Storable, powdered chiral zirconium complex for asymmetric aldol and hetero Diels–Alder reactions

Kazutaka Seki, Masaharu Ueno and Shū Kobayashi*

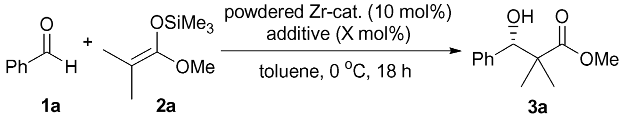
Received 30th January 2007, Accepted 22nd March 2007
First published as an Advance Article on the web 10th April 2007
DOI: 10.1039/b701466j

A storable, powdered chiral zirconium catalyst for asymmetric aldol and hetero Diels–Alder reactions has been developed. The catalyst has the same activity as that prepared *in situ* even after being stored for 3 months. Moreover, this chiral Zr catalyst worked efficiently not only for asymmetric aldol reactions but also for asymmetric hetero Diels–Alder reactions affording the corresponding addition products with high enantioselectivities.

Catalytic asymmetric carbon–carbon bond-forming reactions with chiral catalysts provide powerful tools for synthesis of optically active compounds.[1] While a wide variety of metal and non-metal based catalysts have been investigated for such transformations, these systems suffer from drawbacks associated with preparation and handling of the species concerned. In recent years, our group has focused on the development of chiral zirconium complexes prepared from zirconium alkoxide and chiral 1,1′-binaphthalene-2,2′-diol (BINOL) derivatives,[2] which were found to catalyze several asymmetric reactions such as Mannich reactions,[3] aza Diels–Alder reactions,[4] Strecker reactions,[5] allylation of imine,[6] Mukaiyama aldol reactions,[7] hetero Diels–Alder reactions,[8] [3 + 2] cycloaddition,[9] and others. These reactions proceeded smoothly to afford the desired products in high yields with high selectivities under mild conditions; however, the catalysts required preparation *in situ* under anhydrous conditions immediately prior to use due to the moisture sensitivity typical of most Lewis acids. In order to address these issues, we have developed air-stable, storable chiral zirconium catalysts stabilized on powdered molecular sieves (ZrMS) for Mannich reactions, aza Diels–Alder reactions, Mukaiyama aldol reactions, and hetero Diels–Alder reactions.[10] More recently, we have developed isolable, air-stable, storable, and highly selective chiral zirconium catalysts prepared from zirconium tetrakis-*tert*-butoxide ($Zr(Ot\text{-}Bu)_4$), 6,6′-bis(pentafluoroethyl)-1,1′-binaphthalene-2,2′-diol ($6,6'\text{-}(C_2F_5)_2$-BINOL), and *N*-methylimidazole which promote asymmetric Mannich reactions.[11] Remarkably, these catalysts can be stored for at least 6 months in air at room temperature, and recovered and reused after use in asymmetric Mannich reactions without significant loss of activity. Inspired by this we decided to investigate the applicability of this solid stabilized catalyst to other reactions. Herein we report storable, powdered chiral zirconium complexes for the promotion of asymmetric Mukaiyama aldol reactions and hetero Diels–Alder reactions.

The original catalyst for asymmetric Mukaiyama aldol reactions was prepared from $Zr(Ot\text{-}Bu)_4$, 3,3′-diiodo-1,1′-binaphthalene-2,2′-diol ($3,3'\text{-}I_2$-BINOL), *n*-propanol and water.[7,12] Accordingly, we first tried to prepare a solid-stabilized form of this catalyst using the same method as that to isolate the catalysts for asymmetric Mannich reactions. The catalyst so prepared was partially soluble in dry toluene after stirring for 3 h at room temperature, and following the addition of dry hexane it was precipitated as a slightly yellowish powder. After being stirred for 12 h, the solid was collected by filtration and dried. The activity of this powdered catalyst was tested in the aldol reaction of the benzaldehyde (**1a**) with the ketene silyl acetal (**2a**) derived from methyl isobutyrate. The reaction proceeded smoothly in the presence of 10 mol% of the isolated catalyst to afford the desired adduct in 96% yield with moderate enantioselectivity (Table 1, entry 1). In order to improve the enantioselectivity, we investigated the effect of varying the alcohol added to the reaction. In the presence of normal primary alcohols such as ethanol, *n*-propanol and *n*-butanol, the aldol product was obtained in high yields with high enantioselectivities (entries 3–7). However, in the cases of methanol or *n*-pentanol as an additive, the yield was decreased (entries 2 and 8). The use of a secondary alcohol also led to decreased yield and the selectivity fell slightly (entry 9). As the amount of alcohol was increased, the yield dropped slightly, although gratifyingly the enantioselectivity was increased (entries 4–6). The best results were obtained with 80 mol% of the alcohol (entry 4).

Table 1 Investigation of the effect of adding alcohols

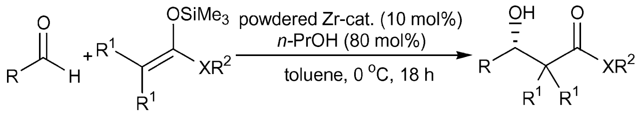


Entry	Additive (mol%)	Yield (%)	Ee (%)
1	—	96 (95)[a]	74 (98)[a]
2	MeOH (80)	11	87
3	EtOH (80)	96	96
4	*n*-PrOH (80)	95	98
5	*n*-PrOH (40)	99	91
6	*n*-PrOH (160)	90	98
7	*n*-BuOH (80)	96	97
8	*n*-Pentanol (80)	71	97
9	i-PrOH (80)	89	88

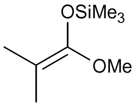
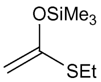
[a] Values in parentheses refer to a catalyst prepared from $Zr(Ot\text{-}Bu)_4$ (10 mol%), (*R*)-$3,3'\text{-}I_2$-BINOL (12 mol%), *n*-PrOH (80 mol%) and H_2O (20 mol%) *in situ*.

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan. E-mail: skobayas@mol.f.u-tokyo.ac.jp; Fax: +81 3 5684 0634; Tel: +81 3 5841 4790

Table 2 Asymmetric aldol reactions using the powdered zirconium catalyst



1a-f **2a,b** **3a-g**

Entry	Aldehyde	Silyl enolate	Product	Yield (%)[b]	Ee (%)[b]
1	Ph (**1a**)	 **2a**	**3a**	95 (95)	98 (98)
2	*p*-MeOC$_6$H$_4$ (**1b**)		**3b**	93 (92)	93 (96)
3	PhCH=CH (**1c**)		**3c**	97 (94)	95 (95)
4	CH$_3$CH=CH (**1d**)		**3d**	95 (76)	96 (97)
5	Ph (**1a**)	 **2b**	**3g**	93 (91)	86 (95)
6[a]	PhCH$_2$CH$_2$ (**1e**)		**3e**	92 (92)	78 (80)
7[a]	*n*-C$_5$H$_{11}$ (**1f**)		**3f**	87 (93)	79 (84)

[a] The aldehyde and silyl enolate were added at 0 °C to a stirred solution of the powdered Zr catalyst and *n*-PrOH at 60 °C over 1 h. [b] Yields in parentheses refer to reactions obtained using the *in situ* prepared catalyst.

We then turned our attention to the use of other substrates, and the results are summarized in Table 2. While aromatic aldehydes gave high yields and selectivities (entries 1–5), aliphatic aldehydes showed high yields and relatively lower selectivities (entries 6 and 7). It is noteworthy that this catalyst has almost the same activity as that of the catalyst prepared *in situ.*

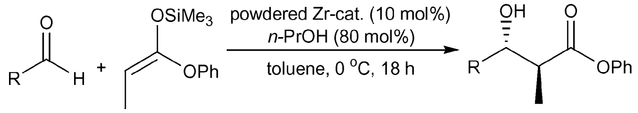
Next, our attention turned to the use of the catalyst in the promotion of diastereoselective aldol reactions (Table 3). We were gratified to find that in all cases the reactions proceeded smoothly to afford the desired *anti*-aldol adducts in high yields with high diastereo- and enantioselectivities.[13]

In the original chiral zirconium catalyst system, the combination of Zr(O*t*-Bu)$_4$, 3,3′-I$_2$-BINOL, *n*-propanol and water, was also effective for asymmetric hetero Diels–Alder reactions.[7,14] Therefore, we employed this isolated catalyst for the asymmetric hetero Diels–Alder reactions of aldehydes with Danishefsky's diene (Table 4). Pleasingly, in all cases the reactions proceeded smoothly to afford the desired products in high yields with high enantioselectivities.

Finally, we investigated the storage properties of the powdered catalyst.[15] Remarkably we found that this catalyst was stable under an argon atmosphere and that no significant loss of activity in the aldol reaction of benzaldehyde **1a** with ketene silyl acetal **2a** was observed after storage for 3 months (Table 5).

In conclusion, we have developed an isolable, storable and highly stereoselective chiral zirconium catalyst for asymmetric aldol reactions and hetero Diels–Alder reactions. This catalyst is readily prepared and handled, and can be stored for more than 3 months without significant loss of activity.

Table 3 Diastereoselective aldol reactions

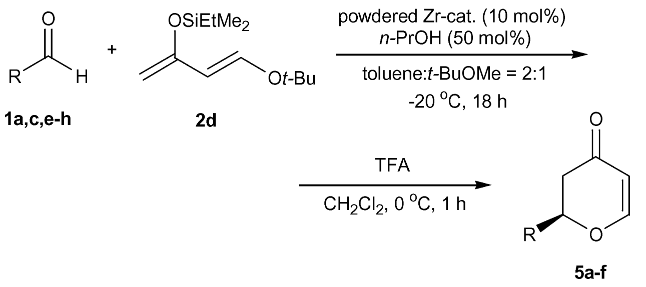


1a-e,g **2c** (E/Z = 95/5) **4a-f**

Entry	Aldehyde	Product	Yield (%)[a]	*syn–anti*[a,b]	Ee (%) [*anti*][a]
1	Ph (**1a**)	**4a**	Quant (94)	5 : 95 (5 : 95)	99 (99)
2	*p*-ClC$_6$H$_4$ (**1g**)	**4b**	Quant (96)	9 : 91 (9 : 91)	97 (96)
3	*p*-MeOC$_6$H$_4$ (**1b**)	**4c**	84 (89)	6 : 94 (7 : 93)	97 (98)
4	PhCH=CH (**1c**)	**4d**	96 (92)	17 : 83 (15 : 85)	99 (98)
5	CH$_3$CH=CH (**1d**)	**4e**	90 (65)	14 : 86 (11 : 89)	99 (92)
6	PhCH$_2$CH$_2$ (**1e**)	**4f**	63 (61)	18 : 82 (14 : 86)	80 (89)

[a] Yields in parentheses refer to reactions using the *in situ* prepared catalyst. [b] Determined by ^{1}H NMR analysis.

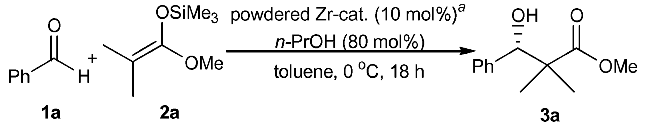
Table 4 Asymmetric hetero Diels–Alder reaction using the powdered zirconium catalyst



Entry	Aldehyde	Product	Yield (%)[b]	Ee (%)[b]
1	Ph (**1a**)	**5a**	96 (Quant)	95 (97)
2	*p*-ClC_6H_4 (**1g**)	**5b**	90 (90)	81 (84)
3	*p*-MeC_6H_4 (**1h**)	**5c**	92 (95)	91 (95)
4	PhCH=CH (**1c**)	**5d**	92 (97)	88 (90)
5	$PhCH_2CH_2$ (**1e**)	**5e**	94 (Quant)	88 (90)
6[a]	*n*-C_5H_{11} (**1f**)	**5f**	93 (98)	92 (93)

[a] 10 mol% $Sc(OTf)_3$ was used instead of TFA (rt, 12 h). [b] Yields in parentheses refer to reactions using the *in situ* prepared catalyst.

Table 5 Storage time and activity of the powdered zirconium catalyst



	Yield (%)	Ee (%)
Fresh	98	97
0.5 Month	96	97
1 Month	95	97
3 Month	96	94

[a] Stored under argon.

Preparation of powdered zirconium catalysts

All reactions were carried out under argon atmosphere in well-dried glassware. A solution of *n*-PrOH (8.0 mmol) in dry toluene (2 mL) and H_2O (2.0 mmol) was added to a dry toluene (2 mL) solution of (*R*)-3,3′-I_2-BINOL (1.2 mmol) and $Zr(Ot\text{-}Bu)_4$ (1.0 mmol) at room temperature. After the mixture was stirred for 3 h at the same temperature, dry *n*-hexane (100 mL) was added and a white precipitate formed. The suspended mixture was further stirred overnight. Filtration of the white suspension and washing with hexane in argon afforded a Zr catalyst as a white powder (535 mg).

Determination of the zirconium content in the powdered zirconium catalysts

The powdered Zr catalyst (15.0 mg) was placed in a 30 mL test tube, and sulfuric acid (1.0 mL) was added. The mixture was heated at 180 °C for 1 h, and then nitric acid (0.5 mL) was added. The mixture was further heated for 1 h to give a clear solution. The solution was diluted with water, and the amount of the Zr metal was measured by ICP analysis. Zr content: 1.093 mmol g^{-1}.

Typical experimental procedure for asymmetric aldol reactions using isolated powdered chiral zirconium catalysts

A solution of *n*-PrOH (0.32 mmol) in dry toluene (1.0 mL) was added to a suspension of powdered Zr catalyst (0.040 mmol) in dry toluene (1.0 mL), and the mixture was stirred for 30 min at room temperature. After cooling to 0 °C, the aldehyde (0.40 mmol) in toluene (0.75 mL) and the ketene silyl acetal (0.60 mmol) in toluene (0.75 mL) were successively added. The mixture was stirred for 18 h at 0 °C, and then saturated aqueous $NaHCO_3$ (5 mL) was added to quench the reaction. After addition of dichloromethane (10 mL), the organic layer was separated and the aqueous layer was extracted twice with dichloromethane (10 mL × 2). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the residue so obtained was treated with THF–1 N HCl (9 : 1, 10 mL) for 1 h at 0 °C. The solution was then basified with 5% $NaHCO_3$ (10 mL) and extracted with dichloromethane (10 mL × 2). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by preparative thin layer chromatography (benzene–ethyl acetate = 20 : 1) to afford the desired aldol adduct. The optical purity was determined by HPLC analysis using the appropriate chiral column. For some compounds, the optical purity was determined after acetylation or benzoylation of the hydroxy groups.[7]

(*S*)-Methyl-3-hydroxy-2,2-dimethyl-3-phenylpropanoate (3a). $[\alpha]_D^{25}$ +5.70 (*c* 2.49 in MeOH, 97% ee). ^1H NMR (600 MHz; solvent $CDCl_3$; standard Me_4Si (0 ppm)) δ 1.12 (s, 3H), 1.15 (s, 3H), 3.73 (s, 3H), 4.90 (s, 1H), 7.25–7.36 (m, 5H). ^{13}C NMR (600 MHz; solvent $CDCl_3$; standard $CDCl_3$ (77.0 ppm)) δ 19.0, 23.1, 47.6, 52.1, 78.7, 127.6, 127.8, 139.9, 178.2. HPLC (Daicel Chiralcel OJ, hexane–iPrOH = 9 : 1, flow rate = 0.5 mL min^{-1}): *t*R = 18.3 min (*S*), *t*R = 22.0 min (*R*). TLC R_f = 0.09 (hexane–ethyl acetate = 8 : 1).

Typical experimental procedure for asymmetric hetero Diels–Alder reactions using the isolated powdered chiral zirconium catalyst

n-PrOH (0.20 mmol) in dry toluene (0.8 mL) was added to a suspension of powdered Zr catalyst in dry toluene (0.5 mL), which was then stirred for 30 min at room temperature. After cooling to −78 °C, the aldehyde (0.40 mmol) in *t*-BuOMe (0.35 mL) and the diene (0.48 mmol) in *t*-BuOMe (0.35 mL) were successively added. The mixture was warmed to −20 °C and stirred for 18 h before saturated aqueous $NaHCO_3$ (10 mL) was added to quench the reaction. After addition of dichloromethane (10 mL), the organic layer was separated and the aqueous layer was extracted twice with dichloromethane (10 mL × 2). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the residue was treated with trifluoroacetic acid (TFA, 0.5 mL) in dichloromethane (8 mL) for 1 h at 0 °C. In the case of the reaction using cinnamaldehyde, scandium triflate ($Sc(OTf)_3$, 0.040 mmol, 10 mol% with respect to the aldehyde) in dichloromethane for 12 h at room temperature was used instead of TFA. After the solution was basified with saturated aqueous $NaHCO_3$ (20 mL), the organic layer was separated and the aqueous layer was extracted with dichloromethane (10 mL × 2). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by preparative thin layer chromatography (benzene–ethyl acetate = 20 : 1) to afford the desired product. The optical purity was determined by HPLC analysis using a chiral column.[8]

(*R*)-2-Phenyl-2,3-dihydro-4*H*-pyran-4-one (5a). $[\alpha]_D^{26}$ −97.1 (*c* 0.69 in $CHCl_3$, 97% ee). ^1H NMR (600 MHz; solvent $CDCl_3$; standard Me_4Si (0 ppm)) δ 2.66 (dd, 1H), 2.90 (dd, 1H), 5.42 (dd, 1H), 5.52 (d, 1H), 7.3–7.4 (m, 5H), 7.48 (d, 1H). ^{13}C NMR (600 MHz; solvent $CDCl_3$; standard $CDCl_3$ (77.0 ppm)) δ 43.3, 81.0, 107.3, 126.0, 128.8, 128.9, 137.8, 163.1, 192.1. HPLC (Daicel Chiralcel OD, hexane–iPrOH = 40 : 1, flow rate = 1.0 mL min^{-1}): tR = 25.1 min (S), tR = 30.1 min (R). TLC $R_f = 0.24$ (benzene–ethyl acetate = 20 : 1).

Acknowledgements

This work was partially supported by Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Sciences (JSPS).

References

1 Review: (*a*) *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley-VCH, New York, 2nd edn, 2000; (*b*) *Lewis Acids in Organic Synthesis*, ed. H. Yamamoto, Wiley-VCH, Weinheim, Germany, 2000, vol. 1.

2 For other examples of zirconium-based asymmetric catalysts: (*a*) E.-I. Negishi, *Pure Appl. Chem.*, 2001, **73**, 239; (*b*) S. Huo, J.-C. Shi and E.-I. Negishi, *Angew. Chem., Int. Ed.*, 2002, **41**, 2141; (*c*) T. Okachi, N. Murai and M. Onaka, *Org. Lett.*, 2003, **5**, 85.

3 (*a*) H. Ishitani, M. Ueno and S. Kobayashi, *J. Am. Chem. Soc.*, 1997, **119**, 7153; (*b*) S. Kobayashi, M. Ueno and H. Ishitani, *J. Am. Chem. Soc.*, 1998, **120**, 431; (*c*) H. Ishitani, M. Ueno and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 8180; (*d*) Y. Ihori, Y. Yamashita, H. Ishitani and S. Kobayashi, *J. Am. Chem. Soc.*, 2005, **127**, 15528; (*e*) S. Kobayashi, Y. Hasegawa and H. Ishitani, *Chem. Lett.*, 1998, 1131; (*f*) H. Ishitani, T. Kitazawa and S. Kobayashi, *Tetrahedron Lett.*, 1999, **40**, 2161.

4 (*a*) S. Kobayashi, S. Komiyama and H. Ishitani, *Angew. Chem., Int. Ed.*, 1998, **37**, 979; (*b*) S. Kobayashi, K. Kusakabe, S. Komiyama and H. Ishitani, *J. Org. Chem.*, 1999, **64**, 4220; (*c*) S. Kobayashi, K. Kusakabe and H. Ishitani, *Org. Lett.*, 2000, **2**, 1225; (*d*) Y. Yamashita, Y. Mizuki and S. Kobayashi, *Tetrahedron Lett.*, 2005, **46**, 1803.

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

6 T. Gastner, H. Ishitani, R. Akiyama and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2001, **40**, 1896.

7 (*a*) H. Ishitani, Y. Yamashita, H. Shimizu and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 5403; (*b*) Y. Yamashita, H. Ishitani, H. Shimizu and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 3292.

8 (*a*) Y. Yamashita, S. Saito, H. Ishitani and S. Kobayashi, *Org. Lett.*, 2002, **4**, 1221; (*b*) Y. Yamashita, S. Saito, H. Ishitani and S. Kobayashi, *J. Am. Chem. Soc.*, 2003, **125**, 3793.

9 (*a*) S. Kobayashi, H. Shimizu, Y. Yamashita, H. Ishitani and J. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 13678; (*b*) Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 11279.

10 (*a*) M. Ueno, H. Ishitani and S. Kobayashi, *Org. Lett.*, 2002, **4**, 3395; (*b*) S. Kobayashi, S. Saito, M. Ueno and Y. Yamashita, *Chem. Commun.*, 2003, 2016; (*c*) S. Kobayashi, M. Ueno, S. Saito, Y. Mizuki, H. Ishitani and Y. Yamashita, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, **101**, 5476.

11 K. Saruhashi and S. Kobayashi, *J. Am. Chem. Soc.*, 2006, **128**, 11232.

12 Recent reviews of Mukaiyama aldol reactions: *Modern Aldol Reactions*, ed. R. Mahrwald, Wiley-VCH, Weinheim, Germany, 2004.

13 Recent examples of *anti*-selective aldol reactions: (*a*) N. Yoshikawa, T. Suzuki and M. Shibasaki, *J. Org. Chem.*, 2002, **67**, 2556; (*b*) S. E. Denmark and S. Fujimori, *Org. Lett.*, 2002, **4**, 3473; (*c*) T. Ooi, M. Taniguchi, K. Doda and K. Maruoka, *Adv. Synth. Catal.*, 2004, **346**, 1073; (*d*) S. Saito and S. Kobayashi, *J. Am. Chem. Soc.*, 2006, **128**, 8704.

14 Recent reports of catalytic asymmetric hetero Diels–Alder reactions: (*a*) P. M. Doyle, M. Valenzuela and P. Huang, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, **101**, 5391; (*b*) X. Zhang, H. Du, Z. Wang, Y.-D. Wu and K. Ding, *J. Org. Chem.*, 2006, **71**, 2862; (*c*) L. Lin, Q. Fan, B. Qin and X. Feng, *J. Org. Chem.*, 2006, **71**, 4141.

15 Other storable chiral catalysts: (*a*) Y. S. Kim, S. Matsunaga, J. Das, A. Sekine, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2000, **122**, 6506; (*b*) T. Hayano, T. Sakaguchi, H. Furuno, M. Ohba, H. Okaw and J. Inanaga, *Chem. Lett.*, 2003, **32**, 608.