Investigation of bispidines as the stoichiometric ligand in the two-ligand catalytic asymmetric deprotonation of *N*-Boc pyrrolidine

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Dedicated to William F. Bailey on the occasion of his 65th anniversary

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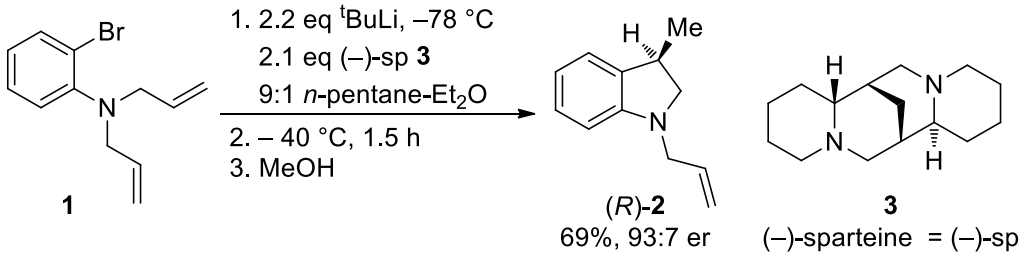
Abstract
A range of achiral bispidines have been synthesized and evaluated as the stoichiometric ligand in the two-ligand catalytic asymmetric deprotonation of *N*-Boc pyrrolidine.

Keywords: Asymmetric synthesis, organolithium reagents, (–)-sparteine, nitrogen heterocycles

Introduction

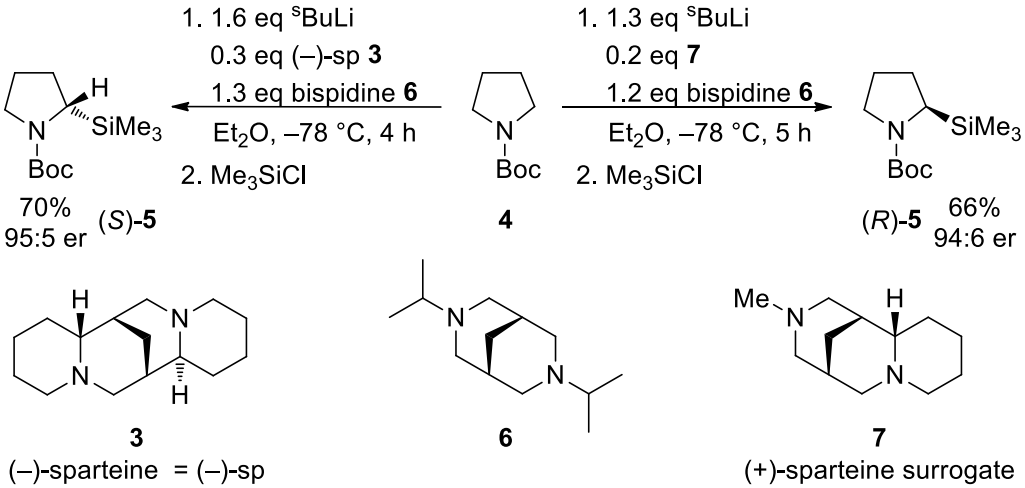
Organolithium/chiral diamine complexes are now established as versatile and useful reagents for the asymmetric synthesis of chiral molecules.[1,2] In this context, (–)-sparteine is the most widely-investigated diamine[3] following the pioneering work by Hoppe[4] and Beak.[5] Indeed, reagents comprising organolithium reagents (*e.g. s*-BuLi or *n*-BuLi) and (–)-sparteine have been used for the asymmetric synthesis of a diverse range of compounds including amines,[6] alcohols,[7] phosphines,[8] ferrocenes[9] and paracyclophanes.[10] An example from Bailey and Mealy[11,12] is representative of the synthetic potential afforded by organolithium/(–)-sparteine reagents. Treatment of di-allylated bromoaniline **1** with *t*-BuLi/(–)-sparteine **3** followed by incubation at –40 °C and quenching with MeOH delivered chiral indoline (*R*)-**2** in 69% yield and 93:7 er (Scheme 1). The reaction proceeds *via* bromine-lithium exchange and subsequent intramolecular carbolithiation in which the facial attack onto the alkene is controlled by coordination of (–)-sparteine to the aryllithium intermediate.



Scheme 1

Our interest in organolithium/(–)-sparteine reagents has focused on their use in the asymmetric deprotonation of *N*-Boc heterocycles. Such asymmetric reactions were first reported by Kerrick and Beak in 1991.[5,13] The contributions to this area from our group have included the development of effective (+)-sparteine surrogates,[14-16] the introduction of two-ligand catalytic asymmetric deprotonation protocols,[17-20] the high yielding asymmetric deprotonation of *N*-Boc piperidine[21] and the introduction of a diamine-free lithiation method.[22]

Two examples of the asymmetric deprotonation of *N*-Boc pyrrolidine **4** using sub-stoichiometric amounts of chiral diamine are shown in Scheme 2. Thus, lithiation of *N*-Boc pyrrolidine **4** with 1.6 eq. *s*-BuLi, 0.3 eq. (–)-sparteine **3** and 1.3 eq. bis-*i*-Pr-bispidine **6** and trapping with Me_3SiCl gave silyl adduct (*S*)-**5** in 70% yield and 95:5 er.[19] If bis-*i*-Pr-bispidine **6** was omitted from the reaction then there was no turn-over of the (–)-sparteine ligand and poor yield and poor enantioselectivity results.[13,17] Interestingly, we have found that (+)-sparteine surrogate **7** can be used in lower loadings than (–)-sparteine to achieve essentially the same level of enantioselectivity. For example, use of 1.3 eq. *s*-BuLi, 0.2 eq. (+)-sparteine surrogate **7** and 1.2 eq. bis-*i*-Pr-bispidine **6** gave silyl adduct (*R*)-**5** in 66% yield and 94:6 er. It is known[18] that *s*-BuLi/(+)-sparteine surrogate **7** lithiates *N*-Boc pyrrolidine **4** faster than *s*-BuLi/(–)-sparteine **3** and we believe that this facilitates more efficient catalytic turn-over.

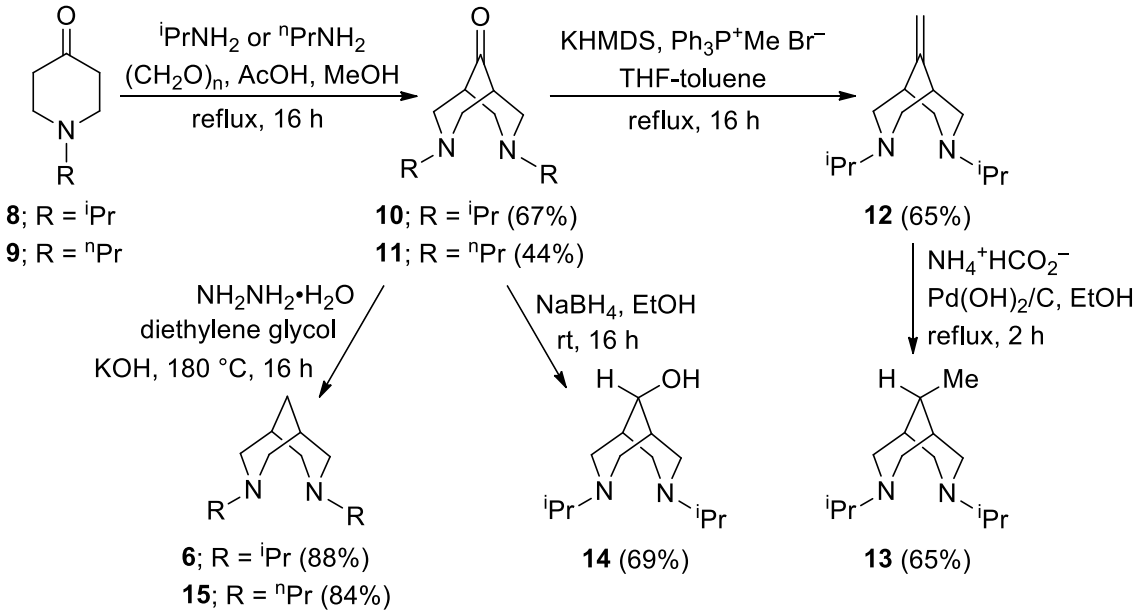


Scheme 2

In both of the examples shown in Scheme 2, success was achieved using a designed recycling diamine, bis-*i*-Pr-bispidine **6**. The idea was that the steric hindrance in *s*-BuLi/bispidine **6** would lead to slow lithiation of *N*-Boc pyrrolidine **4**. However, despite the steric hindrance of bispidine **6**, we hoped that it would participate in ligand exchange and thus recycle the chiral diamine. The successful examples of two-ligand catalysis supported our conjecture. Unfortunately, as disclosed in our original report, bispidine **6** was prepared in a disappointing 26% yield *via* a known[23] two-step route. As a result, we screened several other diamines in an attempt to find a recycling diamine that was easier to synthesise[19] and ultimately concluded that the bispidine framework exemplified by **6** was optimum. Hence, in this paper, we present our efforts at identifying an alternative recycling bispidine ligand to bispidine **6**.

Results and Discussion

To start with, a range of different bispidines was prepared as outlined in Scheme 3. A double Mannich reaction using freshly distilled *N*-*i*-Pr-piperidone **8**, *i*-propylamine and formaldehyde gave bispidone **10** in 67% yield (~21 g scale of product, purified by fractional distillation). In the same way, the *n*-Pr analogue **11** was prepared in 44% yield from *N*-*n*-Pr-piperidone **9** and *n*-propylamine. Our plan was to investigate different methodology for removing or masking the carbonyl functionality in bispidone **10**. A Wittig reaction using the ylid from $Ph_3PMe^+Br^-$ required some optimisation. Eventually, it was found that use of KHMDS as the base and refluxing for 16 hours delivered alkene **12** in 65% yield. Subequent hydrogenation of alkene **12** using $NH_4^+HCO_2^-$ and $Pd(OH)_2/C$ gave bispidine **13** in 65% yield. The ketone in bispidone **10** was readily reduced using $NaBH_4$ to give alcohol **14** (69% yield).



Scheme 3

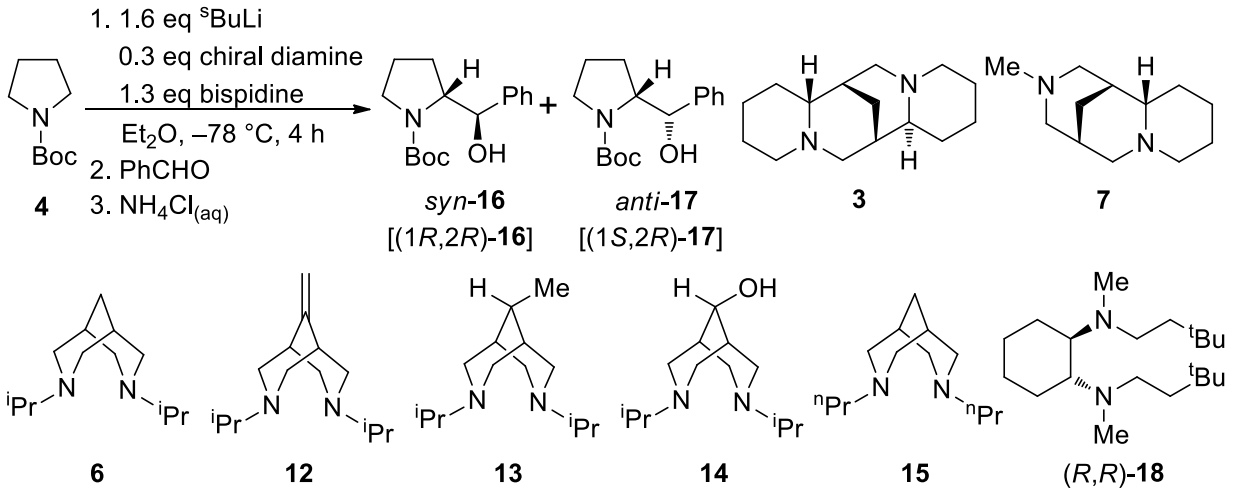
Finally, as part of this study, we re-evaluated the Wolff-Kishner reduction of bispidone **10** to bis-*i*-Pr-bispidine **6**. In our reported method, reaction with hydrazine/KOH was carried out at 180 °C for 4 hours.[17] It transpired that the reaction was incomplete after 4 hours and a simple change to a reaction time of 16 hours led to a significant improvement in yield (88% compared to 38%). In addition, during the work-up, it was necessary to cool the reaction mixture to ~60 °C and transfer it to a separating funnel and then add water. If the diethylene glycol solution was cooled to room temperature before addition of water then the reaction mixture became very viscous and difficult to work with. The bis-*n*-Pr-bispidine **15** was prepared in 84% yield in the same way.

Ultimately, none of the newly prepared analogues of bis-*i*-Pr-bispidine **6** were easier to synthesise than **6** itself. However, we were curious to see whether the other bispidines **12**-**14** would also perform satisfactorily in the two-ligand catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **4**. In addition, using bis-*n*-Pr-bispidine **15**, it would be possible to establish whether steric hindrance on the two nitrogen atoms was required for effective two-ligand catalysis. In order to evaluate the two-ligand catalysis, we utilized the lithiation-benzaldehyde trapping[20] of *N*-Boc pyrrolidine **4** → hydroxy pyrrolidines *syn*-**16** and *anti*-**17**, which can be separated by chromatography (Scheme 4 and Table 1). As a point of reference, a stoichiometric reaction using 1.3 eq. *s*-BuLi/(–)-sparteine **3** was carried out and delivered *syn*-**16** (62% yield, 97:3 er) together with *anti*-**17** (18% yield, 97:3 er) (entry 1). Using 1.6 eq. *s*-BuLi, 0.3 eq. (–)-sparteine **3** and 1.3 eq. bis-*i*-Pr-bispidine **6** gave *syn*-**16** (91:9 er) in 62% yield and *anti*-**17** (91:9 er) in 33% yield (entry 2) indicating successful two-ligand catalytic deprotonation. Slightly lower enantioselectivity (88:12 er) was observed using 1.0 eq. *s*-BuLi, 0.25 eq. (–)-sparteine **3** and 1.0 eq. bis-*i*-Pr-bispidine **6** (entry 4). Under comparable conditions, the (+)-sparteine surrogate **7** engendered higher enantioselectivity (94:6 er, entry 3 and 93:7 er, entry 5) in the expected opposite sense. This confirms that (+)-sparteine surrogate **7** is a better catalyst than (–)-sparteine **3**, probably due to a higher reactivity of the *s*-BuLi/**7** complex.

Next, we investigated the use of new bis-*i*-Pr-bispidines **12**, **13** and **14** as the stoichiometric recycling ligand. Use of alkene bispidine **12** (1.3 eq.) with 0.3 eq. (–)-sparteine led to comparable results to those obtained using bis-*i*-Pr-bispidine **6**: the reaction gave *syn*-**16** (61% yield, 92:8 er) and *anti*-**17** (30% yield, 88:12 er) (entry 6). In contrast, methyl bispidine **13**, which is structurally very similar to bis-*i*-Pr-bispidine **6**, was far less successful giving *syn*-**16** in 79:21 er and *anti*-**17** in 78:22 er (entry 7). It is not clear why methyl bispidine **13** performed so poorly, although there may be subtle conformational differences between methyl bispidine **13** and bis-*i*-Pr-bispidine **6**. A similarly low level of enantioinduction was observed with the lithium alkoxide derived from bispidol **14** (formed *in situ* with an extra equivalent of *s*-BuLi) (entry 8).

The importance of the *i*-propyl groups in bis-*i*-Pr-bispidine **6** was shown by the essentially racemic products (*syn*-**16**, 55:45 er; *anti*-**17**, 55:45 er) generated from the reaction using bis-*n*-Pr-bispidine **15** (entry 9). Clearly, in this case, the background deprotonation using *s*-BuLi/bis-*n*-Pr-bispidine **15** is competitive with deprotonation using *s*-BuLi/(–)-sparteine **3** and essentially no enantioselectivity results. Finally, we also investigated two-ligand catalysis using the Alexakis diamine (*R*,*R*)-**18**[16,24] (0.3 eq.) and bis-*i*-Pr-bispidine **6**. This gave a slightly disappointing result

with *syn*-**16** and *anti*-**17** being formed in 84:16 er and 85:15 er respectively (entry 10). Clearly, the bispidine chiral ligands, (–)-sparteine **3** and (+)-sparteine surrogate **7**, in tandem with bis-*i*-Pr-bispidine **6** are optimal for these types of two-ligand catalytic asymmetric deprotonations.



Scheme 4

Table 1

Entry	Chiral diamine	Bispidine	Yield (%) of *syn*-**16**[b]	er of *syn*-**16**[c]	Yield (%) of *anti*-**17**[b]	er of *anti*-**17**[c]
1	**3**[a]	–	62	97:3	18	97:3
2	**3**	**6**	62	91:9	33	91:9
3	**7**	**6**	65	6:94[d]	29	6:94[d]
4	**3**[e]	**6**[e]	58	88:12	29	88:12
5	**7**[e]	**6**[e]	56	7:93[d]	25	7:93[d]
6	**3**	**12**	61	92:8	30	88:12
7	**3**	**13**	60	79:21	32	78:22
8	**3**	**14**[f]	54	83:17	31	77:23
9	**3**	**15**	61	55:45	34	55:45
10	(*R*,*R*)-**18**	**6**	63	84:16	27	85:15

[a]Stoichiometric (–)-sparteine conditions: 1.3 eq. *s*-BuLi and 1.3 eq. (–)-sparteine **3** used. [b]Yield after purification by column chromatography. [c]Enantiomer ratio (er) determined by CSP-HPLC. [d]Opposite enantiomer of *syn*-**16** and *anti*-**17** obtained as the major product. [e]1.0 eq. *s*-BuLi, 0.25 eq. chiral diamine and 1.0 eq. bispidine used. [f]An additional 1.3 eq. *s*-BuLi was used to deprotonate the hydroxyl group.

Conclusion

In conclusion, we have optimised the two-step synthesis of bis-*i*-Pr-bispidine **6** and carried out the synthesis of other bispidines for use in the two-ligand catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **4**. Although alkene bispidine **12** worked well, we believe that bis-*i*-Pr-bispidine **6** remains the best stoichiometric recycling diamine for such catalytic asymmetric deprotonation reactions.

Experimental Section

General. H_2O is distilled water. Brine refers to a saturated aqueous solution of NaCl. Et_2O, THF or Methyl-THF were freshly distilled from sodium and benzophenone ketyl. All diamines and *N*-Boc pyrrolidine were distilled over CaH_2 before use. Petrol refers to the fraction of petroleum ether boiling in the range 40-60 °C. All reactions were carried out under O_2-free Ar using oven-dried and/or flame-dried glassware. *n*-Butyllithium and *s*-butyllithium were titrated against *N*-benzylbenzamide before use.[25]

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using Merck F_{254} aluminium-backed silica plates. ^1H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument with an internal deuterium lock. Chemical shifts are quoted as parts per million and referenced to $CHCl_3$ (δ_H 7.27) and or $CDCl_3$ (δ_C 77.0, central line of triplet). ^{13}C NMR spectra were recorded with broadband proton decoupling. ^{13}C NMR spectra were assigned using DEPT experiments. Coupling constants (*J*) are quoted in Hertz. IR spectra were recorded on an ATI Matteson Genesis FT-IR spectrometer. Boiling points given for compounds purified by Kügelrohr distillation correspond to the oven temperature during distillation. Electrospray high and low resolution mass spectra were recorded on a Bruker Daltronics microOTOF spectrometer. Optical rotations were recorded at room temperature on a Jasco DIP-370 polarimeter (using sodium D line; 259 nm) and $[\alpha]_D$ given in units of 10^{-1} deg cm^3 g^{-1}. Chiral stationary phase (CSP)-HPLC was performed on an Agilent 1200 series instrument and a multiple wavelength, UV/Vis diode array detector; integration was normally performed at 230 nm.

General procedure for two-ligand deprotonation of *N*-Boc pyrrolidine (4)

s-BuLi (1.3 M solution in hexanes, 1.0 or 1.6 eq.) was added dropwise to a stirred solution of chiral diamine (0.2 or 0.3 eq.) and bispidine (1.0 or 1.3 eq.) in Et_2O (6 mL) at –78 °C under Ar. After stirring at –78 °C for 15 min, a solution of *N*-Boc pyrrolidine **4** (230 mg, 235 μL, 1.34 mmol, 1.0 eq.) in Et_2O (1 mL) was added dropwise. The resulting pale yellow solution was stirred at –78 °C for 4 h. Then, benzaldehyde (282 mg, 270 μL, 2.68 mmol, 2 eq.) was added and the resulting solution was allowed to warm to rt over 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and

the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9-one (10). *i*-Propylamine (12.2 mL, 142.0 mmol) was added dropwise to a stirred solution of *N*-*i*-propyl-4-piperidone **8** (21.1 mL, 142.0 mmol, freshly distilled), paraformaldehyde (12.78 g, 426.0 mmol) and AcOH (8.46 mL, 148.0 mmol) in MeOH (200 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 16 h. The solvent was evaporated under reduced pressure. Then, 50% w/v $KOH_{(aq)}$ solution (500 mL) and Et_2O (500 mL) were added to the residue and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 500 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by fractional distillation gave bispidone **10** (21.39 g, 67%) as a colourless oil, bp 128-130 ºC/2.0 mmHg (lit.,[23] bp 110-120 ºC/10^{-5} mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (dd, *J* 10.5, 3.0 Hz, 4H, NCH_AH$_B$), 2.86 (dd, *J* 10.5, 7.0 Hz, 4H, NCH$_A$$H_B$), 2.85-2.76 (m, 2H, NCH), 2.61-2.54 (m, 2H, COCH), 0.99 (d, *J* 6.5 Hz, 12H, Me). Spectroscopic data consistent with those reported in the literature.[23]

3,7-Di-*n*-propyl-3,7-diazabicyclo[3.3.1]nonan-9-one (11). *n*-Propylamine (5.83 mL, 70.81 mmol) was added dropwise to a stirred solution of *N*-*n*-propyl-4-piperidone **9** (10.7 mL, 10 g, 70.81 mmol), paraformaldehyde (6.38 g, 212.4 mmol) and AcOH (4.22 mL, 73.8 mmol) in MeOH (100 mL) at rt under Ar. The resulting solution was stirred and heated at reflux for 16 h. The solvent was evaporated under reduced pressure. Then, 50% $KOH_{(aq)}$ solution (250 mL) and Et_2O (250 mL) were added to the residue and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 250 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by fractional distillation gave bispidone **11** (7.01 g, 44%) as a yellow oil, bp 95-100 °C/0.2 mmHg; IR (film) 2958, 1739 (C=O), 1469, 1359, 1208, 1137, 1087, 1036, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (dd, *J* 11.0, 2.0 Hz, 4H, NCH_AH$_B$), 2.79 (dd, *J* 11.0, 6.5 Hz, 4H, NCH$_A$$H_B$), 2.56 (br s, 2H, COCH), 2.31 (t, *J* 7.5 Hz, 4H, NCH_2CH$_2$), 1.50-1.40 (m, 4H, NCH$_2$CH_2), 0.89 (t, *J* 7.5 Hz, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 215.1 (C=O), 58.5 (NCH_2), 58.4 (NCH_2), 46.6 (*C*HCO), 20.3 (*C*H_2Me), 11.8 (Me); MS (ESI) *m/z* 257 [(M + MeOH + H)$^+$, 100], 225 [(M + H)$^+$, 1]; HRMS (ESI) *m/z* calcd for $C_{14}H_{24}N_2O$ (M + H)$^+$ 225.1961, found 225.1970 (3.7 ppm error); *m/z* calcd for $C_{14}H_{24}N_2O$ (M + MeOH + H)$^+$ 257.2224, found 257.2220 (1.3 ppm error).

3,7-Diisopropyl-9-methylene-3,7-diazabicyclo[3.3.1]nonane (12). KHMDS (65.4 mL of a 0.5 M solution in toluene, 32.7 mmol) was added dropwise to a stirred solution of $MePh_3P^+Br^–$ (11.68 g, 32.7 mmol) in THF (240 mL) at 0 °C under Ar. After stirring at 0 °C for 30 min, a solution of bispidone **10** (7.00 g, 31.2 mmol) in THF (60 mL) was added dropwise. The resulting solution was stirred at 0 °C for 15 min and then stirred and heated at reflux for 16 h. The solvent was evaporated under reduced pressure and 5 M $HCl_{(aq)}$ solution (250 mL) was added to the residue. The aqueous solution washed with CH_2Cl_2 (2 × 500 mL) and then basified to pH 14 by addition of 5 M $NaOH_{(aq)}$. The aqueous solution was stirred at rt for 1 h and then extracted with Et_2O (8 x 200 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under

reduced pressure to give the crude product as a yellow oil. Purification by Kügelrohr distillation gave alkene bispidine **12** (4.48 g, 65%) as a colourless oil, bp 120-130 °C/1.2 mmHg; IR (film) 3069, 2931, 1670 (C=C), 1469, 1386, 1358, 1176, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 2H, C=CH_2), 2.78-2.68 (m, 2H, NCH), 2.68-2.60 (m, 8H, NCH_2), 2.58-2.40 (m, 2H, NCH_2C*H*), 0.99 (d, *J* 6.5 Hz, 12H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 151.4 (*C*=CH_2), 104.7 (C=*C*H_2), 53.8 (NCH_2), 53.4 (NCH), 39.0 (NCH_2*C*H), 18.1 (Me); MS (ESI) *m/z* 223 [$(M + H)^+$, 100], 150 (15), 123 (30); HRMS (ESI) *m/z* calcd for $C_{14}H_{26}N_2$ $(M + H)^+$ 223.2169, found 223.2169 (0.3 ppm error).

3,7-Diisopropyl-9-methyl-3,7-diazabicyclo[3.3.1]nonane (13). A solution of alkene bispidine **12** (4.48 g, 20.1 mmol) and $NH_4^+HCO_2^-$ (4.16 g, 66.0 mmol) in EtOH (130 mL) was stirred and heated at reflux under Ar. Then, 20% $Pd(OH)_2$/C (1.22 g, 1.4 mmol) was added in one portion. The resulting mixture was stirred and heated at reflux for 2 h. After cooling to rt, the resulting mixture was basified to pH 14 by addition of 5 M $NaOH_{(aq)}$ solution. The aqueous solution was stirred at rt for 1 h. Then, the solids were removed by filtration through a minimum amount of Celite® and washed with 5 M $NaOH_{(aq)}$ solution (20 mL). The EtOH was evaporated under reduced pressure and the aqueous residue was extracted with Et_2O (8 × 200 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by Kügelrohr distillation gave methyl bispidine **13** (2.87 g, 65%) as a colourless oil, bp 130-140 °C/0.4 mmHg; IR (film) 2963, 2932, 1381, 1179, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.79-2.60 (m, 8H, NCH_2), 2.40-2.34 (m, 2H, NCH), 1.86-1.78 (m, 1H, C*H*Me), 1.66 (br s, 2H, NCH_2C*H*), 1.05-0.95 (m, 15H, CH*Me* + C*H*Me_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 53.9 (NCH), 53.6 (NCH), 53.5 (NCH_2), 47.1 (NCH_2), 34.2 (CH), 30.2 (CH), 18.2 (Me), 17.9 (Me), 16.5 (Me); MS (ESI) *m/z* 225 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}N_2$ $(M + H)^+$ 225.2325, found 225.2326 (0.4 ppm error).

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonan-9-ol (14). A solution of $NaBH_4$ (37 mg, 1.0 mmol) in H_2O (1.5 mL) was added dropwise to a stirred solution of bispidone **10** (200 mg, 0.9 mmol) in EtOH (3.0 mL) at rt under air. The resulting solution was stirred at rt for 16 h. The EtOH was evaporated under reduced pressure and the residue was basified to pH 14 by addition of 5 M $NaOH_{(aq)}$ solution. The solution was stirred at rt for 1 h and then extracted with Et_2O (8 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give bispidol **14** (138 mg, 69%) as a colourless oil, bp 170-180 ºC/5 mmHg; IR (film) 3328 (OH), 2965, 2924, 1469, 1382, 1360, 1221, 1174, 1096, 1069, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (br s, 1H, OH), 3.31 (br s, 1H, C*H*OH), 2.99 (br t, *J* 10.5 Hz, 2H), 2.72-2.62 (m, 2H), 2.62-2.42 (m, 4H), 2.28-2.15 (m, 4H), 0.99 (d, *J* 6.5 Hz, 6H, Me), 0.94 (d, *J* 6.5 Hz, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 73.2 (CHOH), 53.3 (NCH), 52.9 (NCH), 52.4 (NCH_2), 48.5 (NCH_2), 34.6 (NCH_2*C*H), 18.2 (Me), 18.1 (Me); MS (ESI) *m/z* 227 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{13}H_{26}N_2O$ $(M + H)^+$ 227.2118, found 227.2124 (2.9 ppm error).

3,7-Diisopropyl-3,7-diazabicyclo[3.3.1]nonane (6). Hydrazine monohydrate (6.22 mL, 127.9 mmol) was added dropwise to a stirred mixture of bispidone **10** (5.17 g, 23.0 mmol) and KOH (15.1 g, 269.0 mmol) in diethylene glycol (130 mL) at rt under Ar. The resulting mixture was

stirred and heated at 180 °C for 16 h. After cooling to 60 °C (if the diethylene glycol solution is cooled to rt before addition of H_2O then the mixture becomes very viscous and difficult to work with), the mixture was transferred to a separating funnel and H_2O (155 mL) was added. Then, Et_2O (85 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (6 × 85 mL) and the combined organic layers were washed with 20% $NaOH_{(aq)}$ (6 × 100 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give bis-*i*-Pr-bispidine **6** (4.29 g, 88%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68-2.57 (m, 2H, NCH), 2.53 (dd, *J* 10.5, 5.5 Hz, 4H, NCH_2), 2.46 (br d, *J* 10.5 Hz, 4H, NCH_2), 1.97-1.92 (m, 2H, NCH_2CH), 1.46-1.41 (m, 2H, NCH_2CHCH_2), 0.97 (d, *J* 6.5 Hz, 12H, $NCHMe_2$). Spectroscopic data consistent with those reported in the literature.[17] Bis-*i*-Pr-bispidine **6** was purified by Kügelrohr distillation (bp 110-120 °C, 0.4 mmHg) immediately before use.

3,7-Dipropyl-3,7-diazabicyclo[3.3.1]nonane (15). Hydrazine monohydrate (4.72 mL, 86.5 mmol) was added dropwise to a stirred mixture of bispidone **11** (3.5 g, 15.6 mmol) and KOH (9.11 g, 182.0 mmol) in diethylene glycol (90 mL) at rt under Ar. The resulting mixture was stirred and heated at 180 °C for 16 h. After cooling to 60 °C (if the diethylene glycol solution is cooled to rt before addition of H_2O then the mixture becomes very viscous and difficult to work with), the mixture was transferred to a separating funnel and H_2O (80 mL) was added. Then, Et_2O (60 mL) was added and the layers separated. The aqueous layer was extracted with Et_2O (6 × 60 mL) and the combined organic layers were washed with 20% $NaOH_{(aq)}$ (6 × 90 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give bis-*n*-Pr-bispidine **15** (2.77 g, 84%) as a colourless oil, bp 100-110 °C/2.0 mmHg; IR (film) 2955, 2932, 1462, 1375, 1290, 1272, 1148, 1106, 1068, 1001 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (br d, *J* 10.5 Hz, 4H, NCH_AH_B), 2.28 (dd, *J* 10.5, 4.5 Hz, 4H, NCH_AH_B), 2.19 (t, *J* 7.5 Hz, 4H, NCH_2CH_2), 1.91 (br s, 2H, NCH_2CH), 1.52-1.41 (m, 6H, NCH_2CH_2 + CH_2CHCH_2), 0.87 (t, *J* 7.5 Hz, 6H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 61.0 (NCH_2), 57.9 (NCH_2), 29.9 (bridge CH_2), 29.2 (NCH_2CH), 20.1 (NCH_2CH_2), 11.9 (Me); MS (ESI) *m/z* 211 [(M + H)$^+$, 100], 199 (12); HRMS (ESI) *m/z* calcd for $C_{13}H_{26}N_2$ (M + H)$^+$ 211.2169, found 211.2162 (3.0 ppm error).

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R*,2*R*)-16 and (1*S*,2*R*)-17 (Table 1, entry 1). *s*-BuLi (2.0 mL of a 1.3 M solution in hexanes, 2.6 mmol, 1.3 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **4** (342 mg, 350 μL, 2.0 mmol, 1.0 eq.) and (–)-sparteine **3** (607 mg, 595 μL, 2.6 mmol, 1.3 eq.) in Et_2O (7 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Then, benzaldehyde (423 mg, 405 μL, 4.0 mmol, 2.0 eq.) was added dropwise and the resulting solution was warmed to rt over 16 h. Saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 75:25 mixture of (1*R*,2*R*)-**16** and (1*S*,2*R*)-**17** by ^{1}H NMR spectroscopy. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**16** (343 mg, 62%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –3.1 (*c* 1.0 in $CHCl_3$) (lit.,[20] $[\alpha]_D$ –1.9 (*c* 1.0 in $CHCl_3$) for (1*R*,2*R*)- **16** of 97:3 er); R_F (98:2 CH_2Cl_2-acetone) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.39-7.25 (m, 5H, Ar), 5.93 (br s, 1H, OH), 4.53 (br d, *J* 8.0 Hz, 1H, CHO), 4.10 (td, *J* 8.0, 3.5 Hz, 1H, NCH), 3.51-3.42 (m, 1H, NCH), 3.41-3.33 (m, 1H, NCH), 1.79-1.15 (m, 2H, CH_2), 1.14-1.45 (m, 2H, CH_2), 1.53 (s, 9H, CMe_3); CSP-HPLC: Chiralpak OD (98:2 hexane:*iso*-PrOH, 0.5 $mLmin^{-1}$) (*R*,*R*)-**16** 24.12 min, (*S*,*S*)-**16** 28.85 min and (1*S*, 2*R*)-**17** (100 mg, 18%, 97:3 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +75.4 (*c* 1.0 in $CHCl_3$) (lit.,[20] $[\alpha]_D$ +95.3 (*c* 1.0 in $CHCl_3$) for (1*S*,2*R*)-**17** of 97:3 er); R_F (98:2 CH_2Cl_2-acetone) 0.3; ^1H NMR (400 MHz, $CDCl_3$) (75:25 mixture of rotamers) δ 7.41-7.23 (m, 5H, Ar), 5.52 (br s, 0.75H, OH), 5.15 (br s, 0.25H, OH), 4.87 (br s, 0.75H, CHO), 4.31 (br s, 0.75H, NCH), 4.00 (br s, 0.25H, CHO), 3.56 (br s, 0.25H, NCH), 3.30 (br s, 1H, NCH), 2.82 (br s, 0.75H, NCH), 2.51 (br s, 0.25H, NCH), 2.01-1.86 (m, 1H, CH_2), 1.85-1.72 (m, 1H, CH_2), 1.68 (s, 2.25H, CMe_3), 1.66-1.46 (m, 1H, CH_2), 1.52 (s, 6.75H, CMe_3), 1.21-1.13 (m, 1H, CH_2); CSP-HPLC: Chiralpak OD (98:2 hexane-*iso*-PrOH, 0.5 $mLmin^{-1}$) (*S*,*R*)-**17** 19.61 min, (*R*,*S*)-**17** 24.00 min. Spectroscopic data consistent with those reported in the literature.[20]

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R*,2*R*)-16 and (1*S*,2*R*)-17 (Table 1, entry 2). Using the general procedure, *s*-BuLi (1.65 mL of a 1.3 M solution in hexanes, 2.14 mmol, 1.6 eq.), (–)-sparteine **3** (94 mg, 0.40 mmol, 0.3 eq.), bis-*i*-Pr-bispidine **6** (366 mg, 1.74 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **4** (230 mg, 235 μL, 1.34 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (282 mg, 270 μL, 2.68 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**16** (221 mg, 62%, 91:9 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –1.24 (*c* 1.0 in $CHCl_3$ and (1*S*, 2*R*)-**17** (116 mg, 33%, 91:9 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +93.0 (*c* 1.0 in $CHCl_3$).

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*S*,2*S*)-16 and (1*R*,2*S*)-17 (Table 1, entry 3). Using the general procedure, *s*-BuLi (2.64 mL of a 1.3 M solution in hexanes, 3.43 mmol, 1.6 eq.), (+)-sparteine surrogate **7** (112 mg, 0.64 mmol, 0.3 eq.), bis-*i*-Pr-bispidine **6** (585 mg, 2.78 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **4** (366 mg, 375 μL, 2.14 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (455 mg, 435 μL, 4.28 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*S*,2*S*)-**16** (370 mg, 65%, 94:6 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ +0.04 (*c* 1.0 in $CHCl_3$) and (1*R*, 2*S*)-**17** (166 mg, 29%, 94:6 er by CSP-HPLC) as a colourless oil, $[\alpha]_D$ –106.3 (*c* 1.0 in $CHCl_3$).

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R*,2*R*)-16 and (1*S*,2*R*)-17 (Table 1, entry 4). Using the general procedure, *s*-BuLi (1.06 mL of a 1.3 M solution in hexanes, 1.38 mmol, 1.0 eq.), (–)-sparteine **3** (81 mg, 0.34 mmol, 0.25 eq.), bis-*i*-Pr-bispidine **6** (290 mg, 1.38 mmol, 1.0 eq.) and *N*-Boc pyrrolidine **4** (234 mg, 240 μL, 1.38 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (293 mg, 280 μL, 2.76 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**16** (214 mg, 58%, 88:12 er by CSP-HPLC) as a colourless oil and (1*S*, 2*R*)-**17** (106 mg, 29%, 88:12 er by CSP-HPLC) as a colourless oil.

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*S*,2*S*)-16 and (1*R*,2*S*)-17 (Table 1, entry 5). Using the general procedure, *s*-BuLi (1.13 mL of a 1.3 M solution in hexanes, 1.47 mmol, 1.0 eq.), (+)-sparteine surrogate **7** (64 mg, 0.37 mmol, 0.25 eq.), bis-*i*-Pr-bispidine **6** (309 mg, 1.47 mmol, 1.0 eq.) and *N*-Boc pyrrolidine **4** (254 mg, 260 μL, 1.47 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (313 mg, 300 μL, 2.94 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*S*,2*S*)-**16** (220 mg, 56%, 93:7 er by CSP-HPLC) as a colourless oil and (1*R*, 2*S*)-**17** (96 mg, 25%, 93:7 er by CSP-HPLC) as a colourless oil.

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R*,2*R*)-16 and (1*S*,2*R*)-17 (Table 1, entry 6). Using the general procedure, *s*-BuLi (1.66 mL of a 1.3 M solution in hexanes, 2.16 mmol, 1.6 eq.), (–)-sparteine **3** (95 mg, 0.41 mmol, 0.3 eq.), alkene bispidine **12** (391 mg, 1.76 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **4** (234 mg, 240 μL, 1.35 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (287 mg, 275 μL, 2.70 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**16** (220 mg, 61%, 92:8 er by CSP-HPLC) as a colourless oil and (1*S*, 2*R*)-**17** (107 mg, 30%, 88:12 er by CSP-HPLC) as a colourless oil.

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R*,2*R*)-16 and (1*S*,2*R*)-17 (Table 1, entry 7). Using the general procedure, *s*-BuLi (1.15 mL of a 1.3 M solution in hexanes, 1.50 mmol, 1.6 eq.), (–)-sparteine **3** (66 mg, 0.28 mmol, 0.3 eq.), methyl bispidine **13** (274 mg, 1.22 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **4** (161 mg, 165 μL, 0.94 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (198 mg, 190 μL, 1.88 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**16** (149 mg, 60%, 79:21 er by CSP-HPLC) as a colourless oil and (1*S*, 2*R*)-**17** (81 mg, 32%, 78:22 er by CSP-HPLC) as a colourless oil.

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R*,2*R*)-16 and (1*S*,2*R*)-17 (Table 1, entry 8). Using the general procedure, *s*-BuLi (1.27 mL of a 1.3 M solution in hexanes, 1.63 mmol, 2.9 eq.), (–)-sparteine **3** (40 mg, 0.17 mmol, 0.3 eq.), bispidol **14** (167 mg, 0.74 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **4** (98 mg, 100 μL, 0.57 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (199 mg, 190 μL, 1.88 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**16** (82 mg, 54%, 83:17 er by CSP-HPLC) as a colourless oil and (1*S*, 2*R*)-**17** (47 mg, 31%, 77:23 er by CSP-HPLC) as a colourless oil.

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R*,2*R*)-16 and (1*S*,2*R*)-17 (Table 1, entry 9). Using the general procedure, *s*-BuLi (1.22 mL of a 1.3 M solution in hexanes, 1.59 mmol, 1.6 eq.), (–)-sparteine **3** (70 mg, 0.30 mmol, 0.3 eq.), bis-*n*-Pr-bispidine **15** (271 mg, 1.29 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **4** (171 mg, 175 μL, 0.99 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (209 mg, 200 μL, 1.99 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**16** (160 mg, 61%, 55:45 er by CSP-HPLC) as a colourless oil and (1*S*, 2*R*)-**17** (90 mg, 34%, 55:45 er by CSP-HPLC) as a colourless oil.

2-(Hydroxyphenylmethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (1*R*,2*R*)-16 and (1*S*,2*R*)-17 (Table 1, entry 10). Using the general procedure, *s*-BuLi (0.96 mL of a 1.3 M solution in hexanes, 1.25 mmol, 1.6 eq.), cyclohexane diamine (*R*,*R*)-**18** (58 mg, 0.23 mmol, 0.3 eq.), bis-*i*-Pr-bispidine **6** (214 mg, 1.02 mmol, 1.3 eq.) and *N*-Boc pyrrolidine **4** (134 mg, 137 μL, 0.78 mmol, 1.0 eq.) in Et_2O (8 mL) and then benzaldehyde (167 mg, 160 μL, 1.57 mmol, 2.0 eq.) gave the crude product. Purification by flash column chromatography on silica with 98:2 CH_2Cl_2-acetone as eluent gave (1*R*,2*R*)-**16** (131 mg, 63%, 84:16 er by CSP-HPLC) as a colourless oil and (1*S*, 2*R*)-**17** (57 mg, 27%, 85:15 er by CSP-HPLC) as a colourless oil.

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