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Palladium-Catalyzed Decarboxylation of Benzyl Fluorobenzoates

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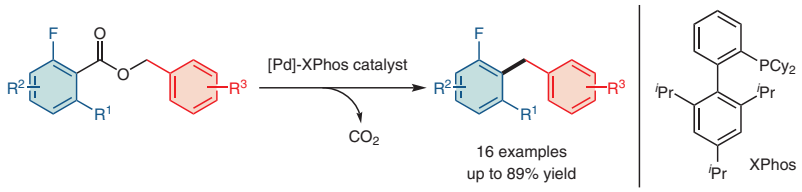

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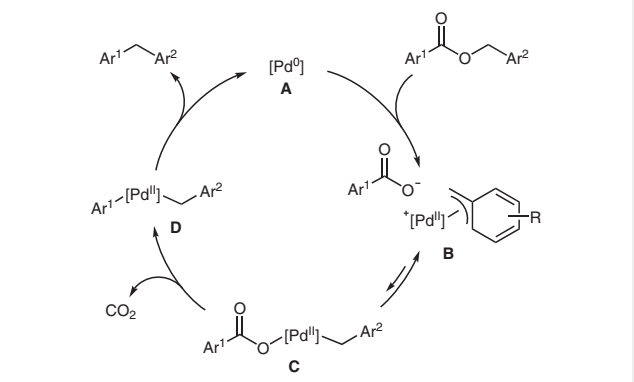
Abstract The decarboxylation of benzyl fluorobenzoates has been developed by using the palladium catalyst prepared in situ from Pd(η³-allyl)Cp and bulky monophosphine ligand XPhos. The catalytic reaction afforded a range of fluorinated diarylmethanes in good yields with broad functional-group compatibility. The substrates were readily synthesized by condensation of the corresponding benzoic acid with benzyl alcohol. Therefore, the transformation is formally regarded as a cross-coupling reaction between fluorine-containing benzoic acids and benzyl alcohols.

Key words decarboxylation, benzylation, palladium catalyst, diarylmethane, fluoroarene, C–O activation, benzyl palladium intermediate

Palladium-catalyzed cross-coupling reactions between organometals and organo(pseudo)halides are currently one of well-studied and reliable methods for carbon–carbon bond formation.[1] However, the catalytic transformation is fate to generate a stoichiometric amount of metal salts as byproducts. The salts may make a great impact on the environment. For avoiding the generation of the inevitable metallic byproduct, a new surrogate of the organometallic substrate is highly attractive. Carboxylic acids are a strong candidate for the organometal alternative, because their transition-metal salts eliminate carbon dioxide to give arylmetal species.[2] This decarboxylative process can be equivalent to the transmetalation in the classical cross-coupling mechanisms. Tremendous efforts have been devoted to achieving the cross-coupling reaction using carboxylic acids as the nucleophilic substrates.[3]

Diarylmethane is an important structural motif in organic chemistry, because the skeleton is often seen in many useful compounds.[4] The cross-coupling reaction of benzylic esters with arylmetal compounds has been developed by us[5] and others.[6,7] However, the use of carboxylic acids remains in premature for the benzylic cross-couplings.[3e,8] In this context, we envisioned that the diarylmethanes are efficiently obtained from the corresponding benzyl benzoates through the decarboxylation. The decarboxylation may proceed with the palladium catalysis through the pathway as depicted in Scheme 1: (i) the oxidative addition of the benzylic C–O bond to palladium(0) **A**, (ii) the decarboxylation of the resulting palladium benzoate **C** to form arylbenzylpalladium(II) **D**, (iii) the reductive elimination from **D** to produce the desired diarylmethane.[9] Herein, we successfully developed the palladium-catalyzed decarboxylative carbon–carbon bond formation of the benzyl esters. The catalytic reaction proceeds without any additives other than the palladium catalyst and emits carbon dioxide as the sole byproduct.

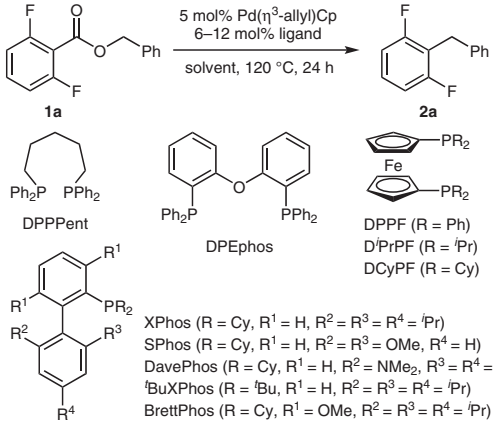


Scheme 1 Working hypothesis for the palladium-catalyzed decarboxylation of benzyl benzoate

To develop the decarboxylative carbon–carbon bond formation, we chose benzyl 2,6-difluorobenzoate (**1a**) as the model substrate for the following catalyst screening, because the *ortho*-fluorine atoms were known to facilitate the decarboxylation of the metal benzoate (Table 1).[10] First, the

decarboxylation of **1a** was attempted using Pd(η³-allyl)Cp and some bidentate bisphosphines, which were reported as the useful ligands for the related catalytic alkylations with benzylic carbonates (Table 1, entries 1–3).[11] However, these ligands did not allow the palladium catalyst to efficiently provide the desired diarylmethane **2a**. Use of the alkyl variants of DPPF is favorable for the decarboxylative reaction (Table 1, entries 4 and 5). Furthermore, a series of bulky monodentate dialkylarylphosphine ligands[12] were evaluated to the palladium-catalyzed decarboxylation of **1a**. The palladium catalyst produced **2a** in the highest yield when XPhos was used as the spectator ligand with 2.4 molar equivalents to palladium (Table 1, entry 6). Decrease in the molar equivalent of the ligand caused the formation of black precipitates during the reaction and led to the significant low yield of **2a** (Table 1, entry 7). Other biarylyldicyclohexylphosphines, SPhos and DavePhos, are comparable to XPhos (Table 1, entries 8 and 9). However, the palladium catalyst bearing bulkier and/or more electron-donating ligand failed to selectively and efficiently promote the desired reaction (Table 1, entries 10 and 11). The catalysis of XPhos–palladium complex is scarcely affected by the solvent (Table 1, entries 12–15). Toluene is the solvent of choice for the present reaction. The palladium-catalyzed decarboxylation was slightly improved by elevating temperature (Table 1, entry 16). It is noteworthy that catalyst loading can be reduced to 1 mol% without loss of the yield of **2a** (Table 1, entry 17).

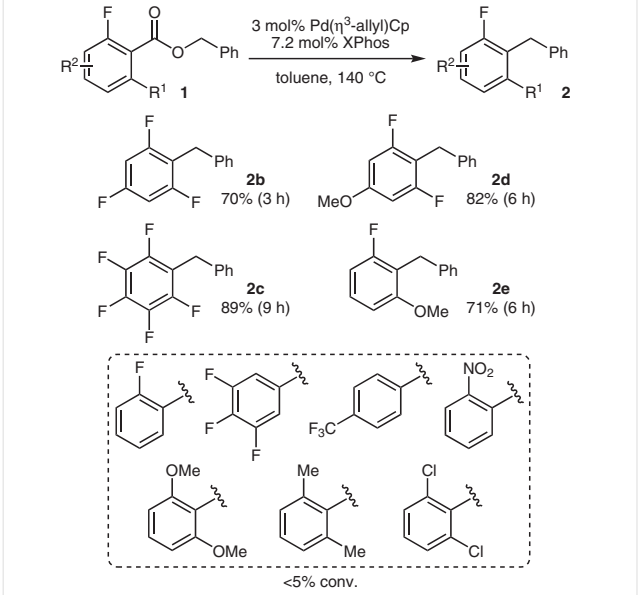
Table 1 Effect of Ligand and Solvent on the Decarboxylation of Benzyl 2,6-Difluorobenzoate (**1a**)[a]



Entry	Ligand (mol%)	Solvent	Conv. (%)[b]	Yield (%)[b]
1	DPPPent (6)	toluene	49	17
2	DPEphos (6)	toluene	49	4
3	DPPF (6)	toluene	70	6
4	D*i*PrPF (6)	toluene	88	37
5	DCyPF (6)	toluene	100	61
6	XPhos (12)	toluene	100	74
7	XPhos (6)	toluene	57	16
8	SPhos (12)	toluene	60	63
9	DavePhos (12)	toluene	100	54
10	*t*-BuXPhos (12)	toluene	47	4
11	BrettPhos (12)	toluene	27	trace
12	XPhos (12)	DMF	99	54
13	XPhos (12)	*t*-AmOH	100	50
14	XPhos (12)	CPME	100	69
15	XPhos (12)	1,4-dioxane	100	61
16[c]	XPhos (12)	toluene	100	75
17[c,d]	XPhos (2.4)	toluene	100	80[e]

[a] Unless otherwise noted, all reactions were carried out with 0.20 mmol of **1a** in 0.50 mL of solvent under N_2 at 120 °C for 24 h.
[b] Determined by GC analysis.
[c] At 140 °C.
[d] The reaction was conducted on a 0.50 mmol scale with 1 mol% of Pd(η³-allyl)Cp and 2.4 mol% of XPhos in 0.50 mL of toluene for 15 h.
[e] Yield of isolated product **2a**.

Next, we attempted the reaction of various substituted benzoates to investigate the substituent effect on the benzoate moiety of **1** (Scheme 2). As with **1a**, the substrates **1b–d**, which have fluorine atoms on both *ortho*-carbons, were transformed into the corresponding diarylmethanes **2b**, **2c**, and **2d** in 70%, 89% and 82% yields, respectively. The reaction of benzyl 2-fluoro-6-methoxybenzoate (**1e**) also proceeded smoothly to afford diarylmethane **2e** in 71% yield. Meanwhile, benzyl 2-fluorobenzoate remained intact under the reaction conditions. The XPhos–palladium catalyst failed to transform the electron-deficient substrates

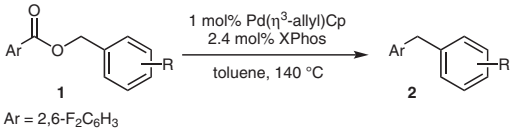


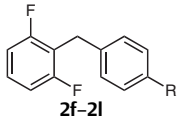
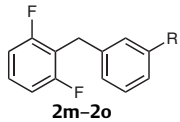
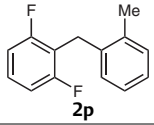
Scheme 2 Substituent effects on benzoate moiety of **1**

having no *ortho*-fluorine atoms into the diarylmethane products. In addition, bis-*ortho*-substituted benzoates without fluorine atoms also gave no decarboxylation products, while the corresponding metal benzoates are amenable to the decarboxylation.[10f,13] These results suggest that the present palladium catalysis requires one *ortho*-fluorine atom and the steric constraint on another *ortho*-position to induce the decarboxylative carbon–carbon bond formation.

The scope of the benzyl moiety is summarized in Table 2. The catalytic decarboxylation tolerated a broad spectrum of functionalities (e.g., ether, ketone, ester, nitrile) and was virtually unaffected by the electronic property of the benzyl moiety. The benzyl esters **1** bearing an electron-donating (Me and MeO) or electron-withdrawing group (CF_3, Ac, CO_2Me, CN, and NO_2) at the *para* position were converted into the corresponding diarylmethanes **2** in good yields (Table 1, entries 1–7). The reaction of *meta*-substituted benzyl esters (**1m**, **1n**, and **1o**) also proceeded in comparable yields to the *para*-substituted ones (Table 1, entries 8–10). Moreover, sterically congested **1p** was compatible with the decarboxylative diarylmethane synthesis, but required higher catalyst loading for the efficient production of **2p** (Table 1, entry 11).

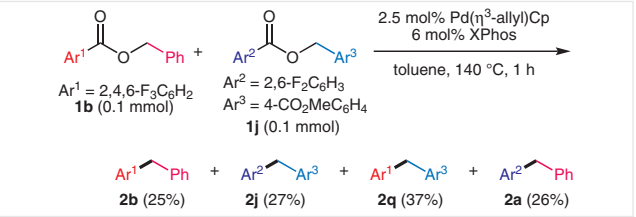
Table 2 Decarboxylation of Benzyl Fluorobenzoates **1**[a]



Entry	1	Time (h)	2		Yield (%)[b]
1	**1f**	14	 **2f–2l**	**2f** R = Me	76
2	**1g**	6		**2g** R = OMe	76
3	**1h**	3		**2h** R = CF_3	86
4	**1i**	9		**2i** R = Ac	73
5	**1j**	17		**2j** R = CO_2Me	78
6[c]	**1k**	6		**2k** R = CN	86
7	**1l**	4		**2l** R = NO_2	73
8[d]	**1m**	3	 **2m–2o**	**2m** R = Me	75
9	**1n**	6		**2n** R = OMe	82
10	**1o**	4		**2o** R = CF_3	80
11[e]	**1p**	9	 **2p**		73

[a] Unless otherwise noted, all reactions were carried out with 0.50 mmol of **1** in 0.50 mL of toluene under N_2 at 140 °C.
[b] Yield of isolated product **2**.
[c] 2 mol% of Pd(η3-allyl)Cp and 4.8 mol% of XPhos were used.
[d] 3 mol% of Pd(η3-allyl)Cp and 7.2 mol% of XPhos were used.
[e] 5 mol% of Pd(η3-allyl)Cp and 12 mol% of XPhos were used.

In order to get a mechanistic insight into the current decarboxylative carbon–carbon bond formation, an equimolar mixture of benzyl fluorobenzoates **1b** and **1j** was heated in toluene in the presence of 2.5 mol% of XPhos–palladium catalyst at 140°C for 1 h (Equation 1). Interestingly, the reaction gave not only **2b** (25%) and **2j** (27%), but also the crossover products **2q** (37%) and **2a** (26%). This observation suggests that the (π-benzyl)palladium and benzoate anion of intermediate **B** in Scheme 1 form a weak ion pair during the course of the reaction. Moreover, the decarboxylation from **C** to **D** might be relatively slow. As a result, the carboxylate counter anion in the (π-benzyl)palladium **B** would be scrambled rapidly, because the (σ-benzyl)palladium **C** is in equilibrium with the ion pair **B**. The scrambling may cause the formation of the equimolar mixture of four possible products.



Equation 1 Crossover experiment using **1b** and **1j**

In summary, we have successfully developed the decarboxylation of benzyl fluorobenzoates by using XPhos–palladium catalyst, which gives fluorinated diarylmethanes in good yields with broad functional-group compatibility.[14,15] The carbon–carbon bond formation is formally regarded as the cross-coupling reaction between benzoic acids and benzyl alcohols, because the benzoate substrates are readily prepared through the esterification. It is noteworthy that the reaction generates only a nontoxic and easily removable byproduct, carbon dioxide. However, the current decarboxylation requires high reaction temperature and has severe benzoate limitations at this moment. Investigations to remove these drawbacks are ongoing in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588572.

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(14) **General Procedure; Palladium-Catalyzed Decarboxylation**
In a nitrogen-filled glove box, Pd(η^3-allyl)Cp (1.1 mg, 5.0 μmol), XPhos (5.7 mg, 12 μmol), and toluene (0.5 mL) were placed in a vial containing a magnetic stirring bar. After 5 min stirring at r.t., benzyl benzoate **1** (0.5 mmol) was added. Then, the vial was sealed with a cap equipped with a PTFE-coated silicone rubber septum and removed from the glove box. The mixture was stirred at 140 °C until starting material consumed monitored by GC analysis. The resulting mixture was evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel eluting with EtOAc/hexane to give the desired diarylmethane **2**. Characterization data for selected product **2a** (for all data, see Supporting Information) is described as follows.

(15) **1-Benzyl-2,6-difluorobenzene (2a)**
Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 4.02 (s, 2 H), 6.87 (t, *J* = 7.6 Hz, 2 H), 7.10–7.22 (m, 2 H), 7.23–7.33 (m, 4 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 28.1 (t, *J* = 3 Hz), 111.2 (dd, *J* = 7, 19 Hz), 116.8 (t, *J* = 20 Hz), 126.3, 127.8 (t, *J* = 10 Hz), 128.4, 128.5, 139.2, 161.4 (dd, *J* = 9, 247 Hz). IR (neat): 3064, 3031, 2940, 1593, 1470, 1265, 1009 cm^{-1}. Anal. Calcd for $C_{13}H_{10}F_2$: C, 4.94; H, 76.46. Found: C, 4.92; H, 76.55.