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An air-stable chiral Hf-based catalyst for asymmetric Mannich-type reactions

Shū Kobayashi,* Ryo Yazaki, Kazutaka Seki and Masaharu Ueno

Department of Chemistry, School of Science, 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

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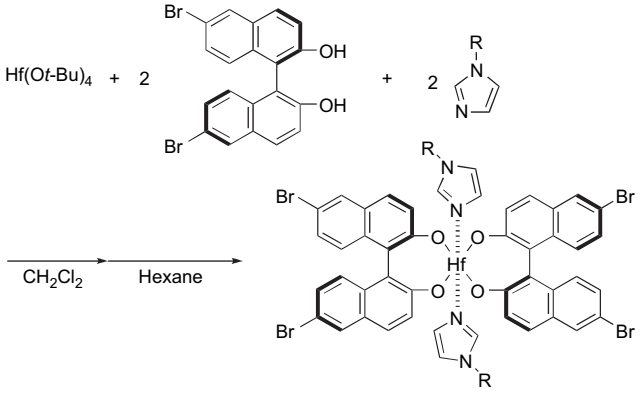
Abstract—A new class of isolable, air-stable, storable, and Hf-based catalyst has been developed. In the presence of 10 mol % of the powdered Hf catalyst, the asymmetric Mannich-type reactions of imines with silicon enolates derived from esters proceeded smoothly to afford the corresponding Mannich-type adducts in high yields with high enantioselectivities. Hafnium single crystals for X-ray analysis were obtained, and the crystals also showed high performance in the asymmetric Mannich-type reactions.

1. Introduction

Asymmetric Mannich reactions provide efficient routes to optically active β-amino carbonyl compounds, which can be converted to versatile biologically important compounds including β-amino acids, β-lactams, β-amino alcohols, and [1,3]oxazinan-2-ones.[1] While many chiral catalysts for these reactions have been developed, recent advances have allowed use of carbonyl compounds directly in the presence of catalytic amounts of activators.[1c,2] However to date, the carbonyl compounds applicable to this reaction are limited to ketones in most cases, and for synthetically useful esters preformed enolates are required. In this context Mukaiyama-type reactions using silicon enolates are the most promising, and several chiral catalysts for these reactions have been developed.[3] However, a drawback is that most chiral Lewis acids are moisture sensitive and have to be prepared just before use.

We have already reported chiral zirconium-catalyzed enantioselective Mannich-type reactions of imines with silicon enolates.[4,5] While chiral zirconium catalysts have been widely used in enantioselective reactions,[6] the first-generation catalyst for the asymmetric Mannich-type reactions was prepared in situ from a zirconium alkoxide, a BINOL derivative, and an imidazole derivative in dichloromethane just before use.[4] Subsequent to these examples we described the synthesis of stable chiral zirconium catalysts, which can be isolable, air-stable, storable, and effective for several reactions.[5,7] Interestingly, while the Zr catalysts have high activity in these reactions, preliminary results showed that related Ti catalysts had lower activity.[6d] Then, we have been interested in catalytic activity of Hf complexes.[8]



In this paper, we describe the synthesis and characterizations of air-stable, chiral Hf catalysts that promote asymmetric Mannich-type reactions.

2. Results and discussion

A chiral Hf complex was prepared from $Hf(O^tBu)_4$ (1 equiv), (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol (6,6′-Br-BINOL, 2 equiv), and *N*-methyl or *N*-benzylimidazole (2 equiv). The three components were first combined in dichloromethane at room temperature for 1 h, and hexane was added to form white powder. The Hf contents of the powder were determined by ICP analysis (Table 1).

Keywords: Hafnium; Asymmetric catalysis; Imines; Mannich-type reactions.
* Corresponding author. Tel.: +81 3 5841 4790; fax: +81 3 5684 0634; e-mail: shu_kobayashi@chem.s.u-tokyo.ac.jp

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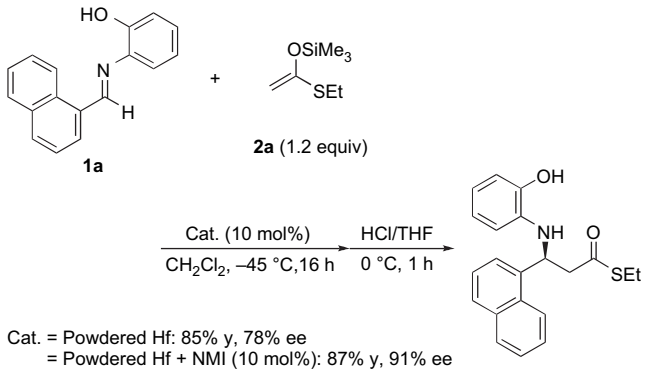
Table 1. Preparation of chiral Hf catalysts

Entry	R	Yield (%)	Hf content (mmol/g)	
			Calcd	Found
1	Bn	98	0.73	0.69
2	Me	94	0.82	0.82

The powdered complex prepared from $Hf(O^tBu)_4$ (10 mol%), (*R*)-6,6′-Br-BINOL (20 mol%), and *N*-methylimidazole (20 mol%) was used as a catalyst in the Mannich-type reaction of imine **1a** with thioketene silyl acetal **2a** (Scheme 1). The reaction proceeded in dichloromethane at –45 °C for 16 h to afford the corresponding Mannich-type adduct in 85% yield with 78% ee. The yield and the enantioselectivity were slightly lower compared with those obtained using the Hf catalyst prepared in situ from $Hf(O^tBu)_4$ (10 mol%), 6,6′-Br-BINOL (20 mol%), and *N*-methylimidazole (30 mol%) in dichloromethane (84% yield, 93% ee). It should be noted that the yield and the selectivity were improved when the powdered Hf complex (10 mol%) was combined with NMI (10 mol%) (87% yield, 91% ee).



Scheme 1. Powdered Hf and effect of NMI.

The powdered Hf catalyst combined with NMI was used in asymmetric Mannich-type reactions with other substrates (Table 2).

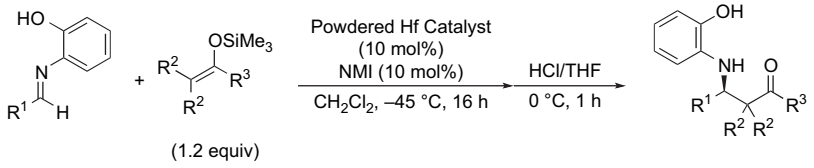
Thioketene silyl acetal **2a** as well as ketene silyl acetal **2b** derived from methyl isobutyrate reacted with some aromatic imines to afford the desired Mannich-type adducts in high yields with high enantioselectivities. In the reaction of an aliphatic imine, a three-component protocol provided the desired adduct in good yield with good enantioselectivity (Scheme 2).

While a powder was obtained from a dichloromethane solution of $Hf(O^tBu)_4$, (*R*)-6,6′-Br-BINOL, and *N*-methyl or *N*-benzylimidazole by adding hexane, crystals were formed from a hexane–ethyl acetate solution. The crystals were suitable for X-ray crystallographic analysis (Fig. 1).

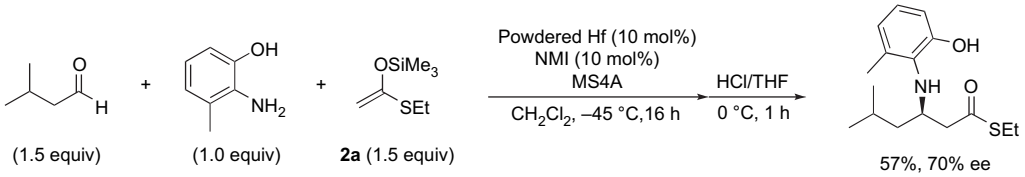
Interestingly, the X-ray structure shows $Hf_4(\mu\text{-BINOLate})_6(\mu_3\text{-OH})_4$, wherein four hexa-coordinated Hf atoms and six BINOL ligands are present. It is worth noting that no imidazole derivatives were included in the single crystals, although NMI was included in the powdered Hf catalysts. While this is the first X-ray crystallographic structure of Hf–BINOL complexes, the structure is similar to that of the known Ti and Zr complexes.[5a] The Hf single crystals were found to show high catalytic activity for the asymmetric Mannich-type reaction (Scheme 3). In the presence of 10 mol% of the crystals, imine **1a** reacted with ketene silyl acetal **2b** in dichloromethane at –45 °C for 132 h to afford the corresponding Mannich-type adduct in 67% yield with 85% ee. Furthermore, the enantioselectivity was slightly improved to 89% ee even in the presence of 10 mol% of the catalyst when NMI (20 mol%) was added.

It was noted that the yield and the enantioselectivity were comparable to those obtained using the powdered zirconium catalyst, albeit longer reaction time was needed. It is also

Table 2. Powdered Hf-catalyzed asymmetric Mannich-type reactions



Entry	R^1	R^2	R^3	Yield (%)	ee (%)
1	Ph	Me	OMe	83	79
2	1-Naphthyl	Me	OMe	93	85
3	Ph	H	SEt	66	82
4	1-Naphthyl	H	SEt	87	91
5	*p*-ClC_6H_4	H	SEt	77	84



Scheme 2. Powdered Hf-catalyzed three-component Mannich-type reactions.

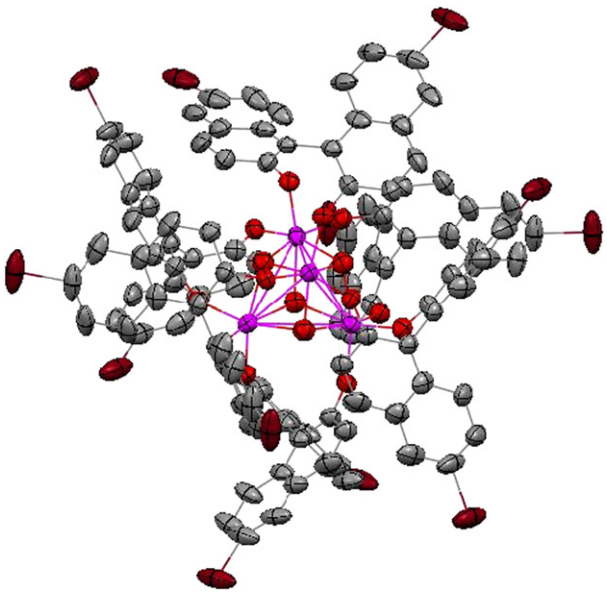
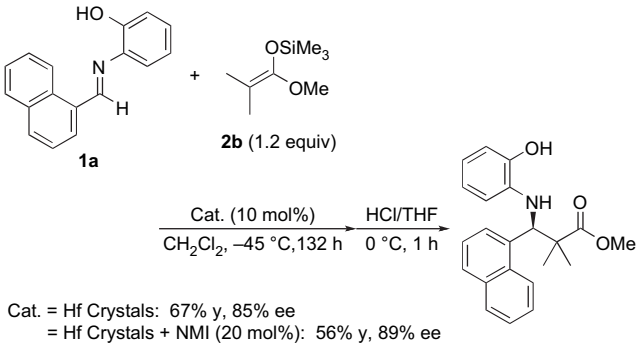


Figure 1. Molecular structure of $Hf_4(\mu\text{-BINOLate})_6(\mu_3\text{-OH})_4$ crystal with thermal ellipsoids at the 50% probability level. The disordered solvent molecules (hexane and ethyl acetate) and hydrogen atoms are omitted for clarity.



Scheme 3. Hf single crystals catalyzed asymmetric Mannich-type reactions.

noteworthy that in the reactions using single crystals high yields and the selectivities were obtained without the addition of NMI.

3. Conclusion

In summary, we have developed two types of isolable, air-stable, and storable Hf catalysts; powdered Hf and Hf crystals. Both catalysts have high activity for asymmetric Mannich-type reactions of imines with silicon enolates to afford the corresponding Mannich-type adducts in high yields with high stereoselectivities. The X-ray structure shows $Hf_4(\mu\text{-BINOLate})_6(\mu_3\text{-OH})_4$, which is similar to the corresponding Zr complex. Further investigations aimed at developing chiral Hf-catalyzed enantioselective reactions are now in progress.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a JEOL ECX400, or ECX600 spectrometer in $CDCl_3$, unless otherwise noted. Tetramethylsilane (TMS) served as internal standard (0 ppm) for ^1H NMR, and $CDCl_3$ was used as internal standard (77.0 ppm) for ^{13}C NMR. HPLC was carried out using the following apparatuses; SHIMADZU LC-10AT (liquid chromatograph), SHIMADZU SPD-10A (UV detector), and SHIMADZU C-R6A or C-R8A Chromatopac. Column chromatography was conducted on Silica gel 60 (Merck), and preparative thin layer chromatography was carried out using Wakogel B-5F. Commercially available chemicals purchased from Aldrich, Kanto Chemical, Tokyo Chemical Industry and Wako Pure Chemical Industry, were purified according to standard procedures. Hafnium *tert*-butoxide ($Hf(O^tBu)_4$) was purchased from Strem Chemical Inc. (*R*)-6,6′-Dibromo-1,1′-bi-2-naphthol ((*R*)-6,6′-Br_2-BINOL) was synthesized according to the literature's method.[4f] Ketene silyl acetals were prepared according to the literature's methods.[4f]

4.2. Preparation of powdered Hf catalysts

All reactions were carried out under argon atmosphere in well-dried glassware. A solution of *N*-methylimidazole (NMI, 1.0 mmol) in dichloromethane (1.0 mL) was added to a dichloromethane (1.0 mL) solution of a ligand (1.0 mmol) and $Hf(O^tBu)_4$ (0.50 mmol) at room temperature. After the mixture was stirred for 1 h at the same temperature, hexane (100 mL) was added and white precipitates were formed. The suspended mixture was further stirred overnight. Filtration of white suspension and washing with hexane afforded an Hf catalyst as white powder.

4.3. Determination of the Hf contents in the powdered Hf catalysts

The powdered Hf catalyst (15.0 mg) was placed in a 10 mL test tube, and sulfuric acid (1.0 mL) was added. The mixture was heated at 180 °C for 30 min, 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 Hf metal was measured by ICP analysis.

4.4. Typical experimental procedure for asymmetric Mannich-type reactions using an isolated powdered chiral Hf catalyst

4.4.1. Without NMI. The powdered Hf catalyst (0.040 mmol) was dissolved in dichloromethane (1.00 mL), and then aldimine (0.40 mmol) and silicon enolate (0.48 mmol) in dichloromethane (0.75 mL) were added at −45 °C. The mixture was stirred for 16 h, and hexane (10 mL) was added to quench the reaction. Precipitates were formed, which were removed by filtration. The filtrate was concentrated and treated with THF–1 M HCl (10:1) at 0 °C for 1 h. The solution was then basicified with a saturated aqueous $NaHCO_3$ solution, and the aqueous solution was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by preparative thin layer chromatography to afford the desired product. The optical purity was determined by HPLC analysis using a chiral column (vide infra).

4.4.2. With NMI. A solution of *N*-methylimidazole (NMI, 0.040 mmol) in dichloromethane (1.0 mL) was added to

the powdered Hf catalyst (0.040 mmol), and the mixture was used for the reaction.

4.4.2.1. Methyl 2,2′-dimethyl-3-(2-hydroxyphenyl)-amino-3-(1′-naphthyl)propionate.[4f] Mp 135–136 °C. IR (neat): 3052, 1691, 1604, 1578, 1270, 798 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.18 (s, 3H), 1.25 (s, 3H), 3.66 (s, 3H), 5.62 (s, 3H), 6.28–6.62 (m, 4H), 7.22–8.00 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 19.9, 25.1, 48.4, 52.4, 57.8, 113.4, 114.2, 117.9, 121.2, 122.1, 123.2, 125.2, 125.3, 125.4, 126.1, 128.1, 129.1, 133.6, 135.3, 135.5, 144.1, 177.9. HPLC: Daicel Chiralcel OD, hexane/^{i}PrOH=19/1, flow rate=0.8 mL/min, t_R=25.8 min (3*S*), t_R=29.0 min (3*R*).

4.4.2.2. Methyl 2,2′-dimethyl-(2-hydroxyphenyl)-amino-3-phenylpropionate.[4f] Mp 112.5–114 °C. IR (KBr): 3401, 1709, 1611, 1514, 1453, 1391 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21 (s, 3H), 1.24 (s, 3H), 3.68 (s, 3H), 4.57 (s, 1H), 6.36–6.76 (m, 4H), 7.21–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 19.9, 24.2, 47.3, 52.3, 64.3, 113.2, 114.1, 117.6, 120.8, 127.3, 127.9, 128.3, 135.6, 138.9, 144.0, 178.0. HPLC: Daicel Chiralpak AD, hexane/^{i}PrOH=9/1, flow rate=1.0 mL/min, t_R=9.3 min (3*R*), t_R=16.0 min (3*S*).

4.4.2.3. *S*-Ethyl 3-(2-hydroxyphenyl)amino-3-phenylpropanethioate.[4f] Mp 79.5–80.5 °C. IR (KBr): 3396, 1647, 1608, 1520, 1449, 1362 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.67 (t, 3H, *J*=7.3 Hz), 2.83 (q, 2H, *J*=7.3 Hz), 2.97 (dd, 1H, *J*=5.4, 14.9 Hz), 3.07 (dd, 1H, *J*=8.1, 14.9 Hz), 4.81 (dd, 1H, *J*=5.4, 8.1 Hz), 6.44–6.71 (m, 4H), 7.20–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 14.4, 23.6, 51.4, 56.1, 114.4, 114.6, 118.8, 121.1, 126.3, 127.4, 128.6, 134.9, 141.7, 144.7, 198.4. HPLC: Daicel Chiralpak AS, hexane/^{i}PrOH=19/1, flow rate=1.0 mL/min, t_R=26.6 min (3*S*), t_R=38.2 min (3*R*).

4.4.2.4. *S*-Ethyl 3-(2-hydroxyphenyl)amino-3-(1′-naphthyl)propane thioate.[4f] Mp 40.5–41.5 °C. IR (KBr): 3380, 1645, 1605, 1514, 1446, 1362 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.18 (t, 3H, *J*=7.3 Hz), 2.86 (q, 2H, *J*=7.3 Hz), 3.03 (dd, 1H, *J*=9.4, 14.8 Hz), 3.20 (dd, 1H, *J*=3.3, 14.8 Hz), 5.68–5.70 (m, 1H), 6.30–6.71 (m, 4H), 7.29–8.23 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 14.4, 23.7, 50.7, 51.9, 113.5, 114.4, 118.1, 121.3, 122.1, 123.1, 125.6, 125.7, 126.5, 128.0, 129.2, 130.3, 134.0, 135.3, 136.7, 143.9, 198.5. HPLC: Daicel Chiralpak AD, hexane/^{i}PrOH=9/1, flow rate=1.0 mL/min, t_R=15.5 min (3*S*), t_R=21.0 min (3*R*).

4.4.2.5. *S*-Ethyl 3-(4′-chlorophenyl)-3-[(2′-hydroxyphenyl)amino]propanethioate.[4f] IR (neat): 3412, 1665, 1610, 1516, 1447, 742 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21 (t, 2H, *J*=7.4 Hz), 2.87 (q, 2H, *J*=7.4 Hz), 2.96 (dd, 1H, *J*=5.1, 14.9 Hz), 3.05 (dd, 1H, *J*=8.3, 14.9 Hz), 4.78 (dd, 1H, *J*=5.1, 8.3 Hz), 6.39–6.78 (m, 4H), 7.22–7.28 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.5, 23.7, 51.2, 55.6, 114.5, 115.0, 119.3, 121.2, 127.8, 128.9, 133.2, 134.6, 140.3, 144.7, 197.8. HPLC: Daicel Chiralpak AD, hexane/^{i}PrOH=9/1, flow rate=1.0 mL/min, t_R=19.5 min (3S), t_R=24.3 min (3*R*).

4.4.2.6. *S*-Ethyl 3-[(2-hydroxy-6-methylphenyl)-amino]-5-methylhexanethioate.[4f] IR (neat): 3356, 2957, 2871, 1681, 1588, 1472, 1366 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.81 (d, 3H, *J*=6.4 Hz), 0.88 (d, 3H, *J*=6.6 Hz), 1.26 (t, 3H, *J*=7.4 Hz), 1.35 (dd, 2H, *J*=6.6, 7.7 Hz), 1.63 (7, 1H, *J*=6.7 Hz), 2.25 (s, 3H), 2.64 (dd, 1H, *J*=8.0, 15.9 Hz), 2.80 (dd, 1H, *J*=4.2, 15.8 Hz), 2.92 (q, 2H, *J*=7.5 Hz), 3.62 (dq, 1H, *J*=4.2, 7.1 Hz), 6.66 (dd, 1H, *J*=0.6, 7.4 Hz), 6.76 (dd, 1H, *J*=1.4, 7.8 Hz), 6.88 (t, 1H, *J*=7.7 Hz). ^{13}C NMR ($CDCl_3$): δ 14.6, 18.1, 22.0, 23.2, 23.6, 25.1, 44.5, 48.4, 52.5, 113.3, 121.8, 124.6, 131.2, 132.5, 151.9, 200.3. HPLC: Daicel Chiralpak OD, hexane/^{i}PrOH=60/1, flow rate=1.0 mL/min, t_R=14.9 min (3*S*), t_R=17.2 min (3*R*).

4.5. Preparation of the single crystals

The powdered Hf catalyst containing *N*-benzylimidazole (20 mg) was dissolved in AcOEt (2 mL). This solution was allowed to stand in a sealed vial filled with hexane. After standing the solution for 1 day, colorless single crystals were formed.

4.5.1. Crystal data of Hf crystal. $C_{136}H_{92}Br_{12}Hf_4O_{24}$: *Fw*=3783.02, D_{calcd} (g cm^{-3})=1.566, crystal system=cubic, space group=*F*432, *a*(Å)=31.7745(8), *b*(Å)=31.7745(8), *c*(Å)=31.7745(8), α(deg)=90.000, β(deg)=90.000, γ(deg)=90.000, *V*(Å^3)=32080.3(14), *Z*=8, *T*(°C)=–180, λ(Å)=0.7107, *R* factor [all data]=0.0472, *R*1 factor [$I>2.0\,\sigma(I)$]=0.0428, *Rw* factor [all data]=0.1362, goodness of fit=1.136.

4.6. Procedure for asymmetric Mannich-type reactions using single crystals

4.6.1. Without NMI. The crystal Hf catalyst (8.6 mg, 0.010 mmol) was suspended in dichloromethane (0.25 mL). After the mixture was stirred for 1 h at room temperature, aldimine (0.10 mmol) and silicon enolate (0.12 mmol) in dichloromethane (0.25 mL) were added at –45 °C. The reaction mixture was stirred for 132 h, and hexane (10 mL) was added to quench the reaction. Precipitates were formed, which were removed by filtration. The filtrate was concentrated and treated with THF–1 M HCl (10:1) at 0 °C for 1 h. The solution was then basicified with a saturated aqueous $NaHCO_3$ solution, and the aqueous solution was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by preparative thin layer chromatography to afford the desired product.

4.6.2. With NMI. *N*-Methylimidazole (1.64 mg, 0.02 mmol) was added to a white suspension of crystals of the Hf catalyst (8.6 mg, 0.010 mmol) in dichloromethane (0.25 mL). After stirring for 3 h, the crystals were partially dissolved, and the slightly suspended mixture was used for the reaction.

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