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MULTI-COMPONENT REACTIONS OF 2-ISOPROPYLIDENE-AZIRIDINES: APPLICATION TO THE SYNTHESIS OF ENANTIOPURE NEOPENTYLAMINES¶

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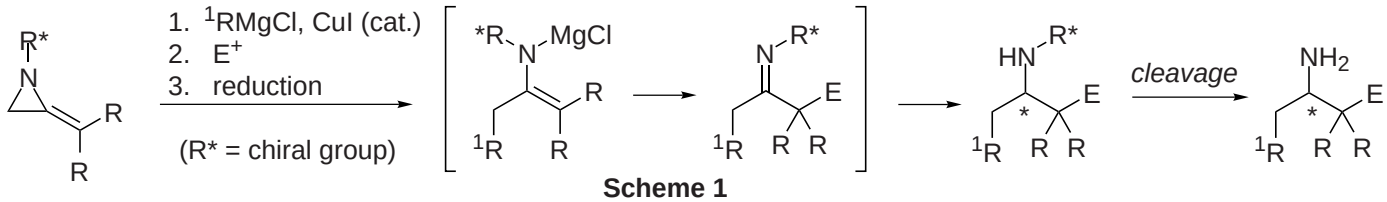
Abstract - Neopentylamines {(1*S*,1'*S*)-**7a**,**b**} are made from (*S*)-2-isopropylidene-1-(1-phenylethyl)aziridine (**4**) in 73% and 56% yields respectively, and as single diastereomers, using a multi-component reaction (M–CR). The structure of (1*S*,1'*S*)-**7a** is confirmed by X-Ray crystallography. Cleavage of the chiral control element {(*S*)-PhMeCH} from **7a** yields neopentyl type amine (**8**•HCl) (≥95%ee). Further experiments reveal the scope and limitations of this M–CR.

¶Dedicated to my friend and research mentor, Professor Albert I. Meyers.

Multi-component reactions (M–CRs) are emerging as important tools for the efficient synthesis of a wide variety of organic molecules.[1] Recently, we reported a new M–CR involving 2-methyleneaziridines.[2] Opening of this highly strained yet readily accessible heterocyclic system with a Grignard reagent in the presence of copper(I) iodide, produces a metalloenamine in a regiocontrolled manner which can be further *C*–alkylated with an electrophile (E^+) to yield a 1,3-disubstituted propanone after imine hydrolysis. Detailed studies have revealed that this M–CR is quite general and tolerates considerable variation in the structure of the three reaction partners.[3] In view of the prominence of chiral, nonracemic amines in organic chemistry as chiral auxiliaries, ligands and resolving agents,[4] we wanted to determine if this M–CR could be used to develop a flexible route for the synthesis of homochiral amines. We planned to achieve this by effecting the ring-opening/alkylation steps of the M–CR using 2-methyleneaziridines bearing chiral, nonracemic nitrogen substituents, then reduce the resultant imine in a stereocontrolled fashion (Scheme 1).

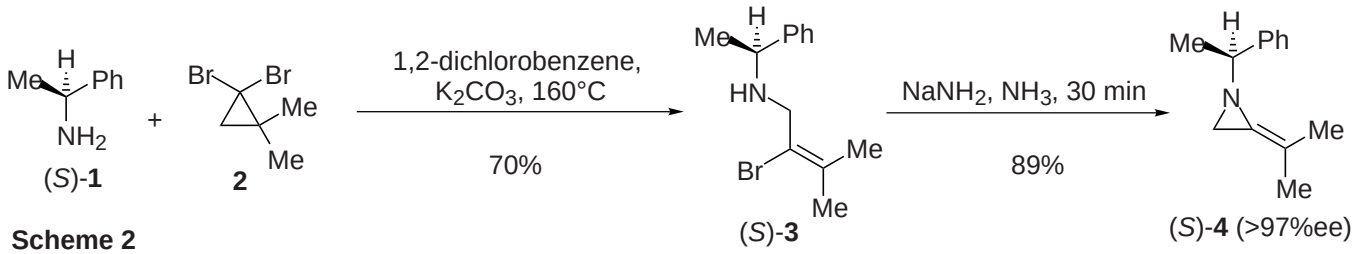


Scheme 1

In refining the reaction design, we elected to use the α-methylbenzyl group as the chiral control element (R* = –CHMePh, Scheme 1). This selection was made on the basis of several factors. Firstly, we knew that enantiomerically pure methyleneaziridines bearing this *N*-substituent can be produced.[5] Secondly, it is well known that this group can be readily removed by hydrogenation, thus providing access to the corresponding primary amines (Scheme 1).[6] Finally, reductions of imines bearing the α-methylbenzyl group can be achieved with good levels of diastereocontrol provided the two imine α-carbons possess sufficiently different patterns of substitution.[6,7] Taking into account this latter observation, we elected to examine the synthesis of neopentylamines (R = Me, Scheme 1) from isopropylidineaziridines in the first instance.

RESULTS AND DISCUSSION

Isopropylidineaziridines and related structures have been made previously by ring closure of 3-bromo-2-methyl-4-alkylamino-2-butenes using either sodium amide in liquid ammonia,[8] or butyllithium in THF.[9] However, prior to this study, the enantiocontrolled synthesis of isopropylidineaziridines bearing chiral *N*-substituents had not been examined. Chiral, nonracemic isopropylidineaziridine {(*S*)-**4**} was made in two steps from (*S*)-1-phenylethylamine (**1**) and 1,1-dibromo-2,2-dimethylcyclopropane (**2**)[10] by modification of the method reported by Quast (Scheme 2).[8b] Thermolysis of (*S*)-**1** and **2** at 160°C in 1,2-dichlorobenzene provided vinyl bromide {(*S*)-**3**} in 70% yield. Further ring closure to isopropylidineaziridine {(*S*)-**4**} was achieved by treatment of (*S*)-**3** with excess sodium amide in liquid ammonia for 30 min. Butyllithium in THF[9] could not be used to effect this interconversion. The enantiomeric purity of (*S*)-**4** was established to be ≥97% ee by chiral HPLC using (±)-**4**[3] for comparison purposes (see EXPERIMENTAL). From a practical standpoint, it is noteworthy that *gem*-dimethyl substitution renders the heterocyclic system more stable with respect to silica gel chromatography. For example, **4** can be easily purified by this method whereas (*S*)-*N*-(1-phenylethyl)-2-methyleneaziridine (**5**) can only be efficiently purified by distillation.[5]

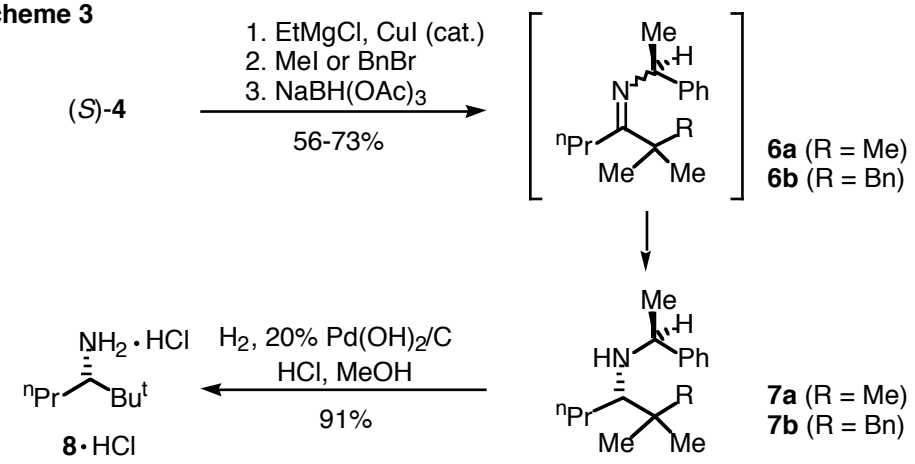


Scheme 2

With (*S*)-**4** in hand, we examined its use in the preparation of enantiomerically pure amines *via* M–CRs. Treatment of isopropylidineaziridine {(*S*)-**4**} with ethylmagnesium chloride in THF in the presence of copper(I) iodide (20 mol%), then methyl iodide and finally sodium triacetoxyborohydride furnished amine {(1*S*,1'*S*)-**7a**} in 73% yield and ≥98% de after silica gel chromatography using this "one-pot" process (Scheme 3). Careful GC analysis prior to purification revealed that traces of the chromatographically separable diastereomer had been produced (crude dr = 91:9). Treatment of (*S*)-**4** under similar conditions using benzyl bromide as the electrophile provided (1*S*,1'*S*)-**7b** in 56% yield, again as a single diastereomer (Scheme 3). Further conversion of (1*S*,1'*S*)-**7a** into neopentyl type amine {(*S*)-**8**·HCl} was achieved by catalytic hydrogenation of the corresponding hydrochloride salt. The enantiomeric excess of (*S*)-**8** was determined to be ≥95% ee by analysis of the ^{1}H NMR spectrum of the corresponding MTPA amide derived

from (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid. Worryingly, the physical data obtained for (*S*)-**8**•HCl prepared using our M–CR did not closely agree with those reported by Moss *et al.* for the (*R*)-enantiomer [mp 218-220°C {lit., mp 150-152°C[7b]}; $[\alpha]_D^{26}$ –25°(*c* 1.0, MeOH) {lit., $[\alpha]_D^{23}$ +31.9°(*c* 1, MeOH)}[7b]]. These workers had made (*R*)-**8**•HCl *via* (1*R*,1'*R*)-**7a** by reduction of imine {(*R*)-**6a**} (made by the classical method of condensation of (*R*)-**1** with 2,2-dimethylhexan-3-one) with sodium borohydride, followed by reductive cleavage of the α-methylbenzyl group. To ensure that our stereochemical assignments were correct, additional verification of the structure of (1*S*,1'*S*)-**7a** produced in the M–CR was sought. Gratifyingly, formation of the hydrochloride salt of **7a** produced crystals suitable for X-Ray crystallographic analysis which unambiguously confirmed the (1*S*,1'*S*)-stereochemistry (Figure 1). By analogy, we assume **7b** also possesses the (1*S*,1'*S*)-stereochemistry.

Scheme 3



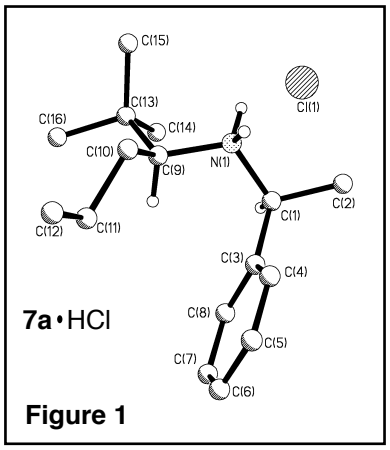
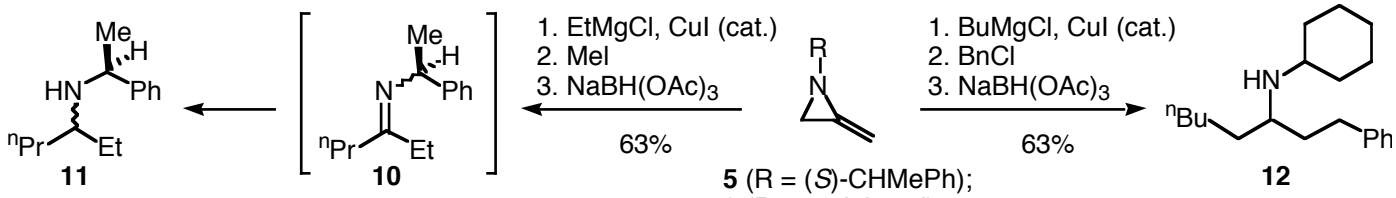


Figure 1

As anticipated, using enantiomerically enriched 2-methyleneaziridines bearing no substituents on the exocyclic double bond, much lower levels of diastereocontrol were observed. For example, (*S*)-**5**[5] was transformed into **11** as a near equal mixture of diastereomers (≤25% de) (Scheme 4). These conditions were essentially identical to those used for the conversion of (*S*)-**4** into (1*S*,1'*S*)-**7a** (Scheme 3). The use of other reducing agents ($NaBH_4$ or $LiAlH_4$) resulted in even lower levels of diastereocontrol. Presumably, the near equal steric size of the propyl and ethyl groups attached to intermediate imine (**10**), results in little facial selectivity in the reduction. This limitation aside, the methodology can be used to make racemic amines in a highly efficient manner. For example, 2-methyleneaziridine (**9**)[11] was converted into amine (**12**) using this "one–pot" process in 63% yield (Scheme 4).



5 (R = (*S*)-CHMePh);
9 (R = cyclohexyl)

Scheme 4

CONCLUSIONS

From our earlier studies on ketone synthesis using this M–CR,[2,3] we know that a diverse range of Grignard reagents and electrophiles can be employed. Hence, we conclude that the method reported herein could be

used to assemble a wide range of enantiomerically pure amines in a very concise fashion by simply varying the three reaction partners in the M–CR. The only significant limitation being that R≠H for high levels of diastereocontrol to be achieved in the imine reduction (Scheme 1). However, whilst the requirement for R≠H is likely to hold in most instances, it should be noted that in a recent synthesis of the hemlock alkaloid (*S*)-coniine achieved in our laboratory, high levels of diastereocontrol (≥90% de) were observed when R=H.[12]

EXPERIMENTAL

General. All experiments were performed under an inert atmosphere in oven-dried glassware. Copper (I) iodide was purified prior to use.[3] Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. All other solvents and reagents were purified by standard protocols. Petroleum ether refers to that boiling in the 40-60°C. Chromatography was performed on Fisher Matrex 60 silica gel. Other general details have been reported previously.[11]

(*S*)-*N*-(2-Bromo-3-methyl-2-butenyl)-1-phenylethylamine (3). To 1,1-dibromo-2,2-dimethyl-cyclopropane (**2**)[10] (10.0 g, 0.044 mol) in a 2-necked flask was added 1,2-dichlorobenzene (80 mL) then (*S*)-(–)-1-phenylethylamine (**1**) (12.5 mL, 0.097 mol) dropwise. After addition of potassium carbonate (6.08 g, 0.044 mol) the mixture was heated for 72 h at 160°C. On cooling to rt, aq. sodium hydroxide solution (2 M, 50 mL) was added followed by ether (100 mL). The organic layer was separated, washed with brine (2 x 50 mL) then dried ($MgSO_4$). After removal of the ether on a rotary evaporator, the 1,2-dichlorobenzene was removed by distillation (60°C/15 mmHg). Column chromatography (5% ethyl acetate / pet. ether) of the residue on silica pretreated with triethylamine gave **3** (8.27 g, 70%) as a yellow oil. $[\alpha]_D^{27}$ –41° (*c* 1.05, $CHCl_3$); IR (film) 3340, 3022, 2914, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.20 (5H, m), 3.75 (1H, q, *J* = 6.5 Hz), 3.44 (1H, d, *J* = 14.4 Hz), 3.34 (1H, d, *J* = 14.4 Hz), 1.96 (1H, br s, NH), 1.89 (3H, s), 1.55 (3H, s), 1.35 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 145.2 (s), 133.4 (s), 128.4 (d), 127.0 (d), 126.9 (d), 121.8 (s), 55.8 (d), 51.1 (t), 25.5 (q), 24.8 (q), 20.5 (q); MS (CI) *m/z* 270 and 268 (MH^+), 190 (MH^+-Br); HRMS (ES^+): calcd for $C_{13}H_{19}NBr$ 268.0701; found 268.0701. Anal. Calcd for $C_{13}H_{18}NBr$: C, 58.22; H, 6.76; N 5.22. Found C, 58.29; H, 6.81; N, 4.91.

(*S*)-2-Isopropylidene-1-(1-phenylethyl)aziridine (4). To a 3-necked flask fitted with a dry-ice condenser and gas inlet was added sodium amide (17.5 g, 0.45 mol) and the system flushed with calcium chloride dried ammonia. Ammonia (100 mL) was condensed into the flask, and then (*S*)-**3** (4.00 g, 14.9 mmol) was added slowly and the mixture stirred for 30 min. Ether (10 mL) was added to the flask, then the reaction was quenched by the dropwise addition of water (CAUTION). After the ammonia had evaporated, water (10 mL) and diethyl ether (10 mL) were added and the mixture stirred for 5 min. The organic phase was separated and the aqueous layer extracted with ether (3 x 20 mL). The combined organic extracts were washed with 10% NaOH solution (2 x 20 mL), 0.1 M acetic acid (20 mL), saturated sodium hydrogen carbonate (20 mL), water (20 mL) then brine (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Subsequent Kugelrohr distillation (100°C/1 mmHg) gave (*S*)-**4** (2.50 g, 89%) as a clear,

colorless oil. $[\alpha]_D^{26}$ –170° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, d_6-DMSO) δ7.14-7.00 (5H, m), 2.68 (1H, q, *J* = 6.5 Hz), 1.80 (1H, br s), 1.68 (1H, br s), 1.42 (3H, s), 1.14 (3H, d, *J* = 6.5 Hz), 1.02 (3H, br s); MS (EI) *m/z* 187 (M^+), 105; HRMS (ES^+): calcd for $C_{13}H_{18}N$ 188.1439; found 188.1440. Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15; N, 7.48. Found C, 83.38; H, 9.57; N, 7.48. Data consistent with those reported for (±)-**4**.[3] HPLC analysis using a Diacel OD column (0.5% IPA in hexanes; 0.7 mL min^{-1}; λ = 252 nm) established (*S*)-**4** to be ≥97% ee {retention times: (*S*)-**4** = 5.51 min, (*R*)-**4** = 6.25 min). (±)-**4**[3] was used for comparison purposes.

General Procedure for M–CR. Copper(I) iodide (0.20 molar equivalents) in a round-bottomed flask was heated under vacuum then purged with nitrogen (3 cycles performed). Freshly distilled THF (2-4 mL) was added and the mixture cooled to –30°C whereupon the Grignard reagent (2.5 molar equivalents) was added. After stirring for 10 min, the 2-alkylidineaziridine (1.0 molar equivalent) in THF (1-2 mL) was added. The mixture was allowed to warm up to rt and stirred for 24 h. The flask was then cooled to 0°C and the electrophile (2.0-2.5 molar equivalents) added dropwise. A reflux condenser was fitted and the reaction mixture heated at 40°C overnight. After cooling to rt, the reaction mixture was added *via* cannula to a solution of sodium borohydride (3.0 molar equivalents) in glacial acetic acid (1.5-2.5 mL) at 10°C. After stirring for 2 h, water (2-4 mL) was added slowly, followed by aq. sodium hydroxide (2 M, 2-4 mL) and EtOAc (2-4 mL). After stirring for 10 min, the mixture was extracted with EtOAc (2 x 20 mL), the combined organic layers washed with saturated aqueous NH_4Cl solution (2 x 20 mL), saturated aqueous $NaHCO_3$ solution (2 x 20 mL) then brine (2 x 20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Column chromatography on alumina (0.1% MeOH in CH_2Cl_2) gave the amines detailed below.

(1*S*,1'*S*)-[1-(1,1-Dimethylethyl)butyl]-(1'-phenylethyl)amine (7a). CuI (29 mg, 0.152 mmol) in THF (4 mL), EtMgCl (2.0 M in THF, 0.94 mL, 1.88 mmol), (*S*)-**4** (140 mg, 0.75 mmol) in THF (2 mL), methyl iodide (116 μL, 1.86 mmol), and sodium borohydride (85 mg, 2.25 mmol) in glacial acetic acid (2.5 mL) were reacted according to the general procedure. Work up and purification gave (*S*,*S*)-**7a** (128 mg, 73%) as a pale yellow oil. $[\alpha]_D^{24}$ –31° (*c* 1.0, $CHCl_3$); IR (film) 3456, 3027, 2960, 1598, 1465, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.34-7.23 (5H, m), 3.81 (1H, q, *J* = 6.6 Hz), 2.10 (1H, dd, *J* = 3.0, 8.4 Hz), 1.47-1.37 (1H, m), 1.32 (3H, d, *J* = 6.6 Hz), 1.26-1.13 (1H, m), 1.10-0.88 (12H, m), 0.70 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 147.2 (s), 128.2 (d), 127.0 (d), 126.7 (d), 63.4 (d), 58.1 (d), 35.7 (s), 35.2 (t), 27.1 (q), 23.7 (q), 20.9 (t), 14.4 (q); MS (FI) *m/z* 233 (M^+), 176 (M^+-^{t}Bu); HRMS (FI): calcd for $C_{16}H_{27}N$ 233.2144, found 233.2141. Anal. Calcd for $C_{16}H_{27}N$: C, 82.34; H, 11.66; N, 6.00. Found C, 82.17; H, 11.91; N, 5.94.

(1*S*,1'*S*)-[1-(1,1-Dimethyl-2-phenylethyl)butyl]-(1'-phenylethyl)amine (7b). CuI (41 mg, 0.215 mmol) in THF (4 mL), EtMgCl (2.0 M in THF, 1.34 mL, 2.68 mmol), (*S*)-**4** (200 mg, 1.07 mmol) in THF (2 mL), benzyl bromide (255 μL, 2.14 mmol) and sodium borohydride (121 mg, 3.20 mmol) in glacial acetic acid (2.5 mL) were reacted according to the general procedure. Work up and purification gave (1*S*,1*S*')-**7b** (187

mg, 56%) as a viscous, pale yellow oil. $[\alpha]_D^{24}$ –29° (*c* 1.1, $CHCl_3$); IR (film) 3027, 2960, 1598, 1496, 1455 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$) δ7.43-7.20 (10H, m), 3.87 (1H, q, *J* = 6.6 Hz), 2.76 (1H, d, *J* = 12.8 Hz), 2.64 (1H, d, *J* = 12.8 Hz), 2.29 (1H, dd, *J* = 2.9, 8.4 Hz), 1.70-1.59 (1H, m), 1.39 (3H, d, *J* = 6.6 Hz), 1.35-1.22 (1H, m), 1.20-1.11 (1H, m), 1.10-0.96 (2H, m), 0.91 (3H, s), 0.90 (3H, s), 0.80 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 147.1 (s), 139.9 (s), 131.0 (d), 128.3 (d), 127.6 (d), 127.0 (d), 126.9 (d), 125.6 (d), 63.2 (d), 58.1 (d), 45.0 (t), 39.7 (s), 35.2 (t), 24.0 (q), 23.7 (q), 23.6 (q), 21.0 (t), 14.6 (q); MS (FAB) *m/z* 310 (MH^+), 266; HRMS (ES^+): calcd for $C_{22}H_{32}N$ 310.2535; found 310.2526. Anal. Calcd for $C_{22}H_{31}N$: C, 85.38; H, 10.10; N, 4.53. Found C, 85.47; H, 10.42; N, 4.37.

(1*S*,1'*S*)- and (1*R*,1'*S*)-1-ethylbutyl-(1'-phenylethyl)amine (11). CuI (24 mg, 0.126 mmol) in THF (2 mL), EtMgCl (2.0 M in THF, 0.79 mL, 1.58 mmol), (*S*)-**5**[5] (100 mg, 0.63 mmol) in THF (1 mL), methyl iodide (98 μL, 1.57 mmol), and sodium borohydride (71 mg, 1.88 mmol) in glacial acetic acid (1.5 mL) were reacted according to the general procedure. Work up and purification gave **11** (81 mg, 63%) as a viscous, pale yellow oil and as a 42:58 mixture of diastereomers as judged by analysis of the ^1H NMR spectrum (GC analysis before purification indicated ≤25% de). IR (film) 3027, 2960, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.25-7.10 (5H, m), 3.83-3.76 (1H, m), 2.25-2.16 (1H, m), 1.40-1.05 (11H, m), 0.82 (1.74H, t, *J* = 7.2 Hz), 0.78-0.69 (4.26H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 146.9 (s), 146.8 (s), 128.7 (d), 127.1 (d), 55.8 (d), 55.5 (d), 55.3 (d), 55.1 (d), 36.9 (t), 36.1 (t), 27.5 (t), 26.0 (t), 25.4 (q), 25.2 (q), 19.4 (t), 18.9 (t), 14.9 (q), 14.6 (q), 10.5 (q), 9.6 (q); MS (FAB) *m/z* 206 (MH^+); HRMS (ES^+): calcd for $C_{14}H_{24}N$ 206.1909; found 206.1910.

(±)-[1-(2-Phenylethyl)hexyl](cyclohexyl)amine (12). CuI (56 mg, 0.294 mmol) in THF (4 mL), BuMgCl (2.0 M in THF, 1.83 mL, 3.66 mmol), **9**[11] (200 mg, 1.46 mmol) in THF (2 mL), benzyl chloride (336 μL, 2.92 mmol), and sodium borohydride (166 mg, 4.39 mmol) in glacial acetic acid (2.5 mL) were reacted according to the general procedure. Work up and purification gave **12** (261 mg, 63%) as a viscous, pale yellow oil. IR (film) 3058, 3027, 2930, 2848, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.30-7.16 (5H, m), 2.66-2.62 (3H, m), 2.46-2.44 (1H, m), 1.85-1.78 (2H, m), 1.78-1.55 (5H, m), 1.46-1.12 (12H, m), 1.10-0.95 (2H, m), 0.90 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 142.8 (s), 128.4 (d), 128.3 (d), 125.6 (d), 53.9 (d), 53.7 (d), 36.5 (t), 34.8 (t), 34.4 (t), 34.3 (t), 32.17 (t), 32.16 (t), 26.2 (t), 25.5 (t), 25.3 (t), 22.7 (t), 14.1 (q); MS (CI) *m/z* 288 (MH^+), 216; HRMS (CI): calcd for $C_{20}H_{34}N$ 288.2691; found 288.2690. Anal. Calcd for $C_{20}H_{33}N$: C, 83.56; H, 11.57; N, 4.87. Found C, 83.69; H, 11.92; N, 4.71.

X-Ray data for (1*S*,1'*S*)-7a · HCl. X-Ray diffraction studies on a colourless crystal of (1*S*,1'*S*)-**7a**·HCl grown from dichloromethane/ether were performed at 293 K using a Bruker SMART diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods. $C_{16}H_{28}NCl$, *M* = 269.84, orthorhombic, space group $P2_12_12_1$, *a* = 7.200(7), *b* = 12.047(21), *c* = 19.396(25) Å, *U* = 1683(4) $Å^3$, Z = 4, D_c = 1.065 Mgm^{-3}, μ = 0.214 mm^{-1}, *F* (000) = 592, crystal size = 0.10 x 0.10 x 0.02 mm, Flack parameter -0.03(10). Of 3467 measured data, 2154 were unique (R_{int} = 0.0286) and 4108 observed ($I > 2\sigma(I)$]) to give R_1= 0.0388 and wR_2 = 0.1000. All non-hydrogen atoms were refined with

anisotropic displacement parameters; both NH protons were located from a Δ*F* map and allowed to refine isotropically subject to a distance constraint (N-H = 0.98 Å). All remaining hydrogen atoms bound to carbon were idealised and fixed. The assignment of the chiral centres is unambiguous. Structural refinements were by the full-matrix least-squares method on F^2. Full lists of structure refinement data, atomic co-ordinates, bond lengths and angles, anisotropic displacement parameters and hydrogen atom parameters have been deposited as supplementary material, C.C.D.C. No. 179329 at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk].

(1*S*)-[1-(1,1-Dimethylethyl)butyl]amine hydrochloride (8•HCl). To a solution of **7a** (70 mg, 0.300 mmol) in ether (2 mL) was added 1 M HCl in ether (2 mL). The mixture was stirred for 5 min, then the solvent removed. Anhydrous methanol (10 mL) was added to the resulting white solid, followed by 20% palladium hydroxide on carbon (20 mg), and the mixture stirred overnight at rt under an atmosphere of hydrogen. The mixture was filtered through Celite then concentrated. Recrystallisation (CH_2Cl_2 / ether) gave **8**•HCl (45.2 mg, 91%) as a white crystalline solid. mp 218-220°C; $[\alpha]_D^{26}$ –25° (*c* 1.0, MeOH); IR (film) 3432, 2966, 1603, 1521, 1271 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.27 (3H, br s), 2.90-2.76 (1H, m), 1.93-1.81 (1H, m), 1.70-1.55 (2H, m), 1.52-1.37 (1H, m), 1.08 (9H, s), 0.93 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 61.9 (d), 33.7 (s), 31.2 (t), 26.5 (q), 20.4 (t), 13.9 (q); MS (ES^+) *m/z* 130 (MH^+); HRMS (ES^+): calcd for $C_8H_{20}N$ 130.1596; found 130.1595.

Determination of the enantiomeric purity of (*S*)-8. To a stirred solution of (*S*)-**8**•HCl (5 mg, 0.030 mmol) and diisopropylethylamine (12.2 µL, 0.070 mmol) in dichloromethane (0.5 mL) was added (S)-(+)-(α)-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (9.7 mg, 0.038 mmol). The reaction was stirred at rt overnight then concentrated under reduced pressure. Aqueous ammonium chloride (1 M, 2 mL) was added and the mixture stirred for 30 min, then extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) then concentrated. Column chromatography (10% ethyl acetate / pet. ether) on silica gave the corresponding MPTA amide (11 mg, 100%) as a colourless oil. IR (film) 3421, 2960, 1696, 1516, 1168 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ7.74 (2H, d, *J* = 7.5 Hz), 7.16-7.00 (3H, m), 6.34 (1H, br d, *J* = 9.4 Hz), 3.92 (1H, m), 3.12 (3H, m), 1.48-1.33 (3H, m), 0.95-0.82 (1H, m), 0.88 (3H, t, *J* = 7.0 Hz), 0.70 (9H, s); MS (CI) *m/z* 346 (M^+), 288; HRMS (CI): calcd for $C_{18}H_{27}NO_2F_3$ 346.1994; found 346.1993. Integration of the ^{1}H NMR signals at: 3.12 (maj), 3.21 (min); and 0.79 (min) and 0.70 (maj) established (*S*)-**8** to be ≥95%ee. The MTPA amide derived from (±)-**8** was made and used for comparison purposes.

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