Direct Catalytic Asymmetric Aldol Reaction: Synthesis of Either *syn*- or *anti*-α,*β*-Dihydroxy Ketones

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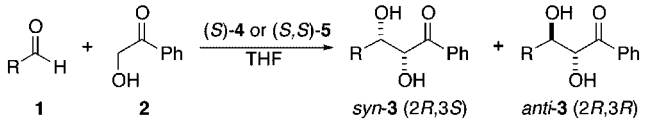
The development of a range of catalytic asymmetric aldol reactions has proven to be a valuable contribution to asymmetric synthesis.[1] In all of these catalytic asymmetric aldol reactions, however, preconversion of the ketone moiety to a more reactive species such as an enol silyl ether and ketene silyl acetal is an unavoidable necessity. Thus, the development of a direct catalytic asymmetric aldol reaction is highly desirable in terms of atom economy.[2] In 1997, we achieved success in carrying out the direct catalytic asymmetric aldol reactions of aldehydes with unmodified ketones using heterobimetallic asymmetric catalysis.[3] List et al.[4] and Trost et al.[5] also reported direct asymmetric aldol reactions using L-proline or a chiral semi-crown Zn complex as a catalyst. In this communication we report the synthesis of either *syn*- or *anti*-α,*β*-dihydroxy ketones in a highly enantioselective manner using two types of bimetallic asymmetric catalysis (Scheme 1).

Scheme 1. General Scheme for the Direct Catalytic Asymmetric Aldol Reaction of 2-Hydroxyacetophenone and Aldehydes



The fact that the 1,2-diol unit occurs in many natural products, for example, carbohydrates and alkaloids, and that 1,2-diols are very important as ligands in asymmetric synthesis makes the demand for the asymmetric synthesis of these compounds even bigger. Due to the impressive work of Sharpless on the asymmetric dihydroxylation (AD) of (*E*)-olefins, the synthesis of *syn*-1,2-diols can be accomplished easily.[6a] However, (*Z*)-olefins leading to *anti*-1,2-diols show low enantioselectivities in the AD.[6b] Recently List et al. reported the first catalytic asymmetric synthesis of *anti*-1,2-diols using hydroxyacetone in the aldol reaction, giving rise to products in high enantiomeric excesses and high diastereomeric ratios.[7−9] However, except for 3,3-dimethylbutanal, no example for normal primary aldehydes has been reported. Therefore, we planned to develop a general direct catalytic asymmetric aldol reaction of primary aldehydes, leading to *anti*-α,*β*-dihydroxy ketones in a highly enantioselective manner.

On the basis of our previous results we started to investigate the aldol reaction of 2-hydroxyacetophenone (**2**, 2 equiv) and 4-phenylbutanal (**1a**) using heterobimetallic asymmetric catalysts. After the screening of many catalysts and reaction conditions, we were pleased to find that the corresponding aldol product (**3a**) could be obtained in 87% yield in a ratio of 5 (*anti*, 95% ee) to 1 (*syn*, 74% ee) using 10 mol % of **4** (Figure 1) prepared from $LaLi_3$tris((*S*)-binaphthoxide) ((*S*)-LLB)[3a,b] (10 mol %), KHMDS (9 mol %) and H_2O (20 mol %) (entry 1, Table 1).[10,11] Moreover,

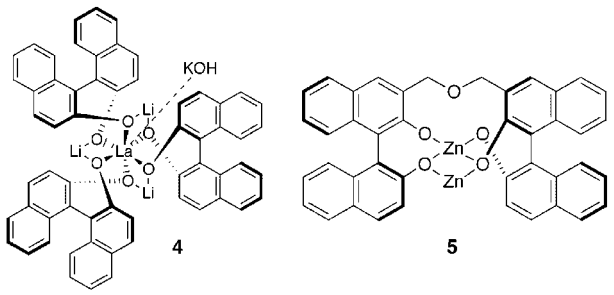


Figure 1. Structure of (*S*)-heterobimetallic catalyst **4** and the proposed structure of (*S,S*)-Zn−Zn-linked-BINOL complex **5**.

Table 1. Aldol Reaction Using Heterobimetallic Catalyst **4**[a]

entry	R	product	catalyst (mol %)	time (h)	yield[b] (%)	dr[c] (*anti*:*syn*)	ee[d] (*anti*/*syn*)
1	Ph (**1a**)	**3a**	10	24	87 (84)	5:1	95 / 74
2[e]	**1a**	**3a**	5	40	78 (78)	4:1	92 / 70
3	(**1b**)	**3b**	10	24	90 (84)	3:1	94 / 84
4	(**1c**)	**3c**	10	28	92 (90)	3:1	94 / 83
5	(**1d**)	**3d**	10	24	92 (86)	2:1	90 / 83
6	Ph (**1e**)	**3e**	10	24	89 (89)	2:1	95 / 87

[a] All reactions were carried out at −50 °C. [b] The yield was determined by ^{1}H NMR of the crude reaction mixture with anisole as an internal standard. The isolated yields after conversion to acetonides are given in parentheses. [c] The dr was determined by ^{1}H NMR of the crude reaction mixture. [d] The ee was determined after conversion to the corresponding acetonide. See Supporting Information. [e] The reaction was carried out at −40 °C.

(1) For a general review on the enantioselective aldol reaction, see: (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, Chapter 29.1. See also: (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374. (c) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137−1141. (d) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357−389.

(2) For a general discussion of atom economy in organic synthesis, see: (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.

(3) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871−1873. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168−4178. (c) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561−5564. For a partially successful attempt, see: (d) Nakagawa, M.; Nakao, H.; Watanabe, K.-I. *Chem. Lett.* **1985**, 391−394.

(4) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.

(5) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003−12004.

(6) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568−7570.

(7) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386−7387.

(8) For the catalytic asymmetric synthesis of *syn*-1,2-diols by Mukaiyama aldol reactions, see: Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, 911−913.

(9) For the synthesis of *syn*- or *anti*-1,2-diols by aldolases or catalytic antibodies, see: (a) Bednarski, M. D.; Simon, E. S.; Bischofberger, N.; Fessner, W.-D.; Kim, M.-J.; Lees, W.; Saito, T.; Waldmann, H.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 627−635. (b) Fessner, W.-D.; Sinerius, G.; Schneider, A.; Dreyer, M.; Schulz, G. E.; Badia, J.; Aguilar, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 555−558. (c) List, B.; Shabat, D.; Barbas, C. F., III.; Lerner, R. A. *Chem. Eur. J.* **1998**, *4*, 881−885. (d) 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*, 2768−2779.

(10) The use of LLB showed less satisfactory results in terms of reactivity and diastereoselectivity.

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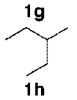
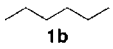
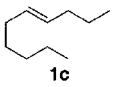
Table 2. Aldol Reaction Using Zn−Zn-linked-BINOL Complex **5**[a]

entry	R	product	catalyst (mol %)	time (h)	yield[b] (%)	dr[c] (*anti*:*syn*)	ee[d] (*anti*/*syn*)
1	 **1f**	**3f**	10	36	92	1:5	67 / 86[e]
2	 **1g**	**3g**	10	48	89	1:6	78 / 85[e]
3	 **1h**	**3h**	10	48	79	1:7	72 / 79
4	 **1b**	**3b**	10	60	80	1:2	73 / 77
5	 **1c**	**3c**	10	60	81	1:2	75 / 79
6	 **1d**	**3d**	10	36	80	1:2	79 / 83
7	 **1e**	**3e**	10	48	89	1:3	81 / 81

[a] All reactions were carried out at −40 °C. [b] Isolated yield after conversion to the corresponding acetonide. [c] The dr was determined by ^{1}H NMR. [d] The ee was determined after conversion to the corresponding acetonide. For full details see Supporting Information. [e] The ee was determined at the stage of the free diol.

as shown in Table 1, the reaction of **2** with a variety of aldehydes produced the corresponding *anti*-aldols stereoselectively in good yields and excellent ees, and even by the use of 5 mol % **4** the *anti*-aldol **3a** was obtained in a ratio of 4 (*anti*, 92% ee) to 1 (*syn*, 70% ee) (entry 2, Table 1).

Due to the instability of some *anti*-1,2-diols, we decided to determine the ee of the aldol products after conversion to the corresponding acetonides.[12,13] The relative and absolute configuration of the *syn*-isomers was revealed by conversion to the acetonides and comparison with authentic samples obtained after Sharpless AD followed by acetonide formation.[13] Determination of the relative and absolute configuration of the *anti*-isomers was performed after epimerization of the acetonides obtained from the *anti*-aldol products.[13] To the best of our knowledge, this is the first example of a general, *anti*-selective, direct catalytic asymmetric aldol reaction using primary aldehydes and 2-hydroxyacetophenone.

Unfortunately, secondary or tertiary aldehydes gave no satisfactory results, and therefore we turned our attention to the development of a new catalyst system. Using (*S*,*S*)-linked-BINOL[14] as a ligand of choice we first investigated various catalysts, for example, Ln-linked-BINOL[14a] (Ln = La, Gd or Yb) or Ln−Ln-linked-BINOL (Ln = La or Yb), but the results were not satisfactory. On the basis of the results obtained by Trost et al.[5] and in our group[14c] in bimetallic asymmetric catalysis, Zn metal was expected to be effective for the direct asymmetric aldol reaction, and after trying many catalysts, for example, Ln−Zn-linked-BINOL[14c] (Ln = La, Gd, Y or Yb) we found that the (*S*,*S*)-Zn−Zn-linked-BINOL complex **5** prepared from linked-BINOL and 2 equiv of Et_2Zn (see Figure 1) showed promising results. The structure of **5** is discussed in detail in the Supporting Information. Surprisingly, the *syn*-aldol **3f** was selectively obtained in a ratio of 5 (*syn*, 86% ee) to 1 (*anti*, 67% ee) on treatment of 2-methylpropanal (**1f**) with 2-hydroxyacetophenone (**2**, 2 equiv) in the presence of **5** (10 mol %) and triphenylphosphine oxide (20 mol %)[15] (entry 1, Table 2).[16] Moreover, as shown in Table 2, the reaction of **2** with a variety of aldehydes afforded the corresponding *syn*-aldols stereoselectively in good ees. It is noteworthy that the reaction of the aldehyde **1c** with a C−C double bond was efficiently promoted by **5** to give the *syn*-aldol product **3c** (entry 5, Table 2), which may be inaccessible by Sharpless AD due to a chemoselectiviy problem.[6a]

The observed stereoselectivities (see Scheme 1) can be understood by assuming the following mechanism. The formation of a chelate complex between catalyst (*S*)-**4** or (*S*,*S*)-**5** and the enolate generated from **2** can result in an efficient shielding of the *Si* face of the enolate from the attack of aldehydes. Thus, *anti*- and *syn*-product were obtained with an identical configuration at the α-position (2*R*) in good to excellent selectivities. This mechanism differs from that of direct asymmetric aldol reaction of acetophenone, in which the enantioface of the *aldehyde* is differentiated.[3a,b] On the other hand, the stereochemistry at the *β*-position can be effected by the enantioface selection of the aldehyde.[13]

In summary, we were able to synthesize either *syn*- or *anti*-1,2-diols using the heterobimetallic catalyst **4** or the newly developed (*S*,*S*)-Zn−Zn-linked-BINOL complex **5**. Although the diastereomeric ratios are not very high, these catalysts can be seen as a new tool to synthesize optically active 1,2-diols. Further investigations on the use of tertiary aldehydes and on the precise mechanism are currently ongoing.

Note Added in Proof. For the *syn*-selective direct catalytic asymmetric aldol reaction of 2-hydroxyacetophenone, see: Trost, B. M.; Oi, Shiuchi *J. Am. Chem. Soc.* **2001**, *123*, 1230−1231.

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Supporting Information Available: Spectral data of the acetonides, the detailed experimental procedure, a discussion about the stereoselectivities and the structural determination studies of **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) General procedure: To a solution of KHMDS in toluene (0.027 mmol, 0.5 M) at 0 °C, was added H_2O in THF (0.06 mmol, 1 M). After stirring for 15 min a solution of (*S*)-LLB in THF (0.03 mmol, 300 μL) was added, and the stirring was continued at 0 °C for 30 min. The resulting solution was cooled to −50 °C, and a solution of **2** (0.6 mmol in 2 mL THF) and **1a** (0.3 mmol) were added successively. The stirring was continued for 24 h at −50 °C and quenched by addition of 1 M HCl. The mixture was extracted with ether, and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of solvent gave a crude mixture of the aldol products.

(12) No change of ee and dr was observed during this conversion.

(13) See Supporting Information.

(14) For catalytic asymmetric syntheses using linked-BINOL as ligand, see: (a) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506−6507. (b) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252−2260. (c) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 8473−8478.

(15) For interesting effects of phosphine oxide, see: (a) Daikai, K.; Kamaura, M.; Inanaga, J. *Tetrahedron Lett.* **1998**, *39*, 7321−7322. (b) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* In press. (c) Yamasaki, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 1256−1257. The result in the absence of $Ph_3P(O)$: 48 h, y. 71%, *anti*:*syn* = 1:3, *anti* = 78% ee, *syn* = 73% ee.

(16) General procedure: To a stirred solution of (*S*,*S*)-linked-BINOL (0.03 mmol) in THF (0.3 mL) at −78 °C, was added Et_2Zn (60 μL, 0.06 mmol, 1.0 M in hexane). The resulting solution was stirred for 30 min at −20 °C before a solution of $Ph_3P(O)$ (0.06 mmol) in THF (0.1 mL) was added. The resulting mixture was stirred for 20 min at −20 °C, and a solution of **2** (0.6 mmol in 1.6 mL THF) was added. After the mixture was cooled to −40 °C, **1f** (0.3 mmol) was added, and the reaction mixture was stirred for 36 h. The reaction was worked up using the same procedure as described in ref 11.