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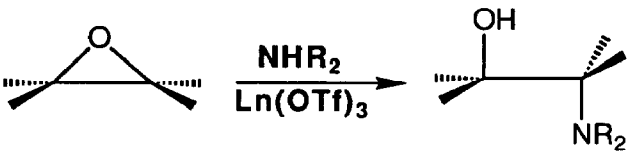
Lanthanide(III) Trifluoromethanesulfonates as Extraordinarily Effective New Catalysts for the Aminolysis of 1,2-Epoxides

Marco Chini, Paolo Crotti,* Lucilla Favero, Franco Macchia, and Mauro Pineschi
Dipartimento di Chimica Bioorganica, Università di Pisa, via Bonanno 33, 56126 Pisa, Italy

Abstract: *Lanthanide(III) trifluoromethanesulfonates (triflates), such as $Yb(OTf)_3$, $Nd(OTf)_3$ and $Gd(OTf)_3$, catalyze in a extraordinarily efficient way the aminolysis of 1,2-epoxides, affording the corresponding β-amino alcohols, at room temperature and in a non-protic solvent (CH_2Cl_2 or toluene), in very good yields. The reactions are completely anti stereoselective and highly regioselective.*

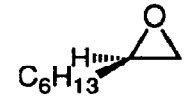
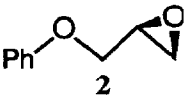
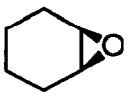
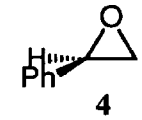
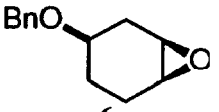
β-Amino alcohols are compounds of undoubted synthetic interest in organic chemistry. By far the most common method for their preparation, that is the direct aminolysis of 1,2-epoxides in protic solvents, suffers from some limitations when sterically hindered amines and/or epoxides are used. Recently we found in our laboratories that common metal salts, *e.g.* $LiClO_4$, promote in an efficient way the direct aminolysis of different 1,2-epoxides with a large variety of primary and secondary amines. This new protocol was effective both with hindered amines and/or epoxides. However an equimolar amount of the catalyst ($LiClO_4$) had to be used.[1,2]

Searching for new, even more efficient catalysts for this reaction, we have now found that lanthanide(III) trifluoromethanesulfonates [lanthanide triflates, $Ln(OTf)_3$] such as $Yb(OTf)_3$, $Nd(OTf)_3$ and $Gd(OTf)_3$,[3,4] promote in an extraordinarily effective way the aminolysis of 1,2-epoxides in low polar non-protic solvents such as toluene or CH_2Cl_2 at room temperature, in quite nice yields (85-100%), using



only a low amount of the catalyst (10% mol). The Table shows the results of the aminolysis of several primary and secondary amines with some representative 1,2-epoxides (**1**-**6**) in the presence of different $Ln(OTf)_3$. The use of less than 10% amount of the catalyst markedly slows down the reaction rate; only in the case of the faster reacting epoxides (**2** and **4**), does the aminolysis reaction proceed smoothly even in the presence of a lower amount of the catalyst (5% mol, results not shown in the Table), whereas a 50% molar amount of $Yb(OTf)_3$ was necessary in the case of the highly hindered epoxide **5** and the

Table. Aminolysis of Some Representative 1,2-Epoxides (1-6) in the Presence of $Ln(OTf)_3$ [$Yb(OTf)_3$, $Gd(OTf)_3$ and $Nd(OTf)_3$].

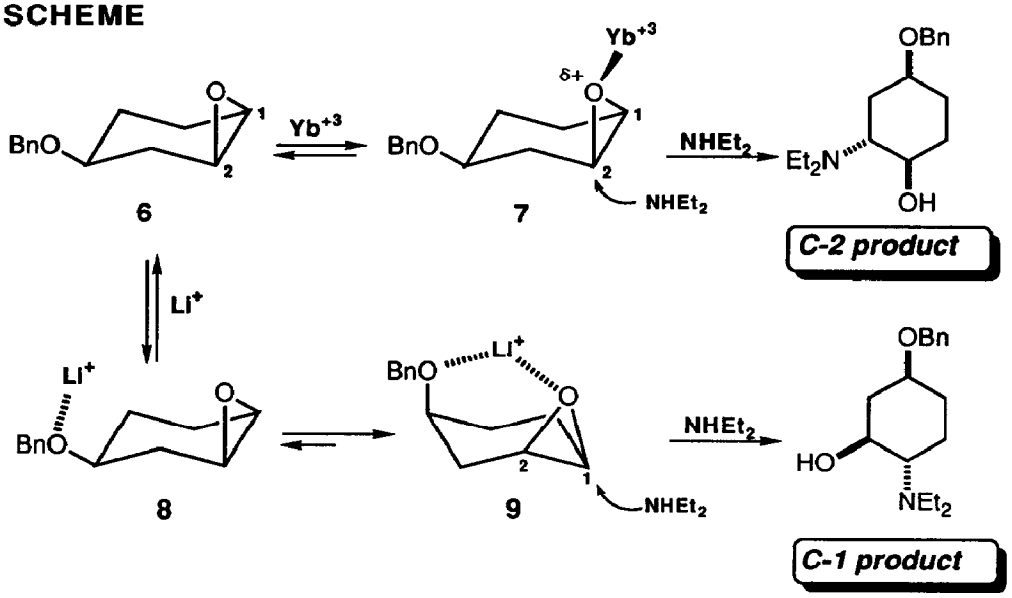
entry	epoxide	$Ln(OTf)_3$[a]	amine	solvent[b]	reaction time (°C)[c]	α attack[d]	β attack[e]	yield %
1		$Yb(OTf)_3$	$NHEt_2$	CH_2Cl_2	20 min	>99	<1	97
2		$Yb(OTf)_3$	$(i\text{-Pr})_2NH$	CH_2Cl_2	3 h	>99	<1	95
	1							
3		$Yb(OTf)_3$	$NHEt_2$	CH_2Cl_2	30 sec	>99	<1	100
4		$Yb(OTf)_3$	$t\text{-BuNH}_2$	CH_2Cl_2	30 min	>99	<1	95
5		$Yb(OTf)_3$	$(i\text{-Pr})_2NH$	CH_2Cl_2	30 min	>99	<1	95
	2							
6		$Yb(OTf)_3$	$NHEt_2$	CH_2Cl_2	1 h			98
7		$Yb(OTf)_3$	$t\text{-BuNH}_2$	CH_2Cl_2	5 h			97
8		$Gd(OTf)_3$	$t\text{-BuNH}_2$	CH_2Cl_2	6 h			98
9		$Nd(OTf)_3$	$t\text{-BuNH}_2$	CH_2Cl_2	18 h			85
10		$LiClO_4$	$t\text{-BuNH}_2$	CH_3CN	18 h			95[f]
11		$Yb(OTf)_3$	$(i\text{-Pr})_2NH$	CH_2Cl_2	18 h			90
12	3	$LiClO_4$	$(i\text{-Pr})_2NH$	CH_3CN	64 h (80)			86[f]
13		$Yb(OTf)_3$	$t\text{-BuNH}_2$	CH_2Cl_2	1 h	49	51	96
14		$Yb(OTf)_3$	$(i\text{-Pr})_2NH$	CH_2Cl_2	1 h	90	10	97
15		$Gd(OTf)_3$	$(i\text{-Pr})_2NH$	CH_2Cl_2	1 h	92	8	96
16		$Nd(OTf)_3$	$(i\text{-Pr})_2NH$	CH_2Cl_2	2 h	92	8	97
17		$LiClO_4$	$(i\text{-Pr})_2NH$	CH_3CN	24 h	89	11	93[g]
18		$Yb(OTf)_3$	Et_2NH	CH_2Cl_2	5 min	55	45	98
19	4	$Gd(OTf)_3$	Et_2NH	CH_2Cl_2	5 min	57	43	98
20		$Nd(OTf)_3$	Et_2NH	CH_2Cl_2	5 min	58	42	97
21		$Yb(OTf)_3$	$(Cy)_2NH$	CH_2Cl_2	2 h	95	5	95
22		$LiClO_4$	$(Cy)_2NH$	CH_3CN	72 h	93	7	88[g]
23		$Yb(OTf)_3$ 10%	$BnNH_2$	CH_2Cl_2	24 h	no	reaction	
24		$Yb(OTf)_3$ 50%	$BnNH_2$	CH_2Cl_2	24 h			95
25	5	$LiClO_4$	$BnNH_2$	CH_3CN	72 h (60)			95[f]
						C-1 product[h]	*C-2 product*[h]	
26		$Yb(OTf)_3$ 50%	$NHEt_2$	CH_2Cl_2	1 h	3	97	98
27		$LiClO_4$	$NHEt_2$	CH_3CN	1.5 h (55)	92	8	98[h]
28			$NHEt_2$	EtOH	5 days (55)	5	95	50[h]
	6							

[a] 10% mol, unless otherwise stated. [b] In the case of the $Ln(OTf)_3$-catalyzed aminolysis, the use of toluene as the solvent, gave the same results. [c] All the reactions were carried out at r.t., unless otherwise stated. [d] Attack of the nucleophile on the less substituted oxirane carbon. [e] Attack of the nucleophile on the more substituted oxirane carbon. [f] See ref. 1. [g] Due to a previous mistake, the corresponding regiochemical result of ref. 2 should be replaced by the present one. [h] See ref.4.

functionalized epoxide **6** (entries 23, 24 and 26, Table). The $Ln(OTf)_3$-catalyzed aminolyses appear to be faster and more efficient than the $LiClO_4$-promoted ones.[1,2] In this way, for example, the reactions of the cyclohexene oxide (**3**) with $t\text{-BuNH}_2$ or $(i\text{-Pr})_2NH$ carried out following this new protocol occurred at room temperature in 5 and 18 hours, respectively, whereas the corresponding $LiClO_4$-promoted reactions took place in 18 hours at room temperature with $t\text{-BuNH}_2$ and only after 64 hours at 80°C in the case of the more

hindered (*i*-Pr)2NH (entries 7,10-12, Table; see also entries 21 and 22,). As in the case of the $LiClO_4$-catalyzed reactions, the reaction rates depend both on the structure of the amine and/or of the epoxide: the use of more hindered epoxides and/or low nucleophilic amines slows the reactions down, but the reaction times are not superior to 24 h. The reactions are usually carried out efficiently in the presence of a slight excess of the amine (20% mol); however the use of larger amounts of the nucleophile increases the reaction rate. Among the lanthanide(III) triflates tested, the order of effectiveness observed is Yb(III) ≡ Gd(III) > Nd(III) (entries 7-9, Table). These $Ln(OTf)_3$-catalyzed aminolyses can best be carried out in anhydrous non-protic non-coordinating solvents, such as toluene or CH_2Cl_2, where the reactions proceed in suspension. In CH_3CN, the reactions are somewhat slowed down, even if in this case they occur in solution, due to the complete solubility of the catalyst in this solvent. The use of more coordinating solvents (DMF, THF or THF/H_2O mixtures) almost annulles the catalytic effects of the Ln(III) salts. Also the presence of increasing amounts of water in a non-protic solvent, such as toluene, markedly and gradually reduces the reaction rate.

SCHEME



As previously observed in common metal salt-promoted reactions, the $Ln(OTf)_3$-catalyzed aminolyses are completely anti stereoselective and, in the case of unsymmetrically substituted epoxides, completely regioselective with the attack of the nucleophile on the less substituted oxirane carbon. The only exception is given by styrene oxide (**5**), in which both regioisomers are formed in substantial amounts, which, however, depend largely on the type of the amine. Beyond the above-mentioned similarities, a quite striking difference exists between the $LiClO_4$- and $Ln(OTf)_3$ [such as $Yb(OTf)_3$]-catalyzed reactions in the control of the regioselectivity of the aminolysis of 1,2-epoxides bearing remote heterofunctionalities by means of chelating processes, as clearly shown by the following example. The reaction of *cis*-4-benzyloxy-1,2-epoxycyclohexane (**6**) (Scheme)[5,6] with $NHEt_2$ in CH_3CN in the presence of 2M $LiClO_4$ (entry 27, Table) largely proceeds through the chelate intermediate **9** and affords a reaction mixture in which the regioisomer ***C-1 product*** predominates (***C-1 product/C-2 product*** ratio=92:8).[5] On the contrary, when the same reaction

is carried out in CH_2Cl_2 in the presence of $Yb(OTf)_3$ (entry 26, Table), the alternative regioisomeric ***C-2 product*** is almost the exclusive reaction product (97%). Evidently, the Yb^{+3} species is not able to fit in effectively between the two oxygen functionalities of **6**, as Li^+ does. However, the two combined reactions offer a very effective, regioalternating synthetic method. The regiochemical result obtained in the $Yb(OTf)_3$-catalyzed aminolysis of **6** is practically identical to the one obtained in the aminolysis carried out under standard conditions (refluxing EtOH), but the operating and the reaction conditions are largely different, thus confirming the strong catalytic effect of the ytterbium salt (entries 26 and 28, Table).

The quite excellent catalytic effect of the lanthanide(III) triflates in the present aminolysis of 1,2-epoxides may reasonably be attributed to the strong oxophilicity of the lanthanide(III) in these compounds, which allows the metal to tightly coordinate to the oxirane oxygen, thus directly favoring the nucleophilic ring opening process. As an alternative rationalization, the catalytic effect of $Ln(OTf)_3$ in these reactions could be ascribed to the increased acidity of the proton of water, present as traces in the reaction medium, strongly coordinated to the lanthanide(III). However, the fact that the presence of increasing small amounts of water (vide supra) constantly reduces gradually the catalytic effects of $Ln(OTf)_3$ points in favor of a direct interaction of the lanthanides(III) with the oxirane oxygen in these reactions.

As a conclusion, this new method appears to have a valuable synthetic application for the aminolysis of 1,2-epoxides in consideration of its simplicity, applicability and efficiency, which could make this new protocol to be largely preferred to other ones previously described.[1,2,5]

General Procedure and Identification of β-Amino Alcohols.

A solution of the epoxide (1.0 mmol) in the solvent (1 ml) was treated with the amine (1.2 mmol) and $Ln(OTf)_3$ (10% mol).[3] The reaction mixture was stirred at r.t. till complete consumption of the epoxide (TLC and/or GC). Dilution with water, extraction with ether and evaporation of the washed (water) ether extracts afforded a crude reaction product consisting of the corresponding β-amino alcohols, practically pure (GC), whose structure was determined by ^{1}H NMR and confirmed by comparison with authentic samples prepared in accordance with literature procedures.[1,2,5] The structure of the new compounds [entries 2,5 (α attack) and 14 and 21(β attack)] was confirmed by ^{1}H NMR analysis and satisfactory microanalytical results (C,H,N ±0.3% of the calculated value). ***Entry 2*** (α attack): ^{1}H NMR δ 3.40-3.57 (m,1H), 3.04 (7 lines, 2H, *J*=6.6 Hz), 2.53 (dd, 1H, *J*=3.5 and 13.2 Hz), 2.15 (dd,1H, *J*=10.5 and 13.2 Hz), 1.14-1.60 (m, 10H), 1.05 and 0.99 (1d each, 12H, *J*=6.6 Hz), 0.88 (t, 3H, *J*=6.7 Hz). ***Entry 5*** (α attack): ^{1}H NMR δ 7.17-7.25 (m, 2H), 6.83-6.90 (m, 3H), 3.78-3.98 (m, 3H), 2.97 (7 lines, 2H, *J*=6.6 Hz), 2.64 (dd, 1H, *J*=4.0 and 13.4 Hz), 2.40 (dd, 1H, *J*=9.3 and 13.4 Hz), 1.00 and 0.95 (1d each, 12H, *J*=6.6 Hz). ***Entry 14*** (β attack, separated by TLC): ^{1}H NMR δ 7.13-7.32 (m, 5H), 3.95 (dd, 1H, *J*=5.52 and 10.2 Hz), 3.71(t, 1H, *J*=10.2 Hz), 3.40 (dd, 1H, *J*=5.5 and 10.2 Hz), 3.30 (7 lines, 2H, *J*=6.6 Hz), 1.08 and 0.88 (1d each, 12H, *J*=6.6 Hz). ***Entry 21*** (β attack, separated by TLC):^{1}H NMR δ 7.24-7.41 (m, 5H), 4.03 (dd, 1H, *J*=5.4 and 10.3 Hz), 3.77 (t, 1H, *J*=10.3 Hz), 3.44 (dd, 1H, *J*=5.4 and 10.3 Hz), 2.70-2.92 (m, 2H), 0.90-2.00 (m, 20H).

References and Notes

1. Chini. M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661-4664, and references therein.
2. Chini. M.; Crotti, P.; Macchia, F. *J.Org.Chem.* **1991**, *56*, 5939-5942.
3. Forsberg, J.H.; Spaziano,V.T.; Balasubramanian, T.M.; Liu, G.K.; Kinsley, S.A.; Duckworth, C.A.; Poteruca, J.J.; Brown, P.S.; Miller, J.L. *J.Org.Chem.* **1987**, *52*, 1017-1021.
4. For recent noteworthy applications of lanthanide(III) salts to the ring opening reactions of 1,2-epoxides with nucleophiles, see: a) Vougioukas, A.E.; Kagan, H.B. *Tetrahedron Lett.* **1987**, *28*, 6065-6068; b) Matsubara, S.; Onishi, H.; Utimoto, K. *ibid.* **1990**, *31*, 6209-6212.
5. Chini, M.; Crotti, P.; Flippin, L.A.; Macchia, F. *J.Org.Chem.* **1991**, *56*, 7043-7048.
6. For the sake of simplicity, only the more stable conformation of epoxide **6** is shown in the Scheme.

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