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Enantioselective Catalysis of Hetero Diels–Alder Reaction and Diethylzinc Addition Using a Single Catalyst

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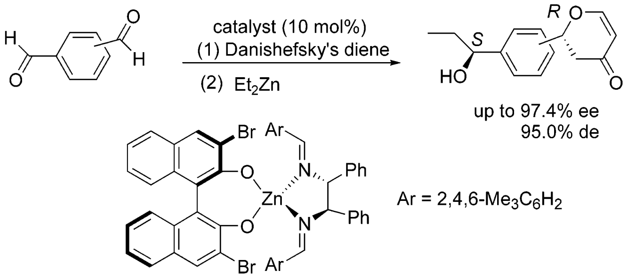
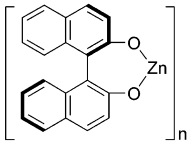
ABSTRACT

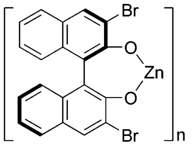


Integration of two asymmetric reactions in one pot with the promotion of a single catalyst has been achieved in high efficiency and excellent stereoselectivity for hetero Diels–Alder reaction of Danishefsky's diene and diethylzinc addition to aldehydes. The strategy described in the present work demonstrated the ability of a single catalyst to promote two distinct enantioselective reactions in one pot.

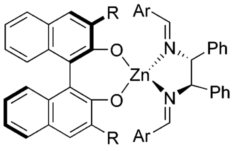
The development of organometallic catalysts that are capable of catalyzing multiple, mechanistically distinct reactions directly or by simple modification has been an increasing demand for expedient and efficient synthetic processes.[1] Asymmetric catalysis of organic reactions has provided a powerful strategy for multiamplification of chirality to obtain optically active compounds.[2] However, there were very few reports on the tandem catalysis of two distinct enantioselective reactions using a single chiral catalyst.[3] Therefore, the integration of two reactions in one pot with the promotion of a single catalyst is a great challenge for chemists. As an example of such a system, we demonstrate the ability of a single catalyst to promote two different reactions in one pot through a tandem method.



1



2



3 R = Ph
Ar = 2,4,6-Me$_3$C$_6$H$_2$

Zinc complexes of 1,1′-bi-2-naphthol (BINOL-Zn, **1**) have been reported to promote enantioselective cyclization of unsaturated aldehydes and Diels−Alder reaction of *N*-alkoxyacrylamides with cyclopentadiene in a stoichiometric manner.[4] Very recently, we found that 3,3′-dibromo-1,1′-bi-2-naphthol (3,3′-Br$_2$BINOL-Zn, **2**) was an efficient catalyst

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[1] For leading examples of tandem catalysis, see: (a) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. (b) Bielawski, C. W.; Louie, J. R.; Grubbs, H. *J. Am. Chem. Soc.* **2000**, *122*, 12872. (c) Drouin, S. D.; Zamanian, F.; Fogg, D. E. *Organometallics* **2001**, *20*, 5495. (d) Orita, A.; Nagano, Y.; Nakazawa, K.; Otera, J. *Adv. Synth. Catal.* **2002**, *344*, 548. (e) Chen, J.; Otera, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 91.

[2] (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, 1992; Vol. 8. (d) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vols. I−III. (e) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: New York, 2001.

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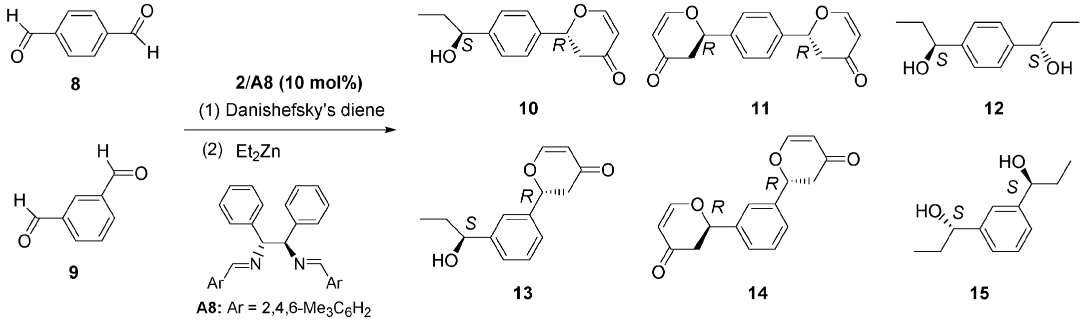
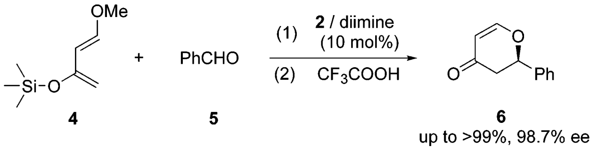
Scheme 1. Tandem Asymmetric Catalysis of Hetero Diels−Alder Reaction and Diethylzinc Addition Using a Single Catalyst

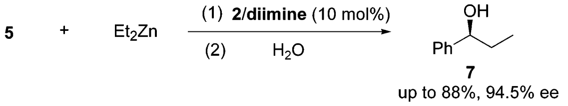


for the hetero Diels−Alder (HDA) reaction of aldehydes with Danishefsky's diene.[5] The asymmetric activation of 3,3′-Ph$_2$-BINOL-Zn complex (**3**) with diimine has been found to be a useful strategy for achieving high efficiency and enantioselectivity in catalytic asymmetric diethylzinc addition to aldehydes.[6] As an effort to explore the application of activated Zn catalyst for two distinct asymmetric reactions, we first investigated its possibility for the promotion of HDA reaction of Danishefsky's diene (**4**) with benzaldehyde (**5**) (eq 1).[7]

The investigation using **1** in combination with diimine prepared by condensation of (*S*,*S*)-1,2-diaminocyclohexane with benzaldehyde as the catalyst for HDA reaction between **4** and **5** (eq 1) showed that the reaction proceeded smoothly at 0 °C to give (*S*)-2-phenyl-2,3-dihydro-4*H*-pyran-4-one **6** with moderate enantioselectivity (63.6% ee). This result prompted us to further improve the enantioselectivity of the reaction by tuning the steric and electronic modifications in the diol ligands and diimine activators through a combinatorial approach.[8] Accordingly, a library of chiral diol ligands (with 12 members), including commercially available or easily prepared BINOL and biphenol derivatives, and a library of diimines (with 20 members) derived from enantiopure 1,2-diaminocyclohexane were created. High throughput screening of the chiral Zn catalyst library (240 members) generated by assembling the members of diol ligand and diimine activator libraries with Zn showed that all of the catalysts could promote the HDA reaction of **4** with **5** at 0 °C to give the desired product **6**. The details of the results were presented in Supporting Information. It was found that the absolute configuration of product was mainly controlled by the chirality of diol ligands and that the level of enantioselectivity of the reaction might be affected by the chirality and steric environment of diimine activators. We were pleased to find that complex **2** in the presence of various diimines was particularly efficient for the reaction, affording adduct **6** in up to quantitative yield and 94.2% ee. The reaction catalyzed by the lead catalysts discovered above was further optimized by decreasing the reaction temperature to −20 °C. Under the optimized conditions, adduct **6** could be obtained in quantitative yield with up to 98.7% ee.



(1)



(2)

With these leading results in hand, we switched our attention to the screening of highly efficient and enantioselective catalysts for diethylzinc addition to benzaldehyde (eq 2) by combining **2** with a variety of diimine activators. The literature results showed that in the catalysis of diethylzinc addition to aldehydes, the steric hindrance of diimine activators was critical for getting maximum activation of BINOL-Zn catalyst.[6] Accordingly, a library of diimines with eight members (see Supporting Information) was created by condensation of enantiopure 1,2-diphenylethylenediamine or 1,2-diaminocyclohexane with 2 equiv of 2,6-dichloro- and 2,4,6-trimethylbenzaldehydes. A rapid screening of the chiral catalyst library composed of **2** and the chiral activators for diethylzinc addition to benzaldehyde at 0 °C disclosed that **2**/**A8** was the best combination, affording (*S*)-1-phenylpropanol ((*S*)-**7**) with 72% ee. The enantioselectivity of the reaction could be improved to 94.5% at a lower reaction temperature (−20 °C). Reexamination of the **2**/**A8** catalyst system for HDA reaction at −20 °C resulted in the formation of (*R*)-**6** with 97.4% ee and quantitative yield.

So far, we have discovered such a catalyst (**2**/**A8**) that is highly efficient and enantioselective for both HDA reaction and diethyl zinc addition of benzaldehyde. This catalyst system provided an excellent opportunity to conduct two asymmetric reactions in one pot using a single catalyst. Then terephthalaldehyde **8** was taken as a substrate for tandem asymmetric HDA reaction and diethylzinc addition to generate dihydropyranone and secondary alcohol moieties in one substrate (Scheme 1). The HDA reaction was first carried out in the presence of 10 mol % **2**/**A8** for 30 h at −20 °C in toluene, and then 3 equiv of diethyl zinc was introduced to

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(3) For leading references on tandem asymmetric catalysis, see: (a) Yu, H.-B.; Hu, Q.-S.; Pu, L. *J. Am. Chem. Soc.* **2000**, *122*, 6500. (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636.

(4) (a) Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1985**, *26*, 5535. (b) Corminboeuf, O.; Renaud, P. *Org. Lett.* 2002, *4*, 1735.

Table 1. Tandem Asymmetric Reaction of Dialdehydes Catalyzed by **2**/**A8**[a]

entry	substrate	Et_2Zn (%)	yield (%)[d]	ee (%)[b,e]	de (%)[c,e]
1	**8**	14[b] + 300[c]	**10** (92)	**10** (97.4)	**10** (95.0)
			11 (<3)	**11** (>99)	**11** (96.9)
			12 (<3)	**12** (nd)	**12** (nd)
2	**9**	14[b] + 300[c]	**13** (82)	**13** (95.9)	**13** (94.9)
			14 (6.5)	**14** (>99)	**14** (96.6)
			15 (10)	**15** (nd)	**15** (nd)

[a] All of the reactions were carried out at −20 °C in toluene with a molar ratio of dialdehyde:Danishefsky's diene:3,3′-Br_2-BINOL:**A8** = 1:1.3:0.1:0.1. [b] For the first step HDA reaction. [c] For diethylzinc addition. [d] Isolated yields. [e] Determined by HPLC on Chiralcel OD or AD column. The de is the diastereoselectivity of the second alkylation step.

continue the second step, asymmetric addition, under the same experimental conditions without workup of the first HDA step product. As shown in Table 1, two asymmetric reactions proceeded efficiently and selectively to give product **10**. It was found that the ee for the HDA reaction was 97.4%, and the de for the diethylzinc addition step was 95.0%, which were essentially the same as those obtained using benzaldehyde as a substrate. The configurations of two chiral centers in product **10** are tentatively assigned to be *R* and *S* as shown in Scheme 1 on the basis of the results obtained using benzaldehyde as a substrate mentioned above. The conversion and chemical selectivity for the first HDA step was very high (monoadduct:diadduct > 96:4). The high chemical selectivity of the first step is probably due to the fact that the formyl group is strongly electron withdrawing, which facilitates the first HDA reaction. After HDA reaction, the substrate is much less reactive than the starting dialdehyde because of electron-donating property of α-dihydropyranyl moiety in the monoadduct. We have also carried out tandem asymmetric HDA reaction and diethylzinc addition of isophthalaldehyde **9** using the catalyst system of **2**/**A8** and observed excellent stereoselectivity for the formation of product **13** (entry 2 in Table 1).

In summary, a new type of chiral zinc catalyst has been found to show excellent stereoselectivity in asymmetric catalysis of both HDA reaction of Danishefsky's diene and diethylzinc addition to aldehydes. The strategy described in the present work demonstrated the ability of a single catalyst to promote two distinct enantioselective reactions in one pot, which might provide a new direction to the design of chiral catalysts for asymmetric synthesis. Research on the extension of the scope of substrates for this reaction and use of achiral diimine activators in the catalyst system is underway in our laboratory.

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Supporting Information Available: Experimental details and spectral data for products, chiral HPLC analysis of the products, and data of the screening of the chiral catalyst library. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Du, H.; Hu, J.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 4349.

(6) For asymmetric activation of BINOL-Zn catalysts, see: (a) Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 497. (b) Mikami, K.; Angelaud, R.; Ding, K.; Ishii, A.; Tanaka, A.; Sawada, N.; Kudo, K.; Senda, M. *Chem. Eur. J.* **2001**, *7*, 730. (c) Costa, A. M.; Jimeno, C.; Gavenonis, J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 6929.

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

(8) For reviews on combinatorial asymmetric catalysis, see: (a) Jandeleit, B.; Schaefer, D. J.; Powers, T. S., Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2494. (b) Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885. (c) Francis, M. B.; Jamison, T. F.; Jacobsen, E. N. *Curr. Opin. Chem. Biol.* **1998**, *2*, 422. (d) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284. (e) Reetz, M. T.; Jaeger, K.-E. *Chem. Eur. J.* **2000**, *6*, 407. (f) Tsukamoto, M.; Kagan, H. B. *Adv. Synth. Catal.* **2002**, *344*, 453.