JOC Note

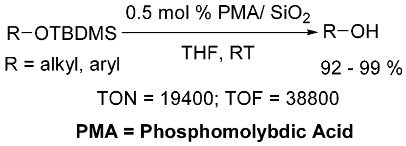
A Facile, Catalytic, and Environmentally Benign Method for Selective Deprotection of *tert*-Butyldimethylsilyl Ether Mediated by Phosphomolybdic Acid Supported on Silica Gel

G. D. Kishore Kumar and Sundarababu Baskaran*

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600 036, India

sbhaskar@iitm.ac.in

Received February 10, 2005



An environmentally benign PMA supported on SiO_2 is found to be an efficient catalyst for the chemoselective deprotection of TBDMS ethers under very mild conditions. Various labile functional groups such as isopropylidene acetal, OTBDPS, OTHP, Oallyl, OBn, alkene, alkyne, OAc, OBz, *N*-Boc, *N*-Cbz, *N*-Fmoc, mesylate, and azide are found to be stable under the reaction conditions. This "truly catalytic" heterogeneous reaction does not require aqueous workup, and the supported catalyst and the solvent can be readily recovered and recycled.

Green chemistry emphasizes the need for environmentally clean synthesis, which involves improvement in selectivity, high atom efficiency, elimination of hazardous reagents, and easy separation with recovery and reuse of reagents.[1] The key to waste minimization in fine chemical synthesis is the widespread substitution of classical organic reactions employing stoichiometric amounts of reagents with cleaner and catalytic alternatives.[2] While many supported reagents are stoichiometric in nature, the successful development of "truly catalytic" supported reagents will greatly enhance their application in "green" synthesis.[3] Heteropoly acids (HPAs) are promising solid acids, redox and bifunctional catalysts in homogeneous as well as in heterogeneous conditions.[4] They exhibit high catalytic activities and unique selectivities, allow for cleaner processing compared to conventional liquid catalysts, and hence are regarded as green catalysts.[5] The supported HPAs are more active than typical solid acids. Acidic or neutral substances such as silica gel, active carbon, and acidic ion-exchange resin are suitable supports, the most often used being silica gel.[6] Phosphomolybdic acid supported on silica gel (PMA/SiO_2) is found to be an excellent catalyst for vapor-phase organic reactions, and most of the processes have already been commercialized.[7] However, the synthetic potential of PMA/SiO_2 in liquid-phase reactions is yet to be explored fully.[8]

The TBDMS (*tert*-butyldimethylsilyl) ether has become one of the most popular silyl protective groups used in organic synthesis.[9] It is easily introduced as well as readily removed under a variety of conditions.[10] A vast array of acidic, neutral, basic, reducing, oxidizing, and fluoride-based reagents have been reported for the removal of the TBDMS group.[11] However, most of these deprotection methods require hazardous reagents and aqueous workup procedures that are detrimental to the environment, and perhaps least attractive is that in nearly all cases the reagent cannot be recovered and recycled. These limitations prompted us to investigate an environmentally benign reagent that can catalyze the cleavage of TBDMS ether under very mild conditions.

Our continued interest[12] in exploring the synthetic potential of heteropoly acid as a novel green catalyst has

---

(1) Anastas, P. T.; Williamson, T. C. *Green Chemistry, Designing for the Environment*; Anastas, P. T., Williamson, T. C., Eds.; American Chemical Society: Washington, DC, 1996; pp 1−17.

(2) Anastas, P. T.; Kirchhoff, M. M.; Williamson, T. C. *Appl. Catal., A* **2001**, *221*, 3.

(3) Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev.* **2004**, *104*, 199.

(4) (a) Kozhevnikov, I. V. *Chem. Rev.* **1998**, *98*, 171. (b) Mizuno, N.; Misono, M. *Chem. Rev.* **1998**, *98*, 199.

(5) (a) Misono, M.; Ono, I.; Koyano, G.; Aoshima, A. *Pure Appl. Chem.* **2000**, *72*, 1305. (b) Wilson, K.; Clark, J. H. *Pure Appl. Chem.* **2000**, *72*, 1313.

(6) (a) Pizzio, L. R.; Vázquez, P. G.; Cáceres, C. V.; Blanco, M. N. *Appl. Catal., A* **2003**, *256*, 125. (b) Izumi, Y.; Hasebe, R.; Urabe, K. *J. Catal.* **1983**, *84*, 402.

(7) Izumi, Y.; Urabe, K.; Onaka, M. *Zeolite, Clay and Heteropoly Acid in Organic Reactions*; Kodansha/VCH: Tokyo, 1992; p 99.

(8) (a) Vázquez, P.; Pizzio, L.; Cáceres, C.; Balnco, M.; Thomas, H.; Alesso, E.; Finkielsztein, L.; Lantaño, B.; Moltrasio, G.; Aguirre, J. *J. Mol. Catal. A: Chem.* **2000**, *161*, 223. (b) Wang, Y.; Liu, J.; Li, W. *J. Mol. Catal. A: Chem.* **2000**, *159*, 71. (c) Majumder, P. L.; Basak, M. *Tetrahedron* **1991**, *47*, 8601.

(9) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

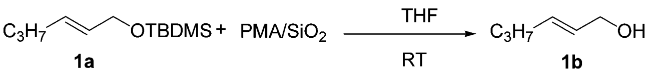
(10) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999 p 17. (b) Crouch, R. D. *Tetrahedron*, **2004**, *60*, 5833. (c) Kocienski, P. *Protecting Groups*, 1st ed.; Gerog Thieme: Stuttgart, 1994.

(11) (a) Khan, A. T.; Ghosh, S.; Choudhury, L. H. *Eur. J. Org. Chem.* **2004**, *10*, 2198. (b) Ikawa, T.; Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6901. (c) Karimi, B.; Zamani, A.; Zareyee, D. *Tetrahedron Lett.* **2004**, *45*, 9139. (d) Arumugam, P.; Karthikeyan, G.; Perumal, P. T. *Chem. Lett.* **2004**, *33*, 1146. (e) Crouch, R. D.; Romany, C. A.; Kreshock, A. C.; Menconi, K. A.; Zile, J. L. *Tetrahedron Lett.* **2004**, *45*, 1279. (f) Sajiki, H.; Ikawa, T.; Hattori, K.; Hirota, K. *Chem. Commun.* **2003**, 654. (g) Khan, A. T.; Mondal, E. *Synlett* **2003**, 694. (h) Rani, S.; Lokesh Babu, J.; Vankar, Y. D. *Synth. Commun.* **2003**, *33*, 4043. (i) Sharma, G. V. M.; Srinivas, B.; Radha Krishna, P. *Tetrahedron Lett.* **2003**, *44*, 4689. (j) Bartoli, G.; Cupone, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Sambri, L.; Tagarelli, A. *Tetrahedron Lett.* **2002**, *43*, 5945. (k) Chen, M.-Y.; Lu, K.-C.; Lee, A. S.-Y.; Lin, C.-C. *Tetrahedron Lett.* **2002**, *43*, 2777. (l) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 2109. (m) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron Lett.* **2000**, *41*, 5711. (n) Bajwa, J. S.; Vivelo, J.; Slade, J.; Repiè, O.; Blacklock, T. *Tetrahedron Lett.* **2000**, *41*, 6021. (o) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 4177. (p) Kartha K. P. R.; Field, R. A. *Synlett* **1999**, 311. (q) Sabitha, G.; Syamala, M.; Yadav, J. S. *Org. Lett.* **1999**, *1*, 1701. (r) Ranu, B.; Jana, U.; Majee, A. *Tetrahedron Lett.* **1999**, *40*, 1985. (s) Bartoli, G.; Bosco, M.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Synlett* **1998,** 209. (t) Oriyama, T.; Kobayashi, Y.; Noda, K. *Synlett* **1998**, 1047. (u) Wilson, N. S.; Keay, B. A. *Tetrahedron Lett.* **1997**, *38*, 187. (v) Wilson, N. S.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 2918. (w) Varma, R. S.; Lamture, J. B.; Varma, M. *Tetrahedron Lett.* **1993**, *34*, 3029. (x) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1993**, *58*, 5130. (y) Feixas, J.; Capdevila, A.; Camps, F.; Guerrero, A. *J. Chem. Soc., Chem. Commun.* **1992**, 1451. (z) Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2997.

(12) (a) Kishore Kumar, G. D.; Baskaran, S. *Chem. Commun.* **2004**, 1026. (b) Kishore Kumar, G. D.; Baskaran, S. *Synlett* **2004**, 1719.

10.1021/jo0502697 CCC: $30.25

TABLE 1. Turnover Number (TON) and Turnover Frequency (TOF) of the PMA/SiO$_2$-Catalyzed Cleavage of TBDMS Ether



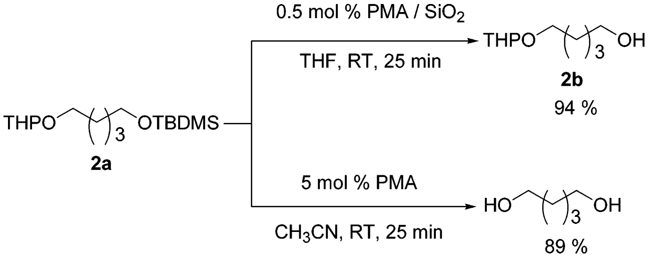
entry	PMA/SiO$_2$ (mol %)	time (h)	yield (%)[a]	TON	TOF (h^{-1})
1	0.1[b]	0.5	95	95000	190000
2	0.1[c]	8	67	67000	8370
3	0.1	4.5	96	96000	21330
4	0.2	3.2	94	47000	14680
5	0.3	2.5	95	31670	12670
6	0.4	1.0	92	23000	23000
7	0.5	0.5	97	19400	38800
8	0.5 (1st cycle)	0.5	95	19000	38000
9	0.5 (2nd cycle)	0.5	94	18800	37600
10	0.5 (3rd cycle)	0.5	92	18400	36800

[a] Yield refers to pure isolated product. [b] Reaction is carried out in CH_3CN under homogeneous conditions. [c] Reaction is carried out in hexane.

resulted in the development of a catalytic method for the selective cleavage of TBDMS ether. Initial experiments have indicated that, under homogeneous conditions, the cleavage of TBDMS ether with 0.1 mol % PMA in CH_3CN is very facile. However, it was our perception that the use of supported catalyst under heterogeneous conditions would lead to better selectivity and facilitate easy separation and recovery of the catalyst for immediate reutilization. The solvent-dependent cleavage of TBDMS ether (**1a**) with PMA/SiO$_2$ is shown in Table 1. The reaction was slow when hexane was used as the solvent (entry 2, Table 1). However, a faster rate and better recyclability was observed in THF. The catalyst was reused without any pretreatment.[13] The efficiency (turnover frequency) and stability (turnover number) of the catalyst were found to be very good even after 3 cycles (entries 8−10, Table 1).[14] Upon screening, it was found that 0.5 mol % of PMA/SiO$_2$ efficiently catalyzes the cleavage of TBDMS ether in THF at room temperature to give the corresponding alcohol in good yield.

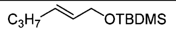
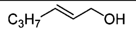
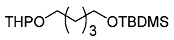
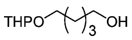
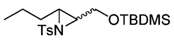
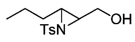
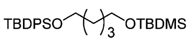
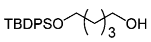
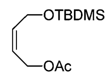
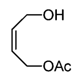
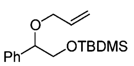
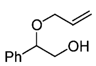
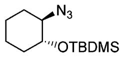
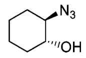
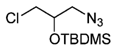
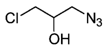
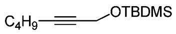
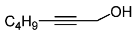
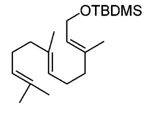
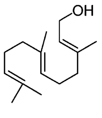
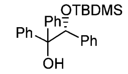
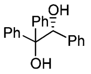
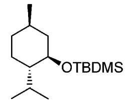
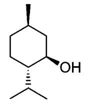
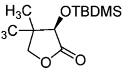
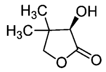
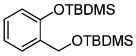
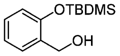
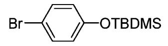
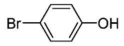
Our initial study focused on the chemoselective cleavage of TBDMS ether in the presence of acid-labile functional groups. Using 0.5 mol % of PMA/SiO$_2$ in THF, the TBDMS ether was chemoselectively cleaved in the presence of THP ether (Scheme 1).[15] However, under homogeneous conditions, with 5 mol % of bulk PMA in CH_3CN, both TBDMS ether as well as THP ether underwent cleavage simultaneously.[16] This transformation clearly shows that the supported PMA is more selective than the bulk PMA.

SCHEME 1. Chemoselective Cleavage of TBDMS Ether in the Presence of THP Ether



Encouraged by this observation, a wide range of structurally varied TBDMS ethers were subjected under these conditions, and the results are summarized in Table 2. Although aziridines are known to undergo regioselective ring opening with different nucleophiles mediated by PMA/SiO$_2$,[12b] surprisingly, tosyl aziridine was found to be stable under the reaction conditions (entry 3). The usefulness of this method was further extended to a chemoselective cleavage of TBDMS ether in the presence of *tert*-butyldiphenylsilyl (TBDPS) ether (entry 4). The compatibility of several sensitive functional groups such as olefin, azide, and allyl ether was further demonstrated during the cleavage of TBDMS ethers (entries 5−8). Highly acid-labile functional groups such as propargyl, farnesyl, and triphenylethanediol deriva-

TABLE 2. PMA/SiO$_2$ Catalyzed Cleavage of TBDMS Ethers

Entry	Substrate (**a**)	Time (min)	Product (**b**)	Yield (%)
1		30		97
2		25		94
3		90		94
4		25		97
5		15		93
6		30		93
7		35		92
8		15		93
9		30		94
10		15		97
11		20		96
12		20		96
13		12h		94
14		15		94
15		18h		99

[a] Yield refers to pure isolated product.

---

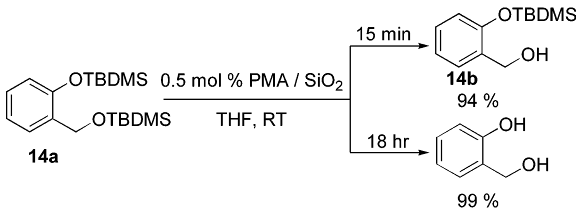
(13) XRD powder pattern of PMA on silica gel was unaltered even after the deprotection reaction. Please see Supporting Information.

(14) Balser, H.-U.; Indolese, A.; Schnyder, A. *Curr. Sci.* **2000**, *78*, 1336.

(15) The THP ether is stable under the reaction condition; however, a longer reaction time (4 h) resulted in the partial deprotection of the THP ether.

(16) (a) Romanelli, G. P.; Baronetti, G.; Thomas, H. J.; Autino, J. C. *Tetrahedron Lett.* **2002**, *43*, 7589. (b) Molnár, A.; Beregszászi, T. *Tetrahedron Lett.* **1996**, *37*, 8597.

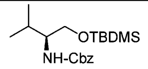
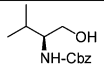
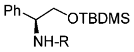
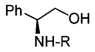
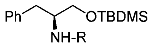
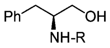
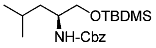
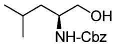
SCHEME 2. Facile Cleavage of Aliphatic TBDMS Ether in the Presence of Aromatic TBDMS Ether



tives were also found to be stable under the reaction conditions (entries 9−11). The cleavage of sterically crowded TBDMS ether required longer time, but the corresponding alcohol was isolated in good yield (entry 13). In addition, chemoselective deprotection of aliphatic TBDMS ether was readily achieved in the presence of aryl TBDMS ether (Scheme 2).

Furthermore, the synthetic potential of this mild method was exemplified in amino alcohol derivatives (Table 3). Protecting groups such as *N*-Boc, *N*-Cbz, and *N*-Fmoc are found to be compatible with the reaction conditions.

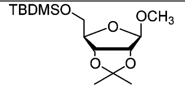
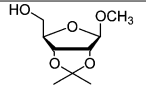
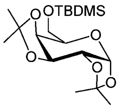
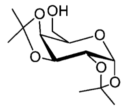
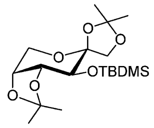
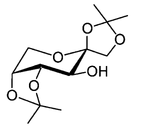
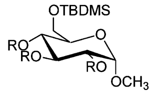
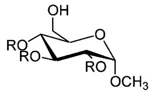
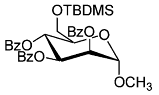
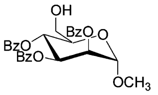
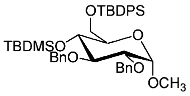
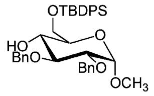
TABLE 3. PMA/SiO$_2$-Catalyzed Deprotection of TBDMS Ethers in *N*-Protected Amino Alcohols

Entry	Substrate (**c**)	Time (min)	Product (**d**)	Yield (%)[a]
1		30		94
				
2	R = Boc	40	R = Boc	96
3	R = Fmoc	15	R = Fmoc	95
				
4	R = Boc	40	R = Boc	93
5	R = Cbz	20	R = Cbz	98
6		20		97

[a] Yield refers to pure isolated product.

The remarkable selectivity and mildness of this method was further tested in carbohydrate substrates having acid-sensitive functional groups (Table 4). The TBDMS ethers of isopropylidene *β*-glucofuranoside (**1e**) and diisopropylidene galactopyranoside (**2e**) were readily deprotected to give the corresponding alcohols in excellent yields. Unlike the supported reagents such as montmorillonite K10[17] and CAN/SiO$_2$,[18] isopropylidene acetal and Boc protecting groups are found to be stable under the reaction conditions (entries 1 and 2). Similarly, differently protected TBDMS ether of α-methyl glucopyranoside and α-methyl mannopyranoside derivatives were also subjected to these conditions, and the result are shown in Table 4. The reactive functional groups such as OAc, OMs, OBz, and OBn are also found to be stable under the reaction conditions (entries 5−8).

TABLE 4. Selective Cleavage of TBDMS Ether in Carbohydrates

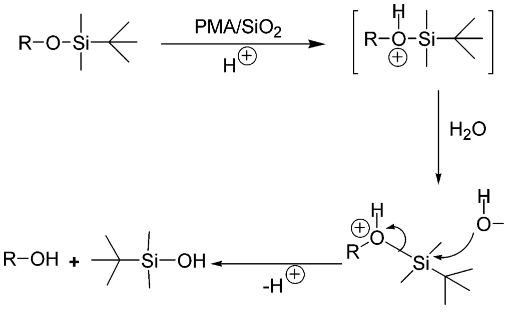
Entry	Substrate (**e**)	Time (min)	Product (**f**)	Yield (%)
1		25		97
2		30		98
3		45		94
				
4	R = H	10	R = H	97[b]
5	R = OAc	25	R = OAc	97
6	R = OMs	15	R = OMs	98
7		10		98
8		90		92

[a] Yield refers to pure isolated product. [b] Reaction is carried out under homogeneous condition using 0.5 mol % of PMA in CH$_3$CN.

A plausible mechanism underlying the cleavage of TBDMS ether is shown in Scheme 3. It is likely that the PMA/SiO$_2$ protonates the TBDMS ether, which in turn could facilitates the attack of water present in the catalyst, leading to the formation of the product.

In conclusion, a catalytic and environmentally benign method for the selective deprotection of TBDMS ether has been developed. The significant advantages offered by this procedure are: (i) the catalyst can be readily recovered and recycled, (ii) reaction conditions are mild (room temperature, faster rate, and excellent yield). (iii) the method is compatible with a variety of sensitive functional groups such as isopropylidene acetal, OTBDPS, OTHP, allyl ether, OBn, alkene, alkyne, *N*-Boc, *N*-Cbz, *N*-Fmoc, OAc, OBz, mesylate, and azide.

SCHEME 3. Proposed Mechanism for the Cleavage of TBDMS Ether



---

(17) Asakura, J.-i.; Robins, M. J.; Asaka, Y.; Kim, T. H. *J. Org. Chem.* **1996**, *61*, 9026.

(18) Hwu, J. R.; Jain, M. L.; Tsai, F.-Y.; Tsay, S.-C.; Balakumar, A.; Hakimelahi, H. G. *J. Org. Chem.* **2000**, *65*, 5077.

Certainly, this method is a better and a practical alternative to the existing procedures, and we believe it will find wide application particularly when selective cleavage of TBDMS ether is required in complex molecules containing more than one protecting groups.

Experimental Section

Preparation of PMA/SiO$_2$ (10% w/w) Catalyst. To a solution of $H_3PMo_{12}O_{40}\cdot 24H_2O$ (100 mg, 0.1 equiv by wt) in MeOH (5 mL) was added slowly silica gel (900 mg, 0.9 equiv by wt, 100−200 mesh), and the mixture was stirred at room temperature for 6 h. Evaporation of MeOH under reduced pressure gave a dry yellowish powder, which contained 10% w/w of PMA.

General Experimental Procedure for the Preparation of TBDMS Ether. To a solution of alcohol (1 mmol) and imidazole (2.5 mmol) in DMF (3 mL) was added portionwise *tert*-butyldimethylsilyl chloride (1.2 mmol), and the resultant mixture was stirred at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with EtOAc. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude compound. Purification of the crude compound by column chromatography over silica gel (100−200 mesh) afforded pure TBDMS ether in good yield.

General Experimental Procedure for the Deprotection of TBDMS Ether. A mixture of TBDMS ether (1 mmol) and PMA/SiO$_2$ (113 mg, 0.005 mmol based on PMA) in THF (3 mL) was stirred at room temperature. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered. The filtrate was concentrated under reduced pressure, and the crude compound was purified by column chromatography over silica gel (100−200 mesh) to afford the pure alcohol.

Acknowledgment. We thank DST and CSIR, New Delhi for financial support, and G.D.K. (SRF) thanks CSIR, New Delhi, for a research fellowship. We are grateful to the DST-FIST program for a NMR facility.

Supporting Information Available: Detailed experimental procedure and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0502697