CHEMCATCHEM

DOI: 10.1002/cctc.201000420

Selective Debenzylation of Benzyl Protected Groups with Silia*Cat* Pd(0) under Mild Conditions

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Protection of functional groups such as alcohols, acids, and amines in the manufacture of pharmaceuticals and fine chemicals is often necessary to avoid possible side reactions during the typical multi-step syntheses of complex organic molecules carried out by these industries.^[1] Formation of benzyl esters and ethers (O-protection)^[2] is a commonly used protection method in numerous drugs syntheses, as the Bn protecting group features ease of preparation and chemical stability toward a number of reaction conditions. Selective and smooth deprotection is critical, and the commonly used method makes use of catalytic hydrogenolysis of protecting benzylic groups with H₂ under pressure in the presence of a heterogeneous Pd/C^[3] catalyst or Raney Ni.^[4] Often, however, the deprotection reaction conditions are not compatible with other functional groups, such as nitro, unsaturated bonds, and halogen groups. For example, the state of the art Pd/C catalyst for the O-debenzylation of benzyl protected alcohols and acids makes use of the following recommended reaction conditions:^[5]

- · Catalyst: 5–10% Pd/C
- · Catalyst loading: 2-10% weight substrate
- · Solvent: THF, ethyl acetate, ethanol
- Temperature: 25–50 °C
- H_2 Pressure: 0.1–1 MPa (0.1 MPa = 1 bar)

Moreover, the pyrophoric nature of these catalysts renders their handling relatively complex, whereas leaching of toxic transition metal nanoparticles often occurs, which requires costly removal of the metal from the product.

An alternative route for the selective debenzylation of aromatic benzyl ethers^[6] and esters^[7] makes use of silica-supported sodium hydrogen sulfate (NaHSO₄·SiO₂). Here, however, reaction conditions are even harsher employing toxic solvents, such as thiophene or anisole under reflux (typically at 115– 140 °C).

There is a clear need of more selective and efficient methods for the debenzylation of protecting groups and in particular of more selective heterogeneous catalysts that, according to green chemistry principles,^[8] can be easily separated from the reactants at the end of the reaction and reused in further reac-

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tion runs. We now report that a new series of sol-gel entrapped Pd⁰ heterogeneous catalysts trademarked Silia*Cat* Pd(0) is a highly selective and versatile heterogeneous catalyst for the O- and N-debenzylation of benzyl protected groups under remarkably mild conditions (0.1 MPa H₂ at room temperature).

We first tested the SiliaCat Pd(0) catalyst under a hydrogen balloon at room temperature with three different substrates, namely an ether, carboxylic acid, and heterocycle. Shown in Table 1 are the debenzylation products that were obtained in more than 98% isolated yields in a time interval ranging from 1 through 20 h.



Solvent choice is known to be critical for any debenzylation reaction, therefore, in order to optimize the reaction conditions, 1-(benzyloxy)-4-methoxybenzene (Scheme 1) was used



Scheme 1. Debenzylation reaction of 1-(benzyloxy)-4-methoxybenzene, the substrate used for optimization.

as our substrate of choice, and a series of commonly employed solvents (THF, methanol, ethanol, ethyl acetate, and hexane) were screened under hydrogen balloon room temperature conditions at different solvent concentrations (Table 2).

The best results were achieved with methanol and ethanol (HPLC grade). Reaction rates in order from the fastest were methanol>ethanol>THF>hexane \gg ethyl acetate. For ethyl

Table 2. Catalytic debenzylation reactions with SiliaCat Pd(0) Hydrogel. Reaction conditions optimization.							
Entry	Catalyst [mol %]	Solvent ^[a]	<i>t</i> [h]	Conversion (yield) $[\%]^{[b]}$			
		(concentration [м])		Product	Other		
1	2	EtOH (0.1)	16	17	0		
2	2	MeOH (0.1)	16	15	0		
3	2	EtOH (0.07)	4	100	0		
4	2	MeOH (0.07)	0.5	100	0		
5	1	MeOH (0.07)	1	100	0		
6	0.5	MeOH (0.07)	2	100 (99.5)	0		
7	0.2	MeOH (0.07)	24	50	0		
8	0.1	MeOH (0.07)	24	25	0		
9	2	THF (0.07)	20	10	0		
10	2	MTHF (0.07)	20	15	0		
11	2	ethyl acetate (0.07)	20	20	0		
12	2	hexane (0.07 м)	20	21	0		
[a] Molar concentration with respect to the substrate. [b] Conversion eval- uated by GC/MS analysis. Isolated yield.							

acetate the reaction barely proceeded. The molar concentration of the solvent with respect to the substrate is crucial with higher concentration slowing or even preventing reaction. The best results were achieved by using a methanol concentration of 0.07 μ and 0.5–1 mol% Silia*Cat* Pd(0) catalyst, with complete conversion obtained after 1–2 h (Table 2, entries 5 and 6).

We investigated the versatility of the Silia*Cat* Pd(0) catalyst by studying debenzylation reactions of different substrates using MeOH or EtOH solvents with 0.5–2 mol% catalyst (Table 3). For comparison (entry 1) we also tested commercial catalyst Pd⁰ EnCat, namely a polyurea-entrapped catalyst that, in general, has its catalytic action attributed to homogeneous Pd leached during reaction (and then readsorbed).^[9]

Results in Table 3 show that Silia*Cat* Pd(0) is an efficient catalyst for the selective debenzylation under hydrogen balloon room temperature conditions of different aryl benzyl ethers (entries 1–6), benzyl amino-acids (entries 7–10), and benzyl-protected sugars (entries 11 and 12) leaving other sensitive groups intact. We have not observed N-debenzylation of benzyl amines (entries 13–15) except for 1-BOC-(4-benzyl)piperazine that is completely reduced after 24 h (entry 16). We have not observed N-debenzylation of benzyl amide (entry 17), alkyl benzyl ether (entry 18), and of benzyl pyridine ether (entry 19). Remarkably, however, O-debenzylation of benzyl indol ether (entry 20) took place quantitatively after 20 h.

Different benzyl-protected molecules tested in Table 3 in the debenzylation reaction were used as substrates to assess whether the results could be extended to other substrates and also to determine possible leaching of Pd and Si from the Silia-*Cat* Pd(0) catalyst during conversion, as well as to obtain actual reaction yields. Again, methanol was used as reaction solvent (0.07 $\,$ m with respect to the substrate) with 1–2 mol% Silia*Cat* Pd(0) catalyst (Table 4). At the end of the reaction, the reactants mixture was analyzed for Pd and Si by ICP-MS.

In general the leaching values are $<5\,\,\rm{ppm}$ execpt for amines entries 3 and 5, pointing to some dissolution effect to-

wards entrapped Pd⁰ nanocrystals most likely due to coordination of the electron pair of the sp³ nitrogen atoms.

Finally, we investigated catalyst stability and recycle, a crucial feature of any catalyst seeking commercial application. The Silia*Cat* Pd(0) was thus reused six consecutive times in the Odebenzylation reaction of 1-(benzyloxy)-4-methoxybenzene under the standard mild conditions mentioned in the Experimental Section. After completion of the reaction, the catalyst was recovered by filtration, rinsed with MeOH and dried under vacuum prior to reuse.

Results in Table 5 show that the catalyst affords a noticeable loss in activity after three reaction runs, but then the activity remained approximately constant and it was enough to expand the reaction time to 1 h and 30 min to afford complete debenzylation of the substrate. In conclusion, we have discovered a new series of sol-gel entrapped Pd⁰ catalysts suitable for the selective debenzylation of numerous substrates under mild conditions with a modest 1-2 mol% catalyst amount. Benzyl-protected sugars, aminoacids, ethers, and esters are smoothly debenzylated under 0.1 MPa H₂ at room temperature. In brief, contrary to Pd/C traditional catalysis, efficient debenzylation with SiliaCat Pd(0) does not lead to the development of a range of more active and selective catalysts with reduced metal loadings designed for O-debenzylation of specific substrates; but rather offers a single versatile catalytic material that can be used in modest (1-2 mol% amount) to smoothly convert different substrates under the mildest reaction conditions thus far reported in the chemical literature. The catalyst is stable and can be reused with a single and unique moderate loss in activity after 3 reaction runs. Like any other organosilica-based material,^[11] these SiliaCat hydrogenation catalysts offer a number of additional advantages over traditional Pd/C catalysts, including:

- · Easy and safe to handle vs Pd/C (free flowing, no static charge)
- · Non pyrophoric
- · High density (suitable for small volume work)
- $\cdot\,$ Leach-proof (ultra low metal contamination of product)
- Fast simple recovery of catalyst from process vessel (the catalyst does not stick to glassware; and it is mechanically and thermally stable)
- Solvent independent (organosilica neither shrinks nor swells in any solvent)
- \cdot Low catalytic amount required (<1 mol%) due to fast kinetics and high turnover
- Excellent storage stability

Finally, the molecular sol–gel entrapment^[12] at the origin of the preparation of the Silia*Cat* organosilica-based matrix offers lot-to-lot reproducibility, owing to accurate catalyst loading.

Experimental Section:

The sol-gel Silia*Cat* Pd(0) catalyst consists of an organosilica matrix doped with entrapped Pd⁰ nanocrystals and has been prepared as described elsewhere.^[13] In general the debenzylation reactions

Table 3. Catalytic debenzylation reactions with SiliaCat Pd(0) Hydrogel. Different substrates.							
	Substrates	Catalyst [mol%]	<i>t</i> [h]	Product	Conv. ^[a] [%]	Select. ^[a] [%]	
1 ^(b)	,o-√o	Pd⁰ EnCat 10	16	о- Он	100	100	
2	,o-()-0	SiliaCat Pd(0) 0.5	1 2	о- Он	95 100	100	
3	,o-()	Silia <i>Cat</i> Pd(0) 1	0.5 1	о- Он	75 100	100	
4		SiliaCat Pd(0) 2	1	ОН	100	100	
5		Silia <i>Cat</i> Pd(0) 1	3	ОН	100	100	
6		Silia <i>Cat</i> Pd(0) 1	2	о — — — — он	100	100	
7		Silia <i>Cat</i> Pd(0) 1	1	о но NH BOC	100	100	
8		Silia <i>Cat</i> Pd(0) 1	4	о но NH BOC	100	95	
9	N-(tert-butoxycarbonyl)-O- benzyl-L-serine	Silia <i>Cat</i> Pd(0) 1	0.5	×o [↓] [↓] , ^{OH}	100	-	
10	HO O carboxybenzyloxy-L- valine	Silia <i>Cat</i> Pd(0) 1	1		100	-	
11 ^(c)	RO RO OR OH COH	SiliaC <i>at</i> Pd(0) 1	24	но он	100 ^[d]	-	
12 ^[c]		Silia <i>Cat</i> Pd(0) 1	24	HO OH	100	100	
13		Silia <i>Cat</i> Pd(0) 1	24	NH	no reaction		
14		Silia <i>Cat</i> Pd(0) 2	24		no reaction		
15		Silia <i>Cat</i> Pd(0) 2	24	NH N	no reaction		

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[a] Conversion/Selectivity evaluated by GC/MS analysis. [b] The substrate (1 mmol, 1 equiv) and the catalyst (Pd^0 EnCat were combined in 10 mL EtOH solvent HPLC grade (0.1 M with respect to the substrate)^[10] [c] Solvents used are MeOH/THF 2:1 (0.03 M with respect to the substrate). [d] Conversion evaluated by ¹H NMR spectroscopy.

herein were performed on a 1 mmol scale. The substrate was dissolved in 15 mL of MeOH or EtOH (0.07 μ) and 1 or 2 mol% of the Silia*Cat* Pd(0) catalyst was added. The mixture was degassed two

times and each time replacing the vacuum by hydrogen. The reaction mixture, connected to a balloon of hydrogen, was stirred at room temperature until GC/MS analysis show maximum conver-

Table 4. Catalytic debenzylation reactions with SiliaCat Pd(0) Hydrogel. Leaching test.								
Entry	Substrates	Catalyst [mol %]	<i>t</i> [h]	Product	Conv. ^[a] [%]	Yield ^[b] [%]	Leaching Pd	[ppm] ^[c] Si
1	p-{	1	1	о- С-он	100	99.7	3.4	1.3
2		1	1	о — — — — — — — — — — — — — — — — — — —	100	98.6	1.7	5
3		2	4	о НО NH BOC	100	99	40	1.4
4	N-(tert-butoxycarbonyl)-O- benzyl-L-serine	1	1	Vot N, OH	100	96	1.5	20
5	O OH HO O carboxybenzyloxy-L- valine	1	1		100	97	18 ^[d]	3.1 ^(d)
6	RO RO OR OR COR COR COR COR COR COR COR	2	20	HO OH HO OH	100	98.7	0. 3	17
7	N CO	1	20	N	100	98	0.4	7
[a] Conversion evaluated by GC/MS analysis. [b] Isolated yield. [c] Leaching determined by ICP analysis. The solvent was evaporated and replaced by DMF								

 $\label{eq:calibration} \begin{array}{l} \textbf{Table 5.} \ \text{Reusability of Silia} Cat \ \text{Pd}(0) \ \text{Hydrogel heterogeneous catalyst in} \\ \text{O-debenzylation reactions of 1-(benzyloxy)-4-methoxybenzene.}^{[a]} \end{array}$

Run	Catalyst [mol %]	<i>T</i> [h]	Conversion ^[b] [%]	Yield ^[c] [%]	Leaching [ppm] ^[d] Pd Si
1	1	1	100	99.7	0.7 (7.5) 2.5 (25)
2	1	1	100	99.4	0.3 (3.7) 1.3 (14)
3	1	1	95		
		1.5	100	99.5	0.3 (4) 2.3 (26)
4	1	1	95		
		1.5	100	99.1	0.2 (3.6) 1.4 (19)
5	1	1	94		
		1.5	99	99.2	0.2 (2.5) 0.8 (11)
6	1	1	94		
		1.5	100	99.4	0.1 (1.5) 0.5 (7)

[a] Reaction conditions: the substrate, 1 mol% catalyst with respect to the substrate and the MeOH solvent (HPLC grade) 0.07 μ (molar concentration with respect to the substrate) were stirred at room temperature, 1 MPa H₂. [b] Conversion in final product determined by GS/MS analysis. [c] Isolated yield of the crude product. [d] Leaching determined by ICP analysis in solution, DMF solvent (0.7 μ), and in solid crude product (crude values in parentheses).

sion. After reaction, the catalyst was filtered off and washed with EtOH or MeOH solvent. The filtrate was concentrated to give a crude product. The conversion in the desired product was determined by GC/MS analysis and by ¹H NMR.

Acknowledgements

This paper is dedicated to Maria Pia Carducci Artenisio, mother to one of us.

Keywords: hydrogenolysis · debenzylation · nanoparticles · ormosil · palladium

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Received: November 25, 2010 Revised: January 17, 2011 Published online on April 21, 2011