Accepted Manuscript

Isothiourea-catalysed chemo- and enantioselective [2,3]-sigmatropic rearrangements of *N*,*N*-diallyl allylic ammonium ylides

Thomas H. West, Stéphanie S.M. Spoehrle, Andrew D. Smith

PII: S0040-4020(17)30097-2

DOI: 10.1016/j.tet.2017.01.062

Reference: TET 28432

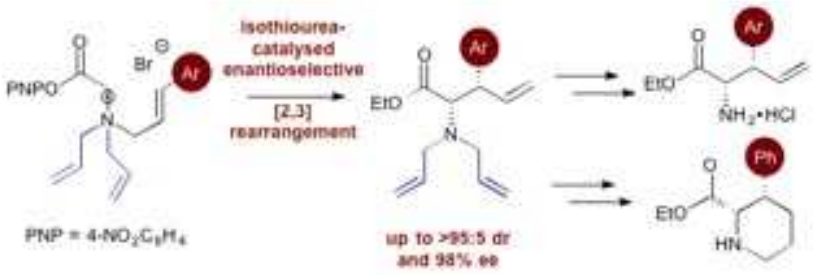
To appear in: *Tetrahedron*

Received Date: 25 August 2016

Revised Date: 5 December 2016

Accepted Date: 26 January 2017

Please cite this article as: West TH, Spoehrle SSM, Smith AD, Isothiourea-catalysed chemo- and enantioselective [2,3]-sigmatropic rearrangements of *N*,*N*-diallyl allylic ammonium ylides, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.01.062.



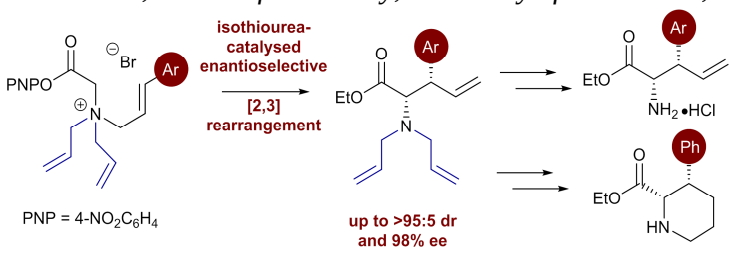
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Isothiourea-catalysed chemo- and enantioselective [2,3]-sigmatropic rearrangements of *N*,*N*-diallyl allylic ammonium ylides

Leave this area blank for abstract info.

Thomas H. West, Stéphanie S. M. Spoehrle and Andrew D. Smith
EaStCHEM, School of Chemistry, University of St Andrews, UK. KY16 9ST



Tetrahedron
journal homepage: www.elsevier.com

Isothiourea-catalysed chemo- and enantioselective [2,3]-sigmatropic rearrangements of *N*,*N*-diallyl allylic ammonium ylides

Thomas H. West, Stéphanie S. M. Spoehrle and Andrew D. Smith *

[a] *EaStCHEM, School of Chemistry, University of St Andrews, UK. KY16 9ST*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
[2,3]-rearrangement
Isothiourea catalysis
allylic ammonium ylides
enantioselective catalysis
α-amino esters

ABSTRACT

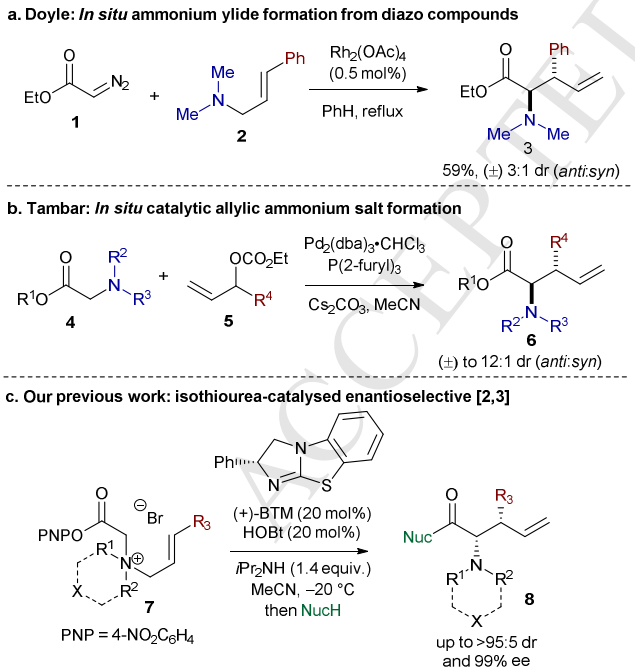
The isothiourea-catalysed chemo- and enantioselective [2,3]-sigmatropic rearrangement of *N*,*N*-diallyl allylic ammonium ylides is explored as a key part of a route to free functionalised α-amino esters and piperidines. The [2,3]-sigmatropic rearrangement proceeds with excellent diastereo- and enantiocontrol (>95:5 dr, up to 97% ee), with the resultant *N*,*N*-diallyl α-amino esters undergoing either *mono*- or *bis*-*N*-allyl deprotection. *Bis*-*N*-allyl deprotection leads to free α-amino esters, while the mono-deprotection strategy has been utilised in the synthesis of a target functionalised piperidine.

* Corresponding author. Tel.: +44 (0)1334 463896; e-mail: ads10@st-andrews.ac.uk

1. Introduction

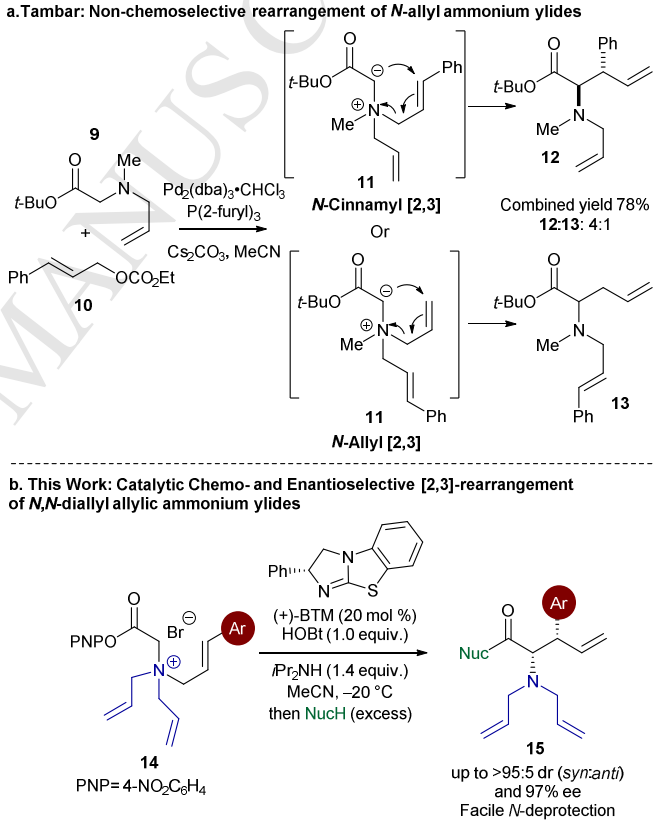
[2,3]-Sigmatropic rearrangements are concerted symmetry allowed processes that proceed through a five-membered, six-electron transition state with an envelope conformation. Stereoselective [2,3]-sigmatropic rearrangements have found great utility in organic synthesis,[1] with their ability to form carbon-carbon bonds through well-defined and predictable transition states under often mild reaction conditions making them attractive for the synthesis of highly functionalised molecular building blocks.[2]

In this context, the [2,3]-rearrangement of allylic ammonium ylides leads to the formation of substituted α-amino acid derivatives. Initially investigated by Ollis,[3] only limited variants of this process that use a sub-stoichiometric amount of a catalyst in the formation of the reactive ylide have been explored to date.[1e] The most common approach utilizes an intermediate metal carbenoid to generate the reactive ylide intermediate as shown by Doyle (Scheme 1a),[4] yet catalytic enantioselective variants have remained elusive.[1b] In 2011, Tambar and co-workers[5] reported an alternative strategy in the catalytic [2,3]-rearrangements of allylic ammonium ylides through Pd-catalysed allylic substitution of allylic carbonates **5** with tertiary amino esters **4** and *in situ* rearrangement (Scheme 1b). This process generates functionalized α-amino esters **6** with high diastereocontrol but in racemic form.[5] Building upon this work, we demonstrated an isothiourea-promoted[6,7] catalytic enantioselective [2,3]-rearrangement of allylic ammonium ylides, leading to a range of α-amino acid derivatives **8** bearing either *N*,*N*-dimethyl or cyclic-*N*-alkyl substituents (Scheme 1c).[8] This process allows for the synthesis of a variety of α-amino ester derivatives and the incorporation of pharmacological relevant amine motifs such as the morpholine unit, although the preparation of free α-amino esters was not possible as suitable *N*-substituents amenable to facile deprotection were not incorporated.



Scheme 1: Catalytic stereoselective [2,3]-rearrangements of allylic ammonium ylides

In this manuscript this limitation is addressed through the application of this methodology to *N*-substituents amenable to either *mono*- or *bis*-*N*-deprotection. At the onset of these investigations, the use of *N*,*N*-dibenzyl, *N*-methyl-*N*-allyl-, and *N*,*N*-diallyl substituents were considered to allow *N*-deprotection under standard laboratory conditions. Sweeney and Coldham have independently utilized *N*,*N*-diallyl groups in the synthesis of α-amino acids, via base mediated [2,3]-rearrangement and subsequent *N*-deprotection.[9] Notable previous work by Tambar has shown that treatment of *N*-methyl-*N*-allyl amine **9** with cinnamyl carbonate **10** in the presence of $Pd_2(dba)_3 \cdot CHCl_3$, P(2-furyl)$_3$ and Cs_2CO_3 gave ammonium ylide **11**, bearing a stereogenic nitrogen.[5] [2,3]-Rearrangement of ammonium ylide **11** proceeded through the *N*-cinnamyl unit and the *N*-allyl unit, resulting in non-chemoselective [2,3]-rearrangement to give a 4:1 mixture of *N*-cinnamyl rearranged product **12** and *N*-allyl rearranged product **13** in a combined 78% yield (Scheme 2a).[5] We report herein that isothiourea-mediated catalysis of *N*,*N*-diallyl allylic ammonium ylides proceeds chemoselectively, generating *N*,*N*-diallyl amino esters **15** with high diastereo- and enantiocontrol that can be readily *bis*-deprotected to generate free α-amino esters (Scheme 2b). *Mono*-*N*-allyl deprotection, followed by metathesis, leads to valuable piperidine building blocks.



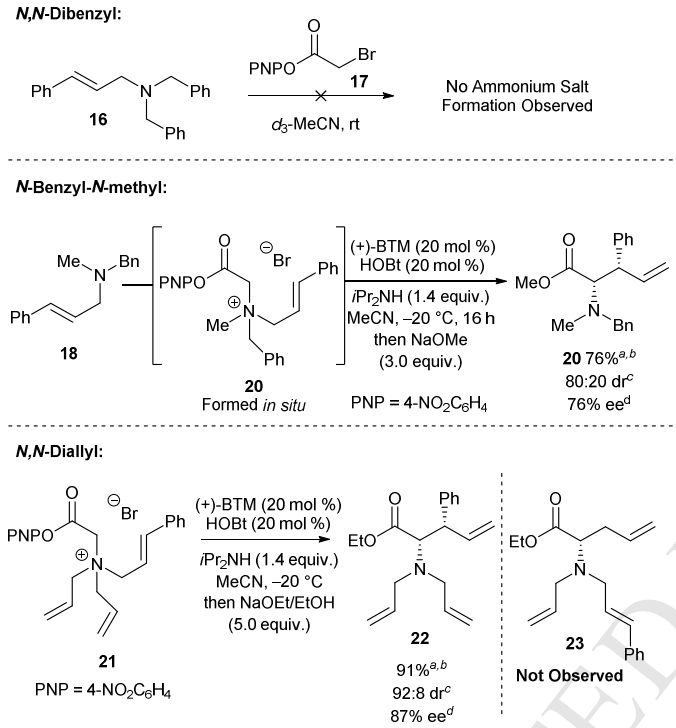
Scheme 2: Proposed chemoselective [2,3]-rearrangement of *N*,*N*-diallyl allylic ammonium ylides.

2. Results and Discussion

Initial Studies and Optimisation

To avoid any potential chemoselectivity issues initial studies probed the use of *N*,*N*-dibenzyl substituents in the isothiourea-catalysed [2,3]-rearrangement methodology. Treatment of *N*,*N*-dibenzyl cinnamyl amine **16** with 4-nitrophenyl bromoacetate **17** resulted in no ammonium salt formation, presumably due to the sterically hindered *N*,*N*-dibenzyl substituent. To reduce the steric bulk around the *N*-substituent, an *N*-methyl-*N*-benzyl substitution was employed **18**. While the corresponding ammonium salt could not be isolated, *in situ* ammonium salt formation and subsequent [2,3]-rearrangement gave, after treatment with sodium methoxide, *N*-methyl-*N*-benzyl-α-amino ester **20** in good yield

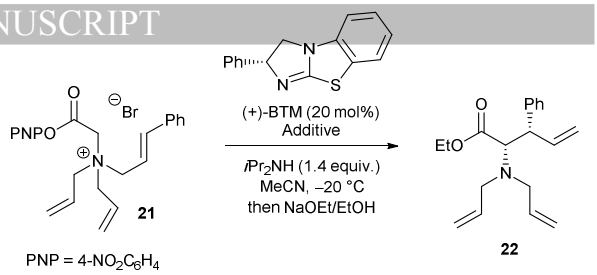
(76%) but modest stereocontrol (80:20 dr, 76% ee). The modest stereocontrol is likely to be due to the formation of a stereogenic nitrogen within the presumed ammonium salt and (+)-BTM bound-diastereoisomeric ammonium ylides within the [2,3]-rearrangement step. Due to the low sterecontrol achieved with an unsymmetrical *N*,*N*-substituent, symmetrical *N*,*N*-diallyl substitution was investigated. Treatment of *N*,*N*-diallyl cinnamyl amine with 4-nitrophenyl bromoacetate **17** gave the corresponding quaternary ammonium salt **21** in 50% isolated yield (Scheme 3). Isothiourea-promoted rearrangement of **21**, followed by addition of sodium ethoxide, resulted in chemoselective [2,3]-rearrangement to give *N*,*N*-diallyl-α-amino ester **22** in excellent yield (91%) and good stereocontrol (92:8 dr, 87% ee).



[a]Isolated yield, [b]Isolated as a mixture of diastereoisomers, [c]Determined by ^{1}H NMR analysis of crude material, [d]Determined by HPLC analysis on chiral stationary phase.

Scheme 3: Evaluation of alternative *N*-substituents.

Further optimisation was performed to improve the stereocontrol of the process (Table 1). The requirement for the HOBt co-catalyst was examined, with rearrangement in the absence of HOBt resulting in reduced product yield and stereocontrol (81%, 89:11 dr, 76% ee, *entry 2*, *table 1*). 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 3*). However, the use of stoichiometric HOBt as an additive resulted in a dramatic enhancement in enantiocontrol (82%, 94:6 dr, 97% ee, *entry 4*, *table 1*). In this process, we postulate that HOBt aids catalyst turnover from an acyl ammonium intermediate after [2,3]-rearrangement, although the reason for enhanced enantiocontrol is not clear and is the subject of ongoing mechanistic investigations. These optimized conditions were taken forward to examine the substrate scope of the reaction. Notably this process could be readily performed on a reasonable laboratory scale without erosion of stereocontrol, with 479 mg (1.60 mmol) of ethyl ester **22** (76% isolated yield) being generated from 1.0 g of *N*,*N*-diallyl ammonium salt **21** (entry 5).



Entry[a]	Additive (mol%)	Yield(%)[b]	dr[c]	ee (%)[d]
1	HOBt (20)	91	92:8	87
2	-	81	89:11	76
3	NBu_4OPNP (100)	77	88:12	74
4	HOBt (100)	82	94:6	97
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 on chiral stationary phase, [e]Performed on 2.11 mmol scale.

Table 1: Reaction additive optimization.

The relative and absolute configuration within **22** was assigned by analogy to that previously unambiguously determined on an *N*,*N*-dimethyl substituted analogue. This configurational outcome is consistent with a Lewis base mediated mechanism involving enantioselective [2,3]-rearrangement that occurs through a BTM-bound intermediate ylide **24** via an *endo*-type pre-transition state assembly such as **25**. In this arrangement the carbonyl oxygen preferentially adopts a coplanar and *syn*-orientation to the S atom within the isothiouronium ion, allowing a stabilizing electrostatic or non-bonding O-S interaction (n_O to $\sigma^*_{C\text{-}S}$).[10,11] The stereodirecting *C*(2)-phenyl unit within BTM adopts a pseudoaxial position to minimize 1,2-steric interactions, with rearrangement occurring *anti* to this substituent. A π-cation interaction between the allylic *C*(3)-phenyl substituent and the acyl ammonium ion provides an additional interaction that is essential for high stereocontrol (Figure 1).

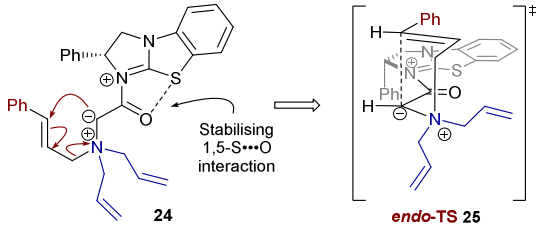
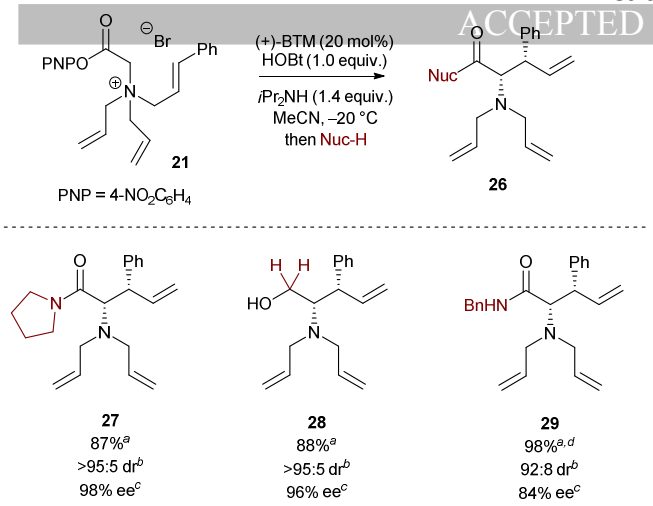


Figure 1: Stereochemical Rationale.

Reaction Scope and N,N-diallyl deprotection

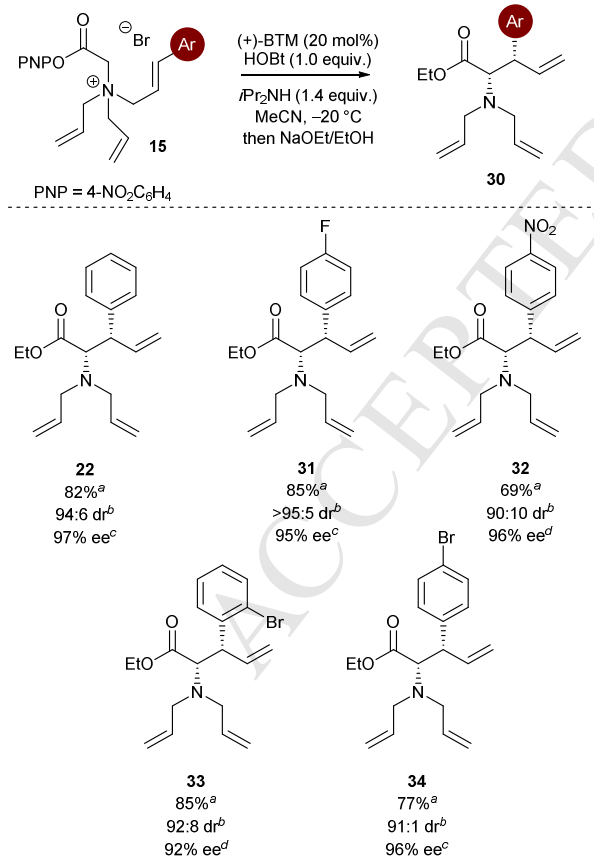
With these optimised conditions in hand, the scope of *in situ* nucleophilic derivatization was examined. The [2,3]-rearrangement of *N*,*N*-diallyl ammonium salt **21** could be derivatised *in situ* using pyrrolidine or $LiAlH_4$ to give amide **27** and amino-alcohol **28** respectively in excellent yield and stereocontrol (*Scheme 4*). However, using 100 mol% HOBt in the catalysis followed by derivatization with benzylamine to give **29**, produced inseparable unidentified allyl-derived side products. However, the use of a catalytic amount of HOBt (20 mol %) allowed the isolation of benzyl amide **29** in excellent yield with good levels of stereocontrol (92:8 dr, 84% ee).



[a]Isolated yield after flash column chromatography, combined yield of mixture of diastereomers [b]Determined by ^{1}H NMR of crude material, [c]Determined by HPLC analysis on chiral stationary phase [d]Reaction performed using HOBt (20 mol%).

Scheme 4: Scope of *in situ* nucleophilic derivatization.

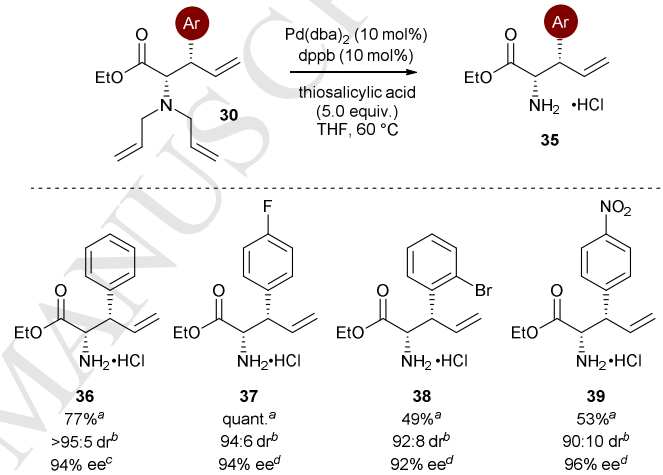
Variation of the C(3)-substituent within the *N*,*N*-diallyl ammonium salt **15** was next investigated. Electron-neutral and electron-withdrawing aromatic substituents could be well tolerated giving ethyl esters **31**, **32** and **34** in excellent yield and good to excellent stereocontrol. Incorporation of a sterically demanding *ortho*-substituent in the C(3)-aryl group was well tolerated giving **33** in good yield and stereocontrol (*Scheme 5*).



[a]Isolated yield after flash column chromatography, combined yield of mixture of diastereomers [b]Determined by ^{1}H NMR of crude material, [c]Determined by HPLC analysis on chiral stationary phase, [d]Enantiopurity determined after *N*,*N*-deallylation and *N*-Boc protection.

Scheme 5: Scope of C(3)-substituent. [a]Enantiopurity determined after *N*,*N*-deallylation and *N*-Boc protection.

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 deallylation chemistry developed by Bernard and co-workers[12] treatment of **22** with $Pd(dba)_2$ (10 mol%), dppb (1,4 bis(diphenylphosphino)butane) (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 **36** as its hydrochloride salt,[13] in excellent yield and without erosion of stereochemical purity, without the need for flash column chromatography. This was applied to a small range of *N*,*N*-diallyl rearrangement products **31**-**33** giving the desired deallylation products **37**-**39** in good to excellent yield without erosion of diastereo- or enantiopurity (Scheme 6).[14] The relative and absolute configurations of the *bis*-deallylated products was confirmed through derivatization of **36** to the known corresponding *N*-acetamide.[15]



[a]Isolated yield, [b]Determined by ^{1}H NMR analysis, [c]Determined by HPLC analysis on chiral stationary phase after filtration through K_2CO_3 plug, [d]Determined by HPLC analysis on chiral stationary phase after *N*-Boc protection.

Scheme 6: Scope of *N*,*N*-deallylation of [2,3]-rearrangement products, [a]Enantiopurity determined after *N*-Boc protection.

Application to piperidine synthesis

To further demonstrate the synthetic utility of this [2,3]-rearrangement process, it was postulated that a highly functionalised piperdine architecture could be accessed through selective *mono*-*N*-allyl deprotection, followed by ring-closing metathesis and hydrogenation. Piperidine core structures are ubiquitous among bioactive molecules,[16] with an analysis of launched drugs within the integrity database showing 320 registered drugs that contain piperidines.[17] For example, the piperidine motif is central to Merck's factor XIa inhibitor **40**.[18] To showcase the utility of this [2,3]-rearrangement methodology we next targeted the preparation of the (2*S*,3*S*)-piperidine 2-carboxylate **41** that maps directly to this core structure.

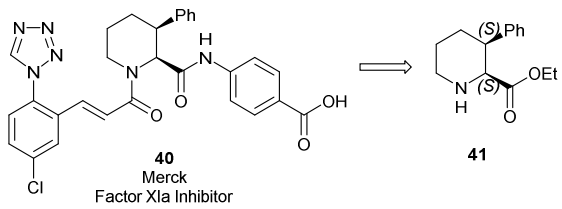
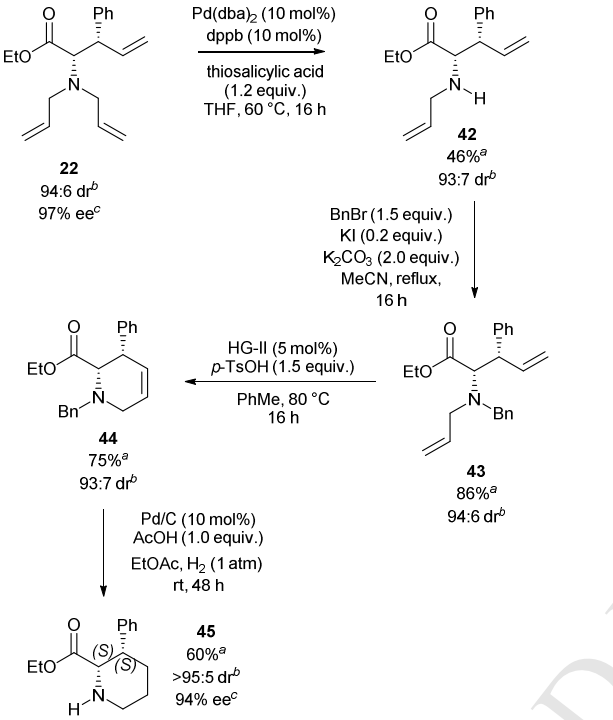


Figure 2: Merck Factor XIa inhibitor and target (2*S*,3*S*)-piperidine 2-carboxylate **41**

Mono-deallylation of **22** following Bernard's methodology,[12] through treatment with $Pd(dba)_2$ (10 mol %), dppb (10 mol %), thiosalicylic acid (1.2 equiv.) in THF at 60 °C, gave **42** in modest yield (46% yield) but with retention of diastereomeric purity. Subsequent *N*-benzyl protection to give **43**, followed by treatment with Hoveyda-Grubbs 2nd generation catalyst (HG-II) (5 mol%) in the presence of *p*-toluenesulfonic acid[19] (1.5 equiv.) in toluene at 80 °C gave ring-closed product **44** in good yield and as a single diastereoisomer after purification. Finally, treatment of **44** with Pd/C and H_2 resulted in hydrogenation and hydrogenolysis to give functionalised piperidine **45** in good yield and with excellent levels of stereocontrol (>95:5 dr, 94% ee).



[a]Isolated yield, [b]Determined by ^{1}H NMR analysis after flash coloumn chromatography, [c]Determined by HPLC analysis on chiral stationary phase.

Scheme 7: *Mono*-*N*-deallylation and synthesis of a target functionalized (2*S*,3*S*) piperidine motif.

3. Conclusions

The isothiourea-catalysed enantioselective [2,3]-rearrangement of *N*,*N*-diallyl cinnamic ammonium ylides proceeds chemoselectivity and with excellent enantioselectivity. The use of stoichiometric HOBt allowed excellent levels of diastereo- and enantiocontrol to be achieved (up to >95:5 dr, up to 97% ee). The substrate scope of this process has been examined across a small number of different aryl and nucleophile variations. The *N*,*N*-diallyl substituents can be readily removed to generate the parent free α-amino ester, and this methodology has been applied to the synthesis of a functionalised target piperdine motif.

4. Experimental Section

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. 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 (100 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 (100 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 triplets 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.

Isothiourea Catalysts; (+)-BTM and (±)-BTM were synthesised according to literature procedures.[20] Allylic Alcohols 4-nitrocinnamyl alcohol, 4-bromocinnamyl alcohol, 2-bromocinnamyl alcohol and 4-fluorocinnamyl alcohol were synthesised according to previously reported procedure.[6]

Authentic racemic samples of the [2,3]-rearrangement products **22**, **27**-**29** and **31**-**34** were synthesised using (±)-BTM.

(*E*)-*N*,*N*-Dibenzyl-3-phenylprop-2-en-1-amine 16

A solution of *N*,*N*-dibenzylamine (6.1 mL, 31.7 mmol, 2.5 equiv.) in THF (12.5 mL) was treated dropwise with a solution of cinnamyl bromide (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) was added and 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.[21]

(*E*)-*N*-Benzyl-*N*-methyl-3-phenylprop-2-en-1-amine 18

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 (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.[22]

Methyl (2*S*,3*S*)-2-(benzyl(methyl)amino)-3-phenylpent-4-enoate 20

A solution of 4-nitrophenyl-2-bromoacetate (63 mg, 0.24 mmol, 1.0 equiv.) and (*E*)-*N*-Benzyl-*N*-methyl-3-phenylprop-2-en-1-amine (60 mg, 0.252 mmol, 1.05 equiv.) in MeCN (1.75 mL) was stirred for 24 h at rt, then cooled to −20 °C and a solution of (+)-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) was added and the reaction sitrred for 24 h at −20 °C, then quenched with NaOMe (1 M in MeOH, 0.72 mL, 0.72 mmol, 3.0 equiv.) and stirred at rt for 1 h. Aq. 1 M NaOH (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were washed with aq. 1 M NaOH (2 × 20 mL), then brine (20 mL), dried over $MgSO_4$ and concentration *in vacuo*. 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); 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, PhC*H*H), 3.70 (1H, d, *J* 11.8, C(2)*H*), 3.75 (1H, d, *J* 13.7, PhCH*H*), 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 (NCH_3), 50.2 (*C*(3)H), 51.0 (*C*(2)H), 58.2 (PhCH_2), 69.4 (OCH_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, PhC*H*H), 3.68 (1H, d, *J* 11.6, C(2)*H*)), 3.75 (1H, d, *J* 13.6 PhCH*H*), 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 (NCH_3), 49.6 (*C*(3)H), 50.8 (*C*(2)H), 58.3 (PhCH_2), 70.5 (OCH_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 (−2.6 ppm).

General Procedure A: 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 B: 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 46

A solution of cinnamyl bromide (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 rt 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; ^{1}H 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 (Ar*C*(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 47

Following general procedure **A**, 4-nitrocinnamyl alcohol (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%) was used without further purification; υ_{max} (film, cm^{-1}) 2978, 1595, 1512, 1339, 1109, 968, 918, 858; ^1H 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*); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) 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 (−2.7 ppm).

(*E*)-*N*,*N*-diallyl-3-(4-bromophenyl)prop-2-en-1-amine 48

Following general procedure **A**, 4-bromocinnamyl alcohol (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%) was used without further purification; υ_{max} (film, cm^{-1}) 2976, 1487, 1400, 1072, 1009, 968, 918; ^1H 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*); $^{13}C\{^1H\}$ 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 (−2.4 ppm).

(*E*)-*N*,*N*-diallyl-3-(2-bromophenyl)prop-2-en-1-amine 49

Following general procedure **A**, 2-bromocinnamyl alcohol (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%) was used without further purification; υ_{max} (film, cm^{-1}) 2976, 1643, 1466, 1435, 1256, 1113, 1047, 1022, 966, 918; ^1H 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*); $^{13}C\{^1H\}$ 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 (−2.4 ppm).

(*E*)-*N*,*N*-diallyl-3-(4-fluorophenyl)prop-2-en-1-amine 50

Following general procedure **A**, 4-fluorocinnamyl alcohol (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) was used without further purification; υ_{max} (film, cm^{-1}) 2918, 2803, 1603, 1508, 1227, 1157, 1119, 966, 917, 841; ^1H 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*); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ_F −114.9 (Ar*F*); $^{13}C\{^1H\}$ 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 (−3.5 ppm).

(*E*)-*N*,*N*-Diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide 21

Following general procedure **B**: (*E*)-*N*,*N*-diallyl-3-(phenyl)prop-2-en-1-amine (5.0 g, 23.47 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl bromoacetate (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; ^1H 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*); $^{13}C\{^1H\}$ NMR (126 MHz, d_6-DMSO) δ_C 56.2 (CO*C*H_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 51

Following general procedure **B**: (*E*)-*N*,*N*-diallyl-3-(4-nitrophenyl)prop-2-en-1-amine (1.0 g, 3.88 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl bromoacetate (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}) 2945, 1773, 1593, 1516, 1452, 1343, 1197, 1167, 1069, 1012, 951, 880; ^1H 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), 4.77 (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*); $^{13}C\{^1H\}$ 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 (−2.1 ppm).

(*E*)-*N*,*N*-Diallyl-3-(2-bromophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 52

Following general procedure **B**: (*E*)-*N*,*N*-diallyl-3-(2-bromophenyl)prop-2-en-1-amine (1.1 g, 3.77 mmol, 1.0 equiv.) was reacted with 4-nitrophenyl bromoacetate (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 53

Following general procedure **B**: (*E*)-*N*,*N*-diallyl-3-(4-fluorophenyl)prop-2-en-1-amine (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 (−1.7 ppm).

(E)-*N*,*N*-Diallyl-3-(4-bromophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide 54

Following general procedure **B**: (*E*)-*N*,*N*-diallyl-3-(4-bromophenyl)prop-2-en-1-amine (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} 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 C: Catalytic asymmetric [2,3]-rearrangement of *N*,*N*-diallyl ammonium salts and subsequent nucleophilic quench

A flame dried Schlenk flask was charged with a 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 22

Following general procedure **C**, (*E*)-*N*,*N*-diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide (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, 10.6 mL, 10.6 mmol, 5.0 equiv.) and stirred for a further 24 h at rt. Crude dr >95:5. The residue was 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, $CHCl_3$); υ_{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, NC*H*H), 3.37 (2H, ddt, *J* 14.5, 4.1, 1.9, NCH*H*), 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{^{1}H} 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 29

Following general procedure **C**, (*E*)-*N*,*N*-diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide (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 was 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, $CHCl_3$); υ_{max} (film, cm^{-1}) 3296, 2928, 1631, 1506, 1452, 1334, 1246, 1120, 912; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 2.92 (2H, dd, *J* 14.6, 8.0, NC*H*H), 3.38-3.46 (2H, m, NCH*H*), 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{^{1}H} 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 (+0.8 ppm).

(2*S*,3*S*)-2-(Diallylamino)-3-phenylpent-4-en-1-ol 28

Following general procedure **C**, with slight modification (*E*)-*N*,*N*-diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide (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, $CHCl_3$); υ_{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*H), 3.23 (2H, ddt, *J* 14.1, 4.4, 1.7, NCH*H*), 3.30 (1H, app. t, *J* 10.0, C*H*HOH), 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*H*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 (100 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 (+0.4 ppm).

(2*S*,3*S*)-2-(Diallylamino)-3-phenyl-1-(pyrrolidin-1-yl)pent-4-en-1-one 27

Following general procedure **C**, (*E*)-*N*,*N*-diallyl-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)-3-phenylprop-2-en-1-ammonium bromide (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 pyrrolidine (100 µL, 1.20 mmol, 5.0 equiv.) and stirred for a further 24 h at rt. Crude dr >95:5. The residue was 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*H), 3.36-3.45 (3H, m, NCH*H* +C(2′)*H*H), 3.49 (2H, t, *J* 6.9, C(5′)H_2), 3.58 (1H, dt, *J* 9.8, 6.5, C(2′)H*H*), 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 (−2.8 ppm).

Ethyl (2*S*,3*S*)-3-(2-bromophenyl)-2-(diallylamino)pent-4-enoate 33

Following general procedure **C**, (*E*)-*N*,*N*-diallyl-3-(2-bromophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide (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_2NH (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 was 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 **38** and *N*-Boc protection 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, NC*H*H), 3.38 (2H, ddt, *J* 14.4, 4.0, 1.9, NCH*H*), 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 (N*C*H_2), 60.2 (O*C*H_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 (−2.9 ppm).

Ethyl (2*S*,3*S*)-2-(diallylamino)-3-(4-nitrophenyl)pent-4-enoate 32

Following general procedure **C**, (*E*)-*N*,*N*-diallyl-3-(4-nitrophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide (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 was 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 **39** and *N*-Boc protection, 96% ee; $[\alpha]_D^{20}$ +54.7 (*c* 1, $CHCl_3$); υ_{max} (film, cm^{-1})

2980, 1724, 1518, 1343, 1155, 920, 854; ^{1}H 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, NC*H*H), 3.35 (2H, ddt, *J* 14.4, 4.0, 1.9, NCH*H*), 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{^{1}H} 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 34

Following general procedure **C**, (*E*)-*N*,*N*-diallyl-3-(4-bromophenyl)-*N*-(2-(4-nitrophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide (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 was 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; ^{1}H 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, NC*H*H), 3.33 (2H, ddt, *J* 14.4, 4.1, 1.9, NCH*H*), 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{^{1}H} 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 31

Following general procedure **C**, (*E*)-*N*,*N*-diallyl-3-(4-nitrophenyl)-*N*-(2-(4-fluorophenoxy)-2-oxoethyl)prop-2-en-1-ammonium bromide (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 was 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; ^{1}H 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, NC*H*H), 3.34 (2H, ddt, *J* 14.5, 4.0, 1.9, NCH*H*), 3.65-3.84 (2H, m, C(2)*H* + C(3)*H*), 4.09-4.34 (2H, m, OCH_2CH_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_2CH_3), 49.5 (*C*(3)H), 53.1 (NCH_2), 60.2 (OCH_2CH_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 D: 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 E: *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 36

Following general procedure **D**, $Pd(dba)_2$ (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 (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-acetamido-3-phenylpent-4-enoate 55

A solution of ethyl (2*S*,3*S*)-2-amino-3-phenylpent-4-enoate hydrochloride (276 mg, 1.08 mmol, 1.0 equiv.) in dry CH_2Cl_2 (6 mL) was treated with Et_3N (300 µL, 2.15 mmol, 2.0 equiv.) and acetic anhydride (200 µL, 2.12 mmol, 2.0 equiv.) and stirred for 16 h at room temperature. The reaction mixture was then diluted by the addition of EtOAc (50 mL). The resulting solution was washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by Biotage® Isolera™ 4 [SNAP Ultra 25 g, 75 mL/min, PE:EtOAc (90:10 1 CV, 90:10 to 40:60 10 CV, 40:60 1 CV)] to give the title product as a white solid (273 mg, 97%, >95:5 dr); HPLC analysis, Chiralpak AD-H (10% IPA/hexane, flow rate 0.7 mL/min, 211 nm, 30 °C) t_R Minor 10.0 min, Major 12.2 min, 95% ee; $[\alpha]_D^{20}$+89.8 (*c* 1, $CHCl_3$), lit.[15] $[\alpha]_D^{20}$+77.3 (*c* 0.98, $CHCl_3$); mp: 64-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.21 (3H, t, *J* 7.1, OCH_2CH_3), 1.93 (3H, s, C(O)CH_3), 3.82 (1H, t, *J* 7.4, C(3)*H*), 4.13 (2H, q, *J* 7.1, OCH_2CH_3), 4.98 (1H, dd, *J* 8.7, 6.6, C(2)*H*), 5.15 – 5.23 (2H, m, C(5)H_2), 5.72 (1H, d, *J* 8.7, N*H*), 6.01 – 6.12 (1H, m, C(4)*H*), 7.18 – 7.34 (5H, Ar*H*); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ_C 14.2 (OCH_2CH_3), 23.3 (C(O)CH_3), 52.3 (*C*(3)H), 55.9 (*C*(2)H), 61.4 (OCH_2CH_3), 117.9 (*C*(5)H_2), 127.5 (Ar*C*(4)H), 128.2 (Ar*C*H), 128.8 (Ar*C*H), 136.3 (*C*(4)H), 138.9 (Ar*C*(1)), 169.8 (*C*=O ester), 171.4 (NH*C*=O). Data consistent with literature.[15]

Ethyl (2*S*,3*S*)-2-amino-3-(2-bromophenyl)pent-4-enoate hydrochloride 38

Following general procedure **D**, $Pd(dba)_2$ (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 (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 *N*-Boc protection, 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 (−1.0 ppm).

Ethyl (2*S*,3*S*)-2-amino-3-(4-nitrophenyl)pent-4-enoate hydrochloride 39

Following general procedure **D**, $Pd(dba)_2$ (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 (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 *N*-Boc protection, 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, OCH_2CH_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_2CH_3), 52.5 (*C*(3)H), 57.6 (*C*(2)H), 63.7 (OCH_2CH_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 37

Following general procedure **D**, $Pd(dba)_2$ (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 (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 *N*-Boc protection, 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_2CH_3), 3.86 (1H, t, *J* 8.4, C(3)*H*), 4.24 (2H, q, *J* 7.1, OCH_2CH_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_2CH_3), 52.2 (*C*(3)H), 58.0 (*C*(2)H), 63.5 (OCH_2CH_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 56

Following general procedure **D** ethyl (2*S*,3*S*)-2-amino-3-(2-bromophenyl)pent-4-enoate hydrochloride (48 mg, 0.14 mmol, 1.0 equiv.), NEt_3 (58 µL, 0.42 mmol, 3.0 equiv.) and Boc_2O (153 mg, 0.7 mmol, 5.0 equiv.) were reacted in CH_2Cl_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; ^{1}H 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{^{1}H} 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 57

Following general procedure **D** ethyl (2*S*,3*S*)-2-amino-3-(4-fluorophenyl)pent-4-enoate hydrochloride (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; ^{1}H 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 (−1.9 ppm).

Ethyl (2*S*,3*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-nitrophenyl)pent-4-enoate 58

Following general procedure **D** ethyl (2*S*,3*S*)-2-amino-3-(4-nitrophenyl)pent-4-enoate hydrochloride (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 42

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 (300 mg, 1.0 mmol, 1.0 equiv.) in degassed THF (10 mL) was added *via* syringe. 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 (20 mL) and EtOAc (20 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 × 30 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; ^{1}H 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, NC*H*H), 3.23 (1H, ddt, *J* 14.0, 5.6, 1.4, NCH*H*), 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 43

A solution of ethyl (2*S*,3*S*)-2-(allylamino)-3-phenylpent-4-enoate (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 at 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) added, 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; ^{1}H 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, NC*H*H), 3.27 (1H, d, *J* 14.1, PhC*H*H), 3.31 (1H, ddt, *J* 14.2, 4.0, 1.9, NCH*H*), 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, PhC*H*H), 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 (−2.6 ppm).

Ethyl (2*S*,3*S*)-1-benzyl-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate 44

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 (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 to 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, NC*H*H), 3.57 (1H, ddt, *J* 17.0, 3.8, 2.4, NCH*H*), 3.62-3.81 (4H, m, OCH_2CH_3 + C(3)*H* + PhC*H*H), 3.84, (1H, d, *J* 6.9, PhCH*H*), 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*); $^{13}C\{^1H\}$ 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, reuiqres: 322.1802 (−2.2 ppm).

Ethyl (2*S*,3*S*)-3-phenylpiperidine-2-carboxylate 45

A solution of ethyl (2*S*,3*S*)-1-benzyl-3-phenyl-1,2,3,6-tetrahydropyridine-2-carboxylate (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, 1452, 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*H), 1.78 (1H, dddt, *J* 12.8, 9.0, 7.7, 3.7, C(6)H*H*), 1.89 (1H, ddt, *J* 13.2, 8.8, 4.3, C(5)H*H*), 1.98 (1H, br. s, N*H*), 2.11 (1H, dtd, *J* 13.6, 7.1, 3.7, C(5)*H*H), 2.82 (1H, ddd, *J* 11.6, 7.9, 3.6, C(4)H*H*), 3.20-3.34 (2H, m, C(3)*H* + C(4)*H*H), 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 (−2.6 ppm).

Acknowledgments

The research leading to these results (T.H.W.) has received funding from the ERC under the European Union's Seventh Framework Programme (FP7/2007-2013) / E.R.C. grant agreement n° 279850 and the European Union (Marie Curie ITN "SubiCat" PITN-GA-2013-607044) (S. S. M. S.).[23] A.D.S. thanks the Royal Society for a Wolfson Research Merit Award. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University.

References and notes

1. (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885-902 (b) Bao, H.; Tambar, U. K. *[2,3]-Rearrangements of Ammonium Zwitterions, in Molecular Rearrangements in Organic Synthesis*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2015 (c) Murphy, G. K.; Stewart, C.; West, F. G. *Tetrahedron* **2013**, *69*, 2667-2686 (d) Sweeney, J. B. *Chem. Soc. Rev.* **2009**, *38*, 1027-1038 (e) West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith, A. D. *ACS Catal.* **2015**, *5*, 7446-7479.
2. Wu, Y. D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421-1423.
3. Jemison, R. W.; Ollis, W. D. *J. Chem. Soc. Chem Commun.* **1969**, 294-295.
4. Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094-5102.
5. Soheili, A. Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133*, 12956-12959.
6. For pioneering reports on isothiourea catalysis, see: a) Birman, V. B;. and Li, X. *Org. Lett.* **2006**, *8*, 1351-1354. b) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.*, **2006**, *128*, 6536-6537. c) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347-4350. d) Joannesse, C.; Johnston, C. P.; Concellón, C; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 8914-8918. For recent reviews, see: e) Morrill, L. C.; Smith, A. D. *Chem. Soc. Rev.*, **2014**, *43*, 6214-6226. f) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109-2121. g) Merad, J.; Pons, J.-M.; Chuzel, O.; Bressy, C. *Eur. J. Org. Chem.*, DOI: 10.1002/ejoc.201600399
7. For selected examples of isothiourea-catalysed processes from this laboratory see a) Simal, C; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. *Angew. Chem. Int. Ed.* **2012**, *51*, 3653-3657. b) Morrill, L. C.; Douglas, J.; Lebl, T.; Slawin, A. M. Z.; Fox, D. J.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 4146-4155. c) Stark, D. G.; Morrill, L. C.; Yeh, P.-P.; Slawin, A. M. Z.; O'Riordan, T. J. C.; Smith, A. D.; *Angew. Chem. Int. Ed.* **2013**, *52*, 11642-11646. d) Yeh, P.-P.; Daniels, D. S. B.; Fallan, C.; Gould, E.; Simal, C.; Taylor, J. E.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.*, **2015**, *13*, 2177-2191
8. West,T. H.; Daniels, D. S. B.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2014**, *136*, 4476-4479.
9. (a) Workman, J. A.; Gaarrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1066-1067 (b) Arboré, A. P. A.; Cane-Honeysett, D. J.; Coldham, I.; Middleton, M. L. *Synlett* **2000**, 236-238.
10. For the initial postulate of 1,5-S•••O interactions as a control element in isothiourea catalysis see (a) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.*, **2007**, *9*, 37-40. For other manuscripts of interest see (b) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.*, **2014**, *136*, 4492-4495. (c) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. *Org. Lett.*, **2012**, *14*, 3288–3291. (d). Robinson, E. R. T.; Walden, D. M.; Fallan, C.; Greenhalgh, M. D.; Cheong, P. H.-Y.; Smith, A. D. *Chem. Sci.* **2016**,. DOI: 10.1039/C6SC00940A. Romo and Tantillo (ref 9b) have probed the nature of 1,5-S•••O interactions of α,β-unsaturated acyl ammonium species with NBO and postulate this interaction is due to a number of orbital interactions. In particular, unfavorable $n_S \Leftrightarrow \sigma^*_{C\text{-}H}/\sigma_{C\text{-}H}$ interactions disfavor alternative conformations with an O-C-N-C dihedral angle of 180°.
11. See the following publications for a selection of discussions on the origin of this interaction: (a) Zhang, X.; Gong, Z.; Li, J.; Lu, T. *J. Chem. Inf. Model.*, **2015**, *55*, 2138-2153; (b) Ángyán, J. G.; Kucsman, Á.; Poirier, R. A.; Csizmadia, I. G. *J. Mol. Struct.: Theochem* **1985**, *123*, 189−201; (c) Murray, J. S.; Lane, P.; Politzer, P.; *Int. J. Quantum Chem.* **2008**, *108*, 2770−2781; (d) Iwaoka, M.; Takemoto, S.; Tomoda, S.; *J. Am. Chem. Soc.* **2002**, *124*, 10613−10620; (e). Brameld, K. A.; Kuhn, B.; Reuter, D. C.; Stahl, M. *J. Chem. Inf. Model.*, **2008**, *48*, 1-24.
12. Lemaire-Audoire, S.; Savignac, M.; Genêt, J. P.; Bernard, J.-M. *Tetrahedron Lett.* **1995**, *36*, 1267-1270.
13. Duthion, B.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2010**, *12*, 4620-4623.
14. For recent methodology for the synthesis of α-amino-β-aryl amino acids see: (a) Zhang, X.; He, G.; Chen, G. *Org. Biomol, Chem.*, **2016**, *14*, 5511-5515. (b) He, F.-S.; Jin, J.-H.; Yang, Z.-T.; Yu, X.; Fossey, J. S.; Deng, W.-P., *ACS Catal.* **2016**, *6*, 652-656. (c) He, Z.-T; Zhao, Y.-S.; Tian, P.; Wang, C.-C.; Dong, H.-Q.; Lin, G.-Q. *Org. Lett.* **2014**, *16*, 1426-1429. (d) Gilfillan, L.; Artschwager, R.; Harkiss, A. H.; Liskamp, R. M.; Sutherland, A. *Org. Biomol. Chem.* **2015**, *13*, 4514-4523. (e) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q *Science*, **2014**, *343* 1216-1220.
15. Liu, M.; Shen, A.; Sun, X.-W.; Deng, F.; Xu, M.-H.; Lin, G.-Q. *Chem. Commun.* **2010**, *46*, 8460-8462.
16. (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752-6756. (b) Meanwell, N. A. *Chem. Res. Toxicol.* **2011**, *24*, 1420-1456. (c) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Educ.* **2010**, *87*, 1348-1349.
17. Ye, S.; Yang, W.; Coon, T.; Fanning, D.; Neubert,T.; Stamos, D.; Yu, J. Q. *Chem. Eur. J.* **2016**, *22*, 4748-4752.
18. (a)Mertz, E.; Edmondson, S. D.; Shao, N.; Neelamkavil, S.; Poker, C.; Hussain, Z.; Guo, Z.; Kevin, N. J.; Zang, Y.; He, J. *WO2015047973 (A1)*, US, **2015**. For other examples of piperidine analogues in drug discovery see: (b)Yu, Q.-Y.; Zhong, H.-M; Sun, W,-W; Zhang, S.-J.; Cao, P.; Dong, X.-P.; Qin, H.-B.; Liu, J.-K.; Wu, B. *Asian J. Org. Chem.* **2016**, *5*, 608-612. (c) Stauffer, S. R *WO2008036316 (A2)*, US, **2008**.
19. Nash, A.; Soheili, A.; Tambar, U. K. *Org. Lett.* **2013**, *15*, 4770-4773.

20. Daniels, D. S. B.; Smith, S. R.; Lebl, T.; Shapland, P.; Smith, A. D. *Synthesis* **2015**, *47*, 34-41.
21. Emayavaramban, B.; Roy, M.; Sundararaju, B. *Chem. Eur. J.* **2016**, *22*, 3952-3955.
22. Blart, E.; Genêt, J. P.; Safi, M.; Savignac, M.; Sinou, D. *Tetrahedron* **1994**, *50*, 505-514.
23. The data underpinning this publication can be found at DOI: http://dx.doi.org/10.17630/f522b48d-ed02-42b3-a161-54687ea5af57

Supplementary Material

Supplementary material containing HPLC traces and NMR spectra of all novel compounds can be found in Supplementary Material.