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One-Pot Palladium(II)-Catalyzed Synthesis of Fluorenones via Decarboxylative Cyclization

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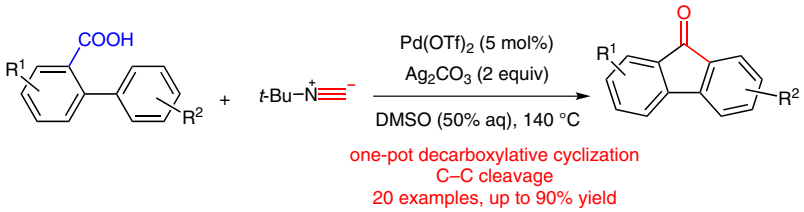

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Abstract A one-pot palladium-catalyzed synthesis of fluorononeses via decarboxylative cyclization is reported. This protocol offers good yields and tolerates a broad range of functional groups. Based on the extensive experimental data, we propose a plausible decarboxylative insertion mechanism.

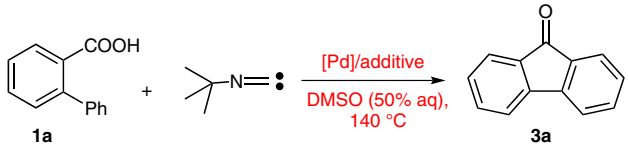
Key words palladium-catalyzed, decarboxylative insertion, C–C cleavage, control experiment, mechanism

Fluorenones are prominent structural motifs of many electronic and optical materials[1] and bioactive natural products.[2] Thus, intense efforts have focused on the development of novel methods to synthesize these compounds. Traditionally, they are synthesized by Friedel–Crafts acylation,[3] remote metalation,[4] and oxidation of fluorenes[5] or fluorenols.[6] Recently, some new metal-catalyzed strategies are reported, including radical cyclization,[7] coupling reactions of arylpalladium,[8] carbonylation,[9] and decarboxylation.[10]

Although diverse successful synthesis of fluorenones has been afforded, the scope of carbonyl source reported were always focused on acyl substrates and CO. More recently, carboxylic acids,[11] organic nitrile,[12] and aldoxime[13] were developed as new novel carbonyl source to attach fluorenones. In the catalytic system of organic nitrile[12] or aldoxime,[13] the carbonyl group was derived from the hydrolysis of C=N bonds. On the other hand, metal-catalyzed insertion of isocyanide[14] could form the similar C=N bonds, which inspired us that isocyanide may be a new carbonyl source in the synthesis of fluorenones. Herein, a one-pot palladium(II)-catalyzed synthesis of fluorenones via decarboxylative cyclization using *tert*-butyl isocyanide as a new carbonyl source is reported (Scheme 1). The control experiments suggested a decarboxylative insertion mechanism.

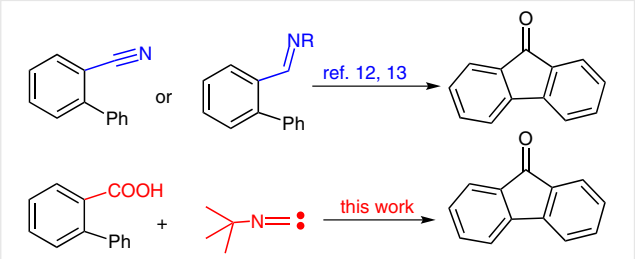
We initiated our studies by using 2-phenylbenzoic acid (**1a**) and *tert*-butyl isocyanide as a model substrate (Table 1, entry 1), which was treated with 5 mol% of $Pd(OAc)_2$ in DMSO (50% aq) at 140 °C for 24 hours. However, very poor yield (<5%) of **3a** was afforded (Table 1, entry 1). When two

Table 1 Optimization of the Conditions



Entry[a]	Catalyst (mol%)	Additive (equiv)	Yield (%)[b]
1	$Pd(OAc)_2$ (5)	–	<5
2	$Pd(OAc)_2$ (5)	AgOAc (2)	38
3	$Pd(OAc)_2$ (5)	Ag_2CO_3 (2)	74
4	$Pd(OAc)_2$ (5)	Ag_2O (2)	57
5	$Pd(OAc)_2$ (5)	$Cu(OAc)_2$ (2)	23
6	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (2)	41
7	$Pd(OAc)_2$ (5)	BQ (2)	0
8	$Pd(OAc)_2$ (5)	AcOH (2)	<5
9	$Pd(OAc)_2$ (5)	K_2CO_3	0
10	$Pd(OTf)_2$ (5)	Ag_2CO_3 (2)	80
11	$PdCl_2$ (5)	Ag_2CO_3 (2)	36
12	Pd/C (5)	Ag_2CO_3 (2)	12

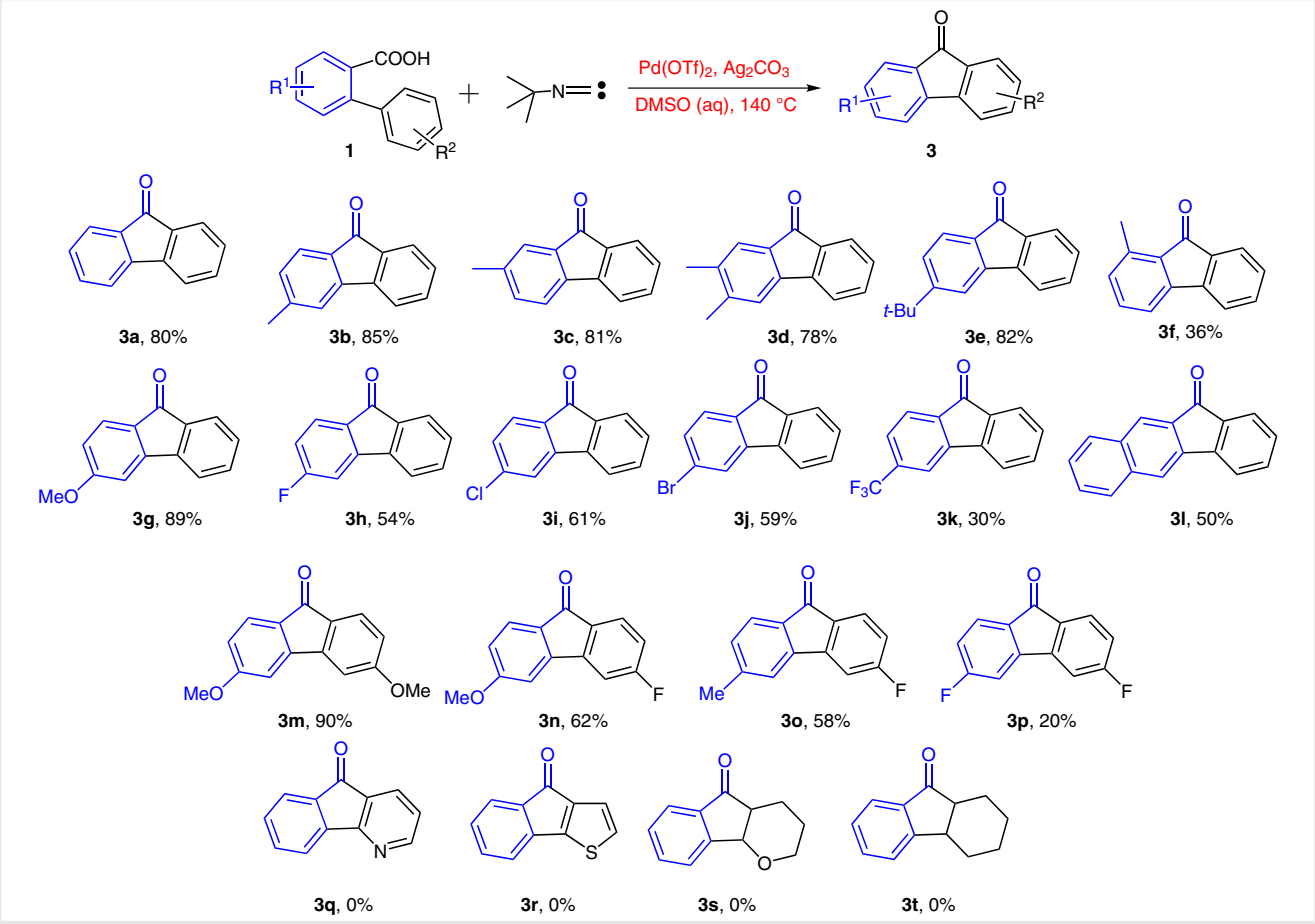
[a] Reaction conditions: **1a** (0.5 mmol), *tert*-butyl isocyanide (1 mmol), catalyst (5 mol%), oxidant (1 mmol), DMSO (50% aq) 3 mL, 140 °C for 24 h.
[b] Isolated yields.



Scheme 1 Metal-catalyzed insertion synthesis of fluorenones

equivalents of AgOAc were added, the yield increased to 38% (Table 1, entry 2), which suggested that oxidants might increase the yield. After studying other oxidants carefully, Ag_2CO_3 showed the best activity (Table 1, entries 3–7). The addition of acid or base did not give good results (Table 1, entries 8 and 9). Subsequently, screening of other palladium catalysts, $Pd(OTf)_2$ gave the best catalytic efficiency, increasing the yield of **3a** to 80% (Table 1, entries 10–12). The use of other solvents or increasing the amount of loading catalyst and additive led to no significant improvement on the yield (Supporting Information, SI-Tables 1, 2).

Encouraged by the preliminary results, we tried to explore the functional-group tolerance for the synthesis of fluorenones. The reaction showed a good tolerance to many functional groups, including electron-donating and electron-withdrawing groups (Scheme 2, 3a–p, e. g., Me, OMe, Cl, Br, F, CF_3). Benzoic acids with electron-donating groups on the 4- or/and 3-positions afforded the corresponding products in good to excellent yields (**3a**–**e**,**g**,**m**). But 2-substituted substrate resulted in a poor yield (**3f**, 36%), which might be due to steric hindrance. Notably, halogen substituents could also be tolerated in moderate yields (**3h**–**j**), which provided opportunities for further functionalization. However, benzoic acids with strong electron-withdrawing groups (**3k**,**p**) showed poor activity. In general, benzoic acids with electron-donating groups gave the better yields. Hetero- or nonaromatic substrates showed no activity (**3q**–**t**).

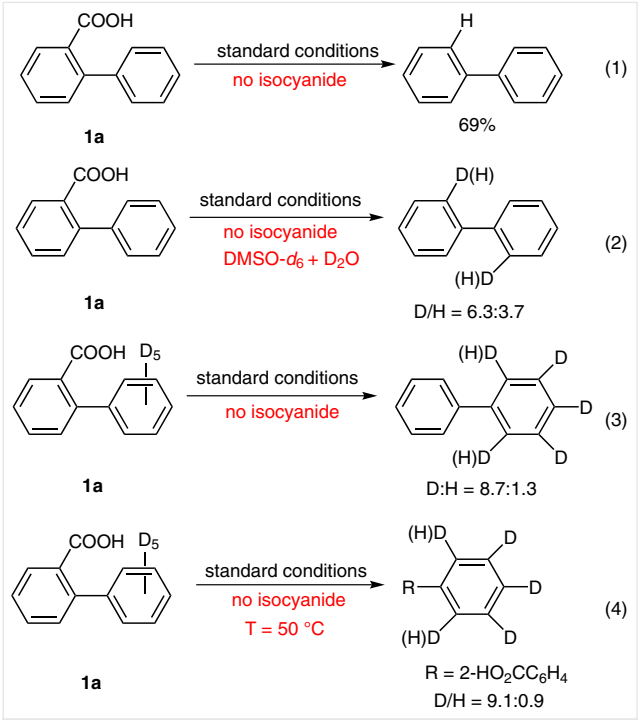


Scheme 2 Exploring the utility of this transformation. *Reagents and conditions*: **1** (0.5 mmol), *tert*-butyl isocyanide (1 mmol), $Pd(OTf)_2$ (5 mol%), Ag_2CO_3 (1 mmol), DMSO (50% aq) 3 mL, 140 °C for 24 h.

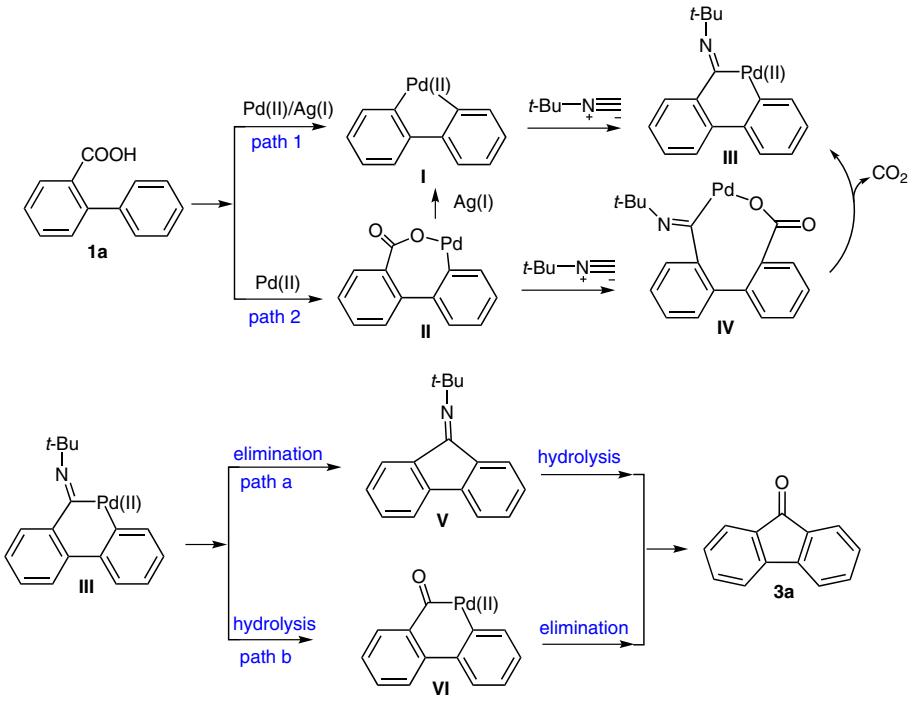
To gain some preliminary insight into the reaction mechanism, control experiments were employed as shown in Scheme 3. Firstly, the reaction of **1a** under standard conditions in the absence of isocyanide afforded 69% yield of xenene (Scheme 3, eq. 1). However, using the deuterated solvent (DMSO-d_6/D_2O = 1:1) gave the appropriate deuterated xenene with D/H = 6.3:3.7 (Scheme 3, eq. 2). Secondly, the parallel reaction of **1a**–**d**[5] in the absence of isocyanide at 140 °C and 50 °C afforded the appropriate deuterated xenene with D/H = 8.7:1.3 and D/H = 9.1:0.9, respectively (Scheme 3, eq. 3 and eq. 4). These results suggests a decarboxylation insertion mechanism via C–H activation.[15]

Based upon the experimental and literature results,[14,15] a plausible mechanism is proposed in Scheme 4. Firstly, the decarboxylation insertion of **1a** catalyzed by the palladium/silver catalyst via two possible paths (path 1 or 2) generated intermediate **III**.[15] Subsequently, the domino elimination and hydrolysis of **III** (path a or path b) generated **3a** to finish the catalytic cycle.[14]

In summary, we have developed a one-pot palladium(II)-catalyzed synthesis of fluorenones via decarboxylative cyclization using *tert*-butyl isocyanide as a new carbonyl source.[16,17] This direct C–COOH cleavage and C–H activation is suitable for a broad range of substrates. The control experiments suggested a possible decarboxylative insertion mechanism. Further studies concerning the detailed mechanism and the broader scope of substrates are currently under way in our laboratory.



Scheme 3 Control experiments for the mechanism



Scheme 4 The possible mechanism

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560527.

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(16) A mixture of **1** (0.5 mmol), DMSO (50% aq, 3 mL), $Pd(OTf)_2$ (5 mol%), and Ag_2CO_3 (2 equiv) was stirred at 140 °C under air atmosphere for 24 h. The reaction mixture was washed H_2O, and the aqueous phase was extracted with EtOAc (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to give the corresponding products (**3a–i**,[17] **3k–m**,[17] **3o–p**[17] according to the literature).

3-Bromo-9*H*-fluoren-9-one (3j)

Yield: 59%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.2 Hz, 1 H), 7.57 (d, *J* = 8.2 Hz, 1 H), 7.52–7.47 (m, 3 H), 7.35–7.31 (m, 1 H), 7.25 (t, *J* = 6.4 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.3, 146.1, 143.1, 140.9, 134.8, 134.3, 132.3, 129.8, 128.9, 125.3, 124.5, 120.9, 120.5. HRMS: *m/z* calcd for $C_{13}H_7BrO$: 259.0981; found: 259.0980

3-Fluoro-6-methoxy-9H-fluoren-9-one (3n)

Yield: 62%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.49 (m, 1 H), 7.42 (d, *J* = 8.2 Hz, 1 H), 7.16 (s, 1 H), 7.02 (m, 2 H), 6.83 (m, 1 H), 3.76 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.7, 167.2 (d, *J* = 254 Hz), 147.3 (d, *J* = 10.2 Hz), 145.8, 143.2 (d, *J* = 2.4 Hz), 132.3, 130.3, 126.2 (d, *J* = 10.2 Hz), 124.2, 121.4, 115.3 (d, *J* = 22.8 Hz), 108.2 (d, *J* = 24.4 Hz), 56.5. HRMS: *m/z* calcd for $C_{14}H_9FO_2$: 228.2185; found: 228.2189.

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