Asymmetric synthesis of β-pyridyl-β-amino acid derivatives

Steven D. Bull, Stephen G. Davies,* David. J. Fox, Massimo Gianotti, Peter M. Kelly, Camille Pierres, Edward D. Savory and Andrew D. Smith

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY. E-mail: steve.davies@chemistry.ox.ac.uk

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The conjugate additions of homochiral lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide to *tert*-butyl 3-(3-pyridyl)- and *tert*-butyl 3-(4-pyridyl)-prop-2-enoates proceed in 84% de, and after subsequent recrystallisation and oxidative *N*-deprotection furnish the (*S*)-3-(3-pyridyl)- and (*S*)-3-(4-pyridyl)-β-amino acid derivatives in 97% ee and 98% ee respectively. Conjugate additions of lithium *N*-benzyl-*N*-α-methyl-4-methoxybenzylamide to *tert*-butyl 3-(2-pyridyl)prop-2-enoates proceed with low levels of diastereoselectivity unless the 3-(2-pyridyl) ring is substituted. Application of this methodology allows the asymmetric synthesis of (*R*)-*tert*-butyl 3-(2-chloro-3-methoxymethoxy-6-pyridyl)-3-aminopropanoate, the protected β-amino ester component of kedarcidin, in 97% ee.

Introduction

Homochiral β-amino acids have attracted much academic and commercial interest, primarily due to their existence in naturally occurring peptides and pseudopeptides and as key fragments within potential drug candidates.[1] Within this growing field, 3-pyridyl-β-amino acid derivatives have emerged as a specific sub-class of β-amino acid which have been shown to possess potent pharmacological activity.[2] As representative examples of this molecular class, a substituted 3-(2-pyridyl)-β-amino acid moiety has been identified as the β-amino acid component of kedarcidin **1**, a potent antitumour antibiotic.[3] Similarly, the 3-(3-pyridyl)-β-amino acid is a key component of elarofiban (RWJ-53308) **2**, an orally active antagonist of the platelet fibrinogen receptor (GP IIb/IIIa antagonist),[4] whilst the 3-(4-pyridyl)-β-amino paclitaxel analogue **3** has been shown to have cytoxicity comparable to that of Taxol[5] (Fig. 1).

Due to this diverse array of biological activity, a variety of routes towards the asymmetric synthesis of β-pyridyl-β-amino acid derivatives have been reported. For instance, Davis *et al.* have used the diastereoselective addition of the lithium enolate of ethyl acetate to homochiral sulfinimine **4** (78% de) and subsequent diastereoisomer separation and sulfinamide hydrolysis to prepare β-3-pyridyl-β-amino acid derivative **5** in >97% ee.[6] In an alternative approach, Bovy *et al.* have shown that conjugate addition of lithium (*R*)-*N*-α-methylbenzyl-*N*-trimethylsilyl amide to the 3-(3-pyridyl)-α,β-unsaturated ester **7** proceeds to give β-amino ester **6** with high diastereoselectivity,[7] although removal of the stereodirecting α-methylbenzyl protecting group to give the amino ester occurred with partial racemisation, giving **5** in moderate yield and 90% ee (Scheme 1).

An alternative approach, recently reported by Zhang *et al.*, has shown that the stereoselective reduction of chiral enamine **8** to furnish **9** proceeds with moderate stereoselectivity, although recrystallisation to homogeneity, followed by removal of the *N*-protecting group *via* treatment with formic acid, offers a route to **10** in >95% ee (Scheme 2).[8]

We have previously developed efficient routes to a range of homochiral β-amino acid derivatives utilising the conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated esters and subsequent *N*-deprotection.[9] The application of this strategy for the asymmetric synthesis of the set of 3-(2-pyridyl)-, 3-(3-pyridyl)- and 3-(4-pyridyl)-β-amino acid derivatives is reported herein.

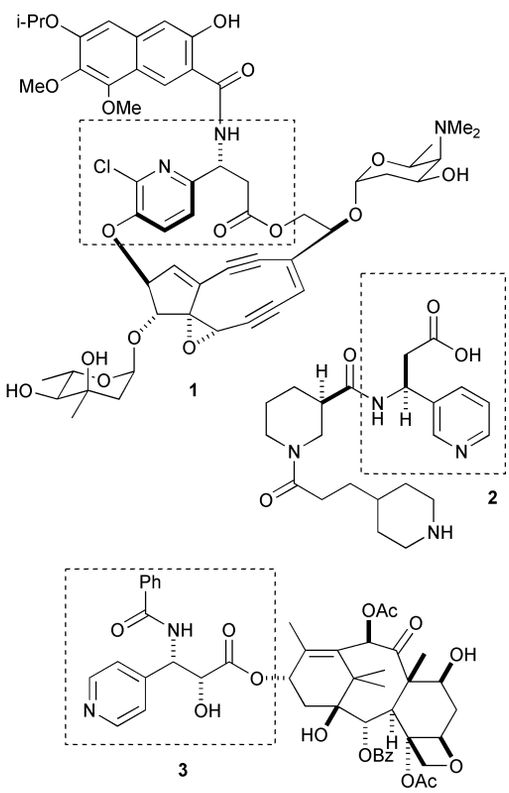

Fig. 1

Results and discussion

Asymmetric synthesis of 3-(3-pyridyl)-β-amino ester 14

Synthesis of a 3-(3-pyridyl)-β-amino acid derivative was chosen as the initial synthetic target for investigation. Thus, *tert*-butyl 3-(3-pyridyl)prop-2-enoate **12** was prepared by Wittig reaction of pyridine-3-carbaldehyde **11** with (*tert*-butyloxycarbonylmethylene)triphenylphosphorane, furnishing (*E*)-**12** as a single diastereoisomer in 75% yield after purification. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide afforded (3*S*,α*R*)-*tert*-butyl 3-(3-pyridyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate **13** in 83% yield and 98% de.[10] Attempted removal of the *N*-benzyl protecting groups of

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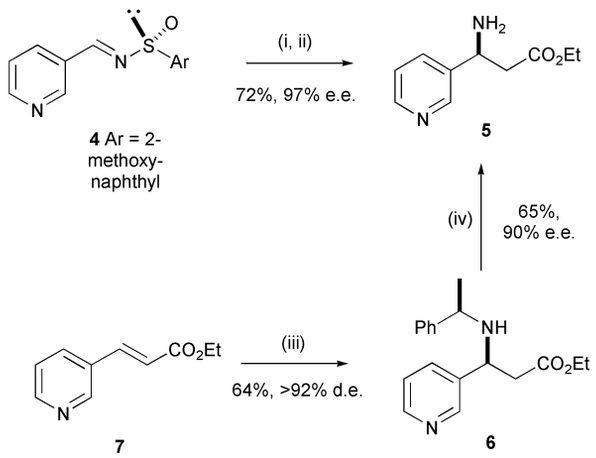
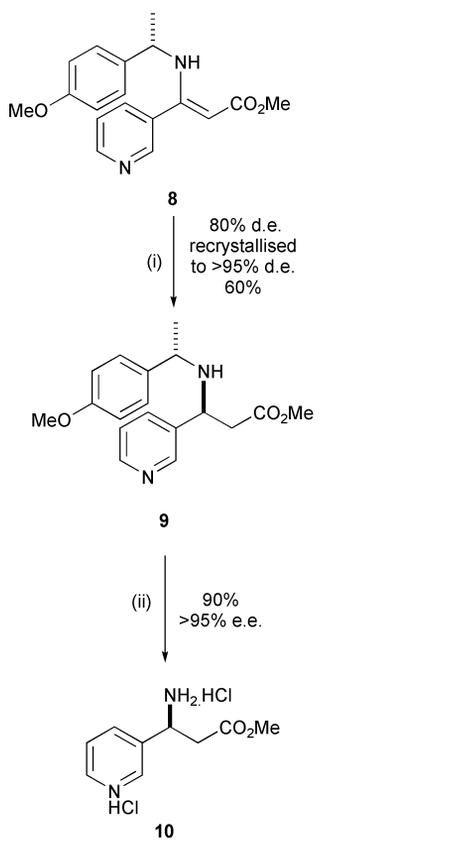


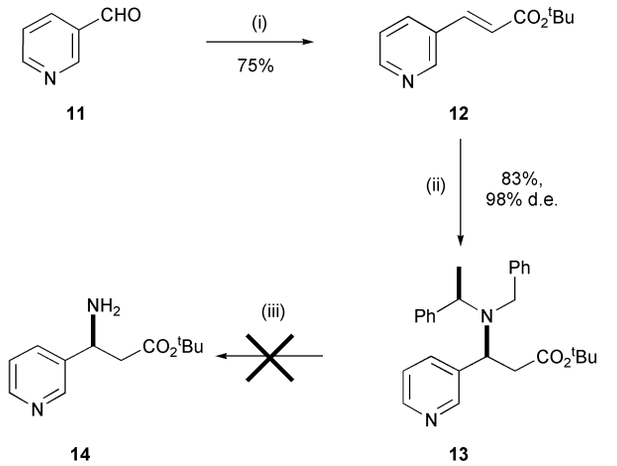
Scheme 1 *Reagents and conditions:* (i). CH_3CO_2Et, LiHMDS; (ii). TFA, EtOH; (iii). lithium (*R*)-*N*-α-methylbenzyl(trimethylsilyl)amide (1.6 eq), −78 °C, THF; (iv). Pd/C, cyclohexa-1,3-diene, AcOH.



Scheme 2 *Reagents and conditions:* (i). $Pd(OH)_2/C$, AcOH–MeOH, 1 atm H_2, rt then recrystallisation; (ii). HCO_2H, Et_3SiH then HCl, MeOH, EtOAc.

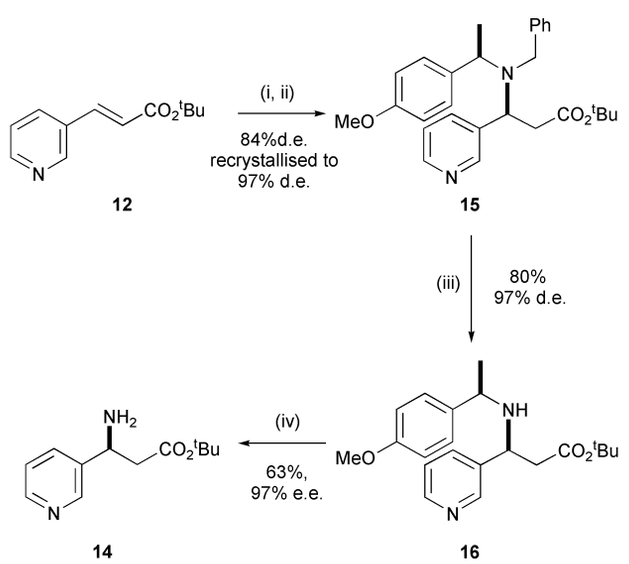
β-amino ester **13** *via* palladium catalysed hydrogenation[11] under a range of conditions gave a complex mixture of inseparable products, primarily arising from partial reduction of the pyridyl ring. Further attempts at *N*-benzyl deprotection *via* transfer hydrogenation, as previously described by Bovy *et al.*.[7] for the related mono-*N*-benzylated ester **6** led to pyridyl-reduction (Scheme 3).

The susceptibility of the pyridine ring to reduction upon hydrogenation led us to an alternative approach for the synthesis of β-(3-pyridyl)-β-amino acid derivatives based on our recent demonstration that tertiary *N*-benzyl amines are susceptible to oxidative deprotection with CAN.[12] Thus, addition of lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide[13] to α,β-unsaturated ester **12** proceeded to give (3*S*,α*R*)-*tert*-butyl 3-(3-pyridyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxy-



Scheme 3 *Reagents and conditions:* (i). (*tert*-butyloxycarbonylmethylene)triphenylphosphorane (1.1 eq), DCM, rt; (ii). lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (1.6 eq), THF, −78 °C; (iii). H_2 (1–5 atm), MeOH, $Pd(OH)_2/C$.

benzylamino)propanoate **15** in 84% de.[10] While the level of diastereoselectivity observed upon addition of lithium (*R*)-*N*-benzyl-*N*-4-methoxy-α-methylbenzylamide to the 3-pyridyl acceptor **12** is lower then that observed for the addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, β-amino ester **15** was readily purified to homogeneity (97% de) by recrystallisation. Subsequent treatment with CAN[12,13] (2.1 eq) afforded (3*S*,α*R*)-*tert*-butyl 3-(*N*-α-methyl-4-methoxybenzylamino)-3-(3-pyridyl)propanoate **16** in 80% yield, which upon further treatment with CAN[12,13] (4.0 eq) resulted in removal of the *N*-α-methyl-4-methoxybenzyl protecting group to afford the required (*R*)-*tert*-butyl 3-amino-3-(3-pyridyl)propanoate **14** in 63% yield.[14] The enantiomeric excess of β-amino ester **14** was shown to be 97% *via* derivatisation with Mosher's acid chloride and comparison of both ^1H and ^{19}F NMR spectra of the resulting amides with that of an authentic scalemic sample (Scheme 4).[15]

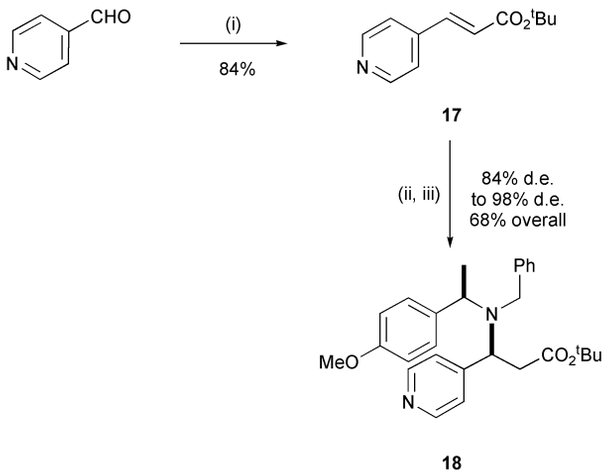


Scheme 4 *Reagents and conditions:* (i). lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide (1.6 eq), −78 °C, THF; (ii). recrystallisation (hexane : Et_2O); (iii). CAN (2.1 eq), MeCN : H_2O (5 : 1), rt; (iv). CAN (4.0 eq), MeCN : H_2O (5 : 1), rt.

Asymmetric synthesis of 3-(4-pyridyl)-β-amino ester 20

Reaction of pyridine-4-carbaldehyde with the lithium anion of *tert*-butyl diethylphosphonoacetate gave (*E*)-*tert*-butyl 3-(4-pyridyl)prop-2-enoate **17** in 84% yield. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide to

α,β-unsaturated ester **17** furnished (3*S*,α*R*)-*tert*-butyl 3-(4-pyridyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)-propanoate **18** in 84% de,[10] which was purified to homogeneity (98% de) by recrystallisation to afford homochiral (3*S*,α*R*)-**18** in 68% overall yield (Scheme 5).



Scheme 5 *Reagents and conditions:* (i). *tert*-butyl diethylphosphonoacetate (1.2 eq), *n*-BuLi (1.1 eq), THF, −78 °C to rt; (ii). lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide, THF, −78 °C then NH_4Cl(aq); (iii). recrystallization (hexane–Et_2O).

Single crystal X-ray crystallographic analysis established the (3*S*,α*R*)-configuration of **18** relative to the known (*R*)-configuration of the α-methyl-4-methoxybenzyl fragment. The (3*S*,α*R*)-configuration is consistent with that predicted by analogy with previous models developed to explain the stereoselectivity observed during addition of homochiral lithium amides to α,β-unsaturated acceptors (Fig. 2).[16]

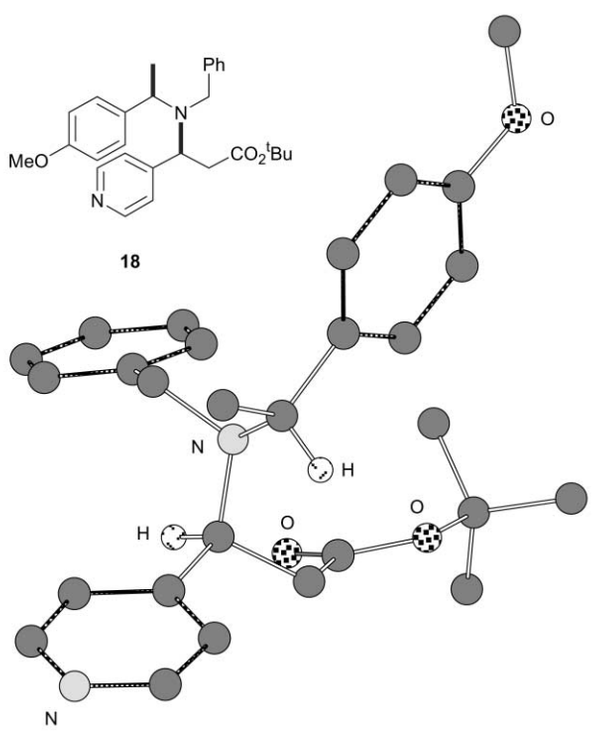
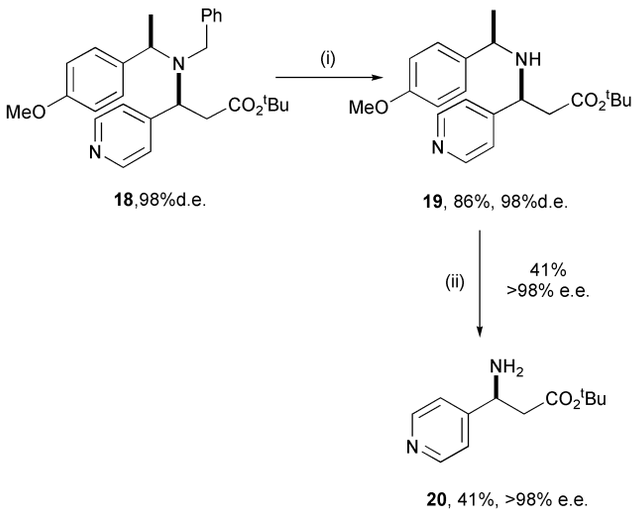


Fig. 2 Chem-3D representation of X-ray crystal structure of **18** (some H atoms omitted for clarity).

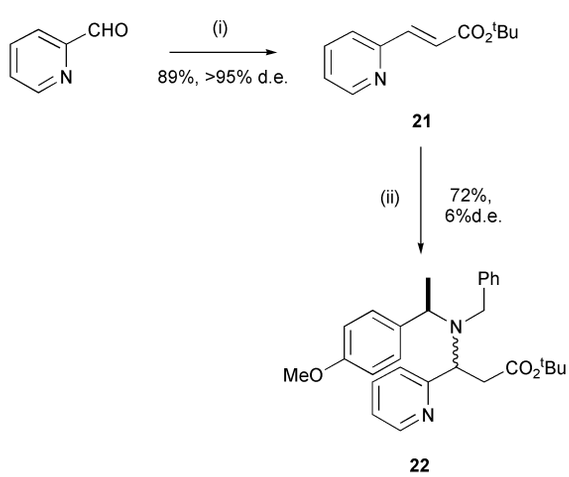
Treatment of 3-(4-pyridyl)-β-amino ester **18** with CAN (2.1 eq) gave (3*S*,α*R*)-*tert*-butyl 3-(*N*-α-methyl-4-methoxybenzylamino)-3-(4-pyridyl)propanoate **19** in 86% yield. Further treatment of (3*S*,α*R*)-**19** with aqueous CAN (4.0 eq) afforded (*S*)-*tert*-butyl 3-amino-3-(4-pyridyl)propanoate **20** in 41% yield. The enantiomeric excess of β-amino ester **20** was shown to be >98% *via* derivatisation with Mosher's acid chloride and comparison of both ^1H and ^{19}F NMR spectroscopic analysis of the resulting amides with that of an authentic racemic sample (Scheme 6).



Scheme 6 *Reagents and conditions:* (i). CAN (2.1 eq), MeCN : H_2O (5 : 1), rt; (ii). CAN (4.0 eq), MeCN : H_2O (5 : 1), rt.

Attempted asymmetric synthesis of a 3-(2-pyridyl)-β-amino ester

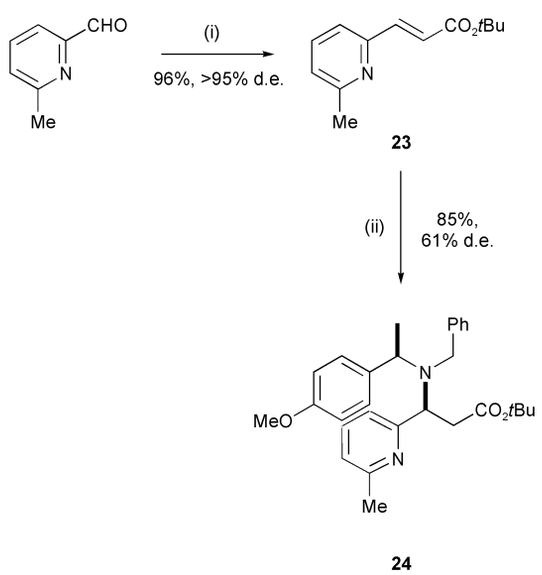
The applicability of this methodology towards the synthesis of the β-2-pyridyl system was similarly investigated. (*E*)-*tert*-Butyl 3-(2-pyridyl)prop-2-enoate **21** was prepared as a single diastereoisomer in 89% yield *via* Horner–Emmons methodology from pyridine-2-carbaldehyde. However, conjugate addition of 1.6 equivalents of lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide to 2-pyridyl acceptor **21** proceeded to only 50% conversion to furnish a crude product containing an inseparable 50 : 50 mixture of starting material and products. Addition of 3.0 equivalents of lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide were required to drive the conjugate addition reaction to completion, furnishing **22** as an inseparable 53 : 47 mixture of diastereoisomeric products in 72% isolated yield (Scheme 7).[17]



Scheme 7 *Reagents and conditions:* (i). *tert*-butyl diethylphosphonoacetate (1.2 eq), *n*-BuLi (1.1 eq), THF, −78 °C to rt; (ii). lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide, THF, −78 °C then NH_4Cl (aq).

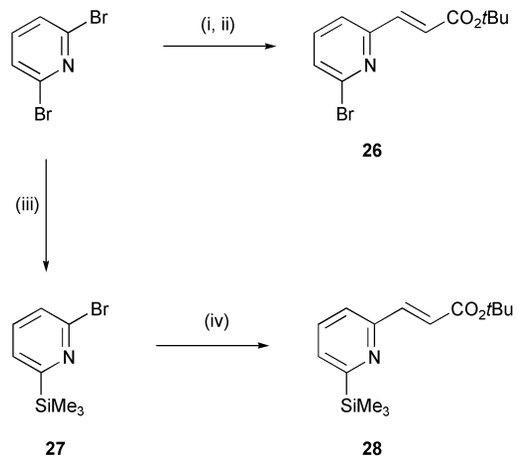
The low level of diastereoselectivity observed upon addition of lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide to β-2-pyridyl acceptor **21** is surprising since conjugate addition of homochiral secondary lithium amides to α,β-unsaturated acceptors typically occurs with very high levels of diastereo-

selectivity. However, low levels of diastereoselectivity for addition reactions to functionalised pyridines have been noted in the literature. For instance, Knochel *et al.* have shown that organozinc reagents add to a variety of aldehydes in the presence of a chiral ligand, furnishing secondary alcohols in high ee,[18] while nucleophilic addition of dipentylzinc to pyridine-3-carbaldehyde in the presence of a chiral ligand proceeded in 0% ee.[19] The low levels of diastereoselectivity observed for conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide to the 3-(2-pyridyl)-α,β-unsaturated acceptor **21** may be due to disruption of the normal chelation controlled lithium amide transition state[16] by chelation of the pyridyl nitrogen to a lithium amide complex, affording a competing, non-stereoselective pathway for conjugate addition. In order to probe further the factors affecting the stereoselectivity of the conjugate addition of homochiral lithium amides to 3-(2-pyridyl)-α,β-unsaturated acceptors, a variety of methods designed to minimise any coordination between the pyridine lone pair and lithium amide were investigated. Initial efforts within this area concentrated upon attempts to pre-coordinate α,β-unsaturated acceptor **21** with LiCl, $MgBr_2$ or BEt_3[19] prior to lithium amide addition. In each case, however, the level of diastereoselectivity remained at around 5% de. It was proposed that the introduction of a methyl group at the 6-position of the pyridyl ring of the conjugate acceptor might serve to sterically impede the coordinating ability of the pyridyl nitrogen. Thus, Wadsworth–Emmons reaction of the lithium anion of *tert*-butyl diethylphosphonoacetate with 3-methylpyridine-2-carbaldehyde gave *tert*-butyl 3-(6-methyl-2-pyridyl)prop-2-enoate **23** in 96% yield and >95% de. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide gave (3*S*,α*R*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)-3-(6-methyl-2-pyridyl)-propanoate **24** in 85% yield as an inseparable mixture of diastereoisomers, but with an improved facial selectivity of 61% de (Scheme 8).



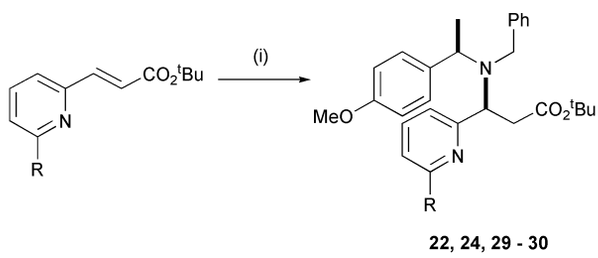
Scheme 8 *Reagents and conditions:* (i). *tert*-butyl diethylphosphonoacetate, *n*-BuLi, THF, −78 °C to rt; (ii). lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide, THF, −78 °C then NH_4Cl (aq).

The increase in diastereoselectivity observed upon conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide to the 3-(6-methyl-2-pyridyl) acceptor **23** relative to the addition to the parent system **21** led to both *tert*-butyl 3-(6-bromo-2-pyridyl)prop-2-enoate **26** and *tert*-butyl 3-(6-trimethylsilyl-2-pyridyl)prop-2-enoate **28** being screened for their capacity to undergo diastereoselective conjugate addition. Thus, **26** and **28** were prepared from 2,6-dibromopyridine using standard procedures (Scheme 9).



Scheme 9 *Reagents and conditions:* (i). *n*-BuLi, −78 °C to −40 °C, then DMF; (ii). *tert*-butyl diethylphosphonoacetate, *n*-BuLi, THF, −78 °C to rt; (iii). *n*-BuLi, −78 °C to −40 °C, then TMSCl; (iv). $Pd(OAc)_2$, *tert*-butyl acrylate, PPh_3, NEt_3, Δ.

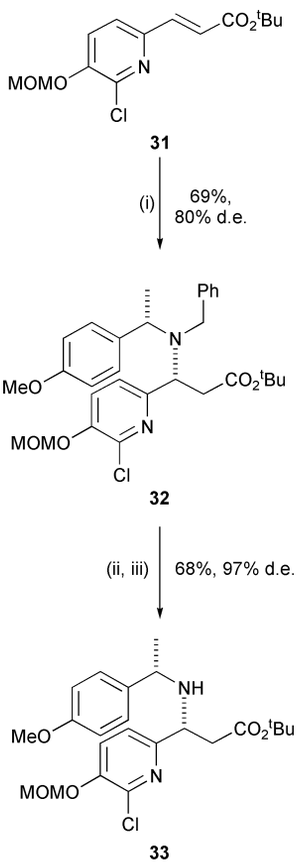
Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide to 3-(6-bromo-2-pyridyl) acceptor **26** gave (3*S*,α*R*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)-3-(6-bromo-2-pyridyl)propanoate **29** in 81% de, but in a poor 45% yield.[20] Similarly, addition to 3-(6-trimethylsilyl-2-pyridyl) acceptor **28** gave (3*S*,α*R*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)-3-(6-trimethylsilyl-2-pyridyl)propanoate **30** in 86% yield and 83% de. While addition to both substituted α,β-unsaturated acceptors **26** and **28** proceeds with improved facial selectivity relative to the parent unsubstituted acceptor **21**, neither (3*S*,α*R*)-**29** nor (3*S*,α*R*)-**30** could be purified to homogeneity by attempted fractional crystallisation or repeated column chromatography (Scheme 10).



R		Yield (%)	d.e. (%)
H	**22**	72	5
Me	**24**	81	61
Br	**29**	45	81
$SiMe_3$	**30**	86	83

Scheme 10 *Reagents and conditions:* (i). lithium (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide, THF, −78 °C then NH_4Cl (aq).

Having shown that substitution of the 2-pyridyl system results in increased levels of diastereoselectivity upon conjugate addition, the application of this methodology for the asymmetric synthesis of the protected β-amino ester of kedarcidin was investigated.[21] Thus, conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide to (*E*)-*tert*-butyl 3-(2-chloro-3-methoxymethoxy-6-pyridyl)prop-2-enoate **31**[22] gave (3*R*,α*S*)-*tert*-butyl 3-(2-chloro-3-methoxymethoxy-6-pyridyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate **32** in 69% yield and 80% de.[10] Mono-debenzylation of β-amino ester **32** with CAN gave (3*R*,α*S*)-*tert*-butyl 3-(2-chloro-3-methoxymethoxy-6-pyridyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate **33** in 68% yield and 97% de after chromatographic purification and fractional recrystallisation (Scheme 11).



Scheme 11 *Reagents and conditions:* (i). lithium (*S*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide, THF, −78 °C then NH_4Cl (aq); (ii). CAN (2.1 eq), MeCN : H_2O (5 : 1), rt; (iii). recrystallization (hexane–Et_2O).

The (3*R*,α*S*)-configuration of **33** was unambiguously assigned by single crystal X-ray analysis relative to the known (*S*)-configuration of the α-methyl-4-methoxybenzyl fragment (Fig. 3).

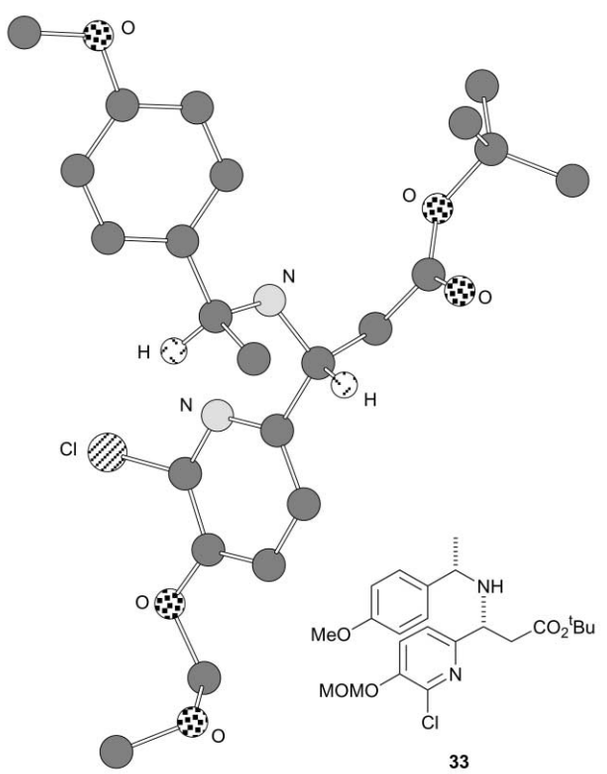
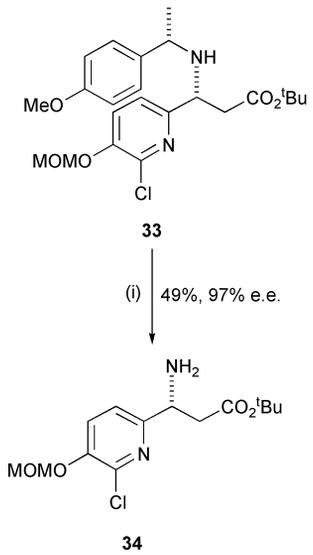


Fig. 3 Chem-3D representation of X-ray crystal structure of **33** (some H atoms omitted for clarity).

Further treatment of secondary β-amino ester **33** with CAN gave the required β-amino ester **34** in 49% yield and 97% ee as shown by derivatisation with homochiral and racemic Mosher's acid chloride and comparison of the ^{19}F NMR spectra of the resulting amides (Scheme 12).



Scheme 12 *Reagents and conditions:* (i). CAN (4.0 eq), MeCN : H_2O (5 : 1), rt.

Conclusion

Lithium *N*-benzyl-*N*-α-methyl-4-methoxybenzyl amide may be employed for the asymmetric synthesis of β-(4-pyridyl)- and β-(3-pyridyl)-β-amino acid derivatives *via* a conjugate addition and oxidative deprotection strategy. However, conjugate addition of lithium *N*-benzyl-*N*-α-methyl-4-methoxybenzyl amide to *tert*-butyl 3-(2-pyridyl)prop-2-enoate proceeds with low levels of diastereoselectivity (6% de), due to disruption of the normal lithium amide transition state [16] by chelation of the pyridyl nitrogen to a lithium amide complex. The incorporation of a substituent onto the 3-(2-pyridyl) ring has been shown to minimise any such chelation, and results in enhanced levels of diastereoselectivity. Application of this methodology allows the asymmetric synthesis of (*R*)-*tert*-butyl 3-(2-chloro-3-methoxymethoxy-6-pyridyl)-3-aminopropanoate, the protected β-amino ester of kedarcidin, to be prepared in 97% ee.

Experimental

General experimental

All reactions involving organometallic or other moisture sensitive reagents were performed under an atmosphere of nitrogen *via* standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. THF was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. Water was distilled. *n*-Butyllithium was used as a solution in hexanes at the molarity stated. Ceric ammonium nitrate (A.C.S. grade) was used as supplied. All other solvents and reagents were used as supplied (Analytical or HPLC grade), without prior purification. Reactions were dried with $MgSO_4$. Thin layer chromatography (tlc) was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Gemini 200 (^1H: 200 MHz and ^{13}C: 50 MHz), Bruker DPX 400 (^1H: 400 MHz and ^{13}C: 100.6 MHz) or a Bruker AMX 500 (^1H: 500 MHz and ^{13}C: 125.3 MHz) spectrometers in the deuterated solvent stated. All chemical

shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. Infrared spectra were recorded on a Perkin–Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted. Low resolution mass spectra (*m*/*z*) were recorded on VG MassLab 20–250 or Micromass Platform 1 spectrometers and high resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer or on a Waters 2790 Micromass LCT Exact Mass Electrospray Ionisation Mass Spectrometer. Techniques used were chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) or electrospray ionisation (ESI) using partial purification by HPLC with methanol : acetonitrile : water (40 : 40 : 20) as eluent. Specific optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g per 100 ml. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford.

Representative procedure 1

n-BuLi (1.55 eq) was added dropwise to a stirred solution of amine (1.55 eq) in THF at −78 °C and stirred for thirty minutes before addition of the α,β-unsaturated acceptor in THF at −78 °C *via* cannula. After two hours NH_4Cl (aq) was added and after warming to rt the resulting solution was partitioned between brine and 1 : 1 Et_2O : DCM, and the organic layer washed successively with 10% citric acid solution, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated *in vacuo*.

Representative procedure 2

CAN (2.1 eq) was added to a solution of the amine (1.0 eq) in 5 : 1 MeCN : H_2O and the solution stirred for two hours at room temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution and partitioned between brine and Et_2O, dried and concentrated *in vacuo*.

Representative procedure 3

CAN (4.0 eq) was added to a solution of the amine (1.0 eq) in 5 : 1 MeCN : H_2O and the solution stirred overnight at room temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution and partitioned between brine and Et_2O, dried and concentrated *in vacuo*.

Representative procedure 4

n-BuLi (1.05 eq) was added dropwise to a solution of *tert*-butyl diethylphosphonoacetate (1.1 eq) in THF (20 ml) at −78 °C before the addition of the requisite aldehyde (1 eq) in THF (20 ml) and warmed to rt. After two hours NH_4Cl (aq) was added and the resulting solution was partitioned between brine and 1 : 1 Et_2O : DCM, dried ($MgSO_4$) and concentrated *in vacuo*.

Preparation of (*E*)-*tert*-butyl 3-(3-pyridyl)prop-2-enoate 12

(*tert*-Butyloxycarbonylmethylene)triphenylphosphorane (5.79 g, 15.4 mmol) was added to a stirred solution of pyridine-3-carbaldehyde (1.50 g, 14.0 mmol) in DCM (20 ml) under nitrogen at rt and stirred for sixteen hours before being diluted with DCM (30 ml) and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexane : Et_2O 1.5 : 1) yielded a mixture of stereoisomers (2.53 g, 88%). The (*E*)-isomer was purified to homogeneity by recrystallisation (hexane : Et_2O) to give **12** as white needles (2.12 g, 74%); mp 58 °C (hexane : Et_2O); $C_{12}H_{15}NO_2$ required C, 70.2; H, 7.4; N, 6.8%; found C, 69.9; H, 7.45; N, 6.7%; ν_{max} (KBr)/cm^{-1} 1700 (s, C=O), 1639 (s, C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, OC*(Me)$_3$*), 6.44 (1H, d, *J* 16.1, HC=C*H*CO$_2$), 7.31–7.34 (1H, m, Ar(5)*H* C_5H_4N), 7.57 (1H, d, *J* 16.1, *H*C=CHCO$_2$), 7.81–7.84 (1H, m, Ar(4)*H* C_5H_4N), 8.59 (1H, d, *J* 4.0, Ar(6)*H* C_5H_4N), 8.71 (1H, s, Ar(2)*H* C_5H_4N); δ_C (50 MHz, $CDCl_3$) 28.1 (OC*(Me)$_3$*), 81.0 (O*C*(Me)$_3$), 122.4, 123.6 (*Ar(5)* C_5H_4N and HC=*C*HCO$_2$), 130.6 (C_{ipso}), 134.1 (*Ar(4)* C_5H_4N), 139.8 (H*C*=CHCO$_2$), 149.6, 150.7 (*Ar(2)* and *Ar(6)* C_5H_4N), 165.6 (*C*=O); *m*/*z* (APCI$^+$) 206.1 (MH$^+$, 80%), 149.9 (MH$^+$ − C_4H_8, 100%); ^1H NMR spectroscopic analysis of the crude reaction mixture showed that the de for the reaction was 88%.

Preparation of (3*S*,α*R*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-(3-pyridyl)propanoate 13

Following representative procedure 1, *n*-BuLi (2.5 M, 5.2 ml, 12.9 mmol), (*R*)-*N*-benzyl-*N*-α-methylbenzylamide (2.80 g, 13.3 mmol, 1.6 eq) in THF (20 ml) and **12** (1.70 g, 8.3 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane : Et_2O 1 : 1), **13** (2.90 g, 83%) as a colourless oil; $[\alpha]_D^{24}$ +4.2 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 1732 (s, C=O); δ_H (500 MHz, $CDCl_3$) 1.27 (9H, s, OC*(Me)$_3$*), 1.32 (3H, d, *J* 7.1, C(α)*Me*), 2.55 (2H, app d, *J* 7.4, C(2)H_2), 3.69 (2H, app s, NCH_2), 3.98 (1H, q, *J* 7.1, C(α)*H*), 4.50 (1H, app t, *J* 7.4, C(3)*H*), 7.20–7.40 (11H, m, 2 × *Ph*, Ar(5)*H* C_5H_4N), 7.71–7.74 (1H, m, Ar(4)*H* C_5H_4N), 8.49–8.50 (1H, m, Ar(6)*H* C_5H_4N), 8.68 (1H, m, Ar(2)*H* C_5H_4N); δ_C (50 MHz, $CDCl_3$) 17.4 (C(α)*Me*), 27.7 (OC*(Me)$_3$*), 37.0 (*C(2)*H$_2$), 50.8 (N*C*H$_2$). 57.0, 57.6 (*C(3)*H and *C(α)*H), 80.7 (O*C*(Me)$_3$), 123.2 (*Ar(5)* C_5H_4N), 127.0, 127.3, 127.9, 128.1, 128.5 (*Ph*), 135.5 (*Ar(4)* C_5H_4N), 137.6, 141.2, 143.7, (C_{ipso}) 148.6, 150.4 (*Ar(2)*, *Ar(6)* C_5H_4N), 171.0 (*C*=O); *m*/*z* (APCI$^+$) 417.6 (MH$^+$, 100%); HRMS (CI$^+$) $C_{27}H_{33}N_2O_2$ requires 417.2542; found 417.2551.

Preparation of (3*S*,α*R*)-*tert*-butyl 3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)-3-(3-pyridyl)propanoate 15

Following representative procedure 1, *n*-BuLi (2.5 M, 5.2 ml, 12.9 mmol), (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide (3.21 g, 13.3 mmol, 1.6 eq) in THF (20 ml) and **12** (1.70 g, 8.3 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane : Et_2O 1 : 1) and recrystallisation (Et_2O : hexane), **15** (3.05 g, 83%) as white blocks; mp 66 °C (Et_2O : hexane); $[\alpha]_D^{24}$ +16.8 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 1725 (s, C=O), 1249 (s, C–OMe), 1151 (s, C–OMe); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, OC*(Me)$_3$*), 1.28 (3H, d, *J* 6.9, C(α)*Me*), 2.51–2.53 (2H, m, C(2)H_2), 3.65 (2H, app s, NCH_2), 3.81 (3H, s, O*Me*), 3.91 (1H, q, *J* 6.9, C(α)*H*), 4.47 (1H, app t, *J* 7.5, C(3)*H*), 6.88 (2H, d, *J* 8.6, Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 7.18–7.32 (8H, m, *Ph*, Ar(2)*H*, Ar(6)*H* C_6H_4OMe, Ar(5)*H* C_5H_4N), 7.71–7.73 (1H, m, Ar(4)*H* C_5H_4N), 8.49 (1H, d, *J* 4.0, Ar(6)*H* C_5H_4N), 8.67 (1H, s, Ar(2)*H* C_5H_4N); δ_C (50 MHz, $CDCl_3$) 17.7 (C(α)*Me*), 27.8 (OC*(Me)$_3$*), 37.0 (*C(2)*H$_2$), 50.7 (N*C*H$_2$) 55.0, 56.9, 77.6 (O*Me*, *C(3)*H and *C(α)*H), 80.5 (O*C*(Me)$_3$), 113.6 (*Ar(3)*, *Ar(5)* C_6H_4OMe), 123.0 (*Ar(5)* C_5H_4N), 126.7, 127.8, 128.2, 128.7 (*Ph* and *Ar(2)*, *Ar(6)* C_6H_4OMe), 135.3, 135.4, 137.5, 141.0 (C_{ipso} and *Ar(4)* C_5H_4N), 148.3, 150.1 (*Ar(2)*, *Ar(6)* C_5H_4N), 158.6 (*Ar(4)* C_6H_4OMe), 170.6 (*C*=O); *m*/*z* (APCI$^+$) 469.2 (MNa$^+$, 10%), 447.0 (MH$^+$, 100%), 135.0 ($C_9H_{11}O^+$, 45%); HRMS (CI$^+$) $C_{28}H_{35}N_2O_3$ requires 447.2648; found 447.2638.

Preparation of (3*S*,α*R*)-*tert*-butyl 3-(*N*-α-methyl-4-methoxybenzylamino)-3-(3-pyridyl)propanoate 16

Following representative procedure 2, CAN (5.76 g, 9.4 mmol) and **15** (2.00 g, 4.5 mmol) in 5 : 1 MeCN : H_2O (36 ml) gave,

after purification by column chromatography on silica gel (hexane : Et_2O 1 : 1 to 1 : 2), **16** as a yellow oil (1.26 g, 80%); $[\alpha]_D^{24}$ +15.7 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3323 (br, N–H), 1725 (s, C=O), 1243 (s, C–OMe), 1151 (s, C–OMe); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.6, C(α)*Me*), 1.37 (9H, s, OC*(Me)$_3$*), 1.78 (1H, br s, N*H*), 2.56 (1H, dd, $J_{2A,2B}$ 15.0, $J_{2A,3}$ 6.2, C(2)H_A), 2.67 (1H, dd, $J_{2B,2A}$ 15.0, $J_{2B,3}$ 7.6, C(2)H_B), 3.63 (1H, q, *J* 6.6, C(α)*H*), 3.78 (3H, s, O*Me*), 4.14 (1H, app t, *J* 6.9, C(3)*H*), 6.77–6.81 (2H, m, Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 7.11–7.15 (2H, m, Ar(2)*H*, Ar(6)*H* C_6H_4OMe), 7.19–7.22 (1H, m, Ar(5)*H* C_5H_4N), 7.59–7.61 (1H, m, Ar(4)*H* C_5H_4N), 8.47–8.51 (2H, m, Ar(2)*H*, Ar(6)*H* C_5H_4N); δ_C (50 MHz, $CDCl_3$) 22.8 (C(α)*Me*), 28.0 (OC*(Me)$_3$*), 43.2 (*C(2)*H_2), 54.5, 55.0, 55.2 (O*Me*, *C(3)*H and *C(α)*H), 80.9 (O*C*(Me)$_3$), 113.7 (*Ar(3)*, *Ar(5)* C_6H_4OMe), 123.3 (*Ar(5)* C_5H_4N), 127.6 (*Ar(2)*, *Ar(6)* C_6H_4OMe), 134.5 (*Ar(4)* C_5H_4N), 137.5, 138.3 (C_{ipso}), 148.6, 149.1 (*Ar(2)*, *Ar(6)* C_5H_4N), 158.5 (*Ar(4)* C_6H_4OMe), 170.4 (*C*=O); *m/z* ($APCI^+$) 379.2 (MNa^+, 10%), 357.2 (MH^+, 100%), 223.1 ($MH^+ - C_9H_{11}O$, 20%), 134.8 ($C_9H_{11}O^+$, 70%); HRMS (CI^+) $C_{21}H_{29}N_2O_3$ requires 357.2178; found 357.2189.

Preparation of (*S*)-*tert*-butyl 3-amino-3-(3-pyridyl)propanoate 14

Following representative procedure 3, CAN (1.04 g, 1.91 mmol, 4.0 eq) and **16** (170 mg, 0.48 mmol, 1.0 eq) in 5 : 1 MeCN : H_2O (6 ml) gave, after work up and purification by column chromatography on silica gel (Et_2O : MeOH 10 : 1), **14** as a yellow oil (67 mg, 63%); $[\alpha]_D^{24}$ −17.6 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3323 (br, N–H), 1725 (s, C=O), 1243 (s, C–OMe), 1151 (s, C–OMe); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, OC*(Me)$_3$*), 1.95 (2H, br s, NH_2), 2.57–2.64 (2H, m, C(2)H_2), 4.41 (1H, br s, C(3)*H*), 7.26 (1H, m, Ar(4)*H* C_5H_4N), 7.71 (1H, m, Ar(5)*H* C_5H_4N), 8.50, 8.60 (2 × 1H, br s, Ar(2)*H*, Ar(6)*H* C_5H_4N); δ_C (100 MHz, $CDCl_3$) 28.0 (OC*(Me)$_3$*), 44.9 (*C(2)*H_2), 50.5 (*C(3)*H), 81.1 (O*C*(Me)$_3$), 123.5 (*Ar(5)* C_5H_4N), 134.0 (*Ar(4)* C_5H_4N and C_{ipso}), 148.4, 148.8 (*Ar(2)*, *Ar(6)* C_5H_4N), 170.7 (*C*=O); *m/z* ($APCI^+$) 223.0 (MH^+, 20%), 166.9 ($MH^+ - C_4H_8$, 100%); HRMS (CI^+) $C_{12}H_{19}N_2O_2$ requires 223.1446; found 223.1442.

Preparation of (*E*)-*tert*-butyl 3-(4-pyridyl)prop-2-enoate 17

Following representative procedure 4, *tert*-butyl diethylphosphonoacetate (12.95 g, 51.5 mmol), *n*-BuLi (2.5 M, 19.6 ml, 49.5 mmol) in THF (20 ml) and pyridine-3-carbaldehyde (5.00 g, 46.7 mmol) in THF (15 ml) gave, after purification by column chromatography on silica gel (hexane : EtOAc 4 : 1), **17** (8.01 g, 84%) as white crystals; mp 73–74 °C; $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%; found C, 70.0; H, 7.4; N, 6.9%; ν_{max} (KBr disc)/cm^{-1} 1710 (s, C=O), 1645 (s, C=C); δ_H (400 MHz, $CDCl_3$) 1.53 (9H, s, OC*(Me)$_3$*), 6.51 (1H, d, *J* 16.0, HC=C*H*CO_2), 7.34 (2H, m, Ar(3)*H*, Ar(5)*H* C_5H_4N), 7.49 (1H, d, *J* 16.0, *H*C=$CHCO_2$), 8.64 (2H, m, Ar(2)*H*, Ar(6)*H* C_5H_4N); δ_C (100 MHz, $CDCl_3$) 27.9 (OC*(Me)$_3$*), 81.2 (O*C*(Me)$_3$), 121.9 (*Ar(3)*, *Ar(5)* C_5H_4N), 124.9 (HC=*C*HCO_2), 140.8 (H*C*=$CHCO_2$), 142.0 (*Ar(4)* C_5H_4N), 150.7 (*Ar(2)*, *Ar(6)* C_5H_4N), 165.5 (*C*=O); *m/z* ($APCI^+$) 206 (MH^+, 100%), 150 ($MH^+ - C_4H_8$, 40%). ^1H NMR spectroscopic analysis of the crude reaction mixture showed that the de of the reaction was >98%.

Preparation of (3*S*,α*R*)-*tert*-butyl 3-(4-pyridyl)-3-(*N*-benzyl-*N*-4-methoxy-α-methylbenzylamino)propanoate 18

Following representative procedure 1, *n*-BuLi (2.5 M, 7.6 ml, 19.0 mmol), (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide (940 mg, 3.90 mmol) in THF (20 ml) and (*E*)-*tert*-butyl 3-(4-pyridyl)prop-2-enoate **17** (2.00 g, 9.76 mmol) in THF (20 ml) gave, after purification by column chromatography on silica gel (hexane : Et_2O 1 : 1) and recrystallisation (Et_2O–hexane), **18** (2.35 g, 54%) as white crystals; mp 62–63 °C (Et_2O–hexane); $[\alpha]_D^{22}$ +39.3 (*c* 1.1, $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 1725 (s, C=O), 1512 (s, C–OMe), 1248 (s, C–OMe); δ_H (400 MHz, $CDCl_3$) 1.29 (9H, s, OC*(Me)$_3$*), 1.30 (3H, d, *J* 7.0, C(α)*Me*), 2.50 (1H, dd, $J_{2A,2B}$ 15.2, $J_{2A,3}$ 4.5, C(2)H_A), 2.52 (1H, dd, $J_{2B,2A}$ 15.2, $J_{2B,3}$ 10.0, C(2)H_B), 3.64 (2H, s, NCH_2Ph), 3.81 (3H, s, O*Me*), 3.90 (1H, q, *J* 7.0, C(α)*H*), 4.44 (1H, dd, $J_{3,2B}$ 10.0, $J_{3,2A}$ 4.5, C(3)*H*), 6.89 (2H, d, *J* 8.7, Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 7.20–7.31 (7H, m, Ar(2)*H*, Ar(6)*H* C_6H_4OMe, *Ph*), 7.35 (2H, d, *J* 6.0, Ar(3)*H*, Ar(4)*H* C_5H_4N), 8.56 (2H, d, *J* 6.0, Ar(2)*H*, Ar(6)*H* C_5H_4N); δ_C(100 MHz, $CDCl_3$) 18.1 (C(α)*Me*), 27.8 (OC*(Me)$_3$*), 36.4 (*C(2)*H_2), 51.0 (N*C*H_2Ph), 55.2, 57.0, 57.5 (*C(3)*H, *C(α)*H, O*Me*), 80.7 (O*C*(Me)$_3$), 113.6 (*Ar(3)*, *Ar(5)* C_6H_4OMe), 123.2, 126.8, 128.0, 128.3, 128.7 (*Ar*), 135.2, 140.7 (C_{ipso}), 149.6 (*Ar(3)*, *Ar(5)* C_5H_4N), 151.7, 158.6 (*Ar(4)* C_5H_4N, *Ar(4)* C_6H_4OMe), 170.8 (*C*=O); *m/z* ($APCI^+$) 447 (MH^+, 90%), 135 ($C_9H_{11}O^+$, 50%); HRMS (CI^+) $C_{28}H_{35}N_2O_3$ requires 447.2648, found 447.2649; ^1H NMR spectroscopic analysis of the crude reaction mixture showed that the de of the reaction was 84%.

X-Ray crystal structure data for 18.† Data were collected using an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at room temperature. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[23] Crystal data for **18** [$C_{28}H_{34}N_2O_3$], colourless block, $M = 446.59$, orthorhombic, space group $P\,2_12_12_1$, $a = 11.4818(13)$ Å, $b = 12.894(3)$ Å, $c = 17.1468(18)$ Å, $U = 2538.5(1)$ Å^3, $Z = 4$, $\mu = 0.598$, crystal dimensions 0.6 × 0.8 × 0.8 mm. A total of 2927 unique reflections were measured for $4.29 < \theta < 74.20$ and 2838 reflections were used in the refinement. The final parameters were $wR_2 = 0.0437$ and $R_1 = 0.0427$ [$I > 3\sigma(I)$]. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre, CCDC number 184753.

Preparation of (3*S*,α*R*)-*tert*-butyl 3-(4-pyridyl)-3-(*N*-α-methyl-4-methoxybenzylamino)propanoate 19

Following representative procedure 2, CAN (3.94 g, 7.18 mmol), **18** (1.53 g, 3.42 mmol) in 5 : 1 MeCN : H_2O (24 ml) gave, after work up and purification by column chromatography on silica gel (hexane : Et_2O (1 : 2)–1% Et_3N), **19** (1.04 g, 86%) as a pale green oil; $[\alpha]_D^{22}$ +11.2 (*c* 0.41, $CHCl_3$); ν_{max} (film)/cm^{-1} 3419 (w, N–H), 1729 (s, C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.5, C(α)*Me*), 1.37 (9H, s, OC*(Me)$_3$*), 2.52 (1H, dd, $J_{2A,2B}$ 15.1, $J_{2A,3}$ 6.5, C(2)H_A), 2.60 (1H, dd, $J_{2B,2A}$ 15.1, $J_{2B,3}$ 6.5, C(2)H_B), 3.63 (1H, q, *J* 6.5, C(α)*H*), 3.77 (3H, s, O*Me*), 4.08 (1H, t, *J* 6.5, C(3)*H*), 6.80 (2H, m, Ar(2)*H*, Ar(6)*H* C_6H_4OMe), 7.14 (2H, m, Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 7.20 (2H, d, *J* 6.0, Ar(3)*H*, Ar(5)*H* C_5H_4N), 8.50 (2H, d, *J* 6.0, Ar(2)*H*, Ar(6)*H* C_5H_4N); δ_C(100 MHz, $CDCl_3$) 22.8 (C(α)*Me*), 28.0 (OC*(Me)$_3$*), 42.7 (*C(2)*H_2), 54.5, 55.2, 56.3 (*C(3)*H, *C(α)*H, O*Me*), 81.0 (O*C*(Me)$_3$), 113.7 (*Ar(3)*, *Ar(5)* C_6H_4OMe), 122.3, 127.5 (*Ar*(2), *Ar*(6) C_6H_4OMe, *Ar*(3), *Ar*(5) C_5H_4N), 137.5 (C_{ipso}), 149.8 (*Ar(2)*, *Ar(6)* C_5H_4N), 152.1, 158.6 (*Ar*(4) C_5H_4N, *Ar*(4) C_6H_4OMe), 170.3 (*C*=O); *m/z* 357 (MH^+, 90%), 135 ($C_9H_{11}O^+$, 90%); HRMS $C_{21}H_{29}N_2O_3$ requires 357.2178, found 357.2177.

Preparation of (*S*)-*tert*-butyl 3-(4-pyridyl)-3-aminopropanoate 20

Following representative procedure 3, CAN (4.59 g, 8.37 mmol), **19** (745 mg, 2.09 mmol) in 5 : 1 MeCN : H_2O (24 ml) gave, after work up and purification by column chromatography on silica

† CCDC reference numbers 184753 and 184754. See http://www.rsc.org/suppdata/p1/b2/b204653a/ for crystallographic files in .cif or other electronic format.

gel ($CHCl_3$–3% MeOH), **20** (191 mg, 41%) as a pale yellow oil; $[\alpha]_D^{22}$ −17.3 (*c* 0.91, $CHCl_3$); ν_{max} (film)/cm^{-1} 3370 (w, N–H), 1732 (s, C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, OC*(Me)*$_3$), 2.12 (2H, br s, N*H*$_2$), 2.52 (1H, dd, $J_{2A,2B}$ 15.9, $J_{2A,3}$ 5.5, C(2)H_A), 2.56 (1H, dd, $J_{2B,3}$ 8.0, $J_{2B,2A}$ 15.9, C(2)H_B), 4.34 (1H, dd, $J_{3,2B}$ 8.0, $J_{3,2A}$ 5.5, C(3)*H*), 7.29 (2H, d, *J* 6.1, Ar(3)*H*, Ar(5)*H* C_5H_4N), 8.54 (2H, d, *J* 6.1, Ar(2)*H*, Ar(6)*H* C_5H_4N); δ_C(100 MHz, $CDCl_3$) 28.0 (OC*(Me)*$_3$), 44.5 (C(2)H_2), 51.7 (*C(3)*H), 81.2 (O*C*(Me)$_3$), 121.5 (*Ar(3)*, *Ar(5)* C_5H_4N), 149.9 (*Ar(2)*, *Ar(6)* C_5H_4N), 153.4 (*Ar(4)* C_5H_4N), 170.6 (*C*=O); *m*/*z* (APCI$^+$) 223 (MH^+, 60%), 167 ($MH^+ - C_4H_8$, 100%); HRMS $C_{12}H_{19}N_2O_2$ requires 223.1447, found 223.1436.

Preparation of (*E*)-*tert*-butyl 3-(2-pyridyl)prop-2-enoate 21

Following representative procedure 4, *tert*-butyl diethylphosphonoacetate (5.18 g, 20.5 mmol) in THF (20 ml) *n*-BuLi (1.6 M, 12.3 ml, 19.6 mmol) and pyridine-2-carbaldehyde (2.00 g, 18.7 mmol) in THF (20 ml) gave, after column chromatography on silica gel (hexane : Et_2O (4 : 1)), **21** (3.42 g, 89%) as a colourless oil; ν_{max} (film)/cm^{-1} 1714 (s, C=O), 1644 (s, C=C); δ_H (400 MHz, $CDCl_3$) 1.53 (9H, s, OC*(Me)*$_3$), 6.83 (1H, d, *J* 15.8, HC=C*H*CO_2), 7.25 (1H, m, Ar(5)*H* C_5H_4N), 7.43 (1H, d, *J* 7.8, Ar(3)*H* C_5H_4N), 7.59 (1H, d, *J* 15.8, *H*C=CHCO$_2$), 7.70 (1H, m, Ar(4)*H* C_5H_4N), 8.63 (1H, m, Ar(6)*H* C_5H_4N); δ_C (100 MHz, $CDCl_3$) 27.9 (OC*(Me)*$_3$), 80.6 (O*C*(Me)$_3$), 123.8, 124.0, 124.5 (*Ar(5)*, *Ar(3)* C_5H_4N, HC=*C*HCO$_2$), 136.8 (*Ar(4)* C_5H_4N), 142.4 (H*C*=CHCO$_2$), 150.1 (*Ar(6)* C_5H_4N), 153.3 (*Ar(2)* C_5H_4N), 166.1 (*C*=O); *m*/*z* (APCI$^+$) 206.0 (MH^+, 80%), 150.0 ($MH^+ - C_4H_8$, 100%); HRMS (CI$^+$) $C_{12}H_{16}NO_2$ requires 206.1181, found 206.1179; ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that the de of the reaction was >95%.

Preparation of (3*R*,α*S*)- and (3*S*,α*S*)-*tert*-butyl 3-(2-pyridyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 22

Following representative procedure 1, *n*-BuLi (1.6 M, 2.7 ml, 4.3 mmol), (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide (1.06 g, 4.4 mmol) in THF (10 ml) and (*E*)-*tert*-butyl 3-(2-pyridyl)prop-2-enoate **21** (300 mg, 1.5 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane : Et_2O 8 : 1), **22** (482 mg, 74%) as a colourless oil; ν_{max} (film)/cm^{-1} 1725 (s, C=O), 1511 (s, C–OMe), 1248 (s, C–OMe); δ_H (400 MHz, $CDCl_3$) 1.34 (9H, s, OC*(Me)*$_3$), 1.39 (3H, d, *J* 6.9, C(α)*Me*), 2.82 (1H, dd, $J_{2A,2B}$ 15.2, $J_{2A,3}$ 4.1, C(2)H_A), 3.25 (1H, dd, $J_{2B,2A}$ 15.2, $J_{2B,3}$ 10.3, C(2)H_B), 3.73 (4H, AB, NCH_2Ph), 3.80 (3H, s, O*Me*), 4.46 (1H, dd, $J_{3,2B}$ 10.3, $J_{3,2A}$ 4.1, C(3)*H*), 6.84 (2H, m, Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 7.04–7.29 (15H, m, *Ar*), 7.52–7.66 (3H, m, *Ar*), 8.46 (1H, m, Ar(6)*H* C_5H_4N); δ_C(100 MHz, $CDCl_3$) 17.0, 19.5 (C(α)*Me*), 27.9, 27.9 (OC*(Me)*$_3$), 36.2, 34.5 (*C(2)*H_2), 50.3, 51.0 (N*C*H_2Ph), 55.2, 55.2, 56.5, 57.1, 58.3, 58.5 (*C(3)*H, *C(α)*H, O*Me*), 79.8, 80.0 (O*C*(Me)$_3$), 113.3, 113.6 (*Ar(3)*, *Ar(5)* C_6H_4OMe), 121.6, 121.7, 123.8, 124.2, 126.5, 128.0, 128.1, 128.3, 128.7, 128.9, 135.7, 135.8 (*Ar*), 135.9, 136.7, 141.3, 141.5 (C_{ipso}), 147.8, 148.0 (*Ar(6)* C_5H_4N), 158.5, 158.3 (*Ar(4)* C_6H_4OMe), 161.1, 161.7 (*Ar(2)* C_5H_4N), 171.8, 171.8 (C=O); *m*/*z* (APCI$^+$) 447 (MH^+, 20%), 313 ($MH^+H^+ - C_9H_{11}O^+$, 100%); HRMS (CI$^+$) $C_{28}H_{35}N_2O_3$ requires 447.2648, found 447.2634. ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that the de of the reaction was 6%.

Preparation of (*E*)-*tert*-butyl 3-(6-methyl-2-pyridyl)prop-2-enoate 23

Following representative procedure 4, *tert*-butyl diethylphosphonoacetate (4.80 g, 19.0 mmol) in THF (10 ml), *n*-BuLi (1.6 M, 11.4 ml, 18.2 mmol) and 6-methylpyridine-2-carbaldehyde (2.00 g, 16.5 mmol) in THF (15 ml) gave, after column chromatography on silica gel (hexane : EtOAc 9 : 1), **23** (3.50 g, 96%) as a colourless oil; $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%, found C, 71.2; H, 7.3; N, 6.2%; ν_{max} (film)/cm^{-1} 1708 (s, C=O); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, OC*(Me)*$_3$), 2.48 (3H, s, *Me*), 6.74 (1H, d, *J* 15.7, HC=C*H*CO_2), 7.02 (1H, d, *J* 7.4, Ar(5)*H* C_5H_3N), 7.14 (1H, d, *J* 7.6, Ar(3)*H* C_5H_3N), 7.46–7.51 (2H, m, Ar(4)*H* C_5H_3N, *H*C=CHCO$_2$); δ_C (100 MHz, $CDCl_3$) 24.5 (*Me*), 28.0 (OC*(Me)*$_3$), 80.4 (O*C*(Me)$_3$), 120.8 (HC=*C*HCO$_2$), 123.7, 123.9, 136.7 (*Ar*), 142.5 (H*C*=CHCO$_2$), 152.4, 158.7 (*Ar(2)*, *Ar(6)* C_5H_3N), 165.9 (*C*=O); *m*/*z* (APCI$^+$) 220 (MH^+, 30%), 164 ($MH^+ - C_4H_8$, 100%); ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that the de of the reaction was >95%.

Preparation of (3*S*,α*R*)-*tert*-butyl 3-(6-methyl-2-pyridyl)-3-(*N*-benzyl-*N*-4-methoxy-α-methylbenzylamino)propanoate 24

Following representative procedure 1, *n*-BuLi (1.6 M, 6.6 ml, 10.6 mmol), (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide (2.60 g, 11.0 mmol) in THF (10 ml) and (*E*)-**23** (1.50 g, 6.9 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane : Et_2O 8 : 1), **24** (2.70 g, 85%) as a colourless oil; ν_{max} (film)/cm^{-1} 1727 (s, C=O), 1511 (s, C–OMe), 1247 (s, C–OMe); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.8, C(α)*Me*), 1.34 (9H, s, OC*(Me)*$_3$), 2.30 (1H, dd, $J_{2A,2B}$ 15.3, $J_{2A,3}$ 3.6, C(2)H_A), 2.46 (3H, s, C–*Me*), 2.97 (1H, dd, $J_{2B,2A}$ 15.3, $J_{2B,3}$ 10.3, C(2)H_B), 3.65 (2H, AB, NCH_2Ph), 3.82 (3H, s, O*Me*), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.55 (1H, dd, $J_{3,2B}$ 10.3, $J_{3,2A}$ 3.6, C(3)*H*), 6.89 (2H, d, *J* 11.4, Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 6.95 (1H, d, *J* 7.7, Ar(5)*H* C_5H_3N), 7.18–7.37 (8H, m, Ar(2)*H*, Ar(6)*H* C_6H_4OMe, *Ph*, Ar(3)*H* C_5H_3N), 7.53 (1H, t, *J* 7.7, Ar(4)*H* C_5H_3N); δ_C 100 MHz, $CDCl_3$) 24.4 (C(α)*Me*), 28.0 (OC*(Me)*$_3$), 34.8 (*C(2)*H_2), 51.2 (N*C*H_2), 55.2, 57.0, 58.2, (O*Me*, *C(α)*H, *C(3)*H), 79.5 (O*C*(Me)$_3$), 113.5, 120.3, 120.7, 126.5, 128.0, 128.1 (*Ar*), 128.3 (C_{ipso}), 128.8, 135.9 (*Ar*), 141.4 (C_{ipso}), 156.6, 158.5, 161.1 (*Ar(2)* C_5H_3N, *Ar(6)* C_5H_3N, *Ar(4)* C_6H_4OMe), 172.0 (*C*=O); *m*/*z* (APCI$^+$) 461 (MH^+, 10%), 327 ($MH^+H^+ - C_9H_{11}O^+$, 80%), 135 ($C_9H_{11}O^+$, 100%); HRMS (ESI) $C_{29}H_{37}N_2O_3$ requires 461.2804, found 461.2805.

Preparation of (*E*)-*tert*-butyl 3-(6-bromo-2-pyridyl)prop-2-enoate 26

n-BuLi (2.5 M, 17 ml, 42 mmol) was added dropwise to a stirred solution of 2,6-dibromopyridine (10.0 g, 42 mmol) in Et_2O (75 ml) at −78 °C under N_2, warmed to −40 °C for 20 minutes and then recooled to −78 °C before the dropwise addition of DMF (3.4 ml, 46.4 mmol) in Et_2O (10 ml) *via* cannula. After 2 hours, the solution was allowed to warm to 0 °C, washed with HCl (aq), dried and concentrated *in vacuo*. Recrystallisation (Et_2O : hexane) gave 6-bromopyridine-2-carbaldehyde as a white crystalline solid (4.50 g, 58%); δ_H (200 MHz, $CDCl_3$) 7.72–7.85 (2H, m, *Ar*), 7.92–7.95 (1H, m, *Ar*), 10.0 (1H, s, C*H*O).[24] Following representative procedure 4, *tert*-butyl diethylphosphonoacetate (3.10 g, 12.4 mmol) in THF (20 ml) *n*-BuLi (1.6 M, 7.4 ml, 11.9 mmol) and 6-bromopyridine-2-carbaldehyde (2.00 g, 10.8 mmol) in THF (20 ml) gave, after column chromatography on silica gel (hexane : EtOAc 9 : 1), **26** (2.70 g, 89%) as a viscous yellow oil; ν_{max} (KBr disc)/cm^{-1} 1701 (br, C=O); δ_H (400 MHz, $CDCl_3$) 1.53 (9H, s, OC*(Me)*$_3$), 6.87 (1H, d, *J* 15.6, HC=C*H*CO_2), 7.34 (1H, d, *J* 7.1, Ar(3)*H* C_5H_3N), 7.43 (1H, d, *J* 7.9, Ar(5)*H* C_5H_3N), 7.47 (1H, d, *J* 15.6, *H*C=CHCO$_2$), 7.55 (1H, t, *J* 7.6, Ar(4)*H* C_5H_3N); δ_C 28.1 (OC*(Me)*$_3$), 80.9 (O*C*(Me)$_3$), 122.5, 126.0, 128.0, 138.9, 140.3 (H*C*=*C*HCO$_2$ and *Ar(3)*, *Ar(4)*, *Ar(5)* C_5H_3N), 142.4 (*Ar(6)* C_5H_3N), 154.4 (*Ar(2)* C_5H_3N), 165.6 (*C*=O); *m*/*z* (APCI$^+$) 286, 284 (MH^+, 20%), 230, 228 ($MH^+ - C_4H_8$, 100%); HRMS (ESI) $C_{12}H_{15}{}^{79}BrNO_2$ requires 284.0286, found 284.0291.

Preparation of (*E*)-*tert*-butyl 3-(6-trimethylsilyl-2-pyridyl)prop-2-enoate 28

n-BuLi (2.5 M, 3.4 ml, 8.44 mmol) was added dropwise to a stirred solution of 2,6-dibromopyridine (2.00 g, 8.4 mmol) in

Et_2O (40 ml) at −78 °C under N_2 and subsequently warmed to −40 °C for 20 minutes before being cooled to −78 °C and the dropwise addition of TMSCl (1.2 ml, 9.3 mmol) in Et_2O (10 ml) *via* cannula. After 2 hours, the solution was allowed to warm to rt, filtered through Celite, washed with H_2O (20 ml), dried and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexane : EtOAc 9 : 1) gave 2-bromo-6-trimethylsilylpyridine **27** (1.80 g, 93%) as a colourless oil; δ_H (200 MHz, $CDCl_3$) 0.32 (9H, s, Si*Me*$_3$), 7.35–7.49 (3H, m, Ar) consistent with that previously observed in the literature.[25] **27** (500 mg, 2.2 mmol) was added to a stirred solution of *tert*-butyl acrylate (0.5 ml, 3.5 mmol), PPh_3 (91 mg, 0.35 mmol) and $Pd(OAc)_2$ (19 mg, 0.1 mmol) in NEt_3 (3 ml) and refluxed overnight. After cooling, the resultant mixture was filtered through Celite (Et_2O), washed with H_2O (20 ml), extracted with DCM (3 × 50 ml), dried and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexane : EtOAc 9 : 1) gave **28** as a colourless oil (419 mg, 70%); $C_{15}H_{23}NO_2Si$ requires C, 64.9; H, 8.4; N, 5.05%; found C, 64.55; H, 8.35; N, 4.9%; ν_{max} (film)/cm^{-1} 1711 (s, C=O); δ_H (400 MHz, $CDCl_3$) 0.33 (9H, s, Si*Me*$_3$), 1.55 (9H, s, OC*(Me)*$_3$), 6.91 (1H, d, *J* 15.6, HC=C*H*CO_2), 7.26 (1H, dd, $J_{4,5}$ 8.0, $J_{4,6}$ 1.0, Ar(3)*H* C_5H_3N), 7.45 (1H, dd, $J_{6,5}$ 7.5, $J_{6,4}$ 1.0, Ar(5)*H* C_5H_3N), 7.58 (1H, t, *J* 7.7, C(4)*H* C_5H_3N), 7.62 (1H, d, *J* 15.6, *H*C=CHCO_2); δ_C (100 MHz, $CDCl_3$) −1.9 (Si*Me*$_3$), 28.1 (OC*(Me)*$_3$), 80.6 (O*C*(Me)$_3$), 123.0, 123.8 (*Ar(3)* C_5H_3N, *Ar(5)* C_5H_3N), 128.6 (HC=*C*HCO_2), 134.3 (*Ar(4)* C_5H_3N), 143.1 (H*C*=CHCO_2), 152.9 (*Ar(2)* C_5H_3N), 166.3 (*Ar(6)* C_5H_3N), 169.1 (*C*=O); *m*/*z* (APCI$^+$) 278 (MH$^+$, 20%), 222 (MH$^+$ − C_4H_8, 100%).

Preparation of (3*S*,α*R*)-*tert*-butyl 3-(6-bromo-2-pyridyl)-3-(*N*-benzyl-*N*-4-methoxy-α-methylbenzylamino)propanoate 29

Following representative procedure 1, *n*-BuLi (1.6 M, 0.34 ml, 0.6 mmol), (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide (136 mg, 0.6 mmol) in THF (5 ml) and (*E*)-**26** (100 mg, 0.4 mmol) in THF (5 ml) gave, after purification by column chromatography on silica gel (hexane : EtOAc 4 : 1), **29** (82 mg, 45%) as a colourless oil; ν_{max} (film)/cm^{-1} 1726 (s, C=O), 1511 (s, C–OMe), 1248 (s, C–OMe); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.9, C(α)*Me*), 1.39 (9H, s, OC*(Me)*$_3$), 2.27 (1H, dd, $J_{2A,2B}$ 15.6, $J_{2A,3}$ 3.4, C(2) H_A), 2.93 (1H, dd, $J_{2B,2A}$ 15.6, $J_{2B,3}$ 10.4, C(2)H_B), 3.65 (2H, AB, NCH_2Ph), 3.82 (3H, s, O*Me*), 3.96 (1H, q, *J* 6.9, C(α)*H*), 4.59 (1H, dd, $J_{3,2B}$ 10.4, $J_{3,2A}$ 3.4, C(3)*H*), 6.90 (2H, d, *J* 8.7, Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 7.21–7.34 (8H, m, Ar(2)*H*, Ar(6)*H* C_6H_4OMe, *Ph*, Ar(5)*H* C_5H_3N), 7.51 (1H, t, *J* 7.6, Ar(4)*H* C_5H_3N), 7.57 (1H, d, *J* 7.5, Ar(3)*H* C_5H_3N); δ_C(100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 28.0 (OC*(Me)*$_3$), 34.2 (*C(2)*H_2), 51.4 (N*C*H_2), 55.2, 57.2, 57.7 (O*Me*, *C(α)*H, *C(3)*H), 80.0 (O*C*(Me)$_3$), 113.6, 122.4, 125.9, 126.7, 128.1, 128.7 (*Ar*), 135.3 (C_{ipso}), 138.2 (*Ar*), 140.6, 140.8 (C_{ipso}), 158.6 (*Ar(4)* C_6H_4OMe), 169.0 (*Ar(2)* C_5H_3N), 171.6 (*C*=O); *m*/*z* (APCI$^+$) 393, 391 (MH$^+$ − $C_9H_{10}O$, 10%), 135 ($C_9H_{11}O^+$, 100%); HRMS (ESI) $C_{28}H_{34}{}^{79}BrN_2O_3$ requires 525.1753, found 525.1754.

Preparation of (3*S*,α*R*)-*tert*-butyl 3-(6-trimethylsilyl-2-pyridyl)-3-(*N*-benzyl-*N*-4-methoxy-α-methylbenzylamino)propanoate 30

Following representative procedure 1, *n*-BuLi (2.5 M, 1.6 ml, 4.1 mmol), (*R*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide (1.00 g, 4.2 mmol) in THF (10 ml) and (*E*)-**28** (390 mg, 1.4 mmol) in THF (10 ml) gave, after purification by column chromatography on silica gel (hexane : Et_2O 8 : 1), **30** (622 mg, 86%) as a colourless oil; ν_{max} (film)/cm^{-1} 1729 (s, C=O), 1511 (s, C–OMe), 1248 (s, C–OMe); δ_H (400 MHz, $CDCl_3$) 0.27 (9H, s, Si*Me*$_3$), 1.13 (3H, d, *J* 6.9, C(α)*Me*), 1.31 (9H, s, OC*(Me)*$_3$), 2.38 (1H, dd, $J_{2A,2B}$ 15.7, $J_{2A,3}$ 3.8, C(2) H_A), 3.26 (1H, dd, $J_{2B,2A}$ 15.7, $J_{2B,3}$ 10.0, C(2)H_B), 3.70 (2H, AB, NCH_2Ph), 3.83 (3H, s, O*Me*), 4.06 (1H, q, *J* 6.9, C(α)*H*), 4.54 (1H, dd, $J_{3,2B}$ 10.0,$J_{3,2A}$ 3.8, C(3)*H*), 6.90 (2H, d, *J* 8.7, Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 7.20–7.37 (9H, m, Ar(2)*H*, Ar(6)*H* C_6H_4OMe, *Ph*, Ar(3)*H* C_5H_3N, Ar(5)*H* C_5H_3N), 7.56 (1H, t, *J* 7.9, Ar(4)*H* C_5H_3N); δ_C (100 MHz, $CDCl_3$) −1.8 (Si*Me*$_3$), 18.9 (C(α)*Me*), 27.9 (OC*(Me)*$_3$), 35.2 (*C(2)*H_2), 50.9 (N*C*H_2), 55.2, 56.4, 58.0, (O*Me*, *C(α)*H, *C(3)*H), 79.5 (O*C*(Me)$_3$), 113.4, 122.8, 126.6, 128.0, 128.1, 128.3, 128.8, 133.8 (*Ar*), 136.2, 141.4 (C_{ipso}), 158.4 (*Ar(4)* C_6H_4OMe), 160.6, 166.2 (*Ar(6)* C_5H_3N, *Ar(2)* C_5H_3N), 171.8 (C=O); *m*/*z* (APCI$^+$) 519 (MH$^+$, 60%), 385 (MH$^+$ − $C_9H_{10}O$, 95%), 135 ($C_9H_{11}O^+$, 100%); HRMS (ESI) $C_{31}H_{43}N_2O_3Si$ requires 519.3043, found 519.3037.

Preparation of (*E*)-*tert*-butyl 3-(2-chloro-3-methoxymethoxy-6-pyridyl)prop-2-enoate 31[3f]

2-Chloropyridin-3-ol (2 g, 15.4 mmol) was added to a stirred solution of K_2CO_3 (4.28 g, 30.8 mmol) and iodine (4.03 g, 15.9 mmol) in water (30 ml) at rt and stirred for 1.5 h before acidification with 1 M HCl to pH 6. The resulting solution was filtered, and the residue dried in an oven to give 2-chloro-6-iodopyridin-3-ol (2.54 g, 64%) as a pale brown powder which was used without further purification. Chloromethyl methyl ether (6.34 ml, 83.5 mmol) was added dropwise to a stirred solution of 2-chloro-6-iodopyridin-3-ol (10.69 g, 41.8 mmol) in $^iPr_2NEt$ (50 ml) at rt and stirred overnight before addition of EtOAc. The organic layer was partitioned between water and EtOAc, dried ($MgSO_4$) and concentrated *in vacuo* to give 2-chloro-6-iodo-3-methoxymethoxypyridine (7.11 g, 57%) as a pale brown oil which was used without further purification. To a stirred solution of 2-chloro-6-iodo-3-methoxymethoxypyridine (7.11 g, 23.7 mmol), *tert*-butyl acrylate (5.1 ml, 35.6 mmol), Bu_4NCl (6.59 g, 23.7 mmol) and $NaHCO_3$ (4.98 g, 59.3 mmol) in DMF (30 ml) was added $Pd(OAc)_2$ (107 mg, 0.474 mmol). The resulting solution was stirred at rt overnight, filtered through Celite (Et_2O), washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography on silica gel (5 : 1 hexane : Et_2O) then gave **31** (5.64 g, 79%) as a golden yellow oil which solidified on standing. δ_H (200 MHz, $CDCl_3$) 1.48 (9H, s, OC*(Me)*$_3$), 3.48 (3H, s, O*Me*), 5.26 (2H, s, OCH_2O), 6.69 (1H, d, *J* 15.6, HC=C*H*CO_2), 7.25 (1H, d, *J* 8.3, Ar*H* C_5H_2N), 7.43 (1H, d, *J* 15.6, *H*C=CHCO_2), 7.43 (1H, d, *J* 8.3, Ar*H* C_5H_2N).

Preparation of (3*R*,α*S*)-*tert*-butyl 3-(2-chloro-3-methoxymethoxy-6-pyridyl)-3-(*N*-benzyl-*N*-α-methyl-4-methoxybenzylamino)propanoate 32

Following representative procedure 1, *n*-BuLi (2.5 M, 7.7 ml, 19.3 mmol), (*S*)-*N*-benzyl-*N*-α-methyl-4-methoxybenzylamide (4.80 g, 20.0 mmol) in THF (20 ml) and **31** (2.00 g, 6.7 mmol) in THF (20 ml) gave, after purification by column chromatography on silica gel (hexane : Et_2O 10 : 1), **32** (2.46 g, 68%) as a colourless oil; $[\alpha]_D^{22}$ +25.4 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 1725 (s, C=O), 1511 (s, C–OMe), 1242 (s, C–OMe); δ_H(400 MHz, $CDCl_3$) 1.39 (9H, s, OC*(Me)*$_3$), 1.26 (3H, d, *J* 6.9, C(α)*Me*), 2.26 (1H, dd, $J_{2A,2B}$ 15.5, $J_{2A,3}$ 3.5, C(2)H_A), 2.89 (1H, dd, $J_{2B,2A}$ 15.5, $J_{2B,3}$ 10.4, C(2)H_B), 3.51 (3H, s, CH_2OCH_3), 3.63 (2H, AB, NCH_2Ph), 3.82 (3H, s, C_6H_4OMe), 3.95 (1H, q, *J* 6.9, C(α)*H*), 4.55 (1H, dd, $J_{3,2B}$ 10.4, $J_{3,2A}$ 3.5, C(3)*H*), 6.88 (2H, m, Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 7.18–7.24 (9H, m, Ar(2)*H*, Ar(6)*H* C_6H_4OMe, *Ph*, Ar(4)*H*, Ar(5)*H* C_5H_2N); δ_C(100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 28.0 (OC*(Me)*$_3$), 36.1 (*C(2)*H_2, 51.3 (N*C*H_2Ph), 55.2, 56.4, 57.1, 57.1 (C_{Ar}–O*Me*, *C(3)*H, *C(α)*H, CH_2OCH_3), 80.0 (O*C*(Me)$_3$), 95.1 (O*C*H_2O), 113.6 (Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 122.9, 123.3, 124.1, 128.1, 128.4, 128.9 (*Ar(2)*, *Ar(6)* C_6H_4OMe, *Ar(4)*, *Ar(5)* C_5H_2N, Ph), 135.4, 139.3, 141.0 (2 × C_{ipso}, *Ar(2)* C_5H_2N), 147.8 (*Ar(6)* C_5H_2N), 155.2, 158.6 (*Ar(4)* C_6H_4OMe, *Ar(3)*, C_5H_2N), 171.8 (*C*=O); *m*/*z* (APCI$^+$) 541 (MH$^+$, 15%), 407 (MH$^+$ − $C_9H_{10}O$, 100%);

HRMS (CI$^+$) $C_{30}H_{38}{}^{35}ClN_2O_5$ requires 541.2469, found 541.2468; ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that the de of the reaction was 80%.

Preparation of (3*R*,α*S*)-*tert*-butyl 3-(2-chloro-3-methoxymethoxy-6-pyridyl)-3-(*N*-α-methyl-4-methoxybenzylamino)-propanoate 33

Following representative procedure 2, CAN (4.40 g, 8.0 mmol), **32** (2.16 g, 4.0 mmol) in 5 : 1 MeCN : H_2O (24 ml) gave, after work up and purification by column chromatography on silica gel (hexane : Et_2O 2 : 1–1% NEt_3) and fractional recrystallisation (hexane : Et_2O) **33**, (1.12 g, 63%) as colourless blocks; mp 70–71 °C (hexane–Et_2O), $[\alpha]_D^{21}$ −1.7 (*c* 1.0, $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3312 (s, N–H), 1725 (s, C=O); δ_H(400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 6.5, C(α)*Me*), 1.40 (9H, s, OC*(Me)$_3$*), 2.15 (1H, br s, N*H*), 2.66 (2H, app d, *J* 7.0, C(2)H_2), 3.52 (3H, s, CH_2O*Me*), 3.68 (1H, q, *J* 6.5, C(α)*H*), 3.78 (3H, s, O*Me*), 4.08 (1H, app t, *J* 7.0, C(3)*H*), 5.23 (2H, s, OCH_2OMe), 6.77–6.79 (2H, m, Ar(3)*H*, Ar(5)*H* C_6H_4OMe), 7.10 (2H, d, *J* 8.0, Ar(4)*H* C_5H_2N), 7.14–7.17 (2H, m, Ar(2)*H*, Ar(6)*H* C_6H_4OMe), 7.34 (2H, d, *J* 8.0, Ar(5)*H* C_5H_2N); δ_C(100 MHz, $CDCl_3$) 23.3 (C(α)*Me*), 28.0 (OC*(Me)$_3$*), 41.7 (*C(2)*H_2), 54.9, 55.2, 56.4, 57.3 (O*Me*, *C(3)*H, *C(α)*H, CH_2O*Me*), 80.5 (O*C*(Me)$_3$), 95.2 (O*C*H_2O), 113.6 (*Ar(3)*, *Ar(5)* C_6H_4OMe), 121.6 (*Ar(5)* C_5H_2N), 123.9 (*Ar(4)* C_5H_2N), 127.9 (*Ar(2)*, *Ar(6)* C_6H_4OMe), 137.9 (*C$_{ipso}$*), 140.7 (*Ar(2)* C_5H_2N), 147.9 (*Ar(6)* C_5H_2N), 155.5, 158.4 (*Ar(3)* C_5H_2N, *Ar(4)* C_6H_4OMe), 170.9 (*C*=O); *m*/*z* (APCI$^+$) 451 (MH$^+$, 100%); HRMS (CI$^+$) $C_{23}H_{32}{}^{35}ClN_2O_5$ requires 451.2000, found 451.1992.

X-Ray crystal structure data for 33 †. Data were collected using an Enraf Nonius Kappa CCD diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at rt. The structure was solved by direct methods (SIR92), all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[23] Crystal data for **33** [$C_{23}H_{31}ClN_2O_5$], colourless block, M = 450.96, orthorhombic, space group $P\,2_12_12_1$, a = 10.5644(2) Å, b = 12.7699(3) Å, c = 17.3731(4) Å, U = 2343.74(9) Å^3, Z = 4, μ = 0.199, crystal dimensions 0.15 × 0.2 × 0.2 mm. A total of 5342 unique reflections were measured for 2.34 < θ < 27.46 and 3571 reflections were used in the refinement. The final parameters were wR_2 = 0.0382 and R_1 = 0.0381 [$I > 3\sigma(I)$]. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre, CCDC number 184754.

Preparation of (*R*)-*tert*-butyl 3-(2-chloro-3-methoxymethoxy-6-pyridyl)-3-aminopropanoate 34

Following representative procedure 3, CAN (1.53 g, 2.8 mmol), **33** (300 mg, 0.7 mmol) in 5 : 1 MeCN : H_2O (15 ml) gave, after work up and purification by column chromatography on silica gel (hexane : Et_2O 1 : 1 to Et_2O), **34** (104 mg, 49%) as a yellow oil; $[\alpha]_D^{24}$ +17.6 (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3378 (br, N–H), 1724 (s, C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, OC*(Me)$_3$*), 2.00 (2*H*, br s, NH_2), 2.58 (1H, dd, $J_{2A,2B}$ 15.9, $J_{2A,3}$ 8.5, C(2)H_A), 2.74 (1H, dd, $J_{2B,2A}$ 15.9, $J_{2B,3}$ 5.1, C(2)H_B), 3.49 (3H, s, O*Me*), 4.31 (1H, dd, $J_{3,2A}$ 8.5, $J_{3,2B}$ 5.1, C(3)*H*), 5.23 (2H, s, OCH_2OMe), 7.25 and 7.43 (2 × 1H, d, *J* 8.4, Ar(4)*H* and Ar(5)*H* C_5H_2N); δ_C(100 MHz, $CDCl_3$) 28.0 (OC*(Me)$_3$*), 43.8 (*C(2)*H_2), 52.8, 56.5 (*C(3)*H, CH_2O*Me*), 80.7 (O*C*(Me)$_3$), 95.1 (O*C*H_2O), 120.2, 124.2, (*Ar(4)*, *Ar(5)* C_5H_2N), 140.6 (*Ar(2)* C_5H_2N), 148.1 (*Ar(6)* C_5H_2N), 156.1 (*Ar(3)* C_5H_2N), 171.0 (*C*=O); *m*/*z* (APCI$^+$) 317 (MH$^+$, 40%), 261 (MH$^+$ − C_4H_8); HRMS (CI$^+$) $C_{14}H_{21}{}^{35}ClN_2O_4$ requires 317.1268, found 317.1268.

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