

Aluminium triflate: a remarkable Lewis acid catalyst for the ring opening of epoxides by alcohols†

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Al(OTf)₃ was found to be an extremely effective catalyst (at ppm levels) for ring opening reactions of epoxides using a range of alcohols.

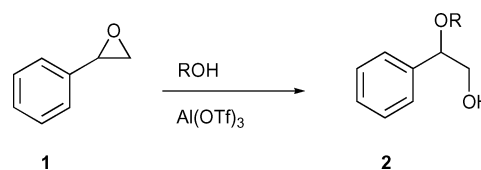
Epoxides are important molecules in organic synthesis and, because of their versatility and reactivity with a range of nucleophiles, are often used as starting materials and intermediates.¹ In general, ring opening reactions of epoxides can be catalysed under basic or acid conditions. The former takes place through an S_N2 type reaction and attack of the nucleophile typically occurs at the less hindered carbon.² Under acidic conditions, the ring opening of the epoxide resembles an S_N1 reaction, sometimes called a borderline S_N2 reaction.² As a result, the nucleophile tends to attack at the more highly substituted carbon atom of the epoxide ring, which bears more of the positive charge and resembles a stable carbocation species.² Therefore, the formation of one product is highly favoured under acidic conditions.²

Recently, metal triflates have received much attention for their role as Lewis acids in a number of reactions. Bismuth triflate has been used as a catalyst in the ring opening of epoxides by aromatic amines under aqueous conditions, and the corresponding β-amino alcohols were afforded in excellent yields.¹ Bismuth triflate has also been employed in the rearrangement

of aryl-substituted epoxides to aldehydes and ketones.³ Yttrium triflate, on the other hand, was used to catalyse the addition of lithium enolates to epoxides to form γ-hydroxy ketones,⁴ and ytterbium(III) triflate catalyses highly regioselective allylation of aromatic epoxides using allyltributyltin in THF.⁵

From our review of the literature, we found that very little work has been done using aluminium triflate. This study, therefore, involved an investigation into the efficacy of Al(OTf)₃ as a Lewis acid for the catalysed ring opening of epoxides by selected alcohols.

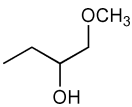
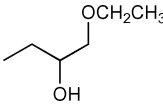
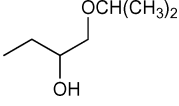
Initially, we conducted our experiments using styrene oxide. Using the protocol set out by Green in a 1987 patent,⁶ six equivalents of methanol or ethanol (with no added solvent) and 0.1% of Al(OTf)₃ were added to styrene oxide and the mixture was heated under reflux for one hour. The reaction afforded excellent yields of the glycol ether where the nucleophile had attacked at the more hindered carbon atom of the epoxide ring (Scheme 1).



Scheme 1

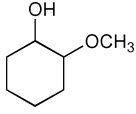
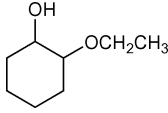
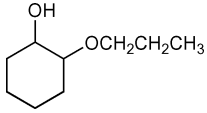
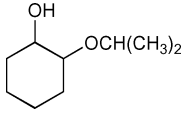
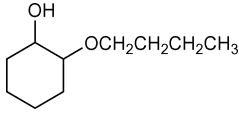
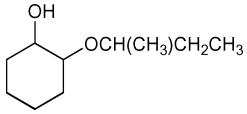
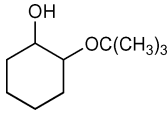
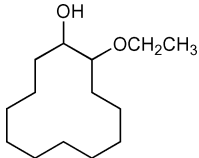
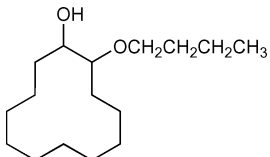
† Electronic supplementary information (ESI) available: Characterisation data. See <http://dx.doi.org/10.1039/b508924g>

Table 1 Yields (%) of products obtained from reactions with selected epoxides in various alcohols^a

Entry	Product	% Yield 0.0005% cat.	% Yield 0.001% cat.	% Yield 0.002 cat.	% Yield 0.003% cat.	% Yield 0.004% cat.
1	2 R = Me	0	1	98	94	— ^b
2	2 R = Et	94	95	—	—	—
3	2 R = nPr	93	97	92 (4) ^c	—	—
4	2 R = iPr	91	92	—	—	—
5	2 R = nBu	—	14	97	96 (4)	92 (8)
6	2 R = 2-Bu	—	0	51	—	85
7	2 R = tBu	—	77	77	—	81
8		—	41 (34)	—	—	—
9		—	31 (24)	—	—	—
10		—	11 (7)	—	—	—

^a Products were characterised using IR, MS, ¹H-, ¹³C- and 2D NMR and GC-FID analysis. See reference 9 for experimental details. ^b Reactions not performed. ^c Yields in parentheses refer to the other regioisomer.

Table 2 Yields (%) of products obtained from reactions with selected epoxides in various alcohols^a

Entry	Product	% Yield 0.001% cat.	% Yield 0.002% cat.	% Yield 0.003% cat.	% Yield 0.004% cat.	% Yield 0.01% cat.	% Yield 0.02% cat.	% Yield 0.04% cat.
1		85	86	— ^b	—	—	—	—
2		77	83	—	—	—	—	—
3		55	88	—	—	—	—	—
4		21	42	62	—	—	—	—
5		—	89	—	—	—	—	—
6		—	45	—	—	—	—	—
7		—	3	—	—	18	—	—
8		—	—	—	7	14	21	49
9		—	—	—	—	—	—	63

^a Products were characterised using IR, MS, ¹H-, ¹³C- and 2D NMR and GC-FID analysis. See reference 9 for experimental details. ^b Reactions not performed.

Satisfied that we were able to repeat the experimental procedures set out in the patent literature, we changed the reaction conditions in order to determine the catalytic ability of Al(OTf)₃, the effects of different alcohols and, finally, the effect of different epoxides on the reaction.

Firstly the effect of temperature on the outcomes of the reactions was investigated. Reactions with styrene oxide and 6 equivalents of MeOH were carried out at 0 °C, room temperature and under reflux for 24 hours and samples were taken and analysed by GC-FID at regular intervals. Al(OTf)₃ was added at 0.001%, 0.002%, 0.003% and 0.004%,⁷ respectively. In each case, for benchmark purposes, the reactions were also performed without added catalyst. The results demonstrated selectivity for the isomer where attack had occurred at the more hindered

carbon, in agreement with prior work.² (The formation of what is believed to be an oligomer was also seen.⁸) At 0 °C, 0.004% of Al(OTf)₃ was needed before a 75% conversion to product **2** was observed. Under these conditions, 7% of the putative oligomer was formed after 24 hours. In contrast, at room temperature, 0.003% of catalyst was required before 85% conversion to **2** was seen and 6% oligomer was formed after only 18 hours. The best conversion observed was under reflux, at which temperature 98% conversion to product **2** was accompanied with only 2% oligomer formation. This was achieved with only 0.002% of the catalyst. The benchmark reactions performed with no catalyst yielded only 5% of the product together with 0.6% of the oligomer after 24 hours under reflux.

As discussed above these reactions tended to form the oligomer by-product and, in order to prevent this, subsequent reactions with styrene oxide were carried out using twenty equivalents of alcohol. This change minimised oligomer formation to only trace amounts.

We also investigated the effects of different alcohols, epoxides and how different catalyst concentrations would influence these reactions (Table 1).⁹ In all cases, except for those performed in the presence of methanol, reactions of styrene oxide required less catalyst to be added than the analogous reactions with other epoxides in order for an appreciable amount of product to be formed. The reactions with styrene oxide were remarkably regioselective, with the formation of only a single regioisomer being detected, namely that where attack of the nucleophile had taken place solely at the more hindered position of the epoxide. In these reactions, electronic effects dominate over steric effects: the intermediate carbocation at the secondary carbon atom is stabilised through resonance with the phenyl ring, thereby promoting nucleophilic attack at this position.

In contrast, butylene oxide provided an almost 50 : 50 ratio of isomers, where the nucleophile had attacked at either end of the epoxide. In these reactions neither steric nor electronic effects played a more dominant role.

Cyclohexene oxide required only 0.001% of the catalyst (0.0005% failed to promote the reaction) to be added to afford an 85% or 77% yield of the monoglycol ether in methanol and ethanol, respectively (Table 2). However, the reactions with cyclododecane epoxide required forty times the amount of Al(OTf)₃ to be added before a 49% conversion to the monoglycol ether was seen when the reaction was performed in ethanol. We believe that this was due to the large, flexible cyclododecane molecule folding over on itself (hydrophobic effects) in the polar solvent (ethanol) making nucleophilic attack difficult. In order to test this hypothesis we repeated the reaction using the less polar solvent 1-butanol, which improved the yield to 63% after one hour under similar conditions.

In general, the reactions with the bulkier alcohols required more Al(OTf)₃ catalyst to be added before appreciable yields of products were obtained. Nonetheless, acceptable yields were achievable for all of the reactions using only ppm levels of the triflate.

Triflic acid is often found in residual amounts in the aluminium triflate used. If triflic acid is present in these reactions, it may be capable of catalysing the ring opening of the epoxide. To test this potential, reactions were performed using triflic acid as the only catalyst, and the results showed that the added triflic acid had a negligible influence. The experimental procedure previously employed was followed, but using triflic acid instead of Al(OTf)₃. After 24 hours under reflux in the presence of 0.005% triflic acid only 4% of product **2** had formed. We could therefore conclude that the catalytic activity observed was ascribable to the Al(OTf)₃.

In order to test Al(OTf)₃ on epoxides containing different structural motifs, glycidyl ethers also were used (Scheme 2), in ethanol, with some surprising results (Table 3).

In contrast to the previous results discussed, the main product formed in these reactions was the 2° alcohol analogue, where the nucleophile strongly favoured attack at the less hindered carbon atom of the epoxide ring. Presumably, this is because the Al(OTf)₃ formed a chelate structure with the two oxygen atoms of the glycidyl ether (Fig. 1). This would decrease the Lewis acidic (electron-withdrawing) effect that the metal would usually have on the internal carbon atom, allowing steric effects

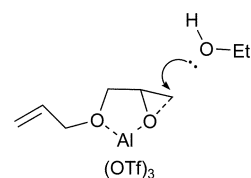
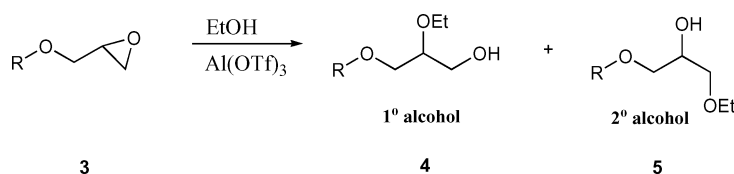


Fig. 1



Scheme 2

Table 3 Yields (%) of products obtained from reactions with glycidyl ethers and ethanol^a

Entry	Product	% Yield 0.002% cat.	% Yield 0.004% cat.	% Yield 0.005% cat.	% Yield 0.01% cat.	% Yield 0.02% cat.	% Yield 0.04% cat.
1	4 R = allyl	6	— ^b	5	14	19	—
	5 R = allyl	22	—	18	49	69	—
2	4 R = tBu	1	—	10	18	21	—
	5 R = tBu	4	—	28	54	63	—
3	4 R = Ph	—	0	—	7	10	12
	5 R = Ph	—	0	—	41	60	80
4		—	30	—	35	26	—
5		—	—	—	24	36	60

^a Products were characterised using IR, MS, ¹H-, ¹³C- and 2D NMR and GC-FID analysis. See reference 9 for experimental details. ^b Reactions not performed.

to play a more dominant role. The nucleophile therefore attacked at the less hindered carbon atom and the 2° alcohol was formed.

The glycidyl ethers required more Al(OTf)₃ to be used in the reactions, when compared with those of styrene oxide and cyclohexene oxide, to observe similar rates of reactions. This is also probably due to the decreased Lewis acid effect of the metal because of the chelate structure that formed. At lower catalyst concentration the reactions with 1,4-butanediol glycidyl ether yielded a significant proportion of the mono glycol ether. Only when 0.04% Al(OTf)₃ was added was the diglycol ether formed as the major product.

In summary, Al(OTf)₃ was found to be a highly effective Lewis acid catalyst (at ppm levels) for the ring opening of a variety of epoxides by a range of alcohols, providing the anticipated products in very high yields with often remarkable selectivity.

Acknowledgements

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Notes and references

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- 7 In all of the reactions the low levels of Al(OTf)₃ were readily obtainable making use of stock solutions in either DME or the alcohol in question and then adding the correctly calculated volume of the solution to the reaction mixture. It was found that there was no difference in the activity of the stock solution due to a solvent effect (DME stock solution vs. alcohol stock solution). In addition, the solutions were found to be stable for over six months, providing identical reactivity after having stood for that period of time.
- 8 The oligomer was tentatively identified as a trimer of the ring-opened product, containing one methoxy residue and three incorporated styrene oxide units, on the basis of ¹H- and ¹³C NMR studies, together with MS analysis.
- 9 Typical experimental procedure; 2 mL (17.5 mmol) of styrene oxide were mixed with 20 eq. of the alcohol in question (0.35 mol). The desired amount of Al(OTf)₃ stock solution (see ref. 7) was then added and the mixture was allowed to stir at the reflux temperature of the mixture or 100 °C (oil bath temperature), whichever was the lower, for one hour, after which the solution was filtered through silica and analysed by GC-FID. Products were isolated using column chromatography and/or vacuum distillation.