# *Communications to the Editor*

## Asymmetric Aldol Reaction via a Dinuclear Zinc Catalyst: α-Hydroxyketones as Donors

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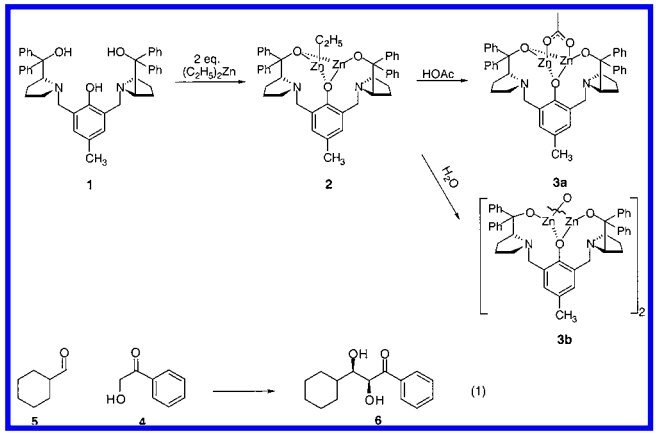
The ability to control the stereoselectivity of the directed aldol condensation has raised this process to prominence in the synthesis of complex molecular targets shared by few reactions.[1] However, these reactions almost invariably require preactivation of the nucleophilic or donor partner. α-Hydroxyketone donors are particularly interesting because of the utility of the polyoxygenated products, yet represent one of the most troublesome donors because of chemoselectivity issues. Only recently have several reports addressed the simple aldol addition involving both chemo- and enantioselectivity using both biological-type (e.g., catalytic antibodies)[2] and nonbiological-type[3,4] catalysis and, in some cases, included α-hydroxyacetone and related derivatives.[2,4b] In these cases, significant excesses of the donor must be employed. We recently reported the development of a new type of asymmetric catalyst which we postulated involves a dinuclear zinc complex.[5] In this paper, we communicate the effectiveness of this catalyst with α-hydroxyketones that permits *use of nearly stoichiometric amounts of both partners in the asymmetric aldol reaction* and the surprising effect of the donor on facial selectivity with respect to the aldehyde.

The catalyst is prepared by reacting the phenol **1** with diethylzinc in THF as in eq 1. Exposure of the complex to acetic acid in the inlet of an electrospray mass spectrometer shows a series of peaks between *m*/*e* 823−833 consistent with the formula $C_{45}H_{47}N_2O_5Zn_2$ that corresponds to the M + $H^+$ peak of **3a**. The combination of these data with our earlier observation regarding the 2:1 stoichiometry of diethylzinc to ligand provides good support for the proposed structures.[6] At the same time, higher aggregates can also form. Thus, direct examination of the catalyst without exposure to acetic acid showed a series of peaks in the electrospray mass spectrometer between 1543 and 1567 consistent with formula $C_{86}H_{87}N_4O_7Zn_4$ that corresponds to the M + $H^+$ peak of the oxo-bridged dimer **3b**. This dimer likely derives from reaction of **2** with trace amounts of adventitious water. Indeed, deliberate addition of trace amounts of water does not adversely affect the selectivity.

Adding a mixture of 1.5 equiv of hydroxyacetophenone (**4**) and 1.0 equiv cyclohexanecarboxaldehyde (**5**) to 5 mol % of the catalyst **2** in THF in the presence of 4 Å MS and $Ph_3PS$ at room temperature, a catalyst system optimized for acetophenone,[5] gave a high yield of the desired aldol product with good diastereoselectivity favoring the syn adduct **6**[7] (eq 1 and Table 1, entry 1).




Disappointingly, the ee was only 30%. However, temperature had a strong effect; as the temperature was lowered to −35°, the ee progressively increased to 90% (Table 1, entries 2−5). Remarkably, the dr was invariant with respect to temperature. Removing $Ph_3PS$ at −35° led to the same result (Table 1, entry 6), that is, no enhancement in conversion in contrast to the opposite observation in the case of acetophenone. Further lowering the temperature to −55° saw a drop in conversion and consequently in yield, but a small increase in ee (Table 1, entry 7). Remarkably, lowering the catalyst loading to 2.5 mol % showed a significant increase in diastereoselectivity with just a modest loss in yield. The conditions of entries 6 and 8 were adopted for further reactions as a compromise between rate/yield and ee. The relative and absolute stereochemistry of the major diastereomer was established by comparison to the product derived from an asymmetric dihydroxylation.[8] Strikingly, the absolute configura-

(1) For the general review on enantioselective Mukaiyama aldol reactions, see: Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, p 998; Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095; Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137; Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357; Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417. Also see: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(2) (a) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352; Takayama, S.; McGarvey, G. J.; Wong, C. H. *Chem. Soc. Rev.* **1997**, *26*, 407; Rasor, J. P. *Chim. Oggi.* **1995**, *13*, 9; Barbas, C. F., III; Heine, A.; Zhong, G.; Hoffmann, T.; Gramatikova, S.; Björnestedt, R.; List, B.; Anderson, J.; Stura, E. A.; Wilson, E. A.; Lerner, R. A. *Science* **1997**, *278*, 2085. Also see: Kajimoto, T. *Yakugaku Zasshi* **2000**, *120*, 42; *Chem. Abstr.* **2000**, *132*, 194551; Hiratake, J.; Oda, J. *Yuki Gosei Kagaku Kyokaishi* **1997**, *55*, 452; *Chem. Abstr.* **1997**, *127*, 17218. (b) Also see: Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768.

(3) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871; Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561; Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168; For a review, see: Shibasaki, M., Sasai, H. *Top. Stereochem.* **1999**, *22*, 201.

(4) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (c) For an intramolecular variant differentiating prochiral carbonyl groups, see: Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615; Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, 358.

(5) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.

(6) For other dinuclear zinc complexes, see: Sakiyama, H.; Mochizuki, R.; Sugawara, A.; Sakamoto, M.; Nishida, Y.; Yamasaki, M. *J. Chem. Soc., Dalton Trans.* **1999**, 997. For other zinc complexes derived from 2,6-di-(dialkylaminomethyl)-*p*-cresol, see: Uhlenbrock, S.; Wegner, R.; Krebs, B. *J. Chem. Soc., Dalton Trans.* **1996**, 3731. For bis-ligated dinuclear zinc complexes, see: Fahrni, C. J.; Pfaltz, A.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1998**, *81*, 507.

(7) This compound has been satisfactorily characterized spectroscopically and elemental composition established.

(8) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1995**, *34*, 1059. For a review, see: Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. The *syn* and *anti* diols for entries 2 and 5 are also known, see: Miyoshi, N.; Fukuma, T.; Wada, M. *Chem. Lett.* **1995**, 999 and referencess therein. Clerici, A. Porta, O. *J. Org. Chem.* **1989**, *54*, 3872; Mukaiyama, T.; Yamaguchi, M. *Chem. Lett.* **1982**, 509.

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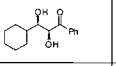
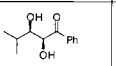
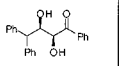
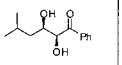
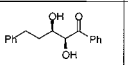
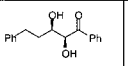
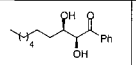
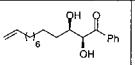
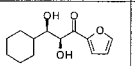
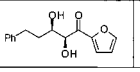
**Table 1.** Optimization of Aldol Reaction of Hydroxyacetophenone[a]

| entry | mol % catalyst | 15 mol % $Ph_3PS$ | temp °C | time (h) | isolated yield (%) | dr | ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | 5.0 | yes | r.t. | 48 | >90 | 5:1 | 30 |
| 2 | 5.0 | yes | 5 | 15 | 82 | 5:1 | 45 |
| 3 | 5.0 | yes | −5 | 48 | >90 | 5:1 | 76 |
| 4 | 5.0 | yes | −25 | 48 | >90 | 5:1 | 88 |
| 5 | 5.0 | yes | −35 | 24 | 94 | 5:1 | 90 |
| 6 | 5.0 | no | −35 | 24 | 97 | 5:1 | 90 |
| 7 | 5.0 | no | −55 | 48 | 77 | 5:1 | 93 |
| 8 | 2.50 | no | −40 | 24 | 83 | 30:1 | 92 |

[a] All reactions were run on 0.5 mmol scale at 0.3 M in aldehyde in the presence of 100 mg of 4 Å MS. [b] Enantiomeric excess determined by chiral HPLC using chiralcel OD column.

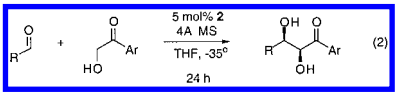
**Table 2.** Asymmetric Aldol Reaction[a]

| entry | R | Ar | Major Product[b] | isolated yield (%) | dr[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | a, b[e] | Ph |  | 83<br>97 | 30:1<br>5:1 | 92<br>90 |
| 2a<br>b[e]<br>c[e,f] | | Ph |  | 89<br>93<br>72 | 13:1<br>5:1<br>6:1 | 93<br>86<br>93 |
| 3a<br>b[e] | Ph, Ph | Ph |  | 74<br>97 | ONLY ONE<br>13:1 | 96<br>81 |
| 4a<br>b[e]<br>c[e,f] | | Ph |  | 65<br>96<br>79 | 35:1<br>3:1<br>4:1 | 94<br>88<br>93 |
| 5a<br>b[e] | Ph | Ph |  | 78<br>98 | 9:1<br>3:1 | 91<br>90 |
| 6[e,g] | Ph | Ph |  | 62 | 3.5:1 | 96 |
| 7[e] | | Ph |  | 89 | 5:1 | 86 |
| 8[e] | | Ph |  | 91 | 5:1 | 87 |
| 9a[e,h]<br>b[e,f] | | |  | 90<br>77 | 6:1<br>6:1 | 96<br>98 |
| 10[e,h] | Ph | |  | 97 | 3.4:1 | 95 |

[a] All reactions as in eq 3 using a 1.5:1.0 ratio of hydroxyketone to aldehyde using 2.5 mol % catalyst unless noted otherwise. [b] See ref 7. [c] Determined by $^1$H NMR spectroscopy on the crude mixture. [d] Determined by chiral HPLC on a Chiracel OD or OJ column. [e] For this run, 5.0 mol % catalyst was employed. [f] Reactions performed using a 1.1:1.0 ratio of hydroxyketone to aldehyde. [g] Reaction performed at −55 °C. [h] Reactions performed using 1.3:1.0 ratio of hydroxyketone to aldehyde.

tion of the stereocenter derived from the aldehyde is opposite to that obtained using acetophenone as donor.[5]

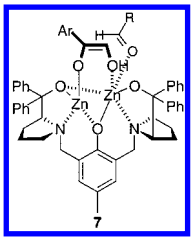
Table 2 and eq 2 summarize the results for a number of




examples. Increasing the size of the α-substituents increases the dr (entry 3). Moving the branch point (entries 4 and 5) or removing it (entries 7 and 8) had no effect on the reaction. Frequently, yields and selectivities plummet with substrates such as those in entries 6−8.[3,4a,b] As noted previously, lowering the temperature for dihydrocinnamaldehyde from −35° (entry 5) to −55° (entry 6) saw an increase in ee from 90% to 96% albeit at the expense of conversion.

Switching hydroxyacetophenone to 2-hydroxyacetylfuran gave excellent results (entries 9 and 10). In these cases, the ratio of substrates was decreased to 1.3:1 with no deleterious effect on conversion or chemoselectivity. While the diastereoselectivity was similar to that of hydroxyacetophenone, a significant increase in ee was observed (entries 1 and 5 vs 9 and 10). The success of a ratio of ketone to aldehyde of only 1.3:1.0 led to our exploration of a further reduction. As shown in entry 2b versus 2c, dropping this ratio to 1.1:1.0 decreased the conversion, resulting in a lower isolated yield of aldol adduct. Nevertheless, both the diastereoselectivity and enantioselectivity increased. A similar trend was observed with 3-methylbutanal (entry 4). This new set of conditions gave the highest ee observed, 98%, in entry 9b. In all cases examined (entries 1−5), dropping the catalyst loading from 5 to 2.5 mol % increased diastereoselectivity and, in some cases (entries 2−4), ee significantly.

The catalyst system reported herein comes closest in reaching the ideal atom economical version of the asymmetric aldol condensation, that is, the ideal being stoichiometric amounts of both reactants and anything else needed only catalytically. Excellent conversion and chemoselectivity was observed with ratios as low as 1.1:1.0 even with simple aldehydes such as dihydrocinnamaldehyde. As pointed out by others,[4b] an advantage of such an asymmetric aldol condensation over the asymmetric dihydroxylation is the formation of both stereocenters simultaneous with carbon−carbon bond formation. Further, chemoselectivity issues may arise in the AD reaction with substrates such as that of Table 2, entry 8. On the basis of our proposed model, it is reasonable to assume that the enolate of the α-hydroxyketone serves as a bidentate ligand bridging the two zincs as depicted in **7** based upon the manner in which carboxylates bridge some



**7**

related dinuclear zinc complexes.[6] Coordination of the aldehyde as shown then delivers the major observed product. The picture that emerges nicely accommodates the unexpected change in facial selectivity with respect to the aldehyde. The enhanced selectivity as a result of lowering the catalyst loading may speak to a role of dimeric type species such as **3b** as well as the monomer with the latter giving higher selectivities.

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**Supporting Information Available:** Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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