Effect of Molecular Sieves and Methanol on the *endo*-Selectivity in $La(OTf)_3$-catalyzed Cyclization of 5-Hydroxy-2-methoxymethyl-1,2-epoxide System

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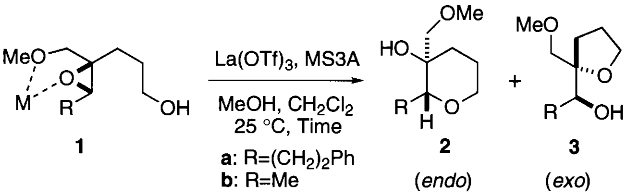
Molecular sieves improved the reproducibility of the cyclization catalyzed by $La(OTf)_3$ in the 5-hydroxy-2-methoxymethyl-1,2-epoxide system, and addition of methanol raised the desired *endo*-selectivity.

endo-Cyclization of hydroxy epoxide is an attractive and straightforward process to construct the frameworks of marine fused polycyclic ethers,[1] such as brevetoxins[2] and ciguatoxins,[3] while the reaction has been known to proceed naturally with an *exo*-mode.[4] We recently reported *endo*-selective cyclizations, which were accomplished by the regioselective activation of an epoxide with the coordination of $La(OTf)_3$ between the oxygen atoms of a directing group and an epoxide (Scheme 1).[5] During the study, we had found that commercial $La(OTf)_3$ did not give the desired selectivity as it stands and that some strictly controlled conditions for the preparation of the catalyst were necessary for reproduction of high *endo*-selectivity of the cyclization.[5b] For increase of the reproducibility in a simple procedure, we have investigated several additives in the reaction with commercial $La(OTf)_3$. It is described here that the addition of molecular sieves and methanol is available in the *endo*-cyclization of 5-hydroxy-2-methoxymethyl-1,2-epoxide system.



Scheme 1.

We examined the respective cyclization of *cis*-7-phenyl-4,5-epoxy-4-methoxymethyl-1-heptanol (**1a**) and *cis*-4,5-epoxy-4-methoxymethyl-1-hexanol (**1b**) to cyclic ethers (**2** and **3**). The conditions and results are shown in Tabel 1. When commercial anhydrous catalysts [$La(OTf)_3$] purchased from different suppliers were used as such without additive in the reaction of **1a**, each catalyst gave a different ratio of the products with the different rate of the reaction (entries 1-3). Addition of pre-dried molecular sieves 3A (MS3A) decreased the differences between the catalysts (entries 4-6). Thus, the problem on the reproducibility with commercial $La(OTf)_3$ was solved, though the *endo*-selectivity was rather low yet. Furthermore, several attempts to improve the selectivity proved addition of methanol to the above reaction system to be effective.

Table 1.

Entry	**1**	$La(OTf)_3$[a] (1.1 eq)	MeOH[b]	MS3A[c]	Time	Ratio[d] of **2/3** (Yield/%)[e]
1	**1a**	A	–	–	1 d	12/88 (100)
2		B	–	–	3 d	63/37 (43) [57]
3		C	–	–	1.4 h	7/91 (99)
4		A	–	+	3 d	41/59 (76)
5		B	–	+	3 d	57/43 (99)
6		C	–	+	3 d	51/49 (99)
7		A	3	+	2 d	60/40 (100)
8		A	11	+	3 d	78/22 (88) [10]
9		A	13	+	7 d	79/21 (99)
10		A	13	–	1 d	19/81 (97)
11		A	15	+	3 d	74/26 (96) [4]
12		B	13	+	3 d	79/21 (83) [17]
13		C	13	+	3 d	79/21 (75) [25]
14	**1b**	A	–	–	3 h	12/88 (93)
15		A	13	+	3 d	91/9 (96)

The concentration was 15 mM. [a] The catalysts were purchased from Aldrich (A), TCI (B), and Strem (C). [b] Equivalent to $La(OTf)_3$. [c] $La(OTf)_3$: MS3A = 1 : 1.5 (w/w). [d] Estimated by GLC. [e] The yield/% of recovered **1** is shown in brackets.

After examined the reaction using one of the catalysts in various amounts of methanol (entries 7-11),[6] it was found that the addition of 13 equivalents of methanol to $La(OTf)_3$ gave the best results in the ratio of **2**:**3**=79:21 (entry 9). When more than 11 equivalents of methanol was added, the rate of the reaction was slowed down, and in the presence of 15 equivalents of methanol the *endo*-selectivity was reduced (entry 11). In the addition of methanol without MS3A, 5-*exo* cyclization was favored (entry 10). These effects of methanol were also observed in other commercial catalysts (entries 12 and 13). The same procedure was applicable to **1b** giving a high *endo*-selectivity (entry 15).

As described above, increasing the amount of methanol tends to prefer the 6-*endo* cyclization and to decrease the rate of the reaction. The effect for *endo*-selectivity might be due to the coordination of methanol to the central metal in the desired chelation. Molecular sieves are suggested to efficiently catalyze the coordination resulting in the constant *endo*-selectivity.[7] In the presence of methanol with MS3A, $La(OTf)_3$ seemed to dissolve very sluggishly or not in CH_2Cl_2. The reaction might proceed on solid surfaces.

In conclusion, it was found that molecular sieves improved the reproducibility of the cyclization catalyzed by commercial $La(OTf)_3$, and the addition of methanol raised the 6-*endo* selectivity in the 5-hydroxy-2-methoxymethyl-1,2-epoxide system. Further applications of the reaction and mechanistic study are now in progress in our laboratory.

References and Notes

1 For reviews, see: a) Y. Shimizu, *Chem. Rev.*, **93**, 1685 (1993). b) T. Yasumoto and M. Murata, *Chem. Rev.*, **93**, 1897 (1993).

2 a) Y.-Y. Lin, M. Risk, S. M. Ray, D. Van Engen, J. Clardy, J. Golik, J. C. James, and K. Nakanishi, *J. Am. Chem. Soc.*, **103**, 6773 (1981). b) Y. Shimizu, H.-N. Chou, H. Bando, G. Van Duyne, and J. C. Clardy, *J. Am. Chem. Soc.*, **108**, 514 (1986). c) J. Pawlak, M. S. Tempesta, J. Golik, M. G. Zagorski, M. S. Lee, K. Nakanishi, T. Iwashita, M. L. Gross, and K. B. Tomer, *J. Am. Chem. Soc.*, **109**, 1144 (1987).

3 a) M. Murata, A. M. Legrand, Y. Ishibashi, and T. Yasumoto, *J. Am. Chem. Soc.*, **111**, 8929 (1989). b) M. Murata, A. M. Legrand, Y. Ishibashi, M. Fukui, and T. Yasumoto, *J. Am. Chem. Soc.*, **112**, 4380 (1990). c) T. Suzuki, O. Sato, M. Hirama, Y. Yamamoto, M. Murata, T. Yasumoto, N. Harada, *Tetrahedron Lett.*, **32**, 4505 (1991). d) M. Satake, A. Morohashi, H. Oguri, T. Oishi, M. Hirama, N. Harada, and T. Yasumoto, *J. Am. Chem. Soc.*, **119**, 11325 (1997).

4 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, **1976**, 734.

5 a) K. Fujiwara, T. Tokiwano, and A. Murai, *Tetrahedron Lett.*, **36**, 8063 (1995). b) K. Fujiwara, H. Mishima, A. Amano, T. Tokiwano, and A. Murai, *Tetrahedron Lett.*, **39**, 393 (1998). c) K. Fujiwara, N. Hayashi, T. Tokiwano, and A. Murai, *Heterocycles*, **50**, 561 (1999).

6 The typical experimental procedure is followed (Table 2, entry 12). A mixture of MS3A (45 mg), which was dried at 250 °C for 3 h *in vacuo* before use, anhydrous La(OTf)$_3$ (53.7 μmol), and methanol (699 μmol) in CH_2Cl_2 (1 ml) were stirred at 25 °C under argon atmosphere. To the mixture, the CH_2Cl_2 (2 ml) solution of **1** (10.9 mg, 46.3 μmol) was added, and the mixture was stirred at 25 °C for 3 days. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (15 ml). After extractive workup and purification by silica gel column chromatography, a mixture of **2** and **3** (9.1 mg, 83%), and recovered **1** (1.8 mg, 17%) were given.

7 For the similar effects of molecular sieves upon the reactivity and selectivity reported in other lanthanide catalysts, see: a) S. Kobayashi, I. Hachiya, H. Ishitani, and M. Araki, *Tetrahedron Lett.*, **34**, 4535 (1993). b) M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, and M. Shibasaki, *J. Am. Chem.Soc.*, **119**, 2329 (1997). c) S. Watanabe, Y. Kobayashi, T. Arai, H. Sasai, M. Bougauchi, and M. Shibasaki, *Tetrahedron Lett.*, **39**, 7353 (1998).