

# Palladium-Catalyzed Benzylation of Active Methine Compounds without Additional Base: Remarkable Effect of 1,5-Cyclooctadiene

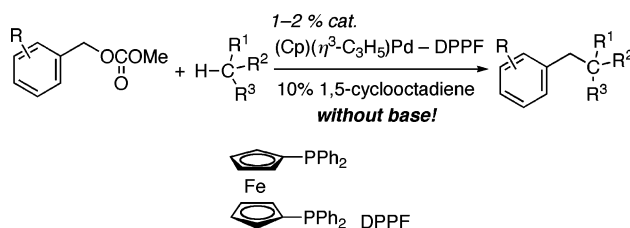
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## ABSTRACT



The palladium complex prepared from DPPF and  $\text{Cp}(\eta^3\text{-C}_3\text{H}_5)\text{Pd}$  is an effective catalyst for the alkylation of active methine compounds with benzylic carbonates under neutral conditions. The addition of 1,5-cyclooctadiene brought about remarkable improvement in the lifetime of the palladium catalyst, which led to high yields of the desired benzylation products.

The alkylation of active methylene and methine compounds is a fundamental reaction in organic synthesis, and has usually been carried out under basic conditions.<sup>1</sup> Recently, we disclosed a palladium-catalyzed benzylation of malonates using various benzylic carbonates.<sup>2,3</sup> A palladium complex generated from DPPF and  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)(\text{cod})]\text{BF}_4$  was the best catalyst for the benzylation, which required a stoichiometric amount of base, *N,O*-bis(trimethylsilyl)acetamide (BSA). A plausible mechanism for catalytic benzylation is shown in Figure 1. DPPF-ligated ( $\eta^3$ -allyl)palladium(II) **A** is reduced to the palladium(0) species **B** via nucleophilic attack of malonate carbanion. Benzyl methyl carbonate (**C**) is activated by palladium(0) **B** and forms a ( $\eta^3$ -benzyl)-

palladium species which can react with soft nucleophiles.<sup>5</sup> It is noteworthy that methoxide is liberated through the oxidative addition of **C** followed by decarboxylation. The methoxide was expected to function as a base for the deprotonation of the malonate. This mechanistic consideration prompted us to develop a new catalytic benzylation of active methine compounds without an additional base. Tsuji et al. had developed palladium-catalyzed allylation under

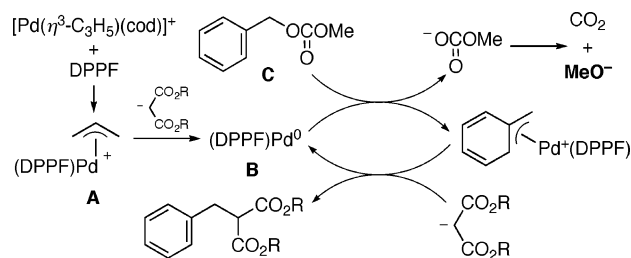


Figure 1. Plausible reaction mechanism of catalytic benzylation.

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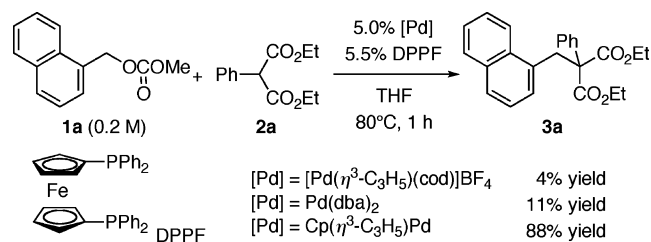
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neutral conditions on the basis of the working hypothesis mentioned above.<sup>6</sup> Herein we report a new palladium catalyst system for conducting the benzylation independent of the additional base.

Our initial work focused on the alkylation of diethyl phenylmalonate (**2a**) with (1-naphthyl)methyl methyl carbonate (**1a**) (Scheme 1). In the presence of BSA base, the

**Scheme 1.** Evaluation of Palladium Catalyst Precursors



reaction of **1a** was complete within 1 h at a catalyst loading of 1 mol % DPPF–[Pd(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)(cod)]BF<sub>4</sub>, yielding the desired product **3a** quantitatively. However, the palladium(II) complex scarcely exhibited catalytic activity for alkylation without an additional base, even if the reaction was conducted in the presence of the 5 mol % palladium. This observation indicates that the DPPF–[Pd(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)(cod)]BF<sub>4</sub> complex is not appropriately reduced to the active palladium(0) catalyst without the malonate carbanion or base. The use of other palladium(II) compounds, Pd(OAc)<sub>2</sub> and PdCl<sub>2</sub>(cod), resulted in no reaction. Pd(dba)<sub>2</sub> (dba = dibenzylideneacetone), which is commonly used as a palladium(0) catalyst precursor, exhibited an insufficient reaction rate. The DBA ligand might inhibit oxidative addition of **1a** to DPPF–palladium(0) because the coordination of the dba ligand is not weak enough to be displaced by **1a**.<sup>7</sup> The in-situ-generated palladium catalyst from DPPF and (η<sup>3</sup>-allyl)-(cyclopentadienyl)palladium(II) [Cp(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Pd], which is known to readily provide palladium(0) species via reductive elimination in the presence of tertiary phosphine,<sup>8</sup> gave the alkylation product **3a** in the highest yield (88%). The catalyst loading was successfully reduced to 1 mol % palladium at a high concentration of the substrates (1.0 M), and the desired product **3a** was obtained in 99% isolated yield.

A wide range of active methine compounds **2** underwent the palladium-catalyzed alkylation with (naphthyl)methyl carbonates **1a** and **1b** as shown in Table 1. The production of **3c** was slower than that of **3a** and **3b**, while acetamido-

**Table 1.** Alkylations of Active Methine Compounds (**2**) with (Naphthyl)methyl Carbonates (**1**)<sup>a</sup>

entry	1	2	Product (3)	yield, %
1	<b>1a</b>	<b>2a</b>	Ar-CH(Ph)-CH(CO <sub>2</sub> Et)-CO <sub>2</sub> Et ( <b>3a</b> ; Ar = 1-Np)	99%
2	<b>1b</b>	<b>2a</b>	Ar-CH(Ph)-CH(CO <sub>2</sub> Me)-CO <sub>2</sub> Me ( <b>3b</b> ; Ar = 2-Np)	>99%
3 <sup>b</sup>	<b>1a</b>	<b>2b</b>	1-Np-CH(Ph)-CH(CO <sub>2</sub> Et)-CO <sub>2</sub> Et ( <b>3c</b> ; R = Me)	91%
4	<b>1a</b>	<b>2c</b>	1-Np-CH(Ph)-CH(CO <sub>2</sub> Et)-CO <sub>2</sub> Et ( <b>3d</b> ; R = AcNH)	98%
5	<b>1a</b>	<b>2d</b>	1-Np-CH(Ph)-CH(CO <sub>2</sub> Me)-CO <sub>2</sub> Me ( <b>3e</b> )	99%
6	<b>1a</b>	<b>2e</b>	Ar-CH(Ph)-CH(EtO-C(=O)-C(=O)-R)-R' ( <b>3f</b> ; Ar = 1-Np)	>99%
7	<b>1b</b>	<b>2e</b>	Ar-CH(Ph)-CH(EtO-C(=O)-C(=O)-R)-R' ( <b>3g</b> ; Ar = 2-Np)	97%
8	<b>1a</b>	<b>2f</b>	1-Np-CH(Ph)-CH(Me-C(=O)-C(=O)-R)-R' ( <b>3h</b> )	97%
9 <sup>c</sup>	<b>1a</b>	<b>2g</b>	1-Np-CH(Ph)-CH(R-C(=O)-C(=O)-R')-R'' ( <b>3i</b> ; R = Ph)	97%
10	<b>1a</b>	<b>2h</b>	1-Np-CH(Ph)-CH(R-C(=O)-C(=O)-R')-R'' ( <b>3j</b> ; R = <i>i</i> -Pr)	>99%

Active methine compounds **2**:

- 2a**: R = Ph
- 2b**: R = Me
- 2c**: R = AcNH
- 2d**: MeO-CO<sub>2</sub>Me
- 2e**: R = EtO, R' = Me
- 2f**: R = Me
- 2g**: R = Ph
- 2h**: R = *i*-Pr

<sup>a</sup> Reactions were conducted on a 1 mmol scale in THF (1.0 mL) at 80 °C for 1 h unless otherwise noted. Isolated yields are given. Np = naphthyl.

<sup>b</sup> The reaction was conducted for 24 h. <sup>c</sup> The reaction was conducted for 3 h.

(**2c**) and methoxymalonate (**2d**) were converted completely into **3d** and **3e** within 1 h the same as the phenylmalonate. These heterosubstituents attached to the reaction site of malonates did not cause deactivation of the palladium catalyst and formation of undesirable side products. Compounds **3f–h** were obtained in high yields through the alkylation of the corresponding β-ketoester and 1,3-diketone using the DPPF–Cp(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Pd catalyst. Azlactones derived from phenylglycine and valine afforded 4,4-dialkylated azlactones **3i** and **3j**, which will be readily converted into α-alkylated α-amino acids.<sup>9</sup> In most cases, the desired alkylation products were obtained in quantitative yields.

We attempted to apply the DPPF–Cp(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Pd catalyst to the alkylation of **2a** with benzyl methyl carbonate (**4a**). However, no benzylation occurred, and the reaction mixture turned into a dark brown solution immediately after heating at 80 °C. This observation suggested that the DPPF–

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palladium(0) complex aggregated to form a palladium cluster because of both its coordinative unsaturation and the low reactivity of benzyl methyl carbonate.<sup>10</sup> Thus, we presumed that the undesirable aggregation could be suppressed by an additional labile ligand such as olefin. Various weak ligands were evaluated for the reaction of *p*-methoxybenzyl methyl carbonate (**4b**) with **2** (Table 2). Both DBA and tri-

**Table 2.** Effects of Additional Labile Ligands on the Reaction of **4b** with **2a**<sup>a</sup>

entry	additive <sup>b</sup>	yield, <sup>c</sup> %
1	none	11
2	dibenzylideneacetone (DBA) ( <b>2</b> )	2
3	Ph <sub>3</sub> P=O ( <b>2</b> )	2
4	1-octene ( <b>10</b> )	20
5	2,5-norbornadiene (NBD) ( <b>2</b> )	15
6	1,5-cyclooctadiene (COD) ( <b>2</b> )	69
7	1,5-cyclooctadiene (COD) ( <b>10</b> )	>99 ( <b>98</b> ) <sup>d</sup>

<sup>a</sup> Reactions were conducted on a 1 mmol scale in THF (1.0 mL) at 80 °C for 3 h. <sup>b</sup> Molar equivalents of additive to Pd are shown in parentheses. <sup>c</sup> GC yields at 3 h. <sup>d</sup> Isolated yield of **5a** is shown in parentheses.

phenylphosphine oxide caused inhibition of the catalytic benzylation. Small change was observed when the benzylation was conducted in the presence of 1-octene or 2,5-norbornadiene. Surprisingly, a catalytic amount of 1,5-cyclooctadiene (COD) brought about a considerable improvement in the lifetime of the catalyst. The benzylation product **5a** was obtained in 98% isolated yield when the catalytic reaction was conducted for 3 h in the presence of 10 mol % additional COD.

The addition of COD to DPPF–Cp(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Pd catalyst was effective for the reaction of diverse benzylic methyl carbonates (Table 3). Benzyl methyl carbonate (**4a**) was less reactive than the other benzylic carbonates. It was converted into **5b** in 84% yield for 24 h at a catalyst loading of 2 mol % palladium. The reactions of electron-poor **4d** and **4e** yielding **5d** and **5e** were as fast as that of electron-rich **4b**. However, an unidentified side product was observed in the reaction of *p*-(trifluoromethyl)benzyl methyl carbonate and seemed to cause a low yield of **5e** (65% yield at a catalyst loading of 1% palladium). The desired **5e** was successfully obtained in 90% isolated yield by use of 2 mol % catalyst. Substituted malonates other than phenylmalonate **2a** underwent the palladium-catalyzed reaction under the present reaction conditions. The palladium catalyst system DPPF–Cp(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Pd–COD was applicable to the benzylations of

**Table 3.** Benzylations of Active Methine Compounds (**2**)<sup>a</sup>

entry	<b>4</b>	<b>2</b>	time, h	Product ( <b>5</b> )	yield, %
1 <sup>b</sup>	<b>4a</b>	<b>2a</b>	24		<b>5b</b> : R = H 84%
2	<b>4c</b>	<b>2a</b>	24		<b>5c</b> : R = <i>p</i> -Me 99%
3	<b>4d</b>	<b>2a</b>	3		<b>5d</b> : R = <i>p</i> -MeO <sub>2</sub> C >99%
4 <sup>b</sup>	<b>4e</b>	<b>2a</b>	3		<b>5e</b> : R = <i>p</i> -CF <sub>3</sub> 90%
5	<b>4f</b>	<b>2a</b>	24		<b>5f</b> : R = <i>o</i> -Me 90%
6 <sup>b</sup>	<b>4b</b>	<b>2b</b>	72		<b>5g</b> 71%
7	<b>4b</b>	<b>2c</b>	3		<b>5h</b> : R = <i>p</i> -MeO 92%
8	<b>4c</b>	<b>2c</b>	24		<b>5i</b> : R = <i>p</i> -Me 85%
9	<b>4d</b>	<b>2c</b>	24		<b>5j</b> : R = <i>p</i> -MeO <sub>2</sub> C 90%
10	<b>4f</b>	<b>2c</b>	3		<b>5k</b> : R = <i>o</i> -Me 91%
11 <sup>b</sup>	<b>4b</b>	<b>2d</b>	24		<b>5l</b> 90%
12 <sup>b</sup>	<b>4b</b>	<b>2e</b>	48		<b>5m</b> : R = EtO <sub>2</sub> C 74%
13 <sup>b</sup>	<b>4b</b>	<b>2f</b>	48		<b>5n</b> : R = Ac 88%

<sup>a</sup> Reactions were conducted on a 1 mmol scale in THF (1.0 mL) at 80 °C. Isolated yields are given. <sup>b</sup> The reactions were conducted with 2 mol % of DPPF–Pd catalyst.

*β*-ketoester **2e** and 1,3-diketone **2f**. However, azlactones failed to react with **4b** by means of the DPPF–palladium catalyst.

In conclusion, the in-situ-generated palladium(0) complex from DPPF and Cp(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Pd is a useful catalyst for the benzylation of active methine compounds in the absence of an additional base. The addition of COD brought about a remarkable improvement in the yields of the desired benzylation products **5**. The additional COD would prevent the DPPF–palladium(0) from aggregating to form inactive palladium species without loss of the catalytic activity and could prolong the lifetime of the catalyst.

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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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