

Remarkably Stable Chiral Zirconium Complexes for Asymmetric Mannich-Type Reactions

Kowichiro Saruhashi and Shū Kobayashi*

Contribution from the Graduate School of Pharmaceutical Sciences, The University of Tokyo, The HFRE Division, ERATO, Japan Science Technology Agency (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received April 21, 2006; E-mail: skobayas@mol.f.u-tokyo.ac.jp

Abstract: Isolable, air-stable, storable, and highly selective chiral zirconium catalysts for asymmetric Mannich-type reactions have been developed. The reactions of imines with silicon enolates proceeded smoothly using 1–10 mol % of the powdered zirconium catalyst to afford the corresponding adducts in high yields with high stereoselectivities. The catalyst could be recovered and reused without significant loss of activity. On the other hand, zirconium single crystals for X-ray analysis were obtained, and the crystals also showed high performance in the asymmetric Mannich-type reactions. Although NMR analyses of these zirconium catalysts showed different structures in dichloromethane, the formation of the same key intermediate from the different catalysts was indicated.

Development of chiral Lewis acids is among the most important tasks in current organic chemistry.¹ While several efficient asymmetric reactions using chiral Lewis acids have been developed, a drawback is that most Lewis acids are unstable in the presence of water and are even sensitive to moisture.² Therefore, many Lewis acid catalysts are prepared in situ in an appropriate dry solvent just before use, and they cannot be stored for extended periods. Contrary to this, we report here remarkably stable chiral zirconium complexes, which are isolable, air-stable, and highly active for asymmetric Mannichtype reactions.

Catalytic asymmetric Mannich-type reactions of imines derived from aldehydes and amines with enolate compounds provide very effective ways to construct optically active β -amino ketones or esters, which are useful chiral building blocks for the synthesis of β -amino acids, β -lactams, β -amino alcohols, [1,3]oxazinan-2-one, and so forth.³ Previously, we have reported chiral zirconium-catalyzed enantioselective Mannich-type reactions of imines with silicon enolates.⁴ Because chiral zirconium catalysts have been widely used in several enantioselective reactions,⁵ we have focused on the structure of the zirconium catalysts.

- (a) Selectivities in Lewis Acid Promoted Reaction; Schinzer, D., Ed.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1989. (b) Lewis acid in Organic Synthesis; Yamamoto, H., Ed.; Wiley-VHC: Weinheim, Germany, 2000.
- (2) For water-compatible Lewis acids, (a) Kobayashi, S.; Nagayama, S.;
 Busujima, T. J. Am. Chem. Soc. 1998, 120, 8287. (b) Kobayashi, S.; Ogino,
 T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K. Org. Lett. 2005, 7,
 4729 and references therein.
- (3) (a) Kobayashi, S.; Ueno, M. In Comprehensive Asymmetric Catalysis, Supplement I; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer: Berlin, 2003; Chapter 29.5. (b) Kobayashi, S. Ishitani, H. Chem. Rev. 1999, 99, 1069. (c) Cordova, A. Acc. Chem. Res. 2004, 37, 102
- (4) (a) Ishitani, H.; Ueno, M.; Kobayashi, S. J. Am. Chem. Soc. 2000, 122, 8180. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. J. Am. Chem. Soc. 1997, 119, 7153. For related work, see (c) Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. Angew. Chem., Int. Ed. 2001, 40, 2271. (d) Wenzel, A. G.; Jacobsen, E. N. J. Am. Chem. Soc. 2002, 124, 12964. (e) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. J. Am. Chem. Soc. 2004, 126, 3734.

The zirconium catalyst for the asymmetric Mannich-type reactions was prepared in situ from a zirconium alkoxide, a 1,1'bi-2-naphthol (BINOL) derivative, and an imidazole derivative in dichloromethane just before use.⁴ In our attempts to obtain single crystals of the zirconium catalyst for X-ray analysis, we discovered that the species prepared from zirconium alkoxides, (*R*)-6,6'-dibromo BINOL, and *N*-methylimidazole (NMI) were soluble in dichloromethane, toluene, or benzene. However, addition of hexane to the dichloromethane solution of the catalyst for X-ray analysis, unfortunately, but was found to be a remarkably stable but highly active catalyst.

The activity of the powdered catalyst was tested in the Mannich-type reaction of the imine (1) prepared from benzaldehyde and 2-aminophenol with the ketene silyl acetal (2) derived from methyl isobutyrate. It was found that the reaction proceeded smoothly in the presence of 10 mol % of the isolated catalyst to afford the desired Mannich adduct in 86% yield with 85% ee. It should be noted that the yield and the enatioselectivity were comparable to those obtained using in situ prepared catalysts.⁴ In addition, the isolated catalyst was found to be remarkably stable to air and moisture. Indeed, it could be stored for at least 6 months in air at room temperature without loss of activity (Table 1), while a significant decrease of yields and selectivities was observed when the in situ prepared catalyst was used after 1 day of storage in air at room temperature.

⁽⁵⁾ For example, (a) Ihori, Y.; Yamashita, Y.; Ishitani, H., Kobayashi, S. J. Am. Chem. Soc. 2005, 127, 15528. (b) Yamashita, Y.; Kobayashi, S. J. Am. Chem. Soc. 2004, 126, 11279. (c) Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi, S. J. Am. Chem. Soc. 2004, 126, 9192. (d) Okachi, T.; Murai, N.; Onaka, M. Org. Lett. 2003, 5, 85. (e) Huo, S.; Shi, J.-C.; Negishi, E.-I. Angew. Chem., Int. Ed. 2002, 41, 2141. (f) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. Angew. Chem., Int. Ed. 2001, 40, 1896. (g) Negishi, E.-I. Pure Appl. Chem. 2001, 73, 239. (h) Kobayashi, S.; Shimizu, H.; Yamashita, Y.; Ishitani, H.; Kobayashi, S. J. Am. Chem. Soc. 2002, 124, 13678. (i) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. J. Am. Chem. Soc. 2002, 124, 13678. (i) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. J. Am. Chem. Soc. 2000, 122, 5403.



Figure 1. Isolated powdered chiral zirconium catalyst.



Table 2. Asymmetric Mannich-Type Reactions of Various Aldimines with Silicon Enolates

	OSiMe₃ ≼ R⁴	(S)-6- (10 CH -45 °	C ₂ F ₅ -Zr mol%) H ₂ Cl ₂ PC, 18 h		0 ↓ R ³	
R ¹	R ²	R ³	R ⁴	yield (%)	syn/anti	ee (%)
Ph (1)	Me	Me	OMe	93	-	87
Naph (3)	Me	Me	OMe	quant	-	89
p-ClPh	Me	Me	OMe	quant	-	87
Ph	Н	Н	SEt	95	-	89
Naph	Н	Н	SEt	quant	-	87
p-ClPh	Н	Н	SEt	95	-	92
iC_4H_9	Η	Н	SEt	63	-	89
Ph	Η	Me	OPh	94	7/93	81
iC_4H_9	Η	Me	OPh	86	12/88	95
$\mathbf{P}\mathbf{h}^{a}$	OBn	Н	OPh	75	5/95	92
$\mathbf{P}\mathbf{h}^{a}$	OTBS	Н	OPr ⁱ	92	92/8	89

^a In toluene at -78 °C.

We also prepared a zirconium catalyst from a zirconium alkoxide, (S)-6,6'-(C₂F₅)₂BINOL, and NMI and found that a similar white powder was formed. We then used this powdered catalyst in several Mannich-type reactions, and the results are summarized in Table 2. Imines derived from aromatic aldehydes reacted with silicon enolates smoothly to afford the desired Mannich-type adducts in high yields with high stereoselectivities. Not only the ketene silvl acetal derived from methyl isobutyrate but also the thicketene silyl acetal from S-ethyl ethanethioate worked well, and the desired products were obtained with high enantioselectivities. Imines prepared from aliphatic aldehydes and 2-aminocresol with a dehydrating agent in situ also reacted smoothly to afford the desired adducts in good yields with excellent enantioselectivities.⁶ As for the catalyst loading, 1-2 mol % of the powdered catalyst was enough to complete the reaction in acceptable levels of yields and selectivities. In all cases, the experimental procedure is simple and convenient; addition of the catalyst directly to the reaction mixture was sufficient for efficient reactions.

	Table 3.	Reuse of the	e Isolated	Catalysts
--	----------	--------------	------------	-----------

			,			
	first		second		third	
	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)
$C_2F_5^b$ Br ^c	quant 87	89 93	quant 89	88 88	88 83	80 79

^{*a*} The reaction of imine **3** with ketene silyl acetal **2** was conducted using 10 mol % of the catalyst in dichloromethane at -45 °C for 18 h. ^{*b*} 6,6'-(C₂F₅)₂BINOL. ^{*c*} 6,6'-Br₂BINOL.



Figure 2. ORTEP diagram of $Zr_4(\mu$ -BINOLate)₆(μ_3 -OH)₄. Hydrogen atoms are omitted for clarity.

In addition to high activity, utility, and handling, it was found that the powdered zirconium catalyst was readily recoverable and reusable.⁷ After the Mannich-type reaction (conducted in dichloromethane) was complete, hexane was added to the reaction mixture. A white precipitate was formed, which could be separated by decantation to give the powdered zirconium catalyst. The recovered catalyst could be reused at least three times without significant loss of activity (Table 3). It is noteworthy that the imidazole parts, which were known to be labile, were also recovered without any damage, and that the addition of NMI was not needed in the second and third runs.

Next, we tried again to obtain single crystals of the zirconium catalyst for X-ray crystallographic analysis. After several trials, single crystals suitable for the X-ray analysis were finally obtained when N-benzylimidazole was used instead of NMI.8,9 Namely, a powdered catalyst was also prepared from Zr(Ot- Bu_{4} , (R)-6,6'-dibromo BINOL, and N-benzylimidazole, and the desired single crystals were formed from a toluene or a hexanes-ethyl acetate solution of the powdered zirconium catalyst. Interestingly, the X-ray structure did not show $(BINOLate)_2 Zr(N-benzylimidazole)_2$ but $Zr_4(\mu-BINOLate)_6(\mu_3-$ OH)4, in which four hexa-coordinated zirconium atoms and six BINOL ligands existed (Figure 2). This is the first X-ray crystallographic structure of a chiral zirconium-BINOL complex that works well in asymmetric Mannich-type reactions.¹⁰ It should be noted that no imidazole derivatives were included in the single crystals, although N-benzylimidazole was included

- (8) Details are shown in Supporting Information.
- (9) When a zirconium catalyst was prepared using N-benzylimidazole instead of NMI, a similar powered catalyst was initially formed. (10) A similar titanium derivative was reported Mikami K Ueki M.
 - 0) A similar titanium derivative was reported. Mikami, K.; Ueki, M.; Matsumoto, Y.; Terada, M. Chirality 2001, 13, 541. It should be noted that zirconium and hafnium are effective in this asymmetric Mannich-type reaction, while titanium does not work well. See ref 4.

⁽⁶⁾ Kobayashi, S.; Kobayashi, J.; Ishitani, H.; Ueno, M. Chem.-Eur. J. 2002, 8, 4185.

⁽⁷⁾ Recently we reported a storable chiral zirconium catalyst; however, the recovery of the catalyst was not enough and NMI had to be added every time for the reuse of the catalyst. Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. Proc. Natl. Acad. Sci. U.S.A. 2004, 101, 5476.



Figure 3. ¹H and ¹³C NMR spectra of Zr catalysts in CD₂Cl₂. (a) Zr catalyst prepared in situ. (b) Isolated Zr catalyst powder. (c) Single crystals of the Zr complex. (d) Single crystals of the Zr complex with NMI. Details are shown in Supporting Information.

in the powdered zirconium catalyst confirmed by elemental analysis before recrystallization. It is assumed that a small amount of water contained in the solvent was replaced with *N*-benzylimidazole. The color of the crystals was gradually changed from colorless to brown under light existence conditions, while no color change was observed under dark conditions.

Very interestingly, the single crystals were found to show high catalytic activity for the asymmetric Mannich-type reaction. In the presence of 20 mol % of the crystals, imine **3** reacted with ketene silyl acetal **2** in dichloromethane at -45 °C for 48 h to afford the corresponding Mannich-type adduct in 80% yield with 85% ee. The yield and the enantioselectivity were comparable to those obtained using the powdered zirconium catalyst. It should be noted that the high yield and the selectivity were obtained without NMI using the single crystals. Furthermore, the enantioselectivity was slightly improved to 87% ee even in the presence of 10 mol % of the catalyst when NMI (20 mol %) was added.

Finally, NMR analyses of the four zirconium catalysts, (a) the in situ prepared catalyst, (b) the isolated powdered catalyst, (c) the single crystals, and (d) the single crystals with NMI, were conducted in dichloromethane- d_2 (Figure 3). Four ¹H and ¹³C NMR spectra showed different signals, indicating that the above four zirconium catalysts have different structures in dichloromethane solutions. On the other hand, because the four

zirconium catalysts gave similar enantioselectivity in the Mannich-type reaction, it was assumed that the same intermediate consisting of the zirconium catalyst and the imine formed. It is quite interesting and noteworthy that the zirconium catalysts with different structures would form the same complex with the imine in the present asymmetric Mannich-type recations.¹¹

In summary, we have developed isolable, air-stable, storable, and highly selective chiral zirconium catalysts for asymmetric Mannich-type reactions. The powdered zirconium catalyst works well with 1-10 mol % loadings in the reactions of imines with silicon enolates to afford the corresponding adducts in high

yields with high stereoselectivities, and the catalyst can be recovered and reused without significant loss of activity. On the other hand, zirconium single crystals for X-ray analysis also show high performance in the asymmetric Mannich-type reactions. NMR analyses of these zirconium catalysts show different structures in dichloromethane, while the formation of the same key intermediate from the different catalysts is indicated.

Acknowledgment. This work was partially supported by a Grant-in-aid for Scientific Research from Japan Society of the Promotion of Science (JSPS).

Supporting Information Available: Experimental section (PDF) and crystallographic information (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA062776R

⁽¹¹⁾ We also conducted NMR analyses of the four zirconium catalysts with an imine. While the charts are rather complicated, independent signals of the zirconium catalysts and the imine were observed as major species in all cases. See Supporting Information.