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Diboron-Assisted Palladium-Catalyzed Transfer Hydrogenation of *N*-Heteroaromatics with Water as Hydrogen Donor and Solvent

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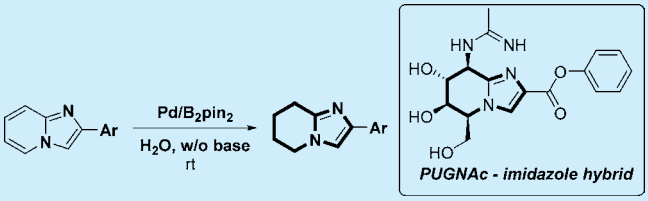
Supporting Information

ABSTRACT: A Pd-catalyzed transfer hydrogenation of various *N*-heteroaromatic compounds with B_2pin_2 as a mediator and environmentally benign water as both solvent and hydrogen donor has been disclosed. This reaction proceeded under ambient temperature with a broad range of *N*-heteroaromatic compounds among which imidazo[1,2-*a*]pyridine derivatives were for the first time selectively reduced to 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines, which are the core structural motifs of an inhibitor of human *O*-GlcNAcase. Mechanistic studies suggested that the new protons in products are from water and Pd−H might be the key intermediate with B_2pin_2 as the H_2O activator.



Since the first transfer hydrogenation (TH) of carbonyl compounds, known as Meerwein−Ponndorf−Verley (MPV) reduction, was published in 1925, various homogeneous and heterogeneous transition-metal catalysts and organocatalysts catalyzed by TH have been successfully developed.[1] However, the "sacrificial" hydrogen sources are limited to alcohols, formic acid, Hantzsch esters, hydrazine, alkanes, and cyclohexene, etc.[2] As the most abundant, environmentally benign, and inexpensive hydrogen-containing source in the world, H_2O would be an ideal hydrogen donor in TH. There is another obvious advantage in the method with water as H donor over other hydrogen sources: deuterium could be easily incorporated into the final products to access D-labeled compounds, which, as we know, are very important materials in pharmaceuticals and life science since D_2O is the most readily accessible deuterium source. However, surprisingly, there are only two elegant methods reported with H_2O as H-donor in TH to date: in 2007, Oltra reported hydrogen/deuterium transfer from H_2O/D_2O to alkenes/alkynes, mediated by Cp_2TiCl with various late transition metals as cocatalysts.[3] Very recently, Stokes developed a Pd/C-catalyzed hydrogen/deuterium transfer from H_2O/D_2O to alkenes/alkynes with $B_2(OH)_4$ as an additive.[4] However, in the above two methods, organic solvents were always required to increase the solubility of the substrates in order to reach high reactivity of the transformations. If water could be served as both solvent and H-donor in TH, it would be even more ideal and desirable.

Saturated and partially saturated *N*-heterocycles play important roles as biologically active building blocks and key intermediates in organic synthesis.[5] Hydrogenation of *N*-heteroaromatic compounds are one of the most important strategies to access these two types of *N*-contained compounds.[6] Many valuable methods had been developed on the reduction of *N*-heteroaromatics. However, transition-metal-catalyzed TH of *N*-heteroaromatics with H_2O as both solvent and hydrogen source has not yet been reported; at the same time, few of the known methods could readily obtain deuterium-labeled *N*-heterocycles with high D-incorportion.

B_2pin_2, which is air stable and inexpensive, has been frequently used as a borylation reagent.[7] Our group is devoted to exploring the new reactivities of B_2pin_2 and has found that α,β-unsaturated ketones can be selectively reduced in the presence of unconjugated C−C unsaturated bonds with Cu/B_2pin_2 system via a domino−borylation−protodeboronation (DBP) strategy with water as the H-donor.[8] Very recently, we successfully converted arylacetylenes into β-phenylethyl boronates with B_2pin_2 under transition-metal-free basic conditions, once again, via DBP strategy.[9] These two results inspired us, and we envisioned that B_2pin_2 might assist the reduction of *N*-heteroaromatic compounds by transferring the hydrogen/deuterium from H_2O/D_2O to the substrates via DBP strategy. As part of our ongoing interest in the new reactivity of diboron reagent, we report herein an expedient pathway for the hydrogenations of *N*-heteroaromatic compounds by employing H_2O as both solvent and hydrogen source at ambient temperature (Scheme 1).

To initiate the study, quinoline (**1a**) was chosen as a model substrate. At first, CuBr in company with Cs_2CO_3 was chosen as catalyst; in the presence of 2 equiv of B_2pin_2, the reaction only gave the hydrogenation product **2a** in 18% yield (Table 1, entry 1). When $Pd(OAc)_2$ was used in place of CuBr, the loading of B_2pin_2 was increased to 3 equiv and the yield of **2a** was improved to 62% (Table 1, entry 3). To our delight, when

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Scheme 1. Our Approach on Transfer Hydrogenation of *N*-Heteroaromatics

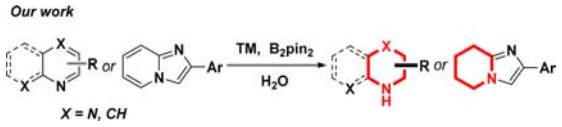
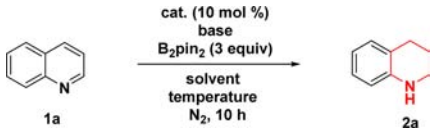


Table 1. Reaction Optimization[a]



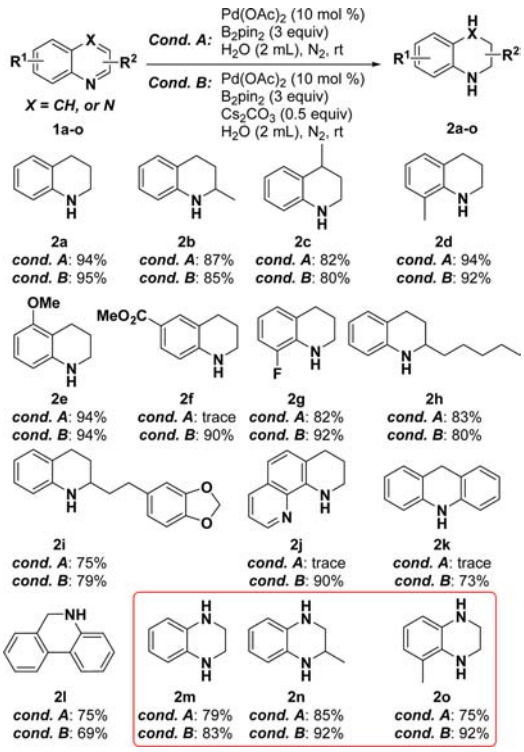
entry	metal	base (x equiv)	solvent	temp (°C)	yield[b] (%)
1[c]	CuBr	Cs_2CO_3 (2)	CH_3CN	60	18
2[c]	$Pd(OAc)_2$	Cs_2CO_3(2)	CH_3CN	60	42
3	$Pd(OAc)_2$	Cs_2CO_3(2)	CH_3CN	60	62
4[d]	$Pd(OAc)_2$	Cs_2CO_3(2)	CH_3CN	60	<10
5	$Pd(OAc)_2$	Cs_2CO_3 (2)	CH_3CN/H_2O (1:1)	60	95
6	$Pd(OAc)_2$	Cs_2CO_3(0.5)	CH_3CN/H_2O (1:1)	60	93
7	$Pd(OAc)_2$	Cs_2CO_3(0.5)	H_2O	60	94
8	$Pd(OAc)_2$	Cs_2CO_3(0.5)	H_2O	rt	94
9	**$Pd(OAc)_2$**		**H_2O**	**rt**	**95**
10		Cs_2CO_3(0.5)	H_2O	rt	42
11[e]	$Pd(OAc)_2$		H_2O	rt	trace
12[f]	$Pd(OAc)_2$		H_2O	rt	92

[a]General procedure: **1a** (0.2 mmol), B_2pin_2 (0.6 mmol), solvent (2 mL), under N_2. [b]Isolated yield. [c]B_2pin_2 (0.4 mmol). [d]PPh_3 (0.04 mmol) was used. [e]Under air. [f]B_2pin_2 was replaced with $B_2(OH)_4$ (0.6 mmol).

the solvent was changed to CH_3CN/H_2O (1:1), the reaction proceeded smoothly, affording **2a** in 95% yield. Next, we attempted to study the effects of the amount of Cs_2CO_3 and the temperature. Seemingly, the amount of Cs_2CO_3 had no impact on the hydrogenation of **1a**, and the reaction proceeded well in water, even at room temperature, to give **2a** in 94−95% yield (Table 1, entries 8 and 9, conditions B and A). However, when the reaction was carried out in the presence of Cs_2CO_3 alone, it could also give **2a** in 42% yield (Table 1, entry 10). It seemed that the reaction mechanism might be different from what we envisioned (entry 9 vs entry 10). In the later research of substrate scope, we found that some substrates can only afford satisfied results in the presence of both $Pd(OAc)_2$ and Cs_2CO_3 (Scheme 2). The result indicated that base, which would promote the transmetalation process of B_2pin_2, indeed had some equivocal effects on our reactions. Air was detrimental to the hydrogenation reaction (Table 1, entry 11), which suggested that an air-sensitive intermediate might be formed in the reaction process. Other metal salts were also screened, but none of them afforded results as satisfying as $Pd(OAc)_2$ did (Supporting Information). $B_2(OH)_4$, which has a bad smell and is more expensive than B_2pin_2, could also give **2a** in 92% yield (Table 1, entry 12).

Subsequently, the optimized conditions were used for further evaluation of the substrate scope (Scheme 2). Various quinoline-derived substrates were subjected to the hydrogenation reactions and smoothly converted into 1,2,3,4-tetrahydroquinolines. The substituents at the 2,4-positions of the quinolines slightly influenced the yields; however, they both

Scheme 2. Hydrogenation of Quinoline- and Quinoxaline-Derived Substrates[a]



[a]All reactions were carried out with **1** (0.2 mmol), and isolated yields are reported.

could afford the desired products in good to excellent yields under conditions A (Table 1, entry 9) and B (Table 1, entry 8). The electronic effects of the substituents on the aromatic ring affected the hydrogenation largely under conditions A (Scheme 2, **2f**). We think that the substrates/products might act as bases and ligands, which could assist the transmetalation process of B_2pin_2. When strong electron-withdrawing groups were present, the basicity of the substrates/products declined and the reaction required extra base. It is noteworthy that **2h** and **2i**, which were isolated from the trunk bark of the South American tree *Galipea officinalis* and showed antimalarial activity, could be successfully accessed under our reaction conditions.[5] Luckily, some polycyclic aromatic compounds could react smoothly, offering the hydrogenated products in good yields (Scheme 2, **2j−l**). It is worth mentioning that **2l**, which could be obtained from phenanthridine, can act as the substitute for Hantzsch esters.[10] Tetrahydroquinoxalines are very useful moieties and present in a wide range of biologically and medicinally active compounds.[11] We were glad to discover that quinoxalines could be smoothly hydrogenated under our conditions and afforded tetrahydroquinoxalines in high yields (Scheme 2, **2m−o**).

Although hydrogenation of quinoline- and quinoxaline-derived substrates has been widely reported,[12] the TH of imidazo[1,2-*a*]pyridines were barely known despite the importance of these compounds in pharmaceutical and synthetic organic chemistry. Delightfully, some imidazo[1,2-*a*]pyridines smoothly underwent a hydrogenation process to afford 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines in excellent yields under our reaction conditions (Scheme 3). We discovered that this reaction process showed an "on-water"

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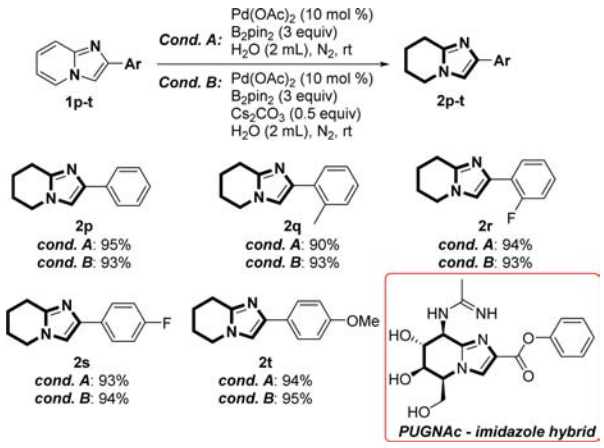
Scheme 3. Hydrogenation of Imidazo[1,2-*a*]pyridine-Derived Substrates[a]



[a]All reactions were carried out with **1** (0.2 mmol) and the reported yields were isolated.

effect (Supporting Information). It is noteworthy that the products **2p−t** are important constitutional units of the PUGNAc−imidazole hybrid, which is an inhibitor of human *O*-GlcNAcase.[13]

Noteworthy and interestingly, other *N*-heteroaromatic compounds could also afford useful products. For example, 5-naphthyridine could selectively hydrogenate one pyridine ring into compound **2u** under conditions A (Figure 1), and

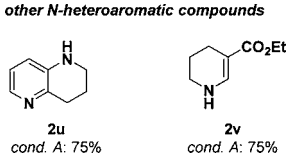


Figure 1. Hydrogenation of other *N*-heteroaromatics under conditions A.

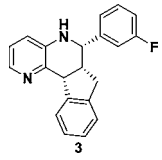


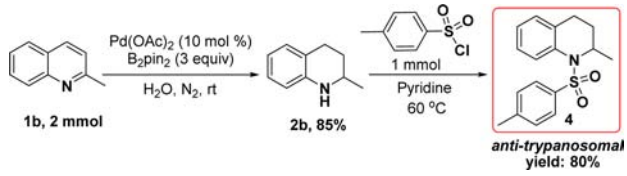
Figure 2. Structure of topoisomerase **I** inhibitor **3**.

compound **2u** is a core unit of compound **3** (Figure 2), which is proven to be able to inhibit topoisomerase I activity.[14] It needs to be pointed out that pyridine with electron-withdrawing CO_2Et at the 3-position could be only partially hydrogenated to afford compound **2v** under conditions A.[15]

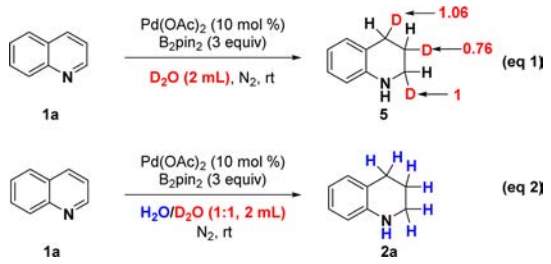
A large-scale experiment was also carried out with 2-methylquinoline (**1b**) under conditions A, and it offered the desired product **2b** in 85% yield. Followed by sulfonylation, compound **4**, which showed antitrypanosomal activity,[5] could be readily obtained in 80% yield (Scheme 4).

In order to understand the origin of hydrogen in the transformations, deuterium-labeled experiments were carried out with **1a** under various conditions (Scheme 5). Trideuterated **5** was obtained with very high deuterium incorporation

Scheme 4. Large Scale Synthesis of *anti*-Trypanosomal 4



Scheme 5. Deuterium-Labeled Experiments



when H_2O was replaced by D_2O under the standard conditions A (eq 1). This result clearly demonstrated that water is the H-donor for this hydrogenation reaction. When the reaction was conducted with the mixture of H_2O/D_2O (1:1), interestingly, only product **2a** was obtained, and no deuterium was incorporated into the final product at all (eq 2). This reaction suggested that H atom transfer might be the rate-determing step (rds) in the entire hydrogenation pathway, which is consistent with the previous report.[3]

There are two possible pathways that could transfer H onto the *N*-heteroaromatic compounds: the first one is domino−borylation−protodeboronation (DBP) as we reported in our previous studies.[8,9] However, as far as we know, all protodeboronation proceeded under basic or F^- anion conditions with elevated temperatures, and in some cases, benzylic positions are critical for the success of protodeboronation.[16] In our transformation, conditions A are neutral, both conditions were conducted at ambient temperature, and the benzylic position is not always used. Therefore, we have reason to believe that our transformation could not proceed via a DBP process. The second pathway is via M−H insertion over *N*-heteroaromatic compounds, in which M−H was formed in situ via transfer hydrogenation from H_2O to transition metal via the assistance of a mediator; in our case, B_2pin_2 acts in that role.

On the basis of all of experiments as well as precedent reports,[3,4] we proposed a tentative mechanism which is shown in Scheme 6: the reaction is initiated by transmetalation between $Pd(OAc)_2$ and B_2pin_2, leading to intermediate **I** in situ. The intermediate **I** would readily form complex **II** with H_2O, which might facilitate the H atom transfer from H_2O to palladium, affording [Pd−H] species **III**. Then, quinoline would coordinate with **III** to give complex **IV**, followed by 1,5-hydride transfer to afford the intermediate **V**. Subsequently, the hydrolysis of intermediate **V** gives enamine **A** and generated $[Pd]^{II}$, which then interacts with B_2pin_2 and H_2O to regenerate [Pd−H] species **III** and release HOBpin.[17] The formed enamine **A** is isomerized to imine **B**, which would coordinate with **III** to give complex **VI**. Subsequent insertion of [Pd−H] to the C=N bond forms intermediate **VII**. Finally, the 1,2,3,4-tetrahydroquinoline is released via hydrolysis with H_2O as the H-donor.

In conclusion, we successfully developed a novel Pd-catalyzed transfer hydrogenation of various *N*-heteroaromatic

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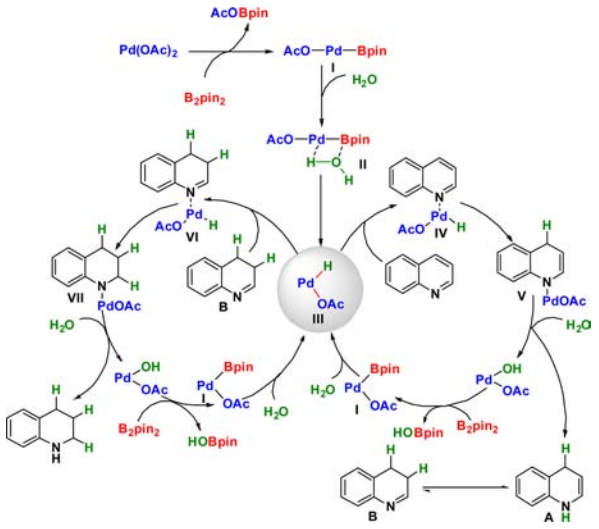
Scheme 6. Plausible Mechanisms



compounds with B_2pin_2 as mediator and H_2O as both solvent and H-donor at ambient temperature. A myriad of *N*-heteroaromatic compounds could be selectively reduced with a broad functional groups tolerance in good to excellent yields. For the first time, imidazo[1,2-*a*]pyridine derivatives have been successfully reduced with good chemoselectivity rendering 5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridines which are the core structure of an inhibitor of human *O*-GlcNAcase. This reaction could be easily scaled up without loss of its efficiency. Broad substrates scope, mild reaction conditions, environmentally benign H-donor, and simple operations feature the reaction and make it an alternative way to the existing TH methods. Further studies on the detailed mechanism and applications on other systems with this novel catalytic system will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01999.

Procedures, characterization, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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(17) HOBpin was detected by ^{11}B NMR spectra in the crude reaction mixture using conditions A. See the Supporting Information for details.

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