DOI: 10.1002/ejoc.200800963

Truly Catalytic and Chemoselective Cleavage of Benzylidene Acetal with Phosphomolybdic Acid Supported on Silica Gel

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Keywords: Chemoselectivity / Heterogeneous catalysis / Protecting groups / Supported catalysts

Phosphomolybdic acid supported on silica gel provides a truly catalytic method for the chemoselective cleavage of benzylidene acetals having sensitive functional groups under mild conditions. It is easy to perform on large scale owing to minimal catalyst loading (0.5 mol-%). Several sensitive functional groups such as TBDPS ether, -OMs, -OAc, allyl ether, *N*-Boc, *N*-Fmoc and *N*-Cbz are stable under the reaction conditions. In addition, benzylidene acetal is selectively cleaved in the presence of isopropylidene ketal.

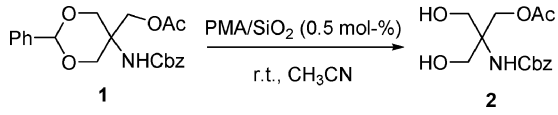
Introduction

One of the foremost challenges currently facing synthetic organic chemistry is the demand for alternative methods that are simple, environmentally friendly, highly chemo- and regioselective and also more convenient for industrial applications. 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. Whereas many supported reagents are stoichiometric in nature, the successful development of "truly catalytic" supported reagents will greatly enhance their application in green synthesis. Recently, heteropoly acids (HPAs) have gained considerable attention in organic synthesis and numerous environmentally benign chemical transformations have been reported.[1] HPAs are environmentally friendly and economically feasible solid acids exhibiting higher catalytic behaviour, unique selectivities, cleaner reaction profiles and well-known bifunctional (acid and redox) catalysts.[2,3] Because bulk HPAs have low specific surfaces, supported heteropoly acids are more widely used than typical solid acids.[1a] In particular, phosphomolybdic acid supported on silica gel (PMA/SiO_2) is found to be an excellent catalyst for various environmentally benign organic transformations.[4,5]

Chemoselective deprotection of benzylidene acetal is one of the most important transformations in carbohydrate chemistry. Various reagent systems are known for the deprotection of benzylidene acetals.[6,7] In addition, supported reagents such as $FeCl_3/SiO_2$,[8a] $HClO_4/SiO_2$,[8b] $NaHSO_4/SiO_2$[8c] and potassium peroxymonosulfate (Oxone) supported on neutral alumina[8d] have also been employed for the deprotection of benzylidene acetals. Most of these methods are difficult to perform on large scale due to the usage of excess amounts of reagent, harsh reaction conditions/reagents, tedious aqueous workup procedure or lack of selectivity.

Results and Discussion

In this communication, we report a truly catalytic, nonaqueous and efficient method for the chemoselective cleavage of benzylidene acetals by using PMA supported on silica gel as a catalyst under mild conditions (Scheme 1). Preliminary studies revealed selective cleavage of six-membered benzylidene acetal **1** with PMA (0.1 mol-%) in CH_3CN under homogeneous conditions.



Scheme 1. Catalytic chemoselective cleavage of benzylidene acetals with PMA supported on silica gel.

In order to improve the efficacy of the reaction, we investigated several variables, and the results are summarized in Table 1. After much experimentation, it was found that 0.5 mol-% of PMA/SiO_2 effectively catalyzed the cleavage of benzylidene acetal **1** under heterogeneous (dichloromethane, DCM) as well as under homogeneous conditions (CH_3CN) at room temperature to give the corresponding diol **2** in good yield. This reaction worked equally well in other organic solvents such as ethyl acetate, THF and hexane, albeit at a slower rate.

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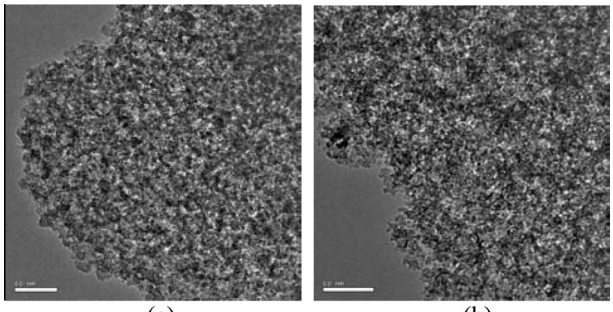
Table 1. The effect of solvent on the cleavage of benzylidene acetal **1** catalyzed by PMA/SiO_2.

Entry	PMA/SiO_2 loading	Solvent	Time [h]	Yield [%] [a]
1	0.1 mol-%	THF	10	61
2	0.1 mol-%	CH_3CN	12	52
3	0.5 mol-%	CH_3CN	3	76
4	0.5 mol-%	DCM	4.5	76[b]
5	1 mol-%	DCM	2	74
6	0.5 mol-% (1st cycle)	DCM	4.5	76
7	0.5 mol-% (2nd cycle)	DCM	4.5	76
8	0.5 mol-% (3rd cycle)	DCM	4.5	75

[a] Yield refers to pure isolated product. [b] TON = 152; TOF = 34 h^{-1}.

Because this method requires only 0.5 mol-% of the catalyst, it can be readily implemented on large scale. In addition, the catalyst can be readily recovered and recycled. The efficiency (turnover frequency, TOF = 34 h^{-1}) and stability (turnover number, TON = 152) of the catalyst were found to be very good even after three cycles. HRTEM studies before and after the reactions of the supported catalyst revealed that the catalyst is uniformly dispersed over the silica support and there is no significant change in the morphology of the catalyst even after three cycles (Figure 1).



(a) (b)

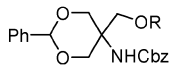
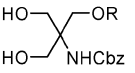
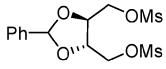
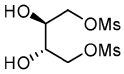
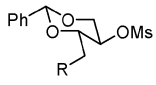
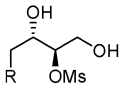
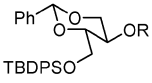
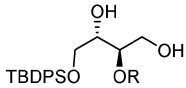
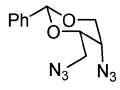
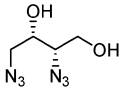
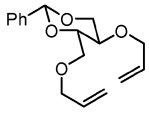
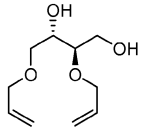
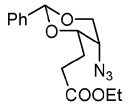
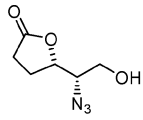
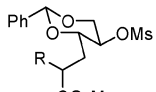
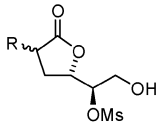
Figure 1. HRTEM studies of the supported catalyst (a) before and (b) after the reaction (three cycles).

Encouraged by these findings, detailed studies towards the deprotection of benzylidene acetals were undertaken, and the results are summarized in Table 2. Labile functional groups such as TBDPS ether, -OMs, -OAc, allyl ether, iodide and azide were found to be stable under the reaction condition. The reactions were usually performed on a multigram scale and the catalyst was readily recovered and recycled.

During these studies, we also observed that compounds **13**, **15** and **15a** underwent smooth deprotection of benzylidene acetal followed by in situ lactonization mediated by PMA/SiO_2 to give the corresponding functionalized chiral lactones **14**, **16** and **16a**, respectively, in good yields (Table 2, entries 7 and 8). These functionalized chiral lactones are important intermediates in the synthesis of various natural products.[9]

Further, the efficiency of the catalytic system was also investigated in the cleavage of benzylidene acetals derived from carbohydrate molecules (Table 3). A high degree of chemoselectivity was observed in these reactions, and the results are summarized in Table 3. Sensitive functional groups such as isopropylidene ketals, -OAc and -OMs were found to be stable under the reaction conditions. Intriguingly, benzylidene acetal was selectively deprotected in the presence of acid-labile isopropylidene ketal under heterogeneous conditions (Table 3, entries 1–3).[10] Furthermore, methyl-2,3,4,6-di-*O*-benzylidene-α-D-mannopyranoside (**25**) having both five- and six-membered benzylidene acetals, re-

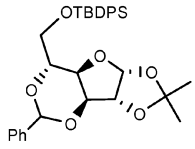
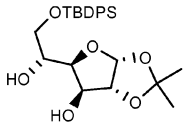
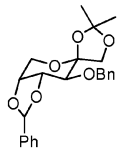
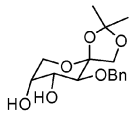
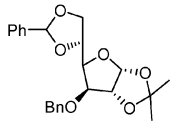
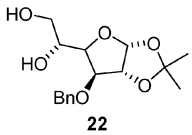
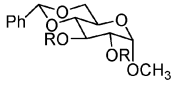
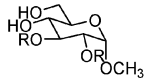
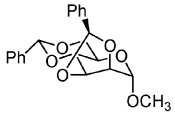
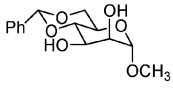
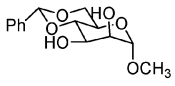
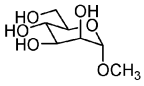
Table 2. PMA/SiO_2 catalyzed cleavage of benzylidene acetals derived from carbohydrates.[a]

Entry	Substrate	Product	Time [h]	Yield [%][b]
1	 **1** R = Ac, **1a** R = H, **1b** R = TBDPS	 **2** R = Ac, **2a** R = H, **2b** R = TBDPS	4.5 3.5 4.5	76 75 83
2	 **3**	 **4**	0.75	92[c]
3	 **5a** R = I, **5b** R = N_3	 **6a** R = I, **6b** R = N3	4 3	78 83
4	 **7a** R = Ms, **7b** R = TBDPS	 **8a** R = Ms, **8b** R = TBDPS	5 4	83 80
5	 **9**	 **10**	4	84
6	 **11**	 **12**	6.5	88
7	 **13**	 **14**	4	89
8	 **15** R = H, **15a** R = COOMe	 **16** R = H, **16a** R = COOMe	3 5.5	86 84

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

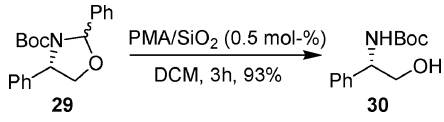
acted readily in a chemoselective manner to give the corresponding methyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**26**) in good yield (Table 3, entry 5).

Table 3. PMA/SiO_2 catalyzed cleavage of *N*-protected-2-phenyl-1,3-oxazolidines.[a]

Entry	Substrate	Product	Time [h]	Yield [%][b]
1	 **17**	 **18**	5	93
2	 **19**	 **20**	3	85
3	 **21**	 **22**	3	86
4	 **23** R = H, **23a** R = Ac, **23b** R = Ms, **23c** R = Bn	 **24** R = H, **24a** R = Ac, **24b** R = Ms, **24c** R = Bn	0.5 4.5 5 5	91[c] 91 95 97
5	 **25**	 **26**	2	94
6	 **27**	 **28**	0.5	93[c]

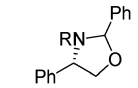
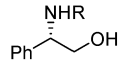
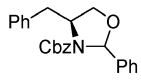
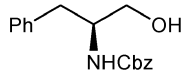
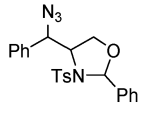
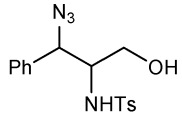
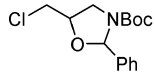
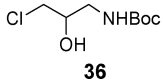
[a] Reaction was carried out in DCM with PMA/SiO_2 (0.5 mol-%) under heterogeneous conditions. [b] Yield refers to pure isolated product.

Similarly, the reactivity of *N*-protected-2-phenyl-1,3-oxazolidines towards PMA/SiO_2 were examined (Scheme 2). As expected, under the reaction conditions 2-phenyl-1,3-oxazolidines underwent smooth cleavage to give the corresponding synthetically useful *N*-protected chiral vicinal amino alcohols in good yields (Table 4).[11] Interestingly, protecting groups such as *N*-Boc, *N*-Fmoc and *N*-Cbz were found to be stable under the reaction conditions.



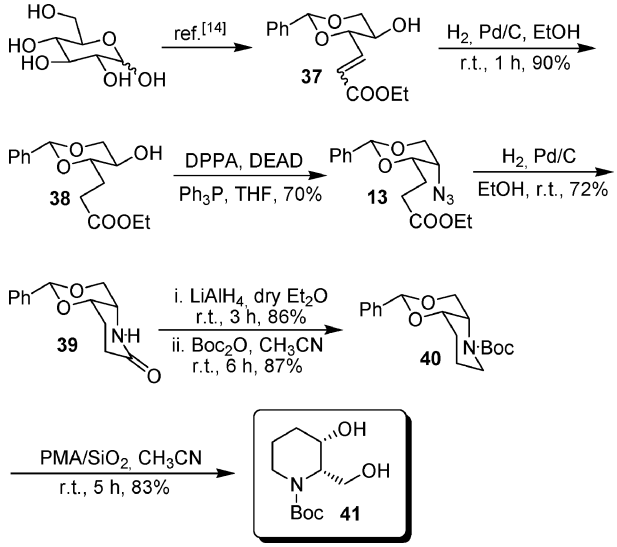
Scheme 2. PMA/SiO_2 catalyzed cleavage of *N*-Boc protected 2-phenyl-1,3-oxazolidine.

Table 4. PMA/SiO_2 catalyzed cleavage of benzylidene acetals.[a]

Entry	Substrate	Product	Time [h]	Yield [%][b]
1	 **29** R =Boc, **29a** R = Fmoc	 **30** R = Boc, **30a** R = Fmoc	3.5 4	93 94
2	 **31**	 **32**	3	95
3	 **33**	 **34**	3	88
4	 **35**	 **36**	4	91

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

The synthetic utility of our novel catalytic system was further explored in the synthesis of 2-hydroxymethyl-3-piperidinol (2-*epi*-4-deoxyfagomine, **41**), which is an important intermediate in the synthesis of several biologically active and pharmaceutically important piperidine alkaloids (Scheme 3).[12] The structure and the relative stereochemistry of 2-*epi*-4-deoxyfagomine (**41**) were unambiguously confirmed by single-crystal X-ray analysis (Figure 2).[13]



Scheme 3. Synthesis of 2-*epi*-4-deoxyfagomine (**41**).

The wide-ranging application of this methodology was further extended towards the synthesis of the δ-lactam derivative of 2-*epi*-4-deoxyfagomine (**42**; Scheme 4), which has

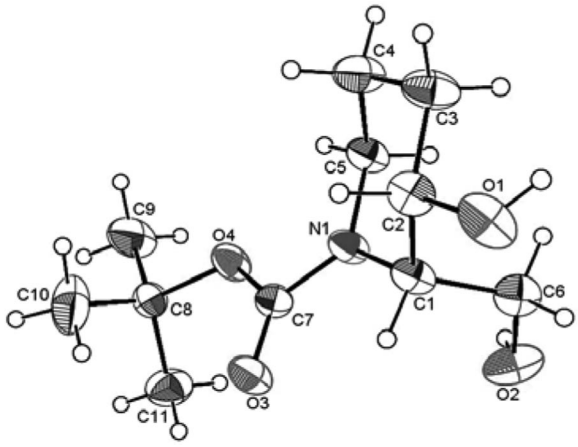
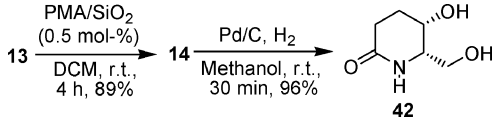


Figure 2. ORTEP diagram of 2-*epi*-4-deoxyfagomine (**41**).

also been found to be an important intermediate in the synthesis of various biologically active 2,3,6-trisubstituted piperidine alkaloids.[15]



Scheme 4. Synthesis of (5*S*,6*S*)-5-hydroxy-6-(hydroxymethyl)piperidin-2-one (**42**).

Conclusions

We developed a simple and an efficient method for the chemoselective cleavage of benzylidene acetal and 2-phenyl-1,3-oxazolidine by using PMA/SiO_2 (0.5 mol-%) as a catalyst under heterogeneous conditions. The remarkable features of our method are mild and clean reaction conditions, simplicity in operation even on large scale and, finally, the active catalyst can be readily recovered and recycled without any loss of activity. The chemoselective nature of the PMA/SiO_2 reagent system was exploited in the stereoselective synthesis of 2-*epi*-4-deoxyfagomine and its analogues. We believe that this truly catalytic method for the selective deprotection of benzylidene acetal will find practical application in organic synthesis.

Experimental Section

General Procedure: A mixture of benzylidene acetal **13** (2 g, 6.56 mmol) and PMA/SiO_2 (740 mg, 0.0327 mmol based on PMA) in DCM (25 mL) was stirred at room temperature for 4 h. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered to recover the catalyst and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; 30–50% EtOAc in hexane) to give the corresponding chiral lactone **14** in good yield (0.998 g, 89%). Physical data for **14**: $[\alpha]_D^{26}$ = +49.8 (*c* = 1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3395, 2925, 2100, 1758, 1268, 1182, 1156, 1060, 916, 809 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.69–4.66 (m, 1 H), 3.87–3.86 (m, 2 H), 3.61–3.59 (m, 1 H), 3.3 (br. s, 1 H), 2.65–2.62 (m, 1 H), 2.59–2.50 (m, 1 H), 2.38–2.36 (m, 1 H), 2.20–2.18 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.14, 78.8, 65.6, 61.9, 28.0, 24.5 ppm. HRMS (ESI): calcd. for $C_6H_9N_3O_3Na$ $[M + Na]^+$ 194.0542; found 194.0546.

Supporting Information (see footnote on the first page of this article): Experimental procedures and full spectroscopic data.

Acknowledgments

This work was financially supported by the Council of Scientific and Industrial Research (CSIR), New Delhi. The authors thank the Department of Science & Technology (DST), New Delhi, for NMR and HRTEM facilities. P. S. K thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, for a research fellowship.

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Received: October 1, 2008
Published Online: November 12, 2008

