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Pd-catalyzed Debenzylation and Deallyation of Ethers and Esters with Sodium Hydride

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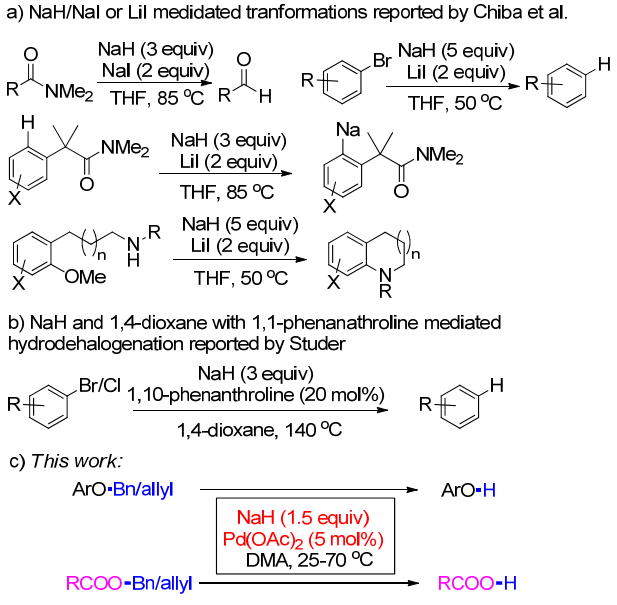
ABSTRACT: Herein we demonstrate simply the addition of $Pd(OAc)_2$ as a promotor switches the reactivity of a commonly used base NaH to a nucleophilic reductant. The reactivity is engineered into a palladium-catalyzed reductive debenzylation and deallylation of aryl ethers and esters. This operationally simple, mild protocol displays a broad substrate scope and a broad spectrum of functional group tolerance (>50 examples) and high chemoselectivity towards aryl ethers over aliphatic structures. Moreover, the dual reactivity of NaH as a base and a reductant is demonstrated in efficient synthetic elaboration.

KEYWORDS: *sodium hydride, palladium, reduction, debenzylation, deallylation.*

Cheap and structurally simple NaH is one of the most widely used reagents in chemical research. It is generally used as a base in organic synthesis.[1] In sharp contrast, it is rarely used as a reductant or a nucleophile.[2,3] In this context, recent elegant studies from the groups of Chiba[4] and Studer[5] reveal such highly sought utility in organic reactions. The Chiba and coworkers developed a series of unique NaH-LiI or NaI composite mediated organic transformations including the reduction of nitriles, amides, and imines,[4a,b] dehalogenation of aryl halides,[4c] amide-directed C-H sodiation,[4d] and nucleophilic amination of methoxy arenes (Scheme 1a).[4e] Studer et al reported an unprecedented radical hydrodehalogenation of aryl bromides and chlorides using NaH and 1,4-dioxane as reagents and 1,10-phenanthroiline as a radical initiator (Scheme 1b). These studies underscore the enormous synthetic potential of cheap and readily stored and handled, but much less explored NaH as a reducing reagent or a nucleophile for organic transformation.

Herein, we report new findings that simply the employment of $Pd(OAc)_2$ as a promotor switches the reactivity of commonly used base NaH to a nucleophilic reductant (Scheme 1c). The new reactivity is transformed into a new palladium-catalyzed reductive debenzylation and deallylation of aryl ethers and esters. This operationally simple, mild protocol displays a broad substrate scope and a broad spectrum of functional group tolerance (>50 examples) and high chemoselectivity towards aryl ethers over aliphatic ones. Moreover, the dual reactivity of NaH as a base and a nucleophile is explored in efficient synthetic elaboration. It is noteworthy that benzyl and allyl functionalities are widely used as protecting groups for hydroxyl and carboxylate groups. General deprotection methods employ Pd-catalyzed hydrogenolysis[6] and Rh-promoted isomerization of double bonds[7] for debenzylation and deallylation, respectively. However, our method unifies the two protocols enabling the removal of both protecting groups under the same reaction conditions.

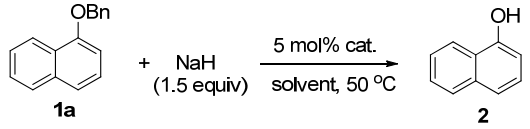
Scheme 1. Reactions mediated by NaH as a reductant or a nucleophile



We commenced the studies by treating 1-(benzyloxy)naphthalene (**1a**) with NaH (1.5 equiv) and various catalysts (5 mol %) in THF (Table 1, entries 1-4 and supporting information) under an N_2 atmosphere. In the absence of catalyst, no conversion was observed after

24 h (entry 1). Nonetheless, when $PdCl_2$ and $Pd(OAc)_2$ were added, the desired deprotection product, 1-naphthol (**2**), was obtained in nearly quantitative yield (entries 2 and 3). Other Pd sources were also tested (see supporting information). The lower yields obtained with these catalysts demonstrated that the presence of ligands on Pd had a negative effect on the process. Furthermore, an attempt to replace palladium by other metals failed to provide any detectable products except $RhCl_3{\cdot}3H_2O$ (entry 4). Subsequently, several solvents were screened (entries 5-6 and supporting information), and DMA (*N*,*N*-dimethylacetamide) was found to be the most effective as the conversion was complete in less than 1 h (entry 6). Notably, other hydrides, such as KH and LiH, could also participate in the debenzylation reaction and afforded **2** in 36% and 98% yields, respectively (entries 7 and 8). Considering the cost of KH and LiH, NaH was still the best choice for the reaction. Lowering loading of NaH and $Pd(OAc)_2$ was then evaluated, and both resulting in substantial decreases in the yield (see supporting information). Finally, the reaction could be carried out at rt without a drop in the yield albeit with a longer reaction time (entry 9).

Table 1. Optimization of reaction parameters[a]

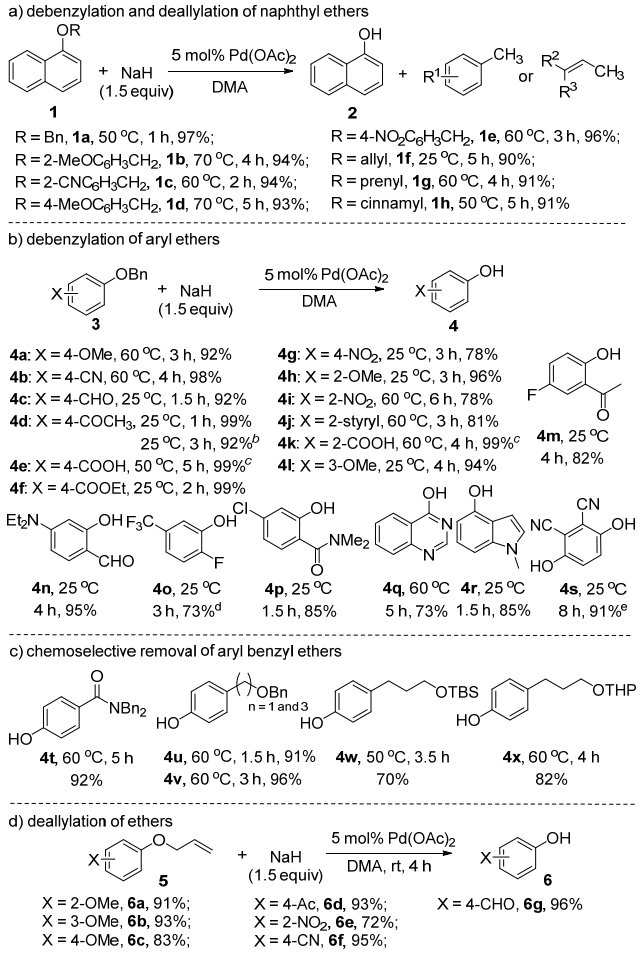


entry	catalyst	solvent	time (h)	yield (%)[b]
1	-	THF	24	0
2	$PdCl_2$	THF	4	97
3	$Pd(OAc)_2$	THF	5	98
4	$RhCl_3{\cdot}3H_2O$	THF	12	12
5	$Pd(OAc)_2$	DMF	12	83
6	**$Pd(OAc)_2$**	**DMA**	**1**	**97**
7[c]	$Pd(OAc)_2$	DMA	15	36
8[d]	$Pd(OAc)_2$	DMA	3.5	98
9[e]	$Pd(OAc)_2$	DMA	3	96

[a]Reaction conditions: NaH (0.45 mmol, 1.5 equiv) and catalyst (0.015 mmol, 5 mol%) in solvent (1.0 mL) was stirred for 5 min under N_2 before **1a** (0.3 mmol) in solvent (0.5 mL) was added, and then the reaction was stirred at 50 °C for the specified time. [b]Isolated yield. [c]KH was used. [d]LiH was used. [e]The reaction was conducted at rt.

With the optimal reaction conditions in hand, we next explored the substrate scope with respect to the alternation of protecting group (Scheme 2a). Various benzyl group-protected substrates bearing electron-neutral, -donating and -withdrawing groups **1a-e** were smoothly converted into 1-naphthol (**2**) in uniformly high to excellent yields. In addition, the reaction system was efficient for the cleavage of allyl, prenyl and cinnamyl protecting groups (**1f-h**). To the best of our knowledge, almost no examples of removing both the electron-rich *p*-methoxybenzyl (PMB) group[8] (**1d**) and electron-deficient *p*-nitrobenzyl (PNB) group[9] (**1e**) by the same reaction conditions have been reported. Moreover, few reagents[10, 11] are capable of simultaneously cleaving both benzyl and allyl groups.

Scheme 2. Scope of debenzylation and deallylation of ethers[a]



[a]Reaction conditions: NaH (0.45 mmol, 1.5 equiv) and catalyst (0.015 mmol, 5 mol%) in DMA (1.0 mL) was stirred for 5 min under N_2 before **1** (0.3 mmol) in DMA (0.5 mL) was added, and then the reaction was stirred at the specified temperature for the specified time. [b]The reaction was conducted on 6 mmol of substrate. [c]2.5 equiv of NaH was used. [d]THF was used as the solvent. [e]3.0 equiv of NaH was used.

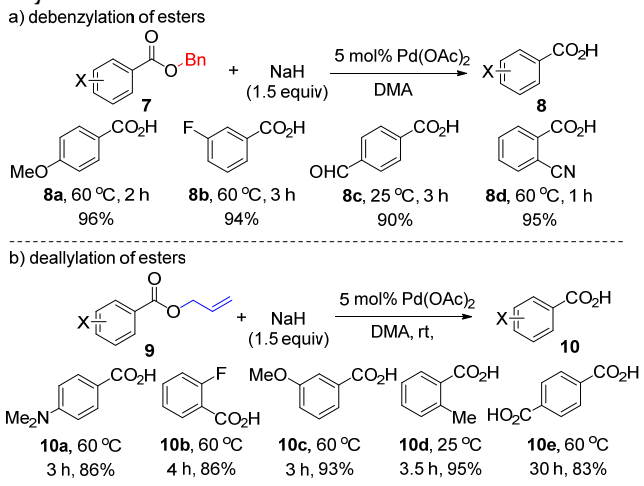
We then turned our attention to the evaluation of the more structurally diverse aryl benzyl ethers (Scheme 2b). Notably, the efficiency of the reaction was not significantly affected by substituents on the phenol portion of the molecule, which was demonstrated by the observation that the electronic nature and substitution pattern on the aromatic ring of the substrates did not impact the results of these reactions (**4a-p**). The mild nature of the combination of NaH/$Pd(OAc)_2$ enlables a variety of reducible functional groups, such as aldehyde (**4c** and **4n**), ketone (**4d** and **4m**), nitro (**4g** and **4i**), alkene (**4j**) and chloride (**4p**) groups, which are usually labile under hydrogenolysis conditions, to be tolerated. When the reaction was conducted on a 6 mmol scale (substrate **3d**), the process proceeded smoothly and afforded **4d** in similar yield as was achieved on a small scale. Heteroaromatic compounds including quinazoline **3q** and indole **3r** proved to be competent substrates and provided the corresponding deprotected products **4q** and **4r**. The procedure was also

applicable to the double debenzylation of **3s** to give diphenol **4s** in high yield.

Next, the chemoselectivity of the methodology was investigated when different benzyl groups appeared in one molecule (Scheme 2c). It was found that cleavage occurred exclusively on the aryl benzyl ether but not on the *N*,*N*-dibenzylbenzamide (**4t**) or the alkyl benzyl ether (**4u** and **4v**).[12] Furthermore, to demonstrate the orthogonal capacity, additional suitable protecting groups such as broadly used TBS and THP were subjected to the standard reaction conditions and gave the desired debenzylation products **4w** and **4x** in good yields. Allyl groups are also easily removed by the established protocol. Some representative substrates **5** bearing common functional groups including OMe, Ac, NO_2, CN, and CHO underwent deallylation under even milder conditions (rt) in 4 h to give desired phenols **6** in good yields (Scheme 2d).

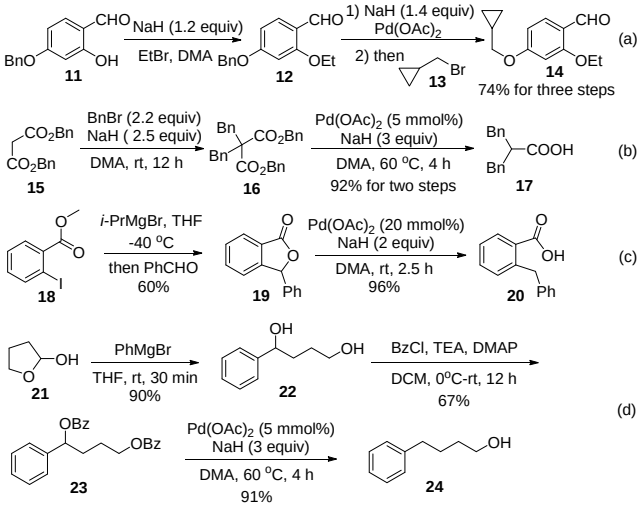
The conversion of esters to carboxylic acids is an meaningful deprotection reaction in synthesis. The deprotection of corresponding benzyl and allyl carboxylates occurs even more easily than the that of the corresponding aryl ethers. Representative benzyl and allyl ester substrates with various substituents were reacted smoothly with NaH/$Pd(OAc)_2$ in DMA and furnished carboxylic acids in good yields (Scheme 3).

Scheme 3. Scope of the deprotection of benzyl and allyl esters



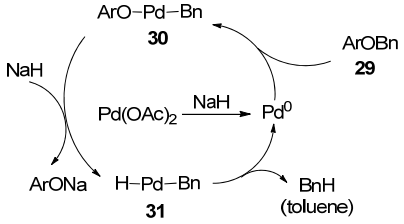
We envisioned that taking advantage of the dual reactivity of NaH as a base and a reductant, the efficient synthesis of more complex structures, which otherwise take multistep process, is feasible. In the first attempt, we selected readily prepared **11** as the starting material for the one-pot synthesis. Treatment of **11** with EtBr and 1.2 equiv of NaH gave **12** as the only product, and subsequent addition of $Pd(OAc)_2$ and an additional 1.4 equiv of NaH led to the formation of sodium phenolate, which was directly reacted with (bromomethyl)cyclopropane **13** to provide the final product **14** in 74% overall yield for the one-pot three step synthesis (Scheme 4a). The second example is the well-known malonic ester synthesis (Scheme 4b). Dialkylation of malonate **15** using BnBr, followed by treatment with NaH/$Pd(OAc)_2$ in one-pot, gave decarboxylation product **17** in 92% yield. To the best of our knowledge, this represents the most efficient synthetic operation to this kind of structure reported to date.[13] The third case is the preparation of 2-benzylbenzoic acid **20** via a two-step pathway (Scheme 4c). The benzyl moiety of **19** was efficiently reduced to a methylene, which is different from the above mentioned reactions since the focus here is on the transformation of the benzyl group instead of the deprotection of a phenol or carboxylic acid. Similarly, this strategy can be employed for the introduction of alkyl fragment at benzyl or allyl position as indicated by the facile syntheses of **24** and **28** (Scheme 4d and Scheme S1, respectively). Key precursor **23** was generated from hemiacetal **21**[14] in straightforward two-step synthesis. The final reduction steps were mild, and efficiently provided the alkylation products in good yields. The atom- and step-economy of the developed methods are clearly demonstrated in these syntheses, highlighting the unique power of NaH in organic synthesis.

Scheme 4. Exploration of NaH as reductant in efficient synthetic elaboration



Based on the general mechanism of a typical Pd-promoted debenzylation reaction, a plausible catalytic cycle for the new transformation was proposed (Scheme 5). Pd(0) is initially formed by reduction of $Pd(OAc)_2$ with NaH.[15] Aryl benzyl ether **29** undergoes oxidative addition followed by ion exchange of ArO^- and hydride anion between **30** and NaH, which provides ArONa and intermediate **31**. Finally, reductive elimination of **31** releases toluene and regenerates the Pd(0) catalyst.

Scheme 5. The proposed catalytic cycle



In conclusion, we have developed a new protocol for the deprotection of aryl benzyl/allyl ethers and benzyl/allyl esters using NaH as a nucleophile in high yield and with a broad substrate scope and a wide spectrum of functional group tolerance. The method exhibits high

chemoselectivity towards aryl ethers over aliphatic ones. These features render the new deprotection methodology potentially useful in the protection of -OH and COOH in organic synthesis. Furthermore, the key component of the process is the uncovering of $Pd(OAc)_2$ as a promoter, capable of switching the reactivity of NaH from base to a nucleophile. Further studies along this direction are currently underway in our laboratories and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experiment details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interests.

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(15) Pd/C can promote the process (see SI, Table S1, entry 7).

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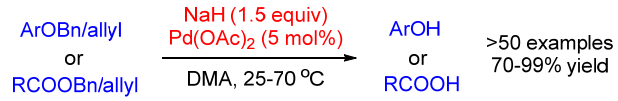

- the first TM catalyzed reduction
- chemoselective removal of aryl ethers
- broad functional group compatibility
- mild reaction conditions
- high reaction yield