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Asymmetric deprotonation of *N*-Boc-piperidines

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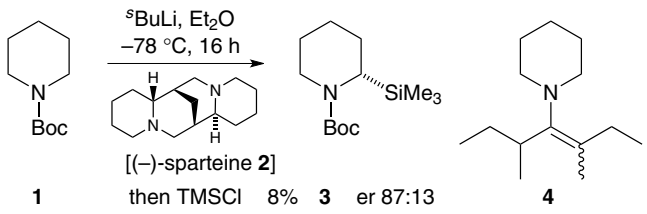
Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

Abstract—A selection of chiral ligands was screened for the asymmetric deprotonation of *N*-Boc-piperidine. The asymmetric deprotonation of this compound is notoriously difficult and reasonable yields are obtained only with non-hindered ligands, such as tetramethylethylene diamine (TMEDA). Chiral versions of TMEDA were investigated but even small increases in steric bulk of the ligand caused significant reduction in the yields of the product after electrophilic quench. The ligands studied focused on diamines or amino-alcohols with one or two stereocentres, including C_2-symmetric ligands. In general these promoted low levels of enantioselectivity in this transformation; however a C_2-symmetric ligand first reported by Alexakis et al. gave a high enantiomer ratio but a low yield of the product. The substrate *N*-Boc-piperidine is therefore much more sensitive to steric factors in comparison with the related and highly enantioselective deprotonation of *N*-Boc-pyrrolidine. The application of the chemistry to two 4-substituted piperidines was also investigated and variable enantiomer ratios were obtained.

1. Introduction

Asymmetric deprotonation is a powerful technique in organic synthesis. Typically, substrates are treated with a chiral lithium amide base or with an organolithium complexed to a chiral ligand, most commonly (−)-sparteine. Using carbamates, proton abstraction occurs α- to either a nitrogen or oxygen atom.[1] One such substrate is *N*-Boc-pyrrolidine, in which the *pro-S* hydrogen atom at C-2 of the pyrrolidine is removed using *sec*-BuLi and (−)-sparteine with very high enantioselectivity [enantiomer ratio (er) 97:3].[2] Kinetic studies have shown that the formation of a three-component complex of the alkyllithium, (−)-sparteine and *N*-Boc-pyrrolidine occurs prior to a rate-determining proton abstraction.[3] The high enantioselectivity arises from the lower activation energy of one diastereomeric transition state due to reduced steric effects.[4] Removal of the *pro-R* hydrogen atom occurs through a more congested and higher energy pathway.

Highly selective asymmetric deprotonation is, however, limited to a small number of substrates. The extension even to the homologous *N*-Boc-piperidine has been found to be very unsatisfactory.[5,6] Thus, treatment of *N*-Boc-piperidine **1** with 1.3 equiv of *sec*-BuLi and (−)-sparteine **2** required 16 h to give only 8% yield of *N*-Boc-2-trimethylsilyl-piperidine **3**, formed after electrophilic quenching with trimethylsilyl chloride (TMSCl) (Scheme 1).[5] The major product was recovered starting material **1**, although at elevated temperatures (−40 °C for 3 h) the enamines **4**, which must arise from competitive addition of *sec*-BuLi to the carbamate group, were formed (43% yield). The er of product



Scheme 1. Deprotonation with ligand (−)-sparteine.

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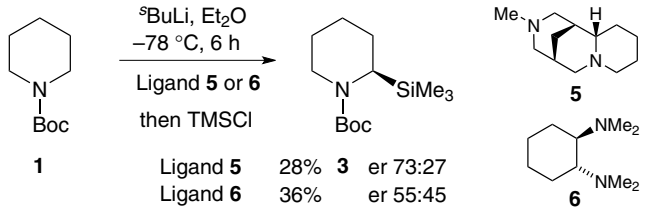
3 was found to be 87:13 in favour of the (*S*)-configuration at C-2. Asymmetric deprotonation of a related cyclic amine (a phenanthroline derivative) with (−)-sparteine has recently been reported with similar enantioselectivity (er 84:16, yield 25–30%).[7]

The ligand (−)-sparteine is fairly bulky and its complex with *sec*-BuLi has been found to be less reactive than that of some simpler diamines.[6] Two such diamines, **5** and **6**, have been screened for the asymmetric deprotonation of *N*-Boc-piperidine. Using 1.4 equiv of *sec*-BuLi and 2.4 equiv of the diamine, the 2-substituted piperidine **3** was obtained with improved yields, although at the expense of enantioselectivity (Scheme 2).[6]

The presence of the piperidine ring system in a large number of alkaloids and biologically active molecules makes the improvement of this chemistry of significant interest. Proton abstraction to give racemic *N*-Boc-2-lithiopiperidine is possible using the ligand tetramethylethylene diamine (TMEDA) and electrophilic quench leads to 2-substituted piperidines in yields of 35–94%.[8,9] This ligand is the least hindered diamine and its complex with *sec*-BuLi is the most reactive.



Scheme 2. Deprotonation with ligands **5** and **6**.

2. Results and discussion

Lithiation of *N*-Boc-piperidine **1** using *sec*-BuLi and TMEDA in Et_2O is known to occur by removal of an equatorial proton.[8–10] No proton abstraction occurs in the absence of a ligand. Of course the ligand TMEDA gives rise to racemic products after electrophilic quenching and as far as we are aware, the only ligands reported for the asymmetric transformation are the diamines (−)-sparteine **2**, **5** and **6**.[5,6,11] These chiral ligands provide only low yields of product **3** after quenching with TMSCl. Unfortunately, the ligand that provides the highest yield (ligand **6**), gives rise to the poorest level of enantioselectivity (Scheme 2). We were therefore interested in exploring ligands that improved the yield of the product and in addition were able to effect asymmetric induction. We selected to investigate the chiral ligands **8**–**21** (Fig. 1), which were prepared using standard methods as described in Section 3 or were available commercially.

Proton abstraction of *N*-Boc-piperidine was carried out under standard conditions using 1.3 equiv of *sec*-BuLi and ligand, and a time of 6 h was allowed for lithiation. The organolithium was quenched with either TMSCl or $PhMe_2SiCl$ to give products **3** or **7** (Scheme 3).

Results (yields and enantiomer ratios) are given in Table 1. In each case, the majority of the mass balance was recovered starting material. The enantiomer ratios of products **3** were determined by chiral stationary phase GC analysis using a β-cyclodextrin-permethylated 120 fused silica capillary column. The absolute configuration of the major enantiomer was established after preparation of an authentic sample of (*S*)-**3** according to Scheme 1 (absolute

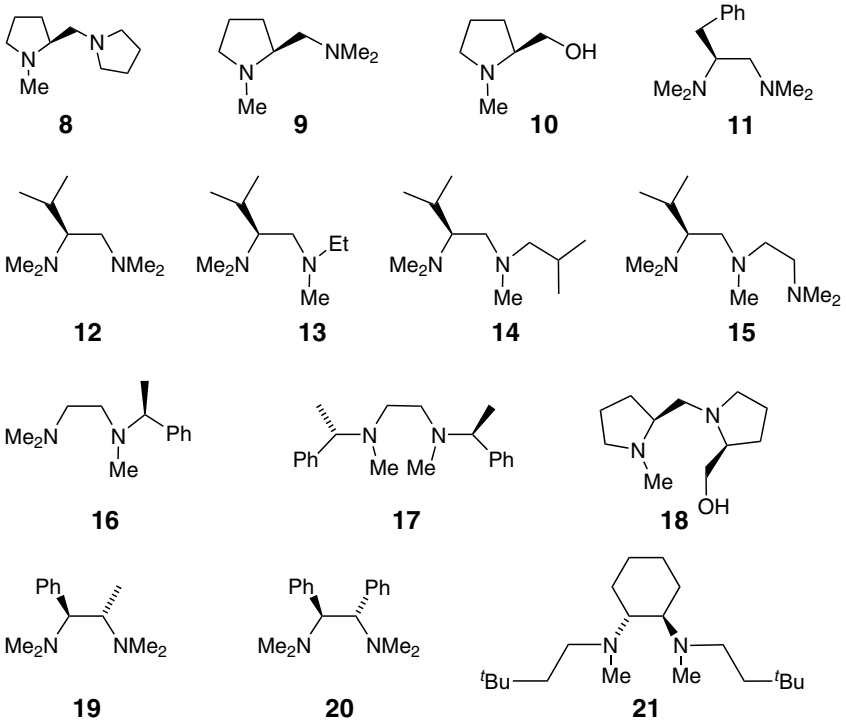
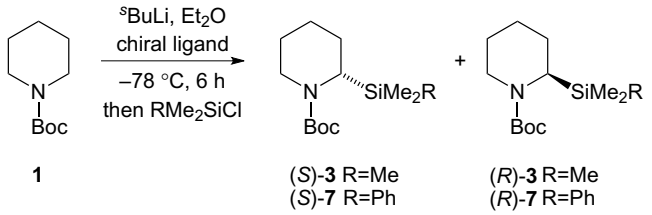


Figure 1. Ligands **8**–**21**.



Scheme 3. Deprotonation with ligands **8**–**21**.

Table 1. Yields and enantiomer ratios using ligands **8**–**21** (Scheme 3)

Entry	Ligand	Product	Yield (%)	er (*S*):(*R*)
1	**8**	**7**	21	52:48
2	**9**	**3**	37	66:34
3	**10**[a]	**7**	18	50:50
4	**11**	**3**	50	65:35
5	**12**	**3**	29	67:33
6	**13**	**3**	11	66:34
7	**14**	**3**	0	—
8	**15**	**3**	0	—
9	**16**	**3**	15	70:30
10	**17**	**7**	0	—
11	**18**[a]	**3**	0	—
12	**19**	**3**	50	59:41
13	**20**	**3**	50	60:40
14	**21**	**3**	13	90:10

[a] One extra equivalent of *sec*-BuLi added to deprotonate the alcohol.

configuration by X-ray structure analysis of the *p*-bromobenzamide).[5] The enantiomer ratios of products **7** were determined by chiral HPLC on a Chiralcel OD column.

From the results in Table 1, several conclusions can be drawn. Firstly, ligand **9** gives higher yields and enantioselectivities than ligand **8**. Therefore the dimethylamino substituent seems preferable to the pyrrolidine. However, the hydroxy substituent (deprotonated with an extra equivalent of base) is unsuitable; some product was obtained with the amino-alcohol **10** but there was no asymmetric induction.

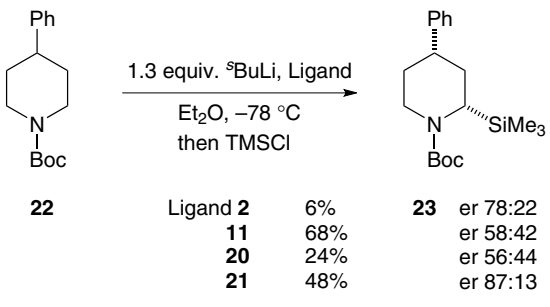
The fairly low yield, even with diamine **9** encouraged us to use a ligand more akin to TMEDA, with two dimethylamino substituents and an asymmetry within the connecting two-carbon chain. Ligands **11** and **12** were studied and gave reasonable yields of product **3** (entries 4 and 5). Using these ligands, enantiomer ratios were moderate, with only about a 2:1 preference for abstraction of the *pro-S* hydrogen atom. Ligand **11** does represent, however, one of the best ligands so far for this transformation, promoting reasonable yield and with some degree of enantioselectivity.

When the nitrogen atom of the ligand bears different substituents then, on complexation to lithium, the configuration of this nitrogen atom could play a role in any asymmetric induction.[12] We therefore prepared ligands **13** and **14** with a view to exploring any such effect. However, yields were reduced substantially on increasing the bulk around the nitrogen atom. With ligand **13**, a low yield of product **3** was obtained, although the enantioselectivity was no different from that using the dimethylamino derivative **12**. Triamine ligand **15** was unsuitable, possibly for the same reason. However, the less hindered ligand **16** did give some of product **3** with reasonable enantioselectivity. With the C_2-symmetric ligand **17**, however, the chemistry once again suffers from lack of any proton abstraction. Ligand **18** (after alcohol deprotonation) is a good ligand for asymmetric substitution of 2-lithiopyrrolidines,[13] but was found to give no product in the attempted asymmetric deprotonation of *N*-Boc-piperidine **1**.

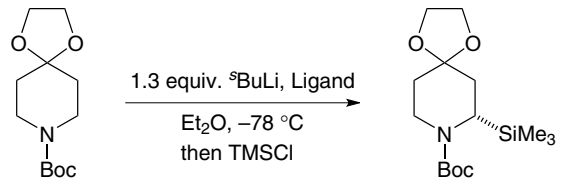
We then studied diamine ligands **19**–**21**.[14] Ligand **19** gave a good yield of product **3** with low enantioselectivity. The C_2-symmetric ligand **20** gave a good yield of the desired product, once again illustrating the lower steric encumbrance of the N-permethylated ligands, although the enantioselectivity was low. Interestingly, ligand **21** gave a high enantioselectivity (er 90:10), although the yield with this bulkier ligand was low.

As an alternative substrate, *N*-Boc-4-phenylpiperidine **22** was tested (Scheme 4). This substrate is reported as being more reactive than *N*-Boc-piperidine towards lithiation.[9] Indeed, using TMEDA as a ligand seems to promote more rapid lithiation and the racemic product **23** could be isolated in high yield (90%). Only one stereoisomer was obtained (assumed to have a cis-configuration as reported[8]). A selection of the chiral ligands was screened for this reaction. Product **23** was formed in variable yield, with the best levels of enantioselectivity (determined by chiral GC analysis) obtained using ligand **21**. The absolute configuration of the major enantiomer of product **23** was not determined but is likely to be consistent with product **3**.

In substrate **22**, a ring-flip of the piperidine causes the phenyl substituent to change between the equatorial and axial locations. If we assume that (in the same way as *N*-Boc-piperidine) the equatorial proton is removed and the resulting organolithium quenches with retention of configuration, then in order to obtain the cis-product, there must be no deprotonation of the axial conformer. For the proton abstraction of **22** with the phenyl group in the equatorial position, it is still possible to obtain high yields of either enantiomeric product but only if there is rotation of the *N*-Boc group. This is by no means rapid at low temperature as the half life for rotation of related *N*-Boc-cyclic amines has been found to be many hours at −78 °C.[15] If the barrier to rotation of the *N*-Boc-piperidines is high at low temperature, then high enantioselectivities would be achieved only



Scheme 4. Deprotonation of *N*-Boc-4-phenylpiperidine.



24 Ligand **2** 0% **25** er –
11 47% er 60:40
20 6% er 60:40
21 53% er 47:53

Scheme 5. Deprotonation of piperidine **24**.

under a kinetic resolution, in which one of the rotamers (of one chair conformation) reacts faster than the other. This theory would be supported if higher enantiomer ratios were obtained by running the reaction to less than 50% yield. Therefore the reaction using ligand **11** was repeated with only 0.65 equiv of *sec*-BuLi. This gave product **23** in 24% yield with a slightly increased enantiomer ratio (er 63:37). Although this increase in enantioselectivity is not large, it is significant and supports the likelihood that there is no rotation of the *N*-Boc group at −78 °C. The enantiomer ratio (er 87:13) for product **23** using ligand **21**, in which 48% yield is obtained, may therefore be about optimal. This represents the best result reported for the asymmetric deprotonation of a piperidine.

Finally, we studied substrate **24**, bearing an acetal at the 4-position of the piperidine ring (Scheme 5). This substrate seems to be less suited to this chemistry and gives similar or lower yields in comparison to that using *N*-Boc-piperidine, although ligand **21** was higher yielding than expected. However in all cases, product **25** was formed with low enantioselectivity (absolute configuration not determined).

It is clear that the asymmetric deprotonation of *N*-Boc-piperidines is more difficult than that of the homologous *N*-Boc-pyrrolidines. Calculations at the B3P86/6-31+G* level suggest that the activation energy for removal of a proton in *N*-Boc-piperidine is some 2–3 kcal/mol higher than that for the removal of a proton in the 5-membered ring analogue.[5] The lithiation is clearly sensitive to sterics within the ligand and this makes it difficult to design a chiral ligand that is efficient both in terms of promoting a high yield and simultaneously a high enantioselectivity in the deprotonation of this substrate. Despite this, some promising results have been obtained, particularly using ligand **21**; this ligand can provide high enantioselectivities and leads to reasonable yields using a substrate, such as *N*-Boc-4-phenylpiperidine, which is more reactive than *N*-Boc-piperidine.

3. Experimental

3.1. General

Experiments were carried out under an inert atmosphere of nitrogen. Solvents were purified using a Grubbs solvent purification system.[16] Petrol refers to light petroleum (bp 40–60 °C). The ligands TMEDA and (−)-sparteine were obtained from commercial suppliers and were distilled under reduced pressure prior to use. Column chromatography was performed on silica gel (230–400 mesh). Infrared spectra were recorded on a Nicolet Magna 550 FT-IR spectrometer or on a Perkin–Elmer Spectrum RX1/FT IR system with a DuraSampl IR-II diamond ATR. ^{1}H and ^{13}C NMR spectra were recorded on Brucker instruments at various field strengths as indicated. Chemical shifts are reported in parts per million (ppm) relative to solvent signals and coupling constants, *J*, are given in Hz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Mass spectra were run on a Micromass GCT instrument or Micromass LCT. Low resolution mass spectra were recorded using a Thermoquest CE Trace GCMS2000 series instrument fitted with a Restek RTX-5MS (Cross bond 5% diphenyl, 95% dimethyl polysiloxane 15 m column) with helium as the carrier gas using either EI or CI mode. Microanalysis was performed on a Carlo Erba 1110 instrument.

3.2. General procedure for the lithiation

To the chiral ligand (0.70 mmol) in Et_2O (2 mL) was added *sec*-BuLi (0.50 mL, 0.70 mmol, 1.4 M) (or 0.97 mL, 1.35 mmol for amino-alcohol ligands **10** and **18**) at −78 °C. After 15 min, *N*-Boc-piperidine (100 mg, 0.54 mmol) was added dropwise. After 6 h, Me_3SiCl (146 mg, 1.35 mmol) or $PhMe_2SiCl$ (138 mg, 0.81 mmol) was added and the mixture was allowed to warm to room temperature over 16 h. MeOH (1 mL) was added, the solvents removed under reduced pressure and the residue purified by column chromatography on silica, eluting with petrol–EtOAc (97:3), to give either product **3** or **7** (yields given in Table 1), as an oil.

Spectroscopic data for compound **3** were identical to that reported.[5] The enantiomer ratio of product **3** was determined by chiral stationary phase GC using β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d. [20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi], retention times 27.6 min (major) and 28.3 min (minor) (at 85 °C). The absolute configuration of the major enantiomer of product **3** was verified by preparation of an authentic sample of (*S*)-**3** according to the literature.[5]

Data for compound **7**: ν_{max} (film)/cm^{-1} 2930 (C–H), 1680 (C=O); δ_H (500 MHz, DMSO-d_6, 80 °C) 7.60–7.55 (2H, m, Ph), 7.41–7.35 (3H, m, Ph), 4.00–3.50 (2H, br, NCH_2), 3.09–2.70 (1H, br, NCH), 1.73–1.57 (2H, m, CH_2), 1.57–1.28 (4H, br, $2 \times CH_2$), 1.41 (9H, s, *t*-Bu), 0.42 (3H, s, SiMe), 0.36 (3H, s, SiMe); δ_C (63 MHz, DMSO-d_6, 80 °C) 153.7, 138.4, 133.2, 128.34, 127.2, 77.9, 44.9, 43.1, 27.7, 25.3, 25.1, 22.4, −2.8, −3.0. Found (ES): MNa^+, 342.1853. $C_{18}H_{29}NO_2NaSi$ requires 342.1865; GC–MS *m/z* (ES) 342 (100%, MNa^+). Found: C, 67.72; H, 8.85; N, 4.18. $C_{18}H_{29}NO_2Si$ requires C, 67.66; H, 9.15; N, 4.38. The enantiomer ratio of product **7** was determined by HPLC on a Chiralcel OD column; the resolution between the enantiomers of the compound was achieved

using a Gilson 300 series system fitted with a Chiralcel OD column (250 mm × 4.6 mm i.d.) as the stationary phase with a mixture of *n*-hexane/isopropanol (99.5:0.5 v/v) as the mobile phase at a flow rate of 0.5 mL/min, ambient temperature, detection by UV absorbance at 254 nm; injection volume 25 μL of the sample prepared in a 2–4 mg/mL solution of eluent; retention times 9.3 min (minor) and 11.9 min (major).

3.3. Preparation of the chiral ligands

Ligands **8** and **9** were prepared according to the reported methods from *N*-Cbz-L-proline.[17] Ligands **10**, **18** and **20** were obtained from commercial suppliers. Ligands **17**, **19** and **21** were prepared as reported.[14,18,19] Other ligands were prepared as described below.

3.3.1. (*S*)-*N*,*N*,*N*′,*N*′-Tetramethyl-3-phenylpropane-1,2-diamine 11. To *N*-Boc-*N*-methyl-phenylalanine[20] (2.3 g, 8.3 mmol) in $CHCl_3$ (60 mL) was added DCC (1.7 g, 8.3 mmol) followed by HOBt (1.12 g, 8.3 mmol) at room temperature. After 20 min, the dimethylamine (1.05 mL, 8.3 mmol, 40% aq solution) was added. After 16 h, the solvent was evaporated under a reduced pressure and EtOAc (50 mL) was added. The white precipitate was removed by filtration and the filtrate was washed with 5% citric acid solution followed by 10% $NaHCO_3$ solution. The organic layer was separated, dried over $MgSO_4$ and evaporated. The crude amide was used in the next step without further purification.

The amide (2.43 g, 7.9 mmol) in THF (60 mL) was added via cannula over 30 min to a suspension of $LiAlH_4$ (1.20 g, 31.7 mmol) in THF (30 mL) at room temperature. The mixture was heated at reflux for 16 h, then was cooled to 0 °C and EtOAc (10 mL) was added slowly, followed by a slurry of Na_2SO_4 in water (with care!). The resulting white precipitate was filtered and washed with EtOAc (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by bulb-to-bulb distillation to give diamine **11** (1.25 g, 74%) as an oil; $[\alpha]_D^{24} = +50$ (*c* 1.6, $CHCl_3$); bp 5 mbar/42 °C; ν_{max} (film)/cm^{-1} 2930, 2855, 2815 and 2765 (C–H); δ_H (250 MHz, $CDCl_3$) 7.16–7.30 (5H, m, Ph), 2.83–2.93 (2H, m, 2 × CH), 2.39–2.52 (2H, m, 2 × CH), 2.35 (6H, s, 2 × CH_3), 2.13 (6H, s, 2 × CH_3), 1.95–2.02 (1H, m, CH); δ_C (63 MHz, $CDCl_3$) 140.0, 129.0, 128.2, 125.6, 63.5, 59.7, 45.7, 40.4, 32.6. Found (ES): MH^+, 207.1858. $C_{13}H_{23}N_2$ requires 207.1861; GC–MS *m*/*z* (ES) 207 (100%, MH^+). For an alternative procedure but no spectroscopic data, see Ref. 21.

3.3.2. (*S*)-*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-diamino-3-methylbutane 12. In the same way as diamine **11**, *N*-Boc-*N*-methyl-valine[20] (3.1 g, 13.4 mmol), DCC (2.7 g, 13.4 mmol), HOBt (1.8 g, 13.4 mmol) and dimethylamine (1.7 mL, 13.4 mmol, 40% aq solution) gave the crude amide, which was used in the next step without further purification.

In the same way as diamine **11**, the amide (3.2 g, 12.5 mmol) and $LiAlH_4$ (1.9 g, 49.8 mmol) gave, after bulb-to-bulb distillation, diamine **12** (1.18 g, 56%) as an oil; $[\alpha]_D^{24} = +28.0$ (*c* 2.5, $CHCl_3$); bp 120 °C/4 mm Hg; ν_{max} (film)/cm^{-1} 2935, 2860, 2815 and 2760 (C–H); δ_H (400 MHz, $CDCl_3$) 2.34–2.40 (2H, m, 2 × CH), 2.27 (6H, s, 2 × CH_3), 2.16 (6H, s, 2 × CH_3), 1.98–2.02 (1H, m, CH), 1.73–1.81 (1H, m, CH), 0.89 (3H, d, *J* 6.5, CH_3), 0.86 (3H, d, *J* 6.5, CH_3); δ_C (100 MHz, $CDCl_3$) 66.4, 57.9, 45.9, 41.6, 28.5, 21.3, 19.3. Found (ES): MH^+, 159.1864. $C_9H_{23}N_2$ requires 159.1861; GC–MS *m*/*z* (ES) 159 (100%, MH^+). Data consistent with that reported, except for lit. $[\alpha]_D = +178$ (*c* 2.61, $CHCl_3$);[22] due to the difference in the specific rotations, we prepared diamine **12** by an alternative procedure: *N*-Boc-valine was coupled with dimethylamine using DCC/HOBt, followed by removal of the Boc group with TFA, Eschweiler–Clark dimethylation of the primary amine then $LiAlH_4$ reduction; this gave the same diamine **12**; $[\alpha]_D^{24} = +22$ (*c* 2.1, $CHCl_3$); we are not able to reconcile the difference between our value and that reported; note however that using our diamine **12**, the er of product **3** was 67:33, indicating that our ligand had at least this level of enantioenrichment and is likely to be enantiomerically pure.

3.3.3. (*S*)-*N*^{1}-Ethyl-*N*,*N*′,*N*′-trimethyl-3-methylbutane-1,2-diamine 13. In the same way as diamine **11**, *N*-Boc-*N*-methyl-valine[20] (2.7 g, 11.8 mmol), DCC (2.4 g, 11.8 mmol), HOBt (1.6 g, 11.8 mmol) and ethylamine (1.0 mL, 13.4 mmol, 70% aq solution) gave the crude amide, which was used in the next step without further purification.

To a suspension of NaH (0.57 g, 14.2 mmol, 60% in oil) in THF (25 mL) was added the amide (2.8 g, 10.9 mmol) and MeI (6.8 mL, 109.3 mmol) in THF (50 mL) at 0 °C over 30 min via cannula. The mixture was allowed to warm to room temperature over 16 h, then water (10 mL) and saturated NH_4Cl (50 mL) were added. The mixture was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with brine solution and dried over $MgSO_4$. The solvent was evaporated to give the crude tertiary amide (3.08 g) which was used in the next step without further purification.

In the same way as diamine **11**, the tertiary amide (3.07 g, 11.3 mmol) and $LiAlH_4$ (1.7 g, 45.2 mmol) gave, after bulb-to-bulb distillation, diamine **13** (1.21 g, 60%) as an oil; $[\alpha]_D^{24} = +26.0$ (*c* 3.1, $CHCl_3$); ν_{max} (film)/cm^{-1} 2955, 2925, 2865 and 2780 (C–H); δ_H (400 MHz, $CDCl_3$) 2.31–2.46 (3H, m, CH and CH_2), 2.29 (6H, s, 2 × CH_3), 2.18–2.23 (1H, m, CH), 2.15 (3H, s, CH_3), 2.11–2.07 (1H, m, CH), 1.81–1.73 (1H, m, CH), 1.00 (3H, t, *J* 7.0, CH_3), 0.90 (3H, d, *J* 6.5, CH_3), 0.88 (3H, d, *J* 6.5, CH_3); δ_C (100 MHz, $CDCl_3$) 66.3, 55.4, 52.0, 42.1, 41.8, 28.8, 21.3, 19.5, 12.2. Found (ES): MH^+, 173.2014. $C_{10}H_{25}N_2$ requires 173.2018; GC–MS *m*/*z* (ES) 240 (100%, MNa^+).

3.3.4. (*S*)-*N*^{1}-Isobutyl-*N*,*N*′,*N*′-trimethyl-3-methylbutane-1,2-diamine 14. In the same way as diamine **11**, *N*-Boc-*N*-methyl-valine[20] (2.65 g, 11.5 mmol), DCC (2.35 g, 11.5 mmol), HOBt (1.55 g, 11.5 mmol) and isobutylamine (1.15 mL, 11.5 mmol) gave the crude amide, which was used in the next step without further purification.

In the same way as diamine **13**, NaH (0.61 g, 15.2 mmol, 60% in oil) and the amide (3.3 g, 11.5 mmol) and MeI (7.3 mL, 117 mmol) gave the crude tertiary amide (3.6 g) which was used in the next step without further purification.

In the same way as diamine **11**, the tertiary amide (3.5 g, 11.5 mmol) and $LiAlH_4$ (1.85 g, 48.8 mmol) gave, after bulb-to-bulb distillation, diamine **14** (1.54 g, 67%) as an oil; $[\alpha]_D^{24} = +11.8$ (*c* 2.8, $CHCl_3$); bp 6 mbar/90 °C; ν_{max} (film)/cm^{-1} 2945, 2925, 2865 and 2770 (C–H); δ_H (400 MHz, $CDCl_3$) 2.36–2.41 (1H, m, CH), 2.29 (6H, s, $2 \times CH_3$), 2.12–2.17 (2H, m, $2 \times CH$), 2.11 (3H, s, CH_3), 1.98–2.0 (1H, m, CH), 1.65–1.77 (2H, m, $2 \times CH$), 0.91 (3H, d, *J* 6.7, CH_3), 0.89 (3H, d, *J* 6.7, CH_3), 0.85 (3H, d, *J* 3.0, CH_3), 0.83 (3H, d, *J* 3.0, CH_3); δ_C (100 MHz, $CDCl_3$) 67.3, 66.5, 57.3, 42.3, 42.0, 29.6, 26.0, 21.1, 20.9, 19.5. Found (EI): M^+, 200.2252. $C_{12}H_{28}N_2$ requires 200.2252; GC–MS *m*/*z* (EI) 200 (5%, M^+), 114 (12), 100 (100).

3.3.5. (*S*)-N^1-(2-Dimethylaminoethyl)-*N*,*N*′,*N*′-trimethyl-3-methylbutane-1,2-diamine 15. In the same way as diamine **11**, *N*-Boc-*N*-methyl-valine[20] (1.7 g, 7.5 mmol), DCC (1.5 g, 7.5 mmol), HOBt (1.0 g, 7.5 mmol) and trimethylethylenediamine (1.0 mL, 7.5 mmol) gave the crude amide, which was used in the next step without further purification.

In the same way as diamine **11**, the amide (2.3 g, 7.4 mmol) and $LiAlH_4$ (1.1 g, 29.6 mmol) gave, after bulb-to-bulb distillation, diamine **15** (1.23 g, 76%) as an oil; $[\alpha]_D^{24} = +23.8$ (*c* 2.2, $CHCl_3$); bp 5 mbar/100 °C; ν_{max} (film)/cm^{-1} 2945, 2850, 2810 and 2765 (C–H); δ_H (400 MHz, $CDCl_3$) 2.35–2.54 (7H, m, CH and $3 \times CH_2$), 2.31 (6H, s, $2 \times CH_3$), 2.23 (6H, s, $2 \times CH_3$), 2.20 (3H, s, CH_3), 1.74–1.84 (1H, m, CH), 0.92 (3H, d, *J* 6.5, CH_3), 0.90 (3H, d, *J* 6.5, CH_3); δ_C (100 MHz, $CDCl_3$) 66.3, 57.4, 56.6, 56.4, 45.8, 42.9, 41.8, 28.9, 19.4, 18.9. Found (ES): MH^+, 216.2435. $C_{12}H_{30}N_3$ requires 216.2440; GC–MS *m*/*z* (ES) 216 (100%, MH^+).

3.3.6. (*S*)-*N*,*N*,*N*′-Trimethyl-*N*′-(1-phenylethyl)ethane-1,2-diamine 16. In the same way as diamine **11**, *N*-Boc-*N*-methyl-glycine (2.5 g, 13.2 mmol), DCC (2.7 g, 13.2 mmol), HOBt (1.8 g, 13.2 mmol) and 1-phenylethylamine (1.7 mL, 13.2 mmol) gave the crude amide, which was used in the next step without further purification. In the same way as diamine **13**, NaH (0.4 g, 16 mmol, 95%) and the amide (3.6 g, 12.3 mmol) and MeI (7.7 mL, 123 mmol) gave the crude tertiary amide (3.7 g) which was used in the next step without further purification.

In the same way as diamine **11**, the tertiary amide (3.7 g, 12.1 mmol) and $LiAlH_4$ (1.83 g, 48.3 mmol) gave, after bulb-to-bulb distillation, diamine **16** as an oil; $[\alpha]_D^{24} = -33.1$ (*c* 2.6, $CHCl_3$); ν_{max} (film)/cm^{-1} 2970, 2940, 2820 and 2770 (C–H); δ_H (400 MHz, $CDCl_3$) 7.22–7.33 (5H, m, Ph), 3.58 (1H, q, *J* 7.0, CH), 2.55–2.61 (1H, m, CH), 2.32–2.41 (3H, m, CH and CH_2), 2.24 (3H, s, CH_3), 2.19 (6H, s, $2 \times CH_3$), 1.39 (6H, d, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 143.5, 128.0, 127.6, 126.7, 63.9, 57.4, 52.0, 45.7, 38.9, 18.5. Found (EI): M^+, 206.1782. $C_{13}H_{22}N_2$ requires 206.1791; GC–MS *m*/*z* (EI) 206 (5%, M^+), 148 (50), 105 (100).

3.4. Procedure for the lithiation of 22

To the chiral ligand (0.70 mmol) in Et_2O (1 mL) was added *sec*-BuLi (0.50 mL, 0.70 mmol, 1.4 M) at −78 °C. After 15 min, *N*-Boc-4-phenylpiperidine **22** (141 mg, 0.54 mmol) in Et_2O (1 mL) was added dropwise. After 6 h, Me_3SiCl (146 mg, 1.35 mmol) was added and the mixture was allowed to warm to room temperature over 16 h. MeOH (1 mL) was added, the solvents were removed under reduced pressure and the residue was purified by column chromatography on silica, eluting with petrol–EtOAc (97:3), to give product **23** (yields given in Scheme 4), as cubes; mp 64–66 °C; $[\alpha]_D^{24} = +4.6$ (*c* 1.1, $CHCl_3$) for **23** er 87:13 (prepared using ligand **21**) based on chiral GC as described below; ν_{max} (film)/cm^{-1} 2925 (C–H), 1675 (C=O); δ_H (250 MHz, $CDCl_3$) 7.40–7.20 (5H, m, Ph), 4.20–4.10 (1H, br, CH), 3.10–2.90 (1H, br, CH), 2.82–2.67 (1H, br, CH), 2.80–2.47 (1H, br, CH), 1.90–1.50 (4H, br, $2 \times CH_2$), 1.50 (9H, s, *t*-Bu), 0.11 (9H, s, $SiMe_3$); δ_C (63 MHz, $CDCl_3$) 155.1, 146.3, 128.5, 126.9, 126.2, 79.0, 51.0, 48.0, 44.8, 34.2, 33.5, 28.4, −0.7. Found (ES): MH^+, 334.2213. $C_{19}H_{32}NO_2Si$ requires 334.2202; GC–MS *m*/*z* (ES) 334 (16%, MH^+), 278 (100), 262 (38). Found: C, 68.38; H, 9.59; N, 3.92. $C_{19}H_{31}NO_2Si$ requires C, 68.42; H, 9.37; N, 4.20.

The enantiomeric ratio of product **23** was determined by chiral stationary phase GC using β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d. [20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, hydrogen carrier at 14 psi], retention times 34.0 min and 34.6 min (isothermal at 140 °C).

3.5. Procedure for the lithiation of 24

To the chiral ligand (0.70 mmol) in Et_2O (1 mL) was added *sec*-BuLi (0.50 mL, 0.70 mmol, 1.4 M) at −78 °C. After 15 min, piperidine **24** (170 mg, 0.54 mmol) in Et_2O (1 mL) was added dropwise. After 6 h, Me_3SiCl (146 mg, 1.35 mmol) was added and the mixture allowed to warm to room temperature over 16 h. MeOH (1 mL) was added, the solvents were removed under reduced pressure and the residue was purified by column chromatography on silica, eluting with petrol–EtOAc (97:3), to give product **25** (yields given in Scheme 5), as an oil; ν_{max} (film)/cm^{-1} 2955, 2875 (C–H), 1690 (C=O); δ_H (500 MHz, DMSO-d_6, 80 °C) 3.94 (2H, s, CH_2), 3.935 (2H, s, CH_2), 3.58–3.50 (1H, br, CH), 3.45–3.30 (1H, br, CH), 3.15–2.95 (1H, br, CH), 1.72–1.52 (4H, m, $2 \times CH_2$), 1.45 (9H, s, *t*-Bu), 0.09 (9H, s, $SiMe_3$); δ_C (125 MHz, DMSO-d_6, 80 °C) 154.9, 107.1, 79.2, 64.3, 64.1, 46.1, 43.8, 35.7, 35.5, 28.5, −0.5; Found (ES): MH^+, 316.1942. $C_{15}H_{30}NO_4Si$ requires 316.1944; GC–MS *m*/*z* (ES) 316 (2%, MH^+), 244 (100), 216 (100).

The enantiomeric ratio of product **25** was determined by chiral stationary phase GC using β-cyclodextrin-permethylated 120 fused silica capillary column 30 m × 0.25 mm i.d. [20% permethylated β-cyclodextrin in SPB-35 poly(35% di-

phenyl/65% dimethyl)siloxane, hydrogen carrier at 14 psi], retention times 40.0 min and 40.8 min (isothermal at 115 °C).

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