Enantioselective Addition of Dimethylzinc to Aldehydes Catalyzed by a Chiral Perhydro-1,3-benzoxazine-Based Amino Alcohol as Ligand

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Abstract: Dimethylzinc undergoes efficient enantioselective addition to a wide variety of aromatic and aliphatic aldehydes in the presence of a catalytic amount of a chiral perhydro-1,3-benzoxazine-based amino alcohol. Methyl carbinols are obtained in good yields and in enantiomeric excesses of 99% or more in the absence of any metal other than zinc.

Key words: asymmetric catalysis, zinc, aldehydes, chiral auxiliaries, amino alcohols

Among the asymmetric catalytic reactions that are available for C–C bond formation, the enantioselective addition of a diorganozinc reagent to an aldehyde in the presence of a catalytic amount of a chiral ligand is a particularly convenient method for obtaining chiral secondary alcohols with high optical purity.[1–4] In this respect, the asymmetric addition of diethylzinc to aldehydes has attracted a great deal of attention. However, although they are more important than ethyl carbinols as building blocks for the synthesis of bioactive compounds,[5] chiral methyl carbinols are usually prepared from ketones through enantioselective reduction. This route is adopted mainly because of the low reactivity of dimethylzinc compared with that of diethylzinc.[6] Significant progress has recently been made in the use of chiral chromium,[7] titanium[8,9] and osmium[10] complexes as catalysts for this reaction; however, these impressive methods depended on the presence of others metals in addition to zinc. Only a few examples of asymmetric methylation reactions of aldehydes, other than benzaldehyde, that employ dimethylzinc and a catalytic amount of chiral ligands in the absence of any additional metals have been reported that provide high yields and high enantiomeric excesses.[11–15] Therefore, the development of a highly enantioselective methylation method remains a challenge.

We have recently introduced the perhydro-1,3-benzoxazine **1** (Figure 1) as an asymmetric ligand and have demonstrated its use as a catalyst in asymmetric ethylation and arylation reactions of a wide range of aldehydes.[16]

Here we report that perhydro-1,3-benzoxazine **1** also catalyzes the asymmetric reaction of aldehydes with dimethylzinc.

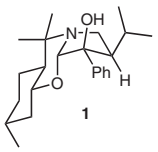
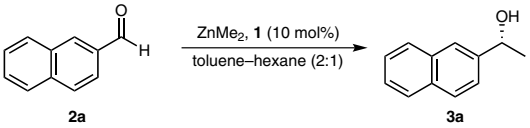


Figure 1 Perhydro-1,3-benzoxazine ligand **1**

We initially examined the experimental conditions for the reaction between two equivalents of dimethyl zinc (1.2 M) and 2-naphthaldehyde in the presence of 10 mol% of ligand **1** in a 2:1 toluene–hexane mixture at various temperatures. The results are listed in Table 1.

Table 1 Screening of Reaction Conditions for Asymmetric Methylation of 2-Naphthaldehyde Catalyzed by Ligand **1**



2a **3a**

Entry[a]	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	25	24	93	87
2	0	24	56	91
3	–10	24	49	93
4	–15	24	22	95
5	–20	24	21	97
6	–20 / r.t.	24/6	75	92

[a] Reactions were carried out with a Me_2Zn/aldehyde/catalyst **1** molar ratio of 2:1:0.1 in 2:1 toluene–hexane. All reactions were performed in duplicate.
[b] Yields of pure compounds after column chromatography.
[c] The ee was determined by HPLC on a Chiralcel AS-H column. The absolute configuration was assigned from the order of elution in HPLC by comparison with literature data.

Under the optimized conditions for the addition of diethylzinc to aldehydes,[16a] carbinol **3a** was obtained in good yield but moderate enantioselectivity (87% ee; Table 1, entry 1). Decreasing the temperature from room temperature to –20 °C increased the enantioselectivity from 87% to 97% (entries 2–5). However, this was accompanied by progressive loss in catalytic activity; the yield fell to 20% at –20 °C with 68% recovery of the starting aldehyde **2a** (entry 5). Good catalytic performance in terms of both the

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yield and enantioselectivity was achieved when the mixture was stirred for 24 hours at –20 °C and then for six hours at room temperature (75% yield, 92% ee; Entry 6). Figure 2 shows the evolution of the conversion and enantiomeric excess with reaction time under these conditions.

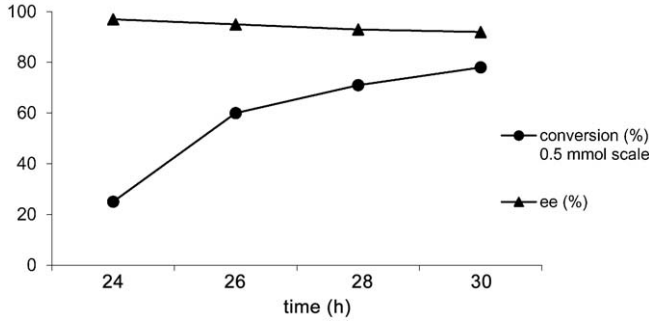


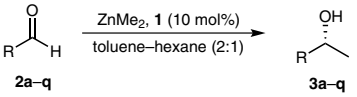
Figure 2 Changes in conversion and enantiomeric excess with reaction time at room temperature

Next, we evaluated the asymmetric catalysis by ligand **1** of addition reactions of dimethylzinc with a variety of aldehydes under the optimized conditions. The results are shown in Table 2.

Optically active 1-arylethanols were obtained in good yields and good-to-excellent enantioselectivities from various aromatic aldehydes, including *ortho*-, *meta*- and *para*-substituted benzaldehydes (Table 2, entries 1–11). In general, there was little dependence on the electronic character of the substituent in *para*-substituted benzaldehydes. 4-Tolualdehyde and 4-methoxybenzaldehyde, which contain electron-donating groups, and 4-chloro- and 4-(trifluoromethyl)benzaldehyde, which contain electron-withdrawing groups, behaved similarly in terms of their enantioselectivities (entries 4, 6, 9, and 11), although there were appreciable differnces in their reactivities. 2-Chloro- and 2-bromo-substituted benzaldehydes gave slightly lower enantiomeric excesses than did other benzaldehydes substituted with donating groups in the *ortho*-position (compare entries 7 and 10 with entries 3 and 5). This is probably due to a combination of the electronic and steric effects of the *ortho*-substituents. In the same way, good enantioselectivity was achieved with the heterocyclic aldehyde 2-furaldehyde (83% ee; entry 12). The best asymmetric inductions were found with 4-(trifluoromethyl)benzaldehyde (which contains a strongly electron-withdrawing 4-trifluoromethyl group) and 3-chlorobenzaldehyde; these gave enantiomeric excesses of up to 97% and 98%, respectively (entries 11 and 8).

Encouraged by these results, we focused our attention on the asymmetric addition of dimethylzinc to several aliphatic aldehydes **2m**–**o** in the presence of chiral ligand **1**. Extremely high enantioselective methylation was achieved with 3-phenylpropanal, although the chemical yield was moderate (entry 13). Cyclohexanecarboxaldehyde also showed a high enantiomeric excess of 88% (entry 14), whereas alkylation of the linear aldehyde heptanal showed moderate enantioselectivity (entry 15). To facilitate the determination of the enantiomeric excess by chiral HPLC, alcohols **3n** and **3o**, obtained by addition of dimethylzinc to cyclohexanecarboxaldehyde and heptanal, respectively, were characterized as their benzoates (**4n** and **4o**, respectively).

Table 2 Asymmetric Addition of Dimethylzinc to Various Aldehydes Catalyzed by Ligand **1**



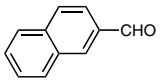
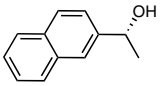
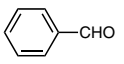
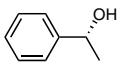
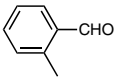
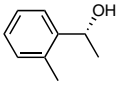
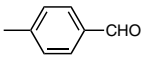
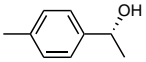
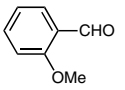
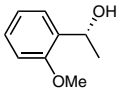
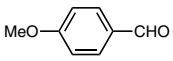
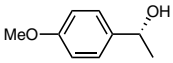
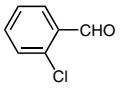
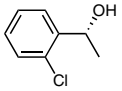
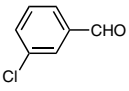
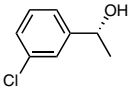
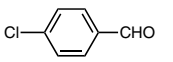
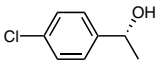
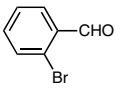
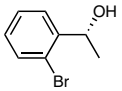
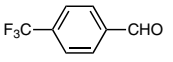
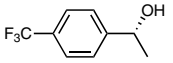
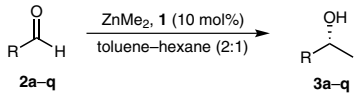
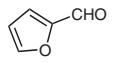
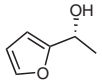
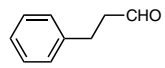
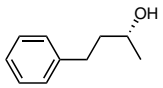
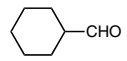
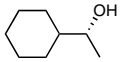
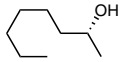
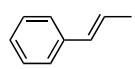
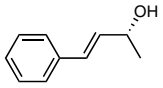
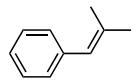
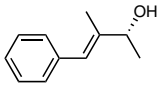
Entry[a]	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
1	 **2a**	 **3a**	75	87
2	 **2b**	 **3b**	96	91
3	 **2c**	 **3c**	58[f]	91
4	 **2d**	 **3d**	67[f]	94
5	 **2e**	 **3e**	90	93
6[d]	 **2f**	 **3f**	72	92
7	 **2g**	 **3g**	70	86
8	 **2h**	 **3h**	70	98
9[d]	 **2i**	 **3i**	97	95
10	 **2j**	 **3j**	74	80
11	 **2k**	 **3k**	98	97

Table 2 Asymmetric Addition of Dimethylzinc to Various Aldehydes Catalyzed by Ligand **1** (continued)



Entry[a]	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
12	 **2l**	 **3l**	51[f]	83
13	 **2m**	 **3m**	40[f]	>99
14	 **2n**	 **3n**	64[e]	88
15	 **2o**	 **3o**	58[e]	74
16[d]	 **2p**	 **3p**	88	74
17	 **2q**	 **3q**	47[f]	86

[a] Reactions were carried out with a Me_2Zn/aldehyde/catalyst **1** molar ratio of 2:1:0.1 in 2:1 toluene–hexane at –20 °C for 24 h and then for 6 h at r.t. unless otherwise indicated.
[b] Yields of pure compounds after column chromatography.
[c] The ee was determined by HPLC on a chiral column. The absolute configuration was assigned by comparing the sign of the specific rotation or the elution order in the HPLC analysis with literature data.
[d] At r.t. for 24 h.
[e] Yield of the benzoylated product.
[f] 22% of **2c**, 12% of **2d**, 20% of **2l**, 38% of **2m**, and 24% of **2q** were recovered.

The catalytic efficiency of ligand **1** for the addition of dimethylzinc to α,β-unsaturated aldehydes was also examined. Allylic alcohol **3p** was obtained in a good yield and moderate enantioselectivity from *trans*-cinnamaldehyde (entry 16), whereas methylation of α-methyl-*trans*-cinnamaldehyde gave allylic alcohol **3q** in a reasonably high 86% enantiomeric excess but with a moderate chemical yield (entry 17).

In all of the cases, the reaction led to alcohols with the *R*-configuration as a result of attack of the methyl group on the *Re* face of the aldehyde carbonyl (Figure 3). The stereochemical course of the reaction can be rationalized in terms of an *anti*-5/4/4-fused tricyclic transition-state structure, related to that proposed by Noyori.[17] This transition structure prevents steric repulsion between the perhydro-1,3-benzoxazine skeleton and the aldehyde and dimethylzinc and it minimizes nonbonded repulsion between the nonreactive $Zn–CH_3$ group and the R substituent on the aldehyde.

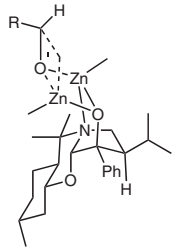


Figure 3 Proposed transition state for the addition of dimethylzinc to aldehydes catalyzed by ligand **1**

In conclusion, we have shown that chiral perhydro-1,3-benzoxazine **1** is an efficient chiral ligand for the enantioselective addition of dimethylzinc to a wide variety of aldehydes under mild conditions and in the absence of additional metals other than zinc. The enantioselectivity is excellent for aromatic aldehydes and good for aliphatic or α,β-unsaturated aldehydes. On the other hand, the yields vary from moderate to high, depending on the starting aldehyde. These results compared favorably with the highest enantioselectivities reported for the asymmetric addition of dimethylzinc to aldehydes.

All reactions were carried out in anhyd solvents under argon in dried glassware by means of Schlenk techniques. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ by using a Bruker AV-400 spectrometer. Chemical shifts for protons are reported in ppm from TMS with the residual $CHCl_3$ resonance as the internal reference. Chemical shifts for carbons are reported in ppm from TMS and are referenced to the carbon resonance of the solvent. Specific rotations were measured by using a 5-mL cell with a 1-dm path length and a Na lamp; the concentration is given in grams per 100 mL. Flash chromatography was carried out using silica gel (230–240 mesh). Chemical yields refer to the pure isolated substances. TLC analysis was performed on glass–backed plates coated with silica gel 60 and an F_{254} indicator, and visualized by either UV irradiation or by staining with I_2 or phosphomolybdic acid soln. Chiral HPLC analysis was performed using a Daicel Chiralcel OD Column, Chiralpak AD-H, or Chiralpak AS–H. UV detection was performed at 220 or 254 nm.

Unless otherwise indicated, all compounds were purchased and used as received. The ligand **1** was prepared according to reported procedures.[16a,18,19]

Asymmetric Addition of Dimethylzinc to Aldehydes; General Procedure

A 1.2 M soln of Me_2Zn in toluene (0.83 mL, 1.0 mmol) was added to an argon-purged flask containing ligand **1** (17.8 mg, 0.05 mmol) and anhyd 1:2 toluene–hexane (0.2–0.5 mL) at r.t. The soln was stirred for 10 min then cooled to –20 °C. The aldehyde (0.5 mmol) was added and the mixture was kept at –20 °C for 24 h then warmed to r.t. and stirred for 6 h. The reaction was quenched by dropwise addition of aq NH_4Cl. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane–EtOAc). The ee values were determined by HPLC on a chiral stationary phase.

(1*R*)-1-(2-Naphthyl)ethanol (3a)
This compound was obtained from 2-naphthaldehyde (78 mg, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:30)] to give a colorless solid; yield: 64 mg (0.37 mmol, 75%), 92% ee.

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (98:02), 1 mL/min, λ = 254 nm]: t_R = 19.1 min for enantiomer *R*, t_R = 21.9 min for enantiomer *S*. The configuration was assigned by comparing the HPLC elution order with literature data.[20]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58 (d, *J* = 6.5 Hz, 3 H), 2.50 (s, 1 H), 5.01 (q, *J* = 6.5 Hz, 1 H), 7.49–7.54 (m, 3 H), 7.79–7.87 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0 (CH_3), 70.3 (CH), 123.7 (CH), 123.8 (CH), 125.7 (CH), 126.0 (CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 132.8 (C), 133.2 (C), 143.1 (C).

(1*R*)-1-Phenylethanol (3b)
This compound was obtained from PhCHO (53 mg, 51 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:60)] to give a colorless liquid; yield: 58 mg (0.48 mmol, 96%), 91% ee.

HPLC [Chiralcel OD, hexane–*i*-PrOH (95:05), 1 mL/min, λ = 220 nm]: t_R = 9.5 min for enantiomer *R*, t_R = 11.3 min for enantiomer *S*. The configuration was assigned by comparing the HPLC elution order with literature data.[20]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.5 Hz, 3 H), 1.93 (br s, 1 H), 4.90 (q, *J* = 6.5 Hz, 1 H), 7.28 (m, 1 H), 7.32–7.42 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (CH_3), 69.6 (CH), 125.1 (2 CH), 126.9 (CH), 128.0 (2 CH), 145.7 (C).

(1*R*)-1-(2-Methylphenyl)ethanol (3c)
This compound was obtained from 2-tolualdehyde (60 mg, 60 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:60)] to give a colorless liquid; yield: 43 mg (0.29 mmol, 58%), 91% ee.

HPLC [Chiralpak AD-H, hexane–*i*-PrOH (99:1), 1 mL/min, λ = 220 nm]: t_R = 18.4 min for enantiomer *R*, t_R = 23.1 min for enantiomer *S*. The configuration was assigned by comparing the HPLC elution order with literature data.[21]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 6.4 Hz, 3 H), 2.36 (s, 3 H), 2.43 (br, 1 H), 5.12 (q, *J* = 6.4 Hz, 1 H), 7.13–7.28 (m, 3 H), 7.54 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 (CH_3), 23.8 (CH_3), 66.6 (CH), 124.4 (CH), 126.2 (CH), 127.0 (CH), 130.2 (CH), 134.0 (C), 143.8 (C).

(1*R*)-1-(4-Methylphenyl)ethanol (3d)
This compound was obtained from 4-tolualdehyde (60 mg, 56 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:60)] to give a colorless liquid; yield: 50 mg (0.33 mmol, 67%), 94% ee; $[\alpha]_D^{20}$ +49.3 (*c* 0.5, $CHCl_3$).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (99:1), 1 mL/min, λ = 220 nm]: t_R = 15.3 min for enantiomer *R*, t_R = 18.2 min for enantiomer *S*. The configuration was assigned by comparing the sign of the optical rotation with the literature value: $[\alpha]_D^{20}$ +53.2 (*c* 0.236, $CHCl_3$, *R*).[22]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 6.4 Hz, 3 H), 2.39 (s, 3 H), 2.69 (br s, 1 H), 4.84 (q, *J* = 6.4 Hz, 1 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9 (CH_3), 24.9 (CH_3), 69.9 (CH), 125.2 (2 CH), 128.9 (2 CH), 136.8 (C), 142.8 (C).

(1*R*)-1-(2-Methoxyphenyl)ethanol (3e)
This compound was obtained from 2-methoxybenzaldehyde (68 mg, 62 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:30)] to give a colorless oil; yield: 74 mg (0.45 mmol, 90%), 93% ee; $[\alpha]_D^{20}$ +26.8 (*c* 0.6, $CHCl_3$).

HPLC [Chiralpak AD-H, hexane–*i*-PrOH (99:1), 1 mL/min, λ = 254 nm]: t_R = 33.3 min for enantiomer *S*, t_R = 34.6 min for enantiomer *R*. The configuration was assigned by comparing the sign of the optical rotation with the literature value: $[\alpha]_D^{25}$ +28.4 (*c* 1.0, $CHCl_3$, *R*).[23]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.4 Hz, 3 H), 2.90 (s, 1 H), 3.86 (s, 3 H), 5.11 (q, *J* = 6.4 Hz, 1 H), 6.89 (m, 1 H), 6.98 (m, 1 H), 7.26 (m, 1 H), 7.37 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8 (CH_3), 55.1 (CH_3), 66.2 (CH), 110.2 (CH), 120.6 (CH), 125.9 (CH), 128.1 (CH), 133.4 (C), 156.3 (C).

(1*R*)-1-(4-Methoxyphenyl)ethanol (3f)
This compound was obtained from 4-methoxybenzaldehyde (68 mg, 61 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:20)] to give a colorless oil; yield: 59 mg (0.35 mmol, 72%), 92% ee.

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (90:10), 1 mL/min, λ = 254 nm]: t_R = 12.2 min for enantiomer *R*, t_R = 15.9 min for enantiomer *S*. The configuration was assigned by comparing the HPLC elution order with literature data.[24]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.6 Hz, 3 H), 2.89 (s, 1 H), 3.78 (s, 3 H), 4.78 (q, *J* = 6.4 Hz, 1 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.26 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8 (CH_3), 55.0 (CH_3), 69.5 (CH), 113.6 (2 CH), 126.5 (2 CH), 138.0 (C), 158.6 (C).

(1*R*)-1-(2-chlorophenyl)ethanol (3g)
This compound was obtained from 2-chlorobenzaldehyde (71 mg, 56 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:45)] to give a colorless oil; yield: 54 mg (0.35 mmol, 70%), 86% ee.

HPLC [Chiralcel OD, hexane–*i*-PrOH (99:1), 1 mL/min, λ = 220 nm]: t_R = 24.7 min for enantiomer *R*, t_R = 27.4 min for enantiomer *S*. The configuration was assigned by comparing the HPLC elution order with literature data.[9]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.4 Hz, 3 H), 3.45 (s, 1 H), 5.19 (q, *J* = 6.3 Hz, 1 H), 7.17 (m, 1 H), 7.21–7.33 (m, 2 H), 7.50 (dd, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4 (CH_3), 66.6 (CH), 126.3 (CH), 127.0 (CH), 128.1 (CH), 129.1 (CH), 131.3 (C), 143.0 (C).

(1*R*)-1-(3-Chlorophenyl)ethanol (3h)
This compound was obtained from 3-chlorobenzaldehyde (71 mg, 58 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:30)] to give a colorless oil; yield: 54 mg (0.35 mmol, 70%), 98% ee; $[\alpha]_D^{20}$ +40.1 (*c* 0.8, $CHCl_3$).

HPLC [Chiralpak AD-H, hexane–*i*-PrOH (99:1), 0.5 mL/min, λ = 220 nm]: t_R = 56.9 min for enantiomer *R*, t_R = 67.6 min for enantiomer *S*. The configuration was assigned by comparing the sign of the optical rotation with the literature value: $[\alpha]_D^{25}$ +40.4 (*c* 1.0, $CHCl_3$, *R*).[23]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.4 Hz, 3 H), 2.57 (br s, 1 H), 4.82 (q, *J* = 6.4 Hz, 1 H), 7.13–7.29 (m, 3 H), 7.34 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1 (CH_3), 69.7 (CH), 123.5 (CH), 125.5 (CH), 127.4 (CH), 129.7 (CH), 134.2 (C), 147.8 (C).

(1*R*)-1-(4-Chlorophenyl)ethanol (3i)
This compound was obtained from 4-chlorobenzaldehyde (71 mg, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:30)] to give a colorless oil; yield: 75 mg (0.48 mmol, 97%), 95% ee; $[\alpha]_D^{20}$ +47.5 (*c* 0.7, $CHCl_3$).

HPLC [Chiralcel OD, hexane–*i*-PrOH (95:5), 1 mL/min, λ = 220 nm]: t_R = 9.2 min for enantiomer *S*, t_R = 10.0 min for enantiomer *R*. The configuration was assigned by comparing HPLC elution order with literature data[25] and the sign of the optical rotation with the literature value: $[\alpha]_D^{25}$ +46.1 (*c* 1.0, $CHCl_3$, *R*).[23]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.5 Hz, 3 H), 2.49 (s, 1 H), 4.74 (q, *J* = 6.5 Hz, 1 H), 7.19–7.29 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0 (CH_3), 69.3 (CH), 126.7 (2 CH), 128.3 (2 CH), 132.7 (C), 144.1 (C).

(1*R*)-1-(2-Bromophenyl)ethanol (3j)
This compound was obtained from 2-bromobenzaldehyde (93 mg, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:45)] to give a colorless oil; yield: 74 mg (0.37 mmol, 74%), 80% ee.

HPLC [Chiralcel OD, hexane–*i*-PrOH (98:2), 1 mL/min, λ = 220 nm]: t_R = 14.7 min for enantiomer *R*, t_R = 16.5 min for enantiomer *S*. The configuration was assigned by comparing the HPLC elution order with literature data.[26]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (d, *J* = 6.4 Hz, 3 H), 2.42 (br s, 1 H), 5.21 (q, *J* = 6.4 Hz, 1 H), 7.12 (m, 1 H), 7.31 (m, 1 H), 7.50 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1 H), 7.57 (dd, J_1 = 7.8 Hz, J_2 = 1.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5 (CH_3), 69.1 (CH), 121.6 (C), 126.6 (CH), 127.8 (CH), 128.7 (CH), 132.6 (CH), 144.5 (C).

(1*R*)-1-[4-(Trifluoromethyl)phenyl]ethanol (3k)
This compound was obtained from 4-(trifluoromethyl)benzaldehyde (87 mg, 69 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:30)] to give a colorless oil; yield: 93 mg (0.49 mmol, 98%), 97% ee; $[\alpha]_D^{20}$ +26.1 (*c* 0.9, $CHCl_3$).

HPLC [Chiralpak AS-H, hexane–*i*-PrOH (99:01), 0.5 mL/min, λ = 220 nm]: t_R = 32.1 min for enantiomer *R*, t_R = 34.2 min for enantiomer *S*. The configuration was assigned by comparing the sign of the optical rotation with the literature value: $[\alpha]_D$ = +24.14 (*c* 1.41, $CHCl_3$, *R*).[9]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 6.5 Hz, 3 H), 3.38 (s, 1 H), 4.86 (q, *J* = 6.5 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1 (CH_3), 69.6 (CH), 124.1 (q, $J_{C\text{-}F}$ = 271.6 Hz, 1C), 125.3 (2 CH), 125.6 (2 CH), 129.5 (q, $J_{C\text{-}CF}$ = 32.1 Hz, 1C), 149.6 (C).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –63.08 (3 F).

(1*R*)-1-(2-Furyl)ethanol (3l)
This compound was obtained from 2-furaldehyde (48 mg, 42 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:20)] to give a colorless oil; yield: 28 mg (0.25 mmol, 51%), 83% ee.

HPLC [Chiralcel OD, hexane–*i*-PrOH (99:1), 1 mL/min, λ = 220 nm]: t_R = 28.6 min for enantiomer *R*, t_R = 30.8 min for enantiomer *S*. The configuration was assigned by comparing the HPLC elution order with literature data.[9]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.5 Hz, 3 H), 2.56 (br s, 1 H), 4.84 (q, *J* = 6.5 Hz, 1 H), 6.21 (d, *J* = 3.2 Hz, 1 H), 6.31 (d, *J* = 3.2 Hz, 1 H), 7.35 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (CH_3), 63.4 (CH), 105.0 (CH), 110.0 (CH), 141.8 (CH), 157.5 (C).

(2*R*)-4-Phenylbutan-2-ol (3m)
This compound was obtained from 3-phenylpropanal (67 mg, 66 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:60)] to give a colorless liquid; yield: 30 mg (0.20 mmol, 40%), >99% ee.

HPLC [Chiralcel OD, hexane–*i*-PrOH (95:05), 1 mL/min, λ = 220 nm]: t_R = 12.7 min for enantiomer *R*, t_R = 20.4 min for enantiomer *S*. The configuration was assigned by comparing the HPLC elution order with literature data.[20]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.3 Hz, 3 H), 1.72–1.90 (m, 2 H), 2.23 (br s, 1 H), 2.66–2.85 (m, 2 H), 3.85 (sext, *J* = 6.3 Hz, 1 H), 7.21–7.26 (m, 3 H), 7.31–7.36 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0 (CH_3), 32.0 (CH_2), 40.7 (CH_2), 67.2 (CH), 125.7 (CH), 128.3 (4 CH), 142.0 (C).

(2*R*,3*E*)-4-Phenylbut-3-en-2-ol (3p)
This compound was obtained from *trans*-cinnamaldehyde (59 mg, 64 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:30)] to give a yellow oil; yield: 65 mg (0.44 mmol, 88%), 74% ee.

HPLC [Chiralcel OD, hexane–*i*-PrOH (90:10), 1 mL/min, λ = 254 nm]: t_R = 10.1 min for enantiomer *R*, t_R = 15.0 min for enantiomer *S*. The configuration was assigned by comparing the HPLC elution order with literature data.[9]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.4 Hz, 3 H), 2.70 (s, 1 H), 4.50 (quint, *J* = 6.4 Hz, 1 H), 6.28 (dd, J_1 = 15.9 Hz, J_2 = 6.4 Hz, 1 H), 6.57 (d, *J* = 15.9 Hz, 1 H), 7.24–7.42 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2 (CH_3), 68.6 (CH), 126.3 (2 CH), 127.4 (CH), 128.4 (2 CH), 129.1 (CH), 133.5 (CH), 136.6 (C).

(2*R*,3*E*)-3-Methyl-4-phenylbut-3-en-2-ol (3q)
This compound was obtained from α-methyl-*trans*-cinnamaldehyde (66 mg, 73 μL, 0.5 mmol) and purified by flash chromatography [EtOAc–hexane (1:20)] to give a colorless oil; yield: 38 mg (0.23 mmol, 47%), 86% ee.

HPLC [Chiralcel OD, hexane–*i*-PrOH (95:05), 1 mL/min, λ = 254 nm]: t_R = 9.8 min for enantiomer R, t_R = 11.0 min for enantiomer S. The configuration was assigned by comparing the HPLC elution order with literature data.[27]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 6.5 Hz, 3 H), 1.93 (s, 3 H), 2.85 (br s, 1 H), 4.41 (q, *J* = 6.5 Hz, 1 H), 6.56 (s, 1 H), 7.23–7.41 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2 (CH_3), 21.6 (CH_3), 73.3 (CH), 124.1 (CH), 126.2 (CH), 127.9 (2 CH), 128.8 (2 CH), 137.5 (C), 141.5 (C).

Benzoates 4n and 4o; General Procedure
BzCl (77 mg, 64 μL, 0.55 mmol) was added under N_2 at r.t. to a soln of 1-cyclohexylethanol (**3n**) or octan-2-ol (**3o**) (0.5 mmol) obtained by adding Me_2Zn to CyCHO or heptanal, respectively, in anhyd pyridine (1.5 mL). The mixture was stirred until the starting material disappeared (TLC) and then the reaction was quenched with sat. aq $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL), washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (silica gel, hexane).

(1*R*)-1-Cyclohexylethyl Benzoate (4n)[28]
This compound was obtainedfrom aldehyde **2n** (66 mg, 0.5 mmol) in two steps: methyl addition and esterification of the intermediate alcohol **3n**. The product was purified by flash chromatography (hexane) to give a colorless oil; yield: 74 mg (0.32 mmol, 64% overall), 88% ee.

HPLC [Chiralpak AS-H, hexane, 1 mL/min, λ = 254 nm]: t_R = 6.4 min for enantiomer *R*, t_R = 7.5 min for enantiomer *S*. The configuration was assigned by assuming an analogous reaction mechanism for the methyl addition stage.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95–1.25 (m, 5 H), 1.27 (d, *J* = 6.4 Hz, 3 H), 1.45–1.90 (m, 6 H), 4.99 (quint, *J* = 6.4 Hz, 1 H), 7.35–7.41 (m, 2 H), 7.48 (m, 1 H), 8.03–8.07 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8 (CH_3), 25.8 (2 CH_2), 26.2 (CH_2), 28.2 (CH_2), 28.4 (CH_2), 42.5 (CH), 74.8 (CH), 128.0 (2 CH), 129.2 (2 CH), 130.7 (C), 132.3 (CH), 165.7 (C).

(1*R*)-1-Methylheptyl Benzoate (4o)

This compound was obtained from aldehyde **2o** (64 mg, 0.5 mmol) in two steps: methyl addition and esterification of the intermediate alcohol **3o**. The product was purified by flash chromatography (hexane) to give a colorless oil; yield: 68 mg (0.28 mmol, 58% overall), 74% ee; $[\alpha]_D^{20}$ –29.1 (*c* 0.8, MeOH).

HPLC [Chiralpak AD-H, hexane, 0.5 mL/min, λ = 220 nm]: t_R = 10.7 min for enantiomer *S*, t_R = 11.7 min for enantiomer *R*. The configuration was assigned by comparing the sign of the optical rotation with the literature value: $[\alpha]_D^{20}$ –40.6 (*c* 1.06, MeOH, *R*).[29]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.90 (m, 3 H), 1.28–1.42 (m, 8 H), 1.34 (d, *J* = 6.3 Hz, 3 H), 1.59 (m, 1 H), 1.73 (m, 1 H), 5.17 (sext, *J* = 6.3 Hz, 1 H), 7.39–7.44 (m, 2 H), 7.53 (m, 1 H), 8.04–8.08 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (CH_3), 19.9 (CH_3), 22.5 (CH_2), 25.3 (CH_2), 29.0 (CH_2), 31.6 (CH_2), 35.9 (CH_2), 71.5 (CH), 128.1 (2 CH), 129.4 (2 CH) 130.8 (C), 132.5 (CH), 166.0 (C).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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