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Aluminium triflate: an efficient recyclable Lewis acid catalyst for the aminolysis of epoxides

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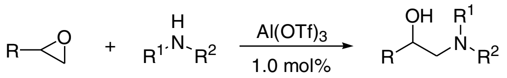
Abstract—Epoxides are powerful starting materials for a range of useful materials and can be converted into, amongst others, amino alcohols. In this work, a range of epoxides was ring-opened using various alkyl- and arylamines under the action of aluminium triflate as a catalyst. This catalyst was found to be highly active, producing the desired amino alcohol products in high yields with low catalyst loadings. Additionally, it was shown that the aluminium triflate catalyst is recyclable by simple extraction into water and may be re-used several times.

1,2-Amino alcohols are important molecules in both organic synthesis and medicinal chemistry.[1] They can be prepared using a variety of routes, most commonly through the ring opening of epoxides,[2] often involving heating of the epoxide in a protic solvent with an excess of amine.[3] Lewis acids, many of which suffer from deactivation of the catalyst due to complex formation with the amine, have also been used for this process.[4–7] A recent report describes the use of $Al(OTf)_3$ present at 5 mol % loading in the preparation of ionic liquids,[8] in which this catalyst was used in the presence of 2-picolylamine as nucleophile with a few epoxides.

Recently, we reported the use of $Al(OTf)_3$ as a remarkably efficient Lewis acid catalyst for the ring opening of epoxides in alcohols.[9] We now report that this versatile catalyst is also highly efficient (when present from as little as 1.0 mol % loading) for the ring opening of a range of epoxides with a variety of amines (Scheme 1). Additionally, we investigated the influence of steric and electronic effects on the outcome of this reaction.

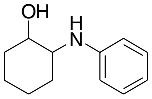
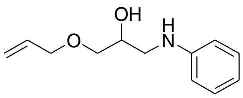
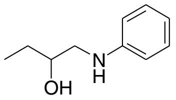
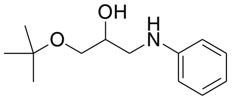


Scheme 1.

First, we examined the effects of different solvents on a standard reaction. Using aniline as the nucleophile with a variety of epoxides, the reactions were carried out in DCM, ether or toluene (Table 1), while limiting the reaction times to 5 h.[10]

The reactions carried out in toluene resulted in highest yields. Both DCM and ether can act as Lewis bases

Table 1. Solvent effect on aminolysis reactions

Entry	Products	Yield[a] (%)		
		DCM	Ether	Toluene
1		55	56	82
2		28	64	90
3		34 (8)[b]	36 (7)[b]	75 (18)[b]
4		45	62	81

[a] 1.0% $Al(OTf)_3$, 1.2 equiv aniline, temp = lower of reflux or 100 °C, 5 h.

[b] Yields in parentheses refer to the other regioisomer.

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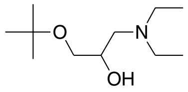
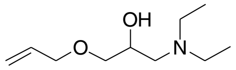
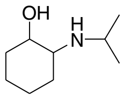
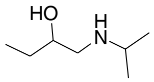
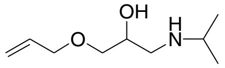
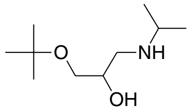
lowering the Lewis acidity of the Al(OTf)$_3$, which could account for the lower yields in these solvents.

These initial experiments also demonstrated that higher concentrations of Al(OTf)$_3$ were required for these reactions than for the alcoholysis reactions.[9] Presumably, this was due to the nitrogen of the amine and the oxygen of the epoxide competing for complexation to the Al(OTf)$_3$, since both oxygen and nitrogen are hard Lewis bases (see below).

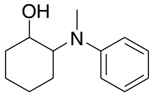
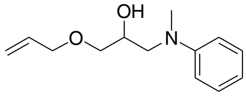
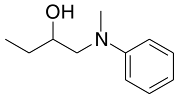
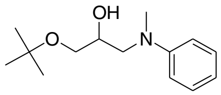
A variety of aryl- and alkylamine nucleophiles were then used in reactions with the same four epoxides, in order to determine the role that steric and electronic effects would play in these reactions. In general, the alkylamines (Table 2) are harder bases than the aromatic amines and therefore more efficiently compete with the epoxides for the catalyst. Longer reaction times and/or higher concentrations of Al(OTf)$_3$ were required for diethylamine and isopropylamine than those for the aromatic amines (Tables 1 and 3) (for isopropylamine, diminished reactivity probably arose due to a combination of steric effects and catalyst deactivation). This is in line with the 'hard–soft acid–base' theory proposed by Pearson.[11] According to this theory, ethers are considered hard bases, as are alkylamines. In contrast, arylamines are considered borderline cases. This being the case, the harder amines will tend to retard the rate of the reaction, in line with our observations, and concomitantly require slightly elevated levels of catalyst to observe similar rates and conversions.

Table 2. Alkylamine reactions with epoxides[a]

Entry	Products	Yield[b] (%)		
		1 mol % Al(OTf)$_3$	2 mol % Al(OTf)$_3$	10 mol % Al(OTf)$_3$
1		48	75[b]	—
2		45	80[b]	—
3		14	—	43[c]
4		8 (3)[c,d]	—	30 (12)[c,d]
5		33 (26)[c,d]	—	38 (30)[c,d]
6		31 (31)[c,d]	—	35 (34)[c,d]

[a] 1.2 equiv amine, 100 °C, 5 h.
[b] Isolated yield (%).
[c] 24 h reaction time.
[d] Yields in parentheses refer to the other regioisomer.

Table 3. *N*-Methylaniline reactions with epoxides[a]

Entry	Products	Yield[b] (%)	
		1 mol % Al(OTf)$_3$	2 mol % Al(OTf)$_3$
1		87	89
2		50	93
3		74 (8)[c]	80 (10)[c]
4		65	91

[a] 1.2 equiv amine, 100 °C, 5 h.
[b] Isolated yield (%).
[c] Yields in parentheses refer to the other regioisomer.

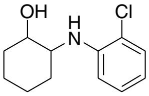
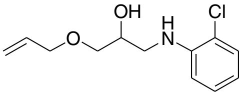
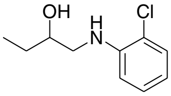
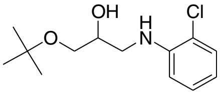
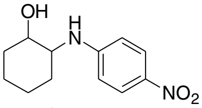
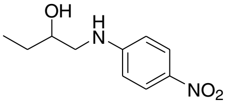
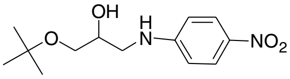
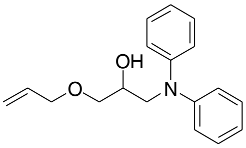
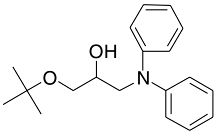
The reactions involving the glycidyl ethers with the alkylamines afforded much higher yields than those with the alkyl epoxides. This is presumably because the glycidyl ethers can form a chelate structure with the aluminium triflate, which is more stable than the simple Al–O complexes formed by regular oxiranes, and are thus able to compete more effectively with the amines for the metal centre.

The aniline reactions (Table 1) that were initially performed showed the best results overall for the aromatic amines, in terms of yield and selectivity at 1.0 mol % catalyst loading. *N*-Methylaniline, which is sterically more hindered than aniline, performed equally well in the presence of 2.0 mol % of Al(OTf)$_3$ (Table 3). Albeit less efficient, even deactivated arylamines can be used in these reactions (Table 4). For example, 2-chloroaniline showed a decrease in the yield when using low catalyst loadings, but afforded good yields of product in the presence of 2 mol % of the catalyst (Table 4, entries 1–4).

The use of deactivated nucleophiles in the form of *para*-nitroaniline (Table 4, entries 5–7) or diphenylamine (Table 4, entries 8–9) also allowed acceptable to good yields of products to be obtained when making use of 10 mol % of the catalyst (Table 4, entries 5–7). In the presence of this nucleophile, the chelate effect, together with the deactivated nucleophile, proved deleterious to the reaction. The latter set of reactions were carried out under solventless conditions (Table 4, entries 5–7) and afforded essentially identical results to those in toluene.[12]

Several reactions also showed that the catalyst is suitable for recovery and re-use without a reduction in efficacy (Table 5). After the first reaction, the catalyst was extracted into water, which was subsequently removed

Table 4. Deactivated arylamine reactions with epoxides

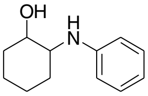
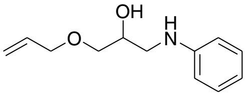
Entry	Product	Yield[a] (%)		Yield[b] (%)
		2 mol % $Al(OTf)_3$	5 mol % $Al(OTf)_3$	5 mol % $Al(OTf)_3$ solventless
1		80	—	—
2		88	—	—
3		63	—	—
4		94	—	—
5		—	52	58
6		—	54	57
7		—	32	16
8		—	57[b]	57[c]
9		—	41[b]	—

[a] 1.2 equiv amine, 100 °C, 5 h, isolated yield.

[b] 1.2 equiv amine, 100 °C, 24 h, isolated yield.

[c] 10 mol % $Al(OTf)_3$, 1.2 equiv amine, 100 °C, 24 h, isolated yield.

Table 5. Yields (%) of catalyst recycling reactions

Product	Yield[a](%)		
	Initial reaction	1st recycle	2nd recycle
	82	90	—
	90	92	88

[a] Isolated yield (%).

under vacuum at elevated temperature. This cycle was repeated for the second recycling reaction. It is clear from Table 5 that the activity and selectivity are retained during three cycles (two recycling steps).

The slightly enhanced reactivity of the catalyst (see first recycle) may be ascribable to the removal of Al-bound water, affording a more active form of the catalyst. Differential scanning calorimetry (DSC) of the commercial $Al(OTf)_3$ used in this study indicated an endotherm at 170 °C and another at 260 °C. We believe these endotherms to arise due to Al-bound water. The first endotherm is allocated to loosely bound water (probably via hydrogen bonding in an outer ligand sphere) and the second to tightly bound water (as a Lewis acid–Lewis base pair); neither endotherm was observed for pre-dried $Al(OTf)_3$ (dried under vacuum at 120 °C for 48 h). In proof thereof, the dried $Al(OTf)_3$ was exposed to the atmosphere for 1 min at ambient temperature, and application to DSC to the sample afforded a scan showing the higher temperature endotherm, which we ascribe to tightly bound water. Longer exposure (5 min) showed a DSC scan demonstrating both endotherms.

In summary, aluminium triflate is an effective, recyclable Lewis acid catalyst for the aminolysis of epoxides, with possible application in 'green chemistry' scenarios by virtue of its activity under solventless conditions and its ability to be recycled. The amine nucleophiles, being hard bases, sometimes effectively compete with the oxygen atom of the oxirane ring for complexation to the aluminium triflate, especially in the cases where alkylamines were employed. The putative stable chelate structures, which presumably formed as intermediates from the glycidyl ethers, were generally able to compete more effectively for the aluminium than the simple alkyl epoxides leading to improved reactions. However, when present together with a strongly deactivated nucleophile, the chelate structures proved deleterious.

We are currently investigating the stereochemical outcome of these reactions to determine whether or not the stereochemistry present in the epoxide is retained in the product.

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10. General experimental procedure for reactions in a solvent: 2.5 mL of toluene was added to the relevant amount of $Al(OTf)_3$ (as shown in the Tables) under an inert atmosphere. Epoxide (3.5 mmol) and 1.2 equiv of the amine were added and the mixture was heated at 100 °C for the time indicated. Aqueous extraction and chromatography over silica or vacuum distillation allowed the pure products to be isolated. All compounds provided satisfactory ^{1}H NMR, ^{13}C NMR, IR, MS and HRMS data consistent with the structures shown. Regioisomers were identified making use of HSQC and HMBC 2D NMR spectra.
11. Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827–1836.
12. General reaction conditions for solventless reactions: 3.5 mmol of the epoxide and 1.2 equiv of the amine were added to the relevant amount of $Al(OTf)_3$ (as shown in the Tables) under an inert atmosphere. The mixture was heated at 100 °C for 24 h. Aqueous extraction and chromatography over silica allowed the pure products to be isolated.