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Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by C_2-symmetric chiral diols

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ABSTRACT

Optically pure C_2-symmetric diols have been synthesized with moderate yields in a straightforward manner, and are used as catalysts in the enantioselective alkylation of aromatic aldehydes with diethylzinc. The addition of diethylzinc to benzaldehyde and sterically hindered 1-naphthaldehyde was achieved with excellent enantioselectivities (97–99% ee) under catalysis with (1*R*,2*R*)-1,2-bis(3,5-dibromophenyl)-ethane-1,2-diol and (1*R*,2*R*)-1,2-bis(3,5-diphenylphenyl)-ethane-1,2-diol.

Enantioselective carbon—carbon bond forming reactions represent an interesting challenge in modern organic chemistry. In this context, the alkylation of aldehydes with organometallic reagents in the presence of a catalytic amount of a chiral molecule gives a new C—C bond in an enantioselective manner. The addition of dialkylzinc to aldehydes catalyzed by β-amino alcohols is a very attractive method to obtain optically active secondary alcohols, which are important building blocks in the synthesis of many biologically and optically active compounds.[1] Since the initial reports by Oguni, Noyori, and Soai, many chiral β-amino alcohol type ligands have been developed.[1,2] Although some of these ligands can be obtained through simple synthetic methods, most are not always easy to prepare. A large number of chiral catalysts have been developed and high selectivities have been achieved. In accordance with these developments, significant research has been devoted toward the synthesis of C_2-symmetric chiral ligands such as diols,[3] diamines and disulfonamides,[4] bisoxazolines,[5] etc., as this symmetry element eliminates the number of possible transition states.[6] These chiral ligands have been used with and without extra metals, such as Ti(IV) for the enantioselective addition of organometallic reagents to aldehydes.[7]

Herein, we report the synthesis of optically pure C_2-symmetric diols with moderate yields in a straightforward manner. One of these chiral C_2-symmetric diols, (1*R*,2*R*)-1,2-bis(3,5-dibromophenyl)-ethane-1,2-diol (**3**) has been previously reported as an intermediate in the synthesis of bisphosphane and bisoxazoline ligands by our group.[8] However, no example of its use as a ligand for enantioselective catalysis has been described so far, to the best of our knowledge. Replacing bromines with phenyl groups via Suzuki cross-coupling reactions has provided a novel more bulky C_2-symmetric diol, (1*R*,2*R*)-1,2-bis(3,5-diphenylphenyl)-ethane-1,2-diol (**4**).[9] As part of our research on enantioselective catalysis, we decided to evaluate these chiral diols in the addition of diethylzinc to various aromatic aldehydes as a general catalytic benchmark reaction.

The C_2-symmetric chiral ligands were prepared according to the synthetic routes outlined in Scheme 1. Tetrabromo-substituted (*E*)-stilbene **1** was not commercially available and needed to be synthesized. This product was obtained in good overall yield via a Horner–Wadsworth–Emmons reaction using a phosphonate ester, according to an earlier reported method by our group.[8] The described method could be easily scaled-up. Diol **3** was synthesized via a Sharpless asymmetric dihydroxylation (63%, >99% ee, 5 days) using THF as a co-solvent in order to solve the solubility problem of **1**.[8a] Next, using a Suzuki cross-coupling, four phenyl groups could be introduced to afford diol **4** (70%) after 24 h. Although, diol **4** was obtained in a short sequence, this method was not pursued due to the poor overall yield and long reaction time. Therefore, a second method was devised (Scheme 1). Thus, tetrabromo-substituted (*E*)-stilbene **1** was treated with phenylboronic acid and K_2CO_3 in the presence of $[Pd(PPh_3)_4]$ in EtOH/H_2O/toluene (1:2:4) at reflux temperature, yielding tetraphenyl substituted (*E*)-stilbene **2** in excellent yield (95%) in 22 h.[10] Next, Sharpless asymmetric dihydroxylation gave chiral C_2-symmetric diol **4** (65%, >99% ee, 5 h).

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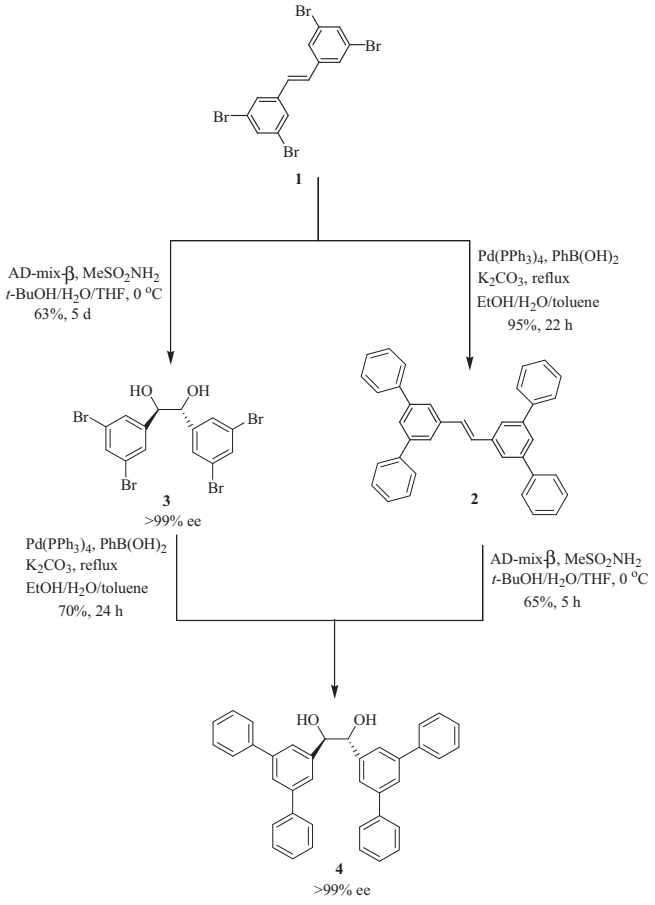
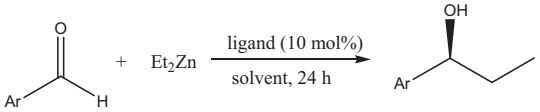


Scheme 1. Synthesis of optically pure C_2-symmetric diols **3** and **4**.

We subsequently focused our attention on the enantioselective alkylation of various aromatic aldehydes catalyzed by newly synthesized chiral C_2-symmetric diols **3** and **4**, in order to determine the efficiency of the ligands (Table 1). This reaction is one of the most versatile methods for the formation of carbon–carbon bonds.[1e–j] Reactions were carried out by using 2 equiv of diethylzinc (1 M solution in hexane) at 0 °C or rt for 24 h in the presence of the ligands (0.1 equiv) in different solvents.[11] The initial test substrate was benzaldehyde, which is regarded as a standard substrate for evaluating newly synthesized enantioselective catalysts. Benzaldehyde gave the corresponding secondary alcohol with excellent enantioselectivities (99% ee) and moderate yields in both dichloromethane and toluene (Table 1, entries 1 and 2) under catalysis by the diol **3**. When the reaction was performed with diol **4** in dichloromethane, we observed a decrease in the enantioselectivity and yield (Table 1, entry 3). Changing the solvent from dichloromethane to toluene resulted in both slightly higher enantioselectivity and yield (Table 1, entry 4). We next examined the influence of these two solvents on the addition of diethylzinc to various aromatic aldehydes catalyzed by diols **3** and **4**. Excellent enantioselectivity, but a moderate yield was obtained on ethylation of sterically hindered 1-naphthaldehyde using diol **4** as the catalyst in toluene (Table 1, entry 8). Using dichloromethane as the solvent led to a slight decrease in both the enantioselectivity and yield (Table 1, entry 7). Changing the catalyst to diol **3** resulted in a parallel outcome. A higher enantioselectivity and yield were observed in toluene than in dichloromethane (Table 1, entries 5 and 6). The electronic nature of the substituent on the phenyl ring seems to have a variable effect on the enantioselectivity in the solvents employed. Thus, aldehydes with electron-withdrawing chlorine at the 2- or 3-positions gave better enantioselectivities in dichloromethane than in toluene (Table 1, entries 9–20), catalyzed by either diol **3** or **4**. The ethylation of 2-chlorobenzaldehyde using diol **3** resulted in better selectivity in dichloromethane than in toluene (Table 1, entries 9 and 11). These reactions were also run at 0 °C in dichloromethane and toluene (Table 1, entries 10 and 12), but significant differences were achieved. Similarly, diol **4** catalyzed the reaction more efficiently in dichloromethane than in toluene (Table 1, entries 13 and 14). The use of 3-chlorobenzaldehyde gave excellent enantioselectivity in dichloromethane with diol **3** (Table 1, entry 16). However, poor selectivity was obtained in toluene (Table 1, entry 17). Performing the reaction at 0 °C in toluene did not result in any improvements (Table 1, entry 18). With diol **4**, we observed similar results; the selectivity was better in dichloromethane than in toluene (Table 1, entries 19 and 20). We also investigated the effect of a strong electron-releasing substituent on the phenyl ring, as in 2- and 3-methoxybenzaldehydes (Table 1, entries 21–32). It was found that changing the solvent made no difference to the enantioselective addition to 2-methoxybenzaldehyde using diols **3** (Table 1, entries 21 and 22) and **4** (Table 1, entries 23 and 24). We observed no enantioselectivities but moderate yields when we alkylated 3-methoxybenzaldehyde in dichloromethane (Table 1, entries 25, 26, and 29–30) with diols **3** and **4**. Changing the solvent to toluene resulted in a slightly higher

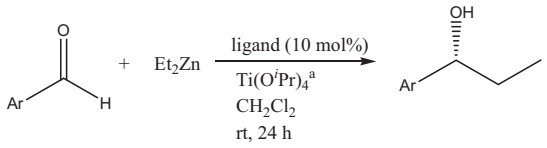
Table 1
Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by chiral diols **3** or **4**



Entry	Ar	Ligand	Solvent	Temperature (°C)	Yield[a] (%)	ee[b] (%)
1	Ph	**3**	CH_2Cl_2	25	43	99
2	Ph	**3**	Toluene	25	49	99
3	Ph	**4**	CH_2Cl_2	25	34	77
4	Ph	**4**	Toluene	25	38	79
5	1-Naphth	**3**	CH_2Cl_2	25	50	81
6	1-Naphth	**3**	Toluene	25	59	89
7	1-Naphth	**4**	CH_2Cl_2	25	47	97
8	1-Naphth	**4**	Toluene	25	53	99
9	2-ClC_6H_4	**3**	CH_2Cl_2	25	59	65
10	2-ClC_6H_4	**3**	CH_2Cl_2	0	61	70
11	2-ClC_6H_4	**3**	Toluene	25	26	52
12	2-ClC_6H_4	**3**	Toluene	0	41	53
13	2-ClC_6H_4	**4**	CH_2Cl_2	25	54	59
14	2-ClC_6H_4	**4**	Toluene	25	24	42
15	2-ClC_6H_4	**4**	Toluene	0	26	47
16	3-ClC_6H_4	**3**	CH_2Cl_2	25	40	93
17	3-ClC_6H_4	**3**	Toluene	25	35	31
18	3-ClC_6H_4	**3**	Toluene	0	43	29
19	3-ClC_6H_4	**4**	CH_2Cl_2	25	45	78
20	3-ClC_6H_4	**4**	Toluene	25	32	71
21	2-$MeOC_6H_4$	**3**	CH_2Cl_2	25	44	59
22	2-$MeOC_6H_4$	**3**	Toluene	25	41	61
23	2-$MeOC_6H_4$	**4**	CH_2Cl_2	25	30	60
24	2-$MeOC_6H_4$	**4**	Toluene	25	38	60
25	3-$MeOC_6H_4$	**3**	CH_2Cl_2	25	43	*rac*
26	3-$MeOC_6H_4$	**3**	CH_2Cl_2	0	45	*rac*
27	3-$MeOC_6H_4$	**3**	Toluene	25	35	10
28	3-$MeOC_6H_4$	**3**	Toluene	0	37	34
29	3-$MeOC_6H_4$	**4**	CH_2Cl_2	25	17	*rac*
30	3-$MeOC_6H_4$	**4**	CH_2Cl_2	0	16	*rac*
31	3-$MeOC_6H_4$	**4**	Toluene	25	16	32
32	3-$MeOC_6H_4$	**4**	Toluene	0	15	9

[a] Isolated yield.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H or Chiralcel OB).

Table 2
Enantioselective addition of diethlyzinc to aromatic aldehydes in the presence of $Ti(O^iPr)_4$ and chiral diols **3** or **4**



Entry	Ar	Ligand	Yield[b] (%)	ee[c] (%)
1	Ph	**3**	56	32
2	Ph	**4**	45	27
3	1-Naphth	**3**	61	62
4	1-Naphth	**4**	60	34
5	2-ClC_6H_4	**3**	73	12
6	2-ClC_6H_4	**4**	65	7
7	3-ClC_6H_4	**3**	54	47
8	3-ClC_6H_4	**4**	57	9
9	2-$MeOC_6H_4$	**3**	56	19
10	2-$MeOC_6H_4$	**4**	42	16
11	3-$MeOC_6H_4$	**3**	53	*rac*
12	3-$MeOC_6H_4$	**4**	26	*rac*

[a] Reactions were carried out with $Ti(O^iPr)_4$ (0.94 equiv).
[b] Isolated yield.
[c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H or Chiralcel OB).

enantioselectivity, but lower yields (Table 1, entries 27, 28, 31, and 32). For this substrate, the highest enantioselectivity was obtained from the reaction catalyzed by diol **3** in toluene at 0 °C (Table 1, entry 28).

We also explored the reactivity and selectivity of the addition of diethylzinc to aromatic aldehydes in the presence of titanium isopropoxide and chiral diols **3** and **4** (Table 2). The process using titanium-based catalysts tends to be more efficient and selective.[3a,12] According to the literature, we used chiral diols in combination with $Ti(O^iPr)_4$. Correspondingly, we examined the effect of $Ti(O^iPr)_4$ on the reaction of aromatic aldehydes with diethylzinc. Dichloromethane was chosen as the solvent since it gave a better enantioselectivity in the absence of an additive. Under our reaction conditions, an aldehyde/Et_2Zn (1 M solution in hexane)/$Ti(O^iPr)_4$/ligand ratio of 1:2:0.94:0.1 was used at room temperature for 24 h. We found that the addition of the titanium species led to significantly decreased enantioselectivities in all cases, but the conversions were noteworthy (Table 2, up to 73%).

In conclusion, we have reported the synthesis of C_2-symmetric chiral diols **3** and **4** in good yields via short synthetic sequences. These ligands were able to catalyze the enantioselective addition of diethylzinc to various aromatic aldehydes. In general, the best results were obtained with benzaldehyde and 1-naphthaldehyde. The use of aromatic aldehydes with substituents on the aryl ring resulted in lower enantioselectivities, however, the yields were very similar. The presence of electron-releasing or electron-withdrawing substituents resulted in similar enantioselectivities, with the exception of 3-methoxy-substituted benzaldehyde, which gave racemic alkylated products and poor yields. These ligands could also catalyze the alkylation reaction in the presence of titanium isopropoxide with lower enantioselectivities, but with higher yields.

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9. *Experimental data for compound* ***4****:* white solid (>99% ee, 65% yield). Mp : 226–227 °C. Anal. Calcd for $C_{38}H_{30}O_2$: C, 88.00; H, 5.83%. Found: C: 87.81; H: 5.89%. IR (KBr disc) ν_{max}/cm^{-1}: 3530 (–OH), 3467 (–OH), 3081, 3056, 3034 (CH_{Ar}), 2860 (CH_{aliph}), 1949, 1887, 1764, 1689, 1594, 1575, 1496, 1453, 1407, 1340, 1264, 1170, 1076, 1040, 1028, 879, 753, 695, 632, 538. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.72 (t, J = 1.75 Hz, 2H, ArH), 7.55–7.52 (m, 8H, ArH), 7.45–7.35 (m, 16H, ArH), 4.97 (s, 2H, CH), 3.03 (s, 2H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.81, 140.90, 128.76, 127.50, 127.27, 125.81, 124.91, 79.44. MS (MALDI-TOF) m/z: 501.10 $[M-OH]^+$, 541.23 $[M+Na]^+$.$[\alpha]_D^{20}$ −98.4 (c, 1.0, EtOH). Conditions for HPLC: Chiralcel OD-H column, solvent: n-hexane/EtOH (90:10), flow rate = 1 mL/min, T = 35 °C, retention times: 30.5 min for (1*R*,2*R*)-**4**, 37.4 min for (1*S*,2*S*)-**4**.
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11. *General procedure for the enantioselective diethylzinc addition to aromatic aldehydes:* Under an argon atmosphere, chiral ligand **3** or **4** (0.025 mmol) was dissolved in dry solvent and $Ti(O^iPr)_4$ (0.23 mmol) was added and the mixture stirred for 1 h. Et_2Zn (0.5 mmol, 1 M in hexane) was added and the resulting yellow solution was stirred for 20 min at room temperature. The mixture was cooled to 0 °C and the aromatic aldehyde was added (0.25 mmol). The mixture was stirred for another 24 h. After quenching with saturated NH_4Cl solution (1 mL), H_2O (25 mL) was added and the mixture 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 HPLC analysis with a chiral stationary phase column (Chiralcel OD-H or Chiralcel OB).
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