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# Direct Catalytic Asymmetric Aldol-Type Reaction of Aldehydes with Ethyl Diazoacetate

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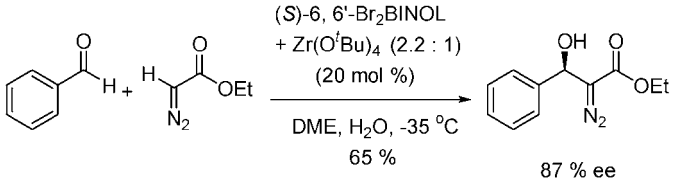
## ABSTRACT

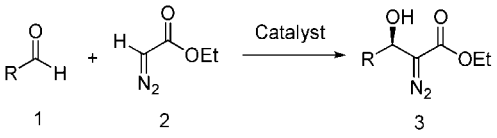



**The direct aldol-type condensation of aldehydes with ethyl diazoacetate catalyzed by the chiral complex of BINOL derivatives–$Zr(O^tBu)_4$ gave *β*-hydroxy α-diazo carbonyl compounds with moderate enantioselectivities (53–87% ee).**

Enantioselective C−C bond formation under catalytic condition remains a challenging task in modern organic synthesis. Because the aldol reaction is generally considered as one of the most powerful and efficient C−C bond-forming reactions, the corresponding catalytic asymmetric aldol reaction has been extensively studied over the past decades, and numbers of highly enantioselective catalytic systems have been developed.[1] However, most of these processes rely on the activation of the ketones or esters by converting them into enol silyl ethers or ketene silyl acetals, namely, Mukaiyama-type aldol condensation. Although it is now possible to achieve high stereocontrol in these processes, considering the requirement of atom efficiency, it would be more desirable to directly apply nucleophiles in catalytic asymmetric aldol reactions. The direct catalytic asymmetric aldol reaction has been studied only recently, and several very practical processes have been developed.[2]

We have recently developed a DBU-catalyzed aldol-type condensation of aldehydes with ethyl diazoacetate.[3] This reaction can give α-diazo carbonyl compounds bearing a *β*-hydroxyl group, which may be transformed to other synthetically useful compounds. We conceived that a catalytic asymmetric system might be developed in this system. In this communication we report our investigation on the catalytic asymmetric aldol condensation with ethyl diazoacetate as nucleophile (Scheme 1).

**Scheme 1**




For the direct condensation of aldehyde with diazoacetate to occur, a transition metal catalyst that can activate aldehyde and bring both the aldehyde and the diazoacetate in close proximity is required. To search for a metal complex that

(1) For recent reviews on the catalytic asymmetric aldol reaction, see: (a) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem.−Eur. J.* **2002**, *8*, 37. (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol.3, Chapter 29.1. (c) Sawamura, M.; Ito, Y. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH, 2000; p 493.

(2) For reviews, see: (a) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989. (b) Alcaide, B.; Almemdros, P. *Eur. J. Org. Chem.* **2002**, 1595. (c) List, B. *Tetrahedron* **2002**, 58, 5573. (d) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. For most recent reports, see: (e) Ooi, T.; Taniguchi, M.; Kemeda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542. (f) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem.*

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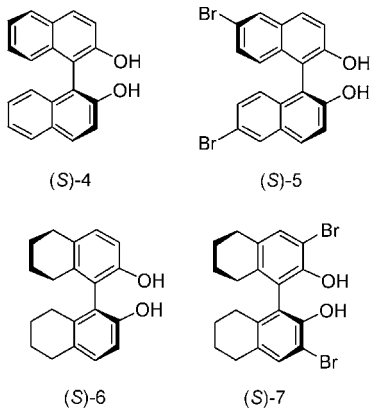
**Table 1.** Effect of Additives, Chiral Ligands, Solvent, and Temperature on $Zr(O^tBu)_4-2L^*$ Catalyzed Aldol-Type Condensation of Benzaldehyde **1** (**a**, R = Ph) with Ethyl Diazoacetate

| entry | additive (mol %) | ligand[a] | solvent | temp (°C) | time (h) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | $CH_3CN$ (20) | (*S*)-**4** | THF | 25 | 24 | 35 | 53 |
| 2 | $CH_3CN$(20), $H_2O$(20) | (*S*)-**4** | THF | 25 | 24 | 40 | 65 |
| 3 | $CH_3CN$(20), $H_2O$(20) | (*S*)-**5** | THF | 25 | 24 | 45 | 58 |
| 4 | $CH_3CN$(20), $H_2O$(20) | (*S*)-**6** | THF | 25 | 24 | 23 | 0 |
| 5 | $CH_3CN$(20), $H_2O$(20) | (*S*)-**7** | THF | 25 | 24 | tr | |
| 6 | $H_2O$(20) | (*S*)-**4** | DME | 25 | 24 | 58 | 70 |
| 7 | $H_2O$(20) | (*S*)-**4** | DME | −23 | 48 | 62 | 83 |
| 8 | $H_2O$(20) | (*S*)-**5** | DME | −35 | 72 | 65 | 87 |

[a] 20 mol % of the catalyst $Zr(O^tBu)_4$−ligand (1:2.2) was applied in all cases. [b] Refer to the isolated yield after separation by silica gel. [c] ee's were determined by chiral HPLC; Chiracel OJ; hexane/2-propanol = 96:4.

could catalyze the condensation, we used benzaldehyde as the substrate and (*S*)-BINOL (*S*)-**4** as the chiral ligand. After examination of various metals,[4] we were pleased to find that Kobayashi's Zr(IV) catalyst,[5] prepared from $Zr(O^tBu)_4$ and 2.2 equiv of (*S*)-**4**,[6] is effective for the condensation. With this catalytic system and THF as solvent and $CH_3CN$ as additive,[7] the condensation gave (*S*)-*β*-hydroxyl α-diazo carbonyl compound **3** (**a**, R = Ph)[8] in 35% yield and 53% ee (Table 1, entry 1).




Since the initial experiments suggested that $Zr(O^tBu)_4$−(*S*)-BINOL could give higher ee value, this catalytic system was chosen, and we proceeded to optimize other conditions. Because Kobayashi et al. reported that Zr(IV) catalysts could be activated by adding small amount of $H_2O$, the first experiment is to test the effect of $H_2O$ additive in our reaction. The enantioselectivity could be indeed increased slightly by adding 20 mol % of $H_2O$, but the yield is still low (Table 1, entry 2).

The chiral ligands of (*S*)-BINOL derivatives were then examined. The hydrogenated (*S*)-BINOL derivatives (*S*)-**6** and (*S*)-**7** were not efficient in promoting the reaction, while (*S*)-BINOL and its (*S*)-6,6′-dibromo derivative (*S*)-**5** gave similar results (Table 1, entries 3−5). The catalytic system with (*S*)-**5** as the chiral ligand was slightly more reactive.

Next, the effect of solvent was studied. Nonpolar solvents, such as $Et_2O$, $CH_2Cl_2$ or $PhCH_3$, were not suitable for this reaction. Polar solvent $CH_3O(CH_2)_2OCH_3$ (DME), in combination with 1 equiv of $H_2O$ as additive, was found to be superior over THF to give aldol product in 58% yield and 70% ee (Table 1, entry 6). In this solvent, 20 mol % of $H_2O$ is critical in activate the catalyst; however, an excess amount of $H_2O$ will have the opposite effect to deactivate the catalyst.

The temperature of the reaction was found to significantly affect the enantioselectivity (Table 1, entries 7 and 8). The reaction at lower temperature could improve the enantioselectivity, but it took a longer time for the reaction to complete. It appeared that at low temperature (*S*)-6,6′-dibromo BINOL is the suitable ligand since it could make a more reactive catalytic system. In any case, at temperatures below −35 °C the reaction was found to be too slow to be practically useful.

This optimized condition was then applied to other aldehyde substrates (Table 2).[9] For some aldehydes (entries 3, 4, 7, 8), we found that the reaction was very slow at −35 °C. We suspected that the product of the condensation might compete with the substrates to bind to the transition metal of the catalyst, thus deactivating the catalytic system. To overcome this possible difficulty, we further added $MgBr_2$

*Soc.*, **2002**, *124*, 6798. (g) Evans, D.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, 392. (h) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169.

(3) Jiang, N.; Wang, J. *Tetrahedron Lett.* **2002**, *43*, 1285.

(4) We have examined B(III), Ti(IV), and Al(III). The catalyst prepared from $Ti(O^iPr)_4$ and 1 equiv of (*S*)-**4** gave the condensation product in 53% yield and 15% ee.

(5) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180.

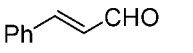
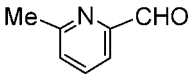
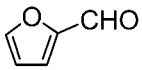
(6) The Zr(IV) catalyst prepared with 1 equiv of (*S*)-**4** gave lower enantioselectivity.

(7) Various additives were examined, including *N*-methylimidazole. $CH_3CN$ gave the best results in terms of ee value.

(8) The absolute configuration was determined by converting **3a** into a known compound of ethyl 3-hydroxy-3-phenylpropionate and comparing the sign of optical rotation. See Supporting Information.

(9) **Typical Procedure.** Chiral ligand (0.056 mmol) was dissolved in 0.5 mL of anhydrous DME, and then $Zr(O^tBu)_4$ (97%, 10 mg, 0.025 mmol) was added to the solution under $N_2$ at room temperature. After the mixture stirred for 1 h, $N_2CHCO_2Et$ (43 mg, 0.375 mmol) was added into the solution, and then water (0.45 uL, 0.025 mmol) was added. After the solution was stirred for another 3 h, it was then cooled by a dry ice/$CCl_4$ bath (−23 °C) or dry ice/$ClCH_2CH_2Cl$ bath (−35 °C). Aldehyde (0.125 mmol) was added under $N_2$. The solution was stirred for 3 days, and the solvent and excess $N_2CHCO_2Et$ were removed with rotovap. The crude residue was purified with silica gel column (petroleum ether/acetone = 8:1).

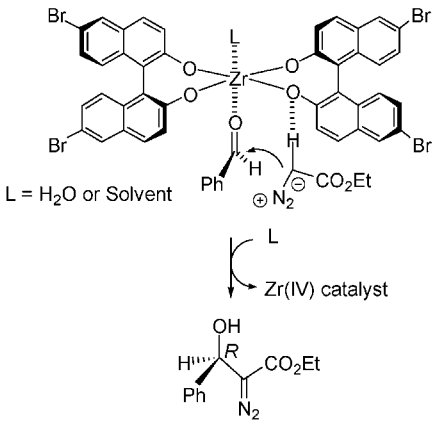
**Table 2.** Direct Catalytic Asymmetric Aldol-Type Condensation Using Zirconium Catalyst[a]

| entry | aldehyde | product | ligand | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | PhCHO **1a** | **3a** | (*S*)-**5** | 65 | 87 |
| 2 | 3-$F_3CC_6H_4CHO$ **1b** | **8b**[d] | (*R*)-**4** | 61 | 65 |
| 3[e] | 4-$ClC_6H_4CHO$ **1c** | **8c**[d] | (*R*)-**4** | 59 | 72 |
| 4[e] | 3-$BrC_6H_4CHO$ **1d** | **8d**[d] | (*S*)-**4** | 47 | 78 |
| 5 |  **1e** | **3e** | (*R*)-**4** | 72 | 79 |
| 6 |  **1f** | **3f** | (*S*)-**5** | 68 | 53 |
| 7[e] |  **1g** | **3g** | (*S*)-**4** | 80 | 86 |
| 8[e] | *n*-$C_3H_7CHO$ **1h** | **3h** | (*R*)-**4** | 82 | 57 |

[a] 20 mol % of the catalyst $Zr(O^tBu)_4$−ligand (1: 2.2) was applied in all cases. [b] Refer to the isolated yield after separation by silica gel. [c] ee's were determined by chiral HPLC; Chiracel OJ; hexane/2-propanol. [d] The crude $\beta$-hydroxyl product was acylated directly. [e] 1.5 equiv of $MgBr_2$ was added.

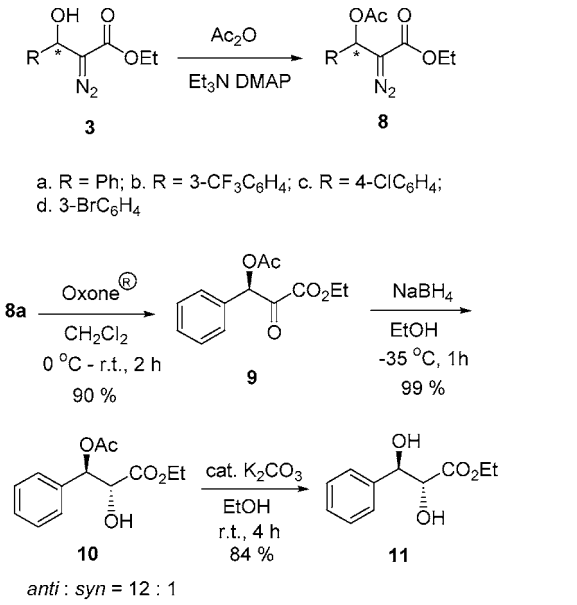
to the reaction, which was expected to bind the product.[10] Adding $MgBr_2$ could indeed enhance the reaction rate, thus allowing the condensation with these substrates to occur at lower temperature. With this modification, moderately high

**Scheme 2**




enantioselectivity could be achieved in general, as shown by the data collected in Table 2. The aromatic aldehydes with electron-withdrawing substituents generally gave moderate yields and enantioselectivities; however, the aromatic aldehyde with an electron-donating group, such as *p*-methoxybenzaldehyde, was a poor substrate in terms of reactivity under this condition. On the other hand, heterocyclic aldehydes worked well in this reaction. It is also worthwhile to note that similar enantioselectivity could be achieved with an aliphatic aldehyde (Table 2, entry 8). For the aldehydes **1b**, **1c**, and **1d**, the $\beta$-hydroxy product could not be separated in a chiral column. The products were converted to $\beta$-acetoxy compounds, which could be separated by chiral OJ column (Scheme 3).

**Scheme 3**




An assumed mechanism of this enantioselective condensation is outlined in Scheme 2. Although it is known that zirconium(IV) alkoxide can function as base to promote aldol condensation,[11] we propose that the Zr(IV) catalyst in the current reaction functions primarily as a Lewis acid to activate the aldehyde. Experimentally, we conformed that in the absence of chiral ligand, the condensation did not occur with 20 mol % of $Zr(O^tBu)_4$ at room temperature. The catalyst ligand may bring the ethyl diazoacetate in close proximity to the aldehyde and further assist the deprotonation of ethyl diazoacetate through hydrogen bonding (Scheme 2).

The chiral $\beta$-substituted α-diazo carbonyl compounds thus obtained could be transformed to some synthetically useful compounds.[12] For example, the diazo group can be trans-

(10) $MgBr_2$ has been shown to efficiently bind to $\beta$-hydroxyl esters. See: Bouzide, A. *Org. Lett.* **2002**, *4*, 1347.

(11) For example, $Zr(O\text{-}n\text{-}Pr)_4$ is reported to catalyze intramolecular Michael−Aldol reaction; see: Attah-Poku, S. K.; Chau, F.; Yadav, V. K.; Fallis, A. G. *J. Org. Chem.* **1985**, *50*, 3418.

(12) For comprehensive reviews on the chemistry of α-diazo carbonyl compounds, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998. (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *44*, 1091.

formed to an oxo group by direct oxidation with Oxone. The $\beta$-keto ester **9** was further converted to *anti* $\alpha,\beta$-dihydroxy ester **10** by stereoselective reduction with $NaBH_4$ following deacylation under basic condition with catalytic potassium carbonate.[13]

In conclusion, we have conducted for the first time the application of ethyl diazoacetate as nucleophile in a direct catalytic asymmetric aldol-type reaction and demonstrated that moderately high enantioselectivity could be achieved. Since the diazo group could be subjected to diverse transformations, there is a possibility that this reaction may be developed into a synthetically useful process, although further work is needed to improve both the chemical yield and the enantioselectivity.

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**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.

OL0343257

(13) Desai, S. B.; Argade, N. P.; Ganesh, K. N. *J. Org. Chem.* **1996**, *61*, 6730.