Highly *anti*-Selective Catalytic Asymmetric Aldol Reactions

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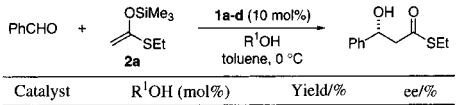
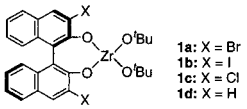
The Lewis acid-mediated aldol reactions of silyl enol ethers with aldehydes (Mukaiyama aldol reaction) provide one of the most convenient carbon−carbon bond-forming processes in organic synthesis.[1] Since the first catalytic asymmetric version of this reaction using chiral tin(II) Lewis acids appeared in 1990,[2] several efficient Lewis acid catalysts based on boron, titanium, copper, etc., have been reported.[3] While these highly selective reactions have been regarded as one of the most efficient reactions for the preparation of chiral *β*-hydroxy ketone and ester derivatives, temperatures of −20 to −78 °C and strict anhydrous conditions are required in most cases.[3−5] In addition, while several excellent *syn*-selective aldol reactions have been developed, few general highly *anti*-selective aldol reactions have been reported.[6] In this paper, we address these problems and report highly *anti*-selective catalytic asymmetric aldol reactions using a novel chiral zirconium catalyst.

Our catalyst shown here is based on a chiral zirconium complex. We have recently shown that catalytic asymmetric Mannich-type,[7] aza Diels−Alder,[8] and Strecker reactions[9] proceeded smoothly in the presence of chiral zirconium catalysts.[10] While the zirconium catalysts effectively activated aldimines in these reactions, it was expected that the catalyst would also activate aldehydes to create excellent asymmetric enivironments. After testing several zirconium catalysts in a model reaction of benzaldehyde with the silyl enol ether of (*S*)-ethyl ethanethioate, it was found that the chiral zirconium catalyst (**1a**) prepared from $Zr(O^tBu)_4$ and (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol ((*R*)-3,3′-BrBINOL)[7c,11] gave promising results. When the reaction was performed using 10 mol % of **1a** in toluene at 0 °C, the desired aldol adduct was obtained in 46% yield with 4% ee. Although the yield and the selectivity were less than satisfactory, an interesting finding was the formation of a monotrimethylsilylated BINOL derivative detected by thin-layer chromatography (TLC). At this stage, it was thought that the catalyst regeneration step (vide infra) was slow and that the monotrimethylsilylated BINOL derivative was detected when the reaction was quenched with water. To accelerate this step, we then decided to add a proton source to convert the monotrimethylsilylated BINOL derivative to a BINOL derivative. After testing several proton sources, it was found that the yield and the enantioselectivity were improved to 54 and 61%, respectively, by using propanol as the source.[12,13] We further tested chiral ligands (BINOL derivatives), and the desired aldol adduct was obtained in 81% yield with 92% ee when (*R*)-3,3′-diiodo-1,1′-bi-2-naphthol ((*R*)-3,3′-IBINOL)[11] was used as the chiral ligand. The amounts and the kinds of alcohols also influenced the yield and the selectivity (Table 1), and it is noted that lower yield and selectivity were obtained when 2-methyl-2-propanol (^{t}BuOH) was used.

Table 1. Effect of Catalysts and Alcohols



Catalyst	R^1OH (mol%)	Yield/%	ee/%
1a	—	46	4
1a	PrOH (50)	54	61
1b	PrOH (50)	81	92
1c	PrOH (50)	48	35
1d	PrOH (50)	72	57
1b	PrOH (20)	78	89
1b	PrOH (100)	85	91
1b	^{i}PrOH (50)	66	77
1b	BuOH (50)	78	86
1b	^{t}BuOH (50)	31	30



We then tested other examples of aldehydes and silyl enolates, and the results are summarized in Table 2.[14] Aromatic aldehydes as well as α,*β*-unsaturated and aliphatic aldehydes reacted with silyl enolates to afford the corresponding aldol adducts in high yields with high ees using **1b** as a catalyst. Only 2 mol % of **1b**

(1) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1012.

(2) (a) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455. (b) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247.

(3) *Review*: (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. 3, p 998. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (c) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. (d) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (e) Bach, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 417.

(4) (a) Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* **1999**, 71. (b) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1999**, *55*, 8739 and references therein.

(5) Some catalytic asymmetric aldol reactions were performed at higher temperatures (−20 to 23 °C): (a) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (b) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (c) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363. Catalytic asymmetric aldol reactions in wet dimethylformamide were reported: (d) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 2648.

(6) Masamune et al. reported *anti*-selective catalytic asymmetric aldol reactions; however, the enantioselectivities of the *anti*-adducts were 60−82% ees. (a) Parmee, E. R.; Hong, Y.; Tempkin, O.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 1729. For other *anti*-selective catalytic asymmetric aldol reactions: (b) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077. (c) Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319. (d) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982. (e) Evans, D. A.; MacMillan, W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859. Although high selectivities are obtained in some of these reactions, substrates are limited in all cases.

(7) (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (b) Kobayashi, S.; Ueno, M.; Ishitani, H. *J. Am. Chem. Soc.* **1998**, *120*, 431. (c) Kobayashi, S.; Hasegawa, Y.; Ishitani, H. *Chem. Lett.* **1998**, 1131.

(8) (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979. (b) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220. (c) Kobayashi, S.; Kusakabe, K.; Ishitani, H. *Org. Lett.* **2000**, *2*, 1225.

(9) (a) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3186. (b) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762.

(10) For other examples of zirconium-based asymmetric catalysts: (a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. (b) Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897. (c) Yu, C.-M.; Yoon, S.-K.; Choi, H.-S.; Baek, K. *Chem. Commun.* **1997**, 763. (d) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262.

(11) Cox, P. J.; Wong, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253.

(12) The aldol adduct was obtained as a free alcohol form mainly, while products were obtained as silylated forms in previous reports on catalytic asymmetric aldol reactions of silyl enolates.

(13) Katsuki et al. reported a fluorinated alcohol accelerated catalytic asymmetric Michael reactions: (a) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568. See also: (b) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595. It should be noted in our case that an alcohol not only accelerates the catalyst regeneration step but also blocks an undesired achiral side reaction. See ref 4.

(14) While the diastereoselectivities were determined by ^{1}H NMR analyses, the enantiomeric excesses were determined using chiral HPLC analyses. The absolute configuration assignments were made by comparison with the authentic samples.[2b]

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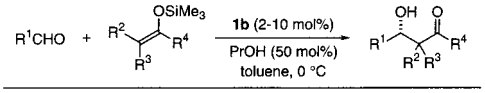
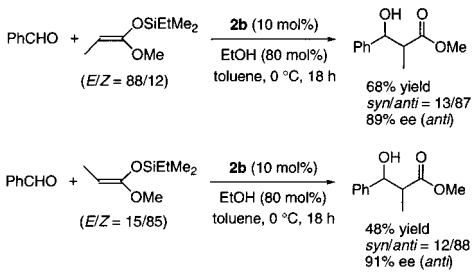
Table 2. Catalytic Asymmetric Aldol Recations Using **1b**[a]



Aldehyde	Silyl Enolate	Yield/%	*syn*/*anti*	ee/%
PhCHO	OSiMe$_3$ SEt (**2a**)	81	—	92
PhCHO	OSiMe$_3$ OMe (**2b**)	89	—	97
		87	—	94[b]
		93	—	89[c]
p-MeOPhCHO	**2b**	90	—	93
CHO	**2b**	74	—	90[d]
Ph(CH$_2$)$_2$CHO	**2a**	69	—	81[e]
PhCHO	OSiMe$_3$ OMe	61	8/92	93[f]
PhCHO	OSiMe$_3$ OPh (**2c**)	98	5/95	99[f]
p-MeOPhCHO	**2c**	70	7/93	95[g]
p-ClPhCHO	**2c**	85	7/93	95[f]
Ph CHO	**2c**	90	14/86	96[f]
Ph(CH$_2$)$_2$CHO	**2c**	38	12/88	85[g]
Ph(CH$_2$)$_2$CHO	**2c**	58	13/87	83[g,h]

[a] **1b** (10 mol%) was used unless otherwise noted. [b] 5 mol%. [c] 2 mol%. [d] BuOH (50 mol%) was used. Toluene−benzotrifluoride (3:2) was used as a solvent. [e] Room temperature. [f] EtOH (80 mol%). [g] PrOH (80 mol%). [h] 2 equiv of **2c** was used.

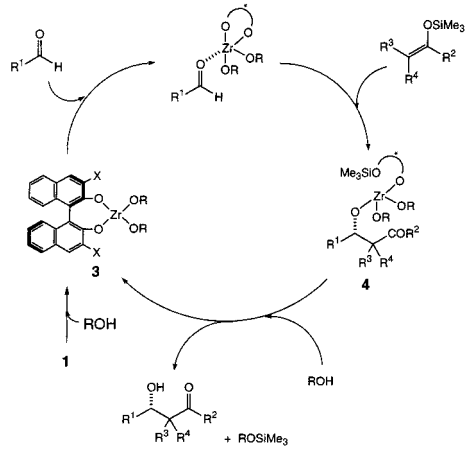
Scheme 1. Effect of Geometrical Isomers



catalyzed the reaction efficiently. It is noteworthy that high yields and selectivities were obtained even at 0 °C to room temperature in the presence of free alcohols, while most previous catalytic asymmetric aldol reactions required temperatures of −20 to −78 °C under strict anhydrous conditions.[5] Moreover, *anti*-aldol adducts were obtained in the reactions of silyl enolates of propionate derivatives with several aldehydes in high selectivities.[15,16] It was also confirmed that the selectivities were independent of the geometry of the silyl enolates. Namely, *anti*-selectivities were obtained using both (*E*)- and (*Z*)-silyl enolates (Scheme 1).[17] Although the precise transition state is not clear at this stage, we assume the acyclic transition state and the rather bulky zirconium catalyst may prefer the *anti*-selectivities.[18]

The assumed catalytic cycle of the present asymmetric aldol reaction is shown in Scheme 2. We postulate the true catalyst as (naphthalenediolato)-dialkoxyzirconium **3** which was suggested by ^{1}H and ^{13}C NMR analysis.[19] In addition, comparable results

Scheme 2. Assumed Catalytic Cycle



were obtained when the aldol reaction of benzaldehyde with **2** was carried out using the catalyst prepared from Zr(OPr)$_4$ and (*R*)-3,3′-IBINOL (72% yield, 84% ee, cf. Table 1, run 6). Catalyst **3** activates an aldehyde, and a silyl enolate attacks the aldehyde to form key intermediate **4**. When no alcohol is present, it is thought that the catalyst regeneration step (from **4** to **3**) would be slow, and when the reaction is quenched with water, **4** forms the monotrimethylsilylated BINOL derivative. On the other hand, **4** immediately reacts with an alcohol to regenerate the catalyst **3** along with formation of the aldol adduct and an alcohol trimethylsilyl ether. The formation of the trimethylsilyl ether was confirmed by GC−MS analysis.

A typical experimental procedure is described for the reaction of benzaldehyde with **2a**. To a suspension of (*R*)-3,3′-diiodo-1,1′-bi-2-naphthol (0.048 mmol) in toluene (1.0 mL) was added Zr(O^{t}Bu)$_4$ (0.04 mmol) in toluene (0.50 mL) at room temperature. The mixture was stirred for 0.5 h at the same temperature, and *n*-propanol (0.20 mmol) in toluene (1.0 mL) was added. The mixture was stirred for 0.5 h, and was then cooled to 0 °C. Toluene solutions (1.5 mL) of benzaldehyde (0.4 mmol) and **2a** (0.48 mmol) were successively added. The mixture was stirred for 18 h, and saturated NaHCO$_3$ was added to quench the reaction. The aqueous layer was extracted with dichloromethane, and the crude adduct was treated with THF−1 N HCl (20:1) at 0 °C for 1 h to hydrolyze a small amount of the silylated adduct. After usual workup, the crude product was chromatographed on silica gel to give the desired adduct. The optical purity was determined by HPLC analysis using a chiral column.[20]

In summary, we have developed *anti*-selective asymmetric aldol reactions that proceeded at 0 °C to room temperature under mild conditions with high yields and high diastereo- and enantioselectivities using a novel chiral zirconium catalyst in the presence of an alcohol additive. Use of the protic additive is key to facilitate catalyst turnover and is a unique feature of this reaction compared to other traditional catalytic asymmetric aldol reactions.

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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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(15) *syn*-Selective catalytic asymmetric aldol reactions were reported. Furuta, K.; Maruyama, T. Yamamoto, H. *Synlett* **1991**, 439.

(16) Bulky aliphatic aldehydes such as pivalaldehyde and isobutyraldehyde reacted with **2c** sluggishly. While α-benzyloxyaldehyde reacted with **2c** to afford the corresponding aldol adduct in a good yield (∼75%), lower selectivities were obtained (*syn*/*anti* = ∼1/4, *anti* = ∼50% ee). Investigations to improve these lower yields and selectivities are in progress.

(17) Evans et al. reported chiral tin(II)-catalyzed aldol-type reactions of pyruvate esters with silyl enolates.[6e] In these reactions, both (*E*)- and (*Z*)-silyl enolates gave *anti*-adducts.

(18) (a) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1985**, 447. (b) Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R.; *Tetrahedron* **1986**, *42*, 893.

(19) ^{1}H NMR (CD_2Cl_2) δ 6.75 (d, 2H, J = 8.2 Hz), 6.89 (d, 2H, J = 8.2 Hz), 7.02−7.10 (m, 4H), 7.21−7.25 (m, 4H), 7.72 (d, 2H, J = 8.2 Hz), 7.80−7.82 (m, 2H), 8.49 (s, 2H), 8.56 (s, 2H); ^{13}C NMR (CD_2Cl_2) δ 92.8, 95.0, 116.8, 119.0, 122.5, 123.1, 125.5, 125.6, 125.7, 126.0, 126.3, 126.8, 130.3, 130.4, 134.1, 134.2, 138.1, 139.4, 154.4, 156.1.

(20) Details are shown in Supporting Information.