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LETTERS

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 debenzylation 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 H_2). 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 debenzylation was not attained in all substrates even after 20 hours (entry 2, 5, 15, 18). On the other hand, an addition of 10%Ti-HMS dramatically promoted debenzylation 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 SiO_2 (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 1. Acceleration of Debenzylation

$$\underset{\textbf{1}\ (100\text{ mg})}{n\text{-}C_{12}H_{25}OBn} \xrightarrow[\text{MeOH, r.t., 6hr}]{\text{5\%Pd-C (wet type, 20 mg)},\ H_2\text{ (1atm), Silicate}} \textbf{1} + \underset{\textbf{2}}{n\text{-}C_{12}H_{25}OH}$$

Entry	Silicate	Amount (mg)	Products (%)	
			1	2
1	-	-	49	49
2	HMS	100	43	47
3	10%Ti-HMS	100	0	94

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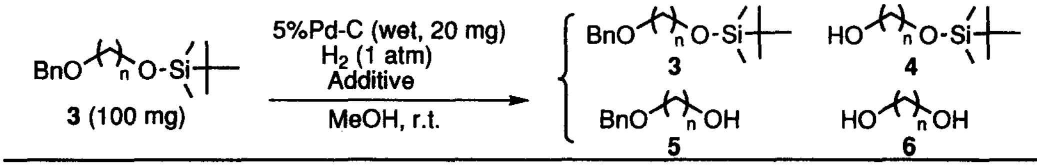
Table 2. Acceleration of Debenzylation in the Presence of t-Butyldimethisilyl Ether Group



Entry	n	Substrates	Additives	(mg)	Time (hr)	Products / Isolated Yield (%)			
						3a	**4a**	**5a**	**6a**
1	2	**3a**	-		4	84	14	0	0
2	2	**3a**	-		20	35	51	0	0
3	2	**3a**	- a)		2	0	0	0	82
4	2	**3a**	10%Ti-HMS	(100)	4	0	71	0	0
						3b	**4b**	**5b**	**6b**
5	3	**3b**	-		4	77	17	4	0
6	3	**3b**	-		20	17	64	6	9
7	3	**3b**	- a)		2	0	0	0	quant.
8	3	**3b**	10%Ti-HMS	(100)	4	0	80	0	7
9	3	**3b**	HMS	(100)	4	59	13	5	0
10	3	**3b**	SiO_2	(100)	4	81	8	3	1
11	3	**3b**	*p*-TsOH	(0.1eq.)	4	0	0	0	70
12	3	**3b**	Amberlite IR-120B	(100)	4	0	0	0	90
13	3	**3b**	Dowex-50W x 8	(100)	4	0	0	0	91
14	3	**3b**	Amberlyst 15	(100)	4	0	0	0	97
15	3	**3b**	Amberlite IRC-50	(100)	4	40	38	6	0
						3c	**4c**	**5c**	**6c**
16	4	**3c**	-		3	71	18	3	0
17	4	**3c**	-		20	0	69	0	29
18	4	**3c**	- a)		2	0	0	0	quant.
19	4	**3c**	10%Ti-HMS	(100)	3	0	83	0	13
						3d	**4d**	**5d**	**6d**
20	5	**3d**	-		4	73	14	2	4
21	5	**3d**	-		20	6	75	3	13
22	5	**3d**	- a)		2	0	0	0	91
23	5	**3d**	10%Ti-HMS	(100)	4	0	82	0	15

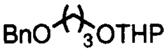
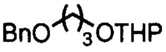
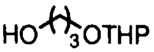
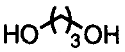
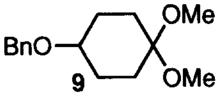
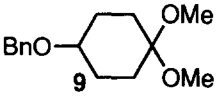
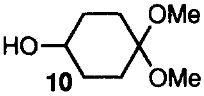
a) $Pd(OH)_2$ was used as a catalyst instead of 5%Pd-C.

tected 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

$$\text{Substrates (100 mg)} \xrightarrow[\text{MeOH, r.t.}]{\text{5\%Pd-C (wet, 20 mg), H}_2\text{ (1 atm), Additive}} \text{Products}$$

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	*p*-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					 9	+	 10
	8	-	-	4	85		12
	9	-	-	20	20		72
	10	- a)	-	2	0		0 b)
	11	10%Ti-HMS	(100)	4	7		87
	12	*p*-TsOH	(0.1eq)	4	0		66
	13	Amberlite IR-120B	(100)	4	0		90
	14	Amberlite IRC-50	(100)	4	39		56

a) $Pd(OH)_2$ was us ed 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 debenzylation 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 ^{29}Si MAS NMR spectra of 10%Ti-HMS and HMS.9) The deconvolution analysis depicted shows that a ratio of $Q^4 / (Q^2+Q^3)$ 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, Brϕnsted acid site, as the original HMS. Although the mechanism for selective acceleration of hydrogenolytic debenzylation 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 debenzylation 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]

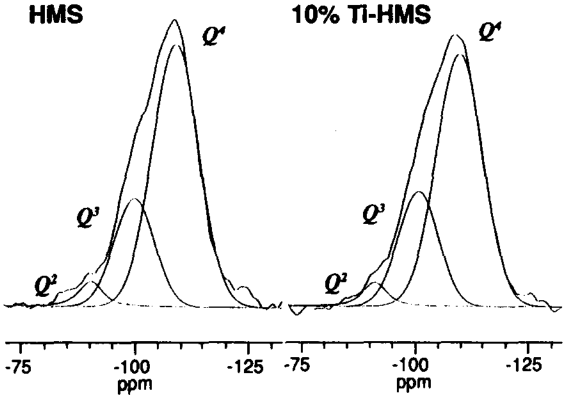
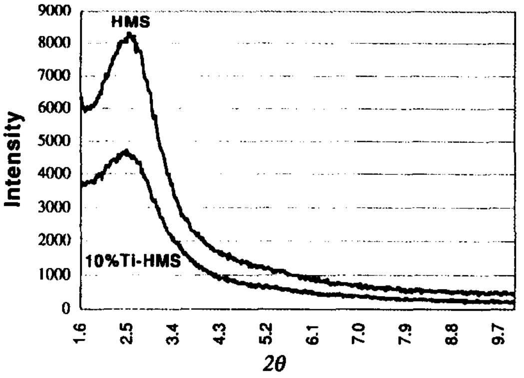


Fig. 2 Powder XRD Patterns of HMS and 10% Ti-HMS [11]



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2. Tanev, P. T.; Pinnavaia, T. J. *Science* **1995**, *267*, 865.
3. 10%Ti-HMS was prepared according to the literatures: Zhang, W.; Froba, M.; Wang, J.; Tanev, P. T.; Wong, J.; Pinnavaia, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9164. Tanev, P. T.; Chibwe, M.; Pinnavaia, T. J. *Nature* **1994**, *368*, 321.
4. A typical procedure follows: To MeOH suspension (10 ml) of 5%Pd-C (Kawaken Fine Chemical Co. (PH) Wet Type, 20 mg) and the benzyl ether (100 mg) a silica (100 mg) was added and the mixture stirred for 10 min at r. t. H_2-filled balloon was fitted to the flask and the mixture stirred for the times indicated. After filtration through celite or membrane filter, the reaction mixture was concentrated and purified by silicagel column chromatography or preparative TLC.
5. Ward J. W. *J. Catal.* **1970**, *16*, 386. Idem. *ibid.* **1967**, *9*, 396. Idem. *ibid.* **1967**, *9*, 225. Parry, J. B. *J. Phys. Chem.* **1965**, *69*, 231.
6. In the case of using *p*-TSA the work-up follows: The reaction mixture was neutralized with saturated aq. $NaHCO_3$ and extracted with ether. The extract was dried, concentrated, and purified by the usual manner.
7. 230-400 mesh of Silicagel 60 (Merck) was used.
8. Some silyl ethers are susceptible to hydrogenolysis: Toshima, K.; Yanagawa, K.; Mukaiyama, S.; Tatsuta, K. *Tetrahedron Lett.* **1990**, *46*, 6697. Rao, V. S.; Perlin, A. S. *Carbohydr. Res.* **1980**, *83*, 175. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975. Dodd, G. H.; Golding, B. T.; Ioannou, P. V. *J. Chem. Soc., Chem. Commun.* **1975**, 249. Corey, E. J.;Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
9. ^{29}Si MAS NMR spectra were measured at 59.6MHz on a JNM-CMX 300 (JEOL) solid state NMR spectrometer equipped with a magic angle spin probe. The quantitative determination of Q^2, Q^3, and Q^4 sites was accomplished by deconvolution of the spectra.
10. Q^n indicates that the framework of the silica is composed of $Si(OSi)_n(OH)_{4-n}$ as an average structural unit. The ratio of $Q^2 : Q^3 : Q^4$ 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.
11. The XRD patterns were measured on a Rigaku RINT-2000 diffractometer equipped with CuKα radiation (λ=1.542 Å). The diffraction data were collected by using a continuous scan mode with a scan speed of 0.5 deg (2θ)/min.