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

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†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.

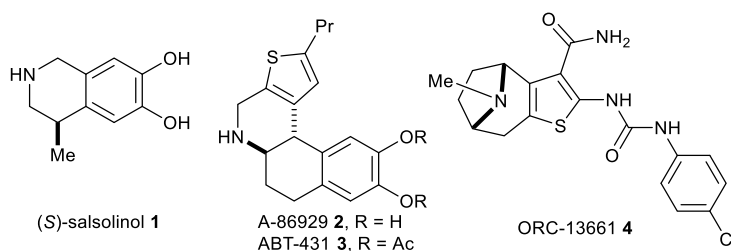
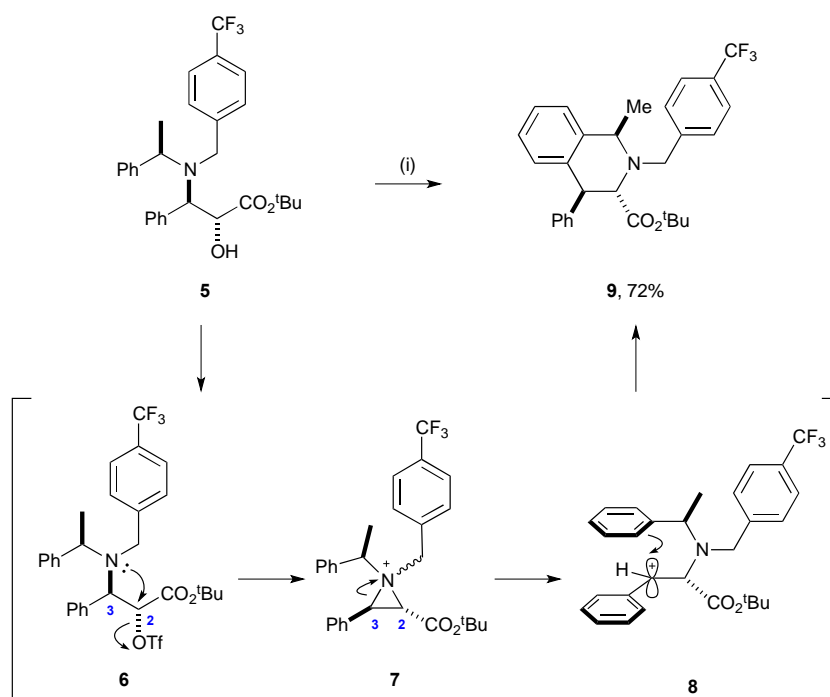


Figure 1. The structures of biologically active arene- and heteroarene-fused cyclic compounds **1–4**

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 Tf₂O 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) Tf₂O, 2,6-di-*tert*-butyl-4-methylpyridine, CH₂Cl₂, 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.

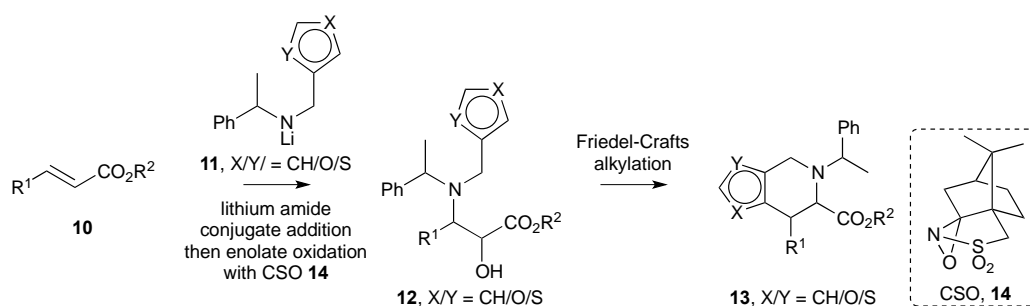
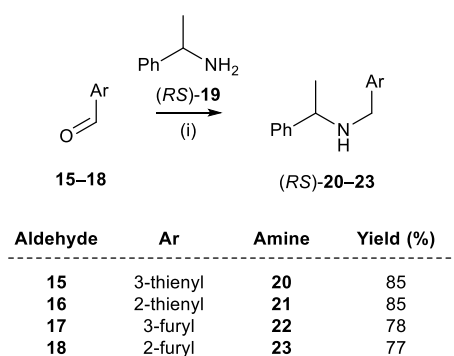


Figure 2. Proposed synthetic route to heteroarene-fused azabicycles

RESULTS AND DISCUSSION

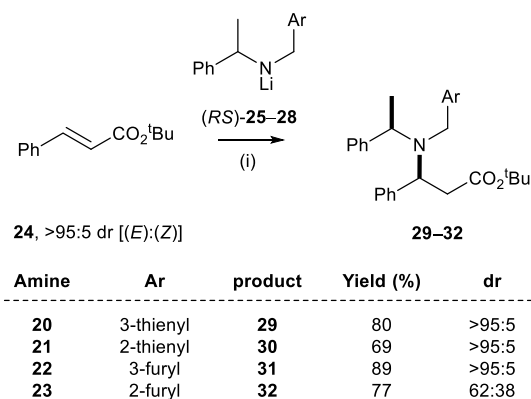
A range of heteroaryl substituted amines [derived from (*RS*)- α -methylbenzylamine] were prepared *via* a standard reductive alkylation procedure upon reaction with the requisite aldehydes.⁶ Commercially available aldehydes **15–18** were treated with racemic α -methylbenzylamine (*RS*)-**19** and subsequent reduction with NaBH₄ gave secondary amines (*RS*)-**20–23** in 77–85% yield (Scheme 2).



Scheme 2. Reagents and conditions: (i) (*RS*)-**19**, EtOH, rt, 24 h then NaBH₄, 0 °C to rt, 48 h

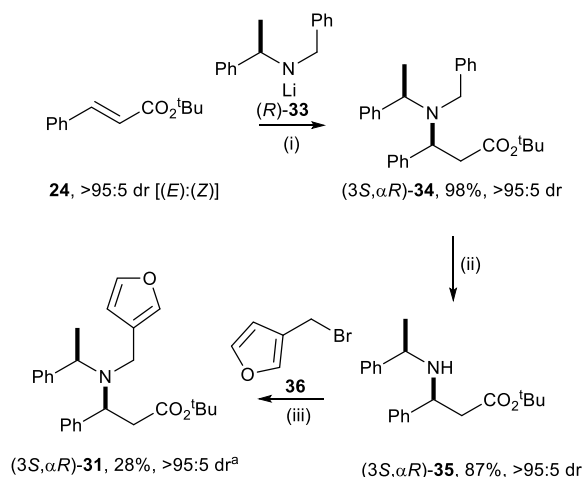
Using a one-pot procedure, addition of *s*-BuLi to a mixture of the requisite amines (*RS*)-**20–23** and α,β -unsaturated ester **24** gave the corresponding lithium amides (*RS*)-**25–28** *in situ*, which underwent conjugate addition to α,β -unsaturated ester **24**: conjugate addition of 3-thienyl, 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 diastereoisomers (>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 state⁷ 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.



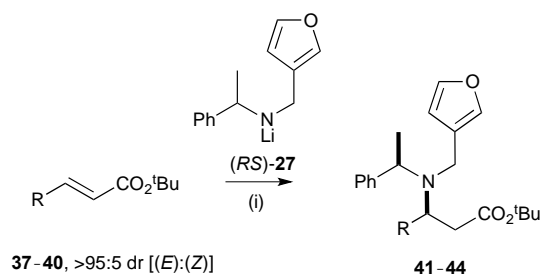
Scheme 3. Reagents and conditions: (i) (*RS*)-**20–23**, *s*-BuLi, THF, $-78\text{ }^{\circ}\text{C}$, 2 h

The relative configuration within β -amino ester product **31** was assigned by chemical correlation to the known β -amino ester (*3S,\alphaR*)-**34**,¹¹ and later unambiguously established *via* single crystal X-ray analysis of enantiopure (*3S,\alphaR*)-**31** (*vide infra*). The known β -amino ester (*3S,\alphaR*)-**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 (*3S,\alphaR*)-configuration within **34** has previously been established *via* single crystal X-ray diffraction analysis.¹² Treatment of (*3S,\alphaR*)-**34** with cerium ammonium nitrate (CAN) promoted chemoselective mono-*N*-debenzylation¹³ to give secondary β -amino ester (*3S,\alphaR*)-**35** in 87% yield. An authentic sample of 3-furyl substituted β -amino ester (*3S,\alphaR*)-**31** was obtained upon *N*-alkylation of (*3S,\alphaR*)-**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 (*3S,\alphaR*)-**31** were identical to those for the sample of (*3RS,\alphaSR*)-**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/H₂O (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.

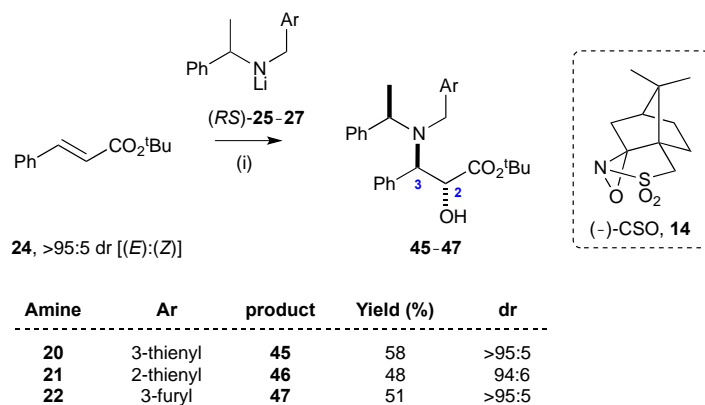


| Precursor | R | β -amino ester | Yield (%) | dr |
|-----------|-------------------------------------|----------------------|-----------|-------|
| 37 | 3-F-C ₆ H ₄ | 41 | 85 | >95:5 |
| 38 | 3-MeOC ₆ H ₄ | 42 | 69 | >95:5 |
| 39 | 4-F-C ₆ H ₄ | 43 | 49 | >95:5 |
| 40 | 4-MeO-C ₆ H ₄ | 44 | 52 | >95:5 |

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

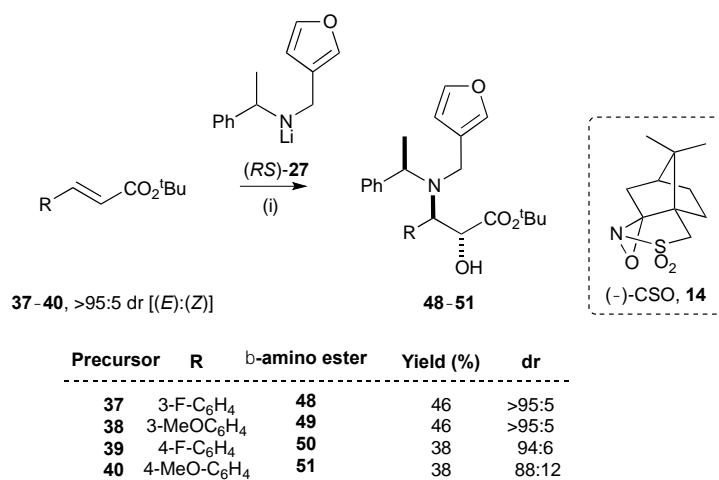
α,β -Unsaturated ester 24 was next treated with *N*-heteroaryl substituted lithium amides (RS)-25–27 followed by subsequent addition of (–)-CSO 14, from which the corresponding *anti*- α -hydroxy- β -amino esters 45–47 were obtained in 48–58% yield and $\geq 94:6$ dr (Scheme 6).⁹ The relative 2,3-*anti*-configurations 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 ^1H NMR 3J coupling constants ($^3J_{2,3} = 2.9\text{--}3.5$ Hz) between the C(2)*H* and C(3)*H* protons within **45–47**.^{14,15}



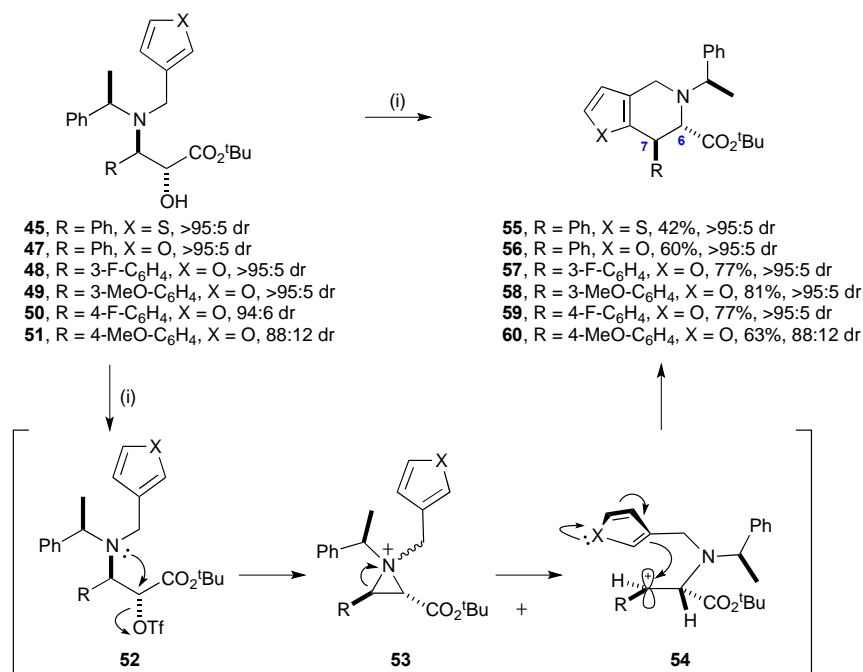
Scheme 6. Reagents and conditions: (i) (RS)-**20–22**, *s*-BuLi, THF, -78 °C, 2 h then (–)-CSO **14**, -78 °C to rt, 16 h

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 ^1H NMR 3J coupling constants ($^3J_{2,3} = 3.0\text{--}3.2$ Hz).



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

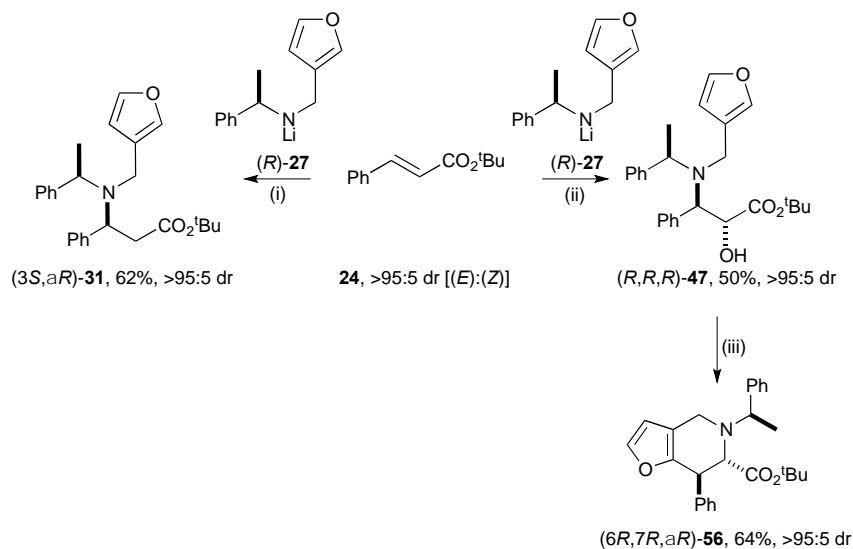
The Friedel-Crafts alkylation type cyclisation protocol employed in our previous syntheses of 1,2,3,4-tetrahydroisoquinolines¹⁵ was applied to *N*-heteroaryl substituted α -hydroxy- β -amino esters **45** and **47–51**: these substrates were treated with Tf₂O and 2,6-di-*tert*-butyl-4-methylpyridine in CH₂Cl₂ 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 \geq 88:12 dr in each case. The relative configurations within **55–60** were tentatively assigned from the ¹H NMR ³*J* coupling constants between the C(6)*H* and C(7)*H* protons of the heteroaryl fused tetrahydropyridines **55–60** (³*J*_{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 Tf₂O 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*-heteroarene ring¹⁷ [with retention of configuration at C(3)] to give the bicyclic compounds **55–60** (Scheme 8).



Scheme 8. Reagents and conditions: (i) Tf₂O, 2,6-di-*tert*-butyl-4-methylpyridine, CH₂Cl₂, 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 (*3S,\alpha R*)-**31** in 62% yield and >95:5 dr. The relative configuration within (*3S,\alpha R*)-**31** was unambiguously established *via* single crystal X-ray diffraction analysis and the absolute (*3S,\alpha 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 (*6S,7R,\alpha R*)-**56** in 64% and >95:5 dr (Scheme 9).



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

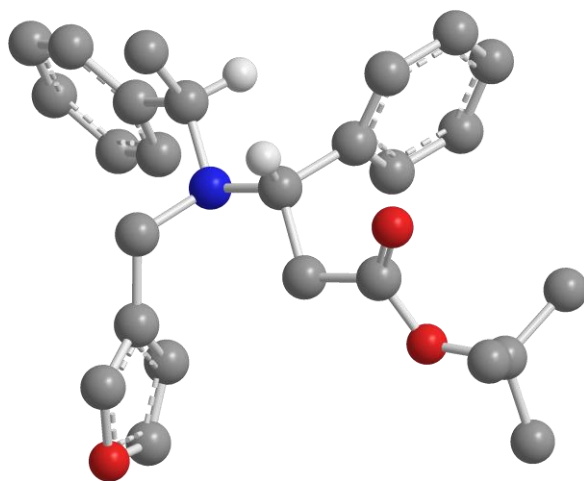


Figure 3. X-Ray crystal structure of (*3S,\alpha R*)-**31** (selected H atoms are omitted for clarity)

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 MgSO₄ or Na₂SO₄. Thin layer chromatography was performed on aluminium plates coated with 60 F₂₅₄ silica. Plates were visualised using UV light (254 nm), iodine, 1% aq KMnO₄, 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 cm² 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 deuterium resonance. ¹H–¹H COSY, ¹H–¹³C HSQC, and ¹H–¹³C 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. NaBH₄ (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 CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂, and the combined aqueous extracts were neutralised with 2.0 M aq NaOH, extracted with CH₂Cl₂, 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 NH₄Cl. The resultant mixture was allowed to warm to rt over 15 min then concentrated *in vacuo*. The residue was then partitioned between CH₂Cl₂ and 10% aq citric acid solution. The aqueous layer was extracted with CH₂Cl₂ and the combined organic extracts were washed sequentially with satd aq NaHCO₃, H₂O 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 NH₄Cl was added and the reaction mixture was stirred at rt for 5 min, then concentrated *in vacuo*. The residue was then partitioned between CH₂Cl₂ and 10% aq citric acid solution. The aqueous layer was extracted with CH₂Cl₂ and the combined organic extracts were washed sequentially with satd aq NaHCO₃, H₂O and brine, then dried and concentrated *in vacuo*.

General procedure 4 - Rearrangement/Friedel-Crafts alkylation: Tf₂O (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 CH₂Cl₂ (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. H₂O was then added and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were then dried and concentrated *in vacuo*. The residue was dissolved in Et₂O 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 NaBH₄ (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, CDCl₃)

1.38 (3H, d, J 6.6, C(α)Me), 3.66 (2H, app s, NCH₂Ar), 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, CDCl₃) 24.4 (C(α)Me), 46.6 (NCH₂Ar), 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⁺) C₁₃H₁₆NS⁺ ([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 NaBH₄ (4.65 g, 122 mmol) to give **21** as a pale yellow oil (23.6 g, 85%); δ_H (400 MHz, CDCl₃) 1.39 (3H, d, J 6.7, C(α)Me), 3.81 (1H, d, J 14.3, NCH_AH_BAr), 3.86 (1H, d, J 14.3, NCH_AH_BAr), 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 NaBH₄ (7.53 g, 198 mmol) to give **22** as a pale yellow oil (31.1 g, 78%); δ_H (400 MHz, CDCl₃) 1.39 (3H, d, J 6.6, C(α)Me), 3.83 (2H, app s, NCH₂Ar), 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 NaBH₄ (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 CHCl₃).

(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 NaBH₄ (7.53 g, 198 mmol) to give **23** as a pale yellow oil (30.6 g, 77%); δ_H (400 MHz, CDCl₃) 1.37 (3H, d, J 6.6, C(α)Me), 3.59 (1H, d, J 14.3, NCH_AH_BAr), 3.67 (1H, d, J 14.3, NCH_AH_BAr), 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 (3RS, 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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.24 (9H, s, CMe₃), 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, NCH₂Ar), 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, CDCl₃) 16.2 (C(α)Me), 27.8 (CMe₃), 38.7 (C(2)), 46.2 (NCH₂Ar), 57.0 (C(α)), 59.6

(C(3)), 80.2 (CMe₃), 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⁺) C₂₆H₃₂NO₂S⁺ ([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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.23 (9H, s, CMe₃), 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, NCH₂Ar), 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, CDCl₃) 15.9 (C(α)Me), 27.8 (CMe₃), 38.7 (C(2)), 46.1 (NCH₂Ar), 56.8 (C(α)), 59.5 (C(3)), 80.2 (CMe₃), 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⁺) C₂₆H₃₂NO₂S⁺ ([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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.25 (9H, s, CMe₃), 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, NCH₂Ar), 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, CDCl₃) 16.2 (C(α)Me), 27.8 (CMe₃), 38.8 (C(2)), 41.5 (NCH₂Ar), 56.6 (C(α)), 59.3 (C(3)), 80.2 (CMe₃), 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⁺) C₂₆H₃₂NO₃⁺ ([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: PPh₃ (3.48 g, 13.3 mmol) was added to a stirred solution of 3-(hydroxymethyl)furan (0.88 mL, 10.2 mmol) and CBr₄ (4.02 g, 12.2 mmol) in CH₂Cl₂ (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/Et₂O/35% aqNH₄OH, 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/Et₂O/35% aqNH₄OH, 90:9:1) gave (3*S*, α *R*)-**31** as a colorless solid (247 mg, 62%, >95:5 dr); [α]_D²² +3.2 (*c* 1.0 in CHCl₃); mp 90–92 °C.

X-Ray crystal structure determination for 31: Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Mo-K α 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** [C₂₆H₃₁NO₃]: *M* = 405.54, monoclinic, space group *P* 2₁, *a* = 10.1926(7) Å, *b* = 9.2926(4) Å, *c* = 12.7488(8) Å, β = 108.134(7)°, *V* = 1147.54(12) Å³, *Z* = 2, μ = 0.076 mm⁻¹, colourless block, crystal dimensions = 0.18 × 0.19 × 0.21 mm³. A total of 5982 unique reflections were measured for 3 < θ < 30 and 4855 reflections were used in the refinement. The final parameters were *wR*₂ = 0.098 and *R*₁ = 0.067 [*I* > 3.0 σ (*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/Et₂O/35% aqNH₄OH, 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, CDCl₃) [selected peaks for the major diastereoisomer] 1.24 (9H, s, CMe₃), 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_BAr), 3.70 (1H, d, *J* 15.9, NCH_AH_BAr), 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, CDCl₃) [selected peaks for the minor diastereoisomer] 1.28 (9H, s, CMe₃), 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_BAr), 3.77 (1H, d, *J* 15.9, NCH_AH_BAr), 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, CDCl₃) [selected peaks for the major diastereoisomer] 16.8 (C(α)Me), 27.8 (CMe₃), 38.5 (C(2)), 43.6 (NCH₂Ar), 57.0 (C(α)), 59.5 (C(3)), 80.1 (CMe₃), 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, CDCl₃) [selected peaks for the minor diastereoisomer] 19.4 (C(α)Me), 27.9 (CMe₃), 38.1 (C(2)), 43.0 (NCH₂Ar), 57.9 (C(α)), 59.6 (C(3)), 80.3 (CMe₃), 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⁺) C₂₆H₃₂NO₃⁺ ([*M*+*H*]⁺) requires 406.2377; found 406.2374.

***tert*-Butyl (3*S*, α *R*)-3-[*N*-benzyl-*N*-(α -methylbenzyl)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 NH₄Cl (10 mL). The resultant mixture was allowed to warm to rt over 15 min, then concentrated *in vacuo*. The residue was then partitioned between CH₂Cl₂ (100 mL) and 10% aq citric acid solution (100 mL). The aqueous layer was extracted with CH₂Cl₂ (2 \times 100 mL) and the combined organic extracts were washed sequentially with satd aq NaHCO₃ (200 mL), H₂O (200 mL) and brine (200 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et₂O, 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 CHCl₃); {lit.^{11c} $[\alpha]_D^{22} +3.9$ (*c* 0.7 in CHCl₃)}; δ_H (400 MHz, CDCl₃) 1.23 (9H, s, *CMe*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*_A*H*_BPh), 3.71 (1H, d, *J* 14.9, *NCH*_A*H*_BPh), 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/H₂O (v/v 5:1, 184 mL) at rt. The reaction mixture was stirred at rt for 2 h before the addition of satd aq NaHCO₃ (130 mL). The resultant mixture was stirred at rt for 30 min. The aqueous layer was extracted with EtOAc (3 \times 100 mL), and the combined organics were then dried and concentrated *in vacuo*. The residue was then stirred in 2.0 M aq NaHSO₃ (100 mL) for 20 min. The resultant mixture was extracted with Et₂O (3 \times 100 mL), and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et₂O/35% aqNH₄OH, 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 CHCl₃); δ_H (400 MHz, CDCl₃) 1.36 (3H, d, *J* 6.5, *C*(α)*Me*), 1.38 (9H, s, *CMe*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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.29 (9H, s, *CMe*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, NCH₂Ar), 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, CDCl₃) 16.8 (C(α)Me), 27.8 (CMe₃), 38.1 (C(2)), 41.6 (NCH₂Ar), 56.8 (C(α)), 58.6 (C(3)), 80.4 (CMe₃), 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, CDCl₃) –113.6 (C(3'')F); m/z (ESI⁺) 424 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₆H₃₁FNO₃⁺ ([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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.27 (3H, d, J 6.8, C(α)Me), 1.29 (9H, s, CMe₃), 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, NCH₂Ar), 3.83 (3H, s, OMe), 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, CDCl₃) 16.4 (C(α)Me), 27.8 (CMe₃), 38.7 (C(2)), 41.6 (NCH₂Ar), 55.2 (OMe), 56.6 (C(α)), 59.1 (C(3)), 80.2 (CMe₃), 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⁺) C₂₇H₃₄NO₄⁺ ([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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.26 (9H, s, CMe₃), 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, NCH₂Ar), 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, CDCl₃) 16.4 (C(α)Me), 27.8 (CMe₃), 38.5 (C(2)), 41.5 (NCH₂Ar), 56.7 (C(α)), 58.7 (C(3)), 80.3 (CMe₃), 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, CDCl₃) –115.8

(C(4'')F); m/z (ESI⁺) 424 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₆H₃₁FNO₃⁺ ([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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.25 (3H, d, *J* 6.8, C(α)Me), 1.27 (9H, s, CMe₃), 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, NCH₂Ar), 3.81 (3H, s, OMe), 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, CDCl₃) 16.2 (C(α)Me), 27.8 (CMe₃), 38.9 (C(2)), 41.4 (NCH₂Ar), 55.2 (OMe), 56.5 (C(α)), 58.7 (C(3)), 80.1 (CMe₃), 110.8 (C(4')), 113.4 (C(3'')), 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⁺) C₂₇H₃₄NO₄⁺ ([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-phenylpropanoate 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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.21 (3H, d, *J* 6.8, C(α)Me), 1.22 (9H, s, CMe₃), 3.84 (1H, d, *J* 15.1, NCH_AH_BAr), 4.03 (1H, d, *J* 15.1, NCH_AH_BAr), 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, CDCl₃) 13.7 (C(α)Me), 27.7 (CMe₃), 47.4 (NCH₂Ar), 57.0 (C(α)), 65.9 (C(3)), 73.3 (C(2)), 82.2 (CMe₃), 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⁺) C₂₆H₃₂NO₃S⁺ ([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-phenylpropanoate 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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.21 (3H, d, *J* 6.8, C(α)Me), 1.21 (9H, s,

CMe_3), 4.11 (1H, d, J 15.4, NCH_AH_BAr), 4.27 (1H, d, J 15.4, NCH_AH_BAr), 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 (CMe_3), 47.3 (NCH_2Ar), 57.1 (C(α)), 64.6 (C(3)), 73.6 (C(2)), 82.3 (CMe_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-phenylpropanoate 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/Et₂O/35% aqNH₄OH, 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, CMe_3), 3.67 (1H, d, J 15.2, NCH_AH_BAr), 3.87 (1H, d, J 15.2, NCH_AH_BAr), 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 (CMe_3), 42.6 (NCH_2Ar), 56.7 (C(α)), 65.9 (C(3)), 73.2 (C(2)), 82.2 (CMe_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-phenylpropanoate 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/Et₂O/35% aqNH₄OH, 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''-fluorophenyl)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/Et₂O/35% aqNH₄OH, 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, CMe_3), 3.71 (1H, d, J 15.2, NCH_AH_BAr), 3.89 (1H, dd, J 15.2, 0.8, NCH_AH_BAr), 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 (CMe₃), 42.6 (NCH₂Ar), 56.8 (C(α)), 64.8 (C(3)), 73.1 (C(2)), 82.5 (CMe₃), 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, CDCl₃) -113.3 (C(3'')F); *m/z* (ESI⁺) 462 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₂₆H₃₁FNO₄⁺ ([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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.22 (3H, d, *J* 6.8, C(α)Me), 1.26 (9H, s, CMe₃), 3.69 (1H, d, *J* 15.2, NCH_AH_BAr), 3.80 (3H, s, OMe), 3.87 (1H, dd, *J* 15.2, 1.0, NCH_AH_BAr), 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, CDCl₃) 13.8 (C(α)Me), 27.7 (CMe₃), 42.6 (NCH₂Ar), 55.2 (OMe), 56.7 (C(α)), 65.5 (C(3)), 73.2 (C(2)), 80.6 (CMe₃), 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⁺) C₂₇H₃₄NO₅⁺ ([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''-fluoro-**

phenyl)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/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.21 (3H, d, *J* 6.8, C(α)Me), 1.24 (9H, s, CMe₃), 3.67 (1H, d, *J* 15.3, NCH_AH_BAr), 3.86 (1H, d, *J* 15.3, NCH_AH_BAr), 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, CDCl₃) 13.7 (C(α)Me), 27.7 (CMe₃), 42.5 (NCH₂Ar), 56.7 (C(α)), 64.9 (C(3)), 73.1 (C(2)), 82.4 (CMe₃), 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, CDCl₃) -114.8 (C(4'')F); *m/z* (ESI⁺) 440 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₆H₃₁FNO₄⁺ ([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/Et₂O/35% aqNH₄OH, 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, CDCl₃) [selected peaks for the major diastereoisomer] 1.20 (3H, d, *J* 6.8, C(α)Me), 1.24 (9H, s, CMe₃), 3.63 (1H, d, *J* 15.2, NCH_AH_BAr), 3.80 (3H, s, OMe), 3.85 (1H, d, *J* 15.2, NCH_AH_BAr), 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, CDCl₃) [selected peaks for the minor diastereoisomer] 1.27 (9H, s, CMe₃), 1.44 (3H, d, *J* 6.8, C(α)Me), 3.78 (3H, s, OMe), 4.00 (1H, dd, *J* 15.9, NCH_AH_BAr), 4.62 (1H, d, *J* 3.2, C(2)*H*); δ_{C} (100 MHz, CDCl₃) [major diastereoisomer] 13.4 (C(α)Me), 27.8 (CMe₃), 42.5 (NCH₂Ar), 55.2 (OMe), 56.6 (C(α)), 65.3 (C(3)), 73.3 (C(2)), 82.1 (CMe₃), 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⁺) C₂₇H₃₄NO₅⁺ ([M+H]⁺) requires 452.2431; found 452.2426.

(6*RS*,7*SR*, α *SR*)-*N*(5)-(α -Methylbenzyl)-6-(*tert*-butoxycarbonyl)-7-phenyl- 4,5,6,7-tetrahydrothieno [3,2-*c*]pyridine **55:** Following *General procedure 4*, Tf₂O (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 CH₂Cl₂ (3.81 mL). Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.13 (3H, d, *J* 6.6, C(α)Me), 1.41 (9H, s, CMe₃), 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, CDCl₃) 21.3 (C(α)Me), 28.2 (CMe₃), 44.6 (C(7)), 47.6 (C(4)), 61.8 (C(α)), 63.5 (C(6)), 81.4 (CMe₃), 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 (CO₂^tBu); *m/z* (ESI⁺) 420 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₆H₃₀NO₂S⁺ ([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*, Tf₂O (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 CH₂Cl₂ (8.91 mL). Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.16 (3H, d, *J* 6.6, C(α)Me), 1.47 (9H, s, CMe₃), 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, CDCl₃) 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 (CO₂^tBu); *m/z* (ESI⁺) 404 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₆H₃₀NO₃⁺ ([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*, Tf₂O (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 CH₂Cl₂ (5.94 mL). Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et₂O/35% aqNH₄OH, 90:9:1) gave (*6S,7R,αR*)-**56** as a pale yellow oil (123 mg, 64%, >95:5 dr); [α]_D²² –12.8 (*c* 1.0 in CHCl₃).

(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*, Tf₂O (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 CH₂Cl₂ (7.69 mL). Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et₂O/35% aqNH₄OH, 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, CDCl₃) 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, CDCl₃) 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 (CO₂^tBu); δ_F (377 MHz, CDCl₃) –113.9 (C(3')*F*); *m/z* (ESI⁺) 422 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₆H₂₉FNO₃⁺ ([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*, Tf₂O (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 CH₂Cl₂ (6.37 mL). Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et₂O/35% aqNH₄OH, 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, CDCl₃) 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, *OMe*), 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, CDCl₃) 21.8 (C(α)Me), 28.2 (CMe₃), 43.4 (C(7)), 44.6 (C(4)), 55.2 (OMe), 61.9 (C(α)), 63.6 (C(6)), 81.5 (CMe₃), 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 (CO₂^tBu); *m/z* (ESI⁺) 434 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₃₂NO₄⁺ ([M+H]⁺) requires 434.2326; found 434.2321.

(6RS,7SR, 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*, Tf₂O (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 CH₂Cl₂ (5.41 mL). Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et₂O/35% aqNH₄OH, 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, CDCl₃) 1.16 (3H, d, *J* 6.6, C(α)Me), 1.47 (9H, s, CMe₃), 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, CDCl₃) 21.6 (C(α)Me), 28.2 (CMe₃), 42.6 (C(7)), 44.6 (C(4)), 61.9 (C(α)), 63.7 (C(6)), 81.6 (CMe₃), 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 (CO₂^tBu); δ_F (377 MHz, CDCl₃) –116.4 (C(4')F); *m/z* (ESI⁺) 422 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₆H₂₉FNO₃⁺ ([M+H]⁺) requires 422.2126; found 422.2122.

(6RS,7SR, 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*, Tf₂O (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 CH₂Cl₂ (6.93 mL). Purification *via* flash column chromatography (eluent 30–40 °C petrol/Et₂O/35% aqNH₄OH, 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, CDCl₃) [selected peaks for the major diastereoisomer] 1.18 (3H, d, *J* 6.8, C(α)Me), 1.47 (9H, s, CMe₃), 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, OMe), 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, CDCl₃) [selected peaks for the minor diastereoisomer] 1.36 (3H, d, *J* 6.6, C(α)Me), 1.41 (9H, s, CMe₃), 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, CDCl₃) [selected peaks for the major diastereoisomer] 21.6 (C(α)Me), 28.2 (CMe₃), 42.6 (C(7)), 44.6 (C(4)), 55.2 (OMe), 61.9 (C(α)), 63.9 (C(6)), 81.4 (CMe₃), 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 (CO₂^tBu); δ_C (125 MHz, CDCl₃) [selected peaks for the minor diastereoisomer] 22.4 (C(α)Me), 28.2 (CMe₃), 42.6 (C(4)), 42.7 (C(7)), 55.4 (OMe), 61.4 (C(α)), 65.2 (C(6)), 81.1 (CMe₃), 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 (CO_2^tBu); *m/z* (ESI⁺) 434 ([*M*+*H*]⁺, 100%); HRMS (ESI⁺) $\text{C}_{27}\text{H}_{32}\text{NO}_4^+$ ([*M*+*H*]⁺) requires 434.2326; found 434.2320.

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