

Metal-Carbon Covalent Bonds Stabilized Palladium Nanoparticles as Expeditious Heterogeneous Catalyst for Oxidative Dehydrogenation of *N*-Heterocycles

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Dedication ((optional))

Abstract: We reveal here the first dehydrogenation of nitrogen heterocycles catalyzed by a palladium nanocatalyst. The carbon-metal covalent bonds-stabilized nanoparticles were proved to be efficient for the dehydrogenation process in the existence of TBHP. A variety of *N*-heterocycles were transformed into functionalized quinolines with medium to excellent yields in water solvent under mild conditions with simple operation.

The quinoline ring is one of the most ubiquitous heterocycles found in numerous natural products, forming the scaffold for compounds that exhibit diverse biological and therapeutic activities.^[1] lts hydrogenation product, 1,2,3,4tetrahydroquinoline, is also a core structural motif in alkaloids and other bioactive molecules, displaying wide applications in agricultural, pharmaceutical and fine chemistry.^[2] Given the importance of these nitrogen-containing heterocycles, the last few years have witnessed the development of various methods to produce compounds containing quinoline as well as 1,2,3,4tetrahydroquinoline skeletons. Catalytic dehydrogenation (CDH) and hydrogenation reactions, most often catalyzed by metal complexes, represent an atom-efficient way for the conversion between these N-heterocycles with only H₂ generated/used.^[3] Sometimes, CDH process is even more challenging and oxidant may be necessary as acceptor for H₂ to promote the equilibrium in CDH reaction, as the dehydrogenation of N-heterocycles was proved to be a thermodynamically uphill process at ambient conditions.^[4] Despite of the various studies on hydrogenations in recent years, CDH process, especially for N-heterocycles, has been less well established as harch condiitons are usually required.

A pioneering work was reported by Fujita and Yamaguchi, in which a homogeneous catalytic system involving [Cp*Ir] catalyst was developed for dehydrogenation-hydrogenation reactions of *N*-heterocycles in refluxing *p*-xylene (Scheme 1a).^[5] Though the reaction condition is not ideal, catalyst capable of both hydrogenation and dehydrogenation is rather rare. After that, metal complexes including iron,^[6] cobalt,^[4a,7] nickel ^[8] and

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ruthenium ^[9] were further developed in addition to some other iridium catalysts ^[10] for dehydrogenation systems. To be noted, the first Cu-catalyzed dehydrogenation system was studied very recently, consisting of homogeneous Cul, di-tert-butyl azodicarboxylate (DBAD) and molecular oxygen (Scheme 1b).^[11] Despite of the great progress, most of these metal catalyzed systems, require harsh conditions such as high temperature, toxic organic solvents and show limited functional-group tolerance. Considering the importance of quinoline and its derivatives as well as the current deficiency, it is still urgent and challenging to develop innovative catalytic de/hydragenation transformations under mild and clean conditions with high efficiency.





Scheme 1. Representative studies on metal catalyzed dehydrogenation process.

During the past decade, a growing interest has been attracted on the development of palladium-based organometallic catalysts for organic synthesis, with de/hydration transformations also involved. For representative examples, Stahl and his coworkers reported a Pd-catalyzed method for dehydrogenation of cyclohexanones to phenols (Scheme 1c),^[12] after which analogous approaches were developed to access other compounds including cyclohexenes,^[13] aryl ethers,^[14], esters and nitriles,^[15] aniline derivatives and so on.^[16] But for *N*-heterocycles and their derivatives, despite of the achievement gained in hydrogenation process, examples are still scarce for CDH transformations.^[17] Recently, we prepared a palladium nanocatalyst stabilized by carbon–metal covalent bonds (Pd=NPs), with which hydrogenation of quinoline was enabled in water under mild condition.^[18] The nano-catalytic heterogeneous

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system was highlighted featuring in the high efficiency as well as catalyst recycling.

Inspired by the leading results, it was thought to be amazing if the reverse reaction could be achieved with the same nanocatalyst to obtain quinoline from dehydrogenation of tetrahydroquinoline. Hence, as our continuous efforts to discover challenging de/hydrogenation transformations,^[19] and to pursue clean, mild and efficient catalytic strategies for sustainable chemistry, herein, we report a highly efficient dehydrogenation process with Pd nanoparticles as catalyst and *tert*-butyl hydroperoxide (TBHP) as oxidant for tetrahydroquinoline and its derivatives in water (Scheme 1d). To the best of our knowledge, this is the first example of palladium catalyzed dehydrogenation of *N*- heterocycles at room temperature in water solvent.

In our initial evaluation of oxidative dehydrogenation conditions, 2-methyl-1,2,3,4-tetrahydroquinoline was used as model substrate with 4 mmol % Pd=NPs as catalyst and 2 equivalents of TBHP as oxidant (see Table S1 in the Supporting Information for full screening data). It was delight to discover that 2-methyl-quinoline was generated in 31% yield in water at room temperature. Excessive TBHP could further increase the result and over 95% yield was achieved with eight equivalents TBHP (Table 1, entries 1-3). TBHP was supposed to play an important role serving as the acceptor of H₂, so as to promote the equilibrium for dehydrogenation. It is noteworthy that Pd=NPs outperformed some other metal precursors such as Iridium nano-catalyst,^[20] palladium-based catalysts,^[21] or copper catalysts^[22] (entries 4-12), suggesting the high efficiency of the nano-catalyst. Afterwards, several oxidants of both organic and inorganic were screened, with TBHP still exhibiting the best performance (entries 13-15). In addition to water, organic CH₃OH, solvents. including toluene, 1.4-dioxane. tetrahydrofuran, and dichloromethane were also tested and though enabled the dehydrogenation, lower yields were obtained ranging from 13 to 73% (entries 16-19). Eventually, the observations indicated that water was the best solvent with Pd=NPs as catalyst and TBHP as oxidant at room temperature, giving the product in yield of over 95%.

Table 1 Optimization of reaction conditions.^[a]

entry	Catalyst	Oxidant /equiv	Solvent	yield (%) ^[b]
1	Pd=NPs	TBHP/2	H ₂ O	31
2	Pd=NPs	TBHP/5	H ₂ O	77
3	Pd=NPs	TBHP/8	H ₂ O	>95
4	Ir=NPs	TBHP/8	H ₂ O	trace
5	Pd/C	TBHP/8	H ₂ O	47
6	Pd(OAc) ₂	TBHP/8	H ₂ O	6
7	Pd(OAc) ₂ /4,5-	TBHP/8	H ₂ O	13
	diazafluoren-9-one		W.	
8	Pd(PPh ₃) ₂ Cl ₂	TBHP/8	H ₂ O	17
9	Pd(PPh ₃) ₄	TBHP/8	H ₂ O	trace
10	Cul/bpy/TEMPO	TBHP/8	H_2O	65
11	CuBr/bpy/TEMPO	TBHP/8	H_2O	91
12	CuCl/bpy/TEMPO	TBHP/8	H_2O	78
13	Pd=NPs	Ag ₂ O/8	H_2O	74
14	Pd=NPs	DTBP/8	H_2O	trace
15	Pd=NPs	H ₂ O ₂ /8	H ₂ O	59
16	Pd=NPs	TBHP/8	CH₃OH	47
17	Pd=NPs	TBHP/8	toluene	13

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18	Pd=NPs	TBHP/8	THF	32	
19	Pd=NPs	TBHP/8	DCM	73	

[a] Reaction conditions: 2-methyltetrahydroquinolines (0.3 mmol), H_2O (2 mL), Pd NP (15 mg, 0.0125 mmol, 4% of substrate), TBHP (8 equiv), r.t., 18 h; [b] Yields were determined by ¹H-NMR.

After the promising initial results, subsequent efforts were devoted to examine the applicability of this protocol. Under the optimized conditions, substrates were extended to various structurally differently substituted tetrahydroquinolines with 8 equivalents of TBHP in water. As shown in Scheme 2, tetrahydroquinloines bearing electron-donating substituents (OMe, NH₂, OH) on both pyridine ring and benzene ring performed well in the system giving corresponding quinolines in good to excellent yields (2a-2m). The outcome showed that the dehydrogenation process was not significantly affected by varying the position of the same substituent, e.g. a methyl group on 2, 3, 4- position of the pyridine moiety or 6-, 7-, 8- position of the benzene moiety. Electron-deficient groups, including carboxylate-, bromo-, and chloro- substitutions, retarded the dehydrogenation process dramatically, but still exhibited great selectivity with these groups remained intact without hydrolysis or cleavage (2n-2p). Only 39% yield of 8-chlorotetrahydroquinolines was observed even improving to temperature to 80°C (2p). It was supposed that electron-deficient groups impair the electron density of aromatic rings, leading to a more difficult coordination of substrates with Pd NP catalyst. These observations highlight the advantages of this palladium nanocatalyst over Pd/C for dehydrogenations reactions, as the latter can promote undesired reactivity with aryl halides, and the -CI and -Br substituents are appealing functional groups for subsequent derivatization.^[7b] 3-phenyl substituted tetraquinoline also performed well in this system, giving the corresponding quinoline in 76% yield.

Scheme 2. Scope of the dehydrogenation of quinoline derivatives $^{\left[a\right] }$



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[a] Reaction conditions: tetrahydroquinolines (0.3 mmol), H_2O (2 mL), Pd NP (15 mg, 0.0125 mmol, 4% of substrate), TBHP (8 eq), r.t., 18 h; [b] Isolated yields.

[c] The reaction was carried out at 80°C.

Encouraged by these results, the substrates scope with regard to other N-heterocycles was further evaluated as listed in Scheme 3. Substituted quinoxaline, acridine, 1.10phenanthroline, benzoquinoline could be obtained in this dehydrogenation process from their corresponding heterocycles. Tetrabenzoquinoline gave excellent vields to dehydrogenation product (2w). Tetrahydroacridine as well as tetrahydro-1.10phenanthroline enabled the reaction with comparable results to tetrahydroquinoline of good to excellent yields (2x-2z). As for Tetrahydroquinoxalines, the yields were relatively impaired and high temperature was needed in some cases to achieve the process (2r-2v). Only 49% yield was obtained for 2-phenyl quinoxaline derivative even at 80°C, probably due to the steric effect.

Scheme 3. Pd-NPs-catalyzed dehydrogenation of nitrogen heterocycles ^[a]



[a] Reaction conditions: tetrahydroquinolines (0.3 mmol), H₂O (2 mL), Pd NP (15 mg, 0.0125 mmol, 4% of substrate), TBHP (8 eq), r.t., 18 h;
[b] Isolated yield.

[c] The reaction was carried out at 80°C.

Elaboration of the detailed mechanistic pathway will undoubtedly allow further optimization of this dehydrogenation system. In the present case, a detailed mechanism for the overall catalytic process cannot be clealy elucidated yet, but a plausible route was proposed as outlined in Scheme 4. The computational results showed that the energy gap between tetraquinoline (1a) and 1,2-dihydroquinoline (3a) (120.8 kJ/mol) is relatively lower compared with that of 2,3-dihydroquinoline (4a) (121.8 kJ/mol) or 3,4-dihydroquinoline (5a) (128.9 kJ/mol). It was deduced that the dehydrogenation started from the coordination of Pd=NPs to nitrogen, followed by beta-hydride elimination with TBHP as accpetor of hydrogen. The result coinsides with the concept that nitrogen atoms strongly promote the dehydrogenation with H_2 evolution.^[4,23] Adsorption is considered to be a crucial and initial step for nano-catalysis and the dehydrogenation was supposed to experience the adsorption of substrate onto the surface of Pd=NPs, as almost no reaction happened with Pd(OAc)₂ catalyts. Afterwards, the isomerization among **3a**, **4a**, **5a** was available due to the small energy gap and the dehydrogenation process occurred again at 2-position to give the target product. This also explains why excessive amount of TBHP is necessary.



Scheme 4. A plausible route for dehydrogenation process.

Eventually, the reusability of this nanocatalyst was examined with 2-methylquinoline as model substrate. After the termination of dehydrogenation process, the product or any substrate remaining in the mixture was extracted with ether before analysis by ¹H NMR. The nano-catalyst was then recovered by extraction with dichloromethane due to the hydrophobicity of Pd=NPs, and reused without further treatment. By the addition a new batch of 2-methylquinoline and TBHP, the recovered nanocatalyst can be used for at least 5 times without obvious loss of reactivity or selectivity.

In summary, a simple and expeditious dehydrogenation process of tetraquinolines as well as derivative *N*-heterocycles was disclosed here using a metal-carbon stabilized palladium nanoparticles as catalyst. The reaction was achieved in mild conditions in water solvent at room temperature. Great substrate tolarance was exhibited including a broad range of quionlines, quinoxaline, acridine, 1,10-phenanthroline, benzoquinoline. In addition to its high efficiency, the Pd=NPs could be easily recovered and reused owning to the heterogeneous nature. It is believed that this protocol, together with the reverse hydrogenation process, may have fundamental implications Pd catalytic chemistry and potential for industrial purpose.

Experimental Section

Preparation of the metal-carbon bond stabilized palladium nanocatalyst was prepared and characterized according to our previous studies.^[18] For the dehydrogenation process, to a 10 mL vial was added *N*-heterocycles (0.3 mmol), water (1 mL), TBHP (8 eq, 303 mg) and Pd=NP (4% of the substrate, 15 mg, 0.0125 mmol). The system was sealed and kept at room temperature for 18 h. After being finished, the product or any substrate left was extracted with ethyl acetate (1 mLx3) before further purification on flash chromatography or analysis by ¹H-NMR.

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Entry for the Table of Contents (Please choose one layout)

Layout 1:

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Text for Table of Contents

The first nano-Pd catalyzed dehydrogenation of *N*-heterocycles was reported, with mild reaction conditions, good substrate tolerance and efficient catalyst recycling.



First Pd nano-catalyzed dehydrogenation of *N*-heterocycles
Up to 26 examples with good to excellent yields
Mild reaction conditions with efficient recycling

Xiao-Tao Sun,⁺ Jie Zhu,⁺ Yun-Tao Xia, Lei Wu^{*}

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