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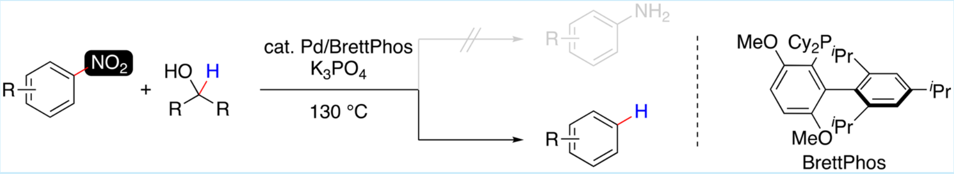
Reductive Denitration of Nitroarenes

Myuto Kashihara, M. Ramu Yadav, and Yoshiaki Nakao*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan

Supporting Information



ABSTRACT: The Pd-catalyzed reductive denitration of nitroarenes has been achieved via a direct cleavage of the C−NO_2 bonds. The catalytic conditions reported exhibit a broad substrate scope and good functional-group compatibility. Notably, the use of inexpensive propan-2-ol as a mild reductant suppresses the competitive formation of anilines, which are normally formed by other conventional reductions. Mechanistic studies have revealed that alcohols serve as efficient hydride donors in this reaction, possibly through β-hydride elimination from palladium alkoxides.

The reductive denitration of nitroarenes via a cleavage of the C−NO_2 bonds is a challenging transformation in organic synthesis. Contrary to the well-established nitration of arenes,[1] examples for the reverse reaction, i.e., the reductive denitration, remain scarce. Previously reported reactions are only applicable to specific substrates, such as highly electron-deficient and amino-substituted nitroarenes, and suffer from low yields of the parent arenes and/or the formation of side products.[2] The difficulties associated with the reductive denitration can be attributed to the inherent reactivity of the nitro group: under reducing conditions nitroarenes are usually converted into anilines and/or other reduced species, such as nitroso compounds and hydroxylamines.[3,4] As a result, the removal of nitro groups on aromatic rings commonly requires the formation of the corresponding anilines and two additional synthetic manipulations, namely diazotization followed by a Sandmeyer-type reaction (Figure 1, path A).[5] Unfortunately, these processes may suffer from a limited substrate scope, as the use of strong acids largely diminishes the functional-group tolerance. Therefore, a more straightforward and general method for the reductive denitration (path B) remains highly attractive. In the chemical industry, the derivatization of fossil aromatic resources often starts with a nitration reaction,[6] and a wide range of nitroarenes is accordingly commercially available from selective nitration reactions followed by S_NAr/S_EAr/VNS and/or *ortho*-selective C−H functionalization reactions,[7,8] which proceed site-selectively thanks to the strong electronic effect of the nitro group. A nitration and decoration sequence for arenes, followed by a single-step denitration reaction under mild conditions, would thus represent an efficient and practical pathway to a diverse range of functionalized arenes starting from simple arenes (Figure 1).

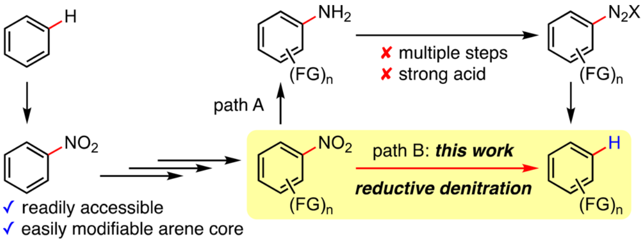


Figure 1. Synthesis of polysubstituted benzenes via the reductive denitration of nitroarenes.

Our group has recently reported Pd-catalyzed C−C and C−N bond-forming coupling reactions using nitroarenes as electrophiles.[9,10] Notably, these reactions proceed via the unprecedented oxidative addition of the Ar−NO_2 bond to Pd(0), where the reduction of the nitro group does not compete. These results inspired us to trap the oxidative adduct with an appropriate hydride source to achieve the single-step denitration. Herein, we report a denitration of nitroarenes that bypasses for the first time the reduction to anilines followed by diazotization and a Sandmeyer-type reaction, using secondary alcohols as sources of the reducing hydride.

Initially, we chose hydrosilanes as hydride sources for the denitration of nitroarenes, given their use in a number of metal-catalyzed defunctionalization reactions.[11] Thus, 4-nitroanisole (**1a**, 0.20 mmol) in DME (1.0 mL) was treated for 12 h at 130 °C with various hydrosilanes in the presence of $Pd(acac)_2$ (5.0 mol %), BrettPhos (**L1**)[12] (10 mol %), and K_3PO_4 (0.50 mmol). Dimethoxymethylsilane (**2a**) and triethylsilane (**2b**) predominantly afforded undesired *p*-anisidine (**3′a**) through the reduction of the nitro group (Table 1, entries 1 and 2), whereas bulkier triisopropylsilane (**2c**) furnished desired anisole (**3a**), albeit only in 3% yield (entry 3). We then focused on the use of alcohols as hydride sources. To our

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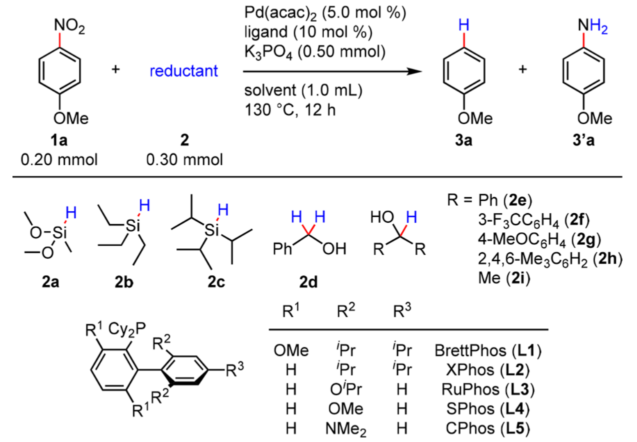
Table 1. Optimization Studies for the Reductive Denitration of 1a

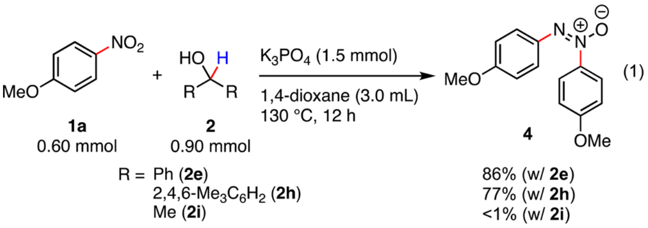


entry	reductant	ligand	solvent	yield (%) 3a[a]	yield (%) 3′a[b]
1	**2a**	**L1**	DME	<1	10
2	**2b**	**L1**	DME	~1	58
3	**2c**	**L1**	DME	3	<1
4	**2d**	**L1**	DME	~1	<1
5	**2e**	**L1**	DME	35	3
6	**2f**	**L1**	DME	<1	6
7	**2g**	**L1**	DME	38	5
8	**2h**	**L1**	DME	60	1
9	**2i**	**L1**	DME	67	~1
10	**2i**	**L1**	1,4-dioxane	68	~1
11	**2i**	**L2**	1,4-dioxane	14	~1
12	**2i**	**L3**	1,4-dioxane	13	~1
13	**2i**	**L4**	1,4-dioxane	6	~1
14	**2i**	**L5**	1,4-dioxane	7	~1

[a] GC yields determined using n-C$_{13}$H$_{28}$ as an internal standard. [b] GC yields estimated based on the yield of p-acetaniside (**3′′a**) after treatment of crude reaction mixtures with acetic anhydride.

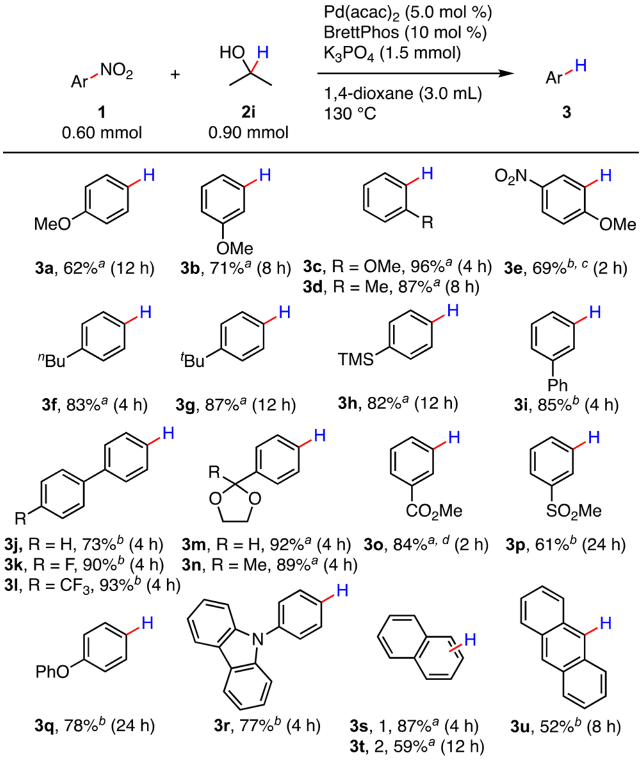
delight, **3a** was obtained in 35% yield with benzhydrol (**2e**), while benzylalcohol (**2d**) generated a trace amount of **3a** (entries 4 and 5). Further optimization studies indicated that a benzhydrol derivative that bears an electron-donating substituent **2g** generates **3a** more effectively than that carrying an electron-withdrawing group **2f** (entries 6 and 7). Sterically demanding dimesitylmethanol (**2h**) significantly improved the yield of **3a** (≤60%), while the formation of **3′a** was suppressed (entry 8). Remarkably, the use of propan-2-ol (**2i**)[13] as a hydride source afforded the best yield of **3a** (67%), accompanied by a mere trace amount of **3′a** (entry 9). The formation of the targeted product was slightly improved in 1,4-dioxane (entry 10). Moreover, other Buchwald-type ligands (**L2**–**L5**)[14] were investigated, but the performance of **L1** was clearly superior (entries 10–14). Hence, we concluded that the conditions shown in entry 10 represent the optimized reaction conditions for this system.

For comparison, control experiments were undertaken in the absence of the catalyst, using various alcohols, which resulted in the formation of azoxy compound **4** as a major product (eq 1).[15] The reaction of **4** with **2i** under the optimized conditions did not give **3a**, showing that it was not a reaction intermediate of the present reductive denitration. The formation of **4** depended significantly on the nature of the alcohol employed: **2e** furnished **4** in high yield (86%), whereas **2h** reacted with **1a** more slowly, while **2i** completely prevented this side reaction (for details, see Supporting Information).



To assess the versatility of this denitration reaction, we probed a wide range of nitroarenes under the optimized conditions (Scheme 1). Electron-rich nitroanisoles were readily converted to the corresponding anisole (**3a**–**3c**) in good to excellent yield. Interestingly, nitro groups in proximity to the methoxy substituent reacted much faster and delivered the product in higher yields. Such rate enhancement was not observed with 2-nitrotoluene to afford toluene (**3d**) after 8 h in 87% yield estimated by GC analysis. This trend is consistent with the denitration of 2,4-dinitroanisole, which selectively furnished 4-nitroanisole (**3e**) in 69% yield. Alkyl, silyl, and phenyl substituents did not interfere with the reaction and furnished arenes **3f**–**3j** in good yields. 4-Fluorobiphenyl (**3k**) and 4-trifluoromethylbiphenyl (**3l**) were obtained from the denitration of the corresponding nitroarenes in 90% and 93% yields, respectively. Nitroarenes bearing protected carbonyl groups or an alkoxycarbonyl functionality were also denitrated

Scheme 1. Substrate Scope for the Reductive Denitration of Nitroarenes



[a] GC yields. [b] Isolated yields. [c] The reaction was undertaken in 1.0 mmol scale, and 1.0 mmol of **2i** was used. The product was accompanied by 8% of 2-nitroanisole (**3e′**). [d] **2h** was used instead of **2i**.

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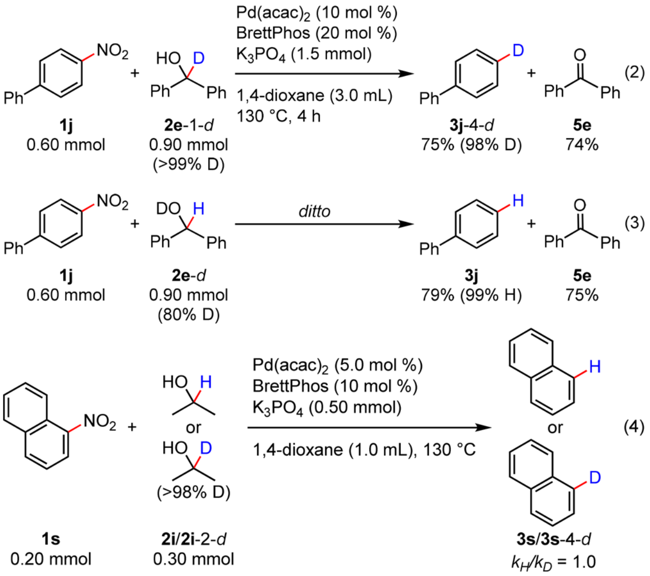
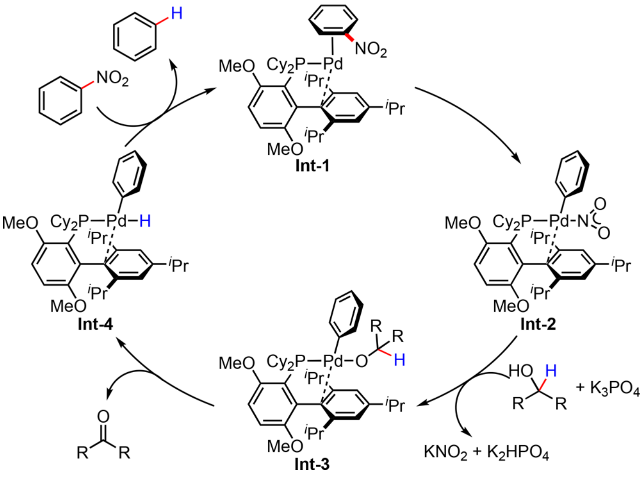
in good yields (**3m**−**3o**); in the latter case, bulky dimesitylmethanol (**2h**) was employed as the reductant in order to avoid a potential ester-exchange reaction. An electron-deficient, sulfonyl-substituted nitrobenzene was also successfully denitrated, although longer reaction times were required to generate **3p**. Phenoxy and carbazolyl moieties, which were easily introduced into the nitroarene core via S_NAr reactions, were also compatible with the applied reaction conditions (**3q** and **3r**). π-Extended nitroarenes, including nitronaphthalenes and nitroanthracene, furnished the corresponding polyaromatics (**3s**−**3u**) in moderate to good yields.[16]

In order to investigate the reaction mechanism underlying this Pd-catalyzed reductive denitration, we carried out deuterium-labeling experiments. The use of benzhydrol deuterated at the benzylic position (Ph_2CDOH, **2e**-1-*d*) as the reductant resulted in the replacement of the nitro group of **1j** by deuterium (97%) and the generation of benzophenone (**5e**) in 74% yield, indicating the involvement of β-hydride elimination (eq 2). Consistently, the use of Ph_2CHOD (**2e**-*d*) as the reductant did not give any deuterated product (eq 3). These reactions giving both arene **3j** and ketone **5e** in comparable yields also support a mass balance of the transformation. Furthermore, we did not observe any kinetic isotopic effect (KIE) when the denitration of **1s** was independently examined using propan-2-ol (**2i**) or deuterated propan-2-ol-2-*d* (**2i**-2-*d*) (eq 4). Based on these results and our previous reports,[9] we postulate a plausible catalytic cycle shown in Scheme 2. The initial formation of a π-complex (**Int-1**) between the nitroarenes and Pd(0) should be followed by the oxidative addition of the C−NO_2 bond to give **Int-2**. The nitrite group on the Pd center would subsequently be substituted by an alkoxide ligand to generate **Int-3**, and ensuing β-hydride elimination would afford arylpalladium hydride **Int-4**. Subsequent reductive elimination would then deliver the corresponding arene and regenerate the Pd(0) catalyst. Our previous studies[9] suggest that a hemilabile coordination of the methoxy group of BrettPhos may not play any important roles throughout the catalytic cycle. The KIE experiment implied that the β-hydride elimination and the reductive elimination are not the rate-determining steps under the stipulated reaction conditions, and that the former is much faster than alternatively possible C−O bond-forming reductive elimination.[17] We cannot discuss a rate-determining step at this stage with available data. Some reactivity differences observed with electronically different nitroarenes as well as our previous theoretical studies[9a] may support that the oxidative addition is rate-determining. The rate acceleration observed with 2-nitroanisole may be derived from the methoxy group serving as a directing group to promote the oxidative addition.



Scheme 2. Plausible Catalytic Cycle for the Reductive Denitration of Nitroarenes



In summary, we have developed the first example of a palladium-catalyzed reductive denitration of nitroarenes. The combination of the Pd/BrettPhos catalyst and appropriate reductants shows good functional-group tolerance and affords denitrated arenes in good to excellent yields. Other important transformations through the direct cleavage of the C−NO_2 bond of nitroarenes are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00430.

Detailed experimental procedures including spectroscopic and analytical data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nakao.yoshiaki.8n@kyoto-u.ac.jp.

ORCID

Yoshiaki Nakao: 0000-0003-4864-3761

Notes

The authors declare no competing financial interest.

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