Palladium-catalyzed Benzylic Substitution of Benzyl Carbonates with Phosphorus Nucleophiles

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A wide range of benzyl carbonates reacted with dimethyl phosphonate or diphenylphosphine oxide in the presence of the palladium catalyst, $[Pd(\eta^3-allyl)Cl]_2$ –DPEphos, to give dimethyl benzylphosphonates and benzyldiphenylphosphine oxides in high yields. The catalytic phosphonylation was applied to the one-pot synthesis of alkenes from the benzyl esters.

Keywords:	Palladium catalyst	Benzylic substitution		
	Phosphorus nucleophiles			

Organophosphorus compounds are of great importance in various phases of organic chemistry, e.g., Wittig and Horner–Wadsworth–Emmons reagents,¹ chiral ligands,² enzyme inhibitors,³ and emitting dyes.⁴ A variety of reactions have been developed for the preparation of organophosphorus compounds.⁵ Among them, the substitution of organohalides with phosphorus nucleophiles through transition-metal catalysis is advantageous in terms of functional group compatibility, because the reactions proceed well under mild conditions.^{5g,5h,5k} However, the organohalides have a great negative impact on the environment as well as the ecosystem. Toward solution of this drawback, the unreactive C–O bond is an attractive alternative to the C–X (X = halogen) bond. However, the use of ethers or carboxylates is not well studied for catalytic C–P bond formation.⁶

We have developed nucleophilic substitutions of benzyl carbonates through palladium catalysis,^{7,8} which involves electrophilic (n³-benzyl)palladium as a key intermediate.⁹ A variety of nucleophilic compounds work as the reaction partners of the benzyl esters. However, the use of phosphorus nucleophiles has been virtually unexplored for the benzylic substitution, while some phosphorus nucleophiles are often used for the nickel- or palladium-catalyzed allylic and propargylic substitutions.¹⁰ As a related study, the reaction of benzyl alcohols with hypophosphorous acid had been developed with a palladium catalyst by Montchamp. The reaction requires an excess amount of the phosphorus nucleophile to obtain the desired products in good yields.^{11,12} Moreover, Chen and Han recently used a benzyl ester as the electrophilic substrate in their study on the nickel-catalyzed C-O/P-H coupling reaction, but the substrate scope was limited to (2-naphthyl)methyl pivalate.^{6e} Here, we have successfully developed the palladium-catalyzed benzylic substitution with dimethyl phosphonate or diphenylphosphine oxide. It is noteworthy that the latter nucleophile efficiently provides a broad range of benzyldiphenylphosphine oxides, which are useful for the synthesis of phosphine ligands^{2,13} or as the substrates of Horner-Wittig reaction.^{1,14}

The reaction of benzyl methyl carbonate (1a) with dimethyl phosphonate (2a) was carried out in DMSO at 80 °C with $[Pd(\eta^3-allyl)Cl]_2$ -DPEphos catalyst (Table 1, Entry 1). The reaction conditions are optimal for the palladium-catalyzed

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Table 1. Effects of solvent and ligand on the palladiumcatalyzed nucleophilic substitution of 1a with $2a^{a}$



Entry	Solvent	Ligand	Temp. /°C	Time /h	Yield /% ^b
1	DMSO	DPEphos	80	5	11
2	DMF	DPEphos	80	5	39
3	^t AmOH	DPEphos	80	5	25
4	EtOAc	DPEphos	80	5	2
5	THF	DPEphos	80	5	4
6	toluene	DPEphos	80	5	5
7	DMF	Xantphos	80	5	2
8	DMF	DPPF	80	5	16
9	DMF	DPPPent	80	5	6
10	DMF	DPPE	80	5	0
11 ^c	DMF	PPh ₃	80	5	0
12 ^d	DMF	DPEphos	80	48	63
13 ^d	DMF	DPEphos	100	24	76 ^e
14 ^d	DMF	DPEphos	120	5	63 ^e

^aUnless otherwise noted, all reactions were carried out with 0.20 mmol of **1a** and 0.24 mmol of **2a** in 1.0 mL of solvent under N₂; [Pd] = 0.5[Pd(η^3 -allyl)Cl]₂. ^bDetermined by ¹H NMR analysis. ^c11.0% of PPh₃ was used. ^d1.0 mmol of **1a** and 1.2 mmol of **2a** were used with 1.0% of [Pd] and 1.1% of DPEphos. ^eYield of isolated **3a**.

benzylic sulfinylation reported by us.^{7c} Formation of the desired benzylphosphonate **3a** was detected in the reaction mixture by ¹HNMR analysis, but the yield of **3a** was only 11%. The yield was improved by conducting the reaction in other polar solvents, such as DMF or *tert*-amyl alcohol (Entries 2 and 3). In particular, the use of DMF resulted in the highest yield. Meanwhile, the benzylic C–P bond formation scarcely took place in less polar solvents (Entries 4–6). The choice of phosphine ligand on the palladium is crucial for the efficient production of **3a** (Entries 7–11). DPPF–palladium complex can work as the catalyst for the benzylic phosphonylation. However, no formation of **3a** was observed when the palladium was modified with a chelate bisphosphine bearing small bite angle or

Ar C	сом	^e + HP((1.0% [Pd] (OMe), 1.1% DPEphos Ar	P(OMe) ₂
1	Ö		2a DMF, 100°C 3	ö
Entry	1	Time /h	3	Yield
1	1h	24	3b : R = Me	74
2	1c	24	3c : R = OMe	77
3	1d	24	3d : R = CO ₂ Me	e 69
4	1e	24	3e : R = CF ₃	71
5	1f	24	$\mathbf{P} = P(O)(OMe)_2$ 3f: R = F	70
6	1g	24	3g : R = Cl	65
7	1h	24	MeO ^H ^H ^H ^H ^H ^H ^H ^H	85
8	1i	24	Me P(OMe) ₂ " 3i	77
9 ^c	1j	72	Me Me Me P(OMe) ₂ O 3j	68
10 ^c	1k	3	P(OMe) ₂ U 3k	78

Table 2. Nucleophilic substitution of benzyl carbonates 1 with dimethyl phosphonate 2a^a

Table 3. Nucleophilic substitution of benzyl carbonates 1 with diphenyphosphine oxide 5^{a}

3.0% [Pd] 3.3% DPEphos

Ar 🔨	OCOM	÷ + HP	(O)Ph ₂ 3.3% DPEphos Ar	PPh ₂
1	ö		5 DMF, 100°C, 24 h	ö
Entry	1	Time /h	6	Yield /% ^b
1	1a	48	Ph PPh ₂ 0 6a	91
2	1b	24	6b : R = Me	96
3	1c	24	6c : R = OMe	94
4	1d	24	6d : R = CO ₂ Me	97
5	1e	24	6e : R = CF ₃	94
6	1f	48	$\mathbf{P} = \mathbf{P}(\mathbf{O})\mathbf{P}\mathbf{h}_2 \qquad \mathbf{6f}: \mathbf{R} = \mathbf{F}$	91
7	1g	24	6g ∶ R = Cl	98
8	1i	48	Me PPh ₂ Ö 6i	96
9°	1j	96	Me Me Me Me 6j	50
10 ^c	1k	24	PPh ₂ Ö 6k	88
11	11	24	PPh ₂ U 0 6l	96
12 ^c	1m	24	PPh ₂ O 6m	92

^aUnless otherwise noted, all reactions were carried out with 1.0 mmol of 1 and 1.2 mmol of 2a in 1.0 mL of DMF at 100 °C under N₂; $[Pd] = 0.5[Pd(\eta^3-allyl)Cl]_2$. ^bYield of isolated 3. °5.0% of [Pd] and 5.5% of DPEphos were used.

monophosphine. As a result of the further optimization of reaction parameters, the product 3a was isolated in 76% yield, when the mixture of **1a** and **2a** was heated at 100 °C for 24 h with 1% palladium loading (Entry 13). Although the related catalytic allylic substitutions with phosphorus nucleophiles are commonly conducted in the presence of a stoichiometric base, ^{10a,10b,10d,10j} the addition of any organic or inorganic bases failed to improve the present benzylic substitution. The bases mostly cause a deterioration of the reproducibility. The substrate 1a was completely consumed within 5 h, when the reaction was conducted at 120 °C. However, the higher reaction temperature caused the formation of unidentified side products (Entry 14).

As described in Table 2, various benzylphosphonates were synthesized through the benzylic phosphonylation with 2a by using the DPEphos-palladium catalyst. Both electron-donating and electron-withdrawing substituents on the para position have little effect on the reactivity of the benzylic esters (Entries 1-6). The halogen functionalities (F and Cl) were tolerant of the palladium catalysis. The halogenated substrates 1f and 1g were converted to 3f and 3g in good yields without formation of the dehalogenated product. As with the para-substituted benzyl substrates, 3-methoxybenzyl ester 1h gave the phosphonylated product 3h in 85% yield (Entry 7). The palladium catalyst is useful for the benzylic phosphonylation of ortho-substituted benzyl esters (Entries 8 and 9). The substrate having one orthomethyl group (1i) was comparable in reactivity to 1a. However, ^aUnless otherwise noted, all reactions were carried out with 0.50 mmol of 1 and 0.60 mmol of 5 in 1.0 mL of DMF at 100 °C under N₂; [Pd] = 0.5[Pd(η^3 -allyl)Cl]₂. ^bYield of isolated 6. °1.2 mmol of 5, 6.0% of [Pd], and 6.6% of DPEphos were used.

the methyl groups of 1j caused significant decrease in the reaction rate. The sufficient conversion of 1j to 3j required longer reaction time (72 h) as well as higher catalyst loading (5%). Naphthylmethyl ester 1k also reacted with 2a to give the desired product 3k (Entry 10).

Some phosphorus compounds other than dimethyl phosphonate 2a worked as the nucleophile for the catalytic benzylic substitution. Diethyl phosphonate 2b can react with 1a to give the benzyl phosphonates in good yields. However, the C-P bond formation was accompanied by a remarkable amount of transesterification (eq 1). The benzylation of diphenylphosphine oxide 5 also proceeded well to afford benzyldiphenylphosphine oxide 6a in 98% yield (eq 2). The catalyst loading can be reduced to 3% without significant loss of the yield (Table 3, Entry 1). No substitution was observed when diphenyl phosphonate and dibutylphosphine oxide were employed as the nucleophile. The former phosphorus compound might be insufficient in nucleophilicity for the attack on the $(\eta^3$ benzyl)palladium intermediate because of the more electronwithdrawing phenyl group.¹⁵ The latter nucleophile might poison the palladium catalysis because its Lewis basicity is so strong that the oxygen atom tightly interacts with the metal center.



Diphenylphosphine oxide (5) also reacted with a wide range of benzyl carbonates 1 to give the phosphinylated products in high yields. The substrate scope is summarized in Table 3. Electron-rich and electron-deficient benzyl carbonates 1b-1gwere transformed into the benzyldiphenylphosphine oxides 6b-6g in high yields (Entries 2–7). The *ortho*-substituent of 1i had no effect on the formation of 6i (Entry 8). However, the reaction of 1j was sluggish and failed to produce 6j in high yield even with higher catalyst loading (6%) and prolonged reaction time (96 h) (Entry 9). Naphthylmethyl esters 6k and 6l were also phosphinylated with 5 in high yields (Entries 10 and 11). Two phosphinyl groups were installed on the dicarbonate of *m*-xylene glycol to give 6m in 92% yield (Entry 12).

The present catalytic C–P bond formation is applicable to the one-pot synthesis of β -substituted styrenes from benzyl carbonate **1c** in combination with Horner–Wadsworth–Emmons reaction (Scheme 1). After the palladium-catalyzed phosphonylation of **1c** with **2a**, a solution of NaO'Bu in DMF was carefully added at 0 °C to the mixture containing **3c** in the presence of an aldehyde **7**. As a result, the alkenes **8** were obtained from the above reactions in good yields with excellent *E*-selectivity.

A possible mechanism of the catalytic substitution of benzyl carbonates with phosphorus nucleophiles is depicted in Scheme 2.⁹ The reaction is initiated by the oxidative addition of the benzylic C–O bond of 1 to palladium(0) species **A** with releasing carbon dioxide. The resulting (η^3 -benzyl)palladium intermediate **B** reacts with deprotonated 2 or 5 by methoxide anion to give the phosphonylated or phosphinylated product. The η^3 -benzyl ligand in **B** can isomerize to η^1 -benzyl to form less electrophilic **C** in equilibrium. The formation of **3** or **6** should proceeds through the attack of the phosphorus nucleophile to the intermediate **B**. However, the η^3 -coodination in **B** would be unfavorable for the (benzyl)palladium species generated from **1j**, because its two *ortho*-methyl groups might sterically disturb the η^3 -coodination. Therefore, the reactivity of **1j** was much lower than those of other benzyl esters.







Scheme 2. Possible mechanism of the palladium-catalyzed benzylic substitution of 1 with 2 or 5.

In summary, we successfully developed the nucleophilic substitution of benzyl carbonates with dimethyl phosphonate or diphenylphosphine oxide by using the palladium catalyst, which was generated in situ from $[Pd(\eta^3-allyl)Cl]_2$ and DPEphos. The benzylic C–P bond formation smoothly proceeded in the presence of a small excess amount of phosphorus nucleophiles without use of base. In addition, a variety of benzyldiphenylphosphine oxides, which were beneficial synthons for phosphine ligands¹³ or used for Horner–Wittig olefination,¹⁴ can be obtained in practically quantitative yields through the palladium catalysis. Moreover, synthetic utility of the catalytic benzylic C–P bond formation was highlighted by the one-pot synthesis of *E*-alkenes from the benzyl carbonate.

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