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Convenient semihydrogenation of azoarenes to hydrazoarenes using H_2 [†]

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The high atom-economical and eco-benign nature of hydrogenation reactions make them much more superior to conventional reduction and transfer hydrogenation. Herein, a convenient and highly selective hydrogenation reaction of azoarenes using molecular hydrogen to access diverse hydrazoarenes is reported. The present catalytic method is general and operationally simple, and it operates under exceedingly mild conditions (room temperature and 1 atm of hydrogen pressure). The reusability of catalysts used in this method is also successfully demonstrated.

Hydrazoarenes are important industrial chemicals used in the manufacture of dyes and pigments.1 These chemicals have numerous applications in pharmaceuticals (Fig. 1),² supramolecular chemistry,³ and synthesis of highly substituted aniline derivatives.⁴ Conventionally, hydrazoarenes are prepared by selective reduction of azo compounds; however, the formation of over-reduced anilines is of primary concern. Classical reduction methods of azoarenes involve the use of a stoichiometric amount of highly reactive metals/metal salts such as Mg, Zn, SmI₂, or toxic trialkyltin hydride, which produce copious metal salt waste (Scheme 1).⁵ Selective reduction of azo compounds to hydrazobenzenes using hydrazine, borane or sodium dithionite as reducing agents is also established.⁶⁻⁸ Wang and co-workers have reported the reduction of azobenzenes using NaBH₄ as a reductant and FeSx/Al₂O₃ as a catalyst.9 Unfortunately, this process has limited substrate scope and poor functional group compatibility due to the use of a stoichiometric amount of the reducing agent. The Schmöger research group reported palladium-catalyzed hydrogenation of azoarenes using hydrazine and H₂ gas; however, the reaction is

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unselective.¹⁰ The research groups of Shiraishi,^{11a} Wu,^{11b} and Zhu^{11c} have independently reported visible-light photocatalytic transfer hydrogenation of azobenzenes to hydrazoarenes. Notably, the research groups of Li^{12a} and Kinjo^{12b} have independently reported catalytic hydrogenation of azoarenes using boranes as the transfer hydrogenating reagent. Borylation or silaborations of azoarenes followed by hydrolysis to access hydrazobenzene is reported by the research group of Spencer.¹³

Recently, the research groups of Landaeta,^{14a} Radosevich,^{14b} and Cornella^{14c} have independently reported catalytic transfer hydrogenation of azoarenes to hydrazobenzenes using ammonia-borane as an efficient reducing agent.



Fig. 1 Importance of hydrazobenzenes (selected examples).



Scheme 1 Hydrogenation/reduction of azoarenes.

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The Landaeta and Radosevich groups have used a phosphorus (III) based precatalyst whereas the Cornella group has used a Bi (I)-pincer complex as the catalyst. However, the use of an expensive reductant in excess amounts and prolonged reaction time are the major limitations. Thus, these methods are neither economical nor environmentally friendly. In this regard, the development of a general catalytic method is highly desired for selective hydrogenation of azoarenes^{15,16} to hydrazoarenes using H₂ gas. Typically, catalytic hydrogenation reactions produce few or zero by-products. The high atomeconomical and eco-benign nature of hydrogenation reactions make them much more superior to conventional reduction and transfer hydrogenation. Herein, an efficient, highly selective hydrogenation of azoarenes at room-temperature using molecular hydrogen to access diverse hydrazoarenes is demonstrated. The present catalytic method is operationally simple and operates under mild conditions. This direct hydrogenation exhibits a wide substrate scope and excellent functional group compatibility that is easy to scale up.

Initially, a simple unsubstituted azobenzene **1a** was chosen as a model substrate for the catalytic hydrogenation reaction. After careful investigation of various parameters, such as the use of catalysts and their loading, additives, and solvents (Table 1), the optimal reaction conditions for the selective hydrogenation of azobenzene (**1a**) to hydrazobenzene (**2a**) were determined (Table 1, entry 1; 0.2% loading of Pd/C, 10 mol% of pyridine, MeOH, and 1 atm of H_2). A series of control experiments were carried out to confirm the necessity of each of the reaction components such as the catalyst, additive or co-catalyst, and solvent. No formation of the product was observed in

 Table 1
 Optimization studies^a

N _{2N}	cat. Pd/C cat. Pyridine H ₂ (1 atm), MeOH		NH ₂
1a	rt, 15 min	2a	2a'

Entry	Variation from initial conditions	Yield % $(2a:2a')^{2}$ 98 (94) ^c	
1	None		
2	In the absence of Pd/C	NR	
3	In the absence of pyridine	23	
4	2-Methylpyridine instead of pyridine	56(50:50)	
5	DMAP instead of pyridine	89	
6	Et ₃ N instead of pyridine	60	
7	5 mol% of pyridine	57	
8	100 mol% of pyridine	36	
9	Toluene instead of MeOH	45	
10	THF instead of MeOH	Trace	
11	DMC instead of MeOH	NR	
12	Ru/C instead of Pd/C	Trace	
13	Rh/C instead of Pd/C	40(50:50)	
14	Pt/C instead of Pd/C	68 (36:65)	
15	Pd/Al ₂ O ₃ instead of Pd/C	28	
16	$Pd(OAc)_2$ instead of Pd/C	NR	
17	0.1 mol ⁹ of Pd loading	72	

^{*a*} Reaction conditions: 0.5 mmol of **1a**, 2.1 mg of 5 wt% Pd/C (0.2% of Pd loading), 10 mol% pyridine, 10 mL of anhydrous MeOH, H₂ (1 atm), room temperature, 15 min. ^{*b*} NMR yield using 1,4-dibromobutane as an internal standard. ^{*c*} Isolated yield. NR = no reaction.

the absence of Pd-catalyst (Table 1, entry 2). The role of an additive is very important for this reaction. Among the various additives screened under standard reaction conditions, pyridine was found to be optimal (Table 1, entries 1, and 4–6). The absence of additive or lowering of its mol% resulted in a lower product yield, and the rate of the reaction was sluggish (Table 1, entries 3 and 7). We did not observe any other side products except for hydrazobenzene, aniline, and unreacted azobenzene under our catalytic conditions.

Among several solvents screened, methanol was found to be optimal for this reaction and offered the maximum yield of the product (Table 1, entries 1, 9-11). It is well understood that hydrogen adsorption and activation have been accelerated by protic solvents.¹⁷ In addition, several possible reasons can be proposed to explain the effect of solvents, such as the solubility of hydrogen in reaction media, competitive adsorption of solvent at active catalyst sites, and intermolecular interaction between the reactant and solvent molecules.¹⁸ Indeed, the other possibility is that the azobenzene protons hydrogenbond with methanol thereby activating the -N=N- bond (diazo bond). A similar solvent effect was also observed by Hirota in the Pd/C-catalyzed cleavage of silyl ethers.¹⁹ Notably, other catalysts including Pd/Al₂O₃ were found unsuitable for this selective hydrogenation reaction (Table 1, entries 1, 12-16). A decrease in Pd/C catalyst loading reduced the yield of 2a (Table 1, entry 18). The research groups of Groppo²⁰ and Xia²¹ have independently demonstrated the effect of surface chemistry on the performances of Pd-based catalysts supported on activated carbons. Based on these reports, we believe that a weak interaction between planar p-electrons of sp² hybridized N-atom and the carbon support helps the adsorption of azocompounds on the carbon matrix, and thus Pd/C shows enhanced activity in the semihydrogenation of azoarenes.

Having optimal reaction conditions in hand, the scope of various aromatic azoarenes was investigated under the optimized reaction conditions. The present direct hydrogenation showed a wide substrate scope and broad functional group tolerance under operationally facile conditions. This reaction offers a mild and environmentally benign approach for the library synthesis of 1,2-diarylhydrazine derivatives in good to excellent yields (up to 96%). Notably, the electron-donating as well as electron-withdrawing groups at different positions of the aromatic ring of the 1,2-diaryldiazene derivatives did not affect the reactivity in the catalytic hydrogenation. The unsymmetrical ortho-substituted azobenzene derivatives (o-Cl and o-Et) proceeded smoothly to selectively afford the semi-hydrogenated products 2b and 2c in excellent yields. Similarly, unsymmetrical meta-substituted substrates (-F, -Cl, and -NHAc) provided the corresponding hydrogenated products in good to excellent yields (up to 95%; Table 2, products 2d-2f). The azoarenes bearing electron-withdrawing groups at the para-position of the aryl ring, such as -F, -Cl, -Br, -CF₃, and -CO₂Me smoothly proceeded the hydrogenation reaction under the optimal reaction conditions and led to the corresponding products in 69%-96% isolated yields (Table 2, pro-

Table 2 Highly selective direct hydrogenation of azoarenes^a



^{*a*} Reaction conditions: 0.5 mmol of **1a–u**, 2.1 mg of 5 wt% Pd/C (0.2% of Pd loading), 10 mol% pyridine, 10 mL of anhydrous MeOH, H₂ (1 atm), room temperature, 15 min and the represented yields are isolated yields. ^{*b*} 30 min. ^{*c*} 4.2 mg of Pd/C (0.4% of Pd loading). ^{*d*} 6.3 mg of Pd/C (0.6% of Pd loading).

ducts 2g-2j, and 2n). It is noteworthy that there is no formation of dehalogenated products under the present catalytic conditions. Similarly, substrates with electron-donating groups also showed excellent reactivity towards the semihydrogenation reaction. Thus, electron-rich para-substituted azoarenes (p-EtO, p-NHPiv, and p-OPiv) proceeded well and yielded the corresponding 1,2-diarylhydrazine derivatives in excellent yields (Table 2, products 2k-2m). Significantly, the reducible acyl group was unaffected under our reaction conditions. Thus, the azoarenes 10 and 1u selectively yielded the -N=Nbond hydrogenated products in very good yields (products 20 and 2u in 88% and 75% yields, respectively). Notably, both symmetrical and unsymmetrical di-substituted azoarenes were reacted efficiently under the optimized conditions to yield the corresponding hydrazo derivatives in good to excellent yields (Table 2, products 2p-2t).

Not only is this catalytic method limited to the aromatic azoarenes but also the heteroaromatic azoarenes are selectively hydrogenated under the optimal conditions and yielded the desired products. Thus, the heteroaromatic azo compounds **3a** and **3b** underwent -N=N- hydrogenation smoothly and gave the corresponding products **4a** and **4b** in 83% and 90%,

Table 3 Highly selective direct hydrogenation of heteroaromatic azoarenes $^{\rm a}$



 a Reaction conditions: 0.5 mmol of 3, 4.2 mg of 5 wt% Pd/C (0.4% of Pd loading), 10 mol% pyridine, 10 mL of anhydrous MeOH, H $_2$ (1 atm), room temperature, 30 min and the represented yields are isolated yields.

respectively (Table 3). Interestingly, a good result was obtained in the case of **3a**, which bears two pyridine groups. This result indicates that the rate adsorption of the diazo bond on Pd/C is better than the pyridyl group. Next, we have successfully demonstrated the scalability of this catalytic hydrogenation under mild conditions (Table 4). In this regard, the present Pd/C catalyzed semihydrogenation of azoarenes was tested for a gram-scale synthesis of **2a**, **2h**, **2n**, and **4a** (5.0 mmol scale) and it worked excellently and afforded the corresponding 1,2diaryldiazene derivatives in very good yields after a reaction time of 25 to 40 min.

The significant advantage of heterogeneous catalysts over soluble homogeneous catalysts is their ability to easily separate and recycle. To demonstrate the versatility and the cost-effectiveness of the present catalytic system, a reusability test of the heterogeneous Pd/C catalyst was carried out. Thus, the recovered heterogeneous Pd/C catalyst exhibits remarkable activity, and its reusability was tested up to six consecutive cycles (Fig. 2a). Indeed, no deactivation of the catalyst was observed. Time-dependent experimental analysis was carried out to monitor the progress of the hydrogenation reaction (Fig. 2b). Monitoring the progress of the direct hydrogenation indicated that the consumption of azoarene **1a** follows an exponential decay.

 Table 4
 Direct hydrogenation of azoarenes: gram-scale synthesis^a

	R	cat. Pd/C cat. pyridine MeOH, H ₂ , rt R $\stackrel{fr}{X}$	or 4 (up to 94% yield)
R	Х	Time (min)	Product (yield %) ^b
H p-Cl p-CO ₂ Me H	C C C N	25 25 25 45	2a (94%) 2h (89%) 2n (84%) 4a (74%)

^{*a*} Reaction conditions: substrate 5.0 mmol, 42 mg of 5 wt% Pd/C (0.4% of Pd loading), 10 mol% pyridine (40 mL), 100 mL of anhydrous MeOH, H_2 (1 atm), room temperature. ^{*b*} The represented yields are isolated yields.



Fig. 2 (a) Recyclability test (left). (b) Kinetic profile of hydrogenation of 1a (right).

The research group of Nag has studied the formation of palladium hydride in a carbon-supported palladium catalyst.²² Notably, the ability to absorb hydrogen in the subsurface region of Pd/C has been explained by the simple Horiuti-Polanyi mechanism.²³ Indeed, a catalytic amount of pyridine accelerates the H-atom transfer by increasing electron density on the metal center and thus increases the catalytic activity in a controlled manner.²⁴ Also, pyridine is known to poison by partially preventing access to the metal center. We believe after semihydrogenation of azobenzene that the additive pyridine prevents the over hydrogenation of hydrazobenzene to aniline by preventing the sterically hindered hydrazobenzene molecules from access to Pd-center. To verify this, we have performed hydrogenation of hydrazo benzene (2a) in the presence and absence of a catalytic amount of pyridine. It was observed that in the presence of pyridine, the hydrogenation of 2a to aniline (2a') is slower (13% yield of aniline 2a'). However, in the absence of pyridine (only Pd/C), hydrogenation proceeded efficiently and 2a' was obtained in 88% yield.²⁵ Recently, Zaera and coworkers demonstrated the effect of additives and the surface chemistry of transition-metal catalysts in the hydrogenation catalysis.²⁶

Based on literature precedents,^{22–27} a plausible mechanism for the Pd/C-catalyzed semihydrogenation of azoarenes using H₂ has been depicted in Scheme 2. Initially, molecular hydrogen and azobenzene can undergo adsorption on the Pd surface. On the Pd atom, H₂ dissociates to reactive hydrogen atoms while azobenzene forms a π -complex with Pd/C. A hydrogen atom from the Pd-surface can transfer to the adjacent N-atom of the azobenzene to form a σ -complex intermediate. Finally, another H-atom from the Pd-surface is transferred to the Pd-attached σ -complex to form hydrazobenzene.



Scheme 2 Mechanism for the Pd/C-catalyzed semihydrogenation of azoarene using H_2 .

In summary, here we have reported a general and efficient catalytic hydrogenation of azoarenes to hydrazoarenes under mild, eco-benign conditions. The use of a reusable Pd/C catalyst, high selectivity, broad substrate scope, functional group compatibility and the absence of copious waste products in this direct hydrogenation make our work attractive.

Conflicts of interest

There are no conflicts to declare.

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