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Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by Ti(IV) complexes of C_2-symmetrical chiral BINOL derivatives

Shaohua Gou, Zaher M. A. Judeh *

School of Chemical and Biomedical Engineering, Nanyang Technological University, 62 Nanyang Drive, N1.2 B1-14, Singapore 637459, Singapore

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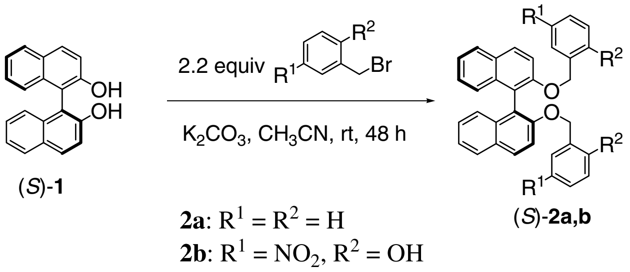
ABSTRACT

Enantioselective addition of diethylzinc to a series of aromatic aldehydes is developed using new chiral C_2-symmetric ligand (*S*)-2,2′-(1,1′-binaphthyl-2,2′-diylbis(oxy))bis(methylene)bis(4-nitrophenol) (*S*)-**2b**. The catalytic system employing 10 mol % of (*S*)-**2b** and 120 mol % of Ti(O*i*Pr)$_4$ was found to promote the addition of diethylzinc to a wide range of aromatic aldehydes with electron-donating and electron-withdrawing substituents, giving up to 89% ee and up to 95% yield of the corresponding secondary alcohol under mild conditions.

Catalytic enantioselective carbon–carbon bond forming reactions are extensively studied reactions in asymmetric synthesis[1] The enantioselective alkylation of aldehydes with organozinc reagents has attracted much attention because of its simplicity and utility for the preparation of chiral secondary alcohols, which are key building blocks in the fine chemical and pharmaceutical industries.[2] Various chiral catalysts based on amino alcohols, diols, thiols, disulfides, diselenides, diamines, oxazaborolidines, bisoxazolidines, sulfinamides, BINOLs, H_4-BINOLs and H_8-BINOLs have been used successfully for the asymmetric addition of dialkylzinc to aldehydes.[3–8] However, studies on BINOLs have focused primarily on the 3-monosubstituted- and the 3,3′-disubstituted derivatives. The rationale behind this design is to keep the 2- and 2′-OH groups free for effective complexation with the dialkylzinc and Ti(O*i*Pr)$_4$.[6–8]

Herein, we report on the synthesis of new 2,2′-disubstituted BINOL ligands (Scheme 1), and examine their effectiveness and application in the asymmetric additions of diethylzinc to various aldehydes. The effect of expansion of the chirality of BINOL on the enantioselectivity will be examined by incorporating substitution at the 2- and 2′-positions.



Scheme 1. Synthesis of chiral ligands (*S*)-**2a**,**b** from (*S*)-BINOL.

Chiral ligands (*S*)-**2a** and (*S*)-**2b** were synthesized[9] in good yields by reacting (*S*)-BINOL with the appropriate benzyl bromide (2.2 equiv) in the presence of K_2CO_3 (4.4 equiv) in CH_3CN at room temperature for 48 h. These ligands are designed intentionally to investigate the effect of expansion of the chirality and to determine the significance of the hydrogens of the 2- and 2′-OH groups. The catalytic activity of these ligands was examined under typical conditions[10] for the addition of diethylzinc to aldehydes in the presence of Ti(O*i*Pr)$_4$ (Table 1). Titanium(IV) complexes with various chiral ligands have been reported extensively as effective promoters for the addition of diethylzinc to aldehydes. Preliminary studies on the alkylation of benzaldehyde **3a** using 10 mol % of (*S*)-**2a** and 120 mol % of Ti(O*i*Pr)$_4$ in dry toluene gave only traces of the corresponding alcohol **4a** (Table 1, entry 1). Fortunately, when the same reaction was repeated using (*S*)-**2b**, secondary alcohol **4a** was obtained in 90% yield and in 67% ee. The complex (*S*)-**2a**–Ti(O*i*Pr)$_4$,

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* Corresponding author. Fax: +65 67947553.
E-mail address: zaher@ntu.edu.sg (Z. M. A. Judeh).

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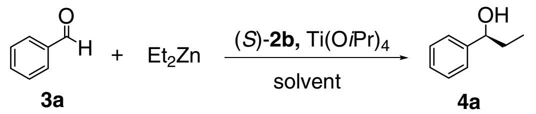
Table 1
Enantioselective addition of diethylzinc to benzaldehyde



Entry[a]	(*S*)-**2** (mol %)	Ti(O*i*Pr)$_4$ (mol %)	Solvent	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	**2a** (10)	120	PhCH$_3$	22	Trace	—
2	**2b** (10)	120	PhCH$_3$	22	90	67
3	**2b** (10)	140	PhCH$_3$	22	87	61
4	**2b** (10)	100	PhCH$_3$	22	93	59
5	**2b** (10)	120	CH$_2$Cl$_2$	22	91	71
6	**2b** (10)	120	THF	22	86	68
7	**2b** (10)	120	Et$_2$O	22	87	64
8	**2b** (10)	120	Hexane	22	88	67
9	**2b** (20)	120	CH$_2$Cl$_2$	22	93	70
10	**2b** (10)	120	CH$_2$Cl$_2$	0	90	77[d]
11	**2b** (10)	120	CH$_2$Cl$_2$	−20	81	74[e]

[a] Reaction conditions: 0.25 M benzaldehyde, 3.0 equiv Et$_2$Zn, 2–3 h.

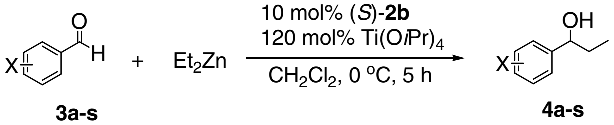
[b] Isolated yields.

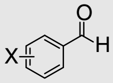
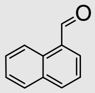
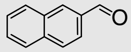
[c] Determined using a chiral GC G-TA column; the (*S*)-configuration was confirmed by comparison with the reported configuration.[6f]

[d] Reaction time was 5 h.

[e] Reaction time was 10 h.

Table 2
Enantioselective addition of diethylzinc to various aromatic aldehydes catalyzed by (*S*)-**2b**



Entry[a]	Aldehyde		Product	Yield[b] (%)	ee[c] (%)
1		X = H (**3a**)	**4a**	90	77 (*S*)
2		X = *o*-CH$_3$ (**3b**)	**4b**	84	73 (*S*)
3		X = *m*-CH$_3$ (**3c**)	**4c**	88	67 (*S*)
4		X = *p*-CH$_3$ (**3d**)	**4d**	92	68 (*S*)
5		X = *p*-C$_2$H$_5$ (**3e**)	**4e**	87	83[g]
6		X = *p*-Ph (**3f**)	**4f**	89	67 (*S*)[d]
7		X = *o*-MeO (**3g**)	**4g**	77	78 (*S*)
8		X = *m*-MeO (**3h**)	**4h**	73	61 (*S*)[e]
9		X = *p*-MeO (**3i**)	**4i**	80	79 (*S*)[e]
10		X = *m*-BnO (**3j**)	**4j**	71	83 (*S*)[e]
11		X = *p*-F (**3k**)	**4k**	70	79 (*S*)
12		X = *p*-Cl (**3l**)	**4l**	93	84 (*S*)
13		X = *p*-Br (**3m**)	**4m**	88	69 (*S*)
14		X = *p*-I (**3n**)	**4n**	92	82 (*S*)
15		X = *p*-F$_3$C (**3o**)	**4o**	76	64 (*S*)[d]
16		X = *o*-I (**3p**)	**4p**	87	72[g]
17		X = *m*-I (**3q**)	**4q**	84	82[g]
18		X = *o*-I (**3p**)	**4p**	76	81[f,g]
19		X = *p*-I (**3n**)	**4n**	81	89 (*S*)[f]
20		(**3r**)	**4r**	92	72 (*S*)[e]
21		(**3s**)	**4s**	95	75 (*S*)[e]

[a] Reaction conditions: 10 mol % (*S*)-**2b**, 120 mol % Ti(O*i*Pr)$_4$, 3.0 equiv Et$_2$Zn, 5 h, 0 °C.

[b] Isolated yields.

[c] The ee was determined using a chiral GC G-TA column. The configuration was confirmed by comparison with literature data.[4d,6f,k]

[d] The ee was determined by using a Chiral OJ-H column (Hex/IPA = 95/5).[6f]

[e] The ee was determined by using a Chiral OD-H column (Hex/IPA = 95/5).[4d,6f]

[f] Reaction performed at −20 °C for 10 h.

[g] Configuration not determined.

in which the ligand does not bear OH groups, did not catalyze the reaction (Table 1, entry 1), whereas an excellent yield and moderate enantioselectivity were obtained when the (*S*)-**2b**–Ti(O*i*Pr)$_4$ complex was employed (Table 1, entry 2). These results indicate that the presence of a free OH, as in (*S*)-**2b**, is indispensable for catalytic activity. Therefore, further reactions were performed using ligand (*S*)-**2b**. Encouraged by the result in entry 2, we employed (*S*)-**2b** to investigate the effect of various solvents and (*S*)-**2b**/Ti(O*i*Pr)$_4$ loading on the yield and enantioselectivity of the products. An increase in the Ti(O*i*Pr)$_4$ loading from 120 to 140 mol % resulted in a slight decrease in both the yield (to 87%) and the ee (to 61%) of **4a** (Table 1, entry 3). A decrease in the Ti(O*i*Pr)$_4$ loading to 100 mol % resulted in a slight increase in the yield to 93% accompanied by a drop in the ee to 59% (Table 1, entry 4). Next, a variety of polar (THF, CH$_2$Cl$_2$ and Et$_2$O) and non-polar (toluene, hexane) solvents were screened. The reaction proceeded well in both polar and non-polar solvents to give comparable yields and enantioselectivities (Table 1, entries 2 and 5–8). The best yield and ee (91% and 71%, respectively) were obtained when CH$_2$Cl$_2$ was used as solvent (Table 1, entry 5). Subsequent reactions were carried out in CH$_2$Cl$_2$ using 120 mol % of Ti(O*i*Pr)$_4$. An increase in (*S*)-**2b** loading to 20 mol % had no significant effect on the yield or ee of **4a** (Table 1, entry 9). A reduction in reaction temperature from 22 °C to 0 °C led to an increase in both the yield and the ee (90% and 77%, respectively) of **4a** (Table 1, entry 10). A further reduction in temperature from 0 °C to −20 °C gave a slight decrease in the yield and the ee of **4a** (Table 1, entry 11). Based on the above-mentioned results, the optimum conditions are 10 mol % of (*S*)-**2b** and 120 mol % of Ti(O*i*Pr)$_4$ in CH$_2$Cl$_2$ at 0 °C.

To study the generality of the ligand (*S*)-**2b** for the enantioselective addition of diethylzinc to various aldehydes, a number of aromatic aldehydes having electron-donating (**3b**–**j**, **3r**, and **3s**) and electron-withdrawing (**3k**–**q**) groups were examined under the optimized conditions reported in Table 1. In comparison to the results obtained with **3a**, the poor electron-donating substituents, Me and Ph, led to a slight decrease in the ees of the products **3b**–**d** and **3f** (Table 2, entries 2–4 and 6 vs entry 1), whereas the *p*-ethyl group in **3e** resulted in an increase in the ee of the product to 83% (Table 2, entry 5 vs entry 1). Interestingly, the position of the substituent on the aromatic ring of **3b**–**d** (Table 2, entries 2–4) had little effect on the ee of **4b**–**d**. In the case of stronger electron-donating substituents, X = MeO and BnO, lower yields but comparable ees of **4g**, **4h**, and **4j** (Table 2, entries 7–10 vs entry 1) were observed, whereas the *m*-MeO substituent in **3h** led to a decrease in the ee of **4h** to 61% (Table 2, entry 8). Electron-withdrawing groups (F, Cl, Br, I, and CF$_3$, Table 2, entries 11–17) showed variation in the yields, but no major differences in the ees of **4k**–**n** and **4p**–**q** except for the strongly electron-withdrawing CF$_3$ group which led to a lower 64% ee for product **4o**. When the reactions in entries 14 and 15 (Table 2) were attempted at −20 °C, an increase in the ee of **4p** (81%) and **4n** (89%) (Table 2, entries 18 and 19) was observed. Reaction of α- and β-naphthaldehydes **3r** and **3s**, respectively, resulted in excellent yields and good ees (Table 2, entries 20 and 21). In general, very good yields and enantioselectivities of the secondary alcohols **4a**–**s** were obtained (Table 2).

In summary, the substituted BINOL ligand (*S*)-**2b**, readily prepared in one step from commercially available starting materials, showed excellent catalytic activities and very good enantioselectivities (up to 89%) in the asymmetric additions of diethylzinc to various aldehydes in the presence of Ti(O*i*Pr)$_4$. The presence of free OH groups on the chiral ligand is essential in delivering good catalytic activity and high enantioselectivities. Further investigation on the applications of these ligands for other asymmetric reactions is ongoing.

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9. *Synthesis of chiral ligand* (*S*)-**2b**: 2-Bromomethyl-4-nitrophenol (508 mg, 2.2 mmol) was added to a stirred mixture of (*S*)-BINOL (286 mg, 1.0 mmol) and K_2CO_3 (607 mg, 4.4 mmol) in CH_3CN (10 mL) at room temperature, and the resulting mixture was stirred for 48 h. The reaction mixture was diluted with ethyl acetate (200 mL), washed with H_2O (3 × 50 mL) and brine (2 × 30 mL). The organic phase was dried over $MgSO_4$, and evaporated to dryness under vacuum pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 1/1, v/v) to afford (*S*)-**2b** as a white amorphous solid in 87% yield; mp 197–199 °C; $[\alpha]_D^{22}$ −24.36 (*c* 0.2, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.01 (s, 2H), 5.15 (s, 2H), 5.25 (s, 2H), 7.10–7.16 (m, 3H), 7.19–7.43 (m, 6H), 7.91–8.02 (m, 5H), 8.26–8.35 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.8, 152.8, 133.4, 131.4, 129.5, 128.4, 127.5, 127.1, 124.9, 124.2, 124.1, 117.8, 113.2, 110.9, 68.4. HRMS(ESI): calcd for $(M^+ +1)$ $C_{34}H_{25}N_2O_8$: 589.1611, found: 589.1624.
10. A typical procedure for the catalytic addition of diethylzinc to aromatic aldehydes: To a solution of (*S*)-**2** (14.7 mg, 0.025 mmol) in CH_2Cl_2 (1.0 mL), $Ti(OiPr)_4$ (89.3 μL, 0.3 mmol) was added under a nitrogen atmosphere, and the reaction mixture was stirred for 30 min at room temperature. A solution of diethylzinc (1.0 M in hexane, 0.75 mL, 0.75 mmol) was added dropwise to the above reaction mixture, and stirring was continued for another 10 min. The reaction mixture was then cooled to 0 °C, and the aldehyde (0.25 mmol) was added and stirring was continued for 5 h. The reaction mixture was quenched with HCl (1.0 M, 2.0 mL), and the product was extracted with (3 × 2 mL) ethyl acetate. The combined ethyl acetate extracts were dried over Na_2SO_4 and evaporated to dryness under vacuum pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate, 10/1, v/v) to afford the secondary alcohol products. The enantioselectivities of the reactions were determined by Chiral GC G-TA using OJ-H or OD-H columns.