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$BiCl_3$-mediated opening of epoxides, a facile route to chlorohydrins or amino alcohols: one reagent, two paths

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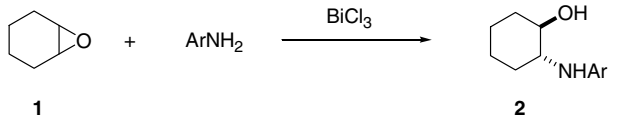
Abstract—Opening of epoxides can be an effective means by which a variety of functional groups can be incorporated. In this letter, we outline how variation of conditions, in particular, that of solvent and concentration, give rise to different products using the Lewis acid catalyst $BiCl_3$.

Medicinal chemistry relies on robust, reliable reactions, facilitating the rapid development of new chemical entities (NCEs) available for bio-evaluation. In this arena, it is imperative that NCEs are generated rapidly, often at the expense of synthetic elegance, perhaps more so with the increasing levels of automation available to the medicinal chemist. Accordingly, we are constantly searching for, and developing, such reactions for medicinal applications. Recently, as part of an on-going series of medicinal chemistry programs in our laboratory, we developed a pharmacophore model that demanded the synthesis of small targeted libraries of β-amino alcohols.[1,2]

There is a considerable literature precedent for the synthesis of β-amino alcohols, with the conversion of epoxides into the corresponding trans amino alcohols being a noteworthy example.[3–5] Ring opening of epoxides is traditionally preferable to the ring opening of aziridines,[6] a function of their higher reactivity and ease of synthesis. An additional concern in our laboratory is waste minimization and the application of green chemistry principles.[7] The pharmaceutical industry has a poor, but improving record in this area with most production processes having high E-factors.[8] Consequently, in evaluating a potential route to our desired targeted libraries, we favored those that occur in benign solvents, have high atom efficiencies and those that are conducted at room temperature and/or catalytically. It was this latter aspect that attracted us to a recent report by Nagaiah et al.[9] in which they reported the aminolysis ring opening of epoxides to amino alcohols catalyzed by $BiCl_3$. Although reports of solvent-free amine epoxide ring openings have been reported,[3,4] many transformations have been conducted utilizing transition metals and rare-earth triflates,[10] each with their own green chemistry issues. $BiCl_3$ is a relatively new catalyst, which has considerable green chemistry advantages, of low toxicity and mild reaction conditions like many useful bismuth based Lewis acids.[9,11,12] Encouraged by these factors, we commenced preliminary evaluations of potential library assembly via a series of model reactions, initially examining the addition of aniline, 2,4-dimethylaniline and 2,4-dichloroaniline to cyclohexene oxide (Scheme 1).

Our curiosity was stimulated when a product other than the expected amino alcohol was obtained in acetonitrile. GC–MS and NMR analysis indicated the conversion of cyclohexene oxide (**1**) to *trans*-2-chlorocyclohexanol (**3**)



1 **2**

Scheme 1.

Keywords: Epoxide; β-Amino alcohol; $BiCl_3$; Green chemistry.
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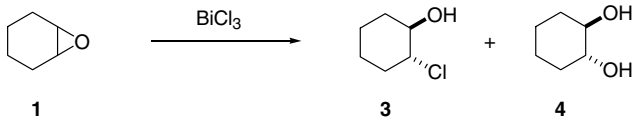
(Scheme 2) in the presence of all the anilines utilized in our initial model reactions (Table 1, entries 1–3). Yields varied between 23% and 33%, which based on the chlorine stoichiometry, equates to essentially a quantitative consumption of the available chlorine atoms in $BiCl_3$ in this unexpected transformation.[13] Increasing the reaction temperature to 40 °C (Table 1, entries 4–6) had no effect on the reaction, but it did, however, allow the introduction of two new nucleophiles, Et_3N and H_2O, which also gave rise to **3** in low yields (5% and 12%, respectively). Conducting the reaction at 60 °C afforded 19% and 25% yields of **3** from Et_3N and H_2O, respectively, whilst $PhNH_2$ still provided good conversions (based on $BiCl_3$ content, Table 1, entries 7–9).



1 **3** **4**

Scheme 2.

Table 1. Effect of amine on yield of chlorohydrin **3**, a $BiCl_3$-mediated epoxide opening in acetonitrile

Entry	Nucleophile	Temp (°C)	$BiCl_3$ (mol %)	**3** Yield (%)
1	Aniline	30	10	30
2	2,4-$(CH_3)_2PhNH_2$	30	10	23
3	2,4-$(Cl)_2PhNH_2$	30	10	29
4	$PhNH_2$	40	10	30
5	Et_3N	40	10	5
6	H_2O[a]	40	10	12
7	$PhNH_2$	60	10	15
8	Et_3N	60	10	19
9	H_2O[a]	60	10	25[b]
10	$PhNH_2$	40	50	94
11	Et_3N	40	50	72
12	H_2O	40	50	69[c]
13	$PhNH_2$	Reflux	10	38[d]
14	Et_3N	Reflux	10	85
15	H_2O[a]	Reflux	10	72[e]
16	H_2O[a]	30	50	64[f]
17	H_2O[a]	0	50	73[g]

[a] 200 μL H_2O added.
[b] 9% diol **4**.
[c] 28% diol **4**.
[d] 0.4% diol **4** + 18% amino alcohol.
[e] 16% diol **4**.
[f] 22% diol **4**.
[g] 9% diol **4**.

Having established that this is a facile conversion, we next investigated the effect of increasing the loading of $BiCl_3$ to 50 mol %, now treating it as a reagent, resulted in 94% and 72% conversion of the epoxide in the presence of $PhNH_2$ and Et_3N, respectively, to **3** (Table 1, entries 10 and 11). These yields were now comparable to other similar literature procedures for the production of chlorohydrins from epoxides.[14] Identification of low yields of cyclohexane-1,2-diol (**4**) suggested a potential role for trace quantities of water (in the solvent), possibly coordinating with $BiCl_3$, facilitating the release of chlorine anion. To explore this further, CH_3CN was spiked with 200 μL of H_2O (Table 1, entry 7) and the amine removed. In this instance, **1** was completely consumed with the concomitant formation of chlorohydrin **3** (69%) and a moderate, but increased, quantity of diol **4** (28%) (Scheme 2). The results tabulated below detail that treatment of cyclohexene oxide with $BiCl_3$/acetonitrile represents a mild and highly efficient route to the corresponding chlorohydrin **3**. A similar Lewis acid mediated transformation also in the presence of acetonitrile/water has been reported,[14e] which suggests that this solvent system may play an important part in the conversion to the chlorohydrin species.

In an effort to obtain the β-amino alcohol **2** (Scheme 1), the reaction mixture was heated at reflux (CH_3CN) overnight with $PhNH_2$ in the presence of $BiCl_3$ (50 mol %) after which we noted some conversion to the amino alcohol. Finally, the reaction with aniline was conducted in anhydrous acetonitrile (dried over CaH_2) with 20 mol % $BiCl_3$ at room temperature (30 °C) in an effort to use milder reaction conditions. After 36 h, we observed some conversion to the amino alcohol by GC–MS and NMR analysis. It is interesting to note that initially 10 mol % $BiCl_3$ was added and by GC–MS analysis no reaction had occurred after 24 h. It was only when a further 10 mol % $BiCl_3$ was added that the reaction took place. This does not parallel the 1–1.5 h reported by Nagaiah and co-workers using 5 mol % catalyst.[9]

Contrastingly, Ollevier et al.[11] report the opening of epoxides to afford the corresponding trans amino alcohols in moderate to high yields with the use of 10 mol % $BiCl_3$ in cyclohexane. By applying this method to cyclohexene oxide (2 M in cyclohexane), we achieved comparable conversion to the amino alcohol within 24 h (Table 2). In all cases, a minor product was observed

Table 2. Conversion to amino alcohol **2** in various solvents

Entry	Reactant	Solvent	Temp (°C)	Concentration[a]	$BiCl_3$ (mol %)	Product ratios **2**:**3**:**4**
1	Aniline	CH_3CN	Reflux	0.1 M	10	0:4.4:1
2	Aniline	CH_3CN[b]	rt	0.1 M	10	1:2:0
3	Aniline	CH_3CN	rt	2 M	10	1:1:0
4	Aniline	DCM	rt	2 M	10	1.7:1:0
5	Aniline	Cyclohexane	rt	2 M	10	5.4:1:0
6	H_2O	CH_3CN	rt	2 M	10	0:2:1

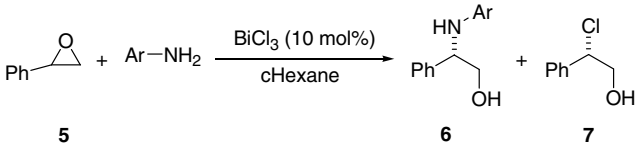
[a] Concentration with respect to starting epoxide.
[b] Anhydrous CH_3CN, dried over CaH_2, reaction left for 36 h.

that being the chlorohydrin. However, this was significantly lower when compared to using acetonitrile as a solvent.

Epoxide ring opening involving a series differently substituted anilines was also examined (Table 3).[15] As previously mentioned, substrates, cyclohexene oxide **1** (Scheme 1) and styrene oxide **5** (Scheme 3) were tested. Good conversion to the amino alcohols (**2** and **6**) can be obtained, even when extremely electron-deficient anilines are used (i.e., 2,4-dinitroaniline, Table 3, entry 5). Slightly lower yields were observed when a more sterically hindered aniline, 2,6-dimethylaniline, was used (Table 3, entries 3 and 9). Similarly, a series non-aromatic amines were also added to styrene oxide (Table 4). Unfortunately, turnover to the β-amino alcohol was slow when reactions were carried out at room temperature. Interestingly, at this temperature the more sterically hindered 1-adamantylamine had one of the highest turnovers (Table 4, entry 5), while in each reaction conducted a large amount of starting material still remained. Increasing the amine stoichiometry and/or catalyst loading, in an effort to improve the yield of these reactions, failed to produce large amounts of the β-amino alcohol. However, increasing the temperature to 40 °C improved the turnover, especially in the case of propylamine, improving the yield from 24% to 91%.

Table 3. Reaction of styrene and cyclohexene oxide with 10% $BiCl_3$ and various anilines: synthesis of amino alcohols **2** and **6**

Entry	Ar-NH_2	Yield (%)
Cyclohexene oxide		
1	Ar=Ph	89
2	*o*-Et-Ph	92
3	2,6-$(CH_3)_2$-Ph	73
4	2-CH_3-6-NO_2-Ph	90
5	2,4-$(NO_2)_2$-Ph	75
6	2,4-$(Cl)_2$-Ph	91
Styrene oxide		
7	Ar=Ph	78
8	*o*-Et-Ph	76
9	2,6-$(CH_3)_2$-Ph	62
10	3-Cl-Ph	82
11	2,4-$(Cl)_2$-Ph	64



5 6 7

Scheme 3.

Table 4. Reaction of styrene oxide with various amines and 10% $BiCl_3$: synthesis of amino alcohols[a]

Entry	Amine	Temperature (°C)	% Conversion[b] (SM)[c]
1	*n*-Propylamine	rt	20 (74)
2	*n*-Propylamine	40	91 (4)
3	*n*-Butylamine	rt	11 (57)
4	*n*-Butylamine	40	30 (11)
5	1-Adamantylamine	rt	34 (50)
6	1-Adamantylamine	40	35 (55)
7	Morpholine	rt	2 (95)
8	Morpholine	40	14 (18)

[a] Reaction carried out in cyclohexane.
[b] % Conversion to the two amino alcohol regioisomers as determined by GC–MS.
[c] Starting material remaining.

Summary: We have demonstrated that bismuth(III) chloride in acetonitrile can be used as a reagent to facilitate the formation of chlorohydrin **3** in excellent yield from the corresponding epoxide **1**, even in the presence of aniline. Conversely, a change in solvent to cyclohexane gives the expected β-amino alcohol **2** or **6**, $BiCl_3$ in this case acting as chelating Lewis acid. These results are currently being incorporated into our program of developing scaffolds for drug design on which a full paper is forthcoming.

Acknowledgments

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15. NMR data for aniline **6** (Table 3, Entry 7)[5f]: ^{1}H NMR: (300 MHz) δ (ppm) 3.81 (dd, $J = 11.3$ and 7.62 Hz, 1H, CH_2), 3.93 (dd, $J = 11.3$ and 7.2 Hz, 1H, CH_2), 4.52 (dd, $J = 7.3$ and 4.1 Hz, 1H, CH) 6.69 (d, $J = 8.3$ Hz, 1H, CH-Ar), 6.76 (m, 1H, CH-Ar), 7.10–7.40 (m, 8H, CH-Ar). ^{13}C NMR (75.5 MHz) δ (ppm) 60.7 (CH), 66.1 (CH_2), 114.6 (CH), 118.6 (CH), 126.5 (CH), 126.6 (CH), 127.2 (CH), 128.2 (CH), 128.6 (CH), 128.7 (CH), 138.6 (C), 145.2 (C).