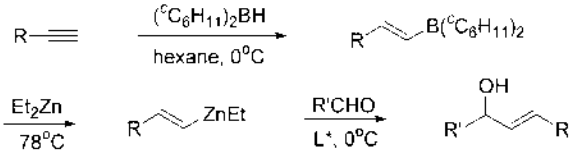
Asymmetric Alkenylzinc Additions to Aldehydes Catalyzed by a Binaphthyl-Based *N,O*-Ligand

Dong-Hyun Ko, Seung-Wan Kang, Kyoung Hoon Kim, Yongseog Chung,† and Deok-Chan Ha*

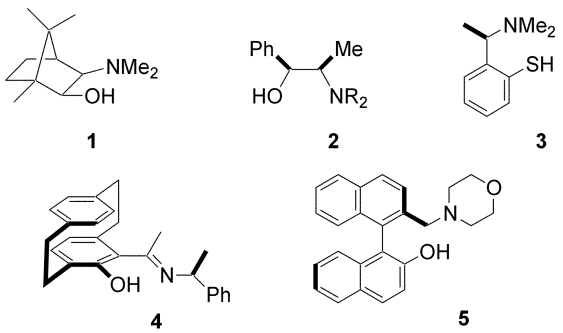
Department of Chemistry, Korea University, Seoul 136-701, Korea
†Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea
Received November 4, 2003

Key Words : Asymmetric synthesis, Chiral ligand, Alkenylzinc, Catalyst, Allylic alcohol

Numerous chiral ligands for enantioselective addition of organozincs to aldehydes have been studied for the last two decades.[1] Despite the very successful catalytic asymmetric inductions, the scope of this reaction is relatively narrow due to the limited availability of the organozinc reagents. Asymmetric addition of vinylzinc to aldehydes can afford the synthetically very useful chiral allylic alcohols. Several methods have been used to generate vinylzinc reagents, including the reactions of alkenyllithium or magnesium reagents with zinc halides,[2] and hydrozirconation of alkynes followed by Zr-Zn transmetallation.[3] Oppolzer and Radinov prepared alkenylzincs by boron-zinc exchange of the alkenylboranes with sequential treatments of terminal alkynes with dicyclohexylborane and diethylzinc, and good enantioselectivitiy was achieved with both aromatic and aliphatic aldehydes by the use of chiral DAIB ligand **1**.[4,5]



Amino alcohols, including the structures of **1** and **2**, are reported to show moderate to high enantioselectivity in the alkenylation of aldehydes with alkenylzinc prepared by boron-zinc exchange.[6] But, the degree of stereoselection depends heavily on the types of aldehydes used and the methods to generate the alkenylzinc compounds. With the alkenylzinc prepared by zirconocene-zinc exchange, these amino alcohol ligands showed very poor asymmetric inductions. Higher enantioselectivity was obtained with the use of 10 mol % of amino thiol ligand **3** and alkenylzinc prepared by the Zr-Zn exchange method, but with decreased reaction yield.[3b] Recently, a paracyclophane-based chiral imino alcohol ligand **4** was reported to give reasonably high enantioselections and reaction yields in the alkenylation of aldehydes.[7]

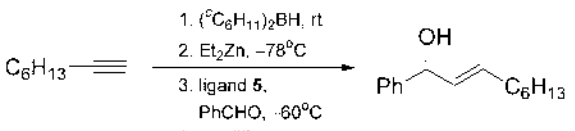


*Corresponding author. Tel.: −82-2-3290-3131; Fax: −82-2-3290-3121; e-mail: dechha@korea.ac.kr

In our previous report, we showed the amino alcohol **5**, a morpholine derivative of the homologs of binaphthyl-based *N,O*-ligand, can be used for highly enantioselective addition of diphenylzinc to different types of aldehydes.[8] Enantioselectivity in the phenylation of aldehyde is usually low because of the rapid competitive uncatalyzed background reaction. One solution to this problem is to use a mixture of Ph_2Zn and Et_2Zn for an *in situ* generation of the less reactive PhZnEt.[9] But the reaction yield using this method and **5**, in our hands, is usually much lower than the use of Ph_2Zn only due to the decreased phenylation rate under the reaction temperature for optimum enantioselection.[8a] Despite the extensive use of the binaphthyl-based chiral ligands in the catalytic asymmetric synthesis, limited number of the ligands are employed in the catalytic asymmetric organozinc additions to aldehydes.[1e] Only one example of binaphthyl-based ligand, 3,3'-diaryl-1,1'-bi-2-naphthol, is known for the phenylation of aldehydes with moderate enantioselectivity by using Ph_2Zn and Et_2Zn mixture and 20 mol % of the ligand.[10] There is no report about the asymmetric alkenylation of aldehyde with the use of binaphthyl-based ligand. Ligand **5** in our study showed high yields and asymmetric induction in the phenylation of aldehydes with Ph_2Zn only and 5 mol % of the ligand. Encouraged with this result, we studied catalytic asymmetric alkenylation of aldehyde with the use of ligand **5**.

Optimum condition for the asymmetric addition of alkenylzinc to aldehyde had been searched for the reaction between 1-octenylzinc and benzaldehyde (Table 1). Dicyclohexylborane, prepared *in situ* with $BH_3{\cdot}SMe_2$ and cyclohexene at 0 °C for 2 h in hexane, was treated with 1-octyne at ambient temperature for 1 h. The resulting 1-octenylborane solution was reacted with Et_2Zn at -78 °C for the boron-zinc exchange to generate 1-octenylethylzinc. It is known that alkenylethylzinc is in equilibrium with diethylzinc and dialkenylzinc above 0 °C and decomposes to the corresponding diene and metallic zinc.[4] When 2 mol % of ligand **5** in toluene was added to the solution of the alkenylzinc at -78 °C and the mixture was slowly warmed to 0 °C followed by the addition of benzaldehyde, only a trace amount of the product was observed. The color of the solution began to

Table 1. Enantioselective Addition of 1-Octenylzinc to Benzaldehyde



Entry	Ligand **5** (mol %)	Conditions[a] (step 4)	Yield[b] (%)	Ee[c] (%)
1	–	0 °C, 12 h	27	
2	2	−30 °C, 3 h	21	49
3	2	0 °C, 3 h	78	61
4	3	−10 °C, 12 h	90	74
5	3	0 °C, 2 h	85	83
6	3	10 °C, 2 h	83	8
7[d]	3	0 °C, 1.5 h	73	69
8	10	0 °C, 1 h	85	89

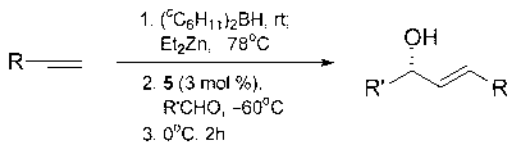
[a]Temperature controlled with low temperature bath with internal magnetic stirrer [b]Isolated yield [c]Determined by HPLC (Chiralcel OD column). [d]Me_2Zn used instead of Et_2Zn.

turn into black at -30 °C and severe decomposition of the alkenylzinc at 0 °C was observed. When benzaldehyde was added at -78 °C without ligand **5** and the reaction mixture was warmed to 0 °C, the allylic alcohol product was obtained in low yield (entry 1, Table 1). Since the alkenylation process was very sensitive to reaction temperature, we added the ligand **5** at -60 °C to the alkenylzinc solution followed by the addition of benzaldehyde. We studied the effect of temperature on the reaction after the addition of benzaldehyde (entries 2 and 3). Reactions under the temperature lower than 0 °C provided poor results both in reaction yields and enantioselection, probably because of the slow alkenylation rate and small rate difference between the catalyzed reaction and uncatalyzed background reaction. Better result was obtained with the use of 3 mol % of **5** and 0 °C alkenylation temperature (entry 5). Higher reaction temperature (entry 6) or the use of Me_2Zn instead of Et_2Zn decreased the selectivity (entry 7). Enantioselectivity of the reaction could be further improved by using 10 mol % of ligand **5** (entry 8).

With the conditions optimized for the 1-octenylation of benzaldehyde, several terminal alkynes were used for the asymmetric alkenylation of aromatic and aliphatic aldehydes with the use of 3 mol % **5** (Table 2). Similar enantioselectivity was observed with aromatic aldehydes, and low enantioselectivity with aliphatic aldehydes. Alkenylation with *t*-butylacetylene was much faster than the use of other alkynes probably because of the unfavorable formation of less reactive aggregates due to steric reason (entries 4 and 5). Many unidentified byproducts were formed with the use of phenylacethylene and caused much decreased reaction yields (entries 6 and 7). Alkenylation of benzaldehyde using a symmetric internal alkyne, 3-hexyne, produced the corresponding allylic alcohol with moderate enantioselectivity.

In conclusion, we demonstrated the first application of binaphthyl-based amino alcohol ligand for the catalytic asymmetric alkenylation of aldehyde. This ligand is successfully applied to the asymmetric synthesis of allylic alcohols

Table 2. Enantioselective Alkenylation of Aldehydes



Entry	R	R'	Yield (%)[a]	% ee[b]
1	*n*-Hx	Ph	85	83 (*R*)[c]
2	*n*-Hx	*p*-Cl-Ph	82	83 (*R*)[c]
3	*n*-Hx	*c*-Hx	77	55 (*S*)[d]
4	*t*-Bu	Ph	87	74 (*R*)[e]
5	*t*-Bu	*p*-Cl-Ph	76	80 (*R*)[e]
6	Ph	Ph	43	72 (*R*)[e]
7	Ph	Et	42	32 (*S*)[e]
8	3-hexyne	Ph	84	77 (*R*)[f]

[a]Isolated yield [b]Absolute configuration assigned by comparison to the literature [c]Determined by chiral HPLC (Chiralcel OD column) [d]Determined by ^{19}F-NMR analysis of the corresponding (*R*)-MTPA ester derivative [e]Determined by chiral HPLC (Chiralpak AD-H column) [f]Determined by chiral HPLC (Chiralcel OJ-H column).

from aromatic aldehydes, and unsatisfactory result was obtained with aliphatic aldehydes. Further study to improve the enantioselectivity of the alkenylation using the ligands having binaphthyl backbone is currently in progress.

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

References

1. Reviews on enantioselective diorganozinc additions to aldehydes: (a) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (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.
2. (a) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645. (b) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.
3. (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.
4. Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170.
5. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
6. (a) Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1257. (b) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766. (c) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225.
7. Dahmen, S.; Brase, S. *Org. Lett.* **2001**, *3*, 4119.
8. (a) Ko, D.-H.; Kim, K. H.; Ha, D.-C. *Org. Lett.* **2002**, *4*, 3759. (b) Kang, S.-W.; Ko, D.-H.; Kim, K. H.; Ha, D.-C. *Org. Lett.* **2003**, *5*, 4517.
9. (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muniz, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3465. (b) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P.; Raabe, G. *Angew. Chem. Int. Ed.* **2001**, *40*, 1488.
10. (a) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222. (b) Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 145.