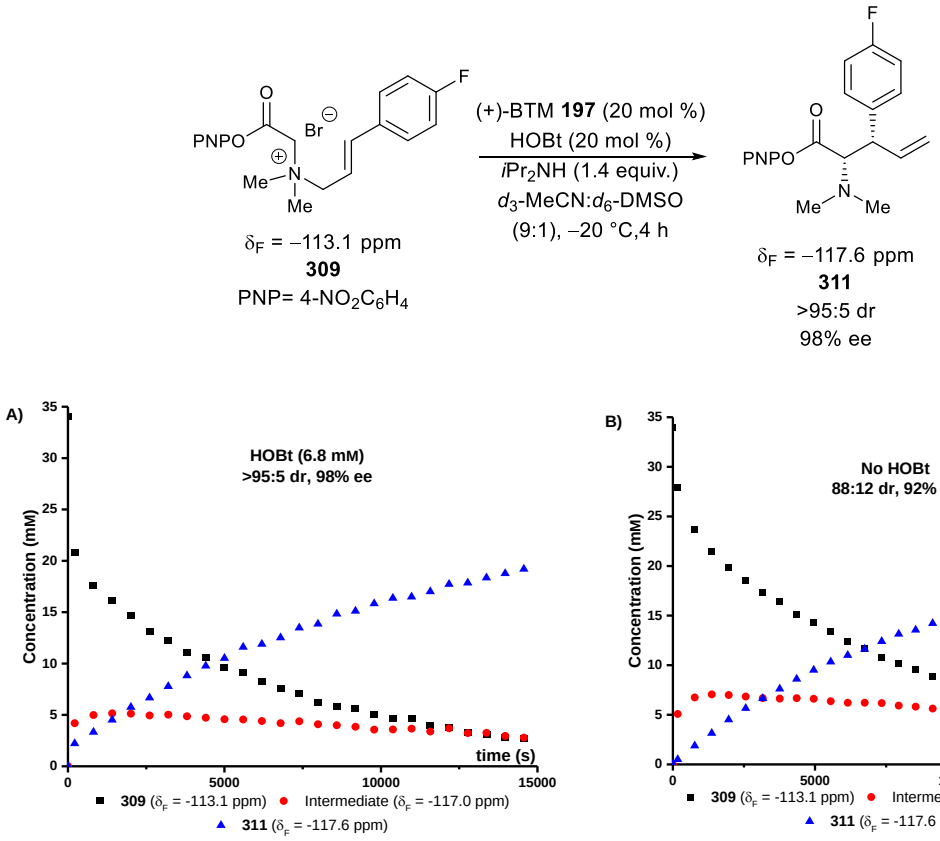
Initial efforts were focused on establishing a kinetic profile of the previously developed [2,3]-rearrangement using ^{19}F NMR as an *in situ* method to monitor the concentrations of substrate and product to identify any potential catalytic intermediates. The "standard" reaction chosen was the [2,3]-rearrangement of isolated ammonium salt **309**, which under the previously optimised reaction conditions, (+)-BTM **197** (20 mol %), HOBt (20 mol %) and *i*Pr$_2$NH (1.4 equiv.) in MeCN at −20 °C, gives **310** in excellent yield and stereoselectivity (95%, >95:5 dr, 98% ee) after the addition of NaOMe.



Scheme 62: Reaction chosen for kinetic analysis.

The 4-fluoro substituent on **309** allows direct monitoring of any species derived from the substrate by ^{19}F NMR *in situ* over time. To analyse this process by ^{19}F NMR some modulation of reaction conditions

had to be made from the original synthetic conditions as ammonium salt **309** is only partially soluble in d_3-MeCN at the synthetic reaction concentration (68 mM). Therefore, the reaction solvent was changed to d_3-MeCN/d_6-DMSO (9:1) and the concentrated halved (34 mM) to allow for full solubility of **309** at −20 °C. Using α,α,α-trifluorotoluene ($PhCF_3$) as an internal standard, a reaction profile could be readily obtained through monitoring of the concentrations of all species containing fluorine over a time period of 4 h at −20 °C, acquiring a $^{19}F\{^1H\}$ NMR spectrum every ten minutes ns = 1, (*Scheme 63A*). $^{19}F\{^1H\}$ single scan was chosen to avoid issues of T_1 relaxation. [47] A typical $^{19}F\{^1H\}$ NMR spectrum of a kinetic analysis is shown in *chapter 6*. *Scheme 63A* shows a typical reaction profile monitoring substrate **309** and product **311**, acid formed from hydrolysis of **309**, *anti*-**311** and HOBt esters are not plotted for clarity. During the early stages of the reaction (<1000 s) a large consumption of substrate (δ_F = −113.1 ppm) is observed, however as the reaction proceeds it enters a pseudo-steady state period (~3000 s onwards) where the substrate decays with good pseudo-first order kinetics. The rearrangement product **311** (δ_F = −117.6 ppm) builds up to high concentrations (~20 mM, >80% conversion) over 4 h. During this kinetic analysis an unknown intermediate species (δ_F = −117.0 ppm) was also observed over the course of the reaction, which builds up to maximum concentration of ~5.2 mM during the initial stages of the reaction and slowly decays as the reaction progresses. Reactive intermediates are rarely observed in kinetic profiles obtained by NMR, so efforts were focused on the identification of this species. If the [2,3]-rearrangement of **309** is performed in the absence of the HOBt additive a similar reaction profile is observed, but slightly lower diastereo- and enantiocontrol is obtained (88:12 dr, 92% ee). Notably, in the absence of HOBt the observed intermediate builds up to higher maximum concentrations (7.1 mM) (*Scheme 63B*) and therefore to facilitate identification of this intermediate further investigations were performed in the absence of HOBt.

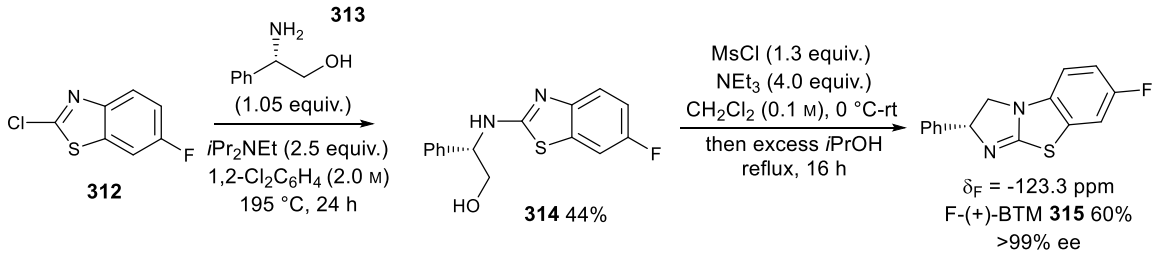


Scheme 63: Reaction profiles monitored by $^{19}F\{^{1}H\}$ NMR, initial concentrations: **309** (34 mM), (+)-BTM **197** (6.8 mM), *i*Pr$_2$NH (47 mM), d_3-MeCN:d_6-DMSO (9:1), −20 °C, 4 h. **A)** HOBt (6.8 mM), **B)** No HOBt. Acid formed from hydrolysis of **309**, *anti*-**311** and HOBt ester not plotted for clarity.

3.4 Identification of the observed intermediate

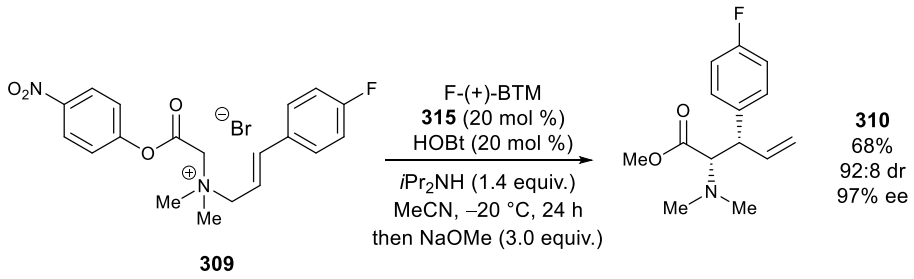
3.4.1 Catalyst Speciation

To monitor all catalyst derived species, the resting state of the catalyst and determine if the observed intermediate is catalyst derived a fluorinated version of (+)-BTM, F-(+)-BTM **315**, was synthesised. F-(+)-BTM **315** was synthesised in two steps from the corresponding chlorobenzothiazole **312** using the chromatography-free route of Daniels *et.al.*[48] (*Scheme 64*).



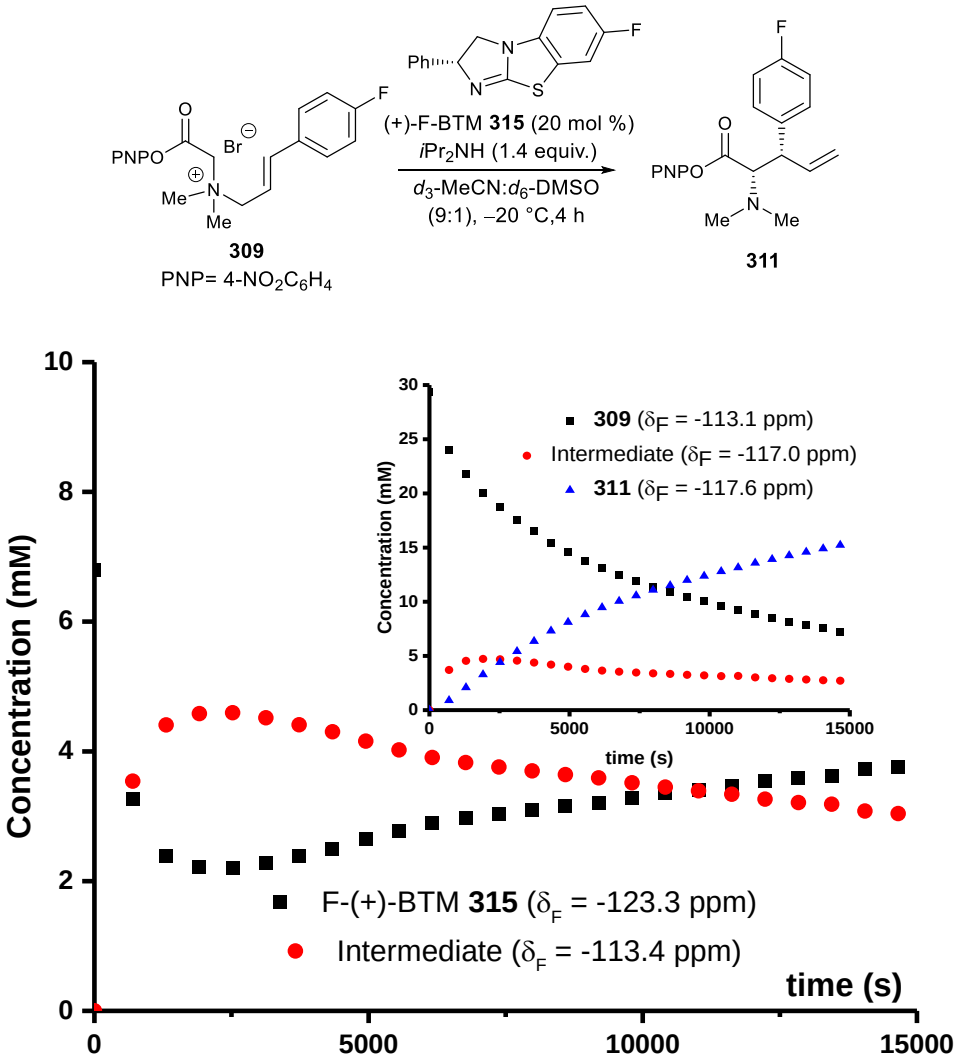
Scheme 64: Synthesis of F-(+)-BTM **315**.

F-(+)-BTM **315** is a competent catalyst for the [2,3]-rearrangement of **309**, giving rearranged product **310**, after the addition of NaOMe, in comparable stereocontrol (92:8 dr, 97% ee) to the reaction using (+)-BTM **197** (>95:5 dr, 98% ee) (*Scheme 65*).



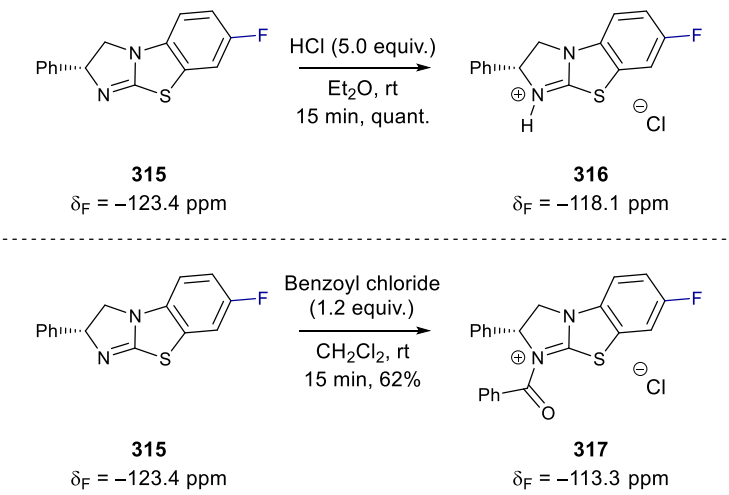
Scheme 65: Demonstration of catalytic competency of F-(+)-BTM **315**, in the [2,3]-rearrangement of **309**.

In situ monitoring of the F-(+)-BTM **315** catalysed process by $^{19}F\{^{1}H\}$ NMR revealed the presence of free F-(+)-BTM **315** (δ_F = −123.3 ppm) and an additional catalyst derived species containing two fluorine signals (δ_F = −113.4 and −117.0 ppm), which integrate equally through the course of the reaction. The latter displayed analogous kinetic behaviour to that of the previously observed reaction intermediate when (+)-BTM **197** is used (*Scheme 66*), suggesting that it is one species derived from a combination of catalyst and substrate. Monitoring of F-(+)-BTM throughout the reaction also revealed the catalyst resting state. The catalyst exists as a mixture of free F-(+)-BTM **315** and catalyst derived intermediate. At the onset of the pseudo-steady-state section of the reaction (>3000 s, 40% conversion), the catalyst exists predominately as the intermediate; as the reaction progresses and the concentration of substrate decreases the resting-state changes to the free F-(+)-BTM (~10000 s, 66% conversion) (*Scheme 66*). Notably, the chemical shift of F-(+)-BTM **315** (δ_F = −123.3 ppm) remains constant throughout the course of the reaction indicating the free catalyst does not become partially protonated.



Scheme 66: Catalyst speciation and identification of reaction intermediate, inset graphic shows the monitoring of substrate derived species, initial concentrations; **309** (29.5 mM), F-(+)-BTM **315** (6.8 mM), *i*Pr$_2$NH (47 mM), d_3-MeCN/d_6-DMSO (9:1), −20 °C, 4 h.

To help elucidate the identity of the catalyst derived reaction intermediate, simplified model species were synthesised. F-(+)-BTM·HCl **316** (δ_F = −118.1 pm) and an *N*-benzoyl acyl ammonium **317** (δ_F = −113.3 pm) were synthesised from F-(+)-BTM **315**, through reaction with ethereal HCl and benzoyl chloride, respectively (*Scheme 67*). Based upon the chemical shift of the fluorine signals it is postulated that the observed intermediate (δ_F = −113.4 ppm) is an acylated isothiourea (model **317** δ_F = −113.3 pm).



Scheme 67: Synthesis of catalyst derived model substrates.

3.4.2 Intermediate identification by isotopic labelling

Given that the observed intermediate is thought to be acyl ammonium derived, based on our previous mechanistic hypotheses, the intermediate could be dication **318**, ammonium ylide **319** or acyl ammonium **320** (*Figure 6*). The nature of the counterion on the observed intermediate is not obvious and is thought to be tough to probe experimentally.

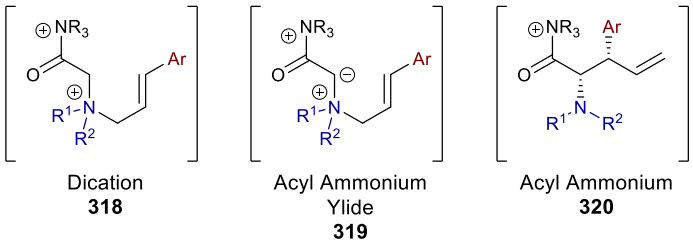


Figure 6: Possible constitution of observed intermediate, possible counterions omitted for clarity.

To fully elucidate the constitution of the observed intermediate an isotopic labelling strategy was employed. In order to utilise this strategy an ^{15}N labelled catalyst, ^{15}N-F-BTM **^{15}N-321**, and $^{13}C_2$ ammonium salt substrate **$^{13}C_2$-322** were identified as necessary (*Figure 7*).

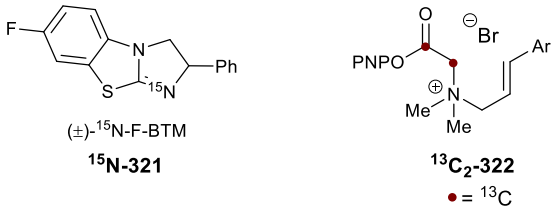


Figure 7: Isotopic labelling strategy.

Double labelling of the substrate **$^{13}C_2$-322** with ^{13}C allowed facile *in situ* monitoring of the reaction by $^{13}C\{^1H\}$ NMR, also necessary to allow identification of potential C-N bond connectivity within the

intermediate. The ^{13}C nucleus has a nuclear spin of I = ½ and a natural abundance of 1.1%, meaning **$^{13}C_2$-322** will exhibit doublets for the ^{13}C=O and $^{13}CH_2$ signals (number of lines = 2nI + 1 = 2(1)(1/2) + 1 = 2) in $^{13}C\{^1H\}$ NMR. The ^{15}N nucleus also has a nuclear spin of I = ½ and a natural abundance of 0.37%, hence if there is ^{15}N-^{13}C connectivity within the observed intermediate a doublet of doublets would be observed within the $^{13}C\{^1H\}$ NMR for the ^{13}C=O signal. This due to the ^{15}N atom causing further splitting of the doublet into a doublet of doublets (*Figure 8*).

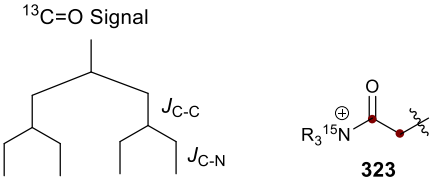
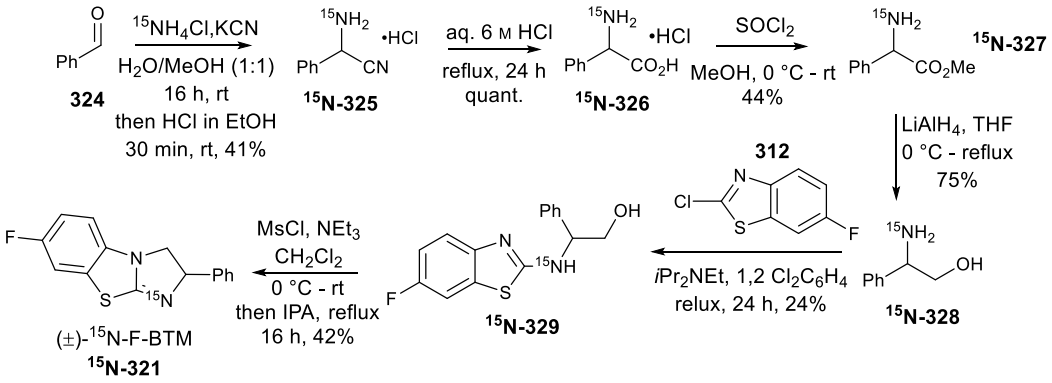


Figure 8: Expected coupling pattern for the presence of ^{15}N-^{13}C connectivity.

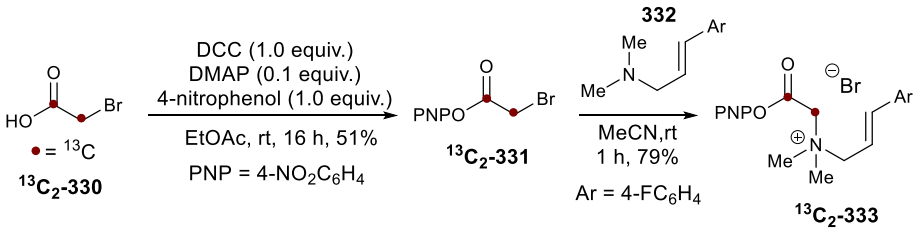
3.4.3 Synthesis of isotopically labelled catalyst and substrate

Racemic ^{15}N-F-BTM **^{15}N-321** was synthesised in six steps from $^{15}NH_4Cl$ and benzaldehyde **324**. Firstly, a three-component Strecker reaction between benzaldehyde, $^{15}NH_4Cl$ and potassium cyanide gave ^{15}N-α-amino nitrile **^{15}N-325** in modest yield, with subsequent hydrolysis under acidic conditions giving ^{15}N-phenylglycine **^{15}N-326** in quantitative yield. Methyl ester formation and $LiAlH_4$ reduction gave ^{15}N-phenylglycinol **^{15}N-328**. S_NAr with 2-chloro-6-fluoro-benzothiazole **312** gave ^{15}N-amino alcohol **^{15}N-329** in poor yield, with subsequent cyclisation using methanesulfonyl chloride and NEt_3 giving ^{15}N-F-BTM **^{15}N-321** in 42% yield (*Scheme 68*).



Scheme 68: Synthesis of ^{15}N-F-BTM **^{15}N-321**.

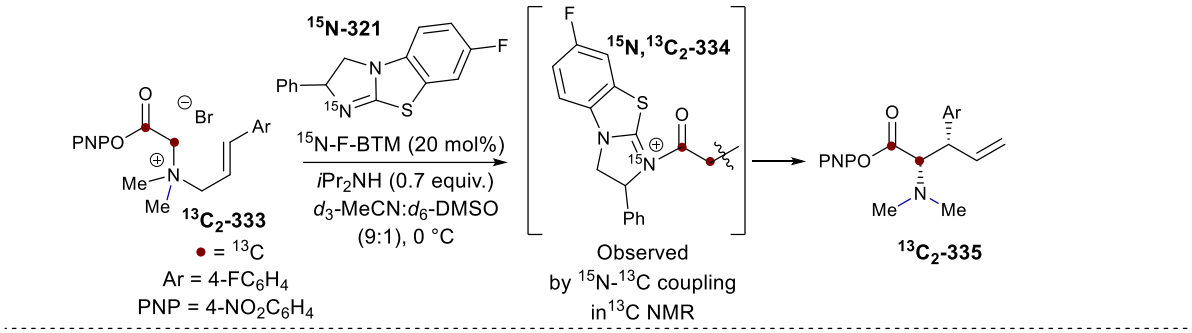
Doubly ^{13}C labelled ammonium salt **$^{13}C_2$-333** was synthesised over two steps from commercially available $^{13}C_2$-bromoacetic acid **$^{13}C_2$-330**. DCC coupling with 4-nitrophenol gave $^{13}C_2$-4-nitrophenyl bromoacetate **$^{13}C_2$-331**, which was reacted with *N*,*N*-dimethyl 4-fluorocinnamyl amine **332** to give $^{13}C_2$ labelled ammonium salt **$^{13}C_2$-333**.

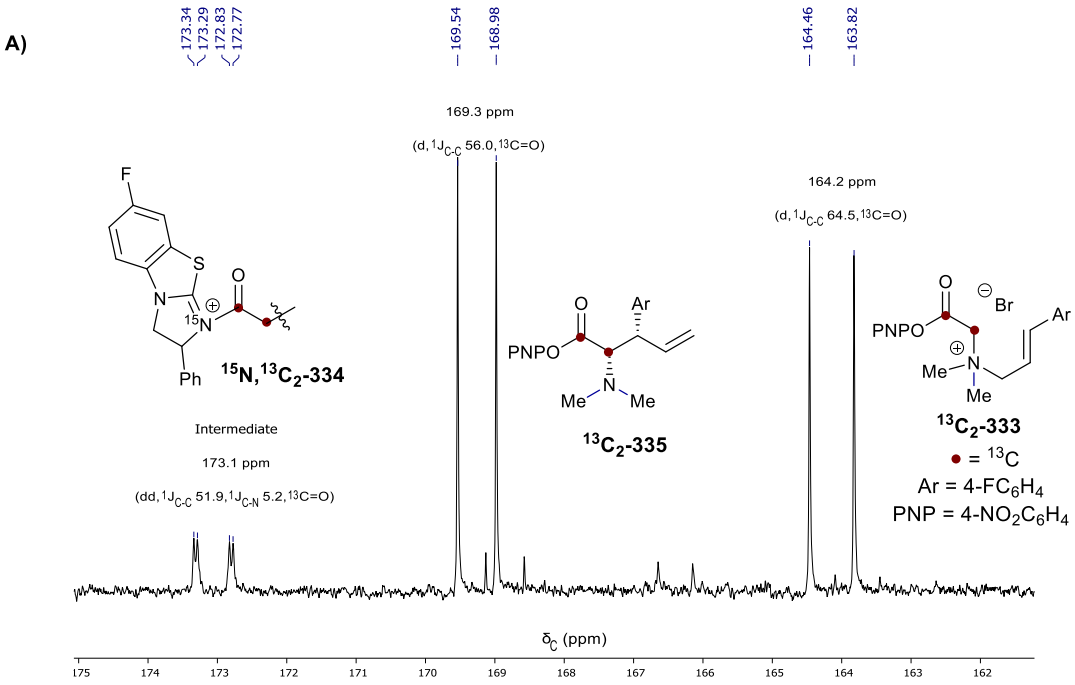


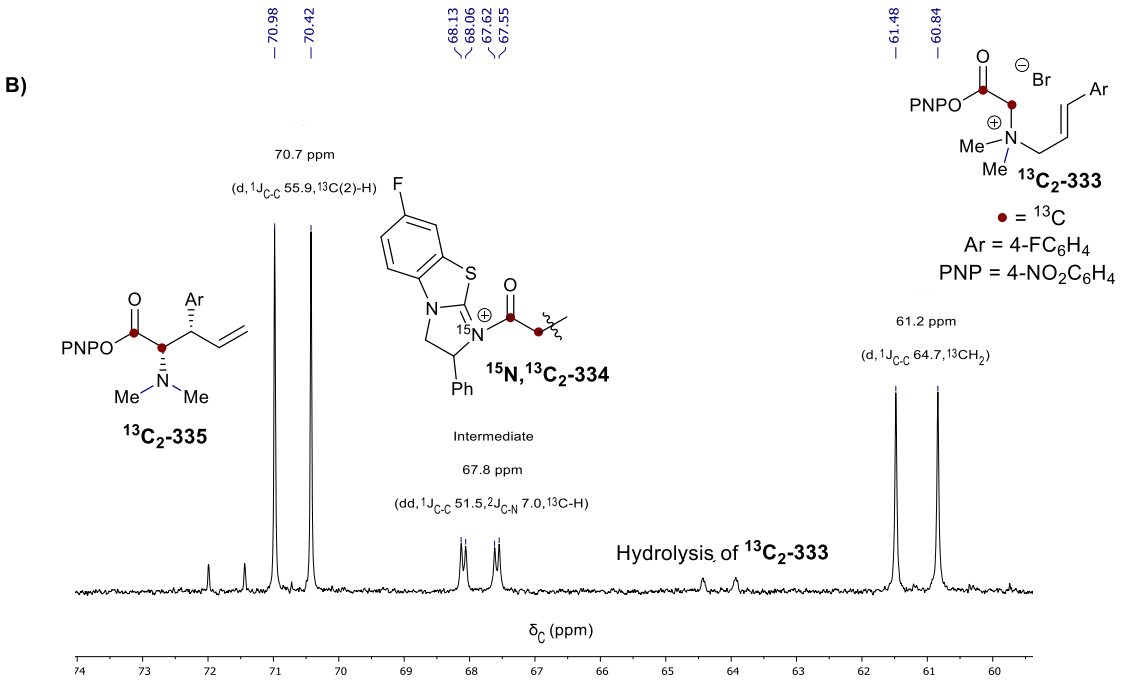
Scheme 69: Synthesis of $^{13}C_2$ ammonium salt **$^{13}C_2$-333**

3.4.4 *In situ* reaction monitoring by ^{13}C NMR Spectroscopy

Using isotopically ^{15}N labelled catalyst **^{15}N-321** and $^{13}C_2$ labelled ammonium salt **$^{13}C_2$-333** the reaction was monitored *in situ* by $^{13}C\{^1H\}$ NMR. Modulation of the concentration of *i*Pr$_2$NH (23.8 mM) prolonged the lifetime of the observed intermediate and facilitated its identification. Following the reaction by $^{13}C\{^1H\}$ NMR, the ^{13}C=O region of the spectrum displayed a doublet of doublets at δ_C = 173.1 ppm ($^1J_{CC}$ = 51.9 Hz, $^1J_{CN}$ = 5.2 Hz), which is consistent with the presence of an acyl ammonium motif within the observed intermediate (*Scheme 70A*). Analysis of the $^{13}CH/^{13}CH_2$ region of the $^{13}C\{^1H\}$ NMR spectrum (60-73 ppm) displayed a doublet of doublets at δ_C = 67.8 ppm ($^1J_{CC}$ = 51.5 Hz, $^2J_{CN}$ = 7.0 Hz) for the intermediate species, further confirming the presence of an acyl ammonium motif within the intermediate (*Scheme 70B*).


15N-321
15N-F-BTM (20 mol%)
iPr2NH (0.7 equiv.)
d3-MeCN:d6-DMSO
(9:1), 0 °C
13C2-333
● = 13C
Ar = 4-FC6H4
PNP = 4-NO2C6H4
15N,13C2-334
Observed
by 15N-13C coupling
in 13C NMR
13C2-335


A)
173.34
173.29
172.83
172.77
169.54
168.98
164.46
163.82
169.3 ppm
(d, 1JC-C 56.0, 13C=O)
164.2 ppm
(d, 1JC-C 64.5, 13C=O)
15N,13C2-334
Intermediate
173.1 ppm
(dd, 1JC-C 51.9, 1JC-N 5.2, 13C=O)
13C2-335
13C2-333
● = 13C
Ar = 4-FC6H4
PNP = 4-NO2C6H4
δC (ppm)


B)
70.98
70.42
68.13
68.06
67.62
67.55
61.48
60.84
70.7 ppm
(d, 1JC-C 55.9, 13C(2)-H)
13C2-335
15N,13C2-334
Intermediate
67.8 ppm
(dd, 1JC-C 51.5, 2JC-N 7.0, 13C-H)
61.2 ppm
(d, 1JC-C 64.7, 13CH2)
13C2-333
● = 13C
Ar = 4-FC6H4
PNP = 4-NO2C6H4
Hydrolysis of 13C2-333
δC (ppm)

Scheme 70: Isotopic labelling studies employing ^{15}N-F-BTM **^{15}N-321** and $^{13}C_2$ ammonium salt **$^{13}C_2$-333**, initial concentrations; **$^{13}C_2$-333** (34 mM), ^{15}N-F-BTM **^{15}N-321** (6.8 mM), *i*Pr$_2$NH (23.8 mM), with partial ^{13}C{^{1}H} NMR (101 MHz, d_3-MeCN/d_6-DMSO (9:1), 273 K) spectra: **A)** (162 -175 ppm), **B)** (60 -74 ppm)

To ascertain the presence of any C(2)-C(3) connectivity within the intermediate, a ^{1}H coupled ^{13}C NMR spectrum was acquired. A doublet of doublets ($^1J_{CH}$ = 138.6 Hz, $^1J_{CC}$ = 51.7 Hz) at δ_C = 67.8 ppm was observed, consistent with the intermediate containing a C(2)H unit, however longer range $^2J_{CH}$ coupling could not unambiguously confirm or exclude C(2)-C(3) connectivity due to significant line broadening within the intermediate in the ^{13}CH/^{13}CH$_2$ region. Notably, long range $^2J_{CH}$ coupling could be readily observed within rearranged product **$^{13}C_2$-335** in the ^{13}CH region, (ddd, $^1J_{CH}$ =143.2 Hz, $^1J_{CC}$ = 56.9 Hz, $^2J_{CH}$ = 2.8 Hz) at δ_C = 70.7 ppm, indicating C(2)-C(3) connectivity within the rearranged product **$^{13}C_2$-333**.

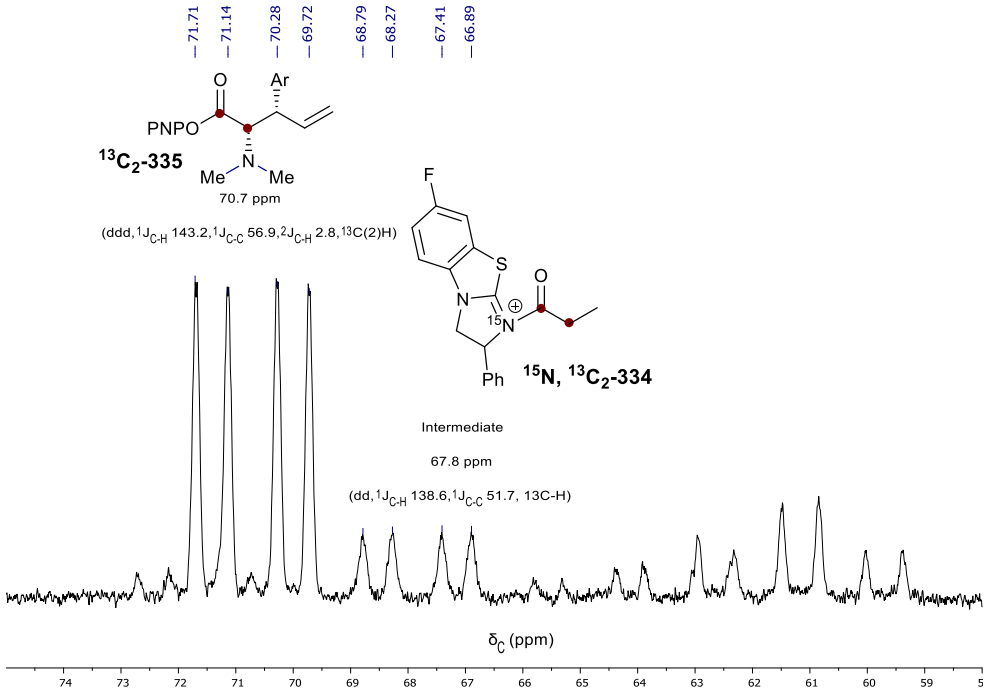
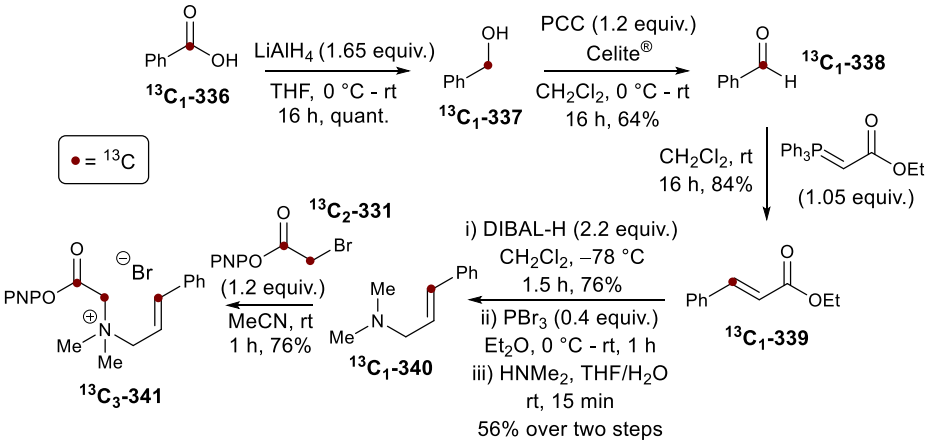


Figure 9: Isotopic labelling studies employing ^{15}N-F-BTM **^{15}N-321** and $^{13}C_2$ ammonium salt **$^{13}C_2$-333** with partial ^{1}H coupled ^{13}C NMR (101 MHz, d_3-MeCN/d_6-DMSO (9:1), 273 K) spectrum (58 -75 ppm). Initial concentrations; **$^{13}C_2$-333** (34 mM), ^{15}N-F-BTM (6.8 mM), *i*Pr$_2$NH (23.8 mM).

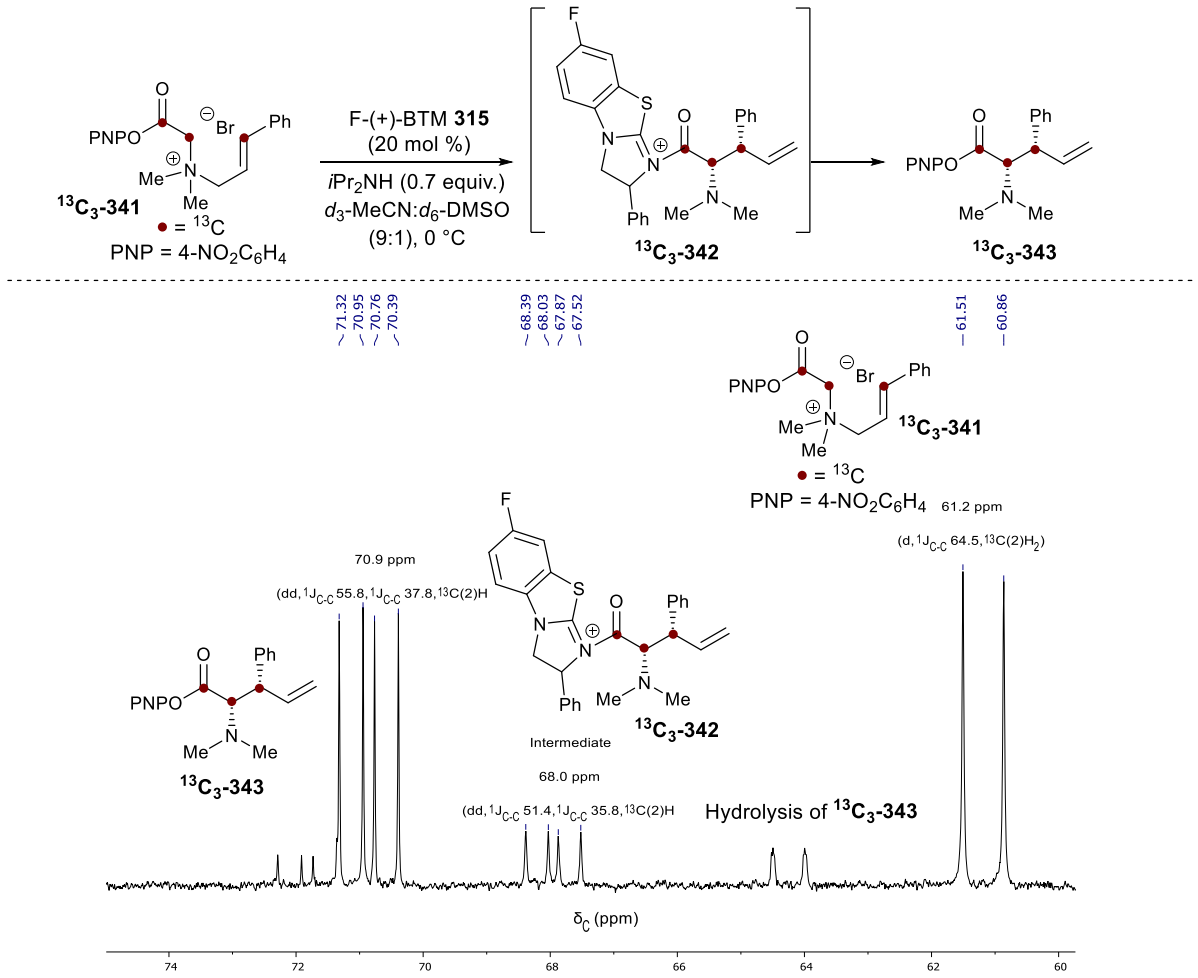
To allow unambiguous elucidation of the constitution of the intermediate an additional ^{13}C isotopic label was installed at the C(3) position of the ammonium salt **$^{13}C_3$-341**. Triply labelled $^{13}C_3$ ammonium salt **$^{13}C_3$-341** was prepared from commercially available α-^{13}C benzoic acid **$^{13}C_3$-336** in seven steps, starting with LiAlH$_4$ reduction to ^{13}C labelled benzyl alcohol **$^{13}C_3$-337** and PCC oxidation to give α-^{13}C benzaldehyde **$^{13}C_3$-338**. Wittig olefination yielded ^{13}C(3)-ethyl cinnamate **$^{13}C_3$-339**, with DIBAL-H reduction followed by bromination and amination giving ^{13}C-*N*,*N*-dimethyl cinnamyl amine **$^{13}C_3$-340**.

Reaction of **$^{13}C_3$-340** with $^{13}C_2$-4-nitrophenyl bromoacetate **$^{13}C_2$-331** gave the desired $^{13}C_3$ ammonium salt **$^{13}C_3$-341** (*Scheme 71*).



Scheme 71: Synthesis of $^{13}C_3$-ammonium salt **$^{13}C_3$-341**

Reacting $^{13}C_3$-ammonium salt **$^{13}C_3$-341** with (+)-F-BTM **315** (20 mol%, 6.8 mM) and *i*Pr$_2$NH (23.8 mM) and monitoring the reaction via *in situ* $^{13}C\{^1H\}$ NMR, the C(2) region (59-72 ppm) displayed a doublet of doublets ($^1J_{CC}$ = 51.4 Hz, $^1J_{CC}$ = 35.8 Hz) at δ_C = 68.0 ppm that is consistent with C(2)-C(3) bond formation (*Scheme 72*). These isotopic labelling studies indicate that the observed intermediate is post-rearrangement acyl ammonium **$^{13}C_3$-342**.

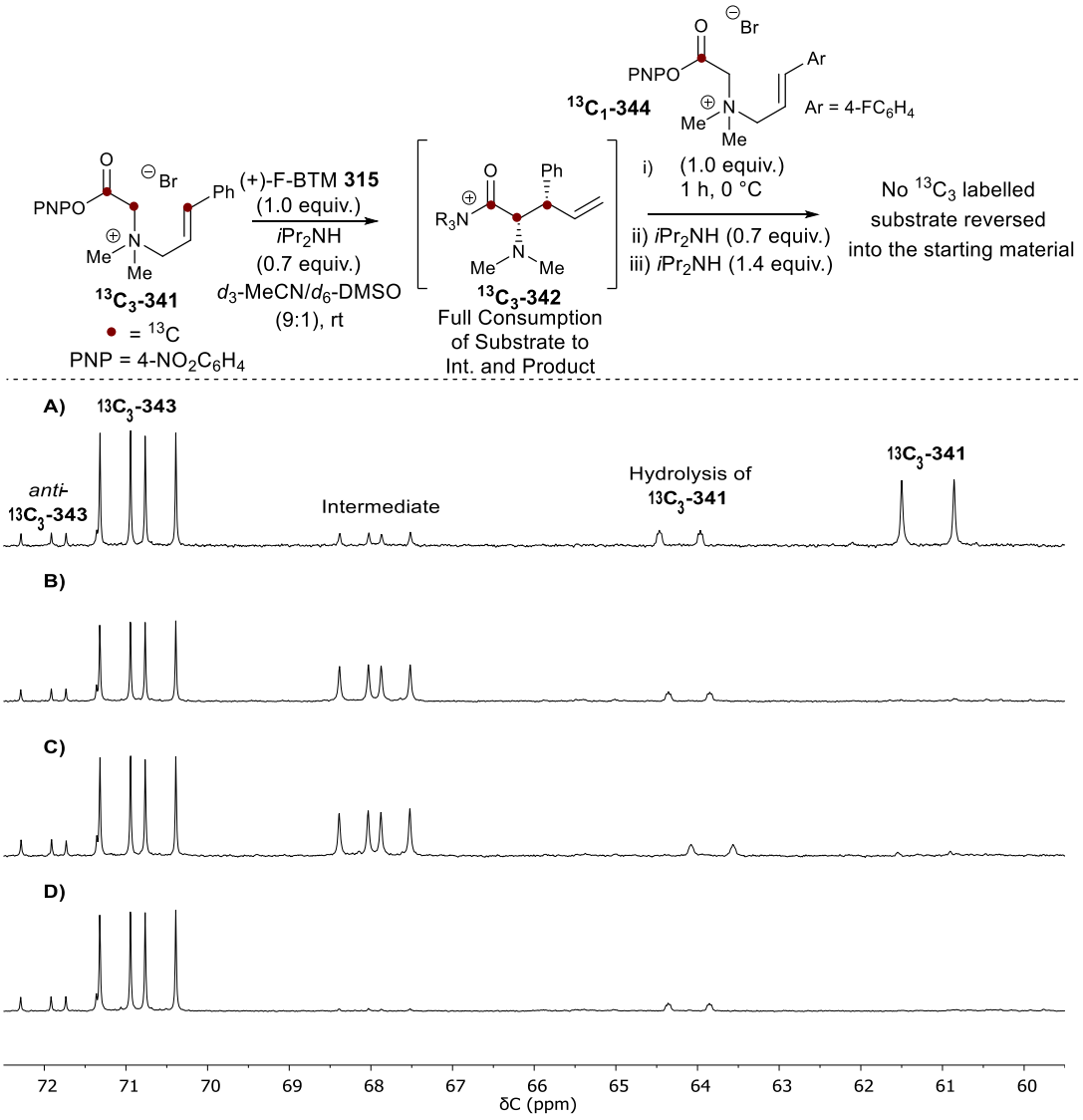


Scheme 72: Isotopic labelling studies employing F-(+)-BTM **315** and $^{13}C_3$ ammonium salt **$^{13}C_3$-341** with partial $^{13}C\{^1H\}$ NMR ((101 MHz, d_3-MeCN/d_6-DMSO (9:1) 273 K) spectrum (60 -74 ppm). Initial concentrations; **$^{13}C_3$-341** (34 mM), F-(+)-BTM **315** (6.8 mM), iPr$_2$NH (23.8 mM).

3.5 Reversibility of Intermediate Formation

Having fully elucidated the constitution of the observed reaction intermediate, the reversibility of its formation and hence the reversibility of the [2,3]-rearrangement step were probed. *In situ* $^{13}C\{^1H\}$ NMR was once again employed to monitor the process, $^{13}C_3$ ammonium salt **$^{13}C_3$-341** was treated with a stoichiometric amount of F-(+)-BTM **315** (34 mM, 1.0 equiv.) and iPr$_2$NH (23.8 mM, 0.7 equiv.) at rt to effect full conversion of **$^{13}C_3$-341** into a mixture of **$^{13}C_3$-343** and intermediate **$^{13}C_3$-342** (*Scheme 73B*). Once full conversion of **$^{13}C_3$-341** was achieved, an equivalent of **$^{13}C_1$-344** (34 mM, 1.0 equiv.), synthesised from $^{13}C_1$ bromoacetic acid, was added and the system allowed to equilibrate in the spectrometer at 273 K for 1 h (*Scheme 73C*). Over this time period no $^{13}C_3$ material was observed to revert back into **$^{13}C_3$-341** from either the intermediate or product. The reaction was subsequently treated with additional iPr$_2$NH (23.8 mM then 47.6 mM) and still no $^{13}C_3$ material was observed reversing into substrate; remaining $^{13}C_3$ intermediate was converted into product **$^{13}C_3$-343** (*Scheme 73D*). This is

consistent with the irreversible formation of the intermediate **$^{13}C_3$-342** and hence the [2,3]-rearrangement step of the process is highly irreversible (*Scheme 73*).



Scheme 73: Intermediate reversibility studies, **A)** $^{13}C\{^1H\}$ NMR spectrum (101 MHz, d_3-MeCN/d_6-DMSO (9:1), 273K) of the $^{13}C(2)$-H region (59-73 ppm). Conditions, **$^{13}C_3$-341** (34 mM), (+)-F-BTM **315** (6.8 mM), iPr$_2$NH (23.8 mM), **B) $^{13}C_3$-341** (34 mM), (+)-F-BTM **315** (34 mM), iPr$_2$NH (23.8 mM), **C) $^{13}C_3$-341** (34 mM), (+)-F-BTM **315** (34 mM), iPr$_2$NH (23.8 mM) and **$^{13}C_1$-344** (34 mM), 273K, 1 h., **D)** After the addition of further iPr$_2$NH (23.8 mM, then a further 47.6 mM).

3.6 Intermediate On or Off Productive Pathway?

Isotopic entrainment studies

To ascertain if the observed acyl ammonium intermediate **342** is off (*figure 10, Case A*) or on (*figure 10, Cases B-D*) the productive catalytic cycle, an isotopic entrainment experiment was performed to distinguish between these four cases. Isotopic entrainment is an experiement in which, once a catalytic reaction has reached pseudo-steady-state, a labelled substrate is added into the reaction and followed through the catalytic cycle. Analysis of the changes of labelled populations within the substrate, intermediate and product allows distinction between each of the four proposed cases. (*Figure 10*).

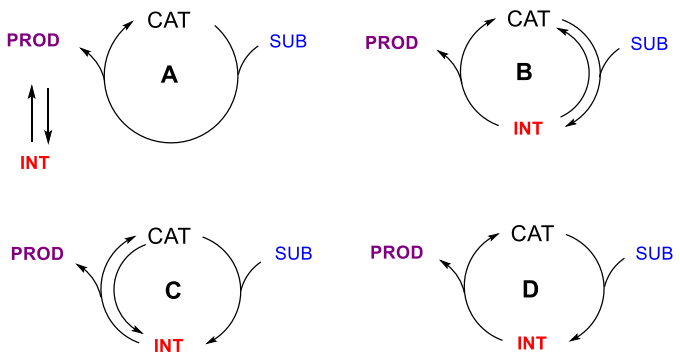
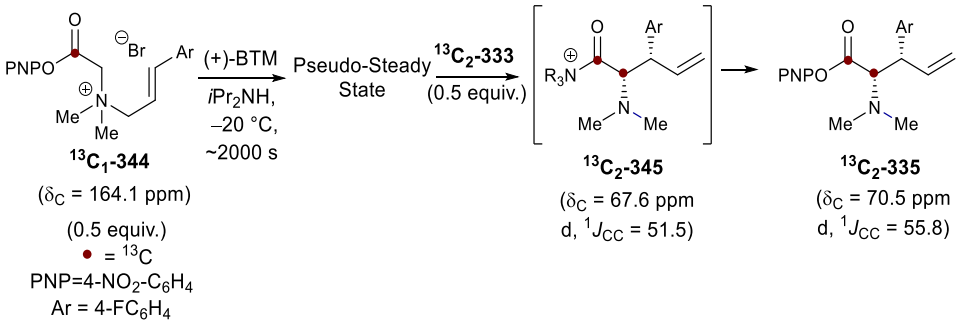


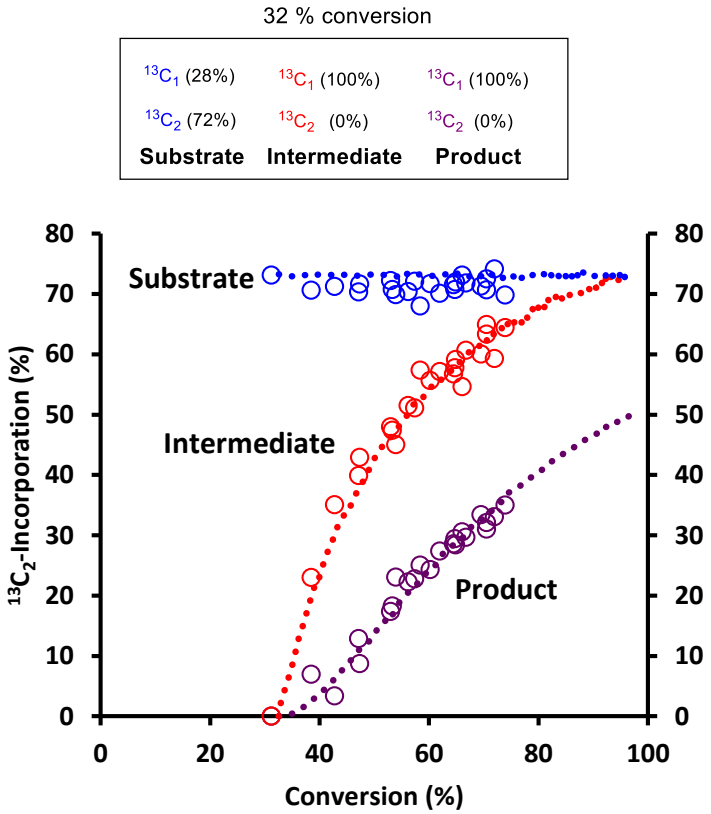
Figure 10: Possible productive and non-productive cases for the observed intermediate **342**.

Applying this strategy, $^{13}C_1$-ammonium salt **$^{13}C_1$-344** (0.5 equiv., 17 mM, δ_C = 164.1 (^{13}C=O)) was treated with (+)-BTM **197** (20 mol%, 6.8 mM) and *i*Pr$_2$NH (1.4 equiv., 47 mM) in 9:1 d_3-MeCN/d_6-DMSO at −20 °C and monitored by *in situ* quantitative (ns = 16, d1 = 30 s) $^{13}C\{^1H\}$ NMR spectroscopy. Once the reaction had reached the pseudo-steady-state period of the reaction ~2700 s, $^{13}C_2$-ammonium salt **$^{13}C_2$-333** (0.5 equiv., 17 mM, δ_C = 60.9 (d, $^1J_{CC}$ 64.6, $^{13}CH_2$)) was added to the reaction, and the $^{13}C_2$-matieral monitored by *in situ* quantitative (ns = 16, d1 =30 s) $^{13}C\{^1H\}$ NMR, $^{13}C_2$-intermediate **$^{13}C_2$-345** (δ_C = 67.6 (d, $^1J_{CC}$ 51.5, ^{13}C(2)H)) and $^{13}C_2$-product **$^{13}C_2$-335** (δ_C = 70.5 (d, $^1J_{CC}$ 55.8, ^{13}C(2)H)).

At the point of addition of **$^{13}C_2$-333**, there has been 32% net conversion of substrate (**$^{13}C_1$-344** and **$^{13}C_2$-333**), but neither the product nor the intermediate yet contain any $^{13}C_2$-labelled material. All $^{13}C_2$-material exists as unreacted substrate with is made up of 28% **$^{13}C_1$-344** and 72% **$^{13}C_2$-333**. Analysis of the $^{13}C_2$-populations in substrate, intermediate and products allowed us to distinguish between cases A-D (*figure 10*). Regardless of case (A-D) the $^{13}C_2$-population of the product must finally rise from 0 to 50%, as equal amounts of **$^{13}C_1$-344** and **$^{13}C_2$-333** were used. For case A where intermediate **342** is non-productive and is in equilibrium with the product, the $^{13}C_2$-incorportation with be lower or equal to that of the product (≤50%). For case B where the intermediate is productive but is in equilibrium with the substrate, the $^{13}C_2$-population of the substrate will be reduced, from 72% to 55%, as $^{13}C_1$-material reverses from the intermediate back into the substrate. For case C where the formation of the

intermediate ([2,3]-rearrangement) is irreversible, the $^{13}C_2$-population in the substrate will remain constant (72%).The $^{13}C_2$-population of the intermediate will be limited to 50% as it is in full equilibrium with the product. For case D the $^{13}C_2$-population in the substrate will also remain constant (72%), the $^{13}C_2$-population in the intermediate will rise to reach 72%, due to its irreverisble decay, the $^{13}C_2$-population in the intermediate will rise in advance of that of the product, due to it being on the productive pathway. Analysis of experimental and predicted $^{13}C_2$-populations as a function of net conversion (*Scheme 74*), confirms that intermediate **342** is a productive catalytic intermediate and occurs from two irreversible first-order interconversions (*figure 10*, *Case D*).



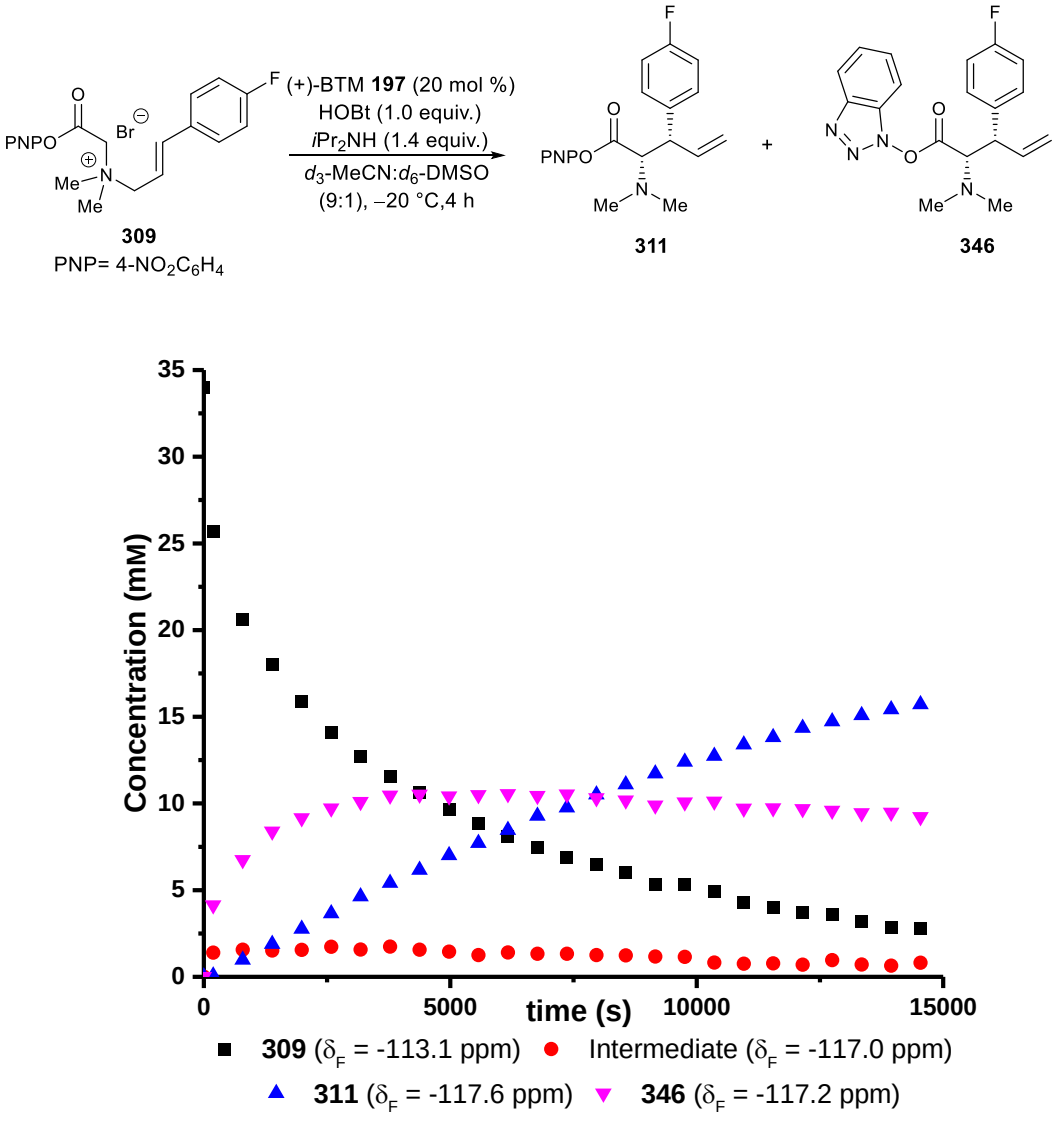


Scheme 74: Entrainment of $^{13}C_2$ substrate **$^{13}C_2$-333** into $^{13}C_1$ catalytic cycle [a]Conditions, **$^{13}C_1$-344** (17 mM), (+)-BTM **197** (6.8 mM), *i*Pr$_2$NH (47.6 mM), d_3-MeCN/d_6-DMSO (9:1), **$^{13}C_2$-333** (17 mM) added at 32% net conversion of substrate. Open circles: experimental ($^{13}C\{^1H\}$ NMR) data, dashed

lines: kinetic simulation where **342** is a productive intermediate in two-irreversible pseudo-first order interconverisons. Kinetic simulations performed by Prof. Guy C. Lloyd-Jones.

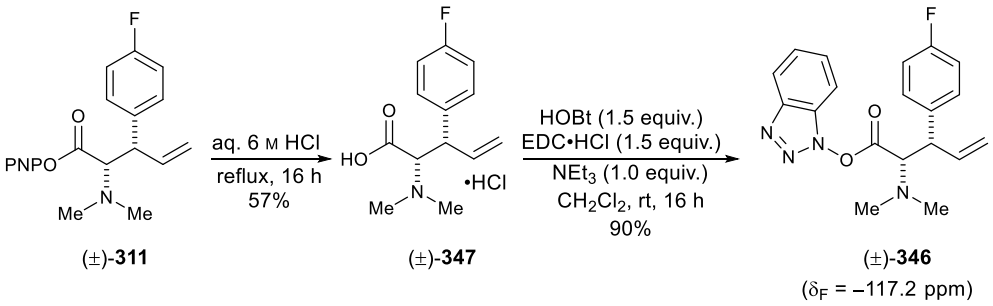
3.7 Effect of HOBt on the Acyl Ammonium Intermediate

To gain insight into the role of the co-catalytic HOBt used within the synthetic reaction, its effect upon the observed acyl ammonium intermediate **342** and kinetic profile was studied. Firstly, the rearrangement was studied in the presence of a stoichiometric amount of HOBt (34 mM, t= 0), which resulted in the suppression of acyl ammonium **342** formation and formation of the corresponding HOBt ester **346** was observed (*Scheme 75*).



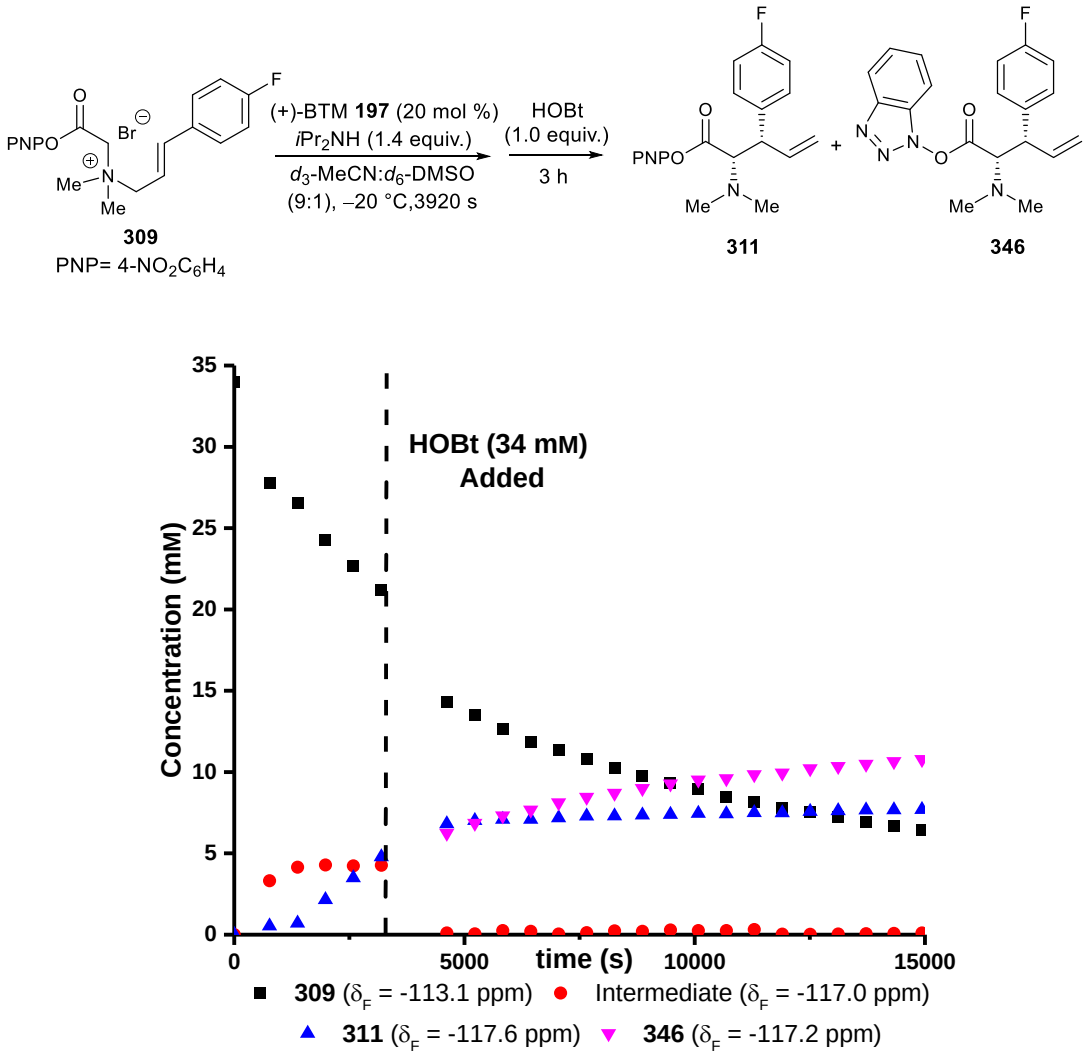
Scheme 75: Addition of stoichiometric HOBt (34 mM) at t=0, initial concentrations **309** (34 mM), (+)-BTM **197** (6.8 mM), HOBt (34 mM) *i*Pr$_2$NH (47.6 mM), d_3-MeCN/d_6-DMSO (9:1).

The identity of the HOBt ester **346** was confirmed through synthesis of an authentic sample, obtained through hydrolysis of **311** under acidic conditions followed by EDC·HCl mediated coupling with HOBt (*Scheme 76*).



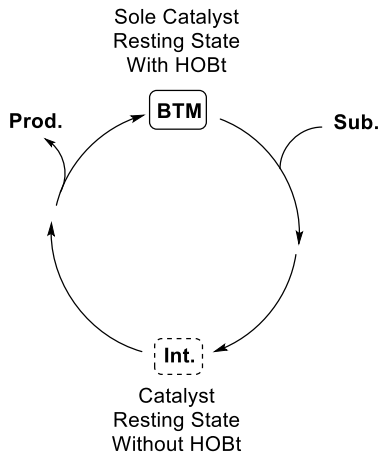
Scheme 76: Synthesis of racemic authentic sample of HOBt ester **346**.

To further examine the effect of HOBt upon acyl ammonium intermediate **342**, a stoichiometric amount of HOBt (34 mM) was added once the reaction has reached its pseudo-steady state (t= 3920 s) at which acyl ammonium **342** has reached its maximum concentration. This resulted in immediate formation of the HOBt ester **346** through esterification of acyl ammonium **342**. After this HOBt addition no further acyl ammonium intermediate **342** was observed by $^{19}F\{^{1}H\}$ NMR.



Scheme 77: Addition of stoichiometric HOBt (34 mM) at t = 3920 s, initial concentrations **309** (34 mM), (+)-BTM **197** (6.8 mM), *i*Pr$_2$NH (47.6 mM), d_3-MeCN/d_6-DMSO (9:1).

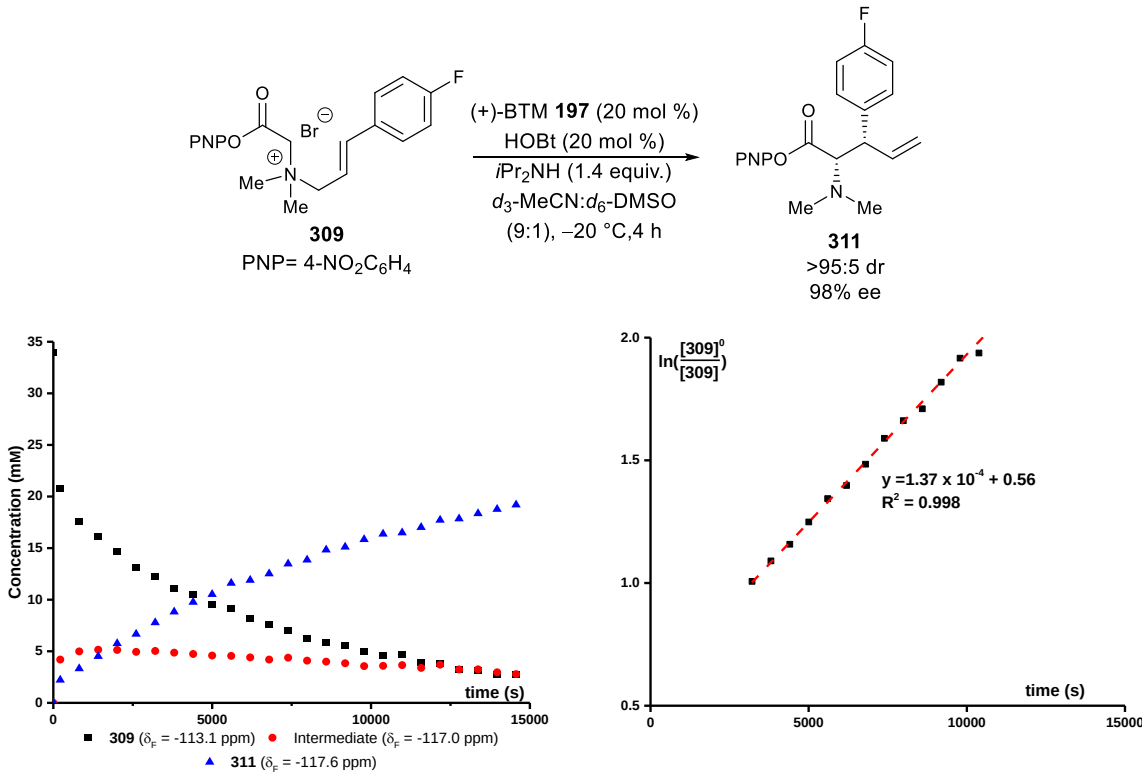
Examination of the reaction profiles of reactions with and without HOBt indicates that the addition of high concentrations of HOBt (13.6-34 mM) changes the resting state of the catalyst from acyl ammonium **342** to free (+)-BTM **197** (*Scheme 78*). This suggests that HOBt accelerates the breakdown of acyl ammonium **342** through transesterification, enabling product release *via* the corresponding HOBt ester **346**.



Scheme 78: Cartoon representation of change in catalyst resting state upon addition of HOBt. Sub., ammonium salt substrate, Int., acyl ammonium intermediate, Prod., 4-nitrophenyl ester product.

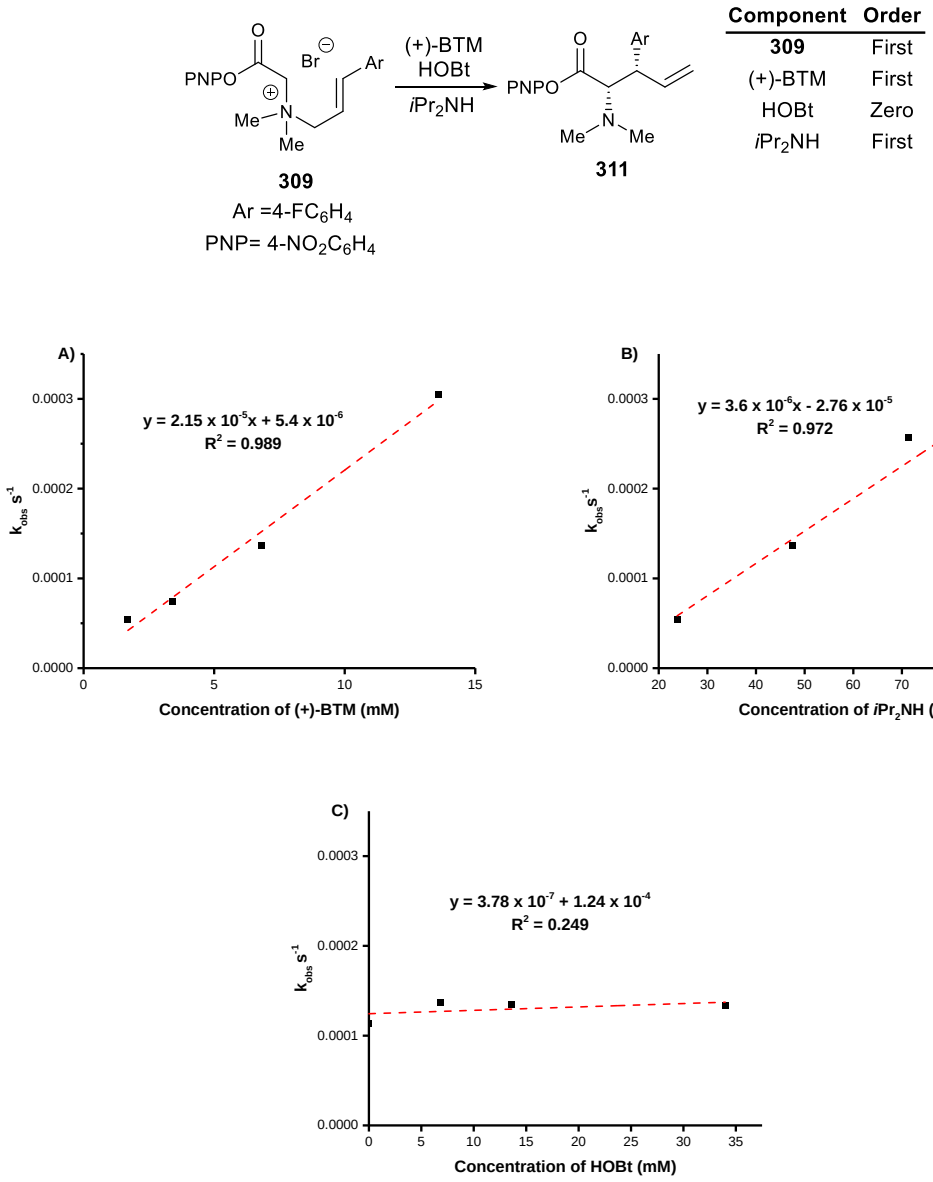
3.8 Reaction Kinetics

Having successfully identified all the species present in the reaction mixture by ^{19}F NMR, a full kinetic analysis was undertaken to determine the rate order of each of the components of the reaction. In the initial period of the reaction there is a significant drop in concentration of substrate, whilst the reaction slowly enters a pseudo-steady state section at ~3000 s. Once in the pseudo steady state, the substrate **309** decays with good pseudo-first order kinetics, which can be shown by plotting a first order log plot (*Scheme 79*). Under the standard conditions ((+)-BTM **197** (6.8 mM), HOBt **216** (6.8 mM), *i*Pr$_2$NH (47 mM), substrate (34 mM)) a k_{obs} of 1.37 × 10^{-4} s^{-1} was observed for the pseudo-steady section of the catalysis. The observed rate (k_{obs}) is determined from the gradient of the first order log plot discarding the data points within the induction period (the first five data points) (*Scheme 79*).



Scheme 79: Kinetic reaction profile and first-order log-plot for the [2,3]-rearrangement of **309**, initial concentrations; **309** (34 mM), (+)-BTM **197** (6.8 mM, 20 mol%), HOBt **216** (6.8 mM, 20 mol%), *i*Pr$_2$NH (47.6 mM, 1.4 equiv.), d_3-MeCN/d_6-DMSO (9:1), −20 °C, 4 h.

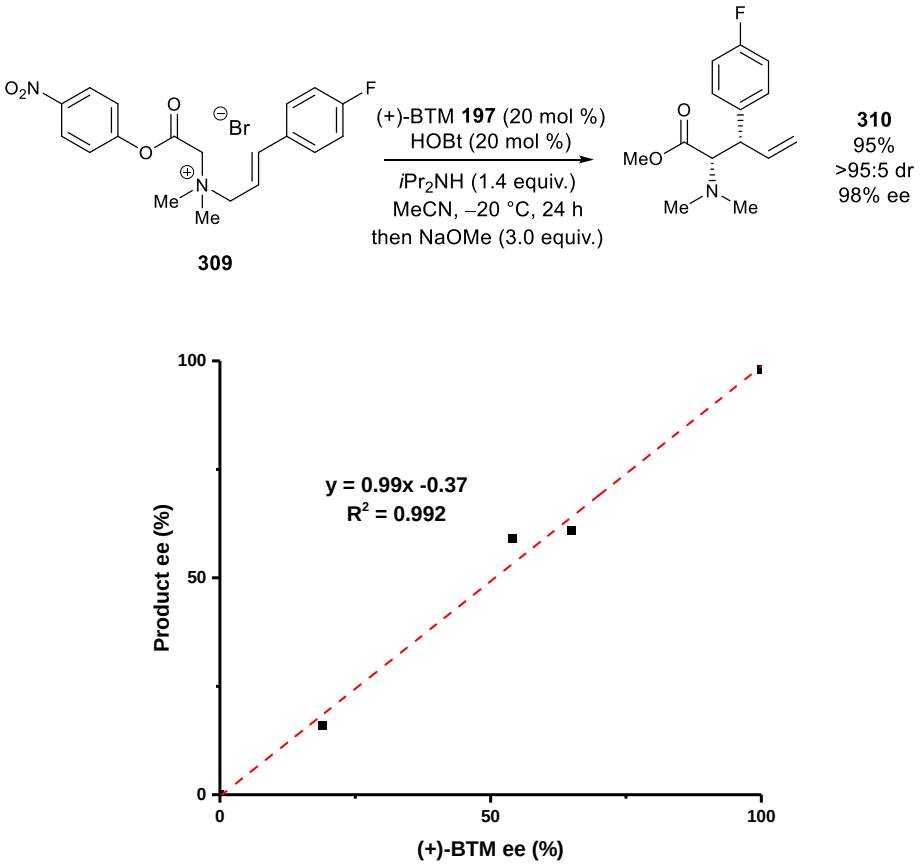
Firstly, the order of the catalyst (+)-BTM **197** was examined across a range of concentrations (1.7-13.6 mM) whilst maintaining the initial concentrations of all other components constant. The observed rate k_{obs}, determined by first-order log-plots for the decay of ammonium salt **309**, from each of the kinetic runs was plotted as a function of concentration. This process was repeated for the other components of the reaction, *i*Pr$_2$NH (23.8-95.2 mM) and HOBt **216** (0-34 mM), revealing a first-order rate dependency upon both (+)-BTM **197** and *i*Pr$_2$NH, and a zero-order rate dependency upon co-catalyst HOBt.



Scheme 79: A) First-order rate dependency on (+)-BTM **197**, **B)** First-order rate dependency on *i*Pr$_2$NH, **C)** Zero-order rate dependency on HOBt .

3.9 Non-Linear Effect of Catalyst Enantiopurity

To probe confirm the first-order rate dependency of (+)-BTM **197**, the effect of the enantiopurity of (+)-BTM **197** on enantiopurity of rearrangement product **310** was probed. Non-linear effects in asymmetric catalysis originate from interactions of chiral catalysts or ligands on or off the catalytic cycle to generate diastereomeric species which result in non-linear correlation between catalyst and product enantiopurity.[49] A good linear relationship was found between the two, further confirming the first-order rate dependency and monomeric nature of the active catalyst (+)-BTM **197** (*Scheme 81*).

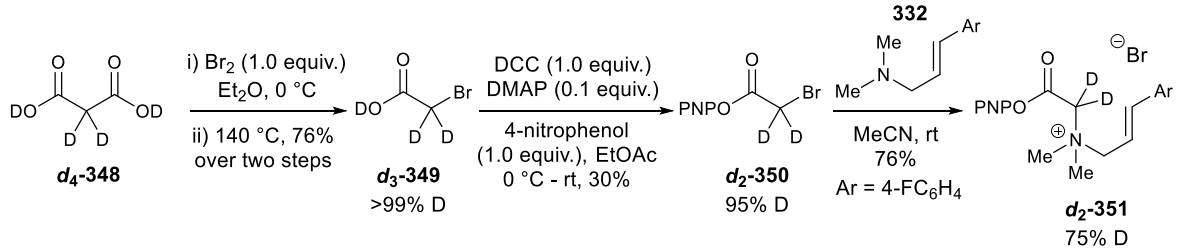


Scheme 81: Probing non-linear effects of catalyst enantiopurity.

Based upon order analysis it is thought that HOBt is not involved in any pre-equilibria with or in the turnover-rate limiting step of the process. Order analysis indicates that deprotonation of dication **318**, [2,3]-rearrangement of **319** or product release from **320** maybe turnover-rate limiting.

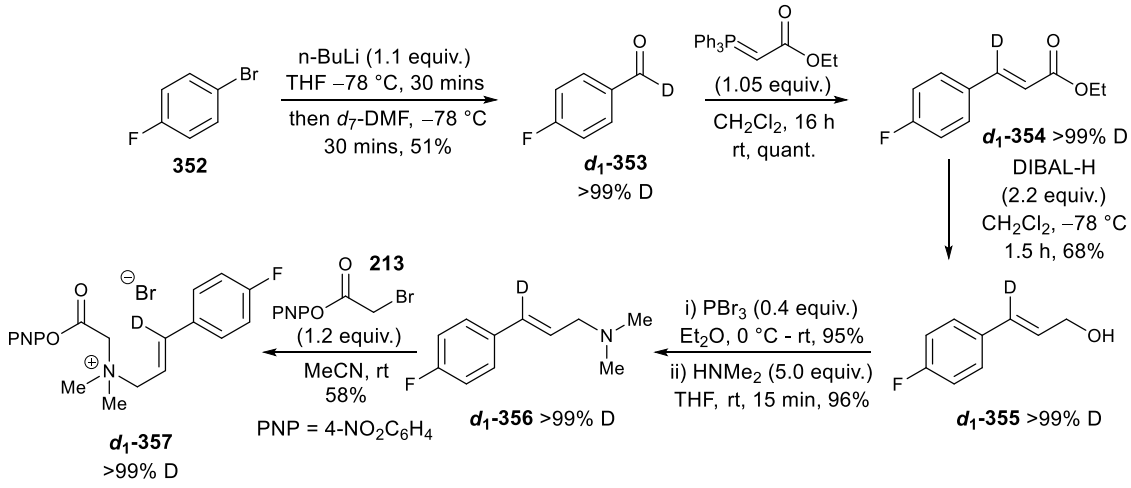
3.10 Deuterium kinetic isotope effects

To probe the turnover-limiting step of the process, deuterium kinetic isotope effects were employed. Firstly, the kinetic relevance of the deprotonation of dication **318** into the reactive ammonium ylide **319** was probed. α-Dideuterio ammonium salt ***d*$_2$-351** was synthesised from d_4-malonic acid, starting with bromination and decarboxylation to give d_3-bromoacetic acid ***d*$_3$-349**. Subsequent DCC mediated coupling with 4-nitrophenol gave d_2-4-nitrophenyl bromoacetate ***d*$_2$-350** (95% D), and addition of *N*,*N*-dimethyl 4-fluorocinnamyl amine **332** gave d_2-ammonium salt ***d*$_2$-351** (*Scheme 82*). Unfortunately, ammonium salt formation led to H/D exchange and ***d*$_2$-351** was obtained with 75% D incorporation as judged by ^{1}H NMR. A range of alternative solvents was trailed for the ammonium salt formation step, including d_3-MeCN and d_2-dichloromethane, however a higher deuterium incorporation could not be achieved. Notably, d_2-ammonium salt ***d*$_2$-351** undergoes facile H/D exchange in NMR solvent (d_3-MeCN/d_6-DMSO (9:1)), losing ~10% D over 4 h at rt. Consequently, ***d*$_2$-351** was deemed unsuitable for precise kinetic analysis.



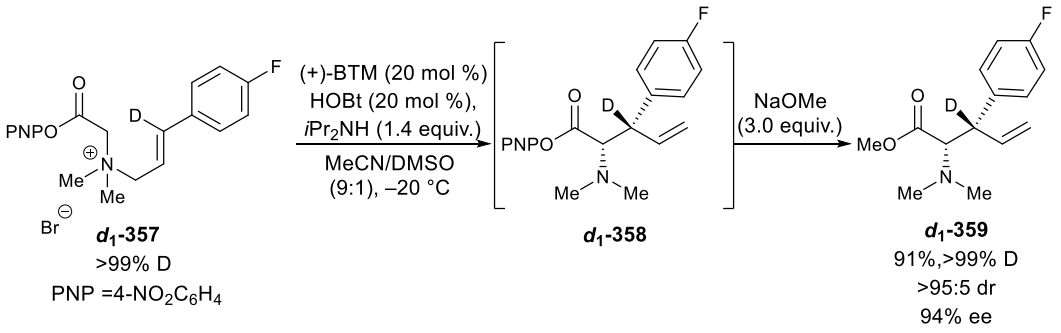
Scheme 82: Synthesis of d_2-ammonium salt ***d*$_2$-351**

As a result, efforts were switched to the measurement of a secondary kinetic isotope effect at the C(3) position to assess the kinetic significance of the [2,3]-rearrangement step. To achieve this, C(3)-D- ***d*$_1$-357** was synthesised in six steps from 4-fluoro-1-bromobenzene **352**, starting with lithium-halogen exchange and quenching with d_7-DMF to give *d*-4-fluorobenzaldehyde ***d*$_1$-353**. Wittig olefination between ***d*$_1$-353** and ethyl 2-(triphenyl-λ5-phosphanylidene)acetate gave α,β-unsaturated ester ***d*$_1$-355**, DIBAL-H reduction, followed by bromination and amination with *N*,*N*-dimethylamine gave C(3)-D amine ***d*$_1$-356**. Reaction of ***d*$_1$-356** with 4-nitrophenyl bromoacetate **213** gave C(3)-D ammonium salt ***d*$_1$-357** with excellent deuterium incorporation (>99% D).



Scheme 83: Synthesis of C(3)-D ammonium salt ***d*$_1$-357**.

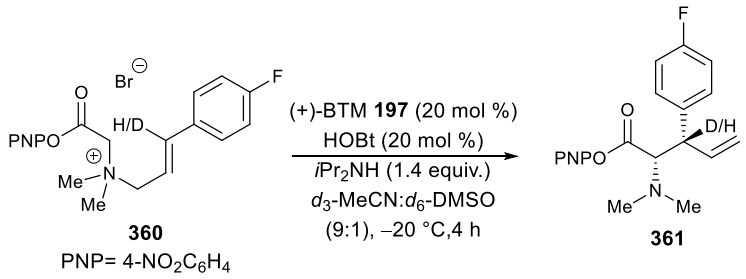
Firstly, the impact of C(3)-deuteration on the yield and stereoselectivity of the [2,3]-rearrangement was probed. Pleasingly, C(3)-D ammonium salt ***d*$_1$-357** underwent [2,3]-rearrangement with comparable yield and stereocontrol (91%, >95:5 dr, 94% ee, >99% D) with that of C(3)-H isotopologue **309**, importantly no H/D exchange was observed under the reaction conditions (*Scheme 84*).

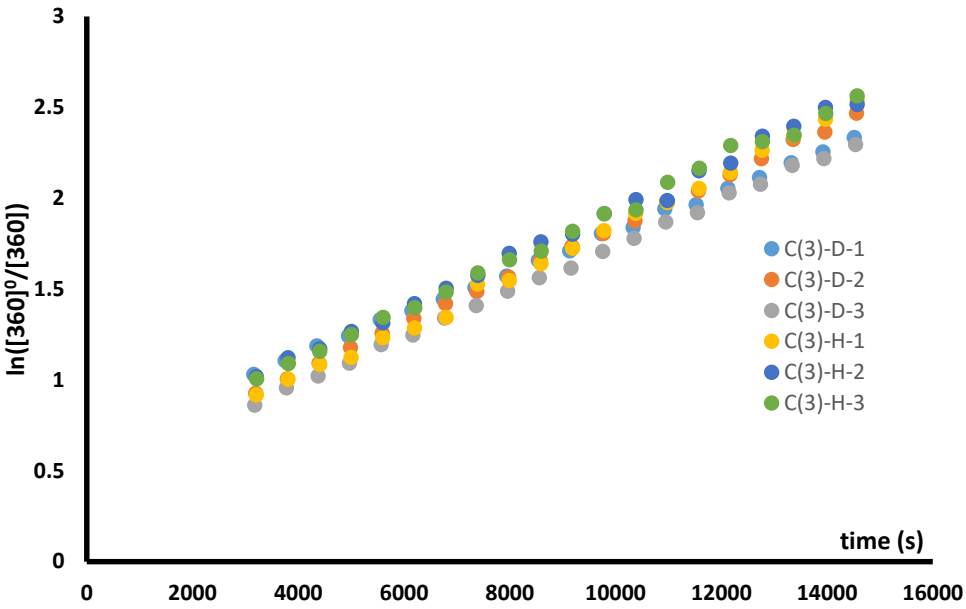


Scheme 84: [2,3]-Rearrangement of C(3)-D allylic ammonium salt ***d*$_1$-357**.†

Measurement of a secondary kinetic isotope effect (SKIE) was first attempted through independent rate measurement of C(3)-D ***d*$_1$-357** vs C(3)-H **309**. The rate of decay of either isotopologue (k_{obs}) was determined from first-order log-plots within the pseudo-steady state period of the reaction (>3000 s). This analysis was performed in triplicate and an average k_{obs} was calculated for both isotopologues. A $k_H/k_D = 1.11$ (SKIE) could be calculated, however the variation in k_{obs} for each kinetic run of the C(3)-D isotopologue ***d*$_1$-357** was larger than the calculated SKIE so therefore measurement by independent rate measurement was deemed to be inconclusive.†

† A genuine authentic sample of C(3)-D PNP ester was synthesised and characterised see *chapter 6*.





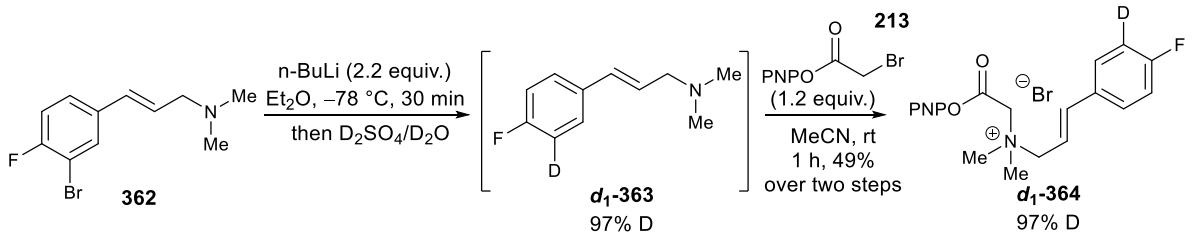
Run	C(3)H k_{obs} s^{-1}	C(3)D k_{obs} s^{-1}
1	1.42×10^{-4}	1.26×10^{-4}
2	1.37×10^{-4}	1.35×10^{-4}
3	1.37×10^{-4}	1.13×10^{-4}
Average	1.39×10^{-4}	1.25×10^{-4}
	k_H/k_D	1.11

Scheme 85: Attempted measurement of C(3)-SKIE by independent rate measurement. Initial concentrations: **360** (34 mM), (+)-BTM **197** (6.8 mM), *i*Pr$_2$NH (47 mM), HOBt **216** (6.8 mM), d_3-MeCN/d_6-DMSO (9:1), −20 °C, 4 h.

3.10.1 Competition SKIE

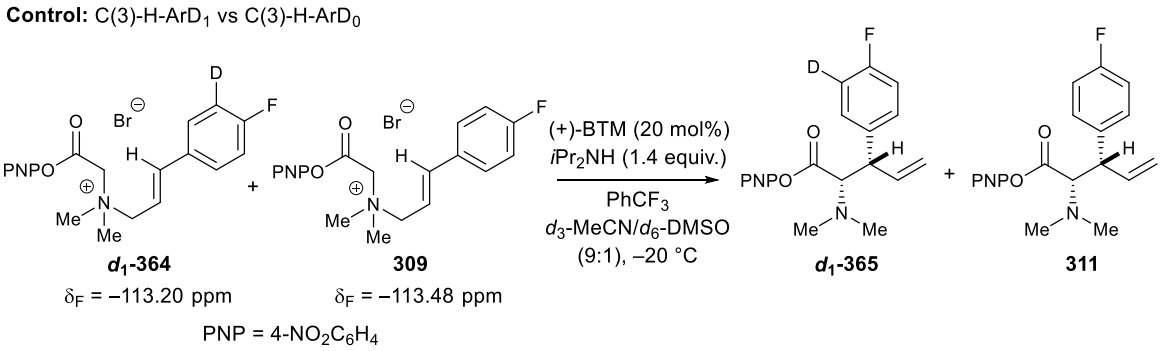
As measurement of a small SKIE at the C(3)-position via independent rate measurement was inconclusive, attention was switched to a competition SKIE strategy. In order to measure a competition KIE by *in situ* ^{19}F NMR the δ_F signals of the C(3)-D ***d*$_1$-357** and C(3)-H **309** isotopologues must be distinct. To achieve this distinction, a deutero-substituent was installed *ortho* to the fluorine on the aryl ring in the C(3)-H isotopologue **309**. Deuteration *ortho* to an aryl fluoride is known to have a dramatic effect upon the δ_F signal, whilst having minimal effect upon the electronic character of the aromatic

ring.[50] A similar double labelling strategy has previously been employed by Lloyd-Jones and co-workers to measure small $^{11}B/^{10}B$, $^{12}C/^{13}C$ and $^{14/15}N$ KIEs via competition in the hydrolysis of MIDA-boronates.[51] The ArC(3)-deutero substituent was installed via lithium-halogen exchange methodology, with the starting allylic amine **362** synthesised from the corresponding benzaldehyde in an analogous method to that described in *chapter 2*. Lithium-halogen exchange of **362** followed by quenching with D_2SO_4/D_2O provided ArD_1-C(3)-H amine ***d*$_1$-363**. Subsequent reaction with 4-nitrophenyl bromoacetate **213** yielded the desired ArD_1-C(3)-H ammonium salt ***d*$_1$-364** in 49% yield with high deuterium incorporation (97% D).



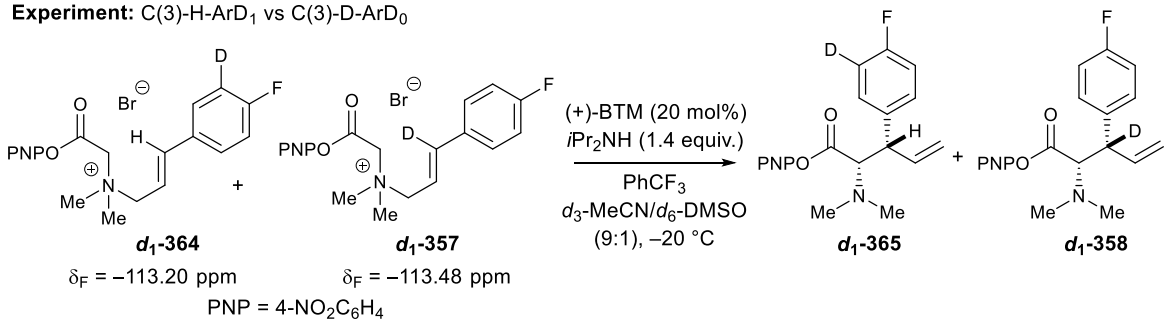
Scheme 86: Synthesis of ArD_1-C(3)-H ammonium salt ***d*$_1$-364**.

The installation of a deutero-substituent *ortho* to the fluorine resulted in a $\Delta\delta_F = 0.28$ ppm (ArD_1-ArD_0), meaning that ArD_1-C(3)-H ***d*$_1$-364** and ArD_0-C(3)-D ***d*$_1$-357** are distinct by ^{19}F NMR and therefore a competition experiment can be performed. First, the KIE resulting from the installation of the deutero-substituent was assessed as a control experiment.[52] A equimolar mixture of ArD_1-C(3)-H ***d*$_1$-364** (17 mM) and ArD_0-C(3)-H **309** (17 mM) were reacted with (+)-BTM **197** (6.8 mM) and *i*Pr_2NH (47.6 mM) and monitored by *in situ* ^{19}F NMR over 4 h (*Scheme 87*). The ratio of ArD_1-C(3)-H ***d*$_1$-364** and ArD_0-C(3)-H **309** was plotted as a function of fractional conversion and the data was fitted to a first-order exponential equation. From this, the KIE resulting from *ortho*-deuteration could be calculated as $k_{C(3)\text{-}H}(ArD_1)/k_{C(3)\text{-}H}(ArD_0) = 0.963$ (*Scheme 88*).

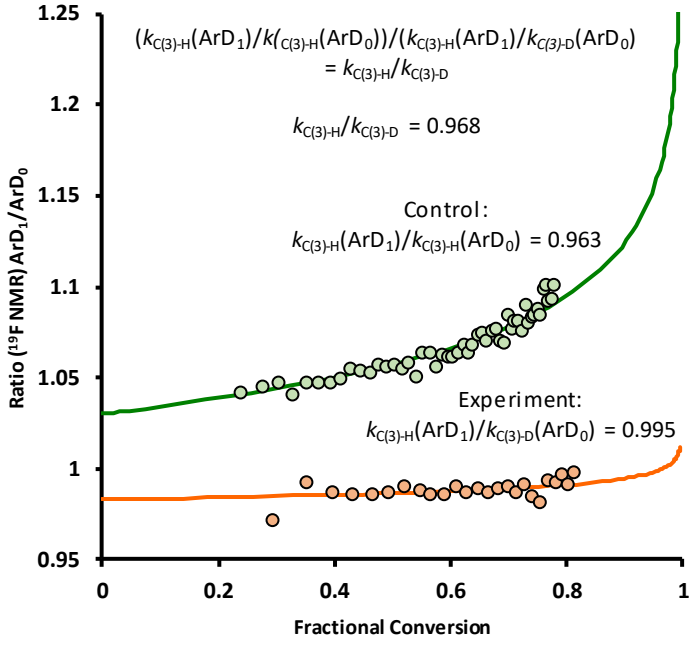


Scheme 87: Competition experiment to calculate the KIE of *ortho*-dueteration.

Having determined the KIE of *ortho*-deuteration, the competition C(3) KIE experiment could be performed. An equimolar mixture of ArD_1-C(3)-H ***d*$_1$-364** (17 mM) and ArD_0-C(3)-D ***d*$_1$-357** (17 mM) were reacted with (+)-BTM (6.8 mM) and *i*Pr_2NH (47.6 mM) and monitored by *in situ* ^{19}F NMR over 4 h (*Scheme 88*). The ratio of ArD_1-C(3)-H ***d*$_1$-364** and ArD_0-C(3)-D ***d*$_1$-357** was plotted as a function of fractional conversion and the data was fitted to a first-order exponential equations **(1)** and **(2)**, allowing the calculation of $k_{C(3)\text{-}H}(ArD_1)/k_{C(3)\text{-}D}(ArD_0)$ = 0.995. Taking into account the effect of the *ortho*-deuterium, the C(3) SKIE could be calculated. $k_{C(3)\text{-}H}/k_{C(3)\text{-}D}$: ($k_{C(3)\text{-}H}(ArD_1)$/ $k_{C(3)\text{-}H}$ (ArD_0)) / ($k_{C(3)\text{-}H}(ArD_1)$/ $k_{C(3)\text{-}D}$ (ArD_0)) = $k_{C(3)\text{-}H}/k_{C(3)\text{-}D}$ = 0.968 (*Scheme 88*). The magnitude of this inverse SKIE is consistent with the [2,3]-rearrangement proceeding though an early exogenic transition state.



(1) $[C(3)\text{-}D\text{-}D_0]_t = [C(3)\text{-}D\text{-}D_0]_0 e^{((kD/kH)*t)}$ **(2)** $[C(3)\text{-}H\text{-}D_1]_t = [C(3)\text{-}H\text{-}D_1]_0 e^{((kD/kH)*t)}$

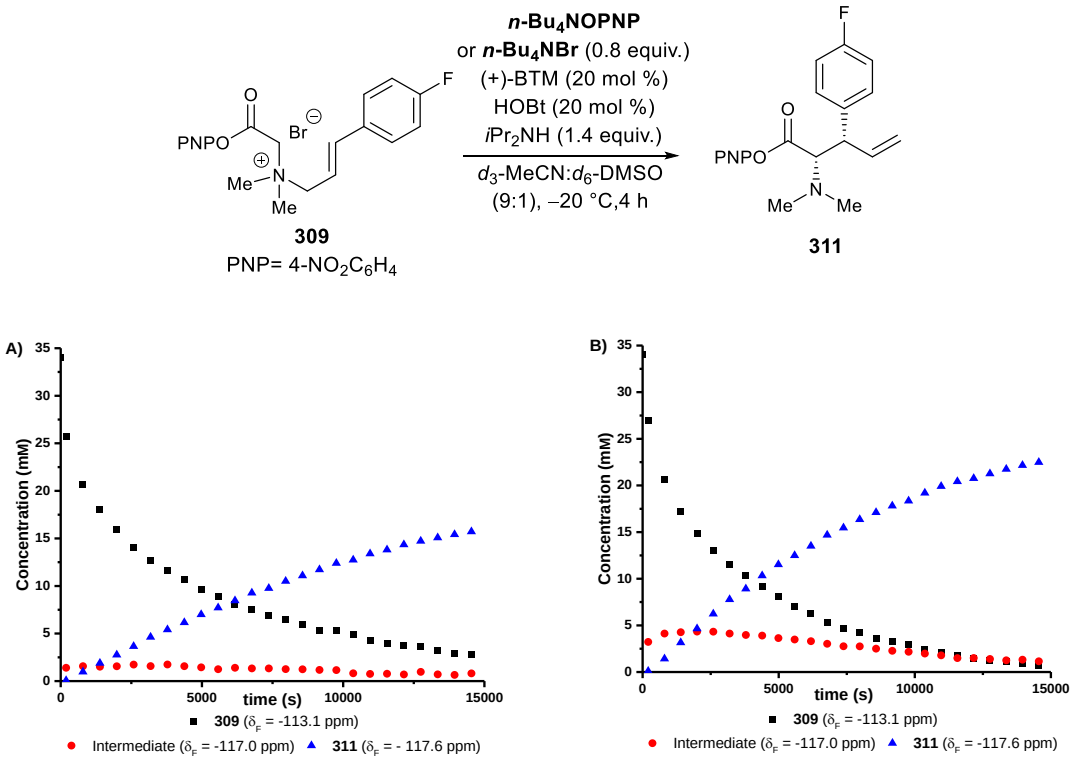


Scheme 88: C(3) competition SKIE, graph showing plots of control and experiment, Ratio of ArD_1/ArD_0 as a function of fractional conversion, fitted to first order exponential functions, using equations 1 & 2. Fitting performed by Prof. Guy C. Lloyd-Jones.

As the observed SKIE was measured by competition, for the SKIE to be "expressed" the substrates ***d*$_1$-364** and ***d*$_1$-357** must be in full equilibrium with the intermediate prior to the first irreversible step and that the irreversible step must involve reaction at the C(3)-position. This competition SKIE does not necessarily indicate that the [2,3]-rearrangement step is turnover-rate limiting.

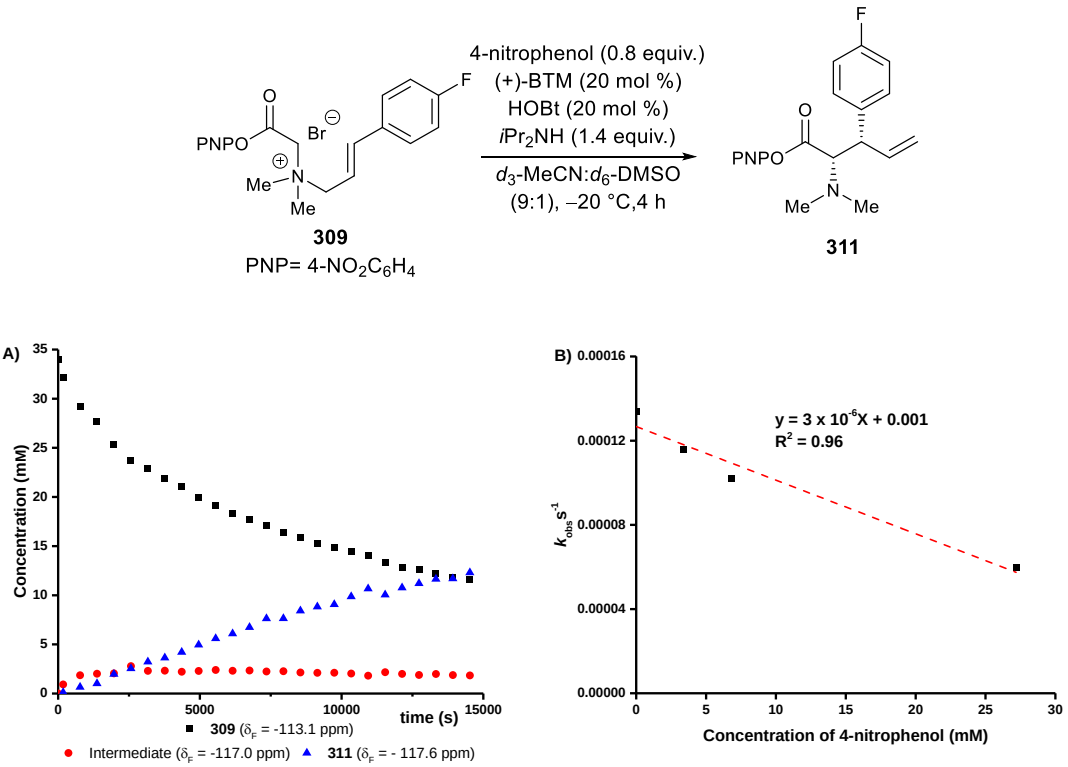
3.11 Effect of additives on reaction rate

The effect of additives upon both reaction rate and acyl ammonium turnover was next probed through kinetic analysis (*Scheme 89*). Addition of *n*-Bu_4N 4-nitrophenoxide (27.2 mM, 0.8 equiv.) to the rearrangement of **309**, resulted in a rapid increase in rate (k_{obs} = 2.42 × 10^{-4} s^{-1}) compared to standard (k_{obs} = 1.37 × 10^{-4} s^{-1}). This was coupled with a significant reduction in the concentration of acyl ammonium intermediate **342** (maximum concentration 2mM). A control experiment using *n*-Bu_4NBr (27.2 mM, 0.8 equiv.) as an additive resulted in a similar reaction rate enhancement (k_{obs} = 2.35 × 10^{-4} s^{-1}), however acyl ammonium **342** was readily observed in higher concentrations (maximum concentration 5 mM). Consistent with these studies, it is postulated that *n*-Bu_4N 4-nitrophenoxide promotes esterification of acyl ammonium **342** into product **311**. The increase in observed reaction rate (k_{obs}) can be accounted for due to the increase in ionic strength of the reaction medium in both cases.



Scheme 89: A) Kinetic profile with additional *n*Bu_4N 4-nitrophenoxide (27.2 mM, 0.8 equiv.) **B)** Kinetic profile with additional *n*Bu_4NBr (27.2 mM, 0.8 equiv.). Standard initial conditions: **309** (34 mM), (+)-BTM **197** (6.8 mM), HOBt (6.8 mM), *i*Pr_2NH (47.6 mM), d_3-MeCN/d_6-DMSO (9:1), −20 °C, 4 h.

Addition of varying concentrations (0-34 mM) of 4-nitrophenol showed a decrease in observed rate (k_{obs}) with a negative first-order rate-dependency. Significant concentrations of acyl ammonium intermediate **342** were observed when 4-nitrophenol is added, consistent with 4-nitrophenol itself being unable to effect product release (*Scheme 90*). In contrast, when high concentrations of *i*Pr$_2$NH (>47 mM) are employed, acyl ammonium intermediate **342** decays much more readily into rearranged product **311**. This suggests that either 4-nitrophenoxide or benzotriazololate are required to mediate product release from observable acyl ammonium intermediate **342**.



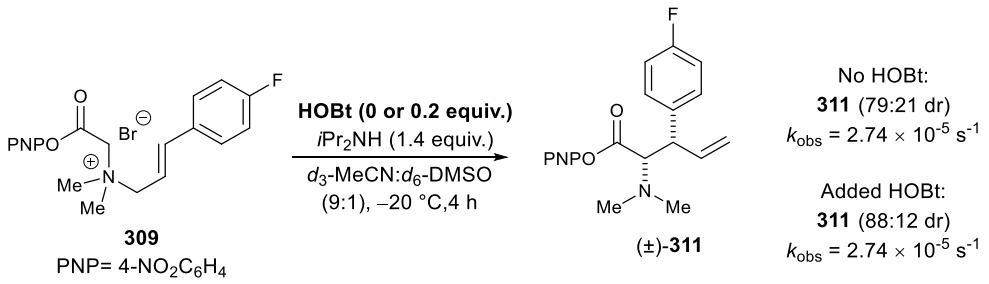
Scheme 90: Effect of additional 4-nitrophenol, **A)** Effect on reaction profile, **309** (34 mM), (+)-BTM **197** (6.8 mM), HOBt (6.8 mM), *i*Pr$_2$NH (47.6 mM), d_3-MeCN/d_6-DMSO (9:1), 4-nitrophenol (27.2 mM), −20 °C, 4 h. **B)** Negative first-order dependency on 4-nitrophenol.

The kinetic significance of deprotonation was further confirmed by the use of (+)-BTM·HCl as a pre-catalyst. In this case rearrangement of **309** proceeded smoothly (performed as an NMR experiment, >95:5 dr, ee not determined), but again with a significant decrease in observed rate (k_{obs} = 8.5 × 10^{-5} s^{-1}).

3.11.1 Influence of HOBt

HOBt is used in the optimal synthetic reaction conditions as it results in increased diastereo- and enantiocontrol, however how it affects the stereocontrol is unclear. Kinetic analysis has shown a zero-order rate dependency upon HOBt across a wide range of concentrations (0-34 mM), which implies that HOBt effects the mechanism after the turnover-limiting step. To probe if HOBt enhances the

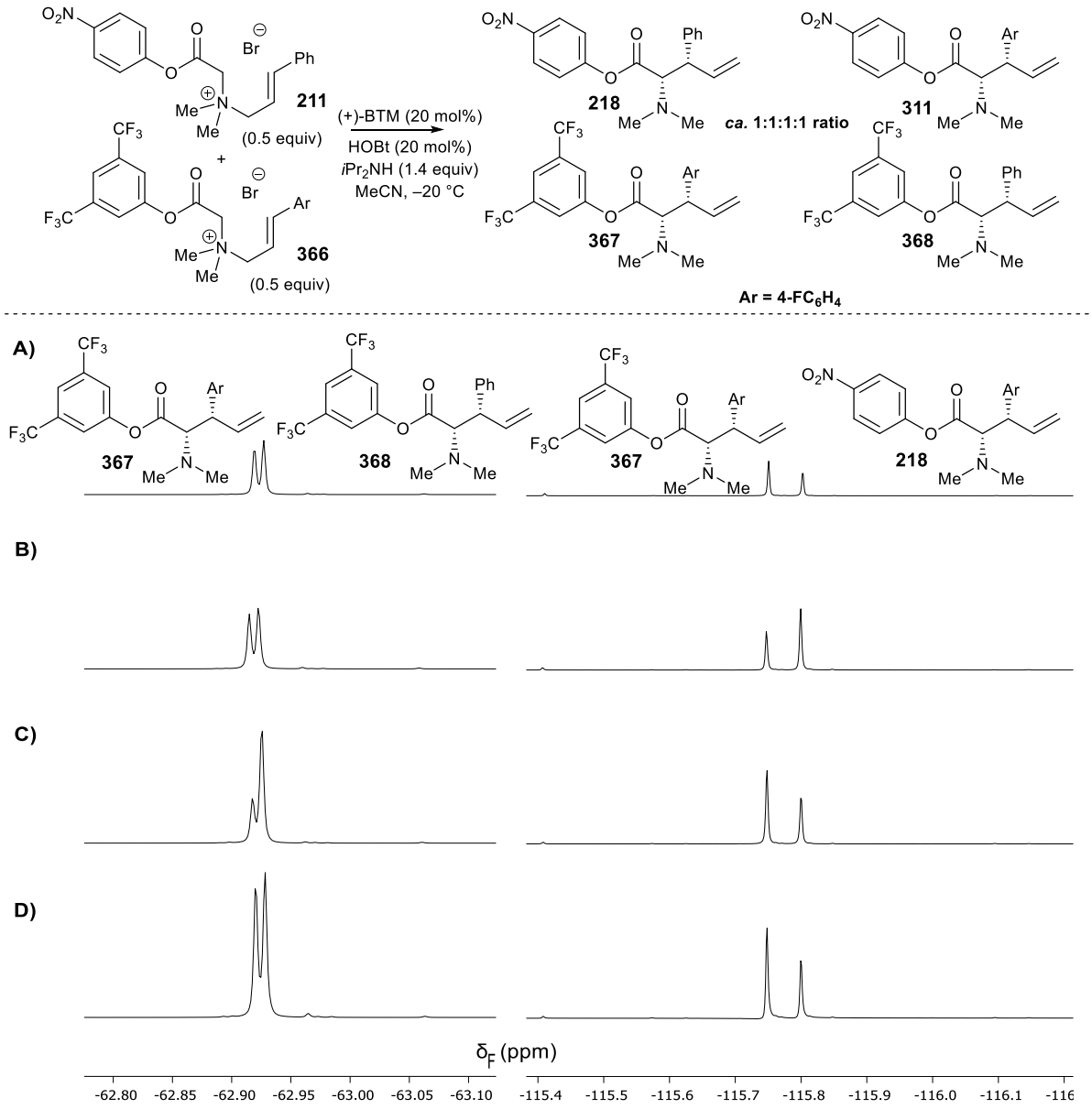
stereocontrol *via* suppression of any base mediated background reaction, the *i*Pr_2NH-mediated rearrangement of **309** was examined with and without HOBt. Treating ammonium salt **309** with *i*Pr_2NH (47 mM) resulted in slow formation of rearrangement product (±)-**311** with low diastereocontrol (79:21 dr, *syn*:*anti*) and an observed rate of $k_{obs} = 2.74 \times 10^{-5}$ s^{-1}. Addition of a catalytic amount of HOBt (0.2 equiv., 6.8 mM) resulted in a similar observed rate ($k_{obs} = 2.70 \times 10^{-5}$ s^{-1}), however a significant improvement in diastereocontrol was observed (88:12 dr, *syn*:*anti*) (*Scheme 91*). This suggests that HOBt does not enhance the stereocontrol of the reaction through suppression of *i*Pr_2NH-mediated background reaction. Although the diastereocontrol of the catalytic process may be enhanced by improvement of the diastereoselectivity of the base-mediated background reaction in the presence of HOBt, this does not account for the increased enantiocontrol. Attempts to analyse the enantiocontrol the [2,3]-rearrangement of **309** as a function of time unfortunately proved impractical, due to the need to derivatise **311** for HPLC analysis. Hence the role of HOBt in enhancing stereocontrol remains unclear.



Scheme 91: Effect of added HOBt (0.2 equiv, 6.8 mM) on rate and stereocontrol of base mediated background rate.

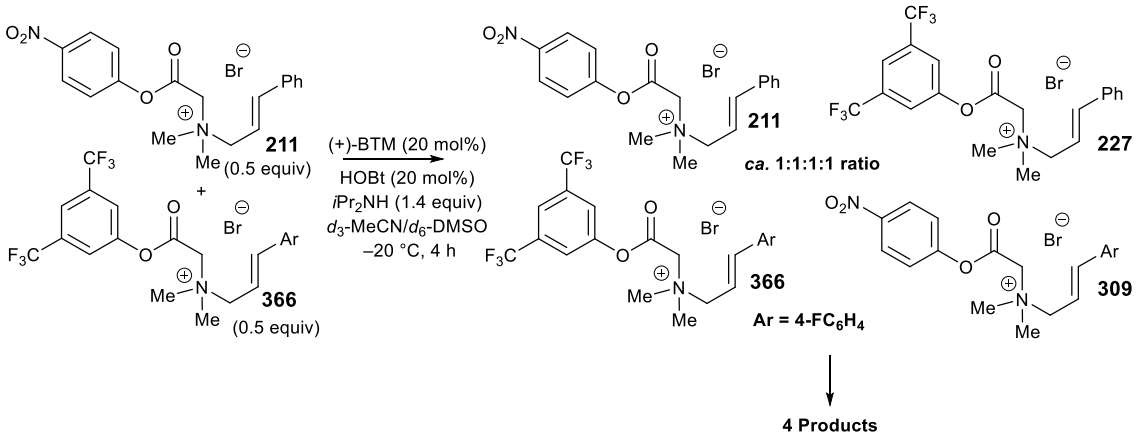
3.12 Crossover and Reversibility Studies

Kinetic analysis has given mechanistic insight into the overall process, however the finer details regarding each of the key steps of the catalytic cycle are unclear. Firstly, the reversibility of the initial acylation step was probed through a crossover-experiment using two ammonium salts **211** and **366** bearing distinct activated esters and C(3)-aryl units. An equimolar amount of **211** and **366** was reacted under previously optimised conditions ((+)-BTM **197** (20 mol %), HOBt (20 mol %), *i*Pr_2NH (1.4 equiv.), MeCN, −20 °C, 16 h), and the crude reaction was analysed after aqueous work-up. The $^{19}F\{^1H\}$ NMR in the aryl-F region revealed the presence of two distinct rearrangement products. The identity of the rearrangement products was confirmed through spiking the same NMR sample with authentic samples of the possible fluorinated products **311**, **367** and **368** and re-analysing the NMR sample by $^{19}F\{^1H\}$ NMR (*Scheme 92*). The presence of **311**, **367** and **368** confirms that the activated esters in ammonium salt **366** and **211** readily crossover under the reaction conditions.



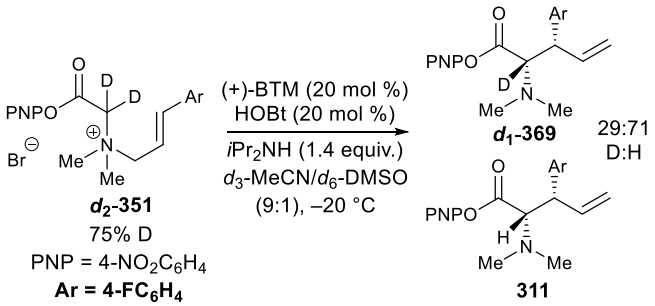
Scheme 92: Crossover experiment of ammonium salts **211** and **366**. $^{19}F\{^{1}H\}$ NMR (471 MHz, $CDCl_3$) analysis of crude material and spiking experiments, showing Ar-CF_3 region (−62 - −63 ppm) and Ar-F region (−115 - −116 ppm) **A)** Crude reaction mixture **B)** A spiked with **218**. **C**) B spiked with **367**. **D)** C spiked with **368**.

Whilst it is known that the activated esters in **211** and **366** readily crossover under the reaction conditions, it is not known whether the generated phenoxides crossover during the initial acylation step or later on in the catalytic cycle. To probe when the phenoxides crossover, the reaction between **211** and **366** was monitored by *in situ* $^{19}F\{^{1}H\}$ NMR. This revealed the rapid formation of four distinct ammonium salts, which subsequently rearrange to form the four crossover products. This is consistent with the initial acylation step with (+)-BTM **197** being highly reversible (*Scheme 93*).



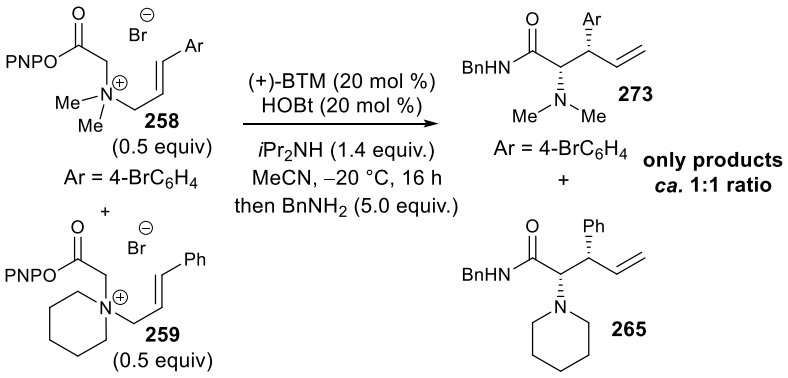
Scheme 93: Crossover of **211** and **366** monitored by *in situ* $^{19}F\{^{1}H\}$ NMR.

The deprotonation step of the catalytic cycle was probed using previously prepared α-dideuterio ammonium salt ***d*₂-351** (75% D). *In situ* monitoring of the rearrangement of ***d*₂-351** by $^{19}F\{^{1}H\}$ NMR revealed incomplete deuterium transfer from α-dideuterio ammonium salt ***d*₂-351** to rearrangement product ***d*₁-369**, with the α-deutero and α-proto-isotopologues distinguishable by $^{19}F\{^{1}H\}$ NMR. Exposure of isolated PNP ester **218** to the reaction conditions resulted in no change in dr and so hence no epimerisation. This indicates the highly reversible nature of the deprotonation step of the process, and also the high acidity of the α-protons on ammonium salt **309**.



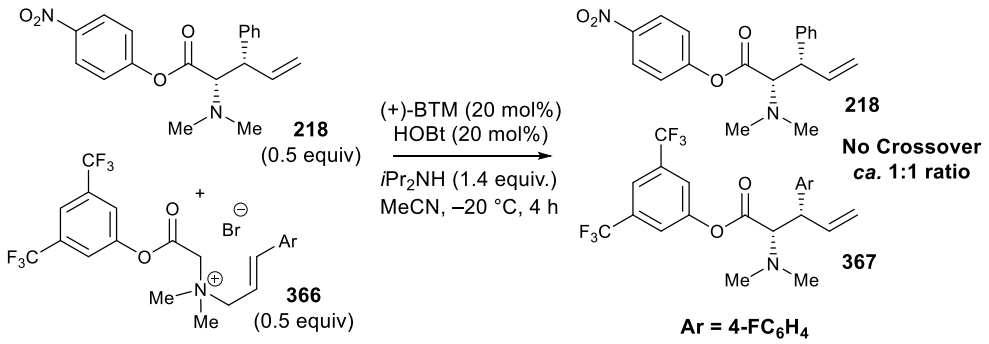
Scheme 94: Incomplete deuterium transfer from α-dideutero ammonium salt ***d*₂-351**.

To probe if the [2,3]-rearrangement step of the process is an intramolecular [2,3]-rearrangement or an intermolecular allylic transfer process, two ammonium salts **258** and **259** bearing distinct *N*-substituents and C(3)-aryl units were reacted together under optimal reaction conditions, followed by addition of benzylamine. Analysis of the crude reaction mixture by ^{1}H NMR demonstrated only two rearrangement products **273** and **265**, consistent with the [2,3]-rearrangement being intramolecular with no competitive intermolecular allylic transfer. Subsequent spiking of the crude reaction mixture and re-analysis of the NMR sample by ^{1}H NMR confirmed the identity of the observed rearrangement products **273** and **265**.



Scheme 95: Crossover experiment between **258** and **259** demonstrating the intramolecular nature of [2,3]-rearrangement. Crossover and spiking experiments performed by Dr. David S. B. Daniels.

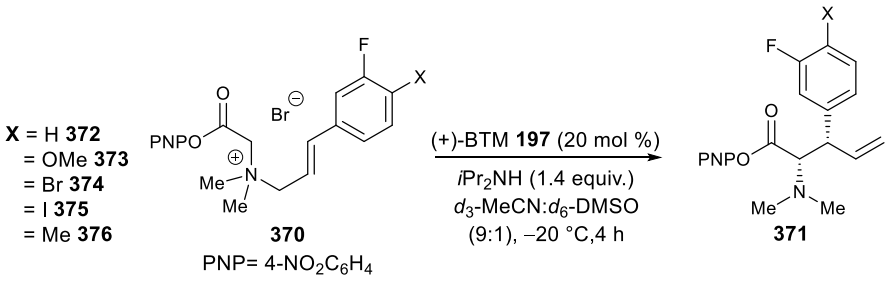
To examine the reversibility of product release from acyl ammonium **342**, a crossover of rearrangement product **218** and ammonium salt **366** bearing distinct C(3)-aryl units and activated esters was performed. The process by monitored by *in situ* $^{19}F\{^{1}H\}$ NMR and only one fluorinated rearrangement product **367** was observed. This is consistent with product release from acyl ammonium **342** being irreversible (*Scheme 96*).



Scheme 96: Crossover of **211** and **366**

3.13 Hammett Plot

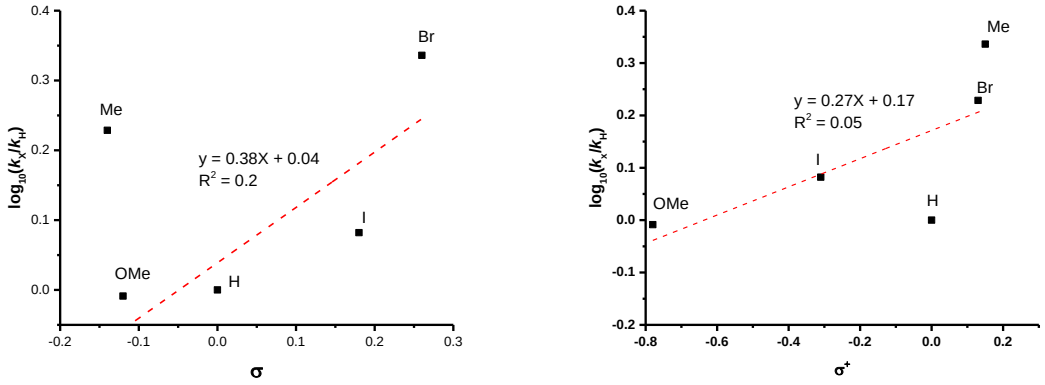
Next, to gain experimental insight into the electronic influence of substituents on the C(3)-position in transition state of the turnover rate-limiting step, a Hammett analysis was performed. To kinetically analyse the reactions by *in situ* $^{19}F\{^{1}H\}$ NMR, a fluoro-substituent was retained in each of the substrates. Variation of the *para*-substituent typically has the largest electronic effect,[53] hence the to allow facile monitoring of the process a fluorine substituent was installed in the *meta*-position of the aryl ring (*Scheme 97*). This allowed facile variation of the *para*-substituent, which has the largest electronic substituent effect on the C(3) position of ammonium salt **370**. The substrates examined were synthesised using previously developed route from the requisite *meta*-fluoro-substituted benzaldehyde and authentic racemic samples of the rearranged products were prepared.



Scheme 97: Ammonium salts and rearrangement for Hammett analysis.

Hammett analysis was first performed using independent rate measurements, with the observed rate, (k_{obs}) for each substrate determined by examination of the first-order log-plot of the decay of the substrate. The plots of $\log_{10}(k_x/k_H)$ against *standard* σ and σ^+ values showed poor correlation (*Scheme 98*).[53]

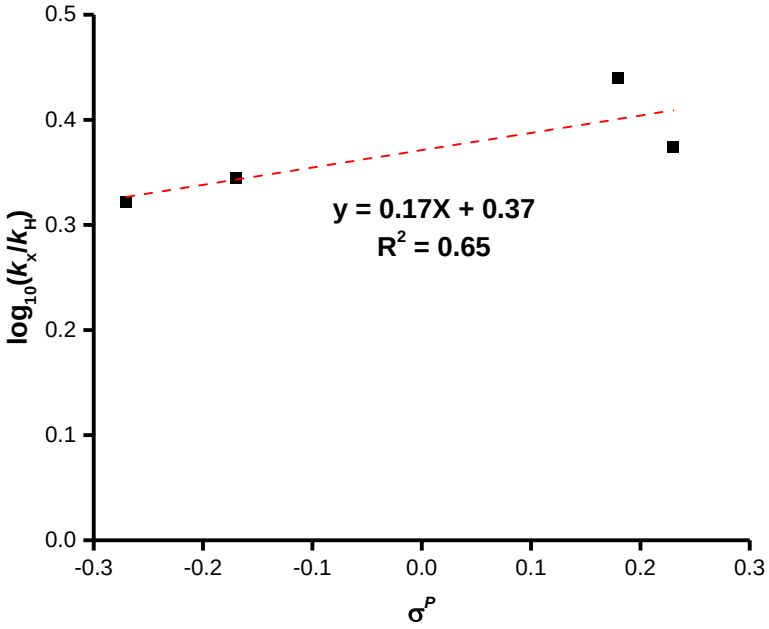
X =	$k_{obs} \times 10^{-4}$ s^{-1}	$\log_{10}(k_x/k_H)$	σ	σ^+
H	1.01	0	0	0
OMe	0.99	−0.087	−0.12	−0.78
Br	2.19	0.336	0.26	0.15
I	1.71	0.229	−0.14	−0.31
Me	1.22	0.082	0.18	0.13



Scheme 98: Hammett plot *via* independent rate measurement.

Due to the ambiguous outcome of the Hammett analysis through independent rate measurement, a competition strategy was employed. As ammonium salts **372-376** had significantly different chemical shifts (δ_F = −96.0 - −136.5 ppm), a five-way competition could be carried out where all five reactions were monitored concurrently in a single NMR tube, minimising the error between each experiment.

X =	$k_{obs} \times 10^{-4}$ s^{-1}	$\log_{10}(k_x/k_H)$	σ
H	0.52	0	0
OMe	1.09	−0.087	−0.27
Br	1.23	0.336	0.23
I	1.43	0.229	0.18
Me	1.15	0.082	−0.17



Graph 1: Hammett Plot, *via* five-way competition experiment. Data analysis performed without X = H.

The plot of $\log_{10}(k_x/k_H)$ against *standard* σ values from the competition experiment displays good correlation (*Graph 1*). The observed ρ value (gradient of the fitted line) 0.17, is very small, indicating there is a minimal substituent effect at the C(3)-position of the ammonium salt, in the absence of HOBt. This small observed ρ value indicates that in the absence of HOBt there is no charge redistribution around the C(3)-aryl position in the turnover-rate limiting events.

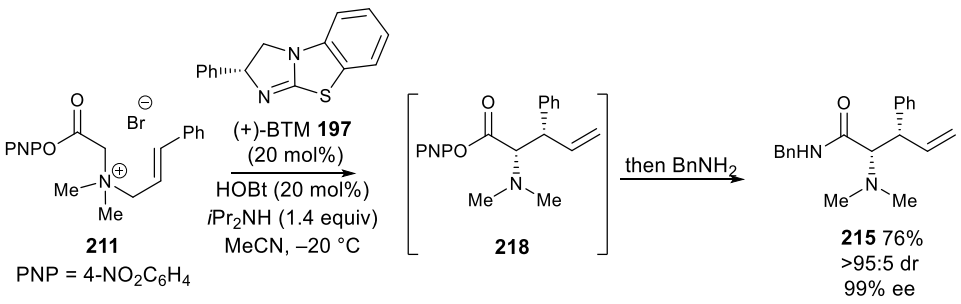
3.14 Computational Studies

3.14.1 Reaction Coordinate Modelling

In collaboration with Daniel M. Walden and Prof. Paul Ha-Yeon Cheong at Oregon State University all intermediates, transitions structures (TSs), and possible salt complexes involved in the mechanism were computed. Exhaustive conformational searches located all pertinent conformations. Geometries and thermodynamic corrections were computed at the M06-2X[54]/6-31G(d) level of theory.[55] Further energy refinement was completed using M06-2X/6-311+G(2df,p).[56] Implicit solvation corrections were applied using the polarized continuum model (PCM)[57] with UFF radii for acetonitrile in both the geometry optimizations and the single-point energy refinements. The hybrid meta-GGA functional M06-2X is more robust than B3LYP at accounting for dispersion interactions, i.e. non-bonding interactions routinely found in organocatalytic systems[58]

Kinetic isotope effects were calculated using the theory of Bigeleisen and Mayer[59] along with the rigid-rotor harmonic oscillator approach (ΔHΔS).[60] Quantum-mechanical tunnelling effects were also computed for both methods using the one-dimensional parabolic approximation.[61] Vibrational frequencies and thermal corrections to the Gibbs free energy were completed using M06-2X/6-31G(d) at –20 °C and 1 atm, matching the experimental conditions. Our collaborators have developed in-house software for automating and expediting the calculation of the KIE, rendering this analysis routine (See SI for more details). The Bigeleisen-Mayer equation gave theoretical KIE values in slightly better agreement with experimental data, and are therefore reported herein as the computed KIE.

To examine the mechanism computationally and probe the origins of stereochemical control, the rearrangement of *N*,*N*-dimethyl cinnamyl ammonium salt **211** was chosen as standard (S*cheme 99*). Computational reaction coordinate modelling was performed in the absence of the HOBt additive to simplify calculations.



Scheme 99: Model system chosen for computational analysis.

The reaction coordinate begins with direct acylation of (+)-BTM **197** with the substrate **211** to form to tetrahedral intermediate **379** (**TS-378**, $\Delta G^{\ddagger}$ = 14.4 kcal/mol). Release of 4-nitrophenoxide forms dication **318** (**TS-380**, $\Delta G^{\ddagger}$ = 15.5 kcal/mol). The significant energy barrier (ΔG = 2.4 kcal/mol) between

substrate **211** and dication **318** is consistent with experimentally observed reversible nature of the acylation step, and with the greater population of the substrate **211** and free (+)-BTM **197**. Dication **318** is reversibly deprotonated at the α-position by 4-nitrophenoxide ($\Delta G^{\ddagger}$ = 10.5 kcal/mol, kinetically favoured over deprotonation by *i*Pr_2NH), released upon acylation, to give ammonium ylide **319** (ΔG = 0.7 kcal/mol). NBO analysis of ylide intermediate **319** shows it to have significant enolate character. Formation of ammonium ylide **319** *via* ammonium ketene **290** was ruled out computationally due to it being thermodynamically unstable (ΔG = 21.1 kcal/mol). Ammonium ylide **319** subsequently undergoes stereodetermining [2,3]-rearrangement (**TS-377-*(2S,3S)*-Major**, $\Delta G^{\ddagger}$ = 16.4 kcal/mol) to give acyl ammonium **320**. The computed KIE for [2,3]-rearrangement, k_H/k_D = 0.966, matches excellently with experiment, k_H/k_D = 0.968, further corroborating the transition state of the stereodetermining [2,3]-rearrangement. After which turnover-rate limiting ($\Delta G^{\ddagger}$ = 16.9 kcal/mol) product release occurs directing mediated by 4-nitrophenoxide *via* tetrahedral intermediate **383**, which can release (+)-BTM **197** to give PNP ester **218** (*Scheme 102*).

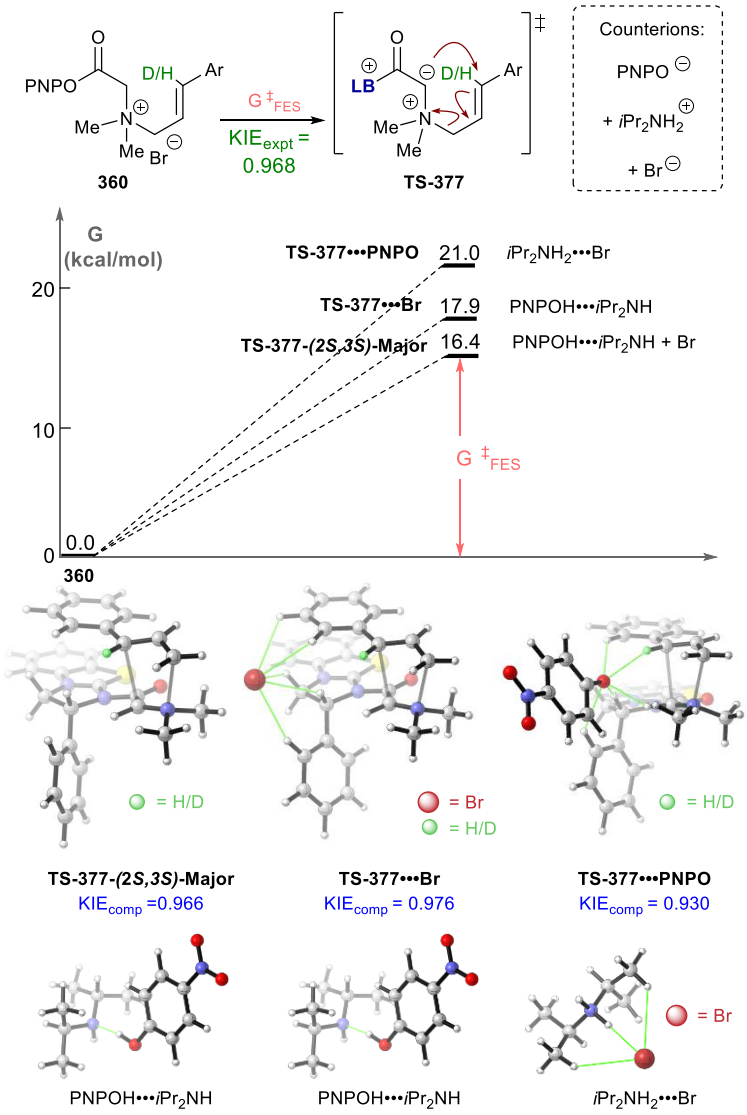
3.14.2 Effect of Counterions on the Theoretical Kinetic Isotope Effect and Energy Barriers

The inclusion of counterions poses a significant challenge to accuracy of the DFT calculations, and exponentially increases the complexity of the conformational search and number of relevant structures to consider.[62] As all proposed reaction intermediate bear a positive charge, the stabilising nature of the counterion is thought to play a role on the energy of relevant intermediates.

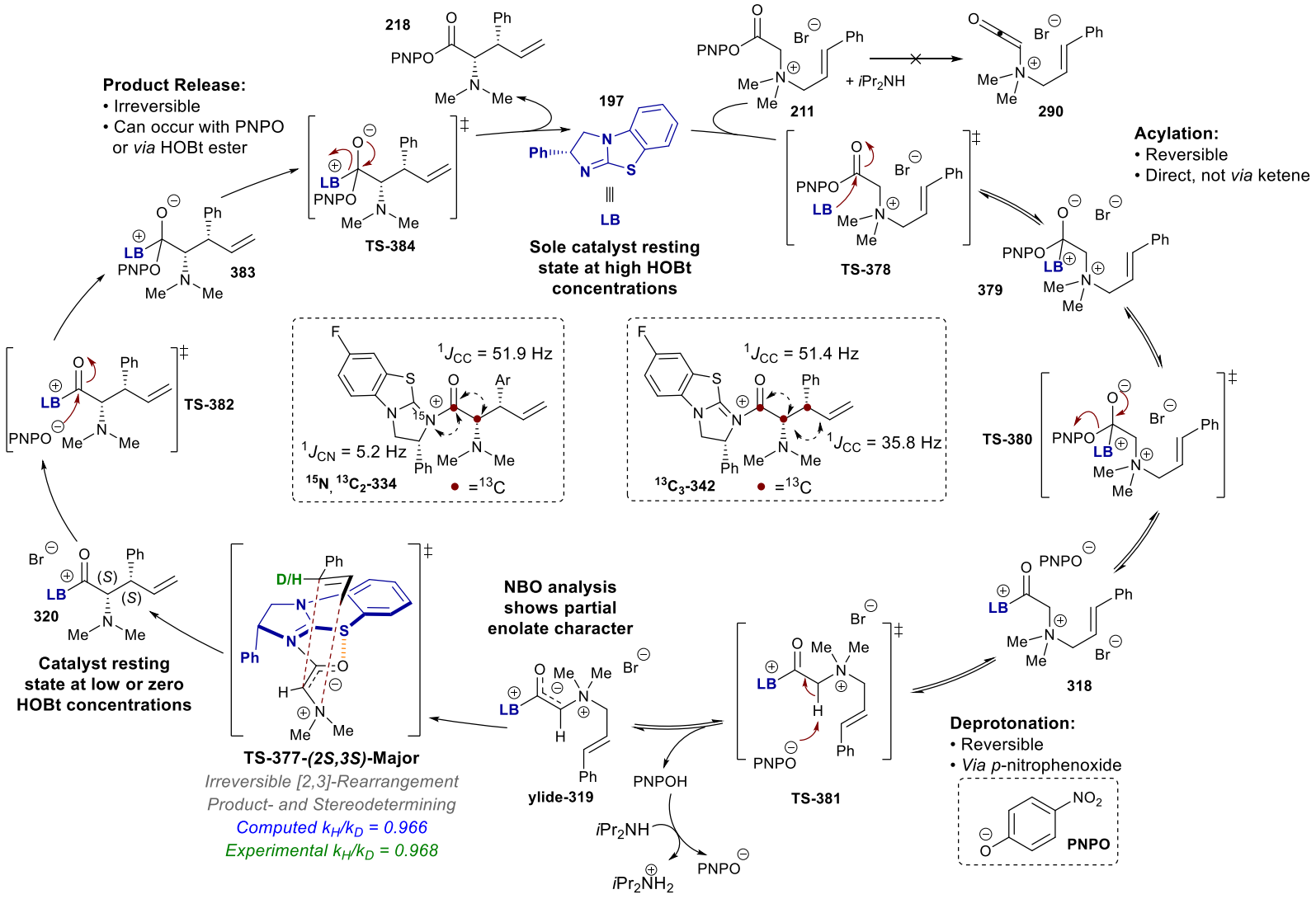
The kinetic isotope effect is computed using vibrational frequencies of the catalyst resting state **211** and the highest energy transition state of the catalytic cycle **TS-377**. These two structures compose the free-energy span (FES) of the catalytic cycle, their difference giviong the barrier of the reaction ($\Delta G^{\ddagger}_{FES}$).[63] Given the charged nature of the species present in the reaction, for identification of the structures that compose the free energy span (($\Delta G^{\ddagger}_{FES}$) all possible counterion coordination combinations were considered. Since the computed KIE depends upon the vibrational frequencies of the most stable reaction intermediate and the TS of the turnover-limiting step, it can be utilised independently of any computed thermodynamics and barriers and the error associated therein.[64] In a reaction with highly charged intermediate, leveraging the calculated KIE allows a route to determine the structures which make up the FES and which counterion are associated with them.[65]

In order to identify the counterion and coordination state of **TS-377-*(2S,3S)*-Major** calculated energy barriers and KIEs were compared for all possible counterion combinations, in the absence of HOBt. After deprotonation of dication **318** to form ylide **319** three possible counterions exist $PNPO^-$, *i*$Pr_2NH_2^+$ and Br^-; the equilibrium between these couterions effects drastically affects the barrier going from substrate **211** to **TS-377-*(2S,3S)*-Major**. With no counterion coordination to **TS-377-*(2S,3S)*-Major**, the computed KIE = 0.966, a 0.3% error compared to experiment. Within this coordination motif eight combinations of resulting counterions were identified; the lowest in energy is when 4-nitrophenol

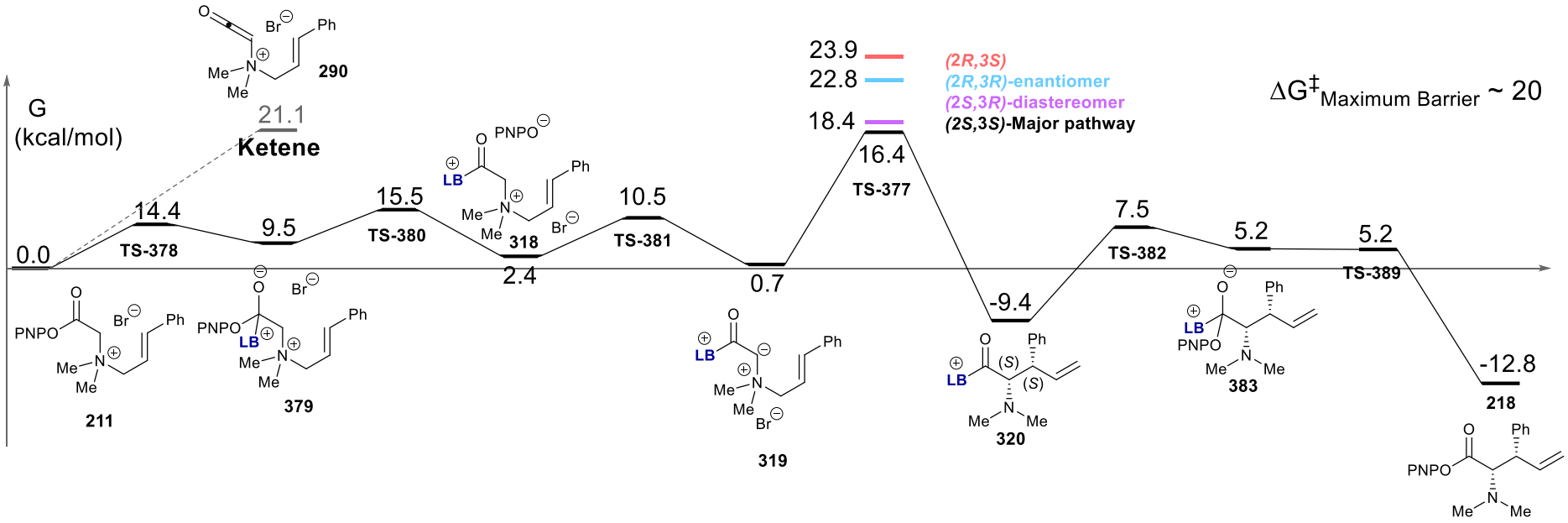
hydrogen bonds to *i*Pr$_2$NH (PNPOH●●●*i*Pr$_2$NH), leaving Br$^-$ free to act as a non-coordinating anion, giving an overall $\Delta G^{\ddagger}_{FES}$ = 16.4 kcal/mol. Coordination of Br$^-$ and PNPO$^-$ to **TS-377-*(2S,3S)*-Major** resulted in $\Delta G^{\ddagger}_{FES}$ = 17.9 kcal/mol and $\Delta G^{\ddagger}_{FES}$ = 21.0 kcal/mol respectively and result in calculated KIEs of 0.976 and 0.930, which are in poor agreement with experiment (*Scheme 100*).



Scheme 100: Effect of counterion coordination on computed KIEs and energy barriers.



Scheme 101: Proposed mechanistic cycle.



Scheme 102: Computed reaction coordinate.

3.14.3 Turnover-Rate Limiting Step

Collaborative reaction coordinate modelling (*Scheme 102*) suggests that in the absence of HOBt once the system has reached pseudo-steady-state the resting-state should be acyl ammonium **320** which is readily observed by ^{19}F and ^{13}C NMR spectroscopy, the formation of which has been shown to be irreversible. The energy barrier to product release from acyl ammonium **320** is thought to be turnover-rate limiting (ΔG = 16.9 kcal/mol), in the absence of HOBt. Addition of HOBt to the reaction been shown to change the resting-state of the system, previously two-catalyst derived species were observed, and shown not to be in equilibrium, by ^{13}C isotopic labelling. When significant concentrations of HOBt are added only one catalyst derived species is observed, thus the distribution of rate governance must have changed. Acyl ammonium **320** is no longer a catalyst resting state and its accelerated breakdown is not significantly turnover-rate limiting. In this case the turnover-rate limiting step is now prior to acyl ammonium **320**, and likely involves a species generated in equilibrium with the catalyst and substrate. This is further corroborated by zero-order rate dependence in HOBt concentration, suggesting that HOBt is not involved in any pre-equilibrium or in the turnover-rate limiting step.

3.13.4 Proposed Mechanism

The data presented above allows for a more detailed catalytic cycle to be proposed (*Scheme 101*). Initial reversible acylation of (+)-BTM **197** forms dication **318** directly and not *via* ketene **290**, as shown by computation. Subsequent deprotonation of **318** into ylide **319** is reversible and is likely to occur using the 4-nitrophenoxide liberated in the acylation step. Stereodetermining [2,3]-rearrangement of **319** proceeds in an intramolecular fashion and irreversibly to give acyl ammonium **320**. Competition kinetic isotope analysis showed there is an inverse SKIE at the C(3) position and is thought to be stereo- and product determining step of the process. Acyl ammonium **320** is an observed genuine intermediate which is on the catalytic pathway, and is the catalyst resting-state when a low concentration of HOBt is employed. At high concentrations of HOBt the resting state of the catalyst change to free (+)-BTM **197**. Product release from **320** can proceed either directly through 4-nitrophenoxide to form **218** and release (+)-BTM **197**, product release is postulated as the turnover-rate limiting step step in the absence of HOBt by computational analysis. Alternatively, **320** can be esterified by HOBt, which can be slowly transesterified by 4-nitrophenoxide to give **218**.

3.14.5 Stereochemical Studies

There are four major factors that impact upon the stereochemical control of the reaction, *E* vs. *Z* configuration of the ylide and its enolate character, n_0 to $\sigma^*_{C\text{-}s}$ catalyst-substrate interaction, *endo* versus *exo* allyl [2,3]-rearrangement, and the facial selectivity of [2,3]-rearrangement. The four lowest energy calculated transition states of the eight possible are detailed in *figure 11*. In these four transition states the rearrangement occurs *anti* to the stereodirecting phenyl substituent upon the acyl ammonium;

rearrangement *syn* to the phenyl substituent was considered too high in energy to be considered significant in accounting for stereocontrol. All stereodetermining transition states proceed with the highly preferred *Z* configuration of the ylide, with phenyl on the cinnamyl group participating in a variety of aromatic interactions as a function of its resulting placement in a given TS. Of the two transition states that lead to the formation of the *anti*-diastereoisomer, **TS-392-(2*R*,3*S*)** ($\Delta G^{\dagger}$ = 23.9 kcal/mol) is significantly higher in energy than **TS-390-(2*S*,3*R*)**. In **TS-377-(2*S*,3*S*)-Major** ($\Delta G^{\dagger}$ = 16.4 kcal/mol) the rearrangement occurs in an *endo* fashion with the carbonyl oxygen in a *syn* orientation to the sulfur atom of the acyl ammonium (S•••O distance = 2.79 Å). In **TS-390-(2*S*,3*R*)** ($\Delta G^{\dagger}$ = 18.4 kcal/mol), the same sulfur-oxygen orientation is observed (S•••O distance = 2.77 Å), however rearrangement occurs in an *exo* fashion, whereas **TS-391-(2*R*,3*R*)** ($\Delta G^{\dagger}$ = 22.8 kcal/mol) rearrangement occurs in an *endo* fashion with sulfur-oxygen in an *anti*-orientation. The computed diastereoselectivity ($\Delta\Delta G^{\dagger}$ = 2.0 kcal/mol) of 95:5 dr (*syn*:*anti*) and enantioselectivity (>99% ee) are in excellent agreement with experimental results.

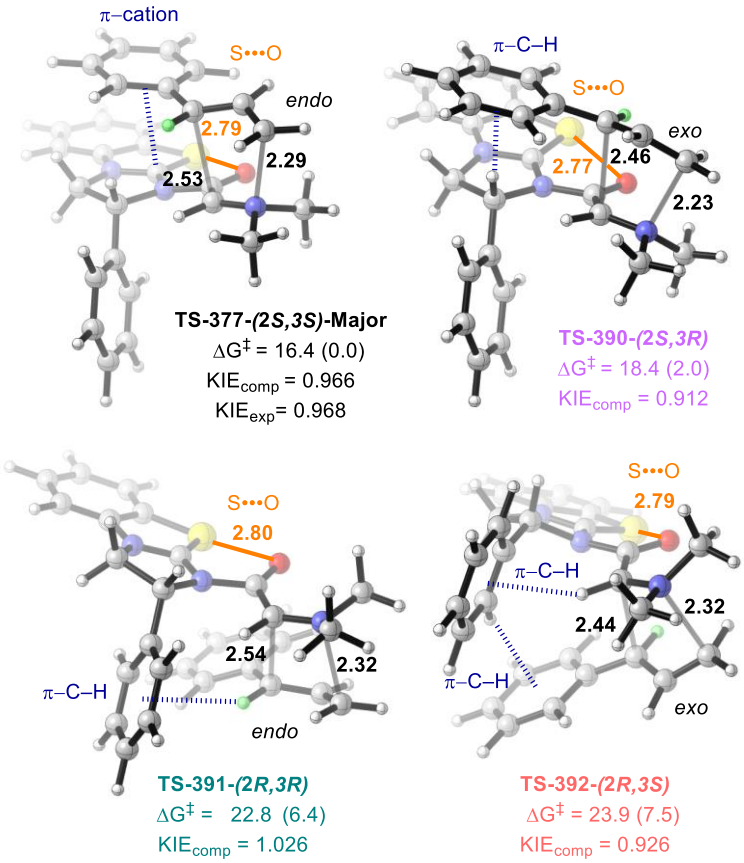


Figure 11: Four lowest calculated transition states for rearrangement of **319**. All energies in kcal/mol and distances in Å. Shaded grey lines represent forming/breaking bonds. Solid orange lines represent non-bonding S•••O interactions. Dashed blue lines represent aromatic interactions.

NBO analysis indicates that both the ylide **319** and **TS-377-(2*S*,3*S*)-Major** have significant enolate character, with ylide **319** displaying C=O bond order of 1.39 and a C-C bond order of 1.52. Early exogenic **TS-377-(2*S*,3*S*)-Major** displays a C=O bond order of 1.54 and C-C bond order of 1.21. The diastereocontrol of the process can be rationalised due to differences in electrostatic interactions found in **TS-377-(2*S*,3*S*)-Major** and **TS-390-(2*S*,3*R*)**. To further probe these differences simplified model systems were examined (*Figure 12*). In these model systems there is a clear preference for C(3)-aryl unit to sit above the cation (π-cation) versus the adjacent C-H (π-C-H) bond, $\Delta\Delta G^{\dagger}$ = 0.9 kcal/mol, (*Figure 12*).[66] Interestingly there is no energy difference between *endo* and *exo* rearrangement, which is how many related [2,3]-rearrangement processes are rationalised. As a result, it is postulated that the observed diastereocontrol can be rationalised the stabilising π-cation interaction of the C(3)-aryl unit with the positively charged acyl ammonium cation.[67] Such an interaction is not possible in the transition state for the *anti*-diastereomer **TS-390-(2*S*,3*R*)**.

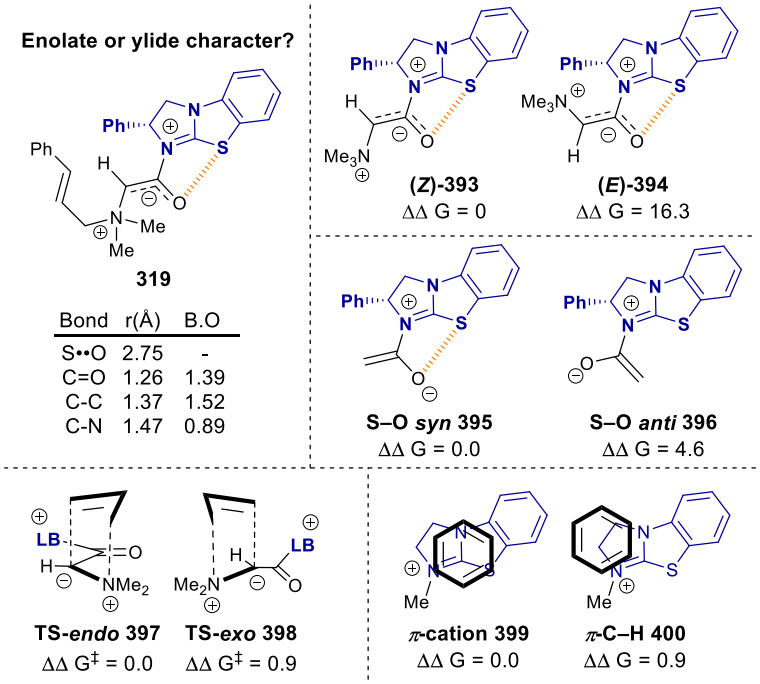
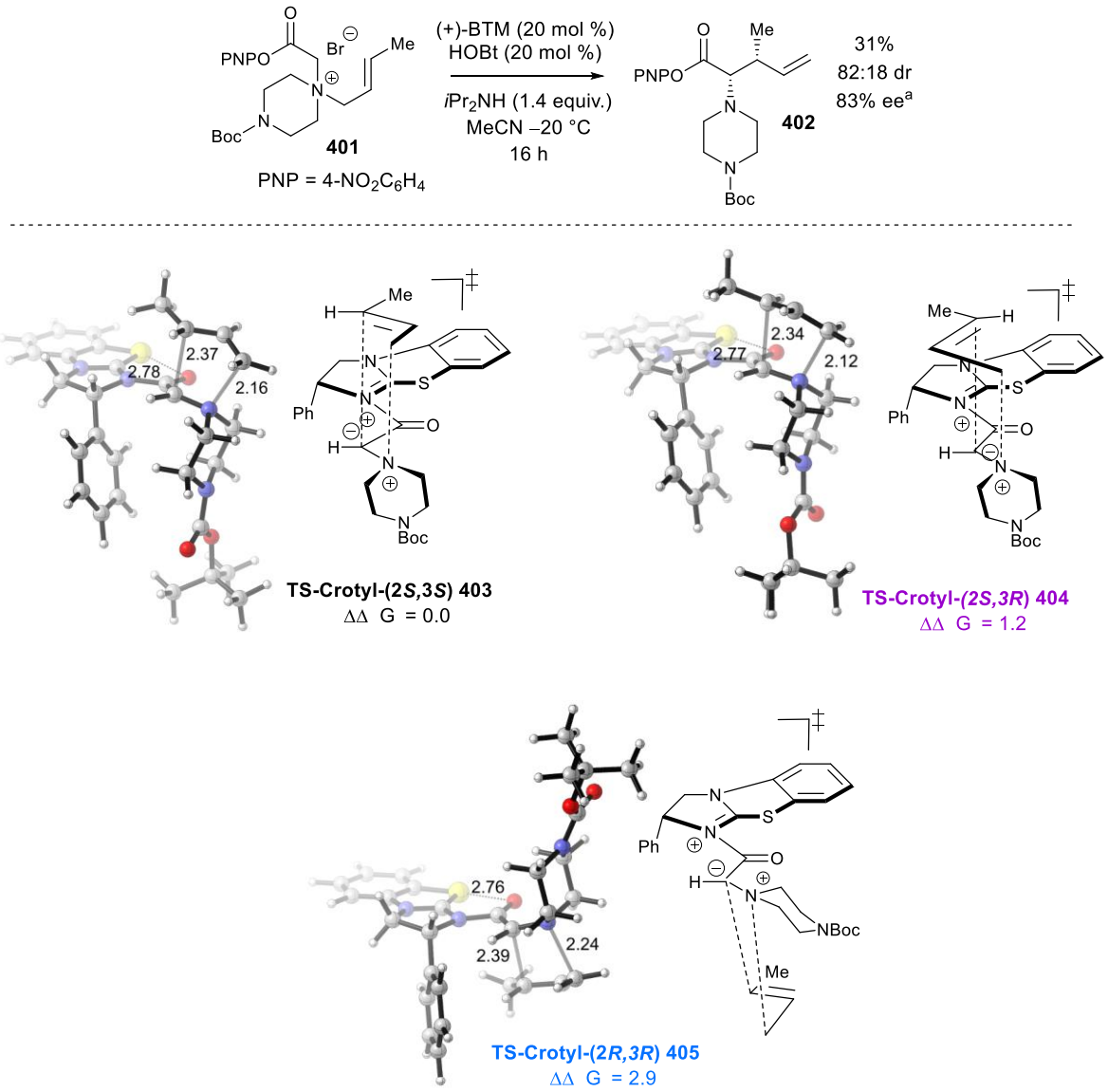


Figure 12: Computed simplified model systems, probing key interactions.

The excellent enantiocontrol of the rearrangement process can be rationalised by a strong non-covalent interaction between the sulfur atom on the acyl ammonium and oxygen atom of the carbonyl unit in the substrate.[68] Calculated model systems show that the *syn* orientation between the sulfur and oxygen is completely selective ($\Delta\Delta G^{\dagger}$ =4.6 kcal/mol). The transition state leading to the minor enantiomer **TS-391-(2*R*,3*R*)** undergoes *endo* rearrangement while maintaining a strong π-cation interaction, the energy differece between that and the major transition state **TS-377-(2*S*,3*S*)-Major** ($\Delta\Delta G^{\dagger}$ = 7.2 kcal/mol) is a direct result of the loss of the S•••O interaction. The conformational preference for the *syn*-sulfur-oxygen orientation is thought to arise from n_0 to $\sigma^*_{C\text{-}S}$ delocalisation in conjunction with an electrostatic

interaction between the partially positively charged sulfur and the partially negatively charged oxygen atom.[69] The S•••O distance in the major transition state **TS-377-(2*S*,3*S*)-Major** is 2.79 Å significantly below that of the sum of the van der Waals radii of sulfur and oxygen (3.4 Å), consistent with a strong non-bonding interaction between sulfur and oxygen in the transition state.

To further experimentally probe the effect of the π-cation interaction crotyl ammonium salt **401** was synthesised. After treatment of **4-1** under the previously optimised reaction conditions rearranged PNP ester **402** was isolated in modest yield (31%) with modest stereocontrol (82:18 dr, 83% ee). This system was also examined computationally; the competed diastereoselectivity of the reaction matches very well with experiment (89:11 dr). The loss of diastereocontrol relative to the cinnamyl model system, is likely a result of the favourable π-cation interaction. The enantioselectivity of the reaction is over estimated computationally (99% ee), but the energy difference between the enantiomeric transition states **TS-Crotyl-(2*S*,3*S*) 403** and **TS-Crotyl (2*R*,3*R*) 405** is small making calculation of enantioselectivity computationally difficult. Notably the calculated transition state for the minor enantiomer **TS-Crotyl (2*R*,3*R*) 404**, shows rearrangement occurring *syn* to the stereodirecting phenyl unit of the acyl ammonium. This suggests the C(3)-aryl unit also has a part to play in controlling the enantiocontrol of the reaction, stabilising facial selectivity.



Scheme 103: Rearrangement of crotyl ammonium salt **401** and calculated transition states. [a] Enantiopurity determined after derivatisation to the corresponding benzylamide.

3.15 Conclusions

The joint mechanistic and computational study reported in this chapter has provided mechanistic and stereochemical insight into the enantioselective isothiourea-catalysed [2,3]-rearrangement of allylic ammonium ylides. Kinetic analysis using ^{19}F NMR has built up reaction profiles and has identified an intermediate species. Isotopic labelling of catalyst (^{15}N) and of the substrate (^{13}C) has elucidated the constitution of the catalytic intermediate as **320** by *in situ* ^{13}C NMR. Isotopic entrainment studies have shown **320** to be a genuine intermediate which is on the productive pathway towards catalysis. The effect of co-catalytic HOBt has been investigated and it has found to change the resting-state of the catalyst and deviation away from the turnover-rate limiting step proposed by computation, when employed in high concentrations. A number of detailed crossover experiments have provided insight

into the reversibility of the key steps of the mechanism. Product release was found to be the turnover-limiting step of the process in the absence of HOBt through computation, the turnover limiting step of the process was found to switch to [2,3]-rearrangement when HOBt was employed. Computational calculation has validated experimental mechanistic experiments through reaction coordinate modelling. Transition state modelling has provided insight into the key interaction which govern the stereochemical outcome of the reaction.

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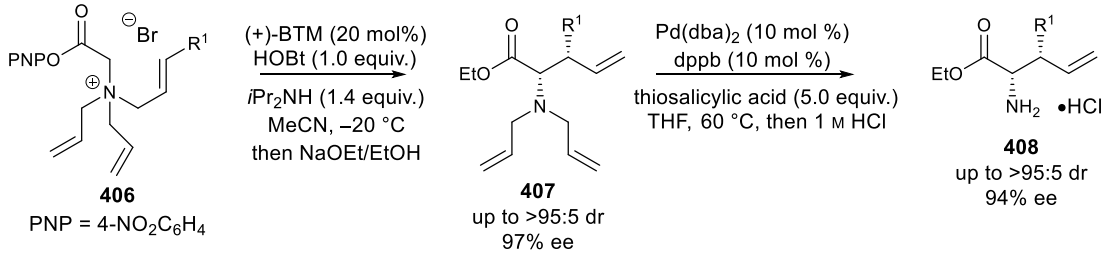
Chapter 4: Application of Removable *N*-Substituents

4.1 Summary

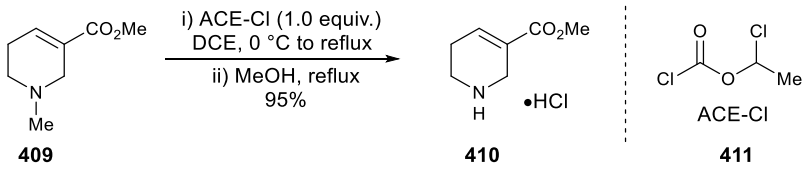
This chapter describes the design and development of an enantioselective synthesis of free α-amino esters *via* [2,3]-rearrangement of *N*,*N*-diallyl allylic ammonium ylides. Isothiourea-catalysed enantioselective [2,3]-rearrangement of *N*,*N*-diallyl quaternary ammonium salts **406** gave a range of *N*,*N*-diallyl-α-amino acid derivatives in excellent yield with excellent levels of diastereo- and enantiocontrol (to >95:5 dr, 97% ee). *N*,*N*-diallyl esters **407** could be readily selectively *mono*- or *bis*-*N*-deprotected to give free α-amino esters using literature reported Pd-catalysed methodology.



Scheme 104: Enantioselective synthesis of free α-amino esters *via* [2,3]-rearrangement of *N*,*N*-diallyl allylic ammonium ylides.

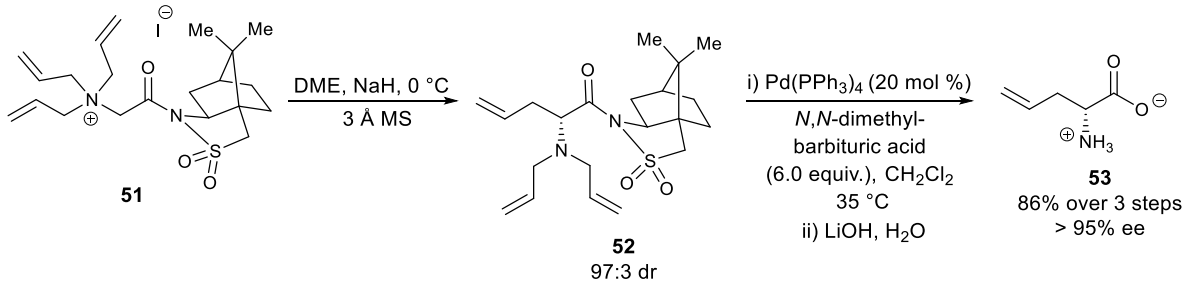
4.2 Concept and Aims

The isothiourea-catalysed [2,3]-rearrangement of allylic ammonium ylides previously described in *chapter 2* allows access to a range of α-amino acid derivatives bearing *N*-alkyl substituents. Whilst this allows for the synthesis of various pharmacological motifs, such as morpholine, the preparation of free α-amino esters was not possible. The removal of these *N*-alkyl substituents is by no means a trivial exercise, often requiring harsh conditions. For example, Olofson and Senet reported the development of 1-chloroethyl chloroformate (ACE-Cl) as an *N*-dealkylating reagent. *N*-Me tetrahydropyridine **409** could be readily demethylated, through treatment was ACE-Cl in refluxing DCE, followed by treatment with methanol, to give guvacoline·HCl **410** in 95% yield (*Scheme 105*).[70]



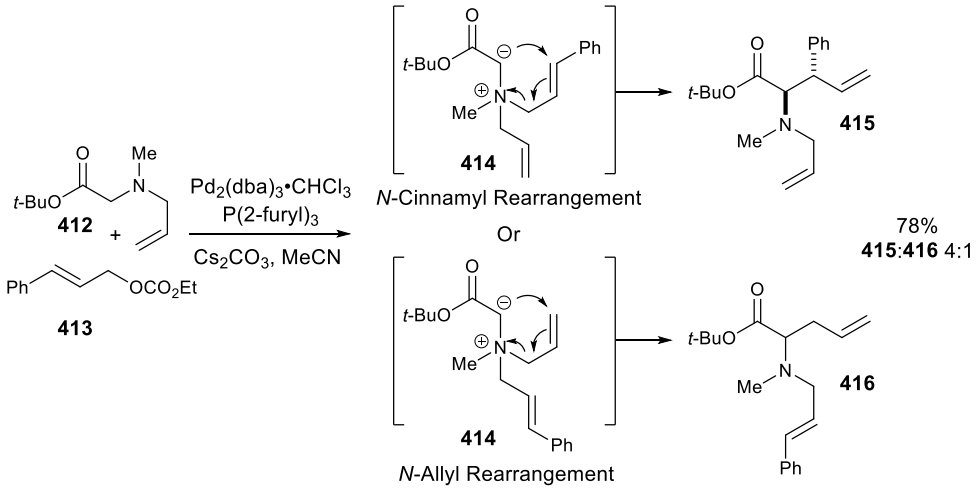
Scheme 105: Deprotection of *N*-Me group using ACE-Cl **411**.[70]

As highlighted in *chapter 1* Sweeney and co-workers[71] have demonstrated the asymmetric [2,3]-rearrangement of triallyl ammonium salts bearing a camphorsultam auxiliary to give *N*,*N*-diallyl α-amino acid derivatives in excellent yield and stereocontrol. It was found that the *N*,*N*-diallyl substituents could be readily removed, utilising Pd-catalysed methodology developed by Guibe (*Scheme 106*).[72]



Scheme 106: [2,3]-Rearrangement of triallyl ammonium salts, and subsequent *N*,*N*-diallyl deprotection.[71]

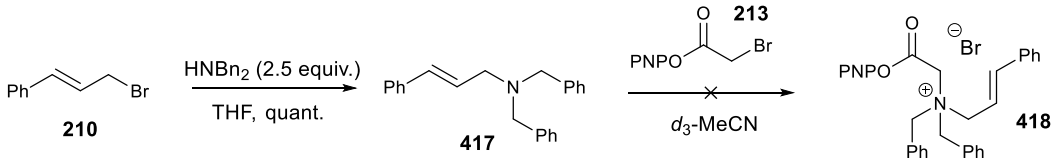
Building on this work, in 2011 Tambar and co-workers[73] demonstrated an elegant Pd-catalysed allylic substitution methodology towards the *in situ* synthesis of allylic ammonium salts. Treatment of *N*-methyl-*N*-allyl amine **412** with cinnamyl carbonate **413** in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$, P(2-furyl)$_3$ and Cs_2CO_3 gave ammonium ylide **414**, bearing a stereogenic nitrogen. [2,3]-Rearrangement of ammonium ylide **414** can proceed through the *N*-cinnamyl unit or the *N*-allyl unit; this resulted in non-chemoselective [2,3]-rearrangement to give a 4:1 mixture of *N*-cinnamyl rearranged product **415** and *N*-allyl rearranged product **416** in a combined 78% yield (*Scheme 107*).



Scheme 107: Non-chemoselective Pd-Catalysed ammonium salt formation, and [2,3]-rearrangement of *N*-methyl-*N*-allyl amino ester **412**.[73]

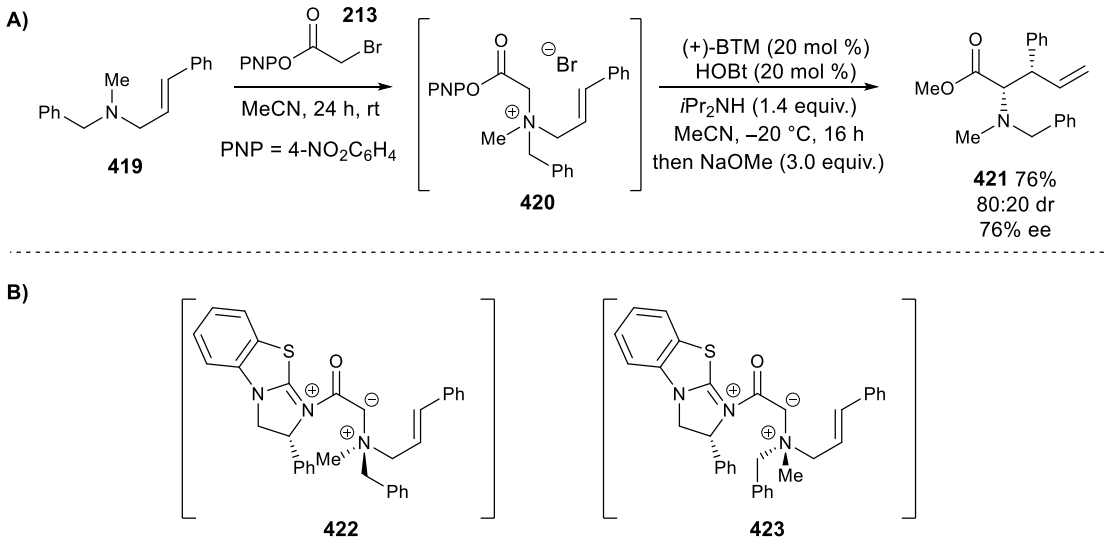
4.3 Initial Studies

To avoid any potential chemoselectivity issues the first removable *N*-substituents trialled in the isothiourea-catalysed [2,3]-rearrangement methodology were *N*,*N*-dibenzyl. Treatment of *N*,*N*-dibenzyl cinnamyl amine **417**, synthesised from cinnamyl bromide **210** in quantitative yield, with 4-nitrophenyl bromoacetate **213** resulted in no ammonium salt formation. This reaction was further monitored by *in situ* ^{1}H NMR, using d_3-MeCN and no ammonium salt formation was observed over 16 h at rt, indicating that the *N*,*N*-dibenzyl substituent may be too sterically hindered to allow ammonium salt formation (*Scheme 108*).



Scheme 108: Attempted synthesis of *N*,*N*-dibenzyl ammonium salt **418**.

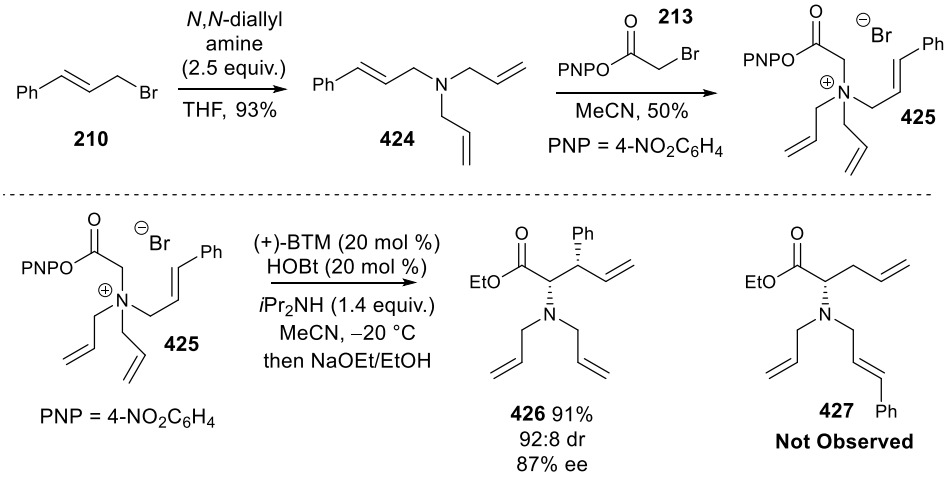
To reduce the steric bulk around the *N*-substituent, an *N*-methyl-*N*-benzyl substituent was employed. The corresponding ammonium salt **420** could not be readily isolated, but pleasingly it was found that *N*-methyl-*N*-benzyl cinnamyl amine **419** could be quaternised using the *in situ* ammonium salt formation and [2,3]-rearrangement methodology outlined in *chapter 2*. Treatment of **419** with 4-nitrophenyl bromoacetate in MeCN followed by (+)-BTM (20 mol %), HOBt (20 mol %) and *i*Pr$_2$NH (1.4 equiv.) at −20 °C, then sodium methoxide gave rearranged *N*-methyl-*N*-benzyl-α-amino ester in good yield (76%), albeit with modest stereocontrol (80:20 dr, 76% ee). The modest diastereocontrol is likely to be due to the formation of a stereogenic nitrogen within the ammonium salt **420** and (+)-BTM bound-diastereomeric ammonium ylides within the [2,3]-rearrangement step. However, it is not currently possible to fully discount the possibility of epimerisation through treatment with sodium methoxide or competing base-mediated background [2,3]-rearrangement. We have previously demonstrated that all steps prior to [2,3]-rearrangement within the mechanism are thought to be readily reversible. As there is some level of diastereocontrol it is likely that the energy barrier for the formation of, and [2,3]-rearrangement of each of the diastereomeric ylides is slightly different.



Scheme 109: A) *In situ N*-methyl-*N*-benzyl ammonium salt **420** formation and isothiourea-catalysed [2,3]-rearrangement. B) Diastereomeric ammonium ylide intermediates **422** and **423**.

4.3.1 [2,3]-Rearrangement of *N*,*N*-Diallyl Ammonium Salts

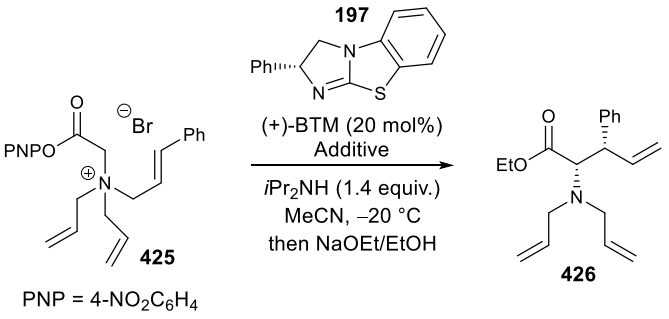
Due to the low diastereocontrol achieved when two different *N*-substituents were employed, a systemetrical *N*,*N*-subsitutent was desired and *N*,*N*-diallyl was postulated. *N*,*N*-diallyl cinnamyl amine was subsequently examined. It was found *N*,*N*-diallyl cinnamyl amine **424** could be readily synthesised from cinnamyl bromide **210**; subsequent treatment with 4-nitrophenyl bromoacetate gave the corresponding quaternary ammonium salt **425** which could be readily isolated in 50% yield (*Scheme 110*. Treatment of **425** under the reaction conditions previously developed in *chapter 2* followed by the addition of sodium ethoxide gratifyingly resulted in chemoselective [2,3]-rearrangement to give *N*,*N*-diallyl-α-amino ester **426** in excellent yield (91%) and good stereocontrol (92:8 dr, 87% ee) (*Scheme 110*).



Scheme 110: Chemoselective [2,3]-rearrangement of *N*,*N*-diallyl ammonium salt **425**.

4.4 Reaction Optimisation

With this initial hit in hand reaction optimisation was performed to attempt to improve the stereocontrol of the process. The requirement for the co-catalyst was examined, removal of HOBt resulted in a reduced yield and stereocontrol (81%, 89:11 dr, 76% ee, *entry 3, Table 3*). The use of a stoichiometric amount of NBu_4OPNP as an additive also resulted in a loss in both diastereo- and enantiocontrol (88:12 dr, 74% ee, *entry 4, Table 3*). However, pleasingly the use of a stoichiometric quantity of HOBt as an additive resulted in a dramatic enhancement in enantiocontrol (82%, 94:6 dr, 97% ee, *entry 2, Table 3*). These conditions were hence taken forward to examine the substrate scope of the reaction. Notably it was demonstrated that this process could be readily performed on a multi-gram scale without erosion of stereocontrol, with 479 mg (1.60 mmol) of ethyl ester **426** being generated from 1.0 g of *N*,*N*-diallyl ammonium salt **425**.



Entry[a]	Additive (mol %)	Yield (%)[b]	dr[c]	ee (%)[d]
1	HOBt (20)	91	92:8	87
2	HOBt (100)	82	94:6	97
3	-	81	89:11	76
4	NBu_4OPNP (100)	77	88:12	74
5[e]	HOBt (100)	76	>95:5	97

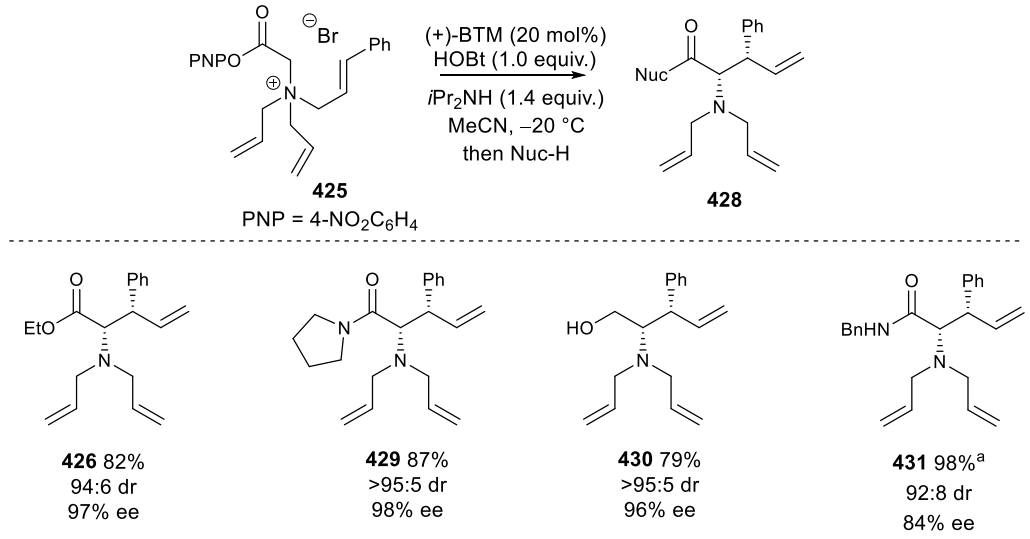
[a]Reactions performed on 0.24 mmol scale, [b]Isolated yield after flash column chromatography, combined yield of mixture of diastereomers [c]Determined by ^{1}H NMR of crude material, [d]Determined by HPLC analysis of chiral stationary phase, [e]Performed on 2.11 mmol scale.

Table 3: Reaction optimization

4.5 Scope of *in situ* Nucleophilic Derivatisation

Next the scope of *in situ* nucleophilic derivatization was examined under previously optimized conditions. The [2,3]-rearrangement product of *N*,*N*-diallyl ammonium salt **425** could be *in situ* derivatised using pyyrolidine or $LiAlH_4$ to give amide **429** and amino-alcohol **430** respectively in excellent yield and stereocontrol (*Scheme 111*). However, derivatization with benzylamine to give **431**, produced inseparable unidentified allyl-derived side products, under the optimal reaction conditions.

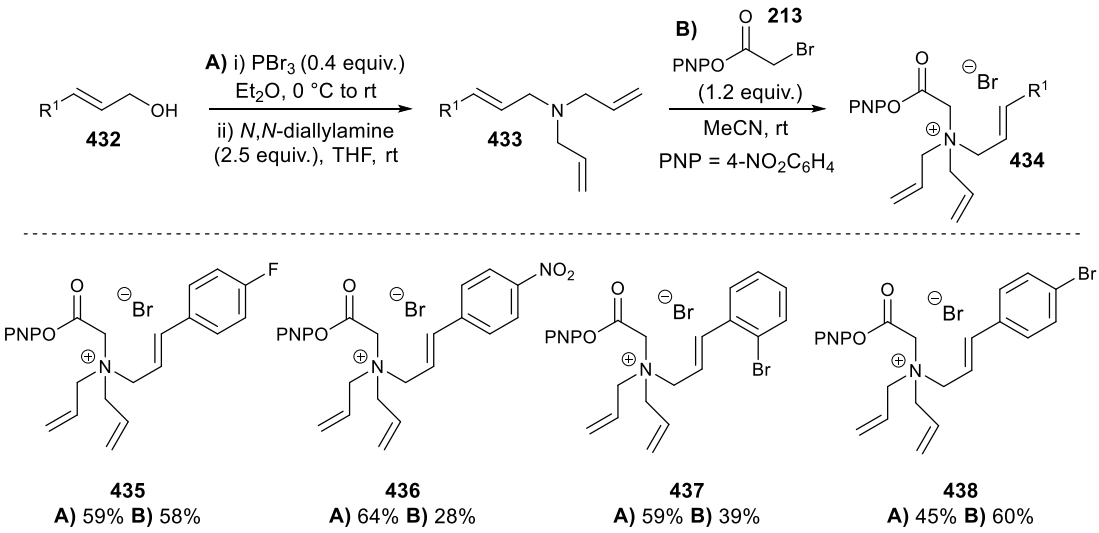
The use of a catalytic amount of HOBt (20 mol %) allowed the isolation of benzyl amide **431** in excellent yield with good levels of stereocontrol (92:8 dr, 84% ee).



Scheme 111: Scope of *in situ* nucleophilic derivatisation [a]HOBt, 20 mol % used instead of 1.0 equiv..

4.6 Synthesis of *N*,*N*-Diallyl Ammonium Salts

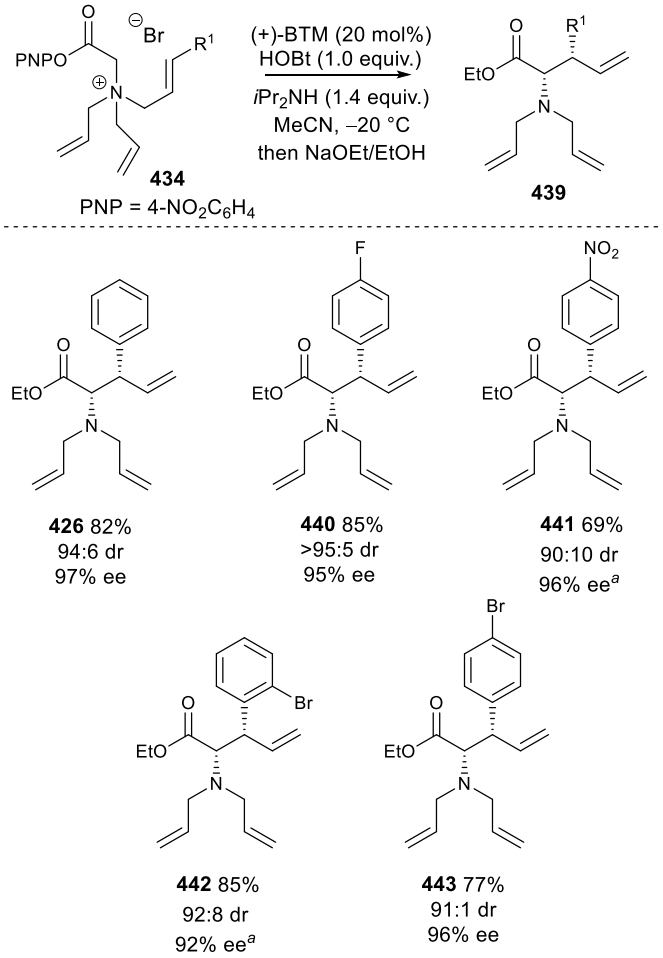
To examine the reaction scope with respect to the C(3)-aryl unit a range of electronically and sterically diverse ammonium salts were synthesised, utilising the method previously developed in *chapter 2*. Allylic alcohols **432** were readily converted to the corresponding *N*,*N*-diallyl cinnamyl amines **433**, which upon treatment with *p*-nitrophenyl bromoacetate **213** gave the desired *N*,*N*-diallyl ammonium salts **434** in modest yields (28-60%) (*Scheme 112*).



Scheme 112: Synthesis of *N*,*N*-diallyl ammonium salts.

4.7 Substrate Scope: Variation of the C(3) Aryl Unit

Variation of the C(3)-substituent within the *N*,*N*-diallyl ammonium salt **434** was next investigated. It was shown that electron-neutral and electron-withdrawing aromatic substituents could be well tolerated giving ethyl esters **440**, **441** and **443** in excellent yield and good to excellent stereocontrol. Incorporation of a sterically demanding *ortho*-substituent in the C(3)-aryl group was well tolerated giving **442** in good yield and stereocontrol (*Scheme 113*).

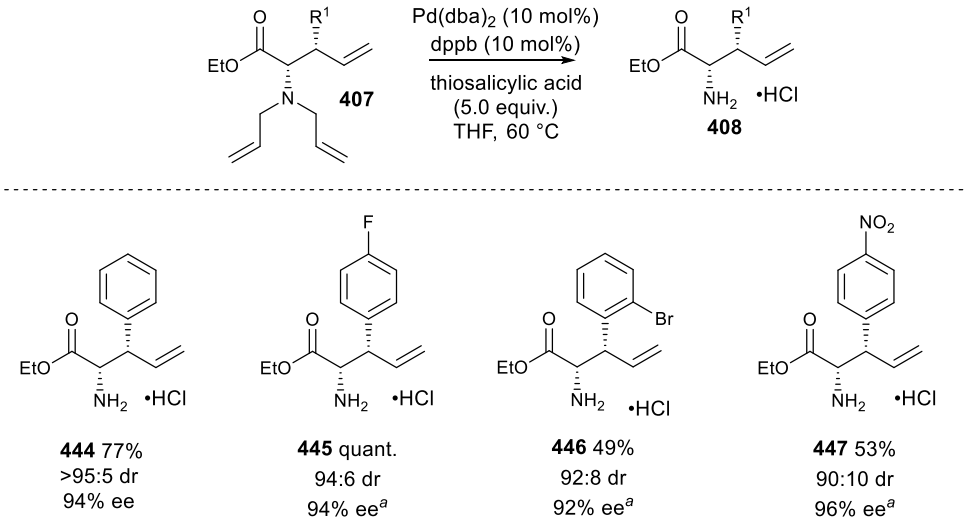


Scheme 113: Substrate scope of C(3)-aryl unit within *N*,*N*-diallyl ammonium salt, [a]Enantiopurity determined after *bis*-*N*-deallylation and *N*-Boc protection.

4.8 Deprotection of *N*,*N*-diallyl rearrangement products

With a range of *N*,*N*-diallyl ethyl esters in hand, efforts were turned to removal of the *N*,*N*-diallyl groups to synthesise a range of α-amino esters. Utilising the Pd-catalysed *bis*-*N*-deallylation chemistry developed by Bernard and co-workers[74] treatment of **426** with $Pd(dba)_2$ (10 mol %), dppb (10 mol %) and thiosalicylic acid (5.0 equiv.) in THF at 60 °C followed by aq. 1 M HCl allowed facile isolation of the desired free amine **444** as its hydrochloride salt,[75], without the need for flash column chromatography. This was applied to a small range of *N*,*N*-diallyl rearrangement products **407** giving

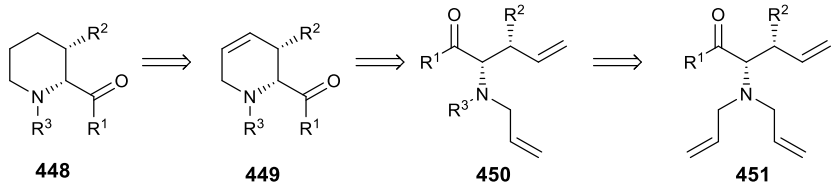
the desired *bis*-*N*-deallylation products **408** in good to excellent yield without erosion of diastereo- or enantiopurity (*Scheme 114*).



Scheme 114: *N*,*N*-deallylation of [2,3]-rearrangement products, [a]enantiopurity determined after *N*-Boc protection.

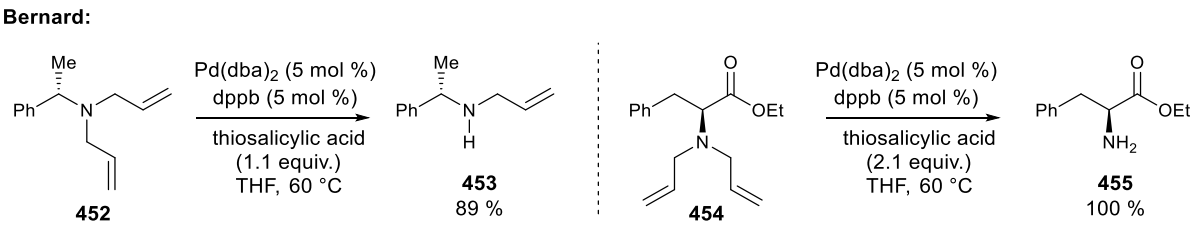
4.9 Application to the Synthesis of Functionalised Piperidines

It was postulated that if one *N*-allyl could be selectively removed, this could allow access to a highly functionalised piperidine architecture, through ring-closing metathesis followed by hydrogenation. Piperidine core structures are ubiquitous among bioactive molecules;[76] analysis of launched drugs within the integrity database shows 320 registered drugs contain saturated piperidines.[77] However, the synthesis of stereodefined functionalised saturated piperdines is often non-trivial.



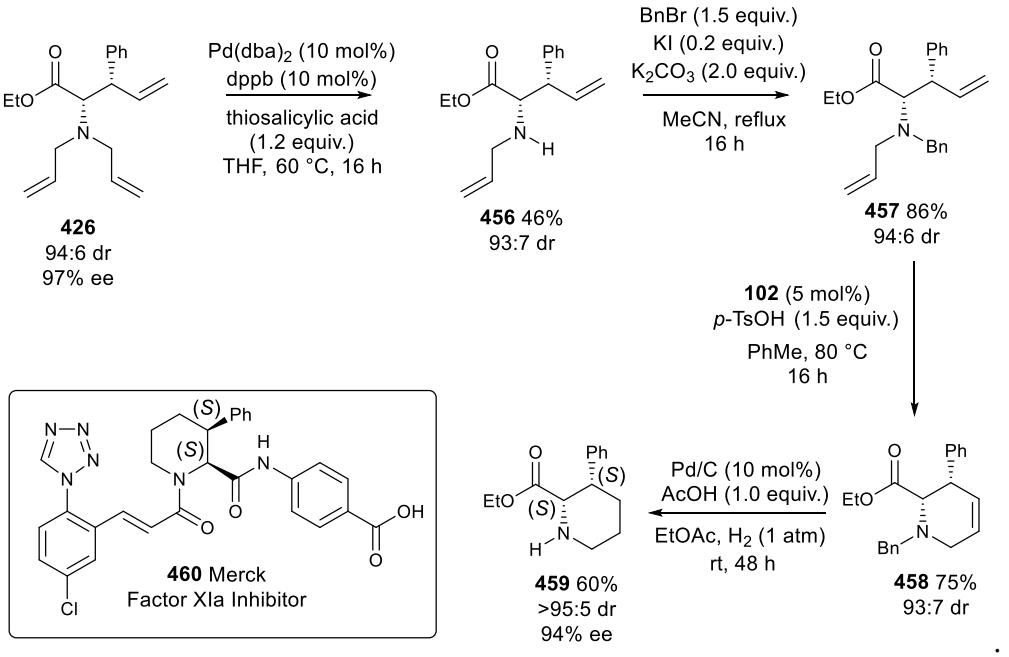
Scheme 115: Retrosynthetic analysis of piperidine core to *N*,*N*-diallyl ester.

Bernard and co-workers[74] have previously demonstrated that it is possible to selectively *mono*- or *bis*-deallylate *N*,*N*-diallyl amines, through simple tuning of equivalents of thiosalicylic acid utilised in the Pd-catalysed deallylation reaction. For example, treatment of **454** with thiosalicylic (2.1 equiv.) in the presence of $Pd(dba)_2$ (5 mol %) and dppb (5 mol %) resulted in *bis*-*N*-deallylation, whereas treatment of **452** with thiosalicylic acid (1.1 equiv.) in the presence of $Pd(dba)_2$ (5 mol %) and dppb (5 mol %) resulted in selective *mono*-*N*-deallylation (*Scheme 116*).[74]



Scheme 116: Bernard's selective *mono*- or *bis*-*N*-deallylation of *N*,*N*-diallylamines.[74]

Utilisng Bernard's methodology **426** was *mono*-*N*-deallylated, through treatment with $Pd(dba)_2$ (10 mol %), dppb (10 mol %), thiosalicylic acid (1.2 equiv.) in THF at 60 °C, to give **456** in modest yield (46%) but with retention of diastereomeric purity. Subsequent *N*-benzyl protection gave **457** in excellent yield; subsequent treatment of **457** with Hoveyda-Grubbs 2nd generation catalyst **102** (5 mol %) in the presence of *p*-toluenesulfonic acid (1.5 equiv.) in toluene at 80 °C gave ring-closed product **458** in good yield and as a single diastereoisomer after purification by flash column chromatography. Finally, Pd/C catalysed hydrogenation of **458** resulted in reduction of the alkene bond and concomitant *N*-benzyl deprotection to give functionalised piperidine **459** in good yield and with excellent levels of stereocontrol (>95:5 dr, 94% ee). It is thought that piperidine core **459** could be further diversified to form a library of bioactive compounds such as Merck's factor XIa inhibitor **460**[78] (*Scheme 117*).



Scheme 117: Further manipulation of [2,3]-rearrangement product **426**.

4.10 Conclusions

The previously developed isothiourea-catalysed enantioselective [2,3]-rearrangement of allylic ammonium ylides has been further developed to allow removable *N*,*N*-diallyl substituents to be incorporated. Excellent chemoselectivity was observed for [2,3]-rearrangement through the *N*-cinnamyl unit over the *N*-allyl unit. The use of stoichiometric HOBt allowed excellent levels of diastereo- and enantiocontrol to be achieved (up to >95:5 dr, up to 98% ee). The substrate scope of this process has been examined across a number of different aryl and nucleophilic variations. It has been shown the *N*,*N*-diallyl substituents can be readily *mono*- or *bis*-*N*-deprotected and this methodology has been applied to the synthesis of a functionalised piperdine motif.

4.11 References

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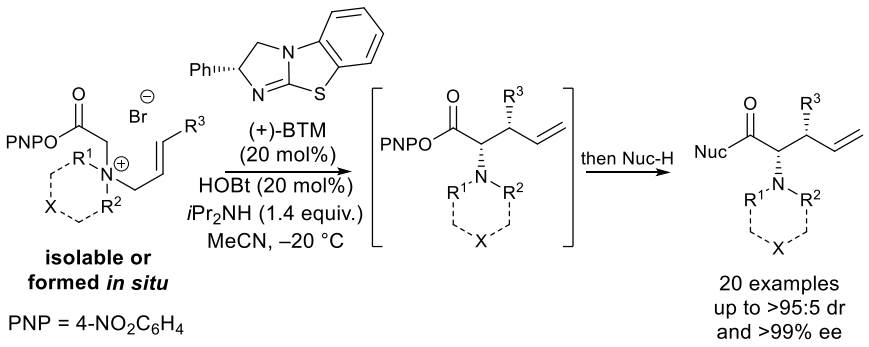
Chapter 5: Conclusions and Outlook

This thesis has described the design and development of an isothiourea-catalysed enantioselective [2,3]-rearrangement of allylic ammonium ylides. Initially a proof of concept methodology was developed and fully investigated. Subsequent experimental mechanistic work has given great insight into complex mechanism of this process. Collaborative computational studies have provided understanding of the origins of stereocontrol in the reaction and has validated experimental mechanistic proposals. The synthetic utility of this process has been demonstrated through the removal of *N*-substituents, which has allowed application of this methodology to the synthesis of free α-amino esters.

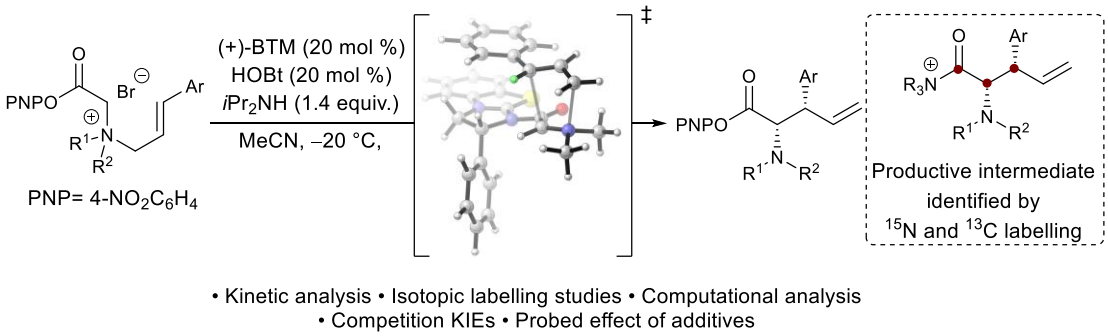
Firstly, the use of isothioureas to facilitate an enantioselective [2,3]-rearrangement was demonstrated. Optimisation and development found that catalytic (+)-BTM in combination with co-catalytic HOBt was optimal for the [2,3]-rearrangement of quaternary ammonium salts bearing 4-nitrophenyl esters (isolated or generated *in situ*) to give a range of *syn*-α-amino acid derivatives in good to excellent yield (33-89%) and with excellent levels of stereocontrol (up to >95:5 dr and >99% ee) (*Scheme 118*).



Scheme 118: Summary of isothiourea-catalysed enantioselective [2,3]-rearrangement of allylic ammonium ylides.

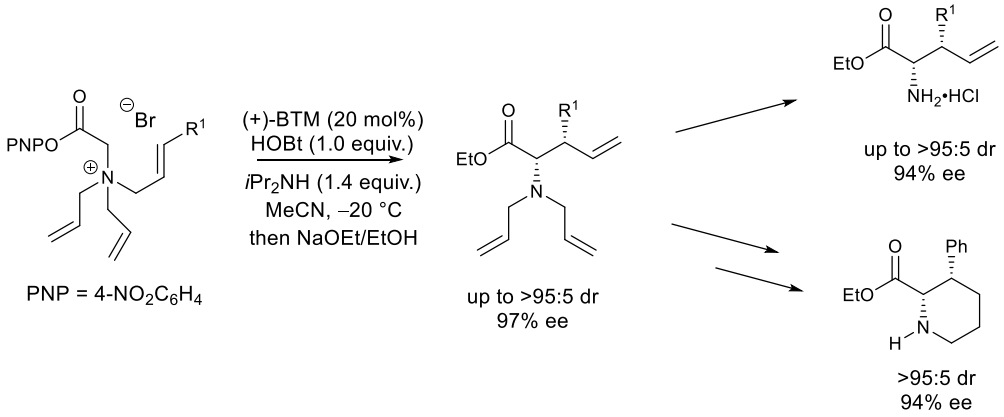
Mechanistic studies into the isothiourea-catalysed enantioselective [2,3]-rearrangement of allylic ammonium ylides were undertaken allowing a detailed catalytic cycle to be proposed. Reaction kinetic analysis using ^{19}F NMR spectroscopy proved to be a powerful tool in the elucidation of a detailed reaction profile including the reaction order of each component and the resting-state of the catalyst. A catalytically productive acyl ammonium intermediate has been observed, with isotopic labelling of both catalyst (^{15}N) and substrate (^{13}C) allowing unambiguous identification of the observed intermediate using *in situ* ^{13}C NMR spectroscopy. Isotopic entrainment has shown the acyl ammonium intermediate to be on-cycle and productive towards catalysis. Kinetic isotope effect analysis has shown [2,3]-rearrangement to be the turnover-limiting step of the process. The effect of the HOBt additive on the reaction and catalyst resting-state has been probed, through *in situ* ^{19}F NMR spectroscopic analysis. Crossover experiments have allowed the reversibility of each step of the proposed catalytic cycle to be examined. Collaborative computational analysis has found key transition state stabilising cation-π and

1,5-S●●●O interactions to be the origins of the excellent observed stereocontrol. Computational reaction coordinate modelling has ruled out alternative mechanistic possibilities and has further validated the experimentally proposed catalytic cycle (*Scheme 119*).



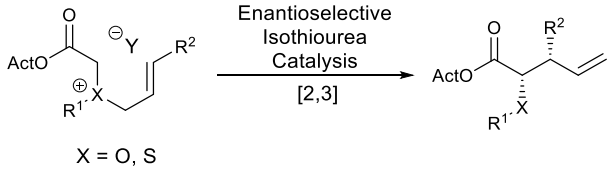
Scheme 119: Summary of mechanistic and computational investigations.

Finally, this methodology was extended to substrates bearing *N*-substituents which could be readily removed under mild conditions. Evaluation of a small range of removable *N*-substituents, showed that isolated *N*,*N*-diallyl ammonium salts underwent chemoselective [2,3]-rearrangement in excellent yields and stereocontrol (up to >95:5 dr and 97% ee). The resulting *N*,*N*-diallyl α-amino esters could undergo Pd-catalysed selective *mono*- or *bis*-*N*-allyl deprotection. *Bis*-*N*-allyl deprotection has allowed the synthesis of a range of stereodefined free α-amino esters, whilst *mono*-*N*-allyl deprotection has allowed this methodology to be applied to the synthesis of a target functionalised piperidine motif.



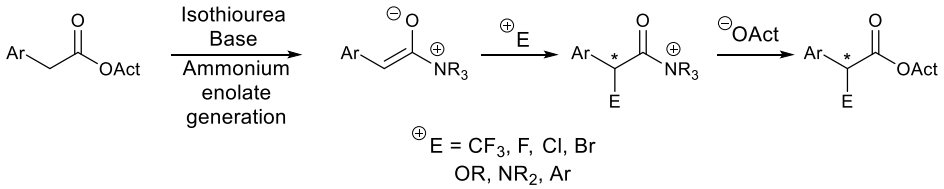
Scheme 120: Summary of isothiourea-catalysed enantioselective [2,3]-rearrangement of *N*,*N*-diallyl ammonium ylides and subsequent selective *N*-deprotection strategies

Future work will likely focus on the extension of this methodology to other develop [2,3]-"onium" ylides rearrangements, such as oxonium or sulfonium ylides (*Scheme 121*). Whilst catalytic enantioselective variants have previously been developed, organocatalytic variants still remain a significant challenge within the area. Such [2,3]-rearrangements would provide access to a range of stereodefined homoallylic ethers and sulfides.



Scheme 121: Proposed isothiourea catalysed [2,3]-rearrangements of oxonium and sulfonium ylides.

At the out-set on this work in 2012 there were no examples of C(1)-acyl ammonium intermediates undergoing turnover from an external nucleophile after α-functionalisation with an electrophile. The work is thesis has demonstrated that electron poor phenoxides can act as suitable C(1)-acyl ammonium turnover agents. Further work could focus on the reaction of C(1)-ammonium enolates with a variety electrophilic partners which do not contain an intramolecular turnover mechanism. For example, it is envisaged that aryl acetic activated esters could react with an isothiourea to generate a C(1)-ammonium enolates; such ammonium enolates could react with a range of electrophiles to form a stereodefined C(1)-acyl ammonium intermediates. Product release from such intermediates could generate a range of enantioenriched carboxylic acid derivatives (*Scheme 122*).



Scheme 122: Potential isothiourea-catalysed enantioselective α-functionalisation of aryl acetic activated esters.

Chapter 6: Experimental Details

General Experimental

Reactions were performed in flame-dried glassware under an N_2 atmosphere unless otherwise stated. Anhydrous CH_2Cl_2 and Et_2O were obtained from an MBraun SPS-800 system, MeCN was HPLC grade stored over 4 Å MS. All other solvents and commercial reagents were used as received without further purification unless otherwise stated. d_3-MeCN and d_6-DMSO for kinetic experiments were used as received. Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C, −20 °C and −78 °C were obtained using ice/water bath, an immersion cooler and CO_2(s)/acetone bath, respectively.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F_{254} silica). Plates were visualised under UV light (254 nm) or by staining with either phosphomolybdic acid or $KMnO_4$ followed by heating. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

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

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

HPLC analyses were obtained on a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatography SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven that allows the temperature to be set from 25-40 °C. Separation was achieved using a Chiralcel OJ-H, or Chiralpak AD-H, AS-H, IA, IB, and ID columns. The columns were flushed with 40% IPA/hexane for 15 mins before switching to the indicated solvent mixtures, as this ensured reproducibility of chromatograms.

Infrared spectra (ν_{max}) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer using either thin film or solid using Pike MIRacle ATR accessory. Analysis was carried out using Shimadzu IRsolution v1.50 and only characteristic peaks are reported.

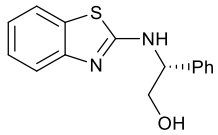
^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H} and ^{19}F NMR spectra were acquired on either a Bruker Avance 300 {δ_H: (300 MHz), δ_C: (75 MHz), δ_F: (282 MHz)}, a Bruker Avance II 400 {δ_H: (400 MHz), δ_C: (101 MHz), δ_F:

(376 MHz)}, a Bruker Ultrashield 500 {δ_H: (500 MHz), δ_C: (126 MHz), δ_F: (471 MHz)}, a Bruker Ascend 400 {δ_H: 400 MHz, δ_C: (101 MHz), δ_F: (471 MHz)} or a Bruker Avace III 700 {δ_H: (700 MHz), δ_C: (179 MHz), δ_F: (659 MHz)} spectrometer at ambient temperature (unless otherwise stated) in the deuterated solvent stated. Chemical shifts, δ, are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants, *J*, are quoted in Hertz (Hz) to the nearest 0.1 Hz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; ddt, doublet of doublets of triplets; dtt, doublet of triplets of triplets; dq, doublet of quartets; td, triplet of doublets; tdd, triplet of doublets of doublets; tt, triplet of triplets; m, multiplet; br, broad; and *apt*, apparent.

Mass spectrometry (HRMS) data were acquired by electrospray ionisation (ESI), electron impact (EI), chemical ionisation (CI), atmospheric pressure chemical ionisation (APCI) or nanospray ionisation (NSI) at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Synthesis of (+)-BTM

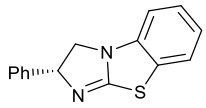
(*R*)-2-(Benzo[*d*]thiazol-2-ylamino)-2-phenylethan-1-ol 461 [79]



Following the procedure of Daniels *et. al*.[79] a solution of 2-Chlorobenzothiazole (8.6 mL, 69.43mmol, 1.0 equiv.), (*R*)-phenylglycinol (10.0 g, 72.8 mmol, 1.05 equiv.) and *i*Pr_2NEt (31.0 mL, 173.6 mmol, 2.5 equiv.) in *o*-dichlorobenzene (34.5 mL, 2.0 M) were heated to 195 °C for 24 h. After cooling to rt, the mixture was treated with H_2O (100 mL) and toluene (75 mL) and vigorously stirred for 30 mins, the resulting precipitate filtered and dried *in vacuo*. The resulting solid was recrystallized from toluene to give the title product as a white solid (11.2 g, 60%);

$[\alpha]_D^{20}$ −98.3 (*c* 1.0 MeOH); {lit. [80]$[\alpha]_D^{20}$ −98.7 (*c* 1.0 MeOH)}; m.p 156-158 °C (PhMe), {lit. 159-160 °C};^{1}H NMR (500 MHz, d_4-MeOH) δ_H: 3.77-3.89 (2H, m, C(1)H_2), 5.00 (1H, dd, *J* 7.5, 5.0, C(2)*H*), 7.03 (1H, td, *J* 7.5, 1.2, Ar(4)*H*), 7.19-7.29 (2H, m, Ar*H*), 7.31-7.40 (3H, m, Ar*H*), 7.44 (2H, dd, *J* 8.1, 1.2, Ar(6,7)*H*), 7.55 (1H, dd, *J* 8.1, 1.2, Ar(8)*H*); Data in accordance with the literature.[79]

(*R*)-2-Phenyl-2,3-dihydrobenzo[*d*]imidazo[2,1-*b*]thiazole ((+)-*Benzotetramisole*), (+)-BTM 197 [79]

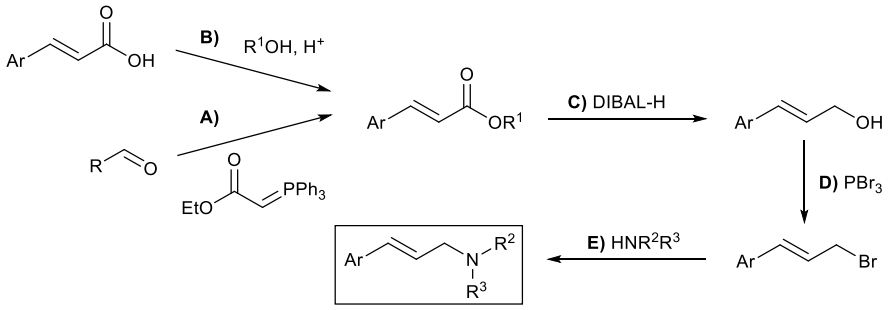


(2*R*)-2-Phenyl-2-(1-thia-3-aza-2-indanylamino) ethanol **461** (11.2 g, 41.5 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (415 mL) and cooled to 0 °C and treated with NEt_3 (23.1 ml, 166 mmol, 4.0 equiv.) followed by MsCl (4.19 mL, 54.0 mmol, 1.3 equiv.). The mixture was then warmed to rt and stirred for 15 mins. After which *i*PrOH (9.0 mL) was added and the mixture heated to reflux for 16 h. The reaction mixture was allowed to cool to rt, then quenched by the addition of aq. 1 M NaOH (200 mL) and stirred for 30 min. The layers separated and the aqueous layer extracted with CH_2Cl_2 (100 mL). The combined organic layers were washed with brine (100 mL) dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was azeotroped with PhMe (3 × 50 mL). The residue was triturated with Et_2O (200 mL) and filtered this was repeated twice. The combined filtrates were extracted with aq. 1 M HCl (5 × 50 mL) and the combined aqueous layers were basified with aq. 2 M NaOH to *ca*. pH>14. The aqueous was extracted with Et_2O (3 × 100 mL) and the combined organic layers washed with brine (100 mL). The organic layer was then treated with activated charcoal (~5 g) and $MgSO_4$ and filtered through Celite® (eluent 200 mL Et_2O), the resulting filtrate was concentrated *in vacuo*. The resulting solid residue was recrystallized from Et_2O/PE to give the title product as a white solid (5.34 g, 51%);

$[\alpha]_D^{20}$ +257.9 (*c* 1.0, MeOH); {lit.[80] $[\alpha]_D^{20}$ +256.7 (*c* 1.0, MeOH)}; m.p 89-90 °C (Et_2O:PE), {lit. 94.5-95.0 °C (Et_2O:hexanes)}; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 3.72 (1H, dd, *J* 8.9, 8.1, C(3)H^AH^B), 4.28 (1H, dd, *J* 10.2, 8.9, C(3)H^AH^B), 5.67 (1H, dd, *J* 10.2, 8.1, C(2)*H*), 6.67 (1H, dd, *J* 7.7, 1.2, Ar(3)*H*), 6.97 (1H, td, *J* 7.7, 1.2, Ar(4)*H*), 7.19 (1H, td, *J* 7.7, 1.2, Ar(2)*H*), 7.27-7.33 (2H, m, Ar*H*), 7.34-7.41 (4H, m, Ar*H*); Data in accordance with the literature.[79]

Experimental Details for Chapter 2

Amine Synthesis General Scheme:



General Procedure A: Synthesis of α,β-Unsaturated Esters from Aldehydes:

To a stirred solution of the aldehyde (1.0 equiv.) in CH_2Cl_2 (10 mL / g aldehyde) was added ethyl 2-(triphenylphosphoranylidene)acetate (1.05 equiv.). The reaction was stirred overnight at rt, concentrated *in vacuo*, the residue triturated with PE/Et_2O (9:1), and the solids removed by filtration. The solvent was removed *in vacuo* and the crude residue purified by flash chromatography on silica gel to give the pure α,β-unsaturated esters.

General Procedure B: Synthesis of α,β-Unsaturated Esters from Acids:

To a stirred solution of the α,β-unsaturated acid (1.0 equiv.) in ethanol (10 mL / g acid) was added conc. H_2SO_4 (0.1 mL / g acid). The reaction was heated at reflux for 3 h, allowed to cool, and concentrated *in vacuo*. The residue was neutralised with sat aq $NaHCO_3$, extracted with EtOAc (3 × equal volume) and the combined organics washed with brine (equal volume). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the pure α,β-unsaturated esters.

General Procedure C: Synthesis of Allylic Alcohols:

To a stirred solution of the α,β-unsaturated ester (1.0 equiv.) in anhydrous CH_2Cl_2 (0.2 M) at −78 °C under N_2 was added DIBAL-H (1.0-1.2 M in toluene *or* hexane, 2.2 equiv.) dropwise. The reaction was stirred for 1.5 h at −78 °C, and quenched with 10% aq NaOH (equal volume). The resultant mixture was allowed to warm to rt and stirred for 1 h. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × equal volume). The combined organics were washed with brine (equal volume), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the pure allylic alcohols.

General Procedure D: Synthesis of Allylic Bromides:

To a stirred solution of the allylic alcohol (1.0 equiv.) in anhydrous Et_2O (0.33 M) at 0 °C was added PBr_3 (0.4 equiv.). The reaction was stirred until complete by TLC analysis (typically 0.25-1 h), and

poured into sat aq $NaHCO_3$ (equal volume). The layers were separated and the aqueous layer extracted with Et_2O (2 × equal volume). The combined organics were washed with sat aq $Na_2S_2O_3$ and brine (1:1, equal volume), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the pure allylic bromides.

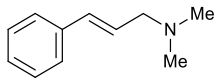
General Procedure E: Synthesis of *N*,*N*-Dimethyl Allylic Amines:

A solution of the allylic bromide (1.0 equiv.) in THF (0.5 M) was added dropwise to a solution of dimethylamine in water (40% wt., 5.0 equiv.) *via* a dropping funnel at rt. After addition was complete, the funnel was rinsed with a small portion of THF and the reaction stirred for 10 mins. 1 M aq NaOH (2 equiv.) was then added in one portion, and the reaction stirred for a further 10 mins. The reaction was diluted with Et_2O (equal volume), the layers separated and the aqueous layer extracted with Et_2O (2 × equal volume). The combined organics were washed with brine (equal volume), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was triturated with Et_2O, any solids removed by filtration, and the solution concentrated *in vacuo* to afford the dimethyl allylic amines that were used as isolated, or purified further by flash chromatography on silica gel or distillation (as indicated).

General Procedure F: Synthesis of Other Tertiary Allylic Amines:

A solution of the allylic bromide (1.0 equiv.) in THF (0.5 M) was added dropwise to a solution of the secondary amine (2.5 equiv.) in THF (2.5 M) *via* a dropping funnel at rt. After addition was complete, the funnel was rinsed with a small portion of THF and the reaction stirred for 10 mins. 1 M aq NaOH (2 equiv.) was then added in one portion, and the reaction stirred for a further 10 mins. The reaction was diluted with Et_2O (equal volume), the layers separated and the aqueous layer extracted with Et_2O (2 × equal volume). The combined organics were washed with brine (equal volume), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was triturated with Et_2O, any solids removed by filtration, and the solution concentrated *in vacuo* to afford the tertiary allylic amines that were used as isolated, or purified further by flash chromatography on silica gel (as indicated).

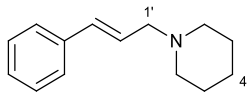
(*E*)-*N*,*N*-Dimethyl-3-phenylprop-2-en-1-amine[81] 212



Following general procedure **E**, the reaction of cinnamyl bromide (25.0 g, 126.9 mmol, 1.0 equiv.) in THF (250 mL) and dimethylamine (80.2 mL, 634.5 mmol, 5.0 equiv.) gave the title compound (15.7 g, 77%, 97:3 *E/Z* by ^{1}H NMR) after distillation under vacuum to give a colourless oil.

bp 80-82 °C at 1 mmHg {Lit.[82] 120 °C at 10 mmHg} ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.28 (6H, s, N(C*H*$_3$)$_2$), 3.08 (2H, dd, *J* 6.7, 1.4, C(1)*H*$_2$), 6.27 (1H, dt, *J* 15.8, 6.7, C(2)*H*), 6.52 (1H, dt, *J* 15.8, 1.4, C(3)*H*), 7.19-7.25 (1H, m, ArC(4)*H*), 7.28-7.34 (2H, m, ArC(3,5)*H*), 7.36-7.41 (2H, m, ArC(2,6)*H*); Data consistent with literature.[81]

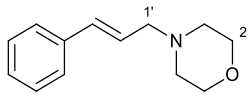
1-Cinnamylpiperidine[83]† 239



Following general procedure **F**, the reaction of cinnamyl bromide (1.00 g, 5.1 mmol, 1.0 equiv.) in THF (10 mL) with piperidine (1.25 mL, 12.7 mmol, 2.5 equiv.) in THF (5 mL) gave the title compound (1.01 g, 99%, >98:2 *E/Z* by ^{1}H NMR) as an orange oil that was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.41-1.49 (2H, m, C(4)*H*$_2$), 1.57-1.65 (4H, m, C(3,5)*H*$_2$), 2.44 (4H, br s, C(2,6)*H*$_2$), 3.12 (2H, dd, *J* 6.7, 1.3, C(1')*H*), 6.31 (1H, dt, *J* 15.9, 6.7, C(2')*H*), 6.50 (1H, dt, *J* 15.9, 1.3, C(3')*H*), 7.18-7.24 (1H, m, Ar(4)*H*), 7.27-7.33 (2H, m, Ar(3,5)*H*), 7.35-7.39 (2H, m, Ar(2,6)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 24.5, 26.1, 54.7, 62.0, 126.4, 127.4 (2 × C), 128.6, 132.7, 137.2. Data consistent with literature.[83]

4-Cinnamylmorpholine[84]† 240



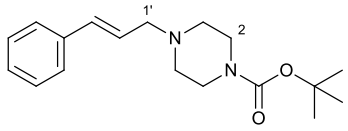
Following general procedure **F**, the reaction of cinnamyl bromide (1.00 g, 5.1 mmol, 1.0 equiv.) in THF (10 mL) with morpholine (1.11 mL, 12.7 mmol, 2.5 equiv.) in THF (5 mL) gave the title compound (1.02 g, 99%, >98:2 *E/Z* by ^{1}H NMR) as an orange oil that was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.49-2.54 (4H, m, C(3,5)*H*$_2$), 3.17 (2H, dd, *J* 6.8, 1.3, C(1')*H*), 3.73-3.77 (4H, m, C(2,6)*H*$_2$), 6.27 (1H, dt, *J* 15.9, 6.8, C(2')*H*), 6.55 (1H, dt, *J* 15.9, 1.3, C(3')*H*), 7.21-7.27

† Synthesised and characterised by Dr David S. B. Daniels

(1H, m, Ar(4)*H*), 7.29-7.35 (2H, m, Ar(3,5)*H*), 7.36-7.41 (2H, m, Ar(2,6)*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 53.8, 61.6, 67.1, 126.1, 126.4, 127.7, 128.7, 133.5, 136.9. Data consistent with literature.[84]

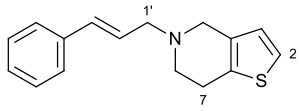
tert-Butyl 4-cinnamylpiperazine-1-carboxylate[85]† 241



Following general procedure **F**, the reaction of cinnamyl bromide (1.00 g, 5.1 mmol, 1.0 equiv.) in THF (10 mL) with 1-Boc-piperazine (2.36 g, 12.7 mmol, 2.5 equiv.) in THF (5 mL) gave the title compound (1.47 g, 4.86 mmol, 96%, >96:4 *E/Z* by ^{1}H NMR) as a white solid after purification by flash chromatography on silica gel (3:1→1:1 PE/EtOAc).

mp 58-60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.46 (9H, s, C(CH_3)$_3$), 2.42-2.47 (4H, m, C(3,5)H_2), 3.16 (2H, dd, *J* 6.8, 1.3, C(1')*H*), 3.42-3.48 (4H, m, C(2,6)H_2), 6.26 (1H, dt, *J* 15.9, 6.8, C(2')*H*), 6.52 (1H, dt, *J* 15.9, 1.3, C(3')*H*), 7.20-7.25 (1H, m, Ar(4)*H*), 7.28-7.34 (2H, m, Ar(3,5)*H*), 7.35-7.39 (2H, m, Ar(2,6)*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 28.6, 43.6, 53.1, 61.3, 79.8, 126.3, 126.5, 127.7, 128.7, 133.5, 136.9, 154.9. Data consistent with literature.[85]

5-Cinnamyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine† 242

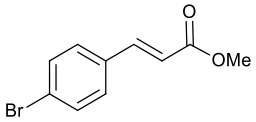


To a stirred solution of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride (1.0 g, 5.69 mmol, 1.2 equiv.) in water (10 mL) at 0 °C was added a solution of NaOH (209 mg, 5.22 mmol, 1.1 equiv.) in water (10 mL). The resulting solution was stirred for 10 min at rt, and to it added THF (5 mL) and Et_3N (1.39 mL, 9.95 mmol, 2.1 equiv.). A solution of cinnamyl bromide (934 mg, 4.74 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise *via* dropping funnel over *ca*. 10 min. The funnel was rinsed with THF (2 mL), the reaction stirred for a further 10 min, and quenched with aq. 1 M NaOH (10 mL). The reaction was diluted with Et_2O (20 mL), the layers separated, and the aqueous layer extracted with Et_2O (2 × 20 mL). The combined organics were washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by flash chromatography on silica gel (9:1→2:1 PE/EtOAc) to the title compound as a viscous orange oil (925 mg, 76%, >98:2 *E/Z* by ^{1}H NMR).

† Synthesised and characterised by Dr David S. B. Daniels

ν_{max} (film, cm^{-1}): 2905, 2772, 1597, 1495, 1449, 1356, 1329, 1167, 1107, 1013, 966, 903; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.85-2.97 (4H, m, C(6 and 7)H_2), 3.38 (2H, dd, *J* 6.7, 1.3, C(1')H_2), 3.63 (2H, t, *J* 1.6, C(4)H_2), 6.36 (1H, dt, *J* 15.9, 6.7, C(2')*H*), 6.60 (1H, dt, *J* 15.9, 1.3, C(3')*H*), 6.73 (1H, d, *J* 5.1, C(3)*H*), 7.08 (1H, d, *J* 5.1, C(2)*H*), 7.22-7.27 (1H, m, Ar(4)*H*), 7.30-7.36 (2H, m, Ar(3,5)*H*), 7.39-7.43 (2H, m, Ar(2,6)*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 25.6, 50.8, 53.2, 60.3, 122.9, 125.4, 126.5, 126.9, 127.7, 128.7, 133.2, 133.5, 133.8, 137.0; HRMS (NSI^+): $C_{16}H_{18}NS$ $[M+H]^+$ found 256.1156, requires 256.1154 (+0.6 ppm).

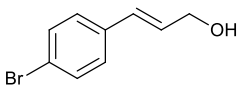
(*E*)-Methyl 3-(4-bromophenyl)acrylate[86] 462



Following the procedure of Jørgenson and co-workers,[87] (*E*)-3-(4-bromophenyl)acrylic acid (10.0 g, 44.1 mmol, 1.0 equiv.) was suspended in anhydrous methanol (100 mL) and cooled to 0 °C. The suspension was treated with thionyl chloride (4.8 mL, 66.1 mmol, 1.5 equiv.) dropwise, and heated to reflux for 2 h. The reaction was allowed to cool to rt and concentrated *in vacuo* to give the title compound (9.58 g, 90%) as a white crystalline solid that was used without further purification.

mp 86-88 °C, {Lit. 88 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.80 (3H, s, OCH_3), 6.42 (1H, d, *J* 16.0, C(2)*H*), 7.38 (2H, d, *J* 8.2, ArC(2,6)*H*), 7.51 (2H, d, *J* 8.2, ArC(3,5)*H*), 7.62 (1H, d, *J* 16.0, C(3)*H*). Data consistent with literature.[86]

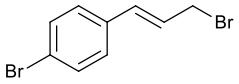
(*E*)-3-(4-Bromophenyl)prop-2-en-1-ol[88] 463



Following general procedure **C**, the reaction of (*E*)-methyl 3-(4-bromophenyl)acrylate **462** (3.00 g, 12.5 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (60 mL) with DIBAL-H (1.0 M in hexane, 22.8 mL, 27.4 mmol, 2.2 equiv.) gave the title compound (2.60 g, 98%) as a white solid that was used without further purification.

mp 65-67 °C {Lit. 63-65 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.59 (1H, br s, O*H*), 4.32 (2H, d, *J* 5.6, C(1)*H*), 6.35 (1H, dt, *J* 15.9, 5.6, C(2)*H*), 6.56 (1H, d, *J* 15.9, C(3)*H*), 7.24 (2H, d, *J* 8.6, ArC(2,6)*H*), 7.44 (2H, d, *J* 8.6, ArC(3,5)*H*). Data consistent with literature.[88]

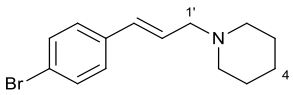
(*E*)-1-Bromo-4-(3-bromoprop-1-en-1-yl)benzene[89]† 464



Following general procedure **D**, the reaction of (*E*)-3-(4-bromophenyl)prop-2-en-1-ol **463** (2.60 g, 12.1 mmol, 1.0 equiv.) in anhydrous Et_2O (36 mL) with PBr_3 (0.46 mL, 4.85 mmol, 0.4 equiv.) gave the title compound (3.00 g, 90%) as an off-white solid that was used without further purification.

mp 70-73 °C {Lit. 72-76 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.14 (2H, d, *J* 7.8, C(3)*H*), 6.39 (1H, dt, *J* 15.5, 7.8, C(2)*H*), 6.58 (1H, d, *J* 15.5, C(1)*H*), 7.25 (2H, d, *J* 8.5, ArC(2,6)*H*), 7.45 (2H, d, *J* 8.5, ArC(3,5)*H*). Data consistent with literature.[89]

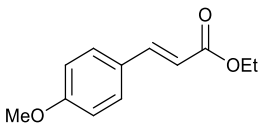
(*E*)-1-(3-(4-Bromophenyl)allyl)piperidine† 243



Following general procedure **F**, the reaction of (*E*)-1-bromo-4-(3-bromoprop-1-en-1-yl)benzene **464** (1.00 g, 3.62 mmol, 1.0 equiv.) in THF (7 mL) with piperidine (0.89 mL, 9.06 mmol, 2.5 equiv.) in THF (4 mL) gave the title compound (910 mg, 90%, >98:2 *E/Z* by ^{1}H NMR) as a colourless oil after purification by flash chromatography on silica gel (2:1 PE/EtOAc→EtOAc).

ν_{max} (film, cm^{-1}): 2932, 2795, 2752, 1487, 1344, 1153, 1109, 1072, 1040, 1009, 966; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.40-1.49 (2H, m, C(4)H_2), 1.56-1.65 (4H, m, C(3,5)H_2), 2.37-2.47 (4H, m, C(2,6)H_2), 3.10 (2H, dd, *J* 6.6, 1.1, C(1')*H*), 6.29 (1H, dt, *J* 15.8, 6.6, C(2')*H*), 6.43 (1H, dd, *J* 15.8, 1.1, C(3')*H*), 7.22 (2H, d, *J* 8.5, ArC(2,6)*H*), 7.41 (2H, d, *J* 8.5, ArC(3,5)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 24.4, 26.1, 54.8, 61.9, 121.2, 127.9, 128.3, 131.5, 131.7, 136.2; HRMS (ESI$^+$): $C_{14}H_{19}N^{79}Br$ $[M+H]^+$ found 280.0691, requires 280.0695 (−1.6 ppm).

(*E*)-Ethyl 3-(4-methoxyphenyl)acrylate[90]† 465

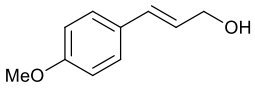


Following general procedure **A**, the reaction of *p*-anisaldehyde (2.0 g, 14.7 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) with the phosphorane (5.37 g, 15.4 mmol, 1.05 equiv.) gave the title compound (2.91 g, 96%) as a white solid after purification by flash chromatography on silica gel (19:1→4:1 PE/Et_2O).

† Synthesised and characterised by Dr David S. B. Daniels

mp 47-48 °C {lit. 47-49 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.33 (3H, t, *J* 7.1, OCH_2CH_3), 3.84 (3H, s, OCH_3), 4.25 (2H, q, *J* 7.1, OCH_2CH_3), 6.31 (1H, d, *J* 16.0, C(2)*H*), 6.90 (2H, d, *J* 8.9, ArC(3)*H*), 7.48 (2H, d, *J* 8.9, ArC(2)*H*), 7.64 (1H, d, *J* 16.0, C(3)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 14.5, 55.5, 60.5, 114.5, 115.9, 127.4, 129.8, 144.4, 161.5, 167.5. Data consistent with literature.[90]

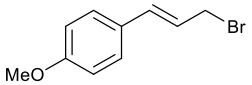
(*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol[91]† 466



Following general procedure **C**, the reaction of (*E*)-ethyl 3-(4-methoxyphenyl)acrylate (1.0 g, 4.85 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (25 ml) with DIBAL-H (1.2 M in toluene, 8.89 mL, 10.67 mmol, 2.2 equiv.) gave the title compound (790 mg, 4.81 mmol, 99%) as a white solid that was used without further purification.

mp 77-78 °C {lit. 78-80 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.43 (1H, br s, O*H*), 3.81 (3H, s, OCH_3), 4.28-4.32 (2H, m, C(1)H_2), 6.56 (1H, d, *J* 15.9, C(3)*H*), 6.24 (1H, dt, *J* 15.9, 5.9, C(2)*H*), 6.86 (2H, d, *J* 8.5, ArC(3)*H*), 7.33 (2H, d, *J* 8.5, ArC(2)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 55.4, 64.1, 114.2, 126.4, 127.8, 129.6 131.1, 159.5. Data consistent with literature.[91]

(*E*)-1-(3-Bromoprop-1-en-1-yl)-4-methoxybenzene[92]† 467

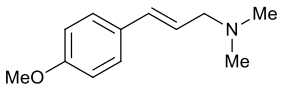


Following general procedure **D** with slight modification, the reaction of (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol **466** (1.0 g, 6.09 mmol, 1.0 equiv.) in anhydrous Et_2O (18 mL) with PBr_3 (0.24 mL, 2.44 mmol, 0.4 equiv.), with CH_2Cl_2 replacing Et_2O in the work up, gave the title compound (890 mg, 60%) as a white solid that was used without further purification.

mp 76-78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.82 (3H, s, OCH_3), 4.17 (2H, dd, *J* 7.9, 1.0, C(3)*H*), 6.27 (1H, dt, *J* 15.6, 7.9, C(2)*H*), 6.60 (1H, dt, *J* 7.9, 1.0, C(1)*H*), 6.86 (2H, d, *J* 8.7, ArC(3)*H*), 7.33 (2H, d, *J* 8.7, ArC(2)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 34.4, 55.5, 114.2, 123.1, 128.2, 128.7, 134.4, 160.0. Data consistent with literature.[92]

† Synthesised and characterised by Dr David S. B. Daniels

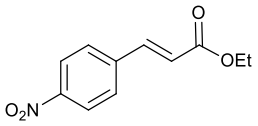
(*E*)-3-(4-Methoxyphenyl)-*N*,*N*-dimethylprop-2-en-1-amine[93]† 245



Following general procedure **E**, the reaction of (*E*)-1-(3-bromoprop-1-en-1-yl)-4-methoxybenzene **467** (880 mg, 3.87 mmol, 1.0 equiv.) in THF (8 mL) with dimethylamine (2.46 mL, 19.4 mmol, 5.0 equiv.) gave the title compound (170 mg, 0.89 mmol, 23%) as a colourless oil after purification by flash chromatography on silica gel (CH_2Cl_2→1:9 MeOH/CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.27 (6H, s, N(C*H*$_3$)$_2$), 3.05 (2H, dd, *J* 6.6, 1.3, C(1)*H*), 3.80 (3H, s, OC*H*$_3$), 6.12 (1H, dt, *J* 15.8, 6.6, C(2)*H*), 6.45 (1H, dt, *J* 15.8, 1.3, C(3)*H*), 6.85 (2H, d, *J* 8.7, ArC(3)*H*), 7.31 (2H, d, *J* 8.7, ArC(2)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 45.4, 55.4, 62.3, 114.1, 125.4, 127.6, 130.0, 132.1, 159.2. Data consistent with literature.[93]

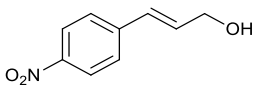
(*E*)-Ethyl 3-(4-nitrophenyl)acrylate[94]† 468



Following general procedure **A** with slight modification, the reaction of 4-nitrobenzaldehyde (2.0 g, 13.23 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (20 mL) with the phosphorane (4.84 g, 13.90 mmol, 1.05 equiv.) gave the title compound (2.47 g, 11.17 mmol, 84%) as a yellow crystalline solid after recrystallisation of the crude residue from hot EtOH.

mp 129-131 °C {Lit. 130-132 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.35 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 4.29 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 6.56 (1H, d, *J* 16.1, C(2)*H*), 7.67 (2H, d, *J* 8.7, ArC(2)*H*), 7.71 (1H, d, *J* 16.1, C(3)*H*), 8.25 (2H, d, *J* 8.7, ArC(3)*H*). Data consistent with literature.[94]

(*E*)-3-(4-Nitrophenyl)prop-2-en-1-ol[92]† 469

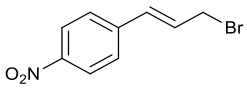


Following general procedure **C**, the reaction of (*E*)-ethyl 3-(4-nitrophenyl)acrylate **468** (2.0 g, 9.04 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (45 mL) with DIBAL-H (1.2 M in toluene, 16.6 mL, 19.89 mmol, 2.2 equiv.) gave the title compound (1.53 g, 94%) as a yellow solid that was used without further purification.

† Synthesised and characterised by Dr David S. B. Daniels

mp 106-107 °C {Lit.[15] 107 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.55 (1H, t, *J* 5.8, O*H*), 4.41 (2H, ddd, *J* 5.8, 5.0, 1.7, C(1)*H*), 6.54 (1H, dt, *J* 16.0, 5.0, C(2)*H*), 6.72 (1H, dt, *J* 16.0, 1.7, C(3)*H*), 7.52 (2H, d, *J* 8.7, ArC(2)*H*), 8.19 (2H, d, *J* 8.7, ArC(3)*H*). Data consistent with literature.[92]

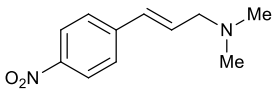
(*E*)-1-(3-Bromoprop-1-en-1-yl)-4-nitrobenzene[95]† 470



Following general procedure **D** with slight modification, the reaction of (*E*)-3-(4-nitrophenyl)prop-2-en-1-ol **469** (1.25 g, 6.98 mmol, 1.0 equiv.) in anhydrous Et_2O (20 mL) with PBr_3 (0.26 mL, 2.79 mmol, 0.4 equiv.), with CH_2Cl_2 replacing Et_2O in the work up, gave the title compound (1.06 g, 63%) as an orange solid that was used without further purification.

mp 55-56 °C {Lit.[19] 58-62 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.16 (2H, dd, *J* 7.4, 0.8, C(3)*H*), 6.56 (1H, dt, *J* 15.6, 7.4, C(2)*H*), 6.71 (1H, dt, *J* 15.6, 0.8, C(1)*H*), 7.52 (2H, d, *J* 8.8, ArC(2)*H*), 8.20 (2H, d, *J* 8.8, ArC(3)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 32.0, 124.2, 127.4, 130.0, 132.2, 142.3, 147.5. Data consistent with literature.[95]

(*E*)-*N*,*N*-Dimethyl-3-(4-nitrophenyl)prop-2-en-1-amine† 249

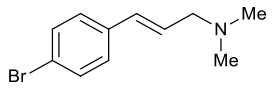


Following general procedure **E**, the reaction of (*E*)-1-(3-bromoprop-1-en-1-yl)-4-nitrobenzene **470** (1.05 g, 4.34 mmol, 1.0 equiv.) in THF (9 mL) with dimethylamine (2.74 mL, 21.7 mmol, 5.0 equiv.) gave the title compound (830 mg, 93%, >98:2 *E/Z* by ^{1}H NMR) as an orange oil that was used without further purification.

ν_{max} (film, cm^{-1}): 2941, 2768, 1595, 1512, 1454, 1337, 1107, 1022, 974, 851; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.29 (6H, s, N(C*H*$_3$)$_2$), 3.12 (2H, dd, *J* 6.3, 1.2, C(1)*H*), 6.45 (1H, dt, *J* 15.9, 6.3, C(2)*H*), 6.59 (1H, dt, *J* 15.9, 1.2, C(3)*H*), 7.49 (2H, d, *J* 8.8, ArC(2)*H*), 8.17 (2H, d, *J* 8.8, ArC(3)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 45.6, 62.0, 124.2, 126.9, 130.4, 133.1, 143.7, 147.0. HRMS (NSI$^+$): $C_{11}H_{15}N_2O_2$ $[M+H]^+$ found 207.1127, requires 207.1128 (−0.5 ppm).

† Synthesised and characterised by Dr David S. B. Daniels

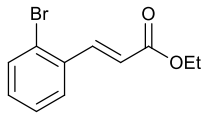
(*E*)-3-(4-Bromophenyl)-*N*,*N*-dimethylprop-2-en-1-amine[†] 244



Following general procedure **E**, the reaction of (*E*)-1-bromo-4-(3-bromoprop-1-en-1-yl)benzene **464** (500 mg, 1.81 mmol, 1.0 equiv.) in THF (4 mL) with dimethylamine (1.15 mL, 9.06 mmol, 5.0 equiv.) gave the title compound (403 mg, 93%, >98:2 *E/Z* by ^{1}H NMR) as a waxy yellow solid that was used without further purification.

mp <30 °C; ν_{max} (film, cm^{-1}): 2940, 2766, 1587, 1485, 1452, 1400, 1360, 1173, 1070, 1007, 968, 835; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.27 (6H, s, N(C*H*$_3$)$_2$), 3.06 (2H, dd, *J* 6.6, 1.2, C(1)*H*$_2$), 6.25 (1H, dt, *J* 15.9, 6.6, C(2)*H*), 6.45 (1H, d, *J* 15.9, C(3)*H*), 7.23 (2H, d, *J* 8.3, ArC(2,6)*H*), 7.42 (2H, d, *J* 8.3, ArC(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 45.5, 62.1, 121.3, 128.0, 128.5, 131.5, 131.8, 136.1; HRMS (ESI$^+$): $C_{11}H_{15}N^{79}Br$ [M+H]$^+$ found 240.0378, requires 240.0382 (−1.8 ppm).

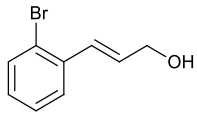
(*E*)-Ethyl 3-(2-bromophenyl)acrylate[96][†] 471



Following general procedure **B**, the reaction of (*E*)-3-(2-bromophenyl)acrylic acid (2.85 g, 12.55 mmol, 1.0 equiv.) with conc. H_2SO_4 (0.30 mL) in EtOH (30 mL) gave the title compound (3.04 g, 95%) as a colourless oil that was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.35 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 4.28 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 6.38 (1H, d, *J* 16.0, C(2)*H*), 7.22 (1H, t, *J* 7.7, ArC*H*), 7.32 (1H, t, *J* 7.7, ArC*H*), 7.57-7.63 (2H, m, ArC*H*), 8.04 (1H, d, *J* 16.0, C(3)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 14.4, 60.8, 121.3, 124.5, 127.8, 127.9, 131.3, 133.6, 134.7, 143.0, 166.5. Data consistent with literature.[96]

(*E*)-3-(2-Bromophenyl)prop-2-en-1-ol[97][†] 472



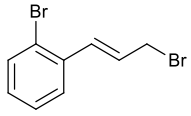
Following general procedure **C**, the reaction of (*E*)-ethyl 3-(2-bromophenyl)acrylate **471** (3.00 g, 11.76 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (60 mL) with DIBAL-H (1.2 M in toluene, 21.6 mL, 25.87

[†] Synthesised and characterised by Dr David S. B. Daniels

mmol, 2.2 equiv.) gave the title compound (2.37 g, 95%) as a colourless oil that was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.68 (1H, br s, O*H*), 4.36 (2H, dd, *J* 5.6, 1.7, C(1)H_2), 6.31 (1H, dt, *J* 15.8, 5.6, C(2)*H*), 6.96 (1H, dt, *J* 15.8, 1.7, C(3)*H*), 7.10 (1H, td, *J* 7.7, 1.7, ArC*H*), 7.27 (1H, *J* 7.8, 1.3, 0.6, ArC*H*), 7.49-7.57 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 63.7, 123.8, 127.3, 127.6, 129.1, 129.9, 131.8, 133.1, 136.7. Data consistent with literature.[97]

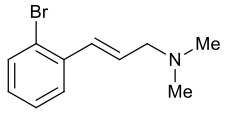
(*E*)-1-Bromo-2-(3-bromoprop-1-en-1-yl)benzene[89]† 473



Following general procedure **D**, the reaction of (*E*)-3-(2-bromophenyl)prop-2-en-1-ol **472** (1.0 g, 4.69 mmol, 1.0 equiv.) in anhydrous Et_2O (15 mL) with PBr_3 (0.18 mL, 1.88 mmol, 0.4 equiv.) gave the title compound (850 mg, 66%) as a pale yellow oil that was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.18 (2H, dd, *J* 7.7, 1.1, C(3)*H*), 6.35 (1H, dt, *J* 15.5, 7.8, C(2)*H*), 7.00 (1H, dt, *J* 15.5, 1.1, C(1)*H*), 7.13 (1H, td, *J* 7.7, 1.7, ArC*H*), 7.27-7.30 (1H, m, ArC*H*), 7.52-7.57 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 32.9, 124.0, 127.4, 127.7, 128.1, 129.7, 133.1, 133.2, 135.7. Data consistent with literature.[89]

(*E*)-3-(2-Bromophenyl)-*N*,*N*-dimethylprop-2-en-1-amine† 248

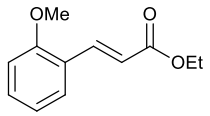


Following general procedure **E**, the reaction of (*E*)-1-bromo-2-(3-bromoprop-1-en-1-yl)benzene (830 mg, 3.01 mmol, 1.0 equiv.) in THF (6 mL) with dimethylamine (1.90 mL, 15.0 mmol, 5.0 equiv.) gave the title compound (616 mg, 85%, >98:2 *E/Z* by ^{1}H NMR) as a yellow oil that was used without further purification.

ν_{max} (film, cm^{-1}): 2940, 2768, 1464, 1452, 1435, 1360, 1172, 1042, 1020, 961, 868; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.30 (6H, s, N(CH_3)$_2$), 3.13 (2H, dd, *J* 6.7, 1.5, C(1)H_2), 6.20 (1H, dt, *J* 15.7, 6.7, C(2)*H*), 6.85 (1H, dt, *J* 15.7, 1.5, C(3)*H*), 7.07-7.11 (1H, m, ArC*H*), 7.24-7.28 (1H, m, ArC*H*), 7.51-7.55 (2H, m, ArC*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 45.4, 62.1, 123.6, 127.2, 127.6, 128.9, 130.6, 131.6, 133.0, 137.0; HRMS (ESI$^+$): $C_{11}H_{15}N^{79}Br$ $[M+H]^+$ found 240.0377, requires 240.0382 (−2.2 ppm).

† Synthesised and characterised by Dr David S. B. Daniels

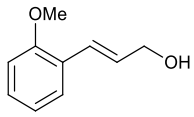
(*E*)-Ethyl 3-(2-methoxyphenyl)acrylate[98]† 474



Following general procedure **B**, the reaction of (*E*)-3-(2-methoxyphenyl)acrylic acid (2.50 g, 14.03 mmol, 1.0 equiv.) with conc. H_2SO_4 (0.25 mL) in EtOH (25 mL) gave the title compound (2.85 g, 98%) as a white solid that was used without further purification.

mp 31-32 °C {Lit. 35 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 7.1, OCH_2CH_3), 3.89 (3H, s, OCH_3), 4.26 (2H, q, *J* 7.1, OCH_2CH_3), 6.53 (1H, d, *J* 16.2, C(2)*H*), 6.89-6.99 (2H, m, ArC*H*), 7.35 (1H, ddd, *J* 8.2, 7.4, 1.7, ArC*H*), 7.48-7.53 (1H, m, ArC*H*), 7.99 (1H, d, *J* 16.2, C(3)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 14.5, 55.6, 60.5, 111.3, 119.0, 120.8, 123.6, 129.1, 131.5, 140.1, 158.5, 167.7. Data consistent with literature.[98]

(*E*)-3-(2-Methoxyphenyl)prop-2-en-1-ol[99]† 475

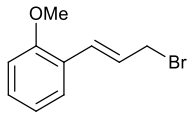


Following general procedure **C**, the reaction of (*E*)-ethyl 3-(2-methoxyphenyl)acrylate **474** (2.50 g, 12.12 mmol, 1.0 equiv.) with DIBAL-H (1.2 M in toluene, 22.2 mL, 26.67 mmol, 2.2 equiv.) in anhydrous CH_2Cl_2 (60 mL) gave the title compound (1.97 g, 12.00 mmol, 99%) as a white solid that was used without further purification.

mp 33-34 °C {Lit. 36-37 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.54 (1H, br s, O*H*), 3.85 (3H, s, OCH_3), 4.33 (2H, dd, *J* 6.1, 1.5, C(1)H_2), 6.39 (1H, dt, *J* 16.1, 6.1, C(2)*H*), 6.88 (1H, d, *J* 8.2, ArC*H*), 6.91-6.96 (2H, m, 1 × ArC*H* and C(3)*H*), 7.21-7.26 (1H, m, ArC*H*), 7.44 (1H, dd, *J* 7.7, 1.7, ArC*H*). Data consistent with literature.[99]

† Synthesised and characterised by Dr David S. B. Daniels

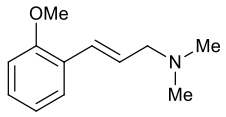
(*E*)-1-(3-Bromoprop-1-en-1-yl)-2-methoxybenzene[92]† 476



Following general procedure **D**, the reaction of (*E*)-3-(2-methoxyphenyl)prop-2-en-1-ol **475** (1.0 g, 6.09 mmol, 1.0 equiv.) in anhydrous Et_2O (18 mL) with PBr_3 (0.23 mL, 2.44 mmol, 0.4 equiv.) gave the title compound (1.29 g, 95%) as a yellow oil that was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.86 (3H, s, OC*H*$_3$), 4.19 (2H, dd, *J* 7.8, 1.0, C(3)*H*$_2$), 6.44 (1H, dt, *J* 15.7, 7.8, C(2)*H*), 6.88 (1H, dd, *J* 8.3, 1.1, ArC*H*), 6.94 (1H, tdd, *J* 7.5, 1.0, 0.5, ArC*H*), 6.98 (1H, dt, *J* 15.7, 1.0, C(1)*H*), 7.26 (1H, ddd, *J* 8.2, 7.4, 1.7, ArC*H*), 7.44 (1H, dd, *J* 7.7, 1.7, ArC*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 34.6, 55.6, 111.0, 120.8, 124.8, 125.9, 127.4, 129.6, 129.7, 157.1. Data consistent with literature.[92]

(*E*)-3-(2-Methoxyphenyl)-*N*,*N*-dimethylprop-2-en-1-amine† 247

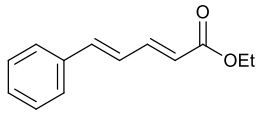


Following general procedure **E**, the reaction of (*E*)-1-(3-bromoprop-1-en-1-yl)-2-methoxybenzene **476** (1.28 g, 5.64 mmol, 1.0 equiv.) in THF (11 mL) with dimethylamine (3.57 mL, 28.2 mmol, 5.0 equiv.) gave the title compound (910 mg, 84%, >98:2 *E*/*Z* by ^{1}H NMR) as a yellow oil that was used without further purification.

ν_{max} (film, cm^{-1}): 2940, 2770, 1597, 1580, 1489, 1462, 1437, 1360, 1288, 1238, 1175, 1111, 1028, 974; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.28 (6H, s, N(C*H*$_3$)$_2$), 3.09 (2H, dd, *J* 6.8, 1.4, C(1)*H*$_2$), 3.84 (3H, s, OC*H*$_3$), 6.28 (1H, dt, *J* 16.0, 6.8, C(2)*H*), 6.83 (1H, dt, *J* 16.0, 1.4, C(3)*H*), 6.86 (1H, d, *J* 8.0, ArC*H*), 6.92 (1H, tdd, *J* 7.5, 1.1, 0.5, ArC*H*), 7.21 (1H, ddd, *J* 8.0, 7.4, 1.7, ArC*H*), 7.45 (1H, dd, *J* 7.6, 1.7, ArC*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 45.4, 55.6, 62.7, 111.0, 120.8, 126.2, 126.9, 127.3, 128.3, 128.5, 156.7; HRMS (NSI$^+$): $C_{12}H_{18}NO$ $[M+H]^+$ found 192.1378, requires 192.1383 (−2.6 ppm).

† Synthesised and characterised by Dr David S. B. Daniels

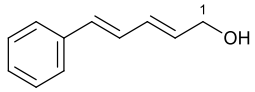
(2*E*,4*E*)-Ethyl 5-phenylpenta-2,4-dienoate[100]† 477



Following general procedure **A**, the reaction of (*E*)-cinnamaldehyde (2.0 g, 15.13 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) with the phosphorane (5.54 g, 15.89 mmol, 1.05 equiv.) gave the title compound (2.52 g, 82%) as a colourless oil after purification by flash chromatography on silica gel (19:1→4:1 PE/Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.32 (3H, t, *J* 7.1, OCH_2CH_3), 4.23 (2H, q, *J* 7.1, OCH_2CH_3), 5.99 (1H, d, *J* 15.3, C(2)*H*), 6.82-6.94 (2H, m, C(4 and 5)*H*), 7.27-7.49 (6H, m, Ar*H* and C(3)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 14.5, 60.5, 121.5, 126.4, 127.3, 128.9, 129.2, 136.2, 140.5, 144.7, 167.2. Data consistent with literature.[100]

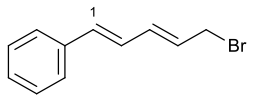
(2*E*,4*E*)-5-Phenylpenta-2,4-dien-1-ol[101]† 478



Following general procedure **C**, the reaction of (2*E*,4*E*)-ethyl 5-phenylpenta-2,4-dienoate **477** (1.50 g, 7.41 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (40 mL) with DIBAL-H (1.2 M in toluene, 13.6 mL, 16.3 mmol, 2.2 equiv.) gave the title compound (1.19 g, 7.40 mmol, 99%) as an off-white solid that was used without further purification.

mp 74-76 °C {Lit. 76-77 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.46 (1H, br s, O*H*), 4.23-4.29 (2H, m, C(1)H_2), 5.97 (1H, dt, *J* 15.2, 5.9, C(2)*H*), 6.43 (1H, ddt, *J* 15.2, 10.4, 1.5, C(3)*H*), 6.56 (1H, d, *J* 15.6, C(5)*H*), 6.80 (1H, dd, *J* 15.6, 10.4, C(4)*H*), 7.23 (1H, t, *J* 7.2, ArC(4)*H*), 7.32 (2H, t, *J* 7.2, ArC(3,5)*H*), 7.38-7.42 (2H, m, ArC(2,6)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 63.6, 126.5, 127.8, 128.3, 128.8, 131.8, 132.6, 132.9, 137.3. Data consistent with literature.[101]

((1*E*,3*E*)-5-Bromopenta-1,3-dien-1-yl)benzene[102]† 479



Following general procedure **D**, the reaction of (2*E*,4*E*)-5-phenylpenta-2,4-dien-1-ol **478** (1.2 g, 7.49 mmol, 1.0 equiv.) in anhydrous Et_2O (25 mL) with PBr_3 (0.28 mL, 2.99 mmol, 0.4 equiv.) gave the title compound as an off-white solid (1.46 g, 6.54 mmol, 87%) that was used without further purification.

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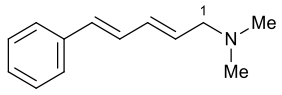
mp 58-59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.11 (2H, dd, *J* 8.0, 0.9, C(5)*H*), 6.00 (1H, dtt, *J* 14.9, 8.0, 0.7, C(4)*H*), 6.46 (1H, ddt, *J* 14.9, 10.4, 0.9, C(3)*H*), 6.60 (1H, d, *J* 15.7, C(1)H_2), 6.77 (1H, ddd, *J* 15.7, 10.4, 0.7, C(2)*H*), 7.22-7.28 (1H, m, Ar(4)*H*), 7.30-7.36 (2H, m, Ar(3)*H*), 7.38-7.42 (2H, m, Ar(2)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 33.6, 126.7, 127.4, 128.2, 128.8, 129.1, 134.6, 135.3, 138.9. Data consistent with literature.[102]

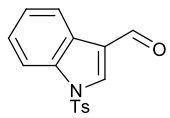
(2*E*,4*E*)-*N*,*N*-Dimethyl-5-phenylpenta-2,4-dien-1-amine[81]† 251



Following general procedure **E**, the reaction of ((1*E*,3*E*)-5-bromopenta-1,3-dien-1-yl)benzene **479** (1.20 g, 5.38 mmol, 1.0 equiv.) in THF (11 mL) with dimethylamine (3.41 mL, 9.06 mmol, 5.0 equiv.) gave the title compound (760 mg, 75%, >98:2 *E,E/other isomers* by ^{1}H NMR) as a yellow oil after purification by flash chromatography on silica gel (CH_2Cl_2→1:9 MeOH/CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.25 (6H, s, N(CH_3)$_2$), 3.01 (2H, dd, *J* 6.8, 0.7, C(1)H_2), 5.84 (1H, dtt, *J* 15.2, 6.8, 0.7, C(2)*H*), 6.33 (1H, ddtd, *J* 15.2, 10.4, 1.4, 0.7, C(3)*H*), 6.51 (1H, d, *J* 15.8, C(5)*H*), 6.79 (1H, ddd, *J* 15.8, 10.4, 0.8, C(4)*H*), 7.21 (1H, t, *J* 7.0, Ar(4)*H*), 7.28-7.34 (2H, m, Ar(3)*H*), 7.37-7.41 (2H, m, Ar(2)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 45.5, 62.0, 126.4, 127.6, 128.7, 128.8, 131.9, 132.0, 133.2, 137.4. Data consistent with literature.[81]

1-Tosyl-1*H*-indole-3-carbaldehyde[103] 480



1*H*-Indole-3-carbaldehyde (2.5 g, 17.2 mmol, 1.0 equiv.) was suspended in CH_2Cl_2 (34 mL) and cooled to 0 °C, Et_3N (4.8 mL, 34.4 mmol, 2.0 equiv.) was then added and the resulting solution stirred for 10 min. 4-toluenesulfonyl chloride (3.6 g, 19.0 mmol, 1.1 equiv.) was added and the reaction mixture stirred at rt for 16 h. The reaction mixture was washed with 10% aq critic acid (20 mL), sat $NaHCO_3$ (20 mL) and brine (20 mL), then dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound (5.1 g, 99%) as a purple solid that was used without further purification.

mp 138-139 °C {Lit.142 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.37 (3H, s, TsCH_3), 7.29 (2H, d, *J* 8.2, TsAr(3,5)*H*), 7.33-7.45 (2H, m, IndAr*H*), 7.85 (2H, d, *J* 8.2, TsArC(2,6)*H*), 7.95 (1H, dd, *J* 7.2, 1.2,

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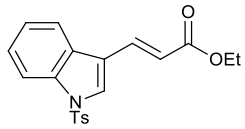
IndAr*H*), 8.21-8.28 (2H, m, IndAr*H* and C(2)*H*), 10.09 (1H, s, C*H*O). Data in consistent with literature.[103]

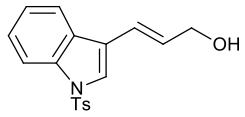
(*E*)-Ethyl 3-(1-tosyl-1*H*-indol-3-yl)acrylate[104] 481



Following general procedure **A**, the reaction of 1-tosyl-1*H*-indole-3-carbaldehyde **480** (2.5 g, 8.36 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) with the phosphorane (3.06 g, 8.78 mmol, 1.05 equiv.) gave the title compound (2.61 g, 85%) as a white solid after purification by flash chromatography on silica gel (1:4 Et_2O/PE).

mp 136-138 °C {Lit. 144-146 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 7.1, OCH_2CH_3), 2.33 (3H, s, $TsCH_3$), 4.28 (2H, q, *J* 7.1, OCH_2CH_3), 6.52 (1H, d, *J* 16.1, C(2)*H*), 7.24 (2H, d, *J* 8.1, TsArC(3,5)*H*), 7.27-7.42 (2H, m, IndArC*H*), 7.70-7.89 (5H, m, 2 × IndArC*H*, 2 × TsArC(2,6)*H* and C(3)*H*), 8.00 (1H, d, *J* 7.7, IndArC(4)*H*). Data consistent with literature.[104]

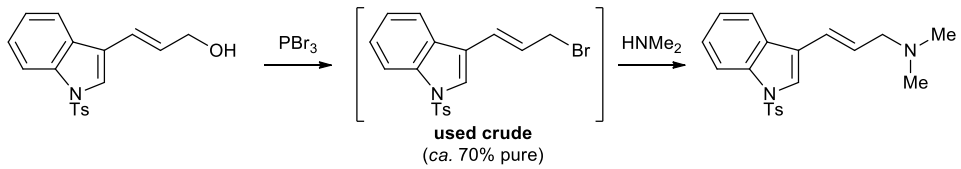
(*E*)-3-(1-Tosyl-1*H*-indol-3-yl)prop-2-en-1-ol[105] 482



Following general procedure **C**, the reaction of (*E*)-ethyl 3-(1-tosyl-1*H*-indol-3-yl)acrylate **481** (2.60 g, 7.05 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) with DIBAL-H (1.2 M in toluene, 12.9 mL, 15.5 mmol, 2.2 equiv.) gave the title compound (2.11 g, 91%) as a white solid that was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.30 (3H, s, $TsCH_3$), 4.34 (2H, t, *J* 5.5, C(1)H_2), 6.43 (1H, dt, *J* 16.0, 5.5, C(2)*H*), 6.67 (1H, d, *J* 16.0, C(3)*H*), 7.14-7.38 (4H, m, 2 × TsArC(3,5)*H* and 2 × IndArC*H*), 7.58 (1H, s, IndArC(2)*H*), 7.70-7.76 (3H, m, 2 × TsArC(2,6)*H* and 1 × IndArC*H*), 7.99 (1H, d, *J* 8.1, IndArC(4)*H*). Data consistent with literature.[105]

(*E*)-*N*,*N*-Dimethyl-3-(1-tosyl-1*H*-indol-3-yl)prop-2-en-1-amine 252

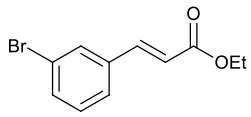


Following general procedure **D**, the reaction of (*E*)-3-(1-tosyl-1*H*-indol-3-yl)prop-2-en-1-ol **482** (2.1 g, 6.42 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) with PBr_3 (0.24 mL, 2.57 mmol, 0.4 equiv.) gave the title compound as a waxy green solid that was used crude (*ca.* 70% pure by ^{1}H NMR) directly in the next step.

Following general procedure E, the reaction of the above crude material in THF (10 mL) with dimethylamine (2.92 mL, 23.1 mmol, 5.0 equiv.) gave the title compound (477 mg, 21%, *2 steps*, >95:5 *E/Z* by ^{1}H NMR) as a yellow oil after purification by flash chromatography on silica gel (1:9 MeOH/CH_2Cl_2).

ν_{max} (film, cm^{-1}): 2945, 1444, 1364, 1169, 1122, 1088, 978; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.31 (6H, s, N(C*H*$_3$)$_2$), 2.32 (3H, s, TsC*H*$_3$), 3.12 (2H, d, *J* 6.7, C(1)*H*$_2$), 6.34 (1H, dt, *J* 16.0, 6.7, C(2)*H*), 6.58 (1H, d, *J* 16.0, C(3)*H*), 7.20 (2H, d, *J* 7.6, TsArC(3,5)*H*), 7.25 (1H, t, *J* 7.7, IndArC(5)*H*), 7.32 (1H, t, *J* 7.7, IndArC(6)*H*), 7.56 (1H, s, IndArC(2)*H*), 7.74-7.77 (3H, m, IndArC(7)*H* and 2 × TsArC(2,6)*H*), 7.99 (1H, d, *J* 8.3, IndArC(4)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 21.7 (Ar*C*H$_3$), 45.3 (N(C*H*$_3$)$_2$), 62.6 (*C*(1)H$_2$), 113.8 (Ind. *C*(4)H), 120.3 (Ind. *C*(3)), 120.6 (Ind. *C*(7)H), 123.6 (*C*(3)H), 123.6 (Ind. *C*(5)H), 124.0 (Ind. *C*(2)H), 125.0 (Ind. *C*(6)H), 127.0 (Ts-Ar*C*(2,6)H), 128.6 (Ind. *C*(9)), 129.1 (*C*(2)H), 130.2 (Ts-Ar*C*(3,5)H), 135.2 (Ts-Ar*C*(1)), 135.6 (Ind. *C*(8)), 145.1 (Ts-Ar*C*(4)); HRMS (CI^+): $C_{20}H_{22}N_2O_2S^+$ $[M]^+$ found 354.1415, requires 354.1402 (+3.7 ppm).

(*E*)-Ethyl 3-(3-bromophenyl)acrylate[106]† 483

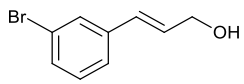


Following general procedure **A**, the reaction of 3-bromobenzaldehyde (2.0 g, 10.81 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) with the phosphorane (3.95 g, 11.35 mmol, 1.05 equiv.) gave the title compound (2.44 g, 88%, 96:4 *E/Z* by ^{1}H NMR) as a colourless oil after purification by flash chromatography on silica gel (24:1→9:1 PE/Et_2O).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 4.27 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 6.43 (1H, d, *J* 16.0, C(2)*H*), 7.25 (1H, t, *J* 7.8, ArC*H*), 7.43 (1H, ddd, *J* 7.8, 2.0, 1.2, ArC*H*), 7.50 (1H, ddd, *J* 7.8, 2.0, 1.0, ArC*H*), 7.60 (1H, d, *J* 16.0, C(3)*H*), 7.65-7.67 (1H, m, ArC*H*). Data consistent with literature.[106]

(*E*)-3-(3-Bromophenyl)prop-2-en-1-ol[97]† 484

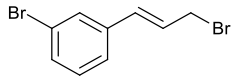
† Synthesised and characterised by Dr David S. B. Daniels



Following general procedure **C**, the reaction of (*E*)-ethyl 3-(3-bromophenyl)acrylate **483** (1.5 g, 5.88 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (30 mL) with DIBAL-H (1.2 M in toluene, 10.8 mL, 12.9 mmol, 2.2 equiv.) gave the title compound (1.22 g, 5.72 mmol, 97%) as a colourless oil that was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.62 (1H, t, *J* 5.8, O*H*), 4.33-4.39 (2H, m, C(1)H_2), 6.39 (1H, dt, *J* 15.9, 5.4, C(2)*H*), 6.58 (1H, dt, *J* 15.9, 1.5, C(3)*H*), 7.21 (1H, t, *J* 7.8, ArC*H*), 7.30-7.34 (1H, m, ArC*H*), 7.39 (1H, ddd, *J* 7.8, 2.0, 1.2, ArC*H*), 7.56 (1H, t, *J* 1.8, ArC*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 63.5, 122.9, 125.2, 129.5, 129.5, 130.2, 130.2, 130.6, 139.0. Data consistent with literature.[97]

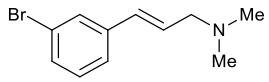
(*E*)-1-Bromo-3-(3-bromoprop-1-en-1-yl)benzene† 485



Following general procedure **D**, the reaction of (*E*)-3-(3-bromophenyl)prop-2-en-1-ol **484** (1.10 g, 5.16 mmol, 1.0 equiv.) in anhydrous Et_2O (15 mL) with PBr_3 (0.19 mL, 2.07 mmol, 0.4 equiv.) gave the title compound (1.15 g, 4.17 mmol, 81%) as an off-white solid that was used without further purification.

ν_{max} (film, cm^{-1}): 3034, 1591, 1560, 1472, 1422, 1202, 1072, 995, 961; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.14 (2H, dd, *J* 7.6, 0.9, C(3)H_2), 6.41 (1H, dt, *J* 15.6, 7.6, C(2)*H*), 6.57 (1H, dt, *J* 15.6, 0.9, C(1)*H*), 7.20 (1H, t, *J* 7.8, ArC*H*), 7.27-7.31 (1H, m, ArC*H*), 7.39 (1H, ddd, *J* 7.8, 2.0, 1.2, ArC*H*), 7.54 (1H, t, *J*, 1.8, ArC*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 32.8, 123.0, 125.5, 126.9, 129.7, 130.3, 131.3, 133.1, 138.1; HRMS (EI$^+$): $C_9H_8{}^{79}Br_2$ [M]$^+$ found 273.8997, requires 273.8998 (−0.5 ppm).

(*E*)-3-(3-Bromophenyl)-*N*,*N*-dimethylprop-2-en-1-amine† 246



Following general procedure **E**, the reaction of (*E*)-1-bromo-3-(3-bromoprop-1-en-1-yl)benzene **485** (1.15 g, 4.17 mmol, 1.0 equiv.) in THF (8 mL) with dimethylamine (2.64 mL, 20.8 mmol, 5.0 equiv.) gave the title compound (850 mg 85%, 96:4 *E*/*Z* by ^{1}H NMR) as a yellow oil that was used without further purification.

ν_{max} (film, cm^{-1}): 2941, 2768, 1589, 1560, 1468, 1452, 1358, 1240, 1172, 1070, 1042, 1020, 993, 961, 845; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.27 (6H, s, N(CH_3)$_2$), 3.06 (2H, dd, *J* 6.6, 1.0, C(1)H_2), 6.26 (1H,

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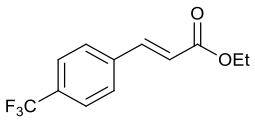
dt, *J* 15.9, 6.6, C(2)*H*), 6.44 (1H, dt, *J* 15.9, 1.0, C(3)*H*), 7.16 (1H, t, *J* 7.8, ArC*H*), 7.28 (1H, dd, *J* 7.8, 1.3, ArC*H*), 7.34 (1H, ddd, *J* 7.8, 2.0, 1.3, ArC*H*), 7.51 (1H, t, *J* 1.8, ArC*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 45.5, 62.0, 122.9, 125.0, 129.4, 129.4, 130.2, 130.4, 131.1, 139.4; HRMS (NSI^+): $C_{11}H_{15}{}^{79}BrN$ $[M+H]^+$ found 240.0382, requires 240.0382 (−0.2 ppm).

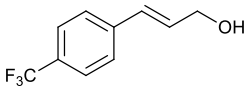
(*E*)-Ethyl 3-(4-(trifluoromethyl)phenyl)acrylate[94]† 486



Following general procedure **B**, the reaction of (*E*)-3-(4-(trifluoromethyl)phenyl)acrylic acid (2.50 g, 11.57 mmol, 1.0 equiv.) with conc. H_2SO_4 (0.25 mL) in EtOH (25 mL) gave the title compound (2.75 g, 97%) as a white solid that was used without further purification.

mp 33-35 °C {Lit.[17] 31-33 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 7.1, OCH_2CH_3), 4.28 (2H, q, *J* 7.1, OCH_2CH_3), 6.50 (1H, d, *J* 16.0, C(2)*H*), 7.60-7.65 (4H, m, ArC*H*), 7.69 (1H, d, *J* 16.0, C(3)*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 14.4, 61.0, 121.0, 124.0 (q, $^{1}J_{CF}$ 272), 126.0 (q, $^{3}J_{CF}$ 4), 128.3, 131.8 (q, $^{2}J_{CF}$ 33), 138.0, 142.8, 166.5; $^{19}F\{^{1}H\}$ NMR (282 MHz, $CDCl_3$) δ_F: −63.4. Data consistent with literature.[94]

(*E*)-3-(4-(Trifluoromethyl)phenyl)prop-2-en-1-ol[107]† 487

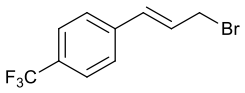


Following general procedure **C**, the reaction of (*E*)-ethyl 3-(4-(trifluoromethyl)phenyl)acrylate **486** (2.50.g, 10.23 mmol, 1.0 equiv.) and DIBAL-H (1.2 M in toluene, 18.8 mL, 22.52 mmol, 2.2 equiv.) in anhydrous CH_2Cl_2 (50 mL) gave the title compound (2.03 g, 98%) as a white solid that was used without further purification.

mp 48-49 °C {Lit. 53-55 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.83 (1H, br s, O*H*), 4.36 (2H, dd, *J* 5.3, 1.6, C(1)H_2), 6.45 (1H, dt, *J* 16.0, 5.3, C(2)*H*), 6.66 (1H, dt, *J* 16.0, 1.6, C(3)*H*), 7.46 (2H, d, *J* 8.2, ArC(2,6)*H*), 7.56 (2H, d, *J* 8.2, ArC(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 63.4, 124.3 (q, $^{1}J_{CF}$ 272), 125.7, (q, $^{3}J_{CF}$ 4), 126.7, 129.4, 129.6 (q, $^{2}J_{CF}$ 32), 131.4, 140.3; $^{19}F\{^{1}H\}$ NMR (282 MHz, $CDCl_3$) δ_F: −63.0. Data consistent with literature.[107]

† Synthesised and characterised by Dr David S. B. Daniels

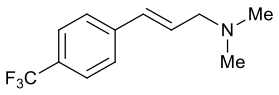
(*E*)-1-(3-Bromoprop-1-en-1-yl)-4-(trifluoromethyl)benzene[95]† 488



Following general procedure **D**, the reaction of (*E*)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol **487** (1.0 g, 4.95 mmol, 1.0 equiv.) in anhydrous Et_2O (15 mL) with PBr_3 (0.19 mL, 1.98 mmol, 0.4 equiv.) gave the title compound (910 mg, 69%) as a white solid that was used without further purification.

mp 29-30 °C {Lit. 35.9-36.8 °C}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.15 (2H, dd, *J* 7.6, 0.9, C(3)H_2), 6.48 (1H, dt, *J* 15.5, 7.6, C(2)*H*), 6.67 (1H, dt, *J* 15.5, 0.9, C(1)*H*), 7.48 (2H, d, *J* 8.3, ArC(2,6)*H*), 7.58 (2H, d, *J* 8.3, ArC(3,5)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 32.6, 124.2 (q, $^1J_{CF}$ 272), 125.8 (q, $^3J_{CF}$ 4), 127.0, 128.0, 130.2 (q, $^2J_{CF}$ 32), 131.4, 140.3; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ_F: −63.1. Data consistent with literature.[95]

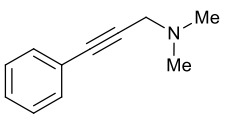
(*E*)-*N*,*N*-Dimethyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine† 250



Following general procedure **E**, the reaction of (*E*)-1-(3-bromoprop-1-en-1-yl)-4-(trifluoromethyl)benzene **488** (890 mg, 3.36 mmol, 1.0 equiv.) in THF (7 mL) with dimethylamine (2.13 mL, 16.8 mmol, 5.0 equiv.) gave the title compound (691 mg, 90%, >98:2 *E/Z* by ^{1}H NMR) as a pale yellow oil that was used without further purification.

ν_{max} (film, cm^{-1}): 2945, 2772, 1614, 1321, 1163, 1119, 1107, 1065, 1015, 972, 845; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.29 (6H, s, N(CH_3)$_2$), 3.10 (2H, dd, *J* 6.5, 1.6, C(1)H_2), 6.36 (1H, dt, *J* 15.9, 6.5, C(2)*H*), 6.55 (1H, dt, *J* 15.9, 1.6, C(3)*H*), 7.46 (2H, d, *J* 8.3, ArC(2,6)*H*), 7.56 (2H, d, *J* 8.3, ArC(3,5)*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 45.5, 62.0, 124.3 (q, $^1J_{CF}$ 272), 125.7 (q, $^3J_{CF}$ 4), 126.7, 129.4 (q, $^2J_{CF}$ 33), 130.5, 131.3, 140.7; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ_F: −63.0; HRMS (ESI$^+$): $C_{12}H_{15}NF_3$ [M+H]$^+$ found 2330.1145, requires 230.1151 (−2.7 ppm).

***N*,*N*-Dimethyl-3-phenylprop-2-yn-1-amine[108]† 489**



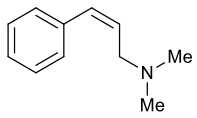
Following the procedure of Consorti *et al.*,[108] dimethylamine (40% wt. in water, 18.6 mL, 146.9 mmol, 1.5 equiv.) was added to a stirred solution of phenylacetylene (10.75 mL, 97.9 mmol, 1.0 equiv.),

† Synthesised and characterised by Dr David S. B. Daniels

paraformaldehyde (3.23 g, 107.7 mmol, 1.1 equiv.) and CuI (93 mg, 0.5 mol%) in 1,4-dioxane (50 mL). The reaction was heated to reflux for 4 h, cooled and the solvent removed *in vacuo*. The residue was diluted with water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by vacuum distillation to give the title compound as a colourless oil (8.40 g, 52.8 mmol, 54%).

bp 106-108 °C at 4 mmHg {Lit. 114 °C at 5 mmHg}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.37 (6H, s, N(C*H*$_3$)$_2$), 3.47 (2H, s, NC*H*$_2$), 7.28-7.32 (3H, m, Ar*H*), 7.42-7.46 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 44.4, 48.7, 84.7, 85.4, 123.4, 128.2, 128.4, 131.8. Data consistent with literature.[108]

(*Z*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine[109]† (*Z*)-283

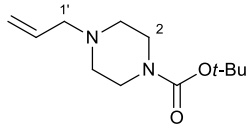


Following the procedure of Jemison *et al*.,[109] H_2 (balloon) was bubbled through a stirred suspension of *N*,*N*-dimethyl-3-phenylprop-2-yn-1-amine **489** (1.00 g, 6.28 mmol, 1.0 equiv.) and Lindlar's catalyst (5% wt. Pd/$CaCO_3$ poisoned with 3.5% Pb, 670 mg, 5 mol %) in EtOH (12.5 mL). Careful bubbling of hydrogen was maintained until full consumption of the starting material was indicated by analytical GC, so as to prevent over-reduction. The reaction mixture was passed through a plug of Celite® (EtOH eluent), and the solvent removed *in vacuo* to give the title compoun as a yellow oil (970 mg, 96%, 97:3 *Z/E* by GC) that was used without further purification.

GC: Column: Agilent DB-5 (30 m, 0.25 mm ID, 0.5 μm film). Method: (Injector 250 °C, FID 305 °C, linear velocity 40 cm/s (He), oven ramps (Initial 60 °C (2 min hold) → 300 °C (40 °C/min, 2 min hold)). t_R over-reduced product (6.32 min), **(*Z*)-283** (6.41 min), **(*E*)-212** (6.62 min), **489** (6.66 min).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.25 (6H, s, N(C*H*$_3$)$_2$), 3.21 (2H, dd, *J* 6.5, 2.0, C(1)*H*$_2$), 5.78 (1H, dt, *J* 11.8, 6.4, C(2)*H*), 6.57 (1H, dt, *J* 11.8, 2.0, C(3)*H*), 7.20-7.37 (5H, m, Ar*H*). Data consistent with literature.[109]

***tert*-Butyl 4-allylpiperazine-1-carboxylate† 287**



Following general procedure **F**, the reaction of allyl bromide (1.00 g, 8.27 mmol, 1.0 equiv.) in THF (16 mL) with 1-Boc-piperazine (3.85 g, 20.66 mmol, 2.5 equiv.) in THF (8 mL) gave the title compound

† Synthesised and characterised by Dr David S. B. Daniels

(1.29 g, 69%) as a colourless oil after purification by flash chromatography on silica gel (4:1→1:1 PE/EtOAc).

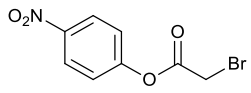
ν_{max} (film, cm^{-1}): 2976, 2797, 1694, 1643, 1456, 1418, 1364, 1238, 1169, 1115, 1003, 918, 866; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.44 (9H, s, $OC(CH_3)_3$), 2.37 (4H, *apt* t, *J* 5.25, C(3)H_2), 2.99 (2H, dq, *J* 6.6, 1.2, C(1')H_2), 3.40-3.45 (4H, m, C(2)H_2), 5.12-5.21 (2H, m, C(3')*H*), 5.77-5.91 (1H, m, C(2')*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 28.6, 43.7, 53.0, 61.9, 79.7, 118.4, 134.7, 154.9; HRMS (NSI^+): $C_{12}H_{23}N_2O_2$ $[M+H]^+$ found 227.1752, requires 227.1754 (−0.9 ppm).

Bromoacetate Synthesis

General procedure G: Synthesis of Bromoacetates from Bromoacetic acids

DCC (1.0 equiv.) was added to a solution of requisite bromoacetic acid (1.0 equiv.), 4-DMAP (0.1 equiv.) and the corresponding phenol (1.0 equiv.) in EtOAc (0.2 M) at 0 °C. The reaction was allowed to warm to rt after 10 min and was stirred for a further 4 h. AcOH (200 µL/g of bromoacetic acid) was added and the reaction mixture cooled to −20 °C for 30 min. The cold suspension was filtered through a pad of Celite® (EtOAc eluent), and the filtrate concentrated *in vacuo*. The residue was dissolved in hot Et_2O, filtered, and the filtrate concentrated *in vacuo*. The resulting solid was recrystallized from Et_2O/hexane to give bromoacetates.

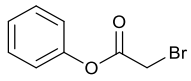
4-Nitrophenyl 2-bromoacetate 213



Following general procedure **G,** bromoacetic acid (30.0 g, 216 mmol, 1.0 equiv.), *p*-nitrophenol (30.0 g, 216 mmol, 1.0 equiv.), DCC (44.5 g, 216 mmol, 1.0 equiv.) and 4-DMAP (2.64 g, 21.6 mmol, 0.1 equiv.) were reacted in EtOAc (1080 mL) to give the title compound (44.1 g, 79%) as a white solid after recrystallization (Et_2O/hexanes).

mp 88-90 °C {Lit 86-87 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.09 (2H, s, C*H*$_2$Br), 7.34 (2H, d, *J* 8.8, ArC(2,6)*H*), 8.30 (2H, d, *J* 8.8, ArC(3,5)*H*); Data consistent with literature.[110]

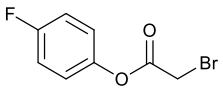
Phenyl 2-bromoacetate[111] 490



Following general procedure **G**, bromoacetic acid (2.50 g, 18.0 mmol, 1.0 equiv.), phenol (1.69 g, 18.0 mmol, 1.0 equiv.), DCC (3.71 g, 18.0 mmol, 1.0 equiv.) and 4-DMAP (220 mg, 1.8 mmol, 0.1 equiv.) were reacted in EtOAc (90 mL) to give the title product (3.31 g, 86%) as a low metling colourless solid, which was used without further purification

mp <30 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.06 (2H, s, C*H*$_2$), 7.12-7.14 (2H, m, Ar*H*), 7.27 (1H, t, *J* 7.8, Ar*H*), 7.36-7.44 (2H, m, Ar*H*); Data consistent with the literature[111]

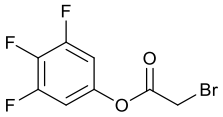
4-Fluorophenyl 2-bromoacetate† 491



Following general procedure **G**, bromoacetic acid (2.50 g, 18.0 mmol, 1.0 equiv.), 4-fluorophenol (2.02 g, 18.0 mmol, 1.0 equiv.), DCC (3.71 g, 18.0 mmol, 1.0 equiv.) and DMAP (220 mg, 1.8 mmol, 0.1 equiv.) in EtOAc (90 mL). to give the title product (4.10 g, 98%) as a low metling yellow solid, which was used without further purification

mp <30 °C; ν_{max} (film, cm^{-1}) 2964, 1755, 1499, 1178, 943; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.05 (2H, s, CH_2), 7.06-7.12 (4H, m, Ar*H*); $^{19}F\{^{1}H\}$ NMR (471 MHz, $CDCl_3$) δ_F: −116.0 (ArC*F*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 25.5 (*C*H_2), 116.4 (d, $^{2}J_{CF}$ 23.6, Ar*C*(3,5)H), 122.7 (d, $^{3}J_{CF}$ 8.5, Ar*C*(2,6)H), 146.3 (d, $^{4}J_{CF}$ 2.7, Ar*C*(1)), 160.6 (d, $^{1}J_{CF}$ 245, Ar*C*-F), 166.0 (*C*=O); HRMS (APCI$^+$): $C_8H_7{}^{79}BrFO_2$ $[M+H]^+$ found 232.9608, requires 232.9608 (+0.0 ppm).

3,4,5-Trifluorophenyl 2-bromoacetate† 492

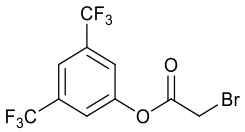


Following general procedure **G**, bromoacetic acid (1.25 g, 9.0 mmol, 1.0 equiv.), 3,4,5-trifluorophenol (1.33 g, 9.0 mmol, 1.0 equiv.), DCC (1.86 g, 9.0 mmol, 1.0 equiv.) and 4-DMAP (110 mg, 0.9 mmol, 0.1 equiv.) were reacted in EtOAc (45 mL) to give the title product (2.26 g, 93%) as pale orange solid after recrystallisation from Et_2O.

mp 46-48 °C; ν_{max} (film, cm^{-1}) 3078, 2955, 1769, 1628, 1522, 1452, 1233, 1126, 1043, 991; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.03 (2H, s, CH_2), 6.86 (2H, dd, *J* 7.7, 5.8, Ar*H*); $^{19}F\{^{1}H\}$ NMR (470 MHz, $CDCl_3$) δ_F: −162.3 (1F, t, J_{FF} 20.7, ArC(4)-*F*), −132.0 (2F, d, J_{FF} 20.7, ArC(3,5)-*F*); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 24.9 (*C*H_2), 106.8 (dd, $^{2}J_{CF}$ 17.2, $^{3}J_{CF}$ 6.2, Ar*C*(2,6)H), 138.6 (dt, $^{1}J_{CF}$ 250, $^{2}J_{CF}$ 15.2, Ar*C*(4)F), 145.0 (dt, $^{3}J_{CF}$ 11.5, $^{4}J_{CF}$ 5.8, Ar*C*(1)O), 151.2 (ddd, $^{1}J_{CF}$ 250, $^{2}J_{CF}$ 11.5, $^{3}J_{CF}$ 5.8, Ar*C*(3,5)F), 165.2 (*C*=O);HRMS (APCI$^+$): $C_8H_5{}^{79}BrF_3O_2$ $[M+H]^+$ found 268.9420, requires 268.9420 (+0.0 ppm).

† Synthesised and characterised by Dr David S. B. Daniels

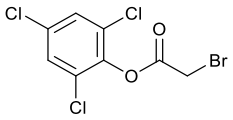
3,5-Bis(trifluoromethyl)phenyl 2-bromoacetate 493



Following general procedure **G**, bromoacetic acid (5.0 g, 36.0 mmol, 1.0 equiv.) was reacted with DCC (7.41 g, 36.0 mmol, 1.0 equiv.), 3,5 bis-trifluoromethyl phenol (5.47 mL, 36.0 mmol, 1.0 equiv.) and DMAP (439 mg, 3.6 mmol, 0.1 equiv.) in EtOAc (180 mL) to give the title product (12.34 g, 98%) as pale orange solid after recrystallization from Et_2O/hexane.

mp 50-51 °C; ν_{max} (film, cm^{-1}) 2963, 1773, 1364, 1273, 1171, 1103, 991; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 4.09 (2H, s, C*H*$_2$), 7.64 (2H, s, Ar(2,6)*H*), 7.81 (1H, s, Ar(4)*H*); $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$) δ_F: −62.9 (C*F*$_3$); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 24.8 (*C*H$_2$), 120.4-120.5 (m, Ar*C*(4)H), 122.2-122.3 (m, Ar*C*(2,6)H), 122.8 (q, $^1J_{CF}$ 273, *C*F$_3$), 133.3 (q, $^2J_{CF}$ 34, Ar*C*CF$_3$), 150.9 (Ar*C*(1)O), 165.2 (*C*=O); HRMS (APCI$^+$): $C_{10}H_6{}^{79}BrF_6O_2$ $[M+H]^+$ found 350.9450, requires 350.9450 (+0.0 ppm).

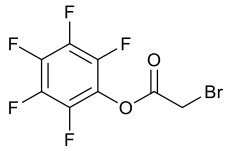
2,4,6-Trichlorophenyl 2-bromoacetate 494



A solution of bromoacetic acid (2.5 g, 18 mmol, 1.0 equiv.), 2,4,6-trichlorophenol (3.55 g, 18 mmol, 1.0 equiv.) and 4-DMAP (0.22 g, 1.8 mmol, 01 equiv.) in EtOAc (90 mL) was treated with DCC (3.71 g, 18 mmol, 1.0 equiv.) and stirred at rt for 16 h. The resulting mixture was filtered through celite®, washed with aq. 1 M HCl (20 mL) then sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was dissolved in Et_2O (20 mL) and filtered then concentrated *in vacuo*, the residue was recrystallized from Et_2O/petanes to give the title product (0.69 g, 12%)as an off white solid

mp 37-39 °C; ν_{max} (film, cm^{-1}) 3082, 1767, 1560, 1447, 1387, 1234, 1204, 1090, 922; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 4.14 (2H, s, C*H*$_2$), 7.39 (2H, s, Ar*H*);$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 24.2 (*C*H$_2$), 128.9 (Ar*C*(3,5)H), 129.5 (Ar*C*(2,6)Cl), 132.7 (Ar*C*(4)Cl), 142.4 (Ar*C*(1)), 163.6 (*C*=O); HRMS (APCI$^+$): $C_8H_5{}^{79}Br{}^{35}Cl_3O_2$ $[M+H]^+$ found 316.8536, requires 316.8533 (+0.9 ppm).

Perfluorophenyl 2-bromoacetate[112] 495



A solution of bromoacteyl bromide (474 μL, 5.44 mmol, 1.0 equiv.) in CH_2Cl_2 (9 mL) was treated with a solution of *i*Pr_2NEt (946 μL, 5.44 mmol, 1.0 equiv.) and pentafluorophenol (1.0 g, 5.44 mmol, 1.0 equiv.) over 15 min. The reaction mixture was then allowed to warm to rt and stirred for a further 1 h, the reaction was quenched with water and the layers separated, the organic layer was washed with brine (15 mL) dried over $MgSO_4$ and concentrated *in vacuo* to give the title product (1.49 g, 90%) as a colourless liquid.

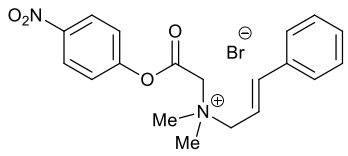
^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.14 (2H, s, C*H*$_2$); ^{19}F NMR (282 MHz, $CDCl_3$) δ_F: −162.09 (2F, dd, *J* 21.7, 17.2, ArC(3,5)*F*), −157.18 (1F, t, 21.7, ArC(4)*F*), −152.88 (2F, d, *J* 17.2, ArC(2,6)*F*); Data consistent with the literature.[112]

Ammonium Salt Synthesis

General Procedure H: Synthesis of activated ammonium salts:

A flame-dried flask was charged with 4-nitrophenyl 2-bromoacetate (1.1-3.0 equiv.) under N_2 and the indicated solvent added. A solution of amine (1.0 equiv.) in the indicated solvent was then added and the reaction mixture stirred at rt for 1-24 h. The resulting precipitate was filtered and washed with Et_2O (× 3) and dried *in vacuo* to give the ammonium salts that were used as isolated, or recrystallised from the stated solvent if necessary.

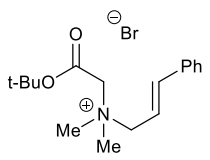
(*E*)-*N*,*N*-Dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide 211



Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (4.44 g, 17.1 mmol, 1.1 equiv.) in MeCN (10.0 mL) with (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **212** (2.50 g, 15.5 mmol, 1.0 equiv.) in MeCN (5.5 mL) for 1 h gave the title compound (5.90 g, 90%) as a white solid.

mp 122 °C (*dec*); ν_{max} (film, cm^{-1}): 2957, 1765, 1530, 1483, 1352, 1179, 1148, 1035, 982; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 3.34 (6H, s, $N^+(CH_3)_2$), 4.40 (2H, d, *J* 7.5, C(1)H_2), 4.82 (2H, s, COCH_2), 6.60 (1H, dt, *J* 15.6, 7.5, C(2)*H*), 6.97 (1H, d, *J* 15.6, C(3)*H*), 7.32-7.47 (3H, m, ArC*H*), 7.50-7.59 (2H, m, *p*-NO_2ArC(2,6)*H*), 7.64 (2H, dd, *J* 8.1, 1.6, ArC*H*), 8.28-8.45 (2H, m, *p*-NO_2ArC(3,5)*H*); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ_C: 50.1 ($N^+(CH_3)_2$), 60.5 (CO*C*H_2), 67.2 (*C*(1)H_2), 116.1 (*C*(2)H), 123.1 (Ar*C*(3,5)H), 125.5 (Ar*C*(2,6)H), 127.4 (C(3)Ar*C*(4)H), 128.8 (C(3)Ar*C*(2,6)H), 129.2 (C(3)Ar*C*(3,5)H), 135.1 (C(3)Ar*C*(1)), 141.7 (*C*(3)H), 145.6 (Ar*C*(4)-NO_2), 154.0 (Ar*C*(1)-O), 163.2 (*C*=O); HRMS (ESI^+): $C_{19}H_{21}O_4N_2^+$ $[M]^+$ found 341.1489, requires 341.1496 (−2.0 ppm).

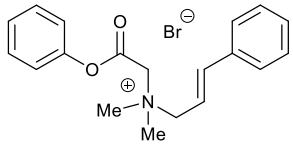
(*E*)-*N*-(2-(*tert*-Butoxy)-2-oxoethyl)-*N*,*N*-Dimethyl-3-phenylprop-2-en-1-ammonium bromide 221



Following general procedure **H**, the reaction of *tert*-butyl 2-bromoacetate (1.1 mL, 7.45 mmol, 1.2 equiv.) with (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **212** (1.0 g, 6.21 mmol, 1.0 equiv.) in MeCN (6.21 mL) for 1 h gave the title compound (1.58 g, 71%) as a white solid.

m.p 138-140 °C; ν_{max} (film, cm^{-1}) 2940, 1732, 1250, 1167, 1150, 968, 895; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.45 (9H, s, C(C*H*$_3$)$_3$), 3.63 (6H, s, N$^+$(C*H*$_3$)$_2$), 4.57 (2H, s, COC*H*$_2$), 4.82 (2H, d, *J* 7.7, C(1)*H*$_2$), 6.28 (1H, dt, *J* 15.7, 7.7, C(2)*H*), 7.03 (1H, d, *J* 15.7, C(3)*H*), 7.39-7.29 (3H, m, Ar*H*), 7.40-7.49 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ_C: 28.1 (*C*(C*H*$_3$)$_3$), 50.9 (N$^+$(*C*H$_3$)$_2$), 61.0 (CO*C*H$_2$), 66.9 (*C*(1)H$_2$), 85.5 (*C*(CH$_3$)$_3$), 113.7 (*C*(2)H), 127.4 (Ar*C*H), 129.0 (Ar*C*H), 129.8 (Ar*C*H), 134.5 (C(3)Ar*C*(1)), 144.6 (*C*(3)H), 163.8 (*C*=O); HRMS (NSI$^+$) $C_{17}H_{26}O_2N^+$ [M$^+$] found: 276.1955, requires: 276.1958 (−1.1 ppm).

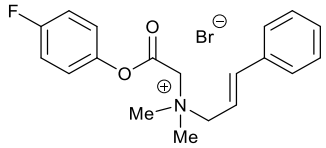
(*E*)-*N*,*N*-Dimethyl-*N*-(2-oxo-2-phenoxyethyl)-3-phenylprop-2-en-1-ammonium bromide 222



Following general procedure **H**, the reaction of phenyl 2-bromoacetate **490** (1.0 g, 4.65 mmol, 1.2 equiv.) with (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **212** (624 mg, 3.88 mmol, 1.0 equiv.) in MeCN (4 mL) for 1 h gave the title compound (1.22 g, 84%) as a white solid.

mp 141°C (dec.); ν_{max} (film, cm^{-1}) 2997, 1757, 1483, 1386, 1184, 983; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 3.34 (6H, s, N$^+$(C*H*$_3$)$_2$), 4.41 (2H, d, *J* 7.4, C(1)*H*$_2$), 4.81 (2H, s, COC*H*$_2$), 6.60 (1H, dt, *J* 15.5, 7.4, C(2)*H*), 6.96 (1H, d, *J* 15.5, C(3)*H*), 7.09-7.28 (2H, m, Ar*H*), 7.29-7.53 (6H, m, Ar*H*), 7.64 (2H, d, *J* 6.7, Ar*H*);^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ_C: 50.8 (N$^+$(*C*H$_3$)$_2$), 60.4 (CO*C*H$_2$), 67.0 (*C*(1)H$_2$), 116.2 (*C*(2)H), 121.5 (Ar*C*H), 126.7 (Ar*C*H), 127.4 (Ar*C*H), 128.7 (Ar*C*H), 129.1 (Ar*C*H), 129.7 (Ar*C*H), 135.1 (C(3)Ar*C*(1)), 141.5 (*C*(3)H), 149.3 (Ar*C*(1)O), 163.9 (*C*=O); HRMS (NSI$^+$) $C_{19}H_{22}NO_2^+$ [M]$^+$ found 296.1644, requires 296.1645 (−0.4 ppm).

(*E*)-*N*-(2-(4-Fluorophenoxy)-2-oxoethyl)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-ammonium bromide 223

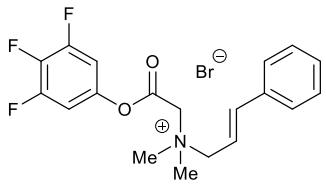


Following general procedure **H**, (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **212** (250 mg, 1.55 mmol, 1 equiv.) was reacted with 4-fluorophenyl 2-bromoacetate **491** (434 mg, 1.86 mmol, 1.2 equiv.) in MeCN (1.5 mL), to give the title coumpound (543 mg, 89%) as a white solid.

mp 156-158 °C; ν_{max} (film, cm^{-1}) 2955, 1762, 1501, 1396, 1172, 1036, 982; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 3.34 (6H, s, N$^+$(C*H*$_3$)$_2$), 4.41 (2H, br. s, C(1)*H*$_2$), 4.80 (2H, br. s, COC*H*$_2$), 6.60 (1H, dt, *J* 15.5, 7.3, C(2)*H*), 6.96 (1H, d, *J* 15.5, C(3)*H*), 7.15-7.52 (7H, m, Ar*H*), 7.63 (2H, d, *J* 7.0, Ar*H*);

$^{19}F\{^{1}H\}$ NMR (282 MHz, $CDCl_3$) δ_F: −116.5 (ArC-*F*); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6) δ_C: 50.8 ($N^+(CH_3)_2$), 60.4 ($COCH_2$), 67.0 ($C(1)H_2$), 116.2 (*C*(2)H), 116.4 (d, $^2J_{CF}$ 23.7, Ar*C*(3,5)H), 123.5 (d, $^3J_{CF}$ 8.8, Ar*C*(2,6)H), 127.4 (Ar*C*H), 128.8 (Ar*C*H), 129.1 (Ar*C*H), 135.1 (C(3)Ar*C*(1)), 141.6 (*C*(3)H), 145.3 (Ar*C*(1)O), 160.0 (d, $^1J_{CF}$ 243, Ar*C*-F), 163.9 (*C*=O); HRMS (NSI^+) $C_{19}H_{21}FNO_2^+$ $[M]^+$ found 314.1549, requires 314.1551 (−0.6 ppm).

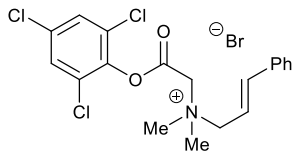
(*E*)-*N*,*N*-Dimethyl-*N*-(2-oxo-2-(3,4,5-trifluorophenoxy)ethyl)-3-phenylprop-2-en-1-ammonium bromide 224



Following general procedure **H**, (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **212** (250 mg, 1.55 mmol, 1.0 equiv.) and 3,4,5-trifluorophenyl 2-bromoacetate **492** (500 mg, 1.86 mmol, 1.2 equiv.) were reacted in MeCN (1.5 mL) to give the title compound (528 mg, 79%) as a white solid

m.p 156-158 °C; ν_{max} (film, cm^{-1}) 2972, 1769, 1634, 1520, 1452, 1177, 1144, 1047, 982; ^1H NMR (500 MHz, DMSO-d_6) δ_H: 3.31 (6H, s, $N^+(CH_3)_2$), 4.37 (2H, d, *J* 6.6, C(1)H_2), 4.73 (2H, s, $COCH_2$), 6.58 (1H, dt, *J* 15.6, 7.6, C(2)*H*), 6.96 (1H, d, *J* 15.6, C(3)*H*), 7.27-7.47 (5H, m, Ar*H*), 7.63 (2H, d, *J* 7.1, Ar*H*); $^{19}F\{^{1}H\}$ NMR (470 MHz, DMSO-d_6) δ_F: −163.0 (1F, td, *J* 22.1, 7.2, Ar(4)*F*), −133.5 (2F, dd, *J* 22.1, 5.5, Ar(3,5)*F*); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ_C: 50.8 ($N^+(CH_3)_2$), 60.4 ($COCH_2$), 67.1 ($C(1)H_2$), 108.1 (d, $^2J_{CF}$ 23.9, Ar*C*(2,6)H), 116.1 (*C*(2)H), 127.4 (C(3)Ar*C*H), 128.8 (C(3)Ar*C*H), 129.1 (C(3)Ar*C*H), 135.1 (C(3)Ar*C*(1)), 137.7 (dt, $^1J_{CF}$ 250, $^2J_{CF}$ 15.3, Ar*C*(4)F), 141.7 (*C*(3)H), 144.2 (td, $^3J_{CF}$ 12.1, $^4J_{CF}$ 3.6, Ar*C*(1)O), 150.1 (ddd, $^1J_{CF}$ 250, $^2J_{CF}$ 10.5, $^3J_{CF}$ 4.9, Ar*C*(3,5)F), 163.2 (*C*=O); HRMS (NSI^+) $C_{19}H_{19}F_3NO_2^+$ $[M]^+$ found 350.1361, requires 350.1362 (−0.4 ppm).

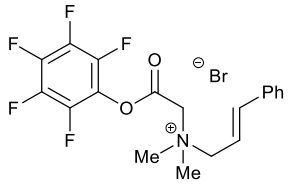
(*E*)-*N*,*N*-Dimethyl-*N*-(2-oxo-2-(2,4,6-trichlorophenoxy)ethyl)-3-phenylprop-2-en-1-ammonium bromide 226



Following general prodcedure **H**, *E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **212** (135 mg, 0.84 mmol, 1.0 equiv.) and 2,4,6-trichlorophenyl 2-bromoacetate **494** (400 mg, 1.26 mmol, 1.5 equiv.) were reacted in MeCN (1.0 mL) to give the title compound (217 mg, 54%) as a white solid

mp 154 °C (dec.);ν_{max} (film, cm^{-1}) 2940, 1776, 1445, 1165, 1120, 974; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 3.41 (6H, s, $N^+(CH_3)_2$), 4.49 (2H, d, *J* 7.5, C(1)H_2), 5.27 (2H, s, COCH_2), 6.58 (1H, dt, *J* 15.5, 7.5, C(2)*H*), 6.90 (1H, d, *J* 15.5, C(3)*H*), 7.34-7.42 (3H, m, Ar*H*), 7.59-7.62 (2H, m, Ar*H*), 7.92 (2H, s, Ar(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ_C: 51.4 ($N^+(CH_3)_2$), 59.6 (CO*C*H_2), 67.0 (*C*(1)H_2), 116.4 (*C*(2)H), 127.8 (C(3)Ar*C*H), 128.9 (C(3)Ar*C*H), 129.1 (C(3)Ar*C*H), 129.6 (OAr*C*(4)Cl), 129.6 (OAr*C*(3,5)H), 133.1 (OAr*C*(2,6)Cl), 135.5 (C(3)Ar*C*(1)), 141.5 (Ar*C*(1)O), 141.9 (*C*(3)H), 162.9 (*C*=O); HRMS (NSI^+): $C_{19}H_{19}{}^{35}Cl_3NO_2^+$ $[M]^+$ found: 398.0476, requires 398.0476 (+0.0 ppm).

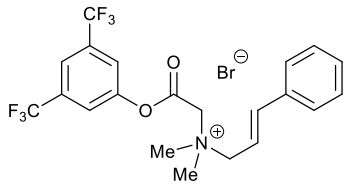
(*E*)-*N*,*N*-Dimethyl-*N*-(2-oxo-2-(perfluorophenoxy)ethyl)-3-phenylprop-2-en-1-ammonium bromide 225



Following general prodcedure **H**, *E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **212** (0.52 g, 3.25 mmol, 1.0 equiv.) and perfluorophenyl 2-bromoacetate **495** (1.48 g, 4.88 mmol, 1.5 equiv.) were reacted in MeCN (7.0 mL) to give the title compound (0.60 g, 39%) as a white solid

mp 161 °C (dec.); ν_{max} (film, cm^{-1}) 2762, 1788, 1520, 1139, 1122, 1030, 1002, 977, 885; ^{1}H NMR (300 MHz, CD_3CN) δ_H: 3.42 (6H, s, $N^+(CH_3)_2$), 4.48 (2H, d, *J* 7.7, C(1)H_2), 5.09 (2H, s, COCH_2), 6.45 (1H, dt, *J* 15.6, 7.7, C(2)*H*), 7.02 (1H, d, *J* 15.6, C(3)*H*), 7.28-7.49 (3H, m, Ar*H*), 7.56-7.60 (2H, m, Ar*H*); $^{19}F\{^{1}H\}$ NMR (282 MHz, CD_3CN) δ_F: −153.7 (2F, d, *J* 16.8, Ar(2,6)*F*), −159.0 (1F, t, *J* 21.0, Ar(4)*F*), −164.2 (2F, dd, *J* 21.0, 16.8, Ar(3,5)*F*); HRMS (NSI^+): $C_{19}H_{17}F_5NO_2^+$ $[M]^+$ found: 386.1164, requires 386.1174 (−2.6 ppm); A good quality $^{13}C\{^{1}H\}$ NMR spectrum could not be readily obtained.

(*E*)-*N*-(2-(3,5-Bis(trifluoromethyl)phenoxy)-2-oxoethyl)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-ammonium bromide 227

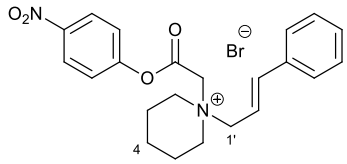


Following general procedure **H**, (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **212** (250 mg, 1.55 mmol, 1.0 equiv.) was reacted with 3,5-bis(trifluoromethyl)phenyl 2-bromoacetate **493** (653 mg, 1.86 mmol, 1.2 equiv.) in MeCN (1.5 mL) to give the title product (598 mg, 75%) as a white solid.

mp 160 °C (dec.); ν_{max} (film, cm^{-1}): 2928, 1780, 1458, 1364, 1275, 1130, 1016, 896; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 3.34 (6H, s, $N^+(CH_3)_2$), 4.39 (2H, d, *J* 7.4, C(1)H_2), 4.74 (2H, s, COCH_2), 6.60

(1H, dt, *J* 15.6, 7.4, C(2)*H*), 6.97 (1H, d, *J* 15.6, C(3)*H*), 7.32-7.44 (3H, m, Ar*H*), 7.63 (2H, d, *J* 7.1, Ar*H*), 8.09 (2H, s, OAr(2,5)*H*), 8.19 (1H, s, OAr(4)*H*); ^{19}F NMR (470 MHz, DMSO-d_6) δ_F: -61.3 (CF_3); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ_C: 50.9 (N$^+$(*C*H$_3$)$_2$), 60.6 (CO*C*H$_2$), 67.1 (*C*(1)H$_2$), 116.1 (*C*(2)H), 120.5-121.1 (m, OAr*C*(4)H), 122.7 (q, $^1J_{CF}$ 273.0, *C*F$_3$), 123.7 (OAr*C*(2,6)H), 127.3 (C(3)Ar*C*(3,5)H), 128.7 (C(3)Ar*C*(2,6)H), 129.1 C(3)Ar*C*(4)H), 131.6 (q, $^2J_{CF}$ 33.7, Ar*C*(3,5)CF$_3$), 135.1 (C(3)Ar*C*(1)), 141.8 (*C*(3)H), 150.0 (Ar*C*(1)O), 163.3 (*C*=O); HRMS (NSI$^+$): $C_{21}H_{20}F_6NO_2^+$ [M-Br]$^+$ found 432.1386, requires 432.1393 (−1.6 ppm).

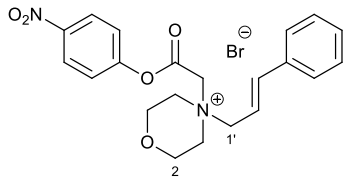
1-Cinnamyl-1-(2-(4-nitrophenoxy)-2-oxoethyl)piperidin-1-ium bromide 259



Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (1.94 g, 7.46 mmol, 3.0 equiv.) in MeCN (5.0 mL) with 1-cinnamylpiperidine **239** (0.50 g, 2.49 mmol, 1.0 equiv.) in MeCN (5.0 mL) for 24 h gave the title compound (0.80 g, 69%) as a white solid.

mp 168 °C (*dec*); ν_{max} (film, cm^{-1}): 2957, 1763, 1522, 1346, 1196, 1150, 974; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.56-1.68 (2H, m, C(4)H_2), 1.88-2.02 (4H, m, C(3,5)H_2), 3.61 (2H, dt, *J* 12.3, 5.5, C(2,6)H^AH^B), 3.79 (2H, dt, *J* 11.4, 5.5, C(2,6)H^A*H*^{B}), 4.45 (2H, d, *J* 7.4, C(1')H_2), 4.83 (2H, s, COCH_2), 6.53-6.65 (1H, m, C(2')*H*), 6.96 (1H, d, *J* 15. 6, C(3')*H*), 7.33-7.51 (5H, m, 2 × OArC(2,6)*H* and 3 × Ar*H*), 7.59-7.65 (2H, m, Ar*H*), 8.36 (2H, d, *J* 9.1, OAr(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ_C: 19.2 (*C*(4)H$_2$), 20.6 (*C*(3,5)H$_2$), 56.0 (CO*C*H$_2$), 59.5 (*C*(2,6)H$_2$), 62.4 (*C*(1')H$_2$), 115.8 (*C*(2')H), 123.1 (OAr*C*(3,5)H), 125.5 (OAr*C*(2,6)H), 127.4 (C(3)Ar*C*(2,6)H), 128.8 (C(3)Ar*C*(3,5)H), 129.2 (C(3)Ar*C*(4)H), 135.2 (C(3)Ar*C*(1)), 141.1 (*C*(3)H), 145.6 (Ar*C*(4)-NO$_2$), 153.8 (Ar*C*(1)-O), 163.3 (*C*=O); HRMS (NSI$^+$): $C_{22}H_{25}O_4N_2^+$ [M]$^+$ found 381.1803, requires 381.1809 (−1.5 ppm).

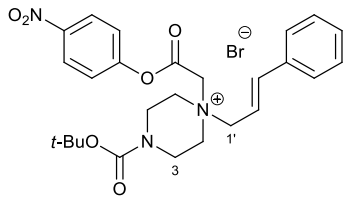
4-Cinnamyl-4-(2-(4-nitrophenoxy)-2-oxoethyl)morpholin-4-ium bromide 260



Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (1.92 g, 7.40 mmol, 3.0 equiv.) in MeCN (5 mL) with 4-cinnamylmorpholine **240** (0.50 g, 2.46 mmol, 1.0 equiv.) in MeCN (5 mL) gave the title compound (0.80 g, 70%) as a white solid.

mp 151 °C (*dec*); ν_{max} (film, cm^{-1}): 2959, 1767, 1524, 1348, 1169, 880; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 3.75 (2H, d, *J* 13.5, C(2,6)H^AH^B), 3.88 (2H, d, *J* 13.5, C(2,6)H^AH^B), 4.04-4.13 (4H, m, C(3,5)*H*), 4.63 (2H, d, *J* 7.4, C(1')*H*), 5.02 (2H, s, COCH_2), 6.61 (1H, dt, *J* 15.5, 7.4, C(2')*H*), 7.00 (1H, d, *J* 15.5, C(3')*H*), 7.46-7.33 (3H, m, Ar*H*), 7.49 (2H, d, *J* 9.1, *p*-NO_2ArC(2)*H*), 7.58-7.69 (2H, m, Ar*H*), 8.36 (2H, d, *J* 9.1, OArC(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ_C: 56.2 (CO*C*H_2), 58.3 (*C*(2,6)H_2), 59.7 (*C*(3,5)H_2), 62.4 (*C*(1')H_2), 115.4 (*C*(2')H_2), 123.0 (OAr*C*(2,6)H), 125.5 (OAr*C*(3,5)H), 127.4 (C(3)Ar*C*(2,6)-H), 128.8 (C(3)Ar*C*(3,5)H), 129.2 (C(3)Ar*C*(4)H), 135.1 (C(3)Ar*C*(1)), 141.6 (*C*(3')H), 145.6 (Ar*C*(4)-NO_2), 153.7 (Ar*C*(1)-O), 163.1 (*C*=O); HRMS (NSI$^+$): $C_{21}H_{23}O_5N_2^+$ $[M]^+$ found 383.1592, requires 383.1601 (−2.5 ppm).

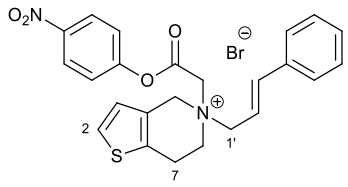
4-(*tert*-Butoxycarbonyl)-1-cinnamyl-1-(2-(4-nitrophenoxy)-2-oxoethyl)piperazin-1-ium bromide 261



Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (1.29 g, 4.97 mmol, 3.0 equiv.) in MeCN (3 mL) with *tert*-butyl 4-cinnamylpiperazine-1-carboxylate **241** (0.50 g, 1.66 mmol, 1.0 equiv.) in MeCN (3.75 mL) for 24 h gave the title compound (0.60 g, 64%) as a white solid.

mp 153 °C (*dec*); ν_{max} (film, cm^{-1}): 2953, 1767, 1711, 1528, 1416, 1167, 1142, 852; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.44 (9H, s, OC(CH_3)$_3$), 3.69-3.93 (8H, m, C(2,6 and 3,5)H_2), 4.58 (2H, d, *J* 7.4, C(1')*H*) 4.99 (2H, s, COCH_2), 6.61 (1H, dt, *J* 15.4, 7.4, C(2')*H*), 7.00 (1H, d, *J* 15.6, C(3')*H*), 7.44-7.36 (3H, m, Ar*H*), 7.50 (2H, d, *J* 9.1, *p*-NO_2ArC(2,6)*H*), 7.63 (2H, d, *J* 7.2, Ar*H*), 8.36 (2H, d, *J* 9.1, *p*-NO_2ArC(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ_C: 28.0 ((*C*H_3)$_3$), 36.6 and 37.7 (rotameric *C*(3,5)H_2), 55.9 (CO*C*H_2), 58.0 (*C*(2,6)H_2), 61.8 (*C*(1')H_2), 80.1 (*C*(CH$_3$)$_3$), 115.4 (*C*(2')H), 123.1 (Ar*C*(2,6)H), 125.5 (Ar*C*(3,5)H), 127.4 (C(3)Ar*C*(2,6)H), 128.8 (C(3)Ar*C*(3,5)H), 129.2 C(3)Ar*C*(4)H), 135.1 (C(3)Ar*C*(1)), 141.6 (*C*(3')H), 145.6 (Ar*C*(4)-NO_2), 153.5 (Ar*C*(1)-O), 153.7 (N*C*=O), 163.1 (*C*=O); HRMS (NSI$^+$): $C_{26}H_{32}O_6N_3^+$ $[M]^+$ found 482.2276, requires 482.2286 (−2.0 ppm).

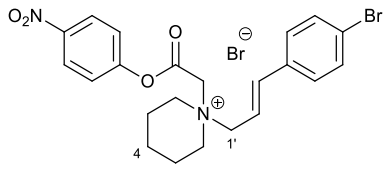
5-Cinnamyl-5-(2-(4-nitrophenoxy)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-ium bromide[†] 262



Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (764 mg, 2.94 mmol, 3.0 equiv.) in MeCN (0.5 mL) with 5-cinnamyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridine **242** (250 mg, 0.98 mmol, 1.0 equiv.) in MeCN (0.5 mL) for 2 h gave the title product (355 mg, 70%) as an off-white solid.

mp 169-170 °C (*dec*); ν_{max} (film, cm^{-1}): 2945, 2926, 1767, 1649, 1614, 1592, 1528, 1487, 1443, 1350, 1192, 1153, 1059, 980, 866, 856; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 3.36-3.38 (2H, m, C(7)*H*), 3.96-4.03 (1H, m, C(6)H^AH^B), 4.25-4.30 (1H, m, C(6)H^AH^B), 4.48-4.53 (2H, m, C(1')*H*), 4.76-4.87 (2H, m, COCH_2), 4.87-4.96 (2H, m, C(4)*H*), 6.69 (1H, dt, *J* 15.5, 7.6, C(2')*H*), 7.00 (1H, d, *J* 15.5, C(3')*H*), 7.00 (1H, d, *J* 5.2, C(3)*H*), 7.37-7.41 (1H, m, Ar(4)*H*), 7.42-7.45 (2H, m, Ar(3)*H*), 7.48 (2H, d, *J* 9.1, OArC(2,6)*H*), 7.61 (1H, d, *J* 5.2, C(2)*H*), 7.63-7.65 (2H, m, C(3)Ar(2,6)*H*), 8.35 (2H, d, *J* 9.1, OArC(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ_C: 20.5, 55.7, 56.9, 59.5, 63.4, 115.8, 123.1, 125.5 (2 × *C*), 126.3, 126.5, 127.4, 128.8, 129.2, 130.6, 135.1, 141.6, 145.6, 153.8, 163.4; HRMS (ESI$^+$): $C_{24}H_{23}N_2O_4S$ $[M]^+$ found 435.1367, requires 435.1373 (−1.4 ppm).

(*E*)-1-(3-(4-Bromophenyl)allyl)-1-(2-(4-nitrophenoxy)-2-oxoethyl)piperidin-1-ium bromide[†] 263



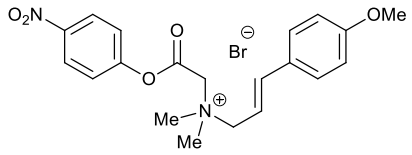
Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (1.39 g, 5.35 mmol, 3.0 equiv.) in MeCN (6.0 mL) with (*E*)-1-(3-(4-bromophenyl)allyl)piperidine **243** (500 mg, 1.78 mmol, 1.0 equiv.) in MeCN (6.0 mL) for 16 h gave the title compound (330 mg, 34%) as a white solid after purification by trituration with hot $CHCl_3$ (5.0 mL), washing with cold $CHCl_3$ (5.0 mL) and drying *in vacuo*.

mp 166-168 °C (*dec*); ν_{max} (film, cm^{-1}): 2957, 1763, 1616, 1589, 1518, 1489, 1350, 1196, 1152, 1011, 978, 856; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.59-1.65 (2H, m, C(4)H_2), 1.91-1.98 (4H, m, C(3,5)H_2), 3.56-3.59 (2H, m, C(2,6)H^AH^B), 3.76-3.83 (2H, m, C(2,6)H^AH^B), 4.45 (2H, d, *J* 7.2, C(1')*H*), 4.87 (2H,

[†] Synthesised and characterised by Dr David S. B. Daniels

s, COC*H*$_2$), 6.65 (1H, dt, *J* 15.5, 7.2, C(2')*H*), 6.94 (1H, d, *J* 15.5, C(3')*H*), 7.49 (2H, d, *J* 8.6, *p*-NO_2ArC(2)*H*), 7.57-7.64 (4H, m, C(3)ArC(2,6 and 3,5)*H*), 8.36 (2H, d, *J* 8.6, OArC(3,5)*H*); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ_C: 19.1, 20.6, 56.1, 59.6, 62.2, 117.0, 122.3, 123.0, 125.5, 129.3, 131.7, 134.5, 139.7, 145.6, 153.8, 163.3; HRMS (ESI+): $C_{22}H_{24}O_4N_2{}^{79}Br$ $[M]^+$ found 459.0906, requires 459.0914 (−1.7 ppm).

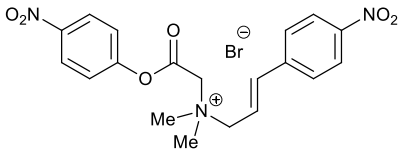
(*E*)-3-(4-Methoxyphenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 256



Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (260 mg, 1.00 mmol, 1.2 equiv.) in CH_2Cl_2/Et_2O (1:4 v:v, 0.85 mL) with (*E*)-3-(4-Methoxyphenyl)-*N*,*N*-dimethylprop-2-en-1-amine **245** (158 mg, 0.830 mmol, 1.0 equiv.) in CH_2Cl_2/Et_2O (1:4 v:v, 0.85 mL) for 16 h gave the title compound (239 mg, 64%) as a pale yellow solid.

mp 114 °C (*dec*); ν_{max} (film, cm^{-1}): 2958, 1765, 1609, 1530, 1514, 1348, 1251, 1177, 980; ^1H NMR (500 MHz, CD_3CN) δ_H: 3.37 (6H, s, $N^+(CH_3)_2$), 3.81 (3H, s, OC*H*$_3$), 4.41 (2H, d, *J* 7.7, C(1)*H*$_2$), 4.81 (2H, s, COC*H*$_2$), 6.32 (1H, dt, *J* 15.5, 7.7, C(2)*H*), 6.94-6.99 (3H, m, C(3)Ar(3,5)*H* and C(3)*H*), 7.47 (2H, d, *J* 9.1, OArC(2,6)*H*), 7.54 (2H, d, *J* 8.8, C(3)ArC(2,6)*H*), 8.30 (2H, d, *J* 9.1, OAr(3,5)*H*); $^{13}C\{^1H\}$ NMR (126 MHz, CD_3CN) δ_C: 51.8 ($N^+(CH_3)_2$), 56.0 (O*C*H$_3$), 61.5 (CO*C*H$_2$), 68.8 (*C*(1)H$_2$), 113.2 (*C*(2)H), 115.0 (C(3)Ar*C*(3,5)H), 123.8 (OAr*C*(2,6)H), 126.3 (OAr*C*(3,5)H), 128.7 (C(3)Ar*C*(1)), 129.9 (C(3)Ar*C*(2,6)H), 143.8 (*C*(3)H), 147.0 (Ar*C*(4)-NO_2), 154.9 (Ar*C*(1)-O), 161.5 (C(3)Ar*C*(4)-OCH_3), 164.3 (*C*=O); HRMS (NSI^+): $C_{20}H_{23}N_2O_5^+$ $[M]^+$ found 371.1591, requires 371.1601 (−2.8 ppm).

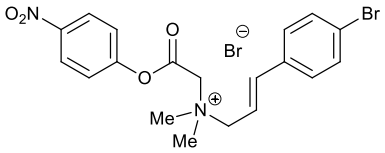
(*E*)-*N*,*N*-Dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-(4-nitrophenyl)prop-2-en-1-ammonium bromide 257



Following general procedure **H**, the reaction of 4-nitrophenyl bromoacetate **213** (617 mg, 2.37 mmol, 1.2 equiv.) in CH_2Cl_2 / Et_2O (1:4 v:v, 1.6 mL) with (*E*)-*N*,*N*-dimethyl-3-(4-nitrophenyl)prop-2-en-1-amine **249** (405 mg, 1.98 mmol, 1.0 equiv.) in CH_2Cl_2 / Et_2O (1:4 v:v, 1.6 mL) for 3 h gave the title compound (331 mg, 36%) as a pale brown solid after recrystallisation from $CHCl_3$ / CH_3CN / Et_2O.

mp 101 °C (*dec*); ν_{max} (film, cm^{-1}): 2930, 1775, 1539, 1516, 1483, 1344, 1202, 1161, 860; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 3.37 (6H, s, $N^+(CH_3)_2$), 4.51 (2H, d, *J* 7.3, C(1)H_2), 4.93 (2H, s, COCH_2), 6.97-6.80 (1H, m, C(2)*H*), 7.12 (1H, d, *J* 15.7, C(3)*H*), 7.58 (2H, d, *J* 9.1, OArC(2,6)*H*), 7.93 (2H, d, *J* 8.8, C(3)ArC(2,6)*H*), 8.26 (2H, d, *J* 8.8, C(3)ArC(3,5)*H*), 8.37 (2H, d, *J* 9.1, OArC(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ_C: 51.1 ($N^+(CH_3)_2$), 60.7 (CO*C*H_2), 66.6 (*C*(1)H_2), 121.4 (*C*(2)H), 123.1 (OAr*C*(2,6)H), 123.9 (C(3)Ar*C*(3,5)H), 125.5 (OAr*C*(3,5)H), 128.5 (C(3)Ar*C*(2,6)H), 139.1 (*C*(3)H), 141.7 (C(3)Ar*C*(1)), 145.6 (Ar*C*(4)-NO_2), 147.3 (C(3)Ar*C*(4)-NO_2), 153.9 (Ar*C*(1)-O), 163.2 (*C*=O); HRMS (NSI^+): $C_{19}H_{20}N_3O_6^+$ $[M]^+$ found 386.1336, requires 386.1347 (−2.7 ppm).

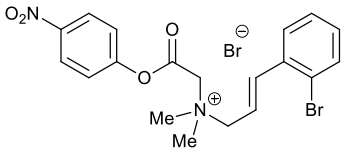
(*E*)-3-(4-Bromophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 258



Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (406 mg, 1.56 mmol, 1.5 equiv.) in MeCN (0.5 mL) with (*E*)-3-(4-bromophenyl)-*N*,*N*-dimethyl-prop-2-en-1-amine **244** (250 mg, 1.04 mmol, 1.0 equiv.) in MeCN (0.5 mL) for 1 h gave the title compound (435 mg, 0.87 mmol, 84%) as a white solid.

mp 160 °C (*dec*); ν_{max} (film, cm^{-1}): 2936, 1771, 1616, 1591, 1526, 1485, 1385, 1204, 1157, 1070, 959, 899; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 3.32 (6H, s, $N^+(CH_3)_2$), 4.37 (2H, d, *J* 7.6, C(1)*H*), 4.79 (2H, s, COCH_2), 6.64 (1H, dt, *J* 15.3, 7.6, C(2)*H*), 6.94 (1H, d, *J* 15.3, C(3)*H*), 7.56 (2H, d, *J* 9.1, OArC(2,6)*H*), 7.58-7.64 (4H, m, C(3)ArC*H*), 8.38 (2H, d, *J* 9.1, OArC(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ_C: 50.9 ($N^+(CH_3)_2$), 60.5 (CO*C*H_2), 67.0 (*C*(1)H_2), 117.2 (*C*(2)H), 122.3 (C(3)Ar*C*(4)-Br), 123.1 (OAr*C*(2,6)H), 125.5 (OAr*C*(3,5)H), 129.4 C(3)Ar*C*(2,6)H), 131.7 (C(3)Ar*C*(3,5)H), 134.4 (C(3)Ar*C*(1)), 140.3 (*C*(3)H), 145.6 (Ar*C*(4)-NO_2), 153.8 (Ar*C*(1)-O), 163.2 (*C*=O); HRMS (NSI^+): $C_{19}H_{20}{}^{79}BrN_2O_4$ $[M]^+$ found 419.0592, requires 419.0601 (−2.1 ppm).

(*E*)-3-(2-Bromophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 254

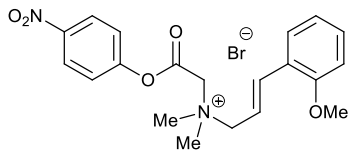


Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (260 mg, 1.00 mmol, 1.2 equiv.) in CH_2Cl_2 / Et_2O (1:4 v:v, 0.8 mL) with (*E*)-3-(2-bromophenyl)-*N*,*N*-dimethyl-prop-2-en-1-

amine **248** (200 mg, 0.83 mmol, 1.0 equiv.) in CH_2Cl_2 / Et_2O (1:4 v:v, 0.8 mL) for 1 h gave the title compound (310 mg, 75%) as a white solid.

mp 112 °C (*dec*); ν_{max} (film, cm^{-1}): 2938, 1767, 1520, 1346, 1195, 1150, 1024, 950; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 3.37 (6H, s, $N^+(CH_3)_2$), 4.50 (2H, d, *J* 6.0, C(1)*H*), 4.88 (2H, s, $COCH_2$), 6.62 (1H, ddt, *J* 15.4, 6.0, C(2)*H*), 7.20 (1H, d, *J* 15.4, C(3)*H*), 7.32 (1H, td, *J* 7.8, 1.5, C(3)ArC(4)*H*), 7.46 (1H, t, *J* 7.3, C(3)ArC(5)*H*), 7.58 (2H, d, *J* 9.1, OArC(2,6)*H*), 7.64-7.73 (1H, m, C(3)ArC(6)*H*), 7.95 (1H, d, *J* 7.8, C(3)ArC(3)*H*), 8.38 (2H, d, *J* 9.1, OArC(3,5)*H*); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6) δ_C: 50.9 ($N^+(CH_3)_2$), 60.5 ($COCH_2$), 66.7 (*C*(1)H_2), 119.9 (*C*(2)H), 123.1 (Ar*C*(2,6)H), 123.2 (C(3)Ar*C*(2)-Br), 125.5 (Ar*C*(3,5)H), 128.1 (C(3)Ar*C*(4)H), 128.4 (C(3)Ar*C*(6)H), 130.9 (C(3)Ar*C*(5)H), 132.9 (C(3)Ar*C*(3)H), 134.7 (C(3)Ar*C*(1)), 139.5 (*C*(3)H), 145.6 (Ar*C*(4)-NO_2), 153.9 (Ar*C*(1)-O), 163.2 (*C*=O); HRMS (APCI$^+$): $C_{19}H_{20}O_4N_2{}^{79}Br^+$ $[M]^+$ found 419.0598, requires 419.0601 (−0.7 ppm).

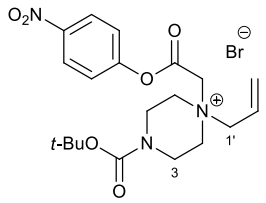
(*E*)-3-(2-Methoxyphenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 255



Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (445 mg, 1.71 mmol, 1.5 equiv.) in MeCN (2.3 mL) with (*E*)-3-(2-methoxyphenyl)-*N*,*N*-dimethylprop-2-en-1-amine **247** (217 mg, 1.14 mmol, 1.0 equiv.) for 24 h gave the title compound (402 mg, 78%) as an off-white solid.

mp 141 °C (*dec*); ν_{max} (film, cm^{-1}): 2936, 1765, 1518, 1489, 1344, 1244, 1148, 1026, 986; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 3.34 (6H, s, $N^+(CH_3)_2$), 3.83 (3H, s, OCH_3), 4.43 (2H, d, *J* 7.5, C(1)*H*), 4.83 (2H, s, $COCH_2$), 6.53 (1H, dt, *J* 15.5, 7.5, C(2)*H*), 7.00 (1H, t, *J* 7.5, C(3)ArC(5)*H*), 7.07 (1H, d, *J* 7.9, C(3)ArC(3)*H*), 7.21 (1H, d, *J* 15.8, C(3)*H*), 7.31-7.45 (1H, m, C(3)ArC(4)*H*), 7.56 (2H, d, *J* 9.2, OAr(2,6)*H*), 7.75 (1H, dd, *J* 7.7, 1.5, C(3)ArC(6)*H*), 8.38 (2H, d, *J* 9.2, OAr(3,5)*H*); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ_C: 50.8 ($N^+(CH_3)_2$), 55.6 (OCH_3), 60.4 ($COCH_2$), 67.5 (*C*(1)H_2), 111.5 (C(3)Ar*C*(3)H), 116.0 (*C*(2)H), 120.6 (C(3)Ar*C*(4)H), 123.1 (OAr*C*(2,6)H), 123.4 (C(3)Ar*C*(1)), 125.5 (OAr*C*(3,5)H), 127.3 (C(3)Ar*C*(6)H), 130.6 (C(3)Ar*C*(4)H), 136.1 (*C*(3)H), 145.6 (Ar*C*(4)NO_2), 153.9 (Ar*C*(1)-O), 156.6 (C(3)Ar*C*(2)-OMe), 163.3 (*C*=O); HRMS (NSI$^+$): $C_{20}H_{23}O_5N_2^+$ $[M]^+$ found 371.1597, requires 371.1601 (–1.2 ppm).

1-Allyl-4-(*tert*-butoxycarbonyl)-1-(2-(4-nitrophenoxy)-2-oxoethyl)piperazin-1-ium bromide 288



Following general procedure **H**, the reaction of 4-nitrophenyl 2-bromoacetate **213** (1.03 g, 3.96 mmol, 3.0 equiv.) in MeCN (0.65 mL) with *tert*-butyl 4-allylpiperazine-1-carboxylate **288** (300 mg, 1.33 mmol, 1.0 equiv.) in MeCN (0.65 mL) for 2 h gave title compound (416 mg, 65%) as an off-white solid.

mp 138 °C (*dec*); ν_{max} (film, cm^{-1}): 2951, 1773, 1709, 1532, 1448, 1144, 858; ^{1}H NMR (500 MHz, DMSO-d_6) δ_H: 1.43 (9H, s, OC(CH_3)$_3$), 3.63-3.85 (8H, m, C(2 and 3)H_2), 4.42 (2H, d, *J* 7.2, C(1')*H*), 4.94 (2H, s, COCH_2), 5.68-5.76 (2H, m, C(3')*H*), 6.11-6.24 (1H, m, C(2')*H*), 7.58 (2H, d, *J* 9.1, ArC(2,6)*H*), 8.38 (2H, d, *J* 9.1, ArC(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (125 MHz, DMSO-d_6) δ_C: 27.9 (C(*C*H_3)$_3$), 36.5 and 37.6 (rotameric *C*(3,5)H_2), 55.9 (CO*C*H_2), 58.1 (*C*(2,6)H_2), 61.9 (*C*(1')H_2), 80.1 (*C*(CH_3)$_3$), 123.1 (Ar*C*(2,6)H), 124.9 (*C*(2')H), 125.6 (Ar*C*(3,5)H), 128.7 (*C*(3')H), 145.7 (Ar*C*(4)-NO_2), 153.5 (N*C*=O), 153.8 (Ar*C*(4)-NO_2), 163.0 (*C*=O); HRMS (ESI^+): $C_{20}H_{28}O_6N_3^+$ $[M]^+$ found 406.1966, requires 406.1973 (−1.6 ppm).

Rearrangement Products

General procedure I: Asymmetric [2,3]-Rearrangement and Sequential Nucleophilic Quench:

A flame-dried flask under N_2 was charged with (+)-BTM (0.2 equiv.) and HOBt (0.2 equiv.) followed by MeCN (0.07 M with respect to ammonium salt). *i*-Pr_2NH (1.4 equiv.) was added and the resulting solution cooled to −20 °C and stirred for five mins. The corresponding ammonium salt (1.0 equiv.) was added and the reaction stirred for 24 h. The corresponding nucleophile (2.0-15.0 equiv.) was added and the reaction allowed to warm to rt and stirred for the time stated. The reaction was quenched with aq. 1 M NaOH (equal volume) and extracted with CH_2Cl_2 (3 × equal volume). The organic layers were washed with aq. 1 M NaOH (2 × equal volume), brine (equal volume), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was analysed by ^{1}H NMR to determine *dr*, then purified by flash column chromatography to yield the rearranged product.

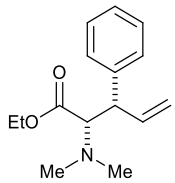
Racemic samples were prepared using (±)-tetramisole·HCl (0.2 equiv.) or (±)-BTM (0.2 equiv.) as catalyst, stirring the rearrangement for 1 h at rt before quenching with the required nucleophile.

General Procedure J: *In situ* Ammonium Salt Formation, Asymmetric [2,3]-rearrangement and Subsequent Nucleophilic Quench:

A flame-dried flask under N_2 was charged with 4-nitrophenyl 2-bromoacetate (1.0 equiv.) and a solution of the corresponding allylic amine (1.05 equiv.) in MeCN (0.14 M with respect to bromoacetate) and the resulting solution was stirred at rt for 24 h. The reaction mixture was cooled to −20 °C, stirred for 5 min, and a pre-cooled solution of (+)-BTM (0.2 equiv.), HOBt (0.2 equiv.) and *i*-Pr_2NH (1.4 equiv.) in MeCN (0.14 M with respect to bromoacetate) was added *via* cannula, and the reaction stirred for 24 h. The corresponding nucleophile (3.0-5.0 equiv.) was added and the reaction allowed to warm to rt and stir (1-16 h). The reaction was quenched with aq. 1 M NaOH (equal volume) and extracted with CH_2Cl_2 (3 × equal volume). The organic layers were washed with aq. 1 M NaOH (2 × equal volume), brine (equal volume), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was analysed by ^{1}H NMR to determine *dr*, then purified by flash column chromatography to yield the rearranged product.

Racemic samples were prepared using (±)-tetramisole·HCl (0.2 equiv.) or (±)-BTM (0.2 equiv.) as catalyst, stirring the rearrangement for 1 h at rt before quenching with the required nucleophile.

(±)-*syn*-Ethyl 2-(dimethylamino)-3-phenylpent-4-enoate[113] 233

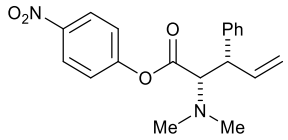


Following general procedure **I**, (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **211** (100 mg, 0.240 mmol, 1.0 equiv.), (±)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 1 h, quenched with NaOEt (1 M in EtOH, 720 µL, 0.72 mmol, 3.0 equiv.) and stirred for a further 1 h. Crude *dr* 92:8. The residue was purified by flash chromatography on silica gel (10% EtOAc/PE) to give the title compound **(**41 mg, 0.166 mmol, 69%, 92:8 *dr* isolated) as a colourless oil.

ν_{max} (film, cm^{-1}): 2938, 1726, 1452, 1257, 1162, 1031, 926; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.29 (3H, t, *J* 7.1, OCH_2CH_3) , 2.26 (6H, s, $N(CH_3)_2$), 3.58 (1H, d, *J* 11.2, C(2)*H*), 3.76 (1H, dd, *J* 11.2, 8.4, C(3)*H*), 4.18 (2H, q, *J* 7.1, OCH_2CH_3), 5.01 (1H, d, *J* 10.1, C(5)H^{cis}), 5.07 (1H, d, *J* 17.1, C(5)H^{trans}), 5.87 (1H, ddd, *J* 17.1, 10.1, 8.4, C(4)*H*), 7.37-7.18 (5H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.7 (OCH_2CH_3), 41.5 ($N(CH_3)_2$), 50.2 (*C*(3)H), 60.0 (OCH_2CH_3), 71.0 (*C*(2)H), 116.7 (*C*(5)H_2), 126.7 (Ar*C*(4)H), 128.0 (Ar*C*(3,5)H), 128.6 (Ar*C*(2,6)H), 138.7 (*C*(4)H), 141.0 (Ar*C*(1)), 170.7 (*C*=O); HRMS (NSI^+): $C_{15}H_{22}O_2N^+$ $[M+H]^+$ found 248.1638, requires 248.1651 (−2.8 ppm).

^1H NMR spectrum of **233** consistent with that given by Doyle *et al*.[113] for the *syn*-diastereomer. Along with the X-Ray crystal structure of **274** (*vide infra*), we assign our major diastereomer in all cases as *syn* by analogy.

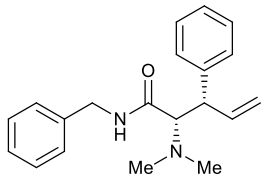
(±)-*syn*-4-Nitrophenyl 2-(dimethylamino)-3-phenylpent-4-enoate 218



Following general procedure **I**, (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **211** (200 mg, 0.480 mmol, 1.0 equiv.), (±)-tetramisole·HCl (23.2 mg, 0.096 mmol, 0.2 equiv.), HOBt (14.4 mg, 0.096 mmol, 0.2 equiv.), *i*Pr_2NH (108 µL, 0.768 mmol, 1.6 equiv.) in MeCN (7.0 mL) were stirred for 1 h. Crude *dr* 92:8. The residue was purified by flash chromatography on silica gel (10→15% EtOAc/PE) to give the title compound (68 mg, 0.200 mmol, 42%, >95:5 *dr* isolated) as a yellow solid.

m.p 103-105 °C; ν_{max} (film, cm^{-1}): 2927, 1755, 1613, 1589, 1518, 1487, 1344, 1204, 1117, 1090; ^1H NMR (500 MHz, CD_2Cl_2) δ_H: 2.39 (6H, s, N(C*H*$_3$)$_2$) 3.93-3.82 (2H, m, C(2)*H* and C(3)*H*), 5.26-5.12 (2H, m, C(5)*H*), 6.00 (1H, ddd, *J* 17.0, 10.1, 7.9, C(4)*H*), 7.31-7.23 (5H, m, Ar*H*), 7.38-7.33 (2H, m, Ar(2,6)*H*), 8.28 (2H, d, *J* 9.1, Ar(3,5)*H*); $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ_C: 41.6, 50.8, 71.3, 117.7, 123.3, 125.7, 127.4, 128.4, 129.2, 139.0, 141.1, 155.8, 168.8; HRMS (NSI^+) $C_{19}H_{21}N_2O_4^+$ $[M+H]^+$ found: 341.1496, requires: 341.1496 (±0.0 ppm).

(2*S*,3*S*)-*N*-Benzyl-2-(dimethylamino)-3-phenylpent-4-enamide 215



Following general procedure **I**, (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **211** (100 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr$_2$NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (50→100% EtOAc/PE) to give the title compound (56 mg, 76%, >95:5 *dr* isolated) as a yellow solid.

HPLC: Chiralcel OJ-H (5% IPA:hexane, flow rate 1.5 mL min^{-1}, 211 nm, 40 °C) t_R minor: 11.6 min, t_R major: 13.7 min, 99% *ee*.

$[\alpha]_D^{20}$ +86.9 (*c* 1.0, $CHCl_3$); mp 110 °C (*dec*); ν_{max} (film, cm^{-1}): 3293, 2922, 1636, 1541, 1452, 1265, 1030, 916; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.30 (6H, s, NC*H*$_3$)$_2$), 3.22 (1H, d, *J* 8.4, C(2)*H*), 3.81-3.89 (1H, m, C(3)*H*),4.44 (2H, d, *J* 5.7, PhC*H*$_2$), 5.02-5.12 (2H, m, C(5)*H*), 6.11 (1H, dt, *J* 17.9, 8.6, C(4)*H*), 6.34 (1H, br s, N*H*), 7.18-7.37 (10H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 42.6 (N(C*H*$_3$)$_2$), 43.4 (Ph*C*H$_2$), 50.2 (*C*(3)H), 73.8 (*C*(2)H), 116.8 (*C*(5)H$_2$), 126.6 (Ar*C*H), 127.6 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 138.3 (Ar*C*(1)), 138.7 (*C*(4)H), 141.9 (C(3)Ar*C*(1)), 170.3 (*C*=O); HRMS (NSI^+): $C_{20}H_{25}ON_2^+$ $[M+H]^+$ found 309.1960, requires 309.1961 (−0.5 ppm).

215 was also synthesized by the *in situ* protocol:

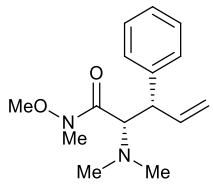
Following general procedure **J**, the reaction of (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **212** (41 mg, 0.250 mmol, 1.05 equiv.) and 4-nitrophenyl 2-bromoacetate (62 mg, 0.24 mmol, 1.0 equiv.) in MeCN (1.75 mL) were stirred for 24 h, followed by addition of (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr$_2$NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (1.75 mL) and stirred for a further 24 h. Quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and

stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (50→100% EtOAc/PE) to give the title compound (44 mg, 0.144 mmol, 60%, >95:5 *dr* isolated, 92% ee) as an off white solid. Spectral data and HPLC analysis identical to that above.

215 was also synthesized from (*Z*)-amine **(*Z*)-283** by the *in situ* protocol:

Following general procedure **J**, the reaction of (*Z*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **(*Z*)-283** (41 mg, 0.250 mmol, 1.05 equiv.) and 4-nitrophenyl 2-bromoacetate **213** (62 mg, 0.24 mmol, 1.0 equiv.) in MeCN (1.75 mL) were stirred for 24 h, followed by addition of (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (1.75 mL) and stirred for a further 24 h. Quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* 87:13. The residue was purified by flash chromatography on silica gel (50→100% EtOAc/PE) to give the title compound (4.0 mg, 5%, >95:5 *dr* isolated, 92% ee) as an off white solid. Spectral data and HPLC analysis identical to that above.

(2S,3*S*)-2-(Dimethylamino)-*N*-methoxy-*N*-methyl-3-phenylpent-4-enamide 229

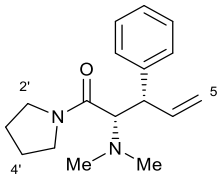


Following general procedure **I**, (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **211** (100 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with *N*,*O*-dimethylhydroxylamine (264 µL, 3.60 mmol, 15.0 equiv.) and stirred for a further 24 h. Crude *dr* 95:5. The residue was purified by flash chromatography on silica gel (10→20% Et_2O/CH_2Cl_2, then 10% $MeOH/CH_2Cl_2$) to give the title compound (41 mg, 65%, >95:5 *dr* isolated) as a yellow oil.

HPLC: Chiralpak AD-H (1% IPA:hexane, flow rate 1.5 ml min^{-1}, 220 nm, 40 °C) t_R minor: 9.4 min, t_R major: 10.5 min, >99% *ee*.

$[\alpha]_D^{20}$ +118.2 (*c* 1.0, $CHCl_3$); ν_{max} (film, cm^{-1}): 2935, 1624, 1454, 1392, 1134, 1024, 987, 918; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.26 (6H, s, N(C*H*$_3$)$_2$), 2.94 (3H, s, MeONCH3), 2.99 (3H, s, MeNOC*H*$_3$), 3.92-3.97 (2H, m, C(2 and 3)*H*), 4.95-5.05 (2H, m, C(5)*H*), 5.93-6.02 (1H, m, C(4)*H*), 7.15-7.38 (5H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 35.6 (N*C*H$_3$), 37.8 (O*C*H$_3$), 41.7 (N(C*H*$_3$)$_2$), 50.3 (*C*(3)H), 65.5 (*C*(2)H), 116.8 (*C*(5)H$_2$), 126.7 (Ar*C*(4)H), 128.5 (Ar*C*(2,6)H), 128.6 (Ar*C*(3,5)H), 138.7 (*C*(4)H), 141.5 (Ar*C*(1)), 170.7 (*C*=O); HRMS (NSI^+): $C_{15}H_{23}O_2N_2$ $[M+H]^+$ found 263.1755, requires 263.1754 (+0.4 ppm).

(2*S*,3*S*)-2-(Dimethylamino)-3-phenyl-1-(pyrrolidin-1-yl)pent-4-en-1-one 230

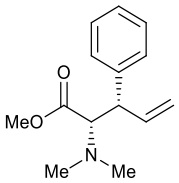


Following general procedure **I**, (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **211** (100 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr$_2$NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with pyrrolidine (100 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* 95:5. The residue was purified by flash chromatography on silica gel (50→100% EtOAc/PE) to give the title compound (40 mg, 61%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralcel OJ-H (5% IPA:hexane, flow rate 1.5 ml min^{-1}, 200 nm, 40 °C) t_R minor: 4.8 min, t_R major: 5.7 min, 99% *ee*.

$[\alpha]_D^{20}$ +114.0 (*c* 1.0, $CHCl_3$); mp 87-90 °C; ν_{max} (film, cm^{-1}): 2874, 1618, 1421, 1227, 1040, 993 921; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.69-1.94 (4H, m, C(3' and 4')H_2), 2.29 (6H, s, N(CH_3)$_2$), 3.19-3.25 (1H, m, C(2')H^AH^B), 3.39-3.53 (3H, m, 2 × C(5')*H* and C(2')H^AH^B), 3.63 (1H, d, *J* 9.4, C(2)*H*), 3.92 (1H, t, *J* 9.4, C(3)*H*), 4.97-5.04 (2H, m, C(5)H_2), 6.08 (1H, ddd, *J* 16.9, 9.4, 8.1, C(4)*H*), 7.18-7.34 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 24.3 (*C*(4')H_2), 26.3 (*C*(3')H_2), 42.0 (N(*C*H_3)$_2$), 45.4 (*C*(5')H_2), 46.9 (*C*(2')H_2), 50.4 (*C*(3)H), 68.8 (*C*(2)H), 116.9 (*C*(5)H_2), 126.7 (Ar*C*(4)H), 128.5 (Ar*C*(2,6)H), 128.6 (Ar*C*(3,5)H), 138.6 (*C*(4)H), 141.5 (Ar*C*(1)), 169.3 (*C*=O); HRMS (NSI$^+$): $C_{17}H_{25}ON_2$ $[M+H]^+$ found 273.1963, requires 273.1691 (+0.6 ppm).

(2*S*,3*S*)-Methyl 2-(dimethylamino)-3-phenylpent-4-enoate 231



Following general procedure **I**, (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **211** (4.00 g, 9.60 mmol, 1.0 equiv.), (+)-BTM (480 mg, 1.92 mmol, 0.2 equiv.), HOBt (256 mg, 1.92 mmol, 0.2 equiv.), *i*Pr$_2$NH (1.88 mL, 13.44 mmol, 1.4 equiv.) in MeCN (140 mL) were stirred for 24 h, quenched with NaOMe (1 M in MeOH, 28.8 mL, 28.8 mmol, 3.0 equiv.) and stirred for a further 1 h. Crude *dr* 95:5. The residue was purified by flash chromatography on silica gel (10→20% EtOAc/PE) to give the title compound (1.95 g, 8.36 mmol, 87%, 95:5 *dr* isolated) as a colourless oil.

HPLC: Chiralcel OJ-H (1% IPA:hexane, flow rate 1.5 mL min^{-1}, 211 nm, 40 °C) t_R minor: 4.3 min, t_R major: 5.4 min, 95% *ee*.

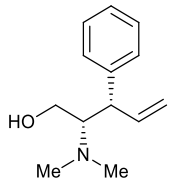
$[\alpha]_D^{20}$ +67.8 (*c* 1.0, $CHCl_3$); ν_{max} (film, cm^{-1}): 2947, 1730, 1454, 1256, 1190, 1143, 982, 918; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.29 (6H, s, N(C*H*$_3$)$_2$), 3.65 (1H, d, *J* 11.3, C(2)*H*), 3.73 (3H, s, OC*H*$_3$), 3.80 (1H, dd, *J* 11.3, 8.3, C(3)*H*), 5.02-5.15 (2H, m, C(5)*H*$_2$), 5.91 (1H, ddd, *J* 16.8, 10.1, 8.3, C(4)*H*), 7.23-7.28 (3H, m, Ar*H*), 7.36 (2H, t, *J* 7.6, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 41.5 (N(*C*H$_3$)$_2$), 50.2 (*C*(3)H), 50.8 (O*C*H$_3$), 71.0 (*C*(2)H), 116.6 (*C*(5)H$_2$), 126.7 (Ar*C*(4)H), 128.0 (Ar*C*(2,6)H), 128.6 (Ar*C*(3,5)H), 138.7 (*C*(4)H), 140.8 (Ar*C*(1)), 171.1 (*C*=O); HRMS (NSI^+): $C_{14}H_{20}NO_2$ $[M+H]^+$ found 234.1482, requires 234.1489 (−2.8 ppm).

The 0.240 mmol scale reaction of (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **211** gave **231** (36 mg, 64%, 95:5 *dr* isolated, 98% ee) as a colourless oil. Spectral data and HPLC analysis identical to the above.

231 was also synthesized by the *in situ* protocol:

Following general procedure **J**, the reaction of (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine **212** (41 mg, 0.250 mmol, 1.05 equiv.) and 4-nitrophenyl 2-bromoacetate (62 mg, 0.24 mmol, 1.0 equiv.) in MeCN (1.75 mL) were stirred for 24 h, followed by addition of (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr$_2$NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (1.75 mL) and stirred for a further 24 h. Quenched with NaOMe (1 M in MeOH, 720 µL, 0.72 mmol, 3.0 equiv.) and stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (10→20% EtOAc/PE) to give the title compound (35 mg, 0.150 mmol, 63%, 95:5 *dr* isolated, 94% ee) as a colourless oil. Spectral data and HPLC analysis identical to that above.

(2*S*,3*S*)-2-(Dimethylamino)-3-phenylpent-4-en-1-ol 232



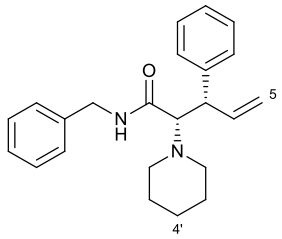
Following general procedure **I** with slight modification, (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **211** (100 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr$_2$NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, concentrated *in vacuo* and the solvent switched to THF (3.5 mL, 2 cycles). The solution was cooled to 0 °C, and $LiAlH_4$ (1.0 M in THF, 0.48 mL, 0.48 mmol, 2.0 equiv.) was added dropwise. The reaction was stirred for 1 h, quenched with aq. 1 M KOH

(10 mL), extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with aq. 1 M KOH (2 × 10 mL), brine (1 × 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (10→20% Et_2O/CH_2Cl_2, then 10% $MeOH/CH_2Cl_2$) to give the title compound (29 mg, 59%, >95:5 *dr* isolated) as a pale yellow oil.

HPLC: Chiralpak AD-H (2% IPA:hexane, flow rate 1.5 ml min^{-1}, 211 nm, 40 °C) t_R minor: 6.1 min, t_R major: 8.2 min, 96% *ee*.

$[\alpha]_D^{20}$ +95.4 (*c* 1.0, $CHCl_3$); ν_{max} (film, cm^{-1}): 3363, 2928, 1452, 1411, 1176, 1059, 1032, 914; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.14 (6H, s, N(C*H*$_3$)$_2$), 3.14 (1H, td, *J* 10.6, 5.0, C(2)*H*), 3.28 (1H, t, *J* 10.7, C(1)*H*^{A}H^B), 3.45 (1H, t, *J* 9.6, C(3)*H*), 3.63 (1H, dd, *J* 10.7, 5.0, C(1)H^A*H*^{B}), 4.89-5.04 (2H, m, C(5)*H*), 5.86 (1H, dt, *J* 16.9, 9.6, C(4)*H*), 7.19-7.32 (5H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 40.7 (N(*C*H$_3$)$_2$), 50.5 (*C*(3)H), 60.1 (*C*(1)H$_2$), 67.7 (*C*(2)H), 115.7 (*C*(5)H$_2$), 126.8 (Ar*C*(4)H), 128.1 (Ar*C*(3,5)H), 128.8 (Ar*C*(2,6)H), 138.8 (*C*(4)H), 143.1 (Ar*C*(1)); HRMS (NSI^+): $C_{13}H_{20}ON$ $[M+H]^+$ found 206.1539, requires 206.1539 (−0.2 ppm).

(2*S*,3*S*)-*N*-Benzyl-3-phenyl-2-(piperidin-1-yl)pent-4-enamide 265



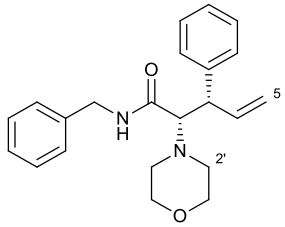
Following general procedure **I**, 1-cinnamyl-1-(2-(4-nitrophenoxy)-2-oxoethyl)piperidin-1-ium bromide **259** (111 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (2→5% Et_2O/CH_2Cl_2), and the resulting solid triturated with Et_2O (2 × 2.0 mL) to give the title compound **21** (70 mg, 0.201 mmol, 84%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralcel OJ-H (1% IPA:hexane, flow rate 1.5 ml min^{-1}, 211 nm, 40 °C), t_R minor: 23.3 min (not observed), t_R major: 29.2 min >99% *ee*.

$[\alpha]_D^{20}$ +71.8 (*c* 1.0, $CHCl_3$); mp 142-145 °C; ν_{max} (film, cm^{-1}): 3281, 2929, 1636, 1557, 1452, 1426, 1360, 1257, 1221, 926; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.28-1.42 (6H, m, C(3',5' and 4')*H*), 2.45-2.56 (4H, br s, C(2',6')*H*), 3.29 (1H, d, *J* 7.8, C(2)*H*), 3.88 (1H, t, *J* 7.8, C(3)*H*), 4.46 (2H, d, *J* 5.5, PhC*H*$_2$), 4.95-5.14 (2H, m, C(5)*H*), 6.12 (1H, dt, *J* 17.1, 8.6, C(4)*H*), 6.61 (1H, br s, N*H*), 7.11-7.55 (10H, m, 10 × Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 24.4 (*C*(4')H$_2$), 26.5 (*C*(3',5')H$_2$), 43.3 (Ph*C*H$_2$), 49.4

(*C*(3)H), 51.8 (*C*(2',6')H_2), 74.1 (*C*(2)H), 116.4 (*C*(5)H_2), 126.3 (Ar*C*H), 127.6 (Ar*C*H), 128.0 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 128.8 (Ar*C*H), 138.6 (Ar*C*(1)), 139.3 (*C*(4)H), 142.6 (C(3)Ar*C*(1)), 170.7 (*C*=O); HRMS (NSI$^+$): $C_{23}H_{29}ON_2$ $[M+H]^+$ found 349.2276, requires 349.2274 (+0.2 ppm).

(2*S*,3*S*)-*N*-Benzyl-2-morpholino-3-phenylpent-4-enamide 266

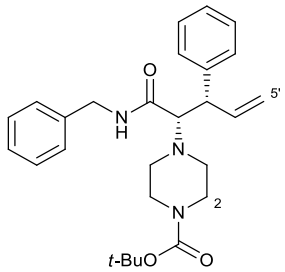


Following general procedure **I**, 4-cinnamyl-4-(2-(4-nitrophenoxy)-2-oxoethyl)morpholin-4-ium bromide **260** (111 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* 94:6. The residue was purified by flash chromatography on silica gel (2→5% Et_2O/CH_2Cl_2), and the resulting solid triturated with Et_2O (2 × 2.0 mL) to give the title compound **22** (70 mg, 83%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralpak AD-H (3% IPA:hexane, flow rate 1.5 ml min^{-1}, 211 nm, 40 °C) t_R minor: 32.5 min, t_R major: 37.7 min, 86% *ee*.

$[\alpha]_D^{20}$ +58.2 (*c* 1.0, $CHCl_3$); mp 180-182 °C; ν_{max} (film, cm^{-1}): 3267, 2853, 1635, 1558, 1448, 1418, 1248, 1111, 999; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.52-2.62 (4H, m, C(2',6')H_2), 3.23 (1H, d, *J* 8.6, C(2)*H*), 3.40-3.54 (4H, m, C(3',5')H_2), 3.87 (1H, t, *J* 8.6, C(3)*H*), 4.44 (2H, d, *J* 5.6, PhCH_2), 5.03-5.09 (2H, m, C(5)*H*),6.06 (1H, ddd, *J* 17.9, 9.7, 8.6, C(4)*H*), 6.24 (1H, br s, N*H*), 7.16-7.38 (10H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 43.5 (Ph*C*H_2), 49.5 (*C*(3)H), 50.9 (*C*(2',6')H_2), 67.3 (*C*(3',5')H_2), 73.8 (*C*(2)H), 116.9 (*C*(5)H_2), 126.6 (Ar*C*H), 127.7 (Ar*C*H), 128.1 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 128.9 (Ar*C*H), 138.3 (Ar*C*(1)), 138.5 (*C*(4)H), 141.6 (*C*(3)Ar*C*(1)), 169.8 (*C*=O); HRMS (NSI$^+$): $C_{22}H_{27}O_2N_2$ $[M+H]^+$ found 351.2070, requires 351.2067 (+0.8 ppm).

***tert*-Butyl 4-((2*S*,3*S*)-1-(benzylamino)-1-oxo-3-phenylpent-4-en-2-yl)piperazine-1-carboxylate 267**

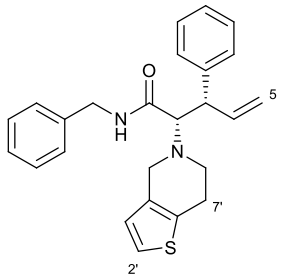


Following general procedure **I**, 4-(tert-butoxycarbonyl)-1-cinnamyl-1-(2-(4-nitrophenoxy)-2-oxoethyl)piperazin-1-ium bromide **261** (135 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* 93:7. The residue was purified by flash chromatography on silica gel (2→5% Et_2O/CH_2Cl_2), and the resulting solid triturated with Et_2O (2 × 2.0 mL) to give the title compound (96 mg, 89%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralcel OJ-H (5% IPA:hexane, flow rate 1.5 ml min^{-1}, 220 nm, 40 °C) t_R major: 7.8 min, t_R minor: 17.8 min, 96% *ee*.

$[\alpha]_D^{20}$ +51.4 (*c* 1.0, $CHCl_3$); mp 155-157 °C; ν_{max} (film, cm^{-1}): 3279, 2970, 1681, 1635, 1558, 1456, 1364, 1248, 1163, 1001, 920; ^{1}H NMR (500 MHz, toluene-d_8, 351 K) δ_H: 1.37 (9H, s, OC(CH_3)$_3$), 2.29 (2H, dt, *J* 10.5, 5.0, C(3,5)H^AH^B), 2.46 (2H, dt, *J* 10.5, 5.0, C(3,5)H^AH^B), 2.89 (1H, d, *J* 9.6, C(2')*H*), 3.01-3.16 (4H, m, C(2,6)H_2), 3.88 (1H, t, *J* 8.6, C(3')*H*), 4.19 (1H, dd, *J* 14.7, 5.9, PhCH^AH^B), 4.28 (1H, dd, *J* 14.7, 5.9, PhCH^AH^B), 4.91-5.01 (2H, m, C(5')*H*), 5.41 (1H, br s, N*H*), 5.96 (1H, ddd, *J* 17.5, 10.2, 7.7, C(4')*H*), 6.95-7.17 (10H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, toluene-d_6, 351 K) δ_C: 28.6 (C(*C*H_3)$_3$), 43.6 (Ph*C*H_2), 44.8 (*C*(3,5)H_2), 49.8 (*C*(3')H), 50.3 (*C*(2,6)H_2), 73.2 (*C*(2')H), 79.0 (*C*(CH_3)$_3$), 116.5 (*C*(5')H), 126.6 (Ar*C*H), 127.6 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 128.8 (Ar*C*H), 129.1 (Ar*C*H), 139.6 (Ar*C*(1)), 139.8 (*C*(4')H), 142.2 (C(3')Ar*C*(1)), 154.7 (Boc,*C*=O), 168.9 (*C*=O); HRMS (NSI$^+$): $C_{27}H_{36}O_3N_3$ $[M+H]^+$ found 450.2749, requires 450.2751 (–0.5 ppm).

(2*S*,3*S*)-*N*-Benzyl-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-3-phenylpent-4-enamide 268

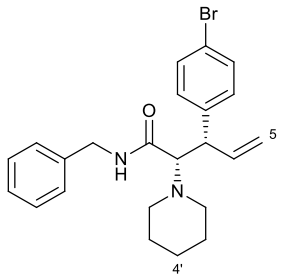


Following general procedure **I**, 5-cinnamyl-5-(2-(4-nitrophenoxy)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-5-ium bromide **262** (124 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (0→10% Et_2O/CH_2Cl_2) to give the title compound (77 mg, 80%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralpak AD-H (4% IPA:hexane, flow rate 1.5 ml min^{-1}, 211 nm, 40 °C) t_R minor: 30.3 min, t_R major: 36.7 min, >99% *ee*.

$[\alpha]_D^{20}$ +70.6 (*c* 1.0, $CHCl_3$); mp 50-52 °C; ν_{max} (film, cm^{-1}): 3273, 2918, 1638, 1559, 1454, 1265, 1039, 912; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.47-2.57 (1H, m, C(7')H^A*H^B*), 2.58-2.67 (1H, m, C(7')H^A*H^B*), 2.74-2.83 (1H, m, C(6')*H^A*H^B), 3.00 (1H, dt, *J* 11.0, 5.1, C(6')H^A*H^B*), 3.53 (1H, d, *J* 8.1, C(2)*H*), 3.64 (1H, d, *J* 14.1, C(4')*H^A*H^B), 3.76 (1H, d, *J* 14.1, C(4')H^A*H^B*), 3.98 (1H, t, *J* 8.1, C(3)*H*), 4.44 (2H, *apt* quintet, *J* 8.9, PhCH_2), 4.99-5.12 (2H, m, C(5)*H*), 6.16 (1H, dt, *J* 18.3, 9.3, C(4)*H*), 6.54 (1H, br s, N*H*), 6.62 (1H, d, *J* 5.0, C(3')*H*), 7.00 (1H, d, *J* 5.0, C(2')*H*), 7.36-7.13 (10H, m, 10 × Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 26.1 (*C*(7')H_2), 43.4 (Ph*C*H_2), 47.8 (*C*(6')H_2), 50.0 (*C*(3)H), 50.7 (*C*(4')H_2), 72.8 (*C*(2)H), 116.8 (*C*(5)H_2), 122.6 (*C*(3')H), 125.2 (*C*(2')H), 126.6 (Ar*C*H), 127.7 (Ar*C*H), 128.1 (Ar*C*H), 128.4 (Ar*C*H), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 133.5 (*C*(9')), 133.8 (*C*(8'),) 138.4 (Ar*C*(1)), 138.9 (*C*(4)H), 142.0 (C(3)Ar*C*(1)), 170.5 (*C*=O); HRMS (ESI$^+$): $C_{25}H_{27}ON_2S$ $[M+H]^+$ found 403.1833, requires 403.1844 (–1.4 ppm).

(2*S*,3*S*)-*N*-Benzyl-3-(4-bromophenyl)-2-(piperidin-1-yl)pent-4-enamide[†] 269

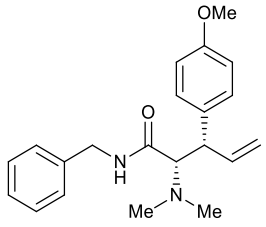


Following general procedure **I**, (*E*)-1-(3-(4-bromophenyl)allyl)-1-(2-(4-nitrophenoxy)-2-oxoethyl)piperidin-1-ium bromide **263** (130 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (0→4% Et_2O/CH_2Cl_2) to give the title compound (89 mg, 87%, >95:5 *dr* isolated) as a white solid.

HPLC: Chiralpak AD-H (5% IPA:hexane, flow rate 1.5 ml min^{-1}, 220 nm, 40 °C) t_R major: 10.6 min, t_R minor: 18.0 min, 98% *ee*.

$[\alpha]_D^{20}$ +69.3 (*c* 1.0, $CHCl_3$); mp 170-172 °C; ν_{max} (film, cm^{-1}): 3271, 2930, 2812, 1659, 1635, 1558, 1487, 1454, 1221, 1103, 1070, 1009, 991, 918, 814; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.28-1.43 (6H, m, C(3',5' and 4')H_2), 2.40-2.57 (4H, m, C(2')*H*), 3.16-3.27 (1H, m, C(2)*H*), 3.83-3.93 (1H, m, C(3)*H*), 4.39-4.51 (2H, m, PhCH_2), 5.00-5.08 (2H, m, C(5)*H*), 6.06 (1H, ddd, *J* 16.7, 10.5, 8.2, C(4)*H*), 6.51 (1H, br s, N*H*), 7.13 (2H, d, *J* 8.4, C(3)ArC(2,6)*H*), 7.25-7.37 (5H, m, Ar*H*), 7.40 (2H, d, *J* 8.4, C(3)ArC(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 24.4, 26.5, 43.4, 48.5, 51.7, 73.8, 117.0, 120.1, 127.6, 128.0, 128.8, 130.3, 131.4, 138.4, 138.7, 141.5, 170.1; HRMS (ESI^+): $C_{23}H_{28}ON_2{}^{79}Br$ $[M+H]^+$ found 427.1365, requires 427.1380 (−3.4 ppm).

(2*S*,3*S*)-*N*-Benzyl-2-(dimethylamino)-3-(4-methoxyphenyl)pent-4-enamide 271



Following general procedure **I**, (*E*)-3-(4-methoxyphenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **256** (108 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4

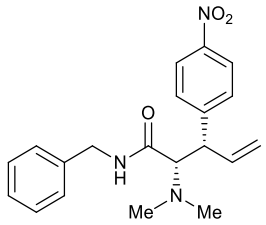
[†] Synthesised and characterised by Dr David S. B. Daniels

equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* 88:12. The residue was purified by flash chromatography on silica gel (50→100% EtOAc/PE) to give the title compound (49 mg, 60%, 93:7 *dr* isolated) as an off white solid.

HPLC: Chiralcel OJ-H (3% IPA:hexane, flow rate 1.5 mL min^{-1}, 211 nm, 40 °C) t_R major: 31.0 min, t_R minor: 36.9 min (not observed), >99% *ee*.

$[\alpha]_D^{20}$ +89.7 (*c* 1.0, $CHCl_3$); mp 94 °C (*dec*); ν_{max} (film, cm^{-1}): 3304, 2932, 2862, 1640, 1545, 1510, 1452, 1248, 1217, 1030, 908; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 2.29 (6H, s, N(CH_3)$_2$), 3.14 (1H, d, *J* 8.3, C(2)*H*), 3.77-3.80 (4H, m, C(3)*H* and OCH_3), 4.43 (2H, d, *J* 5.7, PhCH_2), 5.01-5.07 (2H, m, C(5)*H*), 6.08 (1H, ddd, *J* 17.8, 9.7, 8.5, C(4)*H*), 6.26 (1H, br s, N*H*), 6.84 (2H, d, *J* 8.7, C(3)ArC(3,5)*H*), 7.15 (2H, d, *J* 8.7, C(3)ArC(2,6)*H*), 7.37-7.23 (5H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 42.7 (N(CH_3)$_2$), 43.4 (PhCH_2), 49.3 (*C*(3)H), 55.3 (OCH_3), 74.0 (*C*(2)H), 114.0 (C(3)Ar*C*(3,5)H), 116.5 (*C*(5)H_2), 127.6 (Ar*C*(4)H), 128.2 (Ar*C*(2,6)H), 128.8 (Ar*C*(3,5)H), 129.2 (C(3)Ar*C*(2,6)H), 133.9 (C(3)Ar*C*(1)), 138.4 (Ar*C*(1)), 138.9 (*C*(4)H), 158.2 (C(3)Ar*C*(4)-OMe), 170.4 (*C*=O); HRMS (NSI^+): $C_{21}H_{27}N_2O_2$ $[M+H]^+$ found 339.2069, requires 339.2067 (+0.6 ppm).

(2*S*,3*S*)-*N*-Benzyl-2-(dimethylamino)-3-(4-nitrophenyl)pent-4-enamide 272



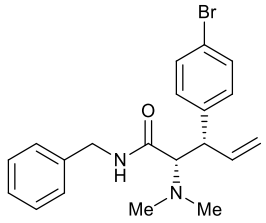
Following general procedure **I**, (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-(4-nitrophenyl)prop-2-en-1-ammonium bromide **257** (112 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (50→100% EtOAc/PE) to give the title compound (60 mg, 71%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralpak AD-H (5% IPA:hexane, flow rate 1.5 mL min^{-1}, 200 nm, 40 °C) t_R major: 20.1 min, t_R minor: 22.4 min, 96% *ee*.

$[\alpha]_D^{20}$ +94.4 (*c* 1.0, $CHCl_3$); mp 128-130 °C; ν_{max} (film, cm^{-1}): 3285, 2922, 1640, 1556, 1510, 1344, 1224, 1180, 1006, 934; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.31 (6H, s, N(CH_3)$_2$), 3.27 (1H, d, *J* 8.4, C(2)*H*), 4.04 (1H, t, *J* 8.4, C(3)*H*), 4.42-4.56 (2H, m, PhCH_2), 5.08-5.19 (2H, m, C(5)*H*), 6.05 (1H, dt,

J 17.8, 9.8, C(4)*H*), 6.37 (1H, br s, N*H*), 7.27-7.40 (5H, m, Ar*H*), 7.42 (2H, d, *J* 8.6, C(3)ArC(2,6)*H*), 8.18 (2H, d, *J* 8.6, C(3)ArC(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 42.3 ($N(CH_3)_2$), 43.5 ($PhCH_2$), 49.4 (*C*(3)H), 73.0 (*C*(2)H), 118.5 (*C*(5)H_2), 123.8 (C(3)Ar*C*(3,5)H), 127.8 (Ar*C*H), 128.2 (Ar*C*H), 128.9 (Ar*C*H), 129.3 (C(3)Ar*C*(2,6)H), 137.2 (*C*(4)H), 138.2 (Ar*C*(1)), 146.6 (C(3)Ar*C*(4)-NO_2), 149.9 (C(3)Ar*C*(1)), 169.1 (*C*=O); HRMS (NSI^+): $C_{20}H_{24}N_3O_3$ $[M+H]^+$ found 354.1816, requires 354.1812 (+1.1 ppm).

(2*S*,3*S*)-*N*-Benzyl-3-(4-bromophenyl)-2-(dimethylamino)pent-4-enamide 273

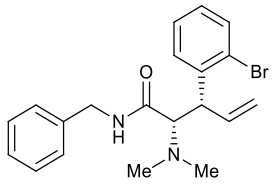


Following general procedure **I**, (*E*)-3-(4-bromophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **258** (120 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* 95:5. The residue was purified by flash chromatography on silica gel (50→100% EtOAc/PE) to give the title compound (71 mg, 76%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralcel OJ-H (2% IPA:hexane, flow rate 1.5 mL min^{-1}, 220 nm, 40 °C) t_R major: 25.4 min, t_R minor: 29.4 min, >99% *ee*.

$[\alpha]_D^{20}$ +93.3 (*c* 1.0, $CHCl_3$); mp 115-117 °C; ν_{max} (film, cm^{-1}): 3291, 2918, 1641, 1552, 1487, 1009, 928; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.31 (6H, s, $N(CH_3)_2$), 3.17 (1H, d, *J* 8.4, C(2)*H*), 3.85 (1H, t, *J* 8.3, C(3)*H*), 4.33-4.57 (2H, m, $PhCH_2$), 5.02-5.13 (2H, m, C(5)H_2), 6.06 (1H, ddd, *J* 16.9, 10.3, 8.3, C(4)*H*), 6.29 (1H, br s, N*H*), 7.14 (2H, d, *J* 8.4, C(3)ArC(2,6)*H*), 7.24-7.41 (5H, m, Ar*H*), 7.44 (2H, d, *J* 8.4, C(3)ArC(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 42.5 ($N(CH_3)_2$), 43.4 ($PhCH_2$), 49.3 (*C*(3)H), 73.5 (*C*(2)H), 117.4 (*C*(5)H_2), 120.4 (C(3)Ar*C*(4)-Br), 127.7 (Ar*C*H), 128.2 (Ar*C*H), 128.8 (Ar*C*H), 130.1 (C(3)Ar*C*(2,6)H), 131.7 (C(3)Ar*C*(3,5)H), 138.2 (*C*(4)H), 138.3 (Ar*C*(1)), 141.0 (C(3)Ar*C*(1)), 169.8 (*C*=O); HRMS (NSI^+): $C_{20}H_{24}ON_2{}^{79}Br$ $[M+H]^+$ found 387.1069, requires 387.1067 (+0.6 ppm).

(2*S*,3*S*)-*N*-Benzyl-3-(2-bromophenyl)-2-(dimethylamino)pent-4-enamide 274



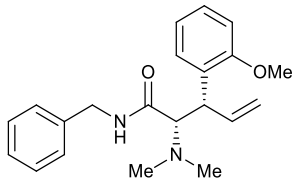
Following general procedure **I**, (*E*)-3-(2-bromophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **254** (120 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr$_2$NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with BnNH$_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (50→100% EtOAc/PE) to give the title compound (51 mg, 55%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralpak AD-H (2.5% IPA:hexane, flow rate 1.5 mL min^{-1}, 200 nm, 40 °C) t_R major: 13.8 min, t_R minor: 19.0 min, 86% *ee*.

$[\alpha]_D^{20}$ +42.0 (*c* 1.0, $CHCl_3$); mp 122-126 °C; ν_{max} (film, cm^{-1}): 3293, 2924, 1638, 1553, 1454, 1267, 1222, 1020, 918; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.33 (6H, s, N(C*H*$_3$)$_2$), 3.27 (1H, d, *J* 7.1, C(2)*H*), 4.40 (1H, t, *J* 8.2, C(3)*H*), 4.46 (2H, d, *J* 5.2, PhC*H*$_2$), 5.08-5.19 (2H, m, C(5)*H*$_2$), 6.11 (1H, dt, *J* 17.5, 9.3, C(4)*H*), 6.43 (1H, br s, N*H*), 7.07-7.13 (1H, m, *o*-BrAr(4)C*H*), 7.25-7.39 (7H, m, 2 × C(3)ArC*H* and 5 × Ar*H*), 7.57 (1H, dd, *J* 8.0, 1.1, C(3)ArC(3)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 42.8 (N(*C*H$_3$)$_2$), 43.4 (Ph*C*H$_2$), 48.7 (*C*(3)H), 72.8 (*C*(2)H), 117.8 (*C*(5)H$_2$), 124.7 (Ar*C*(2)-Br), 127.5 (Ar*C*H), 127.6 (Ar*C*H), 128.1 (C(3)Ar*C*(5)H), 128.2 (Ar*C*H), 128.8 (Ar*C*H), 130.0 (Ar*C*H), 133.2 (C(3)Ar*C*(3)H), 137.0 (*C*(4)H), 138.3 (C(3)Ar*C*(1)), 140.7 (Ar*C*(1)), 170.2 (*C*=O); HRMS (NSI$^+$): $C_{20}H_{24}ON_2{}^{79}Br$ $[M+H]^+$ found 387.1070, requires 387.1067 (+0.9 ppm).

Crystal data for **274**: $C_{20}H_{23}BrN_2O$, M = 378.32, colourless prism, orthorhombic space group *P* 21 21 21; *a* = 8.039(2) Å, *b* = 9.628(2) Å, *c* = 24.585(5) Å, $\alpha = \beta = \gamma = 90°$, *V* = 1902.7(7) Å^3, *Z* = 4, D_c = 1.352 g cm^{-3}, flack parameter = 0.046(5), *R* = 0.0257, R_W = 0.0623 for 3464 data with $I > 2\sigma(I)$ and 255 parameters. Data were recorded at 93 K on Saturn 70 diffractometer using multi-layer mirror monochromated MoKa (I = 0.71075 Å) radiation and the structures were solved by direct methods and refined using full-matrix least square analysis.

(2*S*,3*S*)-*N*-Benzyl-2-(dimethylamino)-3-(2-methoxyphenyl)pent-4-enamide 275

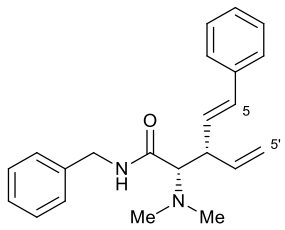


Following general procedure **I**, (*E*)-3-(2-methoxyphenyl)-*N*,*N*-Dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **256** (108 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* 94:6. The residue was purified by flash chromatography on silica gel (50→100% EtOAc/PE) to give the title compound (27 mg, 33%, >95:5 *dr* isolated) as a pale yellow solid.

HPLC: Chiralpak AD-H (1% IPA:hexane, flow rate 1.5 mL min^{-1}, 220 nm, 40 °C) t_R major: 41.6 min, t_R minor: 64.0 min, 95% *ee*.

$[\alpha]_D^{20}$ +61.6 (*c* 0.18, $CHCl_3$); mp 147-149 °C; ν_{max} (film, cm^{-1}): 3933, 2934, 1641, 1492, 1242, 1029, 916; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.28 (6H, s, N(C*H*$_3$)$_2$), 3.32 (1H, d, *J* 7.8, C(2)*H*), 3.83 (3H, s, OC*H*$_3$), 4.25 (1H, t, *J* 8.3, C(3)*H*), 4.43 (2H, d, *J* 5.6, PhC*H*$_2$), 5.01-5.14 (2H, m, C(5)*H*), 6.14-6.25 (1H, m, C(4)*H*), 6.39 (1H, br s, N*H*), 6.85 (1H, d, *J* 8.2, C(3)Ar(3)*H*), 6.92 (1H, t, *J* 7.4, C(3)ArC(4)*H*), 7.13-7.37 (7H, m, C(3)Ar(5 & 6)*H* and 5 × Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 42.7 (N(*C*H$_3$)$_2$), 43.3 (Ph*C*H$_2$), 43.7 (*C*(3)H), 55.5 (O*C*H$_3$), 72.5 (*C*(2)H), 110.8 (Ar*C*H), 116.8 (*C*(5)H$_2$), 120.8 (Ar*C*H), 127.6 (2 × Ar*C*H), 128.2 (Ar*C*H), 128.7 (Ar*C*H), 129.4 (Ar*C*H), 130.4 (C(3)Ar*C*(1)), 138.1 (*C*(4)H), 138.5 (Ar*C*(1)), 156.6 (Ar*C*(2)-OMe), 170.9 (*C*=O); HRMS (NSI$^+$): $C_{21}H_{27}O_2N_2$ $[M+H]^+$ found 339.2070, requires 339.2067 (+0.9 ppm).

(2*S*,3*S*,*E*)-*N*-Benzyl-2-(dimethylamino)-5-phenyl-3-vinylpent-4-enamide 279



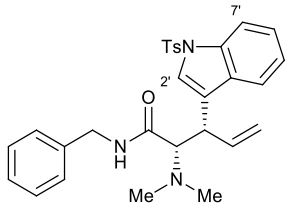
Following general procedure **J**, (2*E*,4*E*)-*N*,*N*-dimethyl-5-phenylpenta-2,4-dien-1-amine **251** (47 mg, 0.250 mmol, 1.05 equiv.) and 4-nitrophenyl 2-bromoacetate **213** (62 mg, 0.24 mmol, 1.0 equiv.) in MeCN (1.75 mL) were stirred for 24 h, followed by addition of (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN

(1.75 mL) and stirred for a further 24 h. Quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* 88:12. The residue was purified by flash chromatography on silica gel (30% EtOAc/PE) to give the title compound (42 mg, 51%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralcel OJ-H (4% IPA:hexane, flow rate 1.5 mL min^{-1}, 254 nm, 40 °C) t_R major: 12.8 min, t_R minor: 16.0 min, 96% *ee*.

$[\alpha]_D^{20}$ +89.5 (*c* 1.0, $CHCl_3$); mp 133-136 °C; ν_{max} (film, cm^{-1}): 3292, 2934, 1641, 1545, 1454, 1213, 1028, 962; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.34 (6H, s, N(C*H*$_3$)$_2$), 2.93 (1H, d, *J* 5.7, C(2)*H*), 3.51 (1H, q, *J* 6.8, C(3)*H*), 4.45 (2H, d, *J* 5.1, PhC*H*$_2$), 5.05-5.20 (2H, m, C(5')*H*), 5.97 (1H, ddd, *J* 17.3, 10.3, 7.1, C(4')*H*), 6.33 (1H, dd, *J* 15.9, 7.7, C(4)*H*), 6.42 (1H, d, *J* 15.9, C(5)*H*), 6.73 (1H, br s, N*H*), 7.18-7.36 (10H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 43.3 (Ph*C*H$_2$), 43.4 (N(*C*H$_3$)$_2$), 47.3 (*C*(3)H), 74.5 (*C*(2)H), 117.1 (*C*(5')H$_2$), 126.5 (Ar*C*H), 127.4 (Ar*C*H), 127.6 (Ar*C*H), 128.1 (Ar*C*H), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 129.5 (*C*(4)H), 131.6 (*C*(5)H), 137.5 (Ar*C*(1')), 137.7 (*C*(4')H), 138.4 (Ar*C*(1)), 170.9 (*C*=O); HRMS (ESI^+): $C_{22}H_{27}ON_2$ $[M+H]^+$ found 335.2114, requires 335.2123 (–1.2 ppm).

(2*S*,3*S*)-*N*-Benzyl-2-(dimethylamino)-3-(1-tosyl-1*H*-indol-3-yl)pent-4-enamide 280



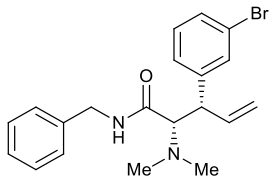
Following general procedure **J**, (*E*)-*N*,*N*-dimethyl-3-(1-tosyl-1*H*-indol-3-yl)prop-2-en-1-amine **252** (89 mg, 0.250 mmol, 1.05 equiv.) and 4-nitrophenyl 2-bromoacetate **213** (62 mg, 0.24 mmol, 1.0 equiv.) in MeCN (1.75 mL) were stirred for 24 h, followed by addition of (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (1.75 mL) and stirred for a further 24 h. Quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (0→5% Et_2O/CH_2Cl_2) to give the title compound (67 mg, 56%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralpak AD-H (10% IPA:hexane, flow rate 1.5 mL min^{-1}, 220 nm, 40 °C) t_R major: 15.5 min, t_R minor: 21.8 min, 92% *ee*.

$[\alpha]_D^{20}$ +39.1 (*c* 1.0, $CHCl_3$); mp 62-64 °C; ν_{max} (film, cm^{-1}): 3290, 2926, 1643, 1447, 1362, 1169, 1120, 1070, 978; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.30 (6H, N(C*H*$_3$)$_2$), 2.30 (3H, s, TsC*H*$_3$), 3.27-3.37 (1H, m, C(2)*H*), 4.10 (1H, t, *J* 7.8, C(3)*H*), 4.40 (2H, d, *J* 5.1, PhC*H*$_2$), 4.98-5.14 (2H, m, C(5)*H*), 6.04 (1H,

dt, *J* 17.6, 8.9, C(4)*H*), 6.39 (1H, br s, N*H*), 7.16 (2H, d, *J* 8.2, TsArC(3,5)*H*), 7.18-7.23 (2H, m, IndArC(5 and 6)*H*), 7.27-7.34 (5H, m, Ar*H*), 7.49 (1H, d, *J* 7.8, IndArC(4)*H*), 7.54 (1H, s, IndArC(2)*H*), 7.71 (2H, d, *J* 8.2, TsArC(2,6)*H*), 7.95 (1H, d, *J* 8.3, IndArC(7)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 21.7, 40.9, 42.7, 43.4, 72.6, 114.0, 117.6, 119.7, 122.1, 123.3, 124.7 (2 × *C*), 126.9, 127.6, 128.1, 128.8, 129.9, 130.6, 135.3, 135.3, 137.0, 138.2, 144.8, 170.0; HRMS (ESI^+): $C_{29}H_{32}O_3N_3S$ $[M+H]^+$ found 502.2155, requires 502.2164 (–0.7 ppm).

(2*S*,3*S*)-*N*-Benzyl-3-(3-bromophenyl)-2-(dimethylamino)pent-4-enamide 281

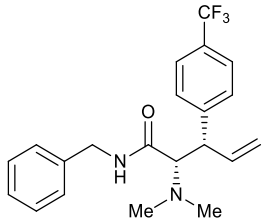


Following general procedure **J**, (*E*)-3-(3-bromophenyl)-*N*,*N*-dimethylprop-2-en-1-amine **246** (61 mg, 0.250 mmol, 1.05 equiv.) and 4-nitrophenyl 2-bromoacetate **213** (62 mg, 0.24 mmol, 1.0 equiv.) in MeCN (1.75 mL) were stirred for 24 h, followed by addition of (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (1.75 mL) and stirred for a further 24 h. Quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (30→70% EtOAc/PE) to give the title compound (65 mg, 70%, >95:5 *dr* isolated) as a pale yellow solid.

HPLC: Chiralcel OJ-H (2% IPA:hexane, flow rate 1.5 mL min^{-1}, 211 nm, 40 °C) t_R major: 20.9 min, t_R minor: 28.8 min, 91% *ee*.

$[\alpha]_D^{20}$ +73.0 (*c* 1.0, $CHCl_3$); mp 113-116 °C; ν_{max} (film, cm^{-1}): 3298, 2922, 1645, 1537, 1474, 1452, 1354, 1255, 918; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.32 (6H, s, N(CH_3)$_2$), 3.22 (1H, d, *J* 7.9, C(2)*H*), 3.85 (1H, t, *J* 8.4, C(3)*H*), 4.46 (2H, d, *J* 5.6, PhCH_2), 5.04-5.10 (2H, m, C(5)*H*), 6.04 (1H, ddd, *J* 16.8, 10.4, 8.4, C(4)*H*), 6.35 (1H, br s, N*H*), 7.15-7.20 (2H, m, C(3)Ar*H*), 7.25-7.31 (3H, m, Ar*H*), 7.31-7.36 (3H, m, 1 × C(3)Ar*H* and 2 × Ar*H*), 7.39 (1H, s, C(3)Ar(2)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 42.5 (N(CH_3)$_2$), 43.4 (PhCH_2), 49.6 (*C*(3)H), 73.3 (*C*(2)H), 117.6 (*C*(5)H_2), 122.6 (Ar*C*(2)-Br), 127.1 (Ar*C*H), 127.7 (Ar*C*H), 128.2 (Ar*C*H), 128.8 (Ar*C*H), 129.8 (Ar*C*H), 130.2 (Ar*C*H), 131.4 (Ar*C*H), 137.9 (*C*(4)H), 138.3 (Ar*C*(1)), 144.3 (C(3)Ar*C*(1)), 169.6 (*C*=O); HRMS (NSI^+): $C_{20}H_{24}ON_2{}^{79}Br$ $[M+H]^+$ found 387.1071, requires 387.1067 (+1.2 ppm).

(2*S*,3*S*)-*N*-Benzyl-2-(dimethylamino)-3-(4-(trifluoromethyl)phenyl)pent-4-enamide 282

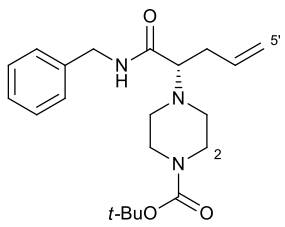


Following general procedure **J**, (*E*)-*N*,*N*-dimethyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine **250** (58 mg, 0.250 mmol, 1.05 equiv.) and 4-nitrophenyl 2-bromoacetate **213** (62 mg, 0.24 mmol, 1.0 equiv.) in MeCN (1.75 mL) were stirred for 24 h, followed by addition of (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in MeCN (1.75 mL) and stirred for a further 24 h. Quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* >95:5. The residue was purified by flash chromatography on silica gel (5→20% Et_2O/CH_2Cl_2) to give the title compound (47 mg, 52%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralpak AD-H (1% IPA:hexane, flow rate 1.5 mL min^{-1}, 211 nm, 40 °C) t_R major: 37.0 min, t_R minor: 44.7 min, 85% *ee*.

$[\alpha]_D^{20}$ +70.6 (*c* 0.5, $CHCl_3$); mp 160-163 °C; ν_{max} (film, cm^{-1}): 3284, 2917, 1641, 1557, 1322, 1152, 1119, 1067, 927; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.31 (6H, s, N(C*H*$_3$)$_2$), 3.26 (1H, d, *J* 8.4, C(2)*H*), 3.96 (1H, t, *J* 8.4, C(3)*H*), 4.47 (2H, *apt* t, *J* 5.7, PhC*H*$_2$), 5.16-5.03 (2H, m, C(5)*H*), 6.07 (1H, ddd, *J* 18.4, 10.1, 8.5, C(4)*H*), 6.39 (1H, br s, N*H*), 7.19-7.44 (7H, m, C(3)ArC(2,6)*H* and 5 × Ar*H*), 7.57 (2H, d, *J* 8.1, C(3)ArC(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 42.4 (N(*C*H$_3$)$_2$), 43.4 (Ph*C*H$_2$), 49.6 (*C*(3)H), 73.2 (*C*(2)H), 117.8 (*C*(5)H$_2$), 124.4 (q, $^1J_{CF}$ 272, *C*F$_3$), 125.5 (q, $^3J_{CF}$ 4, C(3)Ar*C*(3,5)H), 127.7 (Ar*C*H), 128.2 (Ar*C*H), 128.7 (Ar*C*H), 128.7 (q, $^2J_{CF}$ 32, C(3)Ar*C*(4)), 128.9 (Ar*C*H), 137.9 (*C*(4)H), 138.2 (Ar*C*(1)), 146.1 (C(3)Ar*C*(1)), 169.6 (*C*=O); ^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ_F: –62.3 (C*F*$_3$); HRMS (NSI$^+$): $C_{21}H_{24}ON_2F_3$ $[M+H]^+$ found 377.1837, requires 377.1835 (+0.5 ppm).

(*S*)-*tert*-Butyl 4-(1-(benzylamino)-1-oxopent-4-en-2-yl)piperazine-1-carboxylate 289



Following general procedure **J**, 1-allyl-4-(*tert*-butoxycarbonyl)-1-(2-(4-nitrophenoxy)-2-oxoethyl)piperazin-1-ium bromide **288** (117 mg, 0.240 mmol, 1.0 equiv.), (+)-BTM (12.0 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.), *i*Pr_2NH (47 µL, 0.19 mmol, 1.4 equiv.) in

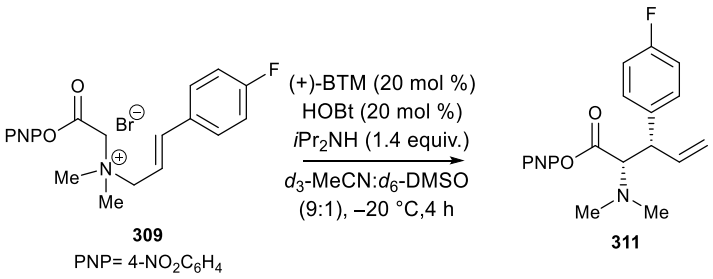
MeCN (3.5 mL) were stirred for 24 h, quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. The residue was purified by flash chromatography on silica gel (0→10% Et_2O/CH_2Cl_2) to give the title compound (68 mg, 76%, >95:5 *dr* isolated) as an off white solid.

HPLC: Chiralpak AD-H (5% IPA:hexane, flow rate 1.5 ml min^{-1}, 211 nm, 40 °C) t_R major: 13.3 min, t_R minor: 16.5 min, 56% *ee*.

$[\alpha]_D^{20}$ +8.7 (*c* 1.0, $CHCl_3$); mp 77-79 °C; ν_{max} (film, cm^{-1}): 3261, 2970, 1695, 1643, 1415, 1244, 1120, 995; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.44 (9H, s, OC(CH_3)$_3$), 2.43-2.50 (3H, m, 2 × C(2,6)H^AH^B and C(3',5')H^AH^B), 2.56-2.65 (3H, m, 2 × C(2,6)H^AH^B and C(3',5')H^AH^B), 3.07 (1H, t, *J* 6.3, C(2')*H*), 3.30-3.44 (4H, m, C(3,5)*H*), 4.37-4.51 (2H, m, PhCH_2), 5.05 (1H, dd, *J* 10.2, 1.5, C(5')H^{cis}), 5.11 (1H, dd, *J* 17.0, 1.5, C(5')H^{trans}), 5.86 (1H, ddd, *J* 17.0, 10.2, 1.5, C(4')*H*), 7.23-7.36 (5H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 28.5 (C(CH_3)$_3$), 32.4 (*C*(2')H), 43.3 (*C*(2,6)H_2), 43.4 (Ph*C*H_2), 50.3 (*C*(3,5)H_2), 69.1 (*C*(3)H), 80.0 (*C*(CH_3)$_3$), 117.5 (*C*(5')H_2), 127.7 (Ar*C*H), 127.8 (Ar*C*H), 128.9 (Ar*C*H), 135.5 (*C*(4')H), 138.5 (Ar*C*(1)), 154.8 (Boc-*C*=O), 172.0 (*C*=O); HRMS (ESI^+): $C_{21}H_{32}O_3N_3$ $[M+H]^+$ found 374.2427, requires 374.2444 (–3.0 ppm).

Experimental Details for Chapter 3

Standard Kinetic Procedure

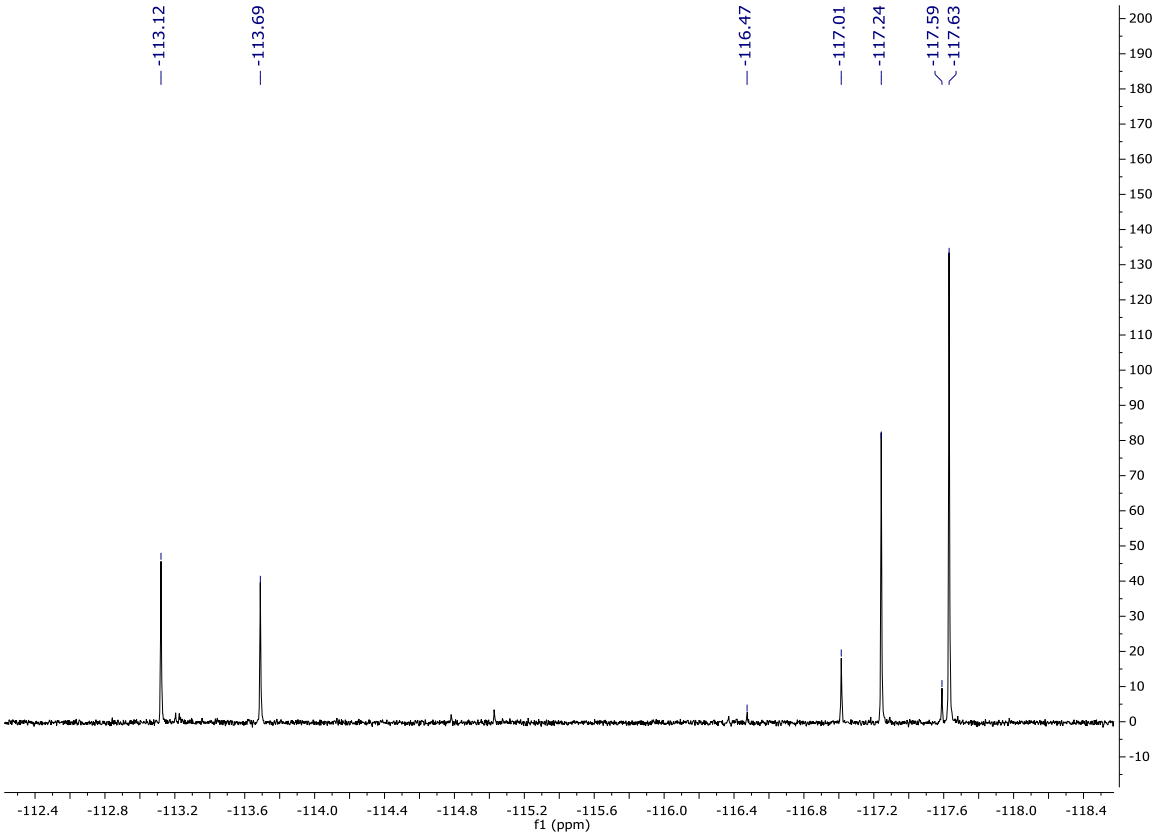


Typical Experiment: (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **309** (10.5 mg, 0.024 mmol) was added to a NMR tube and dissolved in d_3-MeCN (540 µL, spiked with $PhCF_3$ 25 µL/10 mL) and d_6-DMSO (60 µL) with sonication. The NMR tube was loaded into a NMR spectrometer that had been pre-cooled to −20 °C, the sampled locked to d_3-MeCN, shimmed and an initial ^{19}F $\{^1H\}$ spectrum acquired (ns = 1 or ns = 32, d1 = 15 s, sweep width 80 ppm (spectral centre −90 ppm). The sample was then removed from the spectrometer and placed in a −20 °C bath (CO_2 (s)/acetone) before a sample (100 µL) of a 2 mL stock solution containing (+)-BTM (24 mg, 0.96 mmol) and *i*Pr_2NH (94 µL, 0.67 mmol) in d_3-MeCN/d_6-DMSO (9:1) was added. The sample was returned to the NMR spectrometer and the kinetic experiment initiated.

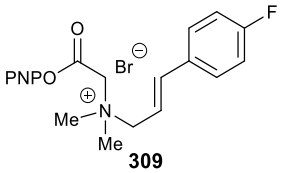
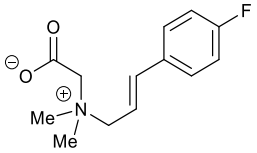
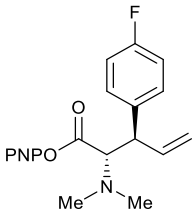
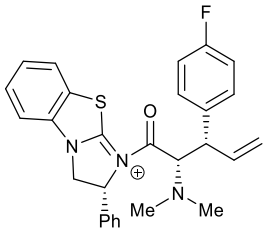
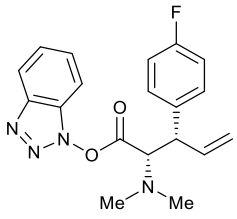
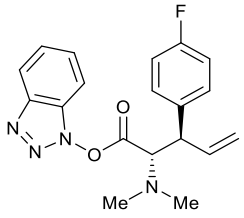
General Considerations: Stock solutions were prepared by adding reagents directly to volumetric glassware. The required stock solution volume was measured using a gas-tight 100 µL syringe. Kinetic experiments were collected at 471 MHz, kinetic experiments (arrays of spectra) were implemented using Bruker Topspin software. Typical experiment 1 scan per spectrum, 598 s delay between the start of each spectrum or 32 scans (15 s delay between scans) per spectrum with 91 s between the start of each spectrum. For typical kinetic runs 24 spectra were collected and processed using MestRe Nova 9.0 software. Time points were taken from NMR spectra timestamps from Bruker Topspin, the time at which the stock solution was added was recorded from Bruker Topspin software.

Typical Kinetic Profile and Analysis

Typical ^{19}F {^{1}H} NMR of Kinetic Run



Scheme 123: Typical $^{19}F\{^{1}H\}$ NMR (471 MHz) (d_3-MeCN/d_6-DMSO (9:1), 253 K) in the ArF region at ~10000 s, (+)-BTM (6.8 mM), HOBt (13.6 mM), *i*Pr$_2$NH (47.6 mM), Ammonium Salt (34 mM)

Component	δ_F: (ppm) (d_3-MeCN/d_6-DMSO, 471 MHz)
 **309** PNP= 4-$NO_2C_6H_4$	−113.12
 **Hydrolysis of 309**	−113.69
 **519**	−116.47
 **320**	−117.02
 **346**	−117.21
 *anti*-**346**	−117.59

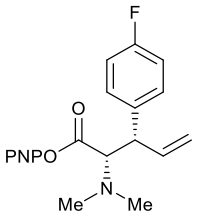
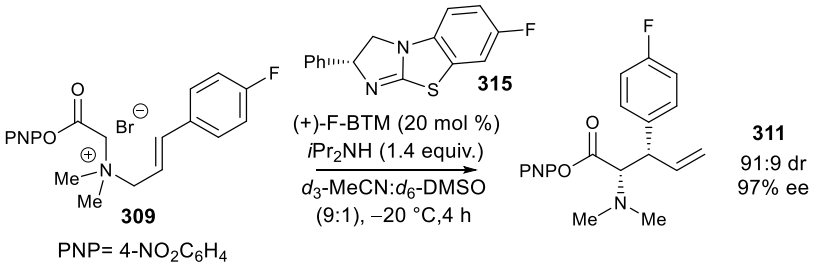
 **311**	−117.63

Table 4: Reaction species and corresponding chemical shifts.

Intermediate Identification

Catalyst Resting State Studies

To identify the unknown intermediate species δ_F: = −117.0 ppm, F-BTM **315** was employed with **309** and the process monitored by ^{19}F {^1H} NMR.



Scheme 124: Rearrangement of **309** using (+)-F-BTM

Following the standard kinetic procedure with slight modification, except using (+)-F-BTM in place of (+)-BTM. Two fluorinated catalyst derived species were observed throughout the reaction a signal at δ_F: −123.35 ppm which corresponds to (+)-F-BTM and a signal at δ_F: −113.44 ppm. Simplified model compounds are synthesised to attempt to identify the signal at δ_F: −113.44 ppm. Based upon the shift of benzoylated F-BTM **317** the unknown species was identified as an acyl ammonium intermediate.

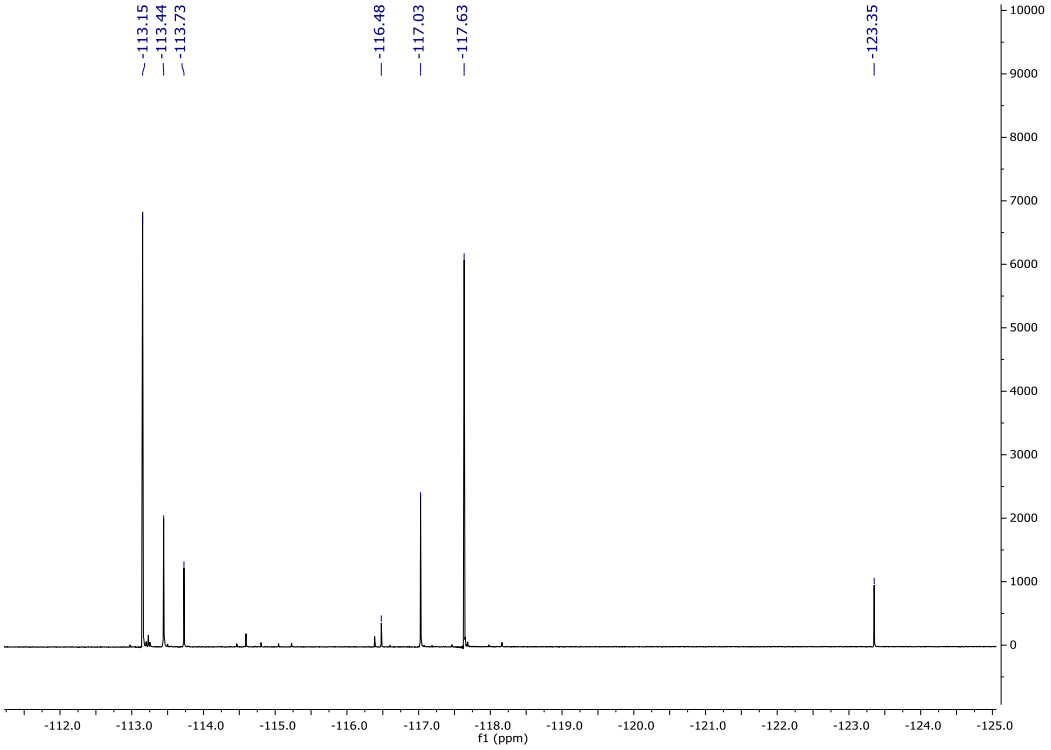
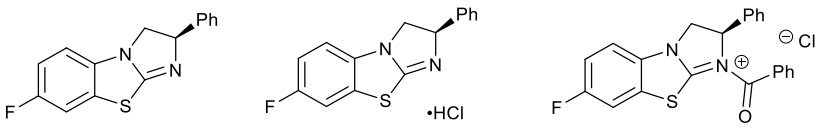


Figure 13: $^{19}F\{^1H\}$ NMR (471 MHz) (d_3-MeCN/d_6-DMSO (9:1), 253 K) in the ArF region, (+)-F-BTM (6.8 mM), iPr$_2$NH (47.6 mM), Ammonium Salt (34 mM)



315
δ_F = –123.3 ppm

316
δ_F = –118.1 ppm

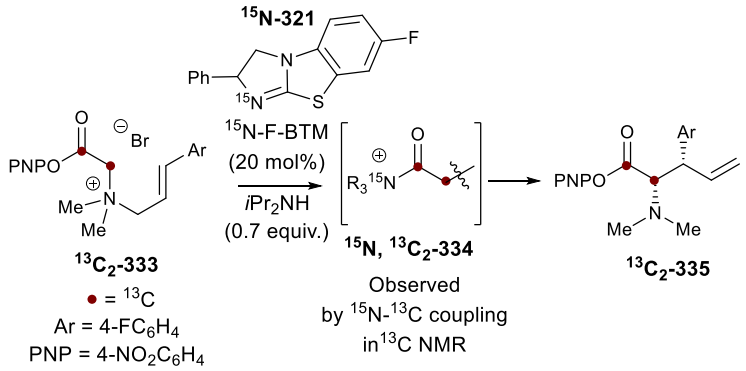
317
δ_F = –113.4 ppm

Figure 14: Fluorinated isothiourea derivatives **315**, **316** and **317** and δ_F

Isotopic Labelling

$^{13}C_2$-322 with ^{15}N-F-BTM ^{15}N-321

To unambiguously identify the acyl ammonium species, an isotopic labelling strategy was used. Firstly, $^{13}C_2$ substrate **$^{13}C_2$-322** and ^{15}N catalyst **^{15}N-321** were employed.

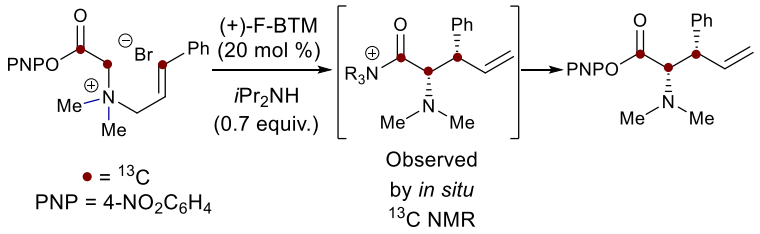


Scheme 125: Isotopic labelling studies of catalyst and substrate

A solution of $^{13}C_2$ ammonium salt **$^{13}C_2$-322** (10.5 mg, 0.024 mmol, 34 mM) in d_3-MeCN/d_6-DMSO (9:1) (600 µL) was prepared in an NMR tube. The NMR tube was loaded into a pre-cooled spectrometer (273 K) and an initial ^{13}C {^{1}H} (101 MHz) spectrum was taken. The solution was treated with a 100 µL sample of a 1 mL stock solution (^{15}N-F-BTM **^{15}N-321** (13 mg, 0.048 mmol) and *i*Pr$_2$NH (23.5 µL, 0.168 mmol) in d_3-MeCN/d_6-DMSO (9:1)) at 0 °C. The sample returned to the spectrometer a ^{13}C {1H} spectrum (ns = 16, d1 = 2 s) were recorded every 10 min for 40 min.

$^{13}C_3$-341 with (+)-F-BTM 315

To unambiguously determine if the intermediate is pre- or post-rearrangement, $^{13}C_3$ substrate **$^{13}C_3$-341** was used.

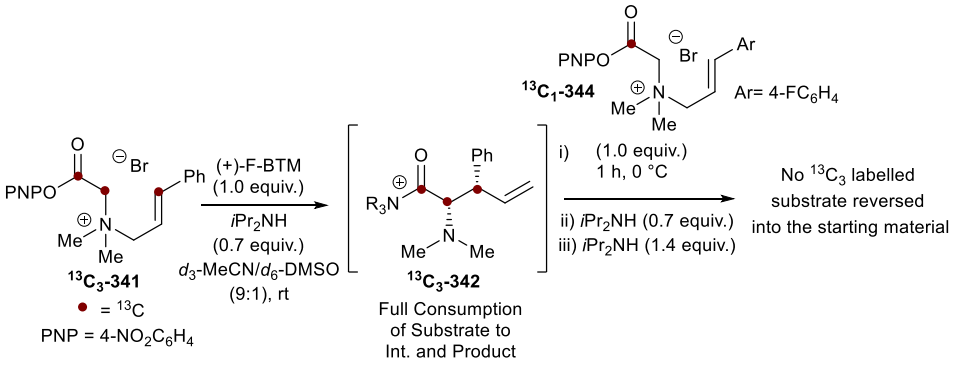


Scheme 126: $^{13}C_3$-341 with (+)-F-BTM catalyst **315**

A solution of $^{13}C_3$ ammonium salt **$^{13}C_3$-341** (10 mg, 0.024 mmol, 34 mM) in d_3-MeCN/d_6-DMSO (9:1) (600 µL) was prepared in an NMR tube. The NMR tube was loaded into a pre-cooled spectrometer (273 K) and an initial ^{13}C {^1H} (101 MHz) spectrum was taken. The solution was then treated with a 100 µL sample of a 1 mL stock solution ((+)-F-BTM **315** (13 mg, 0.048 mmol) and *i*Pr$_2$NH (23.5 µL, 0.168 mmol) in d_3-MeCN/d_6-DMSO (9:1)) at 0 °C. The sample returned to the spectrometer amd ^{13}C{^1H} spectra (ns = 16, d1 = 2 s) were recorded every 10 min for 40 min.

Reversibility of [2,3]-Rearrangement

A solution of (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl-1,2-$^{13}C_2$)-3-phenylprop-2-en-1-ammonium-3-^{13}C bromide **$^{13}C_3$-341** (10.0 mg, 0.024 mmol, 1.0 equiv.) in d_3-MeCN/d_6-DMSO (9:1) (600 µL) in an NMR tube was treated with 100 µL of a 1 mL stock solution ((+)-F-BTM (65 mg, 0.24 mmol) and *i*Pr$_2$NH (24 µL, 0.17 mmol) at rt. The reaction was monitored by ^{19}F and ^{13}C NMR until full conversion **$^{13}C_3$-341** substrate was observed. Once **$^{13}C_3$-341** was fully consumed (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl-2-^{13}C)prop-2-en-1-ammonium bromide **$^{13}C_1$-344** (10 .5 mg, 0.024 mmol, 1.0 equiv.) was added, the resulting solution was monitored by *in situ* ^{13}C NMR, for 1 h and no reversal of $^{13}C_3$ material into the substrate was observed. *i*Pr$_2$NH (2.3 µL, 0.017 mmol, 0.7 equiv.) was added and the reaction monitored for a further 30 mins, again no reversal of $^{13}C_3$ material into the substrate was observed. Further *i*Pr$_2$NH (4.7 µL, 0.034 mmol, 1.4 equiv.) was added and the reaction was monitored for a further 30 mins and no reversal of $^{13}C_3$ material was observed in the substrate. This indicates that the [2,3]-rearrangement step is highly irreversible.

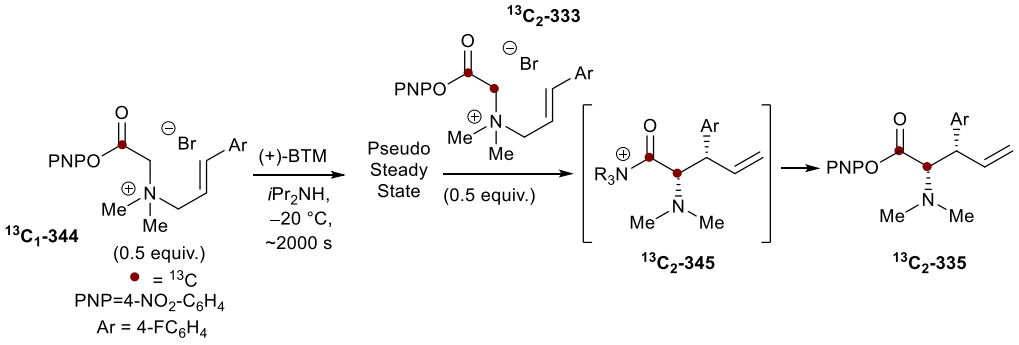


Scheme 127: Reversibility studies of the [2,3]-rearrangement step

Entrainment Study

$^{13}C_2$-333 entrained into **$^{13}C_1$-344** reaction within the pseudo-steady state

In order to determine if the observed intermediate is on or off the catalytic cycle an isotopic entrainment experiment was undertaken. A $^{13}C_1$ catalytic cycle was set up and once it has reached pseudo-steady-state $^{13}C_2$ substrate was entrained into the catalytic cycle and the rate of growth of the $^{13}C_2$ intermediate and $^{13}C_2$ product was monitored.



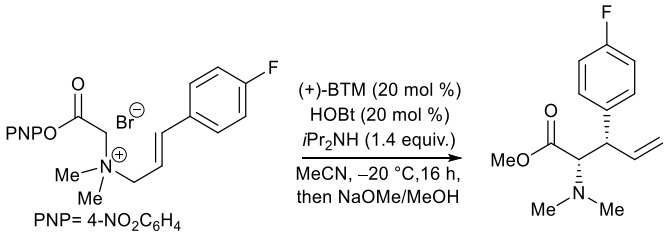
Scheme 128: Isotopic entrainment of $^{13}C_2$ substrate **$^{13}C_2$-333** (17 mM) into $^{13}C_1$ catalytic cycle ($^{13}C_1$ substrate **$^{13}C_1$-344** (17 mM), (+)-BTM (6.8 mM), iPr$_2$NH (47.6 mM)) within the pseudo-steady-state

A solution of $^{13}C_1$ ammonium salt **$^{13}C_1$-344** (5.25 mg, 0.012 mmol, 17 mM) in d_3-MeCN/d_6-DMSO (9:1) (600 µL) was prepared in an NMR tube. The NMR tube was loaded into a pre-cooled spectrometer (253 K) and an initial inverse gated quantitative ^{13}C {^{1}H} (ns = 16, d1 = 30 s) (126 MHz) spectrum was taken. The solution was then treated with a 100 µL sample of a 2 mL stock solution ((+)-BTM (24 mg, 0.096 mmol) and iPr$_2$NH (94 µL, 0.67 mmol) in d_3-MeCN/d_6-DMSO (9:1)) at −20 °C and the sample returned to the spectrometer. The reaction was monitored for ~2000 s taking a ^{13}C {^{1}H} every 606 s, until the reaction reached the pseudo-steady-state, at which point the NMR tube was removed from the spectrometer and $^{13}C_2$ ammonium salt **$^{13}C_2$-333** (5.25 mg, 0.012 mmol, 17 mM) was added at −20 °C,

the NMR tube was then returned to the spectrometer and a kinetic run initiated (ns = 16, d1 = 30 s, 606 s between the start of each spectrum, 25 spectra).

Non-Linear Effects

To probe the relationship between the enantiopurity of the (+)-BTM **197** catalyst the enantiomeric excess of the product, **310** was treated under standard catalytic conditions, using five different samples of catalyst with different enantiopurities. Stock solutions of (+)-BTM **197** with different enantiopurities were prepared by mixing the appropriate quantities of (+)-BTM and (−)-BTM in MeCN (4 mL, 0.055 mmol total of BTM). The enantiopurity of the catalyst stock solutions was measured *via* chiral HPLC analysis.



General Procedure

Stock solution of (+)-BTM (3.5 mL, 0.048 mmol) was treated with HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr$_2$NH (47 μL, 0.34 mmol, 1.4 equiv.) and cooled to −20 °C. The resulting solution was treated with (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide (105 mg, 0.24 mmol, 1.0 equiv.) and stirred for 16 h. Once complete the mixture was treated with NaOMe (1 M in MeOH, 0.72 mL, 0.72 mmol, 3.0 equiv.) and the stirred at rt for 1 h, diluted with CH_2Cl_2 (20 mL) and aq. 1 M NaOH (10 mL), the layers separated and the aqueous extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with aq. 1 M NaOH (10 mL) and brine (10 mL) dried over $MgSO_4$ then concentrated *in vacuo*. The crude residue (>95:5 dr) was purified by flash column chromatography on silica gel (10-15% EtOAc/hexanes) to give the product as a colourless oil (>95:5 dr), ee measured by chiral HPLC analysis.

Entry	(+)-BTM ee (%)	Product ee (%)
1	0	0
2	19	16
3	54	59
4	65	61
5	100	98

[a] Determined by HPLC analysis on a chiral stationary phase

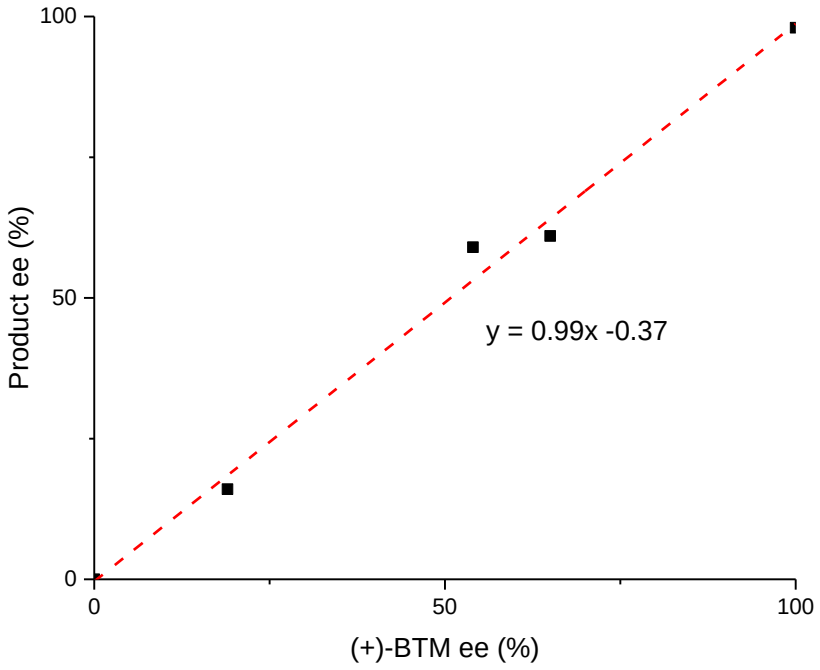
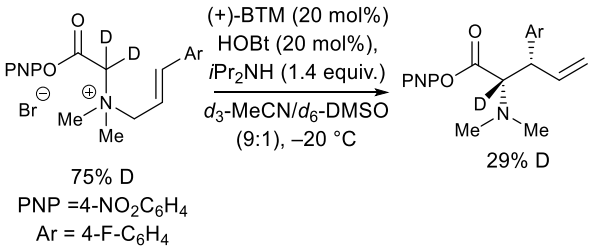


Figure 14: Probing non-linear effects of catalyst enantiopurity

Kinetic Isotope Effects

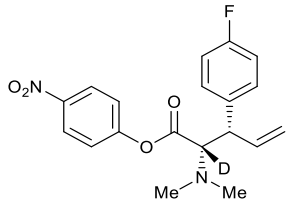
α-Deuterium Primary Kinetic Isotope Effect

To probe if α-deprotonation is kinetically significant, α-D_2 ammonium salt ***d*$_2$-351** was prepared, however only 75% D incorporation was achieved. It was found that significant H/D exchange occurs in d_3-MeCN/d_6-DMSO (9:1). Treating α-D_2 ammonium salt ***d*$_2$-351** under the standrard reaction conditions (*Scheme 129*), further H/D exchange was achieved, 29% D incorporation by $^{19}F\{^1H\}$ NMR, isolated of the α-D product ***d*$_1$-358**, lead to further H/D exchange.



Scheme 129: H/D exchange under reaction conditions of α-D_2 ammonium salt ***d*$_2$-351**

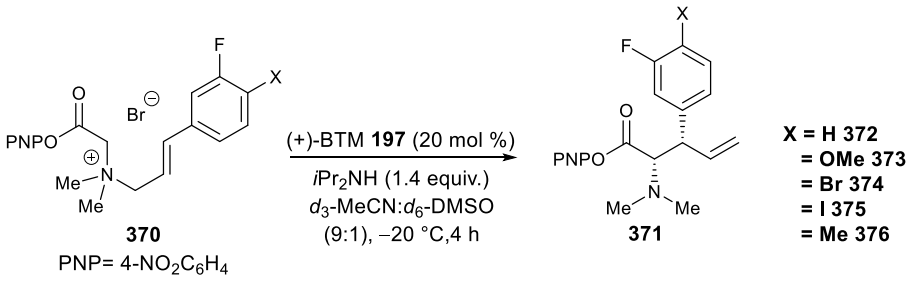
4-Nitrophenyl (2*S*,3*S*)-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate-2-*d* d_1-358



Following general procedure **L**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium-3-*d* bromide ***d*$_2$-351** (105 mg, 0.24 mmol, 1.0 equiv.) was reacted with (+)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr$_2$NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL). Direct purification *via* flash column chromatography (15% EtOAc/hexanes) gave the title product as a pale yellow solid (35 mg, 41%, 10% D)

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (6H, s, N(C*H*$_3$)$_2$), 3.81-3.93 (1.8 H, m, C(2)*H* + C(3)*H*), 5.13-5.30 (2H, m,C(5)*H*$_2$), 5.98 (1H, ddd, *J* 17.6, 10.1, 7.9, C(4)*H*), 7.08 (2H, t, *J* 8.6, C(3)Ar(3,5)*H*), 7.21-7.32 (4H, m, C(3)Ar(2,6)*H* + OAr(2,6)*H*), 8.31 (2H, d, *J* 9.0, OAr(3,5)*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: −115.8 (Ar*F*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 41.4 (N(*C*H$_3$)$_2$ (C(2)D)), 41.4 (N(*C*H$_3$)$_2$ (C(2)*H*)), 49.4 (*C*(3)H (C(2)D)), 49.5 (*C*(3)H (C(2)H), 70.4 (t, $^1J_{CD}$ 22, *C*(2)D), 70.8 (*C*(2)H), 115.7 (d, $^2J_{CF}$ 21, C(3)Ar*C*(3,5)H), 117.6 (*C*(5)H$_2$), 122.8 (OAr*C*(2,6)H), 125.4 (OAr*C*(3,5)H), 129.4 (d, $^3J_{CF}$ 8, C(3)Ar*C*(2,6,)H), 135.8 (d, $^4J_{CF}$ 3, C(3)Ar*C*(1)), 138.3 (*C*(4)H), 145.6 (Ar*C*(1)-O), 155.2 (Ar*C*(4)-NO$_2$), 161.8 (d, $^1J_{CF}$ 245, Ar*C*-F), 168.4 (*C*=O); HRMS: Due to low deuterium incorporation an accurate high resolution mass spectrum could not be obtained.

Hammett Plot



Scheme 130: Ammonium salts and rearrangement for Hammett analysis.

Hammett analysis by indepent rate measurement

Following the standard kinetic procedure, the requiste ammonium salt (0.024 mmol, 1.0 equiv.) was treated with a 100 µL aliquot of a 2 mL stock solution, containing (+)-BTM, and *i*Pr$_2$NH, in d_3-MeCN/d_6-DMSO (9:1). First order rate constants were extracted within the pseudo-steady state and compared.

Hammett analysis by five-way competition

Following the standard kinetic procedure with slight modification, all five ammonium salts **372**-**376** (0.0048 mmol, 6.8 mM) were weiged into an NMR tube then solvated with d_3-MeCN/d_6-DMSO (9:1, 600 µL total volume) and loaded into a pre-cooled spectrometer (471 MHz, 253 K), and a t=0 ^{19}F{^{1}H} NMR spectrum (80 ppm sweep width, spectral centre −100 ppm, ns = 32, d1 = 15 s, expt 8 min 29 s) was taken. The sample was removed from the spectrometer and placed in a −20 °C cooling bath (CO_2 (s), acetone) a 100 µL aliquot of a 2 mL stock solution, containing (+)-BTM (0.096 mmol), and *i*Pr$_2$NH (0.672 mmol), in d_3-MeCN/d_6-DMSO (9:1). The sample returned to the spectrometer and the kinetic run initated (24 spectra, 91 s delay between spectra). First-order rate constants were extracted from the decay of each of the substrates.

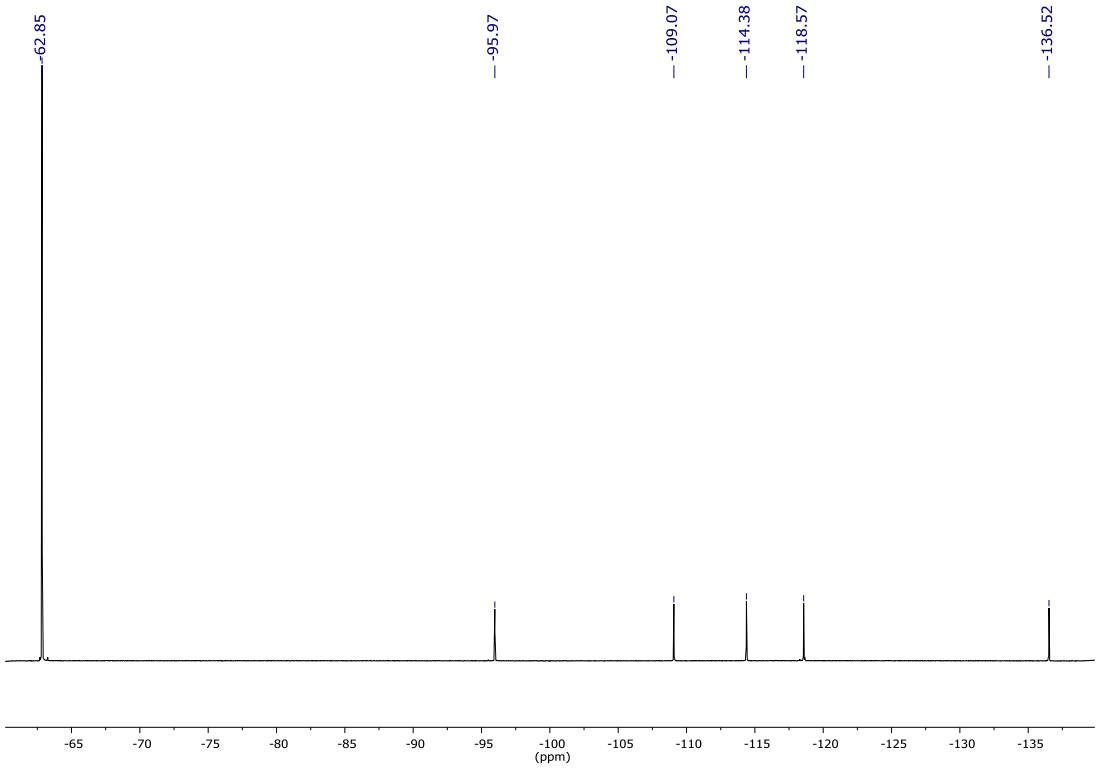
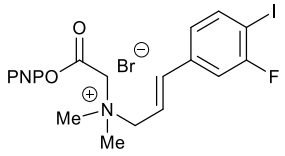
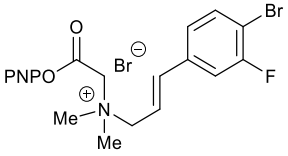
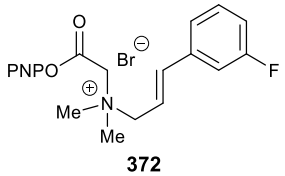


Figure 15: $^{19}F\{^{1}H\}$ NMR spectrum containg internal standrard $PhCF_3$ (−62.9 ppm) and five ammonium salts

Ammonium salt	δ_F: (ppm) (d_3-MeCN/d_6-DMSO, 471 MHz)
 **375** PNP= 4-$NO_2C_6H_4$	−96.0
 **374** PNP= 4-$NO_2C_6H_4$	−109.1
 **372** PNP= 4-$NO_2C_6H_4$	−114.4

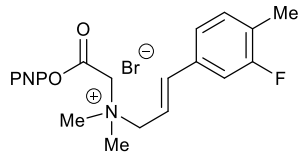
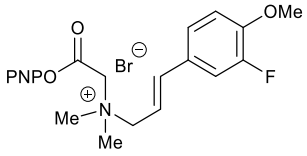
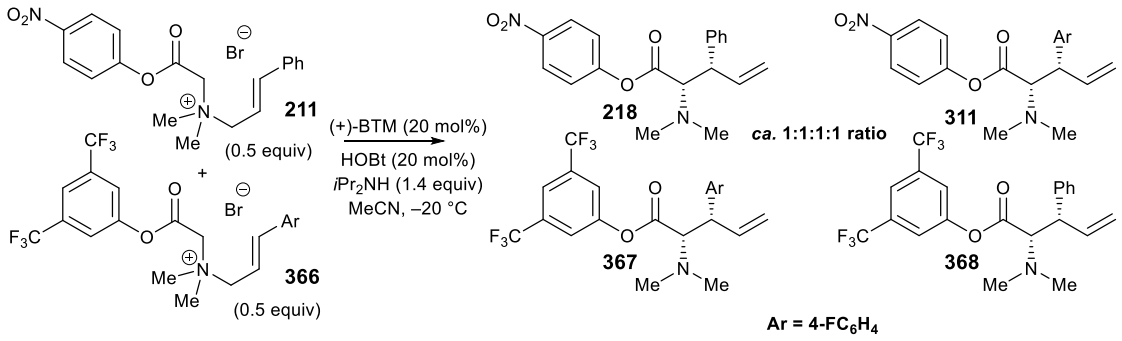
 **376** PNP= 4-$NO_2C_6H_4$	−118.6
 **373** PNP= 4-$NO_2C_6H_4$	−136.5

Table 5: Ammonium salts and δ_F: chemical shift, used in Hammett analysis.

Crossover Experiments

Phenol Crossovers

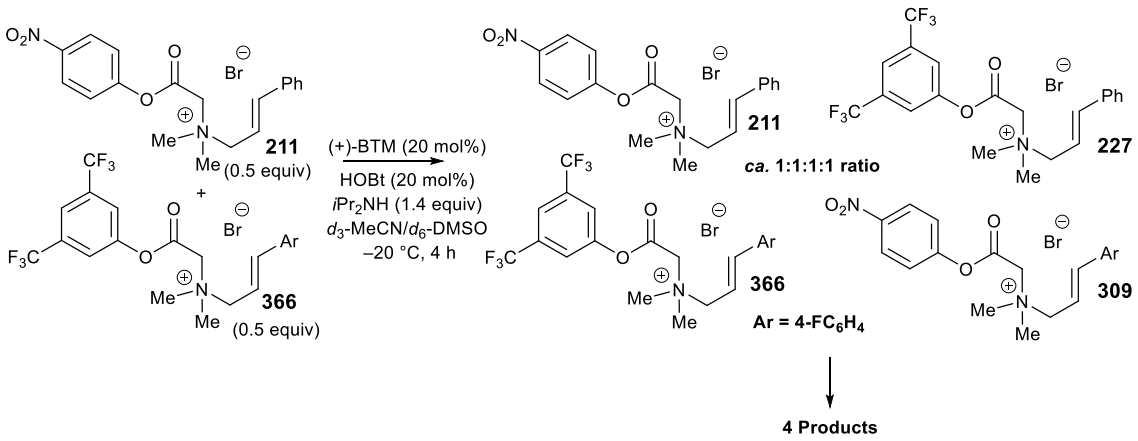
A flamed dried Schlenk under Ar was charged with (+)-BTM (12 mg, 0.24 mmol, 0.2 equiv.) and HOBt (6.4 mg, 0.24 mmol, 0.2 equiv.) in MeCN (3.5 mL) the resulting solution was cooled to −20 °C and stirred for 5 min. (*E*)-*N*-(2-(3,5-bis(trifluoromethyl)phenoxy)-2-oxoethyl)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-ammonium bromide **366** (64 mg, 0.12 mmol, 0.5 equiv.) and (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **211** (50 mg, 0.12 mmol, 0.5 equiv.) were added together and the reaction was stirred for 16 h. The reaction was quenched by the addition of aq. 1 M NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by $^{19}F\{^1H\}$ NMR, genuine samples of the potential crossover products were individually added to the crude residue and then re-analysed by $^{19}F\{^1H\}$ NMR.



Scheme 131. Crossover experiment between activated esters **211** and **366**

Phenol Crossovers following by in situ $^{19}F\{^{1}H\}$ NMR

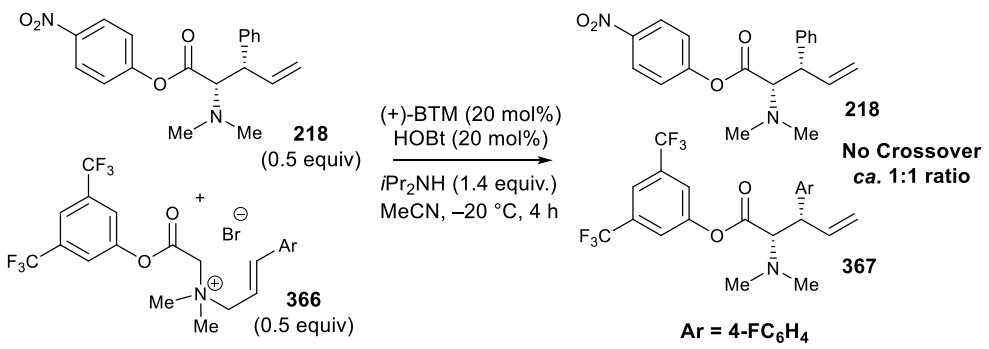
Following the standard kinetic procedure, (*E*)-*N*-(2-(3,5-bis(trifluoromethyl)phenoxy)-2-oxoethyl)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-ammonium bromide **366** (6.4 mg, 0.012 mmol, 0.5 equiv.) and (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **211** (5.0 mg, 0.012 mmol, 0.5 equiv.) were weighed into an NMR tube and solvated with d_3-MeCN/d_6-DMSO (9:1, total volume 600 µL). The NMR tube was then loaded into a pre-cooled spectrometer (500 MHz, 253 K) and a t=0 spectra taken. The NMR tube was removed from the spectrometer and added to a −20 °C (CO_2 (s) acetone) bath and a 100 µL aliquot of a 2 mL stock solution containing (+)-BTM, HOBt, and *i*Pr_2NH in d_3-MeCN/d_6-DMSO (9:1) was added and the NMR tube returned to the spectrometer an kinetic run initiated (24 spectra, 598 s delay between spectra).



Scheme 132: Crossover experiment followed by $^{19}F\{^{1}H\}$ NMR

Reversibility of Product Release

Following standard kinetic procedure A solution of (*E*)-*N*-(2-(3,5-bis(trifluoromethyl)phenoxy)-2-oxoethyl)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-ammonium bromide **366** (6.4 mg, 0.012 mmol, 0.5 equiv.) and 4-nitrophenyl *syn*-2-(dimethylamino)-3-phenylpent-4-enoate **218** (4.1 mg, 0.012 mmol, 0.5 equiv.) in d_3-MeCN/d_6-DMSO (9:1) (600 µL) was prepared and 100 µL of a 2 mL stock solution ((+)-BTM (24 mg, 0.48 mmol), HOBt (12.8 mg, 0.48 mmol) and *i*Pr_2NH (94 µL, 0.68 mmol)) was added at −20 °C and a $^{19}F\{^{1}H\}$ NMR spectrum taken every 10 min. only a single fluorinated rearranged product was observed throughout the reaction.



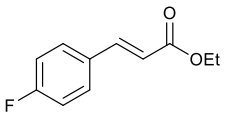
Scheme 133: Crossover experiment a *p*-nitrophenyl ester product and a *bis*-trifluoromethyl ammonium salt, showing no crossover, following by ^{19}F {^{1}H} NMR only one fluorinated rearranged product observed

General Procedure K: Synthesis of *N*, *N*-Dimethyl Amines from Allylic Alcohols

A solution of allylic alcohol (1.0 equiv.) in Et_2O (0.33 M) was cooled to 0 °C and treated with PBr_3 (0.4 equiv.) and stirred for 1 h, the reaction was quenched by the dropwise addition of aq. sat. $NaHCO_3$ (equal volume), the mixture was allowed to warm to rt. The layers were then separated, the aqueous layer extracted with Et_2O (2 × equal volume), the combined organic layers washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in THF (0.5 M) and added to aq. dimethylamine (40% wt., 5.0 equiv.) *via* dropping funnel, upon completion the dropping funnel was rinsed with THF (half volume) and the reaction was stirred at rt for 15 min. The reaction was treated with aq. 1 M NaOH (equal volume) and stirred for 15 min, then Et_2O (equal volume) was added, the layers separated and the aqueous layer extracted with Et_2O (2 × equal volume). The combined organic layers were washed with brine, dried over $MgSO_4$ then concentrated *in vacuo*, the crude residue was purified by high vacuum distillation to give *N*, *N*-dimethyl allylic amines.

Amine Synthesis

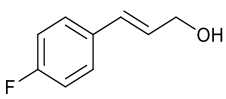
Ethyl (*E*)-3-(4-fluorophenyl)acrylate[114] 496



Following general procedure **A**, 4-fluorobenzaldhyde (4.7 mL, 43.6 mmol, 1.0 equiv.) was reacted with ethyl 2-(triphenyl-λ5-phosphanylidene)acetate (16.0 g, 46.0 mmol, 1.05 equiv.) in CH_2Cl_2 (50 mL) to give the title product (8.46 g, quant.) as a pale yellow oil after flash chromatography on silica gel (0→20% EtOAc/hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.33 (3H, t, *J* 7.1, CH_2CH_3), 4.26 (2H, q, *J* 7.1, CH_2CH_3), 6.35 (1H, d, *J* 16.0, C(2)*H*), 7.07 (2H, t, *J* 8.7, Ar(3,5)*H*), 7.50 (2H, dd, *J* 8.7, 5.4, Ar(2,6)*H*), 7.64 (1H, d, *J* 16.0, C(3)*H*) ; Data consistent with literature.[114]

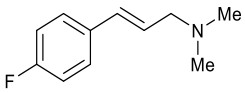
(*E*)-3-(4-Fluorophenyl)prop-2-en-1-ol[115] 497



Following general procedure **C**, ethyl (*E*)-3-(4-fluorophenyl)acrylate **496** (5.0 g, 25.8 mmol, 1.0 equiv.) was reacted with DIBAL-H (56.7 mL, 1.0 M in hexane, 56.7 mmol, 2.2 equiv.) in CH_2Cl_2 (125 mL) to give the title product (3.92 g, quant.) as a white solid, which was used without further purification.

mp 54-56 °C {lit. mp 58-60 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.26-4.36 (2H, m, C(1)H_2), 6.29 (1H, dt, *J* 15.9, 5.7, C(2)*H*), 6.58 (1H, d, *J* 15.9, C(3)*H*), 7.02 (2H, t, *J* 8.7, Ar(3,5)*H*), 7.30-7.40 (2H, m, Ar(2,6)*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: −114.4 (Ar*F*); Data consistent with literature.[115]

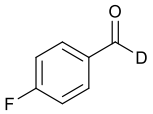
(*E*)-3-(4-Fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine 498



Following general procedure **K**, (*E*)-3-(4-fluorophenyl)prop-2-en-1-ol **497** (6.83 g, 44.9 mmol, 1.0 equiv.) was reacted with PBr_3 (1.70 mL, 18.0 mmol, 0.4 equiv.) in Et_2O (135 mL) then with dimethylamine (aq. 40% wt., 28.5 mL, 225 mmol, 5.0 equiv.) in THF (90 mL) to give the title product (4.54 g, 56% over two steps, 96:4 *E*:*Z*) as a colourless oil after high vacuum distillation

bp 100-102 °C @ 1 mmbar; ν_{max} (film, cm^{-1}): 2943, 2767, 1602, 1508, 1224, 1157, 970; ^{1}H NMR (400 MHz, $CDCl_3$) 2.26 (6H, s, N(CH_3)$_2$), 3.00-3.08 (2H, m, C(1)H_2), 6.17 (1H, dt, *J* 15.8, 6.7, C(2)*H*), 6.46 (1H, d, *J* 15.8, C(3)*H*), 6.99 (2H, t, *J* 8.7, Ar(2,6)*H*), 7.33 (2H, dd, *J* 8.7, 5.4, Ar(3,5)*H*); ^{19}F NMR (472 MHz, $CDCl_3$) δ_F: −114.8 (Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 45.4 (N(CH_3)$_2$), 62.1 (*C*(1)H_2), 115.5 (d, $^{2}J_{CF}$ 21.5, Ar*C*(3,5)H), 127.3 (d, *J* 1.9, *C*(2)H), 127.8 (d, $^{3}J_{CF}$ 7.9, Ar*C*(2,6)H), 131.4 (*C*(3)H), 133.3 (Ar*C*(1)), 162.3 (d, $^{1}J_{CF}$ 246, Ar*C*(4)-F); HRMS (NSI$^+$): $C_{11}H_{15}NF^+$ [M+H]$^+$ found: 180.1181, requires: 180.1183 (−1.1 ppm).

α-Deuterio-4-fluoro-benzaldhyde d_1-353

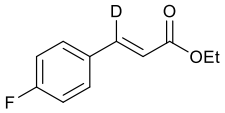


A solution of 4-fluoro-bromobenzene (6.24 mL, 56.8 mmol, 1.0 equiv.) in THF (315 mL) was cooled to −78 °C and treated with *n*-BuLi (32.6 mL, 1.92 M in hexanes, 62.5 mmol, 1.1 equiv.) dropwise. The resulting solution was stirred for 30 min at −78 °C and d_7-DMF (5.0 g, 62.5 mmol, 1.1 equiv.) was added dropwise and stirred for a further 30 min. The reaction was quenched by the addition of sat. NH_4Cl (20 mL) and aq. 1 M H_2SO_4 (3 drops) and allowed to warm to rt. The mixture was extracted with Et_2O (3 × 200 mL), the combined organic layers washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by distillation under vacuum to give the product as a colourless liquid (3.65 g, 51%);

bp 40-42 °C @ 1 mmbar; ν_{max} (film, cm^{-1}): 1678 1593, 1504, 1414, 1222, 1149, 881, 810; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 7.17 (2H, t, *J* 8.6, Ar(3,5)*H*), 7.79-7.93 (2H, m, Ar(2,6)*H*); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −102.3—102.4 (m, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 116.4 (d, $^{2}J_{CF}$ 22,

Ar*C*(3,5)H), 132.3 (d, $^{3}J_{CF}$ 10, Ar*C*(2,6)H), 132.9 (d, $^{4}J_{CF}$ 3, Ar*C*(1)), 166.5 (d, $^{1}J_{CF}$ 257, Ar*C*-F), 189.8-190.5 (m, *C*DO); HRMS (EI^{+}) $C_7H_5DOF^{+}$ $[M+H]^{+}$ found: 126.0464, requires: 126.0465 (−0.8 ppm).

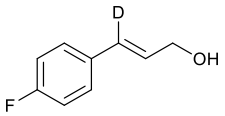
Ethyl (*E*)-3-(4-fluorophenyl)acrylate-3-*d*, d_1-354



Following general procedure **A**, α-deuterio-4-fluoro-benzaldhyde ***d*$_1$-353** (3.0 g, 24.0 mmol, 1.0 equiv.) was reacted with ethyl 2-(triphenyl-λ5-phosphanylidene)acetate (8.8 g, 25.2 mmol, 1.05 equiv.) in CH_2Cl_2 (30 mL) to give the title product (4.42 g, quant., 96:4 *E*:*Z*) as a white solid after flash column chromatography on silica gel (0→20% EtOAc/hexane).

mp <30 °C; ν_{max} (film, cm^{-1}) 2991, 1708, 1625, 1586, 1506, 1311, 1230, 1174, 1078, 881; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.33 (3H, t, *J* 7.1, CH_2CH_3), 4.26 (2H, q, *J* 7.1, CH_2CH_3), 6.35 (1H, *J* 2.1, C(2)*H*), 7.07 (2H, t, *J* 8.7, Ar(3,5)*H*), 7.51 (2H, dd, *J* 8.7, 5.4, Ar(2,6)*H*); ^{19}F NMR (679 MHz, $CDCl_3$) δ_F: −109.7- ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (*C*H$_3$), 60.6 (*C*H$_2$), 116.0 (d, $^{2}J_{CF}$ 22, Ar*C*(3,5)H), 117.9 (*C*(2)H), 129.9 (d, $^{3}J_{CF}$ 8.4, Ar*C*(2,6)H), 130.7 (d, $^{4}J_{CF}$ 3.0, Ar*C*(1)), 142.9 (t, $^{1}J_{CD}$ 24, *C*(3)D), 163.9 (d, $^{1}J_{CF}$ 251, Ar*C*-F), 166.8 (*C*=O); HRMS (NSI^{+}) $C_{11}H_{11}DFO_2^{+}$ $[M+H]^{+}$ found: 196.0876, requires: 196.0879 (−1.3 ppm).

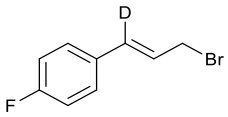
(*E*)-3-(4-Fluorophenyl)prop-2-en-3-*d*-1-ol d_1-355



Following general procedure **C**, ethyl (*E*)-3-(4-fluorophenyl)acrylate-3-*d* ***d*$_1$-354** (3.0 g, 16.95 mmol, 1.0 equiv.) was reacted with DIBAL-H (37.3 mL, 1.0 M in hexane, 37.3 mmol, 2.2 equiv.) in CH_2Cl_2 (85 mL) to give the title product (1.77 g, 68%, 96:4 *E*:*Z*) as a white solid, which was used without further purification.

mp 54-56 °C; ν_{max} (film, cm^{-1}): 3257, 2930, 1598, 1506, 122, 1091, 1019, 977, 837; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.28 (2H, t, *J* 4.2, C*H*$_2$), 6.24 (1H, br. s, C(2)*H*), 6.95-7.00 (2H, m, Ar(3,5)*H*), 7.27-7.33 (2H, m, Ar(2,6)*H*);^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −114.3—114.4 (m, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 63.4 (*C*(1)H$_2$), 115.5 (d, $^{2}J_{CF}$ 22.0, Ar*C*(3,5)H), 128.0 (d, $^{3}J_{CF}$ 8.0, Ar*C*(2,6)H), 128.2 (*C*(2)H), 129.5 (t, $^{1}J_{CD}$ 24.0, *C*(3)D), 132.9 (Ar*C*(1)), 162.4 (d, $^{1}J_{CF}$ 247, Ar*C*-F); HRMS (EI^{+}) C_9H_8DOF $[M]^{+}$ found: 153.0701, requires: 153.0700 (+0.7 ppm).

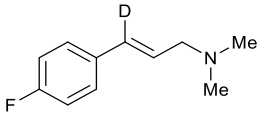
(*E*)-1-(3-Bromoprop-1-en-1-yl-1-*d*)-4-fluorobenzene d_1-499



Following general procedure **D**, (*E*)-3-(4-fluorophenyl)prop-2-en-3-*d*-1-ol ***d*₁-355** (1.5 g, 9.80 mmol, 1.0 equiv.) was reacted with PBr_3 (418 μL, 4.44 mmol, 0.4 equiv.) in Et_2O (33 mL) to give the title product (2.02 g, 95%), as a colourless oil, which was used immediately.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.15 (2H, d, *J* 7.8, C(1)H_2), 6.31 (1H, t, *J* 7.8, C(2)*H*), 7.02 (2H,t, *J* 8.4, Ar(3,5)*H*), 7.36 (2H, dd, *J* 8.4, 5.4, Ar(2,6)*H*).

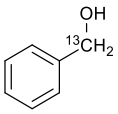
(*E*)-3-(4-Fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine-3-*d*, d_1-356



Following general procedure **E**, (*E*)-1-(3-bromoprop-1-en-1-yl-1-*d*)-4-fluorobenzene ***d*₁-499** (1.80 g, 8.33 mmol, 1.0 equiv.) was reacted with dimethylamine (aq. 40% wt, 5.3 mL, 41.67 mmol, 5.0 equiv.) in THF (18 mL) gave the title product (1.45 g, 96%, 97:3 *E*:*Z*) after high vacuum distillation.

bp 100-102 °C @ 1 mmbar; ν_{max} (film, cm^{-1}): 2770, 1600, 1506, 1225, 1157, 1029, 835; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.89 (6H, s, N(CH_3)$_2$), 2.66 (2H, d *J* 6.8, C(1)H_2), 5.81 (1H, t, *J* 6.8, C(2)*H*), 6.61 (2H, t, *J* 8.7, Ar(3,5)*H*), 6.92-6.95 (2H, m, Ar(2,6)*H*); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ_F: −114.8 (Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 44.4 (N(*C*H_3)$_2$), 61.1 (*C*(1)H_2), 114.6 (d, $^2J_{CF}$ 22.0, Ar*C*(3,5)H), 126.5 (d, $^2J_{CD}$ 2.0, C(2)H), 126.9 (d, $^3J_{CF}$ 7.8, Ar*C*(2,6)*H*), 129.9 (t, $^1J_{CD}$ 24.0, *C*(3)D), 132.5 (d, $^4J_{CF}$ 3.0, Ar*C*(1)), 161.4 (d, $^1J_{CF}$ 246, Ar*C*-F); HRMS (NSI$^+$) $C_{11}H_{14}DNF^+$ $[M+H]^+$ found: 181.1245, requires: 181.1246 (−0.4 ppm).

Phenylmethanol-^{13}C$^{[116]}$ $^{13}C_1$-337

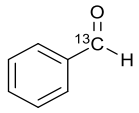


Following the procedure of Blake *et.al*,[116] a solution of [α-^{13}C]-benzoic acid **$^{13}C_1$-336** (1.0 g, 8.13 mmol, 1.0 equiv.) in THF (15 mL) was added dropwise to a solution of $LiAlH_4$ (2.4 M in THF, 5.60 mL, 13.4 mmol, 1.65 equiv.) in THF (15 mL) at 0 °C. The resulting solution was allowed to warm to rt and stirred for 16 h, the reaction was quenched by the addition of aq. 1 M KOH (15 mL) dropwise at 0 °C. Et_2O (30 mL) was then added and the mixture stirred for 30 min at rt, the layers separated and the

aqueous layer extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with aq. 1 M HCl (30 mL), then brine (30 mL) dried over $MgSO_4$ and concentrated *in vacuo* to give the product (972 mg, quant.) as a colourless oil which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.67 (2H, ddd, *J* 142.4, 6.1, 3.2, Ph^{13}C*H*$_2$), 7.27-7.41 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 65.2 (^{13}*C*H$_2$), 127.1 (d, $^3J_{CC}$ 3, Ar*C*(3,5)H), 127.7 (Ar*C*(4)H), 128.6 (d, $^2J_{CC}$ 4, Ar*C*(2,6)H), 140.9 (d, $^1J_{CC}$ 47, Ar*C*(1)); data consistent with the literature.[116]

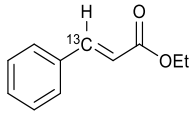
α-^{13}C Benzaldehyde[116] $^{13}C_1$-338



A solution of phenylmethanol-^{13}C **$^{13}C_1$-337** (972 mg, 8.13 mmol, 1.0 equiv.) in CH_2Cl_2 (16 mL) was cooled to 0 °C and treated with Celite® (2.11 g) and PCC (2.11 g, 9.76 mmol, 1.2 equiv.) and the reaction allowed to warm to rt and stirred for 16 h. The mixture was concentrated *in vacuo* and re-dissolved in Et_2O (20 mL) and filtered through a pad of silica gel and washed with Et_2O (100 mL), the filtrate was concentrated *in vacuo* to give the product as a colourless oil (554 mg, 64%);

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.53 (2H, t, *J* 7.6, Ar(3,5)*H*), 7.59-7.69 (1H, m, Ar(4)*H*), 7.79-7.95 (2H, m, Ar(2,6)*H*), 10.04 (1H, d, $^1J_{CH}$ 174.0, C*H*O); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 129.1 (d, $^2J_{CC}$ 5.0, Ar*C*(2,6)H), 129.9 (d, $^3J_{CC}$ 4.0, Ar*C*(3,5)H), 134.6 (Ar*C*(4)H), 136.5 (d, $^1J_{CC}$ 54, Ar*C*(1)), 192.5 (^{13}*C*HO); data consistent with the literature.[116]

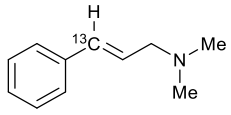
Ethyl cinnamate-3-^{13}C $^{13}C_1$-339



Following general procedure **A**, α-^{13}C benzaldehyde **$^{13}C_1$-338** (554 mg, 5.13 mmol, 1.0 equiv.) was reacted with ethyl 2-(triphenyl-λ5-phosphanylidene)acetate (1.87 g, 5.39 mmol, 1.05 equiv.) in CH_2Cl_2 (6 mL) to give the title product (760 mg, 84%, 97:3 *E*:*Z*) as a yellow oil after purification by flash column chromatography on silica gel (10% EtOAc/hexanes), which was used directly.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.30 (3H, t, *J* 7.2, CH_2CH_3), 4.23 (2H, q, *J* 7.2, CH_2CH_3), 6.41 (1H, dd, *J* 16.0, 1.0, C(2)*H*), 7.29-7.37 (2H, m, Ar*H*), 7.43-7.49 (3H, m, Ar*H*), 7.66 (1H, dd, $^1J_{CH}$ 156.1, $^3J_{HH}$ 16.0, C(3)*H*);

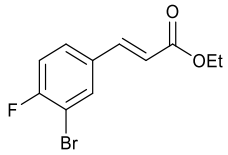
(*E*)-*N*,*N*-Dimethyl-3-phenylprop-2-en-1-amine-3-^{13}C $^{13}C_1$-340



Following general procedure **C**, ethyl cinnamate-3-^{13}C (760 mg, 4.29 mmol, 1.0 equiv.) was reacted with DIBAL-H (1 M in hexane, 9.44 mL, 9.44 mmol, 2.2 equiv.) in CH_2Cl_2 (22 mL), to give crude alcohol (584 mg, 76%, 97:3 *E*:*Z*), which was used immediately. Following general procedure **K**, (*E*)-3-phenylprop-2-en-1-ol-3-^{13}C (584 mg, 3.28 mmol, 1.0 equiv.) was reacted with PBr_3 (123 μL, 1.31 mmol, 0.4 equiv.) in Et_2O (10 mL), then with dimethylamine (40% wt. in H_2O, 2.1 mL, 16.4 mmol, 5.0 equiv.) in THF (7 mL) to give the title product (297 mg, 56% over two steps, 98:2 *E*:*Z*) as a colourless oil after Kugerohlor distillation (140 °C @ 2 mmbar).

ν_{max} (film, cm^{-1}): 2974, 2767, 1495, 1449, 1360, 1127, 1020, 960, 864; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.30 (6H, s, N(CH_3)$_2$), 3.10 (2H, t, *J* 6.4, C(1)H_2), 6.29 (1H, dt, *J* 15.9, 6.4, C(2)*H*), 6.54 (1H, dd, *J* 150.9, 15.9, ^{13}C(3)*H*), 7.21-7.48 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 45.5 (N(*C*H_3)$_2$), 62.2 (d, $^3J_{CC}$ 1.7, *C*(1)H_2), 126.4 (d, $^3J_{CC}$ 2.0, Ar*C*(3,5)H), 127.6 (d, $^1J_{CC}$ 72, *C*(2)H), 128.7 (d, $^2J_{CC}$ 4.3, Ar*C*(2,6)H), 130.9 (Ar*C*(4)H), 132.6 (^{13}*C*(3)H), 137.2 (d, $^1J_{CC}$ 56, Ar*C*(1)); HRMS (ESI$^+$) $C_{10}{}^{13}CH_{16}N^+$ $[M+H]^+$ found: 163.1310, requires: 163.1311 (−0.5 ppm).

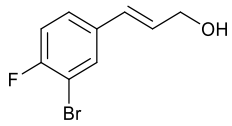
Ethyl (*E*)-3-(3-bromo-4-fluorophenyl)acrylate[117] 500



Following general procedure **A**, the reaction of 3-bromo-4-fluorobenzaldehyde (3.0 g, 14.78 mmol, 1.0 equiv.) with ethyl 2-(triphenylphosphoranylidene)acetate (6.17 g, 17.73 mmol, 1.2 equiv.) in CH_2Cl_2 (30 mL) gave the title product (3.59 g, 89%, 94:6 *E*:*Z*) as a white solid after purification by flash column chromatography (10→20% EtOAc/hexanes);

mp 62-64 °C {lit. 64-65 °C};^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.32 (3H, t, *J* 7.1, CH_2CH_3), 4.26 (2H, q, *J* 7.1, CH_2CH_3), 6.35 (1H,d, *J* 16.0, C(2)*H*), 7.12 (1H, t, *J* 8.4, Ar(5)*H*), 7.38-7.46 (1H, m, Ar(6)*H*), 7.56 (1H, d, *J* 16.0, C(3)*H*), 7.71 (1H, dd, *J* 6.6, 2.2, Ar(2)*H*); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −104.2 (Ar*F*); Data consistent with the literature.[117]

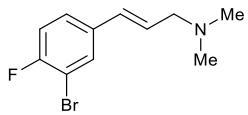
(*E*)-3-(3-Bromo-4-fluorophenyl)prop-2-en-1-ol 501



Following general procedure **C**, the reaction of ethyl (*E*)-3-(3-bromo-4-fluorophenyl)acrylate **500** (1.59 g, 5.82 mmol, 1.0 equiv.) with DIBAL-H (1.0 M in hexane, 12.8 mL, 12.8 mmol, 2.2 equiv.) in CH_2Cl_2 (30 mL) gave the title product (1.18 g, 88%, 94:6 *E*:*Z*) as a colourless oil, which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.33 (2H, dd, *J* 5.5, 1.6, C*H*$_2$OH), 6.29 (1H, dt, *J* 15.9, 5.5, C(2)*H*), 6.53 (1H, d, *J* 15.9, C(3)*H*), 7.06 (1H, t, *J* 8.4, Ar(5)*H*), 7.24-7.32 (1H, m, Ar(6)*H*), 7.57 (1H, dd, *J* 6.6, 2.2, Ar(2)*H*); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −108.8 - −109.0 (m, Ar*F*).

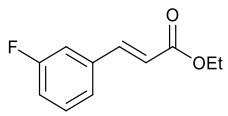
(*E*)-3-(3-Bromo-4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine 362



Following general procedure **K**, the reaction of (*E*)-3-(3-bromo-4-fluorophenyl)prop-2-en-1-ol **501** (6.0 g g, 26.0 mmol, 1.0 equiv.) with PBr_3 (978 µL, 10.4 mmol, 0.4 equiv.) in Et_2O (80 mL), then with aq. dimethylamine (40% wt., 16.4 mL, 130 mmol, 5.0 equiv.) in THF (52 mL) gave the title product (3.52 g, 52%, 95:5 *E*:*Z*) as a colourless liquid after high vacuum distillation.

bp 135-140 °C @ 1mmbar; ν_{max} (film, cm^{-1}): 2770, 1492, 1247, 1043, 962; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.27 (6H, s, N(C*H*$_3$)$_2$), 3.05 (2H, dd, *J* 6.8, 1.4, C*H*$_2$), 6.18 (1H, dt, *J* 15.9, 6.6, C(2)*H*), 6.41 (1H,d, *J* 15.9, C(2)*H*), 7.05 (1H, t, *J* 8.4, Ar(5)*H*), 7.20-7.30 (1H, m, Ar(6)*H*), 7.54 (1H, dd, *J* 6.6, 2.2, Ar(2)*H*); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −109.3 - −109.4 (m, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 45.4 (N(*C*H$_3$)$_2$), 61.9 (*C*(1)H$_2$), 109.2 (d, $^2J_{CF}$ 21.0, Ar*C*-Br), 116.5 (d, $^2J_{CF}$ 23.0, Ar*C*(5)H), 126.7 (d, $^3J_{CF}$ 7.0, Ar*C*(6)H), 128.9 (d, $^3J_{CF}$ 2.0, Ar*C*(2)H), 130.0 (*C*(2)H), 131.2 (*C*(3)H), 134.9 (d, $^4J_{CF}$ 4, Ar*C*(1)), 158.4 (d, $^1J_{CF}$ 248, Ar*C*(4)-F); HRMS (ESI$^+$) $C_{11}H_{14}N^{79}BrF^+$ [M+H]$^+$ found: 258.0286, requires:258.1344 (−0.8 ppm).

Ethyl (*E*)-3-(3-fluorophenyl)acrylate[118] 502

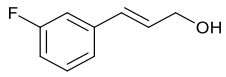


Following general procedure **A**, 3-fluoro-benzaldhyde (2.56 mL, 24.2 mmol, 1.0 equiv.) was reacted with ethyl 2-(triphenyl-λ5-phosphanylidene)acetate (10.1 g, 29.0 mmol, 1.2 equiv.) in CH_2Cl_2 (30 mL)

to give the title product (3.99 g, 85%, 97:3 *E*:*Z*) as a colourless oil after flash column chromatography on silica gel (10→20% EtOAc/hexane).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 7.2, CH_2CH_3), 4.27 (2H, q, *J* 7.2, CH_2CH_3), 6.42 (1H, d, *J* 16.0, C(2)*H*), 7.03-7.11 (1H, m, Ar(2)*H*), 7.21 (1H, dt, *J* 9.7, 2.0, Ar(4)*H*), 7.29 (1H, d, *J* 7.7, Ar(5)*H*), 7.35 (1H, td, *J* 7.9, 5.8, Ar(6)*H*), 7.63 (1H, d, *J* 16.0, C(3)*H*); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −112.6 (Ar*F*); Data consistent with literature.[118]

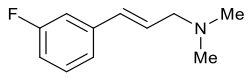
(*E*)-3-(3-Fluorophenyl)prop-2-en-1-ol[119] 503



Following general procedure **C**, the reaction of ethyl (*E*)-3-(3-fluorophenyl)acrylate **502** (3.0 g, 15.5 mmol, 1.0 equiv.) with DIBAL-H (1.0 M in hexane, 34.0 mL, 34.0 mmol, 2.2 equiv.) in CH_2Cl_2 (78 mL) gave the title product (2.08 g, 88%, 97:3 *E*:*Z*) as a colourless oil and was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.35 (2H, d, *J* 5.5, CH_2), 6.39 (1H, dt, *J* 15.9, 5.5, C(2)*H*), 6.61 (1H, d, *J* 15.9, C(3)*H*), 6.96 (1H, td, *J* 8.4, 2.5, Ar(2)*H*), 7.10 (1H, dt, *J* 10.2, 2.1, Ar(4)*H*), 7.16 (1H, d, *J* 7.8, Ar(5)*H*), 7.26-7.35 (1H, m, Ar(6)*H*); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −113.5 (Ar*F*); Data consistent with literature.[119]

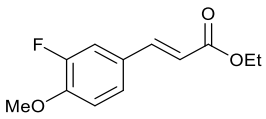
(*E*)-3-(3-Fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine 504



Following general procedure **K**, the reaction of (*E*)-3-(3-fluorophenyl)prop-2-en-1-ol **503** (2.0 g, 13.2 mmol, 1.0 equiv.) with PBr_3 (495 µL, 5.26 mmol, 0.4 equiv.) in Et_2O (39 mL), then with aq. dimethylamine (40% wt., 8.34 mL, 66 mmol, 5.0 equiv.) in THF (26 mL) gave the title product (1.12 g, 47%, 98:2 *E*:*Z*) as a colourless liquid after high vacuum distillation.

bp 85-87 °C @ 1mmbar; ν_{max} (film, cm^{-1}): 2943, 1611, 1591, 1485, 1446, 1359, 1256, 1233, 1175, 1141, 1092, 1022, 964, 872, 856; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H; 2.29 (6H, s, $N(CH_3)_2$), 3.08 (2H, dd, *J* 6.6, 1.3, C(1)H_2), 6.29 (1H, dt, *J* 15.9, 6.6, C(2)*H*), 6.49 (1H, *J* 15.9, C(3)*H*), 6.93 (1H, td, *J* 8.4, 2.7, Ar(2)*H*), 7.08 (1H, dt, *J* 10.2, 2.1, Ar(4)*H*), 7.15 (1H, d, *J* 7.8, Ar(6)*H*), 7.27 (1H, td, *J* 8.0, 6.0, Ar(5)*H*); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −113.6 (td, *J* 9.6, 6.2, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 45.5 ($N(CH_3)_2$), 62.0 (*C*(1)H_2), 112.9 (d, $^2J_{CF}$ 22.0, Ar*C*(2)H), 114.3 (d, $^2J_{CF}$ 21, Ar*C*(4)H), 122.2 (d, $^4J_{CF}$ 2.7, Ar*C*(6)H), 129.1 (*C*(2)H), 130.1 (d, $^3J_{CF}$ 8.3, Ar*C*(5)H), 131.4 (d, *J* 2.6, *C*(3)H), 139.5 (d, $^3J_{CF}$ 7.8, Ar*C*(1)), 163.2 (d, $^1J_{CF}$ 245, Ar*C*-F); HRMS (NSI$^+$) $C_{11}H_{15}NF^+$ $[M+H]^+$ found: 180.1179, requires: 180.1183 (−2.2 ppm).

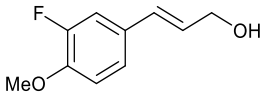
Ethyl (*E*)-3-(3-fluoro-4-methoxyphenyl)acrylate 505



Following general procedure **A**, 3-fluoro-4-methoxybenzaldehyde (5.0 g, 32.5 mmol, 1.0 equiv.) was reacted with ethyl 2-(triphenyl-λ5-phosphanylidene)acetate (13.56 g, 39.0 mmol, 1.2 equiv.) in CH_2Cl_2 (50 mL) to give the title product (6.68 g, 92%, 96:4 *E*:*Z*) as a white solid after flash column chromatography on silica gel (10→20% EtOAc/hexane);

mp 36-38 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 7.1, CH_2CH_3), 3.93 (3H, s, OCH_3), 4.27 (2H, q, *J* 7.1, CH_2CH_3), 6.30 (1H, d, *J* 16.0, C(2)*H*), 6.96 (1H, t, *J* 8.5, Ar(5)*H*), 7.22-7.27 (1H, m, Ar(2)*H*), 7.29 (1H, dd, *J* 12.0, 2.1, Ar(6)*H*), 7.59 (1H, d, *J* 16.0, C(3)*H*); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −134.5 (dd, *J* 11.7, 8.7, Ar*F*).

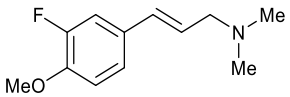
(*E*)-3-(3-Fluoro-4-methoxyphenyl)prop-2-en-1-ol 506



Following general procedure **C**, the reaction of ethyl (*E*)-3-(3-fluoro-4-methoxyphenyl)acrylate **505** (3.0 g, 13.4 mmol, 1.0 equiv.) with DIBAL-H (1.0 M in hexane, 29.5 mL, 29.5 mmol, 2.2 equiv.) in CH_2Cl_2 (67 mL) gave the title product (2.12 g, 87%, 96:4 *E*:*Z*) as a white solid and was used without further purification.

mp 54-56 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.88 (3H, s, O(CH_3)), 4.29 (2H, d, *J* 5.7, C(1)H_2), 6.21 (1H, dt, *J* 15.8, 5.7, C(2)*H*), 6.50 (1H, dt, *J* 15.7, 1.4, C(3)*H*), 6.88 (1H, t, *J* 8.5, Ar(5)*H*), 7.05 (1H, dt, *J* 8.5, 1.5, Ar(6)*H*), 7.13 (1H, dd, *J* 12.5, 2.1, Ar(2)*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: −135.4 (Ar*F*).

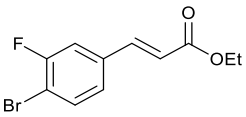
(*E*)-3-(3-Fluoro-4-methoxyphenyl)-*N*,*N*-dimethylprop-2-en-1-amine 507



Following general procedure **K**, the reaction of (*E*)-3-(3-fluoro-4-methoxy-phenyl)prop-2-en-1-ol **506** (2.12 g, 11.65 mmol, 1.0 equiv.) with PBr_3 (438 µL, 4.66 mmol, 0.4 equiv.) in Et_2O (36 mL), then with aq. dimethylamine (40% wt., 7.58 mL, 60 mmol, 5.0 equiv.) in THF (24 mL) gave the title product (1.14 g, 47%, 97:3 *E*:*Z*) as a colourless liquid after high vacuum distillation.

bp 144-148 °C @ 1mmbar; ν_{max} (film, cm^{-1}): 2940, 1618, 1514, 1441, 1300, 1271, 1219, 1121, 1026, 996, 858; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.26 (6H, s, N(CH_3)$_2$), 3.04 (2H, dd, *J* 6.7, 1.4, C(1)H_2), 3.87 (3H, s, O(CH_3)), 6.11 (1H, dt, *J* 15.8, 6.7, C(2)*H*), 6.40 (1H, d, *J* 15.8, C(3)*H*), 6.88 (1H, t, *J* 8.5, Ar(5)*H*), 7.05 (1H, d, *J* 8.5, Ar(6)*H*), 7.12 (1H, dd, *J* 12.5, 2.1, Ar(2)*H*); $^{19}F\{^{1}H\}$ NMR (471 MHz, $CDCl_3$) δ_F: −135.5 (Ar*F*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 45.3 (N(*C*H_3)$_2$), 56.3 (O*C*H_3), 62.0 (*C*(1)H_2), 113.3 (d, $^{4}J_{CF}$ 2.3, Ar*C*(6)H), 113.5 (d, $^{2}J_{CF}$ 19, Ar*C*(2)H), 122.6 (d, $^{3}J_{CF}$ 3.2, Ar*C*(5)H), 126.9 (*C*(2)H), 130.8 (d, $^{3}J_{CF}$ 6.6, Ar*C*(1)), 131.2 (d, $^{4}J_{CF}$ 2.2, *C*(3)H), 147.1 (d, $^{2}J_{CF}$ 11.0, Ar*C*(4)-OMe), 152.6 (d, $^{1}J_{CF}$ 245, Ar*C*-F); HRMS (NSI^{+}) $C_{12}H_{17}FNO$ $[M+H]^{+}$ found: 210.1286, requires: 210.1289 (−1.3 ppm).

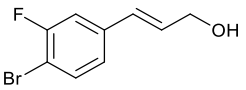
Ethyl (*E*)-3-(4-bromo-3-fluorophenyl)acrylate 508



Following general procedure **A**, 3-fluoro-4-bromobenzaldehyde (5.0 g, 24.6 mmol, 1.0 equiv.) was reacted with ethyl 2-(triphenyl-λ5-phosphanylidene)acetate (10.3 g, 29.6 mmol, 1.2 equiv.) in CH_2Cl_2 (50 mL) to give the title product (7.36 g, quant., 95:5 *E*:*Z*) as a white solid after flash column chromatography on silica gel (10→20% EtOAc/hexane).

mp 32-34 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.33 (3H, t, *J* 7.1, CH_2C*H*$_3$), 4.26 (2H, q, *J* 7.1, C*H*$_2$$CH_3$), 6.42 (1H, d, *J* 15.9, C(2)*H*), 7.17 (1H, dd, *J* 8.2, 1.9, Ar(6)*H*), 7.26 (1H, dd, *J* 9.3, 1.9, Ar(2)*H*), 7.51-7.62 (2H, m, C(3)*H* + Ar(5)*H*); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −106.5 (m, Ar*F*).

(*E*)-3-(4-Bromo-3-fluorophenyl)prop-2-en-1-ol 509

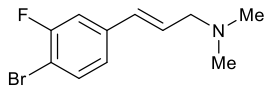


Following general procedure **C**, the reaction of ethyl (*E*)-3-(4-bromo-3-fluorophenyl)acrylate **508** (3.0 g, 11.0 mmol, 1.0 equiv.) with DIBAL-H (1.0 M in hexane, 24.2 mL, 24.2 mmol, 2.2 equiv.) in CH_2Cl_2 (55 mL) gave the title product (2.12 g, 87%, 94:6 *E*:*Z*) as a colourless oil and was used without further purification.

ν_{max} (film, cm^{-1}): 3296, 2920, 1558, 1483, 1419, 1159, 1089, 1039, 962, 869;^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.26-4.46 (2H, m, C(1)H_2), 6.39 (1H, dt, *J* 15.9, 5.3, C(2)*H*), 6.57 (1H, dt, *J* 15.9, 1.7, C(3)*H*), 7.05 (1H, dd, *J* 8.3, 2.0, Ar(6)*H*), 7.16 (1H, dd, *J* 9.8, 2.0, Ar(2)*H*), 7.50 (1H, dd, *J* 8.3, 7.2, Ar(5)*H*); $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ_F: −107.7 (Ar*F*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 63.3 (*C*(1)H_2), 107.9 (d, $^{2}J_{CF}$ 21.0, Ar*C*(4)-Br), 114.0 (d, $^{2}J_{CF}$ 23.0, Ar*C*(2)H), 123.5 (d, $^{4}J_{CF}$ 3.6,

Ar*C*(6)H), 128.8 (*C*(3)H), 130.8 (*C*(2)H), 133.6 (Ar*C*(5)H), 138.4 (d, *J* Ar*C*(1)), 159.3 (d, $^{1}J_{CF}$ 247, Ar*C*-F); HRMS (ASAP^{+}) $C_9H_7OF^{79}Br^{-}$ [M−H]$^{-}$ found: 228.9660, requires: 228.9664 (−0.4 ppm).

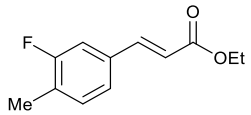
(*E*)-3-(4-Bromo-3-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine 510



Following general procedure **J**, the reaction of (*E*)-3-(3-fluoro-4-bromo-phenyl)prop-2-en-1-ol **509** (2.5 g, 10.82 mmol, 1.0 equiv.) with PBr_3 (407 µL, 4.33 mmol, 0.4 equiv.) in Et_2O (33 mL), then with aq. dimethylamine (40% wt., 6.95 mL, 55 mmol, 5.0 equiv.) in THF (22 mL) gave the title product (1.16 g, 42%, 98:2 *E*:*Z*) as a colourless liquid after high vacuum distillation.

bp 108-110 °C @ 1mmbar; ν_{max} (film, cm^{-1}): 2941, 1570, 1479, 1417, 1358, 1236, 1148, 1040, 966, 858;^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.26 (6H, s, N(C*H*$_3$)$_2$), 3.05 (2H, dd, *J* 6.6, 1.4, C(1)*H*$_2$), 6.27 (1H, dt, *J* 15.9, 6.6, C(2)*H*), 6.43 (1H, d, *J* 15.9, C(3)*H*), 7.01 (1H, dd, *J* 8.3, 2.0, Ar(2)*H*), 7.11 (1H, dd, *J* 9.9, 2.0, Ar(5)*H*), 7.40-7.49 (1H, m, Ar(6)*H*); ^{19}F{^{1}H} NMR (471 MHz, $CDCl_3$) δ_F: −107.8 (Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 45.5 (N(*C*H$_3$)$_2$), 61.9 (*C*(1)H$_2$), 107.6 (d, $^{2}J_{CF}$ 21.2 Ar*C*-Br), 113.9 (d, $^{2}J_{CF}$ 22.7, Ar*C*(2)H), 123.3 (d, $^{4}J_{CF}$ 3.3, Ar*C*(6)H), 129.9 (C(2)*H*), 130.5 (d, $^{3}J_{CF}$ 2.3, Ar*C*(5)H), 133.6 (C(3)*H*), 138.8 (d, $^{3}J_{CF}$ 7.1, Ar*C*(1)), 159.3 (d, $^{1}J_{CF}$ 247, Ar*C*-F); HRMS (NSI^{+}) $C_{11}H_{14}N^{79}BrF^{+}$ [M+H]$^{+}$ found: 259.0288 requires: 259.0288 (−0.1 ppm).

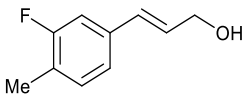
Ethyl (*E*)-3-(3-fluoro-4-methylphenyl)acrylate[120] 511



Following general procedure **A**, 3-fluoro-4-methylbenzaldehyde (5.0 g, 36.2 mmol, 1.0 equiv.) was reacted with ethyl 2-(triphenyl-λ5-phosphanylidene)acetate (15.1 g, 43.5 mmol, 1.2 equiv.) in CH_2Cl_2 (50 mL) to give the title product (7.14 g, 95%, 96:4 *E*:*Z*) as a colourless liquid after flash column chromatography on silica gel (20% EtOAc/hexane).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.33 (3H, t, *J* 7.2, CH_2CH_3), 2.29 (3H, d, *J* 2.0, ArCH_3), 4.26 (2H, q, *J* 7.2, CH_2CH_3), 6.38 (1H, d, *J* 15.9, C(2)*H*), 7.13-7.23 (3H, m, Ar*H*), 7.60 (1H, d, *J* 15.9, C(3)*H*); ^{19}FNMR (471 MHz, $CDCl_3$) δ_F: −116.83 - −116.97 (m, Ar*F*); Data consistent with literature.[120]

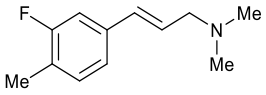
(*E*)-3-(3-fluoro-4-methylphenyl)prop-2-en-1-ol 512



Following general procedure **C**, the reaction of ethyl (*E*)-3-(3-fluoro-4-methylphenyl)acrylate **511** (2.0 g, 9.62 mmol, 1.0 equiv.) with DIBAL-H (1.0 M in hexane, 21.2 mL, 21.2 mmol, 2.2 equiv.) in CH_2Cl_2 (50 mL) gave the title product (1.73 g, quant., 97:3 *E*:*Z*) as a white solid and was used without further purification.

mp 38-40 °C; ν_{max} (film, cm^{-1}): 3310, 2853, 1572, 1506, 1420, 1259, 1115, 1086, 964, 874; ^{1}H NMR (700 MHz, $CDCl_3$) δ_H: 2.25 (3H, d, *J* 2.0, C*H*$_3$), 4.29 (2H, d, *J* 5.6, C(1)*H*$_2$), 6.32 (1H, dt, *J* 15.9, 5.6, C(3)*H*), 6.52 (1H, d, *J* 15.9, C(3)*H*), 6.96-7.04 (2H, m, Ar(2 + 6)*H*), 7.09 (1H, t, *J* 8.0, Ar(5)*H*); ^{19}F NMR (657 MHz, $CDCl_3$) δ_F: −117.84 (t, *J* 9.5, Ar*F*); ^{13}C{^{1}H}NMR (179 MHz, $CDCl_3$) δ_C: 14.5 (d, $^3J_{CF}$ 3.4, Ar*C*H$_3$), 63.7 (*C*(1)H$_2$), 112.6 (d, $^2J_{CF}$ 23.0, Ar*C*(2)H), 122.2 (d, $^4J_{CF}$ 3.7, Ar*C*(6)H), 124.4 (d, $^2J_{CF}$ 18, Ar*C*(4)-Me), 128.9 (*C*(2)H), 130.1 (*C*(3)H), 131.6 (d, $^3J_{CF}$ 5.6, Ar*C*(5)H, 136.6 (d, $^3J_{CF}$ 7.6, Ar*C*(1)), 161.6 (d, $^1J_{CF}$ 244 Ar*C*-F). HRMS (ASAP$^+$) $C_{10}H_{10}OF^-$ [M−H]$^-$ found: 165.0712, requires: 165.0716 (−0.4 ppm).

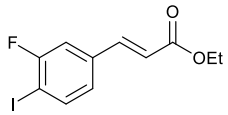
(*E*)-3-(3-fluoro-4-methylphenyl)-*N*,*N*-dimethylprop-2-en-1-amine 513



Following general procedure **K**, the reaction of (*E*)-3-(3-fluoro-4-methyl-phenyl)prop-2-en-1-ol **512** (1.70 g, 10.24 mmol, 1.0 equiv.) with PBr_3 (385 µL, 4.10 mmol, 0.4 equiv.) in Et_2O (30 mL), then with aq. dimethylamine (40% wt., 6.47 mL, 51.2 mmol, 5.0 equiv.) in THF (20 mL) gave the title product (0.87 g, 44%, 97:3 *E*:*Z*) as a colourless liquid after high vacuum distillation.

bp 85-95 °C @ 1mmbar; ν_{max} (film, cm^{-1}): 2943, 1574, 1508, 1454, 1419, 1256, 1113, 1023, 966, 871; ^{1}H NMR (700 MHz, $CDCl_3$) δ_H: 2.24 (3H, d, *J* 2.0, C*H*$_3$), 2.26 (6H, s, N(C*H*$_3$)$_2$), 3.05 (2H, dd, *J* 6.6, 1.5, C(1)*H*$_2$), 6.21 (1H, dt, *J* 15.8, 6.6, C(2)*H*), 6.43 (1H d, *J* 15.8, C(3)*H*), 6.99-7.04 (2H, m, Ar(5 + 6)*H*), 7.09 (1H, t, *J* 8.0, Ar(2)*H*); ^{19}F NMR (659 MHz, $CDCl_3$) δ_F: −117.92 (t, *J* 9.9, Ar*F*); ^{13}C{^{1}H}NMR (179 MHz, $CDCl_3$) δ_C: 14.5 (d, $^3J_{CF}$ 3.5, Ar*C*H$_3$), 45.4 (N(*C*H$_3$)$_2$), 62.0 (*C*(1)H$_2$), 112.5 (d, $^2J_{CF}$ 23.0, Ar*C*(2)H), 121.9 (d, $^4J_{CF}$ 3.2, Ar*C*(6)H), 123.9 (d, $^2J_{CF}$ 18, Ar*C*(4)-Me), 127.9 (*C*(2)H), 131.5-131.5 (m, Ar*C*(5)H + *C*(3)H), 136.9 (d, $^3J_{CF}$ 7.7, Ar*C*(1)), 161.6 (d, $^1J_{CF}$ 245, Ar*C*-F); HRMS (ASAP$^+$) $C_{12}H_{16}FN$ [M] found: 193.1262, requires: 193.1267 (−2.6 ppm).

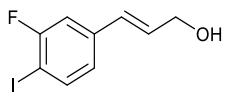
Ethyl (*E*)-3-(3-fluoro-4-iodophenyl)acrylate 514



Following general procedure **A**, 3-fluoro-4-iodobenzaldehyde (1.0 g, 4.0 mmol, 1.0 equiv.) was reacted with ethyl 2-(triphenyl-λ5-phosphanylidene)acetate (1.67 g, 4.8 mmol, 1.2 equiv.) in CH_2Cl_2 (10 mL) to give the title product (1.42 g, quant., 94:6 *E*:*Z*) as a pale yellow oil after flash column chromatography on silica gel (20% EtOAc/hexane).

ν_{max} (film, cm^{-1}): 2980, 1705, 1637, 1560, 1478, 1416, 1313, 1265, 1177, 1026, 978, 856; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 7.1, CH_2CH3), 4.27 (2H, q, *J* 7.1, CH_2CH_3), 6.45 (1H, d, *J* 16.0, C(2)*H*), 7.05 (1H, dd, *J* 8.2, 2.0, Ar(5)*H*), 7.20 (1H, dd, *J* 8.8, 2.0, Ar(2)*H*), 7.57 (1H, d, *J* 16.0, C(3)*H*), 7.76 (1H, dd, *J* 8.2, 6.5, Ar(6)*H*); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −93.2 (dd, *J* 8.5, 6.8, Ar*F*); ^{13}C{^{1}H}NMR (179 MHz, $CDCl_3$) δ_C:14.3 (CH_3), 60.7 (OCH_2), 83.3 (d, $^2J_{CF}$ 26, Ar*C*(4)-I), 114.3 (d, $^2J_{CF}$ 25.0, Ar*C*(2)H), 120.2 (*C*(2)H), 125.2 (d, $^3J_{CF}$ 3.6, Ar*C*(5)H), 136.9 (d, $^3J_{CF}$ 7.1, Ar*C*(1)), 139.8 (d, $^4J_{CF}$ 1.9, Ar*C*(6)H), 142.1 (d, $^4J_{CF}$ 2.5, *C*(3)H), 161.9 (d, $^1J_{CF}$ 246, Ar*C*-F), 166.3 (*C*=O); HRMS (ESI$^+$) $C_{11}H_{10}O_2FINa^+$ $[M+Na]^+$ found: 342.9593, requires: 342.9596 (−2.5 ppm).

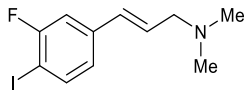
(*E*)-3-(3-fluoro-4-iodophenyl)prop-2-en-1-ol 515



Following general procedure **C**, the reaction of ethyl (*E*)-3-(3-fluoro-4-iodophenyl)acrylate **514** (1.2 g, 3.75 mmol, 1.0 equiv.) with DIBAL-H (1.0 M in hexane, 8.25 mL, 8.25 mmol, 2.2 equiv.) in CH_2Cl_2 (20 mL) gave the title product (0.81 g, 77%, 97:3 *E*:*Z*) as a colourless oil and was used without further purification.

mp 52-54 °C; ν_{max} (film, cm^{-1}): 3225, 2887, 1558, 173, 1406, 1086, 1016, 961, 869;^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.33 (2H, s, C(1)H_2), 6.39 (1H, dt, *J* 15.9, 5.3, C(2)*H*), 6.54 (1H, d, *J* 15.9, C(3)*H*), 6.92 (1H, dd, *J* 8.2, 2.0, Ar(5)*H*), 7.08 (1H, dd, *J* 9.3, 2.0, Ar(2)*H*), 7.67 (1H, dd, *J* 8.2, 6.6, Ar(6)*H*); ^{19}F{^{1}H} NMMR (376 MHz, $CDCl_3$) δ_F: −94.4 (Ar*F*);^{13}C{^{1}H}NMR (179 MHz, $CDCl_3$) δ_C: 63.3 (*C*(1)H_2), 79.6 (d, $^2J_{CF}$ 26.0, Ar*C*(4)-I), 113.2 (d, $^2J_{CF}$ 24.0, Ar*C*(2)H), 123.9 (d, $^4J_{CF}$ 3.1, Ar*C*(5)H), 128.7 (d, $^4J_{CF}$ 2.3, *C*(3)H), 130.8 (*C*(2)H), 139.3 (d, $^4J_{CF}$ 1.6, Ar*C*(6)H), 139.4(d, $^3J_{CF}$ 7.0, Ar*C*(1)), 161.9 (d, $^1J_{CF}$ 245 ArC-F); HRMS (CI$^+$) $C_9H_9OFI^+$ $[M+H]^+$ found: 278.9685, requires: 278.9682 (+1.0 ppm).

(*E*)-3-(3-Fluoro-4-iodophenyl)-*N*,*N*-dimethylprop-2-en-1-amine 516

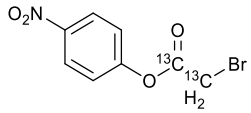


Following general procedure **K**, the reaction of (*E*)-3-(3-fluoro-4-methyl-phenyl)prop-2-en-1-ol **515** (0.81 g, 2.90 mmol, 1.0 equiv.) with PBr_3 (109 µL, 1.16 mmol, 0.4 equiv.) in Et_2O (9 mL), then with aq. dimethylamine (40% wt., 1.83 mL, 14.5 mmol, 5.0 equiv.) in THF (6 mL) gave the title product (0.68 g, 77%, 95:5 *E*:*Z*) as a pale yellow solid, which was used without purification.

mp 49-51 °C; ν_{max} (film, cm^{-1}): 2860, 1555, 1471, 1404, 1257, 1230, 1143, 1038, 1017, 996, 876; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.25 (6H, s, N(C*H*$_3$)$_2$), 3.05 (2H, dd, *J* 6.5, 1.4, C(1)*H*), 6.28 (1H, dt, *J* 15.8, 6.5, C(2)*H*), 6.41 (1H, d, *J* 15.8, C(3)*H*), 6.89 (1H, dd, *J* 8.2, 2.0, Ar(5)*H*), 7.05 (1H, dd, *J* 9.3, 2.0, Ar(2)*H*), 7.63 (1H, dd, *J* 8.2, 6.6, Ar(6)*H*);^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −94.5 - −94.6 (m, Ar*F*);^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 45.5 (N(C*H*$_3$)$_2$), 61.9 (*C*(1)H$_2$), 79.4 (d,$^2J_{CF}$ 26, Ar*C*(4)-I), 113.1 (d, $^2J_{CF}$ 24, Ar*C*(2)H), 123.8 (d, $^3J_{CF}$ 3.1, Ar*C*(1)), 130.0 (*C*(2)H), 130.5 (d, $^4J_{CF}$ 2.1, Ar*C*(6)H), 139.3 (d, $^4J_{CF}$ 1.8, *C*(3)H), 139.8 (d, $^3J_{CF}$ 7.1, Ar*C*(5)H), 162.0 (d, $^1J_{CF}$ 245, Ar*C*-F); HRMS (ASAP$^+$) $C_{11}H_{14}FIN$ $[M + H]^+$ found: 306.0147, requires: 306.0155 (−0.8 ppm).

Bromoacetate Synthesis

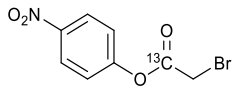
4-Nitrophenyl 2-bromoacetate-$^{13}C_2$ $^{13}C_2$-331



Following general procedure **G**, $^{13}C_2$-bromoacetic acid (400 mg, 2.84 mmol, 1.0 equiv.) was reacted with DCC (585 mg, 2.84 mmol, 1.0 equiv.), 4-nitrophenol (395 mg, 2.84 mmol, 1.0 equiv.) and DMAP (34 mg, 0.28 mmol, 0.1 equiv.) in EtOAc (14 mL) to give the title product (379 mg, 51%) as a white solid after recrystallization from Et_2O/hexane.

mp 83-84 °C; ν_{max} (film, cm^{-1}): 2957, 1724, 1587, 1516, 1338, 1207, 1009, 923; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.11 (2H, dd, *J* 154, 4.8, ^{13}C*H*$_2$), 7.34 (2H, d, *J* 9.1, Ar(2,6)*H*), 8.30 (2H, d, *J* 9.1, Ar(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 25.1 (d, $^1J_{CC}$ 67, ^{13}*C*H$_2$), 122.2 (Ar*C*(2,6)H), 125.5 (Ar*C*(3,5)H), 145.9 (Ar*C*(4)-NO_2), 155.0 (Ar*C*(1)-O), 165.1 (d, $^1J_{CC}$ 67, ^{13}*C*=O); HRMS (APCI$^+$) $C_6{}^{13}C_2H_7BrNO_4^+$ $[M+H]^+$ found: 261.9620, requires 261.9620 (−0.0 ppm).

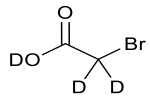
4-Nitrophenyl 2-bromoacetate-1-^{13}C $^{13}C_1$-517



Following general procedure **G**, $^{13}C_1$-bromoacetic acid (500 mg, 3.55 mmol, 1.0 equiv.) was reacted with DCC (731 mg, 3.55 mmol, 1.0 equiv.), 4-nitrophenol (493 mg, 3.55 mmol, 1.0 equiv.) and DMAP (43 mg, 0.36 mmol, 0.1 equiv.) in EtOAc (20 mL) to give the title product (424 mg, 46%) as a white solid after recrystallization from Et_2O/hexane.

mp 80-82 °C; ν_{max} (film, cm^{-1}): 2962, 1726, 1587, 1514, 1487, 1335, 1091, 929;^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.09 (2H, d, $^2J_{CH}$ 4.8, C*H*$_2$), 7.32-7.36 (2H, m, Ar(2,6)*H*), 8.27-8.32 (2H, m, Ar(3,5)*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 25.2 (d, $^1J_{CC}$ 67, *C*H$_2$), 122.2 (Ar*C*(2,6)H), 125.5 (Ar*C*(3,5)H), 145.8 (Ar*C*(4)-NO_2), 155.0 (d, $^2J_{CC}$ 3.4, Ar*C*(1)), 165.1 (^{13}C=O); HRMS (ASAP$^+$) $C_7{}^{13}CH_7NO_4Br$ $[M+H]^+$ found: 260.9598, requires: 260.9502 (+2.3 ppm).

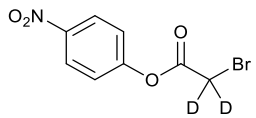
2-Bromoacetic-d_2 acid-d[121] d_3-349



A solution of d_4-malonic acid ***d*$_4$-348** (4.0 g, 36 mmol, 1.0 equiv.) in Et_2O (100 mL) was treated with Br_2 (1.91 mL, 36 mmol, 1.0 equiv.) dropwise at 0 °C. Once the addition was complete the reaction mixture was concentrated *in vacuo*. The resulting solid was heated at 140 °C until bubbling ceased, the residue was purified by distillation to give the product as a colourless liquid (3.90 g, 76%).

bp 82-84 °C @ 2 mmbar; $^{13}C\{^1H\}$ (400 MHz, d_6-DMSO) δ_C: 26.7-28.5 (m, *C*D$_2$), 168.4 (*C*=O); data consistent with the literature.[121]

4-Nitrophenyl 2-bromoacetate-d_2, d_2-350



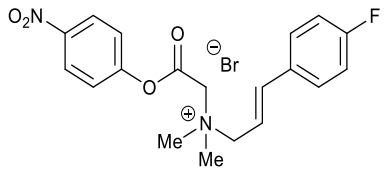
Following general procedure **G**, 2-bromoacetic-d_2 acid-d ***d*$_3$-349** (1.0 g, 7.04 mmol, 1.0 equiv.) was reacted with DCC (1.45 g, 7.04 mmol, 1.0 equiv.), 4-nitrophenol (0.98 mg, 7.04 mmol, 1.0 equiv.) and DMAP (86 mg, 0.70 mmol, 0.1 equiv.) in EtOAc (35 mL) to give the title product (550 mg, 30%, 95% D) as a white solid after recrystallization from Et_2O/hexane.

mp 66-68 °C; ν_{max} (film, cm^{-1}): 2933, 1762, 1589, 1514, 1487, 1336, 1199, 1105, 979;^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 4.09-4.11 (0.1H, m, C(2)*H*D + C(2)*H*$_2$), 7.34 (2H, d, *J* 9.1, Ar(2,6)*H*), 8.30 (2H, d, *J*

9.1, Ar(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 24.4-25.1 (m, *C*D_2), 122.2 (Ar*C*(2,6)H), 125.5 (Ar*C*(3,5)H), 145.8 (Ar*C*(1)O), 155.0 (Ar*C*(4)NO_2), 165.1 (*C*=O); HRMS (APCI$^+$) $C_8H_5{}^2H_2BrNO_4^+$ $[M+H]^+$ found: 261.9672, requires: 261.9679 (−2.5 ppm).

Ammonium Salt Synthesis

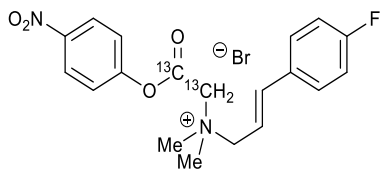
(*E*)-3-(4-Fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 309



Following general procedure **H**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine **498** (4.0 g, 22.4 mmol, 1.0 equiv.) was reacted with *p*-nitrophenyl bromoacetate **213** (6.97 g, 26.8 mmol, 1.2 equiv.) in MeCN (23 mL) to give the title product (8.95 g, 91%) as a white solid.

mp 146 °C (dec.); ν_{max} (film, cm^{-1}): 2918, 1775, 1591, 1510, 1348, 1226, 1205, 1146, 1132, 978, 893;^{1}H NMR (300 MHz, CD_3CN) δ_H: 3.40 (6H, s, $N^+(CH_3)_2$), 4.46 (2H, d, *J* 7.6, C(1)H_2), 4.88 (2H, s, COCH_2), 6.44 (1H, dt, *J* 15.6, 7.6, C(2)*H*), 7.02 (1H, d, *J* 15.6, C(3)*H*), 7.16 (2H, t, *J* 8.9, C(3)Ar(3,5)*H*), 7.48 (2H, d, *J* 9.2, OAr(2,6)*H*), 7.64 (2H, dd, *J* 8.9, 5.5, C(3)Ar(2,6)*H*), 8.30 (2H, d, *J* 9.2, OAr(3,5)*H*);$^{19}F\{^{1}H\}$ NMR (282 MHz, CD_3CN) δ_F: −113.9 (Ar-*F*); $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ_C: 50.8 ($N^+(CH_3)_2$), 60.5 (CO*C*H_2), 67.0 (*C*(1)H_2), 115.6 (d, $^2J_{CF}$ 22, C(3)Ar*C*(3,5)H), 116.1 (*C*(2)H), 123.1 (OAr*C*(3,5)H), 125.5 (OAr*C*(2,6)H), 129.5 (d, $^3J_{CF}$ 7.8, C(3)Ar*C*(2,6)H), 131.8 (d, $^4J_{CF}$ 2.9, C(3)Ar*C*(1)), 140.3 (*C*(3)H), 145.6 (OAr*C*(1)O), 153.9 (OAr*C*(4)NO_2), 162.5 (d, $^1J_{CF}$ 247, Ar*C*-F), 163.2 (*C*=O); HRMS (NSI$^+$): $C_{19}H_{20}FN_2O_4^+$ $[M-Br]^+$ found: 359.1392, requires 359.1402 (−2.7 ppm).

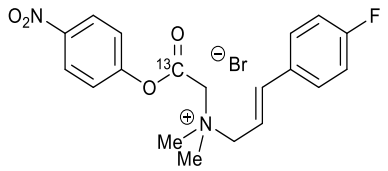
(*E*)-3-(4-Fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl-1,2-$^{13}C_2$)prop-2-en-1-ammonium bromide $^{13}C_2$-333



Following general procedure **H**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine **498** (172 mg, 0.96 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl 2-bromoacetate-$^{13}C_2$ **$^{13}C_2$-331** (300 mg, 1.15 mmol, 1.2 equiv.) in MeCN (1 mL) to give the title product (348 mg, 79%) as a white solid.

mp 129 °C (dec.); ν_{max} (film, cm^{-1}): 2912, 1732, 1508, 1390, 1116, 972;^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 3.34 (6H, s, $N^+(CH_3)_2$), 4.41 (2H, d, *J* 7.3, C(1)H_2), 4.86 (2H, dd, *J* 147, 6.7, $^{13}CH_2$), 6.57 (1H, dt, *J* 15.6, 7.3, C(2)*H*), 6.96 (1H, d, *J* 15.6, C(3)*H*), 7.26 (2H, t, *J* 8.8, C(3)Ar(3,5)*H*), 7.57 (2H, d, *J* 9.1, OAr(2,6)*H*), 7.70 (2H, dd, *J* 8.8, 5.6, C(3)Ar(2,6)*H*), 8.38 (2H, d, *J* 9.1, OAr(3,5)*H*); ^{19}F NMR (471 MHz, d_6-DMSO) δ_F: −112.2 (Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, d_6-DMSO) δ_C: 50.8 ($N^+(CH_3)_2$), 60.5 (d, *J* 64, $^{13}CH_2$), 67.1 (*C*(1)H_2), 115.7 (d, $^{2}J_{CF}$ 21.6, C(3)Ar*C*(3,5)H), 116.1 (*C*(2)H), 123.1 (OAr*C*(3,5)H), 125.5 (OAr*C*(2,6)H), 129.5 (d, $^{3}J_{CF}$ 8.3, C(3)Ar*C*(2,6)H), 131.8 (d, $^{4}J_{CF}$ 2.9, C(3)Ar*C*(1)), 140.4 (*C*(3)H), 145.6 (OAr*C*(1)), 153.9 (OAr*C*(4)NO_2), 162.5 (d, $^{1}J_{CF}$ 247, Ar*C*-F), 163.2 (d, $^{1}J_{CC}$ 64, ^{13}C=O); HRMS (NSI$^+$) $C_{17}{}^{13}C_2H_{20}FN_2O_4^+$ $[M]^+$ found: 361.1459, requires 361.1469 (−2.7 ppm).

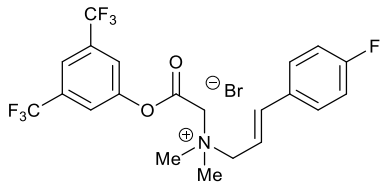
(*E*)-3-(4-Fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl-2-^{13}*C*)prop-2-en-1-ammonium bromide $^{13}C_1$-341



Following general procedure **H**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine **498** (156 mg, 0.87 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl 2-bromoacetate-$^{13}C_1$ **^{13}C$_1$-517** (250 mg, 0.96 mmol, 1.2 equiv.) in MeCN (2 mL) to give the title product (292 mg, 76%) as a white solid.

mp 136 °C (dec.); ν_{max} (film, cm^{-1}): 2995, 1730, 1595, 1508, 1350, 1226, 1203, 1132, 1119, 977, 889, 850;^{1}H NMR (400 MHz, d_6-DMSO) δ_H: 3.34 (6H, s, $N^+(CH_3)_2$), 4.38 (2H, d, *J* 7.5, C(1)H_2), 4.81 (2H, d, *J* 6.8, $^{13}COCH_2$), 6.55 (1H, dt, *J* 15.6, 7.5, C(2)*H*), 6.96 (1H, d, *J* 15.6, C(3)*H*), 7.27 (2H, t, *J* 8.8, C(3)Ar(3,5)*H*), 7.56 (2H, d, *J* 9.1, OAr(2,6)*H*), 7.70 (2H, dd, *J* 8.8, 5.6, C(3)Ar(2,6)*H*), 8.38 (2H, d, *J* 9.1, OAr(3,5)*H*); ^{19}F{^{1}H} NMR (471 MHz, d_6-DMSO) δ_F: −112.1 (Ar*F*); ^{13}C{^{1}H} NMR (101 MHz, d_6-DMSO) δ_C: 50.8 ($N^+C(H_3)_2$), 60.5 (d, $^{1}J_{CC}$ 65, $^{13}COCH_2$), 67.1 (*C*(1)H_2), 115.6 (d, $^{2}J_{CF}$ 21.7, C(3)Ar*C*(3,5)H), 116.0 (*C*(2)H), 123.1 (OAr*C*(3,5)H), 125.5 (OAr*C*(2,6)H), 129.5 (d, $^{3}J_{CF}$ 8.4, Ar*C*(2,6)H), 131.8 (d, $^{4}J_{CF}$ 3, Ar*C*(1)), 140.4 (*C*(3)H), 145.6 (Ar*C*(1)O), 153.8 (Ar*C*(4)NO_2), 162.5 (d, $^{1}J_{CF}$ 247, Ar*C*-F), 163.2 (^{13}C=O); HRMS (ESI$^+$) $C_{18}{}^{13}CH_{20}FN_2O_4^+$ $[M]^+$ found: 360.1425, requires: 360.1435 (−2.8 ppm).

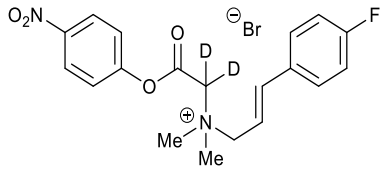
(*E*)-*N*-(2-(3,5-Bis(trifluoromethyl)phenoxy)-2-oxoethyl)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-ammonium bromide 366



Following general procedure **H**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine **498** (1.0 g, 5.59 mmol, 1 equiv.) was reacted with 3,5-bis(trifluoromethyl)phenyl 2-bromoacetate **493** (2.35 g, 6.70 mmol, 1.2 equiv.) in MeCN (5.6 mL) to give the title product (739 mg, 25%) as a white solid, after recrystallization from MeCN/Et_2O.

mp 160 °C (dec.); ν_{max} (film, cm^{-1}): 2904, 1778, 1510, 1363, 1278, 1130, 974, 847; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 3.34 (6H, s, $N^+(CH_3)_2$), 4.41 (2H, d, *J* 7.5, C(1)H_2), 4.78 (2H, s, COCH_2), 6.57 (1H, dt, *J* 15.7, 7.5, C(2)H_2), 6.98 (1H, d, *J* 15.7, C(3)*H*), 7.26 (2H, t, *J* 8.7, C(3)Ar(3,5)*H*), 7.70 (2H, dd, *J* 8.7, 5.6, C(3)Ar(2,6)*H*), 8.09 (2H, s, OAr(2,6)*H*), 8.16 (1H, s, OAr(4)*H*); ^{19}F NMR (376 MHz, d_6-DMSO) δ_F: −112.2 (Ar-*F*), −61.3 (Ar-CF_3); ^{13}C{^{1}H} (126 MHz, d_6-DMSO) δ_C: 50.9 ($N^+(CH_3)_2$), 60.6 (COCH_2), 67.0 (*C*(1)H_2), 115.7 (d, $^2J_{CF}$ 22, C(3)Ar*C*(3,5)H), 116.1 (*C*(2)H), 120.8 (br. s, OAr*C*(4)H), 122.7 (q, $^1J_{CF}$ 273, *C*F_3), 123.7 (d, $^3J_{CF}$ 3, OAr*C*(2,6)H), 129.5 (d, $^3J_{CF}$ 8.3, C(3)Ar*C*(2,6)H), 131.6 (q, $^2J_{CF}$ 34, OAr*C*(3,5)-CF_3), 131.8 (d, $^4J_{CF}$ 3, C(3)Ar*C*(1)), 140.5 (*C*(3)H), 150.0 (Ar*C*(1)-O), 162.5 (d, $^1J_{CF}$ 247, Ar*C*-F), 163.3 (*C*=O); HRMS (NSI$^+$) $C_{21}H_{19}F_7NO_2^+$ [M]$^+$ found: 450.1292, requires: 450.1299 (−1.5 ppm).

(*E*)-3-(4-Fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl-1,1-d_2)prop-2-en-1-ammonium bromide d_2-351

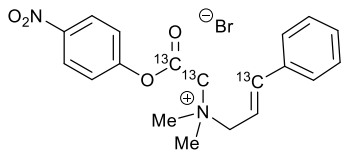


Following general procedure **H**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine **498** (155 mg, 0.95 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl 2-bromoacetate-d_2 ***d*$_2$-350** (300 mg, 1.15 mmol, 1.2 equiv.) in MeCN (2 mL) to give the title product (307 mg, 76%, 75% D) as a white solid.

mp 136 °C (dec.); ν_{max} (film, cm^{-1}): 2913, 1780, 1591, 1508, 1487, 1348, 1227, 1203, 1163, 1064, 975, 852;^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 3.56 (6H, s, $N^+(CH_3)_2$), 4.39 (2H, d, *J* 7.5, C(1)H_2), 4.81-4.85 (0.68H, m, COCH_2/COC*H*D), 6.53 (1H, dt, *J* 15.6, 7.5, C(2)*H*), 6.97 (1H, d, *J* 15.6, C(3)*H*), 7.24 (2H, t, *J* 8.7, C(3)Ar(3,5)*H*), 7.55 (2H, d, *J* 9.1, OAr(2,6)*H*), 7.69 (2H, dd, *J* 8.7, 5.7, C(3)Ar(2,6)*H*), 8.36

(2H, d, *J* 9.1, OAr(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, d_6-DMSO) δ_C: 51.0 (d, $^{3}J_{CD}$ 4.0, $N^{+}(CH_3)_2$), 60.1-60.6 (m, CD_2/CHD/CH_2), 67.3 ($C(1)H_2$), 115.9 (d, $^{2}J_{CF}$ 21.5, Ar*C*(3,5)H), 116.0 (*C*(2)H), 123.3 (OAr*C*(2,6)H), 125.7 (OAr*C*(3,5)H), 129.7 (d, $^{3}J_{CF}$ 8.4, C(3)Ar*C*(2,6)H), 131.9 (d, $^{4}J_{CF}$ 3.1, Ar*C*(1)), 140.8 (*C*(3)H), 145.8 (Ar*C*(1)-O), 154.0 (Ar*C*(4)-NO_2), 162.7 (d, $^{1}J_{CF}$ 247, Ar*C*-F), 163.3-163.4 (m, *C*=O); HRMS (NSI^{+}) $C_{19}H_{18}D_2FN_2O_4^{+}$ $[M]^{+}$ found:361.1517, requires: 361.1527 (−2.8 ppm).

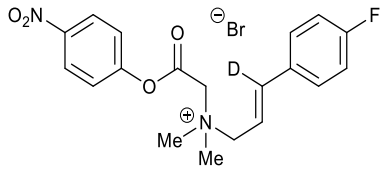
(*E*)-*N*,*N*-Dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl-1,2-$^{13}C_2$)-3-phenylprop-2-en-1-ammonium-3-^{13}C bromide $^{13}C_3$-341



Following general procedure **H**, (*E*)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-amine-3-^{13}C **$^{13}C_1$-340** (155 mg, 0.95 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl 2-bromoacetate-$^{13}C_2$ **$^{13}C_2$-331** (300 mg, 1.15 mmol, 1.2 equiv.) in MeCN (2 mL) to give the title product (307 mg, 76%) as a white solid.

mp 148 °C (dec.); ν_{max} (film, cm^{-1}): 2943, 1722, 1527, 1350, 1166, 1120, 978, 856; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 3.34 (6H, s, $N^{+}(CH_3)_2$), 4.40 (2H, t, *J* 5.8, C(1)H_2), 4.82 (2H, dd, *J* 147.3, 6.7, $^{13}CO^{13}CH_2$), 6.60 (1H, dt, *J* 15.4, 7.5, C(2)*H*), 6.97 (1H, dd, *J* 154.0, 15.6, C(3)*H*), 7.36-7.44 (3H, m, C(3)Ar*H*), 7.56 (2H, d, *J* 9.1, OAr(2,6)H), 7.62-7.65 (2H, m, C(3)Ar*H*), 8.38 (2H, d, *J* 9.1, OAr(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, d_6-DMSO) δ_C: 50.8 ($N^{+}(CH_3)_2$), 60.5 (d, $^{1}J_{CC}$ 64, $^{13}CH_2$), 67.2 ($C(1)H_2$), 116.1 (d, $^{1}J_{CC}$ 71, *C*(2)H), 123.1 (OAr*C*(2,6)H), 125.5 (OAr*C*(3,5)H), 127.4 (d, $^{3}J_{CC}$ 2, C(3)Ar*C*(3,5)H), 128.8 (d, $^{2}J_{CC}$ 4, C(3)Ar*C*(2,6)H), 129.2 (Ar*C*(4)H), 135.1 (d,$^{1}J_{CC}$ 55, C(3)Ar*C*(1)), 141.7 (^{13}C(3)H), 145.6 (Ar*C*(4)-NO_2), 153.9 (Ar*C*(1)-O), 163.2 (d, $^{1}J_{CC}$ 64, ^{13}C=O); HRMS (ESI^{+}) $C_{16}{}^{13}C_3H_{21}N_2O_4^{+}$ $[M]^{+}$ found: 344.1586, requires 344.1596 (−3.1 ppm).

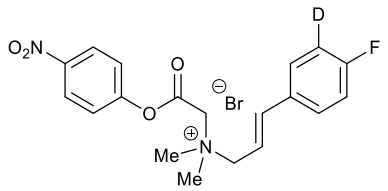
(*E*)-3-(4-Fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium-3-*d* bromide d_1-357



Following general procedure **H**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine-3-*d* ***d*$_1$-356** (407 mg, 2.26 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl 2-bromoacetate **213** (705 mg, 2.71 mmol, 1.2 equiv.) in MeCN (2.5 mL) to give the title product (580 mg, 58%, >99% D) as a white solid.

mp 132 °C (dec.); ν_{max} (film, cm^{-1}): 2897, 1775, 1591, 1510, 1348, 1206, 1147, 1132, 985, 891; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 3.32 (6H, s, $N^+(CH_3)_2$), 4.37 (2H, d, *J* 7.5, C(1)H_2), 4.79 (2H, s, COCH_2), 6.54 (1H, t, *J* 7.5,C(2)*H*), 7.27 (2H, t, *J* 8.9, C(3)Ar(3,5)*H*), 7.56 (2H, d, *J* 9.1, OAr(2,6)*H*), 7.70 (2H, dd, *J* 8.9, 5.6, C(3)Ar(2,6)*H*), 8.38 (2H, d, *J* 9.1, OAr(3,5)*H*); $^{19}F\{^{1}H\}$ NMR (376 MHz, d_6-DMSO) δ_F: −112.2 (Ar-*F*); $^{13}C\{^{1}H\}$ NMR (126 MHz, d_6-DMSO) δ_C: 50.8 ($N^+(CH_3)_2$), 60.5 (CO*C*H_2), 67.0 (*C*(1)H_2), 115.7 (d, $^{2}J_{CF}$ 22, C(3)Ar*C*(3,5)H), 115.9 (*C*(2)H), 123.1 (OAr*C*(2,6)H), 125.5 (OAr*C*(3,5)H), 129.5 (d, $^{3}J_{CF}$ 9, C(3)Ar*C*(2,6)H), 131.7 (d, $^{4}J_{CF}$ 2, C(3)Ar*C*(1)), 141.1 (t, $^{1}J_{CD}$ 21, *C*(3)D), 145.6 (OAr*C*(1)-O), 153.9 (OAr*C*(4)-NO_2), 162.5 (d, $^{1}J_{CF}$ 247, Ar*C*-F), 163.2 (*C*=O); HRMS (NSI^+) $C_{19}H_{19}DO_4N_2F^+$ $[M]^+$ found: 360.1458, requires: 360.1464 (−1.8 ppm).

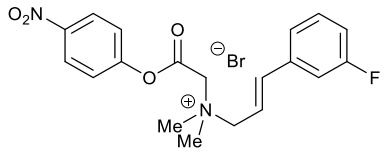
(*E*)-3-(4-Fluorophenyl-3-*d*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide d_1-364



A solution of (*E*)-3-(3-bromo-4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine **362** (250 mg, 0.97 mmol, 1.0 equiv.) in anhydrous Et_2O (10 mL) was cooled to −78 °C and treated with *n*-BuLi (2.31 M in hexanes, 0.93 mL, 2.13 mmol, 2.2 equiv.) dropwise and the resulting solution stirred for 30 min. D_2SO_4 (98% in D_2O, 250 µL, 2.43 mmol, 2.5 equiv.) was added dropwise and the reaction was allowed to warm to rt, D_2O (5 mL) was then added. The mixture was basified with aq. 1 M NaOH (10 mL) to *ca.* pH 14 and extracted with Et_2O (3 × 20 mL), the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeCN (2 mL) and *p*-nitrophenyl bromoacetate (303 mg, 1.16 mmol, 1.2 equiv.) was added and the reaction stirred for 1 h at rt, the resulting precipitate was filtered and dried *in vacuo* to give the title product as a white solid (209 mg, 97% D, 49% over two steps).

mp 143 °C (dec.); ν_{max} (film, cm^{-1}): 2898, 1778, 1591, 1519, 1489, 1348, 1205, 1163, 1143, 977, 854, 823; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 3.34 (6H, s, $N^+(CH_3)_2$), 4.38 (2H, d, *J* 7.5, C(1)H_2), 4.80 (2H, s, CO*C*H_2), 6.55 (1H, dt, *J* 15.5, 7.5, C(2)*H*), 6.96 (1H, d, *J* 15.5, C(3)*H*), 7.27 (1H, t, *J* 9.1, Ar(5)*H*), 7.56 (2H, d, *J* 9.2, OAr(2,6)*H*), 7.70 (2H, td, *J* 5.0, 2.4, C(3)Ar(3,5)*H*), 8.38 (2H, d, *J* 9.2, OAr(3,5)*H*); $^{19}F\{^{1}H\}$ NMR (376 MHz, d_6-DMSO) δ_F: −112.4 (Ar*F*); $^{13}C\{^{1}H\}$ NMR (126 MHz, d_6-DMSO) δ_C: 50.8 ($N^+(CH_3)_2$), 60.5 (CO*C*H_2), 67.1 (*C*(1)H_2), 115.5-116.1 (m, C(3)Ar*C*(5)H + C(3)Ar*C*(3)D), 123.1 (Ar*C*(3,5)H), 125.5 (Ar*C*(2,6)H), 129.6-129.3 (m, C(3)Ar*C*(2)H + C(3)Ar*C*(6)H), 131.8 (d, $^{3}J_{CF}$ 3, C(3)Ar*C*(1)), 140.5 (*C*(3)H), 145.6 (OAr*C*(1)O), 153.9 (OAr*C*(4)NO_2), 162.5 (d, $^{1}J_{CF}$ 247, Ar*C*-F), 163.2 (*C*=O); HRMS (ESI^+) $C_{19}H_{19}DO_4N_2F^+$ $[M]^+$ found: 360.1455, requires: 360.1464 (−2.61 ppm).

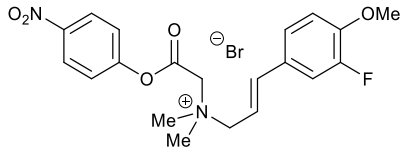
(*E*)-3-(3-Fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 372



Following general procedure **H**, (*E*)-3-(3-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-amine **504** (0.5 g, 2.79 mmol, 1.0 equiv.) was reacted with *p*-nitrophenyl bromoacetate **213** (0.87 g, 3.35 mmol, 1.2 equiv.) in MeCN (3 mL) to give the title product (0.93 g, 76%) as a white solid.

mp 146 °C (dec.); ν_{max} (film, cm^{-1}): 3011, 1751, 1524, 1489, 1346, 1200, 1169, 1144, 984, 882, 852; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 3.35 (6H, s, $N^+(CH_3)_2$), 4.43 (2H, d, *J* 7.5, C(1)H_2), 4.87 (2H, s, COCH_2), 6.70 (1H, dt, *J* 15.5, 7.5, C(2)*H*), 6.98 (1H, d, *J* 15.5, C(3)*H*), 7.13-7.27 (1H, m, Ar(2)*H*), 7.39-7.51 (2H, m, Ar(4)*H* + Ar(5)*H*), 7.48-7.65 (3H, m, Ar(6)*H* + Ar(2,6)*H*), 8.38 (2H, d, *J* 9.1, Ar(3,5)*H*); ^{19}F NMR (471 MHz, d_6-DMSO) δ_F: −113.2 (td, *J* 9.7, 5.5, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, d_6-DMSO) δ_C: 50.9 ($N^+(CH_3)_2$), 60.6 (COCH_2), 66.8 (*C*(1)H_2), 113.4 (d, $^2J_{CF}$ 22.0, Ar*C*(2)H), 115.8 (d, $^2J_{CF}$ 21.0, Ar*C*(4)H), 118.1 (*C*(2)H), 123.1 (Ar*C*(3,5)*H*), 124.0 (d, $^3J_{CF}$ 3, Ar*C*(6)H), 125.5 (Ar*C*(2,6)H), 130.7 (d, $^3J_{CF}$ 9.0, Ar*C*(5)H), 137.7 (d, $^3J_{CF}$ 8, Ar*C*(1)), 140.1 (d, $^4J_{CF}$ 3, *C*(3)H), 145.6 (Ar*C*(1)-O), 153.9 (Ar*C*(4)-NO_2), 162.5 (d, $^1J_{CF}$ 243, Ar*C*-F), 163.2 (*C*=O); HRMS (ASAP$^+$) $C_{19}H_{20}FN_2O_4^+$ $[M]^+$ found: 359.1408, requires: 359.1407 (+0.3 ppm).

(*E*)-3-(3-Fluoro-4-methoxyphenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 373

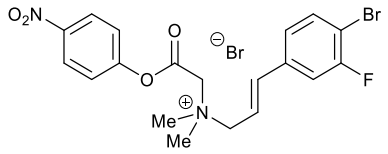


Following general procedure **H**, (*E*)-3-(3-fluoro-4-methoxyphenyl)-*N*,*N*-dimethylprop-2-en-1-amine **507** (0.5 g, 2.39 mmol, 1.0 equiv.) was reacted with *p*-nitrophenyl bromoacetate **213** (0.75 g, 2.87 mmol, 1.2 equiv.) in MeCN (2.5 mL) to give the title product (1.04 g, 93%) as a white solid.

mp 147 °C (dec.); ν_{max} (film, cm^{-1}): 3005, 1762, 1520, 1350, 1287, 1223, 1200, 1174, 1150, 980, 887; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 3.32 (6H, s, $N^+(CH_3)_2$), 3.86 (3H, s, OCH_3), 4.37 (2H, d, *J* 7.5, C(1)H_2), 4.82 (2H, s, COCH_2), 6.51 (1H, dt, *J* 15.5, 7.5, C(2)*H*), 6.88 (1H, d, *J* 15.5, C(3)*H*), 7.19 (1H, t, *J* 8.7, Ar(5)*H*), 7.36 (1H, dd, *J* 8.7, 2.0, Ar(6)*H*), 7.56 (2H, d, *J* 9.1, Ar(2,6)*H*), 7.64 (1H, dd, *J* 12.8, 2.1, Ar(2)*H*), 8.38 (2H, d, *J* 9.1, Ar(3,5)*H*); ^{19}F NMR (471 MHz, d_6-DMSO) δ_F: −135.3 (td, *J* 12.9, 9.0, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, d_6-DMSO) δ_C: 51.2 ($N^+(CH_3)_2$), 56.6 (O*C*H_3), 60.9 (CO*C*H_2), 67.6 (*C*(1)H_2), 114.1 (Ar*C*(6)H), 114.3 (d, $^2J_{CF}$ 19, Ar*C*(2)H), 115.6 (*C*(2)H), 123.6 (Ar*C*(2,6)H), 125.3 (d,

$^{3}J_{CF}$ 3.1, Ar*C*(5)H), 126.0 (Ar*C*(3,5)H), 128.9 (d, $^{3}J_{CF}$ 6.7, Ar*C*(1)), 140.7 (*C*(3)H), 146.1 (Ar*C*(1)-O), 148.3 (d, $^{2}J_{CF}$ 11, Ar*C*(4)-OMe), 152.0 (d, $^{1}J_{CF}$ 244, Ar*C*-F), 154.3 (Ar*C*(4)-NO_2), 163.9 (*C*=O); HRMS (ASAP$^+$) $C_{20}H_{22}FN_2O_5^+$ $[M]^+$ found: 389.1510, requires: 389.1513 (−0.8 ppm).

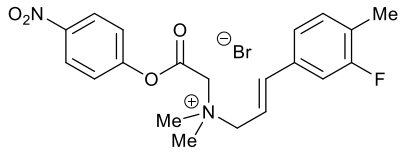
(*E*)-3-(4-Bromo-3-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 374



Following general procedure **H**, (*E*)-3-(3-fluoro-4-bromophenyl)-*N*,*N*-dimethylprop-2-en-1-amine **510** (0.5 g, 1.94 mmol, 1.0 equiv.) was reacted with *p*-nitrophenyl bromoacetate **213** (0.61 g, 2.33 mmol, 1.2 equiv.) in MeCN (2.0 mL) to give the title product (0.82 g, 82%) as a white solid.

mp 148 °C (dec.); ν_{max} (film, cm^{-1}): 3009, 1767, 1522, 1475, 1418, 1342, 1193, 1161, 984, 883; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 3.34 (6H, s, $N^+(CH_3)_2$), 4.41 (2H, d, *J* 7.5, C(1)H_2), 4.84 (2H, s,COCH_2), 6.73 (1H, dt, *J* 15.5, 7.5, C(2)*H*), 6.94 (1H, d, *J* 15.5, C(3)*H*), 7.41 (1H, dd, *J* 8.3, 1.9, Ar*H*), 7.57 (2H, d, *J* 9.1, Ar(2,6)*H*), 7.67-7.85 (2H, m, Ar*H*), 8.38 (2H, d, *J* 9.1, Ar(3,5)*H*); ^{19}F NMR (471 MHz, d_6-DMSO) δ_F: −108.45—108.27 (m, Ar*F*); ^{13}C{^{1}H} NMR (179 MHz, d_6-DMSO) δ_C: 50.9 ($N^+(CH_3)_2$), 60.6 ($COCH_2$), 66.6 (*C*(1)H_2), 108.4 (d, $^{2}J_{CF}$ 21, Ar*C*(4)-Br), 114.8 (d, $^{2}J_{CF}$ 23, Ar*C*(2)H), 119.0 (*C*(2)H), 123.1 (Ar*C*(2,6)H), 125.4 (d, $^{4}J_{CF}$ 2.5, Ar*C*(6)H), 125.5 (Ar*C*(3,5)H), 133.7 (Ar*C*(5)H), 137.2 (d, $^{3}J_{CF}$ 7.4, Ar*C*(1)), 139.1 (*C*(3)H), 145.6 (Ar*C*(1)-O), 153.9 (Ar*C*(4)-NO_2), 158.5 (d, $^{1}J_{CF}$ 244, Ar*C*-F), 163.2 (*C*=O); HRMS (ASAP$^+$) $C_{19}H_{19}{}^{79}BrFN_2O_4^+$ $[M]^+$ found: 437.0511, requires: 437.0512 (−0.2 ppm).

(*E*)-3-(3-Fluoro-4-methylphenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 376

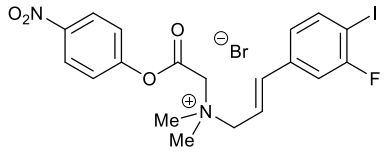


Following general procedure **H**, (*E*)-3-(3-fluoro-4-methylphenyl)-*N*,*N*-dimethylprop-2-en-1-amine **513** (0.5 g, 2.59 mmol, 1.0 equiv.) was reacted with *p*-nitrophenyl bromoacetate **213** (0.81 g, 3.11 mmol, 1.2 equiv.) in MeCN (3.0 mL) to give the title product (0.25 g, 21%) as a white solid.

mp 138 °C (dec.); ν_{max} (film, cm^{-1}): 2957, 1763, 1532, 1348, 1179, 1150, 1116, 980, 856; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 2.24 (3H, s, CH_3), 3.34 (6H, s, $N^+(CH_3)_2$), 4.41 (2H, s, C(1)H_2), 4.86 (2H, s, COCH_2), 6.63 (1H, br. s, C(2)*H*), 6.92 (1H, d, *J* 15.5, C(3)*H*), 7.33 (2H, s, Ar*H*), 7.43-7.66 (3H, m,

Ar*H*), 8.37 (2H, br. s, ArC(3,5)*H*); ^{19}F (657 MHz, d_6-DMSO) δ_F: −117. 6 (br. s, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, d_6-DMSO) δ_C: 14.1 (*C*H$_3$), 50.8 (N$^+$(*C*H$_3$)$_2$), 60.5 (CO*C*H$_2$), 66.9 (*C*(1)H$_2$), 113.0 (d, $^2J_{CF}$ 22.9, Ar*C*(2)H), 116.9 (*C*(2)H), 123.1 (Ar*C*(2,6)H), 123.7 (Ar*C*(6)H), 125.2 (d, $^2J_{CF}$ 17.4, Ar*C*(4)-Me), 125.5 (Ar*C*(2,6)H), 131.8 (d, $^3J_{CF}$ 5.3, Ar*C*(5)H), 135.2 (d, $^3J_{CF}$ Ar*C*(1)), 140.2 (*C*(3)H), 145.6 (Ar*C*(1)-O), 153.9 (Ar*C*(4)-NO$_2$), 160.9 (d, $^1J_{CF}$ 243, Ar*C*-F), 163.2 (*C*=O); HRMS (ASAP$^+$) $C_{20}H_{22}N_2O_4F^+$ [M]$^+$ found: 373.1563, requires: 373.1564 (−0.3 ppm).

(*E*)-3-(3-Fluoro-4-iodophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 375

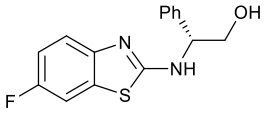


Following general procedure **H**, (*E*)-3-(3-fluoro-4-iodophenyl)-*N*,*N*-dimethylprop-2-en-1-amine **516** (0.4 g, 1.31 mmol, 1.0 equiv.) was reacted with *p*-nitrophenyl bromoacetate **213** (0.41 g, 1.57 mmol, 1.2 equiv.) in MeCN (2.0 mL) to give the title product (0.67 g, 90%) as a white solid.

mp 170 °C (dec.); ν_{max} (film, cm^{-1}); 2930, 1769, 1514, 1481, 1398, 1344, 1221, 1161, 989, 883; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 3.33 (6H, s, N$^+$(C*H*$_3$)$_2$), 4.39 (2H, d, *J* 7.5, C(1)*H*$_2$), 4.82 (2H, s, COC*H*$_2$), 6.73 (1H, dt, *J* 15.5, 7.5, C(2)*H*), 6.92 (1H, d, *J* 15.5, C(3)*H*), 7.25 (1H, dd, *J* 8.2, 1.9, Ar(6)*H*), 7.56 (2H, d, *J* 9.1, Ar(3,5)*H*), 7.64 (1H, dd, *J* 9.6, 1.9, Ar(2)*H*), 7.89 (1H, dd, *J* 8.2, 6.8, Ar(5)*H*), 8.38 (2H, d, *J* 9.1, Ar(2,6)*H*); ^{19}F NMR (471 MHz, d_6-DMSO) δ_F: −95.4 (dd, *J* 9.5, 6.7, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, d_6-DMSO) δ_C: 50.9 (N$^+$(*C*H$_3$)$_2$), 60.6 (CO*C*H$_2$), 66.7 (*C*(1)H$_2$), 83.0 (d, $^2J_{CF}$ 26, C(3)Ar*C*(4)-I), 113.7 (d, $^2J_{CF}$ 25, C(3)Ar*C*(2)H), 118.7 (*C*(2)H), 123.1 (OAr*C*(2,6)H), 125.5 (OAr*C*(3,5)H), 125.6 (d, $^4J_{CF}$ 2.9, Ar*C*(6)H), 137.9 (d, $^3J_{CF}$ 7.6, Ar*C*(1)), 139.3 (*C*(3)H), 139.5 (d, $^3J_{CF}$ 2.0, Ar*C*(5)H), 145.6 (Ar*C*(1)-O), 153.9 (Ar*C*(4)-NO$_2$), 161.5 (d, $^1J_{CF}$ 242, Ar*C*-F), 163.2 (*C*=O); HRMS (NSI$^+$) $C_{19}H_{19}FIN_2O_2^+$ [M]$^+$ found: 485.0360, requires: 485.0368 (−1.7 ppm).

Catalyst Synthesis

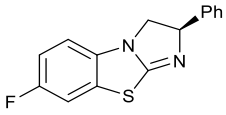
(*R*)-2-((6-Fluorobenzo[*d*]thiazol-2-yl)amino)-2-phenylethan-1-ol 314



A solution of 2-chloro-6-fluoro-benzothiazole **312** (1.50 g, 7.98 mmol, 1.0 equiv.) and (*R*)-phenyl glycinol (1.15 g, 8.37 mmol, 1.05 equiv.) in 1,2 dichlorobenzene (4 mL) was treated with *N*,*N* diisopropylethylamine (3.48 mL, 19.95 mmol, 2.5 equiv.) and heated at refluxed for 24 h. The reaction was cooled to rt and water (12 mL) and toluene (12 mL) were added and the mixture stirred for 30 min, the precipitate was filtered and washed with toluene. The resulting solid was recrystallized from toluene to give the title product as a white solid (1.01 g, 44%).

$[\alpha]_D^{20}$ −94.3 (*c* 1, MeOH); mp 140-142 °C; ν_{max} (film, cm^{-1}): 3209, 3001, 1605, 1562, 1462, 1350, 1194, 1063, 817; ^{1}H NMR (500 MHz, d_4-MeOH) δ_H: 3.82 (2H, ddt, *J* 18.8, 11.3, 6.3, C(1)H_2), 4.99 (1H, t, *J* 6.3, C(2)*H*), 6.97 (1H, t, *J* 8.9, Ar(5)*H*), 7.25 (1H, t, *J* 7.1, C(2)Ar(4)*H*), 7.29-7.37 (4H, m, Ar*H*), 7.42 (2H, d, *J* 7.6, Ar*H*); ^{19}F{^{1}H} NMR (376 MHz, d_4-MeOH) δ_F: −123.7 (Ar*F*); ^{13}C{^{1}H} NMR (101 MHz, d_4-MeOH) δ_C: 62.2 (*C*(2)H), 66.8 (*C*(1)H_2), 108.4 (d, $^2J_{CF}$ 27.5, Ar*C*(7)H), 114.1 (d, $^2J_{CF}$ 24.1, Ar*C*(5)H), 119.6 (d, $^3J_{CF}$ 8.8, Ar*C*(4)H), 128.1 (C(2)Ar*C*(2,6)H), 128.6 (C(2)Ar*C*(4)H), 129.5 (C(2)Ar*C*(3,5)H), 132.4 (d, $^3J_{CF}$ 10.9, Ar*C*-S), 141.0 (C(2)Ar*C*(1)), 149.7 (d, $^4J_{CF}$ 1.3, Ar*C*-N), 159.6 (d, $^1J_{CF}$ 239, Ar*C*-F), 168.6 (*C*=N); HRMS (NSI$^+$): $C_{15}H_{14}FN_2OS$ $[M+H]^+$ found: 289.0807, requires 289.0805 (+0.5 ppm).

(*R*)-7-Fluoro-2-phenyl-2,3-dihydrobenzo[*d*]imidazo[2,1-*b*]thiazole (F-(+)-BTM) 315



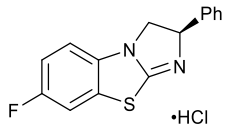
A solution of (*R*)-2-((6-fluorobenzo[*d*]thiazol-2-yl)amino)-2-phenylethan-1-ol **314** (500 mg, 1.74 mmol, 1.0 equiv.) and NEt_3 (966 μL, 6.94 mmol, 4.0 equiv.) in CH_2Cl_2 (17.4 mL) was cooled to 0 °C and MsCl (176 μL, 2.26 mmol, 1.3 equiv.) was added dropwise. The reaction mixture was then allowed to warm to rt and stirred for 15 min, once (*R*)-2-((6-fluorobenzo[*d*]thiazol-2-yl)amino)-2-phenylethan-1-ol was consumed by TLC, *i*PrOH (350 μL) was added. The mixture was then heated to reflux and stirred for 16 h. Once complete, the reaction was cooled to rt and quenched by the addition of aq. 1 M NaOH (15 mL), the layers separated and the aqueous extracted with CH_2Cl_2 (2 × 20 mL), the combined organic layers washed with brine and dried over $MgSO_4$ then concentrated *in vacuo*. The residue was azeotroped with toluene (3 × 20 mL), the residue was purified by flash chromatography on silica gel

(2→15% EtOAc/CH_2Cl_2). The residue was recrystallized (Et_2O/hexane) to give the product as a white solid (281 mg, 60%);

HPLC analysis, Chiralpak AD-H (10% IPA/hexane, flow rate 1.5 mL/min, 254 nm, 40 °C) t_R Major 11.5 min, Minor 15.8 min, >99% ee;

$[\alpha]_D^{20}$ +211.2 (*c* 1, $CHCl_3$); mp 110-112 °C; ν_{max} (film, cm^{-1}): 2885, 1604, 1595, 1573, 1483, 1465, 1259, 1179, 960; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 3.71 (1H, t, *J* 8.5, C(3)H^AH^B), 4.28 (1H, app. t, *J* 9.5, C(3)H^AH^B), 5.69 (1H, dd, *J* 10.1, 8.5, C(2)*H*), 6.60 (1H, dd, *J* 8.5, 4.3, ArC(5)*H*), 6.92 (1H, td, *J* 8.8, 2.5, ArC(6)*H*), 7.10 (1H, dd, *J* 8.0, 2.5, ArC(8)*H*), 7.33, (1H, m, Ar*H*), 7.40 (4H, d, *J* 4.3, Ar*H*); $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$) δ_F: −121.21 (Ar*F*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 53.0 (*C*(3)H_2), 75.7 (*C*(2)H), 108.6 (d, $^3J_{CF}$ 8.4, Ar*C*(5)H), 111.0 (d, $^2J_{CF}$ 27.5, Ar*C*(8)H), 113.3 (d, $^2J_{CF}$ 23.7, Ar*C*(6)H), 126.6 (C(2)Ar*C*(2,6)H), 127.8 (C(2)Ar*C*(4)H), 128.5 (d, $^3J_{CF}$ 9.9, Ar*C*-S), 128.9 (C(2)Ar*C*(3,5)H), 133.8 (d, $^4J_{CF}$ 1.3, Ar*C*-N), 142.6 (C(2)Ar*C*(1), 158.0 (d, $^1J_{CF}$ 241, Ar*C*-F), 166.8 (C=N); HRMS (NSI^+): $C_{15}H_{12}FN_2S$ $[M+H]^+$ found: 271.0697, requires 271.0700 (−1.0 ppm).

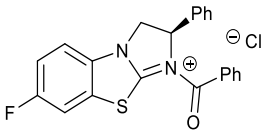
(*R*)-7-Fluoro-2-phenyl-2,3-dihydrobenzo[*d*]imidazo[2,1-*b*]thiaacupzole hydrochloride (F-(+)-BTM·HCl) 316



A solution of (+)-F-BTM **315** (100 mg, 0.37 mmol, 1.0 equiv.) in Et_2O (3.7 mL) was treated with HCl (2 M in Et_2O, 0.92 mL, 1.84 mmol, 5.0 equiv.) at rt and stirred for 15 min. The resulting mixture was concentrated *in vacuo* to give the title product as an off white solid (116 mg, quant.)

$[\alpha]_D^{20}$+112.2 (*c* 1, MeCN); mp 128-130 °C; ν_{max} (film, cm^{-1}) 2991, 2858, 1568, 1501, 1470, 1259, 1203, 1024, 878; ^1H NMR (500 MHz, d_6-DMSO) δ_H: 4.39 (1H, dd, *J* 10.6, 8.5, C(3)H^AH^B), 4.98 (1H, t, *J* 10.6, C(3)H^AH^B), 5.98 (1H, dd, *J* C(2)*H*), 7.41-7.48 (4H, m, Ar*H*), 7.55-7.58 (3H, m, Ar*H*), 8.04 (1H, dd, *J* 8.7, 2.4, ArC(8)*H*), 11.75 (1H, br. s, N*H*); $^{19}F\{^1H\}$ NMR (376 MHz, d_6-DMSO) δ_F: −117.1 (Ar*F*); $^{13}C\{^1H\}$ NMR (126 MHz, d_6-DMSO) δ_C: 53.5 (*C*(3)H_2), 66.3 (*C*(2)H), 112.2 (d, $^2J_{CF}$ 29, Ar*C*(8)H), 113.8 (d, $^3J_{CF}$ 9, Ar*C*(5)H), 115.5 (d, $^2J_{CF}$ 25, Ar*C*(6)H), 127.1 (C(2)Ar*C*(2,6)H), 129.0 (C(2)Ar*C*(3,5)H), 129.2 (d, $^3J_{CF}$ 11, Ar*C*-S), 131.7 (C(2)Ar*C*(4)H), 138.7 (C(2)Ar*C*(1)), 158.6 (d, $^1J_{CF}$ 241, Ar*C*-F), 170.0 (*C*=N); HRMS (ESI^+) $C_{15}H_{12}N_2FS^+$ $[M]^+$ found: 271.0692, requires: 271.3329 (−2.85 ppm).

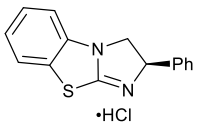
(*R*)-1-benzoyl-7-fluoro-2-phenyl-2,3-dihydrobenzo[d]imidazo[2,1-b]thiazol-1-ium chloride 317



A solution of (+)- F-BTM **315** (100 mg, 0.37 mmol, 1.0 equiv.) in CH_2Cl_2 (3.7 mL) was treated with benzoyl chloride (52 µL, 0.44 mmol, 1.2 equiv.) and stirred at rt for 15 min. Et_2O (4 mL) was added and the precipitate was filtered and dried *in vacuo* to give the title product as a white solid (94 mg, 62%).

$[\alpha]_D^{20}$ −52.0 (*c* 1, DMSO); mp 174-176 °C; ν_{max} (film, cm^{-1}): 2997, 1674, 1485, 1375, 1338, 1201, 1012, 881;^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 4.81 (1H, dd, *J* 11.3, 6.7, C(3)*H*^{A}H^B), 5.45 (1H, t, *J* 11.3, C(2)*H*), 6.72 (1H, dd, *J* 10.5, 6.7, C(3)H^A*H*^{B}), 7.18-7.28 (3H, m, Ar*H*), 7.32 (2H, d, *J* 7.1, Ar*H*), 7.44 (2H, t, *J* 7.7, Ar*H*), 7.58 (1H, t, *J* 7.7, Ar*H*), 7.63 (2H, d, *J* 7.7, Ar*H*), 7.75 (1H, td, *J* 9.0, 2.7, ArC(6)*H*), 8.08 (1H, dd, *J* 9.0, 4.3, ArC(8)*H*), 8.41 (1H, dd, *J* 8.6, 2.7, ArC(5)*H*); ^{19}F NMR (471 MHz, d_6-DMSO) δ_F: −113.0 (td, *J* 8.8, 4.4, Ar*F*); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ_C: 55.9 (*C*(3)H_2), 68.0 (*C*(2)H), 112.5 (d, $^2J_{CF}$ 29, Ar*C*(8)H), 116.7 (d, $^3J_{CF}$ 9.3, Ar*C*(5)H), 117.4 (d, $^2J_{CF}$ 26, Ar*C*(6)H), 127.4 (*PhC*(2,6)H), 127.5 (*PhC*(2,6)H), 128.7 (*PhC*(3,5)H), 128.8 (*PhC*(3,5)H), 129.0 (*PhC*(4)H), 130.3 (Ar*C*H), 130.8 (Ar*C*H), 131.6 (d, $^3J_{CF}$ 12, Ar*C*-S), 132.8 (Ar*C*H), 136.9 (Ar*C*), 159.8 (d, $^1J_{CF}$ 245, Ar*C*-F), 167.8 (*C*=O + *C*=N); HRMS (ESI$^+$) $C_{22}H_{16}ON_2FS^+$ $[M]^+$ found: 375.0951, requires: 375.0962 (−2.90 ppm).

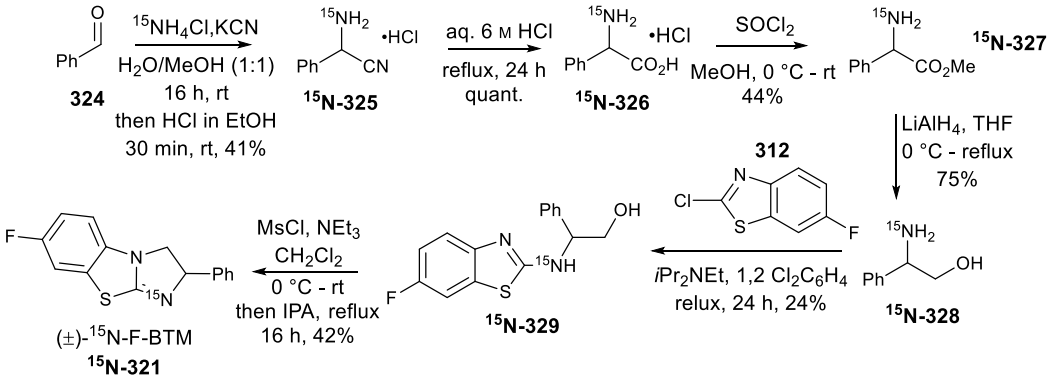
(*R*)-2-Phenyl-2,3-dihydrobenzo[*d*]imidazo[2,1-*b*]thiazole hydrochloride ((+)-BTM·HCl) 517



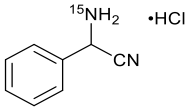
A solution of (+)-BTM **197** (100 mg, 0.40 mmol, 1.0 equiv.) in Et_2O (4 mL) was treated with HCl (2 M in Et_2O, 1 mL, 2.00 mmol, 5.0 equiv.) at rt and stirred for 15 min. The resulting mixture was concentrated *in vacuo* to give the title product as an off white solid (114 mg, quant.).

mp 201-203 °C;$[\alpha]_D^{20}$+132.5 (*c* 1, MeCN); ν_{max} (film, cm^{-1}): 3390, 2723, 1589, 1568, 1497, 1440, 1367, 1271, 1030, 916, 819; ^{1}H NMR (700 MHz, d_6-DMSO) δ_H: 4.40 (1H, dd, *J* 10.6, 8.3 *C*(3)*H*^{A}H^B), 4.99 (1H, t, *J* 10.6, *C*(3)H^A*H*^{B}), 5.97 (1H, dd, *J* 10.6, 8.3, *C*(2)H), 7.36–7.45 (2H, m, Ar*H*), 7.47 (2H, dd, *J* 8.3, 6.6, Ar*H*), 7.53 (1H, dd, *J* 8.1, 1.2, Ar*H*), 7.57 (3H, dt, *J* 7.4, 2.7, Ar*H*), 8.07 (1H, dd, *J* 8.1, 1.0, Ar*H*), 11.53 (1H, s, N$^+$*H*); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ_C: 53.1 (*C*(3)H_2), 66.2 (*C*(2)H), 112.8 (Ar*C*H), 124.6 (Ar*C*H), 124.9 (Ar*C*H), 127.1 (Ar*C*H), 127.6 (Ar*C*), 128.0 (Ar*C*H), 129.0 (Ar*C*H), 129.0 Ar*C*H), 134.8 (Ar*C*), 138.7 (Ar*C*), 169.7 (*C*=N); HRMS (ESI$^+$) $C_{15}H_{13}N_2S^+$ $[M]^+$ found: 253.0784, requires: 253.0788 (−3.9 ppm).

Synthesis of ^{15}N-F-BTM, ^{15}N-321



2-(Amino-^{15}*N*)-2-phenylacetonitrile hydrochloride ^{15}N-325

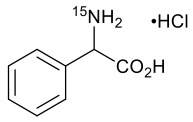


Caution: KCN, potassium cyanide, is a potent poison, which should be handled with gloves in a well-ventilated fume hood. Contact with acid releases HCN, due care should be taken to avoid contact with acid.

A solution of $^{15}NH_4Cl$ (1.0 g, 18.2 mmol, 1.0 equiv.) and KCN (1.24 g, 19.1 mmol, 1.05 equiv.) in H_2O (23 mL) was treated with a solution of benzaldehyde (1.85 mL, 18.2 mmol, 1.0 equiv.) in MeOH (23 mL) and stirred for 16 h at rt. Once complete water (20 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 50 mL), the organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in Et_2O (30 mL) and treated with HCl (2.5 M in EtOH, 11 mL, 27.3 mmol, 1.5 equiv.) then stirred for 30 min at rt, the resulting precipitate was filtered and washed with Et_2O (20 mL) and dried *in vacuo* to give the product as a white solid (1.28 g, 41%);

mp 148 °C (dec.); ν_{max} (film, cm^{-1}) 2843, 2573, 2021, 1595, 1467, 1192, 1115, 991; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 5.99 (1H, s, C*H*CN), 7.49-7.55 (3H, m, Ar*H*), 7.66-7.73 (2H, m, Ar*H*), 9.83 (3H, br. s, N^+H_3); $^{13}C\{^1H\}$ NMR (126 MHz, d_6-DMSO) δ_C: 43.2 (d, $^1J_{CN}$ 6.7, *C*HCN), 116.3 (*C*N), 128.5 (Ar*C*(2,6)H), 129.2 (Ar*C*(3,5)H), 130.3 (Ar*C*(4)H), 130.4 (Ar*C*(1)); HRMS (APCI$^+$): $C_8H_9N^{15}N^+$ $[M]^+$ found: 134.0734, requires 134.0731 (+2.5 ppm).

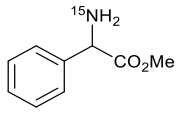
2-(Amino-^{15}N)-2-phenylacetic acid hydrochloride ^{15}N-326



A solution of 2-(amino-^{15}N)-2-phenylacetonitrile hydrochloride **^{15}N-325** (1.2 g, 7.10 mmol, 1.0 equiv.) in aq. 6 M HCl (71 mL) was heated to reflux for 24 h. Once complete the reaction mixture was cooled to rt and concentrated *in vacuo* to give the product as a white solid (1.57 g, quant.).

mp 228 °C (dec.); ν_{max} (film, cm^{-1}): 3105, 2884, 1728, 1476, 1408, 1209, 1180, 1010, 875; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 5.04 (1H, s, ^{15}NC*H*), 7.04-7.63 (5H, m, Ar*H*), 8.95 (1H, br. s, CO_2H), 9.09 (3H, br. s, N^+H_3); ^{13}C{^{1}H} NMR (126 MHz, d_6-DMSO) δ_C: 55.5 (d, $^1J_{CN}$ 6.7, ^{15}N*C*H), 128.2 (Ar*C*(2,6)H), 128.9 (Ar*C*(3,5)H), 129.3 (Ar*C*(4)H), 133.3 (Ar*C*(1)), 169.6 (*C*=O); HRMS (NSI$^+$): $C_8H_{10}O_2{}^{15}N^+$ [M]$^+$ found: 153.0672, requires 153.0676 (−2.9 ppm).

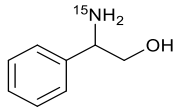
Methyl 2-(amino-^{15}N)-2-phenylacetate ^{15}N-327



A solution of 2-(amino-^{15}N)-2-phenylacetic acid hydrochloride **^{15}N-326** (1.2 g, 6.38 mmol, 1.0 equiv.) in MeOH (14 mL) was cooled to 0 °C and was treated dropwise with thionyl chloride (931 μL, 12.77 mmol, 2.0 equiv.) the resulting reaction mixture was allowed to warm to rt and stirred for 16 h. Once complete the mixture was concentrated *in vacuo*, the residue was partitioned between EtOAc (20 mL) and aq. 1M NaOH (20 mL), the layers separated the aqueous layer extracted with EtOAc (2 × 20 mL), the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the product as a yellow oil (462 mg, 44%).

ν_{max} (film, cm^{-1}): 3244, 2953, 1737, 1670, 1494, 1215, 1127, 1002, 827; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.97 (2H, br. s, NH_2), 3.68 (3H, s, OCH_3), 4.61 (1H, s, PhC*H*), 7.27-7.40 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 52.5 (O*C*H$_3$), 58.8 (d, $^1J_{CN}$ 4.2, ^{15}N*C*H), 126.9 (Ar*C*(2,6)H), 128.1 (Ar*C*(4)H), 128.7 (Ar*C*(3,5)H), 140.3 (Ar*C*(1)), 174.5 (*C*=O); HRMS (NSI$^+$): $C_9H_{12}O_2{}^{15}N^+$ [M+H]$^+$ found: 167.0829, requires 167.0833 (−2.3 ppm).

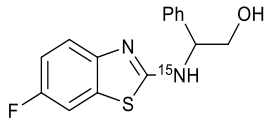
2-(Amino-^{15}*N*)-2-phenylethan-1-ol ^{15}N-328



A solution of methyl 2-(amino-^{15}*N*)-2-phenylacetate **^{15}N-327** (755 mg, 4.55 mmol, 1.0 equiv.) in THF (46 mL) was cooled to 0 °C and treated dropwise with $LiAlH_4$ (2.4 M in THF, 2.85 mL, 6.82 mmol, 1.5 equiv.) after stirring for 15 min, the reaction was heated to reflux for 1 h. Once complete the reaction was cooled to 0 °C and quenched with aq. 1 M KOH (40 mL) dropwise, EtOAc was then added (30 mL) and the mixture stirred at rt for 30 min. The layers separated and the aqueous layer extracted with EtOAc (3 × 30 mL) the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give the product as a yellow oil (473 mg, 75%) which was used directly without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.40 (2H, br. s, NH_2), 3.55 (1H, ddd, *J* 10.7, 8.4, 2.1, C(1)H^AH^B), 3.70-3.77 (1H, m, C(1) H^AH^B), 4.04 (1H, dd, *J* 8.4, 4.3, C(2)*H*), 7.27-7.38 (5H, m, Ar*H*), ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 57.5 (d, $^1J_{CN}$ 4.3, *C*(2)H), 68.0 (d, $^2J_{CN}$ 2.1, *C*(1)H), 126.6 (Ar*C*(2,6)H), 127.7 (Ar*C*(4)H), 128.8 (Ar*C*(3,5)H), 142.7 (Ar*C*(1)).

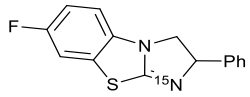
2-((6-Fluorobenzo[*d*]thiazol-2-yl)amino-^{15}*N*)-2-phenylethan-1-ol ^{15}N-329



A solution of 2-chloro-6-fluoro-benzothiazole **312** (590 mg, 3.15 mmol, 1.0 equiv.) and 2-(amino-^{15}*N*)-2-phenylethan-1-ol **^{15}N-328** (457 mg, 3.31 mmol, 1.05 equiv.) in 1,2 dichlorobenzene (1.58 mL) was treated with *N*,*N* diispropylethylamine (1.37 mL, 7.88 mmol, 2.5 equiv.) and heated at reflux for 24 h. The reaction was cooled to rt and concentrated *in vacuo*, the residue was dissolved in CH_2Cl_2 (30 ml) and washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*, the residue was recrystallized from toluene to give the title product as a white solid (218 mg, 24%).

mp 164-165°C; ν_{max} (film, cm^{-1}): 3205, 3016, 1600, 1531, 1460, 1209, 1049, 1029, 852; ^{1}H NMR (500 MHz, MeOH-d_4) δ_H: 3.70-3.91 (2H, m, C(1)H_2), 4.99 (1H, br. s, C(2)*H*), 6.96 (1H, t, *J* 7.9, Ar(5)*H*), 7.22-7.29 (1H, m, C(2)Ar(4)*H*), 7.29-7.38 (4H, m, Ar*H*), 7.39-7.45 (2H, m, Ar*H*); ^{19}F{^{1}H} NMR (376 MHz, MeOH-d_4) δ_F: −123.7 (Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, MeOH-d_4) δ_C: 62.1 (d, $^1J_{CN}$ 21.6, *C*(2)H), 66.8 (*C*(1)H_2), 108.4 (d, $^2J_{CF}$ 27.4, Ar*C*(7)H), 114.1 (d, $^2J_{CF}$ 24.1, Ar*C*(5)H), 119.5 (d, $^3J_{CF}$ 8.7, Ar*C*(4)H), 128.1 (C(2)Ar*C*(2,6)H), 128.6 (C(2)Ar*C*(4)H), 129.5 (C(2)Ar*C*(3,5)H), 132.4 (d, $^3J_{CF}$ 10.8, Ar*C*-S), 141.0 (C(2)Ar*C*(1)), 149.6 (Ar*C*-N), 159.6 (d, $^1J_{CF}$ 239, Ar*C*-F), 168.6 (d, $^1J_{CN}$ 21.6, *C*=N); HRMS (NSI$^+$): $C_{15}H_{14}FN^{15}NOS^+$ $[M+H]^+$ found: 290.0776, requires 290.0776 (+0.1 ppm).

(±)-7-Fluoro-2-phenyl-2,3-dihydrobenzo[*d*]imidazo[2,3-*b*]thiazole-1-^{15}*N*, ^{15}N-321



A solution of 2-((6-fluorobenzo[*d*]thiazol-2-yl)amino-^{15}*N*)-2-phenylethan-1-ol **^{15}N-329** (218 mg, 0.76 mmol, 1.0 equiv.) in CH_2Cl_2 (7.6 mL) was cooled to 0 °C and treated with NEt_3 (423 μL, 3.04 mmol, 4.0 equiv.) followed by MsCl (76 μL, 0.98 mmol, 1.3 equiv.) dropwise. The resulting solution was allowed to warm to rt and stirred for 15 min, once complete the reaction was treated with *i*PrOH (220 μL) and heated to reflux for 16 h. Once complete the reaction was cooled to rt and quenched by the addition of aq. 1 M NaOH (10 mL), the layers separated and the aqueous extracted with CH_2Cl_2 (2 × 20 mL), the combined organic layers washed with brine and dried over $MgSO_4$ then concentrated *in vacuo*. The residue was azeotroped with toluene (3 × 20 mL), the residue was purified by flash chromatography on silica gel (5% *i*PrOH/hexane). The residue was recrystallized (Et_2O/hexane) to give the product as a yellow solid (87 mg, 42%).

mp 111-113 °C; ν_{max} (film, cm^{-1}): 3028, 160, 1490, 1188, 871; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.69 (1H, t, *J* 8.5, C(3)*H*^{A}H^B), 4.13-4.34 (1H, m, C(3)H^A*H*^{B}), 5.57-5.76 (1H, m, C(2)*H*), 6.58 (1H, dd, *J* 8.6, 4.3, Ar(5)*H*), 6.90 (1H, td, *J* 8.8, 2.5, Ar(6)*H*), 7.08 (1H, dd, *J* 8.0, 2.5, Ar(8)*H*), 7.27-7.32 (1H, m, Ar*H*), 7.35-7.40 (4H, m, Ar*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: −121.2 (Ar*F*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 53.0 (*C*(3)H_2), 75.7 (d, $^1J_{CN}$ 4.6, *C*(2)H), 108.6 (d, $^3J_{CF}$ 8.4, Ar*C*(5)H), 111.1 (d, $^2J_{CF}$ 28, Ar*C*(8)H), 113.3 (d, $^2J_{CF}$ 24, Ar*C*(6)H), 126.6 (C(2)Ar*C*(2,6)H), 127.8 (C(2)Ar*C*(4)H), 128.6 (d, $^3J_{CF}$ 9.9, Ar*C*-S) 128.9 (C(2)Ar*C*(3,5)H), 133.8 (d, $^4J_{CF}$ 1.4, Ar*C*-N), 142.9 (d, $^2J_{CN}$ 1.3, C(2)Ar*C*(1)), 158.0 (d, $^1J_{CF}$ 241, Ar*C*-F), 166.8 (d, $^1J_{CN}$ 2.3, *C*=^{15}N); HRMS (NSI$^+$): $C_{15}H_{12}FN^{15}NS^+$ $[M+H]^+$ found: 272.0669, requires 272.0670 (−0.4 ppm).

Catalytic [2,3]-Rearrangements

General Procedure L: Catalytic [2,3]-Rearrangement of Allylic Ammonium Salts

A flamed dried Schlenk was charged with (+)-BTM (0.2 equiv.) and HOBt (0.2 equiv.) in MeCN (0.07 M with respect to the ammonium salt). *i*Pr_2NH (1.4 equiv.) was added and the solution was cooled to −20 °C ad stirred for five min. The corresponding ammonium salt (1.0 equiv.) was added and the reaction stirred for 16 h, after which the reaction was quenched by the addition of aq. 1 M NaOH (equal volume) and extracted with CH_2Cl_2 (3 × equal volume). The combined organic layers were washed with brine (equal volume) dried over $MgSO_4$ and concentrated *in vacuo*, the crude residue was analysed by ^1H and $^{19}F\{^1H\}$ NMR to determine diastereoselectivity then purified by flash column chromatography to give the *syn* rearranged activated ester.

General Procedure M: Racemic Catalytic [2,3]-Rearrangement of Allylic Ammonium Salts

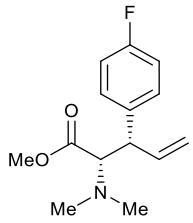
A flamed dried Schlenk was charged with (±)-BTM (0.2 equiv.) and HOBt (0.2 equiv.) in MeCN (0.07 M with respect to the ammonium salt). *i*Pr_2NH (1.4 equiv.) The corresponding ammonium salt (1.0 equiv.) was added and the reaction stirred for 30 min at rt, after which the reaction was quenched by the addition of aq. 1 M NaOH (equal volume) and extracted with CH_2Cl_2 (3 × equal volume). The combined organic layers were washed with brine (equal volume) dried over $MgSO_4$ and concentrated *in vacuo*, the crude residue was analysed by ^1H and ^{19}F NMR to determine diastereoselectivity then purified by flash column chromatography to give the (±)-*syn* rearranged activated ester.

General Procedure N: Catalytic [2,3]-Rearrangement of Allylic Ammonium Salts and sequential Sodium Methoxide Quench

A flamed dried Schlenk was charged with (+)-BTM (0.2 equiv.) and HOBt (0.2 equiv.) in MeCN (0.07 M with respect to the ammonium salt). *i*Pr_2NH (1.4 equiv.) was added and the solution was cooled to −20 °C ad stirred for five min. The corresponding ammonium salt (1.0 equiv.) was added and the reaction stirred for 16 h, after which the reaction was quenched by the addition of NaOMe (1.0 M, 3.0 equiv.) and stirred at rt for 1 h. The reaction mixture was quenched with aq. 1 M NaOH (equal volume) and extracted with CH_2Cl_2 (3 × equal volume), the combined organic layers washed with aq. 1 M NaOH (2 × equal volume), brine (equal volume), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was analysed by ^1H and ^{19}F NMR to determine diastereoselectivity then purified by flash column chromatography to give the rearranged *syn* methyl ester.

1 M NaOMe in MeOH was freshly prepared before use, by dissolving Na metal in anhydrous methanol at 0 °C and stirred for 30 min at rt.

Methyl (2*S*,3*S*)-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate 310

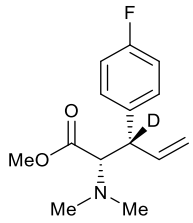


Following general procedure **N** (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **309** (105 mg, 0.24 mmol, 1.0 equiv.) was reacted with (+)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr$_2$NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL) then NaOMe (1 M in MeOH, 0.72 mL, 0.72 mmol, 3.0 equiv.) to give the title product (57 mg, 95%, >95:5 dr) as a white solid after purification by flash column chromatography (10% EtOAc/hexanes).

HPLC analysis, Chiralpak OJ-H (3% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 4.4 min, Minor 3.6 min, >99% ee;

mp 54-56 °C; $[\alpha]_D^{20}$ +56.8 (*c* 1, $CHCl_3$); ν_{max} (film, cm^{-1}): 2949, 1728, 1506, 1346, 1217, 1155, 979, 921; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.24 (6H, s, N(C*H*$_3$)$_2$), 3.54 (1H, d, *J* 11.3, C(2)*H*), 3.70 (3H, s, OC*H*$_3$), 3.74 (1H, dd, *J* 11.3, 8.3, C(3)*H*), 4.69-5.09 (2H, m, C(5)*H*$_2$), 5.82 (1H, ddd, *J* 17.0, 10.2, 8.3, C(4)*H*), 7.01 (2H, t, *J* 8.7, Ar(3,5)*H*), 7.17 (2H, dd , *J* 8.7, 5.4, Ar(2,6)*H*); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −116.4 (Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 41.5 (N(*C*H$_3$)$_2$), 49.3 (*C*(3)H), 50.9 (O*C*H$_3$), 71.0 (*C*(2)H), 115.5 (d, $^2J_{CF}$ 21, Ar*C*(3,5)H), 116.9 (*C*(5)H$_2$) 129.4 (d, $^3J_{CF}$ 7.9, Ar*C*(2,6)H), 136.5 (d, $^4J_{CF}$ 3, Ar*C*(1)), 138.6 (*C*(4)H), 161.7 (d, $^1J_{CF}$ 245, Ar*C*-F), 171.0 (*C*=O); HRMS (NSI$^+$) $C_{14}H_{19}FNO_2^+$ $[M+H]^+$ found: 252.1396, requires: 252.1394 (+0.7 ppm).

Methyl (2*S*,3*S*)-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate-3-*d* d_1-359

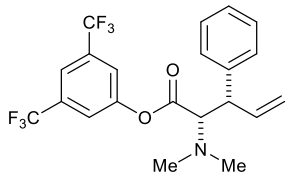


Following general procedure **N**, (*E*)-3-(4-fluorophenyl)-N,N-dimethyl-N-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium-3-*d* bromide ***d*$_1$-357** (105 mg, 0.24 mmol, 1.0 equiv.) was reacted with (+)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr$_2$NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL) then NaOMe (1 M in MeOH, 0.72 mL, 0.72 mmol, 3.0 equiv.) to give the title product (55 mg, 95%, >95:5 dr, >95% D) as a white solid after purification by flash column chromatography (15% EtOAc/hexanes).

HPLC analysis, Chiralpak OJ-H (3% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 4.4 min, Minor 3.6 min, 94% ee;

mp 55-57 °C; $[\alpha]_D^{20}$ +51.0 (*c* 1, $CHCl_3$); ν_{max} (film, cm^{-1}): 2978, 2949, 1726, 1506, 1425, 1215, 1155, 922; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 2.24 (6H, s, $N(CH3)_2$), 3.54 (1H, s, C(2)*H*), 3.70 (3H, s, OCH_3), 4.86-5.20 (2H, m, C(5)H_2), 5.82 (1H, dd, *J* 17.0, 10.2, C(4)*H*), 7.00 (2H, t, *J* 8.8, Ar(3,5)*H*), 7.17 (2H, dd, *J* 8.8, 5.4, Ar(2,6)*H*); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −116.4 (Ar-*F*); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ_C: 41.4 ($N(CH_3)_2$), 48.9 (t, $^1J_{CD}$ 20, *C*(3)D), 50.9 (OCH_3), 71.0 (*C*(2)H), 115.5 (d, $^2J_{CF}$ 21, Ar*C*(3,5)H), 116.8 (*C*(5)H_2), 129.4 (d, $^3J_{CF}$ 7.8, Ar*C*(2,6)H), 136.5 (Ar*C*(1)), 138.5 (*C*(4)H), 161.7 (d, $^1J_{CF}$ 245, Ar*C*-F), 171.0 (*C*=O); HRMS (NSI^+) $C_{14}H_{18}DFNO_2^+$ $[M+H]^+$ found: 253.1460, requires: 253.1457 (+1.1 ppm).

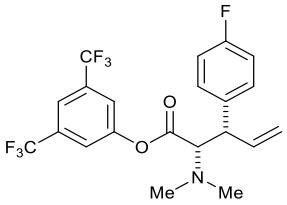
(±)-3,5-Bis(trifluoromethyl)phenyl *syn*-2-(dimethylamino)-3-phenylpent-4-enoate 368



Following general procedure **M**, (*E*)-*N*-(2-(3,5-bis(trifluoromethyl)phenoxy)-2-oxoethyl)-*N*,*N*-dimethyl-3-phenylprop-2-en-1-ammonium bromide **227** (123 mg, 0.24 mmol, 1.0 equiv.) was reacted with (±)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL). to give the title product (73 mg, 71%) as a white solid after flash column chromatography (10→15% EtOAc/hexanes).

mp 88-90 °C; ν_{max} (film, cm^{-1}): 2937, 1755, 1456, 1369, 1275, 1171, 1119, 1105, 902; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (6H, s, $N(CH_3)_2$), 3.88-3.90 (2H, m, C(2)*H* + C(3)*H*), 5.12-5.32 (2H, m, C(5)H_2), 5.91-6.12 (1H, m, C(4)*H*), 7.26-7.30 (3H, m, Ar*H*), 7.32-7.42 (2H, m, Ar*H*), 7.53 (2H, s, Ar(2,6)*H*), 7.78 (1H, s, ArC(4)*H*); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ_F: −62.9 (CF_3); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 41.6 ($N(CH_3)_2$), 50.5 (*C*(3)H), 70.9 (*C*(2)H), 117.6 (*C*(5)H_2), 119.9-120.0 (m, OAr*C*(4)H), 121.7-123.0 (m, OAr*C*(2,6)H), 122.8 (q, $^1J_{CF}$ 273, *C*F_3), 127.2 (C(3)Ar*C*(4)H), 128.0 (C(3)Ar*C*(2,6)H), 128.9 (C(3)Ar*C*(3,5)H), 133.1 (q, $^2J_{CF}$ 34.0, Ar*C*-CF_3), 138.3 (*C*(4)H), 140.1 (C(3)Ar*C*(1)), 151.0 (Ar*C*(1)), 168.8 (*C*=O); HRMS (NSI^+) $C_{21}H_{20}F_6NO_2^+$ $[M+H]^+$ found: 432.1387, requires: 432.1393 (−1.3 ppm).

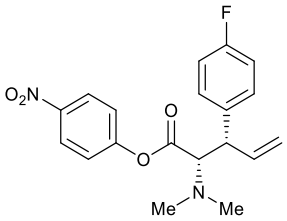
(±)-3,5-Bis(trifluoromethyl)phenyl *syn*-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate 367



Following general procedure **M**, (*E*)-*N*-(2-(3,5-bis(trifluoromethyl)phenoxy)-2-oxoethyl)-3-(4-fluorophenyl)-*N*,*N*-dimethylprop-2-en-1-ammonium bromide **366** (127 mg, 0.24 mmol, 1.0 equiv.) was reacted with (±)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL). to give the title product (51 mg, 40%) as a white solid after flash column chromatography (10→15% EtOAc/hexanes).

mp 58-60 °C; ν_{max} (film, cm^{-1}): 2941, 1761, 1512, 1460, 1366, 1276, 1167, 1119, 933, 891; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.42 (6H, s, $N(CH3)_2$), 3.83-3.94 (2H, m, C(2)*H* + C(3)*H*), 5.14-5.22 (2H, m, C(5)*H*), 5.99 (1H, ddd, *J* 17.5, 10.0, 7.9, C(4)*H*), 7.08 (2H, t, *J* 8.6, Ar(3,5)*H*), 7.22-7.35 (2H, m, Ar(2,6)*H*), 7.56 (2H, s, Ar(2,6)*H*), 7.80 (1H, s, Ar(4)*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: −62.9 (C*F*$_3$), −115.8 (Ar*F*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_H: 41.5 (N(*C*H_3)$_2$), 49.6 (*C*(3)H), 70.8 (*C*(2)H), 115.8 (d, $^2J_{CF}$ 21.3, C(3)Ar*C*(3,5)H), 117.7 (*C*(5)H_2), 119.6-120.3 (m, OAr*C*(4)H), 122.4-122.8 (m, OAr*C*(2,6)H), 122.9 (q, $^1J_{CF}$ 273, *C*F_3), 129.4 (d, $^2J_{CF}$ 7.9, Ar*C*(2,6)H), 133.2 (q, $^2J_{CF}$ 34.1, Ar*C*CF_3), 135.8 (d, $^4J_{CF}$ 3.2, C(3)Ar*C*(1)), 138.3 (*C*(4)H), 151.0 (Ar*C*(1)), 161.9 (d, $^1J_{CF}$ 245.3, C(3)ArC(4)-F), 168.6 (*C*=O); HMRS (NSI$^+$) $C_{21}H_{19}F_7NO_2^+$ $[M+H]^+$ found: 450.1291, requires: 450.1299 (−1.7 ppm).

4-Nitrophenyl *syn*-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate 311

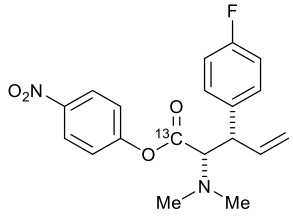


Following general procedure **L**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **309** (105 mg, 0.24 mmol, 1.0 equiv.) was reacted with (+)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL) gave the title product as a pale yellow solid (44 mg, 52%, >95:5 dr); after flash column chromatography (10→20% EtOAc/hexanes).

mp 92-95 °C; $[\alpha]_D^{20}$ +29.0 (*c* 1, MeCN); ν_{max} (film, cm^{-1}): 2951, 1745, 1589, 1508, 1342, 1201, 1069, 921, 846; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.39 (6H, s, N(C*H*$_3$)$_2$), 3.78-3.92 (2H, m, C(2)*H*+C(3)*H*),

5.02-5.39 (2H, m, C(5)H_2), 5.95 (1H, ddd, *J* 17.4, 10.1, 7.7, C(4)*H*), 7.05 (2H, t *J* 8.7, C(3)Ar(3,5)*H*), 7.21-7.27 (4H, m, C(3)Ar(2,6)*H* + OAr(2,6)*H*), 8.28 (2H, d, *J* 9.1, OAr(3,5)*H*); $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$) δ_F: −116.3 (Ar*F*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 41.4 (N(*C*H_3)$_2$), 49.5 (*C*(3)H), 70.8 (*C*(2)H), 115.7 (d, $^2J_{CF}$ 21, C(3)Ar*C*(3,5)H), 117.6 (*C*(5)H_2), 122.8 (OAr*C*(2,6)H), 125.4 (OAr*C*(3,5)H), 129.4 (d, $^3J_{CF}$ 8, C(3)Ar*C*(2,6)H), 135.8 (d, $^4J_{CF}$ 3, C(3)Ar*C*(1)), 138.3 (*C*(4)H), 145.6 (Ar*C*(1)-O), 155.2 (Ar*C*(4)-NO_2), 161.8 (d, $^1J_{CF}$ 245, Ar*C*-F), 168.4 (*C*=O). HRMS (NSI^+) $C_{19}H_{20}FN_2O_4^+$ $[M+H]^+$ found: 359.1402, requires: 359.1402 (+0.1 ppm).

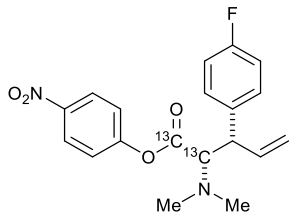
(±)-4-Nitrophenyl (*syn*)-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate-1-^{13}C $^{13}C_1$-518



Following general procedure **M**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl-2-^{13}*C*)prop-2-en-1-ammonium bromide **$^{13}C_1$-344** (105 mg, 0.24 mmol, 1.0 equiv.) was reacted with (±)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL) gave the title product as a pale yellow solid (53 mg, 62%, >95:5 dr); after flash column chromatography (10→20% EtOAc/hexanes).

mp 99-100 °C; ν_{max} (film, cm^{-1}): 2941, 1713, 1591, 1523, 1508, 1346, 1206, 1159, 1080, 923, 864;^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (6H, s, N(C*H*$_3$)$_2$), 3.62-4.02 (2H, m, C(2)*H* + C(3)*H*), 5.03-5.37 (2H, m, C(5)H_2), 5.98 (1H, ddd, *J* 16.9, 10.1, 8.0, C(4)*H*), 7.07 (2H, t, *J* 8.7, Ar(3,5)*H*), 7.16-7.38 (4H, m, Ar(2,6)*H* + Ar(2,6)*H*), 8.31 (2H, d, *J* 9.0, Ar(3,5)*H*); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: −115.74 - −115.86 (m, Ar*F*), $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 41.4 (N(*C*H_3)$_2$), 49.5 (C(3)*H*), 70.8 (d, $^1J_{CC}$ 56, C(2)*H*), 115.7 (d, $^2J_{CF}$ 21, C(3)Ar*C*(3,5)H), 117.6 (*C*(5)H_2), 122.8 (OAr*C*(2,6)H), 125.4 (OAr*C*(3,5)H), 129.4 (d, $^3J_{CF}$ 7.8, C(3)Ar*C*(2,6)H), 135.8 (app. t, *J* 3.9, Ar*C*(1)), 138.3 (*C*(4)H), 145.6 (Ar*C*(4)-NO_2), 155.2 (d, $^2J_{CC}$ 3.8, Ar*C*(1)-O), 161.8 (d, $^1J_{CF}$ 245, Ar*C*-F), 168.4 (^{13}C=O); HRMS (ESI^+) $C_{18}{}^{13}CH_{20}O_4N_2F^+$ $[M+H]^+$ found: 360.1482, requires: 360.1435 (−1.99 ppm).

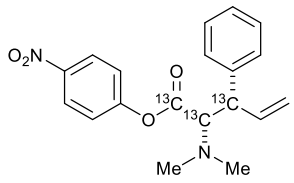
(±)-4-Nitrophenyl (*syn*)-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate-1,2-$^{13}C_2$ $^{13}C_2$-335



Following general procedure **M**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl-1,2-$^{13}C_2$)prop-2-en-1-ammonium bromide **$^{13}C_2$-333** (105 mg, 0.24 mmol, 1.0 equiv.) was reacted with (±)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr$_2$NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL) gave the title product as a pale yellow solid (51 mg, 59%, >95:5 dr); after flash column chromatography (10→20% EtOAc/hexanes).

mp 100-102 °C; ν_{max} (film, cm^{-1}): 2939, 1714, 1591, 1524, 1506, 1346, 1205, 1159, 1078, 916, 864;^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (6H, d, $^2J_{CH}$ 4.2, N(C*H*$_3$)$_2$), 3.83-3.94 (1H, m, C(3)*H*), 3.85 (1H, ddd, $^1J_{CH}$ 142, $^2J_{CH}$ 11.4, $^3J_{CH}$ 5.2, ^{13}C(2)*H*), 5.11-5.35 (2H, m, C(5)*H*$_2$), 5.98 (1H, dddd, *J* 17.0, 10.1, 8.6, 2.6, C(4)*H*), 7.08 (2H, t, *J* 8.7, Ar(3,5)*H*), 7.18-7.29 (4H, m, OAr(2,6)*H* + C(3)Ar(2,6)*H*), 8.29 (2H, d, *J* 9.1, OAr(3,5)*H*); ^{19}F (471 MHz, $CDCl_3$) δ_F: −115.8 (tt, *J* 9.1, 5.2, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 41.4 (N(*C*H$_3$)$_2$), 49.5 (d, $^1J_{CC}$ 38, *C*(3)H), 70.8 (d, $^1J_{CC}$ 57, ^{13}*C*(2)*H*), 115.7 (d, $^2J_{CF}$ 21, C(3)Ar*C*(3,5)H), 117.6 (d, $^4J_{CH}$ 3.6, *C*(5)H$_2$), 122.8 (OAr*C*(2,6)H), 125.4 (OAr*C*(3,5)H), 129.4 (dd, $^3J_{CF}$ 8.1, $^3J_{CC}$ 1.8, Ar*C*(2,6)H), 135.7-135.9 (m, Ar*C*(1)), 138.3 (*C*(4)H), 145.6 (Ar*C*(4)-NO$_2$), 155.2 (dd, *J* 3.5, 1.7, ArC(1)-O), 161.8 (d, $^1J_{CF}$ 245, Ar*C*-F), 168.4 (d, $^1J_{CC}$ 57, ^{13}*C*=O); HRMS (ESI$^+$) $C_{17}{}^{13}C_2H_{20}O_4N_2F^+$ $[M+H]^+$ found: 361.1462, requires: 361.1469 (−1.86 ppm).

(±)-4-Nitrophenyl (*syn*)-2-(dimethylamino)-3-phenylpent-4-enoate-1,2,3-$^{13}C_3$ $^{13}C_3$-343

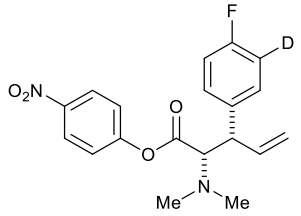


Following general procedure **M**, (*E*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl-1,2-$^{13}C_2$)-3-phenylprop-2-en-1-ammonium-3-^{13}C bromide **$^{13}C_3$-341** (100 mg, 0.24 mmol, 1.0 equiv.) was reacted with (±)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr$_2$NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL) gave the title product as a pale yellow solid (49 mg, 60%, >95:5 dr); after flash column chromatography (10→20% EtOAc/hexanes).

mp 107-109 °C; ν_{max} (film, cm^{-1}): 2984, 1707, 1516, 1487, 1344, 1198, 1155, 1072, 1045, 910, 862; ^{1}H NMR (700 MHz, $CDCl_3$) δ_H: 2.42 (6H, dd, *J* 4.4, 2.2, N(C*H*$_3$)$_2$), 3.75-4.04 (2H, m, ^{13}C(2)*H* + ^{13}C(3)*H*),

5.18 (1H, t, *J* 10.8, C(5)*H*^{cis}H), 5.26 (1H, dd, *J* 17.0, 6.4, C(5)H*H*^{trans}), 5.95-6.09 (1H, m, C(4)*H*), 7.26-7.32 (5H, m, Ar(2,6)*H* + Ar*H*), 7.39 (2H, t, *J* 7.6, Ar*H*), 8.31 (2H, d, *J* 9.1, Ar(3,5)*H*);^{13}C{^{1}H} NMR (179 MHz, $CDCl_3$) δ_C: 41.5 (N(*C*H$_3$)$_2$), 50.4 (d, $^{1}J_{CC}$ 38, ^{13}*C*(3)H, 70.9 (dd, $^{1}J_{CC}$ 57, $^{1}J_{CC}$ 38, ^{13}*C*(2)H), 117.5 (d, $^{3}J_{CC}$ 3.6, *C*(5)H$_2$), 122.8 (Ar*C*(2,6)H), 125.4 (Ar*C*(3,5)H), 127.1 (Ar*C*(4)H), 127.9 (Ar*C*(3,5)H), 128.9 (d, $^{3}J_{CC}$ 3.5, Ar*C*(2,6)H), 138.4 (d, $^{1}J_{CC}$ 41, *C*(4)H), 140.2 (dd, $^{1}J_{CC}$ 45.4, $^{2}J_{CC}$ 3.2, Ar*C*(1)), 145.6 (Ar*C*(4)NO$_2$), 155.3 (d, $^{2}J_{CC}$ 2.0, Ar*C*(1)-O), 168.6 (d, $^{1}J_{CC}$ 57, ^{13}*C*=O); HRMS (ESI$^+$) $C_{16}{}^{13}C_3H_{21}O_4N_2^+$ $[M+H]^+$ found: 344.1589, requires: 344.1596 (−2.17 ppm).

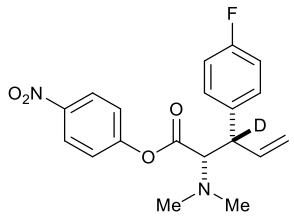
(±)-4-Nitrophenyl (*syn*)-2-(dimethylamino)-3-(4-fluorophenyl-3-*d*)pent-4-enoate *d*$_1$-365



Following general procedure **M**, (*E*)-3-(4-fluorophenyl-3-*d*)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide ***d*$_1$-364** (53 mg, 0.12 mmol, 1.0 equiv.) was reacted with (±)-BTM (6 mg, 0.024 mmol, 0.2 equiv.), HOBt (3.2 mg, 0.024 mmol, 0.2 equiv.) and *i*Pr$_2$NH (24 μL, 0.34 mmol, 1.4 equiv.) in MeCN (1.75 mL) gave the title product as a pale yellow solid (38 mg, 44%, >95:5 dr); after flash column chromatography (15% EtOAc/hexanes).

mp 96-98 °C; ν_{max} (film, cm^{-1}): 2949, 1757, 1589, 1516, 1489, 1342, 1201, 1092, 923, 894;^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.41 (6H, s, N(C*H*$_3$)$_2$), 3.62-4.11 (2H, m, C(2)*H* + C(3)*H*), 4.71-5.42 (2H, m, C(5)*H*$_2$), 5.97 (1H, ddd, *J* 17.6, 10.1, 7.8, C(4)*H*), 7.07 (1H, t, *J* 8.9, Ar(5)*H*), 7.19-7.36 (4H, m, Ar(2,6)*H* + Ar(2)*H* + Ar(6)*H*), 8.31 (2H, d, *J* 9.1, Ar(3,5)*H*); ^{19}F (471 MHz, $CDCl_3$) δ_F: −116.08 (dt, *J* 10.2, 5.3, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 41.4 (N(*C*H$_3$)$_2$), 49.5 (*C*(3)H), 70.8 (*C*(2)H), 115.8 (d, $^{2}J_{CF}$ 21, Ar*C*(5)H), 117.6 (*C*(5)H$_2$), 122.8 (Ar*C*(2,6)*H*), 125.4 (Ar*C*(3,5)H), 129.3 (app. dd, *J* 11, 7.8, Ar*C*(3)-D + Ar*C*(2)H + Ar*C*(6)H), 135.8 (d, $^{4}J_{CF}$ 3.2, Ar*C*(1)), 138.3 (*C*(4)H), 145.6 (Ar*C*(4)-NO$_2$), 155.2 (Ar*C*(1)-O), 161.8 (d, $^{1}J_{CF}$ 245, Ar*C*-F), 168.4 (*C*=O); HRMS (ESI$^+$) $C_{19}H_{19}DO_4N_2F$ $[M+H]^+$ found: 360.1458, requires: 360.1464 (−1.77 ppm).

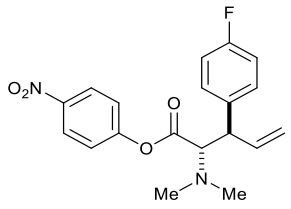
(±)-4-Nitrophenyl (*syn*)-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate-3-*d* d_1-358



Following general procedure **M**, (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium-3-*d* bromide ***d*$_1$-357** (15 mg, 0.03 mmol, 1.0 equiv.) was reacted with (±)-BTM (1.5 mg, 0.006 mmol, 0.2 equiv.), HOBt (0.8 mg, 0.006 mmol, 0.2 equiv.) and *i*Pr$_2$NH (5.8 μL, 0.04 mmol, 1.4 equiv.) in MeCN (0.5 mL) gave the title product as a pale yellow solid (3 mg, 28%, >95:5 dr); after flash column chromatography (15% EtOAc/hexanes).

mp 97-98 °C; ν_{max} (film, cm^{-1}): 2940, 1757, 1525, 1510, 1346, 1206, 1159, 1113,1099, 918;^{1}H NMR (700 MHz, $CDCl_3$) δ_H: 2.38 (6H, s, N(CH3)$_2$), 3.82 (1H, s, C(2)*H*), 5.15 (1H, d, *J* 10.1, C(5)*H*^{A}H^B), 5.21 (1H, d, *J* 17.0, C(5)H^A*H*^{B}), 5.94 (1H, dd, *J* 17.0, 10.1, C(4)*H*), 7.05 (2H, t, *J* 8.4, Ar(3,5)*H*), 7.17-7.27 (4H, m, Ar(2,6)*H* + Ar(2,6)*H*), 8.28 (2H, d, *J* 8.9, Ar(3,5)*H*); ^{19}F (657 MHz, $CDCl_3$) δ_F: −115.82 (m, Ar*F*); ^{13}C{^{1}H} NMR (179 MHz, $CDCl_3$) δ_C: 41.5 (N(*C*H$_3$)$_2$), 48.8-49.3 (m, *C*(3)D), 70.8 (*C*(2)H), 115.8 (d, $^2J_{CF}$ 21, Ar*C*(3,5)H), 117.6 (*C*(5)H$_2$), 122.8 (OAr*C*(2,6)H), 125.4 (OAr*C*(3,5)H), 129.3 (d, $^3J_{CF}$ 7.9, Ar*C*(2,6)H), 135.8 (d, $^4J_{CF}$ 2.9, Ar*C*(1)), 138.3 (*C*(4)H), 145.6 (Ar*C*(4)-NO$_2$), 155.2 (Ar*C*(1)-O), 161.8 (d, $^1J_{CF}$ 245, Ar*C*-F), 168.4 (*C*=O); HRMS (ESI$^+$) $C_{19}H_{19}DO_4N_2F$ [M+H]$^+$ found: 360.1457, requires: 360.1464 (−2.05 ppm).

(±)-4-Nitrophenyl (*anti*)-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate 519



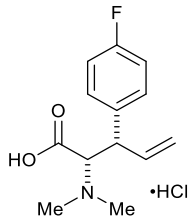
A solution of (*E*)-3-(4-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **309** (1.0 g, 2.28 mmol, 1.0 equiv.) in MeCN (33 mL) was treated with KO*t*Bu (0.31 g, 2.73 mmol, 1.2 equiv.) and the resulting mixture was stirred for 1 h at rt. The reaction mixture was then concentrated *in vacuo* the residue dissolved in CH_2Cl_2 (100 mL) and water (100 mL) the layers separated and the aqueous extracted with CH_2Cl_2 (2 × 50 mL). The combined organic lyaers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* The crude residue was analysed by ^{1}H NMR (2.6:1 *syn*:*anti*). The residue was then purified by flash column chromatography

(10→15% EtOAc/hexane) to give the *syn* diastereoisomer (150 mg, 18%) followed by the *anti* diastereoisomer (49 mg, 6%) as a beige solid;

Data for *anti* diastereoisomer;

mp 99-101 °C; ν_{max} (film, cm^{-1}): 2949, 1747, 1591, 1519, 1346, 1210, 1161, 1093, 908; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.54 (6H, s, $N(CH3)_2$), 3.76-3.88 (2H, m, C(2)*H* + C(3)*H*), 5.08-5.25 (2H, m, C(5)H_2), 6.16 (1H, ddd, *J* 17.6, 10.3, 7.2, C(4)*H*), 6.75 (2H, d, *J* 9.1, Ar(2,5)*H*), 7.05 (2H, t, *J* 8.6, Ar(3,5)*H*), 7.21-7.32 (2H, m, Ar(2,6)*H*), 8.16 (2H, d, *J* 9.1, Ar(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 41.4 ($N(CH3)_2$), 49.0 (*C*(3)H), 72.0 (*C*(2)H), 115.8 (d, $^{2}J_{CF}$ 21, Ar*C*(3,5)H), 117.1 (*C*(5)H_2), 122.6 (OAr*C*(2,6)H), 125.3 (OAr*C*(3,5)H), 130.3 (d, $^{3}J_{CF}$ 8, C(3)Ar*C*(2,6)H), 136.0 (d, $^{4}J_{CF}$ 3, Ar*C*(1)), 138.0 (*C*(4)H), 145.6 (Ar*C*(4)-NO_2), 154.9 (Ar*C*(1)-O), 162.1 (d, $^{1}J_{CF}$ 246, Ar*C*-F), 168.0 (*C*=O); HRMS (ESI^+) $C_{19}H_{20}FN_2O_4^+$ $[M+H]^+$ found: 359.1395, requires: 359.1402 (−1.84 ppm).

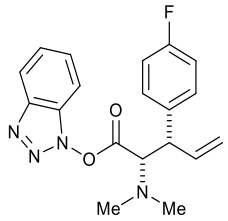
(±)-*Syn*-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoic acid hydrochloride 347



A solution of 4-nitrophenyl *syn*-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate **311** (1.0 g, 3.00 mmol, 1.0 equiv.) in aq. 6 M HCl (30 mL) was heated at reflux for 16 h. Once complete the reaction mixture was cooled to rt and Et_2O (30 mL) added, the layers separated and the aqueous layer washed with Et_2O (2 × 30 mL). The aqueous layer was concentrated *in vacuo* the resulting solid was recrystallized (CH_2Cl_2/EtOAc) to give the product as a white solid (466 mg, 57%, >95:5 dr);

mp 157-159 °C; ν_{max} (film, cm^{-1}): 2907, 2681, 2507, 1728, 1508, 1361, 1224, 1200, 993, 831; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H: 2.80 (6H, s, $N(CH_3)_2$), 3.61 (1H, br. s, N^+H) 4.24 (1H, t, *J* 7.4, C(3)*H*), 4.43 (1H, br. s, C(2)*H*), 5.23-5.41 (2H, m, C(5)H_2), 6.08 (1H, dt, *J* 17.0, 9.8, C(4)*H*), 7.21 (2H, t, *J* 8.8, Ar(3,5)*H*), 7.41-7.53 (2H, m, Ar(2,6)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, d_6-DMSO) δ_C: 41.4 ($N(CH_3)_2$), 46.2 (*C*(3)H), 69.6 (*C*(2)H), 115.5 (d, $^{2}J_{CF}$ 21, Ar*C*(3,5)H), 120.0 (*C*(5)H_2), 130.2 (d, $^{3}J_{CF}$ 8.1, Ar*C*(2,6)H), 134.9 (*C*(4)H), 135.3 (d, $^{4}J_{CF}$ 2.0, Ar*C*(1)), 161.4 (d, $^{1}J_{CF}$ 243, Ar*C*-F), 168.0 (*C*=O); HRMS (NSI^+) $C_{13}H_{17}FNO_2^+$ $[M]^+$ found: 238.1234, requires: 238.1238 (−1.6 ppm).

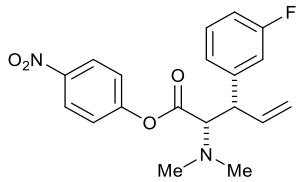
(±)-1*H*-Benzo[*d*][1,2,3]triazol-1-yl *syn*-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoate 346



A solution of *syn*-2-(dimethylamino)-3-(4-fluorophenyl)pent-4-enoic acid hydrochloride **347** (100 mg, 0.37 mmol, 1.0 equiv.) in CH_2Cl_2 (3.7 mL) was treated with NEt_3 (52 μL, 0.37 mmol, 1.0 equiv.) and stirred for 15 min at rt. The mixture was treated with HOBt (75 mg, 0.56 mmol, 1.5 equiv.) and EDC·HCl (108 mg, 0.56 mmol, 1.5 equiv.) and the mixture stirred at rt for 16 h. After which CH_2Cl_2 (20 mL) and sat. aq. $NaHCO_3$ (10 mL) were added, the layers separated, the organic layer washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in EtOAc (30 mL) and filtered through a plug of silica gel washing with EtOAc (50 mL). The filtrate was concentrated *in vacuo* to give the product as a beige solid (118 mg, 90%, >95:5 dr);

mp 51 °C (dec.); ν_{max} (film, cm^{-1}): 2791, 1792, 1602, 1510, 1225, 1037, 894; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.48 (6H, s, N(CH_3)$_2$), 3.93 (1H, dd, *J* 11.5, 8.8, C(3)*H*), 4.10 (1H, d, *J* 11.5, C(2)*H*), 5.29-5.37 (2H, m, C(5)H_2), 6.05 (1H, dt, *J* 17.9, 8.8, C(4)*H*), 7.10 (2H, t, *J* 8.7, Ar(3,5)*H*), 7.28 (2H, dd, *J* 8.6, 5.2, Ar(2,6)*H*), 7.41 (d, *J* 8.3, Ar(4)*H*), 7.45 (1H, t, *J* 7.6, (Ar(6)*H*), 7.57 (1H, t, *J* 7.6, Ar(5)*H*), 8.11 (1H, d, *J* 8.3, Ar(7)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 41.3 (N(*C*H_3)$_2$), 49.3 (*C*(3)H), 69.3 (*C*(2)H), 108.5 (Ar*C*(4)H), 115.8 (d, $^2J_{CF}$ 21, C(3)Ar*C*(3,5)H), 118.6 (*C*(5)H_2), 120.7 (Ar*C*(7)H), 124.9 (Ar*C*(6)H), 128.7 (Ar*C*-N), 128.9 (Ar*C*(5)H), 129.4 (d, $^3J_{CF}$ 8, C(3)Ar*C*(2,6)H), 135.1 (d, $^4J_{CF}$ 3, C(3)Ar*C*(1)), 137.6 (*C*(4)H), 143.5 (Ar*C*-N), 161.9 (d, $^1J_{CF}$ 246, Ar*C*-F), 166.0 (*C*=O); HRMS (NSI$^+$) $C_{19}H_{20}FN_4O_2^+$ $[M+H]^+$ found: 355.1564, requires: 355.1565 (−0.2 ppm).

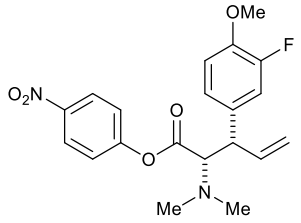
(±)-4-Nitrophenyl (*syn*)-2-(dimethylamino)-3-(3-fluorophenyl)pent-4-enoate 520



Following general procedure **M**, (*E*)-3-(3-fluorophenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **372** (105 mg, 0.24 mmol, 1.0 equiv.) was reacted with (±)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL). to give the title product (45 mg, 52%, >95:5 dr) as a white solid after flash column chromatography (10→20% EtOAc/hexanes);

mp 77-80 °C; ν_{max} (film, cm^{-1}): 2836, 1746, 1614, 1591, 1518, 1487, 1343 1204, 1098, 925;^{1}H NMR (700 MHz, $CDCl_3$) δ_H: 2.39 (6H, s, N(CH_3)$_2$), 3.79-3.91 (2H, m, C(2)*H*+C(2)*H*), 5.14-5.27 (2H, m, C(5)H_2), 5.95 (1H, ddd, *J* 17.0, 10.1, 8.1, C(4)*H*), 6.91-7.00 (2H, m, Ar(4)*H* + Ar(6)*H*), 7.05 (1H, d, *J* 7.6, Ar(2)*H*), 7.26 (2H, d, *J* 9.1, Ar(2,6)*H*), 7.32 (1H, td, *J* 7.9, 5.9, Ar(5)*H*), 8.29 (2H, d, *J* 9.1, Ar(3,5)*H*; ^{19}F NMR (659 MHz, $CDCl_3$) δ_F: −112.9 (q, *J* 8.6, Ar*F*); ^{13}C{^{1}H} NMR (179 MHz, $CDCl_3$) δ_C: 41.5 (N(*C*H_3)$_2$), 50.0 (*C*(3)H), 70.7 (*C*(2)H), 114.0 (d, $^{2}J_{CF}$ 22, Ar*C*(4)H), 114.9 (d, $^{2}J_{CF}$ 22, Ar*C*(2)H), 118.0 (*C*(5)H_2), 122.8 (Ar*C*(2,6)H), 123.7 (d, $^{4}J_{CF}$ 2.7, Ar*C*(6)H), 125.4 (Ar*C*(3,5)H), 130.3 (d, $^{3}J_{CF}$ 8.3, Ar*C*(5)H), 137.8 (*C*(4)H), 142.8 (Ar*C*(1)), 145.6 (Ar*C*(1)-O), 155.2 (Ar*C*(4)-NO_2), 163.1 (d, $^{1}J_{CF}$ 246, Ar*C*-F), 168.2 (*C*=O); HRMS (ESI$^+$) $C_{19}H_{20}O_4N_2F^+$ [M+H]$^+$ found: 359.1396, requires: 359.1402 (−1.56 ppm).

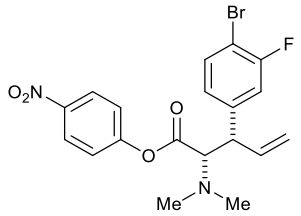
(±)-4-Nitrophenyl (*syn*)-2-(dimethylamino)-3-(3-fluoro-4-methoxyphenyl)pent-4-enoate 521



Following general procedure **M**, (*E*)-3-(3-fluoro-4-methoxy-phenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **373** (113 mg, 0.24 mmol, 1.0 equiv.) was reacted with (±)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr$_2$NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL). to give the title product (49 mg, 53%) as a pale yellow solid after flash column chromatography (10→20% EtOAc/hexanes);

mp 88-90 °C; ν_{max} (film, cm^{-1}): 2938, 1755, 1589, 1516, 1485, 1344, 1276, 1195, 1120, 1098, 925, 858;^{1}H NMR (700 MHz, $CDCl_3$) δ_H: 2.42 (6H, s, N(CH_3)$_2$), 3.78-3.85 (2H, m, C(2)*H* + C(3)*H*), 3.91 (3H, s, OCH_3), 4.96-5.38 (2H, m, C(5)H_2), 5.95 (1H, dddd, *J* 17.1, 10.1, 7.0, 1.3, C(4)*H*), 6.93-7.06 (3H, m, Ar(2,3,5)*H*), 7.28 (2H, d, *J* 9.1, Ar(2,6)*H*), 8.31 (2H, d, *J* 9.1, Ar(3,5)*H*); ^{19}F NMR (659 MHz, $CDCl_3$) δ_F: −134.7 (dd, *J* 12.3, 8.4, Ar*F*); ^{13}C{^{1}H}NMR (179 MHz, $CDCl_3$) δ_C: 41.5 (N(*C*H_3)$_2$), 49.3 (*C*(3)H), 56.3 (O*C*H_3), 70.8 (*C*(2)H), 113.6 (d, $^{3}J_{CF}$ 1.6, ArC(5)H), 115.5 (d, $^{2}J_{CF}$ 19, Ar*C*(2)H), 117.6 (*C*(5)H_2), 122.8 (Ar*C*(2,6)H), 123.6 (d, $^{4}J_{CF}$ 3.4, Ar*C*(6)H), 125.4 (Ar*C*(3,5)H), 133.1 (d, $^{3}J_{CF}$ 6.0, Ar*C*(1)), 138.1 (*C*(4)H), 145.6 (Ar*C*(1)-O), 146.6 (d, $^{2}J_{CF}$ 11, Ar*C*(4)-OMe), 152.5 (d, $^{1}J_{CF}$ 246, Ar*C*-F), 155.2 (Ar*C*(4)-NO_2), 168.4 (*C*=O); HRMS (ESI$^+$) $C_{20}H_{22}O_5N_2F^+$ [M+H]$^+$ found: 389.1499, requires: 389.1507 (−2.12 ppm).

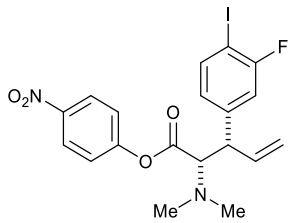
(±)-4-Nitrophenyl (*syn*)-3-(4-bromo-3-fluorophenyl)-2-(dimethylamino)pent-4-enoate 522



Following general procedure **M**, (*E*)-3-(3-fluoro-4-bromo-phenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **374** (124 mg, 0.24 mmol, 1.0 equiv.) was reacted with (±)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL). to give the title product (92 mg, 88%) as a white solid after flash column chromatography (10→20% EtOAc/hexanes);

mp 69-71 °C; ν_{max} (film, cm^{-1}): 2940, 1757, 1523, 1487, 1344, 1203, 1097, 925, 862;^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.38 (6H, s, N(CH_3)$_2$), 3.71-3.90 (2H, m, C(2)*H* + C(3)*H*), 5.11-5.33 (2H, m, C(5)H_2), 5.90 (1H, ddd, *J* 17.0, 10.1, 7.8, C(4)*H*), 6.94 (1H, dd, *J* 8.2, 2.0, Ar(6)*H*), 7.04 (1H, dd, *J* 9.6, 2.0, Ar(2)*H*), 7.26 (2H, d, *J* 9.1, Ar(2,6)*H*), 7.52 (1H,dd, *J* 8.2, 7.2, Ar(5)*H*), 8.29 (2H, d, *J* 9.1, Ar(3,5)*H*); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ_F: −107.1 (Ar*F*); ^{13}C{^{1}H}NMR (126 MHz, $CDCl_3$) δ_C: 41.4 (N(*C*H_3)$_2$), 49.5 (*C*(3)H), 70.5 (*C*(2)H), 107.3 (d, $^2J_{CF}$ 21, Ar*C*(4)-Br), 116.1 (d, $^2J_{CF}$ 22, Ar*C*(2)H), 118.4 (*C*(5)H_2) 122.8 (Ar*C*(2,6)H), 125.0 (d, $^4J_{CF}$ 3.3, Ar*C*(6)H), 125.4 (Ar*C*(3,5)H), 133.7 (Ar*C*(5)H), 137.4 (*C*(4)H), 142.1 (d, $^3J_{CF}$ 6.5, Ar*C*(1)), 145.7 (Ar*C*(1)-O), 155.1 (Ar*C*(4)-NO_2), 159.3 (d, $^1J_{CF}$ 245, Ar*C*-F), 168.0 (*C*=O); HRMS (ESI$^+$) $C_{19}H_{19}O_4N_2{}^{79}BrF^+$ $[M+H]^+$ found: 437.0496, requires; 437.0507 (−2.46 ppm).

(±)-4-Nitrophenyl (*syn*)-2-(dimethylamino)-3-(3-fluoro-4-iodophenyl)pent-4-enoate 523

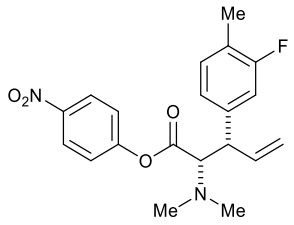


Following general procedure **M**, (*E*)-3-(3-fluoro-4-iodo-phenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **375** (136 mg, 0.24 mmol, 1.0 equiv.) was reacted with (±)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL). to give the title product (109 mg, 94%) as a pale yellow solid after flash column chromatography (10→20% EtOAc/hexanes);

mp 86-88 °C; ν_{max} (film, cm^{-1}): 2940, 1755, 1614, 1591, 1521, 1489, 1344, 1203, 1157, 1095, 1026, 925, 880; ^{1}H NMR (700 MHz, $CDCl_3$) δ_H: 2.38 (6H, s, N(CH3)$_2$), 3.73-3.91 (2H, m, C(2)*H* + C(3)*H*),

5.02-5.32 (2H, m, C(5)*H*), 5.90 (1H, ddd, *J* 17.0, 10.1, 8.2, C(4)*H*), 6.82 (1H, dd, *J* 8.1, 2.0, Ar(6)*H*), 6.99 (1H, dd, *J* 9.0, 2.0, Ar(2)*H*), 7.26 (2H, d, *J* 9.0, Ar(2,6)*H*), 7.71 (1H, dd, *J* 8.1, 6.6, Ar(5)*H*), 8.29 (2H, d, *J* 9.0, Ar(2,6)*H*); ^{19}F NMR (659 MHz, $CDCl_3$) δ_F: −93.72-−93.90 (m, Ar*F*); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ_C: 41.4 (N(*C*H_3)$_2$), 49.6 (*C*(3)H), 70.5 (*C*(2)H), 79.2 (d, $^2J_{CF}$ 26, Ar*C*(4)-I), 115.4 (d, $^2J_{CF}$ 24, Ar*C*(2)H), 118.4 (*C*(5)H_2), 122.8 (Ar*C*(2,6)H), 125.4 (Ar*C*(3,5)H), 125.5 (d, $^3J_{CF}$ 3.1, Ar*C*(1)), 137.4 (*C*(4)H), 139.5 (Ar*C*(5)H), 143.3 (d, $^4J_{CF}$ 6.5, Ar*C*(6)H), 145.7 (Ar*C*(1)-O), 155.1 (Ar*C*(4)-NO_2), 162.0 (d, $^1J_{CF}$ 245, Ar*C*-F), 168.0 (*C*=O); HRMS (ESI^+) $C_{19}H_{19}O_4N_2FI^+$ $[M+H]^+$ found: 485.0360, requires: 485.0368 (−1.66 ppm).

(±)-4-Nitrophenyl (*syn*)-2-(dimethylamino)-3-(3-fluoro-4-methylphenyl)pent-4-enoate 524

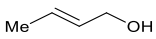


Following general procedure **M**, (*E*)-3-(3-fluoro-4-methyl-phenyl)-*N*,*N*-dimethyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **376** (109 mg, 0.24 mmol, 1.0 equiv.) was reacted with (±)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL). to give the title product (79 mg, 88%) as a pale yellow solid after flash column chromatography (10→20% EtOAc/hexanes);

mp 73-75 °C; ν_{max} (film, cm^{-1}): 2940, 1757, 1616, 1591, 1523, 1489, 1456, 1344, 1204, 1159, 1113, 1095, 923, 862; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.26 (3H, d, *J* 1.8, ArC*H*$_3$), 2.40 (6H, s, N(C*H*$_3$)$_2$), 3.80-3.85 (2H, m, C(2)*H* + C(3)*H*), 5.12-5.25 (2H, m, C(5)H_2), 5.8-6.01 (1H, m, C(4)*H*), 6.86-6.98 (2H, m, Ar(2)*H* + Ar(6)*H*), 7.16 (1H, td, *J* 7.9, 0.9, Ar(5)*H*), 7.26 (2H, d, *J* 9.2, Ar(2,6)*H*), 8.28 (2H, d, *J* 9.2, Ar(3,5)*H*); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ_F: −117.1 (Ar*F*); $^{13}C\{^1H\}$ NMR (179 MHz, $CDCl_3$) δ_C: 14.5 (d, $^3J_{CF}$ 3.3, ArC*H*$_3$), 41.5 (N(*C*H_3)$_2$), 49.7 (*C*(3)H), 70.8 (*C*(2)H), 114.4 (d, $^2J_{CF}$ 23, Ar*C*(2)H), 117.8 (*C*(5)H_2), 122.8 (Ar*C*(2,6)H), 123.3 (d, $^4J_{CF}$ 3.1, Ar*C*(6)H), 123.5 (d, $^2J_{CF}$ 17, Ar*C*(4)-Me), 125.4 (Ar*C*(3,5)H), 131.8 (d, *J* 5.4, Ar*C*(5)H), 138.1 (*C*(4)H), 139.9 (d, $^3J_{CF}$ 7.0, Ar*C*(1)), 145.6 (Ar*C*(1)-O), 155.2 (Ar*C*(4)-NO_2), 161.5 (d, $^1J_{CF}$ 245, Ar*C*-F), 168.4 (*C*=O); HRMS (ESI^+) $C_{20}H_{22}O_4N_2F^+$ $[M+H]^+$ found: 373.1552, requires: 373.1558 (−1.64 ppm).

Stereochemical Model

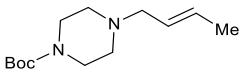
(*E*)-But-2-en-1-ol[122] 525



A solution of $LiAlH_4$ (4.0 M in Et_2O, 12.1 mL, 48.2 mmol, 0.4 equiv.) in THF (30 mL) was cooled to 0 °C then a solution of (*E*)-crotonaldehyde (10 mL, 120.7 mmol, 1.0 equiv.) in THF (20 mL) was added *via* dropping funnel. The resulting solution was allowed to warm to rt and stirred for 2 h, the reaction was quenched by the dropwise addition of aq. 1 M KOH (50 mL). The resulting biphasic mixture was stirred for 30 min at rt, the layers separated and the aqueous layer extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with aq. 2 M HCl (50 mL), then brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled at atmospheric pressure to give the product as a colourless liquid (4.30 g, 59%, 98:2 *E:Z*)

bp 128-130 °C @ 976 mbar {lit. 117-121 °C @ 976 mbar}, ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.68-170 (3H, m, CH_3), 4.06 (2H, d, *J* 5.2, C(1)H_2), 5.59-5.79 (2H, m, C(2)*H* + C(3)*H*); data consistent with the literature.[122]

***tert*-Butyl (*E*)-4-(but-2-en-1-yl)piperazine-1-carboxylate 526**

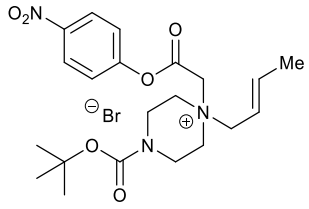


A solution of (*E*)-but-2-en-1-ol **525** (1.0 g, 13.9 mmol, 1.0 equiv.) in Et_2O (42 mL) was cooled to 0 °C and treated with PBr_3 (521 µL, 5.56 mmol, 0.4 equiv.) dropwise, the reaction mixture then stirred for 1 h at 0 °C. The reaction was quenched by the addition of aq. $NaHCO_3$ (20 mL) and allowed to warm to rt, the layers separated and the aqueous layer extracted with Et_2O (2 × 20 mL), the combined organic layers washed with brine (20 mL) dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in THF (14 mL) and added to a solution of *tert*-butyl piperazine-1-carboxylate (6.45 g, 34.7 mmol, 2.5 equiv.) in THF (14 mL) dropwise, the resulting mixture was stirred at rt for 15 min. The reaction mixture was treated with aq. 1 M NaOH (20 mL) and stirred for 15 min, Et_2O (30 mL) as then added the layers separated and the aqueous extracted with Et_2O(2 × 30 mL), the combined organics were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5→20% Et_2O/CH_2Cl_2) to give the product as a yellow oil (678 mg, 20% over two steps, 97:3 E:Z);

ν_{max} (film, cm^{-1}): 2934, 2905, 1694, 1417, 1364, 1244, 1168, 968, 830; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.45 (9H, s, C(CH_3)$_3$), 1.69 (d, *J* 6.3, CH_3), 2.36 (4H, br. s, C(3)H_2), 2.92 (2H, d, *J* 6.7, C(1′)H_2), 3.43 (4H, br. s, C(2)H_2), 5.43-5.54 (1H, m, C(2′)*H*), 5.61 (1H, dd, *J* 12.7, 6.3, C(3′)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 17.9 (*C*H$_3$), 28.5 (C(*C*H$_3$)$_3$), 43.2 and 44.2 (rotameric *C*(3)H$_2$), 52.9 (*C*(2)H$_2$), 61.0

(*C*(1′)H_2) 79.7 (*C*(CH_3)$_3$), 127.2 (*C*(2′)H), 129.7 (*C*(3′)H), 154.9 (*C*=O); HRMS (NSI$^+$) $C_{13}H_{25}O_2N_2^+$ $[M+H]^+$ found: 241.1904, requires: 241.1911 (−2.7 ppm).

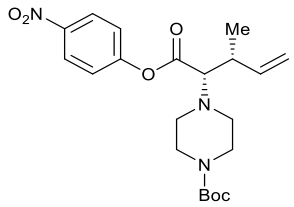
(*E*)-1-(But-2-en-1-yl)-4-(tert-butoxycarbonyl)-1-(2-(4-nitrophenoxy)-2-oxoethyl)piperazin-1-ium bromide 401



Following general procedure **G**, *p*-nitrophenyl bromoacetate **213** (1.30 g, 5.0 mmol, 3.0 equiv.) was reacted with *tert*-butyl (*E*)-4-(but-2-en-1-yl)piperazine-1-carboxylate **526** (0.40 g, 1.67 mmol, 1.0 equiv.) in MeCN (3.3 mL) to give the title product as a white solid (0.51 g, 60%, 94:6 E:Z)

mp 132 °C (dec.); ν_{max} (film, cm^{-1}): 2974, 1757, 1697, 1526, 1489, 1346, 1149, 1010, 972, 858; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 1.43 (9H, s, C(C*H*$_3$)$_3$), 1.81 (3H, d, *J* 6.3, C*H*$_3$), 3.56-3.84 (8H, m, C(2,6 and 3,5)*H*$_2$), 4.32 (2H, d, *J* 7.3 , C(1′)*H*$_2$), 4.86 (2H, s, COC*H*$_2$), 5.78 (1H,dt, *J* 14.1, 7.3, C(2′)*H*), 6.13 (1H, dq, *J* 13.2, 6.3, C(3′)*H*), 7.57 (2H, d, *J* 9.1, Ar(2,5)*H*), 8.39 (2H, d, *J* 9.1, Ar(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, d_6-DMSO) δ_C: 18.2 (*C*H$_3$), 27.9 (C(*C*H$_3$)$_3$), 36.5 and 37.6 (rotameric *C*(2,6)H$_2$), 55.5 (COCH$_2$), 57.7 (*C*(3,5)H$_2$), 61.5 (*C*(1′)H$_2$), 80.1 (*C*(CH$_3$)$_3$), 117.4 (*C*(2′)H), 123.1 (Ar*C*(2,6)H), 125.6 (Ar*C*(3,5)H), 140.7 (*C*(3′)H), 145.7 (Ar*C*(4)-NO$_2$), 153.5 (Ar*C*(1)-O), 153.8 (N*C*=O), 162.1 (*C*=OCH$_2$); HRMS (NSI$^+$) $C_{21}H_{30}N_3O_6^+$ $[M]^+$ found: 420.2121, requires: 420.2129 (−1.9 ppm).

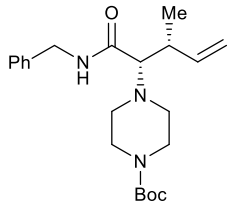
***tert*-Butyl 4-((2*S*,3*R*)-3-methyl-1-(4-nitrophenoxy)-1-oxopent-4-en-2-yl)piperazine-1-carboxylate 402**



Following general procedure **L**, (*E*)-1-(but-2-en-1-yl)-4-(tert-butoxycarbonyl)-1-(2-(4-nitrophenoxy)-2-oxoethyl)piperazin-1-ium bromide **401** (120 mg, 0.24 mmol, 1.0 equiv.) was reacted with (+)-benzotetramisole (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr$_2$NH (47 μL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL) at −20 °C for 16 h. Crude *dr* 82:18, flash coloumn chromatography (10→15% EtOAc/hexanes) gave the title product as a colourless oil (31 mg, 31%, 82:18 dr).

$[\alpha]_D^{20}$ −20.4 (*c* 1, $CHCl_3$); ν_{max} (film, cm^{-1}): 2978, 1757, 1686, 1525, 1346, 1247, 1113, 1009, 909; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.15 (3H, d, *J* 6.7, CH_3), 1.46 (9H, s, C(CH_3)$_3$), 2.53-2.86 (5H, m, C(3)*H* + C(3′,5′)H_2), 3.22 (1H, d, *J* 11.1, C(2)*H*), 3.33-3.54 (4H, m, C(2′)H_2), 5.09-5.22 (2H, m, C(5)H_2), 5.74 (1H, ddd, *J* 17.1, 10.2, 8.5, C(4)*H*), 7.21 (2H, d, *J* 9.2, Ar(2,6)*H*), 8.26 (2H, d, *J* 9.2, Ar(3,5)*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 17.1 (*C*H_3), 28.6 (*C*(CH_3)$_3$), 37.6 (*C*(3)H), 43.8 and 44.8 (rotameric *C*(2′,6′)H_2), 49.5 (*C*(3′,5′)H_2), 72.2 (*C*(2)H), 79.9 (*C*(CH_3)$_3$), 117.1 (*C*(5)H_2), 122.8 (Ar*C*(2,6)H), 125.4 (Ar*C*(3,5)H), 139.8 (*C*(4)H), 145.6 (Ar*C*(4)-NO_2), 154.8 (Ar*C*(1)-O), 155.2 (N*C*=O), 168.6 (*C*=O); HRMS (ESI^+) $C_{21}H_{30}O_6N_3^+$ $[M+H]^+$ found: 420.2126, requires: 420.2129 (−0.7 ppm);

***tert*-butyl 4-((2*S*,3*R*)-1-(benzylamino)-3-methyl-1-oxopent-4-en-2-yl)piperazine-1-carboxylate 527**



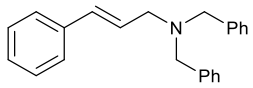
A solution of *tert*-butyl 4-((2*S*,3*R*)-3-methyl-1-(4-nitrophenoxy)-1-oxopent-4-en-2-yl)piperazine-1-carboxylate **402** (31 mg, 0.074 mmol, 1.0 equiv.) in CH_2Cl_2 (3.5 mL) was treated with benzylamine (41 μL, 0.37 mmol, 5.0 equiv.) and *i*Pr_2NH (11 μL, 0.074 mmol, 1.0 equiv.) and stirred at rt for 16 h. Once complete the reaction was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (5→20% Et_2O/CH_2Cl_2) to give the product as a colourless oil (22 mg, 77%, 84:16 dr);

HPLC analysis, Chiralpak OD-H (5% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 19.7 min, Minor 17.1 min, 83% ee;

$[\alpha]_D^{20}$ +1.5 (*c* 1, $CHCl_3$); ν_{max} (film, cm^{-1}): 3292, 2976, 1695, 1649, 1422, 1366, 1248, 1172, 1124, 1007; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.14 (3H, d, *J* 6.7, CH_3), 1.47 (9H, s, C(CH_3)$_3$), 2.48-2.60 (4H, m, C(3',5')H_2), 2.68-2.85 (2H, m, C(2)*H* + C(3)*H*), 3.38 (4H, br. s, C(2',6')H_2), 4.40 (1H, dd, *J* 14.6, 5.5, PhC$H^A$$H^B$), 4.50 (1H, dd, *J* 14.6, 5.5, PhC$H^A$$H^B$), 5.08 (2H, m, C(5)$H_2$), 5.82 (1H, ddd, *J* 17.4, 10.4, 7.0, C(4)*H*), 6.50 (1H, t, *J* 5.5, N*H*), 7.25-7.32 (3H, m, Ar*H*), 7.33-7.38 (2H, m, Ar*H*); $^{13}C\{^1H\}$NMR (126 MHz, $CDCl_3$) δ_C: 17.3 (*C*H_3), 28.5 (*C*(CH_3)$_3$), 36.2 (*C*(3)H), 43.3 (Ph*C*H_2), 43.5 and 44.4 (rotameric *C*(2'6')H_2), 50.6 (*C*(3',5')H_2), 74.6 (*C*(2)H), 79.9 (*C*(CH_3)$_3$, 116.1 (*C*(5)H_2), 127.7 (Ar*C*(4)H), 128.1 (Ar*C*(2,6)H), 128.8 (Ar*C*(3,5)H), 138.4 (Ar*C*(1)), 139.5 (*C*(4)H), 154.8 (Boc-*C*=O), 170.4 (*C*=O); HRMS (ESI^+) $C_{22}H_{34}O_3N_3^+$ $[M+H]^+$ found: 388.2585, requires: 388.2522 (−2.5 ppm).

Experimental Detials for Chapter 4

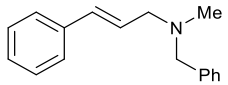
(*E*)-*N*,*N*-Dibenzyl-3-phenylprop-2-en-1-amine 417



A solution of *N*,*N*-dibenzylamine (6.1 mL, 31.7 mmol, 2.5 equiv.) in THF (12.5 mL) was treated dropwise with solution of cinnamyl bromide **210** (2.5 g, 12.7 mmol, 1.0 equiv.) in THF (26 mL) over 10 mins at rt. The resulting mixture for stirred for 16 h, aq. 1 M NaOH (30 mL) added the mixture stirred for a further 5 min, Et_2O (30 mL) was then added, the layers separated and the aqueous layer extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (50 mL) dried over $MgSO_4$ and concentrated *in vacuo*, the resulting residue was purified by flash column chromatography (5→20% EtOAc/PE) to give the title product as a yellow oil (4.23 g, quant., >98:2 *E*:*Z*);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.24 (2H, dd, *J* 6.5, 1.,5 C(1)H_2), 3.64 (4H, s, PhCH_2), 6.24-6.38 (1H, m, C(2)*H*), 6.54 (1H, d, *J* 16.0, C(3)*H*), 7.14-7.49 (15H, m, Ar*H*); data consistent with literature.

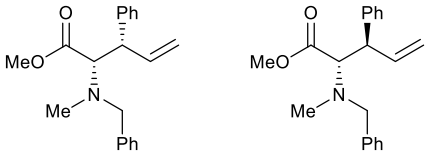
(*E*)-*N*-Benzyl-*N*-methyl-3-phenylprop-2-en-1-amine 419



A solution of *N*-benzyl-*N*-methylamine (8.2 mL, 63.5 mmol, 2.5 equiv.) in THF (26 mL) was treated dropwise with a solution of cinnamyl bromide **210** (5.0 g, 25.4 mmol, 1.0 equiv.) in THF (50 mL) over 10 mins at rt. The resulting mixture was stirred for a further 15 mins, aq. 1 M NaOH (50 mL) added and the mixture stirred for a further 5 min, Et_2O (50 mL) was then added, the layers separated and the aqueous layer extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (50 mL) dried over $MgSO_4$ and concentrated *in vacuo*, the resulting residue was purified by flash column chromatography (5→20% EtOAc/PE) to give the title product as an orange oil (5.2 g, 86%, 98:2 *E*:*Z*);

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.28 (3H, s, NCH_3), 3.23 (2H, dd, *J* 6.7, 1.5, C(1)H_2), 3.58 (2H, s, PhCH_2), 6.36 (1H, dt, *J* 15.9, 6.7, C(2)*H*), 6.57 (1H, dd, *J* 15.9, 1.5, C(3)*H*), 7.20-7.47 (10H, m, Ar*H*); data consistent with literature.

Methyl (2*S*,3*S*)-2-(benzyl(methyl)amino)-3-phenylpent-4-enoate 421



Following general procedure **J**, 4-nitrophenyl -2-bromoacetate **213** (63 mg, 0.24 mmol, 1.0 equiv.) was reacted with (*E*)-*N*-Benzyl-*N*-methyl-3-phenylprop-2-en-1-amine **419** (60 mg, 0.252 mmol, 1.05 equiv.) in MeCN (1.75 mL) for 24 h at rt, then cooled to −20 °C and reacted with (+)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 µL, 0.34 mmol, 1.4 equiv.) in MeCN (1.75 mL) for 24 h, then quenched with NaOMe (1 M in MeOH, 0.72 mL, 0.72 mmo, 3.0 equiv.) and stirred at rt for 1 h. Crude *dr* 80:20, the residue was purified by flash column chromatography (5% EtOAc/PE) to give the title product as a colourless oil (56 mg, 76%, 80:20 *dr*);

HPLC analysis Chiralpak OJ-H (0.5% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 9.5 min, Minor 6.9 min, 76% ee;

$[\alpha]_D^{20}$ −5.7 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 2949, 1728, 1452, 1254, 1190, 1146, 1026, 984, 918; Major (*syn*) diastereoisomer; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.15 (3H, s, NCH_3), 3.39 (1H, d, *J* 13.7, PhCH^AH^B), 3.70 (1H, d, *J* 11.8, C(2)*H*), 3.75 (1H, d, *J* 13.7, PhCH^AH^B), 3.77 (3H, s, OCH_3), 3.87 (1H, dd, *J* 11.8, 8.3, C(3)*H*), 4.94-5.12 (2H, m, C(5)H_2), 5.85 (1H, ddd, *J* 17.1, 10.2, 8.3, C(4)*H*), 6.69-6.86 (2H, m, Ar*H*), 7.10-7.21 (5H, m, Ar*H*), 7.22-7.40 (3H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 38.1 (N*C*H_3), 50.2 (*C*(3)H), 51.0 (*C*(2)H), 58.2 (Ph*C*H_2), 69.4 (O*C*H_3), 116.7 (*C*(5)H_2), 126.6 (Ar*C*H), 126.9 (Ar*C*H), 128.1 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 128.7 (Ar*C*H), 138.8 (*C*(4)H), 139.2 (Ar*C*), 140.7 (Ar*C*), 171.4 (*C*=O); Minor (*anti*) diastereoisomer;^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.29 (3H, s, NCH_3), 3.48 (3H, s, OCH_3), 3.51 (1H, d, *J* 13.6, PhCH^AH^B), 3.68 (1H, d, *J* 11.6, C(2)*H*)), 3.75 (1H, d, *J* 13.6 PhCH^AH^B), 3.83-3.94 (1H, m, C(3)*H*), 5.04-5.10 (2H, m, C(5)H_2), 6.20 (1H, ddd, *J* 17.2, 10.2, 8.2, C(4)*H*), 6.69-6.86 (2H, m, Ar*H*), 7.10-7.21 (5H, m, Ar*H*), 7.22-7.40 (3H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 38.1 (N*C*H_3), 49.6 (*C*(3)H), 50.8 (*C*(2)H), 58.3 (Ph*C*H_2), 70.5 (O*C*H_3), 116.1 (*C*(5)H_2), 126.9 (Ar*C*H), 127.1 (Ar*C*H), 128.4 (Ar*C*H), 128.4 (Ar*C*H), 128.7 (Ar*C*H), 128.9 (Ar*C*H), 138.8 (*C*(4)H), 139.4 (Ar*C*), 141.1 (Ar*C*), 170.6 (*C*=O); HRMS (ESI$^+$) $C_{20}H_{24}O_2N^+$ $[M+H]^+$ found: 310.1794, requires: 310.1802 (−2.4 ppm).

General Procedure O: Synthesis of *N*,*N*-diallylamines from Allylic Alcohols

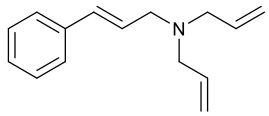
A solution of allylic alcohol (1.0 equiv.) in Et_2O (0.33 M) was cooled to 0 °C and treated with PBr_3 (0.4 equiv.) and stirred for 1 h, the reaction was quenched by the dropwise addition of aq. sat. $NaHCO_3$ (equal volume), the mixture was allowed to warm to rt. The layers were then separated, the aqueous layer extracted with Et_2O (2 × equal volume), the combined organic layers washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in THF (0.5 M) and added to *N*,*N*-diallylamine (2.5 equiv.) in THF (2.5 M with respect to *N*,*N*-diallylamine) *via* dropping funnel, upon completion the dropping funnel was rinsed with THF (half volume) and the reaction was stirred at rt for 15 min. The reaction was treated with aq. 1 M NaOH (equal volume) and stirred for 15 min, then Et_2O (equal volume) was added, the layers separated and the aqueous layer extracted with Et_2O (2 × equal volume). The combined organic layers were washed with brine, dried over $MgSO_4$ then concentrated *in vacuo*, *N*, *N*-diallyl allylic amines were used without further purification.

General Procedure P: Synthesis of *N*,*N* diallyl allylic ammonium salts

A solution of *N*,*N* diallyl amine (1.0 equiv.) in MeCN (1 M) was treated with 4-nitrophenyl bromoacetate (1.2 equiv.) and the reaction mixture was stirred for 16 h. Et_2O (5 × volume) was added and the mixture stirred for 1-16 h, the precipitate was filtered and dried *in vacuo* to give the salts. Ammonium salts were used directly or recrystallized from MeCN/Et_2O if required.

Amine Synthesis

(*E*)-*N*,*N*-Diallyl-3-phenylprop-2-en-1-amine 424

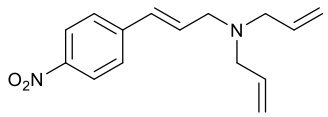


A solution of cinnamyl bromide **210** (25.0 g, 126.9 mmol, 1.0 equiv.) in THF (250 mL) was added dropwise to a solution of *N*,*N* diallylamine (39.1 mL, 317.0 mmol, 2.5 equiv.) in THF (125 mL) dropwise over 10 min at rt. The resulting solution was stirred at 15 min for a further 15 min. aq. 1 M NaOH (200 mL) was then added and the mixture stirred for a further 5 min, Et_2O (200 mL) was then added, the layers separated and the aqueous layer extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with brine (200 mL) dried over $MgSO_4$ and concentrated *in vacuo*, the resulting residue was purified by high vacuum distillation to give the title product as a colourless liquid (25.2 g, 93%).

bp 136-138 °C @ 1mmbar; υ_{max} (film, cm^{-1}): 2800, 1641, 1494, 1448, 1417, 1352, 1119, 995, 964, 916, 873; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 3.17 (4H, d, *J* 6.5, diallyl-C(1)H_2), 3.28 (2H, d, *J* 6.7, C(1)H_2), 5.13-5.27 (4H, m, diallyl-C(3)H_2), 5.92 (2H, ddt, *J* 16.8, 10.2, 6.5, diallyl-C(2)*H*), 6.29 (1H, dt, *J* 15.8,

6.7, C(2)*H*), 6.54 (1H, d, *J* 15.8, C(3)*H*), 7.22-7.44 (5H, m, Ar*H*); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 55.8 (*C*(1)H_2), 56.6 (diallyl-*C*(1)H_2), 117.7 (diallyl-*C*(5)H_2), 126.3 (ArC(2,6)H), 127.3 (Ar*C*(4)H), 127.4 (*C*(2)H), 128.6 (Ar*C*(3,5)H), 132.7 (*C*(3)H), 135.6 (diallyl-*C*(2)H), 137.1 (Ar*C*(1)); HRMS (ESI^+) $C_{15}H_{20}N^+$ $[M+H]^+$ found: 214.1590, requires: 214.1590 (−0.1 ppm).

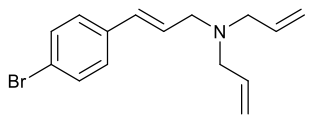
(*E*)-*N*,*N*-diallyl-3-(4-nitrophenyl)prop-2-en-1-amine 528



Following general procedure **O**, 4-nitrocinnamyl alcohol **469** (2.86 g, 15.98 mmol, 1.0 equiv.) was reacted with PBr_3 (601 µL, 6.39 mmol, 0.4 equiv.) in Et_2O (48 mL), then with *N*,*N*-diallylamine (4.93 mL, 40 mmol, 2.5 equiv.) in THF (32 mL) to give the title product as an orange oil (2.63 g, 64%) with was used without further purification.

υ_{max} (film, cm^{-1}): 2978, 1595, 1512, 1339, 1109, 968, 918, 858; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.14 (4H, d, *J* 6.5, diallyl-C(1)H_2), 3.28 (2H, dd, *J* 6.3, 1.4, C(1)H_2), 5.12-5.25 (4H, m, diallyl-C(3)H_2), 5.88 (2H, ddt, *J* 16.8, 10.2, 6.5, diallyl-C(2)*H*), 6.45 (1H, dt, *J* 15.9, 6.3, C(2)*H*), 6.59 (1H, d, *J* 15.9, C(3)*H*), 7.48 (2H, d, *J* 8.8, Ar(2,6)*H*), 8.17 (2H, d, *J* 8.8, Ar(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (100 Mz, $CDCl_3$) δ_C: 55.5 (*C*(1)H_2), 56.8 (diallyl-*C*(1)H_2), 117.9 (diallyl-*C*(3)H_2), 124.0 (Ar*C*(3,5)H), 126.7 (Ar*C*(2,6)H), 130.3 (*C*(2)H), 133.1 (*C*(3)H, 135.3 (diallyl-*C*(2)H), 143.6 (Ar*C*(1)), 146.8 (Ar*C*(4)-NO_2); HRMS (ESI^+) $C_{15}H_{19}O_2N_2^+$ $[M+H]^+$ found: 259.1440, requires: 259.1447 (−0.4 ppm).

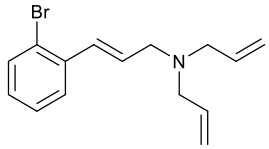
(*E*)-*N*,*N*-diallyl-3-(4-bromophenyl)prop-2-en-1-amine 529



Following general procedure **O**, 4-bromocinnamyl alcohol **463** (1.62 g, 7.59 mmol, 1.0 equiv.) was reacted with PBr_3 (286 µL, 3.04 mmol, 0.4 equiv.) in Et_2O (24 mL), then with *N*,*N*-diallylamine (2.53 mL, 18.97 mmol, 2.5 equiv.) in THF (16 mL) to give the title product as a pale yellow oil (0.99 g, 45%) with was used without further purification.

υ_{max} (film, cm^{-1}): 2976, 1487, 1400, 1072, 1009, 968, 918; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.12 (4H, dt, *J* 6.5, 1.3, diallyl-C(1)H_2), 3.22 (2H, dd, *J* 6.6, 1.4, C(1)H_2), 5.09-5.25 (4H, m, diallyl-C(3)H_2), 5.87 (2H, ddt, *J* 16.8, 10.2, 6.5, diallyl-C(2)*H*), 6.25 (1H, dt, *J* 15.9, 6.6, C(2)*H*), 6.45 (dt, *J* 15.9, 1.4, C(3)*H*), 7.23 (2H, d, *J* 8.5, Ar(2,6)*H*), 7.42 (2H, d, *J* 8.5, Ar(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (100 Mz, $CDCl_3$) δ_C: 55.8 (*C*(1)H_2), 56.8 (diallyl-*C*(1)H_2), 117.9 (diallyl-*C*(3)H_2), 121.2 (Ar*C*(4)-Br), 127.9 (Ar*C*(2,6)H), 128.5 (*C*(2)H), 131.5 (*C*(3)H), 131.8 (Ar*C*(3,5)H), 135.6 (diallyl-*C*(2)H), 136.2 (Ar*C*(1)); HRMS (ESI^+) $C_{15}H_{19}N^{79}Br^+$ $[M+H]^+$ found: 292.0694, requires: 292.0701 (−0.1 ppm).

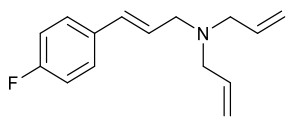
(*E*)-*N*,*N*-diallyl-3-(2-bromophenyl)prop-2-en-1-amine 530



Following general procedure **O**, 2-bromocinnamyl alcohol **472** (1.36 g, 6.37 mmol, 1.0 equiv.) was reacted with PBr_3 (240 µL, 2.55 mmol, 0.4 equiv.) in Et_2O (20 mL), then with *N*,*N*-diallylamine (1.96 mL, 15.93 mmol, 2.5 equiv.) in THF (13 mL) to give the title product as a pale yellow oil (1.10 g, 59%) with was used without further purification.

υ_{max} (film, cm^{-1}): 2976, 1643, 1466, 1435, 1256, 1113, 1047, 1022, 966, 918; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.15 (4H, dt, *J* 6.5, 1.3, diallyl-C(1)H_2), 3.29 (2H, dd, *J* 6.7, 1.5, C(1)H_2), 5.11-5.27 (4H, m, diallyl-C(3)H_2), 5.89 (2H, ddt, *J* 16.8, 10.2, 6.5, diallyl-C(2)*H*), 6.19 (1H, dt, *J* 15.8, 6.7, C(2)*H*), 6.86 (1H, d, *J* 15.8, C(3)*H*), 7.08 (1H, td, *J* 7.7, 1.6, Ar(6)*H*), 7.19-7.32 (1H, m, Ar(5)*H*), 7.53 (2H, td, *J* 8.0, 1.6, Ar(3,4)*H*); ^{13}C{^{1}H} NMR (100 Mz, $CDCl_3$) δ_C: 55.7 (*C*(1)H_2), 56.7 (diallyl-*C*(1)H_2), 118.0 (diallyl-*C*(3)H_2), 123.5 (Ar*C*(2)-Br), 127.2 (Ar*C*(4)H), 127.6 (Ar*C*(5)H), 128.8 (Ar*C*(6)H), 130.6 (*C*(2)H), 131.6 (*C*(2)H), 133.0 (Ar*C*(3)H), 135.6 (diallyl-*C*(2)H), 137.2 (Ar*C*(1)); HRMS (ESI$^+$) $C_{15}H_{19}N^{79}Br^+$ $[M+H]^+$ found: 292.0694, requires: 292.0701 (−0.1 ppm).

(*E*)-*N*,*N*-diallyl-3-(4-fluorophenyl)prop-2-en-1-amine 531

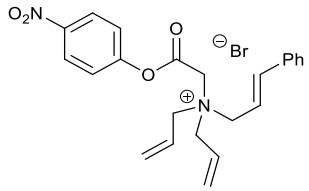


Following general procedure **O**, 4-fluorocinnamyl alcohol **497** (1.36 g, 6.37 mmol, 1.0 equiv.) was reacted with PBr_3 (240 µL, 2.55 mmol, 0.4 equiv.) in Et_2O (20 mL), then with *N*,*N*-diallylamine (1.96 mL, 15.93 mmol, 2.5 equiv.) in THF (13 mL) to give the title product as a pale yellow oil (1.10 g, 59%, 96:4 *E*:Z) with was used without further purification.

υ_{max} (film, cm^{-1}): 2918, 2803, 1603, 1508, 1227, 1157, 1119, 966, 917, 841; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.13 (4H, dt, *J* 6.5, 1.3, diallyl-C(1)H_2), 3.23 (2H, dd, *J* 6.7, 1.4, C(1)H_2), 5.12-5.28 (4H, m, diallyl-C(3)H_2), 5.88 (2H, ddt, *J* 16.8, 10.2, 6.5, diallyl-C(2)*H*), 6.17 (1H, dt, *J* 15.8, 6.7, C(2)*H*), 6.47 (1H, dt, *J* 15.8, 1.4, C(2)*H*), 6.89-7.07 (2H, m, Ar(3,5)*H*), 7.28-7.37 (2H, m, Ar(2,6)*H*); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ_F: −114.9 (Ar*F*); ^{13}C{^{1}H} NMR (100 Mz, $CDCl_3$) δ_C: 55.7 (*C*(1)H_2), 56.6 (diallyl-*C*(1)H_2), 115.4 (d, $^2J_{CF}$ 21.5, Ar*C*(3,5)H), 117.9 (diallyl-*C*(3)H_2), 127.0 (*C*(2)H), 127.7 (d, $^3J_{CF}$ 7.8, Ar*C*(2,6)H), 131.5 (*C*(3)H), 131.9 (d, $^4J_{CF}$ 2.9, Ar*C*(1)), 135.4 (diallyl-*C*(2)H), 162.2 (d, $^1J_{CF}$ 247, Ar*C*(4)-F); HRMS (ESI$^+$) $C_{15}H_{19}NF^+$ $[M+H]^+$ found: 232.1494, requires: 232.1502 (−0.9 ppm).

Ammonium Salt Synthesis

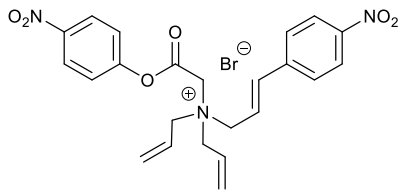
(*E*)-*N*,*N*-Diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide 425



Following general procedure **P**: (*E*)-*N*,*N*-diallyl-3-(phenyl)prop-2-en-1-amine **424** (5.0 g, 23.47 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl bromoacetate **213** (7.32 g, 28.17 mmol, 1.2 equiv.) in MeCN (23.5 mL) to give the title product as a white solid (5.54 g, 50%).

mp 128 °C (dec.); υ_{max} (film, cm^{-1}): 2945, 1771, 1616, 1591, 1528, 1452, 1346, 1996, 166, 1142, 988, 937, 883; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 4.27 (4H, d, *J* 7.3, diallyl-C(1)H_2), 4.37 (2H, d, *J* 7.4, C(1)H_2), 4.73 (2H, s, COCH_2), 5.57-5.89 (4H, m, diallyl-C(3)H_2), 6.24 (2H, ddt, *J* 17.3, 10.0, 7.3, diallyl-C(2)*H*), 6.60 (1H, dt, *J* 15.5, 7.4, C(2)*H*), 7.03 (1H, d, *J* 15.5, C(3)*H*), 7.34-7.46 (3H, m, Ar*H*), 7.49 (2H, d, *J* 9.1, Ar(3,5)*H*), 7.56-7.68 (2H, m, Ar*H*), 8.37 (2H, d, *J* 9.1, Ar(2,6)*H*); ^{13}C{^{1}H} NMR (126 MHz, d_6-DMSO) δ_C: 56.2 (COCH_2), 62.3 (diallyl-*C*(1)H_2), 62.5 (*C*(1)H_2), 115.7 (*C*(2)H), 123.0 (Ar*C*(2,6)H), 125.4 (Ar*C*(3,5)H), 125.6 (diallyl-*C*(3)H_2), 127.4 (C(3)Ar*C*(2,6)H), 128.6 (diallyl-*C*(2)H), 128.8 (C(3)Ar*C*(3,5)H), 129.2 (C(3)Ar*C*(4)H), 135.1 (C(3)Ar*C*(1)), 141.6 (*C*(3)H), 145.7 (Ar*C*(1)-O), 153.7 (Ar*C*(4)-NO_2), 163.3 (*C*=O); HRMS (ESI^+) $C_{23}H_{25}O_4N_2^+$ $[M]^+$ found: 393.1801, requires: 393.1809 (−2.0 ppm).

(*E*)-*N*,*N*-Diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-(4-nitrophenyl)prop-2-en-1-ammonium bromide 436

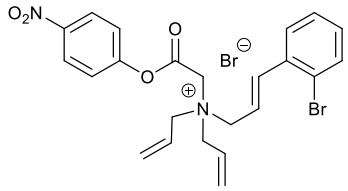


Following general procedure **P**: (*E*)-*N*,*N*-diallyl-3-(4-nitrophenyl)prop-2-en-1-amine **528** (1.0 g, 3.88 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl bromoacetate **213** (1.21 g, 4.66 mmol, 1.2 equiv.) in MeCN (4 mL) to give the title product as a white solid (0.55 g, 28%) after recrystallization from MeCN.

mp 142 °C (dec.); υ_{max} (film, cm^{-1}): 29450, 1773, 1593, 1516, 1452, 1343, 1197, 1167, 1069, 1012, 951, 880; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 4.30 (4H, d, *J* 7.3, diallyl-C(1)H_2), 4.43 (2H, d, *J* 7.4, C(1)H_2), 4.7 (2H, s, COCH_2), 5.71-5.84 (4H, m, diallyl-C(3)H_2), 6.24 (2H, ddt, diallyl-C(2)*H*), 6.87 (1H, dt, *J* 15.5, 7.4, C(2)*H*), 7.17 (1H, d, *J* 15.5, C(3)*H*), 7.51 (2H, d, *J* 9.1, Ar(2,6)*H*), 7.92 (2H, d, *J*

8.9, C(3)Ar(2,6)*H*), 8.29 (2H, d, *J* 8.9, C(3)Ar(3,5)*H*), 8.38 (2H, d, *J* 9.1, Ar(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, d_6-DMSO) δ_C: 56.3 (CO*C*H_2), 61.9 (*C*(1)H_2), 62.5 (diallyl-*C*(1)H_2), 120.9 (*C*(2)H), 123.0 (Ar*C*(2,6)H), 123.9 (Ar*C*(3,5)H), 125.3 (diallyl-*C*(2)H), 125.6 (Ar*C*(3,5)H), 128.5 (Ar*C*(2,6)H), 128.8 (diallyl-*C*(3)H_2), 139.1 (*C*(3)H), 141.7 (C(3)Ar*C*(4)-NO_2), 145.7 (Ar*C*(1)-O), 147.4 (C(3)Ar*C*(1)), 153.7 (Ar*C*(4)-NO_2), 163.2 (*C*=O); HRMS (ESI^+) $C_{23}H_{24}O_6N_3^+$ $[M]^+$ found: 438.1651, requires: 438.1660 (−2.0 ppm).

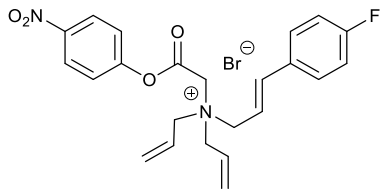
(*E*)-*N*,*N*-Diallyl-3-(2-bromophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 437



Following general procedure **P**: (*E*)-*N*,*N*-diallyl-3-(2-bromophenyl)prop-2-en-1-amine **530** (1.1 g, 3.77 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl bromoacetate **213** (1.18 g, 4.53 mmol, 1.2 equiv.) in MeCN (4 mL) to give the title product as a white solid (0.80 g, 39%) after recrystallization from MeCN.

mp 98 °C (dec.); υ_{max} (film, cm^{-1}): 2954, 1773, 1525, 1348, 1201, 1168, 1066, 1022, 943, 858; ^{1}H NMR (400 MHz, d_6-DMSO) δ_H: 4.31 (4H, d, *J* 7.2, diallyl-C(1)H_2), 4.46 (2H, d, *J* 7.4, C(1)H_2), 4.79 (2H, s, COCH_2), 5.65.-5.84 (4H, m, diallyl-C(3)H_2), 6.24 (2H, ddd, *J* 17.0, 9.8, 5.3, diallyl-C(2)*H*), 6.62 (1H, dt, *J* 15.3, 7.4, C(2)*H*), 7.24 (1H, d, *J* 15.3, C(3)*H*), 7.33 (1H, t, *J* 7.6, Ar(4)*H*), 7.47 (1H, t, *J* 7.7, Ar(5)*H*), 7.52 (2H, d, *J* 8.9, ArC(2,6)*H*), 7.69 (1H, d, *J* 8.0, Ar(6)*H*), 7.96 (1H, d, *J* 7.8, Ar(3)*H*), 8.37 (2H, d, *J* 8.9, ArC(3,5)*H*); $^{13}C\{^{1}H\}$ NMR (126 MHz, d_6-DMSO) δ_C: 56.2 (CO*C*H_2), 62.0 (*C*(1)H_2), 62.4 (diallyl-*C*(1)H_2), 119.5 (*C*(2)H), 123.0 (Ar*C*(2,6)H), 123.3 (C(3)Ar*C*(2)-Br), 125.4 (Ar*C*(3,5)H), 125.6 (diallyl-*C*(3)H_2), 128.1 (C(3)Ar*C*(4)H), 128.6 (C(3)Ar*C*(6)H), 128.6 (diallyl-*C*(2)H), 130.9 (C(3)Ar*C*(5)H), 132.9 (C(3)Ar*C*(3)H), 134.8 (C(3)Ar*C*(1)), 139.4 (*C*(3)H), 145.7 (Ar*C*(1)-O), 153.7 (Ar*C*(4)-NO_2), 163.2 (*C*=O); HRMS (ESI^+) $C_{23}H_{24}O_4N_2{}^{79}Br^+$ $[M]^+$ found: 471.0904, requires: 471.0914 (−2.1 ppm).

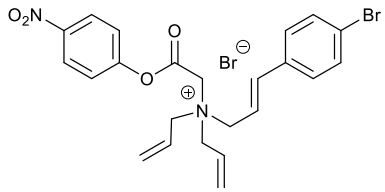
(*E*)-*N*,*N*-Diallyl-3-(4-fluorophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 435



Following general procedure **P**: (*E*)-*N*,*N*-diallyl-3-(4-fluorophenyl)prop-2-en-1-amine **531** (1.0 g, 4.33 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl bromoacetate (1.35 g, 5.19 mmol, 1.2 equiv.) in MeCN (4.3 mL) to give the title product as a white solid (1.23 g, 58%);

mp 132 °C (dec.); υ_{max} (film, cm^{-1}): 2945, 1771, 1591, 1528, 1348, 1200, 1159, 1141, 988, 939, 837; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 4.28 (4H, d, *J* 7.3, diallyl-C(1)H_2), 4.36 (2H, d, *J* 7.5, C(1)H_2), 4.75 (2H, s, COCH_2), 5.71-5.82 (4H, m, diallyl-C(3)H_2), 6.24 (2H, ddt, *J* 17.3, 10.1, 7.2, diallyl-C(2)*H*), 6.56 (1H, dt, *J* 15.5, 7.5, C(2)*H*), 7.02 (1H, d, *J* 15.5, C(3)*H*), 7.27 (2H, t, *J* 8.8, Ar(3,5)*H*), 7.50 (2H, d, *J* 9.1, Ar(2,6)*H*), 7.71 (2H, dd, *J* 8.7, 5.7, Ar(2,6)*H*), 8.37 (2H, d, *J* 9.1, Ar(3,5)*H*); ^{19}F NMR (476 MHz, d_6-DMSO) δ_F: −112.1 (ddt, *J* 14.4, 9.0, 5.6, Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, d_6-DMSO) δ_C: 56.2 (CO*C*H$_2$), 62.2 (diallyl-*C*(1)H$_2$), 62.4 (*C*(1)H$_2$), 115.6 (d, $^2J_{CF}$ 21.4, Ar*C*(3,5)H) + *C*(2)H), 123.0 (Ar*C*(2,6)H), 125.4 (Ar*C*(3,5)H), 125.6 (diallyl-*C*(3)H), 128.6 (diallyl-*C*(2)H), 129.6 (d, $^3J_{CF}$ 8.2, Ar*C*(2,6)H), 131.8 (d, $^4J_{CF}$ 3.1, Ar*C*(1)), 140.4 (*C*(3)H), 145.7 (Ar*C*(1)-O)), 153.7 (Ar*C*(4)-NO_2), 162.5 (d, $^1J_{CF}$ 247, Ar*C*(4)-F), 163.3 (*C*=O); HRMS (ESI$^+$) $C_{23}H_{24}O_4N_2F^+$ $[M]^+$ found: 411.1708, requires: 411.1715 (−1.6 ppm).

(E)-*N*,*N*-Diallyl-3-(4-bromophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 438



Following general procedure **P**: (*E*)-*N*,*N*-diallyl-3-(4-bromophenyl)prop-2-en-1-amine **529** (0.99 g, 3.39 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl bromoacetate (1.06 g, 4.06 mmol, 1.2 equiv.) in MeCN (4 mL) to give the title product as a white solid (1.12 g, 60%)

mp 126 °C (dec.); υ_{max} (film, cm^{-1}): 2943, 1771, 1591, 1526, 1487, 1450, 1346, 1198, 1167, 1142, 939, 883; ^{1}H NMR (500 MHz, d_6-DMSO) δ_H: 4.26 (4H, d, *J* 7.3, diallyl-C(1)H_2), 4.35 (2H, d, *J* 7.4, C(1)H_2), 4.73 (2H, s, COCH_2), 5.68-5.85 (4H, m, diallyl-C(3)H_2), 6.12-6.31 (2H, m, diallyl-C(2)*H*), 6.63 (1H, dt, *J* 15.5, 7.4, C(2)*H*), 6.99 (1H, d, *J* 15.5, C(3)*H*), 7.49 (2H, d, *J* 9.1, Ar(2,6)*H*), 7.55-7.66 (4H, m,

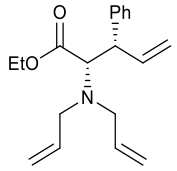
Ar(2,3,5,6)*H*), 8.36 (2H, d, *J* 9.1, Ar(3,5)*H*); $^{13}C\{^{1}H\}$ $\{^{1}H\}$ NMR (126 MHz, d_6-DMSO) δ_C: 56.2 (CO*C*H_2), 62.3 (*C*(1)H_2), 62.3 (diallyl-*C*(1)H_2), 116.8 (*C*(2)H), 122.4 (Ar*C*(4)-Br), 123.0 (Ar*C*(2,6)H), 125.4 (Ar*C*(3,5)H), 125.6 (diallyl-*C*(3)H_2), 128.7 (diallyl-*C*(2)H), 129.5 (Ar*C*(2,6)H), 131.7 (Ar*C*(3,5)H), 134.4 (C(3)Ar*C*(1)), 140.2 (*C*(3)H), 145.7 (Ar*C*(1)-O), 153.7 (Ar*C*(4)-NO_2), 163.3 (*C*=O); HRMS (ESI^+) $C_{23}H_{24}O_4N_{279}Br^+$ $[M]^+$ found: 471.0904, requires: 471.0914 (−2.1 ppm).

[2,3]-Rearrangement Products

General Procedure Q: Catalytic Asymmetric [2,3]-Rearrangement of *N*,*N* diallyl ammonium salts and subsequent nucleophilic quench

A flame dried Schlenk flask was charged with solution of (+)-BTM (0.2 equiv.), HOBt (1.0 equiv.), *i*Pr_2NH (1.4 equiv.) and MeCN (0.07 M) and cooled to −20 °C and stirred for 5 mins. The solution was treated with the requisite ammonium salt (1.0 equiv.) and stirred for a further 16 h, after which the corresponding nucleophile (2.0 – 5.0 equiv.) was added and the reaction allowed to warm to rt and stirred for the time stated. The reaction was quenched with aq. 1 M NaOH (equal volume) and extracted with CH_2Cl_2 (3 × equal volume). The combined organic layers were washed with aq. 1 M NaOH (2 × equal volume), brine (equal volume), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was analysed by ^{1}H NMR to determine *dr*, then purified by flash column chromatography to give the rearranged product.

Ethyl (2*S*,3*S*)-2-(diallylamino)-3-phenylpent-4-enoate 426

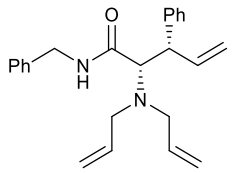


Following general procedure **Q**, (*E*)-*N*,*N*-diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **425** (1.0 g, 2.11 mmol, 1.0 equiv.) was reacted with (+)-BTM (107 mg, 0.42 mmol, 0.2 equiv.), HOBt (285 mg, 2.11 mmol, 1.0 equiv.) and *i*Pr_2NH (413 µL, 2.95 mmol, 1.4 equiv.) in MeCN (30 mL), then quenched with NaOEt (1 M in EtOH, 10.55 mL, 10.55 mmol, 5.0 equiv.) and stirred for a further 24 h at rt. Crude *dr* >95:5. The residue purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to give the title product (479 mg, 76%, >95:5 *dr*) as a colourless oil;

HPLC analysis, Chiralpak AD-H (0.5% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 3.2 min, Minor 3.7 min, 97% ee;

$[\alpha]_D^{20}$+18.8 (*c* 1, $CHCl_3$); ν_{max} (film, cm^{-1}): 2980, 1726, 1640, 1445, 1417, 1246, 1152, 995, 916;^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.33 (3H, t, *J* 7.1, OCH_2CH_3), 2.83 (2H, dd, *J* 14.5,8.3, NCH^AH^B), 3.37 (2H, ddt, *J* 14.5, 4.1, 1.9, NCH^AH^B), 3.76-3.85 (2H, m, C(2)*H* + C(3)*H*), 4.14-4.30 (2H, OCH_2CH_3), 4.88-5.16 (6H, m, C(5)H_2 + diallyl-C(3)H_2), 5.34-5.37 (2H, m, diallyl-C(2)*H*), 5.92 (1H, dddd, *J* 17.1, 10.2, 7.0, 0.9, C(4)*H*), 7.13-7.19 (2H, m, Ar*H*), 7.20-7.26 (1H, m, Ar*H*), 7.26-7.35 (2H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (179 MHz, $CDCl_3$) δ_C: 14.7 (OCH_2CH_3), 50.4 (*C*(3)H), 53.2 (NCH_2), 60.1 (OCH_2CH_3), 65.4 (*C*(2)H), 116.7 (*C*(5)H_2), 117.2 (diallyl-*C*(3)H_2), 126.5 (Ar*C*(4)H), 128.3 (Ar*C*(2,6)H), 128.5 (Ar*C*(3,5)H), 128.5 (Ar*C*(2,6)H), 136.4 (diallyl-*C*(2)H), 138.7 (*C*(4)H), 141.0 (Ar*C*(1)), 171.5 (*C*=O); HRMS (ESI$^+$) $C_{19}H_{26}O_2N^+$ $[M+H]^+$ found: 300.1948, requires: 300.1958 (−3.4 ppm).

(2*S*,3*S*)-*N*-benzyl-2-(diallylamino)-3-phenylpent-4-enamide 431

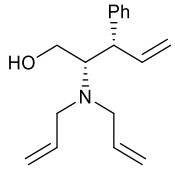


Following general procedure **Q**, (*E*)-*N*,*N*-diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **425** (114 mg, 0.24 mmol, 1.0 equiv.) was reacted with (+)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (6.4 mg, 0.048 mmol, 0.2 equiv.) and *i*Pr_2NH (47 µL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL), then quenched with $BnNH_2$ (131 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h. Crude *dr* 93:7. The residue purified by flash column chromatography on silica gel (0→2% Et_2O/CH_2Cl_2) to give the title product (85 mg, 98%, 92:8 *dr*) as a colourless oil;

HPLC analysis, Chiralpak OJ-H (5% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 6.2 min, Minor 5.2 min, 84% ee;

$[\alpha]_D^{20}$+53.1 (*c* 1.0, $CHCl_3$); ν_{max} (film, cm^{-1}): 3296, 2928, 1631, 1506, 1452, 1334, 1246, 1120, 912; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.92 (2H, dd, *J* 14.6, 8.0, NC*H*^{A}H^B), 3.38-3.46 (2H, m, NCH^A*H*^{B}), 3.51 (1H, d, *J* 9.9, C(2)*H*), 3.94-4.02 (1H, m, C(3)*H*), 4.51 (2H, dd, *J* 5.6, 2.9, PhCH_2), 4.93-5.16 (6H, m, C(5)H_2 + diallyl-CH_2), 5.45 (2H, dddd, *J* 16.8, 10.5, 8.0, 4.4, diallyl-C(1)*H*), 5.95-6.06 (2H, m, C(4)*H* + N*H*), 7.14-7.34 (10H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ_C: 43.4 (Ph*C*H_2), 49.7 (*C*(3)H), 53.5 (diallyl-*C*(1)H_2), 66.7 (*C*(2)H), 117.0 (*C*(5)H_2 + diallyl-*C*(3)H_2), 126.4 (C(3)Ar(*C*(4)H), 127.7 (Ar(*C*(4)H), 128.2 (C(3)Ar(*C*(2,6)H), 128.3 (Ar(*C*(2,6)*H*), 128.6 (C(3)Ar(*C*(3,5)H), 128.8 (Ar(*C*(3,5)H), 137.1 (diallyl-*C*(2)H), 138.4 (C(3)Ar*C*(1)), 139.0 (*C*(4)H), 141.5 (Ar(*C*(1)), 170.2 (*C*=O); HRMS (NSI^+) $C_{24}H_{29}N_2O^+$ $[M+H]^+$ found: 361.2277, requires 361.2274 (+0.7 ppm).

(2*S*,3*S*)-2-(Diallylamino)-3-phenylpent-4-en-1-ol 430



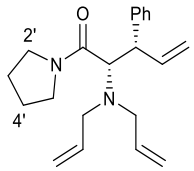
Following general procedure **Q** with slight modification (*E*)-*N*,*N*-diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **425** (114 mg, 0.24 mmol, 1.0 equiv.) was reacted with (+)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (32 mg, 0.24 mmol, 1.0 equiv.) and *i*Pr_2NH (47 µL, 0.34 mmol, 1.4 equiv.) in MeCN, then concentrated *in vacuo* and the solvent switched to THF (3.5 mL, 2 cycles). The solution was cooled to 0 °C and treated with $LiAlH_4$ (1.0 M in THF, 0.48 mL, 0.48 mmol, 2.0 equiv.) dropwise. The reaction was stirred for 1 h, quenched by the addition of aq. 1 M KOH (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with aq. 1

M KOH (2 × 10 mL), dried over $MgSO_4$ then concentrated *in vacuo*. Crude *dr* >95:5. The residue was purified by flash coloumn chromatography on silica gel (0→10% Et_2O/CH_2Cl_2) to give the title product (54 mg, 88%, >95:5 *dr*) as a colourless oil

HPLC analysis, Chiralpak OJ-H (0.5% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 5.5 min, Minor 4.5 min, 96% ee;

$[\alpha]_D^{20}$+27.3 (*c* 1.0, $CHCl_3$); ν_{max} (film, cm^{-1}) 3420, 2924, 1601, 1415, 1265, 1045, 991, 914; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.70 (2H, dd, *J* 14.1, 8.0, NC*H*^{A}H^B), 3.23 (2H, ddt, *J* 14.1, 4.4, 1.7, NCH^A*H*^{B}), 3.30 (1H, app. t, *J* 10.0, C*H*^{A}H^{B}OH), 3.37 (1H, td, *J* 9.5, 9.0, 4.1, C(2)*H*), 3.47 (1H, t, *J* 9.5, C(3)*H*), 3.63 (1H, dd, *J* 10.0, 4.1, CH^A*H*^{B}OH), 4.84-5.11 (6H, m, diallyl-C(3)H_2 + C(5)H_2), 5.64 (2H, dddd, 17.2, 10.2, 8.0, 4.8, diallyl-C(2)*H*), 5.79-6.01 (1H, m, C(4)*H*), 7.21-7.34 (5H, m, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C: 51.4 (*C*(3)H), 52.6 (diallyl-*C*(1)H_2), 60.3 (*C*(1)H_2), 62.2 (*C*(2)H), 115.8 (*C*(5)H_2), 117.4 (diallyl-*C*(3)H_2), 126.9 (Ar*C*(4)H), 128.2 (Ar*C*(2,6)H), 128.8 (Ar*C*(3,5)H), 137.0 (diallyl-*C*(2)H), 138.9 (*C*(4)H), 143.0 (Ar*C*(1)); HRMS (NSI$^+$) $C_{17}H_{24}NO^+$ $[M+H]^+$ found: 258.1853, requires 258.1852 (+0.2 ppm).

(2*S*,3*S*)-2-(Diallylamino)-3-phenyl-1-(pyrrolidin-1-yl)pent-4-en-1-one 430



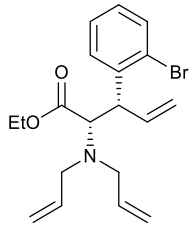
Following general procedure **Q**, (*E*)-*N*,*N*-diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide **425** (114 mg, 0.24 mmol, 1.0 equiv.) was reacted with (+)-BTM (12 mg, 0.048 mmol, 0.2 equiv.), HOBt (32 mg, 0.24 mmol, 1.0 equiv.) and *i*Pr_2NH (47 µL, 0.34 mmol, 1.4 equiv.) in MeCN (3.5 mL), then quenched with pyyrolidine (100 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h at rt. Crude *dr* >95:5. The residue purified by flash column chromatography on silica gel (0→5% Et_2O/CH_2Cl_2) to give the title product (68 mg, 87%, >95:5 *dr*) as a colourless oil;

HPLC analysis, Chiralpak AD-H (5% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 3.8 min, Minor 5.9 min, 98% ee;

$[\alpha]_D^{20}$ +134.0 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 2974, 1629, 1429, 1420, 1157, 991; ^{1}H NMR (700 MHz, $CDCl_3$) δ_H: 1.76-1.93 (4H, m, C(3′ + 4′)H_2), 2.96 (2H, dd, *J* 15.1, 7.9, NC*H*^{A}H^B), 3.36-3.45 (3H, m, NCH^A*H*^{B} +C(2′)*H*^{A}H^B), 3.49 (2H, t, *J* 6.9, C(5′)H_2), 3.58 (1H, dt, *J* 9.8, 6.5, C(2′)H^A*H*^{B}), 3.82-3.98 (2H, m, C(2)*H* + C(3)*H*), 4.84-5.09 (6H, m, C(5)H_2 + diallyl-C(3)H_2), 5.41 (2H, dddd, *J* 17.1, 10.2, 7.9, 4.2, diallyl-C(2)*H*), 5.90 (1H, ddd, *J* 17.0, 10.1, 7.7, C(4)*H*), 7.21 (3H, tt, *J* 8.2, 1.5, Ar*H*), 7.30 (2H, dd, *J* 8.6, 6.6, Ar*H*); ^{13}C{^{1}H} NMR (179 MHz, $CDCl_3$) δ_C: 24.4 (*C*(4′)H_2), 26.4 (*C*(3′)H_2), 45.4 (*C*(5′)H_2), 51.3 (*C*(3)H), 53.3 (diallyl-*C*(1)H_2), 63.5 (*C*(2)H), 116.1 (diallyl-*C*(3)H_2), 116.9 (*C*(5)H_2), 126.4

(Ar*C*(4)H), 128.3 (Ar*C*(2,6)H), 128.8 (Ar*C*(3,5)H), 137.9 (diallyl-*C*(2)H), 138.7 (*C*(4)H), 141.4 (Ar*C*(1)), 171.0 (*C*=O); HRMS (ESI$^+$) $C_{21}H_{29}ON_2^+$ $[M+H]^+$ found: 325.2265, requires: 325.2274 (−2.9 ppm).

Ethyl (2*S*,3*S*)-3-(2-bromophenyl)-2-(diallylamino)pent-4-enoate 442

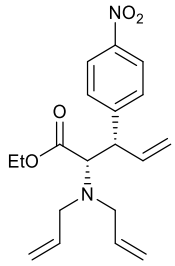


Following general procedure **Q**, (*E*)-*N*,*N*-diallyl-3-(2-bromophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **437** (0.3 g, 0.54 mmol, 1.0 equiv.) was reacted with (+)-BTM (27 mg, 0.11 mmol, 0.2 equiv.), HOBt (73 mg, 0.54 mmol, 1.0 equiv.) and *i*Pr$_2$NH (105 µL, 0.76 mmol, 1.4 equiv.) in MeCN (7.7 mL), then quenched with NaOEt (1 M in EtOH, 2.70 mL, 2.70 mmol, 5.0 equiv.) and stirred for a further 24 h at rt. Crude *dr* 92:8. The residue purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to give the title product (173 mg, 85%, 92:8 *dr*) as a colourless oil;

Enantiopurity determined after derivatisation to **532**, 92% ee;

$[\alpha]_D^{20}$ + 9.6 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 2980, 1728, 1638, 1472, 1244, 1177, 1153, 1020, 918; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.32 (3H, t, *J* 7.1, OCH_2CH_3), 2.79 2H, dd, *J* 14.4, 8.5, NCH^AH^B), 3.38 (2H, ddt, *J* 14.4, 4.0, 1.9, NCH^AH^B), 3.85 (1H, d, *J* 11.6, C(2)*H*), 4.14-4.29 (2H, m, OCH_2CH_3), 4.47 (1H, dd, *J* 11.6, 8.0, C(3)*H*), 4.93-5.17 (6H, m, C(5)H_2 + diallyl-C(3)H_2), 5.40 (2H, dddd, *J* 17.3, 11.3, 8.5, 4.0, diallyl-C(2)*H*), 5.75 (1H, ddd, *J* 17.6, 10.1, 8.0, C(4)*H*), 7.05 (1H, ddd, *J* 8.1, 7.2, 1.7, ArC(4)*H*), 7.15 (1H, dd, *J* 7.7, 1.7, ArC(5)*H*), 7.28 (1H, dd, *J* 7.7, 1.3, ArC(6)*H*), 7.53 (1H, dd, *J* 8.0, 1.3, ArC(3)*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.8 (OCH_2CH_3), 48.5 (*C*(3)H), 53.3 (NCH_2), 60.2 (OCH_2CH_3), 65.1 (*C*(2)H), 117.3 (diallyl-*C*(3)H_2), 117.6 (*C*(5)H_2), 125.3 (Ar*C*(2)-Br), 127.2 (Ar*C*(5)H, 127.8 (Ar*C*(4)H), 129.7 (Ar*C*(6)H, 132.9 (Ar*C*(3)H), 136.2 (diallyl-*C*(2)H), 137.3 (*C*(4)H), 139.8 (Ar*C*(1)), 171.2 (*C*=O); HRMS (ESI$^+$) $C_{19}H_{25}O_2NBr^+$ $[M+H]^+$ found: 378.1052,requires: 378.1063 (−3.0 ppm).

Ethyl (2*S*,3*S*)-2-(diallylamino)-3-(4-nitrophenyl)pent-4-enoate 441

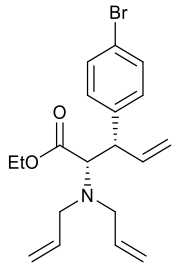


Following general procedure **Q**, (*E*)-*N*,*N*-diallyl-3-(4-nitrophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **436** (0.2 g, 0.39 mmol, 1.0 equiv.) was reacted with (+)-BTM (20 mg, 0.08 mmol, 0.2 equiv.), HOBt (53 mg, 0.39 mmol, 1.0 equiv.) and *i*Pr_2NH (76 µL, 0.55 mmol, 1.4 equiv.) in MeCN (5.6 mL), then quenched with NaOEt (1 M in EtOH, 1.95 mL, 1.95 mmol, 5.0 equiv.) and stirred for a further 24 h at rt. Crude *dr* 90:10. The residue purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to give the title product (92 mg, 69%, 90:10 *dr*) as a yellow oil;

Enantiopurity determined after derivatisation to **534**, 96% ee;

$[\alpha]_D^{20}$ +54.7 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 2980, 1724, 1518, 1343, 1155, 920, 854; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.34 (3H, t, *J* 7.1, OCH_2CH_3), 2.81 (2H, dd, *J* 14.4, 8.4, NCH^AH^B), 3.35 (2H, ddt, *J* 14.4, 4.0, 1.9, NCH^AH^B), 3.82 (1H, d, *J* 11.7, C(2)*H*), 3.98 (1H, dd, *J* 11.7, 7.9, C(3)*H*), 4.24 (2H, dddd, *J* 18.0, 10.8, 7.1, 3.7, OCH_2CH_3), 4.98-5.16 (6H, m, C(5)H_2 + diallyl-C(3)H_2), 5.36 (2H, dddd, *J* 16.9, 10.3, 8.3, 4.1, diallyl-C(2)*H*), 5.86 (1H, ddd, *J* 17.0, 10.3, 7.9, C(4)*H*), 7.33 (2H, d, *J* 8.8, Ar(2,6)*H*), 8.19 (2H, d, *J* 8.8, Ar(3,5)*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.7 (OCH_2CH_3), 50.1 (*C*(3)H), 53.1 (NCH_2), 60.4 (OCH_2CH_3), 64.9 (*C*(2)H), 117.9 (diallyl-*C*(3)H_2), 118.2 (*C*(5)H_2), 123.6 (Ar*C*(3,5)H), 129.4 (Ar*C*(2,6)H), 135.6 (diallyl-*C*(2)H), 137.1 (*C*(4)H), 146.7 (Ar*C*(1)), 149.1 (Ar*C*(4)-NO_2), 170.6 (*C*=O); HRMS (ESI^+) $C_{19}H_{25}O_4N_2^+$ $[M+H]^+$ found: 345.1802, requires: 345.1809 (−2.0 ppm).

Ethyl (2*S*,3*S*)-3-(4-bromophenyl)-2-(diallylamino)pent-4-enoate 443



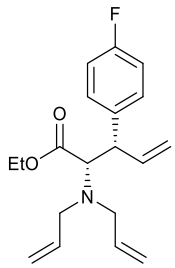
Following general procedure **Q**, (*E*)-*N*,*N*-diallyl-3-(4-bromophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **438** (400 mg, 0.73 mmol, 1.0 equiv.) was reacted with (+)-

BTM (37 mg, 0.15 mmol, 0.2 equiv.), HOBt (99 mg, 0.73 mmol, 1.0 equiv.) and *i*Pr_2NH (142 µL, 1.02 mmol, 1.4 equiv.) in MeCN (10.4 mL), then quenched with NaOEt (1 M in EtOH, 3.65 mL, 3.65 mmol, 5.0 equiv.) and stirred for a further 24 h at rt. Crude *dr* 90:10. The residue purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to give the title product (213 mg, 77%, 91:9 *dr*) as a yellow oil;

HPLC analysis, Chiralpak AD-H (0.5% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 3.2 min, Minor 3.9 min, 96% ee;

$[\alpha]_D^{20}$ +40.5 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 2980, 1726, 1489, 1173, 1153, 1011, 918; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.30 (3H, t, *J* 7.1, OCH_2CH_3), 2.79 (2H, dd, *J* 14.4, 8.4, NCH^AH^B), 3.33 (2H, ddt, *J* 14.4, 4.1, 1.9, NCH^AH^B), 3.67-3.81 (2H, m, C(2)*H* + C(3)*H*), 4.13-4.26 (2H, m, OCH_2CH_3), 4.96-5.09 (6H, m, C(5)H_2 + diallyl-C(3)H_2), 5.38 (2H, dddd, *J* 16.5, 10.8, 8.4, 4.1, diallyl-C(2)*H*), 5.83 (1H, ddd, *J* 17.0, 10.2, 7.7, C(4)*H*), 7.02 (2H, d, *J* 8.4, Ar(2,6)*H*), 7.41 (2H, d, *J* 8.4, Ar(3,5)*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.7 (OCH_2CH_3), 49.7 (*C*(3)H), 53.1 (NCH_2), 60.2 (OCH_2CH_3), 65.1 (*C*(2)H), 117.1 (*C*(5)H_2), 117.5 (diallyl-*C*(3)H_2), 120.0 (Ar*C*-Br), 130.3 (Ar*C*(2,6)H), 131.3 (Ar*C*(3,5)H), 136.1 (diallyl-*C*(2)H), 138.1 (*C*(4)H), 140.1 (Ar*C*(1)), 171.2 (*C*=O); HRMS (ESI^+) $C_{19}H_{25}O_2NBr^+$ $[M+H]^+$ found: 378.1054, requires: 378.1063 (−2.4 ppm).

Ethyl (2*S*,3*S*)-2-(diallylamino)-3-(4-fluorophenyl)pent-4-enoate 440



Following general procedure **Q**, (*E*)-*N*,*N*-diallyl-3-(4-nitrophenyl)-*N*-(2-(4-fluorophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide **435** (400 mg, 0.82 mmol, 1.0 equiv.) was reacted with (+)-BTM (40 mg, 0.16 mmol, 0.2 equiv.), HOBt (111 mg, 0.82 mmol, 1.0 equiv.) and *i*Pr_2NH (160 µL, 1.15 mmol, 1.4 equiv.) in MeCN (12 mL), then quenched with NaOEt (1 M in EtOH, 4.10 mL, 4.10 mmol, 5.0 equiv.) and stirred for a further 24 h at rt. Crude *dr* 94:6. The residue purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to give the title product (222 mg, 85%, 95:5 *dr*) as a colourless oil;

HPLC analysis, Chiralpak AD-H (0.5% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 3.3 min, Minor 4.3 min, 96% ee;

$[\alpha]_D^{20}$ +14.8 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 2980, 1726, 1508, 1223, 1157, 918, 829; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.30 (3H, t, *J* 7.1, OCH_2CH_3), 2.79 (2H, dd, *J* 14.5, 8.3, NCH^AH^B), 3.34 (2H, ddt, *J*

14.5, 4.0, 1.9, NCH^{A}*H*^{B}), 3.65-3.84 (2H, m, C(2)*H* + C(3)*H*), 4.09-4.34 (2H, m, OC*H*$_2$CH$_3$), 4.86-5.14 (6H, m, C(5)*H*$_2$ + diallyl-C(3)*H*$_2$), 5.26-5.50 (2H, m, diallyl-C(2)*H*), 5.85 (1H, ddd, *J* 17.1, 10.2, 7.6, C(4)*H*), 6.98 (2H, t, *J* 8.7, Ar(3,5)*H*), 7.09 (2H, ddt, 8.3, 5.2, 2.5, Ar(2,6)*H*); ^{19}F{^{1}H} NMR (272 MHz, $CDCl_3$) δ_F: −116.9 (Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 14.7 (OCH$_2$*C*H$_3$), 49.5 (*C*(3)H), 53.1 (N*C*H$_2$), 60.2 (O*C*H$_2$CH$_3$), 65.3 (*C*(2)H), 115.1 (d, $^{2}J_{CF}$ 21.2, Ar*C*(3,5)H), 116.8 (*C*(5)H$_2$), 117.4 (diallyl-*C*(3)H$_2$), 129.9 (d, $^{3}J_{CF}$ 7.8, Ar*C*(2,6)H), 136.2 (diallyl-*C*(2)H), 136.7 (d, $^{4}J_{CF}$ 3.2, Ar*C*(1)), 138.5 (*C*(4)H), 161.6 (d, $^{1}J_{CF}$ 244, Ar*C*-F), 171.3 (*C*=O); HRMS (ESI$^+$) $C_{19}H_{25}O_2NF^+$ $[M+H]^+$ found: 318.1854, requires: 318.1864 (−3.1 ppm).

Deallylation of Products

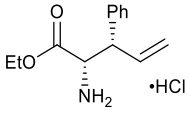
General Procedure **R**: Bis-deallylation of α-*N*,*N* diallyl amino esters

A flamed dried Schlenk tube was charged with $Pd(dba)_2$ (0.1 equiv.), dppb (0.1 equiv.) and thiosalicyclic acid (5.0 equiv.) under Ar. A solution of *N*,*N* diallyl amino ester (1.0 equiv.) in degassed THF (0.1 M) was added and the resulting mixture heated to 60 °C under Ar for 3 h. Once complete the reaction was cooled to rt and aq. 1 M HCl and EtOAc added, the layers separated and the aqueous layer washed with EtOAc (2 × equal volume). The aqueous layer was then concentrated *in vacuo* to give the pure α-amino ester hydrochloride salt.

General Procedure **S**: *N*-Boc protection of α-amino ester hydrochloride salts

A solution of α-amino ester hydrochloride salt (1.0 equiv.) in CH_2Cl_2 (0.07 M) was treated with NEt_3 (3.0 equiv.) and Boc_2O (5.0 equiv.) and stirred for 16 h at room temperature. The resulting mixture was concentrated *in vacuo*, dissolved in MeOH (3 × equal volume) and treated with 4-DMAP (0.1 equiv.) and stirred for 3 h. Once complete the solution was concentrated *in vacuo*, dissolved in EtOAc (5 × equal volume) washed with aq. 1 M HCl (equal volume) and brine (equal volume), dried over $MgSO_4$ and concentrated *in vacuo* to give the *N*-Boc α-amino ester.

Ethyl (2S,3S)-2-amino-3-phenylpent-4-enoate hydrochloride 444



Following general procedure **R**, $Pd(dba)_2$ (19 mg, 0.033 mmol, 0.1 equiv), dppb (14 mg, 0.033 mmol, 0.1 equiv.), thiosalicyclic acid (254 mg, 1.65 mmol, 5.0 equiv.) and ethyl (2*S*,3*S*)-2-(diallylamino)-3-phenylpent-4-enoate **426** (100 mg, 0.33 mmol, 1.0 equiv.) were reacted in THF (3.3 mL) to give the title product as a colourless gum (65 mg, 77%, >95:5 dr).

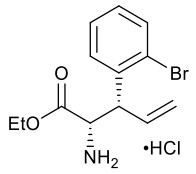
The corresponding free amine was prepared for HPLC analysis by dissolution in HPLC *i*PrOH and filtration through a pipette plug of K_2CO_3.

HPLC analysis, Chiralpak AS-H (5% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 3.5 min, Minor 4.0 min, 94% ee;

$[\alpha]_D^{20}$+59.2 (*c* 1, MeOH); υ_{max} (film, cm^{-1}): 3375, 2870, 1736, 1587, 1495, 1219, 1043, 993, 858; ^{1}H NMR (400 MHz, d_4-MeOH) δ_H: 1.24 (3H, t, *J* 7.1, OCH_2CH_3), 3.88 (1H, t, *J* 8.4, C(3)*H*), 4.23 (2H, q, *J* 7.1, OCH_2CH_3), 4.36 (1H, d, *J* 8.4, C(2)*H*), 5.20-5.33 (2H, m, C(5)H_2), 6.13 (1H, ddd, *J* 17.2, 9.9, 9.1, C(4)*H*), 7.28-7.47 (5H, m, Ar*H*); ^{13}C{^{1}H} (126 MHz, d_4-MeOH) δ_C: 14.3 (OCH_2CH_3), 52.9 (*C*(3)H), 58.0 (*C*(2)H), 63.4 (OCH_2CH_3), 119.9 (*C*(5)H), 129.2 (Ar*C*(4)H), 129.2 (Ar*C*(3,5)H), 1303

(Ar*C*(2,6)H), 136.1 (*C*(4)H), 138.7 (Ar*C*(1)), 169.4 (*C*=O); HRMS (ESI$^+$) $C_{13}H_{18}O_2N^+$ [M]$^+$ found: 220.1327, requires: 220.1332 (−2.3 ppm).

Ethyl (2*S*,3*S*)-2-amino-3-(2-bromophenyl)pent-4-enoate hydrochloride 446

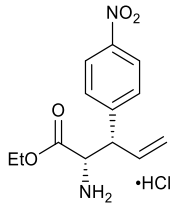


Following general procedure **R**, $Pd(dba)_2$ (16 mg, 0.027 mmol, 0.1 equiv), dppb (12 mg, 0.027 mmol, 0.1 equiv.), thiosalicyclic acid (203 mg, 1.32 mmol, 5.0 equiv.) and ethyl (2*S*,3*S*)-3-(2-bromophenyl)-2-(diallylamino)pent-4-enoate **442** (100 mg, 0.27 mmol, 1.0 equiv., 93:7 dr) were reacted in THF (2.7 mL) to give the title product as a colourless gum (44 mg, 49%, 93:7 dr).

Enantiopurity determined after derivatisation to **532**, 92% ee;

$[\alpha]_D^{20}$ +23.1 (*c* 1, MeOH); υ_{max} (film, cm^{-1}): 3350, 2982, 1736, 1470, 1242, 1219, 1022, 939, 854;^{1}H NMR (500 MHz, d_4-MeOH) δ_H: 1.17 (3H, t, *J* 7.2, OCH_2CH_3), 4.19 (2H, qd, *J* 7.2, 4.2, OCH_2CH_3), 4.36 (1H, dd, *J* 9.4, 7.2, C(3)*H*), 4.47 (1H, d, *J* 7.2, C(2)*H*), 5.29-5.43 (2H, m, C(5)H_2), 6.13 (1H, ddd, *J* 16.7, 10.2, 9.4, C(4)*H*), 7.26 (1H, ddd, *J* 8.0, 5.0, 4.0, Ar(5)*H*), 7.42 (1H, dd, *J* 4.0, 0.7, Ar(4)*H*), 7.68 (1H, dt, *J* 8.0, 0.9, Ar(6)*H*); ^{13}C{^{1}H} NMR (179 MHz, d_4-MeOH) δ_C: 14.2 (OCH_2CH_3), 51.5 (*C*(3)H), 56.3 (*C*(2)H), 63.6 (OCH_2CH_3), 121.9 (*C*(5)H_2), 125.4 (Ar*C*(2)-Br), 129.4 (Ar*C*(5)H), 130.7 (Ar*C*(4)H), 130.8 (Ar*C*(6)H), 133.9 (Ar*C*(3)H), 134.8 (*C*(4)H), 138.0 (Ar*C*(1)), 169.0 (*C*=O); HRMS (ESI$^+$) $C_{13}H_{17}O_2N^{79}Br^+$ [M]$^+$ found: 298.0434, requires: 298.0437 (−1.1 ppm).

Ethyl (2*S*,3*S*)-2-amino-3-(4-nitrophenyl)pent-4-enoate hydrochloride 447



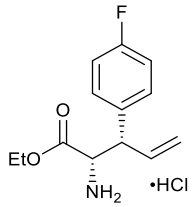
Following general procedure **R**, $Pd(dba)_2$ (8.4 mg, 0.015 mmol, 0.1 equiv), dppb (6.4 mg, 0.015 mmol, 0.1 equiv.), thiosalicyclic acid (116 mg, 0.75 mmol, 5.0 equiv.) and ethyl (2*S*,3*S*)-3-(4-nitrophenyl)-2-(diallylamino)pent-4-enoate **441** (50 mg, 0.15 mmol, 1.0 equiv., 90:10 dr) were reacted in THF (1.5 mL) to give the title product as a colourless gum (24 mg, 53%, 88:12 dr)

Enantiopurity determined after derivatisation to **534**, 96% ee;

$[\alpha]_D^{20}$ +93.6 (*c* 0.25, MeOH); υ_{max} (film, cm^{-1}): 3377, 2905, 1740, 1520, 1346, 1225, 1111, 1014, 852; ^{1}H NMR (500 MHz, d_4-MeOH) δ_H: 1.24 (3H, t, *J* 7.1, OCH_2CH_3), 3.99-4.08 (1H, m, C(3)*H*), 4.25 (2H,

q, *J* 7.1, OC*H*$_2$CH$_3$), 4.51 (1H, d, *J* 7.9, C(2)*H*), 5.24-5.40 (2H, m, C(5)*H*$_2$), 6.14 (1H, ddd, *J* 16.7, 103, 9.2, C(4)*H*), 7.64 (2H, d, *J* 8.7, Ar(2,6)*H*), 8.28 (2H, d, *J* 8.7 Ar(3,5)*H*); ^{13}C{^{1}H} NMR (126 MHz, *d*$_4$-MeOH) δ_C: 14.3 (OCH$_2$*C*H$_3$), 52.5 (*C*(3)H), 57.6 (*C*(2)H), 63.7 (O*C*H$_2$CH$_3$), 121.5 (*C*(5)H$_2$), 125.2 (Ar*C*(2,6)H), 130.6 (Ar*C*(3,5)H), 134.6 (*C*(4)H), 146.4 (Ar*C*(1)), 149.1 (Ar*C*(4)-NO$_2$), 169.0 (*C*=O); HRMS (ESI$^+$) $C_{13}H_{17}O_4N_2^+$ [M]$^+$ found: 265.1176, requires: 265.1183 (−2.6 pm).

Ethyl (2*S*,3*S*)-2-amino-3-(4-fluorophenyl)pent-4-enoate hydrochloride 445

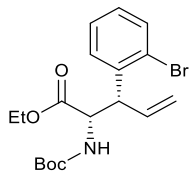


Following general procedure **R**, Pd(dba)$_2$ (9.2 mg, 0.016 mmol, 0.1 equiv), dppb (12.8 mg, 0.016 mmol, 0.1 equiv.), thiosalicyclic acid (122 mg, 0.75 mmol, 5.0 equiv.) and ethyl (2*S*,3*S*)-3-(4-fluorophenyl)-2-(diallylamino)pent-4-enoate **440** (50 mg, 0.16 mmol, 1.0 equiv., 94:6 dr) were reacted in THF (1.5 mL) to give the title product as a oily yellow solid (46 mg, quant., 92:8 dr);

Enantiopurity determined after derivatisation to **533**, 94% ee;

$[\alpha]_D^{20}$ +40.8 (*c* 1, CHCl$_3$); υ_{max} (film, cm^{-1}): 3397, 2864, 1736, 1603, 1508, 1223, 1014, 934, 836;^{1}H NMR (400 MHz, *d*$_4$-MeOH) δ_H: 1.26 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 3.86 (1H, t, *J* 8.4, C(3)*H*), 4.24 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 4.35 (1H, d, *J* 8.4, C(2)*H*), 5.21-5.31 (2H, m, C(5)*H*$_2$), 6.11 (1H, ddd, *J* 16.8, 10.3, 9.0, C(4)*H*), 7.14 (2H, t, *J* 8.8, Ar(3,5)*H*), 7.38 (2H, dd, *J* 8.8, 5.2, Ar(2,6)*H*); ^{19}F{^{1}H} NMR (376, *d*$_4$-MeOH) δ_F: −116.2 (Ar*F*); ^{13}C{^{1}H} NMR (126 MHz, *d*$_4$-MeOH) δ_C: 14.3 (OCH$_2$*C*H$_3$), 52.2 (*C*(3)H), 58.0 (*C*(2)H), 63.5 (O*C*H$_2$CH$_3$), 117.1 (d, $^2J_{CF}$ 21.8, Ar*C*(3,5)H), 120.0 (*C*(5)H$_2$), 131.2 (d, $^3J_{CF}$ 8.2, Ar*C*(2,6)H), 134.8 (d, $^4J_{CF}$ 3.3, Ar*C*(1)), 135.9 (*C*(4)H), 163.9 (d, $^1J_{CF}$ 246, Ar*C*(4)-F), 169.4 (*C*=O); HRMS (ESI$^+$) $C_{13}H_{17}O_2NF^+$ [M]$^+$ found: 238.1232, requires: 238.1238 (−2.5 ppm).

Ethyl (2*S*,3*S*)-3-(2-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)pent-4-enoate 532

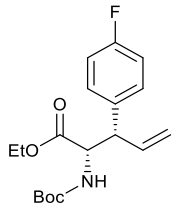


Following general procedure **S** ethyl (2*S*,3*S*)-2-amino-3-(2-bromophenyl)pent-4-enoate hydrochloride **446** (48 mg, 0.14 mmol, 1.0 equiv.), NEt$_3$ (58 µL, 0.42 mmol, 3.0 equiv.) and Boc$_2$O (153 mg, 0.7 mmol, 5.0 equiv.) were reacted in CH$_2$Cl$_2$ (2 mL) to give the title product as a yellow oil (40 mg, 72%, 88:12 dr);

HPLC analysis, Chiralpak AD-H (2% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 12.4 min, Minor 9.4 min, 92% ee;

$[\alpha]_D^{20}$ +38.4 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 3345, 2930, 1717, 1506, 1368, 1161, 1022, 930; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.20 (3H, t, *J* 7.1, OCH_2CH_3), 1.33 (9H, s, $C(CH_3)_3$), 4.06-4.18 (2H, m, OCH_2CH_3), 4.26 (1H, t, *J* 8.9, C(3)*H*), 4.68 (1H, t, *J* 8.9, C(2)*H*), 4.95 (1H, d, *J* 9.3, N*H*), 5.13-5.24 (2H, m, $C(5)H_2$), 6.01 (1H, ddd, *J* 16.9, 10.2, 8.6, C(4)*H*), 7.03-7.15 (1H, m, Ar*H*), 7.25-7.34 (2H, m, Ar*H*), 7.56 (1H, d, *J* 8.0, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.1 (OCH_2CH_3), 28.2 ($C(CH_3)_3$), 51.2 (*C*(3)H), 56.8 (*C*(2)H), 61.2 (OCH_2CH_3), 80.0 ($C(CH_3)_3$), 118.6 ($C(5)H_2$), 125.1 (Ar*C*(2)-Br), 127.6 (Ar*C*(5)H), 128.6 (Ar*C*(4)H), 129.2 (Ar*C*(6)H), 133.1 (Ar*C*(3)H), 135.5 (*C*(4)H), 138.4 (Ar*C*(1)), 154.9 (N*C*=O), 171.5 (*C*=O); HRMS (ESI^+) $C_{18}H_{24}O_4NBrNa^+$ $[M+Na]^+$ found: 420.0773, requires: 420.0781 (−1.9 ppm).

Ethyl (2*S*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-fluorophenyl)pent-4-enoate 533

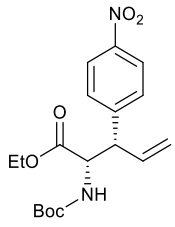


Following general procedure **S** ethyl (2*S*,3*S*)-2-amino-3-(4-fluorophenyl)pent-4-enoate hydrochloride **445** (46 mg, 0.16 mmol, 1.0 equiv.), NEt_3 (67 µL, 0.48 mmol, 3.0 equiv.) and Boc_2O (174 mg, 0.8 mmol, 5.0 equiv.) were reacted in CH_2Cl_2 (2.3 mL) to give the title product as a colourless oil (24 mg, 45%, >95:5 dr);

HPLC analysis, Chiralpak AD-H (5% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 7.4 min, Minor 5.6 min, 94% ee;

$[\alpha]_D^{20}$ +44.7 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 3367, 2980, 2929, 1715, 1510, 1357, 1224, 1161, 1024, 835; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 1.23 (3H, *J* 7.1, OCH_2CH_3), 1.40 (9H, s, $C(CH_3)_3$), 3.79 (1H, t, *J* 7.5, C(3)*H*), 4.14 (2H, qd, *J* 7.1, 1.1, OCH_2CH_3), 4.59-4.71 (1H, m, C(2)*H*), 4.88 (1H, d, *J* 9.2, N*H*), 5.11-5.27 (2H, m, $C(5)H_2$), 6.07 (1H, ddd, *J* 16.9, 10.3, 8.3, C(4)*H*), 7.03 (2H, t, *J* 8.7, Ar(3,5)*H*), 7.19 (2H, dd, *J* 8.7, 5.4, Ar(2,6)*H*); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ_F: −115.5 (Ar*F*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (OCH_2CH_3), 28.4 ($C(CH_3)_3$), 51.8 (*C*(3)H), 57.5 (*C*(2)H), 61.4 (OCH_2CH_3), 80.2 ($C(CH_3)_3$), 115.6 (d, $^2J_{CF}$ 21.3, Ar*C*(3,5)H), 118.0 ($C(5)H_2$), 130.0 (d, $^3J_{CF}$ 7.9, Ar*C*(2,6)H), 134.8 (d, $^3J_{CF}$ 2.4, Ar*C*(1)), 136.4 (*C*(4)H), 155.3 (N*C*=O), 162.1 (d, $^1J_{CF}$ 246, Ar*C*(4)-F), 171.5 (*C*=O); HRMS (ESI^+) $C_{18}H_{24}O_4NFNa^+$ $[M+Na]^+$ found: 360.1575, requires: 360.1582 (−1.8 ppm).

Ethyl (2*S*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-nitrophenyl)pent-4-enoate 534

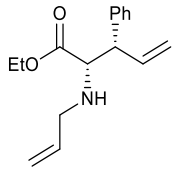


Following general procedure **S** ethyl (2*S*,3*S*)-2-amino-3-(4-nitrophenyl)pent-4-enoate hydrochloride **447** (24 mg, 0.08 mmol, 1.0 equiv.), NEt_3 (33 µL, 0.24 mmol, 3.0 equiv.) and Boc_2O (87 mg, 0.40 mmol, 5.0 equiv.) were reacted in CH_2Cl_2 (1.1 mL) to give the title product as a colourless oil (22 mg, 76%);

HPLC analysis, Chiralpak IB (1% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 10.0 min, Minor 8.7 min, 96% ee;

$[\alpha]_D^{20}$ +52.7 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 3360, 2980, 1736, 1715, 1522, 1346, 1163, 1024, 855;^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.21 (3H, t, *J* 7.1, OCH_2CH_3), 1.37 (9H, s, $C(CH_3)_3$), 3.88 (1H, t, *J* 7.8, C(3)*H*), 4.13 (2H, qd, *J* 7.1, 1.3, OCH_2CH_3), 4.71 (1H, t, *J* 7.8, C(2)*H*), 4.96 (1H, d, *J* 9.2, N*H*), 5.10-5.33 (2H, m, $C(5)H_2$), 6.05 (1H, ddd, *J* 16.9, 10.2, 8.5, C(4)*H*), 7.41 (2H, d, *J* 8.6, Ar(2,6)*H*), 8.18 (2H, d, *J* 8.6, Ar(3,5)*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (OCH_2CH_3), 28.3 ($C(CH_3)_3$), 52.8 (*C*(3)H), 57.4 (*C*(2)H), 61.7 (OCH_2CH_3), 80.5 ($C(CH_3)_3$), 119.5 ($C(5)H_2$), 123.8 (Ar*C*(2,6)H), 129.4 (Ar*C*(3,5)H), 134.9 (*C*(4)H), 147.1 (Ar*C*(1)), 147.2 (Ar*C*(4)-NO_2), 155.2 (N*C*=O), 171.0 (*C*=O); HRMS (ESI^+) $C_{18}H_{24}O_6N_2Na^+$ $[M+Na]^+$ found: 387.1521, requires: 387.1532 (−1.4 ppm).

Ethyl (2*S*,3*S*)-2-(allylamino)-3-phenylpent-4-enoate 456

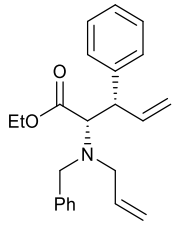


A flame dried two-necked flask was charged with $Pd(dba)_2$ (58 mg, 0.1 mmol, 0.1 equiv.), dppb (43 mg, 0.1 mmol, 0.1 equiv.) and thiosalicylic acid (184 mg, 1.2 mmol, 1.2 equiv.). A solution of ethyl (2*S*,3*S*)-2-(diallylamino)-3-phenylpent-4-enoate **426** (300 mg, 1.0 mmol, 1.0 equiv.) in degassed THF (10 mL) was added *via* cannula. The resulting solution was heated at reflux for 16 h, once complete the reaction was cooled to rt and treated with aq. 1 M HCl (30 mL) and EtOAc (30 mL). The layer separated and the organic layer extracted with aq. 1 M HCl (2 × 20 mL). The combined aqueous layers were basified to ~pH 14 with aq. 2 M NaOH, then extracted with EtOAc (5 × 50 mL), the organics combined, washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by

flash column chromatography (5% EtOAc/PE) to give the title product as a colourless oil (118 mg, 46%).

$[\alpha]_D^{20}$ +56.9 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 3335, 2980, 1728, 1640, 1454, 1178, 1152, 1024, 993, 918; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.21 (3H, t, *J* 7.1, OCH_2CH_3), 3.05 (1H, ddt, *J* 14.0, 6.5, 1.4, NCH^AH^B), 3.23 (1H, ddt, *J* 14.0, 5.6, 1.4, NCH^AH^B), 3.57-3.65 (2H, m, C(2)*H* + C(3)*H*), 4.13 (2H, qd, *J* 7.1, 3.8, OCH_2CH_3), 5.01-5.19 (4H, m, C(5)H_2 + NCH_2CHCH_2), 5.74 (1H, dddd, *J* 16.9, 10.2, 6.5, 5.7, NCH_2CH), 6.03-6.17 (1H, m, C(4)*H*), 7.19-7.25 (3H, m, Ar*H*), 7.27-7.33 (2H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.3 (OCH_2CH_3), 50.9 (NCH_2), 53.6 (*C*(3)H), 60.7 (OCH_2CH_3), 65.3 (*C*(2)H), 116.9 (*C*(5)H), 117.2 (NCH_2CHCH_2), 127.1 (Ar*C*(4)H), 128.2 (Ar*C*(2,6)H), 128.7 (Ar*C*(3,5)H), 136.2 (NCH_2CH), 137.6 (*C*(4)H), 140.3 (Ar*C*(1)), 173.9 (*C*=O); HRMS (ESI^+) $C_{16}H_{22}O_2N^+$ $[M+H]^+$ found: 260.1638, requires: 260.1645 (−2.7 ppm).

Ethyl (2*S*,3*S*)-2-(allyl(benzyl)amino)-3-phenylpent-4-enoate 457

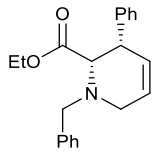


A solution of ethyl (2*S*,3*S*)-2-(allylamino)-3-phenylpent-4-enoate **456** (202 mg, 0.78 mmol, 1.0 equiv.) in MeCN (11.2 mL), was treated with K_2CO_3 (215 mg, 1.56 mmol, 2.0 equiv.), KI (26 mg, 0.156 mmol, 0.2 equiv.), and benzyl bromide (140 µL, 1.17 mmol, 1.5 equiv.), the resulting solution was heated to reflux for 16 h. Once complete the reaction was cooled to rt, and aq. 1 M NaOH (20 mL) and CH_2Cl_2 (20 mL), the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (1→10% EtOAc/PE) to give the title product as a colourless oil (233 mg, 86%, 94:6 dr).

$[\alpha]_D^{20}$ −6.1 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 2978, 1726, 1495, 1454, 1248, 1173, 1153, 1136, 1028, 970; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.35 (3H, t, *J* 7.1, OCH_2CH_3), 2.82 (1H, dd, *J* 14.2, 8.7, NCH^AH^B), 3.27 (1H, d, *J* 14.1, $PhCH^AH^B$), 3.31 (1H, ddt, *J* 14.2, 4.0, 1.9, NCH^AH^B), 3.73 (1H, d, *J* 11.6, C(2)*H*), 3.86 (1H, dd, *J* 11.6, 8.1, C(3)*H*), 3.95 (1H, d, *J* 14.1, $PhCH^AH^B$), 4.18-4.32 (2H, m, OCH_2CH_3), 4.94-5.11 (4H, m, C(5)H_2 + NCH_2CHCH_2), 5.47 (1H, dddd, *J* 17.0, 10.3, 8.7, 4.0, NCH_2CH), 5.83 (1H, ddd, *J* 17.0, 10.2, 8.1, C(4)*H*), 6.69-6.84 (2H, m, Ar*H*), 7.03-7.08 (2H, m, Ar*H*), 7.10-7.18 (3H, m, Ar*H*), 7.22-7.32 (3H, m, Ar*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.8 (OCH_2CH_3), 50.3 (*C*(3)H), 53.4 (NCH_2), 54.0 ($PhCH_2$), 60.1 (OCH_2CH_3), 65.1 (*C*(2)H), 116.7 (*C*(5)H_2), 117.7 (NCH_2CHCH_2), 126.6 (Ar*C*H), 126.8 (Ar*C*H), 128.0 (Ar*C*H), 128.4 (Ar*C*H), 128.7 (Ar*C*H), 128.9 (Ar*C*H), 136.2 (NCH_2CH),

138.7 (*C*(4)H), 139.3 (C(3)Ar*C*(1)), 140.7 (Ar*C*(1)), 171.3 (*C*=O); HRMS (ESI$^+$) $C_{23}H_{28}O_2N^+$ $[M+H]^+$ found: 350.2106, requires: 350.2115 (−2.4 ppm).

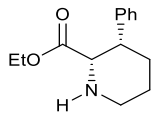
Ethyl (2*S*,3*S*)-1-benzyl-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate 458



A two-neck flask equipped with a reflux condenser with charged with *p*-TsOH (191 mg, 1.01 mmol, 1.5 equiv.) followed by a solution of ethyl (2*S*,3*S*)-2-(allyl(benzyl)amino)-3-phenylpent-4-enoate **457** (233 mg, 0.67 mmol, 1.0 equiv., 94:6 dr) in degassed PhMe (67 mL), the solution was heated to 80 °C and stirred until full dissolution. After which the reaction was treated with Hoveyda-Grubbs 2nd generation catalyst (21 mg, 0.034 mmol, 5 mol%) and the reaction mixture stirred at 80 °C for 16 h. Once complete by TLC, the reaction was cooled to rt and concentrated *in vacuo*, CH_2Cl_2 (50 mL) and aq. 1 M NaOH (50 mL) were added the layers separated and the aqueous layer extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (50 mL) dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by Biotage® Isolera™ 4 [SNAP Ultra 10 g, 36 mL/min, PE:EtOAc (99:1 1 CV, 99:1 → 90:10 10 CV, 80:20 2 CV)] to give the title product as a yellow oil (161 mg, 75%, 92:8 dr);

$[\alpha]_D^{20}$ −127.1 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 2978, 1728, 1493, 1452, 1177, 1144, 1029, 845; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.81 (3H, t, *J* 7.1, OCH_2CH_3), 3.26 (1H, ddt, *J* 17.0, 4.4, 2.4, C(6)H^AH^B), 3.57 (1H, ddt, *J* 17.0, 3.8, 2.4, C(6)H^AH^B), 3.62-3.81 (4H, m, OCH_2CH_3 + C(3)*H* + PhCH^AH^B), 3.84, (1H, d, *J* 6.9, PhCH^AH^B), 4.00-4.08 (1H, m, C(2)*H*), 5.85 (1H, dq, *J* 10.2, 2.4, C(5)*H*), 5.99 (1H, ddt, *J* 10.2, 4.1, 2.5, C(4)*H*), 7.15-7.24 (3H, m, Ar*H*), 7.25-7.31 (3H, m, Ar*H*), 7.31-7.39 (4H, m, Ar*H*); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ_C: 13.9 (OCH_2CH_3), 44.1 (*C*(2)H), 48.6 (NCH_2), 59.5 ($PhCH_2$), 60.2 (OCH_2CH_3), 64.7 (*C*(3)H), 124.9 (*C*(5)H), 126.9 (*C*(4)H), 127.0 (Ar*C*(4)H), 127.4 (Ar*C*(4)H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 128.7 (Ar*C*H), 129.0 (Ar*C*H), 138.2 (Ar*C*(1)), 140.4 (Ar*C*(1)), 170.7 (*C*=O); HRMS (ESI$^+$) $C_{21}H_{24}O_2N^+$ $[M+H]^+$ found: 322.1795, requires: 322.1802 (−2.0 ppm).

Ethyl (2*S*,3*S*)-3-phenylpiperidine-2-carboxylate 459



A solution of ethyl (2*S*,3*S*)-1-benzyl-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate **458** (143 mg, 0.45 mmol, 1.0 equiv., 92:8 dr) in EtOAc (4.5 mL) was treated with AcOH (27 µL, 0.45 mmol, 1.0 equiv.) and Pd/C (47 mg, 10% wt., 0.045 mmol, 0.1 equiv.). The resulting suspension was degassed

with H_2 for 15 min, then left stirring under an atmosphere of H_2 (balloon, 1 atm) for 48 h at rt. The reaction was diluted with EtOAc (30 mL), filtered through Celite® (eluent EtOAc), washed with aq. sat. $NaHCO_3$ (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10→15% Et_2O/CH_2Cl_2) to give the product as a colourless oil (63 mg, 60%, >95:5 dr).

HPLC analysis, Chiralpak AS-H (1% IPA/hexane, flow rate 1.5 mL/min, 211 nm, 40 °C) t_R Major 3.7 min, Minor 3.4 min, 94% ee;

$[\alpha]_D^{20}$ +11.0 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1}): 3348, 2932, 1728, 1493, 14522, 1370, 1246, 1200, 1179, 1128, 1032, 862; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 0.94 (3H, t, *J* 7.1, OCH_2CH_3), 1.52 (1H, ddp, *J* 14.5, 7.3, 3.8, C(6)H^AH^B), 1.78 (1H, dddt, *J* 12.8, 9.0, 7.7, 3.7, C(6)H^AH^B), 1.89 (1H, ddt, *J* 13.2, 8.8, 4.3, C(5)H^AH^B), 1.98 (1H, br. s, N*H*), 2.11 (1H, dtd, *J* 13.6, 7.1, 3.7, C(5)H^AH^B), 2.82 (1H, ddd, *J* 11.6, 7.9, 3.6, C(4)H^AH^B), 3.20-3.34 (2H, m, C(3)*H* + C(4)H^AH^B), 3.82 (1H, d, *J* 4.5, C(2)*H*), 3.92 (2H, qd, *J* 7.1, 3.0, OCH_2CH_3), 7.12-7.21 (1H, m, Ar(4)*H*), 7.22-7.31 (2H, m, Ar(2,6)*H*), 7.40-7.48 (2H, m, Ar(3,5)*H*); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ_C: 14.0 (OCH_2CH_3), 23.3 (*C*(6)H_2), 28.9 (*C*(5)H_2), 42.2 (*C*(3)H), 44.5 (*C*(4)H_2), 60.3 (OCH_2CH_3), 61.5 (*C*(2)H), 126.3 (Ar*C*(4)H), 128.1 (Ar*C*(2,6)H), 128.7 (Ar*C*(3,5)H), 142.7 (Ar*C*(1)), 172.7 (*C*=O); HRMS (ESI^+) $C_{14}H_{20}O_2N^+$ [M+H] found: 234.1483, requires: 234.1489 (−2.4 ppm).

References

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