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[Bmim]BF_4 ionic liquid: a novel reaction medium for the synthesis of β-amino alcohols

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Abstract—Epoxides undergo smooth ring-opening with aryl amines in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids under mild and neutral conditions to afford the corresponding β-amino alcohols in excellent yields with high regioselectivity.

Epoxides are well known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo regioselective ring opening reactions contributes to their synthetic value.[1] β-Amino alcohols are versatile intermediates in natural product synthesis and are also used as β-blockers, insecticidal agents and as chiral ligands in asymmetric synthesis.[2] One of the most straightforward synthetic procedures for the preparation of β-amino alcohols involves the ring opening of epoxides with amines;[3] however, these reactions are generally carried out with large excesses of the amines at elevated temperatures. The high temperature reaction conditions are not only detrimental to certain functional groups, but also to the control of regioselectivity.[4] Subsequently, a variety of activators or promoters such as metal amides, metal triflates and transition metal halides have been developed to perform the epoxide ring opening reactions with amines under mild conditions.[5–7] However, many of these methods often involve the use of expensive and stoichiometric amounts of reagents, poor regioselectivity especially with metal amides derived from primary amines, extended reaction times and also entail undesirable side reactions such as rearrangement of the oxiranes to allyl alcohols under basic conditions[8] or polymerization in strongly acidic conditions resulting in low yields of the desired products. Since β-amino alcohols have become increasingly useful and important in drugs and pharmaceuticals, the development of simple, efficient and environmentally friendly processes for their synthesis, are well appreciated.

Room temperature ionic liquids, especially those based on the 1-*N*-alkyl-3-methylimidazolium cation, have shown great promise as attractive alternatives to conventional solvents.[9] Due to the potential of room temperature ionic liquids as an alternative reaction media for catalytic processes, much attention has been focused on organic reactions promoted by ionic liquids.[10] The unique property of ionic liquids is that they have essentially no vapor pressure, which makes them optimal replacements for the volatile organic solvents traditionally used as industrial solvents. A nice feature of ionic liquids is that yields can be optimized by changing the anions or properties of the cation. In addition, several ionic liquids show enhancement in reaction rates and selectivity, compared to organic solvents with the added benefit of the ease of recovery and reuse of these ionic solvents. Due to these advantages, ionic liquids can make a significant contribution to green chemistry.

In view of the emerging importance of ionic liquids as novel reaction media, we wish to report the use of ionic liquids as efficient promoters for the opening of epoxides with aryl amines under mild conditions (Scheme 1). The treatment of styrene oxide with aniline in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) ionic liquid at ambient temperature afforded the corresponding 2-aminophenyl-2-phenyl-1-ethanol **2** in 90% yield (Scheme 1).

Aryl oxiranes underwent cleavage by a variety of amines in a regioselective manner with preferential attack at the benzylic position (see Table 1). Only a single product was obtained from each of these reactions, the structure of which was confirmed by ^{1}H NMR spectroscopy of the crude product. This method is highly regioselective affording, exclusively, the ring-

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Keywords: ionic liquids; oxiranes; aryl amines; β-amino alcohols.

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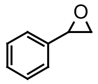
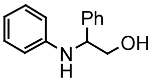
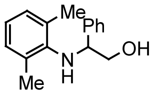
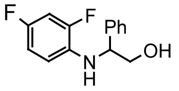
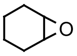
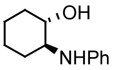
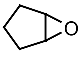
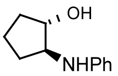
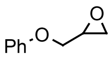
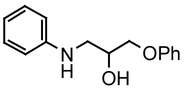
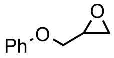
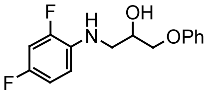
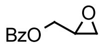
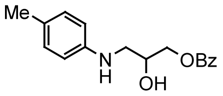
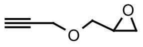
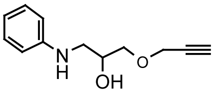
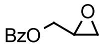
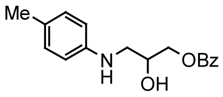
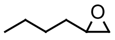
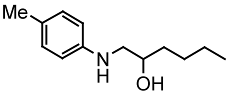
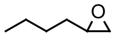
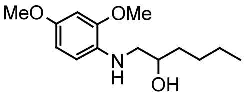
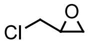
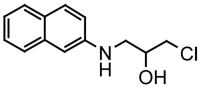
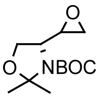
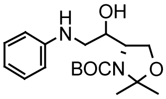
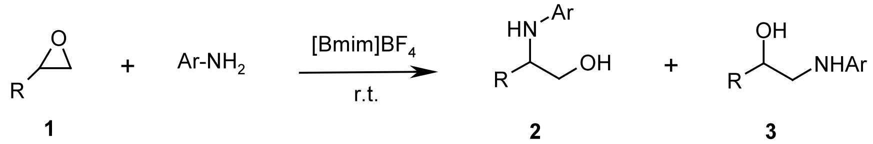
Table 1. Ionic liquid promoted synthesis of β-amino alcohols from epoxides

entry	epoxide	β–amino alcohol[a]	yield (%)[b]	time (h)
a			85	5.0
b	"		90	6.5
c	"		81	7.5
d			83	6.0
e			85	3.5
f			89	6.0
g			82	6.5
h			80	5.5
i			80	6.5
j			87	7.0
k			85	6.0
l			85	6.5
m			89	7.5
n			80	8.0

a: All products were characterized by ^1H NMR, IR and mass spectroscopy.

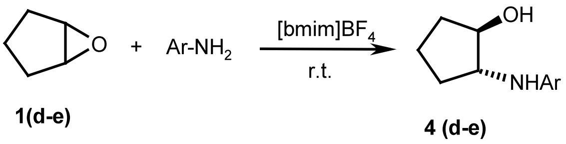
b: Isolated and unoptimized yields



Scheme 1.

opened product **2**. However, glycidyl aryl ethers reacted smoothly with aryl amines to afford the corresponding β-amino alcohols **3** in high yields (entries f, g). In a similar fashion, glycidyl alkyl ethers and esters were also cleaved with aryl amines to produce ring-opened products (entries h, i, j). Alkyl oxiranes (entries k, l, m) underwent cleavage with a range of amines in a regioselective manner with preferential attack at the terminal position (see Table 1). In all cases the reactions proceeded efficiently at ambient temperature with high regioselectivity. Furthermore, cycloalkyl epoxides such as cyclohexene oxide and cyclopentene oxides reacted smoothly with aryl amines to afford the corresponding β-amino alcohols **4** in excellent yields (Scheme 2).

In the case of cyclohexyl epoxide (entry d), the stereochemistry of the ring-opened product **4d** was found to be *trans* from the coupling constants of the ring hydrogen at δ 3.35 (ddd, $J=4.5$, 9.8, 9.8 Hz, 1H) for (CH-OH) in the ^{1}H NMR spectrum. Similarly, the peak at δ 3.15 ppm for (CH-NHPh) showed a similar splitting pattern (ddd, $J=4.0$, 9.5, 10.5 Hz, 1H). A variety of epoxides underwent cleavage with the aryl amines to afford the corresponding β-amino alcohols in high yields. All products were characterized by ^{1}H NMR, IR and mass spectroscopic data and also by comparison with authentic compounds.[6,7] This method does not require any acidic promoters or activators; the reaction conditions are neutral and mild enough to tolerate acid or base labile functionalities. The reactions are clean and highly regioselective affording high yields of products in a short period of time. The reactions of various epoxides with aryl amines were examined in hydrophilic ([bmim]BF_4) and hydrophobic ([bmim]PF_6) ionic liquids.[11] Among these ionic liquids, [bmim]BF_4 was found to be superior in terms of conversion and selectivity. The advantage of the use of ionic liquids as promoters for this transformation is that these ionic solvents can be easily recovered and reused. Since the products were weakly soluble in the ionic phase, they were separated by simple extraction with ether. The rest of the viscous ionic liquid was thoroughly washed with ether and dried at 80°C under reduced pressure and reused in five runs without any loss of activity. The products were obtained of the same purity as in the first run and no decrease in yields occurred in runs carried out using recycled ionic liquid. Furthermore, we have performed these reactions in polar organic solvents such as DMF and *N*-methylpyrrolidine to compare the efficiency of the ionic liquids. The reactions did not proceed in these solvents even under heating (75–80°C). Finally, the efficiency of various quaternary ammonium salts was studied. The epoxide ring opening was not successful when *n*-tetrabutyl ammonium chloride (*n*-Bu_4NCl) or 1-*n*-butyl-3-methylimidazolium chloride (BMImCl) was used as the reaction media. This indicated that both the cation and anion played an important role in this transformation. The scope and generality of this process is illustrated with respect to various epoxides and aryl amines and the results are presented in Table 1.[12]



Scheme 2.

In summary, this paper describes a convenient and efficient method for the synthesis of β-amino alcohols via the regioselective ring opening of epoxides with various aryl amines using ionic liquids as promoters. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this reaction media is expected to contribute to the development of environmentally friendly processes for the synthesis of β-amino alcohols of biological and medicinal importance. The use of ionic liquids as promoters for this transformation avoids the use of moisture sensitive and heavy metal Lewis acids.

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12. **General procedure**: A mixture of epoxide (1 mmol), aryl amine (1 mmol), in [bmim]BF_4 or [bmim]PF_6 (1 mL) was stirred at ambient temperature for the appropriate time (see Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3×10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged on to a small silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:9) to afford pure β-amino alcohol. The rest of the viscous ionic liquid was further washed with ether and dried at 80°C under reduced pressure to retain its activity in subsequent runs.

Recycling of ionic liquid: In the case of the hydrophilic ionic liquid, i.e. [bmim]BF_4, the reaction mixture was diluted water and extracted with ethyl acetate (2×10 mL). The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and concentrated in vacuo and the resulting product was purified either by column chromatography or by recrystallization to afford pure product. The ionic liquid can be recovered either by extracting the aqueous phase with ethyl acetate or by evaporating the aqueous layer in vacuo. The ionic liquid thus obtained was further dried at 80°C under reduced pressure for use in subsequent runs.

Spectral data for selected products:

2-Phenylamino-2-phenyl ethanol (2a): Liquid; IR (neat): ν 3328, 2925, 1542, 1233, 1041, 760; ^{1}H NMR ($CDCl_3$): δ 3.75 (dd, 1H, $J=6.9$, 10.9 Hz), 3.95 (dd, 1H, $J=3.9$, 10.9 Hz), 4.50 (dd, 1H, $J=6.9$, 10.9 Hz), 6.50 (d, 2H, $J=8.0$ Hz), 6.70 (t, 1H, $J=7.8$ Hz), 7.10 (t, 2H, $J=7.9$ Hz) 7.30–7.40 (m, 5H); EIMS *m*/*z*: 213 M$^+$, 195, 107, 91, 77, 57.

***trans*-2-(Phenylamino)cyclohexanol (4d)**: Solid; mp 60–61°C; IR (KBr): ν 3073, 2960, 1547, 1449, 1375, 1263, 1042, 974, 702; ^{1}H NMR ($CDCl_3$): δ 1.0–1.2 (m, 1H), 1.30–1.45 (m, 3H), 1.70–1.90 (m, 2H), 2.10–2.20 (m, 2H), 2.80 (brs, NH, 1H), 3.15 (ddd, 1H, $J=10.5$, 9.5, 4.0 Hz), 3.30 (ddd, 1H, $J=9.8$, 9.8, 4.5 Hz), 6.70–6.80 (m, 3H), 7.15–7.25 (m, 2H); EIMS *m*/*z*: 191 M$^+$, 174, 99, 82, 77, 41.

1-(Phenylamino)-3-phenoxy-2-propanol (3f): Liquid; ^{1}H NMR ($CDCl_3$): δ 3.10 (dd, 1H, $J=7.0$, 12.5 Hz), 3.25 (dd, 1H, $J=4.0$, 12.5 Hz), 3.40–3.55 (m, 2H), 3.95–4.0 (m, 1H), 6.50–6.70 (m, 3H), 7.10–7.40 (m, 7H); EIMS *m*/*z*: 243 M$^+$, 225, 134, 121, 108, 91, 77, 45.

1-(4-Methylphenylamino)hexan-2-ol (3k): Liquid; IR (neat): ν 3027, 2929, 1549, 1447, 1269, 964, 754; ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H, $J=6.8$ Hz), 1.25–1.60 (m, 6H), 2.20 (s, 3H), 2.95 (dd, 1H, $J=8.5$, 12.5 Hz), 3.25 (dd, 1H, $J=3.5$, 12.5 Hz), 3.80 (m, 1H), 6.60 (d, 2H, $J=8.0$ Hz), 6.90 (d, 2H, $J=8.0$ Hz); EIMS *m*/*z*: 207 M$^+$, 190, 178, 135, 121, 107, 91, 84, 57.