論文の内容の要旨

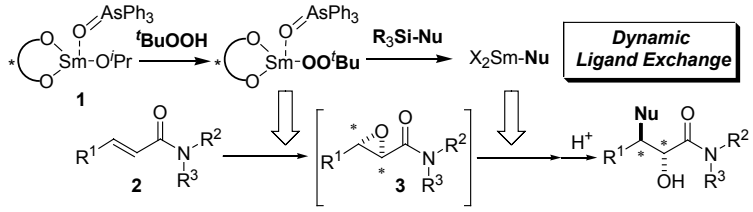
論文題目　**Development of New Reactions Promoted by the Rare-Earth Metal Complexes**

（希土類金属錯体を活用した新規反応の開発）

氏　名　戸﨑 慎也

[1] Dynamic Ligand Exchange of the Rare-Earth Metal Complex

Scheme 1. Dynamic Ligand Exchange of the Rare-Earth Complex and Strategy for One-Pot Sequential Process

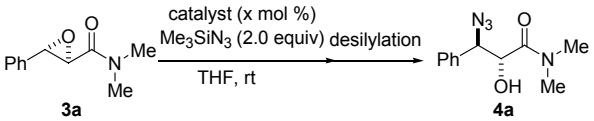


On the basis of the nature of the rare-earth metal complexes, such as moderate Lewis acidity, multifunctionality, large coordination numbers, and fast ligand exchange ability, I anticipated that subsequent addition of other reagents would alter the structure and function of the rare-earth complex in situ through dynamic ligand exchange to promote different reactions successively. In this regard, the rare-earth–BINOL complex appeared to be a suitable catalyst. Our group reported a general and highly enantioselective epoxidation of α,β-unsaturated simple amides **2** catalyzed by the Sm–(*S*)-BINOL–$Ph_3As{=}O$ complex **1**, prepared from $Sm(O^iPr)_3$, (*S*)-BINOL, and $Ph_3As{=}O$ in a ratio of 1:1:1.[1] The highly enantioenriched α,β-epoxy amides **3** (up to >99% ee), in particular α,β-epoxy morpholinyl amides,[2,3] are versatile intermediates because a ring-opening of the epoxide and a modification of the amide moiety provide efficient access to useful chiral building blocks. I assumed that the subsequent addition of another reagent (R_3Si-Nu) after the asymmetric epoxidation would generate another highly reactive complex (X_2Sm-Nu) to promote the catalytic epoxide-opening in one reaction vessel (Scheme 1).

Initial investigation began with the ring-opening reaction of α,β-epoxy amide (Table 1). As expected, treatment of α,β-epoxy amide **3a** with Me_3SiN_3 in the presence of 5 mol % of $Sm(O^iPr)_3$ led to a clean

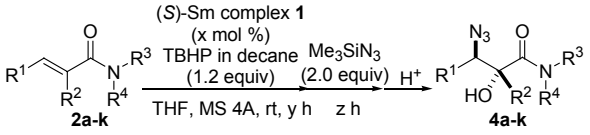
epoxide-opening within 1 h at room temperature, affording the corresponding *anti*-β-azido-α-hydroxyamide **4a** in 99% yield (entry 1). Reduced catalyst loading (0.2 mol %) was sufficient (99%; entry 2). The use of 5 mol % of the (*S*)-Sm complex **1** also completed the reaction (entry 3). In contrast, the reaction with 10 mol % of $Sm(OTf)_3$, a much stronger Lewis acid, proceeded sluggishly to give **4a** in 21% yield after 24 h. (entry 4).

Table 1. Regioselective Ring-Opening of α,β-Epoxy Amide



entry	catalyst	x (mol %)	time (h)	yield (%)
1	$Sm(O^iPr)_3$	5	1	99
2	$Sm(O^iPr)_3$	0.2	2	97
3	(*S*)-Sm complex **1**	5	1	99
4	$Sm(OTf)_3$	10	24	21

Table 2. One-Pot Sequential Process



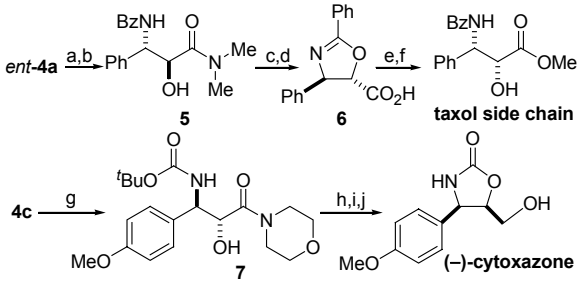
entry	substrate R^1	R^2	NR^3R^4	catalyst (x mol %)	time (y/z h)	yield (%)	ee (%)	product
1	Ph	H	NMe_2	5	12/1	99	99	**4a**
2	Ph	H	NMe_2	2	15/2	70	99	**4a**
3	Ph	H	morpholinyl	5	11/1	99	99	**4b**
4	4-MeO-C_6H_4-	H	morpholinyl	5	12/1	97	99	**4c**
5	4-F-C_6H_4-	H	NMe_2	5	11/1	98	>99	**4d**
6	2-furyl	H	NMe_2	10	11/0.5	45[a]	>99	**4e**
7	Ph	H	NHMe	10	13/8	83	99	**4f**
8	$-(CH_2)_3-$		NHBn	10	12/5	97	96	**4g**
9	$-(CH_2)_4-$		NHBn	10	13/1	86	99	**4h**
10	Ph$(CH_2)_2$-	H	NMe_2	5	6/12	84	98	**4i**
11	Ph$(CH_2)_2$-	H	morpholinyl	5	5/12	92	98	**4j**
12	cyclohexyl	H	NMe_2	10	6/16	75	99	**4k**

[a] The corresponding epoxide is unstable and decomposes on silica gel.

Encouraged by the above results, I examined the extension to a one-pot sequential process. After completion of the catalytic asymmetric epoxidation of **2a** in the presence of 5 mol % of the (*S*)-Sm complex **1**, Me_3SiN_3 was directly added to the reaction mixture. The epoxide-opening proceeded smoothly without adverse effects (99%, 99% ee; Table 2, entry 1). As summarized in Table 2, the present one-pot sequential process had broad substrate generality, and especially noteworthy was the complete regioselectivity of the β-aliphatic substrates (entries 8–12).

Having established the above new one-pot sequential process, the utility was demonstrated by short syntheses of the side chain of the anticancer drug, taxol and a novel cytokine modulator, (–)-cytoxazone (Scheme 2).

Scheme 2. Transformations

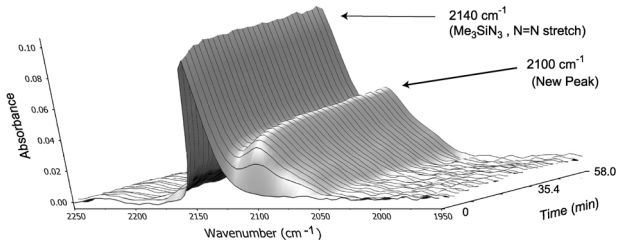


Reagents and Conditions: (a) BzCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 98%; (b) cat. Pd-C, H_2 (1 atm), EtOAc, rt, 96%; (c) $SOCl_2$, $CHCl_3$, rt; (d) 1 N NaOH aq., EtOH, 60 ºC, 70% (2 steps); (e) Me_3SiCHN_2, Et_2O-MeOH, rt; (f) 1 N HCl aq., MeOH, reflux, 89% (2 steps); (g) cat. Pd-C, Boc_2O, H_2 (1 atm), EtOAc, rt, 99%; (h) $LiAlH_4$, THF, –40 to 0 ºC; (i) $NaBH_4$, MeOH-THF, rt; (j) NaH, THF, rt, 58% (3 steps)

Mechanistic Study: I performed spectroscopic experiments to gain precise information of the anticipated rare-earth azide complex, which has never been characterized. When $Sm(O^iPr)_3$ (1 mol equiv) and Me_3SiN_3 (5 mol equiv) were mixed in THF-d_8, the generation of Me_3SiO^iPr was observed on ^1H and ^{13}C NMR spectra, suggesting that a ligand exchange occurs from the isopropoxide to the azide on the samarium metal. Next, I measured in situ IR spectra. When Me_3SiN_3 (20 mol equiv) was treated with $Sm(O^iPr)_3$ (1 mol equiv) in THF, a new peak appeared around 2100 cm^{-1} on in situ IR spectra (Figure 1). Treatment of Me_3SiN_3 with the (*S*)-Sm complex **1** instead of $Sm(O^iPr)_3$ gave similar spectra. DFT calculation (B3LYP/LanL2DZ level) suggested that $Sm(N_3)_3$ has an absorption at 2093 cm^{-1} (N═N stretch). On the other hand, there were no new peaks observed when treated with $Sm(OTf)_3$ in THF. These results indicate that $Sm(O^iPr)_3$ or the (*S*)-Sm complex **1** works in the epoxide-opening reaction, not

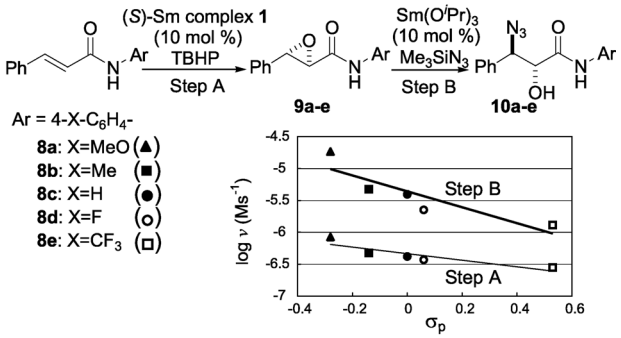
simply as a Lewis acid, but as the active azidation reagent by formation of the highly reactive samarium azide complex. This is the first investigation of the physical property of the rare-earth azide complex.

Figure 1. In Situ IR Spectra



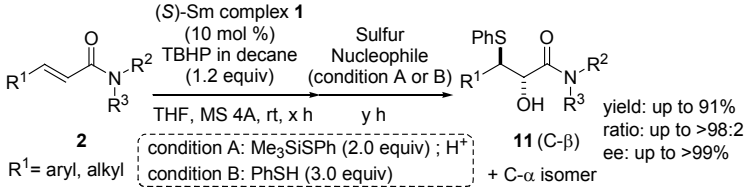
In stark contrast to the success using α,β-epoxy amides, α,β-epoxy ketones and α,β-epoxy esters remained almost unchanged under the reaction conditions shown in Table 1. These facts suggested that the Lewis basicity of the carbonyl moiety has a key role in the epoxide-opening reaction. To investigate the origin of the dramatic difference in reactivity, I performed the ring-opening reaction of α,β-epoxy anilides **9a**–**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 a result, the initial rate (v) of Step B increased as the electron-donating ability of X increased. Remarkably, a similar tendency was observed in the initial rate of the asymmetric epoxidation (Step A). These results suggested that more Lewis-basic amide carbonyl coordinates to the samarium more efficiently and enhances the nucleophilicity of the active samarium–nucleophile complex. In the asymmetric epoxidation of α,β-unsaturated simple amides, the enhancement would be effective enough to overwhelm the potentially low reactivity that derives from the high LUMO energy level, thus achieving the high reactivity.

Scheme 3. Hammett Plot



Exploring other nucleophiles for the sequential process revealed that the use of $PhSSiMe_3$ or PhSH was effective (Scheme 4). Samarium thiolate should be generated through dynamic ligand exchange and act as the active species.

Scheme 4. Application to Sulfur Nucleophile



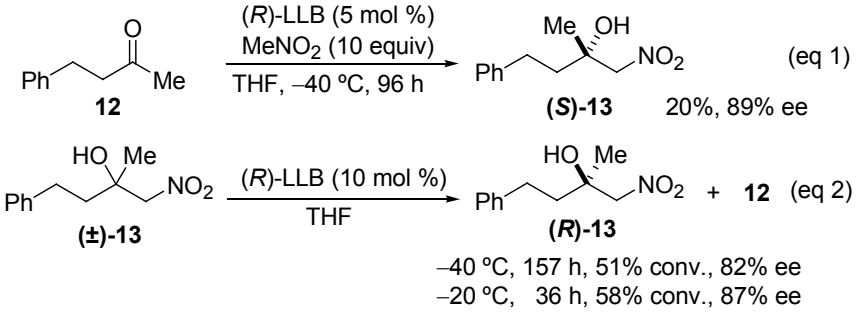
I developed a mild and efficient one-pot sequential catalytic asymmetric epoxidation-regioselective epoxide-opening process promoted by the Sm–BINOL–$Ph_3As{=}O$ complex. The key to the success was the in situ generation of the highly reactive samarium–nucleophile complex through dynamic ligand exchange.[4]

[2] Catalytic Asymmetric Synthesis of Tertiary Nitroaldols

The enantioselective construction of tetrasubstituted carbon centers represents an attractive area in synthetic organic chemistry because they are ubiquitous motif in pharmaceuticals and biologically significant molecules. Catalytic asymmetric Henry reaction (nitroaldol reaction) of ketones would lead to chiral tertiary nitroaldols, which are very useful intermediates. There are, however, no reports on general asymmetric synthesis of tertiary nitroaldols, and very few methodologies even for the racemic version. The difficulty presumably arises from the attenuated reactivity of simple ketones and a strong tendency toward retro-Henry reaction, which makes this subject quite challenging.

In the early 1990s, our group reported the first example of the catalytic asymmetric Henry reaction of aldehydes promoted by the heterobimetallic $LaLi_3$tris(binaphthoxide) complex (LLB). To address the above-mentioned issue, I initially tested LLB for the Henry reaction of ketone **12**. Notably, the reaction proceeded at –40 ºC in the presence of 5 mol % of (*R*)-LLB, affording the corresponding tertiary nitroaldol **(*S*)-13** with 89% ee although the catalytic efficiency was unsatisfactory (20%; Scheme 5, eq 1). Assuming that the low chemical yield was due to fast retro-Henry reaction, I turned my attention to kinetic resolution of racemic **13**, expecting that (*R*)-LLB would preferentially convert the matched enantiomer **(*S*)-13** into **12** and leave the mismatched enantiomer **(*R*)-13** unchanged. As a result, the retro-Henry reaction of **(±)-13** proceeded at –40 ºC in the presence of catalytic (*R*)-LLB, giving **(*R*)-13** with 82% ee at 51% conversion. Raising temperature to –20 ºC increased the reaction rate (eq 2). Further optimization of the reaction conditions and examination of substrate scope are currently in progress.

Scheme 5. Catalytic Asymmetric Synthesis of Tertiary Nitroaldols



[References]

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(4) Tosaki, S.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 2147.