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Air-Stable, Storable, and Highly Selective Chiral Lewis Acid Catalyst

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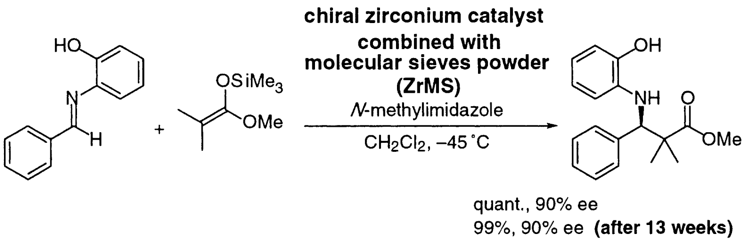
ABSTRACT



An air-stable, storable, and highly selective chiral Lewis acid catalyst for asymmetric Mannich-type reactions has been developed. The catalyst can be stored for more than three months in air at room temperature without loss of activity. Moreover, it has also been demonstrated that the catalyst can be recovered and reused.

Asymmetric synthesis with chiral catalysts has attracted much attention because large quantities of chiral molecules can be prepared from a small amount of a chiral source.[1] While several excellent chiral catalysts have been developed in oxidation and reduction, carbon−carbon bond-forming reactions, and other transformations, they are often unstable in air and/or in the presence of water. This is especially the case in chiral Lewis acid catalysis because most Lewis acids are air- and moisture-sensitive.[2] Therefore, many catalysts are prepared *in situ* in an appropriate solvent just before use, and they cannot be preserved for extended periods. In this paper, we describe an air-stable, storable, and highly selective chiral Lewis acid catalyst for asymmetric Mannich-type reactions.[3] The catalyst can be stored for more than three months in air at room temperature without loss of activity.[4]

The catalyst was prepared from Zr(O^{t}Bu)$_4$ (1 mmol), (*R*)-6,6′-bis(pentafluoroethyl)-1,1′-bi-2-naphthol[5] ((*R*)-6,6′-C$_2$F$_5$-BINOL, 2.0 mmol), *N*-methylimidazole (NMI, 4.0 mmol), and powdered MS 5A (6.0 g/mmol) in benzene at 80 °C for 2 h. After removal of the solvent under reduced pressure at 50 °C for 1 h, *a chiral zirconium catalyst with powdered molecular sieves* (*ZrMS*) was formed. ZrMS thus prepared was first tested in a model Mannich-type reaction of imine **1a** with ketene silyl acetal **2a**. While ZrMS was not effective in the absence of NMI, high yields and selectivities were obtained after adding NMI. The best result was obtained when 10 mol % of ZrMS was combined with 20 mol % of

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(1) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, Y., Eds.; Springer: Berlin, Germany, 1999; Vol. 1−3. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed; Wiley-VCH: New York, 2000.

(2) *Lewis Acid in Organic Synthesis*; Yamamoto, Y., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, p 2.

(3) Recent examples of catalytic enantioselective Mannich-type reactions: (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (c) Kobayashi, S.; Hasegawa, Y.; Ishitani, H. *Chem. Lett.* **1998**, 1131. (d) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180. (e) Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* **2001**, *57*, 861. (f) Kobayashi, S.; Kobayashi, J.; Ishitani, H.; Ueno, M. *Chem. Eur. J.* Submitted for publication. (g) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060. (h) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450. (i) Martin, S. F.; Lopez, O. D. *Tetrahedron Lett.* **1999**, *40*, 8949. (j) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. (k) Yamada, K-i.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504. (l) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (m) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III *J. Am. Chem. Soc.* **2002**, *124*, 1842. (n) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271. (o) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992. (p) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (q) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143. (r) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640.

(4) Shibasaki et al. reported a stable chiral La catalyst: Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506.

(5) (a) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292. (b) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobatyashi, S. *Org. Lett.* **2002**, *4*, 1221. See also ref 3f.

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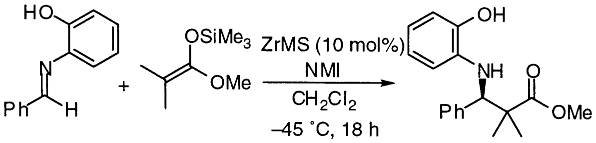
Table 1. Effect of NMI



1a + **2a** → **3a**

entry	NMI/mol %	yield/%	ee/%
1	0	quant.	5[a]
2	12	94	87
3	20	quant.	90
4	30	89	89

[a] Absolute configulation was *S*.

NMI (Table 1, entry 3). In addition, ZrMS was found to be remarkably stable to air and moisture: it was stable at least 13 weeks in air at room temperature (Table 2). It should be noted that a significant decrease of the yield and selectivity was observed when a similar zirconium catalyst, which was prepared from Zr(O^{t}Bu)$_4$, (*R*)-6,6′-C_2F_5BINOL, and NMI, was used after 1-day storage in air at room temperature, presumably due to decomposition of the catalyst.

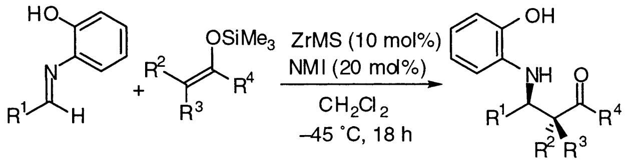
Table 2. ZrMS as a Storable Chiral Lewis Acid[a]

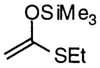
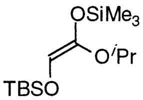
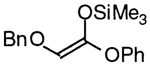
storage time/week	0	2	5	13
yield/%	quant.	quant.	98	99
ee/%	90	90	90	90

[a] The Mannich-type reaction of **1a** with **2a** was performed.

ZrMS was successfully applied to other Mannich-type reactions by using various substrates (Table 3). Imines derived from not only aromatic and heterocyclic but also aliphatic aldehydes reacted smoothly in the presence of a catalytic amount of ZrMS to afford the desired Mannich-type adducts in high yields with high enantiomeric excess. While the *syn*-adduct was obtained in the reaction of α-TBSO enolate **2c**, the *anti*-adduct was produced by using α-BnO enolate **2d**, both in high diastereo- and enantioselectivities. These yields and selectivities were almost comparable to those obtained with use of the chiral zirconium catalyst prepared *in situ* in dichloromethane under Ar atmosphere (Table 3, in parentheses).

Table 3. Catalytic Enantioselective Mannich-Type Reactions with ZrMS



entry	R^1	silicon enolate	yield/%(*syn*/*anti*)[e]	ee/%[e]
1	Ph (**1a**)	**2a**	quant. (quant.	90 89)
2	1-Naph (**1b**)	**2a**	79 (quant.	90 89)
3	(4-Cl)Ph (**1c**)	**2a**	96 (quant.	85 88)
4	Ph (**1a**)	 **2b**	89 (99	90 89)
5	1-Naph (**1b**)	**2b**	93 (quant.	90 88)
6	(4-Cl)Ph (**1c**)	**2b**	91 (98	94 94)
7	2-furyl (**1d**)	**2b**	92 (96	89 89)
8[a]	*i*-C_4H_9 (**1f**)	**2b**	60 (61	92 92)
9[b]	Ph (**1a**)	 **2c**[c]	92 (97/3) (80 (92/8)	96 90)
10	Ph (**1a**)	 **2d**[d]	70 (8/92) (74 (5/95)	89 93)

[a] The imine was prepared from isovaleraldehyde and 2-amino-*m*-cresol. [b] 1,2-Dimethylimidazole was used instead of NMI, and toluene was used as a solvent at −78 °C. [c] *E*/*Z* = >99/<1. [d] *E*/*Z* = <1/>99. [e] Yields and ee values of the Mannich reactions using the chiral zirconium catalyst prepared from Zr(O^{t}Bu)$_4$, (*R*)-6,6′-C_2F_5BINOL, and NMI in dichloromethane are shown in parentheses. Cf. ref 3d.

It is remarkable that easy treatment with powdered molecular sieves has enhanced the stability of the chiral Lewis acid significantly without loss of activity. We then performed NMR experiments to clarify the structure of ZrMS. First, ZrMS was treated with CD_2Cl_2 at room temperature for 30 min, and after filtration, ^{1}H and ^{13}C NMR spectra were measured (Figure 1a). The spectra were complicated, and an oligomeric structure of Zr was assumed, because a similar oligomeric structure was formed by the combination of Zr(O^{t}Bu)$_4$ and (*R*)-6,6′-C_2F_5BINOL (Figure 1b). This oligomeric catalyst was known to give low selectivity in the Mannich-type reaction. On the other hand, rather simple spectra were recorded when ZrMS was combined with NMI in CD_2Cl_2 at room temperature for 30 min (Figure 1c; after filtration). It should be noted that the spectra were similar to those of the chiral zirconium catalyst prepared from Zr(O^{t}Bu)$_4$, (*R*)-6,6′-C_2F_5BINOL, and NMI, which was an efficient catalyst for the Mannich-type reactions of imines with silicon enolates.[3a,c]

Other molecular sieves than MS 5A in ZrMS were also examined.[6] When powdered MS 3A was used in the reaction of **1a** with **2a**, high yield and enantiomeric excess (94% yield,

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(6) Effects of molecular sieves on reactivity and/or selectivity were reported. For example: (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. (c) Mikami, K.; Terada, M.; Matsumoto, Y.; Tanaka, M.; Nakamura, Y. *Microporous Mesoporous Mater.* **1998**, *21*, 461. (d) Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, 1581. (e) Motoyama, Y.; Okano, M.; Narusawa, H.; Mikihara, N.; Aoki, K.; Nishiyama, H. *Organometallics* **2001**, *20*, 1580. (f) Moharram, S. M.; Hirai, G.; Koyama, K.; Oguri, H.; Hirama, M. *Tetrahedron Lett.* **2000**, *41*, 6669. (g) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483. (h) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P.-P. *Tetrahedron Lett.* **1999**, *40*, 2001. (i) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3213.

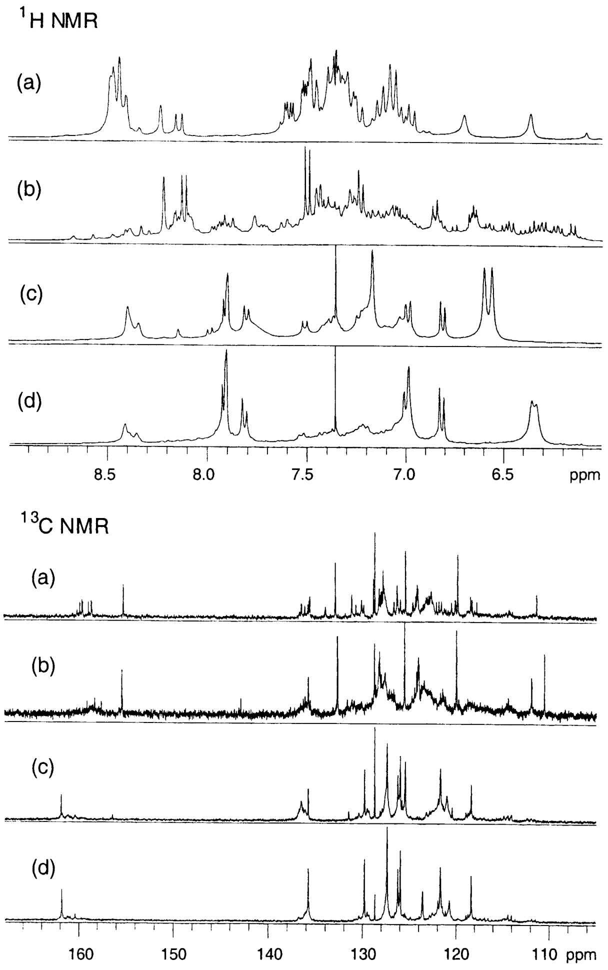

Figure 1. NMR experiments: (a) ZrMS in CD_2Cl_2, (b) $Zr(O^{t}Bu)_4$ and 2.0 equiv of 6,6′-$(C_2F_5)_2$-BINOL in CD_2Cl_2, (c) ZrMS and 2.0 equiv of NMI in CD_2Cl_2, and (d) chiral zirconium catalyst in CD_2Cl_2. See text.

88% ee) were obtained even in the absence of NMI. After 53 days, however, the selectivity decreased (96% yield, 67% ee). Although the selectivity was maintained after 53 days with powdered MS 4A (95% yield, 80% ee), the initial ee was lower (89% yield, 82% ee). On the other hand, when another ZrMS was prepared from $Zr(O^{t}Bu)_4$, (*R*)-3,3′-BrBINOL, and powdered MS 3A (without NMI) and was used in the reaction of **1a** with **2a**, the desired Mannich-type adduct was obtained in 80% yield with 97% ee. The yield and selectivity were maintained after 12 days (79% yield, 96% ee). It is noted that the idea of ZrMS was applied to other chiral zirconium catalyst systems.[7]

Finally, recovery and reuse of ZrMS were investigated. In the presence of ZrMS (10 mol %), imine **1a** was treated with ketene silyl acetal **2a** in dichloromethane at −45 °C. After 18 h, the reaction vessel was warmed to room temperature, and MS 5A was added. After all volatile solvents and materials were removed under reduced pressure (3 h), hexane was added and decantation was conducted three times. While the desired product was isolated from the hexane solution (89% yield, 92% ee), the residue was pumped up under reduced pressure for 3 h and was used for the 2nd run. Almost the same levels of yields and selectivities were obtained (2nd run: 94% yield, 91% ee; 3rd run: 99% yield, 90% ee), although a small amount of the Zr (ca. 5%) was leached for each run according to this procedure.[8]

In summary, we have developed an air-stable, storable, and highly selective chiral Lewis acid catalyst, which was successfully used in asymmetric Mannich-type reactions. Despite many trials to obtain air-stable and storable catalysts, the solution is so simple. It has been revealed that the easy treatment with powdered molecular sieves is the key to create this remarkable Lewis acid. To the best of our knowledge, this is the first example of the use of molecular sieves to stabilize an air- and moisture-sensitive catalyst.[9] The catalyst was stable for more than three months in air at room temperature without loss of activity. Furthermore, the catalyst was recovered and reused. It is noted that other Lewis acids may also be stabilized against air and moisture by using the same concept. Further investigations along this line are now in progress.

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Supporting Information Available: Experimental details and spectra data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[7] In our preliminary experiments, a similar chiral zirconium catalyst with powdered molecular sieves, which was stored for more than three months, efficiently catalyzed asymmetric aza Diels−Alder reactions without loss of activity. (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.

[8] Determined by fluorescence X-ray analysis. All details are shown in the Supporting Information.

[9] It was reported that $AlCl_3$ was protected with cross-linked polystyrene: Neckers, D. C.; Kooistra, D. A.; Green, G. W. *J. Am. Chem. Soc.* **1972**, *94*, 9284. We tested cross-linked polystyrene instead of molecular sieves, but successful results were not obtained.