Tetrahedron: *Asymmetry* 19 (2008) 2218–2221

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of enantiomerically enriched isotopically-labelled anilines by (−)-sparteine directed lithiation

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ARTICLE INFO

Article history:
Received 1 September 2008
Accepted 17 September 2008
Available online 11 October 2008

ABSTRACT

Anilines bearing benzyl or isopropyl groups isotopically labelled (with ^{2}H or ^{13}C) in one of a pair of enantiotopic protons or methyl groups can be made using (−)-sparteine-directed lithiation with an electrophilic quench, followed by deprotection.

1. Introduction

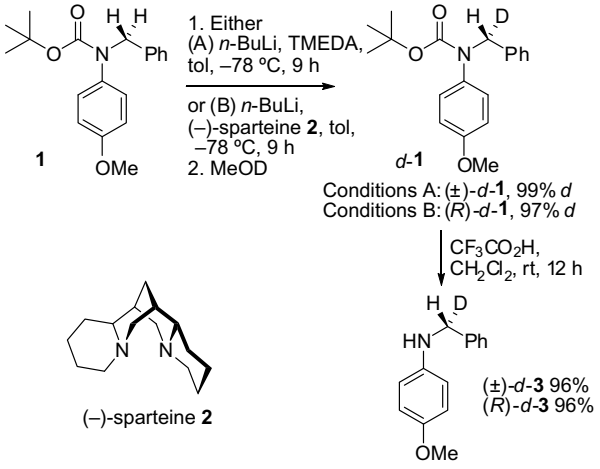
As part of an ongoing program of work in which we have used NMR techniques to study the conformation of putatively helical oligomers ('foldamers')[1–6] built from aromatic amides[7,8] or ureas,[9,10] we required some enantiomerically enriched aniline derivatives in which each of a pair of otherwise enantiotopic nuclei (H or C) is selectively labelled with an NMR active or inactive nucleus (^{1}H vs ^{2}H; ^{12}C vs ^{13}C). Herein we report the methods we used (Scheme 1).

2. Results and discussion

Benzylic amine derivatives may be functionalized enantioselectively by (−)-sparteine directed enantioselective deprotonation of their *N*-Boc-*N*-aryl derivatives,[11,12] or by chiral lithium amide base promoted deprotonation of *N*-benzoyl-*N*-*t*-butyl derivatives.[13] Deuteration of the configurationally stable lithiated intermediates provides a method for the synthesis of isotopically labelled protected amines.

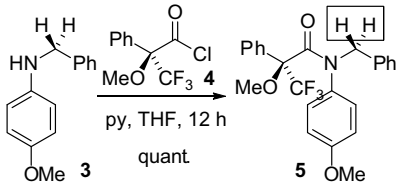
Carbamate **1** was made by the reported method;[11,12] it was deprotonated with *n*-BuLi in the presence of TMEDA and by *n*-BuLi in the presence of (−)-sparteine **2**. The resulting organolithiums were quenched with MeOD to yield racemic and enantiomerically enriched *d*-**1** with 97–99% deuteration (by MS and by ^{1}H NMR). Both samples were deprotected (CF_3CO_2H) to yield anilines *d*-**3** in 96% yield.

Deuteration of **1** via an enantiomerically enriched organolithium has previously been reported to form the (*R*) isomer of *d*-**1**,[12]



Scheme 1. Deuteration by lithiation.

but the enantiomeric purity of neither *d*-**1** nor the amine *d*-**3** has been reported. We chose to establish the er of *d*-**3** by the formation of a diastereoisomeric derivative. Formation of the MTP amide **5** of undeuterated **3** by acylation with Mosher's acid chloride[14]



Scheme 2. MTP amide of aniline **3**.

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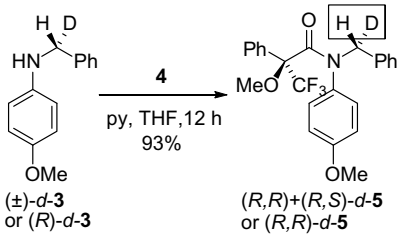
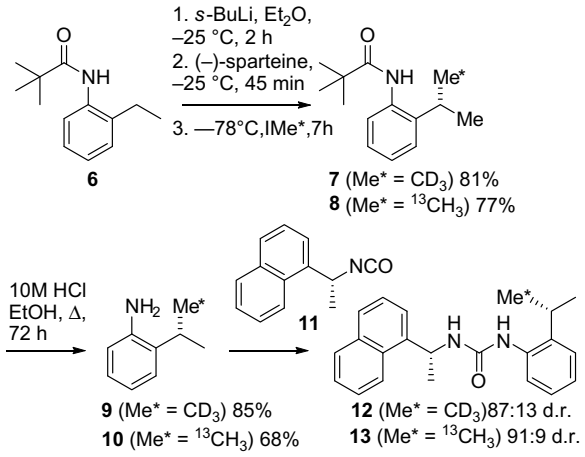
doi:10.1016/j.tetasy.2008.09.014

(*R*)-MTPACl **4** (Scheme 2) gave an excellent yield of the amide **5**, in whose ^{1}H NMR spectrum the benzylic protons showed a clear AB system (J = 14.0 Hz). Repeating the reaction with racemic *d*-**3** (Scheme 3) gave a mixture of (*R,R*) and (*R,S*)-*d*-**5**, which consequently showed a pair of singlets in its NMR spectrum ($\Delta\delta$ = 58 ppb). With (*R,R*)-*d*-**5** derived from enantiomerically enriched (*R*)-*d*-**3**, these singlets were present in a ratio of 70:30, implying that (*R*)-*d*-**1** is formed with a 70:30 er. This value is lower than that reported for related reactions of lithiated **1** with other electrophiles[11,12,15] but nonetheless sufficiently high enough to be useful for our purposes.



Scheme 3. MTP amide of labelled anilines.

For another series of compounds, we required an aniline bearing a ^{13}C or ^{2}H isotopic label in one of the two enantiotopic methyl groups. Given the reported diverse lithiation chemistry[16] of 2-alkylaryl amides,[17–19] anilides,[20] and ureas,[21] we chose 2-isopropyl anilines **9** and **10** as our target compounds (Scheme 4).

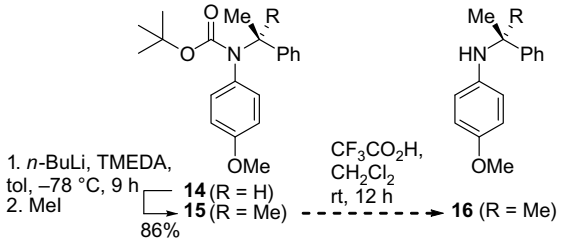


Scheme 4. Synthesis of labelled anilines **9** and **10**.

Amide **6** was made by standard methods, and was lithiated with *s*-BuLi in the presence of (−)-sparteine.[20] Selectivity in the reactions of lithio-**6** results from dynamic thermodynamic resolution of the intermediate organolithium-(−)-sparteine complex,[16] so the lithiation was held at −25 °C to ensure full equilibration before cooling to −78 °C.[20] Two isotopically labelled methyl iodides were then added: ICD_3 and $I^{13}CH_3$, to give an enantiomerically enriched sample of both **7** and **8** in 81% and 77% yield, respectively.

The pivanilide directing group was hydrolysed by refluxing in aqueous hydrochloric acid, to yield the amine **9** in 85% yield and amine **10** in 68% yield. The enantioselectivity of the methylation was determined by formation of the ureas **12** and **13** in quantitative yield with enantiomerically pure (*R*)-2-naphthylethyl isocyanate **11**. As determined by integration of the signals in the ^{1}H NMR spectrum, **12** was formed with a diastereoisomeric ratio of 87:13, and **13** in a diastereoisomeric ratio of 91:9, implying the corresponding er's in **9** and **10**, respectively. Enantioselective methylation of **6** has not previously been reported, but evidently proceeds with enantioselectivity comparable to that reported for alkylation with 1-iodoundecane (89:11).[20] We assigned an (*S*)-absolute stereochemistry to **9** and **10** on the basis of this previous alkylation.

The synthesis of the analogue of **16** (R = Me) of the potentially enantiomerically enriched, isotopically labelled cumylamine derivative **16** (R = Me*) was also attempted (Scheme 5) using the stereospecific deprotonation and methylation of **14**.[11,12] However, the attempted deprotection of the *N*-Boc cumylamine **15** led to decomposition by loss of the stable cumyl cation.[22–24]



Scheme 5. Attempted synthesis of labelled cumylamine derivative **16**.

3. Conclusion

The methods reported here allowed us to obtain gram quantities of labelled amines *d*-**3, 9** and **10** in enantiomerically enriched form. Future reports[25] will detail conformational insights gained by incorporation of the labelled amines *d*-**3, 9** and **10** into oligourea and oligoamide foldamers.

4. Experimental

General experimental details have been reported recently.[26]

4.1. (*R*)-tert-Butyl-α-deuterobenzyl-*p*-methoxyphenylcarbamate, (*R*)-*d*-1

The method reported by Beak[11,12] was employed. To a solution of (−)-sparteine (0.46 cm^3, 2.0 mmol) in toluene (2.0 cm^3) at −78 °C was added *n*-BuLi (1.0 cm^3, 2.0 mmol, 2.0 M). The reaction mixture was stirred for 30 min at −78 °C and then a solution of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine **1** (0.50 g, 1.6 mmol) in toluene (1.6 cm^3) was added. The resulting reaction mixture was stirred at −78 °C for 9 h and methanol-d_1 (0.10 cm^3, 2.20 mmol) added. After stirring for 3 h at −78 °C, the reaction was warmed to room temperature for 10 h. Water (10 cm^3) was added and extracted with EtOAc (3 × 10 cm^3). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; petrol to 5% EtOAc in petrol) to give *tert*-butyl-α-deuterobenzyl-*p*-methoxyphenylcarbamate *d*-**1** (0.49 g, 97%), as a white solid, mp 93–95 °C (EtOAc); R_f (20% EtOAc in petrol) 0.63; ν_{max} (film)/cm^{-1} 2842 (OCH_3) and 1716 (C=O); δ_H (300 MHz; $CDCl_3$) 7.16–7.01 (5H, m, CH-c, CH-d and CH-e), 6.86 (2 H, br, CH-b), 6.61 (2 H, d, J = 9.0, CH-a), 4.60 (1 H, s, CH-f) and 3.54 [3 H, s, ($ArOCH_3$)]; δ_C (75 MHz; $CDCl_3$) 157.6 (C=O), 155.2 (C), 138.7 (C), 135.7 (C), 128.5 (CH), 128.1 (CH), 127.7 (CH), 127.2 (CH), 113.9 (CH), 80.2

(C), 55.4 ($ArOCH_3$), 54.1 (CHD) and 28.4 [$(CH_3) \times 3$]; m/z (ES^+) 315 (100%, $M+H^+$); (found: $M+H^+$, 315.1825, $C_{19}H_{23}D_3NO_3$ requires M+H, 315.1819).

The same compound was made in its racemic form by the following method. To a solution of TMEDA (0.30 cm^3, 2.0 mmol) in toluene (2.0 cm^3) at −78 °C was added *n*-BuLi (1.0 cm^3, 2.0 mmol, 2.0 M). The reaction mixture was stirred for 30 min at −78 °C and a solution of *N*-Boc-*N*-(*p*-methoxyphenyl)benzylamine **1** (0.50 g, 1.6 mmol) in toluene (1.6 cm^3) was added. The resulting reaction mixture was stirred at −78 °C for 9 h and methanol-d_1 (0.10 cm^3, 2.2 mmol) added. After stirring for 3 h at −78 °C, the reaction was warmed to room temperature for 10 h. Water (10 cm^3) was added and extracted with EtOAc (3×10 cm^3). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; petrol to 5% EtOAc in petrol) to give *tert*-butyl-α-deuterobenzyl-*p*-methoxyphenylcarbamate *d*-**1** (0.50 g, 99%), as a white solid, mp 93–95 °C (EtOAc).

4.2. (*R*)-*N*-(*p*-Methoxyphenyl)-α-deuterobenzylamine, (*R*)-*d*-3

tert-Butyl-α-deuterobenzyl-*p*-methoxyphenylcarbamate *(R)-d*-**1** (0.30 g, 0.96 mmol) was dissolved in CH_2Cl_2 (5 cm^3) and trifluoroacetic acid (1 cm^3, 13 mmol) added dropwise. The reaction mixture was stirred at room temperature for 12 h and the solvent evacuated under reduced pressure. The residue was dissolved in EtOAc (20 cm^3), made basic by washing with saturated $NaHCO_3$ and the two phases separated. The organic fraction was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (SiO_2; 10% EtOAc in petrol to EtOAc) to give *N*-(*p*-methoxyphenyl)-α-deuterobenzylamine (*R*)-*d*-**3** (0.20 g, 96%), as a brown oil, R_f (20% EtOAc in petrol) 0.10; ν_{max} (film)/cm^{-1} 3413 (NH) and 2834 (OCH_3); δ_H (300 MHz; $CDCl_3$) 7.46–7.29 (5H, m, CH-c, CH-d and CH-e), 6.84 (2 H, d, J = 9.0, CH-b), 6.67 (2 H, d, J = 9.0, CH-a), 4.32 (1H, s, CH-f) and 3.80 [4H, s, ($ArOCH_3$) and NH]; δ_C (75 MHz; $CDCl_3$) 152.5 (C), 142.8 (C), 139.9 (C), 128.9 (CH), 127.9 (CH), 127.5 (CH), 115.2 (CH), 114.4 (CH), 56.1 ($ArOCH_3$) and 49.2 (CHD); m/z (ES^+) 215 (100%, $M+H^+$); (found: $M+H^+$, 215.1300, $C_{14}H_{15}DNO$ requires M+H, 215.1295).

4.3. N-Benzyl-3,3,3-trifluoro-2-methoxy-*N*-(4-methoxyphenyl)-2-phenylpropanamide, 5

N-Boc-*N*-(*p*-methoxyphenyl)benzylamine **3** (0.04 g, 0.2 mmol) and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.05 g, 0.2 mmol) were dissolved in THF (3.0 cm^3), pyridine (0.11 cm^3, 1.4 mmol) added and stirred for 12 h at room temperature. Water (10 cm^3) was added and extracted with EtOAc (3×10 cm^3). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; petrol to 20% EtOAc in petrol) to give *N*-α-benzyl-3,3,3-trifluoro-2-methoxy-*N*-(4-methoxyphenyl)-2-phenylpropanamide **5** (0.08 g, 97%), as a colourless oil, $[\alpha]_D^{24} = -106$ (*c* 0.4, CH_2Cl_2); R_f (20% EtOAc in petrol) 0.51; ν_{max} (film)/cm^{-1} 2977 (OCH_3), 2842 (OCH_3), 1653 (C=O) and 1265 (C–F); δ_H (500 MHz; $CDCl_3$) 7.26–7.15 (7H, m, Ar), 7.15–7.05 (3H, m, Ar), 6.95 (1H, d, J = 9.0, Ar), 6.84 (1H, d, J = 9.0, Ar), 6.55–6.20 (2H, br, Ar), 4.84 (1 H, d, J = 14.0, CH-a or CH-b), 4.68 (1H, d, J = 14.0, CH-b or CH-a), 3.61 [3H, s, ($ArOCH_3$)] and 3.44 [3H, q, J = 2.0, (OCH_3)]; δ_C (125 MHz; $CDCl_3$) 166.2 (C=O), 158.4 (C), 136.8 (C), 134.7 (C), 133.0 (C), 129.4 (CH), 128.9 (CH), 128.3 (CH), 127.9 (CH), 127.7 (CH), 126.6 (CH), 123.7 [q, J = 289.0, (CF_3)] 114.9 (CH), 114.1 (CH), 84.9 [q, J = 24.9, (C–CF_3)], 55.7 $(OCH_3)_A$, 55.6 (CH_2) and 55.2 $(OCH_3)_B$; m/z (ES^+) 430 (60%, $M+H^+$); (found: $M+H^+$, 430.1635, $C_{24}H_{23}NO_3F_3$ requires M+H, 430.1625).

4.4. *N*-α-Deuterobenzyl-3,3,3-trifluoro-2-methoxy-*N*-(4-methoxyphenyl)-2-phenylpropanamide *d*-5

N-(*p*-Methoxyphenyl)-α-deuterobenzylamine *d*-**3** (0.15 g, 0.69 mmol) and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride **4** (0.18 g, 0.69 mmol) were dissolved in THF (5.0 cm^3), pyridine (0.11 cm^3, 1.4 mmol) added and stirred for 12 h at room temperature. Water (10 cm^3) was added and extracted with EtOAc (3×10 cm^3). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; petrol to 20% EtOAc in petrol) to give *N*-α-deuterobenzyl-3,3,3-trifluoro-2-methoxy-*N*-(4-methoxyphenyl)-2-phenylpropanamide *d*-**5** (0.28 g, 93%), as a pale yellow oil, $[\alpha]_D^{23} = -105.9$ (*c* 0.2, CH_2Cl_2); R_f (20% EtOAc in petrol) 0.51; ν_{max} (film)/cm^{-1} 2982 (OCH_3), 2850 (OCH_3), 1652 (C=O) and 1265 (C–F); δ_H (300 MHz; $CDCl_3$) 7.39–7.26 (14H, m, $Ar^{maj\ and\ min}$), 7.26–7.18 (6H, m, $Ar^{maj\ and\ min}$), 6.94 (2H, d, J = 9.0, $Ar^{maj\ and\ min}$), 6.85 (2H, d, J = 9.0, $Ar^{maj\ and\ min}$), 6.55–6.30 (4H, br, $Ar^{maj\ and\ min}$), 4.95 (1H, s, CH-a^{maj}), 4.89 (1H, s, CH-a^{min}), 3.73 [6H, s, $(ArOCH_3)^{maj\ and\ min}$] and 3.57 [6H, q, J = 2.0, $(OCH_3)^{maj\ and\ min}$]; δ_C (75 MHz; $CDCl_3$) 166.3 $(C{=}O)^{maj}$, 160.0 $(C{=}O)^{min}$, 158.6 $(C)^{maj\ and\ min}$, 137.0 $(C)^{maj\ and\ min}$, 135.6 $(C)^{min}$, 135.0 $(C)^{maj}$, 133.2 $(C)^{maj}$, 131.4 $(C)^{min}$, 129.7 $(CH)^{maj\ and\ min}$, 129.2 $(CH)^{maj\ and\ min}$, 128.6 $(CH)^{maj\ and\ min}$, 128.1 $(CH)^{maj\ and\ min}$, 128.0 $(CH)^{maj\ and\ min}$, 126.8 $(CH)^{maj\ and\ min}$, 124.0 [q, J = 290.0, $(CF_3)^{maj\ and\ min}$], 114.4 $(CH)^{maj\ and\ min}$, 113.2 $(CH)^{maj\ and\ min}$, 85.2 [q, J = 24.8, $(\mathbf{C}–CF_3)^{maj\ and\ min}$], 55.90 $(OCH_3)_A{}^{maj\ and\ min}$, 55.87 $(OCH_3)_B{}^{maj\ and\ min}$, 55.6 $(CHD)^{min}$ and 55.5 $(CHD)^{maj}$; m/z (ES^+) 431 (40%, $M+H^+$); (found: $M+H^+$, 431.1688, $C_{24}H_{22}DNO_3F_3$ requires M+H, 431.1687).

4.5. (*S*)-2-(1-Methyl-2,2,2-trideuterioethyl)pivanilide 7

The method of Beak[20] was employed. Under a nitrogen atmosphere, 2-ethylpivanilide **6** (4.0 g 19.5 mmol, 1 equiv) was dissolved in dry Et_2O (140 mL). *s*-BuLi in hexane 1.3 M (31.5 mL, 41.0 mmol, 2.1 equiv) was added at –25 °C and the solution stirred for 2 h at the same temperature. (−)-Sparteine (13.0 mL, 56.5 mmol, 2.9 equiv) was added and the mixture was kept at −25 °C for 45 min, then cooled to −78 °C for 30 min. Methyl iodide (1.46 mL, 23.4 mmol, 1.2 equiv) was then added. The reaction mixture was maintained at −78 °C for 7 h. MeOH (2 mL) was added followed by water (5 mL). The organic phase was washed with H_3PO_4 0.5 M, dried over $MgSO_4$ and concentrated under reduced pressure. The pure product **7** was obtained after precipitation in Et_2O/petrol (3.5 g, 81%). Mp: 121 °C. IR ν_{max} cm^{-1}: 3319, 2959, 1646, 1504, 755. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.26 (3H, d, J = 6.6 Hz), 1.35 (9H, s), 2.96 (1H, q, 6.6 Hz), 7.23 (3H, m), 7.32 (1H, br s), 7.77 (1H, dd, J = 1.8, 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.70, 27.69, 27.90, 39.66, 124.19, 125.34, 125.55, 126.39, 134.36, 139.57, 176.58. MS (CI/NH_3): 223 (MH^+, 100). HRMS for $C_{14}H_{19}D_3NO$ (MH^+): calcd: 223.1884; found: 223.1884. Elem. Anal. Calcd for $C_{14}H_{18}D_3NO$: C, 75.63; H, 9.52; N, 6.30. Found: C, 75.33; H, 9.34; N, 6.18.

4.6. (*S*)-2-(1-^{13}C-Methylethyl)pivanilide 8

The method reported by Beak[20] was employed. Under nitrogen atmosphere, 2-ethylpivanilide **6** (2.39 g 11.7 mmol, 1 equiv) was dissolved in dry Et_2O (80 mL). *s*-BuLi in hexane 1.3 M (18.9 mL, 24.5 mmol, 2.1 equiv) was added at −25 °C and the solution stirred for 2 h at the same temperature. (−)-Sparteine (7.78 mL, 33.8 mmol, 2.9 equiv) was added and kept at −25 °C for 45 min and then cooled to −78 °C for 30 min before ^{13}C-methyl iodide (2 g, 14.0 mmol, 1.2 equiv) was added. The reaction mixture was maintained at −78 °C until complete reaction (7 h). Then MeOH

(2 mL) was added at −78 °C followed by water (5 mL) at rt. The organic phase was washed with H_3PO_4 (0.5 M) then dried over $MgSO_4$ and concentrated under reduced pressure. The pure product **8** was obtained after precipitation in Et_2O/petrol followed by flash chromatography on silica gel (95/5: DCM/AcOEt) (1.97 g, 77%). Mp: 122 °C. IR ν_{max} cm^{-1}: 3317, 2959, 1644, 1503, 757, 736. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.27 (3H, dd, J = 6.9, 126 Hz), 1.27 (3H, dd, J = 5.3, 6.9 Hz), 1.35 (9H, s), 2.97 (1H, dsept, J = 2.1, 6.9 Hz), 7.15 (1H, dt, J = 1.5, 7.5 Hz), 7.20 (1H, dt, J = 1.5, 7.5 Hz), 7.27 (1H, dd, J = 1.6, 7.5 Hz), 7.32 (1H, br s), 7.77 (1H, d, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.77, 27.68, 27.78 (1C, d, J = 109 Hz), 39.65, 124.24, 125.35, 125.56, 126.38, 134.36, 139.65, 176.58. MS (CI/NH_3): 221 (MH^+, 100). HRMS for $C_{13}{}^{13}CH_{22}NO$ (MH^+): calcd: 221.1729; found: 221.1726. Elem. Anal. Calcd for $C_{13}{}^{13}CH_{21}NO$: C, 76.32; H, 9.61; N, 6.36. Found: C, 76.67; H, 9.84; N, 6.35.

4.7. (*S*)-2-(1-Methyl-2,2,2-trideuterioethyl)aniline 9

Pivanilide **7** (3.1 g, 13.9 mmol, 1 equiv) was dissolved in EtOH (75 mL) and HCl_{aq} 10 M (30 mL). The reaction mixture was heated at reflux for 72 h before NaOH 6 M (50 mL) was added. The aqueous phase was extracted with AcOEt and dried over $MgSO_4$. Acid–base washing provided 1.65 g of pure product **9** (85%). The er was determined by derivatisation with phenylethylisocyanate **11** to be 87:13. IR ν_{max} cm^{-1}: 3467, 3376, 2959, 1621, 1495, 749. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.27 (3H, d, J = 7.0 Hz), 2.89 (1H, q, 7.0 Hz), 3.65 (2H, br s), 6.69 (1H, dd, 1.0, 8.0 Hz), 6.79 (1H, t, J = 7.0 Hz), 7.03 (1H, t, J = 7.5 Hz), 7.15 (1H, d, J = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.16, 27.38, 115.76, 118.97, 125.36, 126.48, 132.61, 143.27. MS (CI/NH_3): 139 (MH^+, 100). HRMS for $C_9H_{11}D_3N$ (MH^+): calcd: 139.1309; found: 139.1311. Elem. Anal. Calcd for $C_9H_{10}D_3N$: C, 78.20; H, 9.48; N, 10.13. Found: C, 78.04; H, 9.89; N, 10.10.

4.8. (*S*)-2-(1-^{13}C-Methylethyl)aniline 10

The pivanilide **8** (1.8 g, 8.18 mmol, 1 equiv) was dissolved in EtOH (25 mL) and HCl_{aq} 10 M (20 mL). The reaction mixture was refluxed for 72 h before NaOH 6 M (50 mL) was added. The aqueous phase was extracted with AcOEt and dried over $MgSO_4$. Acid–base washing provided 750 mg of pure product **10** (68%). The er was determined by derivatisation with phenylethylisocyanate **11** to be 91:9. IR ν_{max} cm^{-1}: 3386, 2958, 1619, 1497, 748. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.27 (3H, dd, J = 6.8, 126 Hz), 1.27 (3H, dd, J = 5.4, 6.8 Hz), 2.92 (1H, dsept, J = 1.9, 6.8 Hz), 3.79 (2H, br s), 6.70 (1H, d, J = 7.9 Hz), 6.80 (1H, t, J = 7.5 Hz), 7.03 (1H, dt, J = 1.4, 7.5 Hz), 7.16 (1H, dd, J = 1.3, 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 22.27, 27.52 (1C, d, J = 109 Hz), 115.91, 119.15, 125.39, 126.50, 135.07, 143.01. MS (CI/NH_3): 137 (MH^+, 100). HRMS for $C_8{}^{13}CH_{14}N$ (MH^+): calcd: 137.1154; found: 137.1158. Elem. Anal. Calcd for $C_8{}^{13}CH_{13}N$: C, 79.37; H, 9.62; N, 10.28. Found: C, 79.30; H, 9.92; N, 10.56.

4.9. *N*-Boc-N-(p-methoxyphenyl)-α,α-dimethylbenzylamine, 15

The method reported by Beak[11,12] was employed. To a solution of TMEDA (0.30 cm^3, 2.0 mmol) in toluene (2.0 cm^3) at −78 °C was added *n*-BuLi (1.0 cm^3, 2.0 mmol, 2.0 M). The reaction mixture was stirred for 30 min at −78 °C and then a solution of *N*-Boc-*N*-(*p*-methoxyphenyl)-α-methylbenzylamine **14** (0.52 g, 1.6 mmol) in toluene (1.6 cm^3) was added. The resulting reaction mixture was stirred at −78 °C for 9 h and then methyl iodide (0.12 cm^3, 2.0 mmol) added. After stirring for 3 h at −78 °C, the reaction was stirred at room temperature for 10 h. Water (10 cm^3) was added and extracted with EtOAc (3 × 10 cm^3). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; petrol to 5% EtOAc in petrol) to give *N*-Boc-*N*-(*p*-methoxyphenyl)-α,α-dimethylbenzylamine **15** (0.59 g, 86%), as a colourless oil; R_f (20% EtOAc in petrol) 0.42; ν_{max} (film)/cm^{-1} 2845 (OCH_3) and 1699 (C=O); δ_H (500 MHz; $CDCl_3$) 7.44 (2H, dd, J = 8.0 and 1.0, CH-c), 7.27 (2H, dd, J = 8.0 and 7.5, CH-d), 7.19 (2H, d, J = 8.5, CH-a), 7.14 (1H, tt, J = 7.5 and 1.0, CH-e), 6.85 (2 H, d, J = 8.5, CH-b), 3.75 [3 H, s, ($ArOCH_3$)], 1.43 [6H, s, (CH_3) × 2] and 1.02 [9H, s, (CH_3) × 3]; δ_C (75 MHz; $CDCl_3$) 158.7 (C=O), 155.9 (C), 150.7 (C), 134.5 (C), 131.3 (CH), 128.3 (CH), 126.0 (CH), 124.7 (CH), 114.2 (CH), 80.2 (C), 61.6 (C), 55.7 ($ArOCH_3$), 30.6 [(CH_3) × 2] and 28.3 [(CH_3) × 3]; m/z (ES^+) 342 (100%, M+H^+); (found: M+H^+, 342.2075, $C_{21}H_{28}NO_3$ requires M+H, 342.2069).

Acknowledgments

We are grateful to the Leverhulme Trust, to the EPSRC and to Pfizer Ltd for support of this project.

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