

# Highly efficient ring opening reactions of epoxides with deactivated aromatic amines catalyzed by heteropoly acids in water

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**Abstract**—Heteropoly acid was found to be an effective and efficient catalyst for the ring opening reaction of epoxides with various aromatic amines to produce the corresponding  $\beta$ -amino alcohols in moderate to excellent yields in water. This method provides a new and efficient protocol in terms of mild reaction conditions, clean reaction profiles, small quantity of catalyst, and simple work-up procedure.  
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## 1. Introduction

It is highly desirable to carry out organic reactions in water from an environmental perspective.<sup>1</sup> On the other hand, heteropoly acids (HPAs) such as tungstophosphoric acid and molybdotophosphoric acid are environment-friendly and economically feasible solid acids due to several advantages such as high catalytic activities and reactivities, ease of handling, cleaner reactions in comparison to conventional catalysts (less waste production), non-toxicity and experimental simplicity.<sup>2</sup> Therefore, organic reactions in water, using a very small quantity of heteropoly acid catalysts will be an ideal methodology, providing that the catalysts show high catalytic activity.

$\beta$ -Amino alcohols are important organic compounds of considerable use in medicinal chemistry and as unnatural amino acids and chiral auxiliaries.<sup>3,4</sup> The most practical and widely used route for synthesizing these compounds is the direct aminolysis of epoxides at elevated temperature with excess of amine.<sup>5</sup> However, this methodology suffers from one or more disadvantages such as high temperature, stoichiometry and moisture sensitive catalyst and hazardous organic solvents. In addition, almost all procedures for the preparation of  $\beta$ -amino alcohols reported so far are restricted to simple aromatic and aliphatic amines and that of deactivated aromatic amines has not been reported in water so far.<sup>6</sup>

## 2. Results and discussion

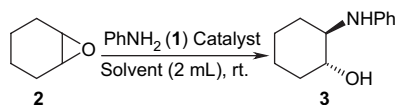
As a part of our research to develop green chemistry by using water as reaction medium<sup>7</sup> or by performing organic transformations under solvent-free conditions,<sup>8</sup> we recently have shown that aliphatic epoxides react with aliphatic amines in water with moderate to high yields and good regioselectivity, without using any catalysts or organic solvents.<sup>9</sup> However, the reactions of aromatic amines with the aliphatic epoxides are very slow in water and give the desired products in low yields. Herein we wish to extend this simple procedure to aromatic amines especially deactivated aromatic amines in water, which has not been reported previously.

Initially, ring opening of cyclohexene oxide was investigated with aniline in water and different organic solvents. Cyclohexene oxide was treated with 1 equiv of aniline at room temperature, and the desired product was obtained in 54% yield within 48 h in water as the sole solvent. As a preliminary study, several promoters were screened in the model reaction of aniline and cyclohexene oxide (Table 1). The starting materials were stirred in water at room temperature in the presence of a promoter (Table 1). The best results were obtained when we used 0.01 mol % of heteropoly acids such as  $H_3PMo_{12}O_{40}$  (Table 1, entry 14) and  $H_3PW_{12}O_{40}$  (Table 1, entry 15) at room temperature for 2 h. Furthermore, we found that common Lewis acids such as  $CeCl_3$ ,  $WCl_6$ ,  $ZrCl_4$  and  $LiClO_4$  also show activity in water (Table 1).

With this promising result in hand, we focused our attention on a study of the scope and limitations of the model reaction of cyclohexene oxide with other deactivated amines such as 3,4-dichloroaniline.

**Keywords:** Amino alcohol; Aromatic amine; Epoxide; Heteropoly acid; Atom economy; Water chemistry.

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**Table 1.** Reaction of cyclohexene oxide with aniline<sup>a</sup>

| Entry | Catalyst   | Mol % | Solvent                              | Time (h) | Yield (%) |
|-------|--|-------|--------------------------------------|----------|-----------|
| 1     | —  | —     | Water                                | 44       | 48        |
| 2     | —  | —     | CH <sub>2</sub> Cl <sub>2</sub>      | 44       | 0         |
| 3     | —  | —     | ClCH <sub>2</sub> CH <sub>2</sub> Cl | 44       | 0         |
| 4     | —  | —     | PhCH <sub>3</sub>                    | 44       | 0         |
| 5     | —  | —     | THF                                  | 44       | 15        |
| 6     | —  | —     | Diethyl ether                        | 44       | 10        |
| 7     | LiClO <sub>4</sub>                               | 200   | Water                                | 24       | 96        |
| 8     | CeCl <sub>3</sub> ·7H <sub>2</sub> O             | 30    | Water                                | 24       | 83        |
| 9     | LiCl   | 200   | Water                                | 24       | 80        |
| 10    | ZrCl <sub>4</sub>                                | 40    | Water                                | 24       | 76        |
| 11    | B(OH) <sub>3</sub>                               | 50    | Water                                | 74       | 92        |
| 12    | WCl <sub>6</sub>                                 | 20    | Water                                | 12       | 86        |
| 13    | Bi(NO <sub>3</sub> ) <sub>3</sub>                | 20    | Water                                | 24       | 83        |
| 14    | H <sub>3</sub> PMo <sub>12</sub> O <sub>40</sub> | 0.1   | Water                                | 2        | 94        |
| 15    | H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub>  | 0.2   | Water                                | 2        | 93        |

<sup>a</sup> Reaction condition: solvent 2 mL, aniline (2 mmol), cyclohexene oxide (2 mmol).

We optimized the reaction conditions by systematic variation of solvent and catalyst in the reaction of **2** with **4**. The results are summarized in Table 2.

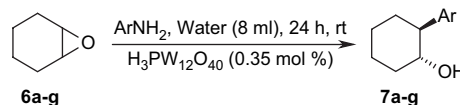
First, we have performed the reaction in organic solvents and in the presence of a heteropoly acid such as tungstophosphoric acid and molybdotungstophosphoric acid. We have found that the reaction can also proceed in low-polar solvents such as toluene and 1,2-dichloroethane. The yield was lower in MeCN and gave byproduct in solvents such as THF. When a mixture of water and an organic solvent, such as toluene and CH<sub>3</sub>CN, was used the yield of adducts did not improve considerably, and in some cases lower yields were observed (Table 2, entries 7–10). We also investigated the effect of adding a surfactant. Interestingly, addition of cetyltrimethylammonium bromide (CTAB) was not effective (Table 2, entry 5), but addition of sodium dodecyl sulfate (SDS) improved the yield of the reaction (Table 2, entries 3 and 4).

**Table 2.** Reaction of cyclohexene oxide with a deactivated amine in the presence of promoter in water

| Entry | Solvent <sup>b</sup>     | Yields (%) | Catalyst | Entry | Solvent                              | Yields (%) | Catalyst |
|-------|--------------------------|------------|----------|-------|--------------------------------------|------------|----------|
| 1     | Water                    | 84         | A        | 13    | THF                                  | 30         | A        |
| 2     | Water                    | 85         | B        | 14    | THF                                  | 25         | B        |
| 3     | Water                    | 88         | A+SDS    | 15    | ClCH <sub>2</sub> CH <sub>2</sub> Cl | 85         | A        |
| 4     | Water                    | 92         | B+SDS    | 16    | ClCH <sub>2</sub> CH <sub>2</sub> Cl | 87         | B        |
| 5     | Water                    | 50         | A+CTAB   | 17    | Diethyl ether                        | 64         | A        |
| 6     | Water                    | 56         | B        | 18    | PhCH <sub>3</sub>                    | 84         | A        |
| 7     | Water/CH <sub>3</sub> CN | 40         | A        | 19    | PhCH <sub>3</sub>                    | 73         | B        |
| 8     | Water/CH <sub>3</sub> CN | 68         | B        | 20    | MeOH                                 | 67         | B        |
| 9     | PhCH <sub>3</sub> /water | 10         | A        | 21    | CH <sub>3</sub> CN                   | 40         | A        |
| 10    | PhCH <sub>3</sub> /water | 22         | B        | 22    | CH <sub>3</sub> CN                   | 60         | B        |
| 11    | PhCH <sub>3</sub> /water | 80         | A        | 23    | MeOH                                 | 62         | A        |
| 12    | Ether/water              | 76         | B        | 24    | EtOH                                 | 76         | B        |

<sup>a</sup> A: H<sub>3</sub>PMo<sub>12</sub>O<sub>40</sub> (0.55 mol %); B: H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> (0.35 mol %).

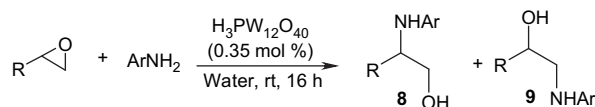
<sup>b</sup> Solvent used in each reaction: 8 mL. The ratio of water to the other solvent is 9:1 in entries 7 and 8, 5:1 in entries 9 and 10 and 1:10 in entries 11 and 12.

**Table 3.** Reaction of cyclohexene oxide with deactivated amines

| Entry          | Aromatic amine | Product | Yield (%)        |
|----------------|----------------|---------|------------------|
| 1              |                |         | 92 <sup>6b</sup> |
| 2              |                |         | 93 <sup>6j</sup> |
| 3 <sup>a</sup> |                |         | 35 <sup>6i</sup> |
| 4 <sup>a</sup> |                |         | 54 <sup>6j</sup> |
| 5              |                |         | 42 <sup>6c</sup> |
| 6              |                |         | 90 <sup>6j</sup> |
| 7 <sup>a</sup> |                |         | 34               |

<sup>a</sup> SDS (0.25 mmol) was added.

Encouraged by the above results we performed the direct ring opening reaction of cyclohexene oxide with various deactivated aromatic amines and the successful results are summarized in Table 3. In the case of amines with

**Table 4.** Aminolysis of epoxides in water in the presence of heteropoly acid<sup>a</sup>

| Entry | Epoxide | Aromatic amine       | Yield (%) | Ratio 8:9 <sup>b</sup> |
|-------|---------|----------------------|-----------|------------------------|
| 1     |         | a R=H                | 92        | 96:4                   |
| 2     |         | b R= <i>n</i> -butyl | 86        | 92:8                   |
| 3     |         | c R=isopropyl        | 84        | 93:7                   |
| 4     |         | d R=OMe              | 90        | 90:10                  |
| 5     |         | e X=Cl               | 84        | 92:8                   |
| 6     |         | f X=Br               | 80        | 90:10 <sup>c</sup>     |
| 7     |         | g R=H                | 90        | 95:5                   |
| 8     |         | h R= <i>n</i> -butyl | 80        | 90:10                  |
| 9     |         | i R=isopropyl        | 84        | 91:9                   |
| 10    |         | j R=OMe              | 88        | 88:12                  |
| 11    |         | k X=Cl               | 80        | 92:8                   |
| 12    |         | l X=Br               | 78        | 90:10 <sup>b</sup>     |
| 13    |         | m R=H                | 93        | 96:4                   |
| 14    |         | n R=isopropyl        | 80        | 85:15                  |
| 15    |         | o R=OMe              | 84        | 84:16                  |
| 16    |         | p X=Cl               | 76        | 90:10                  |
| 17    |         | q R=H                | 80        | 85:15                  |
| 18    |         | r X=Cl               | 76        | 87:13                  |
| 19    |         | s R=H                | 80        | 85:15                  |
| 20    |         | t X=Cl               | 74        | 82:18                  |

<sup>a</sup> All products have been previously reported in the literature.<sup>6</sup>

<sup>b</sup> Ratio was determined by NMR spectroscopy.

<sup>c</sup> SDS (0.2 mmol) was added.

electron-donating groups, such as 4-hydroxyaniline, the corresponding amino alcohols were obtained in good to high yields (Table 3, entry 6). Especially, with a sterically hindered amine, such as 2,4,6-trimethylaniline, the corresponding adduct was produced in moderate yield (Table 3, entry 5). Furthermore, amines with an electron-withdrawing group, such as 2-aminopyridine, 4-nitroaniline and 3-nitroaniline, gave the desired products in moderate yields (Table 3, entries 3, 4, 7).

Finally, this success has encouraged us to extend the generality of the reaction to other aliphatic epoxides with various aromatic amines (Table 4). Aniline, 4-methoxy aniline, 4-chloroaniline, 4-bromoaniline and 4-isopropyl aniline reacted well with aliphatic epoxide such as glycidyl phenyl ether, glycidyl isopropyl ether, 1,2-epoxy butane, 1,2-epoxy propane and allyl 2,3-epoxypropyl ether to give the corresponding amino alcohols in good yields (Table 4).

The *trans* stereochemistry of the  $\beta$ -amino alcohols was determined from the coupling constants of the C–H protons  $\alpha$  to the heteroatoms in the <sup>1</sup>H NMR spectra. For example, the *trans* stereochemistry of compound 3 was assigned from the coupling constants of the peaks at 3.12 ppm (ddd,  $J=10.6$ , 9.4, 4.2 Hz, CH–NHPh) and 3.36 ppm (ddd,  $J=10.6$ , 9.5, 4.3 Hz, CH–OH) in the <sup>1</sup>H NMR spectrum.

Despite the low solubility of both epoxides and amines in water, the heteropoly acid-catalyzed ring opening reactions could still proceed efficiently at ambient temperature. The ring opening reaction might take place at the interface of organic reactants with water in the heterogeneous system. It was found that vigorous stirring was required for the success of the reaction.

There are several interesting implications for the use of heteropoly acids as effective catalysts for the efficient addition of aromatic amines to cyclohexene oxide in water. The reaction itself employs an inexpensive, easily accessed catalyst with low catalyst loading, and it involves a simple experimental procedure.

In summary, the results summarized here constitute the first example of a highly efficient and simple protocol for the ring opening of epoxides catalyzed by HPA, and therefore they expand the chemistry of these versatile catalyst systems to an important new reaction class.

### 3. Experimental

#### 3.1. General

NMR spectra were recorded on a Bruker ACF 500 using CDCl<sub>3</sub>/CCl<sub>4</sub> or CDCl<sub>3</sub>/DMSO-*d*<sub>6</sub> as solvent. Column chromatography was performed on silica gel, Merck grade 60. Ethyl acetate, petroleum ether and other solvents were distilled before use. Epoxides, amines and other chemicals were purchased from Fluka and Merck. H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> and H<sub>3</sub>PMo<sub>12</sub>O<sub>40</sub> are commercially available and were purchased from Merck and used without further purification.

#### 3.2. General procedure of aqueous ring opening of epoxides with aromatic amines catalyzed by HPAs

To a stirred solution of epoxide (2 mmol) and amines (2 mmol) was added water (8 mL) and H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> (20 mg, 0.007 mmol) or H<sub>3</sub>PMo<sub>12</sub>O<sub>40</sub> (20 mg, 0.01 mmol), and the

resulting mixture was stirred at room temperature for 24 h. The mixture was extracted by ethyl acetate (2×10 mL), and the crude product was purified by flash column chromatography to provide the corresponding product. All compounds were characterized on the basis of their spectroscopic data (IR, NMR) and by comparison with those reported in the literature.

**3.2.1. 4-[N-(2-Hydroxycyclohexyl)amino]pyridine.** Yield 34%. <sup>1</sup>H NMR (CDCl<sub>3</sub>+DMSO, 500 MHz): 0.86–1.00 (m, 4H), 1.30–1.32 (m, 2H), 1.64–1.66 (m, 2H), 3.02–3.34 (m, 2H), 5.24 (br s, 2H, NH, OH); <sup>13</sup>C NMR (CDCl<sub>3</sub>+DMSO, 125 Hz): 24.3, 24.8, 31.9, 34.6, 57.6, 75.2, 108.9, 112.4, 137.3, 147.0, 159.3.

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