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Regioselective ring opening of epoxides by nucleophiles mediated by lithium bistrifluoromethanesulfonimide

Janine Cossy,[a,*] Véronique Bellosta,[a] Claire Hamoir[a] and Jean-Roger Desmurs[b]

[a]*Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France*
[b]*Rhodia, 190 avenue Thiers, 69457 Lyon Cedex 06, France*

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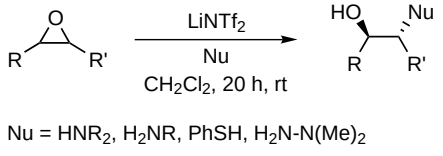
Abstract—In the presence of $LiNTf_2$, epoxides undergo ring opening with high regioselectivity and in good yield when they are treated with nucleophiles such as amines, hydrazines and thiophenol.

Epoxides have been recognized as important and versatile synthetic intermediates in organic synthesis.[1] They can be easily prepared and the strain of their three-membered ring together with the polarization of the C–O bonds make them susceptible to reaction with a large variety of reagents such as electrophiles, nucleophiles, acids, bases, reducing agents and some oxidizing agents. High reactivity with various nucleophiles leads to high regioselective and *trans*-stereospecific ring opening products. Therefore, there is a significant current interest in the ring opening of epoxides. However, this reaction, which is usually carried out with a large excess of nucleophiles at elevated temperature,[2] often fails when poorly nucleophiles and/or sterically hindered nucleophiles or epoxides are used. Several modifications of the classical procedures have been reported. For example, in the case of amines, metal amides (Al,[3] Mg,[4] Li,[5] Pb,[6] Sn[7] and Si[8]) have been employed but an important drawback, associated with these metal amides, is that epoxides frequently undergo rearrangement to produce allylic alcohols as the major products and that primary amines show no regioselectivity. To obviate these problems many activators/promoters such as Lewis acids or lithium salts have been developed to effect the ring opening of epoxides.[9,10] Good regioselectivity of ring opening by nucleophiles has been observed with $MgClO_4$,[9k] $LiClO_4$,[9k] LiOTf,[10e] $LiBF_4$,[9k] $Ti(OiPr)_4$,[9a–d] $Yb(OTf)_3$,[10d] $CoCl_2$.[9f] However, the use of perchlorates is dangerous and the work-up with Lewis acids, which are used very often in stoichiometric quantities, is often difficult due to emulsions. Furthermore, with these catalysts, deactivated aromatic amines and some sterically hindered amines fail to open up epoxides or still require high temperature or pressure. Hence, there is a need for newer versatile activators which could be of great benefit and we would like to report here that the commercially available inexpensive[11] and non-hazardous lithium salt, $LiNTf_2$, can be efficiently used in the ring opening of epoxides with nucleophiles such as amines, hydrazines and thiophenol, at room temperature, in dichloromethane or even without any solvent (Scheme 1).



Scheme 1.

We first examined the reaction of protected glycidol **1** in CH_2Cl_2 with amines in the presence of less than 1 equiv. of $LiNTf_2$. When **1** was treated with 1.2 equiv. of benzylamine in the presence of 0.1 equiv. of $LiNTf_2$ at rt for 20 h, amino alcohol **10** was isolated in 95% yield (Table 1, entry 1). The reaction was highly regioselective as **10** was the only detectable product. Epoxide **1** can be transformed to amino alcohol **11** in 86% yield when treated with 2-phenylethylamine (1.2 equiv.) in the presence of $LiNTf_2$ (0.1 equiv.) (Table 1, entry 2). The replacement of the benzyl protecting group in **1** by a *p*-methoxybenzyl (PMB) has no effect on the reactivity, as **12** was obtained in 85% yield from **2** (Table 1, entry 3). The reaction was extended to epoxides **3–9** and the results are reported in Table 1. Ring opening of

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* Corresponding author. Fax: +33-1-40-79-46-60; e-mail: janine.cossy@espci.fr

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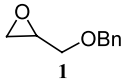
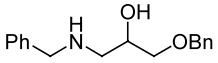
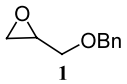
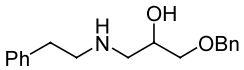
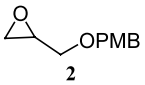
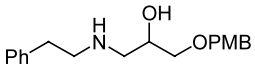
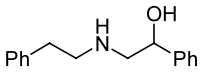
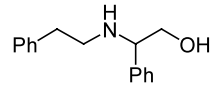
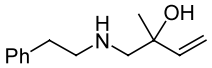
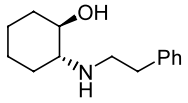
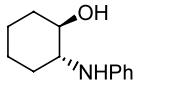
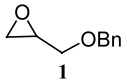
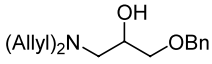
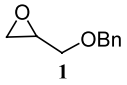
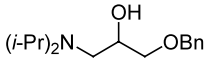
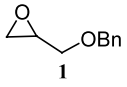
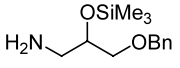
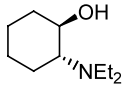
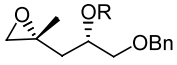
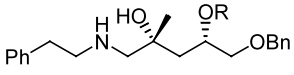
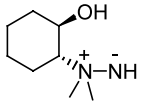
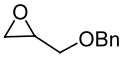
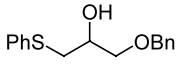
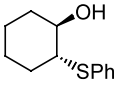
Table 1.

Entry	Epoxide	Amine (equiv)	$LiNTf_2$ equiv	Product Yield in CH_2Cl_2; (Yield without solvent)
1	 **1**	H_2NCH_2Ph (1.2)	0.1	 **10** 95%; (-)
2	 **1**	$H_2N(CH_2)_2Ph$ (1.2)	0.1	 **11** 86%; (86%)
3	 **2**	$H_2N(CH_2)_2Ph$ (1.2)	0.1	 **12** 85%; (-)
4	 **3**	$H_2N(CH_2)_2Ph$ (1.2)	0.1	  **13** + **14** 80/20 77%; (-)
5	 **4**	$H_2N(CH_2)_2Ph$ (1.2)	0.5	 **15** 88%; (-)
6	 **5**	$H_2N(CH_2)_2Ph$ (1.2)	0.1	 **16** 77%; (-)
7	 **5**	H_2NPh (2.0)	0.5	 **17** 89%; (~100%)
8	 **6**	$H_2N(CH_2)_2Ph$ (1.2)	0.5	no reaction
9	 **1**	$HN(Allyl)_2$ (2.0)	0.5	 **18** 60%; (-)
10	 **1**	$HN(i\text{-}Pr)_2$ (2.0)	0.5	 **19** 88%; (-)
11	 **1**	$[(Me)_3Si]_2NH$ (2.0)	0.5	 **20** 74%; (-)
12	 **5**	$HNEt_2$ (2.0)	0.5	 **21** 91%; (-)
		$H_2N(CH_2)_2Ph$ (2.0)		
13	**7** R = TES		0.5	R = TES **22** 60%
			1.0	R = TES **22** ~100%
	8 R = Piv		0.5	R = Piv **23** 86%
	9 R = MOM		1.0	R = MOM **24** ~100%

styrene oxide **3** with 2-phenylethylamine in the presence of $LiNTf_2$ (0.1 equiv.) led to **13** and **14** with a yield of 77% and in a ratio of 80/20 (Table 1, entry 4). Under these conditions, the attack at the terminal carbon was preferred to the attack at the benzylic carbon. It is worth noting that the regioselectivity of the ring opening of epoxide **3** is better in the presence of $LiNTf_2$ than with other activators such as $LiClO_4$ or LiOTf.[12] In the case of epoxide **4**, the attack of 2-phenylethylamine was chemo- and regioselective as amino alcohol **15** was the only obtained product which corresponds to the attack at the terminal position of the epoxide. The best yield (88%) was obtained in the presence of 0.5 equiv. of $LiNTf_2$ (Table 1, entry 5). Cyclohexene oxide **5** was transformed to amino alcohol **16** when treated with 2-phenylethylamine (77% yield) (Table 1, entry 6) and to **17** when reacted with aromatic amine such as aniline (89% yield) (Table 1, entry 7). In contrast, the tetrasubstituted epoxide **6** was not reactive, due probably to steric hindrance.

Secondary amines were also able to open epoxides. The best yields in amino alcohols were obtained when 2 equiv. of amine and 0.5 equiv. of $LiNTf_2$ were used. In all cases, attack of the amines at the terminal carbon of the epoxides was observed and the resulting products were isolated in yields greater than 60%. The attack of diallylamine on epoxide **1** produced **18** in 60% yield and

Table 2.

Entry	Epoxide	Nu (equiv)	$LiNTf_2$ equiv	Product Yield in CH_2Cl_2; (Yield without solvent)
1	 **5**	$(Me)_2N\text{-}NH_2$ (2.0)	0.5	 **25** 70%; (95%)
2	 **1**	PhSH (1.0)	0.5	 **26** 88%; (-)
3	 **5**	PhSH (1.0)	0.5	 **27** 45%; (87%)

the attack of diisopropylamine led to **19** in 88% yield (Table 1, entries 9 and 10). Interestingly, when epoxide **1** was treated with hexamethyldisilazane (HMDS), the amino alcohol **20**, in which the secondary hydroxy group was protected as a silyl ether, was isolated in 74% yield (Table 1, entry 11).

It is worth noting that the use of $LiNTf_2$ is compatible with acid and basic sensitive protecting groups as the treatment of epoxides **7**–**9** with 2-phenylethylamine (2 equiv.) in the presence of $LiNTf_2$ (0.5–1.0 equiv.) led to the corresponding amino alcohols **22**–**24**[13] (Table 1, entry 13). It should be also pointed out that the ring opening of epoxides by amines can be achieved without any solvent and, under these conditions, the amino alcohols were produced with excellent yield (Table 1, entries 2 and 7).

Ring opening of epoxides with other nucleophiles such as *N*,*N*-dimethylhydrazine or thiophenol, in the presence of a catalytic amount of $LiNTf_2$, was also examined. The results are reported in Table 2. When cyclohexene oxide **5** was treated with 2 equiv. of *N*,*N*-dimethylhydrazine, in the presence of $LiNTf_2$ (0.5 equiv.) at rt in CH_2Cl_2 for 20 h, epoxide **5** was transformed to the aminimide **25** in 70% yield.[14] The reaction of epoxides **1** or **5** with thiophenol were also investigated. When **1** and **5** were treated with thiophenol (1 equiv.) at rt in the presence of $LiNTf_2$ (0.5 equiv.) for 20 h, adducts **26** and **27** were obtained in good or acceptable yields. As previously observed with amines, the yield in **25** and **27** was increased when the reaction was performed without any solvent (Table 2, entries 1 and 3).

In summary, we have discovered a novel, mild and efficient activator for the ring opening of epoxides with various nucleophiles (primary and secondary amines, *N*,*N*-dimethylhydrazine and thiophenol). By using less than 0.5 equiv. of $LiNTf_2$,[15,16] the ring opening of epoxides can be achieved with or even without any solvent in excellent yield. Furthermore, when $LiNTf_2$ is used instead of Lewis acids, the work-up is easier as no emulsion was formed.

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References

1. (a) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323; (b) Gorzynsky Smith, J. *Synthesis* **1984**, 629; (c) Mitsunobu, O. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Pattenden, G., Eds.; Pergamon Press: Oxford, 1990; Vol. 6, pp. 88–93; (d) Birkinshaw, T. N. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W.; Roberts, S. M., Eds.; Pergamon Press: Oxford, 1990; Vol. 1, pp. 204–220; (e) Hanson, R. M. *Chem. Rev*. **1991**, *91*, 437; (f) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361.
2. (a) Möller, F. In *Methoden der Organischen Chemie* (*Houben-Weyl*); Müller, E., Ed., 4th ed.; Thieme Verlag: Stuttgart, 1957; Vol. 11/1, pp. 311–326; (b) Mousseron, M.; Jullien, J.; Jolchine, Y. *Bull. Soc. Chim. Fr*. **1952**, 757; (c) Deyrup, J. A.; Moyer, C. L. *J. Org. Chem*. **1969**, *34*, 175; (d) Crooks, P. A.; Szyndler, R. *Chem. Ind. (London)* **1973**, 1111.
3. (a) Overman, L. E.; Flippin, L. A. *Tetrahedron Lett*. **1981**, *22*, 195; (b) Overman, L. E.; Sugai, S. *J. Org. Chem*. **1985**, *50*, 4154.
4. Carré, M. C.; Houmounou, J. P.; Caubère, P. *Tetrahedron Lett*. **1985**, *26*, 3107.
5. Kissel, C. L.; Rickborn, B. *J. Org. Chem*. **1972**, *37*, 2060.
6. Yamada, J.-I.; Yumoto, M.; Yamamoto, Y. *Tetrahedron Lett*. **1989**, *30*, 4255.
7. Fiorenza, M.; Ricci, A.; Taddei, M.; Tassi, D. *Synthesis* **1983**, 640.
8. (a) Papini, A.; Ricci, A.; Taddei, M.; Seconi, G.; Dembech, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2261; (b) Atkins, R. K.; Frazier, J.; Moore, L. L.; Weigel, L. O. *Tetrahedron Lett*. **1986**, *27*, 2451.
9. **$Ti(OiPr)_4$**: (a) Caron, M.; Sharpless, K. B. *J. Org. Chem*. **1985**, *50*, 1557; (b) Chong, J.-M.; Sharpless, K. B. *J. Org. Chem*. **1985**, *50*, 1560; (c) Canas, M.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett*. **1991**, *32*, 6931; (d) Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem*.

1997, *62*, 4970; (e) Sagawa, S.; Abe, H.; Hase, Y.; Inaba, T. *J. Org. Chem.* **1999**, *64*, 4962; (f) **$CoCl_2$**: Iqbal, J.; Pandey, A. *Tetrahedron Lett.* **1990**, *31*, 575; (g) **$Cr(NtBu)Cl_3(dme)$, $Cr(NtBu)_2Cl_2$**: Leung, W.-H.; Chow, E. K. F.; Wu, M.-C.; Kum, P. W. Y.; Yeung, L.-L. *Tetrahedron Lett.* **1995**, *36*, 107. **SmI_2**: (h) Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* **1995**, *36*, 1649; (i) Collin, J.; Giuseppone, N.; Van de Weghe, P. *Coord. Chem. Rev.* **1998**, *178–180*, 117; (j) **$SmCl_3$**: Fu, X.-L.; Wu, S.-H. *Synth. Commun.* **1997**, *27*, 1677. **$LiClO_4$** and **various metal salts**: (k) Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661; (l) Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939; (m) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 7043; (n) **$TaCl_5$**: Chandrasekhar, S.; Ramachandar, T.; Prakash, S. J. *Synthesis* **2000**, 1817; (o) **$InCl_3$**: Reddy, L. R.; Reddy, M. A.; Bhanumathi, N.; Rama Rao, K. *New J. Chem.* **2001**, *25*, 221; (p) **$CeCl_3$**: Reddy, L. R.; Reddy, M. A.; Bhanumathi, N.; Rama Rao, K. *Synthesis* **2001**, 831; (q) **$(iPrO)_2AlOC(O)CF_3$**: Rampalli, S.; Chaudhari, S. S.; Akamanchi, K. G. *Synthesis* **2000**, 78; (r) **Cyclodextrine**: Reddy, L. R.; Reddy, M. A.; Bhanumathi, N.; Rama Rao, K. *Synlett* **2000**, 339.

10. **Ph_4SbOTf**: (a) Fujiwara, M.; Imada, M.; Baba, A.; Matsuda, H. *Tetrahedron Lett.* **1989**, *30*, 739; **$Yb(OTf)_3$**: (b) Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597; (c) Hou, X.-L.; Wu, J.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *Tetrahedron: Asymmetry* **1998**, *9*, 1747; (d) **$Ln(OTf)_3$**: Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433; (e) **LiOTf**: Auge, J.; Leroy, F. *Tetrahedron Lett.* **1996**, *37*, 7715; (f) **$Sn(OTf)_2$** and **$Cu(OTf)_2$**: Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287.
11. $LiNTf_2$ can be purchased from Sigma or Fluka.
12. The regioselectivity of the ring opening of styrene oxide **3** by primary amines is better in the presence of 0.1 equiv. of $LiNTf_2$ (4/1) than in the presence of 2 equiv. of $LiClO_4$ (1/1.3) or than in the presence of 0.5 equiv. of LiOTf (1.5/1). See Refs. 9l and 10e.
13. No reaction occurred when **7** was treated with 2-phenylethylamine (2 equiv.) and $Yb(OTf)_3$ (0.1 equiv.) in CH_2Cl_2 at rt. Attempts to achieve the same reaction with $LiClO_4$ led to **22** always with yields inferior to 40% even by using 2 equiv. of $LiClO_4$, 10 equiv. of amine and by heating.
14. (a) Slagel, R. C. *J. Org. Chem.* **1968**, *33*, 1374; (b) Ikeda, I.; Machii, Y.; Okahara, M. *Synthesis* **1978**, 301; (c) Ikeda, I.; Machii, Y.; Okahara, M. *Synthesis* **1980**, 650; (d) Haywood, L.; McKee, S.; Middleton, W. J. *J. Fluorine Chem.* **1991**, *51*, 419.
15. Yields given in the text refer to isolated pure products after flash chromatography on silica gel. All products were fully characterized by ^1H, ^{13}C NMR, IR and mass spectra.
16. **General procedure:** To a solution of epoxide (2.5 mmol, 1 equiv.) and amine (1.2 or 2 equiv.) in anhydrous CH_2Cl_2 (1 mL), $LiNTf_2$ (0.1–0.5 equiv.) was added. The reaction mixture was stirred under argon at rt for 20 h. After complete conversion, as indicated by TLC, the reaction mixture was diluted with diethyl ether (25 mL), quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and purified by flash chromatography on silica gel.