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A mild and efficient synthesis of β-amino alcohols from epoxides using a mesoporous aluminosilicate catalyst

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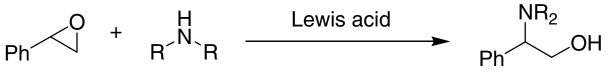
Abstract—Mesoporous aluminosilicates catalyze efficiently the ring-opening reactions of a range of epoxides with aromatic amines to produce β-substituted alcohols in high yields under mild reaction conditions.

The formation of β-amino alcohols from epoxides and amines is an important reaction in medicinal and organic chemistry as they are useful synthetic intermediates for the preparation of β-amino acids, natural products and chiral auxiliaries.[1] Classically, the reaction has been carried out using an excess of the amine and high temperatures, however, these conditions are far from ideal as they are not tolerated by certain functional groups.[2] Therefore, new methods which utilize mild Lewis acid promoters and which work at low temperatures with stoichiometric amounts of amine have continued to be of interest (Scheme 1).[3] The use of ultrasound, microwave irradiation, ionic liquids, solvent free conditions and under aqueous conditions in the absence of a catalyst has been reported.[4] These processes are useful, however, they suffer from disadvantages such as the use of expensive or air sensitive reagents, extended reaction times, the requirement for protracted work-up procedures, or are limited in the range of amines.

Recent developments have focussed on the application of heterogeneous catalysts such as heteropolyacids, zirconium sulfophenyl phosphonates, zeolites and clays for the formation of β-amino alcohols from epoxides and aromatic amines at room temperature.[5] These processes have greatly improved the atom efficiency of the transformation, however, prolonged reaction times or an inert atmosphere are still required.



Scheme 1.

We recently reported that mesoporous aluminosilicates are efficient heterogeneous catalysts for the preparation of β-alkoxy alcohols from epoxides and alcohols.[6] We have extended our studies in this area to show that such catalysts are active for the preparation of β-amino alcohols from aromatic amines and epoxides under extremely mild reaction conditions. The mesoporous aluminosilicate material (Si/Al ratio = 14) was synthesized according to previously reported procedures and used for all subsequent transformations.[6] Our initial experiments with 50 mg/mmol of catalyst utilized simple alkylamines, such as ethylamine or diisopropylamine, with styrene oxide, however, these reactions resulted in no conversion to the β-amino alcohol and the starting material was recovered unchanged. These observations are attributed to a competing interaction of the nitrogen and of the amine with the Lewis acid sites of a catalyst reducing the catalytic activity of the material. To investigate this point further, we next considered the addition reactions of the less nucleophilic aromatic amines under similar conditions. The decreased nucleophilicity of these substrates and the subsequent reduced interaction with the catalyst was expected to free-up the catalytic sites. We were gratified to observe that the reaction of styrene oxide with aniline in dichloromethane at room temperature provided moderate conversion with good selectivity for the expected Markovnikov product pro-

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Keywords: Epoxide ring-opening; Mesoporous aluminosilicates; Heterogeneous catalysis; β-Amino alcohols.

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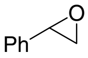
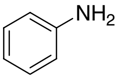
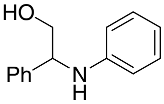
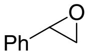
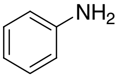
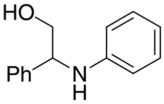
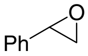
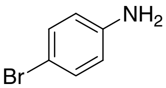
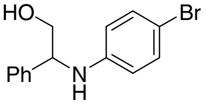
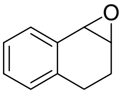
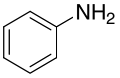
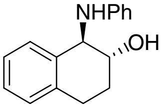
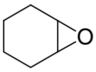
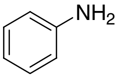
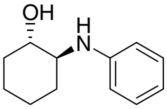
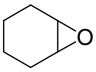
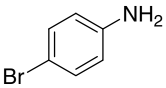
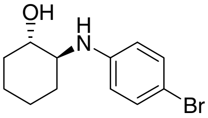
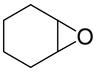
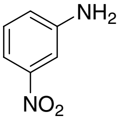
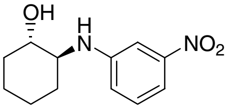
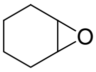
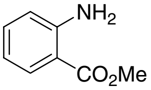
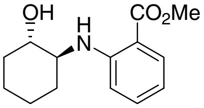
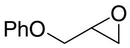
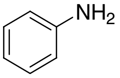
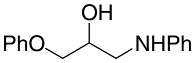
Table 1. Mesoporous aluminosilicate promoted aminolysis of epoxides

Entry	Epoxide	Aniline	Time (h)	Product	Yield[a,b] (%)
1			24		68[c,d]
2			6		70[e]
3			6		65[e]
4			6		79[e]
5			6		85
6			6		65
7			12		69
8			12		57
9			8		80[f]

[a] Isolated yield after column chromatography.

[b] Reactions in CH_2Cl_2 at room temperature utilizing 120 mg/mmol of catalyst unless otherwise stated.

[c] 50 mg/mmol of catalyst used.

[d] Product is an 80:20 mixture of regioisomers as determined by ^{1}H NMR analysis. Major isomer shown.

[e] Products isolated in a 95:5 ratio of regioisomers. Major isomer shown.

[f] Products isolated in an 85:15 ratio of regioisomers. Major isomer shown.

duced by attack at a more stable benzylic position.[7] The decreased interaction of the substrate with a catalyst, and the subsequent improvement in the activity, is analogous to the 'hard-soft acid–base' theory for homogeneous Lewis acid catalysis.[8] In general alkylamines are harder Lewis bases than aromatic amines and compete more efficiently with the epoxide for the catalytic sites resulting in the requirement for longer reaction times and greater amounts of catalyst.[9]

Increasing the quantity of catalyst to 120 mg/mmol led to an improvement in regioselectivity and a subsequent reduction in reaction times for the addition aniline to styrene oxide, and this quantity was used in all subsequent reactions (Table 1). Similarly, 1,2-dihydronaphthalene oxide underwent a facile transformation to give the *anti*-substituted product in good yield with only trace amounts of the corresponding regioisomer. Utilizing this protocol, the aminolysis of cyclohexene oxide also proceeded with a range of anilines to produce the corresponding *anti*-β-amino alcohols in short times and high yields further demonstrating the synthetic utility of this process. Disappointingly, reactions utilizing 4-nitroaniline with these epoxides resulted in no conversion to the desired β-amino alcohol. The application of extended reaction times had no effect on the conversion, and in the case of cyclohexene oxide, the utilization of reflux temperatures led to the production of cyclohexanone produced by a competing Meinwald rearrangement process.[10] This is attributed to the further reduced nucleophilicity of the *para*-substituted aniline compared to aniline and indeed, experiments utilizing the same reaction conditions but with no amine provided the rearrangement product in high yield. In accordance with literature reports,[5d] the addition of aniline to 1,2-epoxy-3-phenyoxypropane resulted in the formation of the product derived from the addition of the amine to the least hindered carbon of the epoxide with good regioselectivity.

In conclusion, we have demonstrated that mesoporous aluminosilicates efficiently catalyze the formation of β-amino alcohols from aromatic amines and epoxides in short reaction times and in high yields under mild reaction conditions. The facile synthesis of these materials, their benign nature, the ease of handling and the simplified reaction and isolation procedures make them a highly attractive alternative to current methodologies.

Typical procedure for aminolysis of epoxides: Cyclohexene oxide (98 mg, 1.0 mmol) and aniline (102 mg, 1.1 mmol) were dissolved in dichloromethane (5 mL) at room temperature. The mesoporous catalyst (120 mg) was added and the reaction mixture stirred at room temperature and monitored by TLC. Upon completion of the reaction, the catalyst was removed by filtration through a Celite plug which was washed with dichloromethane (2 × 5 mL) and the combined solvents were removed under reduced pressure to give a yellow oil which was purified by column chromatography (hexane→20% ethyl acetate–hexane) to give the product *2-(phenylamino)cyclohexanol* (162 mg, 85%) as white solid; mp = 59–61 °C (lit. 60–61 °C[4e]); ^{1}H NMR ($CDCl_3$; 400 MHz) $\delta = 7.11$–7.07 (2H, m), 6.68–6.60 (3H, m), 3.30–3.22 (1H, m), 3.10–2.80 (2H, m), 2.75 (1H, br s), 2.07–1.99 (2H, m), 1.72–1.57 (2H, m), 1.37–1.14 (3H, m), 1.00–0.89 (1H, m); ^{13}C NMR ($CDCl_3$; 100 MHz) $\delta = 148.3$, 129.8, 129.7, 118.7, 118.6, 114.7, 74.9, 60.5, 33.6, 32.0, 25.4, 24.7; ν_{max} (film)/cm^{-1} (neat) = 3394, 3053, 2923, 1599, 1497, 1321, 1054, 740, 688; MS(EI) m/z 192.1 $(M+H)^+$; HRMS (ES) calculated for $C_{12}H_{18}NO$ $(M+H)^+$, 192.1383, found $(M+H)^+$192.1384.

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10. Our initial results for the mesoporous aluminosilicate promoted Meinwald rearrangement of epoxides will be the subject of a subsequent publication.