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# Palladium on Carbon-Catalyzed Benzylic Methoxylation for Synthesis of Mixed Acetals and Orthoesters

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**Abstract:** The palladium on carbon (Pd/C)-catalyzed direct methoxylation of the benzylic positions of linear benzyl and cyclic ether substrates proceeded in the presence of *i*-Pr<sub>2</sub>NEt under oxygen atmosphere to give the corresponding mixed acetals. Cyclic acetal derivatives could also be converted into orthoesters. The present direct methoxylation via a carbon-hydrogen (C-H) functionalization can be accomplished using the easily-removed Pd/C, and molecular oxygen as a green oxidant. The obtained mixed acetals were transformed into the corresponding ether products via the chemoselective substitution of the methoxy group using a silyltriflate, 2,4,6-collidine, and a nucleophile. The orthoester derivative could also be transformed into the cyclic ketal under similar reaction conditions.

#### Introduction

Mixed acetals bearing two different alkoxy groups on one carbon atom are widely utilized as synthetic precursors, and numerous preparation methods have been developed.1-12 Although the acid-catalyzed transacetalization of a symmetrical acetal [-CH(OR<sup>1</sup>)<sub>2</sub>] with an alcohol (R<sup>2</sup>OH) is generally adopted to produce the corresponding mixed acetal [-CH(OR<sup>1</sup>)(OR<sup>2</sup>)] as a simple preparation method, the avoidance of the overreaction into another symmetrical acetal [-CH(OR<sup>2</sup>)<sub>2</sub>] is generally difficult.<sup>1</sup> A reliable preparation method of mixed acetals from symmetrical acetals has been developed by the Fujioka and Kita group via the intermediary pyridinium salts using stoichiometric pyridine and silyltriflate derivatives and the subsequent addition of an alcohol.<sup>2</sup> Although direct alkoxylation reactions of the benzylic positions of the benzyl ether derivatives using a stoichiometric oxidant [e.g., tert-butyl peroxide (TBHP),<sup>3</sup> 2,3dichloro-5,6-dicyano-p-benzoquinone (DDQ),4 bis(trifluoroacetoxy)iodobenzene,<sup>5</sup> nitric oxide/Nor hydroxyphthalimide (NHPI)<sup>6</sup>] could provide mixed acetals, the applicable substrates were quite limited. On the other hand, the intramolecular cyclization of ether substrates bearing a hydroxyl group within the same molecule using DDQ<sup>7</sup>, an iodine oxidant<sup>8</sup> or N-iodosuccinimide (NIS)<sup>9</sup> has been accomplished to synthesize the acetals. While the transition metal (Co<sup>10</sup> or Ru<sup>11</sup>)catalyzed direct transformation methods into mixed acetals from the corresponding allyl alcohols with an additional alcohol has been reported, a catalytic method based on the C-H

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functionalization of the benzylic position of benzyl ethers into mixed acetals has never been developed. We now demonstrate a palladium on carbon (Pd/C)-catalyzed intermolecular methoxylation of linear and cyclic benzyl ethers (1) using oxygen as a green oxidant in the presence of *i*-Pr<sub>2</sub>NEt in MeOH (Scheme 1). Additionally, the methoxylation of cyclic acetals (1') into orthoesters (2') was also accomplished under the present Pd/C-catalyzed reaction conditions. Orthoesters are widely used as dehydrating agents and alcohol sources,<sup>12</sup> and applied to the selective functionalization of steroid derivatives.<sup>13</sup> We have also achieved versatile nucleophilic substitutions based on the elimination of the methoxy group of the prepared 2 and 2' to give the corresponding ether (5) and ketal (5') derivatives.



 $\label{eq:scheme-1} \begin{array}{l} \mbox{Scheme-1.} \mbox{Pd/C-catalyzed benzylic methoxylation under oxygen atmosphere and its application.} \end{array}$ 

### **Results and Discussion**

We have recently accomplished the Pd/C-catalyzed oxygen oxidation of aromatic cyclic acetals to benzoic acid hydroxyalkyl ester derivatives via the direct C-H functionalization of the benzylic positions.<sup>14</sup> Benzyl *n*-butyl ether (1a) also underwent the Pd/C-catalyzed oxidation in MeOH under an oxygen atmosphere at 80 °C for 12 h to give the corresponding esters (3a and 4a) in good total yields (73%, Table 1, entry 1). The addition of inorganic bases, such as NaOH, NaHCO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, NaOtBu and KOtBu, allowed the formation of the mixed acetal (2a) by the direct methoxylation of 1a in low to moderate yields along with the generation of esters (3a and 4a) (entries 2-6). As the result of the further screening using organic bases, such as *N*-methvl *i*-Pr<sub>2</sub>NEt, morpholine, Et₃N, 14-(DABCO) diazabicyclo[2.2.2]octane and 1.8diazabicyclo[5.4.0]undec-7-ene (DBU) (entries 7-12), i-Pr<sub>2</sub>NEt was chosen as a relatively favorable base, although the starting material (1a) was not completely consumed (entry 10). While extension of the reaction time to 24 h was not effective (entry 13), the increased use of Pd/C (15 mol%) could improve the reaction efficiency to give 2a in 84% (entry 14). Meanwhile, heating at 60 °C was not effective for the methoxylation (entry

15), and the reaction hardly proceeded under argon (Ar) and ambient air conditions (entries 16 and 17).

Table 1. Base efficiency in Pd/C-catalyzed methoxylation of benzyl butyl ether  $\left( 1a\right)$ 

Ph <sup>^</sup> O <sup>^</sup> <b>1a</b> (0.25 m	1 <i>_ n-</i> Bu ımol)	0% Pd/C (5 mol%) base (1 equiv) <u>O2</u> MeOH (1 mL) 80 °C, 12 h	OMe Ph └ O <sup>, n-Bu</sup> 2a	0 <sup>J</sup> + Ph	`O <sup>∕n-Bu</sup> +⊺ 3a	O ⊢ OMe 4a	
entry	base		yield (%)				
			SM (1a)	2a	3a	4a	

		SM ( <b>1a</b> )	2a	3a	4a
1	—	0	0	35	38
2	NaOH	0	5	40	40
3	NaHCO <sub>3</sub>	0	54	16	10
4	Na <sub>2</sub> CO <sub>3</sub>	0	28	32	16
5	NaO <i>t</i> Bu	0	56	16	8
6	KO <i>t</i> Bu	0	7	40	19
7	morpholine	98	0	0	0
8	N-methylmorpholine	13	50	14	2
9	Et <sub>3</sub> N	45	18	4	3
10	<i>i</i> -Pr <sub>2</sub> NEt	37	44	7	3
11	DABCO	0	65	13	2
12	DBU	100	0	0	0
13 <sup>[a]</sup>	<i>i</i> -Pr <sub>2</sub> NEt	34	53	7	5
14 <sup>[a,b]</sup>	<i>i</i> -Pr <sub>2</sub> NEt	1	84	6	4
15 <sup>[a,c]</sup>	<i>i</i> -Pr <sub>2</sub> NEt	14	56	13	5
16 <sup>[a,d]</sup>	<i>i-</i> Pr <sub>2</sub> NEt	83	10	0	0
17 <sup>[a,e]</sup>	<i>i-</i> Pr₂NEt	72	16	1	0

[a] For 24 h. [b] 15 mol% of 10% Pd/C was used. [c] At 60  $^{\circ}\text{C}.$  [d] Under Ar. [e] Under air.

The present methoxylation of **1a** could be smoothly catalyzed by only Pd/C to give the desired mixed acetal **(2a)** (Table 2, entry 1), while other platinum group metal on carbon (Pt/C, Ru/C, Rh/C and Ir/C) and Au/C were all ineffective (entries 2-6).

Table 2. Catalyst efficiency.					
Ph 1a (0.25	catalyst (15 mol%) <i>i</i> ·Pr <sub>2</sub> NEt (1 equiv) 0 ^n-Bu 0 2 MeOH (1 mL) 5 mmol) 80 °C, 24 h	OMe Ph O <sup>-n-1</sup> 2a	O Bu <sub>+ Ph</sub> ∬	o <sup>-n-Bu</sup> + Ba	O Ph OMe <b>4a</b>
entry	catalyst	yield (%)			
entry	catalyst	yield (%) SM ( <b>1a</b> )	2a	3a	4a
entry 1	catalyst 10% Pd/C	yield (%) SM ( <b>1a</b> )	<b>2a</b> 84	<b>3a</b> 6	<b>4a</b> 4

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			35 85	C1.007	UE02351203
3	10% Ru/C	96	0	0	0
4	10% Rh/C	96	0	0	1
5	10% lr/C	97	0	0	1
6	10% Au/C	92	0	0	0

The scope of the substrates was next investigated (Table 3). Benzyl ethers (1a-1f) bearing kinds of various alkyl chains were efficiently transformed into the corresponding mixed acetals (2a-2f) (entries 1-6). Phthalane (1g) and isochroman (1h) as cyclic underwent the Pd/C-catalyzed benzylic ethers also methoxylation to be converted into the desired mixed acetals (2g and 2h) in moderate yields along with the over-oxidized cyclic esters (3g and 3h) (entries 7 and 8). 2-Phenyltetrahydrofuran (1i) was also transformed into the corresponding mixed acetal (2i) even in a moderate yield (entry 9). On the other hand, aromatic 5-membered cyclic acetals (1'a and 1'b) efficiently underwent the Pd/C-catalyzed methoxylation to give the corresponding orthoesters (2'a and 2'b) (entries 10 and 11), while the reaction of benzaldehyde dimethyl acetal (1'c) as an acyclic substrate hardly proceeded (entry 12). The steric strain of the benzylic position may be necessary to facilitate the methoxylation of the 5-membered cyclic acetals (1'a and 1'b), therefore, the over-reaction can be suppressed in the methoxylation of the acyclic benzyl ethers (1a-1f) (entries 1-8). However, the structurally distorted cyclic acetal products (2g and 2h) partially underwent the second methoxylation at the benzylic positions into the comparatively unstable orthoesters bearing two methoxy groups,<sup>15</sup> which were converted to esters by partial hydrolysis (3g and 3h). Meanwhile, the relatively flexible 6membered cyclic acetal (1'd) was less reactive. Consequently, the desired orthoester (2'd) was obtained in a low yield, and 83% of the unchanged starting material (1'd) was recovered (entry 13).

Table 3. Scope of substrates.

	10% Pd/C (15 mol%)	
	<i>i-</i> Pr <sub>2</sub> NEt (1 equiv)	
substrate (1)	$O_2$ product (2)	
substrate (1)	MeOH (1 mL)	
	80 °C, 24 h	

entry	substrate	product	yield (%)
		OMe	
	Ph OR	PhOR	
1	R = <i>n-</i> Bu ( <b>1a</b> )	2a	84
2	R = <i>n</i> -C <sub>12</sub> H <sub>25</sub> ( <b>1b</b> )	2b	77
3 <sup>[a]</sup>	R = <i>iso-</i> Am ( <b>1c</b> )	2c	75
4	R = <i>iso</i> -Pr ( <b>1d</b> )	2d	47
5	R = <i>c</i> -Hex ( <b>1e</b> )	2e	80
6 <sup>[a]</sup>	R = <i>tert-</i> Bu ( <b>1f</b> )	2f	78
7 <sup>[a]</sup>			53
	l 1g	OMe	
		2g	19

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OMe

MeOH

Ō,

С



froute al

[route b]

O

MeOH

MeO

H<sub>2</sub>O



[a] 25 mol% of 10% Pd/C was used.[b] 5 mol% of 10% Pd/C was used.[c] The recovered yield of the starting material.

Phenethyl *n*-butyl ether (**1**) without the benzylic position adjacent to the oxygen atom was inactive against the Pd/C-catalyzed methoxylation and remained unchanged (eq. 1). Furthermore, the methoxylation of **1a** was completely inhibited by the addition of 7,7,8,8-tetracyanoquinodimethane (TCNQ) or tetracyanoethylene (TCNE) as a radical scavenger (eq. 2). Based on these results, it is presumed that the present methoxylation of benzyl ethers is initiated via the generation of a benzylic radical intermediate,<sup>16</sup> which is known to be comparatively stable.



A presumable reaction mechanism is shown in Scheme 2. Hydrogen (H<sub>2</sub>) generated by the Pd/C-catalyzed dehydrogenation<sup>17</sup> of MeOH is reacted with oxygen (O<sub>2</sub>) to produce hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>)<sup>18</sup>, which can be transformed to a hydroxyl radical. The benzyl radical intermediate (**A**) produced by the substrate (**1**) and hydroxyl radical is smoothly trapped by a methoxy radical generated from MeOH and a Scheme 2. Proposed reaction mechanism.

Pd/C O<sub>2</sub>

H<sub>2</sub>O<sub>2</sub> H<sub>2</sub>O + HO

MeOH

After the formation of 2a in 84% for 24 h by the Pd/Ccatalyzed methoxylation of 1a (Table 1, entry 14), a very small amount of Pd leaching [0.1% of Pd (1.7 ppm) based on the used Pd amount on 10% Pd/C] was observed (See Supporting Information). When the reaction was stopped in a short time (6 h), 45% of 2a, and 40% of the unreacted starting material (1a) together with total 2% of ester products (3a and 4a) were obtained (eq. 3, X = 0). After hot filtration<sup>19</sup> of the reaction mixture, the filtrate was heated again under oxygen atmosphere for further 18 h to give 2a in 49%, the recovered 1a (29%) and total 8% of ester products (3a and 4a) (eq. 3, X = 18). A small amount of 1a was consumed and the yields of the oxidized products (2a, 3a and 4a) slightly increased, but the reaction was not completed. These results indicated that both leached Pd and supported Pd species could additionally facilitate the oxidation of 1a. Because the property of Pd species activated on carbon may be changed during the heating process, the yields of 2a gradually decreased by the repeated use of recovered Pd/C (eq. 4.)



Chemical modifications of the mixed acetals and orthoesters were also investigated (Scheme 3). The methoxy group of **2e** and **2h** could be chemoselectively activated using a combination of triethylsilyl trifluoromethanesulfonate (TESOTf) and 2,4,6-collidine,<sup>20</sup> and the subsequent nucleophilic substitution using 1-phenyl-1-trimethylsiloxyethylene gave **5e** and **5h** in good yields.

It is noteworthy that the orthoester (2'a) was also transformed into the corresponding ketal (5'a) in 69% yield under similar conditions.



Scheme 3. Chemical modification of mixed acetals and orthoester.

#### Conclusions

We have developed an efficient synthetic method of mixed acetals starting from benzyl ethers by the Pd/C-catalyzed oxidative benzylic methoxylation in the presence of *i*-Pr<sub>2</sub>NEt in MeOH under atmospheric oxygen. Furthermore, the present methoxylation method can also be applied to the orthoester synthesis using aromatic cyclic acetals as substrates. The present first catalytic method combined with molecular oxygen as a clean oxidant is valuable from the viewpoint of green sustainable chemistry.

#### **Experimental Section**

# General Procedure for the Conversion of Benzyl Ester 1a to Mixed Acetal 2a

To a test tube were added benzyl ester (**1a**; 41.1 mg, 0.25 mmol), 10% Pd/C (39.9 mg 0.0125 mmol), *i*-Pr<sub>2</sub>NEt (44.5  $\mu$ L, 0.25 mmol) and MeOH (1 mL), then the test tube was sealed with a septum. The inside air was replaced with O<sub>2</sub> (ballon). The reaction mixture was stirred with a Chemi Station (EYELA, Tokyo Rikakikai Co., Ltd., Tokyo, Japan) and refluxed [80 °C outer aluminum heating block temperature]. After 24 h, the reaction mixture was cooled to room temperature and passed through a membrane filter (Millipore, Millex-LH, 0.20 mm) to remove Pd/C. The filtrate was extracted with Et<sub>2</sub>O (10 mL × 2) and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo. The residue was purified by silica-gel column chromatography using a mixed eluent (hexane/AcOEt = 20/1) to give the corresponding mixed acetal (**2a**; 40.7 mg, 84 %). See the Supporting ionformation for characterization details.

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# **Keywords:** Green chemistry • Heterogeneous catalysis • Oxygen • Palladium

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The direct synthesis of mixed acetals and orthoesters from the corresponding benzylic ethers has been accomplished using palladium on carbon catalyst in MeOH under oxygen atmosphere in the presence of *i*-Pr<sub>2</sub>NEt. The present catalytic method using molecular oxygen as a clean oxidant and easily-recovered Pd/C is valuable from the viewpoint of green sustainable chemistry.

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#### **C-H Methoxylation**

Naoki Yasukawa, Takafumi Kanie, Marina Kuwata, Yasunari Monguchi, Hironao Sajiki\* and Yoshinari Sawama\*

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