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Efficient Catalytic Enantioselective Mannich-Type Reactions Using a Zirconium-Bis(binaphthol)methane Complex

Haruro Ishitani, Takayuki Kitazawa, Shū Kobayashi*†

Graduate School of Pharmaceutical Sciences, The University of Tokyo, CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, and Department of Applied Chemistry, Faculty of Science, Science University of Tokyo (SUT), Kagurazaka, Shinjuku-ku, Tokyo 162-0825

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Abstract: *In the presence of a catalytic amount of a zirconium-bis(binaphthol)methane complex (5), Mannich-type reactions of aldimines with silyl enolates proceeded smoothly to afford the corresponding adducts in high yields with high enantiomeric excesses. (R)-(R)-Bis(3-BINOL)methane 6, that was prepared by linking two binaphthols, was shown to be very effective in these reactions.*

Catalytic asymmetric Mannich-type reactions provide one of the most efficient methods for the synthesis of chiral nitrogen-containing compounds such as β-amino esters, β-lactams, β-amino alcohols, etc.[1] Recently, we reported catalytic enantioselective Mannich-type reactions of aldimines with silyl enolates using a novel chiral zirconium compound (**1**).[2] Chiral zirconium **1** was prepared from $Zr(O^tBu)_4$ and (*R*)-6,6'-dibromo-1,1'-bi-2-naphthol (6,6'-Br-BINOL), and the assumed catalytic cycle of the Mannich-type reactions is shown in Scheme 1. Catalyst **1** is postulated to coordinate aldimine **2** to form zirconium complex **3**.[3] A silyl enolate attacks the aldimine to produce **4**, whose trimethylsilylated oxygen atom attacks the zirconium center to afford the product along with the regeneration of catalyst **1**. To facilitate the formation of **1** from $Zr(O^tBu)_4$ and a BINOL derivative as well as to accelerate the regeneration step of catalyst **1** (from **4** to **1**), we designed novel chiral zirconium catalyst **5**, which could be prepared from $Zr(O^tBu)_4$ and (*R*)-(*R*)-bis(3-BINOL)methane **6** (Scheme 2).[4,5] (*R*)-(*R*)-Bis(3-BINOL)methane **6** was prepared according to Scheme 3. (*R*)-MOM (methoxymethyl)-Protected 3-formyl (CHO)-BINOL **7**[6] was treated with (*R*)-MOM-protected 3-Li-BINOL **8** in THF at -78 °C to room temperature to afford (*R*)-(*R*)-bis(3-BINOL)methanol **9** in a 62% yield. Reduction of **9** with $NaBH_4$/trifluoroacetic acid (TFA) in dichloromethane at 0 °C gave **6** in an 89% yield. During this study, Shibasaki *et al.* reported synthesis of the same ligand (**6**).[5]

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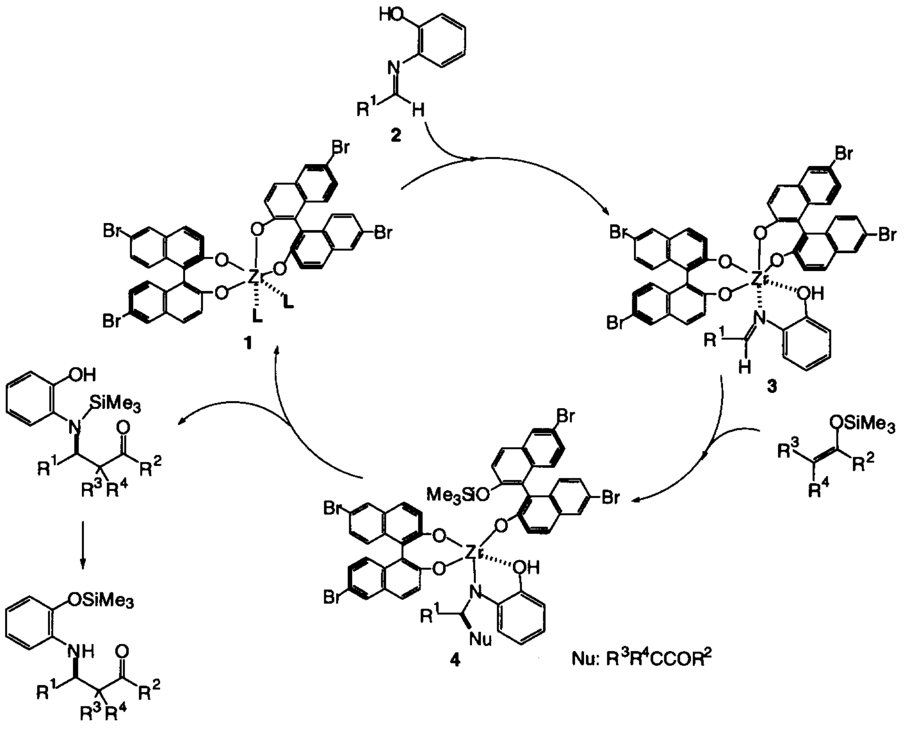
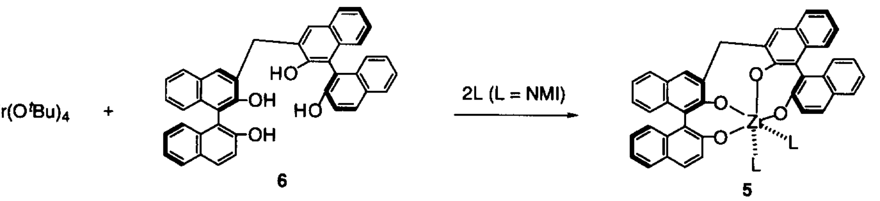
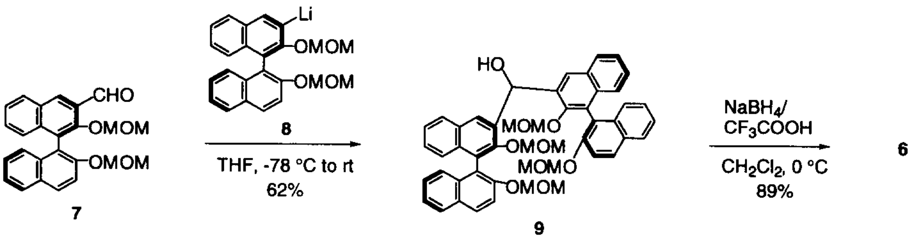


Scheme 1. Assumed Catalytic Cycle of the Mannich-Type Reactions
L = *N*-Methylimidazole (NMI)



Scheme 2. Preparation of Novel Chiral Zirconium Catalyst 5



Scheme 3. Preparation of Bis(3-BINOL)methane 6

Chiral zirconium catalyst **5** was then used in a Mannich-type reaction of aldimine **10** with the ketene silyl acetal derived from methyl isobutyrate (**11**) (Table 1). When the reaction was performed in dichloromethane, the desired adduct was obtained in a 32% ee. However, the enantiomeric excess was improved to 92% when toluene was used as a solvent at -45 °C. It is noted that the use of 2 equivalents of (*R*)-BINOL instead of **6** as ligands gave much lower enantiomeric excess, and that reverse enantioselectivities were obtained by using **6** and (*R*)-BINOL. Satisfactory yield and selectivity were obtained when the reaction was carried out at 0 °C in toluene, and the BINOL ligand **6** was shown to be very effective in this reaction.[7]

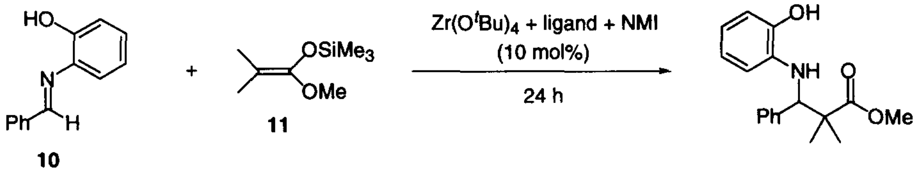
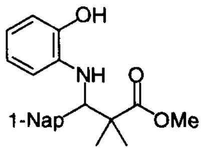


Table 1. Effect of Solvents, Temperatures, and Ligands

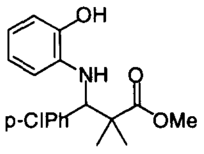
Solvent	Temp/°C	Ligand	Yield/%	ee/%	Config.
CH_2Cl_2	-78	**6**	39	32	*S*
toluene	-45	**6**	26	92	*S*
toluene	0	**6**	59 (75)[a]	94 (95)[a]	*S*
CH_2Cl_2	-45	BINOL (2 eq.)	47	19	*R*
toluene	-45	BINOL (2 eq.)	36	25	*R*

[a] 60 h.

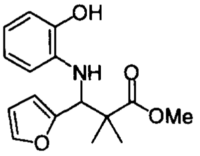
The novel zirconium catalyst (**5**) was then used in other combinations of aldimines and enolates. The aldimines derived from 1-naphthaldehyde, *p*-chlorobenzaldehyde, and 2-furylaldehyde reacted with **11** in the presence of 10 mol% of **5** in toluene at 0 °C to afford the corresponding Mannich-type adducts in high ee's.[8] 1-Ethylthio-1-trimethylsiloxyethene also reacted well as an enolate component in toluene at -45 °C to afford the corresponding adduct in a high ee.[8] The *N*-substituents of the products were easily removed by methylation using methyl iodide and potassium bicarbonate, followed by treatment with cerium ammonium nitrate (CAN).[2a]



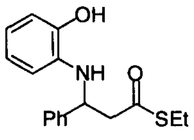
(70%, 85% ee)



(72%, 85% ee)



(98%, 88% ee)



(72%, 82% ee)[a]

[a] -45 °C.

A typical experimental procedure is described for the reaction of aldimine **10** with ketene silyl acetal **11**. To $Zr(O^tBu)_4$ (0.04 mmol) in toluene (0.25 ml) was added ligand **6** (0.06 mmol) in toluene (0.5 ml) and *N*-methylimidazole (NMI, 0.048 mmol) in toluene (0.25 ml) at room temperature. The mixture was stirred for 1 h at the same temperature, and cooled to 0 °C. Toluene solutions (0.75 ml) of **10** (0.8 mmol) and **11** (0.96 mmol) were successively added. The mixture was stirred for 60 h, and saturated $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with ether, and the crude adduct was treated with THF-1N HCl (10:1) at 0 °C for 30 min. After a usual work up, the crude product was chromatographed on silica gel to give the desired adduct in a 75% yield. The optical purity was determined to be 95% ee by HPLC analysis using a chiral column.

In summary, Mannich-type reactions of aldimines with silyl enolates were successfully carried out using a novel zirconium chiral catalyst (**5**). (*R*)-(*R*)-Bis(3-BINOL)methane **6**, that was prepared by linking two BINOLs at the 3-position, was shown to be very effective in these reactions. Further investigations to modify the zirconium catalyst toward more efficient catalytic systems are now in progress.

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References and Notes

† Present address: Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113-0033.

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4 Chiral zirconium catalyst **5** was also indicated by modeling studies. Details will be reported in due course.

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7 The yield and selectivity were higher than those obtained using **1** in dichloromethane at -45 °C (70% yield, 87% ee).[2a] Catalyst **1** gave lower yield when using toluene as a solvent at -45 °C (34% yield, 88% ee).

8 NMI (30 mol%) was used in these cases.