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Reaction-Activated Palladium Catalyst for Dehydrogenation of Substituted Cyclohexanones to Phenols and H₂ without Oxidants and Hydrogen Acceptors

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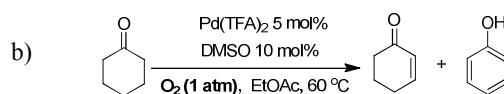
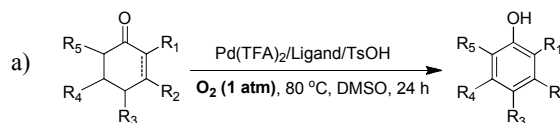
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It is widely believed that dehydrogenation of organic compounds is a thermodynamically unfavorable process, and thus requires stoichiometric oxidants such as dioxygen and metal oxides or sacrificial hydrogen acceptors to remove the hydrogen from the reaction mixture to drive the equilibrium toward the products. Here we report a previously unappreciated combination of common commercial Pd/C and H₂ dehydrogenates a wide range of substituted cyclohexanones and 2-cyclohexenones to the corresponding phenols with high isolated yields, and H₂ as the only byproduct. The reaction requires no oxidants and hydrogen acceptors because instead of removing the generated hydrogen with oxidants or hydrogen acceptors we demonstrated it can be used as a cocatalyst to help power the reaction. The method for phenol synthesis manifests the high atom economy, and is inherently devoid of the complications normally associated with oxidative dehydrogenations.

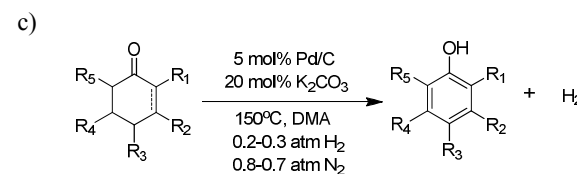
Introduction

Phenols are common precursors and key structural motifs of industrial chemicals ranging from fine (e.g. agrochemicals, dyes, pigments, and pharmaceuticals) to bulk chemicals (polymers).¹ The synthesis of substituted phenols typically relies on introduction of chemical functional groups on the aromatic ring with patterns of nucleophilic and electrophilic aromatic substitution, metal-catalyzed cross-coupling reactions.² However, the nucleophilic reactions of aromatic substitution are largely hampered due to the electron-donating properties of the hydroxyl group. As such, strong electronic directing effects of the hydroxyl group result in limited availability of electrophilic reactions of aromatic substitution to the preparation of ortho- and para-substituted derivatives.³ Although metal-catalyzed cross-coupling reactions are useful approaches to phenols, the methods generally require an expensive metal catalyst,⁴ differential prefunctionalization of the arene coupling partners with a halide and an electropositive group.⁵ Thus achieving a versatile method for facile synthesis of substituted phenols, especially for meta-substituted phenols, remains a key challenge. Recently, the oxidative dehydrogenation of substituted cyclohexanones,⁶ which is designed to be a complementary route for convenient

Existing examples:^{6a,8}



This work:



Scheme 1. Dehydrogenation of substituted cyclohexanones to phenols. The reactions of both (a) and (b) proceeded with Pd(II) complex catalysts requiring molecular oxygen as the oxidant. (c) The palladium(0)-catalyzed reaction for dehydrogenation of cyclohexanones to the phenols under 1 atm of gas mixture

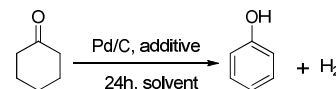
(70-80 vol% N₂ and 30-20 vol% H₂) atmosphere requires no oxidants and hydrogen acceptors, and H₂ is the only side product.

synthesis of meta-substituted phenols, is emerging as a versatile strategy to achieve this goal. However, most of reported methods for synthesis of phenols via oxidative dehydrogenation of cyclohexanones have met with a limited degree of success with regard to atom economy. The existing reactions of this type are typically carried out with stoichiometric oxidizing reagents or hydrogen acceptors, e.g. DDQ,⁷ and/or harsh reaction conditions and limited substrate scope ($\geq 200^\circ\text{C}$ high reaction temperature, and are of limited use for the refinement of more complex substrates) or requiring a stepwise procedure (bromination and dehydrobromination). Very recently Stahl and his co-workers have made a significant progress in oxidative dehydrogenation of cyclohexanones to the phenols.^{6a, 8} They have developed a palladium(II) incorporating a sophisticated ligand catalyst for the dehydrogenation. In the process high conversions and product yields were obtained, and the use of dioxygen as the oxidant is advantageous from a green viewpoint (Scheme 1, a and b). However, the oxidative dehydrogenations for synthesis of phenols are frequently hindered by over-oxidation because phenol products are inherently susceptible to oxidation, giving rise to byproducts.⁹ Moreover, the substrates possessing a chelating function, a nitrogen atom or a sulfur substituent, and/or containing other easily oxidizable functionalities are not compatible with palladium(II) catalyzed oxidation methods, and are therefore of limited use in such oxidative dehydrogenations. Herein we report an oxidant- and hydrogen-acceptor-free dehydrogenation of a wide range of substituted cyclohexanones and 2-cyclohexenones to the phenols with H₂ release. The reaction is catalyzed by a commercial Pd/C in combination with H₂. The incorporation of H₂ into the palladium catalyst not only does not hold back the dehydrogenation reaction, but also it leads to great increase in the catalyst activity for the dehydrogenation in many instances. The method is characterized by requiring no oxidants and hydrogen acceptors, and therefore circumvents the problems of over-oxidation and the compatibility with easily oxidizable functionalities. Likewise, the method provides a promising approach to green hydrogen production from organic compounds, which represents an additional benefit.

Results and Discussion.

Recently, interest in exploring the oxidant- and hydrogen acceptor-free dehydrogenation synthesis has been burgeoning for both economic and environmental benefits. Many milder liquid-phase catalyst systems for the acceptorless dehydrogenations of alcohols to the carbonyl compounds and alcohol dehydrogenation coupling reactions have been reported.¹⁰ It was intriguing to see if an effective catalyst could be developed for oxidant- and acceptor-free dehydrogenation of substituted cyclohexanones and 2-cyclohexenones to the phenols with release of H₂. On the basis of our recently developed, palladium(0) catalyzed dehydrogenation of amines to the imines,¹¹ we anticipated that palladium(0) could also catalytically dehydrogenate cyclohexanones and 2-cyclohexenones to the phenols with release of H₂. Herein we

Table 1: Reaction optimization for dehydrogenation of cyclohexanones^[a]



Entry	conditions	Conv. (%)	Select. (%)
1	DMA/5%Pd/130 °C/ N ₂	89	82
2	DMF/5%Pd/130 °C/ N ₂	85	70
3	DMI/5%Pd/130 °C/ N ₂	65	82
4	DMP/5%Pd/130 °C/ N ₂	67	84
5	Toluene/5%Pd /100 °C/ N ₂	0	-
6	DMA/5%Pd/100 °C/ N ₂	20	93
7	DMA/1%Pd/130 °C/ N ₂	25	84
8	DMA/2.5%Pd/130 °C/ N ₂	80	85
9	DMA/10%Pd/130 °C/ N ₂	99	88
10	DMA/5%Pd/150 °C/ N ₂	99	85
11	DMA/5%Pd/160 °C/ N ₂	99	81
12	DMA/5%Pd/50% Li ₂ CO ₃ /150 °C/ N ₂	88	82
13	DMA/5%Pd/50% Na ₂ CO ₃ /150 °C/ N ₂	99	76
14	DMA/5%Pd/50% K ₂ CO ₃ /150 °C/ N ₂	99	98
15	DMA/5%Pd/50% Cs ₂ CO ₃ /150 °C/ N ₂	82	78
16	DMA/5%Pd/50% NaOH /150 °C/ N ₂	65	62
17	DMA/5%Pd/50% KOH/150 °C/ N ₂	57	49
18	DMA/5%Pd/50% CH ₃ ONa/150°C/ N ₂	99	91
19	DMA/5%Pd/50% NaOEt /150 °C/ N ₂	99	92
20	DMA/5%Pd/50% CF ₃ SO ₃ H/150 °C/ N ₂	90	15
21	DMA/5%Pd/50% TsOH /150 °C/ N ₂	99	5
22	DMA/5%Pd/50% CH ₃ COOH/150°C/ N ₂	99	12
23	DMA/2.5%Pd/10% K ₂ CO ₃ /150 °C/ N ₂	94	85
24	DMA/5%Pd/20% K ₂ CO ₃ /150 °C/ N ₂	99	98
25	DMA/5%Pd/30% K ₂ CO ₃ /150 °C/ N ₂	99	98
26 ^[b]	DMA/5%Pd/10%H ₂ O/20%K ₂ CO ₃ /150 °C/N ₂	55	91
27	DMA/5%Pd/20%K ₂ CO ₃ /150 °C/ O ₂	99	0
28	DMA/5%Pd/20%K ₂ CO ₃ /150 °C/Ar ₂	99	97
29	DMA/5%Pd/20%K ₂ CO ₃ /150°C/ CO ₂	99	92
30 ^[c]	DMA/5%Pd/20% K ₂ CO ₃ /150°C/ H ₂	99	5
31 ^[d]	DMA/5%Pd/20% K ₂ CO ₃ /150 °C/ N ₂	32	-

^[a] Basic reaction conditions: cyclohexanone (1 mmol), solvent (2 mL), 24 h, 1 atm gas atmosphere (gas balloon). The percentage is mol %. Conversion and selectivity are based on gas chromatography(GC) with area normalization. ^[b]The water content of the solvent is volume fraction. ^[c]94% of cyclohexanol was detected. ^[d] With palladium acetate instead of Pd/C. No phenol product was detected.

reported our results toward achieving this goal and give a full account of the influence of the reactions.

To begin our study we investigated reactivity of dehydrogenation of cyclohexanone with 5 mol% of Pd/C, N,N-dimethylacetamide (DMA) as the solvent under 1 atm of N₂ atmosphere (a N₂ balloon) and 130°C reaction for 24h, and the results showed 89% of conversion and 82% of selectivity (Table 1, entry 1). These encouraging results inspired us to further optimize the reaction conditions. A variety of additives were screened for their ability to promote the dehydrogenation reaction. The acidic additives tested were unable to efficiently yield the desired product although some reactions obtained high conversion (Table 1, entries 20-22). On the contrary, most alkaline additives provide excellent product yields. The effects of different solvents were also evaluated. Strong polar aprotic solvents are generally effective for conversion of the substrates to the desired phenols. In contrast, weak polar aprotic solvents, e.g. toluene, are unfavorable to the reaction. The observations could be rationalized in terms of the alkaline additives having relatively low solubility in weak polar aprotic solvents. Although water is conducive to solve the added bases, the addition of water to the reaction system is deleterious to the dehydrogenation.

Several interesting phenomena observed during the gas atmosphere condition screening are worth noting. First, the dehydrogenation of cyclohexanone requires a long time to completely convert the substrate. At first we thought this arises because the dehydrogenation lacked oxidants and hydrogen acceptors. It is widely believed that the dehydrogenation of organic compounds with loss of H₂ is typically unfavorable in thermodynamics and thus requires an oxidant or a hydrogen acceptor to react with the generated hydrogen to provide an external driving force. Control experiments were therefore carried out using O₂ in place of N₂. Indeed, the incorporation of O₂ into the reaction system increases the rates of the dehydrogenation, but molecular oxygen also dramatically reduces the selectivity of the reaction. The reaction under 1 atm of O₂ (a pure O₂ balloon) is totally ineffective in the selectivity to the desired product: only miscellaneous oxidation products were detected (Table 1, entry 27). Thus a variety of gas atmospheres was screened for their effects on the reaction. The results shown in Table 1 displayed that inert gases, e.g. Ar, N₂ and CO₂, enabled the reaction to achieve high selectivity and conversion. When the reaction was carried out under 1 atm of H₂ atmosphere (a H₂ balloon), it provided 94% of hydrogenation product, cyclohexanol, and 5% of desired phenol product (Table 1, entry 30). The reaction can still generate desired dehydrogenation product, phenol, under hydrogenation conditions (1 atm of pure H₂). This was unexpected. To further verify the influence of gas atmospheres on the dehydrogenation reaction for other substrates, we selected another substrate, 3-isobutyl-5-phenyl-cyclohexanone, to carry out the control experiments under a variety of gas atmospheres (N₂, O₂, and a gas mixture of N₂ and H₂). Although the reaction under 1 atm of pure O₂ atmosphere showed a relatively fast rate of dehydrogenation (the starting material was completely consumed within 20 h), the yield of target product is not to 20% (Figure 1, curve ○(green)). This arises because the target

product, 3-isobutyl-5-phenyl-phenol, was further oxidized to by-products during the reaction. When the reaction was carried out under 1 atm of gas mixture (70 vol% of N₂ and 30 vol% of

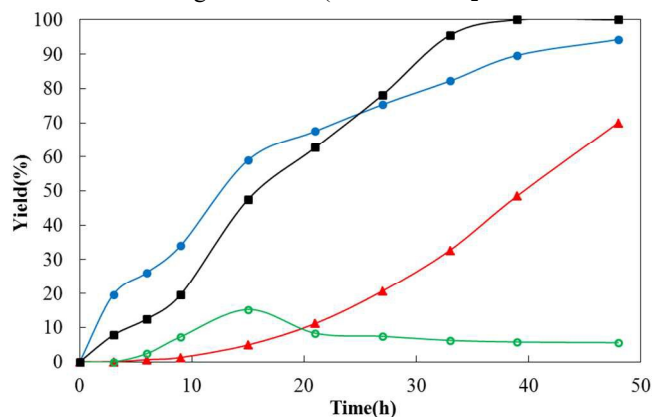


Figure 1. Reaction time course of dehydrogenation of 3-isobutyl-5-phenyl-cyclohexanone to 3-isobutyl-5-phenyl-phenol under variant gas atmosphere conditions. Reaction conditions are as follows: 3-isobutyl-5-phenyl-cyclohexanone (2 mmol), DMA (4 mL), Pd/C (0.1 mmol Pd), K₂CO₃ (0.4 mmol), 150°C. The yields were determined by GC analysis using n-dodecane as the internal standard. Curve ■(black): the reaction was performed under 1 atm of gas mixture (70 vol% N₂ and 30 vol% H₂) atmosphere. Curve ●(blue): the Pd/C catalyst was pretreated with 1 atm H₂ at room temperature for 1 h, and the dehydrogenation reaction with the pretreated Pd/C was performed under 1 atm N₂ atmosphere. Curve ▲(red): the reaction was performed under 1 atm N₂ atmosphere. Curve ○(green): the reaction was performed under 1 atm O₂ atmosphere.

H₂) atmosphere, we only detected dehydrogenation product, 3-isobutyl-5-phenyl-phenol, but detected no hydrogenation product, 3-isobutyl-5-phenyl-cyclohexanol, in the reaction mixture while the starting material was completely converted. We did observe 7% of hydrogenation product, 3-isobutyl-5-phenyl-cyclohexanol, at the initial stages of the reaction, but the hydrogenation product was also completely dehydrogenated to the desired phenol gradually in the following reaction. More surprisingly, such a gas mixture atmosphere did not cause any decrease in dehydrogenation reaction rate, conversion and selectivity, but on the contrary did cause a large increase compared with the reaction under 1 atm of N₂ atmosphere (Figure 1, curve ■(black) vs curve ▲(red)). The observation contradicts the generally accepted point of view that removing the hydrogen from the reaction mixture is beneficial to dehydrogenation reactions. To find out how the Pd/C in combination with H₂ works, we have treated the Pd/C with 1 atm of H₂ at room temperature for 1 h and then use the treated Pd/C to dehydrogenate 3-isobutyl-5-phenyl-cyclohexanone under 1 atm of N₂ atmosphere and 150°C. There were two key findings: (i) A small amount (4%) of hydrogenation product, corresponding cyclohexanol, was generated at the initial stages of the reaction. By contrast, such a hydrogenation product was not observed in the reaction with untreated Pd/C under 1 atm of N₂ atmosphere and 150°C; (ii) The Pd/C treated with H₂ exhibits higher catalytic reactivity for the dehydrogenation (under N₂ atmosphere) compared with the untreated Pd/C

Table 2: Palladium-catalyzed dehydrogenation of cyclic ketones to phenols and H₂ ^[a].

Entry Substrate	Phenol (time/yield)	Entry Substrate	Phenol (time/yield)	Entry Substrate	Phenol (time/yield)
1 1a	 2a (20 h, 92%)	6 1f	 2f (20 h, 92%)	11 1k	 2k (22 h, 85%)
2 1b	 2b (26 h, 80%)	7 1g	 2g (26 h, 63%)	12 1l	 2l (30 h, 70%)
3 1c	 2c (20 h, 84%)	8 1h	 2h (18 h, 93%)	13 1m	 2m (24 h, 81%)
4 1d	 2d (20 h, 85%)	9 1i	 2i (16 h, 90%)	14 1n	 2n (20 h, 83%)
5 1e	 2e (19 h, 82%)	10 1j	 2j (45 h, 73%)	15 1o	 2o (19 h, 86%)

^[a] R₁, R₂, R₃, R₄, R₅: Ar, Me, H. Reaction conditions are as follows: cyclic ketone (1.0 mmol), Pd/C (5 mol% Pd), K₂CO₃ (20 mol%), DMA (N,N-dimethylacetamide, 2 mL), 150°C, 1 atm of gas mixture atmosphere (30 vol% H₂ and 70 vol% N₂). Isolated product yields are reported.

(under N₂ atmosphere) (Figure 1, curve ● (blue) vs curve ► (red)). The Pd/C treated with H₂ is able to convert 3-isobutyl-5-phenyl-cyclohexanone to the corresponding cyclohexanol without reducing reagents (H₂). This result shows that HPd(II)H active species are most likely to be generated during the treatment of Pd/C with H₂ because HPd(II)H can reduce cyclohexanones to cyclohexanols, and the HPd(II)H active species also act as the veritable active catalyst for the dehydrogenation. The rate of the reaction with untreated Pd/C under 1 atm of N₂, by contrast, gradually

increased during the initial stages of the reaction (Figure 1, curve ► (red)), which suggests the catalyst is gradually activated by the generated H₂. Thus we presumed that removing the generated H₂ from the reaction system would suppress the dehydrogenation reaction. To verify it, we performed the reaction under 10 atm of highly pure N₂ in an autoclave and 150°C because nitrogen pressure increase equivalents to reducing the partial pressure of hydrogen generated in the reaction, which equivalents to removing the H₂ from the reaction system. The results showed that the

reaction implemented under 10 atm of N₂ and 150°C for 27 h and 36h provided 0% and 25% yields of target product, respectively compared with the product yield of 20% and 48% respectively but only 1 atm of N₂ atmosphere in the same reaction conditions (Fig. 2, curve c). These observations clearly showed removing the hydrogen from the reaction system (or reducing the partial pressure of hydrogen in the

system) would slow down the reaction and the hydrogen created in the reaction can activate the Pd/C catalyst for the dehydrogenation process. This phenomenon manifests a catalyst could be activated by its reaction products, which is controlled by the reaction, and so we refer to these catalysts as “reaction-activated catalysts”.

Table 3: Palladium-catalyzed dehydrogenation of 2-cyclohexenones to phenols and H₂^[a].

Entry	Substrate	Phenol (time/yield)	Entry	Substrate	Phenol (time/yield)	Entry	Substrate	Phenol (time/yield)
1			7			13		
2			8			14		
3			9			15		
4			10			16		
5			11			17		
6			12			18		

^[a] R₁, R₂, R₃, R₄, R₅: Ar, Me, H. Reaction conditions are as follows: cyclic ketone (1.0 mmol), Pd/C (5 mol% Pd), K₂CO₃ (20 mol%), DMA (N, N-dimethylacetamide, 2 mL), 150°C, 1 atm of gas mixture atmosphere (20 vol% H₂ and 80 vol% N₂). Isolated product yields are reported.

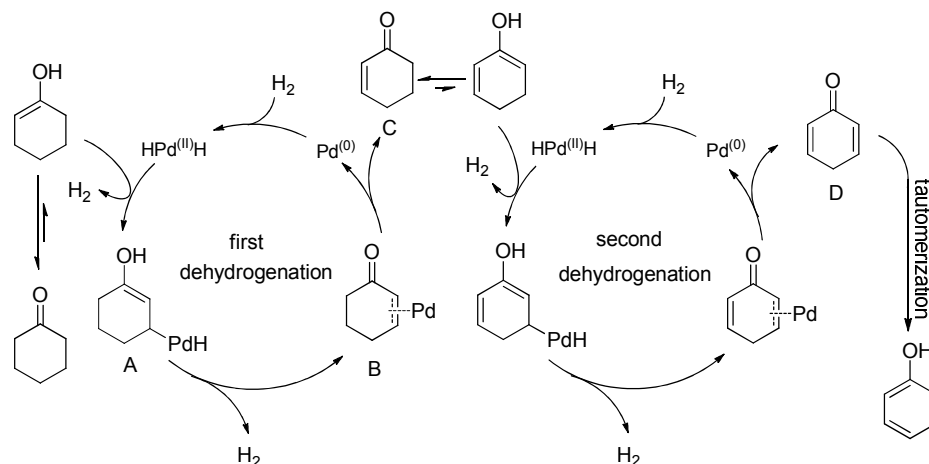
The activation effects of the hydrogen generated in the reaction on Pd/C catalyst might be less obvious in some cases because the resulting partial pressure of hydrogen still may not be high enough. Thus for some specific reactions they still require to extra add a certain amount of hydrogen gas to the

catalytic dehydrogenation systems. The effect of H₂ on the dehydrogenation depends on the use amount of H₂: too high partial pressure of hydrogen could lead to more hydrogenation product generation, which is unfavorable for the dehydrogenation reaction; proper amount of H₂ could help power the

reaction; some dehydrogenation reactions need not extra add H_2 because the generated hydrogen gas is sufficient for the catalyst activation.

The hydrogen-containing gas atmosphere reaction conditions were applied to the dehydrogenation of a variety of substituted cyclohexanones and 2-cyclohexenones. A selection of pertinent examples is displayed in Table 2-3. As can be seen, a broad spectrum of substituted cyclohexanones and cyclohexenones was dehydrogenated to the corresponding phenols with high isolated yields. The outcome of the

dehydrogenation was not significantly affected by varying the position of the same substituent, e.g. methyl group on the cyclohexanones. A number of 3-substituted cyclohexanones, which were readily synthesized with known methods, were efficiently dehydrogenated to the corresponding phenols with the present dehydrogenation method. This may be of great interest in synthesis of meta-fragment substituted phenol derivatives. It is noteworthy that sulfur-, nitrogen- and oxygen-containing

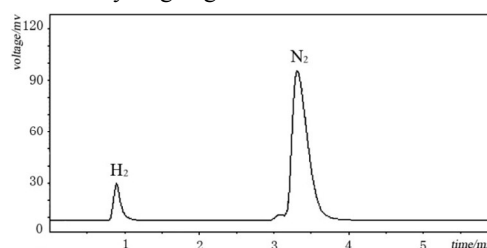


Scheme 2. Proposed mechanistic pathway of palladium-catalyzed dehydrogenation of cyclohexanone to phenol and H_2 .

compounds (typically: Table 2, entries 7, 10, 13 and Table 3, entries 3-6, 8, 15, 18) were also very smoothly converted into the corresponding phenols in high yields with the catalytic system. However, these heteroatom-containing ketones are usually regarded as difficult substrates in most transition metal-catalyzed oxidative protocols due to their strong coordinating abilities. Of particular interest is the fact that under the oxidant- and acceptor-free conditions, highly oxidation-sensitive substrates (Table 2, entries 7, 13 and Table 3, entries 3-6, 8, 15), which are problematic in oxidative dehydrogenations, seldom interfered with the catalytic dehydrogenation reaction, also provide excellent yields. Usually these readily oxidizable ketones are problematic in oxidative dehydrogenations, for example, we attempted to prepare the phenols derived from the substrates (Table 2, 1g and Table 3, 1'q, 1's, 1't), using Stahl's aerobic catalytic system.^{6a,8} The results showed these ketones provided little or no desired products, but a large amount of miscellaneous oxidation products were detected. When the substrate containing a tetrahydrofuran ring was examined, we were pleased to find that not only the cyclohexanone moiety but also the tetrahydrofuran ring were dehydrogenated (Table 2, entry 10). This observation combined with our previous studies, palladium(0) catalyzed acceptorless dehydrogenation,¹¹ suggests the present catalytic dehydrogenation system may be applied to dehydrogenation of substituted tetrahydrofurans to synthesis of furans.

Elucidation of the detailed mechanistic pathway will undoubtedly shed light on the pathway and allow further

optimization of this dehydrogenation system. In present case, a detailed mechanism for the overall catalytic process cannot yet be deduced, but an outline of a potential mechanism is provided in Figure 3. The reaction started with a keto enol tautomerism equilibrium under the alkaline conditions. Metal Pd(0) reacted with hydrogen gas to generate HPd(II)H species. The HPdH species may undergo dehydrogenative palladation of the β -position of cyclohexanone (either keto or enol tautomer) to generate intermediate (A). The palladation with Pd(0) may be difficult compared with use of HPd(II)H species. This may be why H_2 can activate the palladium(0) catalyst. The intermediate (A) was subsequently converted to a key intermediate (B), meanwhile H_2 was released with the directing effects of electron-donating property of hydroxyl groups. The dissociation of intermediate (B) led to Pd(0) and intermediate (C). Sequential the second dehydrogenation of the 2-cyclohexenone (C), a process similar to the first dehydrogenation, resulted in compound (D) generation, which tautomerized into the target product. Gas chromatography (GC) was used to detect the reaction gas atmosphere. As shown in figure 2, we clearly detected the generation of H_2 during the reaction. This demonstrated the hydrogen departed from the substrate formed hydrogen gas.



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Figure 2. GC H₂ detection for the dehydrogenation of cyclohexanone. The gas sample was sampled from the reaction gas atmosphere (reaction conditions: 1 mmol cyclohexanone, 5% mol Pd/C, 150 °C, 1.5 h, 2 ml DMA under 1 atm N₂ atmosphere). The H₂ and N₂ were confirmed by comparing with standard H₂ and N₂ GC spectra.

Conclusions

Dehydrogenation, excluding deprotonation, belongs to an oxidation process. Therefore, to obtain efficient dehydrogenation processes, much attention was naturally turn to developing effective catalysis with oxidants while largely ignoring the advantages inherent in catalysis with a reducing agent (H₂). Our findings unlock opportunities for markedly different synthetic strategies. These reactions achieve high isolated yields, they are intrinsically devoid of complications caused by over-oxidation in oxidative dehydrogenation, and the catalyst tolerates useful substrates with diverse functional groups, including aromatic, susceptible to oxidation and the heteroatom substituents with strong coordinating ability. The dehydrogenation do not need oxidants and hydrogen acceptors, manifests the high atom economy. Moreover, the only by-product H₂ of these reactions is a clean energy carrier. Palladium on active carbon is an industrial commonly used and recycled catalyst. Thus this Pd/C in combination with H₂ catalytic dehydrogenation process displays considerable promise for its practical application in an industrial setting.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and ¹H and ¹³C NMR of new materials. See DOI: 10.1039/b000000x

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