ORGANIC LETTERS

2002
Vol. 4, No. 21
3759−3762

Enantioselective Additions of Diethylzinc and Diphenylzinc to Aldehydes Using 2-Dialkyl-aminomethyl-2′-hydroxy-1,1′-binaphthyls

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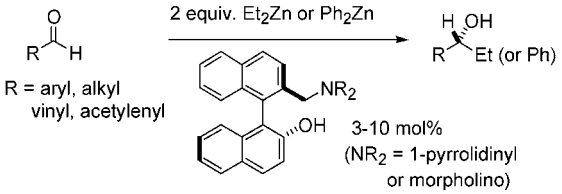
Received August 21, 2002

ABSTRACT



A set of 2-dialkylaminomethyl-2′-hydroxy-1,1′-binaphthyls was prepared and used in the catalytic asymmetric additions of diethylzinc and diphenylzinc to various types of aldehydes. These binaphthyl-based axially chiral amino alcohols show high enantioselectivity in the addition of organozincs to aromatic and aliphatic aldehydes.

Asymmetric addition of organozincs to aldehydes is probably the most successful and still vigorously pursued area in asymmetric C−C bond formation.[1] With the development of diverse ligand structures and reaction conditions for the highly selective catalytic reactions, chiral amino alcohols still remain an attractive choice of catalyst, as a result of their easy availability and simple reaction conditions. Since the use of (*S*)-leucinol by Oguni, numerous amino alcohols, mostly derived from natural chiral resources, have been devised for the asymmetric organozinc addition.[2,3] Despite the enormous success of the axially chiral ligands in asymmetric reactions, a limited number of amino alcohols with 1,1′-biaryl backbone for the organozinc addition are reported, including **1** and **2** (Figure 1).[4]

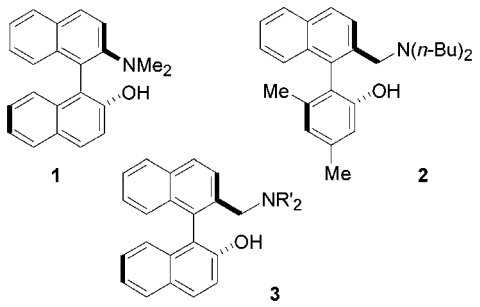


Figure 1. 1,1′-Biaryl amino alcohols for organozinc addition.

In our search for ligands showing high enantioselectivity for both aromatic and aliphatic aldehydes under convenient

(1) Reviews on enantioselective diorganozinc additions to aldehydes: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (c) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: New York, 1996. (d) Soai, K.; Shibata, T. In *Comprensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 911−922. (e) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

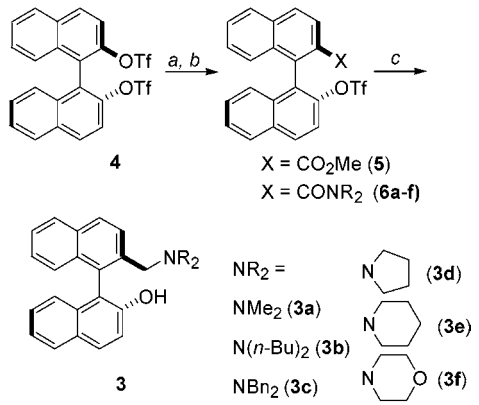
(2) For selected reports on diethylzinc additions, see: (a) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823−2824. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072. (c) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111−7115. (d) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877−7878. (e) Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264−4268. (f) Zhao, G.; Li, X.-G.; Wang, X.-R. *Tetrahedron: Asymmetry* **2001**, *12*, 399−403. (g) DiMauro, F. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 3053−3059. (h) Wipf, P.; Wang, X. *Org. Lett.* **2002**, *4*, 1197−1200. (i) Nugent, W. A. *Org. Lett.* **2002**, *4*, 2133−2136.

10.1021/ol026761j CCC: $22.00
Published on Web 09/14/2002

reaction conditions with easy availability for both enantiomers of the ligand, we prepared axially chiral amino alcohol **3** from chiral binaphthol.

Amino alcohols **3a**−**f** were conveniently prepared from binaphthol bistriflate **4** through a three-step reaction sequence (Scheme 1). Monomethoxycarbonylation of **4** gave ester **5**

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

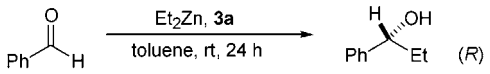


[a] (a) cat. $Pd(OAc)_2$, dppp, CO (1 atm), MeOH, DMSO, 60%; (b) Me_2AlNR_2, toluene, quantitative yields; (c) LAH, THF, 62−79%.

in 60% yield,[5] and the conversion to amide **6**[6] followed by LAH reduction provided amino alcohols **3a**−**f**.

The amino alcohol **3a** was chosen for the initial experiments. Reaction between 2 equiv of diethylzinc and benzaldehyde was carried out in toluene for 24 h to give (*R*)-(+)-1-phenyl-2-propanol (Table 1). The best result was

Table 1. Addition of Diethylzinc to Benzaldehyde Using Ligand **3a**



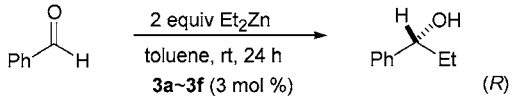
entry	mol % (**3a**)	Et_2Zn (equiv)	convn (%)[a,b]	ee (%)[a,c]
1	2	2	75 (11)	87
2[d]	2	2	78 (11)	88
3[e]	3	2	33 (9)	88
4	3	2	89 (9)	91
5[d]	3	2	88 (7)	92
6	3	1.2	71 (9)	93
7	5	2	45 (17)	88

[a] Determined by chiral GC (Chiraldex G-TA column). [b] Number in the parentheses refers to the amount of benzyl alcohol produced. [c] Absolute configuration assigned by comparison to the literature. [d] Using 5.4 mol % of *n*-BuLi. [e] Reaction was carried out at 0 °C.

obtained with 3 mol % of **3a** at room temperature (entry 4). The ethylation at 0 °C was quite slow, and 58% of the starting benzaldehyde remained unreacted after 24 h (entry 3). The use of *n*-BuLi together with **3a** did not show any appreciable changes in the results (entry 2 and 5).[4a] Despite repeated experiments, a sharp decrease of the conversion yield was observed by increasing the amount of **3a** to 5 mol % (entry 8).

Next, we investigated the substituent effect of the amino part of **3b**−**f** on the level of asymmetric induction in the addition of Et_2Zn to benzaldehyde (Table 2). Under the

Table 2. Addition of Diethylzinc to Benzaldehyde Using Ligands **3a**−**f**



entry	ligand	convn (%)[a,b]	ee (%)[a,c]
1	**3a**	89 (9)	91
2	**3b**	77 (11)	87
3	**3c**	8 (20)	25
4	**3d**	93 (5)	94
5[d]	**3d**	90 (7)	95
6	**3e**	87 (8)	94
7	**3f**	89 (5)	93

[a] Determined by chiral GC (Chiraldex G-TA column). [b] Number in the parentheses refers to the amount of benzyl alcohol produced. [c] Absolute configuration assigned by comparison to the literature. [d] Using 5.4 mol % of *n*-BuLi.

reaction condition optimized for **3a**, di-*n*-butylamino derivative **3b** showed decreased conversion (entry 2), and bulkier dibenzylamino derivative **3c** resulted in only 8% conversion (entry 3). The pyrrolidine analogue **3d** was the most reactive (93% conversion) and selective (94% ee) ligand (entry 4).

Under the same condition, ligand **3d** showed a high level of nonlinear effect in the reaction between diethylzinc and benzaldehyde, 60% ee and 92% ee of the alcohol products with 20% ee and 50% ee of **3d**, respectively.[7] This is in contrast to the structurally related **2**, which was reported to have a fully linear relationship between the enantiomeric excess of **2** and the alcohol products.[4b] The difference can

(3) For selected reports on diphenylzinc additions, see: (a) Zhang, H.; Wue, F.; Mac, T. C.; Chan, K. S. *J. Org. Chem.* **1996**, *51*, 8002−8003. (b) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222−4223. (c) Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 145−149. (d) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muniz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465−3467. (e) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P.; Raabe, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 1488−1490.

(4) (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.

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

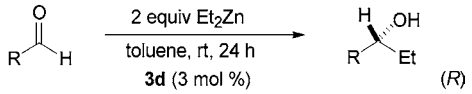
(6) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171−4174. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993.

(7) (a) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S. H.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357. (b) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767−768. (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036. (d) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800−9809. (e) Chen, Y. K.; Costa, A. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 5378−5379.

be due to the difficulty of **2** in forming the heterochiral dinuclear catalyst precursor due to two relatively bulky *n*-butyl groups, compared with the pyrrolidinyl group in **3d**.[7c]

The use of ligand **3d** in the ethylation was extended to other aldehydes (Table 3). High levels of secondary alcohol

Table 3. Addition of Diethylzinc to Aldehydes Using Ligand **3d**



entry	R	isolated yield (%)	ee (%)[a]
1	Ph	89	94[b]
2	*p*-MeO-Ph	97	94[c]
3	*o*-Cl-Ph	97	93[d]
4	*m*-Cl-Ph	95	96[c]
5	*p*-Cl-Ph	97	99[b]
6	1-naphthyl	92	96[c]
7	2-naphthyl	95	96[c]
8	hexyl	96	94[e]
9	cyclohexyl	89	98[e]
10	*trans*-Ph-CH=CH	95	86[c]
11	Ph-C≡C	97	76[c]
12	TIPS-C≡C	84	92[f]

[a] Absolute configuration assigned by comparison to the literatures. [b] Determined by chiral GC (Chiraldex G-TA column). [c] Determined by chiral HPLC (Chiralcel OD column). [d] Determined by chiral HPLC [(*R*,*R*)-Welk-O 1 column]. [e] Determined by chiral GC (Chiraldex G-TA column) of the corresponding acetate derivatives. [f] Determined by ^{19}F NMR of the corresponding (*R*)-MTPA ester derivative.

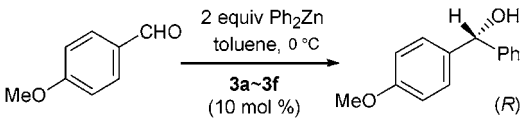
formation and excellent enantiomeric excess were obtained for both aromatic (entries 1−7) and aliphatic aldehydes (entries 8 and 9).

The enantioselectivities for substituted benzaldehydes were generally high, and a slight decrease of the selectivity was observed when the substituent was positioned closer to the aldehyde group as shown in the case of chlorobenzaldehydes (entries 3−5). Ligand **3d** was also applied for the ethylation of α,β-unsaturated aldehydes, but with lower selectivity compared with the cases of aromatic and aliphatic aldehydes (entries 10 and 11). Enantioselectivity in the case of propargyl aldehyde was improved by introducing bulky TIPS group (entry 12).

Enantioselective addition of diphenylzinc to aldehydes is more challenging because of the rapid competitive uncatalyzed phenylation. One of the methods to suppress the undesired background reaction is to use a mixture of diphenylzinc and diethylzinc.[3d] Ligands **3a**−**f** were screened again for the phenylation of *p*-anisaldehyde using diphenylzinc only (Table 4). The best result was obtained with the morpholino derivative **3f** (entry 6). Use of the mixture of diphenylzinc and diethylzinc gave similar enantioselectivity, but with much decreased isolated yield (entry 7).

Various aromatic and aliphatic aldehydes were studied for the phenylation with 10 mol % of **3f** at 0 °C (Table 5).

Table 4. Addition of Diphenylzinc to *p*-Anisaldehyde Using Ligands **3a**−**f**



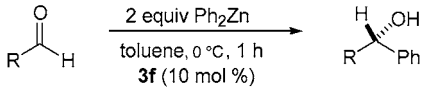
entry	ligand	*t* (h)	isolated yield (%)	ee (%)[a,b]
1	**3a**	1	71	88
2	**3b**	1	93	87
3	**3c**	1	97	95
4	**3d**	1	95	94
5[c]	**3d**	10	94	90
6	**3e**	1	97	98
7[d]	**3f**	24	75	98

[a] Determined by HPLC (Chiralcel OJ column). [b] Absolute configuration assigned by comparison to the literatures. [c] Using 5 mol % of catalyst **3f**. [d] A mixture of Ph_2Zn (1 equiv) and Et_2Zn (2 equiv) was used.

Excellent yields and enantiomeric excesses were accomplished with aromatic aldehydes (entries 1−6), but moderate enantioselectivities were obtained for α,β-unsaturated and aliphatic aldehydes (entries 7−10). Unlike with the reaction between benzaldehyde and diethylzinc catalyzed by **3d**, weak nonlinear effect was observed in the reaction between *p*-tolualdehyde and diphenylzinc catalyzed by **3f** (32% ee and 67% ee of the product alcohols with the use of 25% ee and 50% ee of **3f**, respectively).

In summary, we have prepared a series of chiral amino alcohols from (*R*)-binaphthol and applied them to the asymmetric additions of organozincs to various aromatic,

Table 5. Addition of Diphenylzinc to Aldehydes Using Ligand **3f**



entry	R	isolated yield (%)	% ee (config)[a]
1	*p*-MeO-Ph	97	98[b] (*R*)
2	*p*-Me-Ph	97	97[c] (*R*)
3	*o*-Cl-Ph	95	96[c] (*R*)
4	*m*-Cl-Ph	95	92[d] (*R*)
5	*p*-Cl-Ph	97	95[e] (*R*)
6	2-naphthyl	98	97[c] (*R*)
7	TIPS-C≡C	72	85[f] (*R*)
8	*trans*-Ph-CH=CH	93	75[c] (*S*)
9	hexyl	94	66[c] (*S*)
10	cyclohexyl	97	68[g] (*S*)

[a] Absolute configuration assigned by comparison to the literatures. [b] Determined by HPLC (Chiralcel OJ column). [c] Determined by HPLC (Chiralcel OD column). [d] Determined by HPLC [(*R*,*R*)-Welk-O 1 column]. [e] Determined by HPLC (Chiralcel OB-H column). [f] Determined by ^{1}H NMR of the corresponding (*R*)-MTPA ester derivatives. [g] Determined by HPLC (Chiralcel AD-H column).

aliphatic, and unsaturated aldehydes. Excellent enantioselectivities and yields were accomplished in the ethylations of aromatic and aliphatic aldehydes with Et_2Zn at room temperature. Also, similar results were obtained in the phenylations of aromatic aldehydes by the use of Ph_2Zn only. These amino alcohols may constitute a new set of efficient catalysts in terms of convenient ligand preparations, simple reaction conditions, and high asymmetric induction.

Acknowledgment. This work was financially supported by the Center for Molecular Design and Synthesis (CMDS) at KAIST.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026761J