ORGANIC LETTERS

2005
Vol. 7, No. 21
4729−4731

Bismuth Triflate–Chiral Bipyridine Complexes as Water-Compatible Chiral Lewis Acids

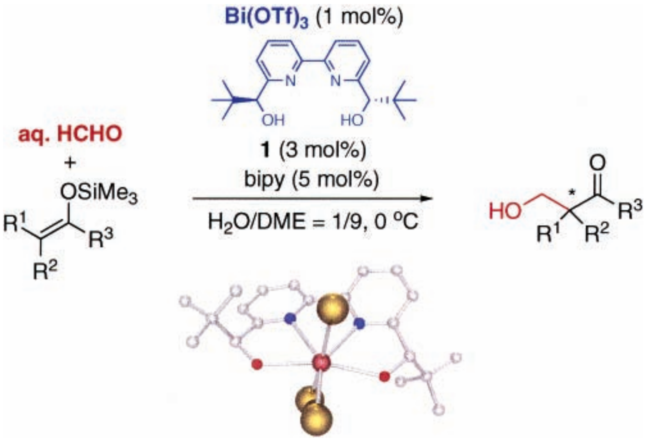
Shū Kobayashi,* Tsuyoshi Ogino, Haruka Shimizu, Shunpei Ishikawa, Tomoaki Hamada, and Kei Manabe

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

skobayas@mol.f.u-tokyo.ac.jp

Received August 14, 2005

ABSTRACT



Catalytic asymmetric hydroxymethylation of silicon enolates with an aqueous formaldehyde solution has been developed using a chiral bismuth complex. This is the first example of highly enantioselective reactions using a chiral bismuth catalyst in aqueous media. In this paper, we have added Bi(OTf)$_3$–1 complex as a "water-compatible Lewis acid". Bi(OTf)$_3$ is unstable in the presence of water but is stabilized by the basic ligand.

Organic reactions in aqueous media are of current interest because water is expected as a key solvent attaining environmentally benign chemical synthesis.[1] Although several interesting reactions with unique reactivity and selectivity have been developed in water or water/organic solvent systems, asymmetric catalysis in such media is difficult because many chiral catalysts are not stable in the presence of water.[2] In particular, chiral Lewis acid catalysis in aqueous media is extremely difficult because most chiral Lewis acids decompose rapidly in the presence of water.[3] To address this issue, we have discovered water-compatible Lewis acids,[4] and catalytic asymmetric reactions using these Lewis acids and chiral ligands have been developed.[5] During this work, we thought that Lewis acids that are decomposed in the presence of water might be stabilized by combining with chiral basic ligands in water. In this paper, we report that bismuth triflate (Bi(OTf)$_3$)−chiral bipyridine complexes work as water-compatible chiral Lewis acids to catalyze hydroxy-

---

(1) (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. (b) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998.

(2) *Aqueous-Phase Organometallic Catalysis*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 2004.

(3) Manabe, K.; Kobayashi, S. *Chem. Eur. J.* **2002**, *8*, 4094.

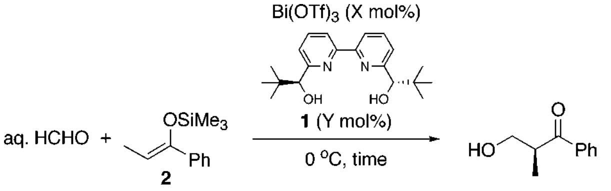
(4) (a) Kobayashi, S. *Chem. Lett.* **1991**, 2187. (b) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590. (c) Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.

10.1021/ol051965w CCC: $30.25

methylation of silicon enolates using an aqueous formaldehyde solution. *A remarkable point is that Bi(OTf)$_3$ is hydrolyzed but is stabilized by the chiral basic ligands in water*.

Recently, we have found that highly enantioselective, catalytic hydroxymethylation of silicon enolates with an aqueous formaldehyde solution proceeded smoothly in the presence of a novel scandium complex prepared from Sc(OTf)$_3$ and chiral bipyridine.[6,7] As an extension of this work, we tested other metal salts (10 mol %) and chiral bipyridine **1**[8] (12 mol %) in the reaction of silicon enolate **2** with an aqueous formaldehyde solution and found that Bi(OTf)$_3$[9] gave promising selectivity (Table 1, entry 2). This result was unexpected because (1) the ionic diameter of bismuth (2.34 Å for 8-coordination) is much bigger than that of scandium (1.74 Å for 8-coordination); (2) Bi(OTf)$_3$ is known to be hydrolyzed.[10] Indeed, only a trace amount of the hydroxymethylated adduct was obtained using Bi(OTf)$_3$ without the chiral bipyridine (entry 1).[11] In this case, silicon enolate **2** was rapidly decomposed by TfOH which is easily generated from Bi(OTf)$_3$ in water. On the other hand, decomposition of silicon enolate **2** was slow and the desired hydroxymethylation proceeded in the presence of Bi(OTf)$_3$ and **1**. Obviously, Bi(OTf)$_3$ was stabilized by chiral bipyridine **1** in water. The yield and the selectivity were improved when 10 mol % of Bi(OTf)$_3$ and 30 mol % of **1** were used (entry 4). When the catalyst loading was decreased, lower yield and selectivity were obtained. For cosolvents, 1,2-dimethoxyethane (DME) and acetone gave promising results. Finally, it was revealed that the desired product was obtained in 94% yield with 91% ee using 1 mol % of Bi(OTf)$_3$ and 3 mol % of **1** in the coexistence of 5 mol % of 2,2′-bipyridine (entry 11). It is noteworthy that the same level of selectivity was attained using 0.5 mol % of Bi(OTf)$_3$, although the yield has not yet been optimized (entry 12). In the presence of 2,2′-bipyridine, the rate of decomposition of silicon enolate **2** was further reduced.

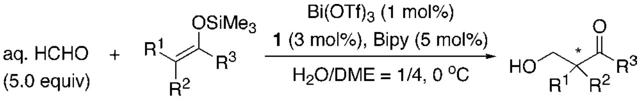
Table 1. Effect of Solvents and Ratios of Bi(OTf)$_3$ and Ligand **1**

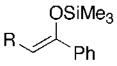
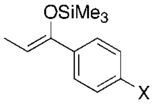
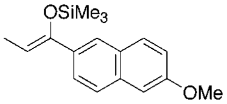
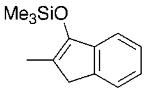
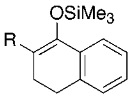
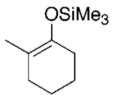
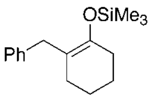
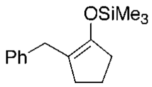


entry	solvent	*x*	*y*	time (h)	yield[a] (%)	ee[b] (%)
1	H_2O/DME = 1/9	10	0	6	trace	-
2	H_2O/DME = 1/9	10	12	4	26	78
3	H_2O/DME = 1/9	10	20	4	36	84
4	H_2O/DME = 1/9	10	30	4	92	93
5	H_2O/DME = 1/9	3	9	4	67	92
6	H_2O/DME = 1/9	1	3	4	63	83
7	H_2O/THF = 1/9	3	9	4	32	80
8	H_2O/CH3CN = 1/9	3	9	4	47	87
9	H_2O/acetone = 1/9	3	9	4	74	90
10	H_2O	3	9	4	7	46
11[c]	H_2O/DME = 1/9	1	3	21	93	91
12[d]	H_2O/DME = 1/9	0.5	1.5	16	76	90

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] 5 mol % of 2,2′-bipyridine was added. [d] 2.5 mol % of 2,2′-bipyridine was added.

Table 2. Bi-catalyzed Hydroxymethylation



entry	silicon enolate		time (h)	yield[a] (%)	ee[b] (%)
1		R = Me	21	93	91
2		R = Et	70	79	92
3		X = MeO	30	80	88
4		X = Cl	34	87	89
5			22	59	92
6			9	89	88
7		R = Me	22	81	95
8		R = C_4H_9	22	68	93
9			20	66	77
10			48	79	92
11			20	82	79

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

Several other substrates were subjected to this catalyst system, and the results are summarized in Table 2. In most cases, the hydroxymethylation proceeded smoothly using an aqueous formaldehyde solution to afford the desired adducts in high yields with high enantioselectivities. The reactions were conducted using 1 mol % of Bi(OTf)$_3$ and 3 mol % of

---

(5) For example: (a) Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* **1999**, 71. (b) Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 11531. (c) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640. (d) Hamada, T.; Manabe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 2989. (e) Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3927. (f) Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7768.

(6) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 12236.

(7) Other examples of asymmetric hydroxymethylation: (a) Manabe, K.; Ishikawa, S.; Hamada, T.; Kobayashi, S. *Tetrahedron* **2003**, *59*, 10439. (b) Ozawa, N.; Wadamoto, M.; Ishihara, K.; Yamamoto, H. *Synlett* **2003**, 2219. (c) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (d) Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 6117, and references therein.

the chiral ligand, and asymmetric quaternary carbons were constructed with high selectivities (entries 6−11).

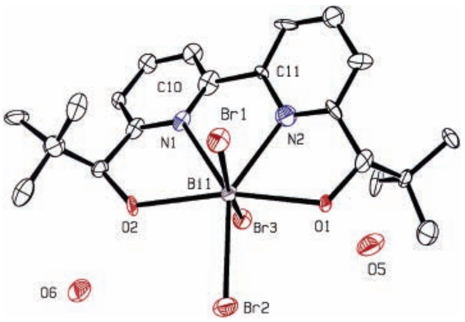
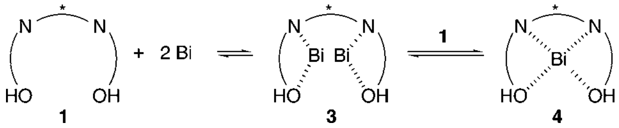


Figure 1. ORTEP drawing of the X-ray crystal structure of [BiBr$_3$·**1**]·(H$_2$O)$_2$·DME. DME is omitted for clarity.

To elucidate the catalyst structure, we conducted X-ray crystal structural analysis, and single crystals suitable for the X-ray analysis were obtained from the BiBr$_3$−**1** complex (Figure 1). The complex adopts a pentagonal bipyramidal structure in which the tetradentate ligand occupies four of the equatorial sites. The structure of the Bi(III)Br$_3$ complex of **1** is closely related to that of the corresponding Sc(III)Br$_3$ complex we previously reported.[12] We also performed in situ NMR analysis of formation of Bi(OTf)$_3$−**1** complexes with different ratios of Bi(OTf)$_3$ and **1**.[13] When Bi(OTf)$_3$ and **1** were combined in a ratio of 1:0.5, a signal at 5.49 ppm was dominant. On the other hand, another signal at 4.72 ppm grew when the ratio of **1** to Bi(OTf)$_3$ increased, and finally the former signal disappeared when Bi(OTf)$_3$ was combined with 3 equiv of **1**. These results indicate that 2 equiv of Bi(OTf)$_3$ and 1 equiv of **1** formed complex **3** and that complex **4** consisting of 1 equiv of Bi(OTf)$_3$ and 1 equiv of **1** was generated when an excess amount of **1** was added (Scheme 1). Complex **4** seemed to be stable even in the presence of 2,2′-bipyridine. When Bi(OTf)$_3$ (1 mol %) and **1** (3 mol %) were combined in DME at room temperature for 30 min and then 2,2′-bipyridine was added at 0 °C, the hydroxymethylation of **2** proceeded at 0 °C in 21 h to afford the desired adduct in 93% yield with 91% ee. On the other hand, the yield and the enantioselectivity decreased (73% y, 85% ee) when Bi(OTf)$_3$ and 2,2′-bipyridine were combined at room temperature for 30 min and then **1** was added, and the mixture was stirred at room temperature for 30 min. However, when the mixture was stirred at room temperature for 1 h, the enantioselectivity was improved (81% yield, 91% ee). These results indicate that complex **4** is stable even in the presence of 2,2′-bipyridine and that **4** is readily formed from Bi(OTf)$_3$−2,2′-bipyridine complex and **1**.[14]

Scheme 1. Formation of Chiral Bi^{3+} Catalysts



In summary, we have developed a chiral Bi^{3+} complex for catalytic asymmetric hydroxymethylation of silicon enolates with an aqueous formaldehyde solution. The reaction proceeded smoothly in the presence of 0.5−1 mol % of the bismuth catalyst to afford the hydroxymethylated adducts in high yields with high enantioselectivities. To the best of our knowledge, this is the first example of highly enantioselective reactions using a chiral bismuth catalyst in aqueous media.[15] It is noted that Sc and Bi with very different ionic diameters gave similar complexes with **1**. In addition to these characteristic points of this reaction, this work provides a new entry to "water-compatible Lewis acids." For a long time, Lewis acids were believed to hydrolyze rapidly in the presence of water. Contrary to this, we found that rare earth and other metal complexes were water-compatible.[4] In this paper, we have added Bi(OTf)$_3$−**1** complex as a water-compatible Lewis acid. Bi(OTf)$_3$ is unstable in the presence of water but is stabilized by the basic ligand.[16] There are many strong Lewis acids unstable in water; however, these Lewis acids may be available in water when combined with basic ligands. In particular, the use of chiral basic ligands leading to new types of water-compatible chiral Lewis acids may enable a wide range of asymmetric catalysis in aqueous media.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Science (JSPS). T.H. thanks the JSPS fellowship for Japanese Junior Scientists.

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

OL051965W

---

[8] (a) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 205. (b) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169.

[9] (a) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517. (b) Répichet, S.; Zwick, A.; Vendier, L.; Le Roux, C.; Dubac, J. *Tetrahedron Lett.* **2002**, *43*, 993.

[10] Répichet, S.; Zwick, A.; Vendier, L.; Le Roux, C.; Dubac, J. *Tetrahedron Lett.* **2002**, *43*, 993.

[11] Sc(OTf)$_3$ is a water-compatible Lewis acid, and it works well for hydroxymethylation even in the absence of a basic ligand. Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472.

[12] The angle of O−Bi−O is 165°, while that of O−Sc−O is 151°. The torsional angle of two pyridines in the Bi complex is 27.0° and that in the Sc complex is 19.4°. For the Sc complex, see ref 6.

[13] Details are shown in the Supporting Information.

[14] The reaction rates using Bi(OTf)$_3$−**1**−2,2′-bipyridine complex and Bi(OTf)$_3$−2,2′-bipyridine complex are comparable. Bi(OTf)$_3$−**1**−2,2′-bipyridine complex: 37% yield for 1.5 h. Bi(OTf)$_3$−2,2′-bipyridine complex: 20% yield for 1.5 h.

[15] Only one example of a chiral bismuth compound, which was used in trimethylsilylcyanation of aldehydes in CH$_2$Cl$_2$, was reported. Wada, M.; Takahashi, T.; Domae, T.; Fukuma, T.; Miyoshi, N.; Smith, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3939.

[16] Whereas it is known that some ligands stabilize metal complexes, this is the first example to be demonstrated that basic ligands stabilize Lewis acids in water. Very recently, Wang and Li reported a related example. See: Li, H.-J.; Tian, H.-Y.; Chen, Y.-J.; Wang, D.; Li, C.-J. *Chem. Commun.* **2002**, 2994.