Enantioselective Ethylation of Various Aldehydes Catalyzed by Readily Accessible Chiral Diols

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ABSTRACT Four chiral C_2-symmetric diols were synthesized in a straightforward three-step reaction and demonstrated excellent enantioselectivities and good overall yields. Their catalytic activities were examined via the addition of diethylzinc to various aldehydes. The enantioselective addition of diethylzinc to 2-methoxybenzaldehyde gave the corresponding chiral secondary alcohol with high yields (up to 95%) and moderate to good enantiomeric excess (up to 88%). All synthesized ligands were evaluated in the addition of diethylzinc to various aldehydes in the presence of an additional metal such as Ti(IV) complexes. *Chirality 28:593–598, 2016.* © 2016 Wiley Periodicals, Inc.

KEY WORDS: chiral diols; enantioselectivity; catalysis; C_2-symmetric; diethylzinc addition

The enantioselective synthesis of various chiral compounds via carbon–carbon bond formation reactions is one of the most fundamental goals of both academia and industry. Among these reactions, the synthesis of optically active pure secondary alcohols via the enantioselective addition of organozinc reagents to aldehydes is a successful method.[1,2] However, much more effort has been devoted towards the synthesis of various chiral secondary alcohols.[3–9] These alcohols are both key compounds in the preparation of pharmaceuticals and agrochemicals and important intermediates in the synthesis of many substrates such as esters, amides, and ethers.[10] Since the pioneering study of Oguni and Omi,[11] the design and development of selective and efficient ligand structures have been significantly investigated for this useful transformation. Several nitrogen- and oxygen-functionalized chiral ligand structures, including amino alcohols,[12,13] diols,[14,15] and diamines,[16,17] have been designed through different synthetic routes. Their catalytic activities have been investigated via the addition of diethylzinc to prochiral aldehydes to yield enantioenriched secondary alcohols.

Hydrobenzoin and its derivatives have wide application in the enantioselective synthesis of chiral ligands, auxiliaries, and chiral synthetic blocks.[18] Due to their usefulness and versatility in chiral technology, significant attention has been paid to short, cheap, and straightforward preparation methods that use these compounds. Hydrobenzoin-type compounds with C_2-symmetry have received special interest because this type of symmetry is generally considered advantageous in that it reduces the number of possible transition states in enantioselective reactions.[19] When used as ligands, these compounds are known to be relatively efficient in several enantioselective reactions and show promise as ligands for enantioselective ethylation of aldehydes. It is noteworthy that we recently reported the simple, low-cost, and easy synthesis of optically active chiral diols.[20] Excellent enantioselectivities were also reported for enantioselective diethylzinc addition to various aldehydes, which is the current benchmark for testing the effectiveness of chiral ligands.

Herein we report the synthesis of four different enantiomerically pure C_2-symmetric diols with good chemical yields under moderate reaction conditions. (1*R*,2*R*)-1,2-bis (4-bromophenyl)-ethane-1,2-diol was synthesized through multiple methods; the first synthesis of (1*R*,2*R*)-1,2-bis (([1,1'-biphenyl]-4-yl)-ethane-1,2-diol obtained by replacing bromines with phenyl groups via a Suzuki cross-coupling is reported here. Additionally, (1*R*,2*R*)-1,2-bis(3-bromophenyl)-ethane-1,2-diol was synthesized via Sharpless asymmetric dihydroxylation with excellent enantioselectivity and good yield. The final newly synthesized diol is (1*R*,2*R*)-1,2-bis ([1,1'-biphenyl]-3-yl)-ethane-1,2-diol. It is notable that there has been no example of using these chiral diols in the addition of enantioselective diethylzinc to aldehydes. All diols were synthesized under mild conditions using short and cheap synthetic steps. Their catalytic activity evaluation was evaluated via the addition of diethylzinc to aldehydes.

MATERIALS AND METHODS

All reactions were carried out under an argon atmosphere in dry solvents. All reagents were purchased and used without purification, unless otherwise noted. Compounds (3-bromobenzyl)phosphonic acid diethyl ester 1, (4-bromobenzyl)phosphonic acid diethyl ester 2, (*E*)-1,2-bis(4-bromophenyl)ethane 4, and (1*R*,2*R*)-1,2-bis(4-bromophenyl)-ethane-1,2-diol 6 were synthesized according to previously described procedures.[21–24] Analytical thin-layer chromatography (TLC) was performed using Macherey-Nagel SIL G-25 UV254 plates. Flash chromatography was carried out with Rocc silica gel (0.040–0.063 mm).^{1}H NMR,^{13}C NMR, and ^{31}P NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer as indicated, with chemical shifts reported in ppm relative to TMS (for^{1}H and^{13}C) and relative to 85% aqueous phosphoric acid (for^{31}P), using the residual solvent signal as a standard.^{13}C NMR spectra were recorded using the attached proton test. IR-spectra were recorded on a Perkin-Elmer Spectrum 65 FT-IR spectrometer. Analytical chiral HPLC separations were performed on a VWR Hitachi Elite LaChrom with DAD detection. Gas chromatography (GC) separations were performed on Shimadzu GC-2010 Plus. Optical rotations were measured with a Rudolph Autopol-I series polarimeter. Mass spectra were acquired using an Agilent LC-MS/MS 6460 Triple Quadrupole spectrometer. Elemental analyses were obtained with a LECO Elemental Analyzer

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(CHNS 0932). Melting points were measured with a Thermo Scientific 9200 melting point apparatus.

(*E*)-3,3'-Dibromostilbene (3). (3-bromobenzyl)phosphonic acid diethyl ester 1 (12.24 g, 40.0 mmol) was dissolved in dry THF (600 mL) was added to a solution of 3-bromobenzaldehyde (14.80 g, 80.0 mmol) in dry THF (300 mL) under an argon atmosphere at room temperature (rt). Next, t-BuOK (6.73 g, 60 mmol) was added to the reaction mixture. The resulting reaction mixture was stirred at room temperature for an additional 40 min. After hydrolysis with water, the mixture was stirred overnight, and the precipitated solid was filtered off, resulting in 12.5 g (92%) of 3 as a pure white solid. mp: 100–101°C; IR (KBr) 3056 (=C-H), 3028 (=C-H), 1857, 1591 (-C=C-), 1562, 1471, 1429, 1073, 970, 873, 770, 681; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.65 (2H, Ar-H, t), 7.40 (4H, Ar-H, dd, *J* = 7.7Hz) 7.22 (2H, Ar-H, t, *J* = 7.8 Hz) 7.00 (2H, -CH, s); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 138.9 (C), 130.8 (CH), 130.2 (CH), 129.4 (CH), 128.6 (CH),125.4 (CH), 122.9 (C).

(1*R*,2*R*)-1,2-Bis(3-bromophenyl)-ethane-1,2-diol (5). First, AD-mix-β (48 g) was dissolved in a mixture of tert-butyl alcohol (120 mL) and water (120 mL). Next, methanesulfonamide (2.21 g, 23.06 mmol) was added, and the reaction mixture was cooled to 0°C, and the inorganic salts were partially precipitated. (*E*)-3,3′-dibromo stilbene 3 (6 g, 17.75 mmol) was added in one portion and the heterogeneous slurry was stirred vigorously at 0°C for 3 days. The mixture was allowed to warm to rt, and Na_2SO_3 (29.81 g, 236.5 mmol) was added. The reaction mixture was stirred at rt for an additional 24 h. Next, EtOAc (100 mL) was added, and the organic phase was separated, whereupon the aqueous phase was further extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with 2 M KOH and dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography over silica gel (Hexane/EtOAc, 80:20) resulting in 5.2 g (>99% enantiomeric excess [ee], 79% yield) of pure diol 5 as a white solid. mp: 49–50°C; $[\alpha]_D^{20}$ =+93.98 (c = 1, $CHCl_3$); IR (KBr) 3399 (OH), 3061 (=C-H), 2897 (-C-H), 1941, 1873, 1569 (-C=C-), 1473 (-C-H), 1426, 1190, 1071(-C-O), 1039, 880, 786, 746; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.40-7.35 (4H, Ar-H, m), 7.10 (2H, Ar-H, t, *J* = 7.7 Hz), 6.94 (2H, Ar-H, dt, *J* = 7.7 Hz), 4.61 (2H, -CH, s), 2.96 (2H, -OH, s); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 141.8 (C), 131.3 (CH), 129.9 (CH), 129.7 (CH), 125.7 (CH), 122.5 (C), 78.2 (CH); MS (ES) MS calculated $[M\text{-}2H]^+$ for $C_{14}H_{10}Br_2O_2$: 369.9 found: 369.0.

(1*R*,2*R*)-1,2-bis([1,1'-biphenyl]-3-yl)-ethane-1,2-diol (7). To a solution of 5 (2 g, 5.37 mmol) and $Pd(PPh_3)_4$ (0.73 g, 0.64 mmol) in toluene (274 mL), phenylboronic acid (1.96 g, 16.11 mmol), EtOH (42 mL), and aq K_2CO_3 (2 M, 80 mL) were added. The resulting reaction mixture was refluxed for 26 h. Water (200 mL) was then added to the reaction mixture. The aqueous layer was further extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography over silica gel (CH_2Cl_2/EtOAc, 95:5) resulting in 1.86 g (>99% ee, 96% yield) pure diol 7 as transparent oil. $[\alpha]_D^{20}$ = +91.97 (c = 1, $CHCl_3$); IR (KBr) 3389 (OH), 3060 (=C-H), 3031 (=C-H), 2902 (-C-H), 1598 (-C=C-), 1574, 1479 (-C-H), 1180, 1046 (-C-O), 895, 803, 758, 701, 615; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.47-7.14 (18H, Ar-H, m), 4.79 (2H, -CH, s), 2.59 (2H, -OH, s); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 141.2 (C), 140.9 (C), 140.4 (C), 128.7 (CH), 128.6 (CH), 127.3 (CH), 127.2 (CH), 126.8 (CH), 126.0 (CH), 125.8 (CH), 79.3 (CH); MS (ES^+) MS calculated $[M]^+$, $[M+Na]^+$, $[M\text{-}OH]^+$ for $C_{26}H_{22}O_2$: 366.2, 389.2, 349.2 found: 366.2, 389.2, 349.2, respectively; Anal. Calcd. for $C_{26}H_{22}O_2$: C 85.22, H 6.05; found C 84.72, H 6.12.

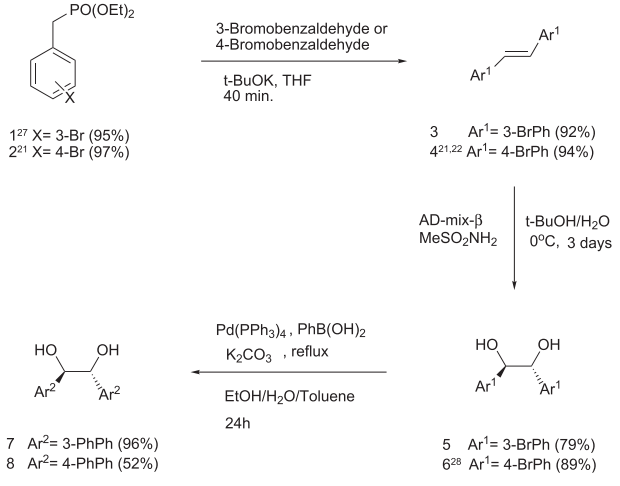
(1*R*,2*R*)-1,2-bis([1,1'-biphenyl]-4-yl)-ethane-1,2-diol (8). To a solution of 6 (2 g, 5.37 mmol) and $Pd(PPh_3)_4$ (0.73 g, 0.64 mmol) in toluene (274 mL), phenylboronic acid (1.96 g, 16.11 mmol), EtOH (40 mL), and aq K_2CO_3 (2 M, 80 mL) were added. The resulting reaction mixture was refluxed for 26 h. Water (200 mL) was added to the reaction mixture. The aqueous layer was further extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography over silica gel (CH_2Cl_2/EtOAc, 95:5), resulting in 0.91 g (>99% ee, 52% yield) pure diol 8 as a white solid. mp: 242-243°C; $[\alpha]_D^{20}$ =+161.90 (c = 1, THF); IR (KBr) 3400 (OH), 3055 (=C-H), 3030 (=C-H), 2893 (-C-H), 1921, 1487 (-C-H), 1386, 1183, 1081 (-C-O), 749, 688; ^{1}H NMR (400 MHz, DMSO-d_6, δ) 7.61 (4H, Ar-H, d, *J* = 7.2 Hz), 7.52 (4H, Ar-H, d, *J* = 8.2 Hz), 7.42 (4H, Ar-H, t, *J* = 7.2 Hz), 7.34-7.27 (6H, Ar-H, m), 5.43 (2H, -CH, s), 4.72 (2H, -OH, s); ^{13}C NMR (100 MHz, DMSO-d_6, δ) 141.8 (C), 140.0 (C), 138.4 (C), 128.9 (CH), 127.8 (CH), 127.2 (CH), 126.5 (CH), 125.6 (CH), 77.1 (CH); MS (ES^+) MS calculated $[M]^+$, $[M+Na]^+$, $[M\text{-}OH]^+$ for $C_{26}H_{22}O_2$: 366.2, 389.2, 349.2 found: 366.2, 389.2, 349.2, respectively.

GENERAL PROCEDURE FOR THE ENANTIOSELECTIVE DIETHYLZINC ADDITION TO ALDEHYDES

Under an argon atmosphere, chiral ligand (0.025 mmol) was dissolved in dry solvent, $Ti(O^iPr)_4$ (0.25 mmol) was added and stirred for 1 h for the Ti-mediated reactions. Et_2Zn (0.5 mmol, 1 M in hexane) was added, and the resulting yellow solution was stirred for 20 min at rt. Aldehyde was then added (0.25 mmol), and the reaction was stirred for another 24 h. After quenching with 1 mL saturated NH_4Cl solution, 25 mL H_2O was added and then extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography to give the corresponding alcohol. Enantiomeric excesses were determined by high-performance liquid chromatography (HPLC) analysis using a chiral stationary phase column (Chiracel OD-H or Chiracel OB) or GC analysis with chiral HP-CHIRAL-B20 column.

RESULTS AND DISCUSSION

The C_2-symmetric chiral diols were prepared in good overall yields according to the synthetic routes outlined in Scheme 1. The key compounds dibromo-substituted (*E*)-stilbene 3 and 4[21,22] were not commercially available and needed to be synthesized. Dibromo-substituted (*E*)-stilbene 3 and 4 were synthesized via different methods such as McMurry coupling[23,24] or Wittig reaction[25,26] by different research groups. The harsh reaction conditions, expensive synthetic steps, or small differences in the E:Z ratio reported in the literature inspired us to devise a different route with milder and more economical synthetic steps. Dibromo-substituted (*E*)-stilbene 3 and 4 were synthesized via Horner-Wadsworth-Emmons (HWE) reaction starting from phosphonates 1[27] and 2,[21] respectively. This route could be easily scaled up.



Scheme 1. Synthesis of optically pure C_2-symmetric diols 5-8.

Next, dibromo-substituted (*E*)-stilbenes 3 and 4 were reacted in a Sharpless asymmetric dihydroxylation reaction to obtain (1*R*,2*R*)-1,2-bis(3-bromophenyl)-ethane-1,2-diol 5 (79%, >99% ee) and (1*R*,2*R*)-1,2-bis(4-bromophenyl)-ethane-1,2-diol 6[28] (89%, >99% ee). Compounds 5 and 6 were treated with phenyl boronic acid and K_2CO_3 in the presence of $[Pd(PPh_3)_4]$ in EtOH/H_2O/toluene (1:2:4) at reflux, affording diphenyl substituted compounds (1*R*,2*R*)-1,2-bis([1,1'-biphenyl]-3-yl)-ethane-1,2-diol 7 with an excellent yield (96%, >99% ee) and (1*R*,2*R*)-1,2-bis([1,1'-biphenyl]-4-yl)-ethane-1,2-diol 8 (52%, >99% ee) in 24 h via a Suzuki cross-coupling.

Although the catalytic effectiveness of hydrobenzoin and their derivatives has been investigated in various enantioselective reactions, only a few examples of these compounds used as ligands in the enantioselective diethylzinc addition to aldehydes are cited in the literature. The initial report of the use of (*S*,*S*)-hydrobenzoin as a chiral ligand with moderate results was published by Salvadori and colleagues.[29] Prasad and Joshi[30] altered the reaction conditions and reported the corresponding chiral alcohol with an ee of 89%. Based on the synthesis and application of chiral diols such as hydrobenzoin in literature data, four chiral C_2-symmetric diols were synthesized in a straightforward manner, and their enantioselective inductions were investigated in the ethylation of aldehydes (Table 1). This enantioselective reaction is a known method for the formation of carbon–carbon bonds.[31] Reactions were carried out by using 2 equiv. of diethylzinc (1M solution in hexane) at rt for 24 h in the presence of 0.1 equiv. of all developed ligands in a variety of solvents.[20] We started by using 2-methoxybenzaldehyde as a test substrate to examine the efficiency of the chiral ligands. 2-Methoxybenzaldehyde gave the corresponding secondary alcohol with an excellent chemical yield and enantioselectivity toluene (Table 1, entry 8) catalyzed by diol 8. However, changing the solvent to dichloromethane resulted in lower enantioselectivity but good yield (Table 1, entry 7). When the reaction was performed with diol 7, we observed good yield and enantioselectivity in toluene (Table 1, entry 6) but moderate enantioselectivity and poor yield in dichloromethane (Table 1, entry 5). Changing the catalyst to diol 6 afforded excellent enantioselectivity in toluene (Table 1, entry 4), but it sharply decreased in dichloromethane (Table 1, entry 3). Moderate enantioselectivity was obtained in the catalysis of 5 in toluene (Table 1, entry 2), despite an almost racemic result in dichloromethane (Table 1, entry 1). Ethylation of 3-methoxybenzaldehyde gave an excellent yield with moderate enantioselectivity in the catalysis of 6 in toluene (Table 1, entry 12); however, a poor yield and moderate enantioselectivity were observed in dichloromethane (Table 1 , entry 11). Changing the catalyst to diol 5 afforded moderate enantioselectivity in toluene (Table 1, entry 10) but sharply decreased in dichloromethane (Table 1, entry 9). We observed a decrease in the catalysis of both diols 7 and 8 in dichloromethane versus in toluene (Table 1, entries 13–16). When we changed the substituent on the phenyl ring to an electron-withdrawing group such as 3- chlorobenzaldehyde, poor selectivities were obtained in catalysis by diols 5–8 (Table 1, entries 17–24). Using benzaldehyde gave unsatisfactory results (Table 1, entries 25–32). It was noted that in the presence of 1-naphtaldehyde, good to excellent enantioselectivities were observed under the catalysis of all four ligands in toluene (Table 1, entries 34, 36, 38, and 40). Changing the solvent to dichloromethane yielded results (Table 1, entries 33, 35, 37, and 39). Ethylation of aliphatic aldehydes in the catalysis of all four ligands was also studied. Ethylation of cyclohexanecarboxaldehyde and isobutyraldehyde in the catalysis of four chiral diols 5–8 gave poor yields and selectivities (Table 1, entries 41-56). Changing solvents was not found to make any difference in the selectivities.

Based on the highest chemical yields and moderate to good enantioselective inductions using chiral diol 8 for the enantioselective ethylation of 2-methoxybenzaldehyde (Table 1, entries 7, 8), the influence of other reaction conditions on the efficacy of the general reaction was studied to generalize the catalytic system (Table 2). Our initial tests were focused on studying the influence of the amount of the ligand 8 at rt. The best enantioselective induction was achieved by applying 10 mol% of ligand 8 (Table 2, entry 5). Using 1 mol% and 5 mol% ligand 8 gave poor selectivities and yields (Table 2, entries 1 and 3). In addition, changing the reaction temperature rt to 0°C during the process of the addition of aldehyde did not influence the selectivities or yields (Table 2, entries 2 and 4). In the presence of 15 mol% ligand 8, good selectivity and chemical yield were observed (Table 2, entry 16). The same reaction conditions without 1 equiv. of Et2Zn showed also good selectivity but poor chemical yield (Table 2, entry 15). We then studied the effect of solvent in a catalytic system (Table 2, entries 6 and 12). Low enantioselectivities were obtained in both dichloromethane and tetrahydrofurane. Another parameter that we studied was the reaction temperature. Lower reaction temperatures gave poor selectivities and yields (Table 2, entries 7–9) than rt (Table 2, entry 5). Adding an additional metal, such as Ti(IV), to the reaction at rt and low temperature gave poor selectivities (Table 2, entries 10 and 11). The amount of Et_2Zn at different temperatures was also studied (Table 2, entries 13 and 14). In the presence of 3 equiv. of Et_2Zn at rt we obtained good selectivity but moderate yield (Table 2, entry 13). Lowering the reaction temperature to 0°C during the process of the addition of aldehyde resulted in almost an almost racemic mixture with poor yield (Table 2, entry 14).

The last investigation of our study was the efficiencies of the chiral diols 5–8 in the presence of an extra metal such as Ti (IV) complex in the addition of diethylzinc to various aromatic and aliphatic aldehydes (Table 3). Titanium-mediated reactions are reported to give more efficient and selective results.[15] Considering the literature data, the efficiencies of the chiral diols with a combination of $Ti(O^iPr)_4$ were examined. In our reaction condition, an aldehyde: Et_2Zn (1M solution in hexane): $Ti(O^iPr)_4$: ligand ratio of 1:2:1:0.1 were used at room temperature for 24 h. Moderate enantioselectivities were observed with 2-methoxybenzaldehyde, 3-methoxybenzaldehyde, 1-naphtaldehyde, and benzaldehyde under the catalysis of all four diols 5–8. (Table 3, entries 1–8 and 13–20). Although moderate results were obtained in the ethylation of 3-chlorobenzaldehyde under the catalysis of 5 and 6 (Table 3, entries 9 and 10), poor results were observed for 7 and 8 (Table 3, entries 11 and 12). We also observed a degree of enantioselectivity with cyclohexanecarboxaldehyde, although almost racemic mixtures were obtained in the absence of Ti(IV) complex (Table 3, entries 21–24). Adding an extra metal resulted in enantioselective induction for all test substrates except isobutyraldehyde (Table 3, entries 25–28).

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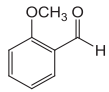
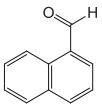
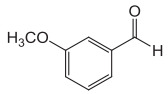
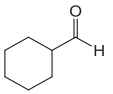
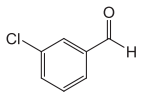
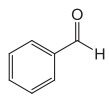
TABLE 1. Enantioselective addition of diethlyzinc to various aldehydes catalyzed by chiral diols 5-8[a]

Entry	Aldehydes	Ligand	Solvent	Yield (%)[b]	ee (%)[c,d]	Entry	Aldehydes	Ligand	Solvent	Yield (%)[b]	ee (%)[c,d]
1		**5**	Dichloromethane	27	7 (*S*)	33		**5**	Dichloromethane	36	15 (*S*)
2			Toluene	40	63 (*S*)	34			Toluene	13	56 (*S*)
3		**6**	Dichloromethane	6	46 (*S*)	35		**6**	Dichloromethane	42	74 (*S*)
4			Toluene	26	88 (*S*)	36			Toluene	40	83 (*S*)
5		**7**	Dichloromethane	25	51 (*S*)	37		**7**	Dichloromethane	33	36 (*S*)
6			Toluene	75	70 (*S*)	38			Toluene	59	68 (*S*)
7		**8**	Dichloromethane	90	56 (*S*)	39		**8**	Dichloromethane	53	37 (*S*)
8			Toluene	95	85 (*S*)	40			Toluene	47	76 (*S*)
9		**5**	Dichloromethane	15	5 (*R*)	41		**5**	Dichloromethane	24	rac
10			Toluene	12	49 (*R*)	42			Toluene	8	rac
11		**6**	Dichloromethane	30	51 (*R*)	43		**6**	Dichloromethane	28	7 (*S*)
12			Toluene	96	61 (*R*)	44			Toluene	2	11 (*S*)
13		**7**	Dichloromethane	28	25 (*R*)	45		**7**	Dichloromethane	36	4 (*S*)
14			Toluene	25	46 (*R*)	46			Toluene	2	7 (*S*)
15		**8**	Dichloromethane	17	32 (*R*)	47		**8**	Dichloromethane	21	7 (*S*)
16			Toluene	22	45 (*R*)	48			Toluene	7	rac
17		**5**	Dichloromethane	31	7 (*S*)	49		**5**	Dichloromethane	58	5 (*S*)
18			Toluene	57	35 (*S*)	50			Toluene	20	9 (*S*)
19		**6**	Dichloromethane	13	4 (*S*)	51		**6**	Dichloromethane	25	13 (*R*)
20			Toluene	26	38 (*S*)	52			Toluene	26	10 (*R*)
21		**7**	Dichloromethane	27	9 (*S*)	53		**7**	Dichloromethane	9	11 (*R*)
22			Toluene	16	11 (*S*)	54			Toluene	18	rac
23		**8**	Dichloromethane	18	4 (*S*)	55		**8**	Dichloromethane	16	5 (*S*)
24			Toluene	54	20 (*S*)	56			Toluene	23	5 (*S*)
25		**5**	Dichloromethane	11	rac						
26			Toluene	2	rac						
27		**6**	Dichloromethane	4	rac						
28			Toluene	2	12 (*S*)						
29		**7**	Dichloromethane	18	10 (*S*)						
30			Toluene	15	11 (*S*)						
31		**8**	Dichloromethane	21	7 (*S*)						
32			Toluene	14	20 (*S*)						

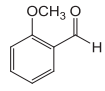
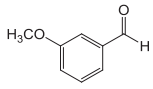
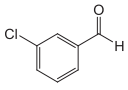
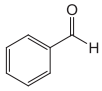
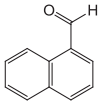
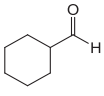
[a]Reaction conditions: 1 equiv. aldehyde, 2 equiv. Et_2Zn, 10 mol% ligand, rt, 24 h.
[b]Isolated yield.
[c]Determined by HPLC analysis with a chiral stationary phase column (Chiracel OD-H or Chiracel OB) or GC analysis with chiral HP-CHIRAL-20B.
[d]Determined by comparison of optical rotations with the literature.

TABLE 2. Enantioselective addition of diethlyzinc to 2-methoxybenzaldehyde catalyzed by 8[a]

Entry	**8** (mol%)	Et_2Zn (equiv)	Temp	Yield (%)[b]	ee (%)[c,d]
1	1	2	rt	36	5 (*S*)
2	1	2	rt-0 °C-rt	39	5 (*S*)
3	5	2	rt	44	21 (*S*)
4	5	2	rt-0 °C-rt	46	12 (*S*)
5	10	2	rt	95	85 (*S*)
6[e]	10	2	rt	90	56 (*S*)
7	10	2	rt-0 °C-rt	34	43 (*S*)
8	10	2	rt-(-30 °C)-rt	45	14 (*S*)
9	10	2	0 °C	31	24 (*S*)
10[f]	10	2	rt	75	38 (*R*)
11[f]	10	2	rt-0 °C-rt	24	29 (*R*)
12[g]	10	2	rt	60	26 (*S*)
13	10	3	rt	65	79 (*S*)
14	10	3	rt-0 °C-rt	27	9 (*S*)
15	15	1	rt	46	80 (*S*)
16	15	2	rt	79	83 (*S*)

[a]Reaction conditions: 1 equiv. aldehyde, x equiv. Et_2Zn, x mol% **8**, toluene, rt, 24 h.
[b]Isolated yield.
[c]Determined by GC analysis with chiral HP-CHIRAL-20B.
[d]Determined by comparison of optical rotations with the literature.
[e]Reactions were carried in CH_2Cl_2.
[f]Reactions were carried out with 1 equiv. of $Ti(O^iPr)_4$ in CH_2Cl_2.
[g]Reactions were carried in THF.

TABLE 3. Enantioselective addition of diethlyzinc to various aldehydes in the presence of $Ti(O^iPr)_4$ and chiral diols 5-8[a]

Entry	Aldehydes	Ligand	Yield (%)[b]	ee (%)[c,d]
1		**5**	78	61 (*R*)
2		**6**	90	55 (*R*)
3		**7**	40	45 (*R*)
4		**8**	76	49 (*R*)
5		**5**	90	46 (*S*)
6		**6**	93	53 (*S*)
7		**7**	54	36 (*S*)
8		**8**	54	42 (*S*)
9		**5**	76	47 (*R*)
10		**6**	23	44 (*R*)
11		**7**	67	31 (*R*)
12		**8**	11	26 (*R*)
13		**5**	42	51 (*R*)
14		**6**	37	46 (*R*)
15		**7**	19	32 (*R*)
16		**8**	37	34 (*R*)
17		**5**	38	64 (*R*)
18		**6**	95	61 (*R*)
19		**7**	58	52 (*R*)
20		**8**	41	48 (*R*)
21		**5**	17	42 (*R*)
22		**6**	3	35 (*R*)
23		**7**	20	17 (*R*)
24		**8**	29	21 (*R*)
25		**5**	2	rac
26		**6**	2	rac
27		**7**	3	4 (*R*)
28		**8**	2	10 (*R*)

[a]Reaction conditions: 1 equiv. aldehyde, 2 equiv. Et_2Zn, 10 mol% ligand, 1 equiv. $Ti(O^iPr)_4$, CH_2Cl_2, rt, 24 h.
[b]Isolated yield.
[c]Determined by HPLC analysis with a chiral stationary phase column (Chiracel OD-H or Chiracel OB) or GC analysis with chiral HP-CHIRAL-20B.
[d]Determined by comparison of optical rotations with the literature.

CONCLUSION

The C_2-symmetric diols 5–8 were readily prepared through short synthetic sequences with good overall yield. The synthesized ligands were evaluated in the alkylation of different aromatic and aliphatic aldehydes with diethylzinc. The best results were obtained with 2-methoxybenzaldehyde and 1-naphthaldehyde. It was found that 2-methoxy substituted benzaldehyde afforded good selectivities, whereas 3-methoxy substituted benzaldehyde showed only moderate selectivities. When the aromatic ring contained an electron-withdrawing substituent, poor results were obtained. Unsatisfactory selectivities were obtained with benzaldehyde, a standard test substrate for this reaction type. Aliphatic aldehydes yielded almost racemic mixtures in all conditions. In addition, with the exception of isobutyraldehyde, the addition of titanium isopropoxide under the same conditions increased enantioselectivities.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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