A Ligand-Accelerated Chiral Lewis Acid Catalyst in Asymmetric Michael Addition of Thiols to α,β-Unsaturated Carbonyls

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Dedicated to Professor Ryoji Noyori in recognition of his remarkable contribution to Synthetic Organic Chemistry.

Abstract: A novel chiral hafnium catalyst, which was readily prepared from $Hf(OTf)_4$ and chiral ligand **1**, has been developed in asymmetric Michael reactions of thiols with 3-(2-alkenoyl)-2-oxazolidinones, affording the corresponding adducts in high yields and enantiomeric excesses. Although chiral Lewis acids are less reactive than their original Lewis acids in many cases, ligand-acceleration has been demonstrated in this asymmetric Michael addition reaction.

Key words: Lewis acid, Michael reaction, asymmetric catalysis

Ligand-acceleration is essential for catalytic asymmetric reactions.[1] In some asymmetric oxidations and alkylations, chiral ligands coordinate to metals and accelerate the catalyzed reactions in a highly enantioselective manner. On the other hand, asymmetric reactions using chiral Lewis acids are now popular and recognized as one of the most efficient methods for the preparation of chiral molecules, especially via enantioselective carbon-carbon bond-forming processes.[2] From the viewpoint of ligand-acceleration, however, this is not the case with most chiral Lewis acid catalysis. Chiral Lewis acids are less reactive than their original Lewis acids in many cases, because basic chiral ligands coordinate to Lewis acids to form chiral Lewis acids, and in this coordination Lewis acids are neutralized to decrease Lewis acidity compared to the original Lewis acids.[3] Development of a ligand-accelerated process in chiral Lewis acid catalysis is important to realize a truly efficient catalytic system. In this paper, we describe such examples of chiral hafnium-catalyzed asymmetric Michael addition of thiols to α,β-unsaturated carbonyl compounds.

Catalytic Michael addition of thiols to α,β-unsaturated carbonyls provides a useful route for the synthesis of chiral sulfur-containing molecules.[4] Bearing in mind the ligand-accelerated chiral Lewis acids, we examined suitable combinations of Lewis acids and chiral ligands (**1**) in the asymmetric Michael reaction of 3-crotonoyl-2-oxazolidinone (**2**) with benzyl mercaptan. Several Lewis acids and ligands were examined and the results are shown in the Table. Among the Lewis acids screened, hafnium triflate ($Hf(OTf)_4$)[5] gave better results, while ytterbium triflate ($Yb(OTf)_3$) or scandium triflate ($Sc(OTf)_3$) was promising.[6]

During this investigation, it was found that the catalytic activity of the chiral hafnium is higher than that of

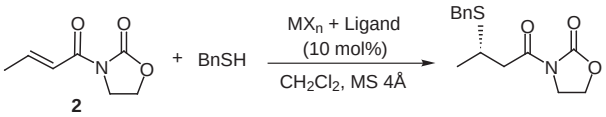

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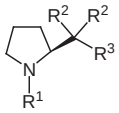
Table Effect of Ligands and Lewis Acids

MX_n	Ligand	Temp (°C)	Yield (%)	ee (%)
$Yb(OTf)_3$	**1a**	-45	75	56
$Yb(OTf)_3$	**1b**	-45	82	61
$Yb(OTf)_3$	**1c**	-45	80	62
$Sc(OTf)_3$	**1c**	-45	73	57
$Hf(OTf)_4$	**1c**	0	82	67
$ScCl_3$	**1d**	0	15	45
$Hf(OTf)_4$	**1d**	0	82	69
$Hf(OTf)_4$	**1e**	0	76	60
$Hf(OTf)_4$	**1f**	0	79	71
$Hf(OTf)_4$	**1g**	0	85	69
$Hf(OTf)_4$	**1h**	0	82	65
$Hf(OTf)_4$	**1i**	0	72	21
$HfCl_4$	**1d**	0	68	59
$TiCl(OTf)_3$	**1d**	0	44	0
$TiCl_4$	**1d**	0	92	6
$MgBr_2$	**1d**	0	25	25



1a: R^1 = H, R^2 = Ph, R^3 = OH
1b: R^1 = COPh, R^2 = Ph, R^3 = OH
1c: R^1 = COPh, R^2 = Ph, R^3 = OMe
1d: R^1 = CO^{t}Bu, R^2 = Ph, R^3 = OMe
1e: R^1 = COMe, R^2 = Ph, R^3 = OMe
1f: R^1 = CO^{t}Bu, R^2 = α-Nap, R^3 = OMe
1g: R^1 = CO^{t}Bu, R^2 = β-Nap, R^3 = OMe
1h: R^1 = CO^{t}Bu, R^2 = *c*-C_6H_{11}, R^3 = OMe
1i: R^1 = CO^{t}Bu, R^2 = Pr, R^3 = OMe

$Hf(OTf)_4$. While the desired Michael adduct was obtained in 58% yield in the addition of benzyl mercaptan to **2** in the presence of 10 mol% of $Hf(OTf)_4$ and MS 4 Å in dichloromethane (CH_2Cl_2) at 0 °C, 82% yield of the adduct was obtained using the chiral hafnium under the same reaction conditions. The difference between the two catalyst systems is the presence and absence of the chiral ligand. This is indeed an example of ligand-accelerated Lewis acid catalysis. We then carefully followed the reaction course in the presence and absence of the chiral ligand in the model Michael addition (Figure 1). It was revealed that the initial rate constant of the chiral hafnium-catalyzed reaction was 1.5 times larger than that of the

achiral reaction. Although the value is not very satisfactory, the origin of the ligand acceleration is interesting from the viewpoint of very rare ligand-accelerated Lewis acid catalysis as well as development of more efficient catalytic systems. We performed kinetic experiments in the reaction of **2** with benzyl mercaptan. Rate constants (k_{obs}) were determined over a range of catalyst concentrations (5-15 mol%), and a linear correlation between k_{obs} vs $[Hf(OTf)_4]^2$ was obtained, which reflected a second-order dependence on the catalyst (Figure 2). These kinetic data provide strong support for a mechanism involving catalyst activation of both the nucleophile and the electrophile[7] that would explain the ligand-accelerated Lewis acid catalysis, although the detailed activation form is not clear at this stage. While $Hf(OTf)_4$ is a white solid and does not dissolve in CH_2Cl_2, a clear solution was obtained after mixing with the ligand in CH_2Cl_2. ^1H and ^{13}C NMR analyses showed formation of a novel chiral hafnium Lewis acid.[8]

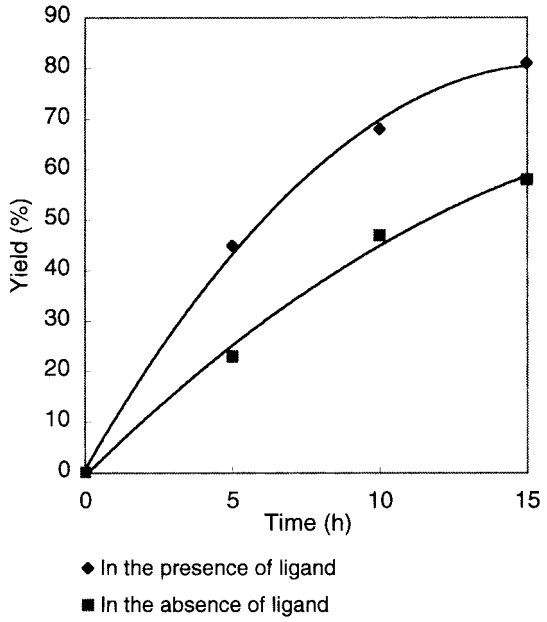


Figure 1 Plot of Isolated Yield vs Time in the Presence and Absence of the Ligand for the Michael Reaction of **2** with Benzyl Mercaptan

Several examples of the catalytic asymmetric Michael reactions are summarized in Table 2. In the presence of a catalytic amount of the chiral hafnium compound, aliphatic thiols reacted with 3-(2-alkenoyl)-2-oxazolidinones to afford the corresponding Michael adducts in high yields with high enantiomeric excesses. In some cases, ligands **1j** and **1k** gave better selectivity. Benzenethiols showed lower selectivity under these conditions.

A typical experimental procedure is described for the reaction of **2** with benzyl mercaptan: To a CH_2Cl_2 suspension (1 mL) of $Hf(OTf)_4$ (0.05 mmol) and MS 4 Å (125 mg) was added chiral ligand **1j** (0.06 mmol) at 0 °C. The mixture was stirred for 30 min at the same temperature.

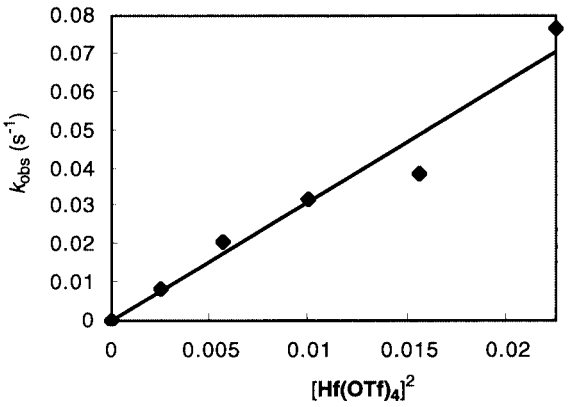


Figure 2 Plot k_{obs} vs $[\mathbf{Hf(OTf)_4}]^2$ for the Michael Reaction of **2** with Benzyl Mercaptan

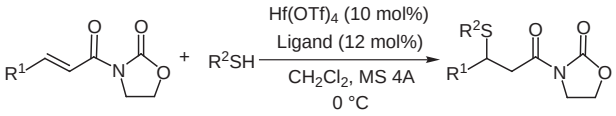
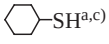
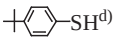
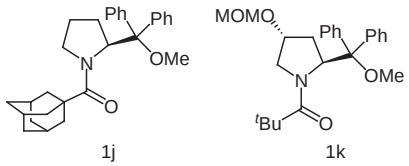


Table 2 Chiral Hafnium Complex-Catalyzed Asymmetric Michael Additions of Thiols

R^1	R^2SH	Ligand	Time (h)	Yieid (%)	ee (%)
CH_3	C_2H_5SH	**1d**	15	90	67
CH_3	 [a,c]	**1d**	15	60	76
CH_3	$PhCH_2SH$	**1d**	15	82	69
CH_3	$PhCH_2SH$	**1j**	22	53	92
CH_3	$PhCH_2SH$	**1j**	48	74	88
CH_3	C_4H_9SH	**1d**	15	92	71
CH_3	C_4H_9SH [b]	**1j**	15	80	90
CH_3	$CH_2=CHCH_2SH$ [c,d]	**1d**	20	71	91
CH_3	$CH_2=CHCH_2SH$ [c,d]	**1k**	20	83	94
C_4H_9	 [d]	**1d**	20	85	50
Ph		**1d**	30	70	43

[a] Twenty mol% of hafnium triflate was used. [b] Fifteen mol% of hafnium triflate was used. [c] Thiol was added slowly over 8 h. [d] The reaction was carried out at 5 °C.



1j 1k

To this mixture, **2** (0.5 mmol) in CH_2Cl_2 (1 mL) and benzyl mercaptan (0.55 mmol) in CH_2Cl_2 (1 mL) were added successively at 0 °C. After the mixture was stirred for 22 h at the same temperature, saturated aqueous $NaHCO_3$ was added to quench the reaction. After the usual work-up, the crude material was purified by preparative TLC to afford the desired Michael adduct. The enantiomeric ex-

cess of the adduct was determined by HPLC analysis using a chiral column. The absolute configuration was determined to be *S* compared with the authentic sample.[4f]

In summary, a novel chiral hafnium catalyst has been developed in asymmetric Michael reactions of thiols with 3-(2-alkenoyl)-2-oxazolidinones. The hafnium catalyst was readily prepared from $Hf(OTf)_4$ and chiral ligand **1**, and to the best of our knowledge, this is the first successful example of the use of chiral hafnium Lewis acids in asymmetric catalysis.[9] Although chiral Lewis acids are less reactive than their original Lewis acids in many cases, ligand-acceleration has been demonstrated in this asymmetric Michael addition reaction. Further studies to clarify the structure of the chiral hafnium catalysts as well as the mechanism of the ligand-acceleration are now in progress.

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(8) $Hf(OTf)_4$: Ligand = 1:1 mixture in CD_2Cl_2 at 0 °C; ^{1}H NMR δ = 1.29 (s, 3.96H), 1.22-1.32 (m, 0.56H), 1.56 (s, 5.04H), 1.66-1.98 (m, 1.76H), 2.21 (m, 0.56H), 2.39-2.64 (m, 1.56H), 3.11 (s, 1.32H), 3.72 (br s, 1.68H), 3.91-4.00 (m, 1H), 4.13 (t, 0.56H, *J* = 10.9), 5.49 (t, 0.44H, *J* = 8.3), 5.59 (dd, 0.56H, *J* = 12.0, 5.6), 7.05 (dd, 1.12H, *J* = 8.0, 1.7), 7.29-7.35 (m, 0.88H), 7.38-7.59 (m, 8H); ^{13}C NMR δ = 23.4, 26.5, 26.9, 27.5, 27.8, 28.5, 36.0, 39.4, 47.4, 52.6, 53.5, 73.2, 76.7, 91.1, 97.5, 118.8, 121.5, 125.2, 126.3, 128.3, 129.2, 129.28, 129.37, 129.42, 129.6, 129.9, 130.0, 130.1, 130.4, 132.1, 133.9, 136.5, 139.0, 178.1, 182.4.

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