

3,3'-Br₂-BINOL-Zn Complex: A Highly Efficient Catalyst for the Enantioselective Hetero-Diels–Alder Reaction

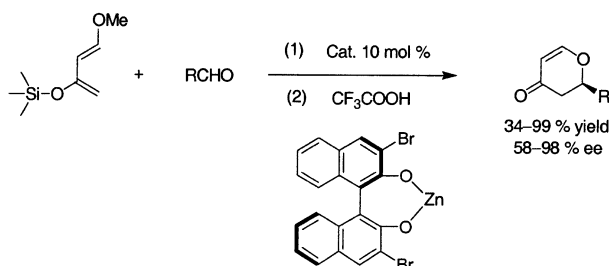
Haifeng Du, Jiang Long, Jieyu Hu, Xin Li, and Kuiling Ding*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, The People's Republic of China

kding@pub.sioc.ac.cn

Received October 5, 2002

ABSTRACT



A BINOLate-zinc complex prepared in situ from Et₂Zn and 3,3'-dibromo-1,1'-bi-2-naphthol (3,3'-Br₂-BINOL) was found to be a highly efficient catalyst for the enantioselective hetero-Diels–Alder reaction of Danishefsky's diene and aldehydes to give 2-substituted 2,3-dihydro-4H-pyran-4-one in up to quantitative yield and 98% ee.

A catalytic asymmetric hetero-Diels–Alder (HDA) reaction between Danishefsky's diene and aldehydes provides a powerful approach for achieving optically active 2-substituted 2,3-dihydro-4H-pyran-4-one, a type of heterocycle with extensive synthetic applications in natural or unnatural products.^{1–3} Since the first HDA reaction of Danishefsky's diene and aldehydes was achieved with the catalysis of

ZnCl₂,⁴ various chiral Lewis acids, such as aluminum, boron, transition and lanthanide metal complexes, and so on, have been employed for this type of reaction.^{5–12} However, the use of chiral zinc catalysts for this reaction has been less successful although the chiral zinc alkoxide **1** and phenoxide **2** have been recently reported to be efficient catalysts for direct asymmetric aldol-type reactions.^{13,14} The Lewis acid **3** obtained from diethylzinc and 1,1'-bi-2-naphthol (BINOL)

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley-Interscience: New York, 1994. (b) *Catalysis Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000. (c) Kagan, H. B. *Comprehensive Organic Chemistry*; Pergamon: Oxford, UK, 1992; Vol. 8. (d) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vols. I–III. (e) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: New York, 2001.

(2) For reviews see: (a) Danishefsky, S. J.; De Ninno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15–23. (b) Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558–3588. (c) Maruoka, K. In *Catalysis Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 8A.

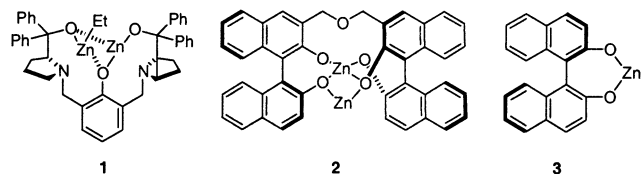
(3) (a) Boger, D. L.; Weinreb, S. N. In *Hetero Diels–Alder Methodology in Organic Synthesis*; Wasserman, H. H., Ed.; Academic Press: San Diego, CA, 1987. (b) Tietze, L. F.; Ketschau, G. In *Stereoselective Heterocyclic Synthesis I*; Metz, P., Ed.; Springer: Berlin, Germany, 1997.

(4) Danishefsky, S.; Kerwin, J. F.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358–360.

(5) (a) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312. (b) Simonsen, K. B.; Svenstrup, N.; Roberson, M.; Jorgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 123–128.

(6) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907–6910.

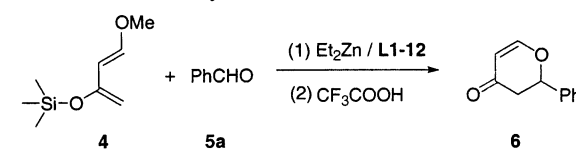
has been reported by Yamamoto to catalyze the enantioselective cyclization of unsaturated aldehydes.¹⁵ Very recently, Renaud reported that Yamamoto's Zn-BINOL complex was an efficient catalyst for enantioselective Diels–Alder reaction of *N*-alkoxyacrylamides with cyclopentadiene.¹⁶ However,



the employment of a stoichiometric amount of Zn-BINOL catalyst is required to obtain acceptable enantioselectivity and reactivity of the reaction. In the present letter, we report our preliminary results on the highly enantioselective HDA reaction of Danishefsky's diene **4** with aldehydes **5** using a catalytic amount of chiral diol ligand-based zinc Lewis acids.

The first trial by using **L1**/zinc complex as the catalyst for the reaction of Danishefsky's diene **4** and benzaldehyde **5a** showed that the reaction proceeded smoothly to give 2-phenyl-2,3-dihydro-4*H*-pyran-4-one (**6a**) in good yield and moderate enantioselectivity (entry 1 in Table 1). This result prompted us to further improve the enantioselectivity of the reaction by tuning the steric and electronic modifications on the diol ligands. Therefore, a series of chiral diol ligands including commercially available or easily prepared BINOL derivatives (**L2**–**L12**) shown in Scheme 1 were submitted

Table 1. Screening of BINOLate-zinc Catalysts for Enantioselective hetero-Diels–Alder Reaction of Danishefsky's Diene **4** and Benzaldehyde **5a**^a



entry	L	cat. (%)	temp. (°C)	yield (%) ^a	ee (%) ^b	conf. ^c
1	L1	10	0	91	59	<i>S</i>
2	L2	10	0	89	60	<i>S</i>
3	L3	10	0	92	42	<i>S</i>
4	L4	10	0	92	0.5	<i>R</i>
5	L5	10	0	50	50	<i>R</i>
6	L6	10	0	>99	93	<i>R</i>
7	L7	10	0	45	20	<i>R</i>
8	L8	10	0	13	58	<i>R</i>
9	L9	10	0	85	64	<i>R</i>
10	L10	10	0	82	43	<i>R</i>
11	L11	10	0	80	43	<i>R</i>
12	L12	10	0	16	17	<i>R</i>
13	L6	10	-10	>99	94	<i>R</i>
14	L6	10	-25	>99	97	<i>R</i>
15	L6	5	-25	90	95	<i>R</i>
16 ^d	L6	1	0	>99	10	<i>R</i>

^a Determined by HPLC with biphenyl as an internal standard. ^b Enantiomeric excesses of products were determined by HPLC on Chiralcel OD column. ^c The configuration of product was determined by retention time of HPLC in comparison with that of an authentic sample prepared according to the literature.^{7d} ^d The reaction was carried out under solvent-free condition.

(7) For BINOL-, H₄-BINOL-, and H₈-BINOL-Ti catalyzed asymmetric HDA of Danishefsky's diene with aldehydes in the presence or absence of molecular sieves (MS), see: (a) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812–2820. (b) Keck, G. E.; Li, X. Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998–5999. (c) Wang, B.; Feng, X.; Cui, X.; Liu, H.; Jiang, Y. *Chem. Commun.* **2000**, 1605–1606. (d) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10–11. (e) Yuan, Y.; Long, J.; Li, X.; Sun, J.; Ding, K. *Chem. Eur. J.* **2002**, *8*, 5033–5042. (f) For BINOL-Zr catalyzed asymmetric HDA of Danishefsky's diene with aldehydes, see: Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 1221–1223.

(8) (a) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403–405. (b) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem.*, **1999**, *38*, 2398–2400. (c) Li, L.-S.; Wu, Y.; Hu, Y.-J.; Xia, L.-J.; Wu, Y.-L. *Tetrahedron: Asymmetry* **1998**, *9*, 2271–2277.

(9) Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, *123*, 5366–5367.

(10) (a) Yao, S.; Johennsen, M.; Audrain, H.; Hazell, R. G.; Jorgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599–8605. (b) Jorgensen, K. A.; Johennsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605–613. (c) Dalko, P. I.; Moisan, L.; Cossy, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 625–628.

(11) (a) Danishefsky, S. J.; Maring, C.; Bednarski, M. *Tetrahedron Lett.* **1983**, *24*, 3451–3454. (b) Danishefsky, S. J.; Bednarski, M. *J. Am. Chem. Soc.* **1983**, *105*, 6968–6969.

(12) (a) Hanamoto, T.; Furuno, H.; Sugimoto, Y.; Inanaga, J. *Synlett* **1997**, 79–80. (b) Qian, C.; Wang, L. *Tetrahedron Lett.* **2000**, *41*, 2203–2206.

(13) (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004. (b) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497–2500. (c) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861–863. (d) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367–3368.

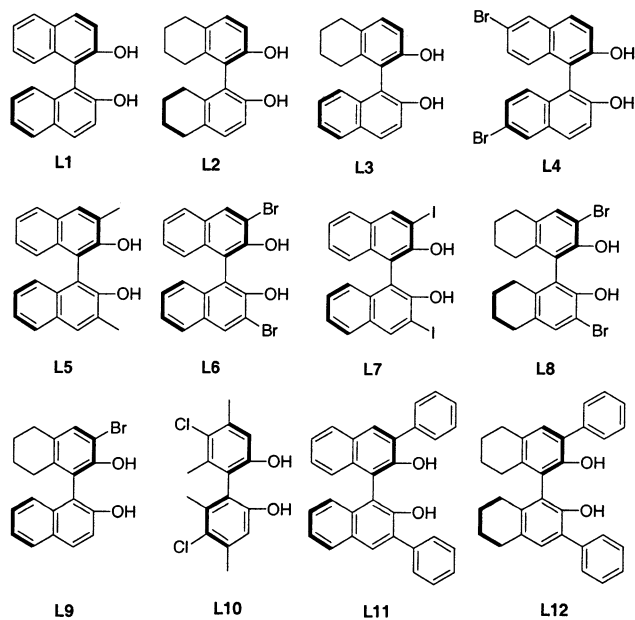
(14) (a) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466–2467. (b) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251–4254.

(15) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1985**, *26*, 5536–5538.

(16) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735–1738.

to asymmetric catalysis. The details of the results were summarized in Table 1, which clearly demonstrated that the enantioselectivity and reactivity of the reaction were significantly influenced by both the electronic effect and steric hindrance of the substituents at 3,3'-positions of BINOL. The serious steric hindrance of phenyl groups at 3,3'-positions of BINOL was proved to be disadvantageous for the reaction (entries 1 and 2 vs 11 and 12, respectively). Moreover, the absolute configuration of product was significantly influenced by the substituents in the binaphthyl unit. The steric hindrance of substituents could switch the asymmetric induction from the formation of *S* product to *R* product (entries 1–3 vs 4–12). The backbone effect of the binaphthyl moiety was not evident in the cases of **L1** and **L2** (entry 1 vs 2). Nevertheless, in the asymmetric induction of 3,3'-substituted BINOL derivatives, partially reduced ligands **L8** and **L12** are inferior to their parent ligands **L6** and **L11** in terms of both enantioselectivity and reactivity (entries 6 and 11 vs 8 and 12, respectively). We were pleased to find that **L6**, (*R*)-3,3'-dibromo-1,1'-bi-2-naphthol (3,3'-Br₂-BINOL), was particularly efficient for the reaction, affording the product in up to quantitative yield and 93% ee. Therefore,

Scheme 1. The Chiral Ligands Employed for Asymmetric Catalysis



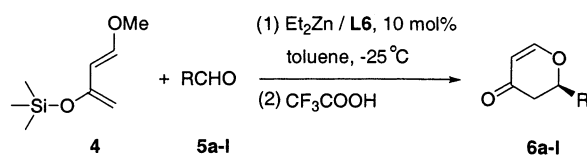
the correct assembly of substituents and backbone of binaphthyl is a key point in designing the chiral diol ligand for the Zn-catalyzed HDA reaction.

The reaction promoted by **L6**-modified catalyst was further optimized via decreasing the reaction temperature. The enantioselectivity of the reaction at -10 and -25 °C could be improved to 94% and 97%, respectively, with quantitative yield (entries 13 and 14). When the catalyst loading was reduced to 5 mol %, the enantioselectivity and yield of the reaction still remain at a high level (entry 15). In our previous work on H_4 -BINOL- and H_8 -BINOL-Ti complexes-catalyzed HDA reactions, the solvent-free condition was found to be critical for reducing the catalyst loading.^{7d} Therefore, 1 mol % of Zn/**L6** was submitted to the reaction in the absence of solvent. Unfortunately the ee (10%) of the product dropped significantly even though the yield of product could be up to >99%, which clearly demonstrated the importance of the solvent effect on the reaction.

Under the optimized conditions, the reactions of a variety of aldehydes, including aromatic, olefinic, and aliphatic derivatives, were carried out under the catalysis of Zn/**L6**. As shown in Table 2, the catalyst was highly efficient for the reaction of aromatic aldehydes to give their corresponding 2-substituted 2,3-dihydro-4H-pyran-4-ones in 82–99% yields with 89–98% ee. The enantioselectivities for the reactions of olefinic and aliphatic aldehydes could be moderate to good, but the yields were found to be relatively lower than those of aromatic aldehydes. The simplicity of the Zn/3,3'-Br₂-BINOL experimental procedure makes it very attractive from a synthetic point of view.

Although the detailed reaction mechanism remains unknown, it can be deduced that there may be a variety of aggregated catalyst species involved in the catalytic system

Table 2. The Reaction of Danishefsky's Diene with Aldehydes Catalyzed by Zn/**L6**



entry	R	yield (%) ^a	ee (%) ^b	conf. ^c
1	phenyl (5a)	>99	97	R
2	3-anisyl (5b)	>99	98	^d
3	3-phenylethyl (5c)	40	58	S
4	<i>E</i> -styryl (5d)	34	86	R
5	2-furfuryl (5e)	>99	96	R
6	3-tolyl (5f)	>99	96	^d
7	4-cyanophenyl (5g)	>99	96	^d
8	3-bromophenyl (5h)	>99	94	^d
9	3-chlorophenyl (5i)	92	98	^d
10	4-bromophenyl (5j)	>99	94	^d
11	4-chlorophenyl (5k)	>99	95	^d
12	2,6-dichlorophenyl (5l)	82	89	^d

Isolated yield. ^b Enantiomeric excesses of products were determined by HPLC on Chiralcel OD or Chiralpak AD column. ^c The configurations of products were determined by the retention times of HPLC in comparison with those of authentic samples prepared according to the literature.^{7d} ^d The absolute configuration was not determined.

on the basis of the observed unusual nonlinear effect.¹⁷ It is obvious that the catalytic system showed both weak positive and strong negative nonlinear effects (Figure 1). The most interesting is that the absolute configuration of the product was switched to *S* from *R* when the enantiomeric excesses of partially resolved (*R*)-**L6** were decreased to <40%, which demonstrated the changes of active species with the decrease of ee of the chiral ligand. The investigation of the solvent effect showed that the reactions carried out in THF and diethyl ether with the catalysis of (*R*)-**L6**/Zn gave the product in the *R* configuration (51% and 46% ee, respectively). On the contrary, the reactions run in dichloromethane and hexane resulted in the product in the *S* configuration (28% and 7% ee, respectively). It can be deduced that the system does not obey Noyori's monomer–dimer model for diethylzinc addition to aldehydes catalyzed by amino alcohols. According to Kagan's ML_n -type model,^{17b} if a catalytic system processes a negative nonlinear effect, the yields for the runs using a low-ee ligand would be higher than that using an enantiopure ligand because the heterochiral complex must necessarily exhibit a higher rate ($k_{RS}/k_{RR} > 1$). In fact, the yields of the

(17) For comprehensive reviews on NLE in asymmetric catalysis, see: (a) Fenwick, D. R.; Kagan, H. B. In *Topics in Stereochemistry*; Denmark, S. E., Ed.; John Wiley & Sons: New York, 1999; Vol. 22, pp 257–296. (b) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922–2959. (c) Bolm, C. In *Advanced Asymmetric Catalysis*; Stephenson, G. R., Ed.; Chapman & Hall: London, UK, 1996; pp 9–26. (d) Heller, D.; Drexler, H.-J.; Fischer, C.; Buschmann, H.; Baumann, W.; Heller, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 495–499. (e) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832–4842. (f) Blackmond, D. G. *J. Am. Chem. Soc.* **1998**, *120*, 13349–13353.

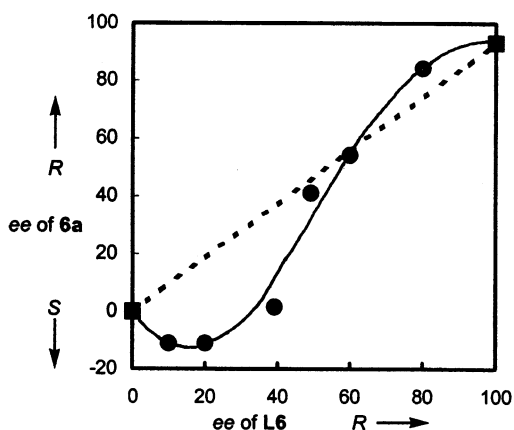


Figure 1. Enantioselectivity for the reaction of **4** with **5a** catalyzed by the zinc complexes of partially resolved (*R*)-**L6**. The broken line indicates the expected values when the reactivity difference between Zn/(*R*)-**L6** and Zn/(*S*)-**L6** was not considered.

reactions dropped with the decrease of enantiomeric excesses of (*R*)-**L6**. Therefore, the ML_n -type model is not applicable to the present catalytic system either. All these facts show that the present catalytic system may not behave in one

particular model and the change of the catalytic species may occur during the course of the reaction with a nonenantiopure catalyst.^{17f} Further insight into the reaction mechanism and research on the application of this type of catalyst in other asymmetric reactions are underway in this laboratory.

In conclusion, a highly efficient enantioselective zinc binaphthoxide-catalyzed hetero-Diels–Alder reaction of Danishefsky's diene with aldehydes has been developed. Under the optimized conditions, up to a quantitative yield and 98% ee of the products were achieved with the catalysis of 10 mol % of Zn/3,3'-Br₂-BINOL.

Acknowledgment. Financial support from the National Natural Science Foundation of China, Chinese Academy of Sciences, the Major Basic Research Development Program of China, and the Ministry of Science and Technology Commission of Shanghai Municipality is gratefully acknowledged.

Supporting Information Available: Experimental details and spectral data for **5a–I** and the data from the search for NLE and the solvent effect in the reaction system. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL027034R