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Graphical Abstract





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Recyclable Pd/C Catalyzed One-Step Reduction of Carbonyls to Hydrocarbons under Simple Conditions without Extra Base

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ABSTRACT

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Keywords: Pd/C Reduction Carbonyls Hydrocarbons The reductions of carbonyls for the synthesis of hydrocarbons were developed with hydrazine hydrate, hydrogen gas and ammonium formate respectively. The simple, mild and efficient conditions were provided by employing recyclable Pd/C as catalyst in normal solvents at 100 °C and the reactions proceeded smoothly to produce the corresponding products with good to excellent yields. And gram-scale reactions and recycling of the catalyst were also demonstrated. Furtherly, the mechanism has been proposed.

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For the synthesis of hydrocarbons from carbonyls, the Clemmensen reduction and Wolff-Kishner reduction are the classic methods. The latter had been an effective method to convert aldehydes and ketones into hydrocarbons under strongly basic conditions at 180-220 °C since it was discovered by Wolff and Kishner¹ in the early 1910s. And dramatic improvements were made by Huang-Minlon,² in which the safer hydrazine hydrate (N₂H₄·H₂O) was introduced in high-boiling-point solvents. The reaction began with a reversible formation of hydrazine and via a deprotonation-tautomerization-proton shuffling process to give an N-anionic intermediate. Then it decomposed to generate the methylene.³ The formation, deprotonation-tautomerization-proton shuffling of hydrazine and N-anionic decomposition process provided a useful tool for new types of chemical transformations, such as deoxygenation of alcohols, ⁴ C-C bond formations with various electrophiles including cross-coupling reactions,5 conjugate addition6 and Grignard-type reaction.⁷

Besides, the further efforts have been devoted into Wolff-Kishner reduction to improve the practicability and operability. For examples, the reduction for sterically hindered carbonyl groups at 210 °C was reported by Barton,⁸ the room temperature reduction and Cope elimination was found by Cram,⁹ the modified deoxygenate reduction with potassium *tert*-butoxide at 100 °C was proved by Grundon¹⁰ and the lithium aluminium hydride promoted reduction of tosylhydrazones at 66 °C was demonstrated by Caglioti,¹¹ respectively. In order to extend the application scope of Wolff-Kishner reduction, many new

strategies and novel reagents also have been applied in this transformation, such as the one-pot reduction of isatin for the synthesis of 2-oxindoles,¹² the multiple-batch reduction based on azeotropic distillation technology,¹³ the modified reductions of *N-tert*-butyldimethylsilylhydrazones at 100 °C,¹⁴ the solar irradiation heated reduction, ¹⁵ the rapid reductions in a silicon carbide microreactor,¹⁶ and the Wolff-Kishner reduction with methyl hydrazinocarboxylate as reagent.¹⁷ However, the limitations were still existed in the improved approaches, like the two- or multi-step procedure, the high-boiling-point solvents, high temperature and the limited practicability. In view of these limitations, the further work is needed to simplify the reaction conditions. And the modified conditions without strong bases in normal solvents may be achieved by employing appropriate catalyst and reductant. Recently, palladium catalyzed C-O hydrogenolysis with polymethylhydrosiloxane^[18] and ruthenium catalyzed hydrogenolysis of carbonyl compounds with hydrogen^[19] have been achieved. These methods provided the practiced strategies for the synthesis of hydrocarbons from carbonyl compounds.

Based on this speculation, our investigation was clear that transition metal could be used as the catalyst for the reduction of ketones and aldehydes (Scheme 1). Our study began by evaluating the reduction of benzophenone (1a, Table 1). Through a period of great effort, we found a Pd/C catalyzed protocol consisting of Pd/C (10.0 mg, 10 wt% palladium on activated carbon paste and 50% moisture, 0.9 mol% [Pd] based on starting material 1a), hydrazine hydrate (4.0 equiv), in ethanol/Water

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(2a) in 95% isolated yield (Entry 1). The result showed that water (Entries 2-4) and 4.0 equivalent hydrazine hydrate (N₂H₄·H₂O, entry 5) were necessary. Notably, the water (10 equivalent) was recommended because the decreased amount of water led to the decreased yield and the excess water had no more positive effects.



Scheme 1. The reduction of carbonyls to hydrocarbons.

Subsequently, the effects of catalyst, solvent, temperature and reductant were screened. In agreement with our previous studies, the palladium catalyst was necessary (Entry 6) and the reducing dosage of Pd/C (5.0 mg, 0.47 mmol% [Pd], 74%, entry 7), Pd(OAc)₂ (89%, entry 8), PdCl₂ (no 2a was detected, entry 9) all showed negative results. It indicated that the Pd/C catalyst may be more compatible with hydrazine hydrate. And the formation of palladium black led to low catalytic activity when Pd(OAc)2 or PdCl₂ was chosen as catalyst. Moreover, the solvent tests revealed that ethanol/water was the best choice (Entries 10-11). And the temperature had been tested and 100 °C was chosen in the standard conditions due to the decreased yields at reduced temperature (80 °C, 73%, entry 12). Lastly, the other reductants, hydrogen (H₂, entries 13-14), sodium formate (HCO₂Na, entries 15-16) and ammonium formate (HCO₂NH₄, entries 17-18), were screened. The facts proved that hydrogen (1 atm-2atm) and ammonium formate (4.0 equiv) also can be applied into this transformation to provide the target product with excellent yields respectively (up to 99%).

Table 1. Conditions optimization ^a							
\land		Cat. (x mo ductant (4.0	I%) 0 equiv)	∕Ph			
Solvent, 100 °C							
1a 2a							
Entry	Cat. (x mol%)	Reductant (y equiv)	Solvent (T °C)	Yiel d (%) ^b			
1	Pd/C (0.9 mol%)	N_2H_4 · H_2O	EtOH/H ₂ O (30/1)	95			
2	Pd/C (0.9 mol%)	$N_2H_4 \cdot H_2O$	EtOH	NA			
3	Pd/C (0.9 mol%)	$N_2H_4 \cdot H_2O$	EtOH/H2O (5/1)	94			
4	Pd/C (0.9 mol%)	$N_2H_4 \cdot H_2O$	EtOH/H2O (2/1)	92			
5^c	Pd/C (0.9 mol%)	$N_2H_4 \cdot H_2O$	EtOH/H2O (30/1)	26			
6		$N_2H_4 \cdot H_2O$	EtOH/H2O (30/1)	NA			
7	Pd/C (0.47 mol%)	N_2H_4 · H_2O	EtOH/H ₂ O (30/1)	74			
8	Pd(OAc) ₂ (5.0 mol%)	$N_2H_4{\cdot}H_2O$	EtOH/H ₂ O (30/1)	89			
9	PdCl ₂ (5.0 mol%)	$N_2H_4{\cdot}H_2O$	EtOH/H2O (30/1)	NA			
10	Pd/C (0.9 mol%)	$N_2H_4 \cdot H_2O$	CH ₃ CN/H ₂ O (30/1)	NA			
11	Pd/C (0.9 mol%)	$N_2H_4{\cdot}H_2O$	1,4-dioxane/H ₂ O (30/1)	NA			
12^{d}	Pd/C (0.9 mol%)	$N_2H_4 \cdot H_2O$	EtOH/H ₂ O (30/1)	73			
13 ^e	Pd/C (0.9 mol%)	H_2	EtOH/H2O (30/1)	99			

e-pr	oofs			9
15	Pd/C (0.9 mol%)	HCO ₂ Na	EtOH/H ₂ O (30/1)	NA
16	Pd/C (0.9 mol%)	HCO ₂ Na	EtOH	NA
17	Pd/C (0.9 mol%)	HCO_2NH_4	EtOH/H2O (30/1)	98
18	Pd/C (0.9 mol%)	HCO_2NH_4	EtOH	99

^{*a*}Reaction conditions: **1a** (91 mg, 0.50 mmol), reductant (100 mg, 4.0 equiv, 2.0 mmol), Pd/C (10 wt% palladium on activated carbon paste and 50% moisture, [Pd] based on starting material **1a**) or Pd(OAc)₂ or PdCl₂ as catalyst, solvent (3.0 mL), 100 °C, 24 h. ^{*b*}Isolated yield. ^c2.0 equiv N₂H₄·H₂O was added. ^{*d*}React at 80 °C. ^{*c*}With H₂ (1 atm–2 atm) as reductant.

With these conditions in hand, we next turned our attention to evaluating the scope of this reaction under the standard conditions A, B and C. As evident from the results compiled in Table 2. the Pd/C catalyzed reduction of carbonyls can be applied to a wide number of ketones (1a-1h, entries 1-8) and aldehydes (1i-1l, entries 9-12). The corresponding products 2a-2l were obtained in good to excellent yields (71%->99%). In particular, the reduction of nitro group can be occurred in the standard conditions as well and this transformation was consistent with our previous results.²⁰ The standard conditions were appropriate for the reduction of 1-(1H-indol-3-yl)ethan-1one 1m (entry 13), 1H-indole-3-carbaldehyde 1n (entry 14) and 1H-indole-2-carbaldehyde 10 (entry 15) to produce 2- or 3alkylindoles with excellent yields. But the cyclic ketones 1tetralone and 1-indanone can't be reduced. Theoretical analysis helds that these carbonyl compounds have higher steric hindrance, which may be the main factors to low reactivity.

In order to expand applicable range of the reaction systems furtherly, the deoxygenation of naphthalen-2-ylmethanol **1p** (Entry 16) under the standard conditions had been conducted. The results showed that the alcohol **1p** can be hydrogenolysed under the standard conditions **A**, **B** and **C** but with lower yields. It is speculated that a dehydrogenative oxidation of alcohol to produce carbonyl^{4a} *in situ* led to lower yields. On the other hand, the reduction of carbonyl **1q** with a bromo-substitutent (Entry 17) had been introduced into the standard conditions. And the dehalogenative product was isolated with good yields.

Table 2. The screen on scope of substrate^{*a*}







"Reaction conditions: 1 (0.50 mmol), Pd/C (10.0 mg, 10 wt% palladium on activated carbon paste and 50% moisture, 0.9 mol% [Pd] based on starting

C-proofs EIOH/H₂O (50/1, 5.0 mL); **B**: H₂ (1 atm-2 atm), EIOH (5.0 mL); **C**: HCO₂NH₄ (126 mg, 4.0 equiv, 2.0 mmol), EtOH (3.0 mL). ^bIsolated yield. ^cN₂H₄·H₂O (200 mg, 8.0 equiv, 4.0 mmol) was added. ^dHCO₂NH₄ (252 mg, 8.0 equiv, 4.0 mmol).

Water is essential ingredient under the standard conditions **A**. In order to explore the active reactant and the role of water, the palladium catalyzed hydrogenation-denitrification of hydrazone **3** were conducted under controlled reaction conditions (**Scheme 2**). It was suggested that hydrazone **6** can be hydrogenation-denitrificated in the presence of 10.0 equivalent water to give high yields of **2a**. And the transformation were failed to produce the target product without the extra water. It firmly proved that a palladium-catalyzed, hydrogenation-deoxygenation of carbonyls was achieved to produce hydrocarbons.



Scheme 2. The controlled experiments

Based on the above results, the known mechanism of ruthenium^{4a} and palladium²¹ catalyzed direct deoxygenation of alcohols and phenols, the possible mechanism of palladium catalyzed reduction of carbonyls and alcohols is proposed in **Figure 1**. The active palladium catalyst H-[Pd]-H (**A**) is produced in the presence of hydrazine hydrate, hydrogen gas or ammonium formate. Then the nucleophilic addition of **A** with carbonyl **1** may occur directly to form a palladium complex **B** and transform to **C**. And a elimination process from **C** may occur directly to provide the product **2**. At the same time, the active [Pd] catalyst is regenerated to catalyze the next catalytic cycle.

3





Figure 1. Proposed mechanism

To test the effect of Pd/C catalyzed reduction of carbonyls under scale-up conditions, benzophenone **1a** (10.0 g) was input into the reaction under standard conditions **A** and 9.1 g **2a** was attained with 98.9% yield (**Table 3**, Entry 1). And the recycle time of Pd/C catalyst was also tested. Pleasingly, the catalytic activity of Pd/C catalyst was decreased slightly at second and third utility (entries 2 and 3, both yields 96.7%). The results indicated that the recyclable Pd/C catalyst may be appropriate for the scale-up practice.

Table 3. Test of scale-up conditions and recycling of Pd/C catalyst^a

Ph + N ₂ H	H ₄ •H ₂ O <u>EtOH/</u>	Pd/C H ₂ O (5/1, 60 r	Ph	
Ŭ 1a, 10.0 g 11.0 g	, 4.0 equiv			2a
Recyclable Times	m (Pd/C)	m (1a)	m (2a)	Yield (%) ^b
1 ^{<i>st</i>}	1.1 g	10.0 g	9.1 g	98.9
2^{nd}	/°	10.0 g	8.9 g	96.7
3 ^{<i>rd</i>}	/°	10.0 g	8.9 g	96.7

^{*a*}**1a** (10.0 g), N₂H₄·H₂O (11.0 g, 4.0 equiv), Pd/C, H₂O (9.9 g, 10.0 equiv), EtOH (50.0 mL), 100 °C, 24 h. ^{*b*}Isolated yield. ^oPd/C was added after washed with water (10 mL) and EtOH (5 mL) respectively after filtered from the previous reaction system.

In summary, we have developed an effective reduction of ketones and aldehydes with Pd/C as catalyst. Hydrazine hydrate, hydrogen gas or ammonium formate can be applied as reductant independently. The simple conditions can be carried out in normal solvent without extra strong base and the good to excellent yields were obtained. The reaction can be scaled-up to 10 grams with excellent yield and the heterogeneous Pd/C can be recovered and recycled with 3 times. Furthermore, the mechanism has been proposed and verified preliminarily according to the controlled experiments.

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Supplementary data associated with this article can be found, in the online version, at

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- Journal Pre-proofs reduction of corbornal reduction of carbonyls for the synthesis of hydrocarbons.
- A reduction of carbonyls to • hydrocarbons in normal solvents without extra base compared with Wolff-Kishner-Huang reduction.
- The catalyst can be recycled three times • with excellent yields.

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