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Benzyl Protection of Phenols under Neutral Conditions: Palladium-Catalyzed Benzylations of Phenols

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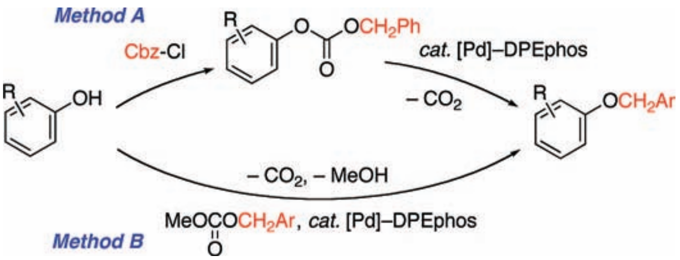
ABSTRACT



Benzyl protection of phenols under neutral conditions was achieved by using a Pd(η^3-C_3H_5)Cp–DPEphos catalyst. The palladium catalyst efficiently converted aryl benzyl carbonates into benzyl-protected phenols through the decarboxylative etherification. Alternatively, the nucleophilic substitution of benzyl methyl carbonates with phenols proceeded in the presence of the catalyst, yielding aryl benzyl ethers.

Benzyl ethers are frequently used as protecting groups for alcohols, including phenols, in organic synthesis.[1] Typically, the benzyl protection has been carried out by treating alcohols with a benzyl halide in the presence of a stoichiometric base, such as potassium hydroxide and sodium hydride.[2] The benzyl protection of alcohols without a base has been achieved by using benzyl trichloroacetimidate[3] or other *O*-benzyl imidates[4,5] in the presence of an acid promoter. Benzyl diphenylphosphinite[6] and 2-benzyloxy-1-methylpyridinium triflate[7] are known as effective benzylating agents of hydroxy groups under neutral conditions. However, the reagents require stoichiometric 2,6-dimethylbenzoquinone or magnesium oxide for producing benzyl ethers in high yield.

We previously reported the nucleophilic substitutions of benzyl methyl carbonates **1** with a palladium catalyst.[8,9] The reaction probably proceeds through the pathway as shown in Scheme 1. Palladium(0) activates the benzylic C−O bond of **1** to form the (η^3-benzyl)palladium intermediate **A**. Concurrent decarboxylation of the leaving group gives methoxide, which will work as a base for generating

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10.1021/ol800548t CCC: $40.75

Scheme 1. Possible Pathway of the Palladium-Catalyzed Nucleophilic Substitution of Benzyl Methyl Carbonates **1**

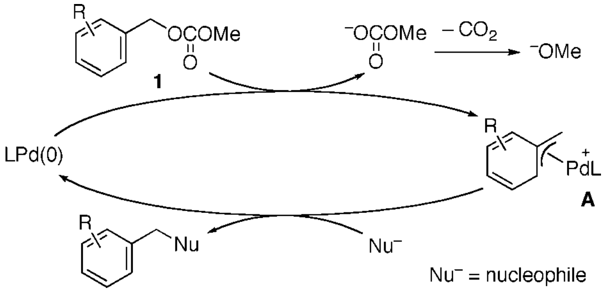
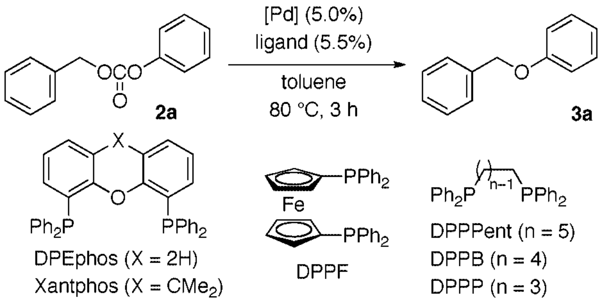


Table 1. Effect of Catalyst on the Reaction of **2a**[a]



entry	[Pd]	ligand	yield (**3a**), %[b]
1	Pd(η^3-C$_3$H$_5$)Cp	DPEphos	99 (99)[c]
2	Pd(η^3-C$_3$H$_5$)Cp	Xantphos	95 (38)[c]
3	Pd(η^3-C$_3$H$_5$)Cp	DPPF	97 (4)[c]
4	Pd(η^3-C$_3$H$_5$)Cp	DPPPent	11
5	Pd(η^3-C$_3$H$_5$)Cp	DPPB	66
6	Pd(η^3-C$_3$H$_5$)Cp	DPPP	6
7	Pd(η^3-C$_3$H$_5$)Cp	PPh$_3$[d]	0
8[e]	Pd(OAc)$_2$	DPEphos	0
9	Pd(dba)$_2$	DPEphos	0

[a] Reactions were conducted on a 0.2 mmol scale in toluene (1.0 mL) at 80 °C for 3 h. The ratio of **2a**/[Pd]/ligand was 20:1.0:1.1. [b] GC yield (average of two runs). [c] Yields in parentheses are GC yields of the reactions at 60 °C. [d] Ratio of [Pd]/PPh$_3$ was 1.0:2.2. [e] Et$_3$N (20 μmol) was added to the reaction mixture to reduce Pd(OAc)$_2$ to Pd(0).

nucleophilic species. We envisioned that in the absence of pronucleophile, the catalytic reaction would provide benzyl methyl ether via alkoxide attack to the η^3-benzyl ligand. Such a decarboxylative etherification would be useful for the benzyl protection of alcohols if the reaction would occur in various alkyl and/or aryl benzyl carbonates. Here, we report a decarboxylative etherification of aryl benzyl carbonates by means of the palladium catalysis, which afforded a broad range of benzyl-protected phenols in high yield. Additionally, the palladium catalyst is effective for the direct benzyl protection of phenols with benzyl methyl carbonate. Both etherifications do not require any additives other than the palladium catalyst.[10]

In a series of our studies on the palladium-catalyzed transformations of **1**,[8] we have never observed the formation of benzyl methyl ether.[11] Consequently, we evaluated various palladium complexes for the reaction of benzyl phenyl carbonate (**2a**), because softer phenoxide would be more reactive to the η^3-benzyl ligand on palladium than harder methoxide (Table 1).[12,13] The quantitative formation of benzyl phenyl ether (**3a**) was observed at 80 °C in the reaction using the palladium catalyst, which was generated in situ from Pd(η^3-C$_3$H$_5$)Cp[14] and a bisphosphine ligand, DPPF,[15] DPEphos,[16] or Xantphos[16] (entries 1−3). In particular, the DPEphos–palladium catalyst produced the desired ether in high yield even at 60 °C. Use of other bisphosphine ligands resulted in lower yields (entries 4−6). No benzyl ether **3a** was produced in the reaction employing monophosphine ligands (entry 7). Choice of palladium precursor was crucial for the catalytic reaction. The substrate **2a** was scarcely consumed when it was treated with the palladium catalyst prepared from Pd(OAc)$_2$ or Pd(dba)$_2$. The hemilabile ligands constituting these catalyst precursors might obstruct the interaction between palladium(0) and the benzyl carbonate. The catalyst loading was successfully reduced to 1.0% without significant loss of the yield of **3a** (Table 2, entry 1).

As shown in Table 2, a wide range of aryl benzyl carbonates **2** were transformed into the benzyl ethers in high yield by Pd(η^3-C$_3$H$_5$)Cp–DPEphos catalyst. Electron-donating or electron-withdrawing property of the *p*-substituent of **2c**−**e** hardly caused significant decrease in the yield of **3** (entries 3−5). The decarboxylative etherification of 4-methyl- or 4-nitrophenyl carbonate failed to give **3b** or **3f** in acceptable yield when the reactions were conducted in the presence of 1.0% palladium. However, higher yield of the benzyl ethers was obtained with 5% catalyst loading (entry 2 and 6). Two ortho-methyl groups of **2h** did not hinder the catalytic production of **3h** (entry 8). Double etherification of **2k** proceeded well, affording benzyl-protected biphenol **3k** (eq 1). Benzyl 2-naphthyl carbonate was converted into the desired ether in only 46% yield. The low yield was caused by undesirable benzylation at the 1-position on the naphthalene ring.[13a] Alkyl benzyl carbonates did not work as substrates for the catalytic reaction. Treatment of benzyl cyclohexyl carbonate with the palladium catalyst yielded no benzyl cyclohexyl ether. Hardness of the alkoxides might reduce their nucleophilicity for the (η^3-benzyl)palladium intermediate. The present decarboxylative formation of benzyl ethers is applicable to protection of phenols with

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(10) Asao et al. reported a gold-catalyzed etherification using *o*-alkynylbenzoates as alkylating agents: Asao, N.; Aikawa, H.; Tago, S.; Umetsu, K. *Org. Lett.* **2007**, *9*, 4299–4302.

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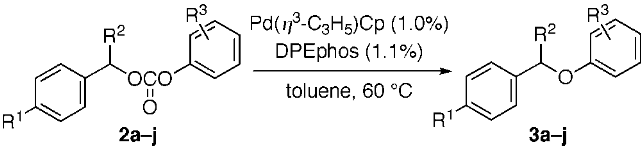
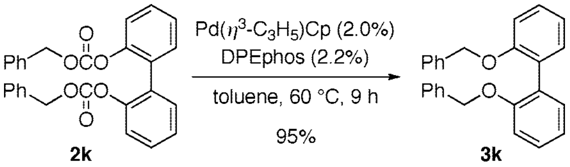
Table 2. Decarboxylative Etherification of Benzyl Aryl Carbonates **2**[a]



entry	R^1	R^2	R^3	**2**	time, h	yield (**3**), %[b]
1	H	H	H	**2a**	3	96
2[c]	H	H	4-Me	**2b**	3	83
3	H	H	4-MeO	**2c**	3	97
4	H	H	4-MeO$_2$C	**2d**	24	95
5	H	H	4-Cl	**2e**	3	96
6[c]	H	H	4-NO$_2$	**2f**	22	89
7	H	H	3-MeO	**2g**	3	94
8	H	H	2,6-Me$_2$	**2h**	3	97
9	MeO	H	H	**2i**	3	97
10[d]	H	Ph	H	**2j**	24	85

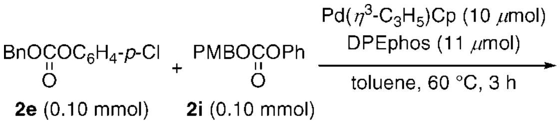
[a] Reactions were conducted on a 1.0 mmol scale in toluene (1.0 mL) at 60 °C unless otherwise noted. The ratio of **2**/Pd(η^3-C$_3$H$_5$)Cp/DPEphos 100:1.0:1.1. [b] Isolated yield. [c] Reaction was conducted on a 0.2 mmol scale with 5% catalyst loading. [d] Reaction was conducted with 2% catalyst loading by using DPPF in place of DPEphos.

p-methoxybenzyl (PMB) or diphenylmethyl group (entries 9 and 10). In the latter case, efficient catalytic etherification was achieved by using DPPF in place of DPEphos ligand.



(1)

A 1:1 mixture of two aryl benzyl carbonates **2e** and **2i** was heated at 60 °C in the presence of the DPEphos–palladium catalyst, yielding the crossover products **3a** and **3i’** as well as **3e** and **3i** (eq 2). The observation indicates that the catalytic cycle of the decarboxylative etherification involved rapid exchange of phenolates. The catalytic reaction might proceed through an ion pair of cationic (η^3-benzyl)palladium and phenolate rather than through neutral (η^1-benzyl)(phenolato)palladium intermediate.

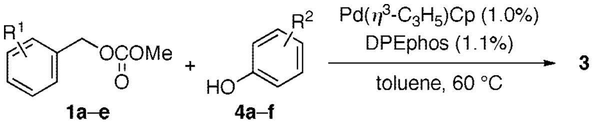


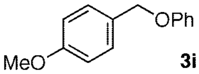
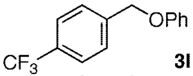
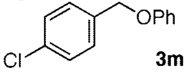
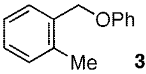
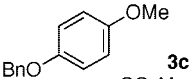
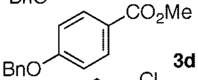
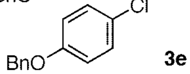
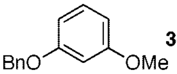
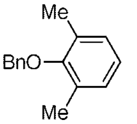
$$\underset{\textbf{2e}\ (0.10\ \text{mmol})}{\mathrm{BnO}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{OC_6H_4\text{-}}\mathit{p}\text{-}\mathrm{Cl}} + \underset{\textbf{2i}\ (0.10\ \text{mmol})}{\mathrm{PMBO}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\mathrm{OPh}} \xrightarrow[\text{toluene, 60 °C, 3 h}]{\substack{\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cp (10 }\mu\text{mol)}\\ \text{DPEphos (11 }\mu\text{mol)}}} \qquad (2)$$

BnOC$_6$H$_4$-*p*-Cl + PMBOPh + BnOPh + PMBOC$_6$H$_4$-*p*-Cl
3e (57%) **3i** (49%) **3a** (43%) **3i'** (43%)

The results of the crossover experiment stimulated us to develop direct etherification of phenols with benzyl methyl carbonates without use of base. The methoxide anion, which was liberated by the oxidative addition of **1a** to palladium(0), might rapidly be replaced with phenol. The resulting phenoxide was expected to attack on (η^3-benzyl)palladium to give the desired benzyl phenyl ether. Consequently, benzyl methyl carbonate (**1a**) was treated with phenol (**4a**) in the presence of the DPEphos–palladium catalyst (Table 3, entry 1). As expected above, benzyl phenyl ether (**3a**) was obtained in 96% yield. Similarly, electron-rich benzylic carbonate **1b** underwent the nucleophilic substitution with **4a** (entry 2). The catalytic substitution was remarkably accelerated by electron-withdrawing substituent of **1c** (entry 3). The methyl group at the ortho-position of **1e** did not hinder the catalytic etherification (entry 5). Various substituted phenols **4b**−**f** were alkylated with **1a** by means of the DPEphos–palladium catalysis (entries 6−10). Electron-deficient phenols required 5% catalyst loading for complete conversion into benzyl ethers. The etherification of **4** with **1a** was generally slow as compared with the decarboxylative reaction of **2** in Table 2. Acidic property of phenolic hydroxy group might retard the catalytic etherification of **4** with **1a**.

Table 3. Nucleophilic Substitution of Benzyl Methyl Carbonates **1** with Phenols **4**[a]



entry	R^1 (**1**)	R^2 (**4**)	time, h	product (**3**)	yield, %[b]
1	H (**1a**)	H (**4a**)	24	BnOPh **3a**	96
2	4-MeO (**1b**)	H (**4a**)	24	 OPh, MeO **3i**	97
3	4-CF$_3$ (**1c**)	H (**4a**)	3	 OPh, CF$_3$ **3l**	96
4	4-Cl (**1d**)	H (**4a**)	24	 OPh, Cl **3m**	78
5	2-Me (**1e**)	H (**4a**)	24	 OPh, Me **3n**	97
6	H (**1a**)	4-MeO (**4b**)	20	 OMe, BnO **3c**	96
7[c]	H (**1a**)	4-MeO$_2$C (**4c**)	22	 CO$_2$Me, BnO **3d**	96
8[c]	H (**1a**)	4-Cl (**4d**)	16	 Cl, BnO **3e**	90
9	H (**1a**)	3-MeO (**4e**)	24	 BnO, OMe **3g**	94
10	H (**1a**)	2,6-Me$_2$ (**4f**)	3	 Me, BnO, Me **3h**	89

[a] Reactions were conducted on a 1.0 mmol scale in toluene (1.0 mL) at 60 °C unless otherwise noted. The ratio of **1**/**4**/Pd(η^3-C$_3$H$_5$)Cp/DPEphos was 100:120:1.0:1.1. [b] Isolated yield. [c] Reactions were conducted on a 0.2 mmol scale with 5% catalyst loading.

In summary, we developed two new protocols for benzyl protection of phenols under neutral conditions using the palladium catalyst, which was generated in situ from Pd(η^3-C_3H_5)Cp and DPEphos. One is the decarboxylative reaction of aryl benzyl carbonates, which are readily prepared by the esterification of phenols with Cbz-Cl. In another protocol, phenols were directly benzylated with benzyl methyl carbonate **1**. Both reactions afforded the desired aryl benzyl ethers **3** in high yield without any additives other than DPEphos–palladium complex. It is of note that only volatile byproducts were generated from the catalytic reaction. However, the palladium-catalyzed methods require heating and are limited to only phenols at this stage. Further investigation is in progress to overcome the disadvantages.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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