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Use of acetate as a leaving group in palladium-catalyzed nucleophilic substitution of benzylic esters

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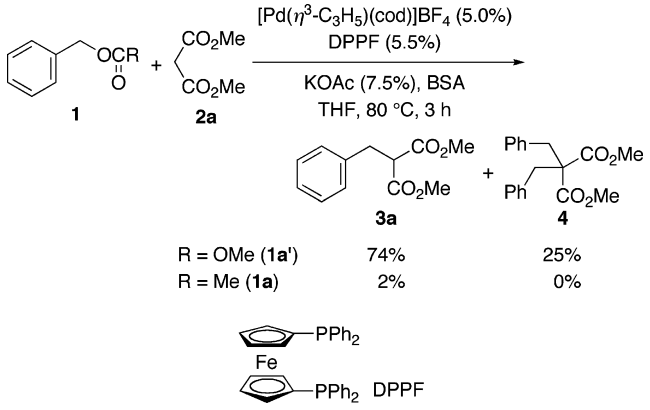
Abstract—The palladium complex prepared in situ from [Pd(η^3-C_3H_5)(cod)]BF_4 and bidentate phosphine DPPF was a good catalyst for the nucleophilic substitution of benzyl acetate. Significant acceleration of the palladium-catalyzed substitution was observed when an alcohol was employed as a reaction solvent. The palladium catalyst was effective for the benzylation of various stabilized carbanions, amines, and benzenesulfinate with benzylic acetates.

Palladium-catalyzed nucleophilic substitutions of allylic carboxylates[1] have often been used for removal of the allyl protective groups[2] as well as carbon–carbon and carbon–heteroatom bond formation in organic synthesis.[3] In the catalytic allylic substitutions, acetate is commonly chosen as a leaving group because of its accessibility as well as simplicity. Recently, we developed a palladium-catalyzed substitution of benzylic carbonates.[4] As with the allylic substitution, the benzylic carbon–oxygen bond of the benzylic carbonate is activated by palladium(0) to form (η^3-benzyl)palladium intermediate, which is readily attacked by various nucleophiles.[5] Fiaud and Legros reported the catalytic benzylic substitution of (naphthyl)methyl acetates,[6] while use of the acetate leaving group remains formidable for the palladium-catalyzed reaction of simple benzyl esters.[7–9] Here, we report that the palladium-catalyzed nucleophilic substitution of benzylic acetates proceeded efficiently in an alcoholic solvent. The palladium catalysis employed in alcohol was effective in a broad range of substrate combinations of benzylic acetates and nucleophiles.

In our recent report, the nucleophilic substitution of benzyl methyl carbonate (**1a′**) with dimethyl malonate (**2a**) was carried out in THF at 80 °C with [Pd(η^3-C_3H_5)-(cod)]BF_4–DPPF[10] catalyst and *N*,*O*-bis(trimethylsilyl)acetamide (BSA)–KOAc base, affording benzylated malonates **3a** and **4** in the highest yield (Scheme 1).[4a] However, the use of benzyl acetate (**1a**) in place of **1a′** under the identical reaction conditions resulted in little production of **3a**. Meanwhile, we found previously that the Suzuki-Miyaura cross-coupling of benzylic acetates is significantly accelerated by use of *tert*-amyl alcohol as a reaction solvent.[11] Thus, we attempted the catalytic benzylic substitution of **1a** in the tertiary alcohol and were pleased to obtain the desired benzylated products **3a** and **4** in 59% and 13% yields, respectively (Table 1, entry 1).[12] The choice of solvent and base was crucial for the palladium catalysis. Product **3a** was scarcely detected in the reaction conducted in non-polar solvents



Scheme 1. Nucleophilic substitution of benzyl esters with dimethyl malonate:benzyl carbonate (**1a′**) versus acetate (**1a**).

Keywords: Palladium; Homogeneous catalysis; Nucleophilic substitution; Benzyl acetate.
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Table 1. Effects of solvent and base on the palladium-catalyzed nucleophilic substitution of **1a** with **2a**[a]

Entry	Solvent	Base	Yield[b] (%)	
			3a	**4a**
1	*t*-AmOH[c]	K_2CO_3	59	13
2	Toluene	K_2CO_3	0	0
3	THF	K_2CO_3	2	0
4	MeCN	K_2CO_3	15	0
5	DMF	K_2CO_3	16	0
6	EtOH	K_2CO_3	0	0
7	*t*-AmOH	K_3PO_4	32	11
8	*t*-AmOH	Cs_2CO_3	43	17
9	*t*-AmOH	Na_2CO_3	14	0
10	*t*-AmOH	DBU	9	0
11[d]	*t*-AmOH	K_2CO_3	59[e]	28[e]

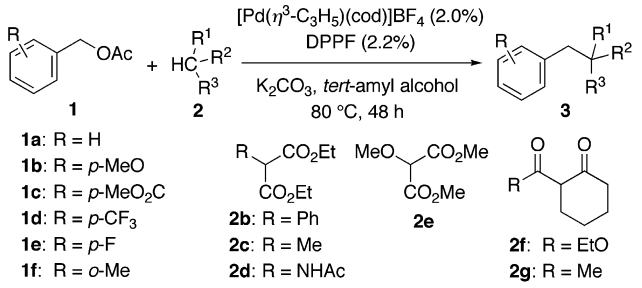
[a] Reactions were conducted on 0.2 mmol scale in a solvent (1.0 mL) at 80 °C for 3 h. The ratio of **1a**:**2a**:base:[Pd(η^3-C_3H_5)(cod)]BF_4:DPPF was 20:30:30:1.0:1.1.
[b] GC yields (average of two runs) were given unless otherwise noted.
[c] *tert*-Amyl alcohol.
[d] The reaction was conducted on 1 mmol scale for 24 h with 1 mol % palladium.
[e] Isolated yield.

(entries 2 and 3). Polar aprotic solvents improved the production of **3a** to some degree (entries 4 and 5). Use of primary alcohol brought about the solvolysis of **1a** in the presence of potassium carbonate (entry 6). In *tert*-amyl alcohol, solvolysis was concurrent with the substitution of **1a** when potassium phosphate and cesium carbonate were used (entries 7 and 8). The side reaction was evaded with sodium carbonate or DBU, while the yield of **3a** was low (entries 9 and 10). The amount of the DPPF–palladium catalyst was successfully reduced to 0.01 equiv of **1a**, and the desired products **3a** and **4** were obtained in high combined yield (entry 11).[13]

The scope of the palladium-catalyzed substitution of benzylic acetates with stabilized carbanions is summarized in Table 2. As with **2a**, 2-phenylmalonate **2b** underwent catalytic benzylation with acetate **1a**, giving product **3b** in 90% yield with 2% catalyst loading (entry 1). The α-substituent of **2b** hardly hindered the reaction with **1a**. Even heteroatom substituents binding to the reaction site of **2d** or **2e** did not decrease the yield of **3** (entries 8–11). These malonate carbanions reacted with a broad range of benzylic acetates. The electron-donating group of **1b** accelerated the catalytic nucleophilic substitution with **2b**, which produced **3c** in 92% yield with 1 mol % catalyst loading (entry 2). The reaction of electron-poor substrates **1c**–**e** required 2 mol % of palladium catalyst for the efficient production of **3d**–**f** (entries 3–5).[14] The *ortho*-methyl group of **1f** did not cause significant deterioration of the reaction rate (entry 6). The catalyst system was effective for the benzylation of 1,3-diketone **2g** as well as β-ketoester **2f** (entries 12 and 13).

Benzylic acetates underwent palladium-catalyzed substitution with secondary amines (Table 3). Initially, the benzylic amination of **1a** with dibutylamine **5a** was attempted in *tert*-amyl alcohol, but yielded **6a** in a trace

Table 2. Nucleophilic substitution of benzylic acetates with stabilized carbanions[a]



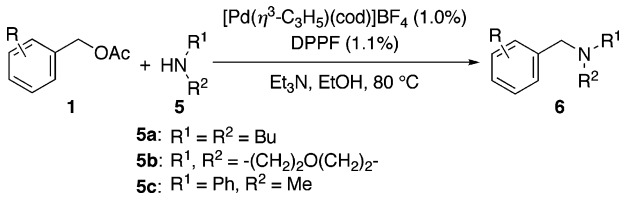
Entry	1	2	Product (3)	Yield[b] (%)
1	**1a**	**2b**	**3b**: R = H	90
2[c]	**1b**	**2b**	**3c**: R = *p*-MeO	92
3[d]	**1c**	**2b**	**3d**: R = *p*-MeO_2C	89
4	**1d**	**2b**	**3e**: R = *p*-CF_3	95
5	**1e**	**2b**	**3f**: R = *p*-F	95
6	**1f**	**2b**	**3g**: R = *o*-Me	90
7	**1b**	**2c**	**3h**	96
8[c]	**1b**	**2d**	**3i**: R = *p*-MeO	88
9[c]	**1d**	**2d**	**3j**: R = *p*-CF_3	86
10[d]	**1e**	**2d**	**3k**: R = *p*-F	90
11[c]	**1b**	**2fe**	**3l**	83
12	**1b**	**2f**	**3m**: R = EtO_2C	87
13	**1b**	**2g**	**3n**: R = Ac	85

[a] Reactions were conducted on 1.0 mmol scale in *tert*-amylalcohol (1.0 mL) at 80 °C for 48 h. The ratio of **1**:**2**:K_2CO_3:[Pd(η^3-C_3H_5)(cod)]BF_4:DPPF was 50:55:55:1.0:1.1.
[b] Isolated yield.
[c] The reactions were conducted with 1 mol % palladium.
[d] The reactions were conducted for 24 h.

amount (entry 1). Using ethanol in place of *tert*-amyl alcohol allowed the catalytic amination to proceed efficiently in the presence of 5% DPPF–palladium (entry 2). The decomposition of **1a** to benzyl alcohol was observed when the catalyst loading decreased to 1%. The competitive solvolysis was successfully suppressed by the addition of triethylamine to the reaction mixture (entry 3).[15] Under the optimized conditions, a variety of *p*- or *o*-substituted benzylic acetates reacted with **5a** in good yields (entries 4–7). Other secondary amines, morpholine (**5b**) and *N*-methylaniline (**5c**), were converted into tertiary amines **6f**–**h** in good yields (entries 8–10). Primary amines were usable as nucleophiles for catalytic substitution but gave the corresponding secondary benzylamines as a mixture with dibenzylamines. The reaction of cyclohexylamine with **1a** gave the mono- and dibenzylated products in 22% and 34% isolated yields, respectively.

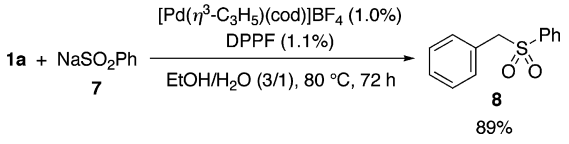
Palladium-catalyzed sulfonylation of **1a** was accomplished using sodium benzenesulfinate (**7**) as a nucleo-

Table 3. Nucleophilic substitution of benzylic acetates with secondary amines[a]



Entry	1	5	Time (h)	Product (6)	Yield[b] (%)
1[c,d]	**1a**	**5a**	3		1[e]
2[c]	**1a**	**5a**	3	**6a**	49[e] (96)[f]
3	**1a**	**5a**	48		85
4	**1b**	**5a**	48	**6b**: R = *p*-MeO	79
5	**1c**	**5a**	72	**6c**: R = *p*-MeO_2C	73
6	**1d**	**5a**	72	**6d**: R = *p*-CF_3	81
7	**1f**	**5a**	72	**6e**: R = *o*-Me	80
8	**1a**	**5b**	48	**6f**: R = H	88
9	**1e**	**5b**	72	**6g**: R = F	73
10	**1a**	**5c**	72	**6h**	82

[a] Reactions were conducted on 1.0 mmol scale in ethanol (1.0 mL) at 80 °C. The ratio of **1**:**2**:Et_3N:[Pd(η^3-C_3H_5)(cod)]BF_4:DPPF was 110:100:110:1.0:1.1.
[b] Isolated yields were given unless otherwise noted.
[c] The reactions were conducted on 0.2 mmol scale in the absence of Et_3N with 5 mol % palladium.
[d] The reaction was conducted in *tert*-amyl alcohol.
[e] GC yield (average of two runs).
[f] GC yield after 24 h is given in the parentheses.



Scheme 2. Nucleophilic substitution of **1a** with **7**.

phile (Scheme 2). The sulfonylation conducted in ethanol or *tert*-amyl alcohol was sluggish because of poor solubility of **7** in these solvents. Addition of water to the reaction mixture allowed the sulfinate salt to dissolve in the reaction solvent, furnishing benzylsulfone **8** in high yield.

In conclusion, the nucleophilic substitution of benzyl acetates proceeded in the presence of [Pd(η^3-C_3H_5)(cod)]BF_4–DPPF catalyst. Use of alcoholic solvent was critical for the palladium catalysis. A variety of nucleophiles were utilized for the palladium-catalyzed substitution. Generally, acetates were readily accessible and treatable as compared to carbonates. The results described here will make the palladium-catalyzed benzylic substitution more useful in organic synthesis.

Acknowledgments

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12. Although the effect of the alcoholic solvent is unclear, we speculate that hydrogen bonding between alcoholic proton and carbonyl oxygen of benzyl acetate may weaken the benzylic carbon–oxygen bond.
13. *General procedure for palladium-catalyzed nucleophilic substitution of* **1** *with* **2**: In a nitrogen-filled drybox, potassium carbonate (152 mg, 1.1 mmol), $[Pd(\eta^3\text{-}C_3H_5)(cod)]BF_4$ (6.8 mg, 20 μmol), and DPPF (12.2 mg, 22 μmol) were put into a 5 mL screw capped vial equipped with a stirring bar. After sealing with a screw cap containing a PTFE/silicone septum, the vial was removed from the drybox. Dry *tert*-amyl alcohol (1.0 mL) was added by a syringe, and then the resulting suspension was stirred at room temperature for 5 min. Benzylic acetate **1** (1.0 mmol) and an active methylene compound **2** (1.1 mmol) were added into the reaction vessel by syringes. The reaction mixture was stirred at 80 °C until **1** disappeared (monitored by GC). On cooling the vial, water was added to the reaction mixture, and then it was extracted several times with hexane or EtOAc. The combined organic layer was washed with brine, dried with $MgSO_4$, and evaporated under reduced pressure. The residue was purified with a flash column chromatography on silica gel (EtOAc/hexane).
14. As with the reaction of benzylic carbonates (Ref. 4a), the reactivity of benzyl acetate **1a** was lower than those of both electron-rich and -poor substrate. We speculated that the electron-donating group of **1** weakened the benzylic C–O bond. Meanwhile, the electron-withdrawing group may favor the pre-coordination of the palladium(0) on the aromatic ring of the benzylic ester.
15. Dibutylamine inherently possesses nucleophilicity enough for attacking the η^3-benzyl ligand on palladium. Triethylamine might be required for neutralizing the acetic acid liberated from benzyl acetate. The reaction conditions were insufficient for the reaction of **1a** with malonates, resulting in no formation of **3**.