J|A|C|S
ARTICLES
Published on Web 01/27/2005

Dynamic Ligand Exchange of the Lanthanide Complex Leading to Structural and Functional Transformation: One-Pot Sequential Catalytic Asymmetric Epoxidation-Regioselective Epoxide-Opening Process

Shin-ya Tosaki, Riichiro Tsuji, Takashi Ohshima,* and Masakatsu Shibasaki*

Contribution from the Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received October 13, 2004; E-mail: ohshima@mol.f.u-tokyo.ac.jp; mshibasa@mol.f.u-tokyo.ac.jp

Abstract: The characteristic property of the lanthanide complex, which easily undergoes a dynamic ligand exchange and alters its structure and function in situ, is described. After the completion of the catalytic asymmetric epoxidation of various α,β-unsaturated amides **2** in the presence of the Sm−(*S*)-BINOL−Ph_3-As═O (1:1:1) complex **1** (2−10 mol %), the addition of Me_3SiN_3 directly to the reaction mixture led to smooth epoxide-opening at room temperature, affording the corresponding *anti*-β-azido-α-hydroxyamide **4** in excellent overall yield (up to 99%) with complete regioselectivity and excellent enantiomeric excess (up to >99%). The key to the success of the sequential process was the in situ generation of the highly reactive samarium azide complex through dynamic ligand exchange. In situ IR spectroscopy and other experiments provided strong evidence that the samarium azide complex was generated. In addition, the relatively high Lewis basicity of the amide moiety had a key role in the high reactivity of both the epoxidation and the epoxide-opening reactions. Examinations of other nucleophiles such as sulfur or carbon nucleophiles as well as transformations of epoxide-opened products are also described.

Introduction

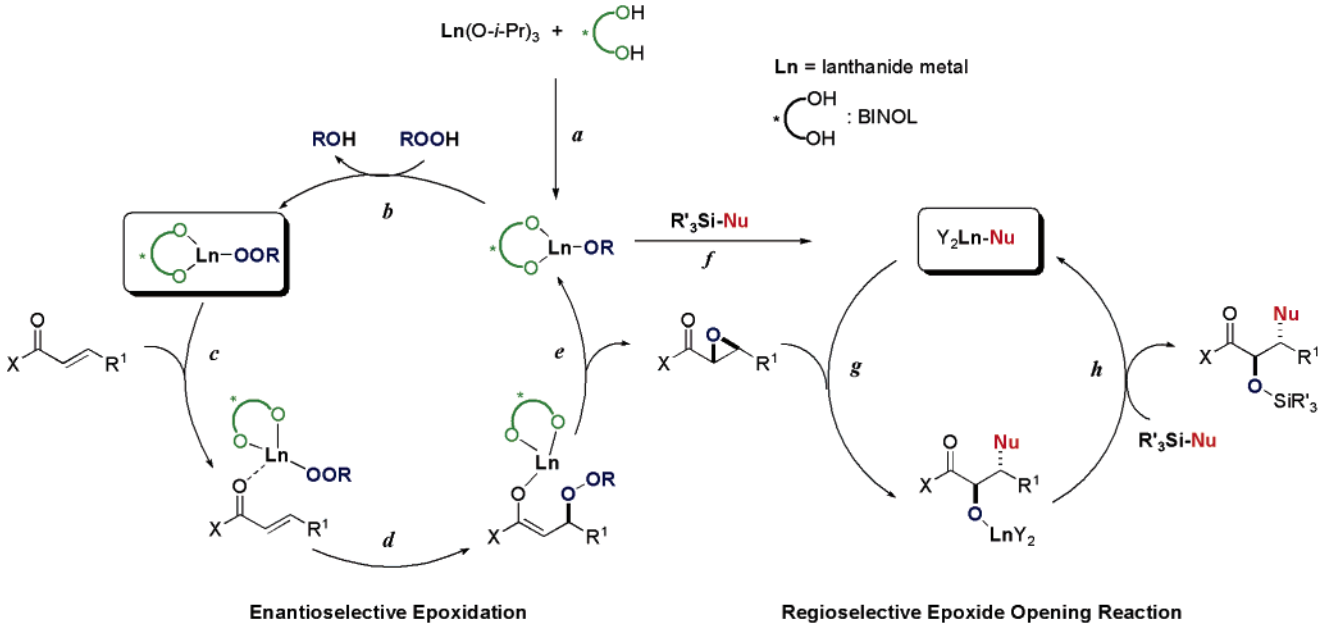
Lanthanide metals are widely utilized for organic reactions. Among them, the large coordination numbers of lanthanide metals allow for the development of lanthanide salt−ligand complexes as Lewis acid catalysts. One role of the ligand is the improvement of existing catalyses. The reaction rate is often increased by the addition of a suitable ligand (ligand-accelerating effect).[1] On the other hand, a nucleophilic reagent can be exchanged for a labile ligand to generate another nucleophilic complex. The nucleophilic complexes of lanthanide metals prepared by modification of the ligand work as highly nucleophilic catalysts compared with conventional Lewis acid catalysts. There are only a few examples of the use of this type of catalyst, however, despite its high reactivity and unique properties. Utimoto et al. reported that the ytterbium catalyst, prepared by the reaction of Bu_3Yb or $Yb(O\text{-}i\text{-}Pr)_3$ with Me_3SiCN, was highly effective for the regioselective ring opening of epoxides and aziridines with cyanide and cyanation of carbonyl compounds.[2] Ytterbium cyanide was postulated to be the active cyanating reagent.[3] Our group recently reported the enantioselective cyanosilylation of ketones[4a] and Strecker reaction of ketoimines[4b−d] catalyzed by the chiral gadolinium complex, in which gadolinium cyanide acts as the nucleophile.[5]

On the basis of the nature of the lanthanide complex, such as moderate Lewis acidity, multifunctionality, large coordination numbers, and fast ligand exchange ability, we anticipated that subsequent addition of other reagents would alter the structure and function of the lanthanide complex in situ through dynamic ligand exchange to promote different reactions successively. In this regard, the lanthanide BINOL complex appeared to be a suitable catalyst. We previously reported a general and highly enantioselective epoxidation of α,β-unsaturated carbonyl compounds catalyzed by alkali-metal free lanthanide BINOL

(1) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.
(2) (a) Matsubara, S.; Onishi, H.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6209. (b) Matsubara, S.; Kodama, T.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6379. (c) Matsubara, S.; Takai, T.; Utimoto, K. *Chem. Lett.* **1991**, 1447.
(3) Schaus and Jacobsen suggested the formation of a ytterbium cyanide species in the asymmetric ring opening of meso-epoxides with Me_3SiCN catalyzed by the (pybox)$YbCl_3$ complex. See: Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001.
(4) (a) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908. (b) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634. (c) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3143. (d) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3153.
(5) The gadolinium catalyst had higher reactivity than the one prepared from $Ti(O\text{-}i\text{-}Pr)_4$, by which Me_3SiCN itself works as a nucleophile. See ref 4a and (a) Hamashima, Y.; Kanai, M.; Shibasaki M. *J. Am. Chem. Soc.* **2000**, *122*, 7412. (b) Hamashima, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 691.
(6) Epoxidation of α,β-unsaturated ketones: (a) Bougauchi, M.; Watanabe, T.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329. (b) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725. For other α,β-unsaturated carbonyl compounds, see: (esters) (c) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323. (d) Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792. *N*-Acylimidazolides: (e) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474. *N*-Acylpyrroles: (f) Kinoshita, T.; Okada, S.; Park, S.-R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4680. (g) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559.

10.1021/ja043770+ CCC: $30.25

Scheme 1. Postulated Catalytic Cycle of Enantioselective Epoxidation (Left Side) and the Following Sequential Epoxide-Opening Reaction (Right Side) through Dynamic Ligand Exchange of the Lanthanide Complex



complexes.[6] The postulated catalytic cycle is illustrated in the left side of Scheme 1. The lanthanide BINOL complex is prepared from Ln(O-*i*-Pr)$_3$ and BINOL in a ratio of 1:1 (step a). Subsequent addition of alkyl peroxide (ROOH) induces an exchange of the alkoxide ligand on the lanthanide metal to generate the active lanthanide peroxide complex (step b). Coordination of the carbonyl to the lanthanide metal to activate the electron-deficient olefin (step c), followed by the enantioselective 1,4-addition of lanthanide peroxide, afforded lanthanide enolate (step d). The subsequent epoxide formation, followed by dissociation from the lanthanide metal, regenerates the lanthanide BINOL complex (step e). We assumed that the subsequent addition of another reagent (R′$_3$Si-Nu) after the enantioselective epoxidation would generate a highly reactive nucleophilic complex (Y$_2$Ln-Nu) in situ through dynamic ligand exchange (step f) and that the newly generated complex would promote the catalytic regioselective epoxide-opening reaction (steps g and h) in one reaction vessel.

The syntheses would be much more efficient if several bonds could be formed in one sequence without isolating the intermediates. The increased demand for a highly efficient and environmentally benign synthetic process requires the development of catalysts that promote different reactions in one reaction vessel.[7,8] This type of catalysis would minimize waste (solvents, reagents, silica gel, etc.) and make waste management unnecessary, because compared to stepwise reactions, the amount of chemicals and energy utilized would substantially decrease.

In this article, we describe the characteristic property of the lanthanide complex, which easily undergoes dynamic ligand exchange and alters its structure and function to promote different reactions. The Sm−BINOL−Ph$_3$As=O complex, a catalyst for highly enantioselective epoxidation of α,β-unsaturated amides, is transformed by the subsequent addition of Me$_3$SiN$_3$ into a highly reactive azidation reagent for regioselective ring opening of α,β-epoxy amide. Thus, a mild and efficient one-pot sequential catalytic asymmetric epoxidation-regioselective epoxide-opening process was developed. In situ IR spectroscopy and other mechanistic studies provide strong evidence for the generation of the samarium azide complex, which should work as the active azidation reagent. This is the first investigation of the physical properties of the lanthanide azide complex. In addition, we report that the high Lewis basicity of the amide moiety has a key role in the unexpectedly high reactivity of both the epoxidation and the epoxide-opening reactions. Variants of this one-pot sequential process utilizing other nucleophiles such as sulfur and carbon nucleophiles were also examined. Finally, *anti*-β-azido-α-hydroxyamides were transformed to biologically active compounds.

Results and Discussion

(A) Catalytic Ring-Opening Reaction of α,β-Epoxy Amides with Azide. We previously reported a general and highly enantioselective epoxidation of α,β-unsaturated simple amides **2** catalyzed by the Sm−(*S*)-BINOL−Ph$_3$As=O complex **1**, prepared from Sm(O-*i*-Pr)$_3$, (*S*)-BINOL, and Ph$_3$As=O in a ratio of 1:1:1 (Scheme 2).[9] The corresponding α,β-epoxy amides **3** were obtained in excellent yield (up to 99%) with excellent

(7) For selected recent examples, see: (a) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609. (b) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. (c) Morimoto, T.; Fuji, K.; Tsutsumi, K.; Kakuuchi, K. *J. Am. Chem. Soc.* **2002**, *124*, 3806. (d) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. (e) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754 and references therein.

(8) For recent examples reported by our group, see: (a) Sakurada, I.; Yamasaki, S.; Göttlich, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 1245. (b) Sakurada, I.; Yamasaki, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 2415. (c) Yamasaki, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 1256. (d) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636.

(9) (a) Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14544. (b) Tosaki, S.-y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495. (c) Ohshima, T.; Nemoto, T.; Tosaki, S.-y.; Kakei, H.; Gnanadesikan, V.; Shibasaki, M. *Tetrahedron* **2003**, *59*, 10485. (d) Kakei, H.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 317. (e) Tosaki, S.-y.; Horiuchi, Y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Chem.−Eur. J.* **2004**, *10*, 1527.

(10) Although H$_8$-BINOL can be used as a ligand for the catalytic asymmetric epoxidation of α,β-unsaturated *N*-acylpyrroles (refs 6f,g), it was not effective for α,β-unsaturated simple amides. **3a** was obtained from **2a** in 10% yield after 48 h when 10 mol % of the Sm−(*S*)-H$_8$-BINOL−Ph$_3$As=O (1:1:1) complex was used.

Scheme 2. Catalytic Asymmetric Epoxidation of α,β-Unsaturated Simple Amides Promoted by the Sm−(*S*)-BINOL−Ph_3As=O Complex **1**

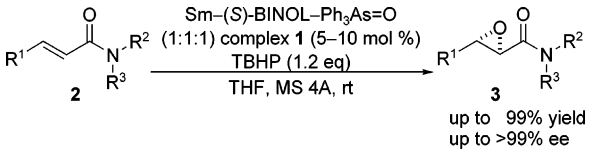
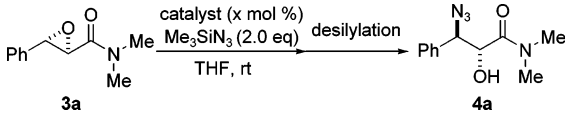


Table 1. Regioselective Ring Opening of α,β-Epoxy Amide with Me_3SiN_3 Using Various Sm Catalysts



entry	catalyst	*x* (mol %)	time (h)	yield[a] (%)
1[b]	Sm(O-*i*-Pr)$_3$	5	1	99
2[b]	Sm(O-*i*-Pr)$_3$	0.2	2	97
3[b]	Sm−(*S*)-BINOL−Ph_3As=O (1:1:1) complex **1**	5	1	99
4[c]	Sm(OTf)$_3$	10	24	21

[a] Isolated yield. [b] Desilylation was conducted with 1 N HCl aq−MeOH. [c] Desilylation was conducted with KF in MeOH.

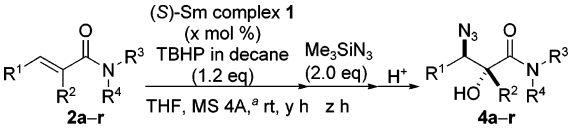
enantiomeric excess (up to >99%).[10] The highly enantioenriched α,β-epoxy amides, in particular α,β-epoxy morpholinyl amides,[9b,e] are versatile intermediates because reductive or nucleophilic epoxide opening and a modification of the amide moiety provide efficient access to useful chiral building blocks. There are few reports on the efficient synthesis of optically active α,β-epoxy amides[11] other than ours, indicating that the ring-opening reaction of α,β-epoxy amides has not been widely investigated, despite its utility. The regioselective epoxide-opening reaction with various nucleophiles is one of the most important transformations in organic synthesis because the epoxide-opened product is obtained with complete control of the vicinal stereochemistry. Chong and Sharpless reported a ring-opening reaction of α,β-epoxy amides with PhSH promoted by 150 mol % of Ti(O-*i*-Pr)$_4$.[12] Secondary amides showed preference for ring opening at the β-position, whereas tertiary amides at the α-position. Aggarwal et al. reported a highly β-selective ring-opening reaction of tertiary α,β-epoxy amides with either PhSH or Me_3SiN_3 promoted by Yb(OTf)$_3$.[11b] Yamamoto et al. reported a regioselective epoxide-opening reaction with Me_3SiN_3 using catalytic Yb(O-*i*-Pr)$_3$.[13] Although α,β-epoxy carbonyl compounds were not utilized in the epoxide-opening reactions reported by Yamamoto et al.[13] and Utimoto et al.,[2] we assumed that Sm(O-*i*-Pr)$_3$ would promote the regioselective ring opening of α,β-epoxy amides to provide β-substituted α-hydroxyamides.

The ring-opening reaction of α,β-epoxy amide with a lanthanide catalyst was examined prior to the one-pot sequential reaction. Table 1 summarizes the results of epoxide-opening reactions with Me_3SiN_3 in the presence of samarium catalysts. As we expected, treatment of α,β-epoxy amide **3a** with 2 equiv of Me_3SiN_3 in the presence of 5 mol % Sm(O-*i*-Pr)$_3$ led to a clean epoxide opening within 1 h at room temperature. Subsequent desilylation gave the corresponding *anti*-β-azido-α-hydroxyamide **4a** in 99% yield with complete regioselectivity (entry 1). Reduced catalyst loading (0.2 mol %) was sufficient to complete the reaction, affording **4a** in 97% yield after 2 h (entry 2). The use of 5 mol % of the (*S*)-Sm complex **1** also completed the reaction with comparable reactivity (entry 3). In contrast, the reaction with 10 mol % Sm(OTf)$_3$, a much stronger Lewis acid, proceeded sluggishly to give **4a** in 21% yield after 24 h (entry 4).[14] Only a trace amount of **4a** was obtained in the absence of the catalyst, even after 48 h.

(B) One-Pot Sequential Catalytic Asymmetric Epoxidation-Regioselective Epoxide-Opening Process. Encouraged by the above results, we examined the extension to a one-pot sequential catalytic asymmetric epoxidation-regioselective epoxide-opening process using the (*S*)-Sm complex **1**. We hypothesized that both the asymmetric epoxidation and the following nucleophilic epoxide-opening reaction would be catalyzed by the Sm complex **1** through a dynamic ligand exchange. After completion of the catalytic asymmetric epoxidation of α,β-unsaturated amide **2a**, 2 equiv of Me_3SiN_3 were directly added to the reaction mixture. The epoxide opening proceeded smoothly at room temperature without significant adverse effects, and subsequent desilylation afforded **4a** in 99% overall yield with 99% ee (Table 2, entry 1). Table 2 summarizes the scope and limitations of the sequential process. The present one-pot sequential process was applicable to various α,β-unsaturated amides **2** with broad substrate generality, and the enantioselectivity was generally excellent (96−>99%). In the presence of 2 to 10 mol % of (*S*)-Sm complex **1**, tertiary amides with various β-aryl substituents (**2a**−**h**, **2j**, entries 1−10, 12) underwent the sequential process at room temperature, affording the corresponding *anti*-β-azido-α-hydroxyamides **4** in good to excellent yield (70−99%). In these cases, the epoxide-opening reaction was completed within 1−3 h, and the overall yield mainly reflected the conversion of the epoxidation reaction. Despite the high instability of the corresponding epoxide of **2i** (entry 11), the present sequential process successfully provided **4i**, representing an advantageous example. The fact that even such a challenging substrate gave 45% chemical yield was very encouraging.[15] The asymmetric epoxidation and the epoxide-opening reaction of α,β,γ,δ-unsaturated amide **2k** occurred regioselectively to afford **4k** (entry 13). Both the epoxidation and epoxide opening of the secondary amide **2l** proceeded slowly compared with that of tertiary amide **2a**, giving **4l** in 83% overall yield (entry 14). α,β-Unsaturated amides with β-aliphatic substituents (**2m**−**r**, entries 15−20) were also applicable to the present sequential process. Even in these cases, the epoxide-opening reactions proceeded smoothly at room temperature, and it was noteworthy that the products were obtained with complete regioselectivity. Cyclic substrates (**2m**, **2n**) gave the corresponding *tert*-alcohols, thereby constructing stereogenic tetrasubstituted carbon centers (entries 15 and 16). Acyclic substrates **2o**−**q** afforded **4o**−**q** as the sole detectable products in good yield (84−92%; entries 17−19). γ-Branched

(11) (a) Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 77. (b) Aggarwal, V. K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9964.
(12) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.
(13) Meguro, M.; Asao, N.; Yamamoto, Y. *Chem. Commun.* **1995**, 1021. The reaction mechanism was not described in this article.
(14) For regioselective epoxide-opening reactions with azide using other Lewis acid catalysts, see: (a) Denis, J.-N.; Green, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46. (b) Azzena, F.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron* **1995**, *48*, 13409. (c) Francesco, F.; Pizzo, F.; Vaccaro, L. *Tetrahedron Lett.* **2001**, *42*, 1131. (d) Francesco, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 3554.
(15) The syn isomer was contaminated with the anti isomer (anti:syn = 11:1). The moderate overall yield was due to the partial decomposition of the corresponding α,β-epoxy amide during the epoxidation reaction.

Table 2. One-Pot Sequential Catalytic Asymmetric Epoxidation-Regioselective Epoxide-Opening Process with Various α,β-Unsaturated Amides



	substrate				catalyst	time	yield[b]	ee[c]	
entry	R^1	R^2	NR^3R^4		(*x* mol %)	(*y*/*z* h)	(%)	(%)	product
1	C_6H_5	H	NMe_2	**2a**	5	12/1	99	99	**4a**
2	C_6H_5	H	NMe_2	**2a**	2	15/2	70	99	**4a**
3	C_6H_5	H	morpholinyl	**2b**	5	11/1	99	99[d]	**4b**
4	4-$MeOC_6H_4$	H	NMe_2	**2c**	5	13/1	95	>99	**4c**
5	4-$MeOC_6H_4$	H	morpholinyl	**2d**	5	12/1	97	99[d]	**4d**
6	4-MeC_6H_4	H	NMe_2	**2e**	5	13/1	93	99	**4e**
7	4-FC_6H_4	H	NMe_2	**2f**	5	11/1	98	>99	**4f**
8	1-naphthyl	H	NMe_2	**2g**	10	11/3	98	98	**4g**
9	2-naphthyl	H	NMe_2	**2h**	5	13/1	99	>99	**4h**
10	2-naphthyl	H	NMe_2	**2h**	2	16/1	71	98	**4h**
11[e]	2-furyl	H	NMe_2	**2i**	10	11/0.5	45[f]	>99	**4i**
12	3-furyl	H	NMe_2	**2j**	5	11/1	94	>99	**4j**
13	(*E*)-PhCH=CH−	H	NMe_2	**2k**	10[g]	12/0.5	90	>99	**4k**
14	C_6H_5	H	NHMe	**2l**	10	13/8	83	99	**4l**
15	$-(CH_2)_3-$		NHBn	**2m**	10	12/5	97	96	**4m**
16	$-(CH_2)_4-$		NHBn	**2n**	10	13/1	86	99	**4n**
17	$Ph(CH_2)_2$-	H	NMe_2	**2o**	5	6/12	84	98	**4o**
18	$Ph(CH_2)_2$-	H	morpholinyl	**2p**	5	5/12	92	98	**4p**
19	*n*-propyl	H	NMe_2	**2q**	5	6/12	85	98[h]	**4q**
20	cyclohexyl	H	NMe_2	**2r**	10	6/16	75	99[h]	**4r**

[a] MS 4A was used without prior activation (1000 mg/mmol of starting material). [b] Isolated yield. The regioselectivity was generally below the detection limit of 500 MHz ^{1}H NMR (>98:2). [c] Determined by chiral HPLC analysis. [d] ee was determined after conversion to the corresponding *N*-Boc amine. [e] The corresponding epoxide is decomposed on silica gel. [f] Isolated yield of the major anti isomer after conversion to TES ether (ref 15). [g] Gd was used as the central metal instead of Sm (ref 9d). [h] ee was determined after conversion to the corresponding benzoate.

substrate **2r** exhibited lower reactivity, probably because of steric hindrance (75% yield; entry 20). While tertiary amides **2o** and **2p** were successful (entries 17 and 18), the corresponding *N*-methylamide **2s** (R^1 = $Ph(CH_2)_2-$, R^2 = H) did not undergo the epoxide-opening reaction under the same reaction conditions.

(C) Mechanistic Study. Although azide complexes of early transition metals are reported to be active nucleophiles toward epoxides,[16] the lanthanide metal azide complex has never been characterized. To gain insight into the structure of the active species in the epoxide-opening reaction promoted by the Sm catalyst, we performed several spectroscopic experiments. First, we performed NMR analysis. When Sm(O-*i*-Pr)$_3$ (1 mol equiv) and Me_3SiN_3 (5 mol equiv) were mixed in THF-d_8, the generation of Me_3SiO-*i*-Pr was observed on ^{1}H and ^{13}C NMR spectra, suggesting that a ligand exchange occurs from the isopropoxide to the azide on the samarium metal. Next, we measured in situ IR spectra to gain more precise information. When Me_3SiN_3 (20 mol equiv) was treated with Sm(O-*i*-Pr)$_3$ (1 mol equiv) in THF, a new peak appeared around 2100 cm^{-1} on in situ IR spectra (Figure 1A). Treatment of Me_3SiN_3 with the (*S*)-Sm complex **1** instead of Sm(O-*i*-Pr)$_3$ gave similar spectra. Density functional theory (DFT) calculation (B3LYP/LanL2DZ level) indicated that $Sm(N_3)_3$ has an absorption at 2093 cm^{-1} (N=N stretch). These data strongly suggested that a samarium azide complex was generated in the mixture. We also performed electrospray ionization mass spectrometry (ESI-MS) analysis of the mixture of Sm(O-*i*-Pr)$_3$ and Me_3SiN_3, but no clear spectrum that supported the generation of samarium azide species was obtained, probably because of its oligomeric nature. When Me_3SiN_3 was treated with (*S*)-Sm complex **1** instead of Sm(O-*i*-Pr)$_3$, on the other hand, two peaks assigned to $[Sm(N_3)_2(Ph_3As{=}O)_3]^+$ (MW 1201) and $[Sm(N_3)_2(Ph_3As{=}O)_4]^+$ (MW 1524) were observed on the spectrum, indicating the generation of samarium azide species.[17]

We also measured the IR spectra of the sequential process to examine whether the same or related species were generated. After the catalytic asymmetric epoxidation of **2a** reached completion in the presence of 10 mol % of (*S*)-Sm complex **1**, Me_3SiN_3 (20 mol equiv to catalyst) was added to the reaction mixture, and the IR scan was started. There was a new broad peak around 2072 cm^{-1} (Figure 1B). DFT calculation (B3LYP/LanL2DZ level) indicated that $Sm(N_3)_2(OMe)$ and $SmN_3(OMe)_2$ have absorptions at 2082 and 2083 cm^{-1}, respectively. These calculations suggested that that samarium azide complex containing alkoxide ligands has an absorption at a lower frequency than $Sm(N_3)_3$ on the IR spectrum. In fact, there should be a lot of TBHP and/or *t*-BuOH present in the reaction mixture of the sequential process. Thus, we conclude that the broad peak at 2072 cm^{-1} corresponds to the samarium azide complex in which the samarium metal is bound or coordinated by other

(16) (a) Choukroun, R.; Gervais, D. *J. Chem. Soc., Dalton Trans.* **1980**, 1800. (b) Blandy, C.; Choukroun, R.; Gervais, D. *Tetrahedron Lett.* **1983**, *24*, 4189. (c) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185. (d) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. (e) McCleland, B. W.; Nugent, W. A.; Finn, M. G. *J. Org. Chem.* **1998**, *63*, 6656. (f) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (g) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924.

(17) The concentration of the monomeric species corresponding to $[Sm(N_3)_2(Ph_3As{=}O)_3]^+$ and $[Sm(N_3)_2(Ph_3As{=}O)_4]^+$ in the mixture would be very low because the treatment of Me_3SiN_3 with either Sm(O-*i*-Pr)$_3$ or (*S*)-Sm complex **1** resulted in similar IR spectra. For details, see the Supporting Information.

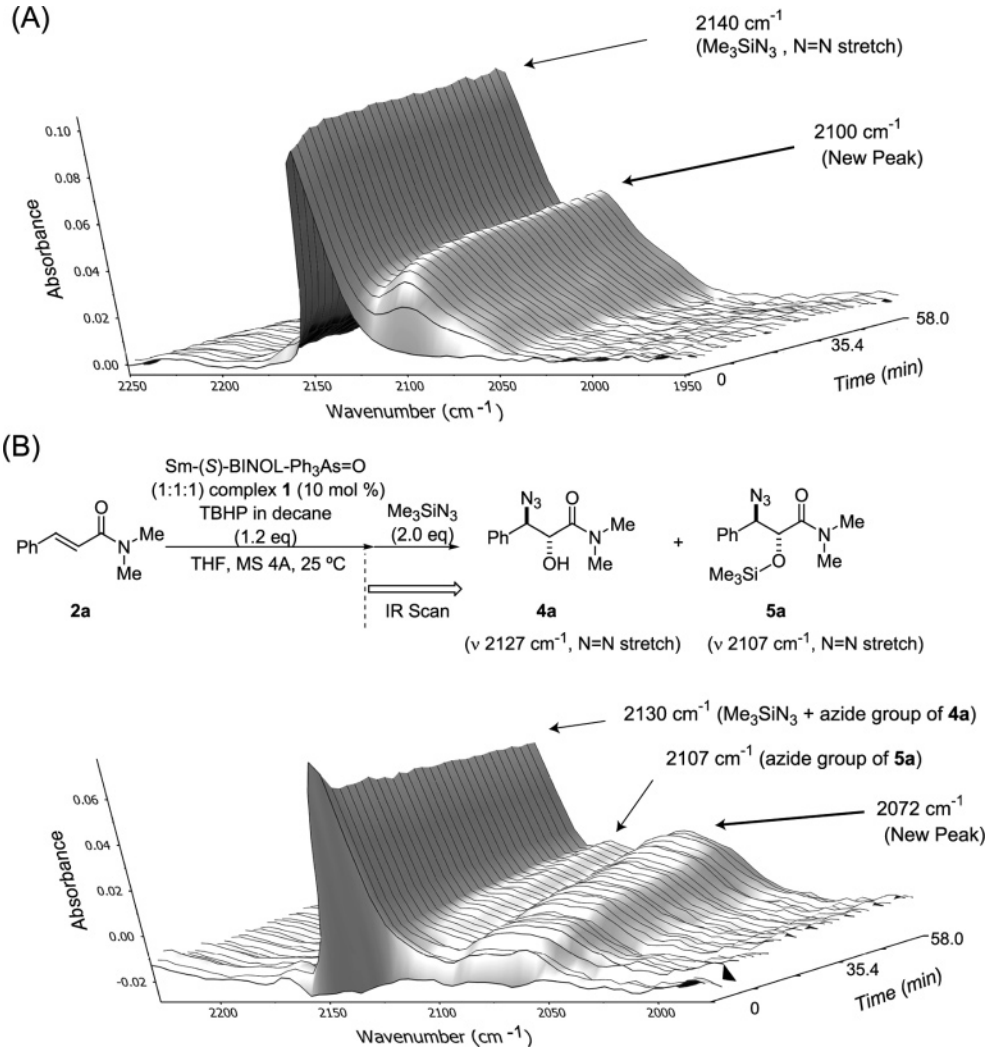


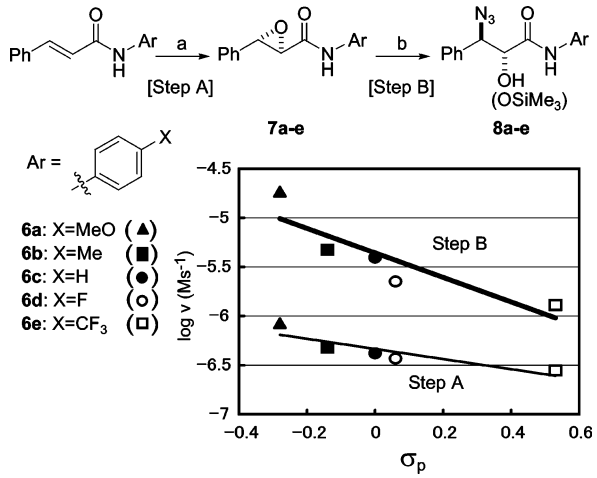
Figure 1. In situ IR experiments. (A) Me_3SiN_3 (20 mol equiv) + Sm(O-*i*-Pr)$_3$ (1 mol equiv). (B) IR spectra in the one-pot sequential process with (*S*)-Sm complex **1**.

ligands such as alkoxide.[18,19] On the other hand, there were no peaks observed, other than the ones corresponding to Me_3SiN_3 (ν = 2140 cm^{-1}, N═N stretch), when treated with Sm(OTf)$_3$ in THF. As mentioned above, the epoxide-opening reaction with Sm(O-*i*-Pr)$_3$ was promoted more smoothly than that with Sm(OTf)$_3$ (Table 1). These results suggest that Sm(O-*i*-Pr)$_3$ or the (*S*)-Sm complex **1** works in the epoxide-opening reaction, not simply as a Lewis acid, but as the active azidation reagent by formation of the highly reactive samarium azide complex. It is noteworthy that the ligand exchange to form the samarium azide complex occurred predominantly even in the presence of other components such as the substrate, TBHP, and/or *t*-BuOH, efficiently promoting the epoxide-opening reaction.

In stark contrast to the success using α,β-epoxy amides that exhibited high reactivity and complete regioselectivity, α,β-epoxy ketones and α,β-epoxy esters remained almost unchanged with Me_3SiN_3 at room temperature in the presence of 10 mol % of Sm(O-*i*-Pr)$_3$.[20] These results suggest that the Lewis basicity of the carbonyl moiety has a key role in the epoxide-opening reaction promoted by the samarium catalyst. In fact, the catalytic epoxide-opening reaction of tertiary amides proceeded more smoothly than that of the secondary amides (Table 2, **2a** vs **2l** and **2o** vs **2s**). To further investigate the origin of the dramatic difference in reactivity, we performed the ring-opening reaction of various α,β-epoxy anilides **7a**−**e**, where the Lewis basicity of the carbonyl moiety was tuned by a para-substituent (X) on the benzene ring (Scheme 3, step B). As shown in the Hammett plot in Scheme 3,[21] the initial rate (v) of step B increased as the electron-donating ability of X increased. These results suggested that more Lewis-basic amide carbonyl coordinates to the samarium more efficiently and enhances the nucleophilicity of the active samarium azide complex, resulting in the high reactivity of α,β-epoxy amides. These findings prompted us to examine the effects of Lewis basicity of the amide moiety in the asymmetric epoxidation. We previously reported that enhancement of the reactivity appeared to be related to the decrease in the energy level of the lowest unoccupied molecular orbital (LUMO) in catalytic asymmetric epoxidation of α,β-unsaturated carboxylic acid imidazolides. *N*-Acyl-4-phenyl-

(18) BINOL would not be involved in the samarium azide complex because all of the BINOL was silylated in the reaction mixture.
(19) The broadened peak at 2072 cm^{-1} suggested that the samarium azide complex exists as a mixture of several oligomeric species in equilibrium.
(20) α,β-Epoxy chalcone: no reaction. α,β-Epoxy methyl cinnamate: trace.
(21) For Hammett substituent constants, see: Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley and Sons: New York, 2002.

Scheme 3. Effect of Amide Moiety on the Reactivity and the Hammett Plot[a]

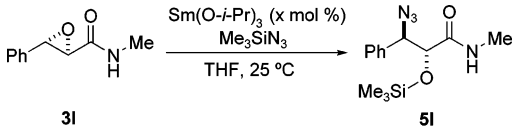


[a] (a) (*S*)-Sm complex **1** (10 mol %), TBHP in decane (1.2 equiv), THF, MS 4A, 25 °C. (b) $Sm(O\text{-}i\text{-}Pr)_3$ (10 mol %), Me_3SiN_3 (2 equiv), THF, 25 °C.

Table 3. Molecular Orbital Calculations (B3LYP/6-31G(d) Level) of α,β-Unsaturated Ester and α,β-Unsaturated Amides

substrate	σ_p	LUMO energy level (eV)
N-methylcinnamamide (**2l**)	−	−1.46
methyl cinnamate	−	−1.72
6a	−0.28	−1.64
6b	−0.14	−1.68
6c	0	−1.72
6d	0.06	−1.78
6e	0.53	−1.96

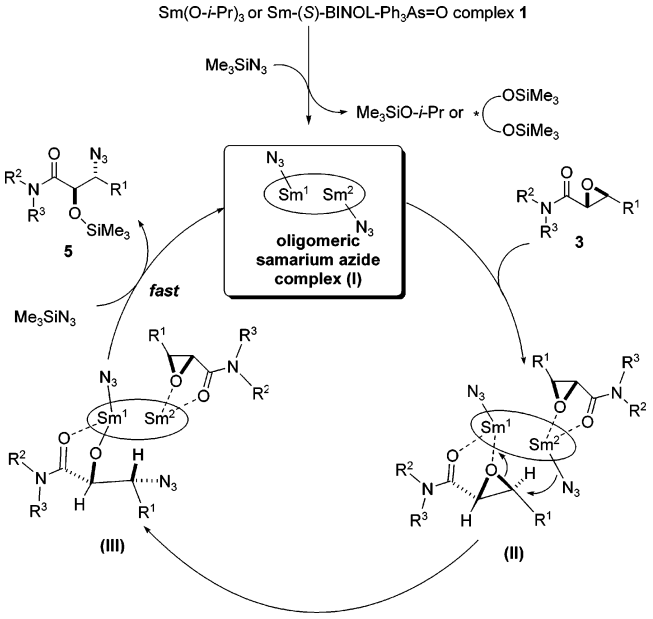
Scheme 4. Initial Rate Kinetics of Epoxide-Opening Reaction of **3l** with Azide



1.08 order dependency on $[Sm(O\text{-}i\text{-}Pr)_3]$
0.04 order dependency on $[Me_3SiN_3]$

imidazolide, which has the lowest LUMO energy level among the other *N*-acylimidazolides, gave the best results in terms of reactivity and enantioselectivity.[6e,9c] Catalytic asymmetric epoxidation of α,β-unsaturated simple amides, however, tended to have relatively high reactivity in contrast to much lower reactive α,β-unsaturated esters, opposite to the expectation based on the LUMO energy calculations (Table 3; B3LYP/6-31G(d) level, *N*-methylcinnamamide: −1.46 eV, methyl cinnamate: −1.72 eV).[9a,c] Thus, we measured the initial rates of the asymmetric epoxidation of various α,β-unsaturated anilides **6a**−**e** using 10 mol % of (*S*)-Sm complex **1** (Scheme 4, step A). As a result, the initial rate (v) of step A increased as the electron-donating ability of X increased, similar to step B. This result indicates that the unexpectedly high reactivity of α,β-unsaturated simple amides for the catalytic asymmetric epoxidation is due to the relatively high Lewis basicity of the amide carbonyl moiety, which would enhance the nucleophilicity of the lanthanide peroxide. In addition, the enhancement of the

Scheme 5. Proposed Catalytic Cycle of the Epoxide-Opening Reaction with Azide



reactivity would be effective enough to overwhelm the potentially low reactivity that derives from the high LUMO energy level.[22−24]

We also performed initial rate kinetic studies of the ring-opening reaction of α,β-epoxy amide **3l** with Me_3SiN_3 using catalytic $Sm(O\text{-}i\text{-}Pr)_3$. The kinetic studies revealed that the reaction rate had a 1.08 order dependency on the concentration of $Sm(O\text{-}i\text{-}Pr)_3$ and a 0.04 order dependency on the concentration of Me_3SiN_3 (Scheme 4). On the basis of these mechanistic studies, the proposed catalytic cycle of the epoxide-opening reaction with Me_3SiN_3 is illustrated in Scheme 5. $Sm(O\text{-}i\text{-}Pr)_3$ or the (*S*)-Sm complex **1** undergoes ligand exchange by the addition of Me_3SiN_3 to generate a highly reactive samarium azide complex (I). Although the precise structure of the samarium azide complex is unclear, it might include at least two samarium metals, and the result of a first-order kinetic dependency on the catalyst suggests that the epoxide opening occurs via cooperative reactivity of those metals.[25] α,β-Epoxy amide **3** coordinates to one samarium metal (Sm^1) of the complex in a bidentate manner (II), by which the direction of

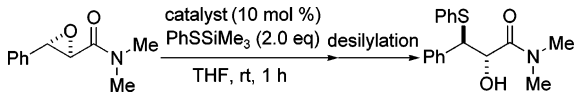
(22) The catalytic asymmetric epoxidation of α,β-unsaturated *N*-acylimidazolides or α,β-unsaturated ketones would proceed easily because of their low enough LUMO energy level and thus would not require the Lewis base enhancements.

(23) The initial rate of step A should be increased as the LUMO energy level decreased (**6a** → **6e**) if the effects of Lewis basicity of carbonyl moiety were ignored. As observed in the Hammett plot of Scheme 3, the range of the initial rate of step A was smaller than that of step B, where only the Lewis basicity defines the reactivity.

(24) For other examples of the superiority of α,β-unsaturated amides to α,β-unsaturated esters in terms of reactivity, see: (a) Concellón, José M.; Rodríguez-Solla, H.; Gómez, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1917. (b) Kamimura, A.; Murakami, N.; Kawahara, F.; Yokota, K.; Omata, Y.; Matsuura, K.; Oishi, Y.; Morita, R.; Mitsudera, H.; Suzukawa, H.; Kakehi, A.; Shirai, M.; Okamoto, H. *Tetrahedron* **2003**, *59*, 9537.

(25) Azide groups can act as bridging ligands between metal atoms leading to di- and polynuclear complexes. For selected examples, see: (a) Fehlhammer, W. P.; Dahl, L. F. *J. Am. Chem. Soc.* **1972**, *94*, 3377. (b) DeMunno, G.; Poerio, T.; Biau, G.; Julve, M.; Lloret, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1459. (c) Goher, M. A. S.; Al-Salem, N. A.; Mautner, F. A.; Klepp, K. O. *Polyhedron* **1997**, *16*, 825. (d) Clegg, W.; Krischner, H.; Saracoglu, A. I.; Sheldrick, G. M. *Z. Kristallogr.* **1982**, *161*, 307. On the basis of the large coordination numbers of lanthanide metals, the samarium azide complex might contain an azido-bridging structure to form the oligomer.

Table 4. Regioselective Epoxide-Opening Reaction by the Sm Catalyst with $PhSSiMe_3$



entry	catalyst	conversion[a] (%)	ratio (C-β:C-α)
1[b]	$Sm(O\text{-}i\text{-}Pr)_3$	100	95:5
2[b]	Sm−(*S*)-BINOL−Ph_3As=O (1:1:1) complex **1**	100	92:8
3[c]	$Sm(OTf)_3$	9	>98:2

[a] Determined by ^1H NMR analysis. [b] Desilylation was conducted with 1 N HCl aq−MeOH. [c] Desilylation was conducted with KF in MeOH.

the nucleophile entry is controlled and preferential attack at the β-position is achieved. The delivery of the bound azide to the epoxide on a single metal center to afford the epoxide-opened product with anti stereochemistry is geometrically impossible.[16e] Thus, the azide ligand, which is bound to another samarium metal (Sm^2) and activated by coordination of another α,β-epoxy amide, would be transferred to the epoxide intramolecularly to give samarium alkoxide(III). The subsequent ligand exchange with Me_3SiN_3 regenerates the samarium azide complex (I) together with the production of silyl ether **5**. This step would proceed very fast so that the rate-determining step of the epoxide opening should be in a part of (I) to (III) (presumably (II) to (III)).

(D) Application to Other Nucleophiles. On the basis of the findings of the regioselective ring-opening reaction of α,β-epoxy amides with Me_3SiN_3 using catalytic $Sm(O\text{-}i\text{-}Pr)_3$, we explored variant reactions using other nucleophiles, such as sulfur and carbon nucleophiles.

Table 4 summarizes the results of catalytic epoxide opening with $PhSSiMe_3$. The epoxide opening of **3a** with 2 equiv of $PhSSiMe_3$ in the presence of 10 mol % of $Sm(O\text{-}i\text{-}Pr)_3$ resulted in the clean consumption of **3a** within 1 h at room temperature. After desilylation, the corresponding β-phenylthio-α-hydroxyamide **9a** was obtained with high regioselectivity (C-β:C-α = 95:5, entry 1). The (*S*)-Sm complex **1** gave the product with similar reactivity and slightly lower regioselectivity (C-β:C-α = 92:8, entry 2). When 10 mol % of $Sm(OTf)_3$ was used instead of $Sm(O\text{-}i\text{-}Pr)_3$ (entry 3), the reaction proceeded with a much lower reaction rate, giving **9a** in 9% conversion after 1 h.[26] Only a trace amount of **9a** was obtained in the absence of the catalyst, even after 48 h. Similar to the epoxide-opening reaction with Me_3SiN_3, α,β-epoxy ketones and α,β-epoxy esters were much less reactive substrates.

A one-pot sequential process with a sulfur nucleophile was then examined. The results are summarized in Table 5. After completion of the catalytic asymmetric epoxidation of **2a** with 10 mol % of (*S*)-Sm complex **1**, the addition of 2 equiv of $PhSSiMe_3$ (condition A) directly to the reaction mixture resulted in smooth epoxide opening within 1 h. Subsequent desilylation gave the epoxide-opened product in 86% overall yield with 92:8 regioselectivity (entry 1). Alternatively, the addition of 3 equiv of PhSH (condition B) was also effective, affording the product with comparable reactivity (93% yield) and regioselectivity (C-β:C-α = 94:6) (entry 2). Morpholinyl amide **2b** was also applicable (entries 3 and 4), and the electron-donating group on the aromatic ring increased the regioselectivity (entries 5 and 6). Secondary amide **2l** gave the epoxide-opened product with higher regioselectivity (C-β:C-α > 98:2) than did tertiary amides. For β-aliphatic substrates, secondary amides gave successful results in terms of regioselectivity.[27] The asymmetric epoxidation of **2s** and the subsequent epoxide opening with either Me_3SiSPh or PhSH proceeded smoothly, giving the corresponding product **9s** with high selectivity (92:8 and 90:10, respectively; entries 9 and 10). γ-Branched substrate **2t** required a longer reaction time for the epoxide opening (>72 h), and **9t** was obtained with modest regioselectivity (C-β:C-α = 85:15, 80:20) (entries 11 and 12). In general, oxidation of the sulfide by the remaining TBHP (ca. 0.2 equiv) was not problematic in the present sequential process.[28]

On the basis of the postulated catalytic cycle shown in Scheme 5, a similar reaction mechanism might occur in the epoxide-opening reaction with $PhSSiMe_3$ or PhSH. The formation of monosilylated BINOL was detected by ESI-MS analysis of the mixture of the (*S*)-Sm complex **1** and $PhSSiMe_3$. This result, as well as the lower catalyst activity of $Sm(OTf)_3$ compared with that of $Sm(O\text{-}i\text{-}Pr)_3$ (Table 4, entry 3), suggests that samarium thiolate (Sm−SPh) is generated through dynamic ligand exchange and acts as the highly nucleophilic reagent.

We also examined the regioselective ring-opening reaction of α,β-epoxy amides with Me_3SiCN using catalytic $Sm(O\text{-}i\text{-}Pr)_3$. On the basis of the reports by Utimoto et al.,[2] we expected that samarium cyanide would be generated and work effectively as an active cyanating reagent. The results are shown in Table 6. The epoxide-opening reaction of **3a** with Me_3SiCN in the presence of 10 mol % of $Sm(O\text{-}i\text{-}Pr)_3$ proceeded smoothly at room temperature, giving the corresponding β-cyano-α-trimethylsilyloxyamide **10a** in 81% yield with good regioselectivity (C-β:C-α = 88:12) after 24 h (entry 1). The reaction of secondary amide **3l** also proceeded smoothly, and the product **10l** was obtained in 80% yield with higher regioselectivity (C-β:C-α = 93:7; entry 2) than that obtained with tertiary amide **3a**. α,β-Epoxy amide with β-alky substituent (**3o**) gave the product **10o** in modest yield (57%) with good regioselectivity (C-β:C-α = 86:14) at room temperature (entry 3). Warming the reaction to 50 °C improved the reactivity to afford **10o** in 71% yield, without a decrease in regioselectivity (C-β:C-α = 85:15) (entry 4).

Extension to the one-pot sequential process was also examined. After completion of the catalytic asymmetric epoxidation of α,β-unsaturated amide, the addition of Me_3SiCN to the reaction mixture resulted in the sluggish epoxide opening, even at 50 °C. Improvement of the reactivity to achieve the sequential process is currently in progress.

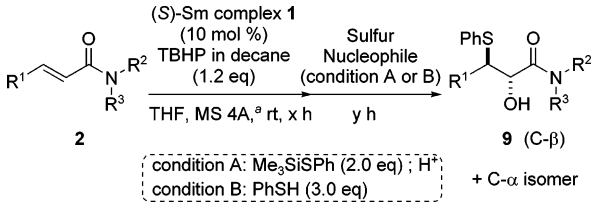
(E) Transformations to Biologically Active Compounds. Regioselective ring opening of the chiral α,β-epoxy amides with azide provides efficient access to chiral β-amino alcohols, which

(26) **9a** was obtained in 75% yield after 48 h.

(27) Tertiary amides gave the epoxide-opened products with low regioselectivity (ca. 1:1) although the reaction proceeded smoothly under the same reaction conditions. For the difference of the regioselectivity between secondary and tertiary amides, see ref 12.

(28) Less than 10% of the oxidized product was formed. When sulfide **9a** was subjected to conditions for the catalytic asymmetric epoxidation [(*S*)-Sm complex **1** (10 mol %), TBHP (1.2 equiv), THF, room temperature], a complex mixture of oxidized products was obtained.

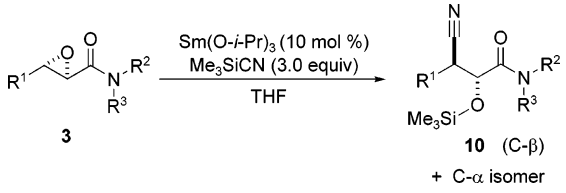
Table 5. One-Pot Sequential Process with a Sulfur Nucleophile



	substrate				time	yield[b]	ratio[c]	ee[d]	
entry	R^1	NR^2R^3		condition	*x*/*y* (h)	(%)	(C-β:C-α)	(%)	product
1	C_6H_5	NMe_2	**2a**	A	11/1	86	92:8	99	**9a**
2	C_6H_5	NMe_2	**2a**	B	11/1	93	94:6	99	**9a**
3	C_6H_5	morpholinyl	**2b**	A	11/1.5	85	95:5	99	**9b**
4	C_6H_5	morpholinyl	**2b**	B	11/1.5	91	96:4	99	**9b**
5	4-$MeOC_6H_4$	NMe_2	**2c**	A	11/1	83	96:4	>99	**9c**
6	4-$MeOC_6H_4$	NMe_2	**2c**	B	11/1	90	98:2	>99	**9c**
7	C_6H_5	NHMe	**2l**	A	15/2	70	>98:2	99	**9l**
8	C_6H_5	NHMe	**2l**	B	13/4	74	>98:2	99	**9l**
9	$Ph(CH_2)_2-$	NHMe	**2s**	A	11/2	76	92:8	99	**9s**
10	$Ph(CH_2)_2-$	NHMe	**2s**	B	6/2	72	90:10	99	**9s**
11	cyclohexyl	NHMe	**2t**	A	15/73	75	85:15	99	**9t**
12	cyclohexyl	NHMe	**2t**	B	14/76	74	80:20	99	**9t**

[a] MS 4A was used without prior activation (1000 mg/mmol of starting material). [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by chiral HPLC analysis.

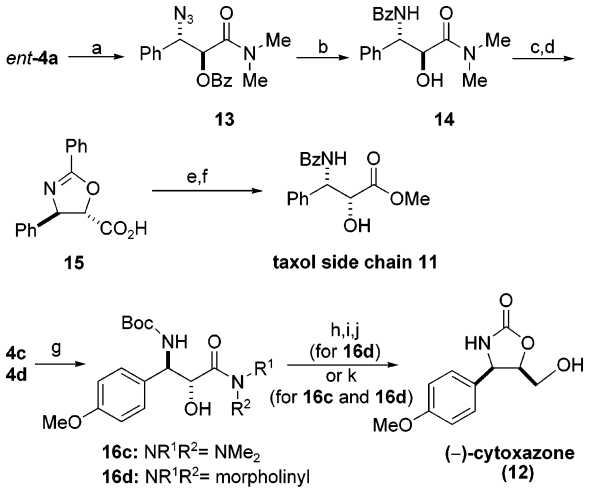
Table 6. Regioselective Epoxide-Opening Reaction by the Sm Catalyst with Me_3SiCN



	substrate							
				temp	time	yield[a]	ratio[b]	
entry	R^1	NR^2R^3		(°C)	(h)	(%)	(C-β:C-α)	product
1	C_6H_5	NMe_2	**3a**	rt	24	81	88:12	**10a**
2	C_6H_5	NHMe	**3l**	rt	39	80	93:7	**10l**
3	$Ph(CH_2)_2$-	NMe_2	**3o**	rt	36	57	86:14	**10o**
4	$Ph(CH_2)_2$-	NMe_2	**3o**	50	36	71	85:15	**10o**

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis.

Scheme 6. Synthesis of Taxol Side Chain and (−)-Cytoxazone[a]



[a] Conditions: (a) BzCl, Et_3N, cat. DMAP, CH_2Cl_2, room temperature, 98%; (b) cat. Pd−C, H_2 (1 atm), EtOAc, room temperature, 96%; (c) $SOCl_2$, $CHCl_3$, room temperature; (d) 1 N NaOH aq, EtOH, 60 °C, 70% (two steps); (e) Me_3SiCHN_2, Et_2O−MeOH, room temperature; (f) 1 N HCl aq, MeOH, reflux, 89% (two steps); (g) cat. Pd−C, Boc_2O, H_2 (1 atm), EtOAc, room temperature, 98% from **4c**, 99% from **4d**; (h) $LiAlH_4$, THF, −40 to 0 °C; (i) $NaBH_4$, MeOH−THF, room temperature; (j) NaH, THF, room temperature, 58% (three steps); (k) *n*-BuLi, $BH_3{\cdot}NH_3$, THF, 0 °C to room temperature, (39% from **16c**, 40% from **16d**).

are ubiquitous in various biologically active compounds.[29] Having established the above new process for the enantioselective synthesis of *anti*-β-azido-α-hydroxyamides, the utility was demonstrated by short syntheses of the side chain **11** of the anticancer drug, taxol,[30] and a novel cytokine modulator, (−)-cytoxazone (**12**)[31] (Scheme 6). For the synthesis of **11**, *ent*-**4a** was converted to azido benzoate **13**, which was hydrogenated to produce benzamide **14** via in situ O → N benzoyl transfer. Treatment of **14** with thionyl chloride to form an oxazoline ring, followed by hydrolysis of the dimethylamide gave known carboxylic acid **15**.[30d] Methylation of **15** and the oxazoline ring opening under acidic conditions afforded the taxol side chain **11**. For the synthesis of (−)-cytoxazone (**12**), morpholinyl amide **4d** was converted to *N*-Boc amine **16d**, which was subjected to stepwise reduction of the morpholinyl amide to primary alcohol. Finally, subsequent cyclization afforded **12** in 58% yield for three steps. Alternatively, **12** was also synthesized from **16c** or **16d** using *n*-BuLi and $BH_3{\cdot}NH_3$,[32] respectively. In these cases, the reduction of the tertiary amide to primary alcohol and the

(29) For reviews of asymmetric synthesis of vicinal amino alcohols, see: (a) Bergmeire, S. C. *Tetrahedron* **2000**, *56*, 2561. (b) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; p 243.

(30) For general review, see: (a) Kingston, D. G. I. *Chem. Commun.* **2001**, 867. (b) Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 726. (c) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451. For synthesis of taxol from baccatin III, see: (d) Kingston, D. G. I.; Chaudhary, A. G.; Gunatilaka, A. A. L.; Middleton, M. L. *Tetrahedron Lett.* **1994**, *35*, 4483.

(31) Madhan, A.; Kumar, A. R.; Rao, B. V. *Tetrahedron: Asymmetry* **2001**, *12*, 2009 and references therein.

(32) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623.

following cyclization proceeded successively, affording **12** in 39% (from **16c**) or 40% (from **16d**) yield.

Summary

The Sm−BINOL−$Ph_3As{=}O$ complex, the catalyst for highly enantioselective epoxidation of α,*β*-unsaturated amide, undergoes dynamic ligand exchange by the subsequent addition of Me_3SiN_3. The newly generated samarium azide complex works as a highly reactive reagent for the regioselective ring opening of α,*β*-epoxy amides. Thus, we developed a mild and efficient one-pot sequential asymmetric epoxidation-regioselective epoxide-opening process with various α,*β*-unsaturated amides, affording *anti*-*β*-azido-α-hydroxyamides in up to 99% yield with complete regioselectivity and up to greater than 99% ee. Strong evidence for generation of the samarium azide complex was obtained by in situ IR spectroscopy and other experiments. This is the first investigation of the physical property of lanthanide azide. The relatively high reactivity of both the asymmetric epoxidation and the epoxide-opening reaction is ascribed to the high Lewis basicity of the amide moiety. The developed sequential process can be extended to other nucleophiles such as thiols. In addition, the epoxide-opened products are versatile intermediates, and *anti*-*β*-azido-α-hydroxyamides were transformed into biologically active compounds.

Acknowledgment. This work was supported by RFTF, Grant-in-Aid for Encouragements for Young Scientists (A), and Grant-in-Aid for Specially Promoted Research from the Japan Society for the Promotion of Science (JSPS) and Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Supporting Information Available: Experimental procedures, characterization of all new compounds with their copies of ^1H and ^{13}C NMR spectra, and other detailed results and discussions (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA043770+