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**Authors:** Sergey Yakukhnov and Valentine Ananikov

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# Catalytic Transfer Hydrodebenzylation with Low Palladium Loading

Sergey A. Yakukhnov<sup>a</sup> and Valentine P. Ananikov<sup>a,\*</sup>

<sup>a</sup> N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninskiy prospect 47, Moscow 119334, Russia  
E-mail: val@ioc.ac.ru

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**Abstract.** A highly-efficient catalytic system for hydrodebenzylation reaction is described. The cleavage of *O*-benzyl and *N*-benzyl protecting groups was performed using an uncommonly low palladium loading (0.02–0.3 mol %; TON up to 5000) in a relatively short reaction time. The approach was used for a variety of substrates including pharmaceutically important precursors, and gram-scale deprotection reaction was shown.

Transfer conditions together with easy-to-make Pd/C catalyst are the key features of this debenzylation scheme.

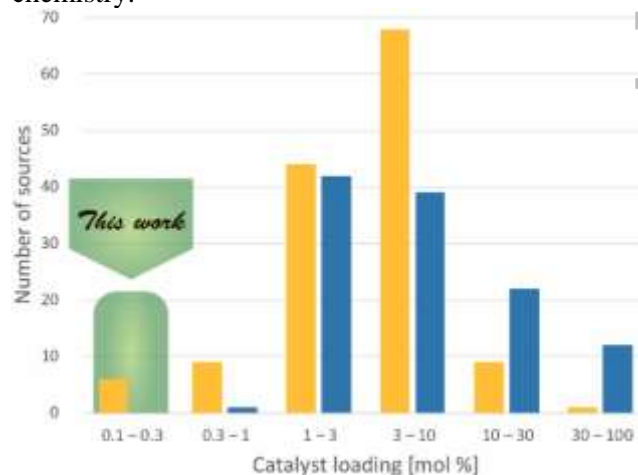
**Keywords:** catalyst efficiency; hydrodebenzylation; hydrodehalogenation; palladium catalysis; transfer conditions; turnover number

## Introduction

Metal catalysis is one of the key engines in chemical research and development. Indeed, it has become an indispensable tool for organic chemists both in academia and industry.<sup>[1–6]</sup> Numerous novel applications of palladium-based homogeneous and heterogeneous catalysts are emerging regularly.<sup>[2–6]</sup> Although homogeneous catalysts typically have higher activities and wider scopes of applicability, the primary advantages of heterogeneous catalysts are their easy separation, the possibility of reuse and tolerance to extreme operating conditions, together with sufficient activity and selectivity. Thus, heterogeneous catalysts have been extensively applied in diverse reactions including oxidation and reduction, C–H bond functionalization, asymmetric synthesis and C–C coupling.<sup>[7]</sup> Development of these highly active catalysts allows to conduct chemical transformations more efficiently, especially in the terms of catalyst loading. However, less attention has been paid to the improvement of hydrodebenzylation deprotection reaction.

Benzyl group is among the most commonly used protecting groups for *O*- and *N*-based functionalities.<sup>[8]</sup> The key features of this protecting group are the ease of formation, relative stability towards both acids and bases and the efficiency of cleavage under mild conditions. Various benzyl protecting groups find numerous applications in

organic transformations, particularly in fine organic chemistry.<sup>[8–10]</sup>



**Figure 1.** A literature overview of catalyst loadings for *O*-benzyl (orange) and *N*-benzyl (blue) bond cleavage for selected most referenced substrates (based on a literature search, see Supporting Information).

For example, a number of pharmaceuticals such as fosamprenavir, lopinavir, lacosamide, repaglinide, lubiprostone, ospemifene, toremifene, ezetimibe, maraviroc, olmesartan, bazedoxifene, lenalidomide, sitaxoxacin, prasugrel, forodesine etc. have debenzylation steps in their synthesis.<sup>[10]</sup>

For more than a century, palladium on carbon (Pd/C) has been a catalyst of choice for hydrodebenzylation reaction.<sup>[11]</sup> In common hydrogenolysis protocols, the catalyst is used as received in its commercially available form. There is a huge number of various forms of Pd/C which differ in metal loading, particle size distribution, oxidation state of the metal, the nature of supporting material, etc. In fact, all these properties influence the course of reaction. Despite the great number of applications described in the literature, hydrogenation *via* standard protocols has several drawbacks. For instance, Pd/C catalysts with metal loading of 5-10% can be pyrophoric and can ignite solvent vapors in the presence of oxygen, causing serious handling issues. An even more crucial issue is related to the loadings of precious metal applied in such reactions. In a typical case, quite high loadings of the metal are applied in order to achieve a certain synthetic result. One of the drawbacks of Pd/C catalysts is the noticeable batch-to-batch variations (it is not uncommon to obtain different results using another batch of catalyst even from the same supplier). An increased Pd loading is a typical solution to compensate for the variations in catalyst activity.

**Table 1.** Screening of reaction conditions.<sup>[a]</sup>

entry	catalyst (mol %)	time (h)	yield <sup>[b]</sup> (%)	TON
1	1	1	100	100
2	0.3	1	100	333
3	0.1	1	100	1000
4	0.05	1	100	2000
5	0.033	1	88	2640
6	0.025	1	37	1480
7	0.02	1	30	1500
8	0.02	6	100	5000
9 <sup>[c]</sup>	0.1	2	73	730
10 <sup>[c]</sup>	0.1	4	100	1000

<sup>[a]</sup> Reaction conditions: Pd/Vulcan catalyst (10.6 mg, 1  $\mu$ mol of palladium), benzyl benzoate (0.1-5 mmol), HCO<sub>2</sub>H and KOH (5 equiv. relative to the substrate), EtOH (concentration of the substrate 0.2 M), reflux;

<sup>[b]</sup> Yields were determined by <sup>1</sup>H NMR spectroscopy;

<sup>[c]</sup> 30 °C.

To illustrate highly varying amounts of catalyst loadings, corresponding data for relevant and most referenced examples of debenzylation is summarized for different types of *O*- and *N*-benzylated substances (Figure 1, see Supporting Information for details). It is evident that the reaction is commonly carried out using 3-10 mol% and 1-3 mol % of a catalyst. However, in several cases the catalyst loading is increased to 10-30 mol% and even stoichiometric amounts are not uncommon. Also, it should be noted

that *N*-benzyl cleavage is considered more challenging and has been hardly attempted with catalyst loadings of less than 1 mol %.

Recent examples of highly efficient catalytic systems for debenzylation reaction are few but noteworthy. A convenient versatile protocol for palladium-catalyzed reductive chemistry with *in situ* forming Pd/C catalyst was reported,<sup>[12]</sup> and its utility for debenzylation of some *O*-benzyl protected substances using palladium loadings from 0.1 to 0.3 mol % (0.05 mol % in the case of Cbz-protected amines; these are benzylic esters too) was demonstrated.<sup>[12]</sup> An unusual catalyst (palladium deposited onto a gold mesh) was reported to retain its activity for the removal of allyl protecting group and also cleaved benzyl benzoate at 0.1 mol % loading within 60 min.<sup>[13]</sup>

Recently, we have reported a handy and rapid approach for preparation of supported palladium-based catalysts, which exhibit promising activity in Suzuki-Miyaura cross-coupling and olefin transfer hydrogenation reactions.<sup>[14]</sup> A specific combination of the properties, such as on-surface location of Pd nanoparticles, easy accessibility of active centers on the surface and convenient preparation, makes these catalysts very promising for synthetic applications.

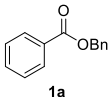
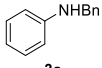
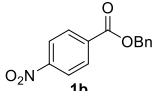
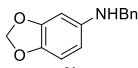
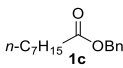
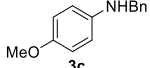
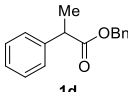
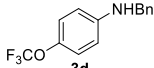
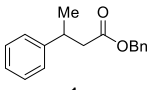
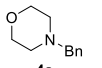
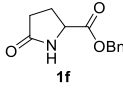
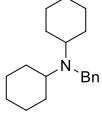
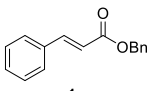
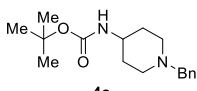
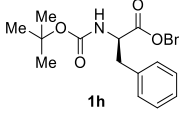
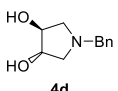
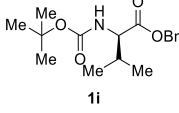
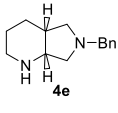
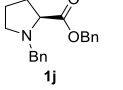
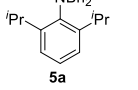
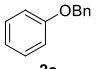
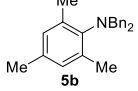
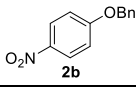
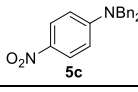
**Table 2.** Optimization of reaction conditions.<sup>[a]</sup>

entry	substrate	HCO <sub>2</sub> H / KOH (mmol / mmol)	yield <sup>[d]</sup> (%)
1 <sup>[b]</sup>		10 / 0	0
		15 / 5	66
		10 / 5	98
		5 / 5	100
		5 / 10	100 <sup>[f]</sup>
2 <sup>[c]</sup>		10 / 0	0
		15 / 5	47
		10 / 5	64
		5 / 5	82
		5 / 10	93
3 <sup>[b,e]</sup>		10 / 0	6; 5
		15 / 5	26; 9
		10 / 5	99; 6
		5 / 5	49; <1
		5 / 10	0
4 <sup>[c]</sup>		10 / 0	24
		15 / 5	54
		10 / 5	72
		5 / 5	22
		5 / 10	0
5 <sup>[c,e]</sup>		10 / 0	3; 2
		15 / 5	18; <1
		10 / 5	51; <1
		5 / 5	11; <1
		5 / 10	0
6 <sup>[c,e]</sup>		10 / 5	99; 13
		6 / 5	99; <1
		5 / 5	63; <1

- [a] Reaction conditions: substrate (1 mmol), Pd/Vulcan catalyst, HCO<sub>2</sub>H, KOH, EtOH (5 mL), 70 °C, 60 min;  
 [b] Loading of the catalyst is 0.1 mol % (10.6 mg)  
 [c] Loading of the catalyst is 0.2 mol % (21.2 mg)  
 [d] Yields were determined by <sup>1</sup>H NMR spectroscopy;  
 [e] The yield of *N*-formylated product is also given (after the semicolon);  
 [f] Saponification of the ester occurred.

Thus, in order to overcome the above-mentioned limitations, development of simple, advantageous and reliable protocols for debenzoylation is urgently required. Experimental procedure, compatible with easy practical preparation of reliable Pd/C catalyst (avoiding complex and difficult-to-reproduce catalyst preparation protocols), is an equally important task. Here, we describe an efficient catalytic system for the transfer hydrodebonylation reaction, which is even more challenging to perform at low metal loadings.

**Table 3.** Substrate scope for the debenzoylation reaction.<sup>[a]</sup>

entry	substrate	time (h)	catalyst (mol %)	yield <sup>[b]</sup> (%)	entry	substrate	time (h)	catalyst (mol %)	yield <sup>[b]</sup> (%)
1 <sup>[d]</sup>		1	0.05	99 (99)	13 <sup>[d]</sup>		1	0.1	99 (92)
2 <sup>[d,e]</sup>		1	0.2	99 (96)	14 <sup>[d]</sup>		1	0.2	99 (97)
3		1	0.2	99 (93)	15		0.5	0.2	99 (83)
4		1	0.2	99 (96)	16		1	0.3	99 (91)
5		1	0.2	99 (95)	17 <sup>[d]</sup>		2	0.3	99 (90)
6		1	0.2	99 (93)	18		2	0.3	99 (93)
7 <sup>[d,f]</sup>		3	0.3	99 (97)	19 <sup>[c]</sup>		3	0.3	99 (81)
8		1	0.2	99 (91)	20 <sup>[d]</sup>		2	0.3	99 (80)
9		1	0.2	99 (89)	21 <sup>[d]</sup>		3	0.3	99 (88)
10 <sup>[c]</sup>		1	0.2	99 (91)	22		2	0.3	99 (94)
11 <sup>[d]</sup>		1	0.3	99 (98)	23		1	0.3	99 (95)
12 <sup>[d,e]</sup>		0.75	0.2	99 (89)	24 <sup>[e]</sup>		2	0.3	99 (93)

[a] Reaction conditions: Pd/Vulcan catalyst (5.3-31.8 mg, 0.5-3 μmol of palladium), substrate (1 mmol), KOH (5 mmol), HCO<sub>2</sub>H (for **1a**, **1c-f**, **1h-i** – 5 mmol; for **2a-b**, **3b** – 6 mmol; for **1b**, **1g**, **4c** – 7 mmol; for **1j**, **3a**, **3c-d**, **4a-b**, **4d-e**, **5a-c** – 10 mmol), EtOH (5 mL), 70 °C;

[b] Conversion of the starting material was determined by <sup>1</sup>H NMR spectroscopy. Isolated yields are shown in the parentheses;

[c] Isolated yields are shown for 5 mmol scale reactions;

<sup>[d]</sup> Isolated yields are shown for 10 mmol scale reactions;

<sup>[e]</sup> Nitro group is reduced to amino group;

<sup>[f]</sup> C-C double bond is reduced.

## Results and Discussion

Using a simple catalyst preparation procedure<sup>[14]</sup> (see Supporting Information), an efficient debenzoylation of benzyl benzoate (**1a**) was carried out (Table 1). The loading of 0.05 mol % was enough to achieve full conversion of the substrate after 60 min only, which corresponded to a turnover number (TON) as high as 2000 and the average reaction rate (turnover frequency, TOF) of more than 2000 h<sup>-1</sup> (Table 1, entries 1-4). Lower catalyst loadings and lower temperatures were acceptable, but a longer reaction time was needed to reach full conversion of the substrate (Table 1, entries 5-10). Nevertheless, utilization of only 0.02 mol % of the catalyst promoted full conversion of the ester within 6 h (Table 1, entry 8). Thus, the process was accomplished with the TON of 5 000. Also, the catalyst activity was examined with regard to possible stirring bar contamination; the experiment confirmed the actual activity of Pd/Vulcan.<sup>[15]</sup>

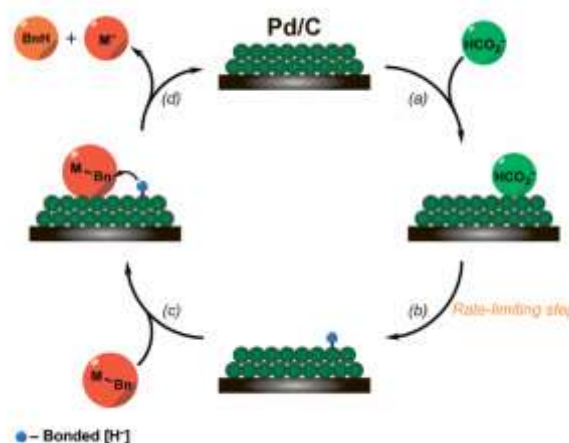
Our further investigation indicated that one of the most significant parameters to be optimized was the ratio of formic acid and base used in preparation of the applied reductant solution. This ratio was shown to have a pronounced influence on the debenzoylation reaction rate as well as on the rate of side processes and the resulting selectivity. It was found that in the case of *O*-benzylated substrates **1a** and **2a** the neutral medium reaction is superior (Table 2, entries 1-2). At the same time, acidic solution of the reductant ensures efficient cleavage of *N*-benzyl bonds in amines **3a**, **4a**, **5a** and **3b** (Table 2, entries 3-6). The accurate and reagent-specific choice of the ratio allows to avoid formation of *N*-formylated side products and to obtain high yields of a single product even in the case of aniline **3b**, which is electron-rich and most susceptible to formylation (Table 2, entry 6).

Next, we evaluated a scope of various *O*- and *N*-benzylated substances **1-5** for debenzoylation in the developed system (Table 3). The *O*-benzyl bonds are readily cleaved under these conditions (Table 3, entries 1-12). Precise control of the reaction progress allows selective deprotection of ester groups in the presence of *N*-Bn group (Table 3, entry 10).

Benzyl-protected amines can be deprotected in a similar manner (Table 3, entries 13-24). However, the issue of optimal pH value is acute. A number of studies dealing with this issue have been reported previously.<sup>[16-19]</sup> In particular, it has been shown that the rate of deprotection for 4-chloro-*N,N*-dibenzylaniline increases greatly when pH of the medium drops below p*K*<sub>a</sub> of the benzyl-protected amine.<sup>[18]</sup> As the reaction is associated with formic

acid consumption, attention should be paid to maintaining a proper pH of the reaction medium.

Another important aspect that should be highlighted for the studied catalytic system is associated with the co-occurring hydrodehalogenation. Selective debenzoylation without the concomitant undesired hydrodehalogenation is a highly sought-after transformation, especially for the synthesis of fine chemicals and pharmaceuticals. Corresponding mechanistic studies and catalytic systems for this transformation with substrates, containing aromatic halogen, are abundant in the literature.<sup>[7p,10,17-19]</sup> A trade-off between the yield of desired product and the catalyst amount was demonstrated.<sup>[17]</sup> Preliminary experiments show that our catalytic system is highly active toward reductive cleavage of Ar-Cl and Ar-Br bonds (Table S1).



**Figure 2.** Plausible mechanism of Pd-catalyzed transfer hydrogenolysis.<sup>[20]</sup>

Palladium-catalyzed transfer hydrogenolysis has been known for a long time, and its well-established mechanism is thoroughly investigated (Figure 2).<sup>[16-18,20]</sup> It involves the following steps: formate anion sorption (a), abstraction of formyl hydrogen as the rate-limiting step (b), approach of the substrate (c) and formation of the product (d). To determine the rate law for the reaction, classical mechanistic Langmuir-Hinshelwood models were derived for hydrodebenzoylation of *N*-benzyl anilines by hydrogen gas as a reductant.<sup>[17,18]</sup>

Kinetic studies were performed with benzyl benzoate as a model substrate and ammonium formate as a reductant (see section 4 of the Supporting Information for details). We have observed a negative influence of the substrate concentration on the reaction rate (*i. e.* inhibition), as well as saturation kinetics for the reductant concentration (Figures S11,S12). If concentration of

the species, which take part in the rate-limiting step (*i. e.*  $\text{Pd}_{\text{surf}}(\text{HCO}_2^-)_{\text{ads}}$ ), is expressed directly through the degree of adsorption  $\theta$ , then these experimental data will be taken into account. Accordingly, the data were fitted with the use of Langmuir adsorption isotherm to derive the rate law (Eq. S4). This newly derived rate law can be converted into the previously reported one in certain cases.<sup>[20]</sup> It also accounts for the presence of various additives, including catalytic inhibitors and poisons.

Further, we investigated the evolution of the catalyst during the operation. We found that the catalyst retained its activity even after 6 h of pretreatment under typical reaction conditions (Table 4, entry 1,2).

**Table 4.** Investigation of the catalyst evolution.<sup>[a]</sup>

entry	additive	pretreatment time	yield, <sup>[b]</sup> (%)
1 <sup>[c]</sup>	–	–	100
2 <sup>[c,d]</sup>	–	6 h	100
3 <sup>[c]</sup>	2.5 mmol $\text{HCO}_2\text{K}$	6 h	100
4 <sup>[d]</sup>	2.5 mmol $\text{HCO}_2\text{K}$	1 h	31
5 <sup>[d]</sup>	2.5 mmol $\text{HCO}_2\text{K}$	2 h	9
6 <sup>[d]</sup>	2.5 mmol $\text{HCO}_2\text{K}$	3 h	< 1
7 <sup>[c]</sup>	212 mg KCl	6 h	37
8 <sup>[d]</sup>	212 mg KCl	6 h	8
9 <sup>[c]</sup>	1000 mg KCl	–	100
10 <sup>[c]</sup>	50 mg KBr	–	100
11 <sup>[c]</sup>	150 mg KBr	–	85
12 <sup>[c]</sup>	5 mg KI	–	< 1

<sup>[a]</sup> Reaction conditions: benzyl benzoate (1 mmol), Pd/Vulcan catalyst (0.1 mol%, 10.6 mg, 1  $\mu\text{mol}$  of palladium),  $\text{HCO}_2\text{H}$  (5 mmol), KOH (5 mmol), EtOH (5 mL), 70 °C, 60 min;

<sup>[b]</sup> The yields were determined by  $^1\text{H}$  NMR spectroscopy;

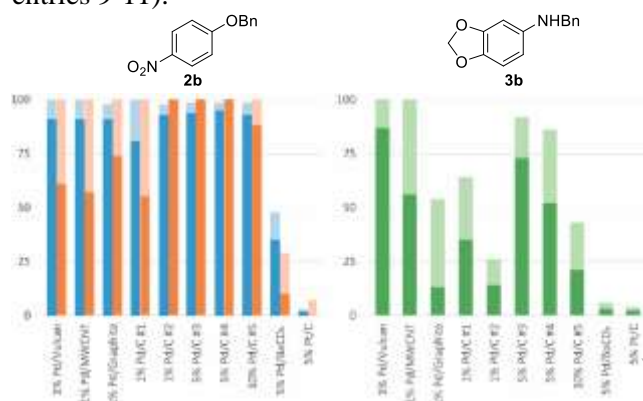
<sup>[c]</sup> The reaction vessel was unsealed;

<sup>[d]</sup> The reaction vessel was sealed.

The presence of  $\text{HCO}_2\text{K}$  had no noticeable influence on the catalytic activity (Table 4, entry 3). However, sealing of the mixture caused rapid deactivation of the catalyst (Table 4, entries 4-6). Thus, the reaction should not be set up in a closed vessel. We assume that this could be related to the poisoning of the surface of palladium by sorption of CO, which could be formed as a result of both thermally-activated side-process of formate-anion fusion to CO and OH<sup>-</sup> and in case of  $\text{CO}_2$  reduction inside the compressed vessel.<sup>[21]</sup>

Also, we estimated the influence of halide anions which may appear in the reaction mixture during debenzilation of amines in the form of salt, as a result of co-occurring dehalogenation processes or for some other accidental reasons. Treatment of the catalyst with KCl leads to its reconstruction and a consequent decrease in the catalytic activity (Table 4,

entries 7,8); however, if the reaction is rapid enough, it could go to completion even in presence of large amounts of chloride and bromide anions (Table 4, entries 9-11).



**Figure 3.** Comparison of efficiency of different catalysts in debenzilation (blue) and nitro-group reduction (orange) of **2b**, and debenzilation of **3b** (green). Reaction times are 30 (deep blue/orange/green colors) and 60 min (light blue/orange/green colors), respectively (see Table S2 for details).

**Table 5.** Recyclability of Pd/Vulcan catalyst.<sup>[a]</sup>

substrate	Run		
	1	2	3
	100	100	100
	100 / 100	91 / 100	90 / 100

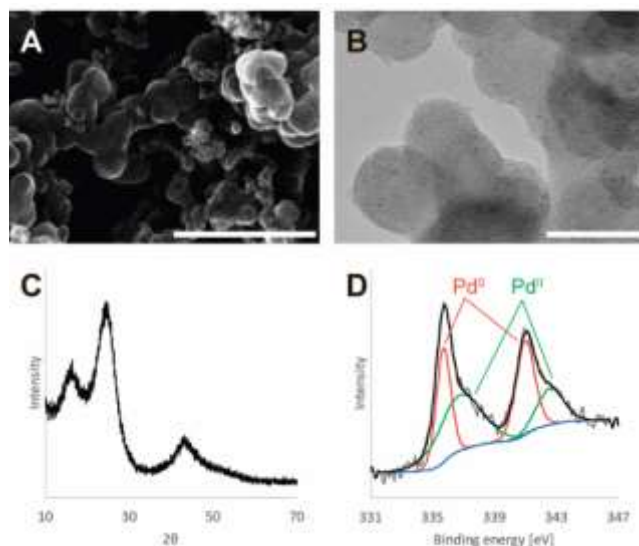
<sup>[a]</sup> Degree of debenzilation and nitro-group reduction in **2b** are shown.

The presence of a small amount of iodide anions stops the debenzilation reaction completely (Table 4, entry 12). All these features can be accounted for when considering the competing adsorption of non-formate anions as a rapidly arising negative factor. It is widely known that halide anions are able to adsorb onto palladium surface, and their affinity increases in the following order:  $\text{Cl}^- < \text{Br}^- < \text{I}^-$ .<sup>[7p]</sup> From our data we may propose that the adsorption energy of formate anion is close to that of chloride anion.

The efficiency of the developed Pd/Vulcan catalyst was compared with other supported catalysts (Figure 3, see also Table S2). Compounds **2b** and **3b** were selected as *O*- and *N*-protected substrates for these studies. On relatively easy case of *O*-benzyl bond cleavage Pd/C catalysts have shown a good performance under optimized conditions. On the other hand, deprotection of much more challenging *N*-benzylated aniline **3b** revealed substantial difference between the applied catalysts. The 1% Pd/C catalyst prepared here in accordance with the “mix-and-stir” approach by using multi-wall carbon

nanotubes (MWCNT) as a supporting material, along with both 5% commercially available Pd/C catalysts, showed good performances. However, 1% Pd/Vulcan catalyst developed in the present study has shown superior catalytic activity.

In many literature examples rather high catalyst loadings are utilized for debenzoylation (Figure 1). This is in a sharp contrast with other Pd-catalyzed synthetic transformations (for example, cross-coupling reactions, hydrofunctionalizations, Heck reaction, substitution reactions, etc.), where around 1 mol% of Pd is applied in high performance process.<sup>[1-7]</sup> For example, it was shown that 0.1-1 mol% of Pd/C catalyst is a reliable amount for high performance cross-coupling and hydrogenation reactions.<sup>[14]</sup> The present study demonstrates that optimized procedure with Pd nanoparticle catalyst made by simple mix-and-stir procedure significantly decreases the catalyst amount. Good activity of the catalyst prompted us to investigate opportunities for re-use the catalyst multiple times. Recycling experiments have successfully shown a possibility to re-use the Pd/Vulcan in the subsequent reactions (Table 5). The same quantitative reaction yield was achieved in three runs.



**Figure 4.** (A) SEM image of 1% Pd/Vulcan catalyst (scale bar-300 nm), (B) TEM image of 1% Pd/Vulcan catalyst (scale bar-50 nm), (C) XRD pattern and (D) XPS pattern of the initial catalyst..

The Pd/Vulcan catalyst represents palladium nanoparticles with small size ( $2.4 \pm 0.4$  nm) and clean surface, dispersed on the surface of Vulcan XC72 carbon black (Figure 4-A,B). As these nanoparticles are small in size and the metal content is 1% by weight, the XRD pattern contains only the signals, associated with the supporting material (Figure 4-C). The presence of Pd(II) species, which could appear during the storage of the catalyst, is indicated by *ex situ* XPS analysis (Figure 4-D). However, we suppose that reduction of such surface palladium

species inevitably takes place under the strongly reductive operation conditions. The catalyst is stored under standard laboratory conditions without any significant changes in its activity.

Additionally, we investigated the status of the catalyst after the recycling experiments. XPS analysis was made, which indicates only minor changes of palladium state. The Pd NPs size distribution pattern changed slightly – mean size increased from 2.4 to 3.2 nm and the distribution became slightly broader.

As an important practical question, some M/C catalysts may exhibit pyrophoric properties on air and require strict inert atmosphere for handling. We have tested the developed catalyst for potential pyrophoric activity. Regular stability tests on air and thermogravimetric analysis on air indicated that Pd/Vulcan catalysts is relatively stable (for more details, see Supporting Information). Therefore, preliminary steps in the reaction setup (handling and weighting) can be performed on air without any noticeable changes in catalytic activity for studied cases.

## Conclusion

In conclusion, we have demonstrated that Pd/Vulcan catalyst, prepared by the “mix-and-stir” approach, has excellent hydrodebenzoylation catalytic reactivity for a wide scope of substrates. The highly reproducible hydrodebenzoylation reactions with low catalyst loading ( $\leq 0.3$  mol %) can be accomplished routinely and in a short time. To the best of our knowledge, the results are superior compared to the generally assumed conditions-to-outcomes for this reaction. The developed catalytic system has an expected functional group tolerance and reactivity, which is similar to that of classically established. Importantly, predictability of the functional groups reactivity pattern is a key requirement for the developed catalytic system to be proposed for widespread use in a regular manner.

The decrease in the amount of precious metal catalyst achieved in this study not only provides a significant increase in cost-efficiency of the overall process, but also allows to reduce the unavoidable environmental contamination with the heavy-metal-containing materials.<sup>[22]</sup>

Of course, one could argue that the concept of Pd/C catalytic systems is known. Indeed, Pd/C catalysts are continuously utilized in organic synthesis for decades and the practical demand has only increased in recent years. Neither have we wanted to bring artificial novelty with extraordinary complex catalyst preparation procedure. Our goal has been to study a classical catalytic system and demonstrate the outstanding potential for improvement it intrinsically has. An order of magnitude increase in the efficiency of exciting and numerous employed supported palladium-on-carbon catalyst makes a strong impact on most significant practically proven applications. The on-

going improvement of diverse catalysts for numerous practical applications gives access to sustainable development.

## Experimental Section

### Pd/C Catalyst preparation

For the synthesis of Pd/C catalysts a freshly made Pd<sub>2</sub>dba<sub>3</sub>·CHCl<sub>3</sub> precursor was prepared *via* recrystallization and its quality was controlled by <sup>1</sup>H NMR.<sup>[23]</sup> The 1% Pd/Vulcan, Pd/MWCNT and Pd/graphite catalysts were obtained following the “mix-and-stir” approach, which was reported recently.<sup>[14]</sup> Palladium content was 1% by weight.

In typical procedure, Pd<sub>2</sub>dba<sub>3</sub>·CHCl<sub>3</sub> (25.0 mg), Vulcan carbon black (500 mg), CHCl<sub>3</sub> (25 mL), and a magnetic stirrer were loaded into a screw-capped reaction vessel and placed in an oil bath at 80 °C under stirring. After the dissolution of Pd<sub>2</sub>dba<sub>3</sub>, a dark red solution was formed, and stirring was performed until the red color of the solution disappears. The Pd/C catalyst was separated from the solution by filtration or centrifugation, washed with acetone (30 mL) to remove free dba, and dried under reduced pressure (0.01 bar, 50 °C). A detailed step-by-step procedure is provided in the dedicated video.<sup>[24]</sup>

### Experimental Procedure for the 1 mmol Scale Hydrodebenzylation

In typical case, an aliquot of 5 mL of reductant solution and a magnetic stirring bar were placed into 15 mL reaction vessel. Then, a portion of substrate (1 mmol) was added. The reaction mixture was placed into a heating block. After a short period of time, a portion of the catalyst was added to the heated reaction mixture. The conversion was monitored by <sup>1</sup>H NMR spectroscopy. After the reaction, the mixture was cooled to room temperature and filtered through PTFE membrane filter. The filter was additionally washed with ethanol; the filtrates were combined, evaporated and the crude product was purified by flash column chromatography on a silica gel column to obtain the desired product.

### Experimental Procedure for the Multi-Gram Scale Hydrodebenzylation (5 or 10 mmol scale)

In typical case, a magnetic stirring bar, a portion of a substrate (X mmol) and 5X mL of reductant solution were placed in a three-necked round-bottom flask. The ratio of formic acid, KOH and ethanol was equal to that for 1 mmol scale hydrodebenzylation reaction. The reaction mixture was heated at reflux conditions. After a short period of time, a portion of the catalyst was added to the heated reaction mixture. The conversion was monitored by <sup>1</sup>H NMR spectroscopy. After the reaction, the mixture was cooled to room temperature and filtered through a pad of Celite®. The pad was additionally washed with ethanol; the filtrates were combined, evaporated and crude product was purified by flash column chromatography on a silica gel column to obtain the desired product.

### Recycling of the Pd/Vulcan catalyst

A 15 mL reaction vessel was loaded with 6 mmol of HCO<sub>2</sub>H, 5 mmol of KOH, 5 mL of ethanol, substrate (1 mmol for **1a**; 0.5 mmol for **2b**) and a magnetic stirring bar. The vessel was placed in heating block with temperature set to 40 °C. A sample of the Pd/Vulcan catalyst (31.8 mg, 3 μmol of palladium) was added to the heated reaction mixture and it was stirred at 40 °C for 60 min. After a probe for <sup>1</sup>H NMR analysis was taken, the reaction mixture was quenched with ethanol (7 mL) and

the catalyst was collected by centrifugation. It was additionally washed twice with water (12 mL) and once again with ethanol (12 mL). The isolated catalyst was used in the next cycle.

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**FULL PAPER****Catalytic Transfer Hydrodebenzylation with Low Palladium Loading***Adv. Synth. Catal.* **Year**, *Volume*, Page-Page

Sergey A. Yakukhnov and Valentine P. Ananikov\*

