Supporting Information for:

Optimized *S*-Trityl-L-Cysteine Based Inhibitors of Kinesin Spindle Protein with potent *in Vivo* Antitumor Activity in Lung Cancer Xenograft Models

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Abbreviations

c/f, *confer*; *dia*-, diastereomeric mixture; DMP, Dess-Martin periodinane; GI_{50}, the concentration required to achieve 50 % growth inhibition; K_i^{app}, apparent K_i value; KSP, kinesin spindle protein; LE, ligand efficiency; MIA, maximum inhibitory activity observed; MTs, microtubules; n.i., no inhibition; NFSI, *N*-fluorobenzenesulfonimide; *rac-,* racemate; RTV, relative tumor volume, STDC, *S*-trityl-*D*-cysteine; STLC, *S*-trityl-*L*-cysteine; n.d.; not determined; n.i., no inhibition;; *T/C*, relative test tumor versus control value;

Contents

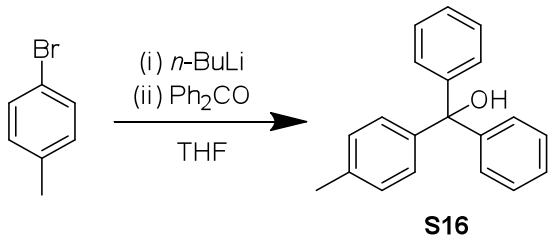
1. Synthetic Procedures

a.) General procedures

Representative procedures and the characterization data for the reported exemplars are provided in this section. Syntheses and characterization for all other compounds are described in section 1b.

General procedure (i): Preparation of trityl alcohols by reduction of benzophenone with lithiated aryl bromides.

Synthesis of intermediate trityl alcohols was achieved by the reduction of benzophenone with lithated aryl bromides. A representative procedure is provided for the synthesis of S**16** (Scheme S1).



S16

Scheme S1

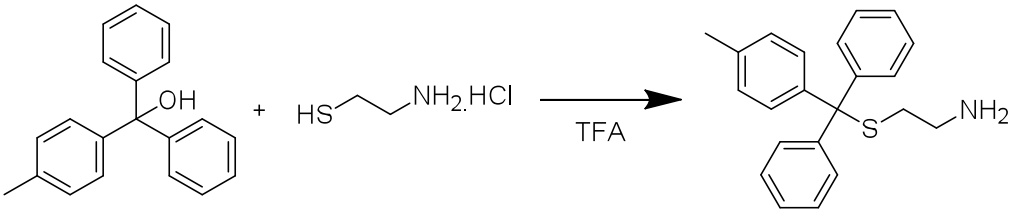
(4-Methylphenyl)(diphenyl)methanol (S16).

n-Butyllithium (2.5 M in hexane, 2.4 mL, 6.00 mmol) was added by slow dropwise addition over 2 min to a cooled (-78 °C) solution of 1-bromo-4-methylbenzene (855 mg, 5.00 mmol) in anhydrous THF (5 mL) and stirred for 30 min at ≤ -70 °C. A solution of benzophenone (1.05 g, 5.75 mmol) in anhydrous THF (5.75 mL) was added by slow dropwise addition over 5 min, and the reaction mixture stirred with the temperature maintained ≤ -70 °C for 6 h, before allowing the reaction to warm to room temperature and stirring for a further 17 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were then washed successively with H_2O and brine (30 mL each), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-9% EtOAc in hexane] afforded the trityl alcohol **S16** as a white solid (707 mg, 43%). Mpt. 65-66 °C (lit. 68-69 °C).[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.34

(s, 3H, CH_3), 2.75 (s, 1H, OH), 7.10-7.17 (m, 4H), 7.24-7.34 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.17, 82.03, 127.32, 128.00, 128.03, 128.78, 137.09, 144.19, 147.15. HRMS (ESI+) calcd. for $C_{20}H_{17}$ = $(M\text{-}OH+H)^+$: 257.1317; found: 257.1325. Anal. calcd. for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.32; H, 6.72.

General procedure (ii): Thioetherification of trityl alcohols

In an adaptation of the procedure reported by Maltese *et al,* thioethers were prepared from trityl alcohols by dehydration in trifluoroacetic acid and subsequent thioetherification with L-cysteine or cysteamine hydrochloride unless otherwise noted.[2] A representative procedure is provided for the synthesis of **17** (Scheme S2).



S16 **17**

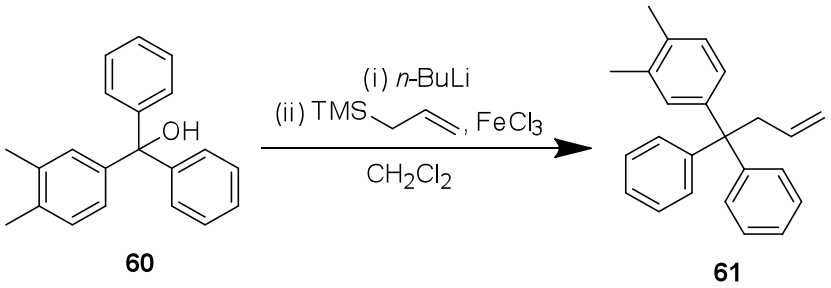
Scheme S2

2-(((4-Methylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (17).

A solution of the tertiary alcohol **S16** (274 mg, 1.0 mmol) with cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1.0 mL) was stirred for 3 h at room temperature. The volatiles were removed *in vacuo*, and the crude basified (*circa.* pH 10) with saturated aqueous sodium carbonate solution. The aqueous mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-12% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **17** as a white solid (229 mg, 69%). Mpt. 72-74 °C. ^{1}H NMR (400 MHz, MeOD) δ = 2.28-2.36 (m, 5H), 2.40-2.45 (m, 2H, CH_2), 7.07-7.11 (m, 2H), 7.17-7.22 (m, 2H), 7.23-7.29 (m, 6H), 7.37-7.42 (m, 4H). ^{13}C NMR (100 MHz, MeOD) δ = 20.93, 36.13, 41.57, 67.54, 127.70, 128.84, 129.48, 130.73, 137.59, 143.31, 146.52. HRMS (ESI+) calcd. for $C_{22}H_{24}NS$ = $(M+H)^+$: 334.1624; found: 334.1624. Anal. calcd. for $C_{22}H_{23}NS$: C, 79.23; H, 6.95; N, 4.13. Found: C, 78.84; H, 7.03; N, 4.13.

General Procedure (iii): Allylation of trityl alcohols.

Intermediate allyls were synthesized from the respective intermediate trityl alcohols in an adaptation of the method reported by Kabalka *et al.* (Scheme S3).[3] A representative procedure is described for alkene **61** in the main text.

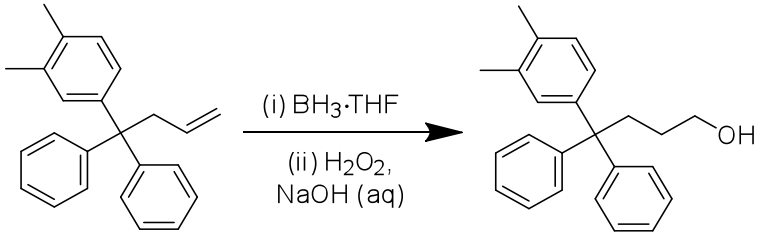


60 61

Scheme S3

General Procedure (iv): Hydroboration-oxidation of but-1-ene-4,4,4-triyltribenzenes.

Intermediate primary alcohols were synthesized from the respective alkenes by Brown hydroboration-oxidation (Scheme S4).[4] A representative procedure is described for the preparation of alcohol **62** in the main text.

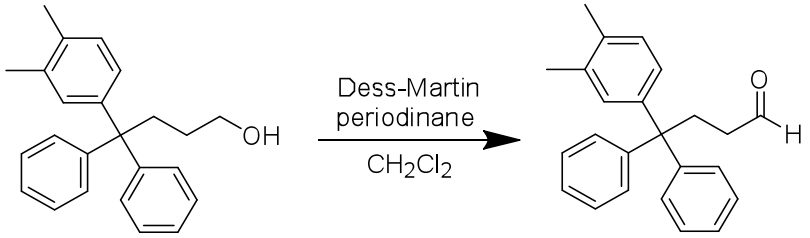


61 62

Scheme S4

General Procedure (v): Dess-Martin oxidation of triphenylbutan-1-ols.

Intermediate primary alcohols were oxidized to the aldehyde with Dess-Martin periodinane (Scheme S5).[5] A representative procedure is described for synthesis of aldehyde **63** in the main text.

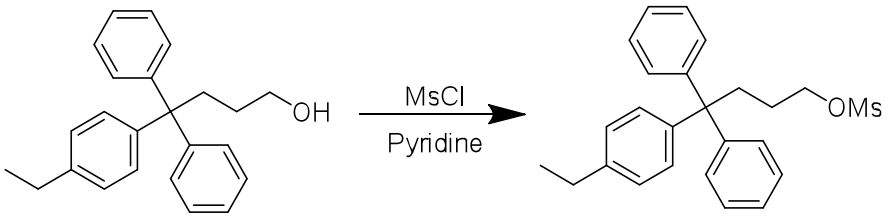


62 **63**

Scheme S5

General Procedure (vi): Mesylation of triphenylbutan-1-ols

Intermediate mesylates were prepared from their respective primary alcohols as reported previously.[6] A representative procedure is provided for the synthesis of **S18** (Scheme S6).



S17 **S18**

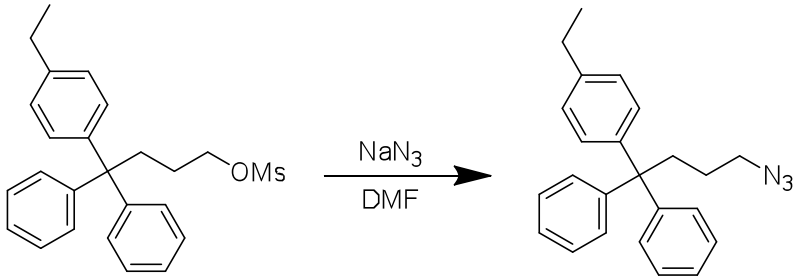
Scheme S6

4-(4-Ethylphenyl)-4,4-diphenylbutyl methanesulfonate (S18).

Methanesulphonyl chloride (0.680 mL, 8.78 mmol) was added to a cooled (0 °C) solution of 4-(4-ethylphenyl)-4,4-diphenylbutan-1-ol **S17** (740 mg, 2.24 mmol) in anhydrous pyridine (15 mL) and stirred for 16 h at room temperature. The volatiles were removed *in vacuo* and the residue extracted with CH_2Cl_2 (30 mL), dried ($MgSO_4$) and concentrated *in vacuo.* Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded the mesylate **S19** as a white oil (280 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (t, 3H, *J* = 7.6 Hz, CH_3), 1.53-1.60 (m, 2H), 2.61 (q, *J* = 7.6 Hz 2H, CH_2), 2.68-2.73 (m, 2H, CH_2), 3.49 (t, 2H, *J* = 6.5 Hz, CH_2), 7.08-7.29 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 15.44, 28.37, 29.06, 37.88, 46.96, 56.03, 126.03, 127.50, 128.01, 129.15, 129.27, 141.87, 144.31, 147.44.

General Procedure (vii): Synthesis of azide intermediates

Intermediate azides were prepared from their respective mesylates by microwave irradiation with sodium azide in DMF (Scheme S7).[6] A representative procedure is provided for the synthesis of **S19**



S18 **S19**

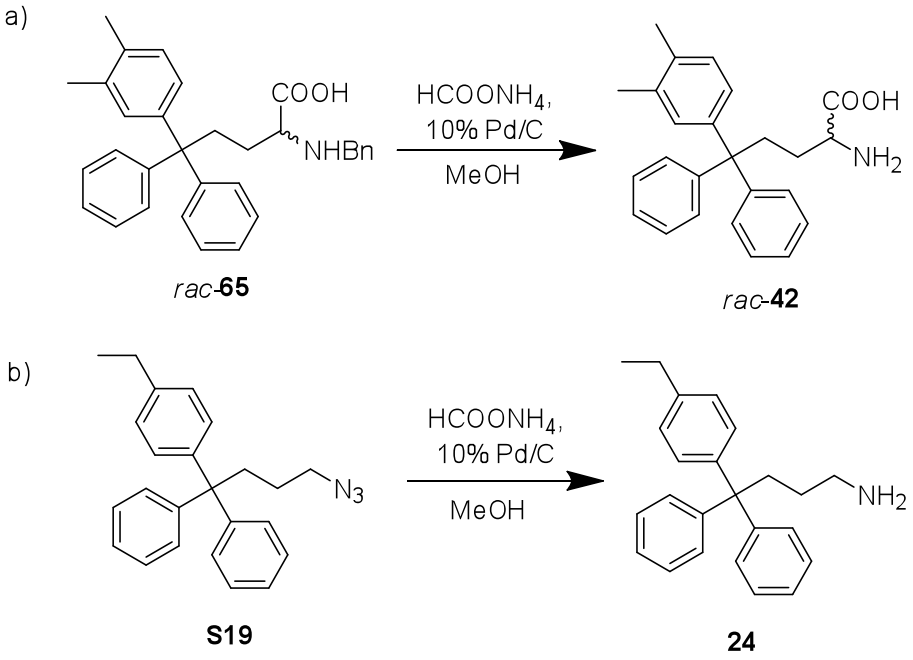
Scheme S7

1-(4-Azido-1,1-diphenylbutyl)-4-ethylbenzene (S19).

Sodium azide (187 mg, 2.88 mmol) was added to a solution of mesylate **S18** (276 mg, 0.68 mmol) in anhydrous DMF (2 mL) and the mixture irradiated with microwave radiation at 175 °C for 10 min. The mixture was cooled, the solid residue filtered off, and the filtrate concentrated *in vacuo.* The crude product was purified by flash chromatography [SiO_2; 2-30% EtOAc in hexane] to afford azide **S19** as a white oil (103 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (t, 3H, *J* = 7.7 Hz, CH_3), 1.53-1.60 (m, 2H, CH_2), 2.61 (q, 2H, *J* = 7.6 Hz, CH_2), 2.69-2.73 (m, 2H, CH_2), 3.49 (t, 2H, *J* = 6.4 Hz, CH_2), 7.08-7.29 (m, 14H).

General Procedure (viii): Ammonium formate based hydrogenation

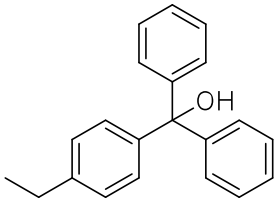
Benzylamines were deprotected by an ammonium formate based hydrogenation (Scheme S8a). This method, developed by Ram *et al*. was also used to reduce azides to their respective primary amines (e.g. Scheme S8b). A representative procedure is described for *rac*-**65** in the main text.



Scheme S8: a) Debenzylation of protected amines.
b) Reduction of 1,1',1''-(4-azidobutane-1,1,1-triyl)tribenzene analogues.

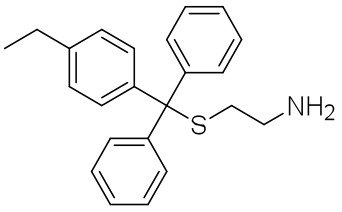
b.) Characterisation and synthetic procedures for all other compounds.

(4-Ethylphenyl)(diphenyl)methanol (S20).



PhMgCl (2.0 M in THF, 7.5 mL, 15.0 mmol) was added slowly by dropwise addition over 5 min to a cooled (0 °C) solution of 4-ethylbenzophenone (1.18 ml, 6.0) in anhydrous THF (10 mL) and the reaction stirred at reflux for 18 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 20 mL). The organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution, H_2O and brine (60 mL each), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-10% EtOAc in hexane] afforded the trityl alcohol **S20** as a white solid (1.51 g, 87%). Mpt. 58-60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.24 (t, 3H, *J* = 7.6 Hz, CH_3), 2.65 (q, 2H, *J* = 7.6 Hz, CH_2), 2.78 (s, 1H, OH), 7.13-7.20 (m, 4H), 7.26-7.35 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 15.54, 28.55, 82.06, 127.30, 127.56, 128.02, 128.05, 143.40, 144.39, 147.18. HRMS (ESI+) calcd. for $C_{21}H_{19}$ = $(M\text{-}OH)^+$: 271.1481; found: 271.1475. Anal. calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.48; H, 7.03.

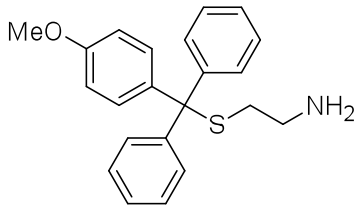
2-(((4-Methylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (18).



The title compound was prepared following general procedure (ii) with (4-ethylphenyl)(diphenyl)methanol **S20** (288 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-12% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **18** as a colourless oil (229 mg, 69%). ^{1}H NMR (500 MHz, MeOD) δ = 1.22 (t, *J* = 7.6 Hz, 3H, CH_3), 2.32-2.36 (m, 2H, CH_2), 2.41-2.46 (m, 2H, CH_2), 2.62 (q, *J* = 7.6 Hz, 2H, CH_2), 7.10-7.14 (m, 2H), 7.18-7.22

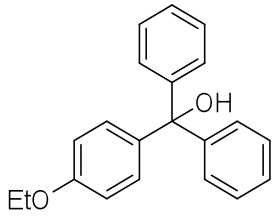
(m, 2H), 7.25-7.32 (m, 6H), 7.39-7.43 (m, 4H). ^{13}C NMR (125 MHz, MeOD) δ = 16.02, 29.29, 36.12, 41.58, 67.57, 127.71, 128.30, 128.84, 130.75, 130.79, 143.58, 144.06, 146.54. HRMS (ESI+) calcd. for $C_{23}H_{26}NS$ = $(M+H)^+$: 348.1780; found: 348.1775. Anal. calcd. for $C_{23}H_{25}NS \cdot \frac{1}{3}H_2O$: C, 78.16; H, 7.32; N, 3.96. Found: C, 78.11; H, 7.03; N, 3.66.

2-(((4-Methoxyphenyl)(diphenyl)methyl)sulfanyl)ethanamine (19).



The title compound was prepared following general procedure (ii) with (4-methoxyphenyl)(diphenyl)methanol (291 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2] afforded the thioether **19** as a colourless oil (63 mg, 18%). ^{1}H NMR (500 MHz, MeOD) δ = 2.32-2.36 (m, 2H, CH_2), 2.41-2.45 (m, 2H, CH_2), 3.77 (s, 3H, CH_3), 6.81-6.84 (m, 2H), 7.17-7.21 (m, 2H), 7.24-7.31 (m, 6H), 7.38-7.42 (m, 4H). ^{13}C NMR (125MHz, MeOD) δ = 36.14, 41.60, 55.72, 67.33, 114.13, 127.70, 128.86, 130.67, 131.99, 138.21, 146.70, 159.78. HRMS (ESI+) calcd. for $C_{22}H_{24}NOS$ $(M+H)^+$: 350.1573; found: 350.1565. Anal. calcd. for $C_{22}H_{23}NOS$: C, 75.61; H, 6.63; N, 4.01. Found: C, 74.77; H, 6.22; N, 3.19.

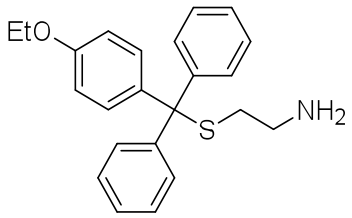
(4-Ethoxyphenyl)(diphenyl)methanol (S8).



The title compound was prepared using general procedure (i) with 1-bromo-4-ethoxybenzene (715 μL, 5.00 mmol) and *n*-butyllithium (2.5 M in hexane, 2.40 mL, 6.00 mmol) in anhydrous THF (5.00 mL), and subsequently benzophenone (1.050 g, 5.75 mmol) in anhydrous THF (5.75 mL). Purification by flash chromatography [SiO_2; 0-14% EtOAc in hexane] afforded the trityl alcohol **S8** as a white solid (0.967 g, 64%). Mpt. 69-71 °C. ^{1}H

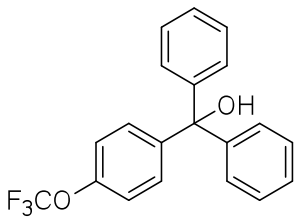
NMR (400 MHz, $CDCl_3$) δ = 1.40 (t, *J* = 7.0 Hz, 3H, CH_3), 2.75 (s, 1H, OH), 4.02 (q, *J* = 7.0 Hz, 2H, CH_2), 6.80-6.84 (m, 2H), 7.13-7.17 (m, 2H), 7.24-7.33 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 14.98, 63.56, 81.89, 113.91127.29, 128.01, 129.36, 139.23, 147.29, 158.26. HRMS (ESI+) calcd. for $C_{21}H_{19}O$ $(M\text{-}OH)^+$: 287.14304; found: 287.14252. Anal. calcd. for $C_{20}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 81.38; H, 6.70.

2-(((4-Ethoxyphenyl)(diphenyl)methyl)sulfanyl)ethanamine (20).



The title compound was prepared following general procedure (ii) with 4-ethoxyphenyl)(diphenyl)methanol **S8** (305 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2 with NH_4OH] afforded thioether **20** as a clear pale brown oil (209 mg, 58%). ^1H NMR (500 MHz, MeOD) δ = 1.37 (t, 3H, *J* = 7.0 Hz, CH_3), 2.32-2.37 (m, 2H, CH_2), 2.41-2.45 (m, 2H, CH_2), 4.01 (q, 2H, *J* = 7.0 Hz, CH_2), 6.79-6.84 (m, 2H), 7.17-7.22 (m, 2H), 7.24-7.30 (m, 6H), 7.38-7.42 (m, 4H). ^{13}C NMR (125 MHz, MeOD) δ = 15.15, 36.13, 41.60, 64.50, 67.34, 114.67, 127.69, 128.85, 130.67, 131.98, 138.09, 146.72, 159.07. HRMS (ESI+) calcd. for $C_{23}H_{26}NOS$ $(M+H)^+$: 364.1730; found: 364.1727. Anal. calcd. for $C_{23}H_{26}NOS \cdot ½H_2O$: C, 74.56; H, 6.53; N, 3.78. Found: C, 74.48; H, 6.93; N, 4.18.

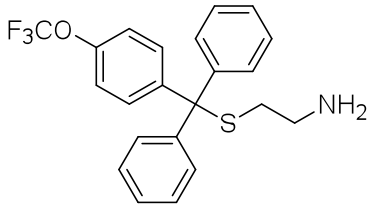
Diphenyl(4-(trifluoromethoxy)phenyl)methanol (S9).



The title compound was prepared using general procedure (i) with 1-bromo-4-(trifluoromethoxy)benzene (743 μL, 5.00 mmol) and *n*-butyllithium (2.5 M in hexane, 2.40 mL, 6.00 mmol) in anhydrous THF (5.00 mL), and subsequently benzophenone (1.050 g, 5.75 mmol) in anhydrous THF (5.75 mL). Purification by flash chromatography [SiO_2; 0-

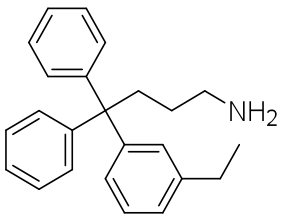
15% EtOAc in hexane] afforded the trityl alcohol **S9** as a white solid (655 mg, 38%). Mpt. 38-39 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.78 (s, 1H, OH), 7.12-7.17 (m, 2H), 7.23-7.36 (m, 12H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -57.77. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 81.78, 120.33, 120.61 (q, J_{CF} = 257.3 Hz), 127.70, 127.94, 128.27, 129.58, 145.53, 146.56, 148.42 (q, J_{CF} = 1.6 Hz). HRMS (ESI+) calcd. for $C_{20}H_{14}F_3O$ $(M\text{-}OH)^+$: 327.09913; found: 327.09848. Anal. calcd. for $C_{20}H_{15}F_3O_2$: C, 69.76; H, 4.39. Found: C, 69.63; H, 4.44.

2-((Diphenyl(4-(trifluoromethoxy)phenyl)methyl)sulfanyl)ethanamine (21).



The title compound was prepared following general procedure (ii) with diphenyl(4-(trifluoromethoxy)phenyl)methanol **S9** (344 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2 with NH_4OH] afforded the thioether **21** as a colourless oil (145 mg, 36%). ^{1}H NMR (400 MHz, MeOD) δ = 2.34 (t, 2H, J = 6.9 Hz), 2.46 (t, 2H, J = 6.9 Hz), 7.17-7.34 (m, 8H), 7.35-7.44 (m, 4H), 7.50-7.54 (m, 2H). ^{19}F NMR (376.5 MHz, MeOD) δ = -59.42. ^{13}C NMR (100 MHz, MeOD) δ = 36.01, 41.48, 67.17, 121.25, 121.92 (q, J_{CF} = 255.4 Hz), 123.18, 128.05, 129.11, 130.66, 132.44, 145.60, 145.85, 149.04. HRMS (ESI+) calcd. for $C_{22}H_{21}F_3NOS$ $(M+H)^+$: 404.1290; found: 404.1291. Anal. calcd. for $C_{22}H_{20}F_3NOS$: C, 65.49; H, 5.00; N, 3.47. Found: C, 65.44; H, 5.04; N, 3.95.

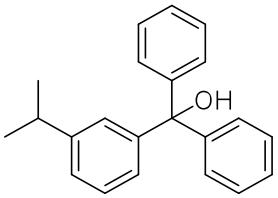
4-(3-Ethylphenyl)-4,4-diphenylbutan-1-amine (22).



The title compound was prepared following the route described for **24** by the methods described in general procedures (iii), (iv) and (vi-viii). A yellow syrup (71 mg) was obtained in an overall yield of 48 %. ^{1}H NMR (400MHz, MeOD): 1.11-1.17 (m, 3H, CH_3), 1.17-1.27

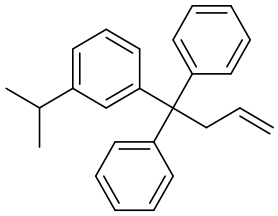
(m, 2H, CH_2), 2.53-2.64 (m, 6H), 7.12-7.27 (m, 14H). ^{13}C NMR (100MHz, MeOD): 14.9, 28.7, 28.8, 37.4, 41.7, 56.4, 125.0, 125.5, 126.2, 127.4, 129.0, 129.7, 143.5, 147.4, 147.6. HRMS (ESI+): calcd. for $C_{24}H_{27}N$ $(M+H)^+$ 330.2216; found: 330.2207. Anal. calcd for $C_{24}H_{27}N$: C, 87.49; H, 8.26; N, 4.25. Found: C, 86.18; H, 7.44; N, 3.87.

Diphenyl(3-(propan-2-yl)phenyl)methanol (S21).



The title compound was prepared using general procedure (i) with 1-bromo-3-(propan-2-yl)benzene (2.60 g, 13.1 mmol) and *n*-butyllithium (6.27 mL, 15.7 mmol) in anhydrous THF (5.00 mL), and subsequently benzophenone (2.90 g, 15.7 mmol) in anhydrous THF (4 mL), with the following modifications. The reaction mixture was stirred for 1 h at -78 °C before addition of the benzophenone solution. Purification by flash chromatography [SiO_2; 0-15% EtOAc in hexane] afforded the afforded trityl alcohol **S21** as a white solid (2.45 g, 62%). Mpt. 51-54 °C. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.22 (d, J = 7.0 Hz, 6H, 2 x CH_3), 2.83-2.92 (m, 2H), 7.03-7.05 (m, 1H), 7.17-7.19 (m, 1H), 7.22-7.26 (m, 2H), 7.29-7.35 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.11, 34.29, 82.28, 125.30, 125.77, 126.33, 127.32, 127.91, 128.01, 128.08, 146.91, 147.17, 148.74. HRMS (ESI+) calcd. for $C_{22}H_{21}$ $(M-OH)^+$: 285.16378; found: 285.16408.

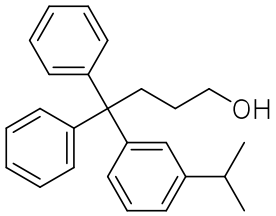
1-(1,1-Diphenylbut-3-en-1-yl)-3-(propan-2-yl)benzene (S22).



The title compound was prepared using general procedure (iii) with diphenyl(3-(propan-2-yl)phenyl)methanol **S21** (4.87 g, 16.1 mmol) and *n*-butyllithium (2.5 M in hexane, 16.1 mL, 40.3 mmol) in anhydrous CH_2Cl_2 (25 mL), and subsequently allyltrimethylsilane (5.14 mL, 32.2 mmol) and iron trichloride (3.13 g, 19.3 mmol) with the following modifications. The reaction mixture was stirred for 24 h before addition of allyltrimethylsilane and iron

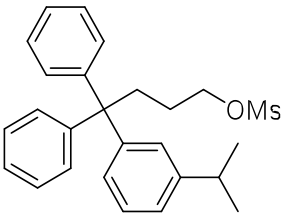
trichloride. Purification by flash chromatography [SiO_2; 0-2% EtOAc in hexane] afforded the alkene **S22** as a yellow oil (3.70 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.19 (d, 6H, *J* = 6.4 Hz, 2 x CH_3), 2.73-2.92 (m, 1H), 3.35-3.51 (m, 1H), 4.94-5.06 (m, 2H), 5.65-5.73 (m, 1H), 6.62-7.31 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.11, 34.29, 47.77, 56.54, 117.26, 123.93, 126.02, 127.09, 127.73, 127.82, 128.09, 129.58, 136.30, 147.19, 147.66, 148.20. GC-MS (CI, methane) t_R = 15.81 min (*m/z* = 355.3, $[M+C_2H_5]^+$).

4-(3-(Propan-2-yl)phenyl)-4,4-diphenylbutan-1-ol (S23).



The title compound was prepared using general procedure (iv) with 1-(1,1-diphenylbut-3-en-1-yl)-3-(propan-2-yl)benzene **S22** (3.70g, 11.3 mmol) and BH_3·THF (1.0 M in THF, 22.7 mL, 22.7 mmol) in anhydrous THF (25 mL), and the reaction mixture stirred at 0 °C for 5 h, and subsequently NaOH (1.0 M, 20.0 mL, 20.0 mmol) and hydrogen peroxide (30% in H_2O, 4.00 mL). The Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded the alcohol **S23** as a yellow oil (2.62 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.19 (d, 6H, *J* = 6.8 Hz, 2 x CH_3), 1.35-1.40 (m, 2H, CH_2), 2.65-2.68 (m, 2H, CH_2), 2.80-2.88 (m, 1H, CH), 3.61-3.66 (m, 2H**,** CH_2), 7.05-7.31 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.12, 29.36, 34.29, 36.62, 56.52, 63.50, 123.75, 125.90, 126.85, 127.81, 127.89, 129.36, 147.20, 147.66, 148.28. GC-MS (CI, methane) t_R = 17.72 min (*m/z* = 343.2, $[M-H]^+$).

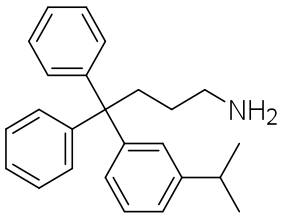
4-(3-(Propan-2-yl)phenyl)-4,4-diphenylbutyl methanesulfonate (S24)



The title compound was prepared using general procedure (vi) with 4-(3-(propan-2-yl)phenyl)-4,4-diphenylbutan-1-ol **S23** (870 mg, 2.53 mmol) and methanesulphonyl chloride (0.78 mL, 10.10 mmol) in anhydrous pyridine (10 ml). Purification by flash chromatography

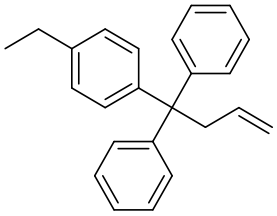
[SiO_2; 0-20% EtOAc in hexane] afforded mesylate **S24** as a white oil (320 mg, 30%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.20 (d, 6H, *J* = 6.9 Hz, 2 x CH_3), 1.56-1.62 (m, 2H, CH_2), 2.73-2.76 (m, 2H, CH_2), 2.80-2.88 (m, 1H, CH), 3.47-3.51 (m, 2H**,** CH_2), 7.06-7.31 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.12, 29.08, 34.31, 37.82, 45.96, 56.42, 123.91, 126.03, 126.85, 127.77, 127.90, 127.99, 129.27, 146.82, 147.45, 148.43.

4-(3-(Propan-2-yl)phenyl)-4,4-diphenylbutan-1-amine (23).



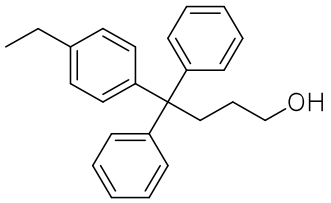
Intermediate azide **S25** was prepared using general procedure (vii) with 4-(3-(propan-2-yl)phenyl)-4,4-diphenylbutyl methanesulfonate **S24** (100 mg, 0.24 mmol) and sodium azide (76 mg, 1.17 mmol) in anhydrous DMF (2.00 mL) and irradiation for 13 min. Purification by flash chromatography [SiO_2; 2-30% EtOAc in hexane] afforded 1-(4-azido-1,1-diphenylbutyl)-3-(propan-2-yl)benzene **S25** as a white oil (72 mg, 82%), which was taken directly to the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (d, 6H, *J* = 7.7 Hz, 2 x CH_3), 1.53-1.60 (m, 2H, CH_2), 2.59-2.63 (m, 2H, CH_2), 2.69-2.73 (m, 1H, CH), 3.49 (t, 2H, *J* = 6.4 Hz, CH_2), 7.08-7.29 (m, 14H). The title compound was then prepared following general procedure (viii) with azide **S25** (200 mg, 0.54 mmol), 10% Pd/C (200 mg) and $HCOONH_4$ (191 mg, 2.70 mmol) in anhydrous MeOH (20 mL). Purification by flash chromatography [SiO_2; 3-15% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded amine **23** as a white oil (59 mg, 32%). ^{1}H NMR (400 MHz, MeOD) δ = 1.16 (d, 6H, *J* = 6.8 Hz, 2 x CH_3), 1.23-1.31 (m, 2H, CH_2), 2.52-2.66 (m, 4H), 2.75-2.82 (m, 1H, CH), 7.03-7.29 (m, 14H). ^{13}C NMR (100 MHz, MeOD) δ = 24.58, 30.22, 35.63, 38.88, 43.13, 57.90, 124.92, 127.02, 127.99, 128.92, 128.99, 130.50, 148.76, 149.08, 149.53. HRMS (ESI+) calcd. for $C_{25}H_{29}N$ $(M+H)^+$: 344.2373; found: 344.2370. Anal. calcd. for $C_{25}H_{29}N$: C, 87.41; H, 8.51; N, 4.08. Found: C, 85.70; H, 7.36; N, 4.86.

1-(1,1-Diphenylbut-3-en-1-yl)-4-ethylbenzene (S26).



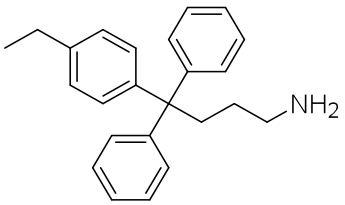
The title compound was prepared using general procedure (iii) with (4-ethylphenyl)(diphenyl)methanol **S16** (4.66 g, 16.2 mmol) and *n*-butyllithium (2.5M in hexanes, 16.17 mL, 40.4 mmol) in anhydrous CH_2Cl_2 (25 mL), and subsequently allyltrimethylsilane (5.16 mL, 32.3 mmol) and iron trichloride (2.89g, 17.8 mmol) with the following modifications. The reaction mixture was stirred for 24 h before addition of allyltrimethylsilane and iron trichloride. Purification by flash chromatography [SiO_2; 0-2% EtOAc in hexane] afforded alkene **S26** as a yellow oil (3.82 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ =1.25 (t, 3H, *J* = 7.6 Hz, CH_3), 2.64 (q, 2H, *J* = 7.7 Hz, CH_2), 3.42-3.47 (m, 2H, CH_2), 4.93-5.08 (m, 2H), 5.63-5.74 (m, 1H), 7.08-7.33 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 15.37, 28.46, 29.10, 75.66, 125.72, 127.93, 128.26, 128.34, 130.09, 130.55, 132.29, 143.22, 144.20, 149.57. GC-MS (CI, methane) t_R = 15.26 min (*m/z* = 313.2, $[M+H]^+$).

4-(4-Ethylphenyl)-4,4-diphenylbutan-1-ol (S17).



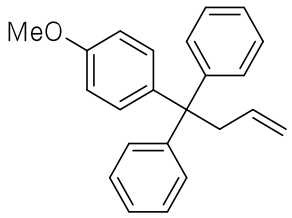
The title compound was prepared using general procedure (iv) with 1-(1,1-diphenylbut-3-en-1-yl)-4-ethylbenzene **S26** (3.82g, 12.2 mmol) and BH_3·THF (1.0 M in THF, 24.5 mL, 24.5 mmol) in anhydrous THF (15 mL), and subsequently NaOH (1.0 M, 20.0 mL, 20.0 mmol) and hydrogen peroxide (30% in H_2O, 4.00 mL). Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded alcohol **S17** as a white oil (2.02 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.25 (t, 3H, *J* = 7.6 Hz, CH_3), 1.36-1.47 (m, 2H), 2.61-2.69 (m, 4H), 3.65 (t, 2H, *J* = 6.3 Hz,CH_2), 7.10-7.33 (m, 14H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 15.44, 28.36, 29.34, 36.66, 56.14, 63.52, 125.90, 127.41, 127.92, 129.22, 129.35, 141.72, 144.60, 147.70. GC-MS (CI, methane) t_R = 17.99 min (*m/z* = 329.2, $[M-H]^+$).

4-(4-Ethylphenyl)-4,4-diphenylbutan-1-amine (24).



The title compound was prepared using general procedure (viii) with azide **S19** (200 mg, 0.56 mmol), 10% Pd/C (200 mg) and $HCOONH_4$ (191 mg, 2.70 mmol) in anhydrous MeOH (20 mL). Purification by flash chromatography [SiO_2; 3-15% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded amine **24** as a white oil (44 mg, 24%). ^{1}H NMR (400 MHz, MeOD) δ = 1.20 (t, 3H, *J* = 7.6 Hz, CH_3), 1.24-1.32 (m, 2H, CH_2), 2.56-2.66 (m, 6H), 7.08-7.28 (m, 14H). ^{13}C NMR (125 MHz, MeOD) δ = 16.23, 29.41, 29.97, 38.89, 43.03, 57.51, 127.00, 128.39, 128.92, 130.47, 143.16, 146.09, 149.11. HRMS (ESI+) calcd. for $C_{24}H_{27}N$ $(M+H)^+$: 330.2216; found: 330.2210. Anal. calcd. for $C_{24}H_{27}N \cdot \frac{2}{3}H_2O$: C, 84.44; H, 8.36; N, 4.10; Found: C, 84.53; H, 8.03; N, 4.30.

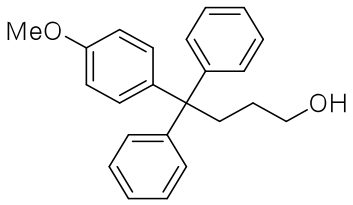
1-(1,1-Diphenylbut-3-en-1-yl)-4-methoxybenzene (S27).



The title compound was prepared using general procedure (iii) with (4-methoxyphenyl)(diphenyl)methanol (10.00 g, 34.4 mmol) and *n*-butyllithium (2.5 M in hexane, 20 mL, 50.0 mmol) in anhydrous CH_2Cl_2 (40 mL), and subsequently allyltrimethylsilane (6.02 mL, 36.9 mmol) and iron trichloride (5.19 g, 32.0 mmol) with the following modifications. The reaction was stirred for 18 h before addition of allyltrimethylsilane and iron trichloride. Purification by flash chromatography [SiO_2; 0-6% EtOAc in hexane] afforded alkene **S27** as a pale brown solid (6.44 g, 60%). Mpt. 71-72.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.42-3.45 (m, 2H, CH_2), 3.81 (s, 3H, CH_3), 4.95-4.98 (m, 1H), 5.03-5.08 (m, 1H), 5.65-5.73 (m, 1H), 6.81-6.84 (m, 2H), 7.13-7.17 (m, 2H), 7.19-7.26 (m, 6H), 7.26.7.30 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 45.84, 55.30, 55.77, 113.16, 117.30, 126.04, 127.86, 127.90, 129.48, 130.58, 136.25, 139.56, 147.76, 157.73. GC-MS

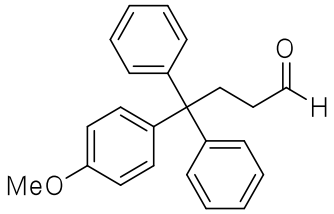
(CI, methane) t_R = 17.12 min (*m/z* = 315.1, $[M+H]^+$). Anal. calcd. for $C_{23}H_{22}O$: C, 87.86; H, 7.05. Found: C, 86.38; H, 6.70.

4-(4-Methoxyphenyl)-4,4-diphenylbutan-1-ol (S28).



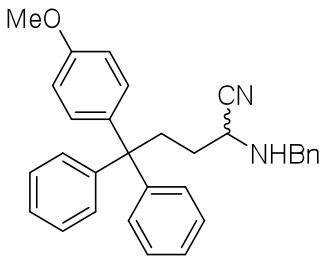
The title compound was prepared using an adaptation of the procedure reported by Starnes.[7] A solution of concentrated sulphuric acid (115 µL, 2.03 mmol) in anhydrous Et_2O (3.0 mL) was added slowly by dropwise addition to a cooled (0 °C) solution of sodium borohydride (115 mg, 4.07 mmol) and alkene **S27** (3.36 g, 10.69 mmol) in anhydrous diglyme (10 mL), and the reaction mixture stirred for 3.5 h at room temperature, then heated at 75 °C for a further 1.5 h. The reaction was cooled (0 °C) and treated successively with water (300 µL), aqueous NaOH (3.0 M, 1.36 mL) and hydrogen peroxide (30% in H_2O, 1.36 mL). The mixture was allowed to warm to room temperature and stirred for 6.5 h, then extracted with Et_2O (50 mL), the organic extracts washed with H_2O (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 10-40% EtOAc in hexane] afforded the primary alcohol **S28** as a white solid (2.33 g, 66%). Mpt. 50-52 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.35-1.41 (m, 2H, CH_2), 2.61-2.66 (m, 2H, CH_2), 3.65 (t, 2H, *J* = 6.5 Hz, CH_2), 3.79 (s, 3H, CH_3), 6.79-6.83 (m, 2H), 7.16-7.22 (m, 4H), 7.24-7.30 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 29.34, 36.78, 55.31, 55.77, 63.50, 113.27, 125.92, 127.95, 129.20, 129.26, 130.36, 139.55, 147.77, 157.64. GC-MS (CI, methane) t_R = 18.34 min (*m/z* = 361.1, $[M+C_2H_5]^+$). Anal. calcd. for $C_{23}H_{24}O_2 \cdot H_2O$: C, 78.83; H, 7.48. Found: C, 79.16; H, 7.23.

4-(4-Methoxyphenyl)-4,4-diphenylbutanal (66).



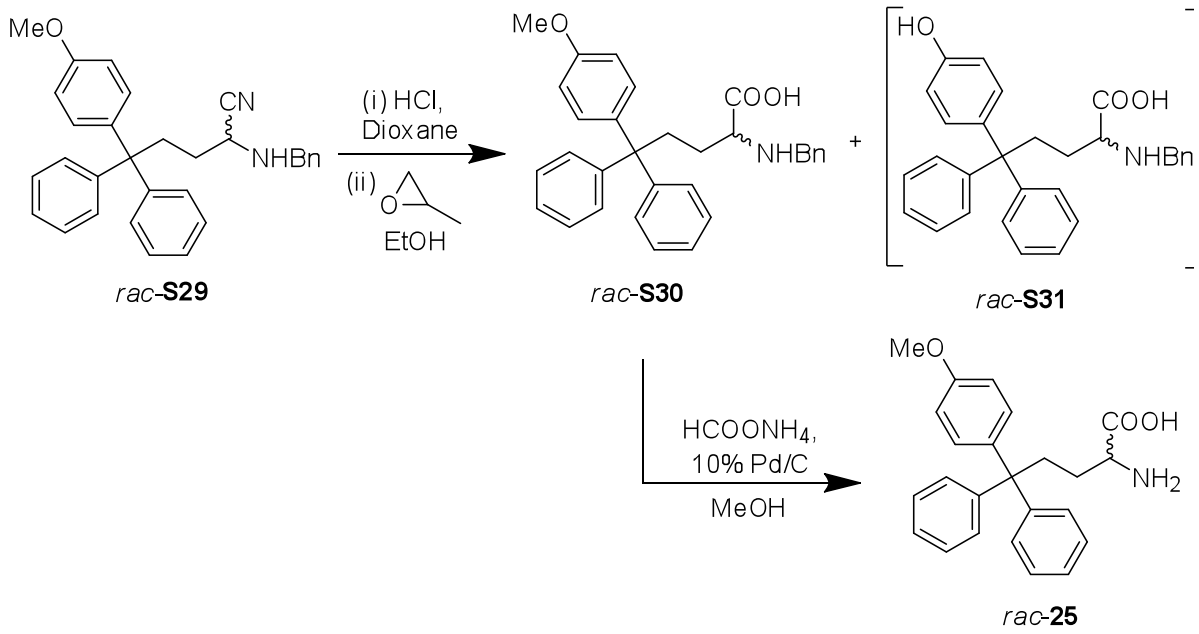
The title compound was prepared using general procedure (v) with **S28** (1.50 g, 4.51 mmol) and Dess-Martin periodinane (2.30 g, 5.42 mmol) in anhydrous CH_2Cl_2 (20 mL). Purification by flash chromatography [SiO_2; 0-35% EtOAc in hexane] yielded the aldehyde **66** as a white solid (1.238 g, 83%). Mpt. 112-113 °C. ^{1}H NMR (400MHz, $CDCl_3$): 2.31-2.35 (m, 2H, CH_2), 2.89-2.93 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 6.80-6.84 (m, 2H), 7.16-7.21 (m, 4H), 7.26-7.29 (m, 8H), 9.63 (s, 1H, CHO). ^{13}C NMR (100MHz, $CDCl_3$): 32.12, 41.27, 55.33, 113.49, 126.22, 128.18, 129.08, 130.21, 138.73, 147.01, 157.84, 201.91. HRMS (ESI+) calcd. for $C_{23}H_{23}O_2$ $(M+H)^+$: 331.1693; found: 331.1690. Anal. calcd. for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.22; H, 6.49.

2-(Benzylamino)-5-(4-methoxyphenyl)-5,5-diphenylpentanenitrile (*rac*-S29).



The title compound was prepared using an adaptation of the method described for *rac*-**65** with **66** (330 mg, 1.0 mmol), benzylamine (129 mg, 132 µL, 1.20 mmol) and trimethylsilyl cyanide (192 µL, 1.40 mmol) in anhydrous CH_2Cl_2 (12 mL). Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded racemic α-aminonitrile **S29** as a pale yellow oil (401 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.59 (q, *J* = 7.8 Hz, 2H, CH_2), 2.70-2.85 (m, 2H), 3.36-3.40 (m, 1H), 3.74-3.81 (m, 4H), 4.01 (d, *J* = 12.9 Hz, 1H), 6.78-6.83 (m, 2H), 7.15-7.36 (m, 17H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 30.12, 36.47, 50.15, 51.78, 55.33, 55.65, 113.47, 120.30, 126.20, 127.73, 128.16, 128.19, 128.49, 128.75, 129.07, 130.21, 138.38, 138.78, 147.07, 157.82.HRMS (ESI+): calcd. for $C_{31}H_{31}N_2O$ $(M+H)^+$ 447.23581; found: 447.23679.

2-Amino-5-(4-methoxyphenyl)-5,5-diphenylpentanoic acid (*rac*-25).



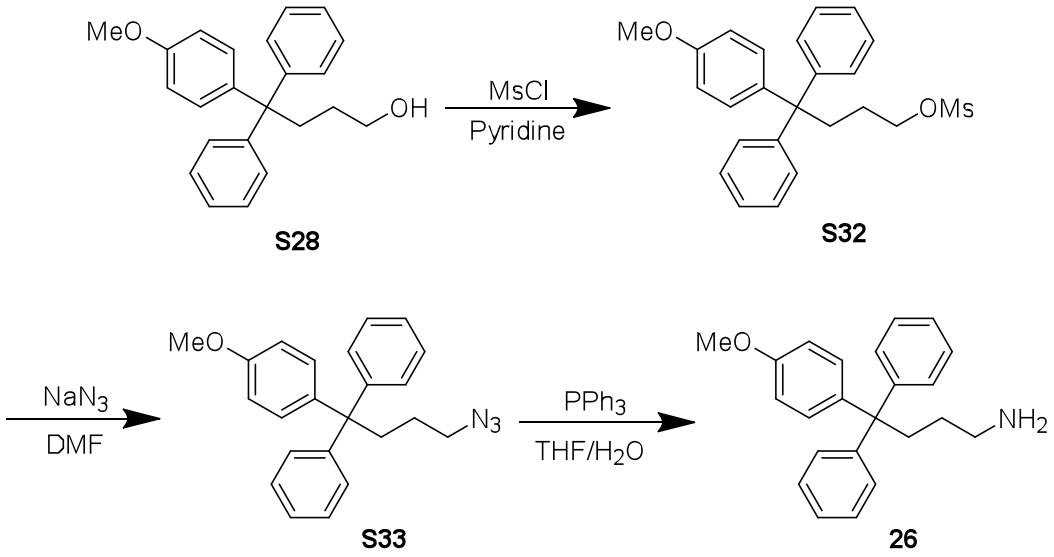
rac-**S29** *rac*-**S30** *rac*-**S31** *rac*-**25**

Scheme S9

Intermediate benzyl amine *rac*-**S30** was prepared by the route depicted in Scheme S9 using an adaptation of the procedures reported by Bigge *et al.* and Warmuth *et al.*[8, 9] A solution of *rac*-**S29** (775 mg, 1.74 mmol) in HCl (6.0 M in dioxane, 15 mL) was heated at reflux for 2 days and then concentrated *in vacuo*. The residue was redissolved in EtOH (10 mL), propylene oxide (2 mL) added and the mixture heated at reflux for 30 min. The volatiles were removed *in vacuo* and the crude product was purified by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to give the protected amino acid *rac*-**S30** as a white solid (485 mg, 60 %). HRMS (ESI+): calcd. for $C_{31}H_{32}NO_3$ $(M+H)^+$ 466.23039; found: 466.23127. As a by-product, 5-(4-hydroxyphenyl)-5,5-diphenylpentanoic acid *rac*-**S31** was also obtained as a white solid (79 mg, 10 %). HRMS (ESI+): calcd. for $C_{30}H_{30}NO_3$ $(M+H)^+$ 452.21474; found: 452.20586. Subsequently, the title compound *rac*-**25** was then prepared using general procedure (viii) with *rac*-**S30** (400 mg, 0.86 mmol), 10% Pd/C (200 mg) and $HCOONH_4$ (273 mg, 4.33 mmol) in anhydrous MeOH (15 mL) and a reaction time of 1 h. Purification by flash chromatography [SiO_2; 3-30% MeOH in CH_2Cl_2 with 0.5% NH_4OH] afforded *rac*-**25** as a white solid (233 mg, 72 %). Mpt 181-184 °C. ^{1}H NMR (400 MHz, MeOD): 1.61-1.63 (m, 2H, CH_2), 2.65-2.82 (m, 2H, CH_2), 3.55-3.59 (m, 1H), 3.72 (s, 3H, CH_3), 6.78-7.28 (m, 14H). ^{13}C NMR (100 MHz, MeOD): 27.6, 35.6, 54.4, 54.9, 55.5,

112.9, 125.7, 127.6, 128.9, 130.1, 138.8, 147.3, 157.9, 173.2. HRMS (ESI+): calcd. for $C_{24}H_{25}NO_3$ $(M+H)^+$ 376.1907; found: 376.1904. Anal. calcd for $C_{24}H_{25}NO_3 \cdot 1.5H_2O$: C, 71.62; H, 7.01; N, 3.48. Found: C, 71.51; H, 5.80; N, 3.25.

4-(4-Methoxyphenyl)-4,4-diphenylbutan-1-amine (26).

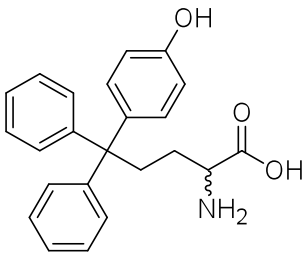


Scheme S10

Mesylate **S32** was prepared using general procedure (vi) with 4-(4-methoxyphenyl)-4,4-diphenylbutan-1-ol **S28** (332 mg, 1.00 mmol) and methanesulphonyl chloride (155 μL, 2.0 mmol) in anhydrous pyridine (8 ml). Purification by flash chromatography [SiO_2; 0-10% EtOAc in hexane] afforded 4-(4-methoxyphenyl)-4,4-diphenylbutyl methanesulfonate **S32** as a white solid (380 mg, 93%), which was taken directly to the next step. Azide **S33** was prepared using general procedure (vii) with **S32** (380 mg, 0.93 mmol) and sodium azide (242 mg, 3.72 mmol) in anhydrous DMF (2.00 mL). Purification by flash chromatography [SiO_2; 0-10% EtOAc in hexane] afforded azide **S33** as a white solid (300 mg, 91%), which was taken directly to the next step. The title compound **26** then was prepared by the triphenylphospine mediated reduction of azide **S33**, in an adaptation of the procedure reported by Dockendorff *et al.*[10] Triphenylphosphine (1.10 g, 4.20 mmol) was added to a solution of **S34** (300 mg, 0.84 mmol) in THF:H_2O (10:1, 11 mL). The reaction mixture was stirred at 60 °C for 12 h and then concentrated *in vacuo*. The crude product was purified by flash chromatography [SiO_2; 3-20% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to afford the title compound **26** as a colorless oil (210 mg, 76%). ^{1}H NMR (400 MHz, MeOD): 1.22-1.26 (m, 2H, CH_2), 2.53-2.62 (m, 4H, CH_2 and CH_2), 3.72 (s, 3H, CH_3), 6.77-7.27 (m, 14H). ^{13}C NMR

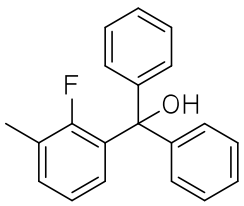
(100 MHz, MeOD): 28.8, 37.6, 41.7, 54.3, 55.7, 112.8, 125.5, 127.5, 129.0, 130.1, 139.4, 147.8, 157.8. HRMS (ESI+): calcd. for $C_{23}H_{26}NO$ $(M+H)^+$ 332.2009; found: 332.2010. LC-MS t_R = 13.00 min (*m/z* = 332.2, $[M+H]^+$; purity = 97.0%).

2-Amino-5-(4-hydroxyphenyl)-5,5-diphenylpentanoic acid (*rac*-27).



The title compound was prepared using general procedure (viii) with *rac*-**S31** (79 mg, 0.17 mmol), 10% Pd/C (40 mg) and $HCOONH_4$ (54 mg, 0.85 mmol) in anhydrous MeOH (8 mL) and a reaction time of 1 h. Purification by flash chromatography [SiO_2; 3-30% MeOH in CH_2Cl_2 with 0.5% NH_4OH] afforded *rac*-**27** as a white solid (42 mg, 69 %). Mpt. 182-184 °C. ^{1}H NMR (400 MHz, MeOD): 1.60-1.62 (m, 2H, CH_2), 2.65-2.82 (m, 2H, CH_2), 3.50-3.53 (m, 1H, CH), 6.67-7.27 (m, 14H). ^{13}C NMR (100 MHz, MeOD): 27.6, 35.6, 55.0, 55.4, 114.3, 125.6, 127.5, 128.9, 130.1, 137.6, 147.5, 155.2, 173.0. HRMS (ESI+): calcd. for $C_{23}H_{23}NO_3$ $(M+H)^+$ 362.1751; found: 362.1749. Anal.calcd for $C_{23}H_{23}NO_3 \cdot ¼CH_2Cl_2$: C, 72.97; H, 6.19; N, 3.66. Found: C, 73.48; H, 5.58; N, 3.54.

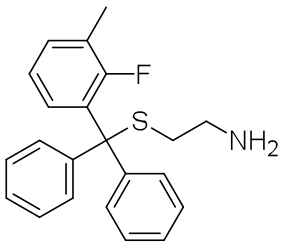
(2-Fluoro-3-methylphenyl)(diphenyl)methanol (S34).



The title compound was prepared using general procedure (i) with 1-bromo-2-fluoro-3-methylbenzene (1.70 g, 9.0 mmol) and *n*-butyllithium (2.5 M in hexane, 3.96 mL, 9.9 mmol) in anhydrous THF (15.0 mL), and subsequently benzophenone (1.37 g, 7.5 mmol) in anhydrous THF (7.5 mL) with the following modifications. The reaction was maintained at ≤ -70 °C for 1 h following addition of *n*-butyllithium, and 2 h after the addition of benzophenone. Purification by flash chromatography [SiO_2; 0-10% EtOAc in hexane]

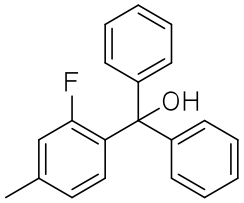
afforded the trityl alcohol **S34** as a white solid (1.74 g, 80%). Mpt. 64-67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.26 (m, 3H, CH_3), 3.61-3.66 (m, 1H, OH), 6.53-6.58 (m, 1H), 6.88-6.92 (m, 1H), 7.14-7.19 (m, 1H), 7.27-7.39 (m, 10H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -114.90. ^{13}C NMR (400 MHz, MeOD) δ = 14.60 (d, J_{CF} = 5.6 Hz), 81.27, 123.19 (d, J_{CF} = 3.6 Hz), 125.74 (d, J_{CF} = 18.4 Hz), 127.59, 127.73, 128.09, 131.49 (d, J_{CF} = 5.3 Hz), 134.11(d, J_{CF} = 11.0 Hz), 145.85, 159.68 (d, J_{CF} = 250.3 Hz). HRMS (ESI+) calcd. for $C_{20}H_{16}F$ $(M\text{-}OH)^+$: 275.1231; found: 275.1229. Anal. calcd. for $C_{20}H_{17}FO$: C, 82.17; H, 5.86. Found: C, 81.55; H, 5.81.

2-((2-Fluoro-3-methylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (28).



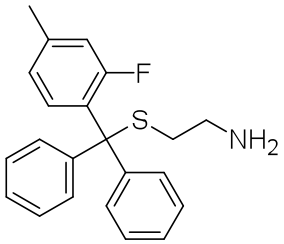
The title compound was prepared following general procedure (ii) with (2-fluoro-3-methylphenyl)(diphenyl)methanol **S34** (292 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2] afforded the thioether **28** as a white solid (226 mg, 64%). Mpt. 165-168 °C. ^{1}H NMR (400 MHz, MeOD) δ = 2.14-2.17 (m, 3H, CH_3), 2.35-2.40 (m, 4H, 2 x CH_2), 7.14-7.19 (m, 1H), 7.23-7.35 (m, 7H), 7.46-7.49 (m, 1H), 7.71-7.76 (m, 1H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -105.84. ^{13}C NMR (400 MHz, MeOD) δ = 14.48 (d, J_{CF} = 5.8 Hz), 31.27, 39.81, 66.39, 124.74 (d, J_{CF} = 4.2 Hz), 127.26 (d, J_{CF} = 19.2 Hz), 128.16, 128.92, 129.13 (d, J_{CF} = 3.6 Hz), 130.27, 131.72 (d, J_{CF} = 10.8 Hz), 132.67 (d, J_{CF} = 5.3 Hz), 143.95, 160.09 (d, J_{CF} = 250.3 Hz). HRMS (ESI+) calcd. for $C_{22}H_{23}FNS$ $(M+H)^+$: 352.1541; found: 352.1528. Anal. calcd. for $C_{22}H_{22}FNS{\cdot}CH_2Cl_2$: C, 63.30; H, 5.54; N, 3.21. Found: C, 62.61; H, 5.11; N, 3.05.

(2-Fluoro-4-methylphenyl)(diphenyl)methanol (S35).



The title compound was prepared using general procedure (i) with 1-bromo-2-fluoro-4-methylbenzene (1.14 mL, 9.0 mmol) and *n*-butyllithium (2.5 M in hexane, 3.96 mL, 9.9 mmol) in anhydrous THF (15.0 mL), and subsequently benzophenone (1.37 g, 7.5 mmol) in anhydrous THF (7.5 mL) with the following modifications. The reaction was maintained at ≤ -70 °C for 2.5 h after the addition of benzophenone. Purification by flash chromatography [SiO_2; 0-10% EtOAc in hexane] afforded the trityl alcohol **S35** as a colourless oil (1.47 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.34 (s, 3H, CH_3), 3.54 (d, J = 10.0 Hz, 1H), 6.62 (t, J = 8.4 Hz, 1H), 6.80-6.84 (m, 1H), 6.90 (dd, J = 0.9, 13.0 Hz, 1H), 7.25-7.36 (m, 10H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -111.20. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.03, 81.01, 116.92 (d, J_{CF} = 29.3 Hz) 124.4 (d, J_{CF} = 2.7 Hz), 127.59, 127.72, 128.09, 130.2 (d, J_{CF} = 3.4 Hz), 131.4 (d, J_{CF} = 9.7 Hz), 140.4 (d, J_{CF} = 8.7 Hz), 145.80, 160.96 (d, J_{CF} = 243.4 Hz). HRMS (ESI+) calcd. for $C_{20}H_{16}F$ $(M\text{-}OH)^+$: 275.1231; found: 275.1228. Anal. calcd. for $C_{20}H_{17}FO$: C, 82.17; H, 5.86. Found: C, 82.27; H, 5.78.

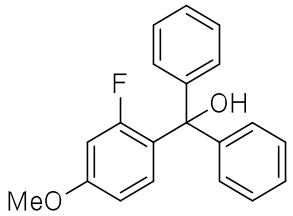
2-((2-Fluoro-4-methylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (29).



The title compound was prepared following general procedure (ii) with **S35** (292 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2] afforded the thioether **29** as a white solid (170 mg, 48%). Mpt. 74-76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.23-2.28 (m, 2H, CH_2), 2.32-2.38 (m, 5H), 6.78-6.83 (m, 1H), 7.03-7.06 (m, 1H), 7.17-7.30 (m, 6H), 7.38-7.44 (m, 4H), 7.69-7.74 (m, 1H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -102.04. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.73, 36.05, 41.38, 65.54 (d, J_{CF} = 2.6 Hz), 117.98 (d, J_{CF} = 23.0 Hz), 125.61 (d, J_{CF} = 2.74 Hz), 127.81, 128.70, 129.60 (d, J_{CF} = 10.6 Hz), 130.25,

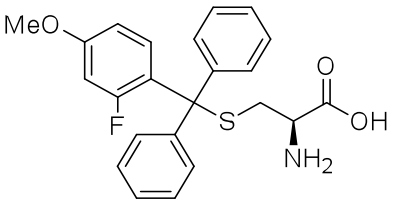
131.63 (d, J_{CF} = 3.3 Hz), 141.71 (d, J_{CF} = 8.0 Hz), 144.60, 161.68 (d, J_{CF} = 250.2 Hz). HRMS (ESI+) calcd. For $C_{44}H_{45}F_2N_2S_2$ $(2M+H)^+$: 703.2987; found: 703.2991. Anal. calcd. for $C_{22}H_{22}FNS \cdot ¼H_2O$: C, 74.23; H, 6.37; N, 3.93. Found: C, 74.27; H, 6.23; N, 3.58.

2-Fluoro-4-methoxyphenyl)(diphenyl)methanol (S10).



The title compound was prepared using general procedure (i) with 1-bromo-2-fluoro-4-methoxybenzene (645 μL, 5.00 mmol) and *n*-butyllithium (2.5 M in hexane, 2.40 mL, 6.00 mmol) in anhydrous THF (5.00 mL), and subsequently benzophenone (1.048 g, 5.75 mmol) in anhydrous THF (5.75 mL). Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded the trityl alcohol **S10** as a white solid (1.165 g, 76%). Mpt. 84-87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.74 (s, 1H, OH), 3.87 (s, 3H, CH_3), 6.85-6.90 (m, 1H), 6.94-6.97 (m, 1H), 7.02-7.07 (m, 1H), 7.23-7.34 (m, 10H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -107.90. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 56.38, 81.61 (d, J_{CF} = 1.5 Hz), 112.62, (d, J_{CF} = 2.4 Hz), 116.22 (d, J_{CF} = 19.7 Hz), 123.84 (d, J_{CF} = 3.6 Hz), 127.59, 127.91, 128.18, 140.17 (d, J_{CF} = 5.1 Hz), 146.70, 146.81 (d, J_{CF} = 10.8 Hz), 151.90 (d, J_{CF} = 245.4 Hz). HRMS (ESI+) calcd. for $C_{20}H_{16}FO$ $(M-OH)^+$: 290.11797; found: 290.11737. Anal. calcd. for $C_{20}H_{17}FO_2 \cdot ⅓H_2O$: C, 76.43; H, 5.66. Found: C, 76.21; H, 5.44.

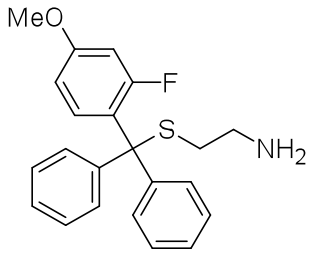
(2*R*)-2-Amino-3-(((2-fluoro-4-methoxyphenyl)(diphenyl)methyl)sulfanyl)propanoic acid (30).



The title compound was prepared following general procedure (ii) with (2-fluoro-4-methoxyphenyl)(diphenyl)methanol **S10** (308 mg, 1.0 mmol) and L-cysteine (133 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-25%

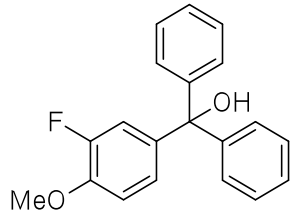
MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **30** as a white solid (204 mg, 50%). Mpt. 152-154.5 °C. ^{1}H NMR (400 MHz, MeOD) δ = 2.68 (dd, 1H, *J* = 8.9, 13.1 Hz), 2.81 (dd, 1H, *J* = 4.3 13.1 Hz), 3.17 (dd, 1H, *J* = 4.2, 8.9 Hz), 3.87 (s, 3H, CH_3), 7.00-7.06 (m, 1H), 7.12-7.20 (m, 2H), 7.23-7.30 (m, 2H), 7.30-7.36 (m, 4H), 7.41-7.46 (m, 4H). ^{19}F NMR (376.5 MHz, MeOD) δ = -136.39. ^{13}C NMR (100 MHz, MeOD) δ = 34.75, 55.17, 56.70, 67.31, 114.20 (d, J_{CF} = 1.4 Hz), 118.42 (d, J_{CF} = 20.1 Hz), 126.69 (d, J_{CF} = 3.2 Hz), 128.15, 129.22, 130.54, 138.63 (d, J_{CF} = 4.9 Hz), 145.54, 145.57, 147.91 (d, J_{CF} = 11.0 Hz), 152.96 (d, J_{CF} = 244.6 Hz), 173.11. HRMS (ESI+) calcd. for $C_{23}H_{23}NO_3FS$ = $(M+H)^+$: 412.1377; found: 412.1377. Anal. calcd. for $C_{23}H_{22}NO_3FS \cdot H_2O$: C, 64.32; H, 5.63; N, 3.26. Found: C, 64.03; H, 5.59; N, 3.26.

2-(((2-Fluoro-4-methoxyphenyl)(diphenyl)methyl)sulfanyl)ethanamine (31).



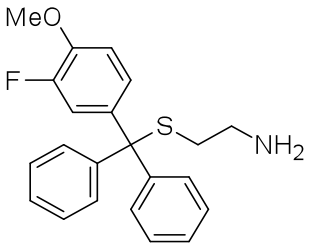
The title compound was prepared following general procedure (ii) with **S10** (308 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-15% MeOH in CH_2Cl_2] afforded the thioether **31** as a brown solid (280 mg, 76%). Mpt. 68-70 °C. ^{1}H NMR (400 MHz, MeOD) δ = 2.32-2.37 (m, 2H, CH_2), 2.43-2.48 (m, 2H, CH_2), 3.85 (s, 3H, CH_3), 6.96-7.02 (m, 1H), 7.08-7.15 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.33 (m, 4H), 7.37-7.42 (m, 4H). ^{19}F NMR (376.5 MHz, MeOD) δ = -136.78. ^{13}C NMR (100 MHz, MeOD) δ = 36.08, 41.55, 56.74, 67.01, 113.79, 118.43 (d, J_{CF} = 20.2 Hz), 126.69 (d, J_{CF} = 2.8 Hz), 127.94, 129.00, 130.61, 139.38 (d, J_{CF} = 5.5 Hz), 146.12, 147.73 (d, J_{CF} = 10.8 Hz), 152.86 (d, J_{CF} = 244.5 Hz). HRMS (ESI+) calcd. for $C_{22}H_{23}FNOS$ $(M+H)^+$: 368.1479; found: 368.1475. Anal. calcd. for $C_{22}H_{22}FNOS \cdot ½H_2O$: C, 70.19; H, 6.16; N, 3.72. Found: C, 70.37; H, 5.80; N, 3.40.

3-Fluoro-4-methoxyphenyl)(diphenyl)methanol (S11).



The title compound was prepared using general procedure (i) with 4-bromo-2-fluoro-1-methoxybenzene (1.03 g, 5.00 mmol) and *n*-butyllithium (2.5 M in hexane, 2.40 mL, 6.00 mmol) in anhydrous THF (5.00 mL), and subsequently benzophenone (1.05 g, 5.75 mmol) in anhydrous THF (5.75 mL). Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded the trityl alcohol **S11** as an off-white solid (0.93 g, 60%). Mpt. 54-55 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.43-3.48 (m, 1H), 3.78 (s, 3H, CH_3), 6.52-6.55 (m, 1H), 6.60-6.67 (m, 2H), 7.24-7.35 (m, 10H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -134.90. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 55.73, 80.85, 102.78 (d, J_{CF} = 26.5 Hz), 108.81 (d, J_{CF} = 2.6 Hz), 126.60 (d, J_{CF} = 10.7 Hz), 127.58, 127.69, 128.10, 130.90 (d, J_{CF} = 5.1 Hz), 160.70 (d, J_{CF} = 11.7 Hz), 161.60 (d, J_{CF} = 245.6 Hz). HRMS (ESI+) calcd. for $C_{20}H_{16}FO$ $(M\text{-}OH)^+$: 290.11797; found: 290.11758. Anal. calcd. for $C_{20}H_{17}FO_2 \cdot ¼H_2O$: C, 76.78; H, 5.64. Found: C, 76.94; H, 5.72.

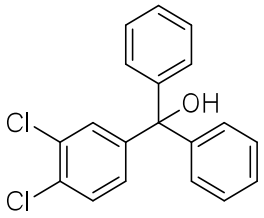
2-(((3-Fluoro-4-methoxyphenyl)(diphenyl)methyl)sulfanyl)ethanamine (32).



The title compound was prepared following general procedure (iii) with 3-fluoro-4-methoxyphenyl)(diphenyl)methanol **S11** (308 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-14% MeOH in CH_2Cl_2 with NH_4OH] afforded the thioether **32** as a pale yellow oil (247 mg, 67%). ^{1}H NMR (400 MHz, MeOD) δ = 2.24-2.29 (m, 2H, CH_2), 2.35-2.40 (m, 2H, CH_2), 3.79 (s, 3H, CH_3), 6.58 (dd, *J* = 2.6, 13.3 Hz, 1H), 6.78 (dd, *J* = 2.6, 8.7 Hz, 1H), 7.17-7.29 (m, 6H), 7.39-7.44 (m, 4H), 7.68-7.74 (m, 1H). ^{19}F NMR (376.5 MHz, MeOD) δ = -99.28. ^{13}C NMR (100 MHz, MeOD) δ = 36.10, 41.43, 56.14, 65.33 (d, J_{CF} = 2.6 Hz), 103.75 (d, J_{CF} = 27.1 Hz), 110.06 (d, J_{CF} = 2.5 Hz), 124.68 (d, J_{CF} = 11.2 Hz), 127.77 128.70 130.21,

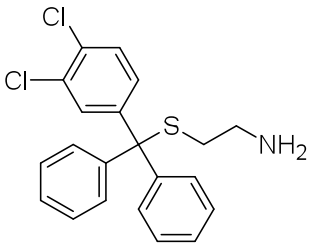
132.42 (d, J_{CF} = 4.1 Hz), 144.83, 162.35 (d, J_{CF} = 250.2 Hz), 162.36 (d, J_{CF} = 11.0 Hz). HRMS (ESI+) calcd. for $C_{22}H_{23}FNOS$ $(M+H)^+$: 368.1479; found: 368.1474. Anal. calcd. for $C_{22}H_{22}FNOS$: C, 71.90; H, 6.03; N, 3.81. Found: C, 72.04; H, 6.05; N, 3.84.

(3,4-Dichlorophenyl)(diphenyl)methanol (S36).



(3,4-Dichlorophenyl)(phenyl)methanone (5.00 g, 20.0 mmol) was dissolved in anhydrous THF (20 mL) and PhMgBr solution (1.0 M in THF, 30 mL) added and the reaction stirred for 48 h at room temperature. The volatiles were removed *in vacuo* and the crude residue extracted with ethyl acetate (3 x 50 mL), the combined extracts dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-10% EtOAc in hexane] afforded the trityl alcohol **S36** as a pale yellow oil (6.10 g, 93%). ^{1}H NMR(400 MHz, $CDCl_3$): 2.77 (s, 1H, OH), 6.91-7.33 (m, 13H). ^{13}C NMR (100MHz, $CDCl_3$): 82.0, 125.6, 127.2, 128.0, 129.1, 129.2, 135.7, 136.3, 144.6, 147.2. HRMS calcd. for $C_{19}H_{13}Cl_2$ $(M-OH)^+$: 311.0389; found: 311.0381.

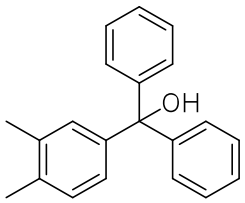
2-(((3,4-Dichlorophenyl)(diphenyl)methyl)sulfanyl)ethanamine (33).



The title compound was prepared following general procedure (iii) with (3,4-dichlorophenyl)(diphenyl)methanol **S36** (165 mg, 0.5 mmol) and cysteamine hydrochloride (57 mg, 0.5 mmol) in trifluoroacetic acid (0.5 mL) with the following modificiations. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1.0 M) and EtOAc was used for extraction (3 x 6 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with NH_4OH] afforded the thioether **33** as white solid (91 mg,

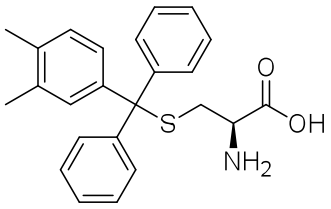
47%). Mpt. 99-102 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.16 (t, J = 7.0 Hz, 2H, CH_2), 2.45 (t, J = 7.1 Hz, 2H, CH_2), 7.25-7.37 (m, 11H), 7.46 (m, 1H), 7.61-7.63 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ = 35.60, 40.78, 64.96, 127.09, 128.23, 128.93 129.49, 129.73, 130.27, 130.64, 130.74, 143.74, 145.90. HRMS (ESI+) calcd. for $C_{21}H_{120}Cl_2NS$ $(M+H)^+$: 388.06880; found: 388.06830. Anal. calcd. for $C_{21}H_{19}Cl_2NS \cdot \frac{1}{3}H_2O$: C, 63.97; H, 5.03; N 3.55. Found: C, 63.99; H, 5.01; N, 3.61.

(3,4-Dimethylphenyl)(diphenyl)methanol (60).



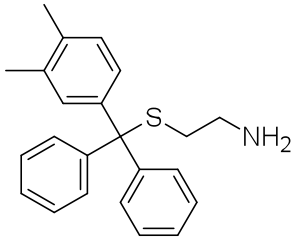
PhMgBr (1.0 M in THF, 22.5 ml, 22.5 mmol) was added slowly by dropwise addition over 10 min to a cooled (0 °C) solution of 3,4-dimethylbenzophenone (3.15 g, 15.0 mmol) in anhydrous THF (5 mL), and the reaction mixture stirred at reflux for 18 h. The reaction was quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (3 x 50 mL). The organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution, H_2O and brine (150 mL each), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude residue by flash chromatography [SiO_2; 0-8% EtOAc in hexane] afforded the trityl alcohol **60** as a colourless oil (3.90 g, 90%). ^{1}H NMR (500MHz, $CDCl_3$) δ = 2.21 (s, 3H, CH_3), 2.25(s, 3H, CH_3), 2.75 (s, 1H, OH), 6.92 (dd, J = 2.0, 7.9 Hz, 1H), 7.04-7.09 (m, 2H), 7.24-7.32 (m, 10H). ^{13}C NMR (125MHz, $CDCl_3$): 19.51, 20.12, 82.03, 125.64, 127.27, 128.00, 128.05, 129.16, 129.25, 135.77, 136.30, 144.61, 147.22. HRMS (ESI+) calcd. for $C_{21}H_{19}$ $(M-OH)^+$: 271.1481; found: 271.1478. Anal. calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.01; H, 6.86.

(2*R*)-2-Amino-3-(((3-,4-dimethylphenyl)(diphenyl)methyl)sulfanyl)propanoic acid (34).



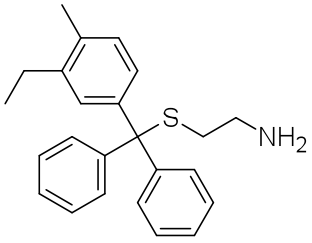
The title compound was prepared following general procedure (ii) with trityl alcohol **60** (500 mg, 1.73 mmol) and L-cysteine (231 mg, 1.1 mmol) in trifluoroacetic acid (1.7 mL). Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2] afforded thioether **34** as a white solid (464 mg, 68%). Mpt. 148-150 °C. ^{1}H NMR (400 MHz, MeOD) δ = 2.19 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.68 (dd, 1H, *J* = 9.2, 13.3 Hz), 2.81 (dd, 1H, *J* = 4.1, 13.3 Hz), 3.05 (dd, 1H, *J* = 4.1, 9.2 Hz), 7.06 (d, 1H, *J* = 8.0 Hz), 7.12 (dd, 1H, *J* = 2.0, 8.0 Hz), 7.17-7.24 (m, 3H), 7.26-7.32 (m, 4H), 7.41-7.46 (m, 4H). ^{13}C NMR (125 MHz, MeOD) δ = 19.30, 20.02, 34.41, 55.12, 67.93, 127.90, 128.17, 129.04, 130.23, 130.69, 130.72, 131.86, 136.45, 137.29, 143.09, 145.92, 145.96, 172.62. HRMS (ESI+) calcd. for $C_{48}H_{51}O_4N_2S_2$ $(2M+H)^+$: 783.3286; found: 783.3295. Anal. calcd. for $C_{24}H_{25}NO_2S \cdot H_2O$: C, 70.39; H, 6.65; N, 3.42. Found: C, 70.31; H, 6.25; N, 3.25.

2-(((3,4-Dimethylphenyl)(diphenyl)methyl)sulfanyl)ethanamine (35).



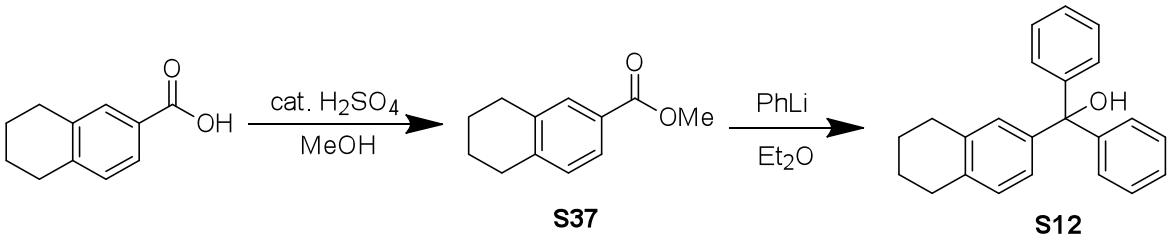
The title compound was prepared following general procedure (ii) with trityl alcohol **60** (289 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1.0 M) and EtOAc was used for extraction (3 x 10mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded thioether **35** a pale yellow oil (273 mg, 79%). ^{1}H NMR (MeOD, 500 MHz) δ 2.17 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.32-2.35 (m, 2H, CH_2), 2.41-2.44 (m, 2H, CH_2), 7.02 (d, *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.16-7.21 (m, 3H), 7.24-7.27 (m, 4H), 7.38-7.41 (m, 4H). ^{13}C NMR (MeOD, 125 MHz) δ 19.30, 20.05, 36.08, 41.56, 67.55, 127.66, 128.21, 128.79, 130.00, 130.76, 131.94, 136.13, 136.97, 143.71, 146.56. HRMS (ESI+) calcd. for $C_{23}H_{26}NS$ $(M+H)^+$: 348.17805; found: 348.17886. Anal. calcd. for $C_{23}H_{25}NS \cdot ¼H_2O$: C, 78.48; H, 7.30; N, 3.98. Found: C, 78.47; H, 7.38; N, 3.82.

2-(((3-Ethyl-4-methylphenyl)(diphenyl)methyl) sulfanyl)ethanamine (37).



The title compound was prepared following general procedure (ii) with trityl alcohol **59** (302 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1.0 M) and EtOAc was used for extraction (3 x 10mL). Purification by flash chromatography [SiO_2; 0-16% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded thioether **37** as a colourless oil (260 mg, 72%). ^{1}H NMR (MeOD, 500 MHz) δ 2.17 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.32-2.35 (m, 2H, CH_2), 2.41-2.44 (m, 2H, CH_2), 7.02 (d, J = 8.0 Hz, 1H), 7.09 (dd, J = 2.0, 8.0 Hz, 1H), 7.16-7.21 (m, 3H), 7.24-7.27 (m, 4H), 7.38-7.41 (m, 4H). ^{13}C NMR (MeOD, 125 MHz) δ 19.30, 20.05, 36.08, 41.56, 67.55, 127.66, 128.21, 128.79, 130.00, 130.76, 131.94, 136.13, 136.97, 143.71, 146.56. HRMS (ESI+) calcd. for $C_{24}H_{28}NS$ $(M+H)^+$: 362.19370; found: 362.19257. Anal. calcd. for $C_{24}H_{27}NS \cdot ⅛CH_2Cl_2$: C, 76.79; H, 7.30; N, 3.70. Found: C, 77.05; H, 7.58; N, 2.93.

(Diphenyl(5,6,7,8-tetrahydronaphthalen-2-yl)methanol (S12).

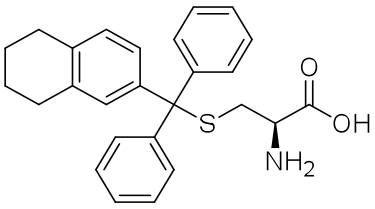


Scheme S11

A solution of 5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (3.52 g, 20 mmol) and conc. sulphuric acid (1 mL) in anhydrous MeOH (20 mL) was refluxed for 17 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*, the crude residue dissolved in EtOAc (50 mL), and washed successively with saturated aqueous $NaHCO_3$, water, brine (50 mL each), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product **S37** as a colourless oil (3.45 g, 91%), which was used without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.79-1.83 (m, 4H, 2 x CH_2), 2.78-2.82 (m, 4H, 2 x CH_2), 3.89

(s, 3H, CH_3), 7.11 (d, J = 7.6 Hz, 1H), 7.72-7.75 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.98, 23.08, 29.40, 29.73, 52.01, 126.63, 127.44, 129.27, 130.53, 137.40, 142.94, 167.54. HRMS (ESI+) calcd. for $C_{12}H_{15}O_2$ $(M+H)^+$: 191.10666; found: 191.10661. Anal. calcd. for $C_{12}H_{14}O_2 \cdot \frac{1}{3}H_2O$: C, 73.47; H, 7.53. Found: C, 73.31; H, 7.39. The intermediate trityl alcohol **S12** was then prepared as follows. Phenyllithium solution (1.8 M in Et_2O, 13.8 mL, 25 mmol) was added to a solution of methyl ester **S37** (1.90 g, 10 mmol) in anhydrous Et_2O (3.5 ml) at -84 °C, and stirred for 1 h whilst maintaining the temperature below -70 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 h, then quenched with saturated aqueous NH_4Cl solution (25 mL) and extracted EtOAc (3 x 20 mL). The combined organic extracts were washed successively with H_2O and brine (50 mL each), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude material by flash chromatography [SiO_2; 0-16% EtOAc in hexane] afforded tertiary alcohol **S12** as a white solid (1.76 g, 56%). Mpt. 101-103 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.77-1.82 (m, 4H, 2 x CH_2), 2.69-2.72 (m, 2H, CH_2), 2.74-2.78 (m, 3H), 6.92 (dd, J = 1.9, 8.0 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 7.26-7.34 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz) 23.33, 29.19, 29.71, 82.02, 125.39, 127.24, 127.98, 128.05, 128.52, 128.74, 136.35, 136.84, 144.19, 147.22. HRMS (ESI+) calcd. for $C_{23}H_{21}$ $(M-OH)^+$: 297.16378; found: 297.16373. Anal. calcd. for $C_{23}H_{22}O \cdot \frac{1}{4}H_2O$: C, 86.62; H, 7.11. Found: C, 86.62; H, 7.23.

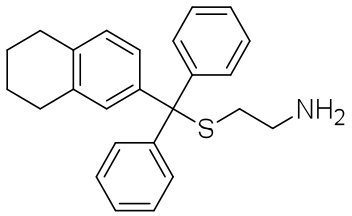
(2*R*)-2-Amino-3-(((5,6,7,8-tetrahydronaphthalen-2-yl)(diphenyl)methyl)sulfanyl) propanoic acid (38).



The title compound was prepared following general procedure (ii) with trityl alcohol **S12** (314 mg, 1.0 mmol) and L-cysteine (133 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2] afforded thioether **38** as a white solid (123 mg, 29%). Mpt. 145-148 °C. ^1H NMR (400 MHz, MeOD) δ = 1.75-1.80 (m, 4H), 2.64-2.75 (m, 5H), 2.82 (dd, 1H J = 4.1, 13.4 Hz), 3.02 (dd, 1H J = 4.1, 9.2 Hz), 6.98 (d, J = 8.2 Hz, 1H), 7.08-7.13 (m, 2H), 7.19-7.24 (m, 2H), 7.26-7.32 (m, 4H), 7.42-7.46 (m, 4H). ^{13}C NMR (100 MHz, MeOD) δ = 24.37, 29.93, 30.53, 34.32, 55.07, 67.94,

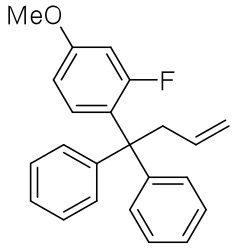
127.90, 128.00, 129.05, 129.76, 130.68, 130.72, 131.17, 136.99, 137.79, 142.67, 145.88, 145.93, 172.55. HRMS (ESI-) calcd. for $C_{26}H_{26}NO_2S$ $(M-H)^-$: 416.1690; found 416.1692. Anal. calcd. for $C_{26}H_{27}NO_2S \cdot \frac{2}{3}H_2O$: C, 72.72; H, 6.65; N 3.26. Found: C, 72.46; H, 6.27; N, 3.15.

2-((Diphenyl(5,6,7,8-tetrahydronaphthalen-2-yl)methyl) sulfanyl)ethanamine (39).



The title compound was prepared following general procedure (iii) with trityl alcohol **S12** (314 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1.0 M) and EtOAc was used for extraction (3 x 10mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded thioether **39** as a colourless oil (262 mg, 70%). ^{1}H NMR (MeOD, 500 MHz) δ 1.76-1.79 (m, 4H, 2 x CH_2), 2.33-2.35 (m, 2H, CH_2), 2.42-2.45 (m, 2H, CH_2), 2.64-2.66 (m, 2H, CH_2), 2.71-2.73 (m, 2H, CH_2), 6.94-6.95 (m, 1H), 7.06-7.08 (m, 2H), 7.17-7.21 (m, 2H), 7.25-7.28 (m, 4H), 7.39-7.41 (m, 4H). ^{13}C NMR (MeOD, 125 MHz) δ 24.40, 29.92, 30.58, 36.02, 41.56, 67.61, 127.66, 128.07, 128.79, 129.51, 130.78, 131.23, 136.72, 137.49, 143.32, 146.57. HRMS (ESI+) calcd. for $C_{25}H_{28}NOS$ $(M+H)^+$: 374.19370; found: 374.19400. Anal. calcd. for $C_{25}H_{27}NS \cdot \frac{3}{4}CH_2Cl_2$: C, 70.73; H, 6.57; N, 3.20. Found: C, 71.00; H, 6.48; N, 3.35.

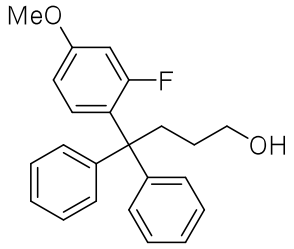
1-(1,1-Diphenylbut-3-en-1-yl)-2-fluoro-4-methoxybenzene (S38)



The title compound was prepared using general procedure (iii) with 2-fluoro-4-methoxyphenyl)(diphenyl)methanol **S10** (4.68 g, 15.2 mmol) and *n*-butyllithium (2.5 M in

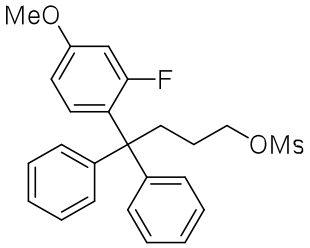
hexane, 15.18 mL, 38.00 mmol) in anhydrous CH_2Cl_2 (25 mL), and subsequently allyltrimethylsilane (4.84 mL, 30.4 mmol) and iron trichloride (2.95g, 18.2 mmol) with the following modifications. The reaction mixture was stirred for 24 h before addition of allyltrimethylsilane and iron trichloride. Purification by flash chromatography [SiO_2; 0-2% EtOAc in hexane] afforded alkene **S38** as a yellow oil (4.19 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.46-3.50 (m, 2H), 3.77 (s, 3H, CH_3), 4.90-5.09 (m, 2H), 5.57-5.67 (m, 1H), 6.55-6.89 (m, 3H), 7.25-7.34 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 44.53, 54.49, 55.61, 102.74 (d, J_{CF} = 27.4 Hz), 108.81, 117.04, 125.90 (d, J_{CF} = 11.8 Hz), 126.19, 127.95, 128.83, 131.51 (d, J_{CF} = 6.3 Hz), 136.33, 146.83, 159.95 (d, J_{CF} = 11.6 Hz), 161.68 (d, J_{CF} = 249.1 Hz). GC-MS (CI, methane) t_R = 17.01 min (*m/z* = 333.1, $[M+H]^+$).

4-(2-Fluoro-4-methoxyphenyl)-4,4-diphenylbutan-1-ol (S39).



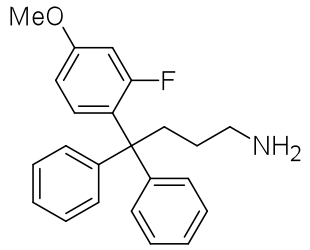
The title compound was prepared using general procedure (iv) with (1-(1,1-diphenylbut-3-en-1-yl)-2-fluoro-4-methoxybenzene **S38** (3.96g, 11.9 mmol) and BH_3·THF (1.0 M in THF, 23.83 mL, 23.8 mmol) in anhydrous THF (29 mL), and subsequently NaOH (1.0 M, 21.0 mL, 21.0 mmol) and hydrogen peroxide (30% in H_2O, 4.20 mL). Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded alcohol **S39** as a yellow oil (2.53 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.30-1.37 (m, 2H, CH_2) 2.67-2.71 (m, 2H, CH_2), 3.60-3.66 (m, 2H, CH_2), 3.77 (s, 3H, CH_3), 6.53-6.61 (m, 2H), 7.02-7.26 (m, 11H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 29.77, 35.85, 54.35, 55.61, 63.36, 102.81 (d, J_{CF} = 27.4 Hz), 109.05, 125.72 (d, J_{CF} = 11.7 Hz), 126.04, 127.96, 128.62, 131.08 (d, J_{CF} = 6.0 Hz), 146.61, 159.85 (d, J_{CF} = 11.3 Hz), 161.74 (d, J_{CF} = 249.7 Hz). GC-MS (CI, methane) t_R = 18.24 min (*m/z* = 379.2, $[M+C_2H_5]^+$).

4-(2-Fluoro-4-methoxyphenyl)-4,4-diphenylbutyl methanesulfonate (S40).



Mesylate **S40** was prepared using general procedure (vi) with 4-(2-fluoro-4-methoxyphenyl)-4,4-diphenylbutan-1-ol **S39** (727 mg, 2.07 mmol) and methanesulphonyl chloride (0.64 mL, 8.28 mmol) in anhydrous pyridine (10 ml). Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded mesylate **S40** as a white oil (349 mg, 39%), which was taken directly to the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.51-1.58 (m, 2H, CH_2) 2.76-2.80 (m, 2H, CH_2), 3.52 (t, 2H, J = 6.4 Hz, CH_2), 3.78 (s, 3H, CH_3), 6.54-6.64 (m, 2H), 7.03-7.30 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 29.54, 37.10 (d, J_{CF} = 2.0 Hz), 45.74, 54.21 (d, J_{CF} = 2.1 Hz), 55.63, 102.89 (d, J_{CF} = 27.2 Hz), 109.13 (d, J_{CF} = 2.4 Hz), 125.46 (d, J_{CF} = 11.7 Hz), 126.16, 128.05, 128.54, 130.96 (d, J_{CF} = 6.3 Hz), 146.31, 159.94 (d, J_{CF} = 11.6 Hz), 161.68 (d, J_{CF} = 249.2 Hz).

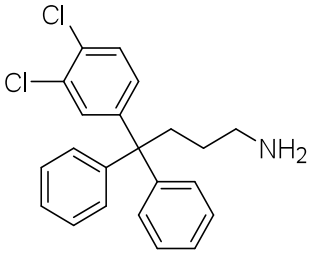
4-(2-Fluoro-4-methoxyphenyl)-4,4-diphenylbutan-1-amine (40).



Intermediate azide **S41** was prepared using general procedure (vii) with mesylate methanesulfonate **S40** (1.746 g, 4.07 mmol) and sodium azide (1.16 g, 17.91 mmol) in anhydrous DMF (20 mL) and irradiation for 15 min. Purification by flash chromatography [SiO_2; 2-30% EtOAc in hexane] afforded 1-(4-azido-1,1-diphenylbutyl)-2-fluoro-4-methoxybenzene **S41** as a white oil (600 mg, 39%) which was taken directly to the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.32-1.40 (m, 2H, CH_2), 2.67-2.73 (m, 2H, CH_2), 3.27 (t, 2H, J = 6.7 Hz, CH_2), 3.78 (s, 3H, CH_3), 6.54-6.65 (m, 2H), 7.00-7.06 (m, 1H), 7.16-7.31 (m, 10H). The title compound was then prepared following general procedure (viii) with azide **S41** (600 mg, 0.54 mmol), 10% Pd/C (600 mg) and $HCOONH_4$ (573 mg, 9.09 mmol) in anhydrous MeOH (20 mL) and a reaction time of 3 h. Purification by flash chromatography

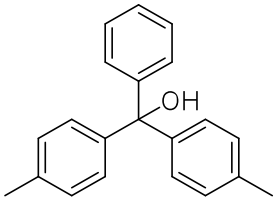
[SiO_2; 3-15% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded amine **40** as a white oil (180 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.20-1.28 (m, 2H, CH_2), 2.60-2.66 (m, 4H), 3.77 (s, 3H, CH_3), 6.57-6.68 (m, 2H), 7.03-7.24 (m, 11H). ^{13}C NMR (100 MHz) δ = 31.08, 38.16 (d, J_{CF} = 2.0 Hz), 43.21, 56.16, 103.66 (d, J_{CF} = 27.6 Hz), 110.03 (d, J_{CF} = 2.3 Hz), 126.92, 127.04, 128.93, 129.76, 132.32 (d, J_{CF} = 6.2 Hz), 148.16, 161.64 (d, J_{CF} = 11.7 Hz), 163.16 (d, J_{CF} = 248.1 Hz). HRMS (ESI+) calcd. for $C_{23}H_{24}FNO$ $(M+H)^+$: 350.1915; found: 350.1910. Anal. calcd. for $C_{23}H_{24}FNO \cdot ½H_2O$: C, 77.07; H, 7.03; N, 3.91; Found: C, 77.16; H, 6.79; N, 3.86.

4-(3,4-Dichlorophenyl)-4,4-diphenylbutan-1-amine (41).



The title compound was prepared following the route described for **24** by the methods described in general procedures (iii), (iv) and (vi-viii). A colorless solid (70 mg) was obtained in an overall yield of 56 %. ^{1}H NMR (400 MHz, MeOD) δ = 1.21-1.24 (m, 2H, CH_2), 2.57-2.63 (m, 4H), 7.15-7.37 (m, 13H). ^{13}C NMR (100 MHz, MeOD) δ = 28.8, 37.2, 41.6, 56.1, 126.1, 127.8, 128.9, 129.0, 129.5, 131.0, 146.3, 148.8. HRMS (ESI+) calcd. for $C_{22}H_{21}NCl_2$ $(M+H)^+$: 370.11238; found: 370.11243. Anal. calcd. for $C_{22}H_{21}NCl_2 \cdot H_2O$: C, 68.04; H, 5.97; N, 3.61. Found: C, 68.36; H, 5.64; N, 3.66.

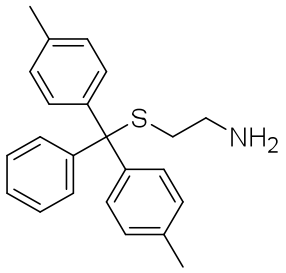
Bis-(4-methylphenyl)(phenyl)methanol (S13).



PhMgCl (2.0 M in THF, 12.5 ml, 25 mmol) was added to a cooled (0 °C) solution of 4,4'-dimethylbenzophenone (2.10 g, 10 mmol) in anhydrous THF (10 mL), and the reaction mixture stirred for 1 h, before allowing the reaction to warm to room temperature and stirring

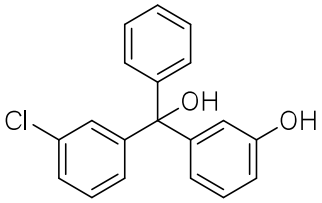
for a further 74 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 25 mL). The organic extracts were washed with successively with H_2O and brine (50 mL each), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-10% EtOAc in pet. ether (60/80)] the trityl alcohol **S13** as a white solid (1.33 g, 46%). Mpt. 70-71 (lit. 75.5-76.4 ^oC).[11] ^1H NMR ($CDCl_3$, 500 MHz) δ 2.35 (s, 6H, 2 x CH_3), 7.10-7.13 (m, 4H), 7.15-7.18 (m, 4H), 7.46-7.33 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.16, 81.90, 127.23, 127.98, 128.74, 136.98, 144.34, 147.31. HRMS (ESI+) calcd. for $C_{21}H_{19}$ $(M\text{-}OH)^+$: 271.1481; found: 271.1479. Anal. calcd. for $C_{21}H_{20}O$: C, 87.46; H, 6.99; Found: C, 87.40; H, 7.06.

2-((Bis(4-methylphenyl)(phenyl)methyl)sulfanyl)ethanamine (44).



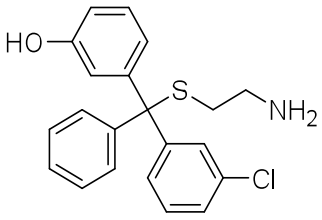
The title compound was prepared using general procedure (ii) with trityl alcohol **S13** (289 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1.0 M) and EtOAc was used for extraction of the aqueous mixture (3 x 10 mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the thioether **44** as a yellow solid (271 mg, 79%). Mpt. 64-67 °C. ^1H NMR (MeOD, 500 MHz) δ 2.30 (s, 6H, 2 x CH_3), 2.32-2.35 (m, 2H, CH_2), 2.41-2.44 (m, 2H, CH_2), 7.07-7.09 (m, 4H), 7.17-7.20 (m, 1H), 7.24-7.27 (m, 5H), 7.38-7.40 (m, 2H). ^{13}C NMR (MeOD, 125 MHz) δ 19.30, 20.05, 36.08, 41.56, 67.55, 127.66, 128.21, 128.79, 130.00, 130.76, 131.94, 136.13, 136.97, 143.71, 146.56. HRMS (ESI+) calcd. for $C_{23}H_{26}NS$ $(M+H)^+$: 348.17805; found: 348.17805. Anal. calcd. for $C_{23}H_{25}NS \cdot ¼H_2O$: C, 78.48; H, 7.30; N, 3.98. Found: C, 78.41; H, 7.49; N, 3.65.

3-((3-Chlorophenyl)(hydroxy)phenylmethyl)phenol (*rac*-S14).



The title compound was prepared using an adaptation of the procedure described by Zhang *et al.*[12] *n*-Butyllithium (2.5 M in hexane, 8.42 mL, 21.05 mmol) was added to a cooled (-78 °C) solution of 1-bromo-3-chlorobenzene (2.11 mL, 18.00 mmol) in anhydrous THF (9 mL). The reaction mixture was stirred for 1 h at -78 °C, treated with a solution of (3-hydroxyphenyl)(phenyl)methanone (1.19 g, 6.00 mmol) in anhydrous THF (6 mL) and stirred for a further 2 h at ≤ -70 °C. The mixture was allowed to warm to room temperature, stirred for 21 h, quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were then washed successively with H_2O and brine (75 mL each), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography [SiO_2; 0-12% EtOAc in petroleum ether (40/60)] afforded trityl alcohol *rac*-**S14** as a white solid (0.73 g, 39%). Mpt 95-96 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.77 (s, 1H, OH), 4.81 (br s, 1H, OH), 6.74-6.75 (m, 1H), 6.77 (ddd, *J* = 0.9, 2.5, 8.0 Hz, 1H), 6.79-6.82 (m, 1H), 7.15-7.27 (m, 5H), 7.30-7.35 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 81.71, 114.71, 115.16, 120.61, 126.33, 127.64, 127.80, 127.96, 128.12, 128.29, 129.29, 129.54, 134.19, 146.15, 148.28, 148.75, 155.46. HRMS (ESI-) calcd. for $C_{19}H_{14}ClO_2$ $(M-H)^-$: 309.06878; found: 309.06894. Anal. calcd. for $C_{19}H_{15}ClO_2$: C, 73.43; H, 4.86. Found: C, 73.55; H, 5.03.

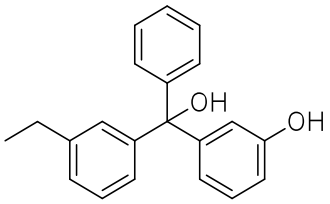
3-(((2-Aminoethyl)thio)(3-chlorophenyl)phenylmethyl)phenol (*rac*-45).



The title compound was prepared following general procedure (ii) with trityl alcohol *rac*-**S14** (311 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1.0 M) and EtOAc was used for extraction (3 x 10mL). Purification by flash chromatography [SiO_2; 0-16% MeOH in CH_2Cl_2 with 1% NH_4OH]

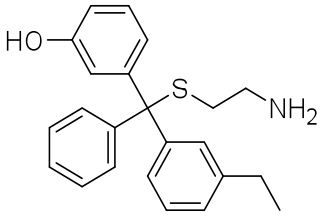
afforded thioether *rac*-**45** as a pale yellow solid (253 mg, 68%). Mpt. 74 °C. ^{1}H NMR (500 MHz, MeOD) δ = 2.36 (t, *J* = 6.9 Hz, 2H, CH_2), 2.48 (t, *J* = 6.9 Hz, 2H, CH_2), 6.67 (ddd, *J* = 0.7, 2.4, 8.1 Hz, 1H), 6.82-6.84 (m, 1H), 6.87-6.88 (m, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.22-7.33 (m, 5H), 7.34-7.36 (m, 1H), 7.39-7.41 (m, 3H). ^{13}C NMR (125 MHz, MeOD) δ = 36.00, 41.48, 67.29, 115.02, 117.08, 121.93, 127.85, 128.05, 129.04, 129.21, 130.00, 130.36, 130.64, 130.70, 134.85, 145.67, 147.04, 148.88, 158.35. HRMS (ESI-) calcd. for $C_{21}H_{19}Cl_2NOS$ $(M-H)^-$: 368.08814; found: 368.08881. Anal. calcd. for $C_{21}H_{20}ClNOS$: C, 68.19; H, 5.45; N, 3.79. Found: C, 68.83; H, 5.45; N, 3.40.

3-((3-Ethylphenyl)(hydroxy)phenylmethyl)phenol (*rac*-S15).



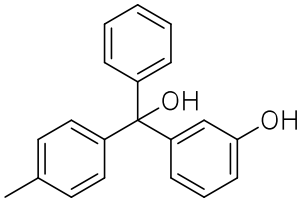
The title compound was prepared using general procedure (i) with 1-bromo-3-ethylbenzene (2.08 ml, 15 mmol) and *n*-butyllithium (2.5 M in hexane, 6.20 mL, 15.6 mmol) in anhydrous THF (15.6 mL), and subsequently (3-hydroxyphenyl)(phenyl)methanone (1.19 g, 6 mmol) in anhydrous THF (6.0 mL) with the following modifications. The reaction was performed at at -84 °C and maintained at the same temperature for 1 h after addition of *n*-butyllithium, and after addition of (3-hydroxyphenyl)(phenyl)methanone for 5 h at ≤ -70 °C. Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded the racemic trityl alcohol **S15** as a yellow oil (1.09 g, 59 %). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.19 (t, *J* = 7.6 Hz, 3H, CH_3), 2.61 (q, *J* = 7.6 Hz, 2H, CH_2), 2.81 (s, 1H, OH), 4.80 (s, 1H, OH), 6.73-6.75 (m, 1H), 6.77-6.78 (m, 1H), 6.81-6.83 (m, 1H), 7.01-7.03 (m, 1H), 7.11-7.13 (m, 1H), 7.16-7.23 (m, 2H), 7.27-7.33 (m, 5H). ^{13}C NMR (MeOD, 125 MHz) δ 15.69, 29.06, 82.09, 114.33, 115.24, 120.76, 125.57, 126.99, 127.42, 127.51, 127.97, 128.05, 129.28, 144.15, 146.72, 146.85, 149.01, 155.30. HRMS (ESI+) calcd. for $C_{21}H_{19}O$ $(M-H-OH)^+$: 287.14304; found: 287.14307. Anal. calcd. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.14; H, 6.69.

3-(((2-Aminoethyl)sulfanyl)(3-ethylphenyl) phenylmethyl)phenol (*rac*-46).



The title compound was prepared following general procedure (ii) with *rac*-**S15** (305 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1.0 M) and EtOAc was used for extraction (3 x 10mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded thioether *rac*-**46** as an off-white solid (186 mg, 51%). Mpt. 50-52 °C. ^{1}H NMR (500 MHz, MeOD) δ = 1.16 (t, *J* = 7.6 Hz, 3H, CH_3), 2.35-2.38 (m, 2H, CH_2), 2.43-2.46 (m, 2H, CH_2), 2.57 (q, *J* = 7.6 Hz, 2H, CH_2), 6.65 (ddd, *J* = 0.8, 2.4, 8.1 Hz, 1H), 6.84-6.86 (m, 1H), 6.90-6.91 (m, 1H), 7.05-7.07 (m, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 7.16-7.21 (m, 3H), 7.26-7.29 (m, 3H), 7.41-7.43 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ = 16.15, 29.93, 36.09, 41.56, 67.80, 118.04, 122.13, 127.21, 127.69, 128.22, 128.78, 129.71, 130.39, 130.82, 144.99, 146.33, 146.47, 147.89, 158.12. HRMS (ESI-) calcd. for $C_{23}H_{24}NOS$ $(M-H)^-$: 362.15841; found: 362.15860 *m/z*. Anal. calcd. for $C_{23}H_{25}NOS \cdot ¼H_2O$: C, 75.06; H, 6.98; N, 3.81. Found: C, 75.04; H, 6.90; N, 3.88.

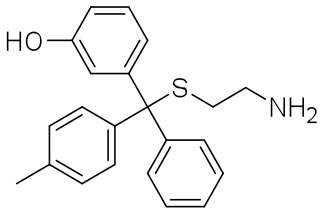
3-(Hydroxy(4-methylphenyl)phenylmethyl)phenol (*rac*-S42).



The title compound was prepared using an adaptation of the procedure for *rac*-**S14** using 1-bromo-4-methylbenzene (3.08 g, 18 mmol) and *n*-butyllithium (2.5 M in hexane, 8.42 mL, 21.6 mmol) in anhydrous THF (9 mL), and subsequently (3-hydroxyphenyl)(phenyl)methanone (1.19 g, 6 mmol) in anhydrous THF (6 mL). Purification by flash chromatography [SiO_2; 0-28% EtOAc in pet. ether (60/80)] afforded the racemic trityl alcohol **S42** as a white solid (0.65 g, 37%). Mpt. 119-122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.35 (s, 3H, CH_3), 2.85 (s, 1H, OH), 5.05 (br s, 1H, OH), 6.73-6.75 (m, 1H), 6.78-6.79 (m, 1H), 6.80-6.82 (m, 1H), 7.11-7.19 (m, 5H), 7.27-7.33 (m, 5H). ^{13}C NMR (125

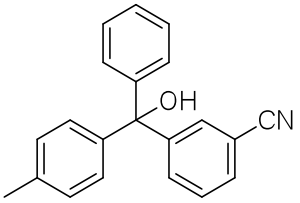
MHz, $CDCl_3$) δ = 21.15, 81.95, 114.34, 115.20, 120.67, 127.40, 127.97, 128.01, 128.04, 128.79, 129.27, 137.18, 143.89, 146.87, 148.97, 155.36. HRMS (ESI-) calcd. for $C_{20}H_{17}O_2$ $(M-H)^-$: 289.12350; found: 289.12340. Anal. calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.09; H, 6.21.

3-(((2-Aminoethyl)sulfanyl)(4-methylphenyl)phenyl methyl)phenol (*rac*-47).



The title compound was prepared following general procedure (ii) with trityl alcohol *rac*-**S42** (290 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL) with the following modifications. Basification of the crude residue (*circa* pH 9) was performed with aqueous NaOH (1.0 M) and EtOAc was used for extraction (3 x 10mL). Purification by flash chromatography [SiO_2; 0-18% MeOH in CH_2Cl_2 with 1% NH_4OH] afforded the racemic thioether **47** as an off-white solid (291 mg, 83%). Mpt. 68 °C. ^{1}H NMR (500 MHz, MeOD) δ = 2.30 (CH_3), 2.34-2.37 (m, 2H, CH_2), 2.44-2.47 (m, 2H, CH_2), 6.63-6.65 (m, 1H), 6.83-6.85 (m, 1H), 6.88-6.89 (m, 1H), 7.06-7.10 (m, 3H), 7.18-7.21 (m, 1H), 7.25-7.29 (m, 4H), 7.39-7.42 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ = 20.93, 36.00, 41.52, 67.51, 114.60, 117.98, 122.09, 127.67, 128.78, 129.41, 129.71, 130.76, 137.55, 143.34, 146.56, 147.99, 158.10. HRMS (ESI+) calcd. for $C_{22}H_{24}NOS$ $(M+H)^+$: 348.14276; found: 348.14307. Anal. calcd. for $C_{22}H_{23}NOS \cdot ¼H_2O$: C, 74.65; H, 6.69; N, 3.96. Found: C, 74.73; H, 6.96; N, 3.73.

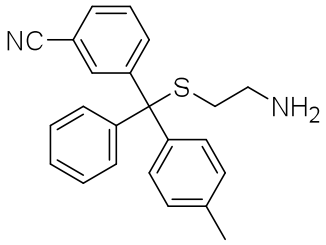
3-(Hydroxy(4-methylphenyl)phenylmethyl)benzonitrile (*rac*-S43).



The title compound was prepared using an adaptation of the reverse addition method developed by Luliński *et al.* and the procedure reported by Neumann *et al.*[13, 14] A solution of

3-bromobenzonitrile (1.18g, 6.50 mmol) in anhydrous THF (6.5 mL) was added by slow dropwise addition over 18 min to a solution of *n*-butyllithium (2.5 M in hexane, 2.73 mL, 6.80 mmol) at -94 °C, and stirred for 1 h whilst maintaining the temperature ≤ -90 °C. After cooling to -94 °C, a solution of (4-methylphenyl)(phenyl)methanone (1.40 g, 7.15 mmol) in anhydrous THF was added by slow dropwise addition over 10 min, and the reaction mixture stirred with the temperature maintained ≤ -75 °C for 5 h. The reaction was allowed to warm to room temperature and stirred for a further 16 h, then with saturated aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed successively with H_2O and brine (50 mL each), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-18% EtOAc in hexane] afforded the trityl alcohol *rac*-**S43** as a colourless oil (1.31 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.36 (s, 3H, CH_3), 2.81 (s, 1H, OH), 7.08-7.11 (m, 2H), 7.13-7.16 (m, 2H), 7.22-7.24 (m, 2H), 7.29-7.36 (m, 3H), 7.39-7.43 (m, 1H), 7.54-7.57 (m, 1H), 7.59-7.61 (m, 1H), 7.64-7.65 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.16, 81.56, 112.13, 119.09, 127.84, 127.88, 127.92, 128.38, 128.41, 128.81, 129.16, 130.94, 131.60, 132.46, 137.84, 143.10, 146.08, 148.60. HRMS (ESI+) calcd. for $C_{21}H_{16}N$ $(M\text{-}OH)^+$: 282.1277; found: 282.1276. Anal. calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N 4.68. Found: C, 82.52; H, 5.33; N, 5.32.

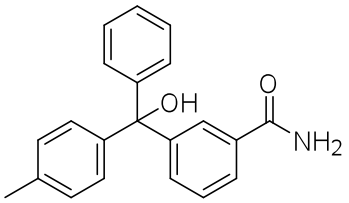
3-(((2-Aminoethyl)sulfanyl)(4-methylphenyl)phenylmethyl)benzonitrile (*rac*-48).



The title compound was prepared following general procedure (ii) with trityl alcohol *rac*-**S43** (299 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-17% MeOH in CH_2Cl_2] afforded thioether *rac*-**48** as an off-white solid (254 mg, 71%). Mpt. 46-48 °C. ^{1}H NMR (500 MHz, MeOD) δ = 2.33 (s, 3H, CH_3), 2.48-2.52 (m, 2H, CH_2), 2.54-2.58 (m, 2H, CH_2), 7.16-7.19 (m, 2H), 7.26-7.30 (m, 3H), 7.33-7.37 (m, 2H), 7.40-7.43 (m, 2H), 7.48-7.52 (m, 1H), 7.61-7.64 (m, 1H), 7.74-7.79 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ = 20.93, 31.44, 39.98, 67.46, 113.30, 119.50, 128.52, 129.45, 130.07, 130.39, 130.52, 131.83, 133.64, 135.36,

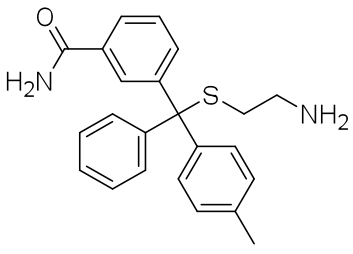
138.64, 141.68, 144.89, 147.98. HRMS (ESI+) calcd. for $C_{23}H_{23}N_2S_2$ $(M+H)^+$: 359.1587; found: 359.1574. Anal. calcd. for $C_{23}H_{22}N_2S{\cdot}CH_2Cl_2$: C, 65.01; H, 5.46; N, 6.32. Found: C, 64.57; H, 5.06; N, 5.99.

3-(Hydroxy(4-methylphenyl)phenylmethyl)benzamide (*rac*-S44).



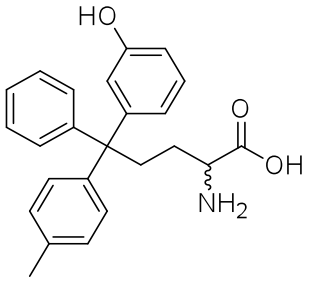
This hydrolysis protocol is a modification of the literature procedure reported by Iso *et al.*[15] Hydrogen peroxide (30% in H_2O, 409 µl, 4.01 mmol) and aqueous NaOH (6.0 M, 400 µL, 2.4 mmol) were added to a solution of nitrile **S43** (400 mg, 1.34 mmol) in EtOH (10mL) and stirred at 60°C for 4 h. After cooling to room temperature, the reaction mixture was partitioned between CH_2Cl_2 (50 mL) and aqueous HCl (0.25 M, 25mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL), and the combined organic layers washed successively with saturated aqueous $NaHCO_3$, H_2O and brine (75 mL each), dried ($MgSO_4$) and concentrated *in vacuo*. Purification [SiO_2; 0-27% MeOH in CH_2Cl_2] afforded amide *rac*-**S44** as a white solid (262 mg, 62%). Mpt. 77-80 °C. ^{1}H NMR (500 MHz, MeOD) δ = 2.32 (s, 3H, CH_3), 4.57 (s, 1H, OH), 7.09-7.12 (m, 4H), 7.22-7.31 (m, 5H), 7.34-7.42 (m, 2H), 7.72-7.75 (m, 1H), 7.86-7.88 (m, 1H), 7.61-7.64 (m, 1H), 7.74-7.79 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ = 21.02, 82.61, 127.01, 128.10, 128.42, 128.75, 129.22, 129.38, 129.41, 132.77, 134.50, 137.95, 145.50, 148.56, 149.74, 172.57. HRMS (ESI+) calcd. for $C_{21}H_{18}NO$ $(M-OH)^+$: 300.1383; found: 300.1380. Anal. calcd. for $C_{21}H_{19}NO_2{\cdot}⅓H_2O$: C, 78.01; H, 6.13; N 4.33. Found: C, 77.70; H, 5.90; N, 4.21.

3-(((Aminomethyl)sulfanyl)(4-methylphenyl)phenylmethyl)benzamide (*rac*-49).



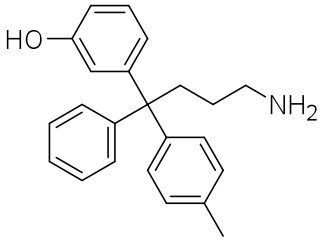
The title compound was prepared following general procedure (iii) with trityl alcohol *rac*-**S44** (224 mg, 0.71 mmol) and cysteamine hydrochloride (88 mg, 0.77 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2] afforded thioether *rac*-**49** as a white solid (254 mg, 71%). Mpt. 95-97 °C. ^{1}H NMR (400 MHz, MeOD) δ = 2.32 (s, 3H, CH_3), 2.47-2.55 (m, 4H, 2 x CH_2), 7.12-7.17 (m, 2H), 7.22-7.35 (m, 5H), 7.37-7.45 (m, 3H), 7.55-7.58 (m, 1H), 7.72-7.76 (m, 1H), 8.07-8.10 (m, 1H). ^{13}C NMR (400 MHz, MeOD) δ = 20.94, 31.97, 40.19, 67.85, 126.86, 128.16, 129.22, 129.25, 129.85, 130.62, 134.26, 134.87, 138.17, 142.43, 145.63, 146.84, 172.14. HRMS (ESI+) calcd. for $C_{23}H_{25}N_2OS_2$ $(M+H)^+$: 377.1682; found: 377.1678. Anal. calcd. for $C_{23}H_{24}N_2OS{\cdot}CH_2Cl_2$: C, 62.47; H, 5.68; N, 6.07. Found: C, 61.92; H, 5.01; N, 5.23.

2-Amino-5-(4-methylphenyl)-5-(3-hydroxyphenyl)-5-phenylpentanoic acid (*dia*-50).



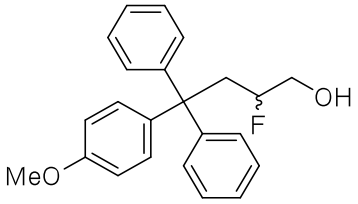
The title compound was prepared following the route described for *rac*-**42** by the methods and procedures described in general procedures (iii-v). A pale yellow solid (77 mg) was obtained with an overall yield of 20%. Mpt. 176 °C. ^{1}H NMR (400 MHz, MeOD) δ = 1.58-1.64 (m, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.63-2.81 (m, 2H, CH_2), 3.48-3.51 (m, 1H, CH), 6.57-6.60 (m, 1H), 6.70-6.76 (m, 1H), 7.04-7.30 (m, 11H). ^{13}C NMR (100 MHz, MeOD) δ = 19.6, 27.7, 35.5, 55.1, 55.7, 112.5, 116.2, 120.4, 125.6, 127.5, 128.1, 128.4, 129.0, 135.2, 144.0, 147.3, 148.7, 156.7, 173.0. HRMS (ESI+) calcd. for $C_{24}H_{25}NO_3$ $(M+H)^+$: 376.19072; found: 376.19064. Anal. Calcd. for $C_{24}H_{25}NO_3{\cdot}⅓CH_2Cl_2$: C, 72.42; H, 6.41; N, 3.47. Found: C, 72.04; H, 6.71; N, 3.17.

3-(4-Amino-1-(4-methylphenyl)-1-phenylbutyl)phenol (*rac*-51).



The title compound was prepared following the route described for **24** by the methods described in general procedures (iii), (iv) and (vi-viii). A white solid (73 mg) was obtained with an overall yield of 25%. ^{1}H NMR (400MHz, MeOD) δ = 1.26-1.28 (m, 2H, CH_2), 2.27 (s, 3H, CH_3), 2.52-2.56 (m, 2H, CH_2), 2.60-2.64 (m, 2H, CH_2), 6.56-6.59 (m, 1H), 6.69-6.73 (m, 1H), 7.02-7.28 (m, 11H). ^{13}C NMR (100MHz, MeOD) δ = 19.5, 28.8, 37.5, 41.7, 55.9, 112.4, 116.4, 120.2, 125.4, 127.4, 128.0, 128.3, 128.9, 129.0, 135.1, 144.4, 147.7, 149.2, 156.7. HRMS (ESI-) calcd. for $C_{23}H_{25}NO(M-H)^-$: 330.18634; found: 330.18665. Anal. calcd for $C_{23}H_{25}NO{\cdot}H_2O$: C, 79.05; H, 7.79; N, 4.01. Found: C, 78.60; H, 7.38; N, 3.83.

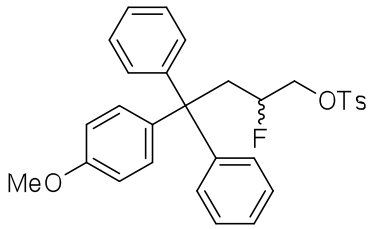
2-Fluoro-4-(4-methoxyphenyl)-4,4-diphenylbutan-1-ol (*rac*-67).



The title compound was prepared by adaptation of the method reported by Beeson *et al.*[16] THF (12.06 mL) and *i*-PrOH (1.34 mL) was added to a flask containing L-proline (62 mg, 0.54 mmol) and *N*-fluorobenzenesulfonimide (2.119 g, 6.72 mmol) and stirred until homogeneous. The mixture was cooled to -10 °C, aldehyde **66** (889 mg, 2.69 mmol) added and stirred for 2 h at ≤ -7.5 °C, before allowing the reaction to warm to room temperature and stirring for a further 21 h. The reaction mixture was cooled to -78 °C, diluted with Et_2O (15 mL) and filtered through a thin pad of silica, eluting with Et_2O. Me_2S (2.5 mL, 34.00 mmol) was added to the filtrate, resulting in formation of a white precipitate. This suspension was washed successively with saturated aqueous $NaHCO_3$ solution (3 x 50 mL) and brine (50 mL), dried (MgSO4), and concentrated *in vacuo*. The residual oil was dissolved in CH_2Cl_2 (15 mL) and EtOH (10 mL), cooled (0 °C), and sodium borohydride added (255 mg, 6.73 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for 4 h. After cooling (0 °C), the reaction mixture was quenched cautiously with saturated

aqueous NH_4Cl solution (100 mL), stirred for 10 min, then extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution (2 x 150 mL) and brine (150 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude residue by flash chromatography [SiO_2; 0-35% EtOAc in hexane] afforded the β-fluorinated alcohol *rac*-**67** as a colourless oil (638 mg, 68%). The β,β-difluorinated alcohol **68** was also obtained as a minor product (165 mg, 17%, *vide infra* for characterisation). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.62-1.66 (m, 1H), 2.55-2.66 (m, 1H), 3.02-3.34 (m, 3H), 3.78 (s, 3H, CH_3), 4.39-4.57 (m, 1H), 6.78-6.83 (m, 2H), 7.16-7.32 (m, 12H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -180.84. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 41.96 (d, J_{CF} = 21.4 Hz), 55.11 (d, J_{CF} = 3.5 Hz), 55.32, 65.54 (d, J_{CF} = 22.4 Hz), 93.06 (d, J_{CF} = 167.4 Hz), 113.48, 126.35, 128.20, 129.06 (d, J_{CF} = 2.2 Hz), 130.24, 138.59, 146.97, 157.90. GC-MS (CI, methane) t_R = 20.20 min (*m/z* = 379.1, $[M+C_2H_5]^+$). Anal. calcd. for $C_{23}H_{23}FO_2$: C, 78.83; H, 6.62. Found: C, 78.15; H, 6.18.

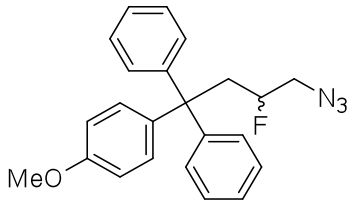
2-Fluoro-4-(4-methoxyphenyl)-4,4-diphenylbutyl-4-methylbenzenesulfonate (*rac*-S45).



The title compound was prepared by an adaptation of the procedure reported by Moussa *et al*.[17] Tosyl chloride (220 mg, 1.73 mmol) and anhydrous pyridine (93 μL, 1.73 mmol) were added to a cooled (0 °C) solution of β-fluorinated alcohol *rac*-**67** in CH_2Cl_2 (4.6 mL) and stirred at room temperature for 3 h. The reaction was quenched with H_2O (5 mL) and saturated aqueous NH_4Cl solution (2.5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude residue by flash chromatography [SiO_2; 0-30% EtOAc in hexane] afforded toyslate *rac*-**S45** as a colourless opaque oil [307 mg, 93% (based on 57% conversion)] and unreacted starting material *rac*-**67** (175 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.45 (s, 3H, CH_3), 2.49-2.61 (m, 1H), 3.22-3.36 (m, 1H), 3.42-3.59 (m, 2H), 3.78 (s, 3H, CH_3), 4.41-4.59 (m, 1H), 6.76-6.82 (m, 2H), 7.10-7.34 (m, 14H), 7.66-7.72 (m, 2H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -177.46. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.80, 41.80 (d, J_{CF} = 21.7 Hz), 54.97 (d, J_{CF} = 3.7 Hz), 55.33, 71.14 (d, J_{CF} = 23.0 Hz), 88.92 (d, J_{CF} = 175.2 Hz), 113.61, 126.48,

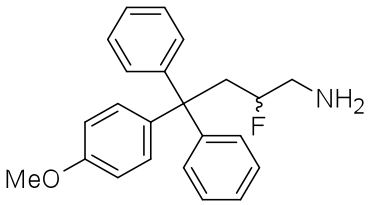
128.08, 128.30, 128.88 (d, J_{CF} = 3.7 Hz), 129.94, 130.08, 132.76, 138.03, 145.04, 146.47, 158.00. GC-MS (CI, methane) t_R = 26.95 min (*m/z* = 503.8, M^-).

1-(4-Azido-3-fluoro-1,1-diphenylbutyl)-4-methoxybenzene (*rac*-S46).



The title compound was prepared by an adaptation of the procedure reported by Jiang *et al.*[18] A solution of tosylate *rac*-**S45** (280 mg, 0.56 mmol) and sodium azide (91 mg, 1.40 mmol) in anhydrous DMSO (2.5 mL) was stirred at 40 °C for 18 h. The reaction mixture was diluted with brine (5 mL), extracted with Et_2O (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-15% EtOAc in hexane] afforded the racemic azide **S46** as a colourless oil, which was used directly in the next step (146 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.53-2.82 (m, 3H), 3.34-3.47 (m, 1H), 3.79 (s, 3H, CH_3), 4.46-4.64 (m, 1H), 6.80-6.85 (m, 2H), 7.16-7.24 (m, 4H), 7.25-7.33 (m, 8H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -174.12. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 42.98 (d, J_{CF} = 21.7 Hz), 54.96 (d, J_{CF} = 21.7 Hz), 55.04, 55.35, 91.46 (d, J_{CF} = 172.2 Hz), 113.62, 126.51 (d, J_{CF} = 2.5 Hz), 128.34 (d, J_{CF} = 4.5 Hz), 128.95, 130.15, 138.23, 146.64, 158.01.

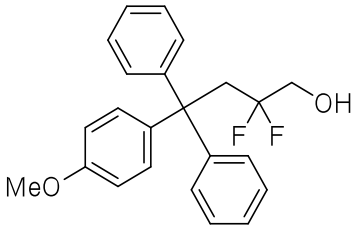
2-Fluoro-4-(4-methoxyphenyl)-4,4-diphenylbutan-1-amine (*rac*-52).



The title compound was prepared using general procedure (viii) with azide *rac*-**S46** (130 mg, 0.35 mmol), 10% Pd/C (142 mg) and $HCOONH_4$ (110 mg, 1.74 mmol) in anhydrous MeOH (3.5 mL). Purification by flash chromatography [SiO_2; 0-20% MeOH in CH_2Cl_2] afforded amine *rac*-**52** as a colourless oil (79 mg, 65%). ^{1}H (400 MHz, $CDCl_3$) δ = 2.09-2.19 (m, 1H), 2.46-2.62 (m, 2H), 3.32-3.35 (m, 1H), 3.76 (s, 3H, CH_3), 4.27-4.42 (m, 1H), 6.80-6.84 (m, 2H), 7.14-7.33 (m, 12H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -180.78. ^{13}C NMR (125 MHz,

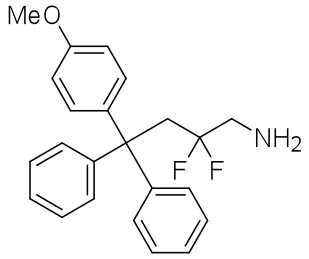
$CDCl_3$) δ = 43.24 (d, J_{CF} = 21.7 Hz), 45.98 (d, J_{CF} = 22.2 Hz), 54.26, 55.00 (d, J_{CF} = 3.2 Hz), 92.99 (d, J_{CF} = 167.7 Hz), 112.88, 125.75, 127.57, 128.80, 130.00, 138.60, 147.07, 147.19, 157.98. HRMS (ESI+) calcd. for $C_{23}H_{25}NOF = (M+H)^+$: 350.1915; found 350.1914. LC-MS t_R = 12.92 min (*m/z* = 350.2, $[M+H]^+$; purity = 100%).

2,2-Difluoro-4-(4-methoxyphenyl)-4,4-diphenylbutan-1-ol (68).



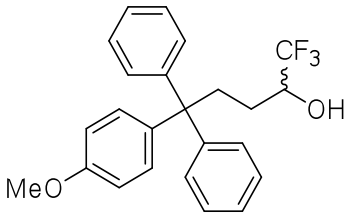
The title compound was prepared using an adaptation of the procedure reported by Enders *et al.*[19] Selectfluor® (0.72 g, 2.05 mmol) was added in one portion to a cooled (0 °C) solution of **66** (435 mg, 1.35 mmol) and L-proline (47 mg, 0.41 mmol) in CH_3CN (5 mL), followed by trifluoroacetic acid (31 μL, 0.41 mmol) added and the reaction mixture stirred for 16 h at room temperature. Methanol (3 mL) and $NaBH_4$ (102 mg, 2.7 mmol) were then added and the reaction mixture stirred at room temperature for 16 h. The volatiles were removed under reduced pressure, and the residue purified by flash chromatography [SiO_2; 0-25% EtOAc in hexane] to afford β, β-difluorinated alcohol **68** as a colourless oil (300 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.76 (t, *J* = 7.0 Hz, 1H), 2.98-3.07 (m, 2H), 3.41 (t, *J* = 16.1 Hz, 2H, CH_2), 3.78 (s, 3H, CH_3), 6.78-6.83 (m, 2H), 7.16-7.21 (m, 2H), 7.24-7.30 (m, 6H), 7.35-7.39 (m, 4H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -98.71. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 42.49 (t, J_{CF} = 22.9 Hz), 54.13, 55.30, 65.03 (t, J_{CF} = 32.0 Hz), 113.16, 122.90 (t, J_{CF} = 243.0 Hz), 126.26, 127.91, 129.16, 130.46, 138.48, 146.88, 157.85. GC-MS (CI, methane) t_R = 20.00 min (*m/z* = 397.1, $[M+C_2H_5]^+$). Anal. calcd. for $C_{23}H_{22}F_2O_2$: C, 74.98; H, 6.02. Found: C, 74.37; H, 6.65.

2,2-Difluoro-4-(4-methoxyphenyl)-4,4-diphenylbutan-1-amine (53).



1-(4-Azido-3,3-difluoro-1,1-diphenylbutyl)-4-methoxybenzene **69** was prepared using general procedure (vii) with primary alcohol **68** (220 mg, 0.60 mmol) and sodium azide (157 mg, 2.42 mmol) in anhydrous DMF (2 mL) and irradiation for 12 min. Purification by flash chromatography [SiO_2; 0-12% EtOAc in hexane] afforded the intermediate azide **69** as a pale yellow oil (195 mg, 83%), which was taken directly to the next step. The title compound was prepared using an adaptation of the procedure reported by Dockendorff *et al.*[10] Triphenylphosphine (410 mg, 1.56 mmol) was added to a solution of azide **69** (120 mg, 0.31 mmol) in THF:H_2O (10:1, 6.6 mL). The reaction mixture was stirred at 60 °C for 12 h and then concentrated *in vacuo*. The crude product was purified by flash chromatography [SiO_2; 0-7% MeOH in CH_2Cl_2 with 0.5% NH_4OH] to afford the title compound **53** as a colorless oil (82 mg, 73%). ^{1}H NMR (400 MHz, MeOD): 2.20-2.28 (m, 2H, CH_2), 3.30-3.39 (m, 2H, CH_2), 3.75 (s, 3H, CH_3), 6.78-7.37 (m, 14H). ^{13}C NMR (100 MHz, MeOD) δ = 44.61 (t, J_{CF} = 23.5 Hz), 55.45, 55.64, 113.95, 124.66 (t, J_{CF} = 243.0 Hz), 127.01, 128.66, 130.30, 131.64, 139.92, 148.48, 159.30. ^{19}F NMR (376.5 MHz, MeOD): -98.21. HRMS (ESI+): calcd. for $C_{23}H_{23}NOF_2$ $(M+H)^+$ 368.18205; found: 368.18195. Anal. calcd. for $C_{23}H_{23}F_2NO \cdot \frac{1}{3}CH_2Cl_2$: C, 70.86; H, 6.03; N, 3.54. Found: C, 70.65; H, 5.75; N, 3.28.

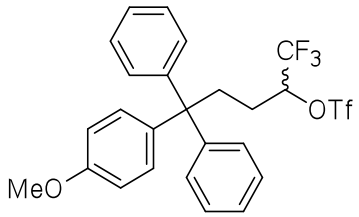
1,1,1-Trifluoro-5-(4-methoxyphenyl)-5,5-diphenylpentan-2-ol (*rac*-70).



The title compound was prepared by an adaptation of the procedure reported by Crich *et al.*[20] TBAF (1.0 M in THF, 0.74 mL, 0.74 mmol) was added to a cooled (0 °C) solution of aldehyde **66** (2.46 g, 7.45 mmol) and trimethyl(trifluoromethyl)silane solution (2.0 M in THF, 7.40 mL, 14.80 mmol) in THF (30 mL), and the reaction mixture stirred at room temperature for 18 h. TBAF (1.0 M in THF, 2.00 mL, 2.00 mmol) was then added, and the

reaction stirred for a further 4.5 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were then washed with brine (80 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-15% EtOAc in hexane] afforded *rac*-**70** as a colourless oil (2.29 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.46-1.53 (m, 2H, CH_2), 2.19-2.24 (m, 1H), 2.50-2.59 (m, 1H), 2.97-3.05 (m, 1H), 3.77-3.85 (m, 4H), 6.80-6.84 (m, 2H), 7.16-7.22 (m, 4H), 7.25-7.31 (m, 8H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -79.75. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 26.23, 35.76, 55.32, 55.72, 71.13 (q, J_{CF} = 30.8 Hz), 113.44, 125.15 (q, J_{CF} = 281.5 Hz), 126.14, 128.11, 129.14, 130.27, 138.97, 147.22, 147.26, 157.78. GC-MS (CI, methane) t_R = 17.62 min (*m/z* = 429.2, $[M+C_2H_5]^+$). Anal. calcd. for $C_{24}H_{23}F_3O_2$: C, 71.99; H, 5.79. Found: C, 72.39; H, 5.57.

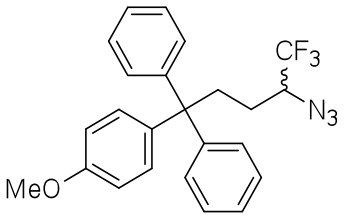
1,1,1-Trifluoro-5-(4-methoxyphenyl)-5,5-diphenylpentan-2-yl trifluoromethanesulfonate (*rac*-S47).



The title compound was prepared by an adaptation of the procedure reported by Jiang *et al.*[18] Trimethylsulphonic anhydride (1.0 M in CH_2Cl_2, 2.43 mL, 2.43 mmol) was added by slow dropwise addition over 15 min to a cooled (-50 °C) solution of alcohol *rac*-**70** (810 mg, 2.02 mmol) and anhydrous pyridine (327 µL, 4.05 mmol) in CH_2Cl_2. The reaction was stirred for 1 h at -50 °C and 1.5 h at ≤ -35 °C before allowing to warm to room temperature and quenching with with brine (15 mL). The aqueous layers were extracted with CH_2Cl_2 (2 x 10 mL), and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded triflate *rac*-**S47** as a colourless oil (834 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.70-1.89 (m, 2H, m, CH_2), 2.59-2.68 (m, 1H), 2.84-2.93 (m, 1H), 3.80 (s, 3H, CH_3), 4.88-4.97 (m, 1H, CH), 6.82-6.86 (m, 2H), 7.14-7.33 (m, 12H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -74.03 (q, *J* = 3.1 Hz), -76.20 (q, *J* = 3.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.40, 34.59, 55.36, 55.50, 82.46 (q, J_{CF} = 34.3 Hz), 113.69, 118.49 (q, J_{CF} = 318.4 Hz), 122.07 (q, J_{CF} = 281.4 Hz), 126.48, 128.37, 128.44, 128.87, 130.03, 138.10, 146.40, 146.43, 158.02. GC-MS (CI,

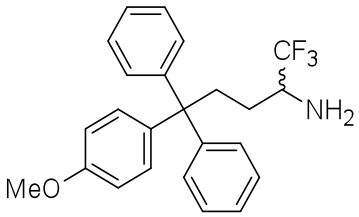
methane) t_R = 16.96 min (*m/z* = 561.2, $[M+C_2H_5]^+$). Anal. calcd. for $C_{25}H_{22}F_6O_4S$: C, 56.39; H, 4.16. Found: C, 56.30; H, 3.97.

1,1,1-Trifluoro-5-(4-methoxyphenyl)-5,5-diphenylpentan-2-yl azide (*rac*-S48).



The title compound was prepared by an adaptation of the procedure reported by Jiang *et al.*[18] A solution of intermediate triflate **S47** (239 mg, 0.45 mmol) and sodium azide (80 mg, 1.23 mmol) in anhydrous DMSO (1.8 mL) was stirred at 40 °C for 18 h. The reaction mixture was diluted with brine (5 mL), extracted with Et_2O (3 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded the azide *rac*-**S48** as a colourless oil (144 mg, 75%), which was used directly in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.47-1.55 (m, 2H), 2.49-2.58 (m, 1H), 2.94-3.03 (m, 1H), 3.42-3.51 (m, 1H), 3.81 (s, 3H, CH_3), 6.82-6.87 (m, 2H), 7.17-7.24 (m, 4H), 7.27-7.32 (m, 8H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -74.96. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.32, 36.19, 55.35, 55.74, 62.82 (q, J_{CF} = 29.8 Hz), 113.56, 124.94 (q, J_{CF} = 282.3 Hz), 126.31, 128.24, 129.05, 130.18, 138.60, 146.90, 146.95, 157.91.

1,1,1-Trifluoro-5-(4-methoxyphenyl)-5,5-diphenylpentan-2-amine (*rac*-54).

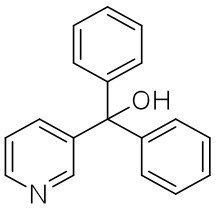


The title compound was prepared using general procedure (vii) with 1,1,1-trifluoro-5-(4-methoxyphenyl)-5,5-diphenylpentan-2-yl azide **S48** (142 mg, 0.33 mmol), 10% Pd/C (142 mg) and $HCOONH_4$ (105 mg, 1.67 mmol) in anhydrous MeOH (3.5 mL). Purification by flash chromatography [SiO_2; 0-40% EtOAc in hexane] afforded the α-trifluoromethyl amine *rac*-**54** as a colourless oil (121 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.14-1.24 (m, 1H), 1.29-1.37 (br s, 2H, NH_2), 1.47-1.55 (m, 1H), 2.51-2.59 (m, 1H), 2.95-3.04 (m, 2H),

3.79 (s, 3H, CH_3), 6.79-6.83 (m, 2H), 7.16-7.21 (m, 4H), 7.24-7.30 (m, 8H). ^{19}F NMR (376.5 MHz, $CDCl_3$) δ = -78.87. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 26.30, 36.81, 54.66 (q, J_{CF} = 29.3 Hz) 55.33, 55.85, 113.39, 126.09, 126.78 (q, J_{CF} = 282.3 Hz), 128.07, 129.17, 130.30, 139.11, 147.36, 147.39, 157.75. GC-MS (CI, methane) t_R = 17.55 min (*m/z* = 400.2, $[M+H]^+$). Anal. calcd. for $C_{24}H_{24}F_3NO$: C, 72.16; H, 6.06; N, 3.51. Found: C, 72.75; H, 6.28; N, 3.10.

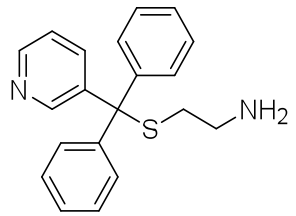
c.) Synthesis and characterization of supplementary compounds

Diphenyl(pyridin-3-yl)methanol (S49).



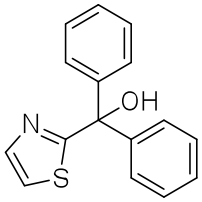
n-Butyllithium (2.5 M in hexane, 3.96 mL, 9.96 mmol) was added by slow dropwise addition over 8 min to a cooled (-94 °C) solution of 3-bromopyridine (722 μL, 7.5 mmol) in anhydrous THF (15 mL) stirred for 1 h at ≤ -70 °C. A solution of benzophenone (1.50 g, 8.25 mmol) in anhydrous THF (8.25 mL) was then added by slow dropwise addition over 10 min, and the reaction mixture stirred with the temperature maintained ≤ -85 °C for 3 h, before allowing the reaction to warm slowly to room temperature and stirring for a further 15 h. The reaction was quenched with aqueous HCl (1.0 M, 15 mL) and washed with Et_2O (50 mL). The organic washings were extracted with aqueous HCl (1.0 M, 3 x 20 mL), and the combined aqueous layers basified (*circa.* pH 9) with saturated aqueous sodium carbonate solution, and extracted with Et_2O (3 x 100 mL). These organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 20-60% EtOAc in hexane] afforded the tertiary alcohol **S49** as a white solid (565 mg, 29%). Mpt. 105-107 °C (lit. 115-116 °C from EtOAc).[21] ^1H NMR (400 MHz, $CDCl_3$) δ = 3.62 (br s, 1H, OH), 7.17-7.35 (m, 11H), 7.62-7.66 (m, 1H), 8.39-8.48 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 80.79, 122.89, 127.77, 127.94, 128.33, 135.62, 142.56, 146.20, 148.27, 149.47. HRMS (ESI+) calcd. for $C_{18}H_{16}NO$ $(M+H)^+$: 262.1226; found: 262.1224. Anal. calcd. for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.54; H, 5.47; N, 5.12.

2-((Diphenyl(pyridin-3-yl)methyl)sulfanyl)ethanamine (S1).



The title compound was prepared following general procedure (ii) with trityl alcohol **S49** (274 mg, 1.05 mmol) and cysteamine hydrochloride (131 mg, 1.15 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2] afforded thioether **S1** as a yellow oil (187 mg, 59%). ^{1}H NMR (400 MHz, MeOD) δ = 2.35-2.40 (m, 2H, CH_2), 2.45-2.50 (m, 2H, CH_2), 7.25-7.30 (m, 2H), 7.32-7.37 (m, 4H), 7.38-7.44 (m, 5H), 7.92 (ddd, *J* = 1.6, 2.5, 8.2 Hz, 1H), 8.40-8.42 (m, 1H), 8.56 (dd, *J* = 0.7, 2.5 Hz, 1H). ^{13}C NMR (400 MHz, MeOD) δ = 35.36, 41.31, 65.73, 124.58, 128.39, 129.38, 130.52, 139.18, 143.04, 145.05, 148.15, 151.05. HRMS (ESI+) calcd. for $C_{20}H_{21}N_2S$ $(M+H)^+$: 321.1431; found: 321.1424. Anal. calcd. for $C_{20}H_{20}N_2S \cdot \frac{1}{3}CH_2Cl_2$: C, 70.07; H, 5.98; N, 8.04. Found: C, 70.14; H, 5.88; N, 7.75.

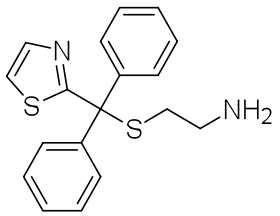
Diphenyl(1,3-thiazol-2-yl)methanol (S50).



The title compound was prepared using general procedure (ii) with 2-bromo-1,3-thiazole (676 μL, 7.50 mmol) and *n*-butyllithium (2.5 M in hexane, 3.15 mL, 7.88 mmol) in anhydrous THF (30 mL), and subsequently benzophenone (1.05 g, 5.75 mmol) in anhydrous THF (5.75 mL) with the following modifications. The reaction was maintained at ≤ -70 °C for 1 h after addition of *n*-butyllithium, and for 2 h after the addition of benzophenone. Purification by flash chromatography [SiO_2; 0-20% EtOAc in hexane] afforded trityl alcohol **S50** as a pale brown solid (825 mg, 41%). Mpt. 107-108 °C (lit. 114-115 °C from pet. ether).[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.20 (s, 1H, OH), 7.29-7.37 (m, 6H), 7.38-7.44 (m, 4H), 7.81 (d, *J* = 3.3 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 80.84, 120.19, 127.58, 128.12, 128.28, 142.81, 145.46, 177.39. HRMS (ESI+) calcd. for $C_{16}H_{12}NS$ $(M-OH)^+$:

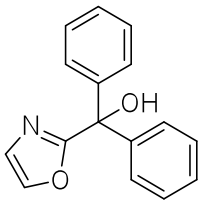
250.0685; found: 250.0683. Anal. calcd. for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 70.85; H, 4.48; N, 5.06.

2-((Diphenyl(1,3-thiazol-2-yl)methyl)sulfanyl)ethanamine (S4).



The title compound was prepared following general procedure (ii) with trityl alcohol **S50** (267 mg, 1.0 mmol) and cysteamine hydrochloride (125 mg, 1.1 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2] afforded thioether **S4** as a brown solid (98 mg, 30%). Mpt 59-61 °C. ^{1}H NMR (400 MHz, MeOD) δ = 2.62-2.66 (m, 2H, CH_2), 2.73-2.77 (m, 2H, CH_2), 7.31-7.40 (m, 6H), 7.39-7.43 (m, 4H), 7.54 (d, *J* = 3.4 Hz, 1H), 7.83 (d, *J* = 3.4 Hz, 1H). ^{13}C NMR (400 MHz, MeOD) δ = 33.99, 40.87, 65.08, 122.16, 128.98, 129.25, 130.46, 143.81, 144.82, 178.61. HRMS (ESI+) calcd. for $C_{18}H_{19}N_2S_2$ $(M+H)^+$: 327.0984; found: 327.0981. Anal. calcd. for $C_{18}H_{18}N_2S_2 \cdot ½CH_2Cl_2$: C, 60.23; H, 5.19; N, 7.59. Found: C, 60.70; H, 4.75; N, 7.63.

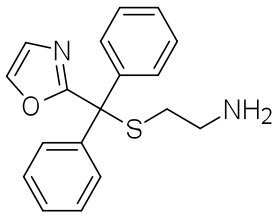
(1,3-Oxazol-2-yl(diphenyl)methanol (S51).



n-Butyllithium (2.5 M in hexane, 3.96 mL, 9.96 mmol) was added by slow dropwise addition over 15 min to a cooled (-94 °C) solution of oxazole (0.59 mL, 9 mmol) in anhydrous THF (25 mL) stirred for 30 min. A solution of benzophenone (1.37 g, 7.50 mmol) in anhydrous THF (7.5 mL) was then added by slow dropwise addition, and the reaction mixture stirred with the temperature maintained ≤ -85 °C for 1.5 h, before allowing the reaction to warm slowly to room temperature and stirring for a further 16 h. The reaction was quenched with saturated aqueous NH_4Cl solution (15 mL) and extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with aqueous HCl (1.0 M, 3 x 10 mL), dried ($MgSO_4$)

and concentrated *in vacuo*. Purification by flash chromatography [SiO_2; 0-15% EtOAc in hexane] afforded tertiary alcohol **S51** as a white solid (507 mg, 27%). Mpt. 97.5-98.5 °C (lit. 100-102 °C).[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.59 (br s, 1H, OH), 7.05 (d, *J* = 0.8 Hz, 1H). 7.31-7.36 (m, 10H), 7.65 (d, *J* = 0.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 78.43, 126.91, 127.32, 128.19, 128.28, 139.78, 143.67, 166.94. HRMS (ESI+) calcd. for $C_{16}H_{12}NO$ $(M+H)^+$: 234.0913; found: 234.0909. Anal. calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N 5.57. Found: C, 76.64; H, 4.95; N, 5.34.

2-((1,3-Oxazol-2-yl(diphenyl)methyl)sulfanyl)ethanamine (S5).

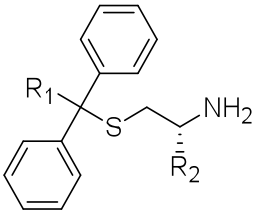


The title compound was prepared following general procedure (ii) with (1,3-oxazol-2-yl(diphenyl)methanol **S51** (201 mg, 0.8 mmol) and cysteamine hydrochloride (100 mg, 0.88 mmol) in trifluoroacetic acid (1 mL). Purification by flash chromatography [SiO_2; 0-25% MeOH in CH_2Cl_2] afforded thioether **S5** as an orange solid (55 mg, 27%). Mpt. 59-61 °C. ^{1}H NMR (400 MHz, MeOD) δ = 2.62-2.70 (m, 4H, 2 x CH_2), 7.21 (d, *J* = 0.7 Hz, 1H), 7.91 (d, *J* = 0.7 Hz, 1H), 7.28-7.37 (m, 10H). ^{13}C NMR (400 MHz, MeOD) δ = 34.40, 40.95, 62.24, 127.76, 129.00, 129.34, 130.05, 141.38, 142.55, 167.68. HRMS (ESI+) calcd. for $C_{18}H_{19}N_2OS$ $(M+H)^+$: 311.1213; found: 311.1210. Anal. calcd. for $C_{18}H_{18}N_2OS \cdot ½CH_2Cl_2$: C, 62.97; H, 5.43; N, 7.94. Found: C, 62.65; H, 4.79; N, 8.04.

2. Supplementary Results

Supplementary Tables

Table S1: Analogues with phenyl ring replacements

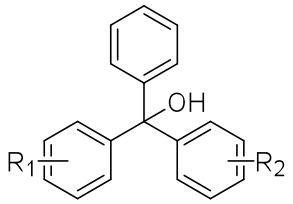


Compd	R_1	R_2	Inhibition of basal ATPase activity K_i^{app} (nM)	L.E.	K562 cells GI_{50} (nM)
S1	3-Pyridine	H	1460.7 ± 73.4	0.35	2442 ± 147
S2[a]	4-Pyridine	H	514.2 ± 66.6	0.37	1832 ± 134
S3[b] (NSC136870)	2-Thienyl	*(R)*-CO_2H	> 50,000	n.d.	n.d.
S4	2-(1,3)-Thiazole	H	3584 ± 381.0	0.34	3750 ± 165
S5	2-(1,3)-Oxazole	H	3013.3 ± 163.0	0.34	2312 ± 122

Notes: L.E. = ligand efficiency; n/a = not applicable; n.d. = not determined;

[a] = synthesised as described previously;[24] [b] = values provided for reference from previous paper.[25]

Table S2: Inhibitory activity of selected trityl alcohols

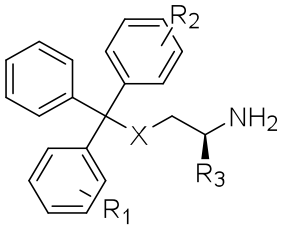


Compd	R_1	R_2	Inhibition of basal ATPase activity K_i^{app} (nM)	L.E.	K562 GI_{50} (nM)
S6[a]	3-Cl	-	n.i.	n/a	n.d.
S7[a]	3-n-Pr	-	1352.4 ± 180.6	0.35	n.d.
S8	4-OEt	-	1020 ± 143	0.36	> 50000
S9	4-OCF_3	-	798 ± 31.6	0.33	> 50000
S10	2-F, 4-OMe		4870 ± 330	0.31	23988 ± 3173
S11	3-F, 4-OMe		1636 ± 138	0.34	> 50000
60	3,4-Me	-	1440.1 ± 204.0	0.36	> 50000
59	3-Et, 4-Me	-	1103.2 ± 135.8	0.35	18197 ± 1898
S12	3,4-$(CH_2)_4$	-	305.6 ± 41.2	0.37	17458 ± 2442
S13	4-Me	4-Me	1689.0 ± 593.6	0.36	n.d.
***rac*-S14**	3-Cl	3-OH	11838 ± 1089	0.31	n.d.
***rac*-S15**	3-Et	3-OH	1001.3 ± 47.6	0.36	n.d.

Notes: n.i. = no inhibition; n/a = not applicable; n.d. = not determined;

[a] = synthesised as reported previously;[6] [b] = values provided for reference from previous paper.[25]

Table S3: Turbidimetric solubility at pH 7.4 of selected analogues.



Compd	X	R_1	R_2	R_3	Turbidimetric solubility (μM)
4	S	H	H	*(R)*-CO_2H	> 100
15	S	H	H	H	65
16	S	3-Et	H	H	37.5
S52[a,b]	S	4-Cl	H	*(R)*-CO_2H	65
6[a]	S	4-Me	H	*(R)*-CO_2H	> 100
17	S	4-Me	H	H	65
7[a]	S	4-OMe	H	*(R)*-CO_2H	> 100
20	S	4-OEt	H	H	3.75
34	S	3-Me	4-Me	(*R*)-CO_2H	65
35	S	3-Me	4-Me	H	3.75
36	S	3-Et	4-Me	(*R*)-CO_2H	65
37	S	3-Et	4-Me	H	3.75
S53[a]	S	3,4-$(CH)_4$	H	*(R)*-CO_2H	37.5
38	S	3,4-$(CH_2)_4$	H	(*R*)-CO_2H	20
S54[c]	C	H	H	CO_2H	> 100
S55[c]	C	H	H	H	> 100
S20[c]	C	3-Cl	H	H	> 100
***rac*-11**[c]	C	3-Me	H	CO_2H	> 100
13[c]	C	3-Me	H	H	> 100
***rac*-12**	C	4-Me	H	CO_2H	> 100
14	C	4-Me	H	H	20
26	C	4-OMe	H	H	> 30
rac-**42**	C	3,4-Me	H	CO_2H	> 100
8	S	3-OH	H	H	> 100
rac-**47**	S	3-OH	4-Me	H	> 100
rac-**46**	S	3-OH	3-Et	H	> 30
dia-**50**	C	3-OH	4-Me	CO_2H	> 100
rac-**51**	C	3-OH	4-Me	H	> 100

Notes: [a] = Compounds 6 (NSC 123139), 7 (NSC123528) S52 (NSC 123139), and S53 (NSC 123529) were obtained from the NCI/DTP Open Chemical Repository (http://dtp.cancer.gov) of the National Cancer Institute. [c] = Values provided for reference from previous paper.[6]

Table S4: Effect of *rac*-**42** on the activity of other human kinesins.

Kinesin	**Kinesin family**	**Inhibition of basal ATPase activity K_i^{app} (μM) [MIA (%)]**	**Inhibition of MT-stimulated ATPase activity K_i^{app} (μM) [MIA (%)]**
Kif5A[a]	Kinesin 1	n.i. (10)	n.i. (10)
Kif5B[b]	Kinesin 1	n.i. (5)	n.i. (5)
Kif3B	Kinesin 2	n.i. (5)	n.i. (20)
MKLP-2[c]	Kinesin 6	n.i. (5)	n.i. (10)
MPP1[d]	Kinesin 6	n.i. (10)	n.i. (15)
Kif7	Kinesin 7	n.i. (5)	n.i. (5)
Kif9	Kinesin 9	n.i. (5)	n.i. (20)

Notes: MIA = maximum inhibitory activity observed. n.i. = no inhibition. [a] = a.k.a. neuronal kinesin heavy chain; [b] = a.k.a. conventional kinesin, kinesin heavy chain; [c] = a.k.a. Kif20A, RabK6; [d] = a.k.a. Kif20B, MPHOSPH1, KRMP1.

Supplementary Figures

Figure S1: Concentration-response curves to determine the specificity of *rac*-**340**. Inhibition of the basal ATPase activity of a) Eg5 and b) Kif3B and inhibition of the MT-stimulated activity of c) Eg5 and d) Kif2B. Measurements were carried out in the concentration range from 0 to 1500 nM for Eg5 and from 0 to 200 μM for Kif3B and Kif2B.

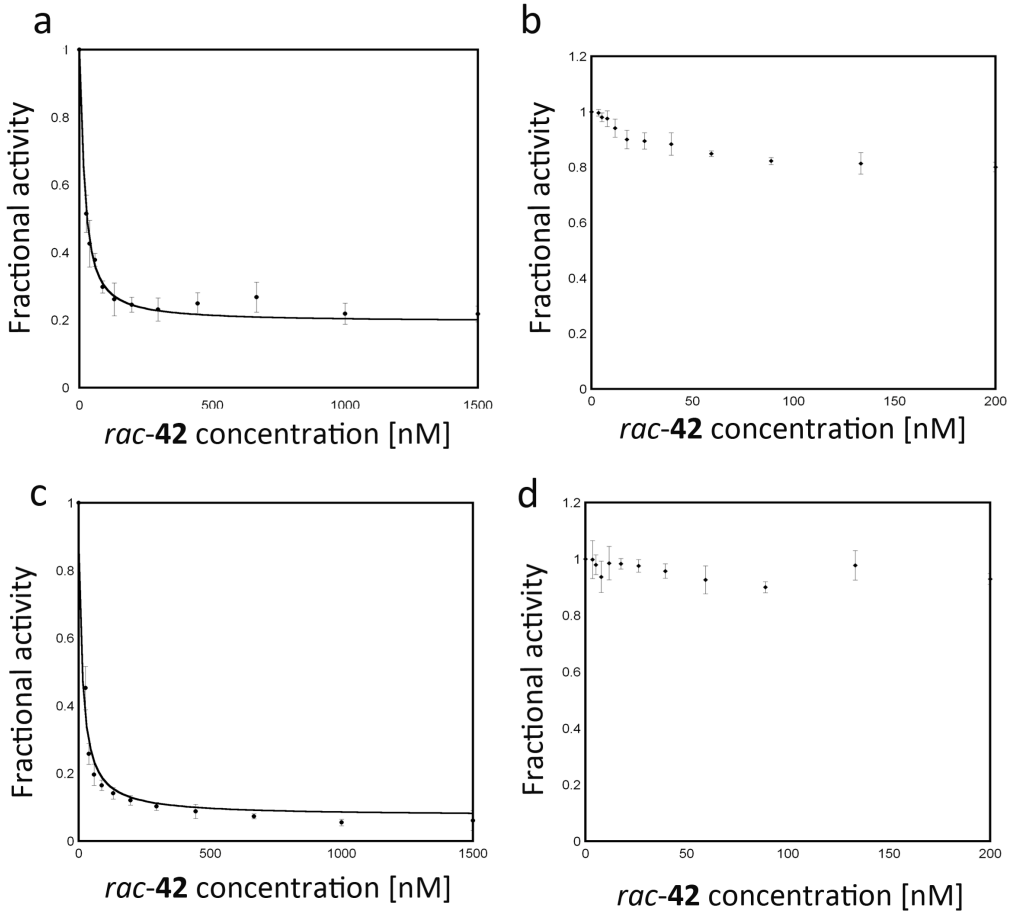
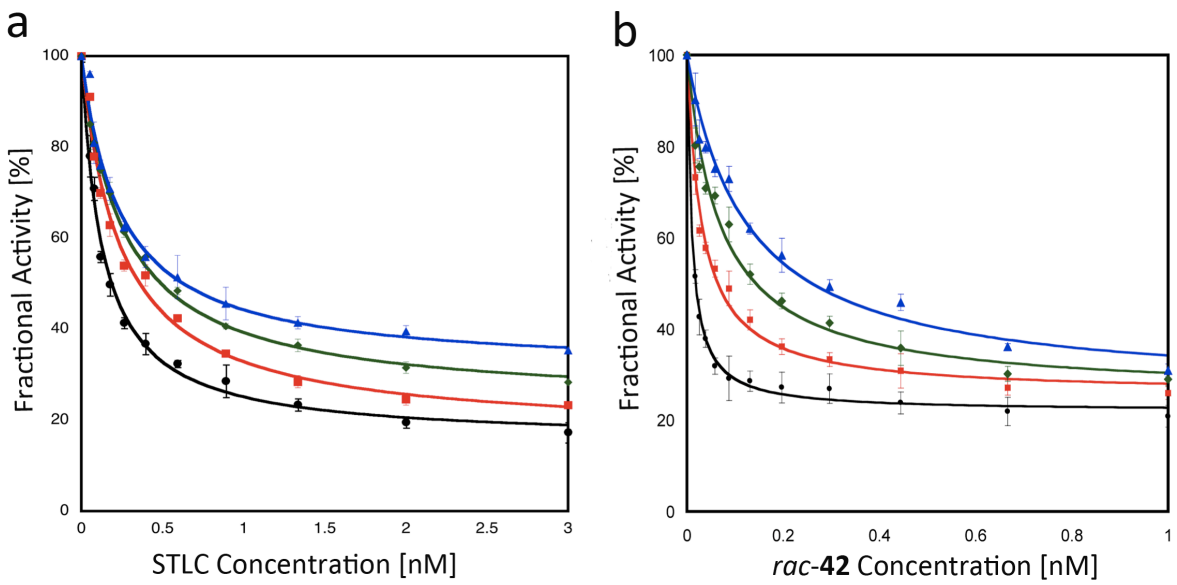


Figure S2: Inhibition of the MT-stimulated Eg5 ATPase activity in the presence of increasing NaCl concentrations. a) Inhibition by **1** in the absence of NaCl (▲) and in the presence of 50 mM NaCl (♦), 100 mM NaCl (■) and 150 mM NaCl (●) leads to improved IC_{50} values of 310 ± 0.2, 267 ± 1.1, 210 ± 2.1 and 132 ± 1.5 nM, respectively. b) Inhibition by *rac*-**42** in the absence of NaCl (▲) and in the presence of 50 mM NaCl (♦), 100 mM NaCl (■) and 150 mM NaCl (●) leads to improved IC_{50} values of 124.8 ± 1.4, 69.5 ± 0.7, 31.1 ± 2.4 and 9.9 ± 0.6 nM, respectively. All reactions were carried out in the presence of 5 nM Eg5 and 1 mM Mg^{2+}ATP.



3. Supplementary References

1. Horn, M.; Mayr, H. Stabilities of Trityl-Protected Substrates: The Wide Mechanistic Spectrum of Trityl Ester Hydrolyses. *Chemistry – A European Journal* **2010,** 16, 7469-7477.

2. Maltese, M. Reductive Demercuration in Deprotection of Trityl Thioethers, Trityl Amines, and Trityl Ethers. *The Journal of Organic Chemistry* **2001,** 66, 7615-7625.

3. Kabalka, G. W.; Yao, M.-L.; Borella, S.; Goins, L. K. Iron Trichloride Mediated Allylation of Lithium Alkoxides through an Unusual Carbon−Oxygen Bond Cleavage. *Organometallics* **2007,** 26, 4112-4114.

4. Brown, H. C.; Rao, B. C. S. A New Technique for the Conversion of Olefins into Organoboranes and Related Alcohols. *Journal of the American Chemical Society* **1956,** 78, 5694-5695.

5. Dess, D. B.; Martin, J. C. Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *The Journal of Organic Chemistry* **1983,** 48, 4155-4156.

6. Wang, F.; Good, J. A. D.; Rath, O.; Kaan, H. Y. K.; Sutcliffe, O. B.; Mackay, S. P.; Kozielski, F. Triphenylbutanamines: Kinesin Spindle Protein Inhibitors with in Vivo Antitumor Activity. *Journal of Medicinal Chemistry* **2012,** 55, 1511-1525.

7. Starnes, W. H. Lead tetraacetate oxidation of 4,4,4-triphenyl-1-butanol, 3,3,3-triphenyl-1-propanol, and 4,4,4-triphenylbutyric acid. *The Journal of Organic Chemistry* **1968,** 33, 2767-2774.

8. Bigge, C. F.; Drummond, J. T.; Johnson, G.; Malone, T.; Probert, A. W.; Marcoux, F. W.; Coughenour, L. L.; Brahce, L. J. Exploration of phenyl-spaced 2-amino-(5-9)-

phosphonoalkanoic acids as competitive N-methyl-D-aspartic acid antagonists. *Journal of Medicinal Chemistry* **1989,** 32, 1580-1590.

9. Warmuth, R.; Munsch, T. E.; Stalker, R. A.; Li, B.; Beatty, A. Enantioselective synthesis of benzocyclic α,α-dialkyl-amino acids: new insight into the solvent dependent stereoselectivity of the TMSCN addition to phenylglycinol derived imines. *Tetrahedron* **2001,** 57, 6383-6397.

10. Dockendorff, C.; Jin, S.; Olsen, M.; Lautens, M.; Coupal, M.; Hodzic, L.; Spear, N.; Payza, K.; Walpole, C.; Tomaszewski, M. J. Discovery of μ-opioid selective ligands derived from 1-aminotetralin scaffolds made via metal-catalyzed ring-opening reactions. *Bioorganic & Medicinal Chemistry Letters* **2009,** 19, 1228-1232.

11. White, W. N.; Stout, C. A. A Determination of the HR Acidity Function for Sulfuric Acid—Aqueous Acetic Acid. *The Journal of Organic Chemistry* **1962,** 27, 2915-2917.

12. Zhang, L.; Zhang, W.; Liu, J.; Hu, J. C−F Bond Cleavage by Intramolecular S_N2 Reaction of Alkyl Fluorides with O- and N-Nucleophiles. *The Journal of Organic Chemistry* **2009,** 74, 2850-2853.

13. Luliński, S.; Zajac, K. Selective Generation of Lithiated Benzonitriles: the Importance of Reaction Conditions. *The Journal of Organic Chemistry* **2008,** 73, 7785-7788.

14. Neumann, W. P.; Penenory, A.; Stewen, U.; Lehnig, M. Sterically hindered free radicals. 18. Stabilization of free radicals by substituents as studied by using triphenylmethyls. *Journal of the American Chemical Society* **1989,** 111, 5845-5851.

15. Iso, Y.; Grajkowska, E.; Wroblewski, J. T.; Davis, J.; Goeders, N. E.; Johnson, K. M.; Sanker, S.; Roth, B. L.; Tueckmantel, W.; Kozikowski, A. P. Synthesis and Structure−Activity Relationships of 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine Analogues as Potent, Noncompetitive Metabotropic Glutamate Receptor Subtype 5

Antagonists; Search for Cocaine Medications. *Journal of Medicinal Chemistry* **2006,** 49, 1080-1100.

16. Beeson, T. D.; MacMillan, D. W. C. Enantioselective Organocatalytic α-Fluorination of Aldehydes. *Journal of the American Chemical Society* **2005,** 127, 8826-8828.

17. Moussa, I. A.; Banister, S. D.; Beinat, C.; Giboureau, N.; Reynolds, A. J.; Kassiou, M. Design, Synthesis, and Structure−Affinity Relationships of Regioisomeric N-Benzyl Alkyl Ether Piperazine Derivatives as σ-1 Receptor Ligands. *Journal of Medicinal Chemistry* **2010,** 53, 6228-6239.

18. Jiang, Z.-X.; Qing, F.-L. Regioselective and Stereoselective Nucleophilic Ring Opening of Trifluoromethylated Cyclic Sulfates: Asymmetric Synthesis of Both Enantiomers of syn-(3-Trifluoromethyl)isoserine. *The Journal of Organic Chemistry* **2004,** 69, 5486-5489.

19. Enders, D.; Hüttl, M. R. M. Direct Organocatalytic α-Fluorination of Aldehydes and Ketones. *Synlett* **2005,** 2005, 0991-0993.

20. Crich, D.; Vinogradova, O. Synthesis and Glycosylation of a Series of 6-Mono-, Di-, and Trifluoro S-Phenyl 2,3,4-Tri-O-benzyl-thiorhamnopyranosides. Effect of the Fluorine Substituents on Glycosylation Stereoselectivity. *Journal of the American Chemical Society* **2007,** 129, 11756-11765.

21. Fuson, R. C.; Miller, J. J. The Condensation of Grignard Reagents with 3-Pyridyl and 3-Quinolyl Ketones. *Journal of the American Chemical Society* **1957,** 79, 3477-3480.

22. Casadio, S.; Donetti, A.; Coppi, G. *N*-trisubstituted methylimidazoles as antifungal agents. *Journal of Pharmaceutical Sciences* **1973,** 62, 773-778.

23. Hodges, J. C.; Patt, W. C.; Connolly, C. J. Reactions of lithiooxazole. *The Journal of Organic Chemistry* **1991,** 56, 449-452.

24. Abualhasan, M. N.; Good, J. A. D.; Wittayanarakul, K.; Anthony, N. G.; Berretta, G.; Rath, O.; Kozielski, F.; Sutcliffe, O. B.; Mackay, S. P. Doing the methylene shuffle – Further

insights into the inhibition of mitotic kinesin Eg5 with *S*-trityl L-cysteine. *European Journal of Medicinal Chemistry* **2012,** 54, 483-498.

25. Kaan, H. Y. K.; Weiss, J.; Menger, D.; Ulaganathan, V.; Tkocz, K.; Laggner, C.; Popowycz, F.; Joseph, B.; Kozielski, F. Structure−Activity Relationship and Multidrug Resistance Study of New *S*-trityl-L-Cysteine Derivatives As Inhibitors of Eg5. *Journal of Medicinal Chemistry* **2011,** 54, 1576-1586.