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Palladium-Catalyzed Synthesis of Fluorenes by Intramolecular C(sp^2)–H Activation at Room Temperature

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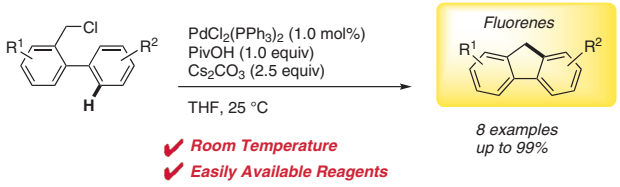

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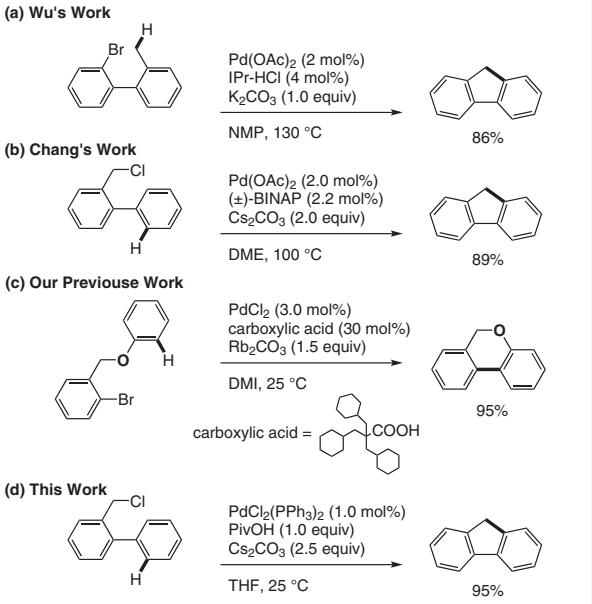
Abstract The synthesis of fluorenes by intramolecular Pd-catalyzed C(sp^2)–H activation of 2-arylbenzyl chlorides was conducted at room temperature by using commercially available triphenylphosphine and pivalic acid as ligands. The desired reactions proceeded efficiently at room temperature, and various substrates were converted into the corresponding fluorene derivatives in excellent yields.

Key words palladium catalysis, ligands, C–H activation, fluorenes, cyclization

Polycyclic aromatic hydrocarbons (PAHs) have attracted significant attention owing to their unique properties and range of applications.[1] Fluorenes are well-known motifs among PAHs, and are of interest in materials science[1e,f,2] and pharmaceutical chemistry applications.[3] Conventional strategies for the synthesis of fluorene derivatives require harsh reaction conditions or multistep procedures.[4] Consequently, the development of more-efficient preparative methods for fluorene derivatives, preferably by the use of easy-to-handle catalysts, is considered to be critical. In this context, the synthesis of fluorenes by using transition-metal catalysts has become the subject of extensive research.[5,6] Using a C–H bond-activation strategy, Wu and co-workers reported a palladium-catalyzed synthesis of fluorenes by C(sp^3)–H bond activation (Scheme 1a),[7] whereas Chang and co-workers described the palladium-catalyzed synthesis of fluorenes by C(sp^2)–H bond activation (Scheme 1b).[8] Although these strategies afforded diverse fluorene derivatives through C–H bond activation, their drawback was a necessity for reaction temperatures of above 100 °C.

We envisioned that carboxylate ligands of appropriate steric bulk might permit efficient catalytic synthesis of fluorenes. Actually, we recently reported that a bulky carboxylic acid bearing three cyclohexylmethyl moieties in the α-position can operate as an efficient carboxylate ligand source in palladium-catalyzed intramolecular C(sp^2)–H bond-arylation reactions (Scheme 1c).[9] It is notable that these reactions proceed at room temperature. After evaluating various carboxylic acids in the fluorene synthesis, commercially available pivalic acid was found to be the best source of the carboxylate ligand, and the desired reactions proceeded efficiently at room temperature (Scheme 1d).



Scheme 1 Pd-catalyzed synthesis of fluorene through C–H bond activation; DMI = 1,3-dimethylimidazolidin-2-one

First, various carboxylic acids **1** with varying steric bulk were screened for the conversion of 2-(chloromethyl)biphenyl (**2a**) to 9*H*-fluorene (**3a**) in the presence of 30 mol%

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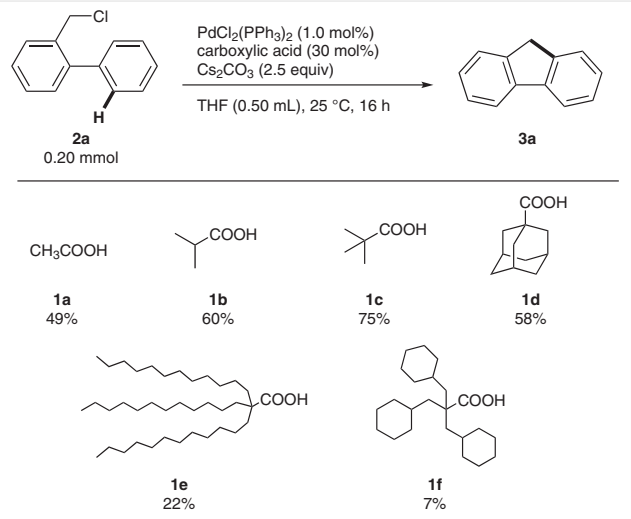
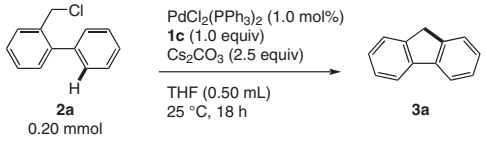
carboxylic acid, $PdCl_2(PPh_3)_2$ (1.0 mol%), and Cs_2CO_3 (2.5 equiv) as a base in THF at 25 °C (Scheme 2). Under these reaction conditions, acetic acid (**1a**) afforded the product **3a** in 49% GC yield. A secondary α-substituted carboxylic acid **1b** also gave **3a** in moderate yield. When pivalic acid (**1c**) was used, **3a** was obtained in 75% yield, whereas adamantane-1-carboxylic acid (**1d**) was noticeably less effective than **1c**. A carboxylic acid bearing three long alkyl chains **1e**[10] was not a good ligand for the reaction. The use of a bulkier carboxylic acid **1f**, which was the best carboxylate ligand source for intramolecular C(sp^2)–H bond-arylation reactions,[9] gave only 7% of **3a**. Thus, we established that **1c** is the best carboxylate ligand source under the reaction conditions.



Scheme 2 Steric effect of carboxylic acids on the palladium-catalyzed synthesis of fluorene (**3a**) from **2a**. *Reagents and conditions*: **2a** (0.20 mmol), $PdCl_2(PPh_3)_2$ (0.0020 mmol, 1.0 mol%), carboxylic acid **1** (0.060 mmol, 30 mol%), Cs_2CO_3 (0.50 mmol, 2.5 equiv), THF (0.50 mL), 25 °C, 18 h. Yields were determined by GC analysis using an internal-standard method.

Next, the reaction conditions were further optimized by using **2a** and **1c** as substrate and carboxylic acid, respectively (Table 1). The desired reaction efficiently proceeded at 25 °C in the presence of $PdCl_2(PPh_3)_2$ (1.0 mol%) and Cs_2CO_3 (2.5 equiv) in THF when the amount of **1c** was increased to 1.0 equivalent. Under these conditions, **3a** was obtained in 99% GC yield (Table 1, entry 1).[11] Employing $PdCl_2(PhCN)_2$ or $Pd_2(dba)_3{\cdot}CHCl_3$ as a Pd source instead of $PdCl_2(PPh_3)_2$ drastically reduced the yield of **3a**, proving that PPh_3 is indispensable in the reaction (entries 2 and 3). There was also a decrease in the yield of **3a** when dppf was used instead of PPh_3 (entry 4). Under these reaction conditions, the use of acetic acid (**1a**) instead of **1c** proved to be ineffective (entry 5). Changing the type of base utilized in the reaction also decreased the yield of **3a** (entries 6–8). Additionally, solvents influenced the outcome of the reaction; DME and benzene were not good solvents (entries 9 and 10). Amide solvents such as DMA gave **3a** in only 2% yield, whereas biphenyl-2-ylmethyl pivalate (**4**) was obtained in 86% yield as a major byproduct (entry 11). The use of 2-(bromomethyl)biphenyl as a substrate afforded **3a** in low yield, and most of the substrate was converted to **4** (entry 12).

Table 1 Optimization of Reaction Conditions for the Palladium-Catalyzed Synthesis of Fluorene[a]



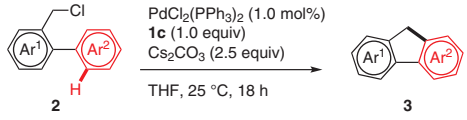
Entry	Change in reaction conditions	Yield[b] of **3a** (%)
1	–	99
2	$PdCl_2(PhCN)_2$ instead of $PdCl_2(PPh_3)_2$	11
3	$Pd_2(dba)_3{\cdot}CHCl_3$	6
4	$PdCl_2$(dppf)	32
5	AcOH (**1a**) instead of **1c**	52
6	Na_2CO_3 instead of Cs_2CO_3	11
7	K_2CO_3	26
8	K_3PO_4	42
9	DME instead of THF	34
10	benzene	4
11	DMA	2[c]
12	2-(bromomethyl)biphenyl instead of **2a**	28[d]

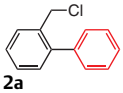
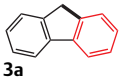
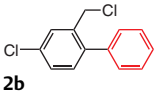
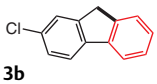
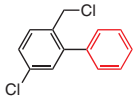
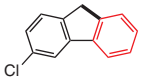
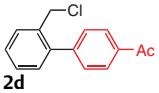
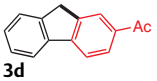
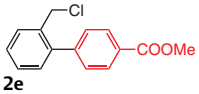
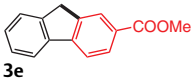
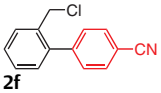
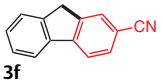
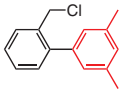
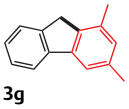
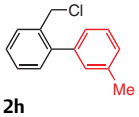
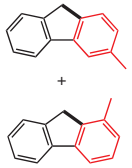
[a] Reaction conditions: **2a** (0.20 mmol), $PdCl_2(PPh_3)_2$ (0.0020 mmol, 1.0 mol %), **1c** (0.20 mmol, 1.0 equiv), Cs_2CO_3 (0.50 mmol, 2.5 equiv), THF (0.50 mL), 25 °C, 18 h.
[b] Determined by GC analysis using an internal-standard method.
[c] Biphenyl-2-ylmethyl pivalate (**4**) was obtained in 86% yield as a major byproduct.
[d] Pivalate **4** was obtained in 41% yield as a major byproduct.

The synthesis of fluorenes from various substrates was carried out at room temperature (Table 2). By using **2a** as the substrate, pure fluorene (**3a**) was successfully isolated in 96% yield (Table 1, entry 1). Substrates that possessed a chloro functionality at the 4- or 5-position of the Ar^1 ring (**2b** and **2c**, respectively) gave the corresponding products **3b** and **3c** in excellent isolated yields (entries 2 and 3). Functionalities such as acetyl, methoxycarbonyl, or cyano groups in the 4-position of the Ar^2 ring (**2d–f**) were also tolerated, affording the corresponding products **3d–f** in high yields (entries 4–6). Under Chang's conditions, **3d–f** were obtained in yields of 48, 0, and 24%, respectively. Thus, our conditions permitted the preparation of several fluorene derivatives with reactive functional groups. When the reaction substrate contained two methyl groups at the 3- and 5-positions of the Ar^2 ring (**2g**), the desired reaction proceeded to completion at 40 °C, giving product **3g** in 95% yield (entry 7). In the reaction using a substrate bearing a methyl

group at the 3-position of the Ar^2 ring (**2h**), the desired product **3h** was obtained as a mixture of two isomers in a 9.3:1 ratio (entry 8). On the other hand, the reaction conditions reported by Chang gave these isomers in a 2.8:1 ratio.[8] This means that our reaction conditions were more efficient, because the reactions proceeded at lower temperatures with good selectivity.

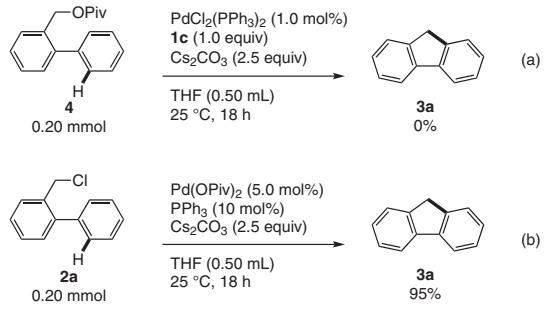
Table 2 Synthesis of Fluorene Derivatives[a]



Entry	Substrate	Product	Yield[b] (%)
1	 **2a**	 **3a**	96
2	 **2b**	 **3b**	99
3	 **2c**	 **3c**	96
4	 **2d**	 **3d**	94
5	 **2e**	 **3e**	99
6	 **2f**	 **3f**	98
7[c]	 **2g**	 **3g**	95
8[d]	 **2h**	 **3h** + **3h′**	92 (9.3:1)

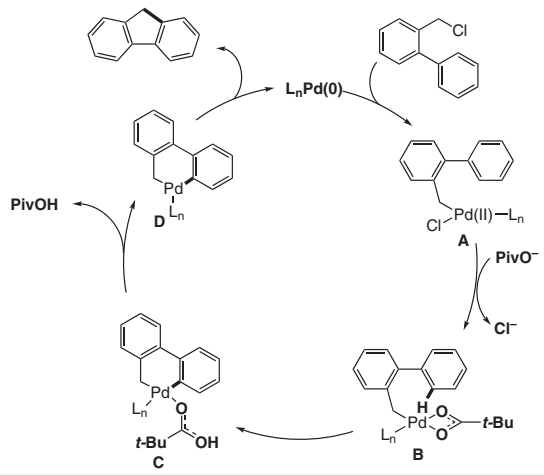
[a] Reaction conditions: **2** (0.20 mmol), $PdCl_2(PPh_3)_2$ (0.0020 mmol, 1.0 mol%), **1c** (0.20 mmol, 1.0 equiv), Cs_2CO_3 (0.50 mmol, 2.5 equiv), THF (0.50 mL), 25 °C, 18 h.
[b] Isolated yield.
[c] At 40 °C.
[d] For 42 h.

To clarify the role of pivalic acid (**1c**), two control experiments were carried out. In our study, **2** might be converted into **4** under basic conditions. Actually, **4** was detected when amide solvents were used. To examine the probability of pivalate acting as an efficient leaving group, the reaction was performed by using **4** as a substrate under the optimum reaction conditions. However, the desired product was not obtained, proving that **1c** is a poor source of the leaving group (Scheme 3a). Next, a mixture of $Pd(OPiv)_2$ and PPh_3 was used as the Pd catalyst instead of $PdCl_2(PPh_3)_2$ and **1c** (Scheme 3b). Although the use of a 1 mol% catalyst loading proved to be ineffective (42% yield), the reaction proceeded efficiently on using 5 mol% of the Pd catalyst, as exemplified by the 95% GC yield obtained for **3a**. Thus, it was shown that **1c** operates as the carboxylate ligand source for the Pd catalyst.



Scheme 3 Control experiments (a) using **4** as a substrate and (b) using $Pd(OPiv)_2$ as a palladium source

Considering the results for these experiments, a plausible reaction mechanism is shown in Scheme 4. Here, the reaction is initiated by an oxidative addition of benzyl chloride to the Pd(0) center to generate a Pd(benzyl) intermediate **A**. A subsequent ligand exchange with pivalate results in intermediate **B**. This is followed by C(sp^2)–H bond activation in the aryl ring through a concerted metalation–depro-



Scheme 4 A plausible reaction mechanism

tonation pathway assisted by the pivalate ligand, affording the palladacycle intermediate **C**. Finally, reductive elimination from **D** leads to the fluorene **3** with regeneration of the Pd(0) species.

In conclusion, a practical method was developed for the synthesis of fluorenes through Pd-catalyzed intramolecular cyclization of 2-arylbenzyl chlorides. Under these reaction conditions, pivalic acid acts as an efficient source of carboxylate ligand for the Pd catalyst. A variety of fluorene derivatives were readily obtained in excellent yields at room temperature.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690812.

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(11) **9*H*-Fluorene (3a); Typical Procedure**

In advance, Cs_2CO_3 was dried by heating under vacuum for 3 h then stored in a glovebox. A 10-mL Schlenk flask was charged with the dried Cs_2CO_3 (0.16 g, 0.50 mmol) in a glovebox, then taken out of glovebox and dried by heating under a vacuum for at least 5 min. The flask was backfilled with argon and then $PdCl_2(PPh_3)_2$ (1.4 mg, 0.0020 mmol, 1.0 mol%) and pivalic acid (**1c**; 20 mg, 0.20 mmol, 1.0 equiv) were added. The flask was then evacuated and backfilled with argon three times. THF (0.50 mL) and **2a** (37 μL, 0.20 mmol) were added, and the mixture was stirred at 25 °C for 18 h. The mixture was then analyzed by GC with tetradecane (50 μL) as an internal standard. H_2O (5 mL) and EtOAc (5 mL) were added, and the mixture was extracted with EtOAc (3 × 5 mL). The collected organic layers were combined, washed with brine (5 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (silica gel, hexane–acetone) to give a colorless solid; yield: 32.1 mg (96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.8 Hz, 2 H), 7.56 (d, *J* = 7.3 Hz, 2 H), 7.39 (t, *J* = 7.3 Hz, 2 H), 7.31 (td, *J* = 7.4, 1.1 Hz, 2 H), 3.92 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 141.7, 126.7, 126.7, 125.0, 119.8, 36.9. EI-HRMS: *m/z*: $[M - H]^+$ calcd for $C_{13}H_9$: 165.0704; found: 165.0702.