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

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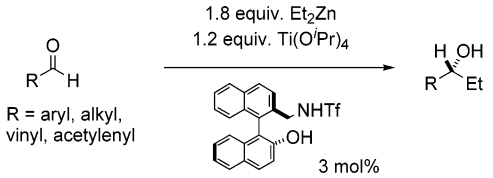
ABSTRACT



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.[1] Since the report by Ohno and co-workers on the highly enantioselective addition of diethylzinc to aldehydes using $Ti(O^iPr)_4$ complexed with chiral bistriflamide **1** ($R = CF_3$),[2] extensive studies have been performed on the structural derivatives of bissulfonamide and sulfonamido alcohol **1**−**3**,[3−5] TADDOLs **4**,[6] and BINOLs **5**.[7−9] 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_2Zn addition to aldehydes.[10] In our previous report, highly enantioselective additions of diethylzinc and diphenylzinc to aldehydes were accomplished using 2-dialkylaminomethyl-2′-hydroxy-1,1′-

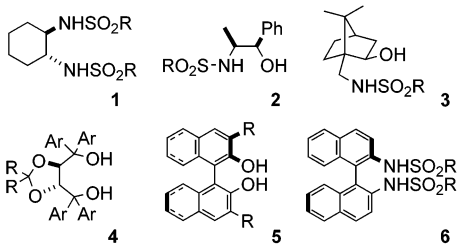


Figure 1. Chiral ligands for Ti-catalyzed dialkylzinc addition to aldehyde.

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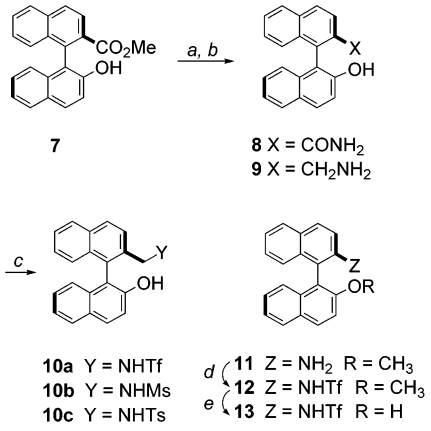
binaphthyl *N*,*O*-ligands,[11] which showed much improved enantioselectivity compared with that of the corresponding 2-dimethylamino-2′-hydroxy-1,1′-binaphthyl.[12]

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).[11,13]

Scheme 1. Synthesis of 2-Sulfonamidomethyl-2′-hydroxy-1,1′-binaphthyl Derivatives[a]

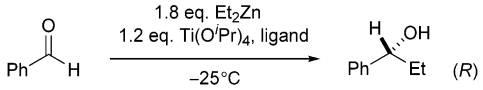


[a] Reagents and conditions: (a) NaCN (0.1 equiv), NH_3, MeOH, 70−80 °C, 48 h, 94%; (b) $LiAlH_4$ (4 equiv), THF, reflux, 24 h, 48%; (c) *n*-BuLi (2 equiv), THF, −78 °C; Tf_2O (2 equiv), −78 °C, 1 h; LiOH−H_2O (12 equiv), rt, 12 h, 89% (for **10a**); (d) Tf_2O (2 equiv), CH_2Cl_2, −78 °C, 1 h, 92%; (e) BBr_3 (3 equiv), CH_2Cl_2, 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.[14] 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 prepared from the known *O*-methyl NOBIN **11**[15] with *N*-triflation followed by demethylation of **12** with BBr_3.

The sulfonamido alcohol ligands **10a**−**c** and **13** were subjected to the ethylation of benzaldehyde with Et_2Zn in the presence of $Ti(O^iPr)_4$ 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[a] (%)	ee[b,c] (%)
1	**10a** (5)	toluene	2	99	96
2	**10b** (5)	toluene	5	60	34
3	**10c** (5)	toluene	5	61	23
4	**13** (5)	toluene	5	79	8
5	**10a** (3)	toluene	2	99	96
6	**10a** (1)	toluene	2	99	95
7	**10a** (1)	hexane	2	99	93
8	**10a** (1)	CH_2Cl_2	2	99	99

[a] Conversion yield (Chiraldex G-TA column). [b] Determined by chiral HPLC (Chiralcel OD column). [c] 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 α,β-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,[10] 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).

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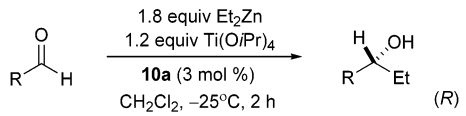
Table 2. Addition of Diethylzinc to Aldehydes Using Ligand **10a**



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

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

Unlike with the BINOL-Ti(O^iPr)$_4$ system, which shows no nonlinear effect under catalytic conditions,[7b] 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[16] that a complex between (BINOLate)Ti(O^iPr)$_2$ and Ti(O^iPr)$_4$ 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.[17]

In summary, we prepared a new binaphthyl-based *N*-triflated amino alcohol ligand and applied it to the enantioselective addition of diethylzinc to aldehyde. This *N*,*O*-ligand−Ti(O^iPr)$_4$ catalyst provides excellent yields and enantioselectivities in the reactions of diethylzinc with a broad range of aromatic, aliphatic, and unsaturated aldehydes.

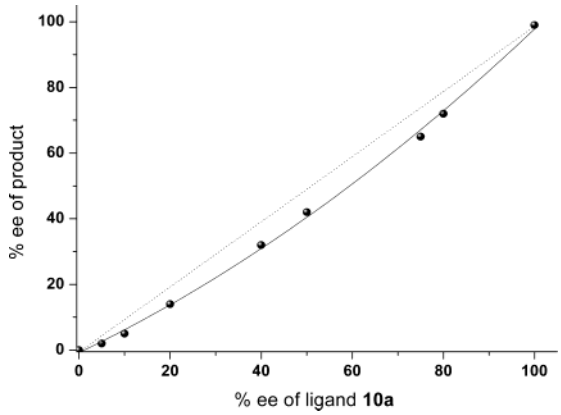


Figure 2. Correlation between the ee of ligand **10a** and the ee of ethylation product of benzaldehyde (1 mol % **10a**, 1.8 equiv of Et_2Zn, 1.2 equiv of Ti(O^iPr)$_4$, −25 °C, 2 h in CH_2Cl_2).

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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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