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# Solvent-Free $Al(OTf)_3$-Catalyzed Aminolysis of 1,2-Epoxides by 2-Picolylamine: A Key Step in the Synthesis of Ionic Liquids

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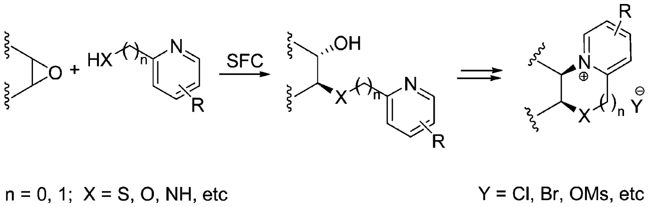
**Abstract:** $\beta$-Amino alcohols *N*-2′-pyridylmethyl substituted **3** have been prepared in excellent yields under mild conditions by the first Lewis acid-catalyzed aminolysis of 1,2-epoxides **1** with the bihaptic amine 2-picolylamine (**2**) with use of 5 mol % of $Al(OTf)_3$ under solvent-free conditions. As a representative of a new class of ionic liquids, *cis*-5-[(4′-methylphenyl)sulfonyl]-1,2,3,4,4a,5,6,11a-octahydropyrido[1,2-*a*]quinoxalin-11-ium methanesulfonate (**6**) and its chloride derivative **7** have been synthesized under environmentally friendly conditions by the one-pot aminolysis of cyclohexene oxide (**1a**) with **2** and intramolecular cyclization of the resulting 2-[(pyridin-2′-yl)methylamino]cyclohexanol (**3a**).

Ionic liquids (ILs), due to the ease of tuning their physical properties, represent an intriguing alternative to common organic reaction media.[1] Since 1999 a variety of ILs have been commercially available[2] and they are essentially imidazolium and pyridinium salts. Only a few examples of optically active ionic liquids have been reported,[3] i.e., imidazolium,[3a,b,d] ammonium, and oxazolinium[3e] salts prepared starting from the chiral pool and chiral pyridinium salts synthesized from achiral substrates following multisteps protocols.[3c,f]

For many years we have been studying the reactions of 1,2-epoxides in water,[4] and recently we also have been paying attention to solvent-free conditions (SFC).[5] Currently we have engaged ourselves in a project aimed at the preparation of new classes of ILs via oxirane ring-opening under SFC by a bihaptic nucleophile and subsequent cyclization of the resulting adduct (Scheme 1). This strategy represents both a stereoselective and a chemically efficient route for preparing new sulfur-, oxygen-, and nitrogen-containing ILs and also a very promising approach for the synthesis of optically active ILs, considering that enantiopure 1,2-epoxides are easily accessible.[6]

**SCHEME 1. Strategy for the Synthesis of Pyridinium-Based ILs Starting from 1,2-Epoxides**



We have initially decided to define the synthesis of pyrido[1,2-*a*]pyrazinium salts (Scheme 1, $n = 1$, X = NH). This goal required, as first step, the study of the aminolysis of 1,2-epoxides with 2-picolylamine (**2**).

The aminolysis protocols of 1,2-epoxides developed in the past few years[7] mainly involve monohaptic nucleophiles and use different acid catalysts such as $Cu(OTf)_2$ (5 mol %),[7a] $Sn(OTf)_2$ (5 mol %),[7a] $InCl_3$ (20 mol %),[7c] $Ca(OTf)_2$ (50 mol %),[7e] $ZnCl_2$ (5 mol %),[7f] $ZrCl_4$ (5 mol %),[7g] $Bi(OTf)_3$ (10 mol %),[7h] and different reaction media such as fluoro alcohols,[7b] ionic liquids,[7d] and water[7h] or SFC.[7g] These procedures suffer some limitations due to the deactivation of the Lewis acid catalyst as a consequence of formation of a stable complex between the metal ion and the amine. Only Zn(II) salts (5 mol %) in acetonitrile[7f] were in some cases truly effective catalysts but they completely failed with bihaptic nucleophiles such as 2-picolylamine (**2**)[7f] because the highly azaphilic Zn(II) cation forms a stable complex with the amine. Hexafluoro-2-propanol and $[bmim]BF_4$ were not effective in the aminolysis with alkylamines.[7b,d]

To the best of our knowledge, no acidic or basic catalyst able to efficiently promote the ring-opening of 1,2-epoxides with a bihaptic nucleophile has been identified to date.

Surprisingly very little attention has been devoted to the use of oxophilic Lewis acids, particularly Al(III), albeit our experience has proved to be particularly

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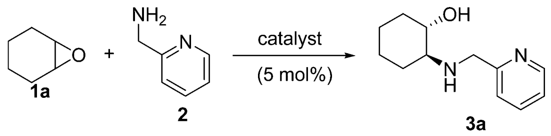
**TABLE 1. Reaction of Cyclohexene Oxide (1a) with 2-Picolylamine (2) (1.02 equiv) at 70 °C after 3 h**



| entry | reaction medium | catalyst | conversion[a] (%) |
|---|---|---|---|
| 1 | SFC | none | <1 |
| 2 | SFC | $Zn(OTf)_2$ | <1 |
| 3 | SFC | $Cu(OTf)_2$ | 33 |
| 4 | SFC | $In(OTf)_3$ | 75 |
| 5 | SFC | $In(OTf)_3$ | 78[b] |
| 6 | SFC | $ZrCl_4$ | 52[c] |
| 7 | SFC | $TiCl_4\cdot(THF)_2$ | 7[c] |
| 8 | SFC | $Yb(OTf)_3$ | 85 |
| 9 | SFC | $Hf(OTf)_4$ | 89 |
| 10 | SFC | $Al(OTf)_3$ | >99[d] |
| 11 | SFC | $Al(OTf)_3$ | 97[b] |
| 12 | DCE | $Al(OTf)_3$ | <1 |
| 13 | MeCN | $Al(OTf)_3$ | 3 |
| 14 | [bmim]$BF_4$ | none | <1 |
| 15 | [bmim]$BF_4$ | $Al(OTf)_3$ | 5 |

[a] By GC and $^1$H NMR analyses; [b] At 30 °C and after 24 h; [c] Additional 18% conversion to *trans*-2-chlorocyclohexanol was obtained; [d] 95% isolated yield after silica gel column chromatography (see the Supporting Information).

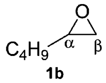
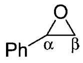
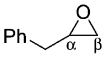
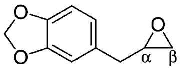
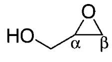
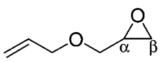
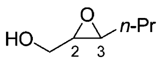
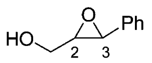
adequate to catalyze the ring-opening of the oxirane ring by a nitrogenous nucleophile.[5e] Therefore we planned to use oxophilic catalysts, such as Al(III), Ti(IV), Zr(IV), Hf(IV), and Yb(III), in the aminolysis of 1,2-epoxides, and considering that under solvent-free conditions (SFC) the efficiency of a chemical process can be strongly increased,[7] we decided to carry out the aminolysis step under SFC. We also decided to investigate the activity of commonly used azaphilic catalysts such as $Zn(OTf)_2$, $Cu(OTf)_2$, and $In(OTf)_3$ that have never been employed in the absence of solvent.

We initially performed the reaction of cyclohexene oxide (**1a**) with 2-picolylamine (**2**) at 70 °C by using different Lewis acid catalysts under SFC in various solvents and in the absence of catalyst for comparison. The results obtained are illustrated in Table 1.

The monoadduct **3a** was the sole isolated product except in the case when chlorinated catalysts were used (Table 1, entries 6 and 7). Trans configuration of **3a** was confirmed by $^1$H NMR analysis.

Under SCF the reaction did not proceed in the absence of catalyst (Table 1, entry 1) and a similar result was obtained in the presence of $Zn(OTf)_2$ (entry 2). $Cu(OTf)_2$ (despite its very high azaphilicity) and $In(OTf)_3$ allowed better conversions (33% and 75% conversion respectively, entries 3, 4) but these reactions also did not proceed to completeness when the reaction time was prolonged, indicating that deactivation of the catalyst occurred.[8] Highly oxophilic Lewis acids such as $ZrCl_4$ and $TiCl_4\cdot(THF)_2$ gave only 52% and 7% conversion to the desired product **3a**, respectively (Table 1, entries 6 and 7). $Yb(OTf)_3$, $Hf(OTf)_4$, and $Al(OTf)_3$ gave 85%, 89%, and the complete conversion respectively after 3 h (entries 8−10).

**TABLE 2. $Al(OTf)_3$-Catalyzed Ring-Opening of 1,2-epoxides 1b−i with 2-Picolylamine (2) under SFC**

| entry | 1,2-epoxide | T (°C) | t[a] (h) | mono-adduct[b] (%) | Yield[c] (%) |
|---|---|---|---|---|---|
| 1 |  **1b** | 70 | 0.5 | **3b** (90) | 87 |
| 2 |  **1c** | 30 | 0.5 | **3c** (85) | 80[d] |
| 3 |  **1d** | 70 | 0.5 | **3d** (85) | 81 |
| 4 |  **1e** | 70 | 0.5 | **3e** (85)[e] | 80 |
| 5 |  **1f** | 30 | 0.5 | **3f** (67) | 98[f] |
| 6 |  **1g** | 30 | 3 | **3g** (67) | 65 |
| 7 |  | 30 | 3 | **3g** (88[g]) | 85 |
| 8 |  | 30 | 3 | **3g** (92[e]) | 90 |
| 9 |  **1h** | 70 | 24 | **3h** (100) | 96[h] |
| 10 |  **1i** | 70 | 0.5 | **3i** (100) | 97 |

[a] Time for complete conversion of 1,2-epoxide; 1.02 equiv of **2** was used. [b] Remaining material was bis-adduct product (see the Supporting Information). [c] Yield of isolated pure product after silica gel column chromatography. [d] α- and β-products were isolated in 17% and 63% yield, respectively. [e] 3 equiv of **2** was used. [f] Overall yield of mono- and bis-adduct products that were not separated; ratio measured by $^{13}$C NMR analysis; [g] 2 equiv of **2** was used. [h] Yield of the 40/60 mixture of $C_2/C_3$ products.

In contrast, only traces of product **3a** were detected when the reaction was performed in the presence of $Al(OTf)_3$ in dichloroethane (DCE), acetonitrile, or [bmim]$BF_4$ (entries 12, 13, and 15), proving that SFC caused an enormous activation.

The reaction protocol is simple (see the Supporting Information) and does not require dry glassware and reagents. This is very important for scaling-up the process. The final amino alcohol **3a** was isolated in ≥99% purity in 95% yield.

$Al(OTf)_3$-catalyzed conditions were then extended to a variety of 1,2-epoxides (Table 2).

All the reactions were fast and completely β- or $C_3$-regioselective except in the case of styrene oxide (**1c**) (α/β ratio = 20/80) and *trans*-2,3-epoxyhexanol (**1h**) ($C_2/C_3$

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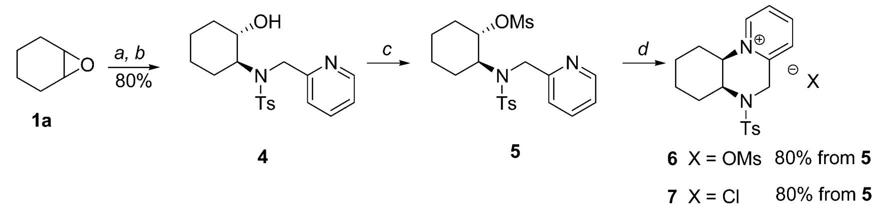
(8) We have found that under SFC and in the presence of 5 mol % of $In(OTf)_3$, cyclohexene oxide **1a** reacts with benzylamine and di-*n*-butylamine, while it is reported that $InCl_3$ in DCM is not effective in these transformations.[7c]

(9) **Representative Experimental Procedure for the Aminolysis of 1,2-Epoxides**: 2.0 mmol (217 mg, 2.04 mmol) of 2-picolylamine (**2**) and 48 mg (0.10 mmol) of $Al(OTf)_3$ were charged into a screw-capped vial and left under magnetic stirring. After complete dissolution of $Al(OTf)_3$ (~5 min), 2.0 mmol (198 mg) of cyclohexene oxide (**1a**) was added and the reaction mixture warmed to 70 °C and left under vigorous magnetic stirring. After 3 h the reaction mixture was cooled to room temperature and the oily mixture was charged on a triethylamine-pretreated silica gel column chromatograph and eluted with EtOAc/MeOH 95/5 solution. The β-amino alcohol **3a** was isolated in 95% yield and recrystallizated from diethyl ether. For a full characterization chart see the Supporting Information.

**SCHEME 2. Synthesis of ILs 6 and 7 from Cyclohexene Oxide (1a)**[a]



[a] Reagents and conditions: (a) $Al(OTf)_3$ (5 mol %), **2** (1,02 equiv), 70 °C, 3 h; (b) $Et_3N$ (1.5 equiv), *p*-TsCl (1.5 equiv), DCM, 0 °C, 1 h; (c) $Et_3N$ (1.5 equiv), MsCl (1.5 equiv), DCM, 0 °C, 4 h; (d) $OMs^-$ of $Cl^-$-exchange resin, $MeOH/H_2O$ 1/1, 40 °C, 15 h.

ratio = 40/60). Monosubstituted 1,2-epoxides (**1b**−**g**) were very reactive toward the nucleophilic attack of **2** and bis-adduct products were formed (see footnotes to Table 2). Improvements in the yield of the monoadducts **3b**−**g** were not observed by varying the catalyst amount or the temperature reaction while an excellent selectivity in the formation of monoadduct was reached by using over-stoichiometric amounts of amine **2** (Table 2, entry 4 and entry 8 vs entries 6 and 7). Bis-adduct formation was not observed in the case of oxirane **1a** and 2,3-substituted 1,2-epoxides **1h** and **1i**.

$\beta$-Amino alcohol products (**3a**−**i**) were isolated in satisfactory to very good yields. All of them are new compounds and have been fully characterized (see the Supporting Information).

Finally we accomplished the synthesis of two new ILs starting from cyclohexene oxide (**1a**) (Scheme 2). The reaction mixture of **1a** with **2** (Table 1, entries 10 or 11) was cooled to 0 °C, DCM was added, and the resulting solution was treated with 1.5 equiv of $Et_3N$ and *p*-toluenesulfonyl chloride to give the corresponding *N*-Ts-$\beta$-amino alcohol **4**, which can be isolated in 80% yield after column chromatography. *O*-Ms derivative **5** was prepared in 70% overall yield in one pot from **1a** by adding 1.5 equiv of $Et_3N$ and methanesulfonyl chloride to the crude **4**. $\beta$-Amino mesilate **5** did not undergo cyclization upon heating at 70 °C for 48 h but only decomposition products were formed. Cyclization of **5** occurred slowly and after 2 weeks at 40 °C, *cis*-pyrido-[1,2-*a*]quinoxalin-11-ium mesylate **6** was obtained in only 25% yield. We were happy to find that by treating **5** with OMs-exchange resin in 1/1 $MeOH/H_2O$ at 40 °C for 15 h, ionic liquid **6** can be satisfactorily obtained in 80% yield.

We have also prepared the chloride derivative **7** by treating **5** with a Cl-exchange resin for 15 h at 40 °C in a 1/1 $MeOH/H_2O$ solution in 80% yield. The pyrido-[1,2-*a*]quinoxalin-11-ium ion formation led to a significant shift of the NMR resonances of pyridine protons (from **5** to **6** and **7**: ortho, 8.49 to 9.33 and 9.74 ppm; para, 7.67 to 8.07 and 8.05 ppm). Salts **6** and **7** are viscous liquids at room temperature and were fully characterized by $^1H$, $^{13}C$ NMR (see the Supporting Information). NOESY and $^{13}C-^1H$ correlation experiments on **6** and **7** confirmed their structure and the expected cis stereochemistry of the fusion at positions 4a,11a (see the Supporting Information).

In conclusion the use of $Al(OTf)_3$ and SFC has allowed for the first time the aminolysis of 1,2-epoxides **1** with the bihaptic 2-picolylamine (**2**) to be carried out under mild conditions. A new class of $\beta$-amino alcohols *N*-2′-pyridylmethyl substituted **3** was prepared in excellent yields. The easy conversion of **3a** into the corresponding octahydropyrido[1,2-*a*]quinoxalin-11-ium methanesulfonate **6** and chloride **7** opens the route to a novel class of ionic liquids starting from 1,2-epoxides by an environmentally friendly procedure. Further investigations are ongoing to synthesize a variety of optically active ionic liquids based on oxygen-, nitrogen-, and sulfur-containing heterocyclic systems.

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**Supporting Information Available:** Experimental procedures and full characterization data ($^1H$ NMR, $^{13}C$ NMR, GC-MS, $R_f$) for all the new mono- and bis-adduct products. This material is available free of charge via the Internet at http://pubs.acs.org.

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