

# Highly Enantioselective Additions of Diethylzinc to Aldehydes Using 2-Triflamido-methyl-2'-hydroxy-1,1'-binaphthyl

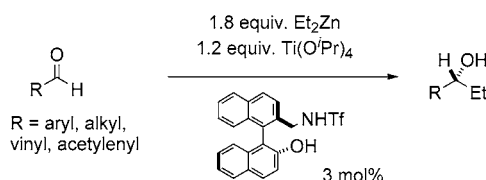
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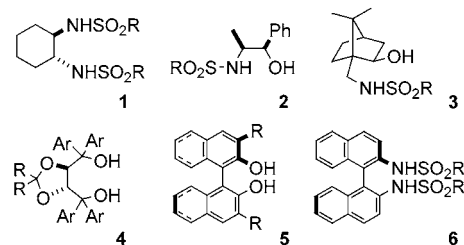
## ABSTRACT



A new *N*-triflated amino alcohol–titanium catalyst was designed for the asymmetric ethylation of aldehydes. This binaphthyl-based sulfonamido alcohol ligand shows uniformly high yield and enantioselectivity in the diethylzinc additions of aromatic, aliphatic, and unsaturated aldehydes.

Synthesis of a chiral secondary alcohol by asymmetric addition of diorganozinc to an aldehyde is one of the most successful areas in asymmetric C–C bond formation.<sup>1</sup> Since the report by Ohno and co-workers on the highly enantioselective addition of diethylzinc to aldehydes using Ti(O<sup>*i*</sup>Pr)<sub>4</sub> complexed with chiral bistriflamide **1** (R = CF<sub>3</sub>),<sup>2</sup> extensive studies have been performed on the structural derivatives of bissulfonamide and sulfonamido alcohol **1–3**,<sup>3–5</sup> TADDOLs **4**,<sup>6</sup> and BINOLs **5**.<sup>7–9</sup> However, few studies have been performed with binaphthyl-based sulfonamides, and bissulfonamides **6** were recently reported to be

poor asymmetric ligands for the Ti-catalyzed Et<sub>2</sub>Zn addition to aldehydes.<sup>10</sup> In our previous report, highly enantioselective



**Figure 1.** Chiral ligands for Ti-catalyzed dialkylzinc addition to aldehyde.

additions of diethylzinc and diphenylzinc to aldehydes were accomplished using 2-dialkylaminomethyl-2'-hydroxy-1,1'-

(1) (a) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 911–922. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.

(2) (a) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657–1660. (b) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095–7098. (c) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691–5700.

(3) (a) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 3250–3251. (b) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1802–1803. (c) Hwang, C.-D.; Uang, B.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3979–3984. (d) Qiu, J.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 2665–2668. (e) Prieto, O.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1629–1644.

(4) Ito, K.; Kimura, Y.; Okamura, H.; Katsuki, T. *Synlett* **1992**, 573–574.

(5) Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2479–2496.

(6) (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321–1323. (b) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473–7484.

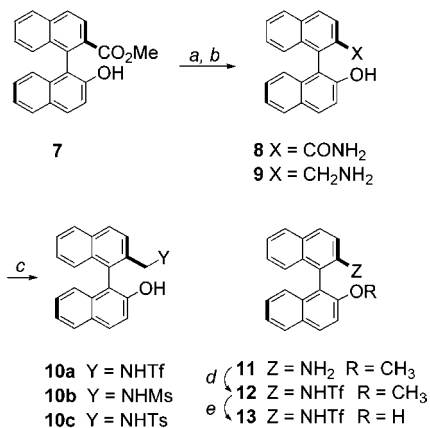
(7) (a) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585–589. (b) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236.

binaphthyl *N,O*-ligands,<sup>11</sup> which showed much improved enantioselectivity compared with that of the corresponding 2-dimethylamino-2'-hydroxy-1,1'-binaphthyl.<sup>12</sup>

In this report, we prepared binaphthyl-based sulfonamido alcohols from chiral binaphthol and used them as ligands for enantioselective Ti(IV)-catalyzed ethylation of aldehydes.

Sulfonamides **10a–c** were prepared by conversion of **7** to the amide **8**, which was reduced to the amine **9** with LAH followed by the corresponding sulfonations (Scheme 1).<sup>11,13</sup>

**Scheme 1.** Synthesis of 2-Sulfonamidomethyl-2'-hydroxy-1,1'-binaphthyl Derivatives<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) NaCN (0.1 equiv), NH<sub>3</sub>, MeOH, 70–80 °C, 48 h, 94%; (b) LiAlH<sub>4</sub> (4 equiv), THF, reflux, 24 h, 48%; (c) *n*-BuLi (2 equiv), THF, –78 °C; Tf<sub>2</sub>O (2 equiv), –78 °C, 1 h; LiOH–H<sub>2</sub>O (12 equiv), rt, 12 h, 89% (for **10a**); (d) Tf<sub>2</sub>O (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 1 h, 92%; (e) BBr<sub>3</sub> (3 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 69%.

Ester **7** was highly resistant toward ammonia or amide for the aminolysis to amide **8**, but the conversion proceeded slowly in methanolic ammonia on heating in the presence of a catalytic amount of NaCN.<sup>14</sup> Selective *N*-sulfonation of amino alcohol **9** to **10a–c** was not possible, probably because of the intramolecular hydrogen bonding between the amino and hydroxy groups. Bis-*N,O*-sulfonation of **9** followed by the selective hydrolysis of the resulting sulfonate moiety provided sulfonamides **10a–c**. For comparative purpose, sulfonamide **13**, not having the methylene unit of **10a**, was

(8) (a) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651–3655. (b) Shen, X.; Guo, H.; Ding, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4321–4327.

(9) (a) Kitajima, H.; Ito, K.; Katsuki, T. *Chem. Lett.* **1996**, 343–344. (b) Kitajima, H.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207–217.

(10) Yus, M.; Ramon, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2003**, *14*, 1103–1114.

(11) Ko, D.-H.; Kim, K. H.; Ha, D.-C. *Org. Lett.* **2002**, *4*, 3759–3762.

(12) (a) Vyskocil, S.; Jaracz, S.; Smrcina, M.; Sticha, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7727–7737. (b) Bringmann, G.; Breuning, M. *Tetrahedron: Asymmetry* **1998**, *9*, 667–679.

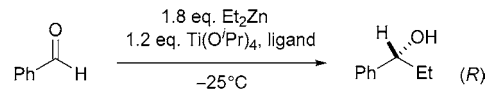
(13) Ohta, T.; Ito, M.; Inagaki, K.; Takaya, H. *Tetrahedron Lett.* **1993**, *34*, 1615–1616.

(14) Hogberg, T.; Strom, P.; Ebner, M.; Ramsby, S. *J. Org. Chem.* **1987**, *52*, 2033–2036.

prepared from the known *O*-methyl NOBIN **11**<sup>15</sup> with *N*-triflation followed by demethylation of **12** with BBr<sub>3</sub>.

The sulfonamido alcohol ligands **10a–c** and **13** were subjected to the ethylation of benzaldehyde with Et<sub>2</sub>Zn in the presence of Ti(O<sup>*i*</sup>Pr)<sub>4</sub> in toluene (Table 1). Ligand **10a**

**Table 1.** Addition of Diethylzinc to Benzaldehyde Using Ligands **10a–c** and **13**



entry	ligand (mol %)	solvent	time (h)	yield <sup>a</sup> (%)	ee <sup>b,c</sup> (%)
1	<b>10a</b> (5)	toluene	2	99	96
2	<b>10b</b> (5)	toluene	5	60	34
3	<b>10c</b> (5)	toluene	5	61	23
4	<b>13</b> (5)	toluene	5	79	8
5	<b>10a</b> (3)	toluene	2	99	96
6	<b>10a</b> (1)	toluene	2	99	95
7	<b>10a</b> (1)	hexane	2	99	93
8	<b>10a</b> (1)	CH <sub>2</sub> Cl <sub>2</sub>	2	99	99

<sup>a</sup> Conversion yield (Chiraldex G-TA column). <sup>b</sup> Determined by chiral HPLC (Chiralcel OD column). <sup>c</sup> Absolute configuration assigned by comparison to the literature.

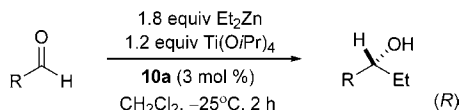
showed a very high enantioselection with the use of 5 mol % in toluene (entry 1). With sulfonamides **10b** and **10c**, much decreased conversion yields were observed despite the extended reaction time under the same condition, and the enantioselections were very poor (entries 2 and 3). As was expected from the result of using **6**, ligand **13** was a very poor chiral ligand for the ethylation (entry 4). Decreasing the amount of ligand **10a** used resulted in almost the same conversion yield and enantioselection (entries 5 and 6). By changing the solvent from toluene or hexane to dichloromethane, almost quantitative conversion and complete enantioselection were accomplished with the use of only 1 mol % of **10a** (entry 8).

With conditions optimized for benzaldehyde, the use of ligand **10a** was extended to the asymmetric ethylation of other aromatic, aliphatic, and  $\alpha,\beta$ -unsaturated aldehydes (Table 2). The yields and enantioselectivities for the substituted benzaldehydes (entries 2–7) and naphthaldehydes (entries 8 and 9) were all excellent regardless of the position of substituents. The additions were completed within 2 h at –25 °C with the use of 3 mol % of ligand **10a**, and the reduced alcohol products, observed in about 2–5% in our previous study using 2-dialkylaminomethyl-2'-hydroxy-1,1'-binaphthyl ligand,<sup>10</sup> were not detected at all.

Excellent reactivity and enantioselection were obtained with both primary and secondary aliphatic aldehydes (entries 10 and 11) and also with *trans*-cinnamaldehyde (entry 12). A slight decrease of enantioselection was observed with phenylpropargyl aldehyde (entry 13).

(15) (a) Hattori, T.; Hotta, H.; Suzuki, T.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 613–622. (b) Hattori, T.; Shijo, M.; Sakamoto, J.; Kumagai, S.; Nakajima, A.; Miyano, S. *J. Chem. Res., Miniprint* **1995**, 124–134.

**Table 2.** Addition of Diethylzinc to Aldehydes Using Ligand **10a**

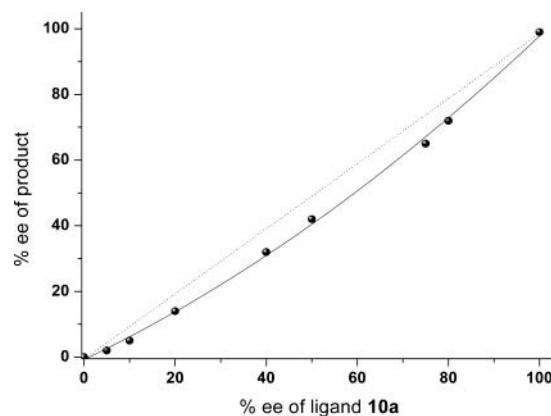


entry	R	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	Ph	99	99 <sup>c</sup>
2	<i>p</i> -MeO-Ph	96	91 <sup>c</sup>
3	<i>o</i> -Cl-Ph	97	96 <sup>d</sup>
4	<i>m</i> -Cl-Ph	95	99 <sup>c</sup>
5	<i>p</i> -Cl-Ph	95	98 <sup>c</sup>
6	<i>o</i> -Me-Ph	96	96 <sup>e</sup>
7	<i>p</i> -Me-Ph	94	99 <sup>e</sup>
8	1-naphthyl	95	98 <sup>c</sup>
9	2-naphthyl	95	98 <sup>c</sup>
10	hexyl	90	98 <sup>f</sup>
11	cyclohexyl	91	99 <sup>f</sup>
12	<i>trans</i> -Ph-CH=CH	97	96 <sup>c</sup>
13 <sup>g</sup>	Ph-C≡C	95	89 <sup>c</sup>

<sup>a</sup> Isolated yields. <sup>b</sup> Absolute configuration assigned by comparison to the literature. <sup>c</sup> Determined by chiral HPLC (Chiralcel OD column). <sup>d</sup> Determined by chiral HPLC (Chiralcel OB-H column). <sup>e</sup> Determined by chiral HPLC (Chiralpak AD-H column). <sup>f</sup> Determined by chiral GC (Chiraldex G-TA column) of the corresponding acetate derivatives. <sup>g</sup> Using 5 mol % of **10a**.

Unlike with the BINOL-Ti(O<sup>*i*</sup>Pr)<sub>4</sub> system, which shows no nonlinear effect under catalytic conditions,<sup>7b</sup> small but distinctive negative nonlinear effect can be seen in the catalytic system using ligand **10a**, as shown in Figure 2. It was clearly demonstrated by Walsh<sup>16</sup> that a complex between (BINOLate)Ti(O<sup>*i*</sup>Pr)<sub>2</sub> and Ti(O<sup>*i*</sup>Pr)<sub>4</sub> is preferentially involved in the catalytic condition. Although the transition structure for the ethylation using **10a**–titanium cannot be drawn at this stage, interactions between the **10a**–ligated titanium intermediates may be present in this catalytic system to induce such a nonlinear effect.<sup>17</sup>

In summary, we prepared a new binaphthyl-based *N*-triflated amino alcohol ligand and applied it to the enantio-



**Figure 2.** Correlation between the ee of ligand **10a** and the ee of ethylation product of benzaldehyde (1 mol % **10a**, 1.8 equiv of Et<sub>2</sub>Zn, 1.2 equiv of Ti(O<sup>*i*</sup>Pr)<sub>4</sub>, –25 °C, 2 h in CH<sub>2</sub>Cl<sub>2</sub>).

selective addition of diethylzinc to aldehyde. This *N,O*-ligand–Ti(O<sup>*i*</sup>Pr)<sub>4</sub> catalyst provides excellent yields and enantioselectivities in the reactions of diethylzinc with a broad range of aromatic, aliphatic, and unsaturated aldehydes.

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**Supporting Information Available:** Experimental details and characterization data for all new compounds and conditions for determining the enantiopurity of the alcohol products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) (a) Balsells, J.; Davis, T. J.; Caroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336–10348. (b) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143–4146.

(17) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922–2959.