A chiral ligand mediated aza-conjugate addition strategy for the enantioselective synthesis of -amino esters that contain hydrogenolytically sensitive functionality

Archer, Robert M.; Hutchby, Marc; Winn, Caroline L.; Fossey, John S.; Bull, Steven D.

DOI:
10.1016/j.tet.2015.08.018

Document Version
Peer reviewed version

Citation for published version (Harvard):
Archer, RM, Hutchby, M, Winn, CL, Fossey, JS & Bull, SD 2015, 'A chiral ligand mediated aza-conjugate addition strategy for the enantioselective synthesis of -amino esters that contain hydrogenolytically sensitive functionality', *Tetrahedron*, vol. 71, no. 46, pp. 8838-8847. https://doi.org/10.1016/j.tet.2015.08.018

Accepted Manuscript

A chiral ligand mediated aza-conjugate addition strategy for the enantioselective synthesis of β-amino esters that contain hydrogenolytically sensitive functionality

Robert M. Archer, Marc Hutchby, Caroline L. Winn, John S. Fossey, Steven D. Bull

PII: S0040-4020(15)01210-7

DOI: 10.1016/j.tet.2015.08.018

Reference: TET 27040

To appear in: *Tetrahedron*

Received Date: 27 May 2015

Revised Date: 3 August 2015

Accepted Date: 10 August 2015

Please cite this article as: Archer RM, Hutchby M, Winn CL, Fossey JS, Bull SD, A chiral ligand mediated aza-conjugate addition strategy for the enantioselective synthesis of β-amino esters that contain hydrogenolytically sensitive functionality, *Tetrahedron* (2015), doi: 10.1016/j.tet.2015.08.018.

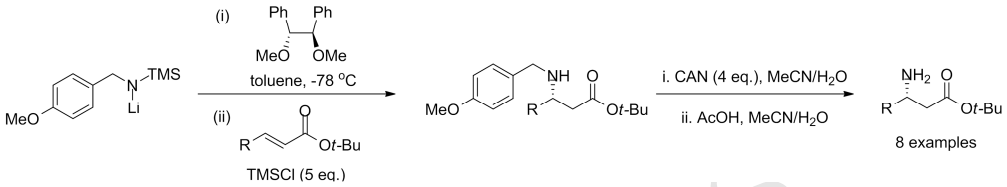
Graphical Abstract

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

A chiral ligand mediated aza-conjugate addition strategy for the enantioselective synthesis of β-amino esters that contain hydrogenolytically sensitive functionality.

Leave this area blank for abstract info.

Robert M. Archer, Marc Hutchby, Caroline L. Winn, John S. Fossey and Steven D. Bull*



Tetrahedron
journal homepage: www.elsevier.com

A chiral ligand mediated aza-conjugate addition strategy for the enantioselective synthesis of β-amino esters that contain hydrogenolytically sensitive functionality.

Robert M. Archer[a], Marc Hutchby[a], Caroline L. Winn[b], John S. Fossey[c] and Steven D. Bull[a*]

[a] *Department of Chemistry, University of Bath, Bath, BA2 7AY, U.K.*
[b] *Syngenta, Jealott's Hill International Research Centre, Bracknell, RG42 6EY, U.K.*
[c] *School of Chemistry, University of Birmingham, Birmingham, West Midlands, B15 2TT, U.K.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
β-Amino esters
Enantioselective synthesis
Aza-conjugate addition
Oxidative deprotection
External chiral ligand

ABSTRACT

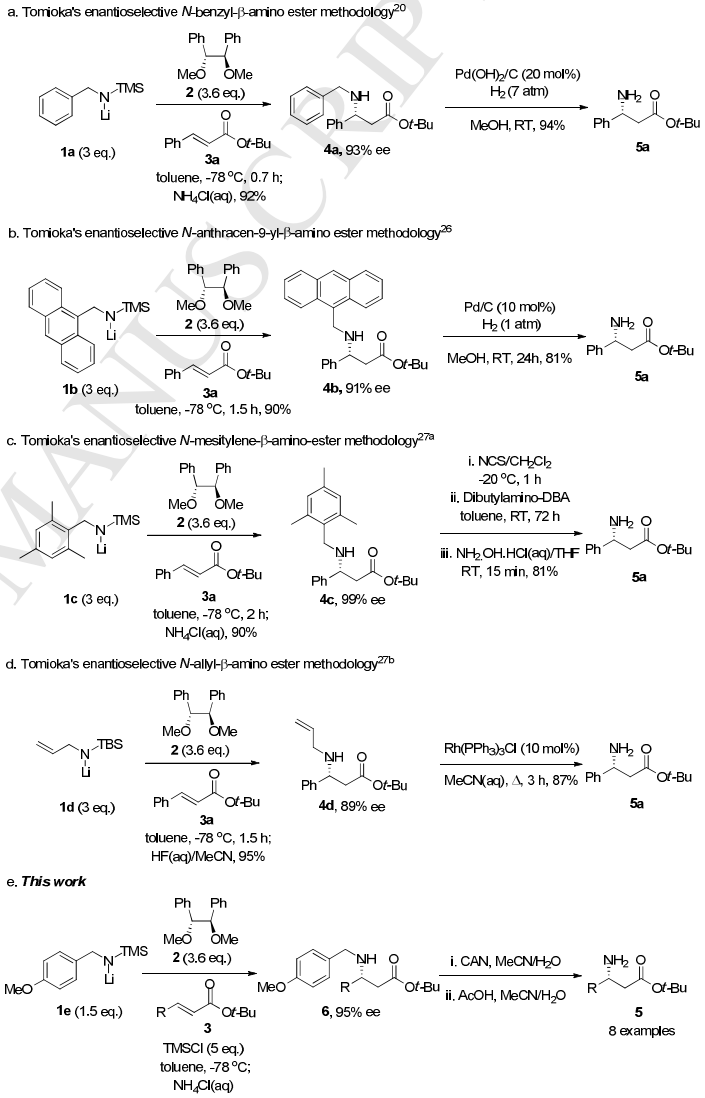
Aza-conjugate addition of the lithium anion of *N*-trimethylsilyl-*p*-methoxybenzylamine to *tert*-butyl enoate acceptors, in the presence of a stoichiometric amount of enantiopure 1,2-dimethoxy-1,2-diphenylethane and excess trimethylsilyl chloride, affords *tert*-butyl-*N*-*p*-methoxybenzyl-β-amino esters with excellent levels of enantiocontrol. These *N*-*p*-methoxybenzyl-β-amino-esters may be deprotected under oxidative conditions *via* treatment with ceric ammonium nitrate, followed by acid hydrolysis of the resultant imine intermediates, to afford enantiopure β-amino-esters containing hydrogenolytically sensitive functionality.

∗ Corresponding author; e-mail: s.d.bull@bath.ac.uk

1. Introduction

Enantiomerically pure β-amino acids and their derivatives are important chiral building blocks for the synthesis of drug molecules and natural products.[1] They are also useful as monomers for the preparation of biologically active β-peptides and αβ-peptides[2] that are more resistant to proteolytic cleavage than peptides derived from α-amino acids.[3] For example, β-peptides have been reported that display antibiotic,[4] antifungal,[5] antiviral,[6] anticancer,[7] and cholesterol uptake inhibitory activities.[8] Relatively short β-peptides sequences are also known to display defined secondary structures,[9] which enables foldameric β-peptides to be used to investigate medicinally relevant protein-protein interactions.[10] However, the range of naturally occurring β-amino acid derivatives available from the chiral pool is limited, and as a consequence methodology is required for their preparation in enantiopure form.[11] Effective strategies that currently exist, include those based on kinetic resolution,[12] stereoselective addition of enolate equivalents to imines,[13] Curtius rearrangement of chiral succinate derivatives,[14] Arndt-Eistert homologation of chiral α-amino acids,[15] and hydrogenation/reduction of *N*-enamine and *N*-acyl-enamide derivatives.[16]

One of the more popular strategies employed for the synthesis of enantiopure β-amino acid derivatives involves the stereoselective conjugate addition of aza-nucleophile equivalents to α-β-unsaturated acid equivalents.[17] Within this area, a range of highly effective protocols have been developed based on the stereoselective addition of lithium amides to enoate acceptors. For example, Yamamoto and coworkers have reported that achiral lithium *N*-trialkylsilylamides such as **1a** add to chiral enoate acceptors that contain γ-stereocentres with good levels of diastereocontrol.[18] Alternatively, Davies and coworkers have employed chiral lithium amides derived from α-methylbenzylamine for the diastereoselective synthesis of an impressive number of β-amino esters.[19] Tomioka and coworkers have developed an elegant external chiral ligand approach that enables achiral lithium amides to be used as aza-nucleophiles for the enantioselective synthesis of β-amino esters. They first reported that addition of lithium *N*-benzyl-*N*-(trimethylsilyl)amide **1a** to α,β-unsaturated esters **3** in the presence of a stoichiometric amount of the chelating C_2-symmetric ligand (*R*,*R*)-1,2-dimethoxy-1,2-diphenylethane **2**, gave protodesilylated *N*-benzyl-β-amino esters **4** with excellent levels of enantiocontrol (e.g. 93% ee for **4a**).[20] These *N*-aryl-β-amino esters could then be *N*-deprotected under hydrogenolytic conditions ($Pd(OH)_2/C$, 7 atm. H_2) to afford their parent β-amino esters **5a** in good yield (Scheme 1a).[20] This external chiral ligand controlled methodology has proven to be useful for the synthesis of a range of cyclic β-amino acid derivatives;[21] and intermediates for the synthesis of the drugs otamixaban, premafloxacin,[22] and the alkaloid natural products (−)-aspidospermidine,[23] (−)-kopsinine[24] and (−)-lycorine.[25] However, the hydrogenolysis conditions used to deprotect *N*-benzyl-β-amino esters **4a** derived from cinnamate acceptors were reported to be problematic because these conditions resulted in competing cleavage of their β-nitrogen bonds to afford unwanted 3-arylpropanoates.[26] In order to address this problem, Tomioka and coworkers introduced a range of lithium *N*-(trialkylsilyl)-amides **1b-d** as second generation aza-nucleophiles for the enantioselective synthesis of *N*-protected-β-amino esters **4b-d** with good levels of enantiocontrol (≥89% ee) (Schemes 1b-d).[26,27] A range of different *N*-deprotection strategies were employed to deprotect these *N*-protected-β-amino esters **4** to afford their parent chiral *N*H-β-amino esters **5a** in good yield. Chiral *N*-anthraceny-9-yl-β-amino-esters **4b** could be deprotected under milder hydrogenolytic conditions using H_2 (1 atm) and 10% Pd/C over a period of 24 h (Scheme 1b).[26] Chiral *N*-mesitylamine-β-amino-esters **4c** was deprotected through a three step *N*-chlorination/regioselective dehydrochlorination/*trans*-oximation protocol (Scheme 1c);[27a] conditions that could also be used to deprotect *N*-benzyl-β-amino ester **4a**.[22] Alternatively, chiral *N*-allyl-β-amino esters **4d** was deprotected using a tandem rhodium catalysed isomerisation/imine hydrolysis approach (Scheme 1d).[27b] Further to these reports, we now report that lithium *N*-*p*-methoxybenzyl-*N*-(trimethylsilyl)amide **1e** can also be used as an achiral aza-nucleophile in these type of chiral ligand mediated aza-conjugate addition reactions to afford chiral *N*-*p*-methoxybenzyl β-amino-esters **6** with excellent levels of enantiocontrol. The *p*-methoxybenzyl (PMB) fragments of these *N*-PMB-β-amino esters **6** may then be oxidatively deprotected using ceric ammonium nitrate (CAN) to afford chiral *N*H-β-amino esters **5** that can contain hydrogenolytically sensitive functionality (Scheme 1e).



Scheme 1: Tomioka's external chiral ligand **2** methodology for the enantioselective synthesis of β-amino esters **5**.

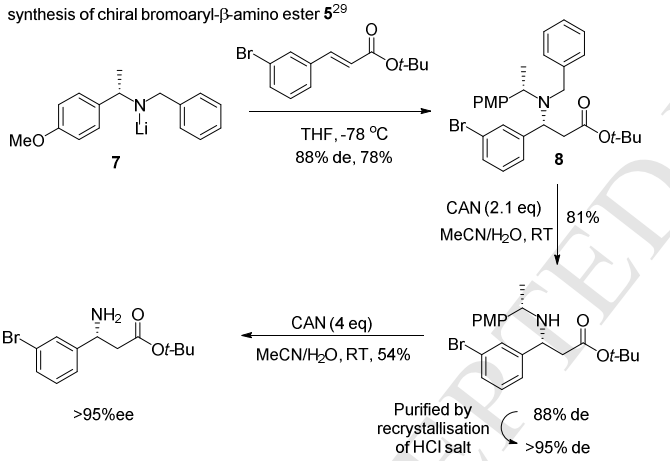
2. Results and Discussion

As part of a research program directed towards the asymmetric synthesis of β-amino acids[28] as chiral precursors for the synthesis of novel heterocyclic scaffolds, we required access to a range of β-amino esters containing hydrogenolytically sensitive functionality. Davies and coworkers had previously reported the use of lithium *N*-benzyl-*N*-α-methyl-*p*-methoxybenzylamide **7** as a chiral aza-nucleophile for the diastereoselective synthesis of chiral haloaryl-β-amino esters such as **8**,[29] whose *N*-benzyl and *N*-PMB protecting groups could be removed under oxidative conditions *via* stepwise treatment with excess CAN (Scheme

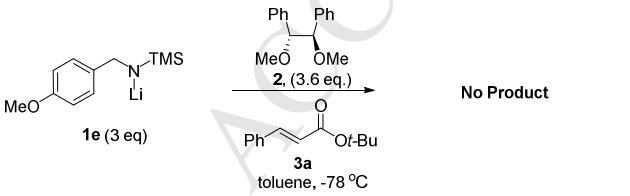
2a).[30] This enabled lithium amide **7** (or its enantiomer) to be used for the asymmetric syntheses of a range of hydrogenolytically sensitive haloaryl and pyridinyl containing β-amino-acids, β-lactams and heterocycles with good levels of stereocontrol.[29,31] Given this precedent, we reasoned that lithium *N*-(4-methoxybenzyl-1,1,1-trimethyl-silanamide **1e** might be useful as an aza-nucleophile for Tomioka's chiral ligand conjugate addition methodology, since it would enable the *N*-PMB groups of its corresponding β-amino-ester adducts **6** to be removed using CAN under oxidative conditions (Scheme 1e).

Tomioka and coworkers previously attempted to employ lithium amide **1e** as an aza-nucleophile using their standard conditions (3 eq. amide, 3.6 eq. chiral ligand **2**, toluene, -78 °C), but reported that it was unsuccessful in delivering any chiral β-amino ester product (Scheme 2b), even when more forcing conditions were employed.[26] However, we noticed that they had reported that addition of an excess of trimethylsilyl chloride (TMSCl) had the potential to improve both the yield and stereoselectivity of these types of aza-conjugate addition reactions. For example, reaction of 1.5 equivalents of lithium amide **1a** with *tert*-butyl-cinnamate **3a** and 1.8 equivalents of ligand **2** in toluene at -78 °C afforded *N*-benzyl-β-amino ester **4a** in 81% yield and 82% ee, which could be improved to 97% yield and 97% ee in the presence of 5.0 equivalents of TMSCl (Scheme 2c).[20] Consequently, we decided to investigate whether carrying out aza-conjugate addition reactions of lithium amide **1e** with **3a** in the presence of excess TMSCl might afford chiral *N*-PMB-β-amino-esters **6** in good yield and high ee.

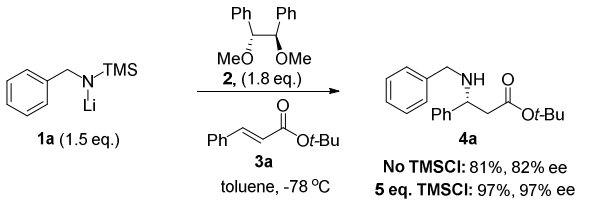
a. Davies' 2nd generation oxidative deprotection methodology for the diastereoselective synthesis of chiral bromoaryl-β-amino ester **5**[29]



b. Tomioka's unsuccessful attempt to use lithium amide **1e** for the asymmetric synthesis of β-amino ester **6a**[26]



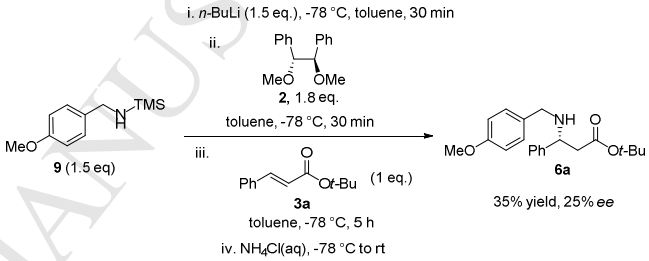
c. Excess trimethylsilylchloride improves the enantioselectivity of conjugate addition reactions of lithium amide **1a**[20]



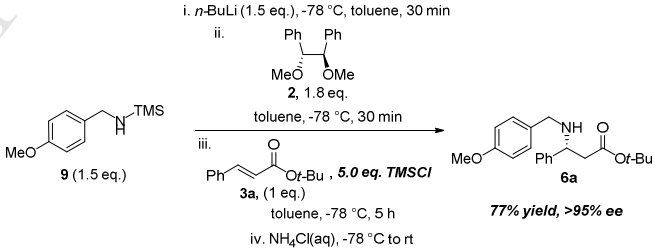
Scheme 2: A range of successful and unsuccessful aza-conjugate addition reactions that have been investigated for synthesis of β-amino esters **4a** and **8**.

N-Trimethylsilyl-*p*-methoxybenzylamine **9** was first prepared by treating *p*-methoxybenzylamine with *n*-butyllithium in THF at 0 °C, followed by addition of TMSCl and heating at reflux for 12 hours. Its corresponding lithium amide **1e** was then generated *via* treatment of 1.5 equivalents of amine **9** with *n*-butyllithium in toluene at -78 °C. A solution of 1.8 equivalents of chiral ligand **2** in toluene was then added to this solution of lithium amide **1e** in toluene at -78 °C, followed by further addition of a solution of *tert*-butyl-cinnamate **3a** in toluene at -78 °C. The reaction was then stirred for 5 h before work-up at -78 °C using NH_4Cl(aq). Promisingly, and in contrast to Tomioka's previous report that no aza-conjugate addition reaction occurred,[26] this reaction produced some of the desired protodesilylated *N*-PMB-β-amino ester **6a**, albeit in low 35% yield and poor enantioselectivity (25% ee) (Scheme 3a). Encouraged by this result, we repeated this aza-conjugate reaction under identical conditions, except that we employed a solution of *tert*-butyl-cinnamate and 5.0 equivalents of TMSCl in the final addition step. To our delight, the presence of excess TMSCl resulted in formation of the desired (*R*)-*N*-PMB-β-amino ester **6a** in a much improved 77% yield and 95% ee (Scheme 3b).

(a) Lithium amide **1e** affords a low yield of scalemic β-amino ester **6a** (25% ee)



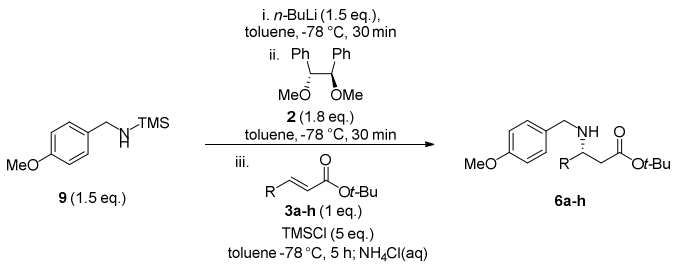
(b) Lithium amide **1e** in the presence of excess TMSCl affords a good yield of enantiopure β-amino ester **6a** (95% ee)

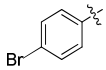
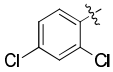
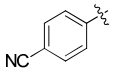
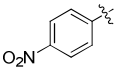


Scheme 3: Chiral ligand **2** mediated aza-conjugate addition reaction of lithium amide **1e** to *tert*-butyl enoate **3a** in the presence of excess TMSCl affords β-amino ester **6a** in good yield and high ee.

The scope and limitation of this aza-conjugate addition reaction was then investigated by reacting lithium amide **1e** with a range of α,β-unsaturated *tert*-butyl enoates **3b-h** in the presence of excess TMSCl, including some substrates that contained hydrogenolytically sensitive functionality (Table 1). Therefore, *tert*-butyl cinnamate ester substrates containing halo-aryl **3b-c** and cyano-aryl substituents **3d** afforded their corresponding β-amino esters **6b-d** in good yields (62-79%) and with 95% ee (Table 1, Entries 2-4). However, (*E*)-*tert*-butyl 3-(4-nitrophenyl)acrylate **3e** proved less reactive, affording *N*-PMB-β-amino ester **6e** in only 40% yield and 95% ee (Table 1, Entry 5), with the poor yield being due to the presence of unreacted *tert*-butyl enoate **3e**. Aza-conjugate addition reactions of heteroatom containing *tert*-butyl enoates were also successful, with (*E*)-*tert*-butyl 3-(thiophen-2-yl)acrylate **3f** and (*E*)-*tert*-butyl 3-(furan-2-yl)acrylate **3g** affording their corresponding β-amino esters **6f** (95% ee) and **6g** (95% ee) in 86% and 73% yield respectively (Table 1, Entries 6-7). Finally, it was shown that the simple acyclic (*E*)-*tert*-butyl hept-2-enoate **3h** afforded its corresponding *N*-PMB-β-amino ester **6h** in 68% yield and 95% ee.

Table 1: Substrate scope of chiral ligand mediated aza-conjugate addition reactions of lithium amide **1e** to α,β-unsaturated ester derivatives **3a-h**.



Entry	Enoate 3[a]	R	*N*-PMB-β-Amino Ester 6a-h	Yield (%)[b]	ee (%)[c,d]
1	**3a**		**6a**	77	95
2	**3b**		**6b**	79	95
3	**3c**		**6c**	76	95
4	**3d**		**6d**	62	95
5	**3e**		**6e**	40[e]	95
6	**3f**		**6f**	86	95
7	**3g**		**6g**	73	95
8	**3h**		**6h**	68	95

a. See experimental section for syntheses of *tert*-butyl enoates **3**; b. Isolated yields of *N*-PMB-β-amino esters **6a-h** after purification by chromatography; c. Ee's of *N*-PMB-β-amino-esters **6a-h** inferred from ee values subsequently determined for their parent *N*-deprotected β-amino esters **5a-h** (*vide infra*); d. Error limit of ±3% ee arising from detection limit of the ^{1}H NMR chiral derivatisation protocol used to determine the ee's of β-amino esters **5a-h**; e. Low yield of *N*-benzyl-β-amino ester **6e** due to poor conversion, with significant amounts of unreacted *tert*-butyl enoate **3e** present in the ^{1}H NMR spectrum of the crude reaction product.

Tomioka and coworkers have recently employed ^{6}Li NMR spectroscopy to demonstrate that addition of chiral ligand **2** to lithium amide **1e** initially results in formation of a mixture of *cis*- and *trans*- cyclic heterodimeric complexes (only *cis*-dimer **10** shown in Figure 1).[32] They proposed that addition of *tert*-butyl enoate **3** results in dissociation of these heterodimeric complexes to afford a new monomeric complex **11** containing one equivalent of lithium amide, one equivalent of chiral ligand and one equivalent of enoate. Intramolecular transfer of the amide fragment of complex **11** to its enoate fragment then occurs in a highly enantiofacial manner to afford a (*Z*)-enolate **12** that is then protonated on work-up with NH_4Cl(aq) to afford the desired *N*-PMB-β-amino ester **6** (Figure 1). The role of TMSCl in improving the yield and enantioselectivity of these type of aza-conjugate addition reactions is unclear, however it is possible that it acts as an electrophilic *O*-silylating agent to trap out (*Z*)-enolate **12** as its corresponding (*Z*)-silyl-ketene acetal **13** *in situ*. This would perturb the equilibria of the potentially reversible intramolecular aza-conjugate addition step (**11** ⇌ **12**), by preventing the reverse E1cB-elimination reaction of (*Z*)-enolate **12** from occurring. Furthermore, it has been shown that enolates such as **12** can react with lithium amide complexes of ligand **2** to afford competing dimeric lithium complexes such as **14**,[33] which could potentially be responsible for competing non-stereoselective aza-conjugate addition pathways that afford *N*-PMB-β-amino ester **6** with poorer levels of control in the absence of TMSCl. Therefore, we propose that the presence of excess TMSCl ensures that (*Z*)-enolate **12** is rapidly trapped out as its *O*-silyl ketene acetal **13**,[34] which ensures that the concentration of free enolate **12** remains sufficiently low to ensure that the enantioselective pathway to *N*-PMB-β-amino ester **6** predominates (Figure 1).

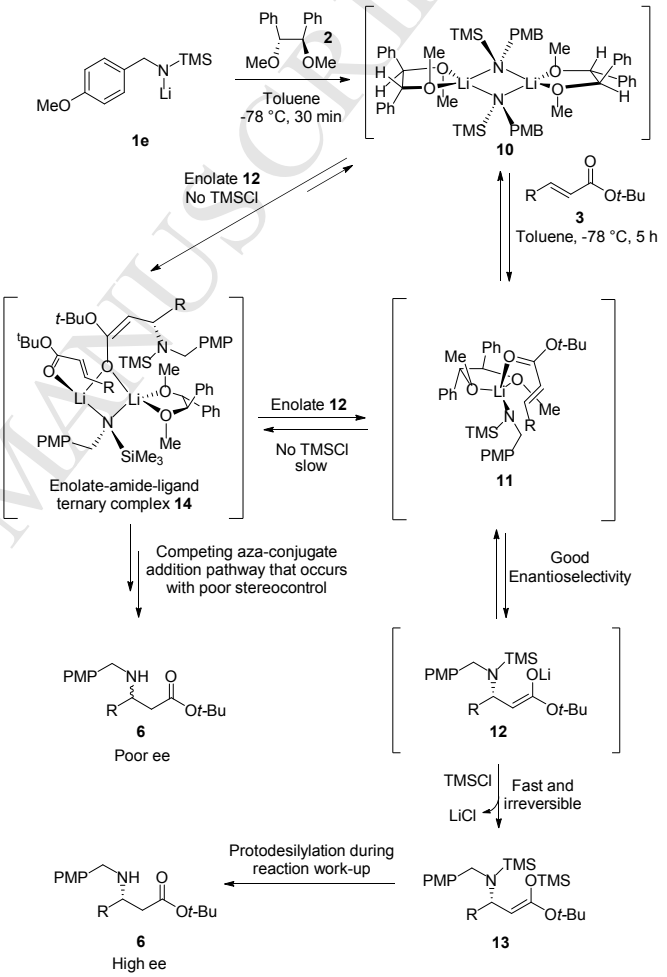
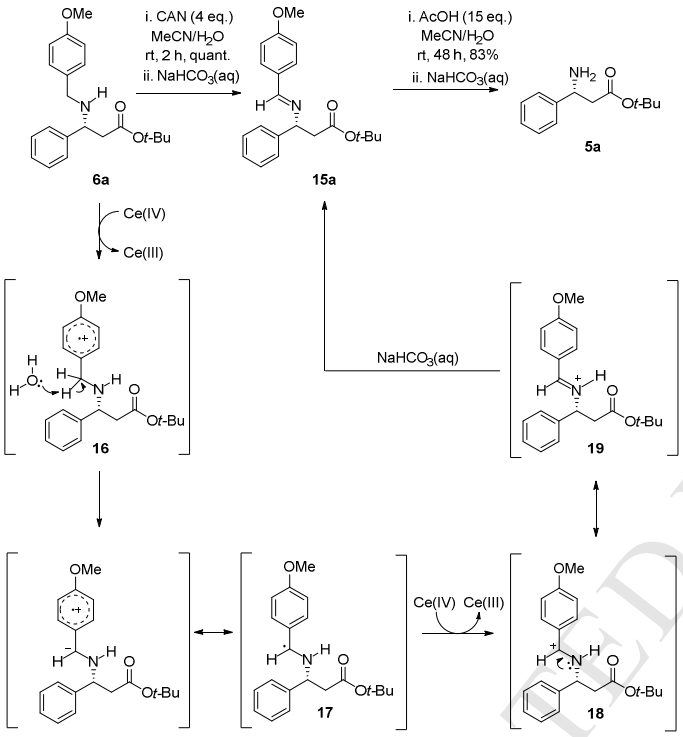


Figure 1: Potential role of TMSCl in improving yields and enantioselectivities of chiral ligand **2** mediated aza-conjugate addition reactions of lithium amide **1e** with *tert*-butyl enoates **3**.

Having successfully identified conditions that enabled lithium amide **1e** to be used as an effective aza-nucleophile for the enantioselective synthesis of *N*-PMB-β-amino esters **6a-h**, we next investigated their *N*-deprotection under oxidative conditions. Treatment of *N*-PMB-β-amino ester **6a** with 4.0 equivalents of CAN in MeCN/H_2O (5:1) solution, followed by basic work up using $NaHCO_3$(aq),[29] afforded *N*-PMB-imine **15a** in essentially quantitative yield (Scheme 4). A plausible mechanism for this CAN mediated oxidative *N*-deprotection step is presented in Scheme 4, whereby CAN first acts an electron acceptor from the *p*-methoxyphenyl (PMP) group to afford a stabilised radical

cation **16**. A benzylic proton of **16** is then deprotonated by water to afford **a** stabilized benzylic radical resonance form **17**. A second equivalent of CAN then oxidises radical **17** to afford benzylic cation **18** which is resonance stabilized as its iminium species **19** that is subsequently isolated as imine **15a** after basic workup. After a short optimisation screen of solvents, acids and reaction time, it was found that stirring a solution of *N*-PMB-imine **15a** in MeCN/H_2O (5:1) in the presence of 15 eq. of acetic acid at room temperature for 48 h followed by neutralisation with $NaHCO_3$(aq) and purification by chromatography, furnished (*R*)-β-amino-*tert*-butyl ester **5a** in 83% yield and 95% ee. The (*R*)-configuration and 95% ee of (*R*)-β-amino-*tert*-butyl ester **5a** was confirmed by comparison of the sign and magnitude of its specific rotation of (*R*)-*N*-benzyl-β-amino of $[\alpha]_D^{23}$ +20.0 (*c* 1.2, $CHCl_3$), with the literature value of $[\alpha]_D^{23}$+19.7 (*c* 0.96, $CHCl_3$).[29]



Scheme 4: CAN mediated oxidative *N*-deprotection of *N*-PMB-β-amino ester **6a** to afford an intermediate imine **15a** that is then hydrolysed under aqueous acidic conditions to afford β-amino ester **5a**.

This oxidative *N*-deprotection methodology was then applied to unmask the remaining *N*-PMB-β-amino esters **6b-h** to afford their corresponding deprotected *N*H-β-amino esters **5b-h** in moderate to good yields (36-73%) over two steps (Table 2). It was found that the <60% yields obtained for formation of *N*H-β-amino esters **5b**, **5e** and **5f** (Entries 2, 4 and 6) were due to competing acid catalysed cleavage of their *tert*-butyl ester fragments to afford their corresponding acids in the imine hydrolysis step. Evidence for this competing *tert*-butyl cleavage pathway was obtained from ^{1}H NMR spectroscopic and mass spectrometric analysis of the aqueous washings of the crude reaction products of the imine hydrolysis reactions, which clearly revealed the presence of their corresponding β-amino acids.[35]

The enantiomeric excesses of β-amino esters **5a-h** were confirmed as 95% ee using a simple three-component chiral derivatisation protocol previously developed in our research group.[36] In this approach, a chiral amine of unknown enantiomeric excess is derivatised with 2-formylphenyl boronic acid and enantiopure BINOL to afford a mixture of diastereomeric imino-boronate

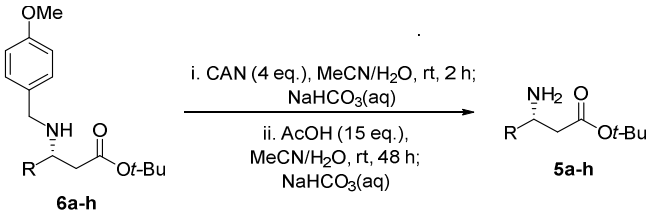
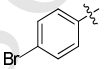
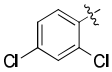
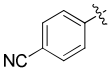
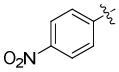
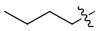


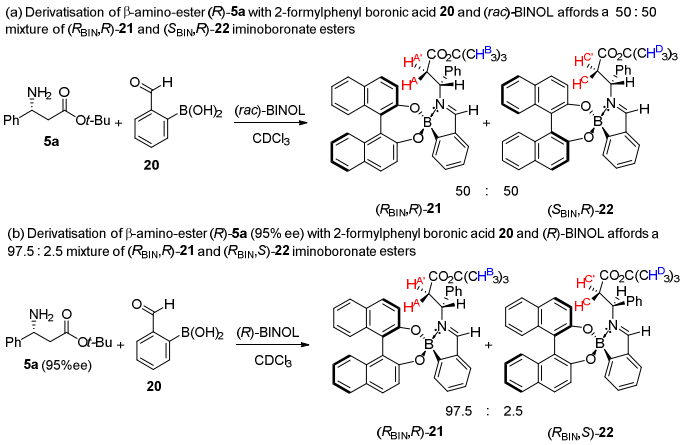
Table 2: CAN deprotection reactions of *N*-PMB-β-amino esters.

Entry	*N*-PMB-β-Amino Ester 6a-h	R	β-Amino Ester 5a-h	Yield (%)[a]	ee (%)[c,d]
1	**6a**		**5a**	68	95
2	**6b**		**5b**	56[b]	95
3	**6c**		**5c**	68	95
4	**6d**		**5d**	51[b]	95
5	**6e**		**5e**	65	95
6	**6f**		**5f**	36[b]	95
7	**6g**		**5g**	73	95
8	**6h**		**5h**	60	95

a. Isolated yields of β-amino esters **5a-h** after purification by chromatography; b. Lower yields of β-amino esters due to competing cleavage of their *tert*-butyl ester fragments in the imine hydrolysis step to give their corresponding β-amino acids; c. Ee's determined by derivatisation of β-amino esters **5a-h** with 2-formylphenylboronic acid and (*R*)-BINOL followed by ^{1}H NMR spectroscopic analysis of the ratio of the resultant mixture of diastereomeric imino-boronate esters;[36] d. Error limit of ±3% in ee arising from the detection limit of the ^{1}H NMR chiral derivatisation protocol.

esters whose ratio can be determined by ^{1}H NMR spectroscopic analysis. Since no kinetic resolution occurs in this derivatisation process, this diasteromeric ratio corresponds to the enantiomeric ratio of the parent chiral amine. For example, β-amino ester (*R*)-**5a** was first derivatised *via* treatment with 2-formylphenylboronic acid **20**, (*rac)*-BINOL, and K_2CO_3 in $CDCl_3$ for 10 min to afford a 50:50 mixture of the diastereomeric iminoboronate esters (R_{BIN},*R*)-**21** and (S_{BIN},*R*)-**22** (Scheme 5a). Analysis of the ^{1}H NMR spectrum of this mixture revealed well resolved resonances corresponding to the diastereotopic methylene and *tert*-butyl ester protons of the (R_{BIN},*R*)-**21** (CH^A, $CH^{A'}$ and $CH^B{}_3$) and (S_{BIN},*R*)-**22** (CH^C, $CH^{C'}$ and $CH^D{}_3$) diastereomers respectively ($\Delta\delta_H$ = 0.1-0.4 ppm), whose integrals could be used to accurately determine their diastereomeric ratio

(Figure 2a). A sample of β-amino ester (*R*)-**5a** generated using our enantioselective aza-conjugate addition protocol, was then derivatised with 2-formylphenylboronic acid **20** and enantiopure (*R*)-BINOL, with ^{1}H NMR spectroscopic analysis revealing that (R_{BIN},*R*)-**21** and (R_{BIN},*S*)-**22** were present in a diastereomeric ratio of 97.5:2.5 (Scheme 5b). This ratio was accurately determined by comparison of the integral ratios of the well resolved *tert*-butyl proton singlet resonances of (R_{BIN},*R*)-**21** (O(CH^B_3) and (R_{BIN},*S*)-**22** (O(CH^D_3) at δ0.85 ppm and δ1.15 respectively (Figure 2b). Therefore, since no kinetic resolution occur in the derivatisation process, it follows that this 97.5:2.5 diasteromeric ratio corresponds to the enantiomeric ratio of chiral amine **5a**, thus allowing us to conclude that it had been formed in 95% ee.



Scheme 5: Chiral derivatisation protocol used to determine the enantiopurity of β-amino ester **5a** as 95% ee.

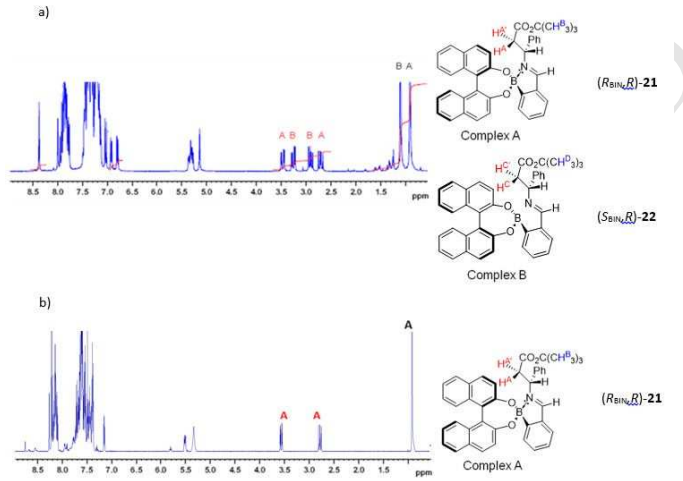


Figure 2. a) ^{1}H NMR spectrum of 50:50 mixture of diastereomeric iminoboronate ester complexes (R_{BIN},*R*)-**21** and (S_{BIN},*R*)-**22**. b) ^{1}H NMR spectrum of a 97.5:2.5 mixture of diastereomeric iminoboronate ester complexes (R_{BIN},*R*)-**21** and (R_{BIN},*S*)-**22**.

3. Conclusions

Aza-conjugate addition of lithium amide **1e** to *tert*-butyl enoates, in the presence of a stoichiometric amount of an external chiral ligand **2** and excess trimethylsilyl chloride, affords *tert*-butyl *N*-PMB-β-amino esters **6a-h** with excellent levels of enantiocontrol. The resultant *tert*-butyl *N*-PMB-β-amino esters **6a-h** may be deprotected *via* treatment with CAN, followed by acid hydrolysis of their resultant imine intermediates, to afford their parent chiral β-amino-esters **5a-h** (95% ee). The ability to deprotect *N*-PMB-β-amino esters **6** under oxidative conditions enables this second generation variant of Tomioka's external chiral ligand mediated lithium amide methodology to be used for the enantioselective synthesis of β-amino esters **6** that contain functionalities that are susceptible to hydrogenolysis.

4. Experimental

General methods

Reactions that required the use of dry solvents were conducted in oven dried glassware under an atmosphere of nitrogen using inert atmosphere techniques. Dry solvents were obtained by passing them through anhydrous alumina columns using an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to the fraction of petroleum ether boiling at 40-60 °C. Hexanes refers to the hexane fraction of petroleum. Solvents were evaporated on a Büchi Rotorvapor. All commercially available compounds were used as obtained from chemical suppliers. ^{1}H and ^{13}C NMR spectra were run in $CDCl_3$ using Bruker Avance 250/300/400/500 MHz spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to the residual solvent peak. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Infra-red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with only selected absorbances quoted as ν in cm^{-1}. Mass spectra were recorded on a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany), using acetonitrile or water to dissolve the sample. TLC was carried out using commercially available polyethylene backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate, ninhydrin or phosphomolybdic acid followed by gentle heating. Flash chromatography was performed under manually generated medium pressure using Merck 60 H silica gel (35-75 μm) unless otherwise stated.

(R,R)-1,2-Dimethoxy-1,2-diphenylethane **2**

(*R,R*)-Hydrobenzoin (1.00 g, 4.67 mmol) was added dropwise (5 min) to a stirred refluxing suspension of sodium hydride (60% dispersion, 0.467 g, 11.7 mmol) in dry THF (10 mL). This mixture was heated at reflux for a further 30 minutes and then cooled to 0 °C prior to the addition of methyl iodide (15.0 mL, 100 mmol). The reaction was then stirred at room temperature overnight, whereupon TLC analysis showed consumption of the starting material. The mixture was cooled to 0 °C and quenched with water (10 mL), extracted with EtOAc (3 x 50 mL), washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was recrystallised from hexane/Et_2O to afford the title compound as a white crystalline solid (0.68 g, 60%). $[\alpha]_D^{25}$-15.1 (*c* 1.8, $CHCl_3$) (Lit.[37] $[\alpha]_D^{23}$ -15.2 (*c* 2.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δH = 7.23-7.15 (6H, m, Ph), 7.08-6.98 (4H, m, Ph), 4.34 (2H, s, $CHOCH_3$), 3.30 (6H, s, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δC = 138.2, 127.9, 127.8, 127.6, 87.7, 57.2; IR (thin film) υmax (cm^{-1}): 1492 (w, C=C), 1455 (w, C=C); HRMS (ESI): m/z 265.1188, $C_{16}H_{18}NaO_2$ $[M+Na]^+$ requires 265.1199.

N-(4-Methoxybenzyl)-1,1,1-trimethylsilanamine **9**

n-Butyllithium solution (2.3 M in hexanes, 6.6 mL, 38.2 mmol) was added to a stirred solution of *para*-methoxybenzylamine (5.00 g, 36.4 mmol) in THF (140 mL) at 0 °C. The reaction was stirred at room temperature for 8 hours before being cooled to 0 °C and a solution of addition of TMSCl (4.67 mL, 36.8 mmol) in

THF (40 mL) added dropwise. The reaction was heated at reflux for 12 hours, concentrated, triturated with pentane (2 x 100 mL) and solvent removed *in vacuo* to afford the title compound as a yellow oil (5.59 g, 73% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.16 (2H, d, *J* = 8.6 Hz, $CH_3OCCHCH$), 6.82 (2H, d, *J* = 8.6 Hz, CH_3OCCH), 3.77 (2H, d, *J* = 7.8 Hz, CH_2N), 3.7 (3H, s, OCH_3), 1.90 (1H, br. s, N*H*), 0.00 (9H, s, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 158.2, 136.5, 129.1, 113.85, 55.2, 45.3, 0.0; IR (thin film) υ_{max} (cm^{-1}): 3305 (w, NH), 1505, 1499 (m, m, C=C).

(E)-tert-Butyl 3-phenylacrylate **3a**

A solution of iodobenzene (2.69 g, 13.2 mmol) diisopropylethylamine (6.90 mL, 39.6 mmol), *tert*-butyl acrylate (2.12 mL, 14.5 mmol), tri(o-tolyl)phosphine (0.40 g, 13.2 mmol) and palladium(II) acetate (0.15 g, 0.66 mmol) in MeCN (80 mL) was heated at reflux for 17 hours. The suspension was then cooled to room temperature, diluted with water (60 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine and water, dried over anhydrous $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash chromatography (EtOAc-petrol, 1:30) to afford the title compound as a yellow oil (1.94 g, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.51 (1H, d , *J* = 16.0 Hz, C*H*=$CHCO_2$), 7.47-7.25 (5H, m, Ph), 6.30 (1H, d, *J* = 16.0 Hz, CH=C*H*CO_2), 1.46 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 166.3, 143.6, 134.7, 123.0, 128.8, 128.0, 120.2, 80.5, 28.2; IR (thin film) υ_{max} (cm^{-1}): 1703 (s, C=O); HRMS (ESI): m/z 227.1025, $C_{13}H_{16}NaO_2$ $[M+Na]^+$ requires 227.1043.

General Procedure 1: Synthesis of *tert*-butyl enoates **3b-g**.

Methylmagnesium bromide (1 eq.) was added to a solution of *tert*-butyl 2-(diethoxyphosphoryl)acetate (1 eq.) in dry THF (0.1 M) at room temperature under an inert atmosphere and the mixture stirred for 15 minutes. A dry THF (0.2 M) solution of the appropriate aryl aldehyde (1 eq) was then added dropwise (5 min) and the reaction mixture heated at reflux for 18 hours. After cooling to room temperature, saturated NH_4Cl(aq) was added and the mixture extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine and water, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified by silica gel chromatography (EtOAc-petrol, 1:30) to afford the desired *tert*-butyl enoate **3**.

(E)-tert-Butyl 3-(4-bromophenyl)acrylate **3b**

4-Bromobenzaldehyde (0.36 g, 2 mmol) was used to prepare the title compound as a white solid (0.404 g, 72% yield) using general procedure 1. Mp. 53-55 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.47 (1H, d, *J* = 15.8 Hz, C*H*=$CHCO_2$), 7.42 (2H, d, *J* = 6.8 Hz, BrCCHC*H*), 7.29 (2H, d, *J* = 6.8 Hz, BrCC*H*CH), 6.31 (1H, d, *J* = 15.8 Hz, CH=C*H*CO_2), 1.46 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 166.1, 142.2, 133.6, 132.1, 129.36, 124.2, 120.9, 80.8, 28.2; IR (thin film) υ_{max} (cm^{-1}): 1704 (s, C=O); HRMS (ESI): *m/z* 305.0129, $C_{13}H_{15}BrNaO_2$ $[M+Na]^+$ requires 305.0153.

(E)-tert-Butyl 3-(2,4-dichlorophenyl)acrylate **3c**

2,4-Dichlorobenzaldehyde (0.52 g, 3 mmol) was used to prepare the title compound as a colourless oil (0.59 g, 78% yield) using general procedure 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.92 (1H, d, *J* = 16.0 Hz, C*H*=$CHCO_2$), 7.54 (1H, d, *J* = 8.5 Hz, C*H*CCl), 7.43 (1H, d, *J* = 2.0 Hz, CClC*H*CCl), 7.25 (1H, dd, *J* = 8.6 and 2.0 Hz, CC*H*CH), 6.35 (1H, d, *J* = 16.1 Hz, CH=C*H*CO_2), 1.54 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 165.6, 138.1, 136.0, 135.4, 131.5, 129.9, 128.3, 127.5, 123.2, 81.0, 28.2; IR (thin film) υ_{max} (cm^{-1}): 1706 (s, C=O); HRMS (ESI): *m/z* 295.0244, $C_{13}H_{14}Cl_2NaO_2$ $[M+Na]^+$ requires 295.0269.

(E)-tert-Butyl 3-(4-cyanophenyl)acrylate **3d**

4-Formylbenzonitrile (0.39 g, 3 mmol) was used to prepare the title compound as a white solid (0.59 g, 82% yield) using general procedure 1. Mp. 140-142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.67 (2H, d, *J* = 7.6 Hz, NCCC*H*), 7.58 (2H, d, *J* = 7.6 Hz, NCCCHC*H*), 7.55 (1H, d, *J* = 16.1 Hz, C*H*=$CHCO_2$), 6.45 (1H, d, *J* = 16.1 Hz, CH=C*H*CO_2), 1.54 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 165.4, 141.1, 139.0, 132.6, 128.3, 123.8, 118.4, 113.1, 81.2, 28.1; IR (thin film) υ_{max} (cm^{-1}): 2226 (m, CN), 1702 (s, C=O); HRMS (ESI): *m/z* 252.0990, $C_{14}H_{15}NNaO_2$ $[M+Na]^+$ requires 252.1000.

(E)-tert-Butyl 3-(4-nitrophenyl)acrylate **3e**

4-Nitrobenzaldehyde (0.30 g, 2 mmol) was used to prepare the title compound as a colourless oil (0.35 g, 70% yield) using general procedure 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 8.14 (2H, d, *J* = 8.7 Hz, O_2NCCH), 7.57 (2H, d, *J* = 8.7 Hz, $O_2NCCHCH$), 7.53 (1H, d, *J* = 16.0 Hz, C*H*=$CHCO_2$), 6.42 (1H, d, *J* = 15.9 Hz, CH=C*H*CO_2), 1.46 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 165.3, 148.3, 140.9, 140.6, 128.5, 124.5, 124.1, 81.5, 28.1; IR (thin film) υ_{max} (cm^{-1}): 1708 (s, C=O); HRMS (ESI): *m/z* 272.0878, $C_{13}H_{15}NNaO_4$ $[M+Na]^+$ requires 272.0899.

(E)-tert-Butyl 3-(thiophen-2-yl)acrylate **3f**

Thiophene-2-carboxaldehyde (0.44 g, 4 mmol) was used to prepare the title compound as a colourless oil (0.60 g, 71% yield) using general procedure 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.67 (1H, d, *J* = 15.7 Hz, C*H*=$CHCO_2$), 7.32 (1H, d, *J* = 5.1 Hz, C*H*S), 7.20 (1H, d, *J* = 3.5 Hz, C*H*CS), 7.02 (1H, dd, *J* = 5.1 and 3.6 Hz, CHC*H*CHS), 6.16 (1H, d, *J* = 15.7 Hz, CH=C*H*CO_2), 1.51 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 166.2, 139.8, 136.1, 130.5, 128.0, 119.0, 80.5, 28.2; IR (thin film) υ_{max} (cm^{-1}): 1699 (s, C=O); HRMS (ESI): *m/z* 233.0591, $C_{11}H_{14}NaO_2S$ $[M+Na]^+$ requires 233.0612.

(E)-tert-Butyl 3-(furan-2-yl)acrylate **3g**

Furan-2-carboxaldehyde (0.48 g, 5 mmol) was used to prepare the title compound as a yellow oil (0.52 g, 65% yield) using general procedure 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.38 (1H, d, *J* = 1.6 Hz, C*H*O), 7.26 (1H, d, *J* = 15.9 Hz, C*H*=$CHCO_2$), 6.50 (1H, d, *J* = 3.4 Hz, C*H*CO), 6.38 (1H, dd, *J* = 3.4 and 1.8 Hz, CHC*H*CHO), 6.18 (1H, d, *J* = 15.9 Hz, CH=C*H*CO_2), 1.44 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 166.4, 151.2, 144.4, 130.1, 118.0, 114.0, 112.1, 80.4, 28.2; IR (thin film) υ_{max} (cm^{-1}): 1701 (s, C=O); HRMS (ESI): *m/z* 217.0875, $C_{11}H_{14}NaO_3$ $[M+Na]^+$ requires 217.0841.

(E)-tert-Butyl hept-2-enoate **3h**

tert-Butyl acrylate (5.92 mL, 40.8 mmol) and Grubbs 2nd generation catalyst (0.10 g) were added to a solution of hex-1-ene (2.89 mL, 13.6 mmol) in CH_2Cl_2 (29 mL) under an inert atmosphere. The reaction mixture was stirred at room temperature for 24 hours and then filtered through celite and concentrated *in vacuo*. Distillation of the residue afforded the title compound as a colourless oil (1.42 g, 55% yield). Bp. 90 °C @ 0.8 Torr; ^{1}H NMR (250 MHz, $CDCl_3$) δ_H = 6.78 (1H, dt, *J* = 15.7 and 6.9 Hz, CH_2CH=CH), 5.66 (1H, dt, *J* = 15.7 and 1.5 Hz, CH_2CH=C*H*), 2.10 (2H, qd, *J* = 7.1 and 1.5 Hz, CH_2-CH_2-CH), 1.49 (9H, s, $C(CH_3)_3$), 1.37-1.18 (4H, m, $CH_3CH_2CH_2$), 0.93 (3H, t, *J* = 7.1 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 166.6, 148.5, 123.3, 80.3, 32.2, 30.6, 28.5, 22.6, 14.2; IR (thin film) υ_{max}

(cm^{-1}): 1706 (s, C=O); HRMS (ESI): *m/z* 207.1343, $C_{11}H_{20}NaO_2$ $[M+Na]^+$ requires 207.1361.

General Procedure 2: Enantioselective Synthesis of *N*-*p*-methoxybenyl-β-amino esters **6a-h**.

n-Butyllithium (2.5 M in hexanes, 1.5 eq.) was added dropwise (5 min) to a solution of *N*-(4-methoxybenzyl)-1,1,1-trimethyl-silanamine **9** (1.5 eq.) in dry toluene (0.33 M) at -78 °C. After stirring the mixture at -78 °C for 30 minutes, a solution of chiral ligand **2** (1.8 eq.) in dry toluene (1 M) was added dropwise (5 min). After stirring the mixture for a further 30 minutes at -78 °C, a solution of the appropriate *tert*-butyl ester **1** (1 eq.) and TMSCl (5 eq.) in dry toluene (2 M) was then added dropwise (5 min). The reaction mixture was stirred for 5 hours at -78 °C and then quenched via the careful addition of saturated NH_4Cl(aq). After allowing the suspension to stir and warm to room temperature, saturated $NaHCO_3$(aq) was added carefully and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine and water, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* and then purified by silica gel chromatography to afford the desired *N*-PMB-β-amino ester **6a-h**.

(R)-tert-Butyl 3-((4-methoxybenzyl)amino)-3-phenylpropanoate **6a**

(*E*)-*tert*-Butyl 3-phenylacrylate **1a** (1.18 g, 5.8 mmol) was used to prepare the title compound as a yellow oil (1.52 g, 77% yield) using general procedure 2. $[\alpha]_D^{26}$ +25.9 (*c* 3.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.43-7.26 (5H, m, Ph), 7.22 (2H, d, *J* = 8.6 Hz, C*H*CHCOCH$_3$), 6.87 (2H, d, *J* = 8.6 Hz, CHC*H*COCH$_3$), 4.09 (1H, dd, *J* = 8.6 and 5.5 Hz, C*H*NH), 3.82 (3H, s, OC*H*$_3$), 3.61 (1H, d, *J* = 12.9 Hz, NHC*H*^{A}H^B), 3.51 (1H, d, *J* = 12.9 Hz, NHCH^A*H*^{B}), 2.68 (1H, dd, *J* = 15.3 and 8.7 Hz, C*H*^{A}CH^{B}CO$_2$), 2.56 (1H, dd, *J* = 15.3 and 5.6 Hz, CH^{A}C*H*^{B}CO$_2$), 2.20 (1H, br. s, N*H*), 1.40 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 171.1, 158.6, 142.8, 132.6, 129.3, 128.5, 127.4, 113.8, 80.6, 59.1, 55.3, 50.8, 44.3, 28.0; IR (thin film) υ_{max} (cm^{-1}): 1721 (s, C=O); HRMS (ESI): *m/z* 364.1911, $C_{21}H_{27}NNaO_3$ $[M+Na]^+$ requires 364.1889.

(R)-tert-Butyl 3-(4-bromophenyl)-3-((4-methoxybenzyl)amino)-propanoate **6b**

(*E*)-*tert*-Butyl 3-(4-bromophenyl)acrylate **1b** (0.55 g, 1.95 mmol) was used to prepare the title compound as a white solid (0.64 g, 79% yield) using general procedure 2. $[\alpha]_D^{26}$ +38.6 (*c* 1.71, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.40 (2H, d, *J* = 8.3 Hz, CHC*H*CBr), 7.18 (2H, d, *J* = 8.3 Hz, C*H*CHCBr), 7.09 (2H, d, *J* = 8.5 Hz, C*H*CHCOCH$_3$), 6.77 (2H, d, *J* = 8.5 Hz, CHC*H*COCH$_3$), 3.95 (1H, dd, *J* = 8.4 and 5.4 Hz, C*H*NH), 3.72 (3H, s, OC*H*$_3$), 3.48 (1H, d, *J* = 12.5 Hz, NHC*H*^{A}H^B), 3.38 (1H, d, *J* = 12.5 Hz, NHCH^A*H*^{B}), 2.52 (1H, dd, *J* = 15.4 and 8.4 Hz, C*H*^{A}CH^{B}CO$_2$), 2.40 (1H, dd, *J* = 15.4 and 5.4 Hz, CH^{A}C*H*^{B}CO$_2$), 1.94 (1H, br. s, N*H*), 1.30 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.8, 158.6, 141.8, 132.2, 131.6, 129.3, 129.1, 121.1, 113.8, 80.9, 58.5, 55.3, 50.8, 44.1, 28.0; IR (thin film) υ_{max} (cm^{-1}): 1739 (s, C=O); HRMS (ESI): *m/z* 442.1006, $C_{21}H_{26}BrNNaO_3$ $[M+Na]^+$ requires 442.0994.

(R)-tert-Butyl 3-(2,4-dichlorophenyl)-3-((4-methoxybenzyl)-amino)propanoate **6c**

(*E*)-*tert*-Butyl 3-(2,4-dichlorophenyl)acrylate **1c** (0.45 g, 1.67 mmol) was used to prepare the title compound as a yellow oil (0.52 g, 76% yield) using general procedure 2. $[\alpha]_D^{27}$ +24.1 (*c* 1.58, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.48 (1H, d, *J* = 8.5 Hz, C*H*CHCCl), 7.29 (1H, d, *J* = 2.1 Hz, CClC*H*CCl), 7.19 (1H, dd, *J* = 8.4 and 2.1 Hz, CHC*H*CCl), 7.09 (2H, d, *J* = 8.6 Hz, C*H*CHCOCH$_3$), 6.75 (2H, d, *J* = 8.6 Hz, CHC*H*COCH$_3$), 4.44 (1H, dd, *J* = 8.6 and 4.5 Hz, C*H*NH), 3.70 (3H, s, OC*H*$_3$), 3.46 (1H, d, *J* = 12.5 Hz, NHC*H*^{A}H^B), 3.41 (1H, d, *J* = 12.8 Hz, NHCH^A*H*^{B}), 2.51 (1H, dd, *J* = 15.6 and 4.7 Hz, C*H*^{A}CH^{B}CO$_2$), 2.40 (1H, dd, *J* = 15.5 and 8.8 Hz, CH^{A}C*H*^{B}CO$_2$), 1.31 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.6, 158.7, 138.5, 134.2, 133.3, 129.4, 129.3, 127.5, 113.8, 81.0, 55.3, 55.1, 51.0, 42.2, 28.1; IR (thin film) υ_{max} (cm^{-1}): 1723 (s, C=O); HRMS (ESI): *m/z* 432.1128, $C_{21}H_{25}Cl_2NNaO_3$ $[M+Na]^+$ requires 432.1110.

(R)-tert-Butyl 3-(4-cyanophenyl)-3-((4-methoxybenzyl)amino)-propanoate **6d**

(*E*)-*tert*-Butyl 3-(4-cyanophenyl)acrylate **1d** (0.23 g, 1 mmol) was used to prepare the title compound as a yellow oil (0.23 g, 62% yield) using general procedure 2. $[\alpha]_D^{26}$ +42.7 (*c* 3.35, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.56 (2H, d, *J* = 8.4 Hz, CHC*H*CCN), 7.42 (2H, d, *J* = 8.4 Hz, C*H*CHCCN), 7.07 (2H, d, *J* = 8.6 Hz, C*H*CHCOCH$_3$), 6.76 (2H, d, *J* = 8.6 Hz, CHC*H*COCH$_3$), 4.03 (1H, dd, *J* = 8.4 and 5.3 Hz, C*H*NH), 3.71 (3H, s, OC*H*$_3$), 3.46 (1H, d, *J* = 12.9 Hz, NHC*H*^{A}H^B), 3.38 (1H, d, *J* = 12.9 Hz, NHCH^A*H*^{B}), 2.53 (1H, dd, *J* = 15.4 and 8.3 Hz, C*H*^{A}CH^{B}CO$_2$), 2.41 (1H, dd, *J* = 15.4 and 5.4 Hz, CH^{A}C*H*^{B}CO$_2$), 2.09 (1H, br. s, N*H*), 1.29 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.4, 158.7, 148.5, 132.4, 131.8, 129.3, 128.2, 118.9, 113.8, 111.2, 81.2, 58.8, 55.3, 50.9, 43.8, 28.0; IR (thin film) υ_{max} (cm^{-1}): 2226 (m, CN), 1703 (s, C=O); HRMS (ESI): *m/z* 389.1855, $C_{22}H_{26}N_2NaO_3$ $[M+Na]^+$ requires 389.1841.

(R)-tert-Butyl 3-((4-methoxybenzyl)amino)-3-(4-nitrophenyl)-propanoate **6e**

(*E*)-*tert*-Butyl 3-(4-nitrophenyl)acrylate **1e** (0. 49 g, 2 mmol) was used to prepare the title compound as a yellow oil (0.33 g, 40% yield) using general procedure 2. $[\alpha]_D^{26}$ +35.7 (*c* 2.6, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 8.12 (2H, d, *J* = 8.7 Hz, CHC*H*CNO$_2$), 7.47 (2H, d, *J* = 8.7 Hz, C*H*CHCNO$_2$), 7.06 (2H, d, *J* = 8.5 Hz, C*H*CHCOCH$_3$), 6.75 (2H, d, *J* = 8.5 Hz, CHC*H*COCH$_3$), 4.08 (1H, dd, *J* = 8.4 and 5.3 Hz, C*H*NH), 3.70 (3H, s, OC*H*$_3$), 3.46 (1H, d, *J* = 12.9 Hz, NHC*H*^{A}H^B), 3.38 (1H, d, *J* = 12.9 Hz, NHCH^A*H*^{B}), 2.53 (1H, dd, *J* = 15.4 and 8.4 Hz, C*H*^{A}CH^{B}CO$_2$), 2.42 (1H, dd, *J* = 15.4 and 5.3 Hz, CH^{A}C*H*^{B}CO$_2$), 2.09 (1H, br. s, N*H*), 1.28 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.4, 158.8, 150.7, 147.3, 131.8, 129.3, 128.3, 123.8, 113.9, 81.3, 58.5, 55.3, 50.9, 43.7, 28.0; IR (thin film) υ_{max} (cm^{-1}): 1722 (s, C=O); HRMS (ESI): *m/z* 409.1777, $C_{21}H_{26}N_2NaO_5$ $[M+Na]^+$ requires 409.1739.

(R)-tert-Butyl 3-((4-methoxybenzyl)amino)-3-(thiophen-2-yl)-propanoate **6f**

(*E*)-*tert*-Butyl 3-(thiophen-2-yl)acrylate **1f** (0.55 g, 2.61 mmol) was used to prepare the title compound as a colourless oil (0.78 g, 86% yield) using general procedure 2. $[\alpha]_D^{26}$ +23.5 (*c* 3.4, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.19-7.12 (3H, m, C*H*CHCOCH$_3$, C*H*S), 6.89-6.86 (2H, m, C*HCH*CS), 6.77 (2H, d, *J* = 8.6 Hz, CHC*H*COCH$_3$), 4.30 (1H, dd, *J* = 8.0 and 5.5 Hz, C*H*NH), 3.72 (3H, s, OC*H*$_3$), 3.63 (1H, d, *J* = 12.8 Hz, NHC*H*^{A}H^B), 3.50 (1H, d, *J* = 12.9 Hz, NHCH^A*H*^{B}), 2.64 (1H, dd, *J* = 15.5 Hz, 8.3, C*H*^{A}CH^{B}CO$_2$), 2.56 (1H, dd, *J* = 15.4 and 5.5 Hz, CH^{A}C*H*^{B}CO$_2$), 2.07 (1H, br. s, N*H*), 1.32 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.7, 158.6, 147.8, 132.2, 129.5, 126.5, 124.5, 124.4, 113.8, 80.1, 55.3, 54.6, 50.6, 44.6, 28.1; IR (thin film) υ_{max} (cm^{-1}): 1722 (s, C=O); HRMS (ESI): *m/z* 370.1450, $C_{19}H_{25}NNaO_3S$ $[M+Na]^+$ requires 370.1453.

(R)-tert-Butyl 3-(furan-2-yl)-3-((4-methoxybenzyl)amino)propanoate **6g**

(*E*)-*tert*-Butyl 3-(furan-2-yl)acrylate **1g** (0. 49 g, 2.57 mmol) was used to prepare the title compound as a yellow oil (0.62 g, 73% yield) using general procedure 2. $[\alpha]_D^{26}$ +57.3 (*c* 3.3, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.37 (1H, d, *J* = 1.9 Hz, C*H*O), 7.21 (2H, d, *J* = 8.7 Hz, C*H*CHCOCH$_3$), 6.84 (2H, d, *J* = 8.7 Hz, CHC*H*COCH$_3$), 6.32 (1H, dd, *J* = 3.1 and 1.9 Hz, C*H*CHO), 6.20 (1H, d, *J* = 3.1 Hz, C*H*CHCHCO), 4.14 (1H, dd, *J* = 7.7 and 6.4 Hz, C*H*NH), 3.79 (3H, s, OC*H*$_3$), 3.68 (1H, d, *J* = 12.6 Hz, NHC*H*^{A}H^B), 3.54 (1H, d, *J* = 12.6 Hz, NHCH^A*H*^{B}), 2.18-2.01 (2H, m, C*H*$_2$CO$_2$), 1.96 (1H, br. s, N*H*), 1.40 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.7, 158.6, 155.3, 141.7, 132.2, 129.4, 113.7, 110.0, 106.8, 80.7, 55.3, 52.3, 50.5, 41.1, 28.0; IR (thin film) υ_{max} (cm^{-1}): 1725 (s, C=O); HRMS (ESI): *m/z* 354.1691, $C_{19}H_{25}NNaO_4$ $[M+Na]^+$ requires 354.1681.

(R)-tert-Butyl 3-((4-methoxybenzyl)amino)heptanoate **6h**

(*E*)-*tert*-Butyl hept-2-enoate **1h** (1.01 g, 5.5 mmol) was used to prepare the title compound as a yellow oil (1.2 g, 68% yield) using general procedure 2. $[\alpha]_D^{26}$ -3.5 (*c* 2.02, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.20 (2H, d, *J* = 8.6 Hz, C*H*CHCOCH$_3$), 6.80 (2H, d, *J* = 8.6 Hz, CHC*H*COCH$_3$), 3.72 (3H, s, OC*H*$_3$), 3.65 (2H, s, NHC*H*$_2$), 2.90 (1H, quintet, *J* = 6.1 Hz, C*H*NH), 2.29 (2H, d, *J* = 6.1 Hz, C*H*$_2$CO$_2$), 1.65 (1H, br. s, N*H*), 1.37 (9H, s, C(C*H*$_3$)$_3$), 1.30-1.14 (6H, m, CH$_3$C*H*$_2$C*H*$_2$C*H*$_2$), 0.82 (3H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 172.4, 158.9, 133.1, 129.7, 114.1, 80.8, 55.7, 54.8, 50.8, 40.8, 34.4, 28.5, 28.3, 23.2, 14.4; IR (thin film) υ_{max} (cm^{-1}): 1722 (s, C=O); HRMS (ESI): *m/z* 322.2377, $C_{19}H_{32}NO_3$ $[M+H]^+$ requires 322.2381.

(R,E)-tert-Butyl 3-((4-methoxybenzylidene)amino)-3-phenylpropanoate **15a**

Cerium ammonium nitrate (1.72 g, 2.94 mmol) was added to a solution of (*R*)-*tert*-Butyl 3-((4-methoxybenzyl)amino)-3-phenylpropanoate **6a** (0.251 g, 0.736 mmol) in MeCN-H_2O (5:1, 9.4 mL) and the bright orange solution stirred at room temperature for 2 hours, before saturated $NaHCO_3$(aq) (50 mL) was added. The mixture was partitioned between brine and Et_2O and the aqueous layer further extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound as a yellow oil (0.204 g, 82% yield). $[\alpha]_D^{22}$ -30.0 (*c* 2.9, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 8.36 (1H, s, C*H*=N), 7.76 (2H, d, *J* = 8.5 Hz, C*H*CHCOCH$_3$), 7.50 (2H, d, *J* = 7.7 Hz, Ph), 7.41- 7.36 (2H, m, Ph), 7.32-7.27 (1H, m, Ph), 6.96 (2H, d, *J* = 8.5 Hz, CHC*H*COCH$_3$), 4.82 (1H, dd, *J* = 9.5 and 4.9 Hz, C*H*N=CH), 3.89 (3H, s, OC*H*$_3$), 2.97 (1H, dd, *J* = 15.0 and 1.5 Hz, C*H*^{A}H^B), 2.86 (1H, dd, *J* = 14.9 and 4.8 Hz, CH^A*H*^{B}), 1.39 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.7, 161.7, 160.5, 143.1, 130.1, 129.2, 128.5, 127.2, 127.0, 113.9, 80.6, 71.4, 55.4, 44.8, 28.1; IR (thin film) υ_{max} (cm^{-1}): 1723 (s, C=O); HRMS (ESI): *m/z* 362.1754, $C_{21}H_{25}NNaO_3$ $[M+Na]^+$ requires 362.1732.

General Procedure 3: Oxidative deprotection of *tert*-butyl *N*-PMB-β-amino esters **6a-h**

Cerium ammonium nitrate (4 eq.) was added to a solution of the appropriate *N*-PMB-β-amino ester **6** (1 eq.) in MeCN-H_2O (5:1, 0.2 M) and the bright orange solution stirred at room temperature for 2 hours before saturated $NaHCO_3$(aq) (50 mL) was added. The mixture was partitioned between brine and Et_2O and the aqueous layer further extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant crude product was dissolved in MeCN-H_2O (5:1, 0.2 M), acetic acid (15 eq.) was then added and the reaction mixture stirred at room temperature for 48 hours. The reaction mixture was then diluted with water (5mL) and washed with Et_2O (3 x 10 mL). The aqueous layer was basified with saturated $NaHCO_3$(aq), extracted with Et_2O (3 x 20 mL), and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude product that was purified by chromatography to afford the desired *tert*-butyl β-amino ester **5a-h**.

(R)-tert-Butyl 3-amino-3-phenylpropanoate **5a**

N-PMB-β-amino ester **6a** (0.1 g, 0.3 mmol) was used to prepare the title compound as a yellow oil (0.044 g, 68% yield) using general procedure 3. $[\alpha]_D^{27}$ +20.0 (*c* 1.2, $CHCl_3$) (Lit.[29] $[\alpha]_D^{20}$ +19.7 (*c* 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.15-7.33 (5H, m, Ph), 4.31 (1H, t, *J* = 6.9 Hz, C*H*NH), 2.52 (2H, d, *J* = 7.0 Hz, C*H*$_2$CO$_2$), 2.41 (2H, br. s, N*H*$_2$), 1.35 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 171.4, 145.4, 128.5, 127.3, 126.3, 80.7, 52.8, 45.4, 28.1; IR (thin film) υ_{max} (cm^{-1}): 3312 (w, N-H), 1725 (s, C=O); HRMS (ESI): *m/z* 222.1500, $C_{13}H_{20}NO_2$ $[M+H]^+$ requires 222.1489.

(R)-tert-Butyl 3-amino-3-(4-bromophenyl)propanoate **5b**

N-PMB-β-amino ester **6b** (0.19 g, 0.46 mmol) was used to prepare the title compound as a colourless oil (0.077 g, 56% yield) using general procedure 3. $[\alpha]_D^{23}$ +21.7 (*c* 0.92, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.37 (2H, d, *J* = 8.5 Hz, CHC*H*CBr), 7.17 (2H, d, *J* = 8.5 Hz, C*H*CHCBr), 4.29 (1H, br. s, C*H*NH$_2$), 2.47 (2H, d, *J* = 6.7 Hz, C*H*$_2$CO$_2$), 1.76 (2H, br. s, N*H*$_2$), 1.34 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 171.0, 143.7, 131.6, 128.2, 121.0, 81.0, 52.2, 45.1, 28.1; IR (thin film) υ_{max} (cm^{-1}): 3662 (m, N-H), 3376 (w, N-H), 1722 (s, C=O); HRMS (ESI): *m/z* 300.0620, $C_{13}H_{19}BrNO_2$ $[M+H]^+$ requires 300.0599.

(R)-tert-Butyl 3-amino-3-(2,4-dichlorophenyl)propanoate **5c**

N-PMB-β-amino ester **6c** (0.14 g, 0.33 mmol) was used to prepare the title compound as a yellow oil (0.066 g, 68% yield) using general procedure 3. $[\alpha]_D^{24}$ +37.6 (*c* 0.85, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.44 (1H, d, *J* = 8.4 Hz, C*H*CHCCl), 7.20 (1H, d, *J* = 1.8 Hz, CClC*H*CCl), 7.8 (1H, dd, *J* = 8.4 and 1.9 Hz, CClC*H*CH), 4.70 (1H, br. s, C*H*NH$_2$), 2.60 (1H, dd, *J* = 16.0 and 4.0 Hz, NHC*H*^{A}H^B), 2.44 (1H, dd, *J* = 16.0 and 9.0 Hz, NHCH^A*H*^{B}), 2.29 (2H, br. s, N*H*$_2$), 1.36 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.8, 136.4, 133.4, 133.3, 129.4, 128.4, 127.5, 81.2, 48.7, 42.8, 28.1; IR (thin film) υ_{max} (cm^{-1}): 3383 (w, N-H), 1725 (s, C=O); HRMS (ESI): *m/z* 312.0525, $C_{13}H_{17}Cl_2NNaO_2$ $[M+Na]^+$ requires 312.0534.

(R)-tert-Butyl 3-amino-3-(4-cyanophenyl)propanoate **5d**

N-PMB-β-amino ester **6d** (0.16 g, 0.45 mmol) was used to prepare the title compound as a yellow oil (0.057 g, 51% yield) using general procedure 3. $[\alpha]_D^{21}$ +16.0 (*c* 0.5, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H = 7.68 (2H, d, *J* = 8.0 Hz, CHC*H*CCN), 7.55 (2H, d, *J* = 8.0 Hz, C*H*CHCCN), 4.50 (1H, br. s, C*H*NH$_2$), 2.63 (2H, d, *J* = 6.6 Hz, C*H*$_2$CO$_2$), 2.14 (2H, br. s, N*H*$_2$), 1.46 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 171.6, 145.2, 132.4, 127.3, 118.8, 111.3, 81.3, 52.5, 44.8, 28.1; IR (thin film) υ_{max} (cm^{-1}): 2228 (m, CN), 1723 (s, C=O); HRMS (ESI): *m/z* 247.1448, $C_{14}H_{19}N_2O_2$ $[M+H]^+$ requires 247.1447.

(R)-tert-Butyl 3-amino-3-(4-nitrophenyl)propanoate **5e**

N-PMB-β-amino ester **6e** (0.13 g, 0.33 mmol) was used to prepare the title compound as a yellow oil (0.057 g, 65% yield)

using general procedure 3. $[\alpha]_D^{25}$ +9.1 (*c* 0.55, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ_H = 8.11 (2H, d, *J* = 8.9 Hz, CHC*H*CNO$_2$), 7.49 (2H, d, *J* = 8.6 Hz, C*H*CHCNO$_2$), 4.42 (1H, br. s, C*H*NH$_2$), 2.51 (2H, d, *J* = 6.7 Hz, C*H*$_2$CO$_2$), 1.78 (2H, br. s, N*H*$_2$), 1.34 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.6, 152.2, 147.2, 127.4, 123.8, 81.3, 52.3, 45.0, 28.1; IR (thin film) υ_{max} (cm^{-1}): 3382 (w, N-H), 1720 (s, C=O); HRMS (ESI): *m/z* 289.1156, $C_{13}H_{18}N_2NaO_4$ $[M+Na]^+$ requires 289.1164.

(R)-tert-Butyl 3-amino-3-(thien-2-yl)propanoate **5f**

N-PMB-β-amino ester **6f** (0.2 g, 0.59 mmol) was used to prepare the title compound as a yellow oil (0.048 g, 36% yield) using general procedure 3. $[\alpha]_D^{25}$ +18.2 (*c* 0.44, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ_H = 7.27 (1H, dd, *J* = 1.7 and 0.7 Hz, C*H*S), 6.23 (1H, dd, *J* = 3.1 and 1.8 Hz, C*H*CHCS), 6.09 (1H, d, *J* = 3.2 Hz, C*H*CCS), 4.31 (1H, dd, *J* = 8.3 and 4.9 Hz, C*H*NH), 2.68 (1H, dd, *J* = 15.8 and 5.0 Hz, C*H*^{A}H^{B}CO$_2$), 2.55 (1H, dd, *J* = 15.4 and 8.4 Hz, *CH*^{A}C*H*^{B}CO$_2$), 2.34 (1H, br. s, N*H*$_2$), 1.3 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.8, 136.9, 128.6, 128.1, 127.1, 81.0, 46.8, 42.1, 28.1; IR (thin film) υ_{max} (cm^{-1}): 1727 (s, C=O); HRMS (ESI): *m/z* 228.1078, $C_{11}H_{18}NO_2S$ $[M+H]^+$ requires 228.1058.

(R)-tert-Butyl 3-amino-3-(furan-2-yl)propanoate **5g**[38]

N-PMB-β-amino ester **6g** (0.1 g, 0.31 mmol) was used to prepare the title compound as a pale green oil (0.048 g, 73% yield) using general procedure 3. $[\alpha]_D^{25}$ +12.4 (*c* 1.05, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ_H = 7.12 (1H, dd, *J* = 4.5 and 1.9 Hz, C*H*CHO), 6.89-6.84 (2H, m, C*H*OCC*H*), 4.58 (1H, dd, *J* = 8.4 and 4.9 Hz, C*H*NH$_2$), 2.65 (1H, dd, *J* = 15.9 and 4.9 Hz, C*H*^{A}H^{B}CO$_2$), 2.57 (1H, dd, *J* = 15.9 and 8.4 Hz, CH^A*H*^{B}CO$_2$), 2.22 (2H, br. s, N*H*$_2$), 1.36 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 170.8, 144.0, 142.6, 124.0, 110.2, 81.0, 48.7, 45.6, 28.1; IR (thin film) υ_{max} (cm^{-1}): 3385 (w, N-H), 1723 (s, C=O); HRMS (ESI): *m/z* 212.1286, $C_{11}H_{18}NO_3$ $[M+H]^+$ requires 212.1287.

(R)-tert-Butyl 3-aminoheptanoate **5h**

N-PMB-β-amino ester **6h** (0.21 g, 0.66 mmol) was used to prepare the title compound as a colourless oil (0.089 g, 60% yield) using general procedure 3. $[\alpha]_D^{23}$ +33.3 (*c* 1.2, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ_H = 3.13-3.00 (1H, m, C*H*NH$_2$), 2.31 (1H, dd, *J* = 15.6 and 4.0 Hz, C*H*^{A}H^{B}CO$_2$), 2.10 (1H, dd, *J* = 15.6 and 8.8 Hz, CH^A*H*^{B}CO$_2$), 1.61 (2H, br. s, N*H*$_2$), 1.39 (9H, s, C(C*H*$_3$)$_3$), 1.36-1.19 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$), 0.83 (3H, t, *J* = 6.3 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C = 172.1, 80.5, 48.4, 43.8, 37.2, 28.2, 28.1, 22.7, 14.0; IR (thin film) υ_{max} (cm^{-1}): 3385 (w, N-H), 1723 (s, C=O); HRMS (ESI): *m/z* 202.1801, $C_{11}H_{24}NO_2$ $[M+H]^+$ requires 202.1807.

General Procedure 4: Determination of the Enantiomeric Excess of (*R*)-*tert*-butyl β-Amino Esters.[36b]

Each (*R*)-*tert*-butyl β-amino ester (1 eq.) and K_2CO_3 (1.1 eq.) were suspended in a minimum amount of $CDCl_3$. 2-Formyl-phenylboronic acid (1.1 eq.), (*R*)-(BINOL) (1.1 eq.), 4 Å molecular sieves, and $CDCl_3$ were then added in order to produce a 0.1 M solution of the β-amino ester. The solution was stirred for 10 min before being filtered through a small pad of Celite and the solution analyzed by ^1H NMR spectroscopy.

5. Acknowledgments

We would like to thank the Engineering and Physical Sciences Research Council (EPSRC) and Syngenta for CASE funding (RMA).

6. References

1. a) Kuhl, A.; Hahn, M. G. *Amino Acids*, 2005, *29*, 89. b) Kiss, L.; Fulop, F. *Chem. Rev.*, 2014, *114*, 1116. c) Kudo, F.; Miyanaga, A.; Eguchi, T. *Nat. Prod. Rep*., 2014, *31*, 1056. d) Lelais, G.; Seebach, D. *Biopolymers*, 2004, *76*, 206.
2. a) Seebach, D.; Gardiner, J. *Acc. Chem. Res.*, 2008, *41*, 1366. b) Aguilar, M. I.; Purcell, A. W.; Devi, R.; Rossjohn, J.; Smith, A. I.; Perlmutter, P. *Org. Biomol. Chem.*, 2007, *5*, 2884. c) Tew, G. N.; Scott, R. W.; Klein, M. L.; DeGrado, W. F. *Acc. Chem. Res.*, 2010, *43*, 30.
3. Frackenpohl, J.; Arvidsson, P. I.; Schreiber, J. V.; Seebach, D. *ChemBioChem*, 2001, *2*, 445.
4. Godballe, T.; Nilsson, L. L.; Petersen, P. D.; Jenssen, H. *Chem. Biol. Drug Des*., 2011, *77*, 107.
5. Karlsson, A. J.; Pomerantz, W. C.; Weisblum, B.; Gellman, S. H.; Palecek, S. P. *J. Am. Chem. Soc.*, 2006, *128*, 12630.
6. English, E. P.; Chumanov, R. S.; Gellman, S. H.; Compton, T. *J. Biol. Chem.*, 2006, *281*, 2661.
7. Kritzer, J. A.; Lear, J. D.; Hodsdon, M. E.; Schepartz, A. *J. Am. Chem. Soc*., 2004 *126*, 9468.
8. Werder, M.; Hauser, H.; Abele, S.; Seebach, D. *Helv. Chim. Acta*, 1999, *82*, 1774.
9. Seebach, D.; Matthews, J. L. *Chem. Commun.*, 1997, 2015.
10. a) Azzarito, V.; Long, K.; Murphy, N. S.; Wilson, A. J. *Nat. Chem.* 2013, *5*, 161. b) Kritzer, J. A.; Stephens, O. M.; Guarracino, D. A.; Reznik, S. K.; Schepartz, A. *Bioorg. Med. Chem.*, 2005, *13*, 11.
11. a) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev*., 2010, *39*, 1656. b) Juaristi, E.; Soloshonok, V. A. (2005) Enantioselective synthesis of β-amino acids. 2nd Edn. Wiley-VCH: New York. c) Liu, M.; Sibi, M. P. *Tetrahedron*, 2002, *58*, 7991.
12. a) Liljeblad, A.; Kanerva, L. T. *Tetrahedron*, 2006, *62*, 5831. b) Goodman, C. G.; Do, D. T.; Johnson, J. S. *Org. Lett.*, 2013, *15*, 2446.
13. a) Hart, D. J.; Ha, D. C. *Chem. Rev.*, 1989, *89*, 1447. b) Tang, T. P.; Ellman, J. A. *J. Org. Chem*., 2002, *67*, 7819.
14. Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem.*, 1999, *64*, 6411.
15. a) Guichard, G.; Abele, S.; Seebach, D. *Helv. Chim. Acta* 1998, *81*, 187. b) Caputo, R.; Longobardo, L. *Amino Acids*, 2007, *32*, 401.
16. a) Ikemoto, N.; Tellers, D. M.; Dreher, S. D.; Liu, J. C.; Huang, A.; Rivera, N. R.; Njolita, E.; Hsiao, Y.; McWilliams, J. C.; Williams, J. M.; Armstrong III J. D.; Sun, Y.; Mathre, D. J.; Grabowski, E. J. J.; Tillyer, R. D. *J. Am. Chem. Soc*., 2004, *126*, 3048. b) Pena, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc*., 2002, *124*, 14552.
17. a) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* 2009, 65, 9657. b) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur*. J., 2009, *15*, 11058. c) Vicario, J. L.; Badia, D.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proc. Int*., 2005, *37*, 513. d) Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc.*, 2007, *129*, 8064.
18. Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.*, 1997, 62, 6274.
19. a) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry*, 2005, 16, 2833. b) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry*, 2012, *23*, 1111.
20. Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc*., 2003, *125*, 2886.
21. Harada, S.; Sakai, T.; Takasu, K.; Yamada, K.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem*., 2012, *77*, 7212.

22. Sakai, T.; Kawamoto, Y.; Tomioka, K. *J. Org. Chem*. 2006, *71*, 4706.
23. Suzuki, M.; Kawamoto, Y.; Sakai, T.; Yamamoto, Y.; Tomioka, K. *Org. Lett*., 2009, *11*, 653.
24. a) Harada, S.; Sakai, T.; Takasu, K.; Yamada, K.; Yamamoto, Y.; Tomioka, K. *Chem. Asian J*., 2012, *7*, 2196. b) Harada, S.; Sakai, T.; Takasu, K.; Yamada, K.; Yamamoto, Y.; Tomioka, K. *Tetrahedron*, 2013, *69*, 3264.
25. Yamada, K.; Yamashita, M.; Sumiyoshi, T.; Nishimura, K.; Tomioka, K. *Org. Lett*., 2009, *11*, 1631.
26. Sakai, T.; Doi, H.; Kawamoto, Y.; Yamada, K.; Tomioka, K. *Tetrahedron Lett*., 2004, *45*, 9261.
27. a) Sakai, T.; Doi, H.; Tomioka, K. *Tetrahedron*, 2006, *62*, 8351. b) Doi, H.; Sakai, T.; Yamada, K.; Tomioka, K. *Chem. Commun*., 2004, 1850.
28. a) Bull, S.D.; Davies, S.G.; Kelly, P.M.; Gianotti, M.; Smith, A. D. *J. Chem. Soc. Perkin Trans. 1*, 2001, 3106. b) Bul
l, S. D.; Davies, S. G.; Smith, A. D. *J. Chem. Soc. Perkin Trans. 1*, 2001, 2931. c) Bull, S. D.; Davies, S. G.; Smith, A. D.; *Tetrahedron:Asymmetry*, 2001, *12*, 2941; d) Bull, S. D.; Davies, S. G.; Roberts, P. M.; Savory, E. D.; Smith, A. D. *Tetrahedron*, 2002, *58*, 4629. e) Koutsaplis, M.; Andrews, P. C.; Bull, S. D.; Duggan, P. J.; Fraser, B. H.; Jensen, P.; *Chem. Commun*., 2007, 3580. f) Evans, C. D.; Mahon, M. F.; Andrews, P. C.; Muir, J.; Bull, S. D. *Org. Lett.* 2011, *13*, 6276.
29. Bull, S. D.; Davies, S. G.; Delgado-Ballester, S.; Fenton, G.; Kelly, P. M.; Smith, A. D. *Synlett*, 2000, 1257.
30. a) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *J. Chem. Soc. Perkin Trans. 1*, 2000, 3765. b) Bull, S. D.; Davies, S. G.; Fenton, G.; Mulvaney, A. W.; Prasad, R. S.; Smith, A. D. *Chem. Commun.*, 2000, 337.
31. a) Bull, S. D.; Davies, S. G.; Delgado-Ballester, S.; Kelly, P. M.; Kotchie, L. J.; Gianotti, M.; Laderas, M.; Smith, A. D. *J. Chem. Soc. Perkin Trans. 1*, 2001, 3112. b) Bull, S. D.; Davies, S. G.; Fox, D. J.; Gianotti, M.; Kelly, P. M.; Pierres, C.; Savory, E. D.; Smith, A. D. *J. Chem. Soc. Perkin Trans.* 1, 2002, 1858. c) Davies, S. G.; Fletcher, A. M.; Lv, L.; Roberts, P. M.; Thomson, J. E. *Tetrahedron:Asymmetry*, 2012, *23*, 910. d) Davies, S. G.; Fletcher, A. M.; Lv, L.; Roberts, P. M.; Thomson, J. E. *Tetrahedron Lett*., 2012, *53*, 3052. e) Davies, S. G, Lee, J. A.; Roberts, P. M.; Thomson, J. E.; West, C. J. *Tetrahedron*, 2012, *68*, 4302.
32. Yamamoto, Y.; Nasu, H.; Tomioka, K. *Tetrahedron*, 2013, *69*, 3836.
33. Yamamoto, Y.; Yasuda, Y.; Oulyadi, H.; Maddaluno, J.; Tomioka, K. *Tetrahedron*, 2010, *66*, 2470.
34. The use of 5 equivalents of TMSCl in these aza-conjugate addition reactions proved optimal, with the use of fewer equivalents of TMSCl leading to lower yields of *N*-PMB-β-amino ester **5a**. This suggests that the presence of excess TMSCl results in efficient formation of a reactive enantioselective lithium amide species, rather than simply acting as a source of LiCl, whose presence is also known to affect the aggregation state and reactivity of lithium amide species. See: Clegg, W.; Greer, J. C.; Hayes, J. M; Mair, F. S.; Nolan, P. M. O'Neil, P. A. *Inorg. Chim. Acta.*, **1997**, *258*, 1.
35. *Tert*-butyl enoate esters **3** were used as acceptors in these studies to ensure that competing 1,2-addition of silyl-lithium amide **1e** to their carbonyl groups did not occur. For a previous report where addition of a lithium amide **1a** to a methyl dienoate acceptor resulted in a mixture of β-amino ester and amide products see: Y.Yamamoto, N. Asao, T. Uyehara, *J. Am. Chem. Soc.*, **1992**, *114*, 5427.
36. a) Perez-Fuertes, Y.; Kelly, A. M.; Johnson, A. L.; Arimori, S.; Bull, S. D.; James, T. D. *Org. Lett*., 2006, *8*, 609. b) Perez-Fuertes, Y.; Kelly, A. M. Fossey, J. S.; Powell, M. E.; Bull, S. D.; James, T. D. *Nat. Prot*., 2008, *3*, 210. c) Powell, M. E.; Kelly, A. M.; Bull, S. D. *Tetrahedron Lett.*, 2009, *50*, 876. d) Perez-Fuertes, Y.; Taylor, J. E.; Tickell, D. A.; Mahon, M. F.; Bull, S. D.; James, T. D. *J. Org. Chem.*, 2011, *15*, 6038.
37. Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.*, 1998, *63*, 9351.
38. Awasthi, A. K.; Boys, M. L.; Cain-Janicki, K. J.; Colson, P. J.; Doubleday, W. W.; Duran, J. E.; Farid P. N. *J. Org. Chem.*, 2005, *70*, 5387.