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PLATINUM ON CARBON–CATALYZED AND CHEMOSELECTIVE AQUEOUS OXYGEN OXIDATION OF AROMATIC ACETALS TO BENZOIC ACIDS

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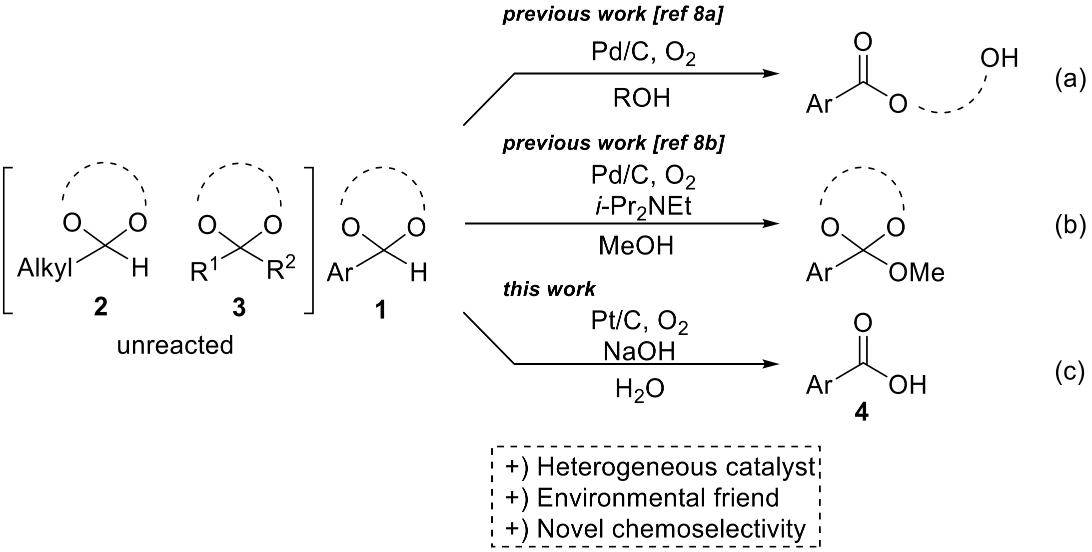
Abstract – Novel chemoselective transformations can diversify the synthetic pathways of the target molecules. The chemoselective oxidation of aromatic acetals to benzoic acid derivatives under platinum on carbon (Pt/C)–catalyzed oxygen oxidation conditions has been newly developed with a tolerance of aliphatic acetals and ketals. The present oxidation was clean and useful from the viewpoint of the easy removal of Pt/C and the use of molecular oxygen as a green oxidant in water as an abundant, non-toxic and environmentally friendly solvent.

The direct transformation of protected compounds without any deprotection process is crucially important for designing step-economical syntheses. Additionally, a chemoselective transformation has contributed to creating a novel synthetic strategy for the target molecules. Acetals and ketals are frequently utilized as protected groups of aldehydes and ketones, respectively, in organic synthesis and generally transformed into various functionalities via the acid-mediated formation of oxonium ion intermediates.[1] Under acidic conditions, ketals are preferentially transformed into oxonium ion intermediates, which smoothly undergo further transformations, in comparison with acetals due to the stabilities of the oxonium ion intermediates.[1] Fujioka and Kita et al. have pioneered the chemoselective transformation of acetals via the specific formation of pyridinium-type salt intermediates using the combination of stoichiometric silyl triflates and an adequate pyridine derivative in the presence of ketals.[2] The pyridinium-type salts derived from acetals were directly and selectively functionalized without changing the coexisting ketal. On the other hand, the transformations of acetals into the corresponding carboxylic acids in one-pot manner have been developed.[3-6] For example, the deprotection of acetals to aldehydes and the subsequent oxidation under aqueous acidic conditions including the stoichiometric oxidant (*e.g.*, CrO_3[3a–d] and O_2[3e]) directly provided the carboxylic acid products. The oxidative cleavage of acetals into the hydroxyalkyl esters by ozone and the subsequent hydrolysis under aqueous conditions also gave the corresponding carboxylic acids.[4] Additionally, the direct oxidations of acetals using the stoichiometric oxidants [OXONE® (potassium peroxomonosulfate)[5] and $AgBr_3/AlCl_3$[6]] were accomplished. The clean oxidation of acetals under an atmosphere of molecular oxygen (O_2) in the presence of $CoCl_2$ and $ZnCl_2$ as a catalyst in dichloromethane was developed.[7a] Also, acetals can be directly converted into carboxylic acids under atmospheric O_2 via the photooxygenation.[7b] However, aliphatic acetals as well as aromatic acetals were equally oxidized into the carboxylic acids under these previously reported reaction conditions, and acid-labile ketals are then likely to be deprotected to the corresponding ketones by the acids generated during the oxidation process. Our research group recently reported the palladium on carbon (Pd/C)–catalyzed chemoselective transformation of aromatic acetals (**1**) via the C–H functionalization of benzylic positions under O_2 atmosphere as a clean oxidant in the presence of aliphatic acetals (**2**) and ketals (**3**) (Scheme 1,a and b).[8] The aromatic acetals (**1**) were transformed into hydroxyalkyl esters in organic solvents, such as ethylene glycol and MeOH, under neutral conditions (Scheme 1,a).[8a] The orthoester products were obtained in the presence of an organic base, such as *i*-Pr_2NEt, under the Pd/C–catalyzed reaction conditions in MeOH (Scheme 1,b).[8b] We now report the direct and chemoselective oxidation of aromatic acetals (**1**) into benzoic acids (**4**) in the presence of platinum on carbon (Pt/C) catalyst and NaOH under atmospheric O_2 in H_2O as an environmentally benign solvent (Scheme 1,c). Meanwhile, aliphatic acetals (**2**) and ketals (**3**) were tolerant under the present conditions.

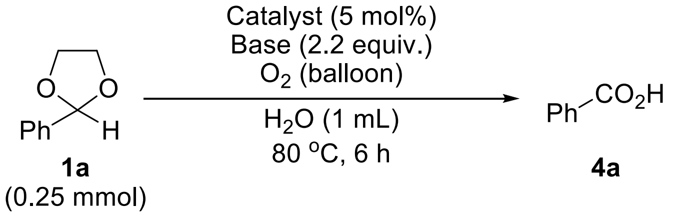


Scheme 1. Metal on Carbon–Catalyzed Chemoselective Oxidation of Aromatic Acetals (**1**)

The direct oxidation of a five–membered cyclic acetal (**1a**), derived from benzaldehyde and ethylene glycol, as an aromatic acetal was successively carried out in the presence of Pd/C and NaOH under O_2 atmosphere in H_2O (1 mL) and the corresponding benzoic acid (**4a**) was obtained at 80 °C for 6 h in 69%

yield (Table 1, Entry 1). Meanwhile, the reaction efficiency under air was moderate (Entry 2), and the oxidation hardly proceeded under argon (Ar) (Entry 3). Pt/C indicated a better catalyst activity in comparison with Pd/C, and **4a** was obtained in 85% isolated yield (Entry 4). Rh/C and Ru/C were inefficient catalysts (Entries 5 and 6), and the reaction using Au/C gave **4a** in a moderate yield (67%) (Entry 7). On the other hand, the Pt/C–catalyzed oxygen oxidation of **1a** in the presence of $NaHCO_3$, Na_2CO_3, or KOH as an inorganic base moderately proceeded (Entries 8–10) and the use of an organic base, such as Et_3N or *i*-Pr_2NEt, dramatically decreased the reaction activity (Entries 11 and 12). Although the Pt/C–catalyzed oxidation of **1a** without a base also reasonably proceeded, the yield of **4a** after 6 h significantly decreased in comparison to that under the NaOH–basic conditions (Entries 4 *vs*. 13). The reaction at 50 °C or 25 °C led the low yields (Entry 4 *vs*. Entries 14 and 15). The used amount of water (0.5 mL or 2 mL) had an insignificant effect to give **4a** in good yield (Entry 4 *vs*. Entries 16 and 17).

Table 1. Reaction Optimization



Entry	Catalyst	Base	Yield (%)[a]	
			1a	**4a**
1	10% Pd/C	NaOH	0	69
2[b]	10% Pd/C	NaOH	32	40
3[c]	10% Pd/C	NaOH	71	0
4	10% Pt/C	NaOH	0	88 (85)[d]
5	10% Rh/C	NaOH	71	10
6	10% Ru/C	NaOH	56	5
7	10% Au/C	NaOH	6	67
8	10% Pt/C	$NaHCO_3$	0	54
9	10% Pt/C	Na_2CO_3	0	60
10	10% Pt/C	KOH	0	75
11	10% Pt/C	Et_3N	75	1
12	10% Pt/C	*i*-Pr_2NEt	94	2
13	10% Pt/C	–	0	71
14[e]	10% Pt/C	NaOH	72	13

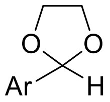
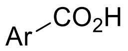
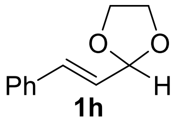
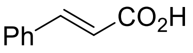
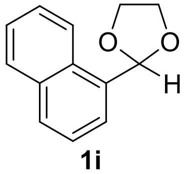
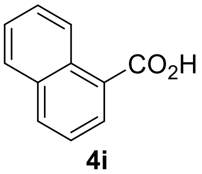
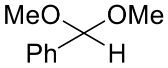
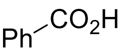
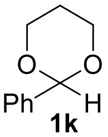
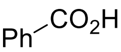
15[f]	10% Pt/C	NaOH	81	7
16[g]	10% Pt/C	NaOH	8	70
17[h]	10% Pt/C	NaOH	6	69

[a] Determined by ^{1}H NMR using 1,4-dioxane as an internal standard. [b] Under Air. [c] Under Ar. [d] Isolated yield. [e] At 50 °C. [f] At 25 °C. [g] In 0.5 mL of H_2O. [h] In 2 mL of H_2O.

The scope of substrates was next investigated (Table 2). Various aromatic five–membered cyclic acetals (**1b**–**1g**) bearing an electron-donating or electron-withdrawing functionality at the *ortho*, *meta* or *para* position of each aromatic nucleus underwent the oxygen oxidation to give the corresponding benzoic acid derivatives (**4b**–**4g**) in good yields. Moreover, the oxidation of the cinnamaldehyde five-membered cyclic acetal (**1h**) also effectively proceeded to give cinnamic acid (**4h**). The naphthalene derivative (**1i**) could be converted to 1-naphthoic acid (**4i**). Furthermore, the present reaction was applicable to the non-cyclic dimethyl acetal (**1j**) derived from benzaldehyde, and the desired benzoic acid (**4a**) could be obtained in good yield, while the six-membered aromatic acetal (**1k**) was less reactive to give the benzoic acid (**4a**) in moderate yield.

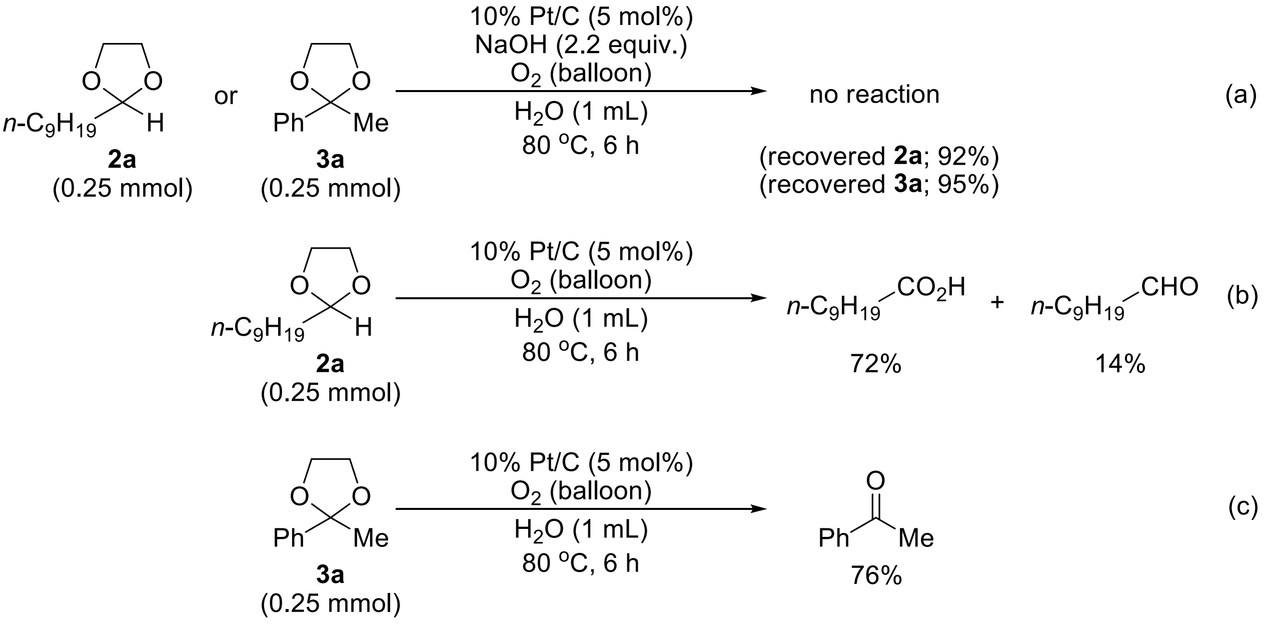
Table 2. Scope of Substrates

$$\underset{(0.25\ \text{mmol})}{\text{Substrate }(\mathbf{1})}\ \xrightarrow[\substack{H_2O\ (1\ \text{mL}) \\ 80\ ^{\circ}\text{C}}]{\substack{10\%\ \text{Pt/C}\ (5\ \text{mol\%}) \\ \text{NaOH}\ (2.2\ \text{equiv.}) \\ O_2\ (\text{balloon})}}\ \text{Product }(\mathbf{4})$$

Substrate (**1**)	Product (**4**)	Yield	Substrate (**1**)	Product (**4**)	Yield
			 **1h**	 **4h**	73% (24 h)
Ar = 4-MeO-C_6H_4 (**1b**)	**4b**	83% (9 h)	 **1i**	 **4i**	74% (24 h)
3-MeO-C_6H_4 (**1c**)	**4c**	76% (12 h)			
2-MeO-C_6H_4 (**1d**)	**4d**	69% (18 h)			
4-Br-C_6H_4 (**1e**)	**4e**	78% (24 h)	 **1j**	 **4a**	82% (24 h)
4-Cl-C_6H_4 (**1f**)	**4f**	78% (24 h)			
4-NO$_2$-C_6H_4 (**1g**)	**4g**	65% (72 h)[a]	 **1k**	 **4a**	45% (72 h)[a,b]

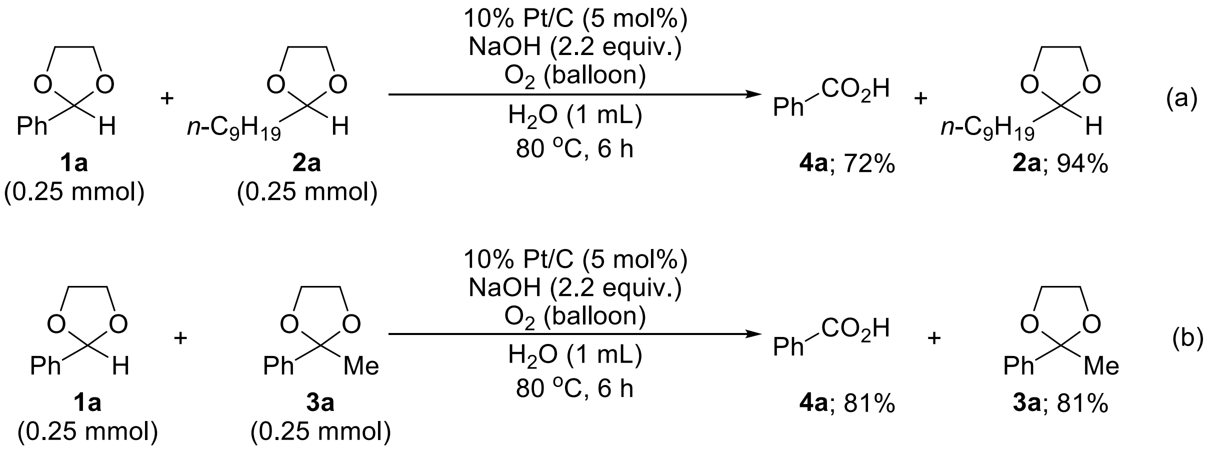
[a] 15 mol% of Pt/C was used. [b] 42% of the starting material was recovered.

As mentioned in the introduction, the chemoselective transformation of acetals coexisting with ketals is a challenging issue due to their reactivity under various reaction conditions,[1,2] and the reactive control between the aromatic and aliphatic acetals was also difficult. In our study, the aliphatic acetal (**2a**) and ketal (**3a**) bearing no benzylic C–H bond within the molecule were inactive substrates for the present Pt/C–catalyzed oxidation in basic H_2O and reminded unchanged (Scheme 2,a). In contrast, the aliphatic acetal (**2a**) was converted to the saturated carboxylic acid in 72% yield under neutral conditions, and the corresponding deprotected aldehyde was also obtained in 14% yield (Scheme 2,b). Presumably, the deprotection of the cyclic acetal proceeded under Pt/C–catalyzed neutral conditions to form an aldehyde, which was further oxidized to give a carboxylic acid.[9] On the other hand, the ketal (**3a**) was completely deprotected under the Pt/C-catalyzed neutral conditions (Scheme 2,c).



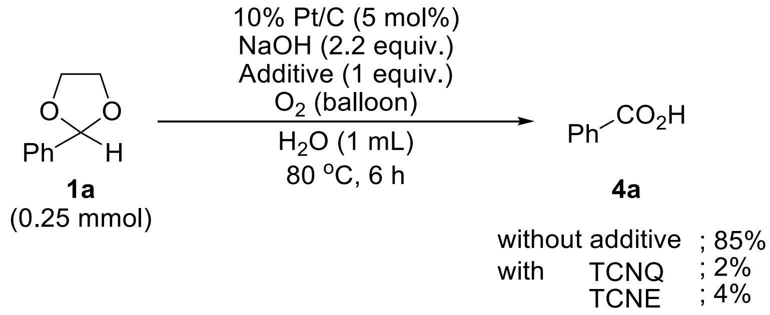
Scheme 2. Reactivities of Aliphatic Acetal and Ketal

Encouraged by the inert results of the aliphatic acetal (**2a**) and ketal (**3a**) under Pt/C–catalyzed basic aqueous conditions (Scheme 2), the chemoselective oxidation of aromatic acetals in the presence of ketals or aliphatic acetals was investigated (Scheme 3). The Pt/C–catalyzed oxygen oxidation of an aromatic acetal (**1a**) coexisting with an aliphatic acetal (**2a**) could selectively proceed in basic H_2O to give **4a** in good yield and the recovered **2a** in 94%. Also, **1a** could be selectively transformed into **4a** under the present oxidation conditions with the suppression of the deprotection of the ketal (**3a**), although the formation of a tiny amount (5%) of acetophenone as a deprotected product could not be avoided.

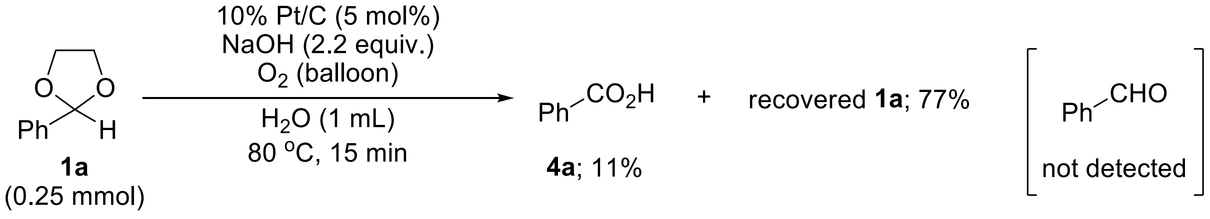


Scheme 3. Chemoselective Reactions of Aromatic Acetals

The present oxygen oxidation of **1a** was depressed by the addition of 7,7,8,8-tetracyanoquinodimethane (TCNQ) or tetracyanoethylene (TCNE) as a radical scavenger (Scheme 4). Furthermore, benzaldehyde was never detected during the Pt/C–catalyzed oxidation even for a short reaction time (15 min.) (Scheme 5). Based on these results, it is plausible that the oxidation of aromatic acetals probably proceeds via the Pt/C and molecular oxygen-mediated formation of benzyl radical intermediates, while the detailed reaction mechanism is unclear.



Scheme 4. Inhibition by the Addition of a Radical Scavenger



Scheme 5. Short Time Reaction

In conclusion, we have developed a catalytic and chemoselective transformation of aromatic cyclic acetals into the corresponding benzoic acid derivatives in the presence of aliphatic cyclic acetals or ketals.

Oxygen is a clean oxidant to be converted into H_2O after the reaction, and H_2O is used as an abundant and environmentally-friendly solvent. Moreover, the Pt/C catalyst could be easily removed by a simple filtration. Therefore, the mild and chemoselective oxidation method of aromatic acetals is valuable from the viewpoint of green sustainable chemistry and methodology to create novel synthetic routes.

EXPERIMENTAL

Typical Procedure: The aromatic acetal (**1a**; 37.5 mg, 0.25 mmol), 10% Pt/C (24.4 mg, 0.013 mmol), NaOH (22.0 mg, 0.55 mmol) and H_2O (1 mL) were stirred in test tube connected with O_2 balloon (1 atm) using a ChemiStation (EYELA, Tokyo Rikakikai Co., Ltd., Tokyo, Japan) at 80 ^{o}C (external aluminum heating block temperature). After 6 h, the reaction mixture was cooled to room temperature and passed through a membrane filter (Millipore, Millex-LH, 0.20 μm) to remove Pt/C. 1N H_2SO_4 (2 mL) was added to the filtrate and the solution was extracted with Et_2O (10 mL X 2) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica-gel column chromatography using a mixed eluent (hexane/AcOEt=4:1) to give the corresponding benzoic acid (**4a**; 26.1 mg, 0.213 mmol, 85%). See the Supporting Information for the characterization details.

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