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Palladium on Carbon-Catalyzed Aqueous Transformation of Primary Alcohols to Carboxylic Acids Based on Dehydrogenation under Mildly Reduced Pressure

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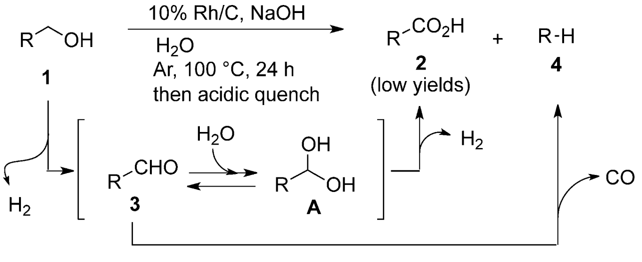
Abstract: The catalytic dehydrogenation of alcohols to carbonyl products is a green sustainable oxidation with no production of waste except for hydrogen, which can be an energy source. Additionally, a reusable heterogeneous catalyst is valuable from the viewpoint of process chemistry and water is a green solvent. We have accomplished the palladium on carbon (Pd/C)-catalyzed dehydrogenation of primary alcohols to carboxylic acids in water under a mildly reduced pressure (800 hPa). The reduced pressure can be easily controlled by the vacuum controller of the rotary evaporator to remove the excess of generated hydrogen, which causes the reduction (reverse reaction) of aldehydes to alcohols (starting materials) and other undesirable side reactions. The present method is applicable to the reaction of various aliphatic and benzylic alcohols to the corresponding carboxylic acids, and the Pd/C could be reused at least 5 times.

Keywords: carboxylic acids; dehydrogenation; primary alcohols; reduced pressure; water

Introduction

The oxidation of alcohols to carbonyl products is important in organic chemistry.[1] Especially, the transition metal-catalyzed dehydrogenation of hydroxy groups is an attractive method to provide the corresponding carbonyl products with less waste except for hydrogen gas,[2–6] and various homogeneous[3] and heterogeneous catalysts[4] have been used for the dehydrogenation of secondary and primary alcohols to the corresponding ketones and aldehydes. The direct transformation of a primary alcohol to the carboxylic acid *via* the double dehydrogenation process requires additional water to form the corresponding hydrate as an intermediate (**A**, Scheme 1) from the aldehyde generated by the first dehydrogenation of a primary alcohol. The pioneer reaction was developed by Milstein et al. using the homogeneous Ru catalyst in water,[5] and we also recently reported the heterogeneous and reusable Rh/C-catalyzed method in water as a non-flammable, clean, cheap and environmentally benign solvent (Scheme 1).[6] While the secondary alcohols were efficiently transformed into ketones under the stated reaction conditions (Rh/C–base–H_2O; Figure 1, style I), the reaction of primary alcohols (**1**) produced lower yields of carboxylic acids (**2**) accompanying by the decarbonylation[7] of the intermediate aldehydes (**3**) to the corresponding alkanes



Scheme 1. Previous results: Rh/C-catalyzed double dehydrogenation of the primary alcohol (**1**) into the carboxylic acid (**2**) in a test tube under atmospheric pressure of argon (Style I).

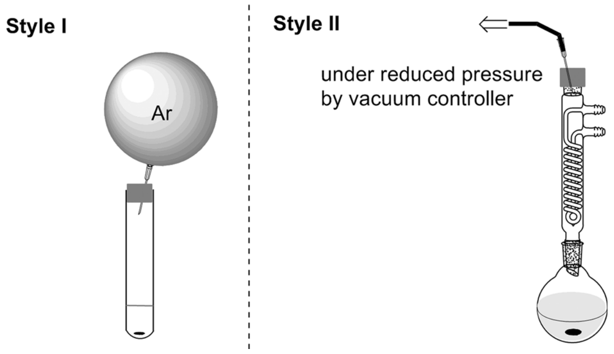


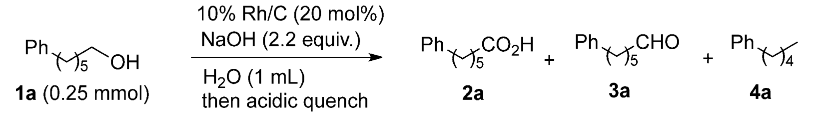
Figure 1. Reaction styles in a test tube under argon (Style I) and a flask connected to a reflux condenser and vacuum controller (Style II).

(**4**) as a side reaction. The undesirable side reaction can be promoted by Rh/C in the presence of excess hydrogen. Additionally, hydrogen stored in the reaction vessel could facilitate the hydrogenation (reverse reaction) of the intermediate aldehyde to the corresponding alcohol (starting material), which delays the consumption of the aldehyde to the carboxylic acid and promotes the undesired decarbonylation of the aldehyde. Therefore, we next investigated the continuous removal of hydrogen generated by the dehydrogenation of the alcohol (**1**) and hydrate (**A**) under reduced pressure by the vacuum controller of a rotary evaporator (Figure 1, Style II).

Results and Discussion

The dehydrogenation of 6-phenyl-1-hexanol (**1a**) as a primary alcohol was initially investigated in the presence of 10% Rh/C (20 mol%) and NaOH (2.2 equiv.) in H_2O at 100 °C under a mildly reduced pressure (Table 1). The reaction, carried out in a flask connected to a reflux condenser or test tube under ambient pressure (1013 hPa), gave the corresponding carboxylic acid (**2a**) in 38% yield within 6 h or 50% yield after 24 h accompanied by the undesirable 1-phenylpentane (**4a**)[8] resulting from the decarbonylation of 6-phenyl-1-hexanal (**3a**), respectively (entries 1 and 2). The use of Pd/C in a test tube (style I) also provided a similar result in comparison with that of Rh/C (entries 3 *vs.* 2). Hydrogen generated during the reaction progress could be removed under reduced pressure at 900 and 800 hPa and **2a** was obtained in good yields (entries 4 and 5).[9] Further reduction of the pressure to 700 and 300 hPa decreased the reaction efficiency of the dehydrogenation and **1a** was not completely consumed (entries 6 and 7). The generated hydrogen also probably plays a role in activating the catalyst metal,[10,11] thus significant removal of hydrogen from the reaction system delays the Rh/C-catalyzed dehydrogenation step. The dehydrogenation also smoothly proceeded at 80 °C under 800 hPa to provide **2a** in 81% yield (entry 9). Meanwhile, the dehydrogenations at 60 °C, room temperature and 120 °C resulted in dramatically decreased reaction efficiency (entries 10–12).

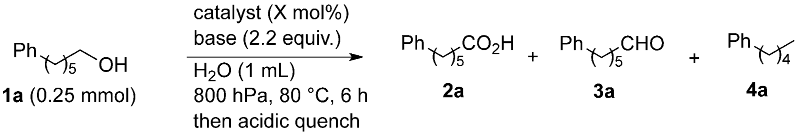
Table 1. Optimization under reduced pressure (Style II).



Entry	Pressure [hPa]	Temperature [°C]	Time [h]	Yield [%][a]			
				1a	**2a**	**3a**	**4a**[b]
1	1013	100	6	20	38	4	7
2[c]	–	100	24	0	50	0	10
3[c,d]	–	100	24	0	51	0	2
4	900	100	6	0	80	0	11
5	800	100	6	0	76	0	13
6	700	100	6	43	33	0	12
7	300	100	6	41	10	0	0
8	900	80	6	24	58	0	6
9	800	80	6	0	81	0	0
10	800	60	6	69	11	0	1
11	800	r.t.	6	87	0	0	0
12	800	120	6	42	16	0	13

[a] Yields were determined by ^1H NMR using 1,4-dioxane as the internal standard.
[b] Alkane **4a** was comparatively easily vaporized under reduced pressure. Therefore, the yield of **4a** may be incorrect due to its loss during the reaction process.
[c] The reaction was carried out in a test tube (Style I).
[d] 10% Pd/C was used instead of 10% Rh/C.

Table 2. Efficiency of catalysts and bases.



Entry	Catalyst	X	Base	Yield [%][a]			
				1a	**2a**	**3a**	**4a**[b]
1	10% Rh/C	20	NaOH	0	81	0	0
2	10% Pd/C	20	NaOH	0	86	0	5
3	10% Pt/C	20	NaOH	0	74	0	0
4	10% Ru/C	20	NaOH	48	46	0	5
5	10% Rh/C	5	NaOH	42	52	0	4
6	10% Pd/C	5	NaOH	4	88	0	4
7	10% Pd/C	5	KOH	14	75	1	1
8	10% Pd/C	5	LiOH	32	50	3	0
9	10% Pd/C	5	Na$_2$CO$_3$	48	40	4	4
10	10% Pd/C	5	NaHCO$_3$	72	19	7	0
11	10% Pd/C	5	–	94	2	4	0
12[c]	10% Pd/C	5	NaOH	10	76	0	1
13	10% Pd/C	1	NaOH	25	50	0	1
14[d]	10% Pd/C	5	NaOH	–	95[e]	–	–

[a] Yields were determined by ^{1}H NMR using 1,4-dioxane as the internal standard.

[b] Alkane **4a** was comparatively easily vaporized under reduced pressure. Therefore, the yield of **4a** may be incorrect due to its loss during the reaction process.

[c] 1.1 equiv. of NaOH was used.

[d] For 9 h.

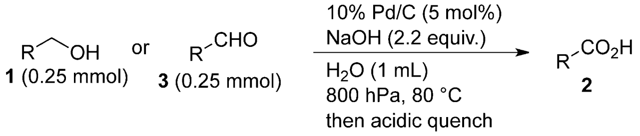
[e] Isolated yield.

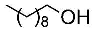
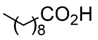
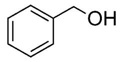
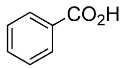
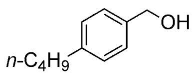
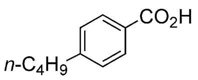
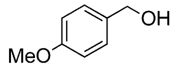
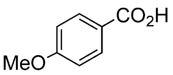
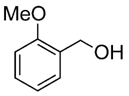
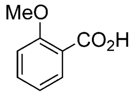
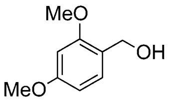
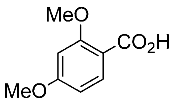
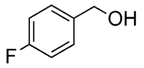
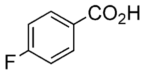
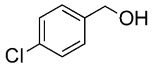
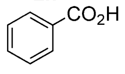
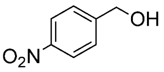
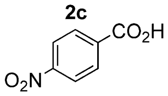
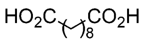
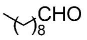
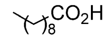
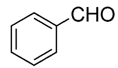
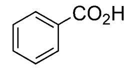
Various platinum metals on carbon (e.g., Pd/C, Rh/C, Ru/C and Pt/C) were found to also possess a catalyst activity for the dehydrogenation of alcohols.[6,10] The double dehydrogenation of a primary alcohol at 80 °C under 800 hPa in the presence of NaOH (2.2 equiv.) was efficiently catalyzed by 20 mol% of 10% Rh/C, Pd/C and Pt/C, except for Ru/C (Table 2, entries 1–4), and the lower catalyst loading of 10% Pd/C (5 mol%) still maintained a high catalyst activity (entry 6), while the use of 5 mol% of Rh/C significantly delayed the dehydrogenation (entry 5). KOH, LiOH, Na$_2$CO$_3$ and NaHCO$_3$, instead of NaOH, were insufficient as a base (entries 7–10) and the reaction without a base hardly proceeded (entry 11). The reduction of NaOH used to 1.1 equiv. or the further decrease of Pd/C to 1 mol% resulted in lower yields of **2a**. Therefore, the combination of 10% Pd/C (5 mol%)–NaOH (2.2 equiv.) under 800 hPa at 80 °C was optimum[12] and prolonging the reaction time to 9 h provided **2a** in 95% isolated yield (entry 14).

The present reaction under reduced pressure was applied to various aliphatic and benzylic alcohols (Table 3). Decanol (**1b**) as a simple aliphatic alcohol and various benzyl alcohols (**1c**–**1j**) bearing electron-donating and electron-withdrawing groups on the aromatic nuclei underwent the double dehydrogenation to the corresponding aliphatic carboxylic acid and benzoic acid derivatives in good to excellent yields (entries 1–9). During the dehydrogenation process, the generated hydrogen may cause the Pd/C-catalyzed hydrogenation of the coexisting reducible functionalities within the same molecule. While aromatic fluoride and nitro groups were totally tolerated under the present reaction conditions (entries 7 and 9), an aromatic chloride was reductively dechlorinated to give benzoic acid (**2c**; entry 8). The yields were dramatically improved in comparison to our previous Rh/C-catalyzed reactions in a test tube (Style I; e.g., **2b**: 53%, **2c**: 54%, **2d**: 44%, **2e**: 38%, **2g**: 23% and **2h**: 33%).[13] 10-Acetoxy-1-decanol (**1k**) underwent the NaOH-mediated hydrolysis, and the diol was dehydrogenated to give the corresponding dicarboxylic acids (**2k**). Furthermore, the reaction of aldehydes (**3b** and **3c**) was also applicable to provide the corresponding carboxylic acids (**2b** and **2c**) in quantitative yields, respectively (entries 11 and 12).

The reuse of the heterogeneous catalysts is important from the viewpoint of green sustainable chemistry. The Pd/C could be reused at least 5 times after simple filtration, washing with H$_2$O and MeOH, then drying [Eq. (1)]. Under the present dehydrogenation in basic media, the carboxylic acids as products were isolated after acidic quench with aqueous 1N H$_2$SO$_4$. The acidic quench before the filtration of Pd/C causes a slight leaching of Pd (2%) from the carbon support as based on an ICP-OES analysis. Meanwhile, the

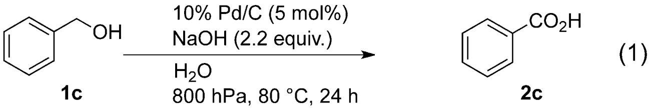
Table 3. Scope of the substrates.



Entry	Substrate	Product	Yield (Time)
1[a]	 **1b**	 **2b**	84% (12 h)
2[a]	 **1c**	 **2c**	quant. (6 h)
3[a]	 **1d**	 **2d**	88% (6 h)
4[a]	 **1e**	 **2e**	quant. (6 h)
5	 **1f**	 **2f**	quant. (6 h)
6[a]	 **1g**	 **2g**	66% (6 h)
7[a]	 **1h**	 **2h**	86% (6 h)
8	 **1i**	 **2c**	55% (6 h)
9	 **1j**	 **2j**	77% (6 h)
10[b]	 **1k**	 **2k**	90% (12 h)
11	 **3b**	 **2b**	99% (6 h)
12	 **3c**	 **2c**	quant. (6 h)

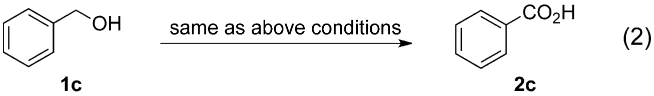
[a] The Rh/C-catalyzed dehydrogenation of **1b**–**1e** and **1g**, **1h** in a test tube (Style I; at 100 °C for 24 h) gave low yields (**2b**: 53%, **2c**: 54%, **2d**: 44%, **2e**: 38%, **2g**: 23% and **2h**: 33%), respectively.

[b] 4 equiv. of NaOH were used.



then acidic quench of the reaction mixture
and subsequent filtration

1st: >99%, 2nd: >99%, 3rd: 99%, 4th: 95%, 5th: >99%



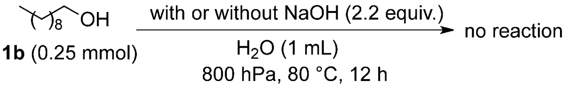
then filtration
and subsequent acidic quench of the filtrate

1st: >97%, 2nd: >99%

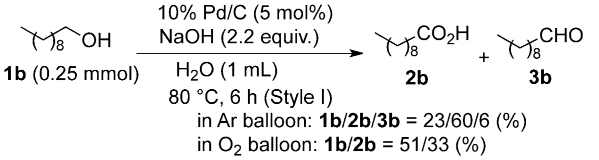
acidic quench of the resulting filtrate after filtration could eliminate the problem and the Pd/C could be reused without leaching [Eq. (2)].

During the dehydrogenation of primary alcohols under reduced pressure, oxygen (O_2) as a component of the air could be an oxidant for the alcohols. The transition metal-catalyzed oxidation of alcohols using O_2 is also a green process to obtain carbonyl products accompanied with H_2O as the only byproduct.[14–16] The reaction of 1-decanol (**1b**) without Pd/C never proceeded [Eq. (3)] and the reaction efficiency of Pd/C under argon was even better in comparison to that under O_2 conditions in a test tube (Style I) [Eq. (4)]. Therefore, the first conversion step of the alcohol to the aldehyde is considered to mainly proceed by the Pd/C-catalyzed dehydrogenation. Furthermore, 1-decanal (**3b**) was completely transformed to decanoic acid (**2b**) in H_2O without Pd/C and NaOH under 800 hPa at 80 °C,[17] while the addition of NaOH rather delayed the transformation of **3b** to **2b** [Eq. (5)]. Meanwhile, the reaction in the presence of Pd/C efficiently proceeded in aqueous basic media as shown in Table 3, entry 11. Since the di-^{18}O-labeled product was efficiently obtained by using $H_2{}^{18}O$ instead of $H_2{}^{16}O$, the present transformation of **3b** to **2b** mainly proceeded by the dehydrogenation of the intermediate hydrate (**A′**) derived from **3b** [Eq. (6)]. While the formation of the hydrate (**A′**) is an equilibrium reaction, the reaction demonstrates a tendency to converge on the ^{18}O-labeled intermediate (**A′**) due to the isotopic effect. Under the O_2 oxidation of the aldehyde, the non-labeled **3b** can be transformed to ^{18}O-labeled **3b′** *via* the hydrate (**A′**), and **3b′** is theoretically converted to the mono-^{18}O-labeled **2b** according to a previous paper.[17a] Nevertheless, the di-^{18}O-labeled **2b** was actually obtained as the main product under the Pd/C–NaOH–$H_2{}^{18}O$ conditions [Eq. (6)]. The ^{18}O-labeling reaction using **2b** as a substrate under the same reaction conditions never proceeded [Eq. (7)]. Therefore, in the present reaction, the two continuous transformations of alcohol to aldehyde and aldehyde to carboxylic acid mainly progressed based on the Pd/C-catalyzed dehydrogenation.[18]

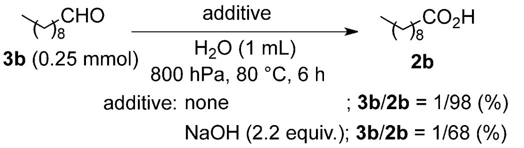
It is noteworthy that the present dehydrogenation could be accomplished using a normal evaporator equipment [Eq. (8), a photograph is also shown in the Supporting Information]. Namely, benzyl alcohol (**1c**; 5 mmol), 10% Pd/C (5 mol%), NaOH (2.2 equiv.) and



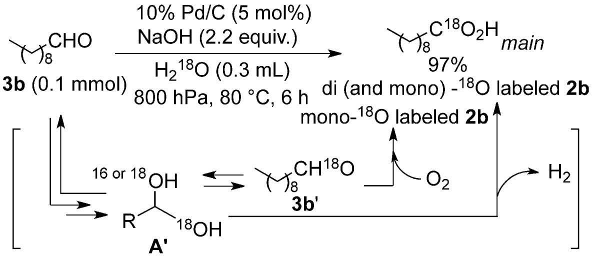
(3)



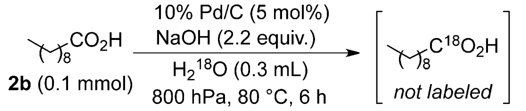
(4)



(5)

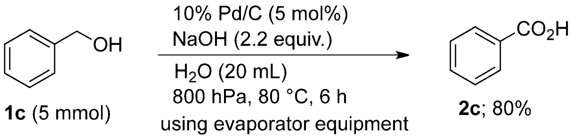


(6)



(7)

H_2O (20 mL) in a 100-mL egg plane flask without a stirring bar attached with an evaporator equipment was rotated under 800 hPa at 80 °C (external oil bath) for 6 h. Consequently, the desired benzoic acid (**2c**) was obtained in 80% yield.



(8)

Conclusions

The clean dehydrogenation of primary alcohols to carboxylic acids has been accomplished using the heterogeneous, reusable and easily available Pd/C in water under 800 hPa at 80 °C. The present method could be achieved by the gentle removal of the hydrogen generated during the double dehydrogenation steps. This is the first efficient oxidation of primary alcohols to carboxylic acids using a heterogeneous catalyst under a gentle reduced pressure and could be verified as a valuable methodology in organic synthesis.

Experimental Section

General Procedure

The primary alcohol (0.25 mmol), 10% Pd/C (13.4 mg, 1.25 μmol), NaOH (22.2 mg, 0.55 mmol) and H_2O (1 mL) were mixed in a flask, in which pressure was reduced to 800 hPa using the vacuum controller of an evaporator (see the photo given in the Supporting Information). After stirring the reaction mixture at 80 °C for the appropriate time, the reaction mixture was quenched with 1 N aqueous H_2SO_4 and passed through a membrane filter (Millipore, Millex-LH, 0.20 μm) to remove the Pd/C. The filtrate was extracted with diethyl ether (10 mL) and H_2O (10 mL), then the aqueous layer was further extracted with diethyl ether (10 mL × 4). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by silica-gel column chromatography using *n*-hexane/EtOAc as the eluent, if necessary.

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[9] Ar bubbling to remove the generated hydrogen in a test tube could not improve the reaction efficiency, because the hydrogen gas, which is required to activate the palladium, may also be removed from the reaction system. It is the same reason in the case of results for the 700 and 300 hPa conditions (Table 1, entries 6 and 7). The reaction of **1a** (0.25 mmol) in the presence of Pd/C (5 mol%) and NaOH (2.2 equiv.) in H_2O (1 mL) at 80 °C for 6 h in a test tube under Ar bubbling conditions gave the desired carboxylic acid (**2a**) in 25% yield, and 65% of **1a** was recovered.

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Palladium on Carbon-Catalyzed Aqueous Transformation of Primary Alcohols to Carboxylic Acids Based on Dehydrogenation under Mildly Reduced Pressure

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