Dehydrative Amination of Alcohols in Water Using a Water-Soluble Calix[4]resorcinarene Sulfonic Acid

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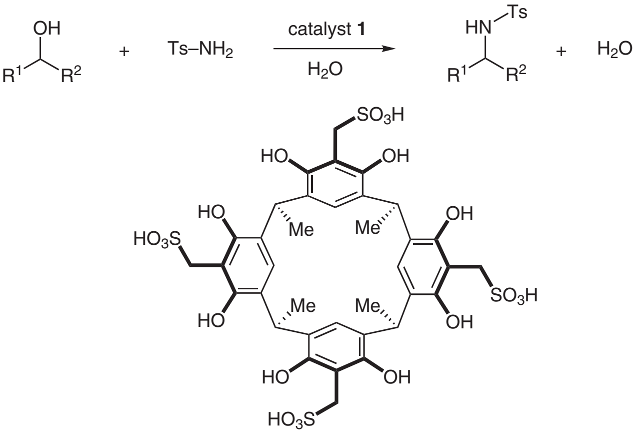
Abstract: A protocol for the dehydrative amination of alcohols in water using a water-soluble calix[4]resorcinarene sulfonic acid as a reusable multifunctional catalyst was developed.

Key words: aminations, calixarenes, green chemistry, host–guest systems, phase-transfer catalysis

The development of efficient methods for forming carbon–nitrogen bonds has received considerable attention in organic synthesis due to the importance of nitrogen-containing compounds in the production of pharmaceuticals and fine chemicals.[1] Substitution reactions of alkyl halides, alkyl acetates, or related compounds with amine nucleophiles are one of the most useful types of carbon–nitrogen bond-forming reactions.[2] The atomic efficiency of substitution reactions may be further enhanced when alcohols, instead of alkyl halides or alkyl acetates, are used as substrates, as is the case when water is the sole by-product of the reaction.[3] Therefore, the development of a procedure for the catalytic amination of alcohols is highly desirable. Consequently, a number of methods using metal catalysts in organic solvent systems have recently been reported.[4,5]

Reducing the use of hazardous solvents is one of the most important challenges presented by the effort to minimize pollution and risks associated with the production of chemicals. Accordingly, organic reactions in water without the use of organic solvents have attracted a great deal of interest in both academic and industrial research.[6] Among such reaction systems, aqueous biphasic systems using water-soluble catalysts have the additional advantage of catalyst recycling after simple decantation or extraction of the organic products.[7] However, because of the low solubility of many organic substrates in water, aqueous biphasic systems often exhibit insufficient reaction rates. To circumvent this problem, polar, water-miscible co-solvents[8] or surfactants[9] are frequently used. However, use of these additives may complicate workup procedures; in particular, product separation and catalyst recovery may be difficult. Recently, our research group developed a new reaction system, which is based on the inverse phase-transfer catalysis[10] of functionalized water-soluble calixarenes, to solve this dilemma.[11,12] More recently, our group found that a water-soluble calix[4]resorcinarene sulfonic acid **1** works as an efficient reusable catalyst for three-component Mannich-type reactions in water.[13,14] In the reaction system, **1** functions not only as a Brønsted acid catalyst, but also as an inverse phase-transfer catalyst, due to its ability to form supramolecular host–guest complexes. In this context, carbon–nitrogen bond-forming reactions in water using a water-soluble calix[4]resorcinarene sulfonic acid **1** have been a focus of our research. This paper presents a method for metal-free dehydrative amination of alcohols in water[15,16] catalyzed by **1**, and it describes the reusability of catalyst **1** (Scheme 1).



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Scheme 1 Dehydrative amination of alcohols in water catalyzed by **1**

Initially, various Brønsted acids were examined as catalysts for the amination reaction of *trans*-1,3-diphenyl-2-propen-1-ol with *p*-toluenesulfonamide in water (Table 1). Common Brønsted acids, such as AcOH, TFA, MsOH, TsOH, and TfOH, were not effective catalysts of this reaction (entries 2–6). However, a water-soluble calix[4]resorcinarene sulfonic acid **1** (10 mol%) was found to efficiently catalyze the reaction, giving the product **2a** in excellent yield (entry 7). Moreover, using only 1 mol% of catalyst **1** in the reaction gave the product **2a** in good yield (entry 9). These results suggest that catalyst **1** bearing the hydrophobic cavity forms host–guest complexes with substrates; these complexes are important for efficient catalysis of the reaction in water. Furthermore, in

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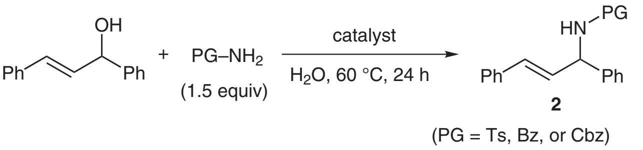
addition to the sulfonamide, the carboxamide and carbamate also could serve as the amine source in the present reaction system, giving the synthetically useful benzoyl- and benzyloxycarbonyl-protected amines **2b** and **2c** in excellent yields (entries 10 and 11).

Table 1 Effect of Catalysts



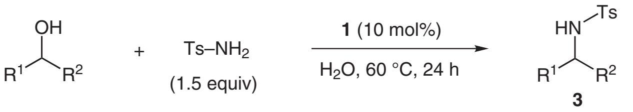
Entry	Catalyst (mol%)	PG	Yield (%)[a]
1	none	Ts	0 (**2a**)
2	AcOH (10)	Ts	0 (**2a**)
3	TFA (10)	Ts	3 (**2a**)
4	MsOH (10)	Ts	2 (**2a**)
5	TsOH (10)	Ts	5 (**2a**)
6	TfOH (10)	Ts	3 (**2a**)
7	**1** (10)	Ts	97 (**2a**)
8	**1** (2)	Ts	96 (**2a**)
9	**1** (1)	Ts	84 (**2a**)
10	**1** (10)	Bz	92 (**2b**)
11	**1** (10)	Cbz	98 (**2c**)

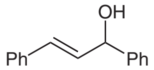
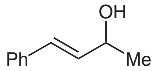
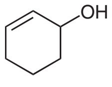
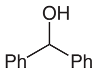
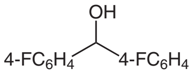
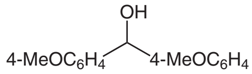
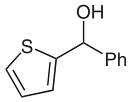
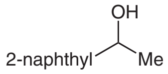
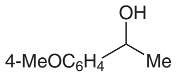
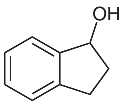
[a] Isolated yield.

Next, the substrate generality of the amination reaction in water catalyzed by **1** was examined using various allyl and benzyl alcohols (Table 2).[17] Both acyclic and cyclic allyl alcohols could be used as substrates in this reaction system (entries 1–3). Also, amination of benzyl alcohols containing electron-donating or -withdrawing groups occurred cleanly and the corresponding products **3c**–**3i** were obtained in moderate to excellent yields (entries 4–10). Substrates containing heteroaromatic alcohols also worked well in this reaction (entry 7).

The reusability of a calix[4]resorcinarene sulfonic acid catalyst **1** was examined (Table 3). After each reaction, the resulting organic products were extracted using ethyl acetate; the aqueous solution containing the catalyst was recovered and reused directly in the next cycle. Activity of catalyst **1** was retained after being recycled multiple times. Even after recycling the catalyst **1** five times, the yields were practically identical to those observed when fresh catalyst was used.

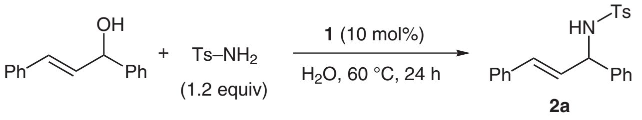
Table 2 Amination of Alcohols in Water



Entry	Alcohol	Yield (%)[a]
1		97 (**2a**)
2		87 (**3a**)
3		63 (**3b**)
4[b]		99 (**3c**)
5[b]		99 (**3d**)
6		97 (**3e**)
7		50 (**3f**)
8[b]		80 (**3g**)
9		96 (**3h**)
10		60 (**3i**)

[a] Isolated yield.
[b] Reaction temperature: 100 °C.

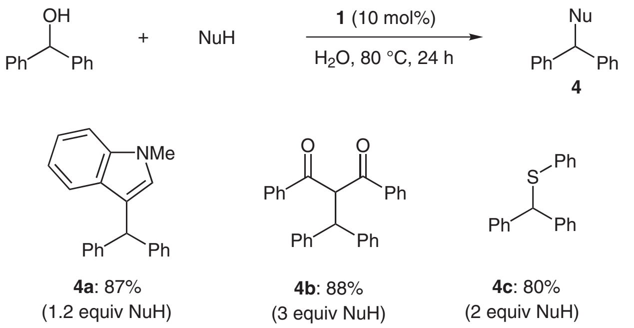
Table 3 Reusability of Catalyst **1**



Recycle number	Fresh	1st	2nd	3rd	4th	5th
Yield of **2a** (%)[a]	93	92	94	95	93	94

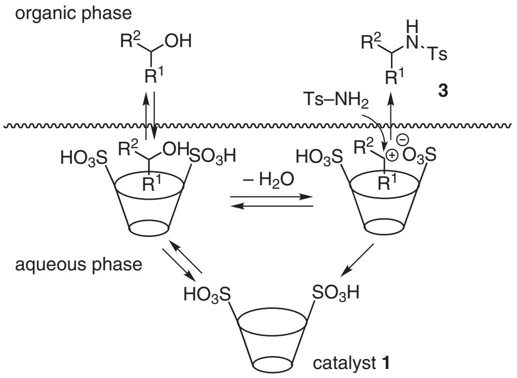
[a] Isolated yield.

The utility and applicability of the present reaction system was extended to nucleophilic substitution reactions of alcohols with carbon nucleophiles (Scheme 2).[16a,18] The Friedel–Crafts-type substitution reaction of benzhydrol with 1-methylindole occurred cleanly and afforded the desired product **4a** in good yield. The substitution reaction using an active methylene compound also proceeded smoothly to give the product **4b**. The present reaction system has been applied to carbon–sulfur bond formation,[16b] giving the desired compound **4c** in good yield.



Scheme 2 Nucleophilic substitution reaction of benzhydrol in water

The proposed mechanism for the calix[4]resorcinarene sulfonic acid **1**-catalyzed dehydrative amination of alcohols is shown in Scheme 3. The water-soluble catalyst **1** forms host–guest complexes with alcohols in the organic–aqueous interfacial layer. The dehydration reaction is promoted by the sulfonic acid moieties on catalyst **1**. The resulting allylic or benzylic cation[18] undergoes nucleophilic attack by the amide, giving the amination product **3** with regeneration of the catalyst **1**.



Scheme 3 Proposed mechanism

In summary, a method for calix[4]resorcinarene sulfonic acid **1**-catalyzed dehydrative amination of alcohols in water was developed.[19] In the reaction system developed in the present study, catalyst **1** worked, not only as a Brønsted acid catalyst, but also as an inverse phase-transfer catalyst. That is to say, **1** performs dual-function catalysis. It is noteworthy that the present reaction proceeded under nonmetallic conditions in water and, furthermore, the aqueous phase containing catalyst **1** could be readily recycled. This reaction system offers an efficient and green method for the synthesis of nitrogen-containing compounds.

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(19) **General Experimental Procedure for Dehydrative Amination in H_2O (Table 2)**: Alcohol (0.30 mmol) and *p*-toluenesulfonamide (0.45 mmol) were added to a solution of water-soluble calix[4]resorcinarene sulfonic acid **1**[13,20] (0.030 mmol) in H_2O (1 mL) with stirring, and the reaction mixture was vigorously stirred at 60 °C for an additional 24 h. After the addition of sat. aq $NaHCO_3$ solution (3 mL), the resulting mixture was extracted with EtOAc (3×3 mL). The combined extracts were dried over anhyd Na_2SO_4 and evaporated. The products were purified by flash chromatography on silica gel to yield the amination product. **Recycling Experiments (Table 3)**: Alcohol (0.90 mmol) and *p*-toluenesulfonamide (1.08 mmol) were added to a solution of water-soluble calix[4]resorcinarene sulfonic acid **1** (0.090 mmol) in H_2O (3 mL) with stirring, and the reaction mixture was vigorously stirred at 60 °C for an additional 24 h. After each reaction, EtOAc (3 mL) was added to the reaction mixture, and the solution was stirred for 5 min. The resulting mixture was allowed to stand for 5 min and then the organic phase was removed via a syringe. This extraction procedure was repeated twice. The remaining aqueous catalyst solution was reused directly in the next cycle. Isolation of the amination product **2a** was performed in a manner similar to that described above.

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