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RAPID STEREOSELECTIVE SYNTHESES OF HETEROARENE-FUSED AZACYCLES VIA DIASTEREOSELECTIVE CONJUGATE ADDITION OF HETEROARYL SUBSTITUTED LITHIUM AMIDES†

Stephen G. Davies,* Ai M. Fletcher, Katherine E. Holder, Paul M. Roberts, James E. Thomson, and David Zimmer

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, U.K. E-mail: steve.davies@chem.ox.ac.uk

†Dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday

Abstract – Conjugate addition of heteroaryl substituted lithium amides to a range of α,β-unsaturated esters followed by *in situ* enolate oxidation with (–)-(camphorsulfonyl)oxaziridine gave the corresponding α-hydroxy-β-amino esters. Subsequent Friedel-Crafts type cyclisation of these α-hydroxy-β-amino esters gave a range of heteroarene-fused azacycles in good yields and high diastereoselectivities.

INTRODUCTION

Arene- and heteroarene-fused azacyclic compounds have been shown to display potent biological activities. For example, (*S*)-salsolinol **1** is a clinical treatment for cancer,[1] and A-86929 **2** and ABT-431 **3** have been used for treatment of Parkinson's disease.[2] Very recently, ORC-13661 **4** was reported as a promising drug candidate for the prevention of aminoglycoside induced hearing loss (Figure 1).[3] Thus, the efficient synthesis and biological evaluation of various analogues of these classes of molecules would benefit drug discovery chemistry significantly.

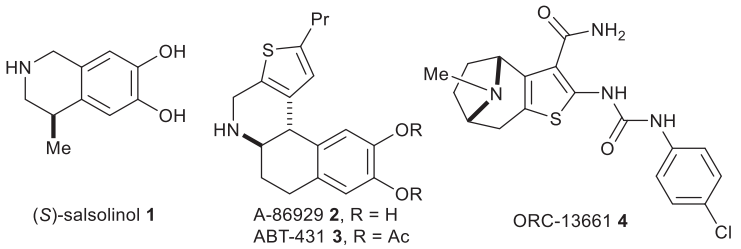
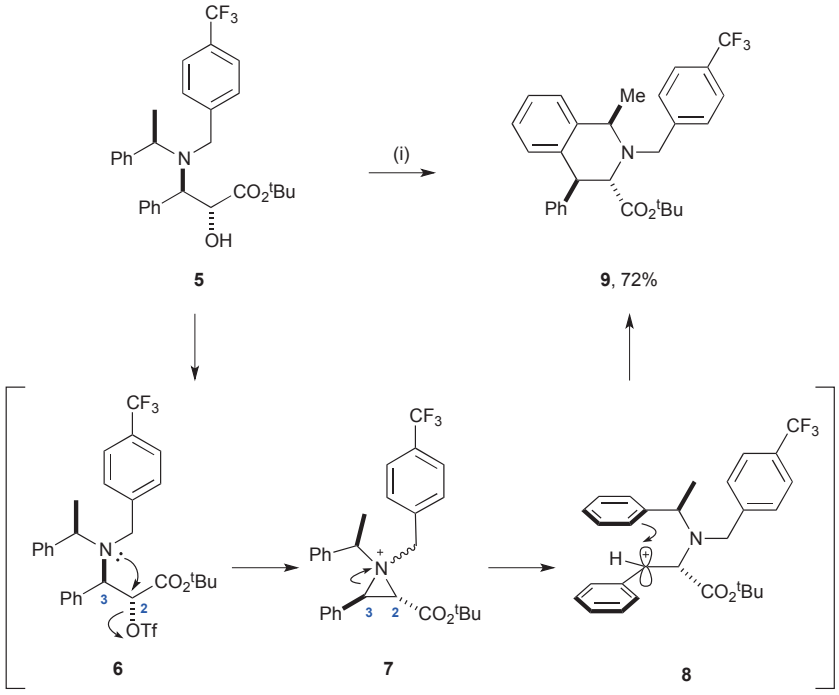


Figure 1. The structures of biologically active arene- and heteroarene-fused cyclic compounds **1**–**4**

We have recently reported the efficient stereoselective syntheses of 1,2,3,4-tetrahydroisoquinolines (i.e., arene-fused azacyclic compounds) *via* the intramolecular Friedel-Crafts type alkylation of the benzylic carbenium ion intermediates derived from *anti*-α-hydroxy-β-amino esters.[4] For example, treatment of α-hydroxy-β-amino ester **5** with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine gave 1,2,3,4-tetrahydroisoquinoline **9** in 72% yield as a single diastereoisomer. This outcome is consistent with a mechanism involving activation of the hydroxyl group within **5** as the corresponding triflate **6**, displacement by the adjacent amino group to give aziridinium intermediate **7** [with inversion of configuration at C(2)], and subsequent rupture of the C(3)–N bond forming the corresponding benzylic carbenium ion **8**, which undergoes rapid Friedel-Crafts type cyclisation to give 1,2,3,4-tetrahydroisoquinoline **9** (Scheme 1).



Scheme 1. *Reagents and conditions:* (i) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C to rt, 6 h

In order to develop further this methodology and to expand the structural diversity of the resultant arene-fused azabicyclic products accessible, α-hydroxy-β-amino esters **12**, bearing a variety of heteroarylmethyl *N*-substituents, were recognised as cyclisation precursors. It was envisaged that α-hydroxy-β-amino esters **12** could be synthesised *via* the conjugate addition of the corresponding heteroaryl substituted lithium amides **11** to α,β-unsaturated esters **10** followed by *in situ* enolate oxidation with (camphorsulfonyl)oxaziridine (CSO) **14**.[5] The resultant α-hydroxy-β-amino esters **12**, incorporating the corresponding heteroaryl motif, would then be exposed to Friedel-Crafts alkylation type conditions to

allow access to novel bicyclic molecular architectures **13** (Figure 2). Herein, we report our investigations in this area.

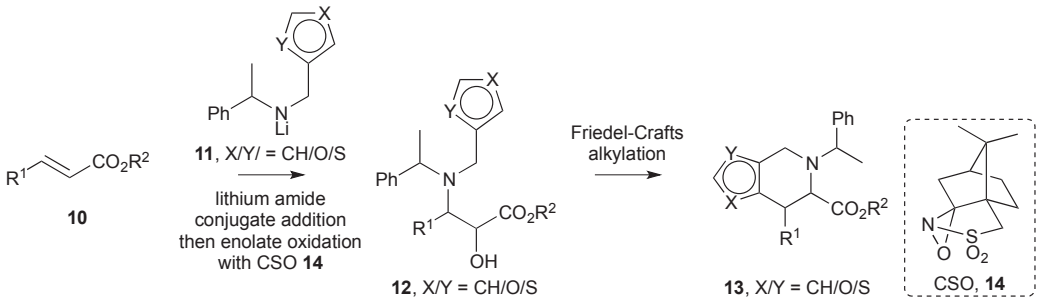
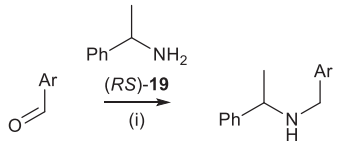


Figure 2. Proposed synthetic route to heteroarene-fused azabicycles

RESULTS AND DISCUSSION

A range of heteroaryl substituted amines [derived from (*RS*)-α-methylbenzylamine] were prepared *via* a standard reductive alkylation procedure upon reaction with the requisite aldehydes.[6] Commercially available aldehydes **15**–**18** were treated with racemic α-methylbenzylamine (*RS*)-**19** and subsequent reduction with $NaBH_4$ gave secondary amines (*RS*)-**20**–**23** in 77–85% yield (Scheme 2).

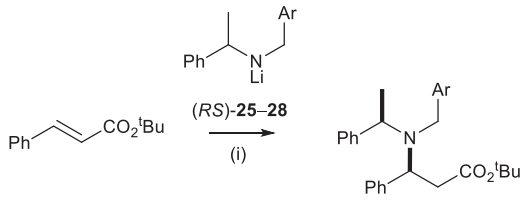


Aldehyde	Ar	Amine	Yield (%)
15	3-thienyl	**20**	85
16	2-thienyl	**21**	85
17	3-furyl	**22**	78
18	2-furyl	**23**	77

Scheme 2. *Reagents and conditions:* (i) (*RS*)-**19**, EtOH, rt, 24 h then $NaBH_4$, 0 °C to rt, 48 h

Using a one-pot procedure, addition of *s*-BuLi to a mixture of the requisite amines (*RS*)-**20**–**23** and α,β-unsaturated ester **24** gave the corresponding lithium amides (*RS*)-**25**–**28** *in situ*, which underwent conjugate addition to α,β-unsaturated ester **24**: conjugate addition of 3-thienyl, 2-thienyl and 3-furyl substituted lithium amides (*RS*)-**25**–**27** to α,β-unsaturated ester **24** gave the corresponding β-amino esters **29**–**31** in 80%, 69% and 89% yield, respectively, as single diasteroisomers (>95:5 dr) in each case. However, conjugate addition of 2-furyl substituted lithium amide (*RS*)-**28** to α,β-unsaturated ester **24** gave the corresponding β-amino ester **32** in 77% yield and 62:38 dr (Scheme 3). The low diastereoselectivity observed upon conjugate addition of the 2-furyl substituted lithium amide reagent (*RS*)-**28** to **24** is presumably due to disruption of the normal mode of chelation in the transition state[7] by the proximal oxygen atom of the 2-furyl group, resulting in a non-selective pathway for conjugate addition. Similar

phenomena have been observed previously when heteroatoms (nitrogen and oxygen atoms) were present in either the lithium amide reagent or the α,β-unsaturated ester, giving rise to a reduction in diastereoselectivity.[8–10] The corresponding reaction with 2-thienyl substituted lithium amide (*RS*)-**26** gave high diastereoselectivity (>95:5 dr), presumably due to the lower lithium chelating ability of the sulfur atom.

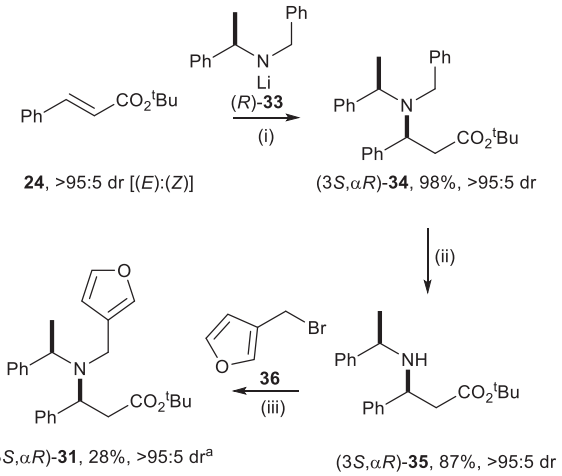


24, >95:5 dr [(*E*):(*Z*)] **29–32**

Amine	Ar	product	Yield (%)	dr
20	3-thienyl	**29**	80	>95:5
21	2-thienyl	**30**	69	>95:5
22	3-furyl	**31**	89	>95:5
23	2-furyl	**32**	77	62:38

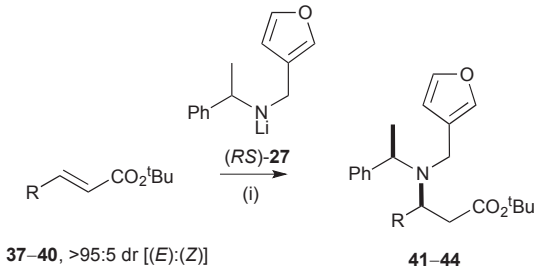
Scheme 3. *Reagents and conditions:* (i) (*RS*)-**20**–**23**, *s*-BuLi, THF, –78 °C, 2 h

The relative configuration within β-amino ester product **31** was assigned by chemical correlation to the known β-amino ester (3*S*,α*R*)-**34**,[11] and later unambiguously established *via* single crystal X-ray analysis of enantiopure (3*S*,α*R*)-**31** (*vide infra*). The known β-amino ester (3*S*,α*R*)-**34** was obtained upon conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**33** to α,β-unsaturated ester **24** in 98% yield as a single diastereoisomer. The (3*S*,α*R*)-configuration within **34** has previously been established *via* single crystal X-ray diffraction analysis.[12] Treatment of (3*S*,α*R*)-**34** with cerium ammonium nitrate (CAN) promoted chemoselective mono-*N*-debenzylation[13] to give secondary β-amino ester (3*S*,α*R*)-**35** in 87% yield. An authentic sample of 3-furyl substituted β-amino ester (3*S*,α*R*)-**31** was obtained upon *N*-alkylation of (3*S*,α*R*)-**35** with the requisite bromide **36**, which was prepared from the corresponding alcohol under Appel conditions (Scheme 4). The spectroscopic data for the enantiopure sample of (3*S*,α*R*)-**31** were identical to those for the sample of (3*RS*,α*SR*)-**31** derived from conjugate addition of 3-furyl substituted lithium amide (*RS*)-**27** to α,β-unsaturated ester **24**. Thus, this unambiguously established the relative configuration within **31**. The relative configurations within the major diastereoisomeric β-amino ester products **29**, **30** and **32** were assigned by analogy to that of **31**.



Scheme 4. *Reagents and conditions:* (i) (*R*)-**33**, THF, –78 °C, 2 h; (ii) CAN, MeCN/H_2O (5:1), rt, 2 h; (iii) **36**, rt, 16 h. [a] Isolated in >80% purity

The conjugate addition of 3-furyl substituted lithium amide (*RS*)-**27**, as a representative heteroaryl substituted lithium amide reagent, to a range of C(3)-aryl substituted α,β-unsaturated esters **37**–**40** was next investigated. In all cases, the corresponding β-amino esters **41**–**44** were obtained as single diastereoisomers (>95:5 dr) in 49–85% yield (Scheme 5). The relative configurations within **41**–**44** were assigned by analogy to C(3)-phenyl substituted β-amino ester **31**.

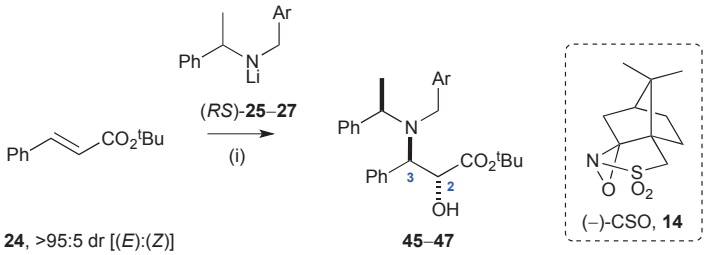


Precursor	R	β-amino ester	Yield (%)	dr
37	3-F-C_6H_4	**41**	85	>95:5
38	3-MeOC_6H_4	**42**	69	>95:5
39	4-F-C_6H_4	**43**	49	>95:5
40	4-MeO-C_6H_4	**44**	52	>95:5

Scheme 5. *Reagents and conditions:* (i) (*RS*)-**22**, *s*-BuLi, THF, –78 °C, 2 h

α,β-Unsaturated ester **24** was next treated with *N*-heteroaryl substituted lithium amides (*RS*)-**25**–**27** followed by subsequent addition of (–)-CSO **14**, from which the corresponding *anti*-α-hydroxy-β-amino esters **45**–**47** were obtained in 48–58% yield and ≥94:6 dr (Scheme 6).[9] The relative 2,3-*anti*-configurations within α-hydroxy-β-amino esters **45**–**47** were assigned by analogy to other aminohydroxylation reactions using lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **33** and CSO **14**,[9] and

were supported by the diagnostic values of the ^{1}H NMR ^3J coupling constants ($^3J_{2,3}$ = 2.9–3.5 Hz) between the C(2)*H* and C(3)*H* protons within **45**–**47**.[14,15]

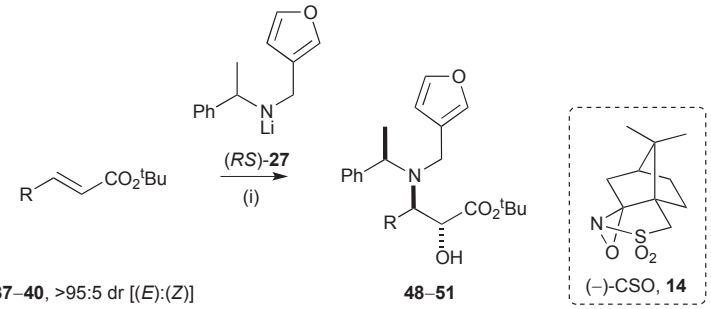


24, >95:5 dr [(*E*):(*Z*)] **45**–**47**

Amine	Ar	product	Yield (%)	dr
20	3-thienyl	**45**	58	>95:5
21	2-thienyl	**46**	48	94:6
22	3-furyl	**47**	51	>95:5

Scheme 6. *Reagents and conditions:* (i) (*RS*)-**20**–**22**, *s*-BuLi, THF, –78 °C, 2 h then (–)-CSO **14**, –78 °C to rt, 16 h

The aminohydroxylation of a range of α,β-unsaturated esters **37**–**40** upon reaction with 3-furyl substituted lithium amide (*RS*)-**27** and (–)-CSO **14** was also examined: conjugate addition of lithium amide (*RS*)-**27** to α,β-unsaturated esters **37**–**40** followed by *in situ* enolate oxidation with (–)-CSO **14** gave the corresponding *anti*-α-hydroxy-β-amino esters **48**–**51** in 38–46% yield (Scheme 7). The relative configurations within **48**–**51** were again assigned by analogy to other aminohydroxylation reactions using lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **33** and CSO **14**[9] and were supported by the diagnostic values of the ^{1}H NMR ^3J coupling constants ($^3J_{2,3}$ = 3.0–3.2 Hz).

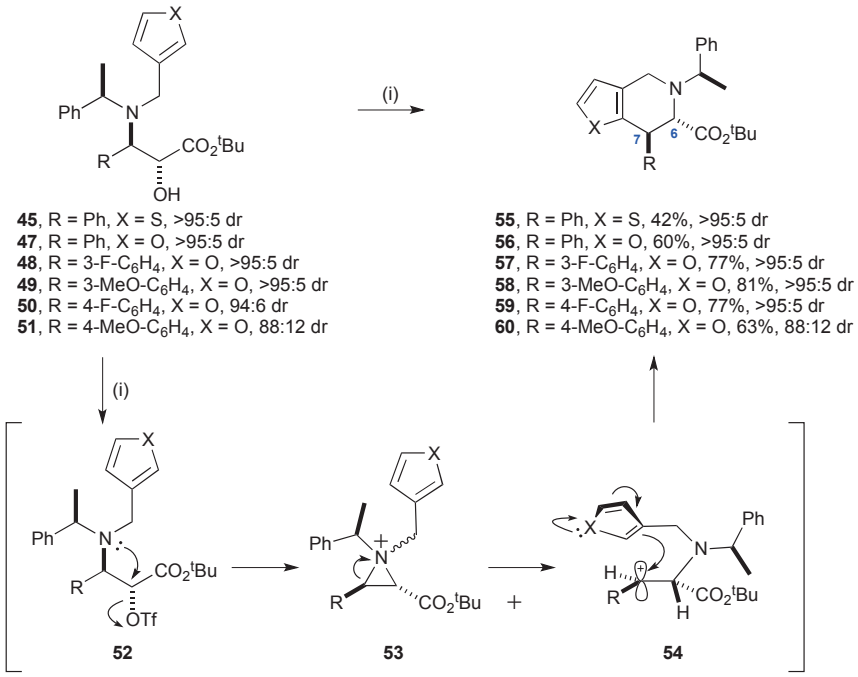


37–**40**, >95:5 dr [(*E*):(*Z*)] **48**–**51**

Precursor	R	β-amino ester	Yield (%)	dr
37	3-F-C_6H_4	**48**	46	>95:5
38	3-MeOC_6H_4	**49**	46	>95:5
39	4-F-C_6H_4	**50**	38	94:6
40	4-MeO-C_6H_4	**51**	38	88:12

Scheme 7. *Reagents and conditions:* (i) **22**, *s*-BuLi, THF, –78 °C, 2 h then (–)-CSO **14**, –78 °C to rt, 16 h

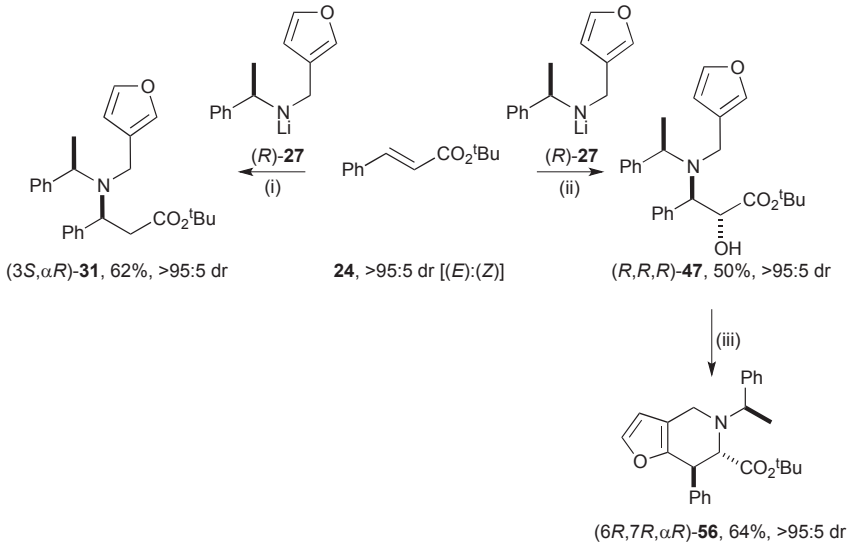
The Friedel-Crafts alkylation type cyclisation protocol employed in our previous syntheses of 1,2,3,4-tetrahydroisoquinolines[15] was applied to *N*-heteroaryl substituted α-hydroxy-β-amino esters **45** and **47**–**51**: these substrates were treated with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine in CH_2Cl_2 to give 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine **55** and 4,5,6,7-tetrahydrofura[3,2-*c*]pyridines **56**–**60** in 42–81% yield and ≥88:12 dr in each case. The relative configurations within **55**–**60** were tentatively assigned from the ^{1}H NMR ^3J coupling constants between the C(6)*H* and C(7)*H* protons of the heteroaryl fused tetrahydropyridines **55**–**60** ($^3J_{6,7}$ = 1.9–2.5 Hz) by analogy to those shown to be diagnostic for the corresponding *anti*-disubstituted 1,2,3,4-tetrahydroisoquinolines.[16] The formation of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine **55** and 4,5,6,7-tetrahydrofura[3,2-*c*]pyridines **56**–**60** and the stereochemical outcomes of these reactions is consistent with the proposed mechanism for 1,2,3,4-tetrahydroisoquinoline formation: treatment of **45** and **47**–**51** with Tf_2O activates the hydroxyl group as the corresponding triflate **52** and intramolecular displacement of the resultant triflate by the amino group [with inversion of configuration of C(2)] forms the corresponding aziridinium intermediate **53**. Regioselective ring-opening of **53** gave carbenium ion **54**, which was rapidly trapped by the most nucleophilic α-position of the *N*-hereoarene ring[17] [with retention of configuration at C(3)] to give the bicyclic compounds **55**–**60** (Scheme 8).



Scheme 8. *Reagents and conditions:* (i) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C to rt, 6 h

The preparation of these heteroarene-fused azacycles in enantiopure form could be readily achieved by employing the analogous synthetic route using an enantiopure heteroaryl substituted lithium amide

reagent in the conjugate addition step. As a representative example, enantiopure amine (*R*)-**22** [prepared in 82% yield from (*R*)-α-methylbenzylamine (*R*)-**19**] was reacted with α,β-unsaturated ester **24** followed by NH_4Cl, which gave the corresponding β-amino ester (3*S*,α*R*)-**31** in 62% yield and >95:5 dr. The relative configuration within (3*S*,α*R*)-**31** was unambiguously established *via* single crystal X-ray diffraction analysis and the absolute (3*S*,α*R*)-configuration of **31** was assigned relative to the known (*R*)-configuration of the *N*-α-methylbenzyl fragment (Figure 3). The corresponding aminohydroxylation of **24** with (*R*)-**27** and (–)-CSO **14** gave α-hydroxy-β-amino ester (*R*,*R*,*R*)-**47** in 50% yield and >95:5 dr. The Friedel-Crafts type cyclisation protocol applied to (*R*,*R*,*R*)-**47** gave enantiopure heteroarene-fused azacycle (6*S*,7*R*,α*R*)-**56** in 64% and >95:5 dr (Scheme 9).



Scheme 9. *Reagents and conditions:* (i) (*R*)-**22**, *s*-BuLi, THF, –78 °C, 2 h; (ii) (*R*)-**22**, *s*-BuLi, THF, –78 °C, 2 h then (–)-CSO **14**, –78 °C to rt, 16 h; (iii) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, 0 °C to rt, 6 h

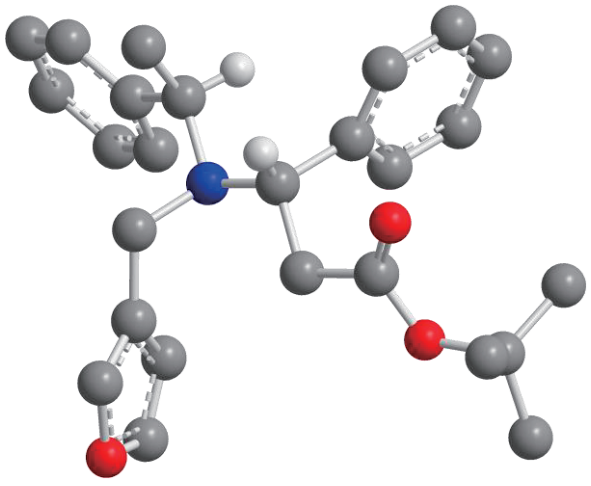


Figure 3. X-Ray crystal structure of (3*S*,α*R*)-**31** (selected H atoms are omitted for clarity)

In conclusion, the stereoselective syntheses of several heteroaryl fused azacyclic compounds were demonstrated. Conjugate addition of thienyl and furyl substituted lithium amides to a range of α,β-unsaturated esters gave the corresponding β-amino esters and the configuration of the newly formed stereogenic centre within the β-amino esters were established *via* chemical correlation. Conjugate addition of heteroaryl substituted lithium amides to α,β-unsaturated esters and subsequent *in situ* enolate oxidation with (–)-(camphorsulfonyl)oxaziridine gave the corresponding *anti*-α-hydroxy-β-amino esters with high diastereoselectivity. Cyclisation of the resultant *anti*-α-hydroxy-β-amino esters *via* a Friedel–Crafts type cyclisation protocol gave a range of heteroaryl fused azacyclic compounds in good yield and high diastereoselectivity. The application of this strategy for the preparation of enantiopure heteroarene-fused azacycles was also demonstrated in one representative case.

EXPERIMENTAL

Reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solutions of *n*-BuLi in hexanes and *s*-BuLi in cyclohexane were purchased and titrated against diphenylacetic acid before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[18] Water was purified by an Elix® UV-10 system. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ or Na_2SO_4. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points were recorded on a Gallenkamp Hot Stage apparatus. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. $^1H-^1H$ COSY, $^1H-^{13}C$ HSQC, and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

General procedure 1 - Preparation of secondary amines: The requisite aryl carboxaldehyde (1.05 equiv) was added to a stirred solution of (*RS*)-α-methylbenzylamine (1.00 equiv) in EtOH (1.77 M with

respect to amine). The resultant mixture was stirred at rt for 24 h before being cooled to 0 °C. $NaBH_4$ (1.00 equiv) was then added and the resultant suspension was stirred at rt for 48 h. The resultant suspension was concentrated *in vacuo* and the residue was partitioned between 10% aq citric acid solution and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined aqueous extracts were neutralised with 2.0 M aq NaOH, extracted with CH_2Cl_2, and washed with brine, then dried and concentrated *in vacuo*.

General procedure 2 - Lithium amide conjugate addition: *s*-BuLi (1.4 M in cyclohexane, 1.55 equiv) was added dropwise *via* syringe to a stirred solution of the requisite secondary amine (1.60 equiv) and the requisite α,β-unsaturated ester (1.00 equiv) in THF (0.4 M with respect to amine) at –78 °C. The reaction mixture was stirred at –78 °C for 2 h before the addition of satd aq NH_4Cl. The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 and 10% aq citric acid solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$, H_2O and brine, then dried and concentrated *in vacuo*.

General procedure 3 - Lithium amide conjugate addition with α-hydroxylation: *s*-BuLi (1.4 M in cyclohexane, 1.55 equiv) was added dropwise *via* syringe to a stirred solution of the requisite secondary amine (1.60 equiv) and the requisite α,β-unsaturated ester (1.00 equiv) in THF (0.4 M with respect to amine) at –78 °C. The resultant solution was stirred at –78 °C for 2 h. (–)-CSO **14** (1.6 equiv) was then added and the reaction mixture was allowed to warm to rt, then stirred at rt for 18 h. Satd aq NH_4Cl was added and the reaction mixture was stirred at rt for 5 min, then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 and 10% aq citric acid solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$, H_2O and brine, then dried and concentrated *in vacuo*.

General procedure 4 - Rearrangement/Friedel-Crafts alkylation: Tf_2O (1.5 equiv) was added to a stirred solution of the requisite α-hydroxy-β-amino ester (1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (3.0 equiv) in CH_2Cl_2 (0.08 M with respect to α-hydroxy-β-amino ester) at 0 °C, and the resultant mixture was stirred at rt for 6 h. H_2O was then added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O then the resultant solution was filtered and concentrated *in vacuo*.

(*RS*)-*N*-(Thiophen-3-ylmethyl)-*N*-(α-methylbenzyl)amine 20: Following *General procedure 1*, **15** (7.81 mL, 89.3 mmol) was reacted with (*RS*)-**19** (10.9 mL, 85.0 mmol) in EtOH (48.0 mL) then $NaBH_4$ (3.23 g, 85.0 mmol) to give **20** as a pale yellow oil (15.8 g, 85%); ν_{max} (ATR) 3330 (N–H); δ_H (400 MHz, $CDCl_3$)

1.38 (3H, d, *J* 6.6, C(α)*Me*), 3.66 (2H, app s, NCH_2Ar), 3.82 (1H, q, *J* 6.6, C(α)*H*), 7.03 (1H, dd, *J* 4.9, 0.9, C(5)*H*), 7.11 (1H, dd, *J* 1.8, 0.9, C(2)*H*), 7.24–7.38 (6H, m, *Ph*, C(4)*H*); δ_C (100 MHz, $CDCl_3$) 24.4 (C(α)*Me*), 46.6 (N*C*H$_2$Ar), 57.5 (*C*(α)), 121.4 (*C*(2)), 125.6, 126.7, 126.9, 128.5 (*C*(4), *o*,*m*,*p*-*Ph*), 127.6 (*C*(5)), 141.6 (*C*(3)), 145.4 (*i*-*Ph*); *m/z* (ESI^+) 218 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{16}NS^+$ ($[M+H]^+$) requires 218.0998; found 218.0999.

(*RS*)-*N*-(Thiophen-2-ylmethyl)-*N*-(α-methylbenzyl)amine 21:[19] Following *General procedure 1*, **16** (12.0 mL, 129 mmol) was reacted with (*RS*)-**19** (15.7 mL, 122 mmol) in EtOH (69.1 mL) then $NaBH_4$ (4.65 g, 122 mmol) to give **21** as a pale yellow oil (23.6 g, 85%); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.7, C(α)*Me*), 3.81 (1H, d, *J* 14.3, NCH_AH$_B$Ar), 3.86 (1H, d, *J* 14.3, NCH$_A$$H_B$Ar), 3.87 (1H, q, *J* 6.7, C(α)*H*), 6.87 (1H, dd, *J* 3.4, 1.0, C(3)*H*), 6.95 (1H, dd, *J* 5.1, 3.4, C(4)*H*), 7.21 (1H, dd, *J* 5.1, 1.0, C(5)*H*) 7.25–7.38 (5H, m, *Ph*).

(*RS*)-*N*-(Furan-3-ylmethyl)-*N*-(α-methylbenzyl)amine 22:[20] Following *General procedure 1*, **17** (18.0 mL, 208 mmol) was reacted with (*RS*)-**19** (25.2 mL, 198 mmol) in EtOH (112 mL) then $NaBH_4$ (7.53 g, 198 mmol) to give **22** as a pale yellow oil (31.1 g, 78%); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.6, C(α)*Me*), 3.83 (2H, app s, NCH_2Ar), 3.87 (1H, q, *J* 6.6, C(α)*H*), 6.38 (1H, d, *J* 0.9, C(4)*H*), 7.25–7.39 (7H, m, C(2)*H*, C(5)*H*, *Ph*).

(*R*)-*N*-(Furan-3-ylmethyl)-*N*-(α-methylbenzyl)amine 22: Following *General procedure 1*, **17** (1.80 mL, 20.8 mmol) was reacted with (*R*)-**19** (2.52 mL, 19.8 mmol) in EtOH (11.7 mL) then $NaBH_4$ (754 mg, 19.8 mmol) to give (*R*)-**22** as a pale yellow oil (3.28 g, 82%); $[\alpha]_D^{22}$+45.9 (*c* 1.0 in $CHCl_3$).

(*RS*)-*N*-(Furan-2-ylmethyl)-*N*-(α-methylbenzyl)amine 23:[20] Following *General procedure 1*, **18** (17.3 mL, 208 mmol) was reacted with (*RS*)-**19** (25.2 mL, 198 mmol) in EtOH (112 mL) then $NaBH_4$ (7.53 g, 198 mmol) to give **23** as a pale yellow oil (30.6 g, 77%); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.6, C(α)*Me*), 3.59 (1H, d, *J* 14.3, NCH_AH$_B$Ar), 3.67 (1H, d, *J* 14.3, NCH$_A$$H_B$Ar), 3.79 (1H, q, *J* 6.6, C(α)*H*), 6.11 (1H, dd, *J* 3.1, 0.6, C(3)*H*), 6.31 (1H, *J* 3.1, 1.8, C(4)*H*), 7.24–7.38 (6H, m, C(5)*H*, *Ph*).

***tert*-Butyl (3*RS*,α*SR*)-3-[*N*-(thiophen-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 29:** Following *General procedure 2*, *s*-BuLi (1.4 M in cyclohexane, 1.72 mL, 2.23 mmol) was reacted with **20** (500 mg, 2.30 mmol) and **24** (294 mg, 1.44 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (5.76 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **29** as a pale yellow oil (488 mg, 80%, >95:5 dr); ν_{max} (ATR) 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (9H, s, C*Me*$_3$), 1.26 (3H, d, *J* 6.8, C(α)*Me*), 2.51 (1H, dd, *J* 14.7, 9.8, C(2)H_A), 2.58 (1H, dd, *J* 14.7, 5.2, C(2)H_B), 3.66 (2H, app s, NCH_2Ar), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.41 (1H, dd, *J* 9.8, 5.2, C(3)*H*), 6.93 (1H, dd, *J* 4.9, 1.2, C(4′)*H*), 7.05 (1H, dd, *J* 2.9, 1.2, C(2′)*H*), 7.19 (1H, dd, *J* 4.9, 2.9, C(5′)*H*), 7.21–7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.2 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.7 (*C*(2)), 46.2 (N*C*H$_2$Ar), 57.0 (*C*(α)), 59.6

(*C*(3)), 80.2 (*C*Me$_3$), 121.2 (*C*(2′)), 125.1 (*C*(5′)), 127.1 (*C*(4′)), 126.8, 127.7, 127.9, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 141.8 (*i*-*Ph*), 143.0 (*C*(3′)), 144.3 (*i*-*Ph*), 171.1 (*C*(1)); *m/z* (ESI$^+$) 422 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{32}NO_2S^+$ ([M+H]$^+$) requires 422.2148; found 422.2144.

***tert*-Butyl (3*RS*,α*SR*)-3-[*N*-(thiophen-2′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 30:** Following *General procedure 2, s*-BuLi (1.4 M in cyclohexane, 1.51 mL, 196 mmol) was reacted with **21** (440 mg, 2.03 mmol) and **24** (295 mg, 1.27 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (5.07 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et$_2$O/35% aqNH$_4$OH, 90:9:1) gave **30** as a pale yellow oil (367 mg, 69%, >95:5 dr); ν_{max} (ATR) 1726 (C=O); δ_H (400 MHz, CDCl$_3$) 1.23 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 6.9, C(α)*Me*), 2.55 (1H, dd, *J* 14.5, 9.8, C(2)*H*$_A$), 2.59 (1H, dd, *J* 14.5, 5.4, C(2)*H*$_B$), 3.86 (2H, app s, NC*H*$_2$Ar), 4.06 (1H, q, *J* 6.9, C(α)*H*), 4.45 (1H, dd, *J* 9.8, 5.4, C(3)*H*), 6.84–6.87 (1H, m, C(3′)*H*), 6.88 (1H, dd, *J* 5.0, 3.5, C(4′)*H*), 7.16 (1H, dd, *J* 5.0, 1.3, C(5′)*H*), 7.22–7.47 (10H, m, *Ph*); δ_C (100 MHz, CDCl$_3$) 15.9 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.7 (*C*(2)), 46.1 (N*C*H$_2$Ar), 56.8 (*C*(α)), 59.5 (*C*(3)), 80.2 (*C*Me$_3$), 123.9 (*C*(3′)), 124.2 (*C*(5′)), 126.3 (*C*(4′)), 126.9, 127.2, 127.8, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 141.7 (*i*-*Ph*), 143.9 (*i*-*Ph*), 147.0 (*C*(2′)), 171.1 (*C*(1)); *m/z* (ESI$^+$) 422 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{32}NO_2S^+$ ([M+H]$^+$) requires 422.2148; found 422.2145.

***tert*-Butyl (3*RS*,α*SR*)-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 31:** Following *General procedure 2*, *s*-BuLi (1.4 M in cyclohexane, 5.43 mL 7.60 mmol) was reacted with **22** (1.58 g, 7.84 mmol) and **24** (1.00 g, 4.90 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (19.6 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et$_2$O/35% aqNH$_4$OH, 90:9:1) gave **31** as a yellow oil (1.76 g, 89%, >95:5 dr); ν_{max} (ATR) 1725 (C=O); δ_H (400 MHz, CDCl$_3$) 1.25 (9H, s, C*Me*$_3$), 1.25 (3H, d, *J* 6.8, C(α)*Me*), 2.55 (1H, dd, *J* 14.6, 9.8, C(2)*H*$_A$), 2.62 (1H, dd, *J* 14.6, 5.2, C(2)*H*$_B$), 3.51 (2H, app s, NC*H*$_2$Ar), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.43 (1H, dd, *J* 9.8, 5.2, C(3)*H*), 6.24 (1H, dd, *J* 1.7, 0.8, C(4′)*H*), 7.22–7.42 (12H, m, C(2′)*H*, C(5′)*H*, *Ph*); δ_C (100 MHz, CDCl$_3$) 16.2 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.8 (*C*(2)), 41.5 (N*C*H$_2$Ar), 56.6 (*C*(α)), 59.3 (*C*(3)), 80.2 (*C*Me$_3$), 110.8 (*C*(4′)), 125.4 (*C*(3′)), 126.7, 127.1, 127.7, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 139.9 (*C*(2′)), 141.8 (*i*-*Ph*), 142.7 (*C*(5′)), 144.5 (*i*-*Ph*), 171.2 (*C*(1)); *m/z* (ESI$^+$) 406 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{32}NO_3^+$ ([M+H]$^+$) requires 406.2377; found 406.2370.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 31:** Method A: PPh$_3$ (3.48 g, 13.3 mmol) was added to a stirred solution of 3-(hydroxymethyl)furan (0.88 mL, 10.2 mmol) and CBr$_4$ (4.02 g, 12.2 mmol) in CH$_2$Cl$_2$ (51.0 mL) at rt. The resultant mixture was left to stir at rt for 3 h, before being poured over hexane (200 mL). The resultant mixture was filtered through Celite® (eluent hexane) then concentrated *in vacuo*. Secondary amine (3*S*,α*R*)-**35** (331 mg, 1.02 mmol, >95:5 dr) was added to the residue, and the resultant mixture was left to stir at rt for 16 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et$_2$O/35% aqNH$_4$OH, 90:9:1) gave (3*S*,α*R*)-**31** as a white solid (114 mg, 28%, >80% purity).

Method B: Following *General procedure 2*, *s*-BuLi (1.4 M in cyclohexane, 1.17 mL 1.52 mmol) was reacted with (*R*)-**22** (315 mg, 1.57 mmol) and **24** (200 mg, 0.98 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (3.92 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave (3*S*,α*R*)-**31** as a colorless solid (247 mg, 62%, >95:5 dr); $[\alpha]_D^{22}$+3.2 (*c* 1.0 in $CHCl_3$); mp 90–92 °C.

X-Ray crystal structure determination for 31: Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Mo-Kα radiation using standard procedures at 150 K. 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.[21,22]

X-Ray crystal structure data for **31** [$C_{26}H_{31}NO_3$]: M = 405.54, monoclinic, space group $P\ 2_1$, a = 10.1926(7) Å, b = 9.2926(4) Å, c = 12.7488(8) Å, β = 108.134(7)°, V = 1147.54(12) Å^3, Z = 2, μ = 0.076 mm^{-1}, colourless block, crystal dimensions = 0.18 × 0.19 × 0.21 mm^3. A total of 5982 unique reflections were measured for $3 < \theta < 30$ and 4855 reflections were used in the refinement. The final parameters were wR_2 = 0.098 and R_1 = 0.067 [I>–3.0σ(I)], with Flack enantiopole = –1.2(11).[23]

***tert*-Butyl (3*RS*,α*SR*)-3-[*N*-(furan-2′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 32:** Following *General procedure 2*, *s*-BuLi (1.4 M in cyclohexane, 1.09 mL 1.52 mmol) was reacted with **23** (315 mg, 1.57 mmol) and **24** (200 mg, 0.98 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (3.92 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 93:6:1) gave **32** as a pale yellow oil (306 mg, 77%, 62:38 dr): ν_{max} (ATR) 1726 (C=O); δ_H (400 MHz, $CDCl_3$) [selected peaks for the major diastereoisomer] 1.24 (9H, s, C*Me*$_3$), 1.27 (3H, d, *J* 6.6, C(α)*Me*), 2.52 (1H, dd, *J* 14.5, 9.8, C(2)H_A), 2.67 (1H, dd, *J* 14.5, 5.2, C(2)H_B), 3.65 (1H, d, *J* 15.9, NCH_AH$_B$Ar), 3.70 (1H, d, *J* 15.9, NCH$_A$$H_B$Ar), 4.05 (1H, q, *J* 6.6, C(α)*H*), 4.43 (1H, dd, *J* 9.8, 5.2, C(3)*H*), 6.10 (1H, dd, *J* 3.2, 0.9, C(3′)*H*), 6.29 (1H, dd, *J* 3.2, 1.9, C(4′)*H*); δ_H (400 MHz, $CDCl_3$) [selected peaks for the minor diastereoisomer] 1.28 (9H, s, C*Me*$_3$), 1.39 (3H, d, *J* 6.6, C(α)*Me*), 2.70 (1H, dd, *J* 14.6, 10.1, C(2)H_A), 2.82 (1H, dd, *J* 14.6, 4.9, C(2)H_B), 3.51 (1H, d, *J* 15.9, NCH_AH$_B$Ar), 3.77 (1H, d, *J* 15.9, NCH$_A$$H_B$Ar), 4.05 (1H, q, *J* 6.6, C(α)*H*), 4.51 (1H, dd, *J* 10.1, 4.9, C(3)*H*), 6.06 (1H, dd, *J* 3.2, 0.9, C(3′)*H*), 6.27 (1H, dd, *J* 3.2, 1.9, C(4′)*H*); δ_C (100 MHz, $CDCl_3$) [selected peaks for the major diastereoisomer] 16.8 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.5 (*C*(2)), 43.6 (N*C*H$_2$Ar), 57.0 (*C*(α)), 59.5 (*C*(3)), 80.1 (*C*Me$_3$), 107.2 (*C*(3′)), 110.3 (*C*(4′)), 140.8 (*i-Ph*), 141.1 (*C*(5′)), 144.6 (*i-Ph*), 154.9 (*C*(2')), 171.2 (*C*(1)); δ_C (100 MHz, $CDCl_3$) [selected peaks for the minor diastereoisomer] 19.4 (C(α)*Me*), 27.9 (C*Me*$_3$), 38.1 (*C*(2)), 43.0 (N*C*H$_2$Ar), 57.9 (*C*(α)), 59.6 (*C*(3)), 80.3 (*C*Me$_3$), 107.4 (*C*(3′)), 110.2 (*C*(4′)), 141.1 (*C*(5′)), 141.4 (*i-Ph*), 144.8

(*i-Ph*), 155.0 (*C*(2′)), 171.3 (*C*(1)); *m/z* (ESI$^+$) 406 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{32}NO_3^+$ ([M+H]$^+$) requires 406.2377; found 406.2374.

***tert*-Butyl (3*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzy)amino]-3-phenylpropanoate 34:**[11c] *n*-BuLi (2.5 M in hexanes, 7.35 mL, 18.4 mmol) was added dropwise *via* syringe to a stirred solution of (*R*)-**33** (4.00 g, 19.0 mmol) in THF (110 mL) at –78 °C. After stirring for 30 min, a solution of **24** (2.42 g, 11.8 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (8 mL) at –78 °C was added dropwise *via* cannula. The reaction mixture was left to stir for 2 h before the addition of satd aq NH_4Cl (10 mL). The resultant mixture was allowed to warm to rt over 15 min, then concentrated *in vacuo*. The residue was then partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid solution (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (200 mL), H_2O (200 mL) and brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O, 15:1) gave **34** as a pale yellow oil (4.80 mg, 98%, >95:5 dr); $[\alpha]_D^{22}$+3.6 (*c* 1.0 in $CHCl_3$); {lit.[11c] $[\alpha]_D^{22}$+3.9 (*c* 0.7 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, C*Me*$_3$), 1.27 (3H, d, *J* 6.8, C(α)*Me*), 2.50 (1H, dd, *J* 14.4, 9.9, C(2)H_A), 2.56 (1H, dd, *J* 14.4, 5.2, C(2)H_B), 3.67 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 3.71 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.41 (1H, dd, *J* 9.9, 5.2, C(3)*H*), 7.17–7.44 (15H, m, *Ph*).

***tert*-Butyl (3*S*,α*R*)-3-phenyl-4-(*N*-α-methylbenzyl)amino-propanoate 35:**[24] CAN (17.6 g, 32.1 mmol) was added to a stirred solution of (3*S*,α*R*)-**34** (6.52 g, 15.7 mmol, >95:5 dr) in MeCN/H_2O (v/v 5:1, 184 mL) at rt. The reaction mixture was stirred at rt for 2 h before the addition of satd aq $NaHCO_3$ (130 mL). The resultant mixture was stirred at rt for 30 min. The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined organics were then dried and concentrated *in vacuo*. The residue was then stirred in 2.0 M aq $NaHSO_3$ (100 mL) for 20 min. The resultant mixture was extracted with Et_2O (3 × 100 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 80:19:1) gave (3*S*,α*R*)-**35** as a pale yellow oil (4.42 g, 87%, >95:5 dr); $[\alpha]_D^{22}$+12.6 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.5, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 2.59 (1H, dd, *J* 14.7, 6.2, C(2)H_A), 2.68 (1H, dd, *J* 14.7, 7.9, C(2)H_B), 3.66 (1H, q, *J* 6.5, C(α)*H*), 4.16 (1H, dd, *J* 7.9, 6.2, C(3)*H*), 7.19–7.33 (10H, m, *Ph*).

***tert*-Butyl (3*RS*,α*RS*)-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-(3''-fluorophenyl)-propanoate 41:** Following *General procedure 2*, *s*-BuLi (1.4 M in cyclohexane, 0.99 mL, 1.40 mmol) was reacted with **22** (290 mg, 1.44 mmol) and **37** (200 mg, 0.90 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (3.61 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **41** as a pale yellow oil (325 mg, 85%, >95:5 dr); ν_{max} (ATR) 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (9H, s, C*Me*$_3$), 1.29 (3H, d, *J* 6.8, C(α)*Me*), 2.52 (1H, dd, *J* 14.8, 9.8, C(2)H_A), 2.57 (1H, dd,

J 14.8, 5.0, C(2)H_B), 3.51 (2H, app s, NCH_2Ar), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.45 (1H, dd, *J* 9.8, 5.0, C(3)*H*), 6.26 (1H, dd, *J* 1.7, 0.7, C(4′)*H*), 6.96 (1H, tdd, *J* 8.4, 2.6, 1.0, C(4″)*H*), 7.13–7.42 (10H, m, C(2′)*H*, C(5′)*H*, C(2″)*H*, C(5″)*H*, C(6″)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.8 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.1 (*C*(2)), 41.6 (N*C*H$_2$Ar), 56.8 (*C*(α)), 58.6 (*C*(3)), 80.4 (*C*Me$_3$), 110.7 (*C*(4′)), 113.9 (d, *J* 21.0, *C*(4″)), 115.0 (d, *J* 21.9, *C*(2″)), 123.6 (d, *J* 2.9, *C*(6″)), 125.0 (*C*(3′)), 126.9, 127.6, 128.2 (*o*,*m*,*p*-*Ph*), 129.5 (d, *J* 8.6, *C*(5″)), 140.0 (*C*(2′)), 142.9 (*C*(5′)), 144.0 (*i*-*Ph*), 145.0 (d, *J* 5.7, *C*(1″)), 162.8 (d, *J* 245.1, *C*(3″)), 170.9 (*C*(1)); δ_F (377 MHz, $CDCl_3$) –113.6 (C(3″)*F*); *m/z* (ESI$^+$) 424 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{31}FNO_3^+$ ([M+H]$^+$) requires 424.2282; found 424.2277.

***tert*-Butyl (3*RS*,α*RS*)-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-(3''-methoxyphenyl)-propanoate 42:** Following *General procedure 2*, *s*-BuLi (1.4 M in cyclohexane, 0.95 mL, 1.33 mmol) was reacted with **22** (275 mg, 1.37 mmol) and **38** (200 mg, 0.86 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (3.42 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **42** as a pale yellow oil (257 mg, 69%, >95:5 dr); ν_{max} (ATR) 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.8, C(α)*Me*), 1.29 (9H, s, C*Me*$_3$), 2.54 (1H, dd, *J* 14.8, 9.6, C(2)H_A), 2.61 (1H, dd, *J* 14.8, 5.4, C(2)H_B), 3.52 (2H, app s, NCH_2Ar), 3.83 (3H, s, O*Me*), 4.05 (1H, q, *J* 6.8, C(α)*H*), 4.42 (1H, dd, *J* 9.6, 5.4, C(3)*H*), 6.17 (1H, dd, *J* 1.7, 0.7, C(4′)*H*), 6.79–7.43 (11H, m, C(2′)*H*, C(5′)*H*, C(2″)*H*, C(3″)*H*, C(5″)*H*, C(6″)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.4 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.7 (*C*(2)), 41.6 (N*C*H$_2$Ar), 55.2 (O*Me*), 56.6 (*C*(α)), 59.1 (*C*(3)), 80.2 (*C*Me$_3$), 110.8 (*C*(4′)), 112.3 (*C*(4″)), 114.0 (*C*(2″)), 120.4 (*C*(6″)), 125.3 (*C*(3′)), 126.7, 127.6, 128.1 (*o*,*m*,*p*-*Ph*), 129.0 (*C*(5″)), 140.0 (*C*(2′)), 142.7 (*C*(5′)), 143.6 (*C*(1″)), 144.4 (*i*-*Ph*), 159.5 (*C*(3″)), 171.0 (*C*(1)); *m/z* (ESI$^+$) 436 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{34}NO_4^+$ ([M+H]$^+$) requires 436.2482; found 436.2475.

***tert*-Butyl (3*RS*,α*RS*)-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-(4''-fluorophenyl)-propanoate 43:** Following *General procedure 2*, *s*-BuLi (1.4 M in cyclohexane, 0.99 mL, 1.40 mmol) was reacted with **23** (290 mg, 1.44 mmol) and **39** (200 mg, 0.90 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (3.61 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **43** as a pale yellow oil (186 mg, 49%, >95:5 dr); ν_{max} (ATR) 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.26 (9H, s, C*Me*$_3$), 1.27 (3H, d, *J* 6.7, C(α)*Me*), 2.51 (1H, dd, *J* 14.6, 10.1, C(2)H_A), 2.60 (1H, dd, *J* 14.6, 4.8, C(2)H_B), 3.50 (2H, app s, NCH_2Ar), 4.00 (1H, q, *J* 6.7, C(α)*H*), 4.41 (1H, dd, *J* 10.1, 4.8, C(3)*H*), 6.23 (1H, dd, *J* 1.6, 0.6, C(4′)*H*), 7.01–7.05 (2H, m, C(3″)*H*, C(5″)*H*), 7.23–7.41 (9H, m, *Ph*, C(2′)*H*, C(5′)*H*, C(2″)*H*, C(6″)*H*); δ_C (125 MHz, $CDCl_3$) 16.4 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.5 (*C*(2)), 41.5 (N*C*H$_2$Ar), 56.7 (*C*(α)), 58.7 (*C*(3)), 80.3 (*C*Me$_3$), 110.7 (*C*(4′)), 114.9 (d, *J* 21.0, *C*(3″), *C*(5″)), 125.3 (*C*(3′)), 126.8, 127.6, 128.2 (*o*,*m*,*p*-*Ph*), 129.6 (d, *J* 7.6, *C*(2″), *C*(6″)), 137.7 (d, *J* 3.8, *C*(1″)), 139.9 (*C*(2′)), 142.8 (*C*(5′)), 144.2 (*i*-*Ph*), 161.9 (d, *J* 245.1, *C*(4″)), 171.0 (*C*(1)); δ_F (377 MHz, $CDCl_3$) –115.8

(C(4″)*F*); *m/z* (ESI$^+$) 424 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{31}FNO_3^+$ ([M+H]$^+$) requires 424.2282; found 424.2279.

***tert*-Butyl (3*RS*,α*RS*)-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-(4''-methoxyphenyl)-propanoate 44:** Following *General procedure 2*, *s*-BuLi (1.4 M in cyclohexane, 0.95 mL, 1.33 mmol) was reacted with **22** (275 mg, 1.37 mmol) and **40** (200 mg, 0.86 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (3.42 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **44** as a pale yellow oil (195 mg, 52%, >95:5 dr); ν_{max} (ATR) 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.8, C(α)*Me*), 1.27 (9H, s, C*Me*$_3$), 2.52 (1H, dd, *J* 14.5, 10.1, C(2)H_A), 2.61 (1H, dd, *J* 14.5, 5.0, C(2)H_B), 3.50 (2H, app s, NCH_2Ar), 3.81 (3H, s, O*Me*), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.38 (1H, dd, *J* 10.1, 5.0, C(3)*H*), 6.24 (1H, dd, *J* 1.7, 0.7, C(4′)*H*), 6.88 (2H, d, *J* 8.5, C(3″)*H*, C(5″)*H*), 7.21–7.43 (9H, m, C(2′)*H*, C(5′)*H*, C(2″)*H*, C(6″)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.2 (C(α)*Me*), 27.8 (C*Me*$_3$), 38.9 (*C*(2)), 41.4 (N*C*H$_2$Ar), 55.2 (O*Me*), 56.5 (*C*(α)), 58.7 (*C*(3)), 80.1 (*C*Me$_3$), 110.8 (*C*(4′)), 113.4 (*C*(3″), *C*(5″)), 125.5 (*C*(3′)), 126.7, 127.6, 128.0 (*o*,*m*,*p*-*Ph*), 129.2 (*C*(2″), *C*(6″)), 133.8 (*C*(1″)), 139.9 (*C*(2′)), 142.6 (*C*(5′)), 144.6 (*i*-*Ph*), 158.6 (*C*(4″)), 171.2 (*C*(1)); *m/z* (ESI$^+$) 436 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{34}NO_4^+$ ([M+H]$^+$) requires 436.2482; found 436.2479.

***tert*-Butyl (*RS*,*RS*,*RS*)-2-hydroxy-3-[*N*-(thiophen-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-phenyl-propanoate 45:** Following *General procedure 3*, *s*-BuLi (1.4 M in cyclohexane, 1.85 mL, 2.41 mmol) was reacted with **20** (540 mg, 2.49 mmol) and **24** (317 mg, 1.56 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (6.22 mL) before the addition of **14** (605 mg, 2.64 mmol). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **45** as a pale yellow oil (394 mg, 58%, >95:5 dr); ν_{max} (ATR) 3493 (O–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.8, C(α)*Me*), 1.22 (9H, s, C*Me*$_3$), 3.84 (1H, d, *J* 15.1, NCH_AH$_B$Ar), 4.03 (1H, d, *J* 15.1, NCH$_A$$H_B$Ar), 4.21 (1H, q, *J* 6.8, C(α)*H*), 4.21 (1H, d, *J* 3.2, C(3)*H*), 4.42 (1H, d, *J* 3.2, C(2)*H*), 6.94 (1H, dd, *J* 4.9, 1.0, C(4′)*H*), 7.04 (1H, dd, *J* 2.9, 1.0, C(2′)*H*), 7.17–7.49 (11H, m, C(5′)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 27.7 (C*Me*$_3$), 47.4 (N*C*H$_2$Ar), 57.0 (*C*(α)), 65.9 (*C*(3)), 73.3 (*C*(2)), 82.2 (*C*Me$_3$), 121.4 (*C*(2′)), 125.5 (*C*(5′)), 126.8, 127.6, 127.8, 128.0, 128.1, 129.8 (*C*(4′), *o*,*m*,*p*-*Ph*), 138.1 (*i*-*Ph*), 143.0 (*C*(3′)), 144.1 (*i*-*Ph*), 171.9 (*C*(1)); *m/z* (ESI$^+$) 438 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{32}NO_3S^+$ ([M+H]$^+$) requires 438.2097; found 438.2096.

***tert*-Butyl (*RS*,*RS*,*RS*)-2-hydroxy-3-[*N*-(thiophen-2′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-phenyl-propanoate 46:** Following *General procedure 3*, *s*-BuLi (1.4 M in cyclohexane, 1.51 mL, 1.97 mmol) was reacted with **21** (440 mg, 2.03 mmol) and **24** (259 mg, 1.27 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (5.07 mL) before the addition of **14** (494 mg, 2.16 mmol). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **46** as a pale yellow oil (267 mg, 48%, 94:6 dr); ν_{max} (ATR) 3491 (O–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.8, C(α)*Me*), 1.21 (9H, s,

C*Me*$_3$), 4.11 (1H, d, *J* 15.4, NC*H*$_A$H$_B$Ar), 4.27 (1H, d, *J* 15.4, NCH$_A$*H*$_B$Ar), 4.27 (1H, d, *J* 2.9, C(3)*H*), 4.27 (1H, q, *J* 6.8, C(α)*H*), 4.47 (1H, d, *J* 2.9, C(2)*H*), 6.88–6.91 (2H, m, C(3′)*H,* C(4′)*H*), 7.18 (1H, dd, *J* 4.8, 1.6, C(5′)*H*), 7.24–7.55 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.4 (C(α)*Me*), 27.7 (C*Me*$_3$), 47.3 (N*C*H$_2$Ar), 57.1 (*C*(α)), 64.6 (*C*(3)), 73.6 (*C*(2)), 82.3 (*C*Me$_3$), 124.4 (*C*(3′), *C*(5′)), 126.4 (*C*(4′)), 126.9, 127.6, 128.0, 128.2, 129.8 (*o*,*m*,*p-Ph*), 138.1, 143.8 (*i-Ph*), 146.8 (*C*(2′)), 172.1 (*C*(1)); *m/z* (ESI$^+$) 460 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{32}NO_3S^+$ ([M+H]$^+$) requires 438.2097; found 438.2094.

***tert*-Butyl (*RS*,*RS*,*RS*)-2-hydroxy-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-phenyl-propanoate 47:** Following *General procedure 3*, *s*-BuLi (1.4 M in cyclohexane, 5.43 mL, 7.60 mmol) was reacted with **22** (1.58 g, 7.84 mmol) and **24** (1.00 g, 4.90 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (19.6 mL) before the addition of **14** (1.91 g, 8.33 mmol). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **47** as a pale yellow oil (1.06 g, 51%, >95:5 dr); ν_{max} (ATR) 3497 (O–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.8, C(α)*Me*), 1.23 (9H, s, C*Me*$_3$), 3.67 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ar), 3.87 (1H, d, *J* 15.2, NCH$_A$*H*$_B$Ar), 4.21 (1H, q, *J* 6.8, C(α)*H*), 4.23 (1H, d, *J* 3.5, C(3)*H*), 4.45 (1H, d, *J* 3.5, C(2)*H*), 6.21 (1H, dd, *J* 1.8, 0.9, C(4′)*H*), 7.22–7.49 (12H, m, C(2′)*H*, C(5′)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 27.7 (C*Me*$_3$), 42.6 (N*C*H$_2$Ar), 56.7 (*C*(α)), 65.9 (*C*(3)), 73.2 (*C*(2)), 82.2 (*C*Me$_3$), 110.6 (*C*(4′)), 126.8 (*C*(3′)), 127.6, 127.9, 128.0, 128.1, 129.7 (*o*,*m*,*p-Ph*), 138.0 (*i-Ph*), 139.9 (*C*(2′)), 143.0 (*C*(5′)), 144.1 (*i-Ph*), 171.9 (*C*(1)); *m/z* (ESI$^+$) 422 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{32}NO_4^+$ ([M+H]$^+$) requires 422.2326; found 422.2320.

***tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-phenyl-propanoate 47:** Following *General procedure 3*, *s*-BuLi (1.4 M in cyclohexane, 1.17 mL, 1.52 mmol) was reacted with (*R*)-**22** (315 mg, 1.57 mmol) and **24** (200 mg, 0.98 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (3.92 mL) before the addition of **14** (382 mg, 1.67 mmol). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave (*R*,*R*,*R*)-**47** as a pale yellow oil (206 mg, 50%, >95:5 dr); $[\alpha]_D^{22}$ −7.7 (*c* 1.0 in $CHCl_3$).

***tert*-Butyl (*RS*,*RS*,*RS*)-2-hydroxy-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-(3′′-fluoro-phenyl)propanoate 48:** Following *General procedure 3*, *s*-BuLi (1.4 M in cyclohexane, 1.62 mL, 2.27 mmol) was reacted with **22** (471 mg, 2.34 mmol) and **37** (325 mg, 1.46 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (5.86 mL) before the addition of **14** (570 mg, 2.49 mmol). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **48** as a pale yellow oil (296 mg, 46%, >95:5 dr); ν_{max} (ATR) 3635 (O–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.9, C(α)*Me*), 1.26 (9H, s, C*Me*$_3$), 3.71 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ar), 3.89 (1H, dd, *J* 15.2, 0.8, NCH$_A$*H*$_B$Ar), 4.22 (1H, q, *J* 6.9, C(α)*H*), 4.24 (1H, d, *J* 3.0, C(3)*H*), 4.43 (1H, d, *J* 3.0, C(2)*H*), 6.26 (1H, d, *J* 0.9, C(4′)*H*), 6.87–7.38 (11H, m, C(2′)*H*, C(5′)*H*, C(2′′)*H*, C(4′′)*H*, C(5′′)*H*, C(6′′)H, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.0 (C(α)*Me*),

27.7 (C*Me*$_3$), 42.6 (N*C*H$_2$Ar), 56.8 (*C*(α)), 64.8 (*C*(3)), 73.1 (*C*(2)), 82.5 (*C*Me$_3$), 110.6 (*C*(4′)), 114.5 (d, *J* 21.0, *C*(4″)), 116.6 (d, *J* 21.9, *C*(2″)), 125.0 (*C*(3′)), 125.3 (d, *J* 2.9, *C*(6″)), 126.9, 127.8, 128.2 (*o*,*m*,*p*-*Ph*), 129.4 (d, *J* 7.6, *C*(5″)), 140.0 (*C*(2′)), 140.9 (d, *J* 6.7, *C*(1″)), 143.0 (*C*(5′)), 143.8 (*i*-*Ph*), 162.5 (d, *J* 245.1, *C*(3″)), 171.9 (*C*(1)); δ_F (377 MHz, $CDCl_3$) –113.3 (C(3″)*F*); *m/z* (ESI$^+$) 462 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{31}FNO_4^+$ ([M+H]$^+$) requires 440.2232; found 440.2227.

***tert*-Butyl (*RS*,*RS*,*RS*)-2-hydroxy-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-(3″-methoxyphenyl)propanoate 49:** Following *General procedure 3*, *s*-BuLi (1.4 M in cyclohexane, 1.54 mL, 2.15 mmol) was reacted with **22** (447 mg, 2.22 mmol) and **38** (325 mg, 1.39 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (5.56 mL) before the addition of **14** (541 mg, 2.36 mmol). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **49** as a pale yellow oil (288 mg, 46%, >95:5 dr); ν_{max} (ATR) 3635 (O–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.8, C(α)*Me*), 1.26 (9H, s, C*Me*$_3$), 3.69 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ar), 3.80 (3H, s, O*Me*), 3.87 (1H, dd, *J* 15.2, 1.0, NCH$_A$*H*$_B$Ar), 4.21 (1H, d, *J* 3.2, C(3)*H*), 4.23 (1H, q, *J* 6.8, C(α)*H*), 4.42 (1H, d, *J* 3.2, C(2)*H*), 6.25 (1H, dd, *J* 1.7, 1.0, C(4′)*H*), 6.82–7.48 (11H, m, C(2′)*H*, C(5′)*H*, C(2″)*H*, C(4″)*H*, C(5″)*H*, C(6″)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.8 (C(α)*Me*), 27.7 (C*Me*$_3$), 42.6 (N*C*H$_2$Ar), 55.2 (O*Me*), 56.7 (*C*(α)), 65.5 (*C*(3)), 73.2 (*C*(2)), 80.6 (*C*Me$_3$), 110.7 (*C*(4′)), 112.8 (*C*(4″)), 115.6 (*C*(2″)), 122.1 (*C*(6″)), 125.3 (*C*(3′)), 126.8, 127.9, 128.1 (*o*,*m*,*p*-*Ph*), 128.9 (*C*(5″)), 139.6 (*C*(1″)), 140.0 (*C*(2′)), 142.9 (*C*(5′)), 144.1 (*i*-*Ph*), 159.3 (*C*(3″)), 172.0 (*C*(1)); *m/z* (ESI$^+$) 452 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{34}NO_5^+$ ([M+H]$^+$) requires 452.2431; found 452.2427.

***tert*-Butyl (*RS*,*RS*,*RS*)-2-hydroxy-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-(4″-fluorophenyl)propanoate 50:** Following *General procedure 3*, *s*-BuLi (1.4 M in cyclohexane, 1.50 mL, 2.10 mmol) was reacted with **22** (435 mg, 2.16 mmol) and **39** (300 mg, 1.35 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (5.41 mL) before the addition of **14** (526 mg, 2.30 mmol). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **50** as a pale yellow oil (225 mg, 38%, 94:6 dr); ν_{max} (ATR) 3635 (O–H), 1724 (C=O); δ_H (500 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.8, C(α)*Me*), 1.24 (9H, s, C*Me*$_3$), 3.67 (1H, d, *J* 15.3, NC*H*$_A$H$_B$Ar), 3.86 (1H, d, *J* 15.3, NCH$_A$*H*$_B$Ar), 4.18 (1H, q, *J* 6.8, C(α)*H*), 4.21 (1H, d, *J* 3.2, C(3)*H*), 4.45 (1H, d, *J* 3.2, C(2)*H*), 6.21 (1H, d, *J* 0.9, C(4′)*H*), 6.98–7.03 (2H, m, C(3″)*H*, C(5″)*H*), 7.24–7.48 (9H, m, C(2′)*H*, C(5′)*H*, C(2″)*H*, C(6″)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 27.7 (C*Me*$_3$), 42.5 (N*C*H$_2$Ar), 56.7 (*C*(α)), 64.9 (*C*(3)), 73.1 (*C*(2)), 82.4 (*C*Me$_3$), 110.6 (*C*(4′)), 114.9 (d, *J* 21.0, *C*(3″), *C*(5″)), 125.3 (*C*(3′)), 126.9, 127.8, 128.2 (*o*,*m*,*p*-*Ph*), 131.3 (d, *J* 7.6, *C*(2″), *C*(6″)), 133.9 (d, *J* 2.9, *C*(1″)), 139.9 (*C*(2′)), 143.0 (*C*(5′)), 144.0 (*i*-*Ph*), 162.3 (d, *J* 246.1, *C*(4″)), 171.8 (*C*(1)); δ_F (377 MHz, $CDCl_3$) –114.8 (C(4″)*F*); *m/z* (ESI$^+$) 440 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{31}FNO_4^+$ ([M+H]$^+$) requires 440.2232; found 440.2223.

***tert*-Butyl (*RS*,*RS*,*RS*)-2-hydroxy-3-[*N*-(furan-3′-ylmethyl)-*N*-(α-methylbenzyl)amino]-3-(4′′-methoxyphenyl)propanoate 51:** Following *General procedure 3*, *s*-BuLi (1.4 M in cyclohexane, 1.77 mL, 2.48 mmol) was reacted with **22** (515 mg, 2.56 mmol) and **40** (375 mg, 1.60 mmol, >95:5 dr [(*E*):(*Z*)]) in THF (6.41 mL) before the addition of **14** (624 mg, 2.72 mmol). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **51** as a pale yellow oil (277 mg, 38%, 88:12 dr); ν_{max} (ATR) 3635 (O–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) [selected peaks for the major diastereoisomer] 1.20 (3H, d, *J* 6.8, C(α)*Me*), 1.24 (9H, s, C*Me*$_3$), 3.63 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ar), 3.80 (3H, s, O*Me*), 3.85 (1H, d, *J* 15.2, NCH$_A$*H*$_B$Ar), 4.17 (1H, d, *J* 3.2, C(3)*H*), 4.19 (1H, q, *J* 6.8, C(α)*H*), 4.43 (1H, d, *J* 3.2, C(2)*H*), 6.20 (1H, dd, *J* 1.7, 0.7, C(4′)*H*), 6.83–6.87 (2H, m, C(3′′)*H*, C(5′′)*H*); δ_H (400 MHz, $CDCl_3$) [selected peaks for the minor diasteroisomer] 1.27 (9H, s, C*Me*$_3$), 1.44 (3H, d, *J* 6.8, C(α)*Me*), 3.78 (3H, s, O*Me*), 4.00 (1H, dd, *J* 15.9, NCH$_A$*H*$_B$Ar), 4.62 (1H, d, *J* 3.2, C(2)*H*); δ_C (100 MHz, $CDCl_3$) [major diastereoisomer] 13.4 (C(α)*Me*), 27.8 (C*Me*$_3$), 42.5 (N*C*H$_2$Ar), 55.2 (O*Me*), 56.6 (*C*(α)), 65.3 (*C*(3)), 73.3 (*C*(2)), 82.1 (*C*Me$_3$), 110.6 (*C*(4′)), 113.4 (*C*(3′′), *C*(5′′)), 125.4 (*C*(3′)), 126.7, 127.9, 128.1 (*o*,*m*,*p*-*Ph*), 129.9 (*C*(1′′)), 130.9 (*C*(2′′), *C*(6′′)), 139.9 (*C*(2′)), 142.9 (*C*(5′)), 144.2 (*i*-*Ph*), 159.0 (*C*(4′′)), 171.9 (*C*(1)); *m/z* (ESI$^+$) 452 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{34}NO_5^+$ ([M+H]$^+$) requires 452.2431; found 452.2426.

(6*RS*,7*SR*,α*SR*)-*N*(5)-(α-Methylbenzyl)-6-(*tert*-butxoycarbonyl)-7-phenyl- 4,5,6,7-tetrahydrothieno [3,2-*c*]pyridine 55: Following *General procedure 4*, Tf_2O (194 mg, 0.686 mmol) was reacted with **45** (200 mg, 0.46 mmol, >95:5 dr) and 2,6-di-*tert*-butyl-4-methylpyridine (281 mg, 1.37 mmol) in CH_2Cl_2 (3.81 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **55** as a pale yellow oil (80 mg, 42%, >95:5 dr); ν_{max} (ATR) 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.6, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 3.67 (1H, d, *J* 15.2, C(4)*H*$_A$), 3.76 (1H, d, *J* 15.2, C(4)*H*$_B$), 4.05 (1H, q, *J* 6.6, C(α)*H*), 4.08 (1H, d, *J* 2.5, C(6)*H*), 4.54 (1H, app s, C(7)*H*), 6.62 (1H, d, *J* 5.1, C(3)*H*), 7.07 (1H, d, *J* 5.1, C(2)*H*), 7.15–7.35 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.3 (C(α)*Me*), 28.2 (C*Me*$_3$), 44.6 (*C*(7)), 47.6 (*C*(4)), 61.8 (*C*(α)), 63.5 (*C*(6)), 81.4 (*C*Me$_3$), 123.8 (*C*(2)), 124.6 (*C*(3)), 126.7, 126.8, 127.1, 127.9, 128.3, 128.4 (*o*,*m*,*p*-*Ph*), 133.9 (*C*(7a)), 135.1 (*C*(3a)), 144.0, 146.2 (*i*-*Ph*), 171.4 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 420 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{30}NO_2S^+$ ([M+H]$^+$) requires 420.1992; found 420.1988.

(6*RS*,7*SR*,α*SR*)-*N*(5)-(α-Methylbenzyl)-6-(tert-butoxycarbonyl)-7-phenyl-4,5,6,7-tetrahydrofuro-[3,2-*c*]pyridine 56: Following *General procedure 4*, Tf_2O (302 mg, 1.07 mmol) was reacted with **47** (300 mg, 0.71 mmol, >95:5 dr) and 2,6-di-*tert*-butyl-4-methylpyridine (438 mg, 2.14 mmol) in CH_2Cl_2 (8.91 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **56** as a pale yellow oil (172 mg, 60%, >95:5 dr); ν_{max} (ATR) 1726 (C=O); δ_H (500 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.6, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 3.52 (1H, d, *J* 14.4, C(4)*H*$_A$), 3.64 (1H, d, *J* 14.4,

C(4)H_B), 4.07 (1H, d, *J* 2.0, C(6)*H*), 4.08 (1H, q, *J* 6.6, C(α)*H*), 4.54 (1H, app s, C(7)*H*), 6.11 (1H, d, *J* 1.7, C(3)*H*), 7.19–7.38 (11H, m, C(2)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.7 (C(α)*Me*), 28.2 (C*Me*$_3$), 43.4 (*C*(7)), 44.6 (*C*(4)), 61.9 (*C*(α)), 63.7 (*C*(6)), 81.4 (*C*Me$_3$), 108.1 (*C*(3)), 117.1 (*C*(3a)), 126.8, 127.0, 128.1, 128.3 (*o*,*m*,*p*-*Ph*), 141.7 (*C*(2)), 141.8 (*i*-*Ph*), 146.4 (*i*-*Ph*), 148.3 (*C*(7a)), 171.4 (*C*O_2^{t}Bu); *m/z* (ESI$^+$) 404 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{30}NO_3^+$ ([M+H]$^+$) requires 404.2220; found 404.2217.

(6*S*,7*R*,α*R*)-*N*(5)-(α-Methylbenzyl)-6-(*tert*-butoxycarbonyl)-7-phenyl-4,5,6,7-tetrahydrofuro-[3,2-*c*]pyridine 56: Following *General procedure 4*, Tf_2O (0.12 mL, 0.71 mmol) was reacted with (*R*,*R*,*R*)-**47** (200 mg, 0.48 mmol, >95:5 dr) and 2,6-di-*tert*-butyl-4-methylpyridine (292 mg, 1.43 mmol) in CH_2Cl_2 (5.94 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave (6*S*,7*R*,α*R*)-**56** as a pale yellow oil (123 mg, 64%, >95:5 dr); $[\alpha]_D^{22}$ −12.8 (*c* 1.0 in $CHCl_3$).

(6*RS*,7*SR*,α*SR*)-*N*(5)-(α-Methylbenzyl)-6-(*tert*-butoxycarbonyl)-7-(3′-fluorophenyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine 57: Following *General procedure 4*, Tf_2O (260 mg, 0.92 mmol) was reacted with **48** (270 mg, 0.62 mmol, >95:5 dr) and 2,6-di-*tert*-butyl-4-methylpyridine (378 mg, 1.85 mmol) in CH_2Cl_2 (7.69 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **57** as a pale yellow oil (199 mg, 77%, >95:5 dr); ν_{max} (ATR) 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.7, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 3.52 (1H, d, *J* 14.4, C(4)H_A), 3.64 (1H, d, *J* 14.4, C(4)H_B), 4.04 (1H, d, *J* 2.0, C(6)*H*), 4.08 (1H, q, *J* 6.7, C(α)*H*), 4.54 (1H, app s, C(7)*H*), 6.12 (1H, d, *J* 2.0, C(3)*H*), 6.96–7.38 (10H, m, *Ph*, C(2)*H*, C(2′)*H*, C(4′)*H*, C(5′)*H*, C(6′)*H*); δ_C (125 MHz, $CDCl_3$) 21.6 (C(α)*Me*), 28.2 (C*Me*$_3$), 43.1 (*C*(7)), 44.6 (*C*(4)), 61.9 (*C*(α)), 63.4 (*C*(6)), 81.7 (*C*Me$_3$), 108.2 (*C*(3)), 113.8 (d, *J* 21.0, *C*(4′)), 115.4 (d, *J* 21.9, *C*(2′)), 117.4 (*C*(3a)), 123.9 (d, *J* 2.9, *C*(6′)), 126.9, 127.1, 128.4 (*o*,*m*,*p*-*Ph*), 129.4 (d, *J* 7.6, *C*(5′)), 141.9 (*C*(2)), 144.5 (d, *J* 7.6, *C*(1′)), 146.1 (*i*-*Ph*), 147.8 (*C*(7a)), 162.8 (d, *J* 245.1, *C*(3′)), 171.2 (*C*O_2^{t}Bu); δ_F (377 MHz, $CDCl_3$) –113.9 (C(3′)*F*); *m/z* (ESI$^+$) 422 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{29}FNO_3^+$ ([M+H]$^+$) requires 422.2126; found 422.2124.

(6*RS*,7*SR*,α*SR*)-*N*(5)-(α-Methylbenzyl)-6-(*tert*-butoxycarbonyl)-7-(3′-methoxyphenyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine 58: Following *General procedure 4*, Tf_2O (216 mg, 0.77 mmol) was reacted with **49** (230 mg, 0.51 mmol, >95:5 dr) and 2,6-di-*tert*-butyl-4-methylpyridine (314 mg, 1.53 mmol) in CH_2Cl_2 (6.37 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **58** as a pale yellow oil (179 mg, 81%, >95:5 dr); ν_{max} (ATR) 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.6, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 3.52 (1H, d, *J* 14.5, C(4)H_A), 3.64 (1H, app d, *J* 14.5, C(4)H_B), 3.82 (3H, s, O*Me*), 4.08 (1H, d, *J* 1.9, C(6)*H*), 4.08 (1H, q, *J* 6.6, C(α)*H*), 4.51 (1H, app s, C(7)*H*), 6.10 (1H, d, *J* 1.9, C(3)*H*), 6.82–7.29 (10H, m, C(2)*H*, C(2′)*H*,

C(4′)*H*, C(5′)*H*, C(6′)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.8 (C(α)*Me*), 28.2 (C*Me*$_3$), 43.4 (*C*(7)), 44.6 (*C*(4)), 55.2 (O*Me*), 61.9 (*C*(α)), 63.6 (*C*(6)), 81.5 (*C*Me$_3$), 108.1 (*C*(3)), 112.3 (*C*(4′)), 114.0 (*C*(2′)), 117.1 (*C*(3a)), 120.8 (*C*(6′)), 126.8, 127.1, 128.3 (*o*,*m*,*p*-*Ph*), 129.0 (*C*(5′)), 141.7 (*C*(2)), 143.5 (*C*(1′)), 143.5 (*i*-*Ph*), 148.2 (*C*(7a)), 159.5 (*C*(3′)), 171.4 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 434 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_4^+$ ([M+H]$^+$) requires 434.2326; found 434.2321.

(6*RS*,7*SR*,α*SR*)-*N*(5)-(α-Methylbenzyl)-6-(*tert*-butoxycarbonyl)-7-(4′-fluorophenyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine 59: Following *General procedure 4,* Tf_2O (183 mg, 0.65 mmol) was reacted with **50** (190 mg, 0.43 mmol, 94:6 dr) and 2,6-di-*tert*-butyl-4-methylpyridine (266 mg, 1.30 mmol) in CH_2Cl_2 (5.41 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **59** as a pale yellow oil (140 mg, 77%, >95:5 dr); ν_{max} (ATR) 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.6, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 3.51 (1H, d, *J* 14.5, C(4)H_A), 3.64 (1H, app d, *J* 14.5, C(4)H_B), 3.99 (1H, d, *J* 1.9, C(6)*H*), 4.08 (1H, q, *J* 6.6, C(α)*H*), 4.52 (1H, app s, C(7)*H*), 6.11 (1H, d, *J* 1.9, C(3)*H*), 7.01–7.29 (10H, m, C(2)*H*, C(2′)*H*, C(3′)*H*, C(5′)*H*, C(6′)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.6 (C(α)*Me*), 28.2 (C*Me*$_3$), 42.6 (*C*(7)), 44.6 (*C*(4)), 61.9 (*C*(α)), 63.7 (*C*(6)), 81.6 (*C*Me$_3$), 108.2 (*C*(3)), 114.8 (d, *J* 21.0, *C*(3′), *C*(5′)), 117.2 (*C*(3a)), 126.9, 127.1, 128.4 (*o*,*m*,*p*-*Ph*), 129.8 (d, *J* 8.6, *C*(2′), *C*(6′)), 137.5 (d, *J* 2.9, *C*(1′)), 141.8 (*C*(2)), 146.2 (*i*-*Ph*), 148.2 (*C*(7a)), 161.9 (d, *J* 245.1, *C*(4′)), 171.2 (*C*O$_2$^{t}Bu); δ_F (377 MHz, $CDCl_3$) –116.4 (C(4′)*F*); *m/z* (ESI$^+$) 422 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{29}FNO_3^+$ ([M+H]$^+$) requires 422.2126; found 422.2122.

(6*RS*,7*SR*,α*SR*)-*N*(5)-(α-Methylbenzyl)-6-(*tert*-butoxycarbonyl)-7-(4′-methoxyphenyl)-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-6-carboxylate 60: Following *General procedure 4*, Tf_2O (234 mg, 0.83 mmol) was reacted with **51** (250 mg, 0.55 mmol, 88:12 dr) and 2,6-di-*tert*-butyl-4-methylpyridine (341 mg, 1.66 mmol) in CH_2Cl_2 (6.93 mL). Purification *via* flash column chromatography (eluent 30−40 °C petrol/Et_2O/35% aqNH_4OH, 90:9:1) gave **60** as a pale yellow oil (150 mg, 63%, 88:12 dr); ν_{max} (ATR) 1724 (C=O); δ_H (500 MHz, $CDCl_3$) [selected peaks for the major diastereoisomer] 1.18 (3H, d, *J* 6.8, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 3.51 (1H, d, *J* 14.5, C(4)H_A), 3.63 (1H, app dd, *J* 14.5, C(4)H_B), 3.83 (3H, s, O*Me*), 4.02 (1H, d, *J* 1.9, C(6)*H*), 4.08 (1H, q, *J* 6.8, C(α)*H*), 4.48 (1H, app s, C(7)*H*), 6.10 (1H, d, *J* 1.9, C(3)*H*); δ_H (500 MHz, $CDCl_3$) [selected peaks for the minor diastereoisomer] 1.36 (3H, d, *J* 6.6, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 3.41 (1H, d, *J* 1.9, C(6)*H*), 4.17 (1H, q, *J* 6.6, C(α)*H*), 4.31 (1H, app s, C(7)*H*), 6.30 (1H, d, *J* 1.9, C(3)*H*); δ_C (125 MHz, $CDCl_3$) [selected peaks for the major diastereoisomer] 21.6 (C(α)*Me*), 28.2 (C*Me*$_3$), 42.6 (*C*(7)), 44.6 (*C*(4)), 55.2 (O*Me*), 61.9 (*C*(α)), 63.9 (*C*(6)), 81.4 (*C*Me$_3$), 108.1 (*C*(3)), 113.5 (*C*(3′), *C*(5′)), 116.8 (*C*(3a)), 126.8, 127.1, 128.3 (*o*,*m*,*p*-*Ph*), 129.3 (*C*(2′), *C*(6′)), 134.0 (*C*(1′)), 141.6 (*C*(2)), 146.4 (*i*-*Ph*), 148.7 (*C*(7a)), 154.5 (*C*(4′)), 171.5 (*C*O$_2$^{t}Bu); δ_C (125 MHz, $CDCl_3$) [selected peaks for the minor diastereoisomer] 22.4 (C(α)*Me*), 28.2 (C*Me*$_3$), 42.6 (*C*(4)), 42.7 (*C*(7)), 55.4 (O*Me*), 61.4 (*C*(α)), 65.2 (*C*(6)), 81.1 (*C*Me$_3$), 108.3 (*C*(3)), 113.3 (*C*(3′), *C*(5′)), 117.3 (*C*(3a)), 126.6, 127.2,

128.0 (*o*,*m*,*p-Ph*), 128.6 (*C*(2′), *C*(6′)), 133.6 (*C*(1′)), 141.8 (*C*(2)), 145.1 (*i-Ph*), 148.6 (*C*(7a)), 158.4 (*C*(4′)), 171.3 (*C*O_2^{t}Bu); *m/z* (ESI$^+$) 434 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{32}NO_4^+$ ([M+H]$^+$) requires 434.2326; found 434.2320.

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