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Catalytic Deprotection of Protected Alcohols in Water Using Low-Loading and Alkylated Polystyrene-Supported Sulfonic Acid

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Abstract: Catalytic deprotection of various protected alcohols was efficiently conducted using a hydrophobic low-loading and alkylated polystyrene-supported sulfonic acid (LL-ALPS-SO_3H) in water as the sole solvent. Transprotection of an alcohol from a silyl ether to the corresponding benzylic ether or ester also proceeded smoothly in water.

The protection−deprotection sequence is one of the most frequently encountered functional-group transformations in organic synthesis.[1,2] In particular, the sequence for hydroxyl groups is extremely important because of enormous demands in natural product synthesis, etc. Although numerous methods for the deprotection of those protected alcohols have been reported, the use of more than equimolar amounts of catalysts or reagents is needed in many cases. In addition, organic solvents are generally used to dissolve the substrates when they are water-insoluble. From the atom-economical[3] and environmental points of view, however, reusable catalyst-mediated deprotection in water without the use of harmful organic solvents is strongly desirable.[4,5]

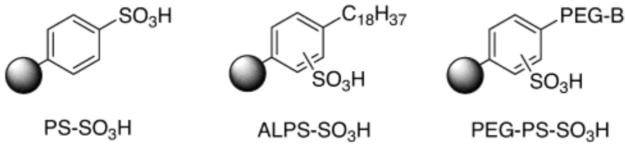
In the course of our investigations on organic reactions in water, we have recently found that a hydrophobic polystyrene-supported sulfonic acid (PS-SO_3H) is an effective and reusable catalyst for formation of esters, hydrolysis of thioesters, and Mannich-type reactions in water.[6] In addition, as a result of continuous studies on the loading levels and the structures of the catalyst, we have developed a low-loading (e.g., 0.17 mmol/g) and alkylated polystyrene-supported sulfonic acid (LL-ALPS-SO_3H), which is one of the best catalysts for several acid-catalyzed organic reactions in water.[7] Thus, we envisaged that LL-ALPS-SO_3H would also be highly effective for deprotection of protected alcohols in water without using organic cosolvents. In this paper, we report an effective and environmentally friendly methodology for the deprotection using LL-ALPS-SO_3H.

TABLE 1. Deprotection of TBS Ether with Various Brϕnsted Acid Catalysts

$$C_{12}H_{25}OTBS \xrightarrow[H_2O,\ 40\ ^{\circ}C,\ 12\ h]{\text{catalyst (5 mol \%)}} C_{12}H_{25}OH$$

entry	catalyst	loading (mmol/g)	yield[a] (%)
1	TsOH		0
2	H_2SO_4		2[b]
3	HCl		7[c] (92)[d]
4	DOWEX 50W-X2	4.41	0
5	PS-SO_3H	0.42	51
6	ALPS-SO_3H	0.41	87
7	ALPS-SO_3H	0.17	90
8	PEG-PS-SO_3H	0.19	4

[a] Isolated yields. [b] In 2 N H_2SO_4 (600 mol %). [c] In 2 N HCl (1200 mol %). [d] In 6 N HCl (3600 mol %).



The *tert*-butyldimethylsilyl (TBS) ether is a frequently used protective group for alcohol functions.[1,8] Therefore, we first examined deprotection of TBS ethers in water. Several Brønsted acids were tested in a model reaction of dodecyl TBS ether in water at 40 °C for 12 h (Table 1). The deprotection did not proceed at all with 5 mol % of TsOH, and surprisingly, the reaction hardly proceeded even when carried out in 2 N H_2SO_4 or HCl despite the presence of excess amounts of the acids (entries 1−3). This is probably because of the insolubility of the substrate in water. On the other hand, hydrophobic polystyrene-supported sulfonic acids were effective for the deprotection (entries 5−7). Interestingly, remarkable effects of the loading levels (entries 4 and 5)[9] and the structures (entries 5 and 6) of the polymer catalysts were revealed. Although the use of amphiphilic polymer-supported catalysts is a traditional approach to realize organic reactions in water,[5] this type of catalyst was less active under these conditions (entry 8). It should be noted that only 5 mol % of LL-ALPS-SO_3H gave almost the same result as 6 N HCl (3600 mol %) (entries 3 and 7).

Next, we investigated substrate generality in the LL-ALPS-SO_3H-catalyzed deprotection of TBS ethers (Table

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[1] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.

[2] For a recent review of protecting groups, see: Jarowicki, K.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2109.

[3] (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233.

[4] (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, 1998. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997.

[5] For recent examples of polymer-supported catalysts which work in water, see: (a) Nagayama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 567. (b) Bergbreiter, D. E.; Liu, Y.-S. *Tetrahedron Lett.* **1997**, *38*, 7843. (c) Bergbreiter, D. E.; Case, B. L.; Liu, Y.-S.; Caraway, J. W. *Macromolecules* **1998**, *31*, 6053. (d) Chen, C.-W.; Chen, M.-Q.; Serizawa, T.; Akashi, M. *Chem. Commun.* **1998**, 831. (e) Danjo, H.; Tanaka, D.; Hayashi, T.; Uozumi, Y. *Tetrahedron* **1999**, *55*, 14341. (f) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919. (g) Tanaka, N.; Masaki, Y. *Synlett* **1999**, 1960. (h) Masaki, Y.; Yamada, T.; Tanaka, N. *Synlett* **2001**, 1311. (i) Sakamoto, T.; Pac, C. J. *Tetrahedron Lett.* **2000**, *41*, 10009. (j) Yamada, Y. M. A.; Ichinohe, M.; Takahashi, H.; Ikegami, S. *Org. Lett.* **2001**, *3*, 1837.

[6] (a) Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2002**, *344*, 270. (b) Iimura, S.; Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 101. (c) Iimura, S.; Nobutou, D.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 1644.

[7] Iimura, S.; Manabe, K.; Kobayashi, S. *Org. Biomol. Chem.* **2003**, *1*, 2416.

[8] Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

[9] DOWEX 50W-X2 is a commercially available polystyrene-supported sulfonic acid, which is regarded as very high-loading PS-SO_3H.

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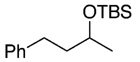
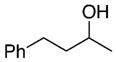
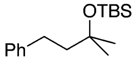
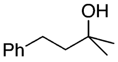
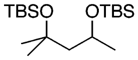
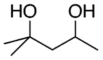
TABLE 2. LL-ALPS-SO$_3$H-Catalyzed Deprotection of Various Protective Alcohols

$$\text{ROPG} \xrightarrow[\text{H}_2\text{O, temp., time}]{\text{5 mol \% LL-ALPS-SO}_3\text{H (0.17 mmol/g)}} \text{ROH} \qquad \text{PG: Protective Groups}$$

entry	ROPG	temp. (°C)	time (h)	ROH	yield (%)[a]
1	$C_{12}H_{25}OTBS$	40	12	$C_{12}H_{25}OH$	90
2	4-EtC_6H_4OTBS	40	24	4-EtC_6H_4OH	87
3		40	12		93
4		40	12		trace
5	 **1**	40	12		89
6	$C_{12}H_{25}OTIPS$	100	12	$C_{12}H_{25}OH$	94
7	$C_{12}H_{25}OTBDPS$	100	24	$C_{12}H_{25}OH$	96
8	$C_{12}H_{25}OTr$	40	24	$C_{12}H_{25}OH$	87
9	$C_{12}H_{25}OMOM$	100	24	$C_{12}H_{25}OH$	96
10[b]	$C_{12}H_{25}OAc$	80	24	$C_{12}H_{25}OH$	87

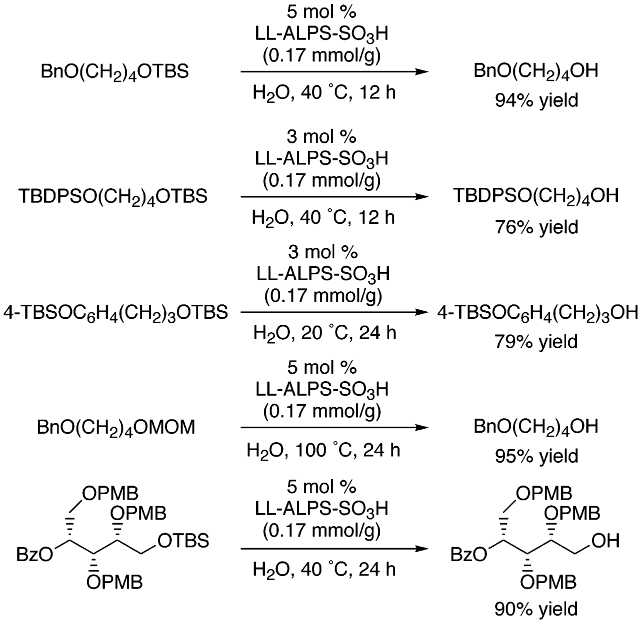
[a] Isolated yields. [b] 1 mol % of the catalyst was used.

2). The reactions proceeded not only for primary but also for aromatic and secondary TBS ethers in high yields under mild conditions in water (entries 1−3). Although a sterically crowded simple tertiary ether was hardly deprotected (entry 4), the double deprotection of compound **1** having a TBS-protected tertiary alcohol moiety proceeded smoothly under mild conditions (entry 5). These results encouraged us to test the deprotection of other protected alcohols in water. As a result, the reactions proceeded smoothly in high to excellent yields with 5 mol % of LL-ALPS-SO$_3$H not only for other silyl ethers such as triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) but also for trityl (Tr) and methoxymethyl (MOM) ethers (entries 6−9). Furthermore, only 1 mol % of the catalyst is enough to catalyze the reaction in the case of an acetyl (Ac)-protected alcohol (entry 10). Therefore, it was revealed that LL-ALPS-SO$_3$H was effective for the catalytic deprotection of various protected alcohols in water as the sole solvent. As expected, the catalyst was easily recovered and reused without any loss of catalytic activity (eq 1).

$$C_{12}H_{25}OTBS \xrightarrow[\text{H}_2\text{O, 40 °C, 12 h}]{\text{5 mol \% LL-ALPS-SO}_3\text{H (0.17 mmol/g)}} C_{12}H_{25}OH \quad \begin{array}{l}\text{1st: 89\% yield}\\ \text{2nd: 91\% yield}\\ \text{3rd: 90\% yield}\end{array} \qquad (1)$$

We then turned our attention to selective deprotection to demonstrate the utility of this methodology (Scheme 1).[10] Although various useful selective deprotection methods have been reported, the present catalytic system also enables the selective deprotection of TBS ethers in the presence of other protective groups such as benzyl (Bn) and TBDPS. In addition, the selective deprotection of an aliphatic TBS ether in the presence of an aromatic TBS ether was attained using LL-ALPS-SO$_3$H in water. Moreover, it was revealed that the selective deprotection of a MOM ether also performed in excellent yield in the presence of a Bn ether moiety. It is particularly noteworthy that the selective deprotection of a substrate with multiple protecting groups such as benzoyl (Bz) and *p*-methoxybenzyl (PMB) was achieved using this catalytic system. These results not only demonstrate an effective selective deprotection methodology but also provide useful information on the use of this novel catalytic system.

SCHEME 1. LL-ALPS-SO$_3$H-Catalyzed Selective Deprotection



Interestingly, transprotection of an alcohol from the corresponding silyl ether to benzylic ether[11] was realized in water by carrying out the deprotection of the TBS ether in the presence of benzhydrol (eq 2).[12] Furthermore, the TBS ether was successfully used directly for the esterification with the carboxylic acid in water (eq 3).[12] Since isolation of the intermediate is not needed, these catalytic transformations are considered as useful and economical processes.

$$C_{12}H_{25}OTBS + \underset{\text{(2.0 equiv.)}}{Ph_2CHOH} \xrightarrow[\text{H}_2\text{O, reflux, 24 h}]{\text{5 mol \% LL-ALPS-SO}_3\text{H (0.17 mmol/g)}} \underset{\text{81\% yield}}{C_{12}H_{25}OCHPh_2} \qquad (2)$$

$$\underset{\text{(2.0 equiv.)}}{Ph(CH_2)_2CO_2H} + C_{12}H_{25}OTBS \xrightarrow[\text{H}_2\text{O, 40 °C, 48 h}]{\text{5 mol \% LL-ALPS-SO}_3\text{H (0.17 mmol/g)}} \underset{\text{91\% yield}}{Ph(CH_2)_2CO_2C_{12}H_{25}} \qquad (3)$$

Finally, it was found that an easy workup process without the use of organic solvents was possible when

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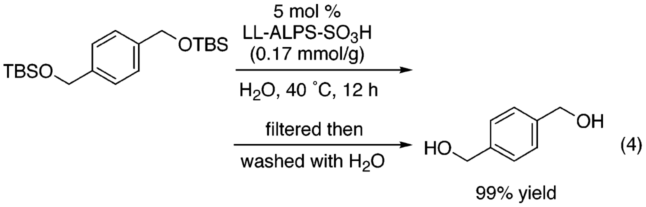
[10] For an excellent review of the selective deprotection of silyl ethers, see: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.

[11] Suzuki, T.; Kobayashi, K.; Noda, K.; Oriyama, T. *Synth. Commun.* **2001**, *31*, 2761.

[12] Recently, we have developed dehydration reactions such as esterification and etherification in water: (a) Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10101. (b) Manabe, K.; Iimura S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971. See also ref 6a. For transprotection in water, see ref 6b.

the products were soluble in water. The pure product was obtained quantitatively after the reaction mixture was filtered, washed with water, and concentrated in the case of deprotection of the TBS ether shown in eq 4. This simple procedure is a remarkable advantage of the present catalytic reaction system.



(4)

In summary, catalytic deprotection of various protected alcohols is efficiently catalyzed by LL-ALPS-SO$_3$H in water as the sole solvent. Remarkable effects of the loading levels and the structures on the polymer-supported sulfonic acid were observed in the deprotection of TBS ethers. Selective deprotection and useful one-pot transformations were also realized in water using this catalytic system. This work will provide an effective and environmentally friendly methodology for the deprotection of various types of protected alcohols and will expand the utility of LL-ALPS-SO$_3$H as a powerful green catalyst.

Experimental Section

Typical Procedure for LL-ALPS-SO$_3$H-Catalyzed Deprotection of Protected Alcohols in Water. A mixture of dodecyl TBS ether (60.5 mg, 0.20 mmol) and the polymer-supported catalyst (LL-ALPS-SO$_3$H (0.172 mmol/g), 58.3 mg, 0.010 mmol) in degassed water (1.2 mL) was stirred for 12 h at 40 °C. The reaction mixture was quenched with saturated aq NaHCO$_3$. The polymer was filtered and washed with water and ethyl acetate. The organic layer was dried over Na$_2$SO$_4$ and evaporated. The mixture was purified by preparative TLC on silica gel to give dodecanol (33.4 mg, 90%).

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Supporting Information Available: General experimental information, experimental details, and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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