

Selective Acceleration for Deprotection of Benzyl Ethers with Ti-HMS

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Abstract: Ti-HMS, a Ti-loaded hexagonal mesoporous silica, was found to accelerate deprotection of benzyl ethers under hydrogenolytic conditions with palladium catalyst. Such acid-sensitive functional groups as silyl ether and acetal moieties in the molecule were little affected by Ti-HMS, which possesses Lewis acid sites due to Ti-atom.

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The benzyl group has been widely used in organic synthesis as a typical hydroxyl protecting group because of its specific advantage of easy deprotection by hydrogenolysis with palladium catalysts.¹⁾ This method is undoubtedly convenient from the view point of easy work-up, but the reproducibility of reductive debenzylolation essentially depends on activity of the catalysts. Use of higher concentrations of Pd catalyst on the carrier, however, sometimes causes serious inflammation or explosion. In the course of our investigation on the utility of heterogeneous catalysts, especially metal-impregnated hexagonal mesoporous silica (HMS),²⁾ Ti-loaded mesoporous silica (Ti-HMS)³⁾ was found to accelerate deprotection of benzyl groups under usual hydrogenolytic conditions (5%Pd-C and 1 atm of H₂). Table 1 shows the results of deprotection of dodecyl benzyl ether **1** with or without the silica under hydrogenolytic conditions.⁴⁾ Although 5%Pd-C was not sufficient catalyst for reductive cleavage of this benzyl ether, the addition of 10%Ti-HMS apparently promoted the reaction (entry 1, 3). On the other hand, HMS,^{2,3)} the original silica, did not exert the acceleration effect (entry 2). This ability of Ti-HMS have been presumed to be due to the properties of acid sites of silica,⁵⁾ which are worth investigating for clarification of their mechanism and further development of their synthetic utility. Now we report selective acceleration of deprotection of benzyl ethers in the presence of acid-sensitive functional groups to evaluate the acid sites of Ti-HMS.

Table 2 shows the results for reactions of benzyl ethers **3** possessing t-butyldimethylsilyloxy group with several acid catalysts or additives under hydrogenolytic conditions.^{4,6)} Under the usual conditions complete debenzylolation was not attained in all substrates even after 20 hours (entry 2, 5, 15, 18). On the other hand, an

Table 1. Acceleration of Debzylolation

n-C ₁₂ H ₂₅ OBn		5%Pd-C (wet type, 20 mg) H ₂ (1atm), Silicate		n-C ₁₂ H ₂₅ OH	
1 (100 mg)		MeOH, r.t., 6hr		1 + 2	
Entry	Silicate	Amount (mg)	Products (%)		
			1	2	
1	-	-	49	49	
2	HMS	100	43	47	
3	10%Ti-HMS	100	0	94	

addition of 10%Ti-HMS dramatically promoted debenzylolation reaction with little influence on the silyl ether moiety and afforded the deprotected mono alcohols **4** in high yields (entry 3, 6, 16, 19). Contrastively no promoting effect was observed with HMS and SiO₂ (entry 7, 8).⁷⁾ When a protic acid, *p*-toluenesulfonic acid (*p*-TSA) was used as a catalyst, both benzyl and silyl ether moieties of the substrate **3b** were depro-

Table 2. Acceleration of Debenzylation in the Presence of *t*-Butyldimethylsilyl Ether Group

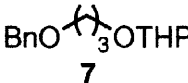
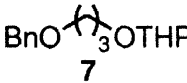
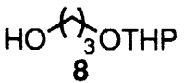
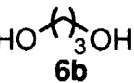
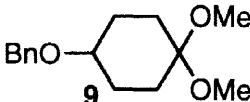
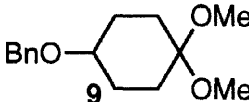
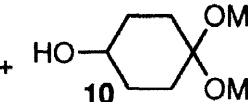
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a) Pd(OH)₂ was used as a catalyst instead of 5%Pd-C.

ected and the corresponding diol **6b** was obtained exclusively (entry 9). When Amberlite IR-120B, Dowex 50W x 8, and Amberlyst 15, which are strongly acidic cation exchange resin, were examined as heterogeneous catalysts instead of Ti-HMS in the reaction of **3b**, the sole product was the diol **6b** in all cases (entry 10, 11, 12). With Amberlite IRC-50, which is weakly acidic cation exchange resin, the appreciable promoting effect could not be observed (entry 13). For **3**, the corresponding diols were obtained in high yields even for 2 hours when using Pd(OH)₂ as a catalyst instead of 5%Pd-C. (entry 3, 7, 18, 22).⁸⁾

Also the results for benzyl ethers **7**, **9** containing acid-sensitive THP ether and acetal moiety under hydrogenoly-

Table 3. Acceleration of Debenzylation in the Presence of THP Ether or Acetal Group

		Substrates (100 mg)	5%Pd-C (wet, 20 mg) H ₂ (1 atm), Additive MeOH, r.t.		Products		
Substrates	Entry	Additives	(mg)	Time (hr)	Products / Isolated Yield (%)		
 7					 7	 8	 6b
	1	-	-	4	78	16	0
	2	-	-	24	32	61	0
	3	- a)	-	2	0	36	36
	4	10%Ti-HMS	(100)	4	7	83	0
	5	<i>p</i> -TsOH	(0.1eq)	4	0	0	74
	6	Amberlite IR-120B	(100)	4	0	0	67
7	Amberlite IRC-50	(100)	4	53	32	0	
 9	8	-	-	4	85	12	
	9	-	-	20	20	72	
	10	- a)	-	2	0	0 ^{b)}	
	11	10%Ti-HMS	(100)	4	7	87	
	12	<i>p</i> -TsOH	(0.1eq)	4	0	66	
	13	Amberlite IR-120B	(100)	4	0	90	
	14	Amberlite IRC-50	(100)	4	39	56	
					 9	+	 10

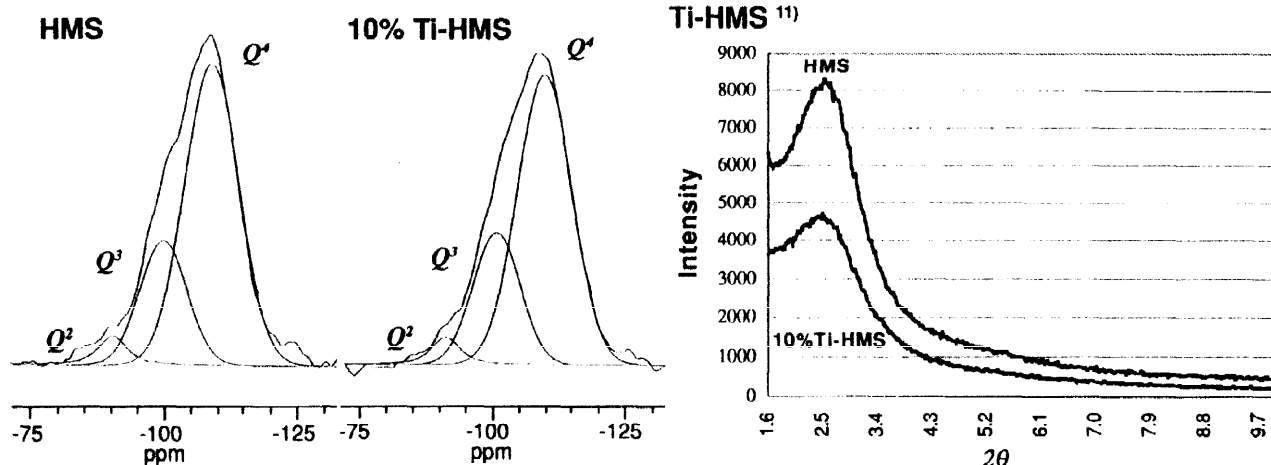
a) Pd(OH)₂ was used as a catalyst instead of 5%Pd-C. b) 4-Hydroxycyclohexanone was obtained quantitatively.

tic conditions are shown in Table 3. The same tendency was observed with several acid catalysts, and 10%Ti-HMS afforded the products **8** and **10** in high yields (entry 3, 9). For **7**, Amberlite IR-120B and *p*-TSA were too strong to deprotect benzyl ether selectively and IRC-50 too weak (entry 4, 5, 6). From the results for **9**, the acceleration effect of debenzylolation with 10%Ti-HMS appears comparable to that with Amberlite IR-120B (entry 9, 11). Surprisingly, for both **7** and **9**, Pd(OH)₂ affected the THP ether and acetal moiety in a similar manner as **3** (entry 3, 10).

Ti-HMS prepared in this study was characterized by NMR spectra and powder XRD patterns.³⁾ Figure 1 shows ²⁹Si MAS NMR spectra of 10%Ti-HMS and HMS.⁹⁾ The deconvolution analysis depicted shows that a ratio of Q⁴ / (Q²+Q³) for 10%Ti-HMS (2.38) is similar to that of HMS (2.19).^{3, 10)} Thus both have almost same short-range framework on microenvironments of surface. On the other hand, the lower intensity of powder XRD of 10%Ti-HMS than that of HMS (Figure 2) shows disorder of bulk structures on solid lattices of the former.¹¹⁾ These evidences imply that 10%Ti-HMS contains almost same proportion of silanol group, Brønsted acid site, as the original HMS. Although the mechanism for selective acceleration of hydrogenolytic debenzylolation by addition of 10%Ti-HMS is obscure yet, the Lewis acid sites due to Ti atom seem to play an important role for this reaction.

In conclusion, Ti-HMS has been found to be a good additive to accelerate selective deprotection of benzyl ether in the presence of acid sensitive functional groups. This method with the silica is also facile from the viewpoint of convenience of the work-up in which the catalyst complex can be removed as an insoluble mass only by filtration of the reaction mixture. Studies on the detailed mechanisms for the selective acceleration of debenzylolation and further applications of Ti-HMS as an additive to other reactions are in progress in our laboratory.

Fig. 1 ^{29}Si MAS NMR of HMS and 10% Ti-HMS ⁹⁾ Fig. 2 Powder XRD Patterns of HMS and 10% Ti-HMS ¹¹⁾



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- Q^n indicates that the framework of the silica is composed of $\text{Si}(\text{OSi})_n(\text{OH})_{4-n}$ as an average structural unit. The ratio of $\text{Q}^2 : \text{Q}^3 : \text{Q}^4$ by the deconvolution analysis is 4.6 : 25.0 : 70.4 for 10% Ti-HMS, and 4.4 : 26.9 : 68.7 for HMS. Thomas, J. M.; Klinowski, J. *Advances in Catalysis* **1985**, 33, 224. Mudrakovskii, I. L.; Mastikhin, U. M.; Shmachkova, V. P.; Kotsarenko, N. S. *Chem. Phys. Lett.* **1985**, 120, 424. Kirkpatrick, R. J.; Smith, K. A.; Schramm, S.; Turner, G.; Yang, W. H. *Ann. Rev. Earth. Planet Sci.* **1985**, 13, 29. Klinowski, J.; Thomas, J. M.; Fyfe, C. A.; Gobbi, G. C.; Hartman, J. S. *Inorg. Chem.* **1983**, 22, 63.
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