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Enantioselective diethylzinc addition to aromatic and aliphatic aldehydes using (3*R*,5*R*)-dihydroxypiperidine derivatives catalyst

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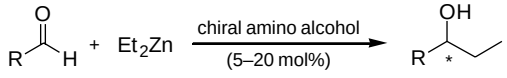
Abstract—A series of chiral (3*R*,5*R*)-dihydroxypiperidine derivatives **3a–f** were conveniently prepared from *trans*-4-hydroxy-L-proline and applied to the catalytic enantioselective addition of diethylzinc to benzaldehyde and heptanal. Among them, **3d** was found to show the best asymmetric induction in promoting the addition of Et_2Zn to various aldehydes, providing (*R*)-secondary alcohols in up to 98% ee.

1. Introduction

Among asymmetric catalysis of C–C bond formation, the enantioselective addition of diorganozinc reagents to aldehydes in the presence of a catalytic amount of a chiral ligand is a convenient method for the preparation of optically active secondary alcohols.[1] Among the numerous chiral catalysts developed for asymmetric organozinc additions, β-amino alcohols hold a prominent position.[1e,2] The use of these catalysts for the addition of diethylzinc to aromatic aldehydes produces 1-aryl-1-ethanols in both excellent chemical yield and enantioselectivity[3,4] (Scheme 1). In contrast, the enantioselectivity for aliphatic aldehydes is usually considerably lower.[5]



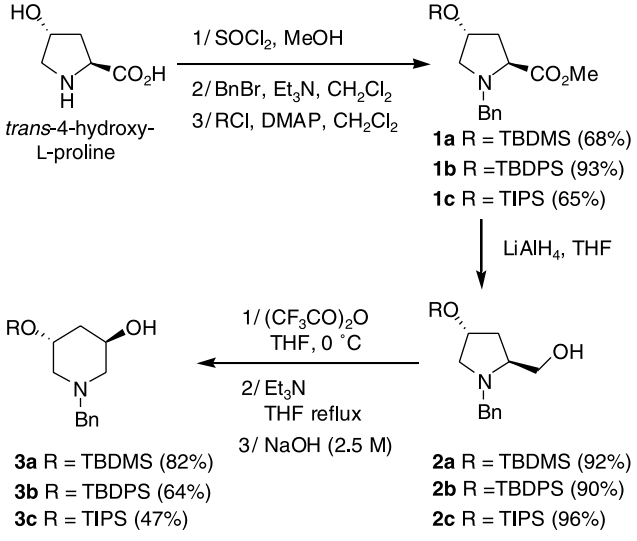
Scheme 1. Enantioselective addition of diethylzinc to aldehydes catalyzed by chiral amino alcohols.

2. Results

In the course of our studies on the synthesis and applications of optically active 3,5-dihydroxy-piperidines,[6] we would like to report here the use of (3*R*,5*R*)-dihydroxypiperidine derivatives on the enantioselective addition of diethylzinc to aryl aldehydes as well as to aliphatic aldehydes.

Ligands **3a–f** were prepared from the commercially available *trans*-4-hydroxy-L-proline by utilizing a ring expansion[7,8] that we have devised previously to synthesize (3*R*,5*R*)-dihydroxypiperidine derivatives.

Compounds **3a**,[7g] **3b**, and **3c** were prepared from the corresponding prolinols **2** by treatment with trifluoroacetic anhydride followed by the addition of triethylamine and then by treatment with sodium hydroxide.[7g] The (3*R*,5*R*)-dihydroxypiperidine derivatives **3a**, **3b**, and **3c** were obtained in 82, 64, and 47% yield, respectively, (Scheme 2). Compound **3a** was then transformed into **3d–f**.



Scheme 2.

Keywords: Enantioselective addition; Aliphatic aldehydes; Chiral ligands.
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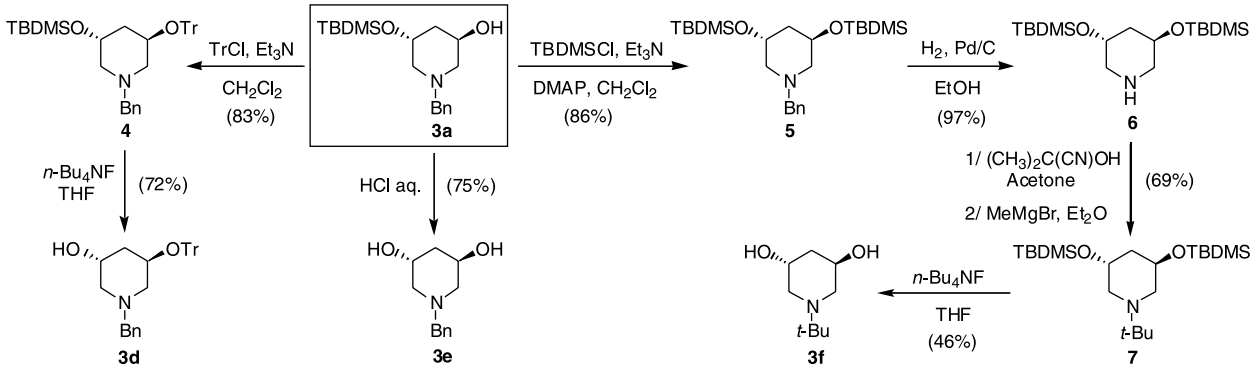


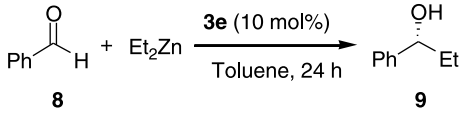
Scheme 3.

For obtaining **3d**, the hydroxypiperidine **3a** was treated with triphenylmethane chloride (CH_2Cl_2, Et_3N, 0 °C) and the resulting piperidine **4** was mono-deprotected with *n*-Bu_4NF (THF, rt) to produce **3d** with an overall yield of 60%. The 3,5-dihydroxypiperidine **3e**[7g] was obtained in 75% yield by deprotection of **3a** using HCl (1.2 N) (Scheme 3).

The synthesis of *N*-*t*-butyl-3,5-dihydoxypiperidine **3f** was achieved from **3a** in four steps. After protection of the hydroxyl group (TBDMSCl, DMAP, Et_3N) and deprotection of the nitrogen (H_2, Pd/C), the amine **6** was treated with acetone cyanohydrin followed by the addition of methylmagnesium bromide[9] and, after addition of *n*-Bu_4NF to the resulting *N*-*t*-butylpiperidine **7** (THF, rt), compound **3f** was isolated with an overall yield of 26% (Scheme 3). It is worth noting that by using this synthetic pathway, a library of chiral ligands should be easily prepared. The novel chiral ligands **3a–f** were then evaluated in the asymmetric induction efficiency of diethylzinc addition to aryl aldehydes and aliphatic aldehydes.

The first test was performed on benzaldehyde using ligand **3e** under standard conditions. The reaction was carried out in dry toluene in the presence of 10 mol% of the chiral ligand **3e** and 2.2 equiv of Et_2Zn at rt for 24 h. The reaction was quenched with HCl (1.2 N) and after extraction and purification by chromatography over silica gel 1-phenylpropan-1-ol **9**[41] was isolated in 84% yield and 89% ee with the (*R*) configuration (Table 1, entry 1). When the temperature was lowered to 0 °C, the yield in **9** was decreased to 73% and the ee remained similar (Table 1, entry 2). By decreasing the number of equivalents of Et_2Zn, from 2.2 to 1.5 or 1.2 equiv, the yield in **9** was increased in the range of 93–99% and the ee was similar and reproducible 87–92%.

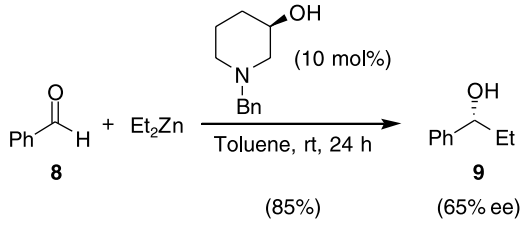
Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by ligand **3e**



Entry	Et_2Zn (equiv)	*T* (°C)	Yield (%)	ee (%)[a]	Conf.[b]
1	2.2	rt	84	89	*R*
2	2.2	0	73	87	*R*
3	1.5	rt	93	87	*R*
4	1.2	rt	99	92	*R*

[a] Determined by using a Chiralcel OD-H column and eluting with hexane–*i*PrOH (99/1) at the flow rate of 1 mL/min.
[b] Determined by comparison with the absolute optical rotation reported in the literature.

We have to point out that the use of (*R*)-*N*-benzyl-3-hydroxypiperidine[7g] led to **9** in 85% yield but the ee was only 65%, which means that 3,5-dihydroxypiperidines were promising (Scheme 4).

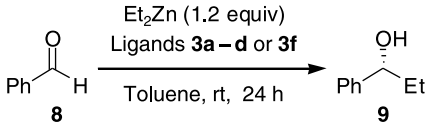


Scheme 4.

Due to these results, ligands **3a–e** were then evaluated to check their asymmetric induction in the addition of diethylzinc to benzaldehyde **8**.

N-Benzyl monoprotected 3,5-dihydroxypiperidine **3a–d** were tested as well as the *N*-*t*-butyl non-protected dihydroxypiperidine **3f**. As reported in Table 2, **3d** shows the best asymmetric induction as 1-phenylpropanol **9** was obtained with 98% ee using 2 mol% of **3d** as catalyst

Table 2. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by ligands **3a–d** and **3f**

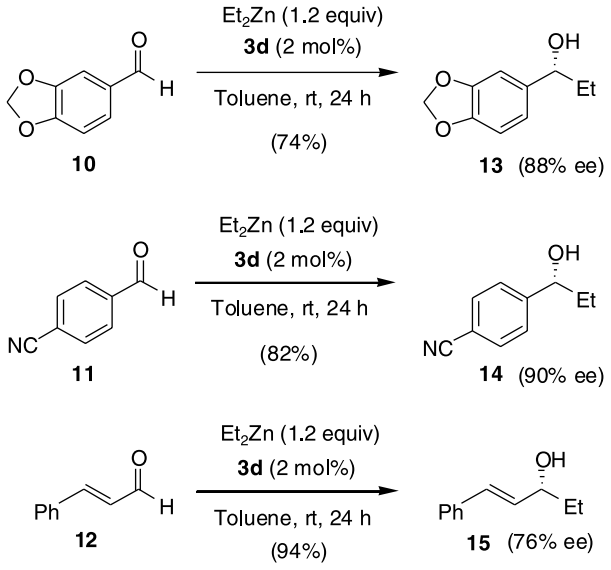


Entry	Ligand	mol%	Yield (%)	ee (%) (conf.)[a]
1	**3a**	10	76	80 (*R*)
2	**3b**	2	94	89 (*R*)
3	**3c**	10	85	88 (*R*)
4	**3d**	2	74	98 (*R*)
5	**3f**	2	77	91 (*R*)

[a] Determined by using a Chiralcel OD-H column and eluting with hexane–*i*PrOH (99/1) at the flow rate of 1 mL/min; the absolute configuration was determined by comparison with the absolute optical rotation given in the literature.

(Table 2, entry 4). Obviously, the presence of a bulky trityl substituent at C3 is crucial to obtain the best asymmetric induction. It is interesting to note that the *N*-*t*-butyl substituent in **3f** also plays an important role in the enantioselectivity (Table 2, entry 5) as **9** was obtained with an ee of 91%.

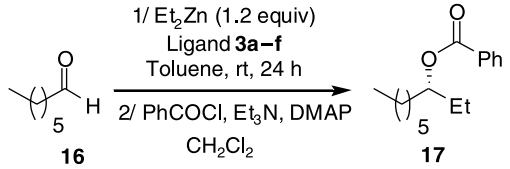
By using **3d** as the catalyst, ethyl alcohol **13**[10] (88% ee), **14**[11] (90% ee) and **15**[3e,12] (76% ee) were obtained with good ee and in good yield from aldehydes **10**, **11**, and **12**, respectively, (Scheme 5).



Scheme 5.

Chiral ligand **3d** was then examined for the asymmetric addition of diethylzinc to the aliphatic aldehyde **16**. In order to facilitate the ee determination by chiral HPLC, the alcohol obtained after the addition of Et_2Zn was benzoylated to produce **17**. The benzoate **17**[13] was obtained with an overall yield of 57% with an ee of 69% (Table 3, entry 4). In the aim of increasing the ee, the chiral ligands **3a**–**c**, **3e**, and **3f** were tested (Table 3). The best ligand for aliphatic aldehydes seems to be the *N*-*t*-butyl-3,5-dihydroxypiperidine **3f** as **17** was obtained with an overall yield of 57% and with an ee of 81% (Table 3, entry 6).

Table 3. Enantioselective addition of diethylzinc to heptanal catalyzed by ligand **3a**–**f**



Entry	Ligand	mol%	Yield (%)[a]	ee (%) (conf.)[b]
1	**3a**	10	34	35 (*R*)
2	**3b**	10	39	59 (*R*)
3	**3c**	10	42	62 (*R*)
4	**3d**	2	57	69 (*R*)
5	**3e**	10	25	60 (*R*)
6	**3f**	2	57	81 (*R*)

[a] Overall yield for addition and benzoylation.
[b] Determined by using a Chiralcel OD-H column and eluting with hexane–*i*PrOH (99/1) at the flow rate of 1 mL/min; the absolute configuration was determined by comparison with the absolute optical rotation given in the literature.

In conclusion, a series of new chiral ligands **3a–f** for the addition of dialkylzinc to aldehydes have been prepared from *trans*-4-hydroxy-L-proline. Compound **3d** was found to be highly efficient for the enantioselective addition of diethylzinc to aromatic aldehydes and good for the enantioselective addition of diethylzinc to aliphatic aldehydes. In the case of aliphatic aldehydes a better ee was obtained with **3f**.

The chiral ligands described in this study might be used in other asymmetric catalytic transformations. Such as for example, the enantioselective Henry reaction of nitromethane with aldehydes.[14]

3. Experimental

3.1. General

All reactions were carried out under argon atmosphere. Commercially available reagents and solvents were used as received. Anhydrous solvents were distilled: tetrahydrofuran and diethyl ether were purified by distillation from sodium and benzophenone, methylene chloride, and toluene were dried by distillation from CaH_2. Flash column chromatography was performed on silica gel (Merck-Kieselgel 60, 230–400 mesh).

Melting points (mp) were not corrected. ^1H and ^{13}C NMR spectra were, respectively, recorded on a Bruker AC 300 at 300 and 75 MHz. Spectra were recorder in $CDCl_3$ as solvent, and chemical shifts (δ) were expressed in ppm relative to residual $CHCl_3$ at $\delta=7.27$ ppm for ^1H and to $CDCl_3$ at $\delta=77.1$ ppm for ^{13}C. ^1H NMR *J* values given in Hz. IR spectra were recorded as neat films (NaCl cell) and KBr pellets for solids on a Perkin-Elmer 298. Mass spectra were obtained by GC/MS with electron impact (EI) ionization by using a 5971 Hewlett Packard instrument at 70 eV: only selected ions are reported. HRMS were performed at the Laboratoire de Spectrochimie de l'Ecole Normale Supérieure in Paris. Optical rotations were measured on a Perkin-Elmer 343 polarimeter in a 10 cm cell. Analytical HPLC was carried out using a Waters 515 solvent-delivery system and a Waters 2487 variable-wavelength absorbance detector operating at 254 nm. The ee of the products were determined using a Chiralcel OD-H column and eluting with hexane–*i*PrOH (99/1) at the flow rate of 1 mL/min. Elemental analysis were performed by the Centre Régional de Microanalyses (Université Pierre et Marie Curie, Paris VI).

3.1.1. (2*S*,4*R*)-1-Benzyl-4-[(*tert*-butyldimethylsilyl)oxy]-2-methoxycarbonylpyrrolidine (1a);[15] typical procedure

To a stirred suspension of (2*R*,4*R*)-4-hydroxy-2-methoxycarbonylpyrrolidine (5.0 g, 38.1 mmol, 1.0 equiv) in MeOH (150 mL) at 0 °C thionyl chloride (3.4 mL, 45.7 mmol, 1.2 equiv) was added dropwise. After 72 h at rt, the organic solvent was removed in vacuo to afford a white solid.

To a stirred suspension of the resulting white solid in CH_2Cl_2 (40 mL) at rt was added Et_3N (21.4 mL, 152.4 mmol, 4 equiv), followed by BnBr (5.5 mL, 45.7 mmol, 1.2 equiv). After 10 min at rt, the reaction mixture was heated at reflux for 5 h and cooled to rt. DMAP (0.5 g, 3.8 mmol, 0.1 equiv) and TBDMSCl (6.9 g, 45.7 mmol, 1.2 equiv) were added. After 12 h at rt, the reaction mixture was quenched with a saturated aqueous Na_2CO_3 solution until pH ~ 10. The aqueous layer was extracted with CH_2Cl_2 and EtOAc and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford an oil, which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 30:70) to give **1a** (9.0 g, 25.8 mmol, 68% yield) as a colorless oil; $[\alpha]_D^{20}$ −49.6 (*c* 3.65, $CHCl_3$); IR (neat): 1740, 1375, 780, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.35–7.21 (5H), 4.41 (m, 1H), 3.91 (d, J=12.5 Hz, 1H), 3.65 (s, 3H), 3.60 (d, J=12.5 Hz, 1H), 3.53 (t, J=8.1 Hz, 1H), 3.27 (dd, J=9.6, 5.7 Hz, 1H), 2.37 (dd, J=9.6, 5.2 Hz, 1H), 2.19 (ddd, J=13.1, 7.5, 7.3 Hz, 1H), 2.03 (ddd, J=12.8, 8.5, 4.0 Hz, 1H), 0.8 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 174.1 (s), 138.0 (s), 129.0 (d), 128.1 (d), 127.0 (d), 70.3 (d), 64.2 (d), 61.5 (t), 59.3 (t), 51.7 (q), 39.4 (t), 25.6 (q), 17.8 (s), −5.0 (q); EI MS *m/z* (relative intensity) 349 ($M^{+\cdot}$, 1), 292 (10), 291 (27), 290 (100), 158 (14), 91 (41).

3.1.2. (2*S*,4*R*)-1-Benzyl-4-[(*tert*-butyldiphenylsilyl)oxy]-2-methoxycarbonylpyrrolidine (1b). Yield: 93% from (2*R*,4*R*)-4-hydroxy-2-methoxycarbonylpyrrolidine; colorless oil; $[\alpha]_D^{20}$ −20.8 (*c* 3.65, $CHCl_3$); IR (neat): 1740, 1375, 740, 710, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.78–7.73 (1H), 7.68–7.60 (4H), 7.48–7.23 (10H), 4.46 (m, 1H), 3.92 (d, J=12.9 Hz, 1H), 3.66 (d, J=12.9 Hz, 1H), 3.62 (s, 3H), 3.61 (dd, J=8.1, 8.1 Hz, 1H), 3.19 (dd, J=9.9, 5.9 Hz, 1H), 2.53 (dd, J=9.9, 4.8 Hz, 1H), 2.13 (m, 1H), 2.04 (m, 1H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 174.0 (s), 138.0 (s), 135.5 (d), 134.7 (d), 133.7 (s), 133.6 (s), 129.7 (d), 129.6 (d), 129.0 (d), 128.1 (d), 127.6 (d), 127.5 (d), 127.0 (d), 71.4 (d), 64.3 (d), 61.5 (t), 59.1 (t), 51.6 (q), 39.4 (t), 26.8 (q), 18.9 (s); EI MS *m/z* (relative intensity) 473 ($M^{+\cdot}$, 1), 458 (1), 414 (100) 199 (11), 183 (6), 158 (11), 135 (5), 91 (49).

3.1.3. (2*S*,4*R*)-1-Benzyl-4-[(triisopropylsilyl)oxy]-2-methoxycarbonylpyrrolidine (1c). Yield: 65% from (2*R*,4*R*)-4-hydroxy-2-methoxycarbonylpyrrolidine; colorless oil; $[\alpha]_D^{20}$ −17.3 (*c* 1.54, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 7.36–7.22 (5H), 4.51 (m, 1H), 3.91 (d, J=12.9 Hz, 1H), 3.64 (s, 3H), 3.62 (d, J=12.9 Hz, 1H), 3.55 (dd, J=8.1, 8.1 Hz, 1H), 3.33 (dd, J=9.7, 5.7 Hz, 1H), 2.43 (dd, J=9.7, 5.0 Hz, 1H), 2.23 (ddd, J=12.9, 8.1, 7.0 Hz, 1H), 2.09 (ddd, J=12.7, 8.7, 4.1 Hz, 1H), 1.06–1.03 (21H); ^{13}C NMR ($CDCl_3$) δ: 174.0 (s), 138.0 (s), 129.0 (d), 128.1 (d), 127.0 (d), 70.5 (d), 64.3 (d), 62.0 (t), 59.1 (t), 51.7 (q), 39.9 (t), 17.8 (q), 17.6 (q), 12.1 (d), 11.8 (d); EI MS *m/z* (relative intensity) 387 (13), 344 (11), 332 ($M^{+\cdot}$−COOMe, 100), 316 (5), 288 (5), 215 (6), 183 (4), 158 (11), 131 (7), 103 (6), 91 (77), 75 (11), 61 (5).

3.1.4. (2*S*,4*R*)-2-{1-Benzyl-4-[(*tert*-butyldimethylsilyl)-oxy]-pyrrolidinyl}methanol (2a);[16] typical procedure To a suspension of $LiAlH_4$ (0.87 g; 23.0 mmol, 2.0 equiv) in THF (15 mL) at 0 °C, a solution of pyrrolidine **1a** (4.0 g, 11.5 mmol, 1.0 equiv) in THF (15 mL) was added dropwise. After stirring at 0 °C for 10 min, the reaction mixture was heated at reflux for 2 h and then cooled to 0 °C. Water (0.09 mL), an aqueous 3.75 M NaOH solution (0.89 mL), and water (2.7 mL) were successively added. The obtained precipitate was collected on a Celite pad and washed with THF. The organic solvent was removed in vacuo to give **2a** (3.4 g, 10.6 mmol, 92% yield) as a colorless oil; $[\alpha]_D^{20}$ −43.4 (*c* 1.00, $CHCl_3$), IR (neat): 3400, 1375, 780, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.37–7.27 (5H), 4.27 (m, 1H), 3.97 (d, J=13.2 Hz, 1H), 3.67 (dd, J=11.0, 3.3 Hz, 1H), 3.47 (d, J=13.2 Hz, 1H), 3.39 (d, J=11.0 Hz, 1H), 3.14 (dd, J=9.9, 5.5 Hz, 1H), 3.07 (m, 1H), 2.65 (s, 1H), 2.37 (dd, J=9.9, 5.7 Hz, 1H), 2.09 (ddd, J=12.9, 7.4, 7.4 Hz, 1H), 1.84 (ddd, J=13.0, 8.6, 4.6 Hz, 1H), 0.8 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 139.0 (s), 128.5 (d), 128.3 (d), 126.9 (d), 70.6 (d), 63.3 (d), 62.1 (t), 60.9 (t), 58.6 (t), 37.7 (t), 25.7 (q), 17.9 (s), −4.9 (q); EI MS *m/z* (relative intensity) 306 ($M^{+\cdot}$−CH3, 3), 292 (7), 291 (24), 290 (100), 158 (14), 91 (61), 75 (7).

3.1.5. (2*S*,4*R*)-2-{1-Benzyl-4-[(*tert*-butyldiphenylsilyl)-oxy]-pyrrolidinyl}methanol (2b). Yield: 90% from **1b**; colorless oil; $[\alpha]_D^{20}$ −1.2 (*c* 2.40, $CHCl_3$); IR (neat): 3350, 1425, 1375, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.73–7.63 (4H), 7.53–7.23 (11H), 4.34 (m, 1H), 3.99 (d, J=12.9 Hz, 1H), 3.63 (dd, J=11.0, 3.7 Hz, 1H), 3.54 (d, J=13.2 Hz, 1H), 3.36 (dd, J=11.0, 1.8 Hz, 1H), 3.14 (tdd, J=8.1, 3.3, 1.8 Hz, 1H), 3.06 (dd, J=10.3, 5.5 Hz, 1H), 2.52 (dd, J=10.1, 4.9 Hz, 1H), 2.48 (br s, 1H), 1.90–1.98 (2H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 139.0 (s), 135.5 (d), 134.4 (s), 129.6 (d), 129.5 (d), 128.5 (d), 128.2 (d), 127.5 (d), 127.4 (d), 126.9 (d), 71.7 (d), 63.4 (d), 62.1 (t), 60.8 (t), 58.7 (t), 37.5 (t), 26.8 (q), 18.9 (s); EI MS *m/z* (relative intensity) 445 ($M^{+\cdot}$, 1), 414 (100), 199 (14), 183 (5), 158 (12), 91 (49); HRMS (CI) calcd for $C_{28}H_{36}O_2NSi$ ($M+H^+$) 446.2515, found 446.2508.

3.1.6. (2*S*,4*R*)-2-{1-Benzyl-4-[(triisopropylsilyl)oxy]-pyrrolidinyl}methanol (2c). Yield: 96% from **1c**; colorless oil; $[\alpha]_D^{20}$ −9.9 (*c* 1.06, $CHCl_3$); IR (neat): 3390, 1460, 1380, 735, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.38–7.24 (5H), 4.37 (m, 1H), 3.97 (d, J=12.9 Hz, 1H), 3.65 (dd, J=10.8, 3.3 Hz, 1H), 3.51 (d, J=13.2 Hz, 1H), 3.40 (d, J=10.7 Hz, 1H), 3.19 (dd, J=8.1, 5.5 Hz, 1H), 3.11 (tdd, J=8.1, 3.3, 1.8 Hz, 1H), 2.91 (br s, 1H), 2.43 (dd, J=9.9, 5.1 Hz, 1H), 2.11 (dt, J=12.9, 7.4 Hz, 1H), 1.88 (ddd, J=12.8, 8.3, 4.1 Hz, 1H), 1.07–1.05 (21H); ^{13}C NMR ($CDCl_3$) δ: 139.0 (s), 128.5 (d), 128.3 (d), 126.9 (d), 70.8 (d), 63.3 (d), 62.6 (t), 60.1 (t), 58.7 (t), 38.0 (t), 17.8 (q), 17.6 (q), 12.2 (d), 11.9 (d); EI MS *m/z* (relative intensity) 332 ($M^{+\cdot}$−CH_2OH, 100), 207 (19), 158 (15), 91 (60), 75 (8), 61 (5); HRMS (CI) calcd for $C_{21}H_{38}O_2NSi$ ($M+H^+$) 364.2672, found 364.2665.

3.1.7. (3*R*,5*R*)-1-Benzyl-5-[(*tert*-butyldimethylsilyl)oxy]-piperidin-3-ol (3a);[6] typical procedure Trifluoroacetic anhydride (1.1 mL, 7.5 mmol, 1.2 equiv) was added dropwise to a solution of pyrrolidine **2a** (2.0 g, 6.2 mmol, 1.0 equiv) in THF (60 mL), cooled to 0 °C. After 1 h, Et_3N (3.5 mL, 24.8 mmol, 4.0 equiv) was added dropwise. The reaction mixture was stirred for 20 min at 0 °C and then heated at reflux for 72 h. After addition of an aqueous 2.5 M NaOH solution (15 mL), the mixture was stirred for 2 h at rt

and then extracted with EtOAc, dried with $MgSO_4$, and evaporated to dryness in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 30:70) to give **3a** (1.65 g, 5.1 mmol, 82% yield) as an oil; $[\alpha]_D^{20}$ +25.3 (*c* 1.75, EtOH); IR (neat): 3450, 1460, 1250, 1150, 1090, 840, 775, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.37–7.24 (5H), 4.05 (h, J=4.8 Hz, 1H), 3.96 (s, 1H), 3.63 (d, J=13.2 Hz, 1H), 3.53 (d, J=13.2 Hz, 1H), 2.90 (m, 1H), 2.75 (m, 1H), 2.50 (br s, 1H), 2.19 (dd, J=11.4, 1.84 Hz, 1H), 2.09 (m, 1H), 1.97 (t, J=10.1 Hz, 1H), 1.38 (ddd, J=13.0, 10.3, 2.6 Hz, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 137.7 (s), 128.8 (d), 128.1 (d), 127.0 (d), 65.8 (d), 65.2 (d), 62.1 (t), 61.0 (t), 58.5 (t), 40.8 (t), 25.7 (q), 18.0 (s), −4.8 (q), −4.9 (q); EI MS *m/z* (relative intensity) 321 ($M^{+\cdot}$, 5), 304 (2), 264 (39), 246 (7), 134 (23), 120 (10), 101 (10), 91 (100), 73 (11).

3.1.8. (3*R*,5*R*)-1-Benzyl-5-[(*tert*-butyldiphenylsilyl)oxy]-piperidin-3-ol (3b). Yield: 64% from **2b**; oil; $[\alpha]_D^{20}$ +46.8 (*c* 1.57, EtOH); IR (neat): 3350, 1420, 1100, 900, 820, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.69–7.61 (4H), 7.48–7.18 (11H), 4.08 (m, 1H), 3.95 (s, 1H), 3.49 (s, 2H), 2.80–2.59 (2H), 2.33–2.23 (2H), 2.10–1.98 (2H), 1.55 (ddd, J=12.9, 9.9, 2.9 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 137.7 (s), 135.6 (d), 135.5 (d), 134.2 (s), 133.9 (s), 129.5 (d), 129.4 (d), 128.7 (d), 128.1 (d), 127.5 (d), 127.4 (d), 127.0 (d), 66.2 (d), 65.8 (d), 62.0 (t), 60.4 (t), 58.9 (t), 53.3 (t), 40.7 (t), 26.8 (q), 19.0 (s); EI MS *m/z* (relative intensity) 445 ($M^{+\cdot}$, 2), 388 (45), 310 (43), 199 (18), 183 (15), 134 (10), 91 (100); HRMS (CI) calcd for $C_{28}H_{36}O_2NSi$ ($M+H^+$) 446.2515, found 446.2514.

3.1.9. (3*R*,5*R*)-1-Benzyl-5-[(triisopropylsilyl)oxy]-piperidin-3-ol (3c). Yield: 47% from **2c**; oil; $[\alpha]_D^{20}$ +17.9 (*c* 2.00, EtOH); IR (neat): 3460, 1450, 1150, 1100, 910, 880, 800, 735, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.36–7.23 (5H), 4.10 (m, 1H), 3.97 (s, 1H), 3.60 (d, J=13.2 Hz, 1H), 3.55 (d, J=13.2 Hz, 1H), 2.96 (m, 1H), 2.77 (m, 1H), 2.53 (br s, 1H), 2.25–2.11 (2H), 1.95 (dd, J=10.3, 9.6 Hz, 1H), 1.40 (ddd, J=13.1, 10.3, 2.6 Hz, 1H), 1.05–1.00 (21H); ^{13}C NMR ($CDCl_3$) δ: 137.8 (s), 128.8 (d), 128.1 (d), 127.0 (d), 66.0 (d), 65.2 (d), 62.1 (t), 61.1 (t), 58.8 (t), 41.0 (t), 17.8 (q), 12.1 (d); EI MS *m/z* (relative intensity) 363 ($M^{+\cdot}$, 6), 320 (28), 190 (9), 172 (7), 134 (14), 120 (10), 91 (100). Anal. Calcd for $C_{21}H_{37}NO_2Si$: C, 69.37; H, 10.26; N, 3.85. Found C, 69.23; H, 10.42; N, 3.82.

3.1.10. (3*R*,5*R*)-1-Benzyl-5-[(*tert*-butyldimethylsilyl)-oxy]-5-trityloxypiperidine (4). To a stirred solution of piperidine **3a** (0.30 g, 0.93 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) at rt was added triphenylmethyl chloride (0.29 g, 1.0 mmol, 1.1 equiv), followed by the addition of Et_3N (0.26 mL, 1.9 mmol, 2.0 equiv). After stirring at rt for 48 h, the reaction was quenched with an aqueous 3.75 M NaOH solution (6 mL). After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a yellow oil, which was purified by flash column chromatography on silica gel (EtOAc/petroleum ether 20:80) to give **4** (0.44 g, 0.78 mmol, 83% yield) as a amorphous solid. ^1H NMR ($CDCl_3$) δ: 7.54–7.47 (5H), 7.34–7.16 (15H), 4.16 (m, 1H), 3.89 (m, 1H), 3.53 (d, J=13.6 Hz, 1H), 3.33 (d, J=13.6 Hz, 1H), 2.65 (dd, J=10.6, 3.3 Hz, 1H), 2.17 (dd, J=11.6, 5.5 Hz, 1H), 2.12 (dd, J=10.8, 3.3 Hz, 1H), 1.86 (dd, J=11.4, 2.6 Hz, 1H), 1.42 (m, 1H), 1.19 (m, 1H), 0.85 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 146.8 (s), 145.1 (s), 138.7 (s), 128.9 (d), 128.8 (d), 128.7 (d), 127.9 (d), 127.8 (d), 127.5 (d), 127.1 (d), 126.7 (d), 126.6 (d), 86.7 (s), 67.7 (d), 66.2 (d), 62.1 (t), 60.2 (t), 57.7 (t), 40.0 (t), 25.8 (q), 18.0 (s), −4.8 (q), −4.9 (q); EI MS *m/z* (relative intensity) 548 ($M^{+\cdot}-CH_3$, 1), 320 (100), 243 (17), 165 (21), 91 (59), 73 (7).

3.1.11. (3*R*,5*R*)-1-Benzyl-5-trityloxypiperidin-3-ol (3d). To a stirred solution of piperidine **4** (0.38 g, 0.68 mmol, 1.0 equiv) in THF (1 mL) at rt was added a solution of tetrabutylammonium fluoride 1 M in THF (2.7 mL, 2.7 mmol, 4.0 equiv). After stirring at rt for 72 h, the reaction was quenched with water (6 mL). After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a yellow gum, which was purified by flash column chromatography on silica gel (EtOAc/cyclohexane 30:70) to give **3d** (0.22 g, 0.49 mmol, 72% yield) as a white solid. Mp 76 °C; $[\alpha]_D^{20}$ +28.7 (*c* 1.23, $CHCl_3$); IR (KBr): 3300, 1440, 1150, 1020, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.52–7.44 (15H), 7.33–7.09 (5H), 3.95–3.82 (2H), 3.37 (d, J=12.9 Hz, 1H), 3.27 (d, J=13.2 Hz, 1H), 2.64 (m, 1H), 2.24–1.94 (4H), 1.84–1.69 (2H); ^{13}C NMR ($CDCl_3$) δ: 144.8 (s), 137.6 (s), 128.8 (d), 128.7 (d), 128.0 (d), 127.6 (d), 126.9 (d), 126.8 (d), 86.8 (s), 66.9 (d), 65.9 (d), 62.1 (t), 59.0 (t), 58.9 (t), 38.9 (t). Anal. Calcd for $C_{31}H_{31}NO_2$: C, 82.82; H, 6.95; N, 3.12. Found C, 82.68; H, 7.14; N, 3.13.

3.1.12. (3*R*,5*R*)-1-Benzylpiperidin-3,5-diol (3e).[7g] To a stirred solution of piperidine **3a** (0.52 g, 1.6 mmol, 1.0 equiv) in EtOAc (0.5 mL) at rt was added an aqueous 1.2 M solution of HCl (10.0 mL, 27.4 mmol, 17.1 equiv). After stirring at rt for 8 h, the reaction was quenched with an aqueous 3.75 M NaOH solution until pH ~ 11. After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a colorless oil, which was purified by flash column chromatography on silica gel (EtOAc/MeOH 95:5) to give **3e** (0.25 g, 1.21 mmol, 75% yield) as a white solid. Mp 109 °C; $[\alpha]_D^{20}$ +15.2 (*c* 0.99, EtOH); IR (KBr): 3440, 1200, 1140, 1100, 1050, 1000, 960, 760 cm^{-1}; ^1H NMR (CD_3OD) δ: 7.60–7.40 (5H), 4.19 (m, 2H), 3.65 (s, 2H), 2.73 (dd, J=10.9, 1.7 Hz, 2H), 2.50 (dd, J=10.9, 6.8 Hz, 2H), 1.38 (t, J=5.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ: 139.0 (s), 130.8 (d), 129.5 (d), 128.5 (d), 66.1 (t), 64.0 (t), 60.9 (t), 41.1 (t); EI MS *m/z* (relative intensity) 207 ($M^{+\cdot}$,14), 189 (2), 134 (12), 130 (10), 120 (14), 116 (27), 91 (100), 65 (8).

3.1.13. (3*R*,5*R*)-1-Benzyl-3,5-di[(*tert*-butyldimethylsilyl)-oxy]-piperidine (5).[6] To a stirred solution of piperidine **3a** (1.30 g, 4.0 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at rt were added TBDMSCl (1.2 g, 8.0 mmol, 2.0 equiv), Et_3N (0.68 mL, 4.8 mmol, 1.2 equiv) and DMAP (0.05 g, 0.4 mmol, 0.1 equiv). After 16 h at rt, the reaction mixture was quenched with a saturated aqueous Na_2CO_3 until pH ~ 10. The aqueous layer was extracted with EtOAc and the combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a yellow oil, which was purified by flash column

chromatography on silica gel (EtOAc/petroleum ether 10:90) to give **5** (1.50 g, 3.45 mmol, 86% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.39–7.21 (5H), 4.11 (m, 2H), 3.73 (d, J=13.6 Hz, 1H), 3.45 (d, J=13.6 Hz, 1H), 2.47 (dd, J=11.0, 3.0 Hz, 2H), 2.33 (dd, J=11.0, 6.3 Hz, 2H), 1.66 (t, J=5.1 Hz, 2H), 0.91 (s, 18H), 0.06 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 138.6 (s), 128.7 (d), 128.0 (d), 126.7 (d), 66.1 (d), 62.2 (t), 59.9 (t), 42.0 (t), 25.8 (q), 18.1 (s), −4.8 (q), −4.9 (q); EI MS *m/z* (relative intensity) 435 ($M^{+\cdot}$, 9), 420 (10), 378 (61), 344 (11), 315 (11), 303 (17), 263 (13), 246 (20), 212 (21), 159 (17), 134 (48), 101 (25), 91 (100), 75 (10), 59 (8).

3.1.14. (3*R*,5*R*)-3,5-Di[(*tert*-butyldimethylsilyl)oxy]-piperidine (6)[6] To a solution of piperidine **5** (1.5 g, 3.45 mmol, 1.0 equiv) in absolute EtOH (10 mL) was added Pd/C (367 mg, 10%, 0.36 mmol, 0.1 equiv). The mixture was stirred under 4 atm of hydrogen at rt for 18 h and was filtered through silica gel. The filtrate was concentrated under reduced pressure to give **6** (1.16 g, 3.36 mmol, 97% yield) as a colorless gum. ^{1}H NMR ($CDCl_3$) δ: 3.95 (m, 2H), 2.97 (br s, 1H), 2.83 (dd, J=14.1, 3.1 Hz, 2H), 2.57 (dd, J=13.4, 6.4 Hz, 2H), 1.73 (t, J=5.3 Hz, 2H), 0.89 (s, 18H), 0.07 (s, 6H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ: 66.3 (d), 52.4 (t), 41.6 (t), 25.7 (q), 18.0 (s), 5.0 (q); EI MS *m/z* (relative intensity) 345 ($M^{+\cdot}$, 1), 330 (6), 301 (23), 288 (100), 156 (34), 116 (10), 101 (10), 82 (40), 75 (15), 73 (32), 59 (7).

3.1.15. (3*R*,5*R*)-1-*tert*-Butyl-3,5-di[(*tert*-butyldimethylsilyl)oxy]-piperidine (7). To a stirred solution of piperidine **6** (0.40 g, 1.2 mmol, 1.0 equiv) in acetone (3 mL) at rt was added acetone cyanohydrin (0.11 mL, 1.2 mmol, 1.0 equiv). After stirring at rt for 16 h, the solvent was removed in vacuo to afford a colorless gum, which was dissolved in ether (2 mL). A 3 M solution of MeMgBr in ether (3.5 mL, 10.5 mmol, 8.75 equiv) was added dropwise to the previously prepared α-aminonitrile solution at 0 °C. After stirring at rt for 20 h, the reaction was quenched with ice. After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a yellow oil, which was purified by flash column chromatography on silica gel (CH_2Cl_2/petroleum ether/Et_3N 50:50:1) to give **7** (0.32 g, 0.8 mmol, 67% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 4.02 (m, 2H), 2.59 (dd, J=11.0, 2.9 Hz, 2H), 2.34 (dd, J=10.7, 6.3 Hz, 2H), 1.61 (t, J=5.5 Hz, 2H), 1.04 (s, 9H), 0.90 (s, 18H), 0.07 (s, 12H); ^{13}C NMR ($CDCl_3$) δ: 66.9 (d), 53.1 (t), 53.0 (s), 42.1 (t), 26.0 (q), 25.8 (q), 18.0 (s), −4.9 (q), −4.8 (q); EI MS *m/z* (relative intensity) 401 ($M^{+\cdot}$, 1), 386 (100), 82 (4), 73 (13), 57 (4).

3.1.16. (3*R*,5*R*)-1-*tert*-Butylpiperidin-3,5-diol (3f). To a stirred solution of piperidine **7** (0.27 g, 0.67 mmol, 1.0 equiv) in THF (2 mL) at rt was added a solution of tetrabutylammonium fluoride 1 M in THF (3.8 mL, 3.8 mmol, 5.6 equiv). After stirring at rt for 72 h, the reaction was quenched with water (6 mL). After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a yellow oil, which was purified by flash column chromatography on silica gel (EtOAc/MeOH/Et_3N 95:5:1) to give **3f** (54.0 mg, 0.31 mmol, 46% yield) as a white solid. Mp 112 °C; $[\alpha]_D^{20}$ +21.3 (*c* 0.94, CH_3OH); IR (KBr): 3300, 1320, 1200, 1060, 960, 830 cm^{-1}; ^{1}H NMR (CD_3OD) δ: 4.14 (m, 2H), 2.88 (dd, J=11.0, 2.9 Hz, 2H), 2.63 (dd, J=11.0, 6.6 Hz, 2H), 1.88 (t, J=5.5 Hz, 2H), 1.29 (s, 9H); ^{13}C NMR (CD_3OD) δ: 66.7 (t), 55.0 (s), 54.3 (t), 41.4 (t), 26.6 (q); HRMS (CI) calcd for $C_9H_{20}O_2N$ ($M+H^+$) 174.1494, found 174.1490.

3.2. Asymmetric addition of diethylzinc to aldehydes; general procedure

Diethylzinc (1.1 M in toluene, 1.2 equiv) was added to ligand **3** in toluene under argon at 0 °C and the mixture was stirred for 0.5 h at 0 °C. After the addition of aldehyde (1.0 equiv) at 0 °C, the mixture was stirred at rt and after 24 h an aqueous 1.2 M solution of HCl was added. After usual work-up, pure alcohols were obtained by flash column chromatography. The ee and the absolute configuration of the resulting alcohol were determined by using HPLC.

3.3. Asymmetric addition of diethylzinc to aldehydes and benzoylation; general procedure

Diethylzinc (1.1 M in toluene, 1.2 equiv) was added to ligand **3** in toluene under argon at 0 °C and the mixture was stirred for 0.5 h at 0 °C. After addition of heptanal (1.0 equiv) at 0 °C, the mixture was stirred at rt and after 24 h an aqueous 1.2 M solution of HCl was added. After extraction with EtOAc, the combined organic layers were dried with $MgSO_4$ and filtered. The solvent was removed in vacuo to afford the crude nonan-3-ol, which was dissolved in CH_2Cl_2. Benzoyl chloride (1.5 equiv), followed by Et_3N (2 equiv) and DMAP (1 equiv) were added to the previously prepared alcohol solution. After stirring at rt for 18 h, the reaction was quenched with an aqueous 1.2 M solution of HCl. After usual work-up, the pure esters were obtained by flash column chromatography. The ee and the absolute configuration of the resulting ester were determined by using HPLC.

References and notes

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