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PALLADIUM ON CARBON–CATALYZED OXIDATIVE TRANSFORMATION OF BENZYLIC ETHERS

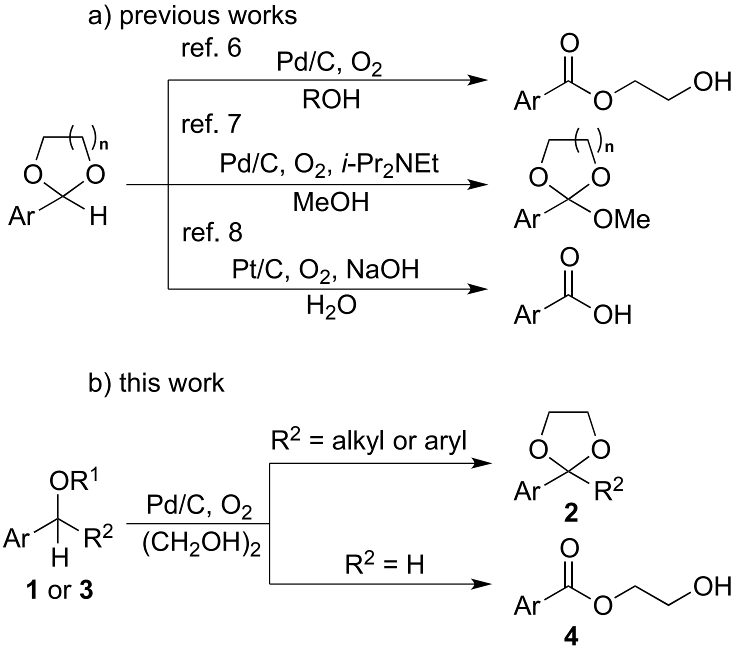
Ryoya Takakura, Shoko Kuwata, Kouki Nakano, Naoki Yasukawa, Hironao Sajiki,* and Yoshinari Sawama*

Laboratory of Organic Chemistry, Gifu Pharmaceutical University 1-25-4 Daigaku-nishi, Gifu 501-1196, Japan
E-mail: sajiki@gifu-pu.ac.jp; sawama@gifu-pu.ac.jp

Abstract - Palladium on carbon (Pd/C)-catalyzed oxidative transformations of primary and secondary benzylic ethers in ethylene glycol as a solvent and reagent in an oxygen atmosphere produced the corresponding hydroxyethyl esters and cyclic ketals, respectively. Commercially-available and heterogeneous Pd/C was easily removed by filtration, and molecular oxygen was used as a clean oxidant.

Various benzylic alcohol derivatives are readily available and used as synthetic precursors based on the activation of the benzylic C-H bonds.[1-4] Oxidative C-C bond formation reactions at the benzylic C-H position adjacent to the oxygen atom have been widely accomplished to construct various useful organic skeletons.[1] While the stoichiometric organic oxidants, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), or peroxide were traditionally used for the C-H bond activation,[1,2] the oxidative transformation using molecular oxygen (O_2) as a mild and green oxidant has been spotlighted from the viewpoint of atom economy and green sustainability due to the advantage that the only by-product is water.[3] Visible-light-mediated C-C bond forming reactions using photocatalysts via benzyl radicals were also developed.[4] Additionally, acetal and ketal derivatives are useful as protecting groups for aldehydes and ketones, respectively, and are usually prepared from aldehydes and ketones under acidic conditions in the presence of an alcohol.[5] To the best of our knowledge, the direct transformation of benzyl alkyl ethers into acetals could not be accomplished. We have recently developed benzylic C-H functionalization reactions of aromatic acetals in the presence of a platinum group metal on carbon using molecular oxygen as a green oxidant (Scheme 1-a).[6-8] Palladium on carbon (Pd/C) effectively catalyzed the oxygen oxidation of aromatic cyclic acetals to corresponding benzoic acid hydroxyethyl ester derivatives in methanol or ethylene glycol as an organic solvent.[6] Furthermore, aromatic cyclic acetals could be selectively transformed into orthoester derivatives in the presence of *N,N*-diisopropylethylamine

(i-Pr_2NEt) as an organic base in methanol via benzylic C-H methoxylation.[7] On the other hand, benzoic acid derivatives could be obtained under platinum on carbon (Pt/C)-catalyzed conditions in the presence of NaOH in atmospheric O_2 and H_2O.[8] We now report the Pd/C-catalyzed oxidative transformation of secondary benzylic ethers (**1**; R^2 = alkyl or aryl) to cyclic acetals (**2**), and primary benzylic ethers (**3**; R^2 = H) to hydroxyethyl esters (**4**) in ethylene glycol under atmospheric O_2.

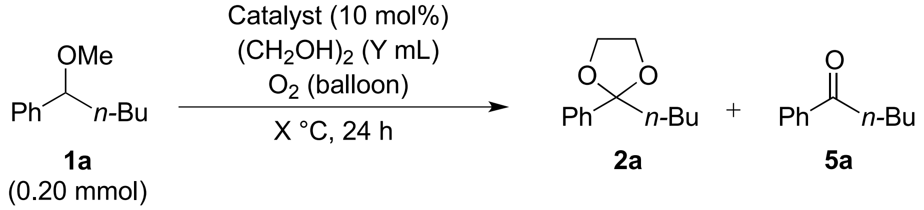


Scheme 1. Oxidative benzylic C-H functionalizations catalyzed by platinum group metal on carbon under atmospheric oxygen

The Pd/C (10 mol%)-catalyzed oxidative annulation of 1-phenyl-1-pentanol methyl ether (**1a**) as a secondary benzylic ether in ethylene glycol (1.0 mL) and an oxygen atmosphere proceeded at 80 °C for 24 h to produce the corresponding 5-membered cyclic ketal (**2a**) in 55% yield together with 15% of unchanged starting material (**1a**, Table 1, entry 1). Pt/C, Ru/C, Rh/C, Ir/C, Ni/C, and Au/C other than Pd/C were all ineffective as a catalyst (entries 2-7). The reaction also smoothly proceeded even if the usage of Pd/C was reduced to 5 mol%, and **2a** was obtained in 60% yield (entry 8). The reactivity also decreases as the reaction temperature decreases from 80 °C to 60 °C, and only 22% of **2a** was obtained together with 62% of the recovered **1a** (entry 9). However, when the reaction temperature increased to 100 °C or 120 °C, the yield of **2a** decreased despite the consumption of **1a** as the starting material (entries 10 and 11). Increasing the use of ethylene glycol from 1 mL to 1.5 or 2.0 mL improves the reaction efficiency (entries 1 *vs.* 12 or 13). In particular, **2a** could be isolated in 72% yield in 2.0 mL of ethylene glycol (entry 13), although further increasing the usage of ethylene glycol (2.5 mL) was ineffective (entry

14). The substrate (**1a**) was not completely consumed even though the reaction time was extended to 48 h (entry 15). It was observed that valerophenone (**5a**), which was a hydrolysis product of **2a**, was gradually and time-dependently generated as a byproduct during the present Pd/C-catalyzed oxygen oxidation (entries 13 and 15).

Table 1. Optimization of reaction conditions using 1-phenyl-1-pentanol methyl ether (**1a**)



Entry	Catalyst	X	Y	Yield (%)[a]	
				1a	**2a**
1	10% Pd/C	80	1.0	15	55
2	10% Pt/C	80	1.0	80	0
3	10% Ru/C	80	1.0	70	0
4	10% Rh/C	80	1.0	80	0
5	10% Ir/C	80	1.0	65	0
6	10% Ni/C	80	1.0	70	0
7	10% Au/C	80	1.0	80	0
8[b]	10% Pd/C	80	1.0	15	60
9	10% Pd/C	60	1.0	62	22
10	10% Pd/C	100	1.0	13	49
11	10% Pd/C	120	1.0	trace	10
12	10% Pd/C	80	1.5	6	71
13	10% Pd/C	80	2.0	10	75 (72)[c,e]
14	10% Pd/C	80	2.5	21	59
15[d]	10% Pd/C	80	2.0	2	68[f]

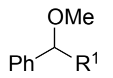
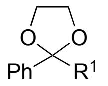
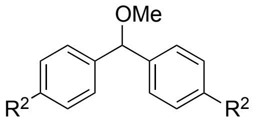
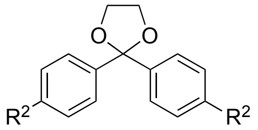
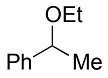
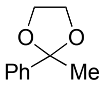
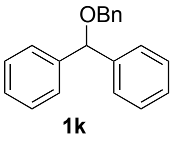
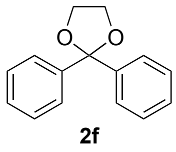
[a]Determined by ^{1}H NMR using 1,2-methylenedioxybenzene as an internal standard. [b]5 mol% of Pd/C was used. [c]Isolated yield. [d]The reaction was stirred for 48 h. [e]**5a** was also generated in 8% yield as a byproduct. [f]**5a** was also generated in 19% yield as a byproduct.

The optimal reaction conditions using 10% Pd/C (10 mol%) in ethylene glycol (2 mL) at 80 °C under O_2 were applied to the oxidative functionalization of various secondary benzylic ethers (Table 2). Secondary benzylic ethers (**1b**-**1d**) derived from 1-phenyl-1-ethanol, 1-phenyl-1-propanol, and 1-phenyl-1-butanol were effectively converted to the corresponding ketal products (**2b**-**2d**) in moderate to high yields.

However, the cyclic ketal formation of a secondary benzylic ether (**1e**) possessing the sterically hindered *tertiary*-butyl (*t*-Bu) group at the benzylic position did not proceed. In the case of 1,1-diphenylmethoxymethane (**1f**), the desired cyclic ketal (**2f**) was smoothly obtained in high yield via the Pd/C-catalyzed oxidative transformation. While a 1,1-diphenylmethoxymethane derivative (**1g**) bearing electron-sufficient methoxy groups at the 4,4'-positions on the aromatic nuclei could be converted to the corresponding ketal product (**2g**) in low yield, substrates each possessing two fluoro and chloro groups at the 4,4'-positions (**1h** and **1i**) were inert. The use of 1-ethoxy-1-phenylethane (**1j**) and benzyl diphenylmethyl ether (**1k**) as a substrate gave corresponding ketal products (**2b** and **2f**) in low yields.

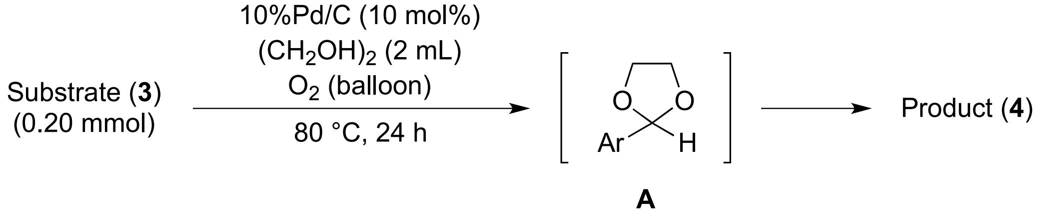
Table 2. Scope and limitation of substrates in ketal formation using secondary benzylic ethers

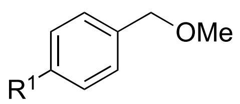
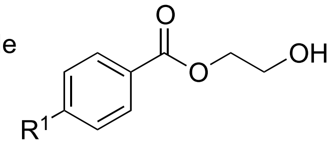
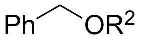
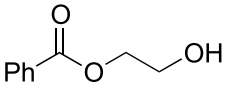
$$\begin{array}{c}\text{Substrate (}\mathbf{1}\text{)}\\ \text{(0.20 mmol)}\end{array} \xrightarrow[\text{80 °C, 24 h}]{\begin{array}{c}\text{10\% Pd/C (10 mol\%)}\\ (CH_2OH)_2 \text{ (2 mL)}\\ O_2 \text{ (balloon)}\end{array}} \text{Product (}\mathbf{2}\text{)}$$

Substrate (**1**)	Product (**2**)	Yield	Substrate (**1**)	Product (**2**)	Yield
					
R^1 = Me (**1b**)	**2b**	44%	R^2 = H (**1f**)	**2f**	83%
Et (**1c**)	**2c**	55%	OMe (**1g**)	**2g**	17%
n-Pr (**1d**)	**2d**	90%	F (**1h**)	**2h**	0%
t-Bu (**1e**)	**2e**	0%	Cl (**1i**)	**2i**	0%
 **1j**	 **2b**	28%	 **1k**	 **2f**	10%

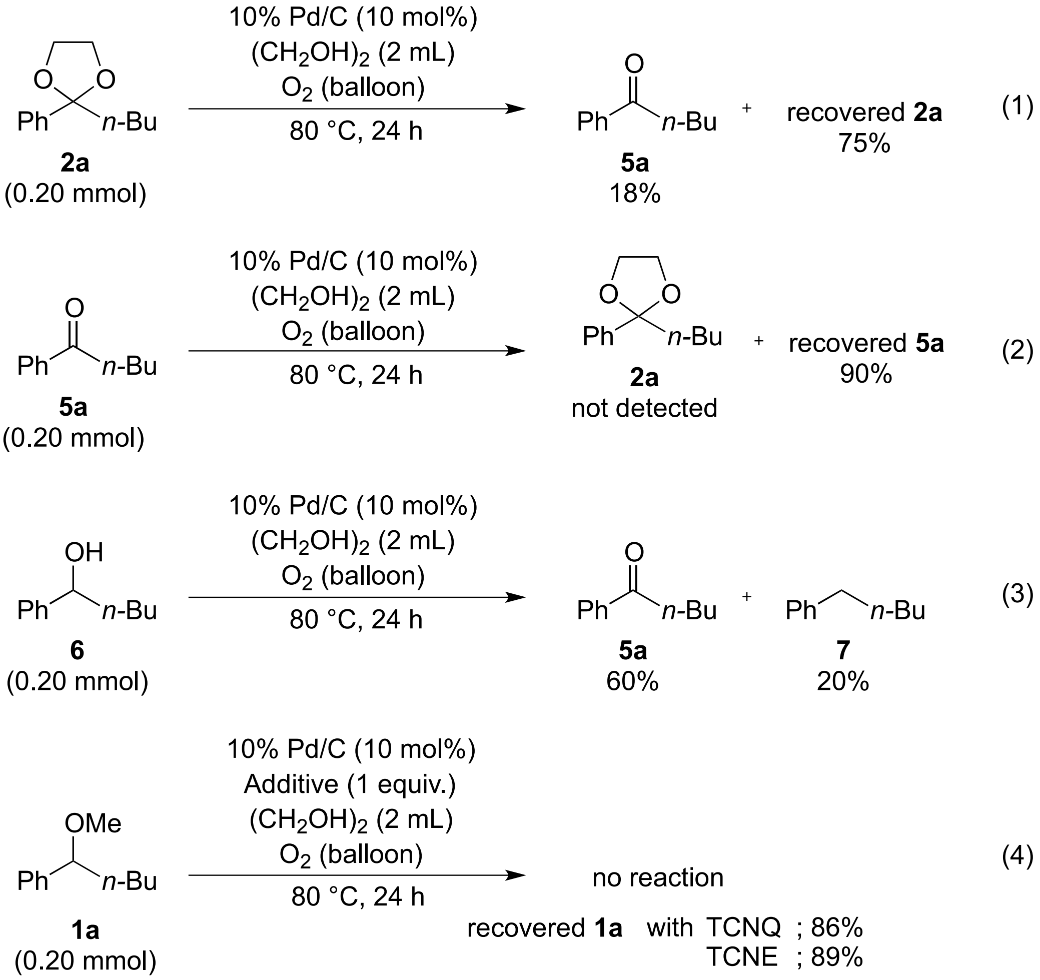
Incidentally, hydroxyethyl esters (**4**) are critical synthetic precursors, such as for the cross-linking of polyesters[9] and the site-selective Diels–Alder reaction of acrylic ester derivatives.[10] Benzyl methyl ether (**3a**) as a primary benzylic ether was transformed into 2-hydroxyethyl benzoate (**4a**) in 78% yield under Pd/C-catalyzed oxygen oxidative conditions in ethylene glycol as the solvent and reactant (Table 3). The oxidative transformation of **3a** should provide the aromatic cyclic acetal (**A**) as a reaction intermediate in a manner similar to the oxidation of secondary benzylic ethers as shown in Table 1, and the subsequent second stage Pd/C-catalyzed oxygen oxidation[6] of **A** continuously proceeded to give the corresponding hydroxyethyl ester (**4**). During the oxidative transformation of **3a** to **4a**, the key intermediate (**A**) was not detected, which indicated that the latter oxidation was faster than the former one. 4-Methyl- and 4-methoxy-benzyl alcohol methyl ethers (**3b** and **3c**) were both effectively converted to the corresponding hydroxyethyl esters (**4b** and **4c**) under present Pd/C-catalyzed double oxidation conditions. In contrast, the oxidation reaction of 4-fluorobenzyl methyl ether (**3d**) never proceeded. Benzyl alkyl ethers (**3e**-**3g**) bearing branched-alkyl chains, such as the *iso*-propyl (*i*-Pr) and *t*-Bu groups, and the *n*-dodecyl (n-$C_{12}H_{25}$) group as a long alkyl chain were also smoothly transformed into corresponding 2-hydroxyethyl benzoate (**4a**) in a good yield, respectively.

Table 3. Scope and limitation of substrates in hydroxyethyl ester formation using primary benzylic ethers



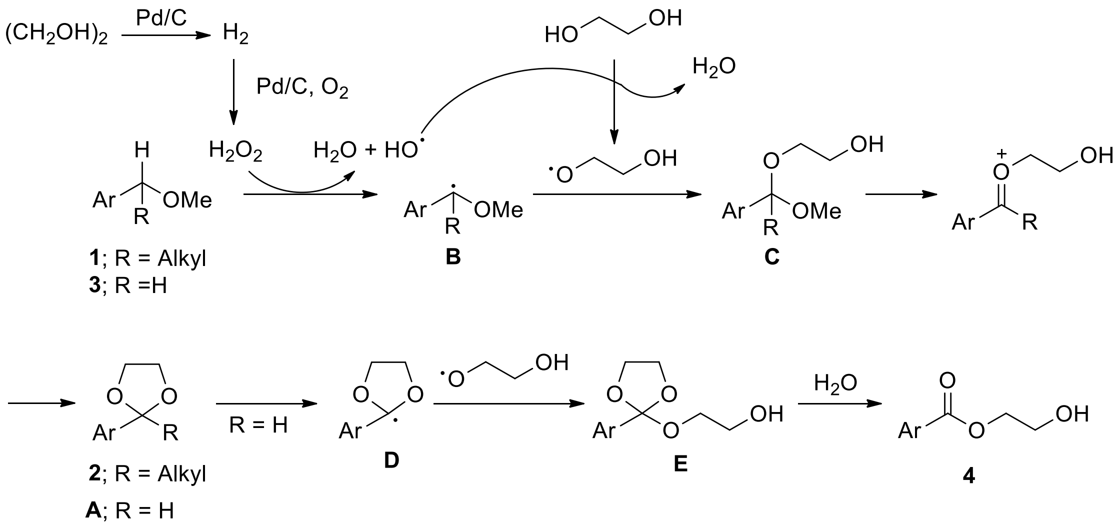
Substrate (**3**)	Product (**4**)	Yield	Substrate (**3**)	Product (**4**)	Yield
					
R^1 = H (**3a**)	**4a**	78%	R^2 = *i*-Pr (**3e**)	**4a**	78%
Me (**3b**)	**4b**	44%	*t*-Bu (**3f**)	**4a**	81%
OMe (**3c**)	**4c**	74%			
F (**3d**)	**4d**	0%	n-$C_{12}H_{25}$ (**3g**)	**4a**	65%

The cyclic acetal moiety of **2a** was partially hydrolyzed to the corresponding ketone under standard Pd/C-catalyzed oxidation conditions in ethylene glycol to give valerophenone (**5a**) in 18% yield [Scheme 2-(1)]. Meanwhile, the ketone moiety of **5a** never converted to the ketal (**2a**) under standard conditions [Scheme 2-(2)]. When using **6** as a substrate possessing the secondary benzylic alcohol moiety instead of benzylic ether, a mixture of a ketone (**5a**) and pentylbenzene (**7**) was obtained accompanied without the formation of the corresponding ketal (**2a**) [Scheme 2-(3)]. These results indicated that cyclic ketal derivatives could be catalytically, oxidatively, and directly prepared from the secondary benzylic ethers without stepwise going through the corresponding alcohol and ketone intermediates. Because the Pd/C-catalyzed oxygen oxidation of **1a** was entirely suppressed by the addition of 7,7,8,8-tetracyanoquinodimethane (TCNQ) or tetracyanoethylene (TCNE) [Scheme 2-(4)], it was suggested that the reaction proceeded via a radical pathway.



Scheme 2. Mechanistic Studies

A proposed reaction mechanism is shown in Scheme 3. Hydrogen (H_2), generated by the Pd/C-catalyzed dehydrogenation[11] of ethylene glycol, was smoothly coupled with oxygen (O_2) under the Pd/C-catalyzed reaction conditions to produce the hydroxy radical via formation of the hydrogen peroxide (H_2O_2).[12] Subsequently, the hydroxyl radical promotes the formation of the benzyl radical intermediate (**B**) from the benzyl ethers (**1**). An alkoxy radical, generated by the reaction of ethylene glycol with the hydroxyl radical, coupled with **B** to give a mixed acetal intermediate (**C**). **C** was further transformed into the cyclic ketal (**2**) via the formation of an oxonium ion intermediate and subsequent intramolecular cyclization. In the case of primary benzylic ethers (**3**) as substrates, the intermediate (**A**) possessing a highly reactive benzylic C-H bond generated during the first oxidation step was continuously converted to **E** via **D** by a reaction mechanism similar to the conversion process from **1** to **C**. Subsequently, the simple hydrolysis of **E** by H_2O generated as the reaction progressed gave benzoic acid hydroxyethyl ester derivatives (**4**).



Scheme 3. Proposed Reaction Mechanism

In conclusion, we have established the selective and clean Pd/C-catalyzed oxidative transformation of benzylic ethers in ethylene glycol under an O_2 atmosphere. Secondary benzylic ethers could be transformed into the corresponding cyclic ketals, and primary benzylic ethers were converted to hydroxyethyl ester derivatives via a two-step oxidation process. The present reaction using Pd/C as an easily removal heterogeneous catalyst from a reaction system and an environmentally benign molecular oxygen supply a straightforward synthetic route to construct the target molecules.

EXPERIMENTAL

Typical Procedure: An alkyl benzyl ether (**1** or **3**; 0.2 mmol), 10% Pd/C (21.3 mg, 0.02 mmol, 10 mol%), and ethylene glycol (2 mL) were placed in a test tube, and the test tube was sealed with a septum. The inside air was replaced with O_2 (balloon). The mixture was stirred using a ChemiStation (EYELA, Tokyo Rikakikai Co., Ltd., Tokyo, Japan) and heated at 80 °C for 24 h. After cooling to room temperature, the reaction mixture was passed through a pad of silica-gel and washed with *n*-hexane/AcOEt. The combined filtrate and washing solvents were concentrated in vacuo. The residue was purified by silica-gel column chromatography using *n*-hexane/AcOEt as an eluent to give the product (**2** or **4**). See Supporting Information for characterization details.

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