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Efficient palladium-catalyzed C(sp^2)–H activation towards the synthesis of fluorenes†

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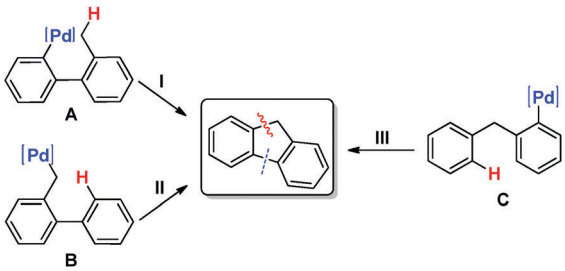
A facile protocol for the synthesis of fluorene derivatives has been developed through palladium-catalyzed cyclization of 2′-halo-diarylmethanes *via* activation of arylic C–H bonds. The reactions occurred smoothly and allowed both electron-rich and electron-deficient substrates to convert into their corresponding fluorenes in good to excellent yields. Studies revealed that this Pd-catalyzed cyclization was also available for the substrates of 2′-chloro-diarylmethanes and no catalyst poisoning occurred for 2′-iodo-diphenylmethane.

The utility of methylene-bridged polyarenes in materials science, such as light-emitting diodes, field-effect transistors and so on,[1–3] has prompted intense research directed at discovering efficient and high-yielding methods for their preparation. Among this class of compounds, fluorene, as an excellent scaffold for organic photoelectric materials, is the most representative structural motif.[4–9] The traditional strategies to synthesize fluorene derivatives include Friedel–Crafts-type reactions,[10–14] radical cyclization,[15–18] and transition metal-mediated cyclization.[19–26] Comparatively, because of its simplicity, cleanliness and atom economy, transition metal-catalyzed cyclization, through a C–H bond activation with subsequent C–C bond formation,[27–29] has emerged as the most efficient strategy and palladium is the most widely used catalyst which has been extensively investigated. Of these synthetic procedures, closing the central five-membered ring is the key step in most employed strategies. As shown in Scheme 1, according to different intermediates, Pd-catalyzed cyclizations which proceed *via* C–H bond activation can be classified into three types. If biphenyl type compounds are used as reactants,



Scheme 1 Different intermediates formed in Pd-catalyzed cyclization to construct fluorene derivatives *via* C–H bond activation.

a new C(sp^2)–C(sp^3) bond will be formed *via* intermediate **A**[22] or **B**[23] in the reaction. 2-Methyl-2′-palladabiphenyl (intermediate **A**) undergoes cyclization through benzylic C–H bond activation (type I), and alternatively, intermediate **B** through aryl C–H bond activation. The crowded environment and the short distance between the palladium moiety and the methyl group or the aryl group cause these processes to be more efficient. However, if a diphenylmethane type compound is used as the reactant, the reaction proceeds *via* aryl C–H bond activation *via* intermediate **C**.[24–26] Differing from intermediate **A** and **B**, in intermediate **C**, due to the existence of a methylene group between two phenyl rings, the distance between the palladium moiety and the aryl group is stretched which makes the C–H bond activation more challenging without a directing group or atom.

To date, most of the research studies have focused on biphenyl type reactants. Only a few examples were reported for diphenylmethane type substrates in the literature. In 2010, Wu and co-workers reported only the unexpected product (1-methyl-fluorene) by the treatment of (2-bromophenyl)-2-tolylmethane with $Pd(OAc)_2$ in the presence of a bulk NHC ligand (IPr) for the activation of benzylic C–H bonds.[22] Furthermore, Fagnou and co-workers developed a new palladium catalyzed direct arylation reaction with an aryl halide in 2006. In his report, also as a special case, fluorene was obtained when 2′-iodo-diphenylmethane was used as the substrate in the presence of $Pd(OAc)_2$, PCy_3-HBF_4,

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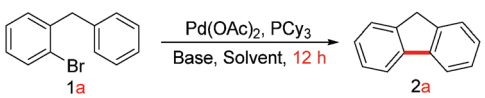
Ag_2CO_3, and K_2CO_3 in DMA.[24–26] Herein, we report our newly developed palladium-catalyzed direct arylation *via* C–H activation adopting diphenylmethane type reactants for the synthesis of fluorene derivatives.

In the previously reported work of Fagnou's group, 0.5 equiv. of Ag_2CO_3 was necessary in the intramolecular cyclization of 2′-iodo-diphenylmethane catalyzed by $Pd(OAc)_2$. They established that the catalyst poisoning occurred with the accumulation of iodide anions in the reaction mixture and could be overcome by the addition of silver salts. Then, was the silver salt necessary if the aryl iodide was replaced by aryl bromide? Accordingly, under the reaction conditions described in Fagnou's work, 2′-bromo-diphenylmethane was treated with $Pd(OAc)_2$, PCy_3, and K_2CO_3 in DMA at 130 °C. Disappointedly, the yield of fluorene was only 35%. This result prompted us to initiate our efforts on a new efficient palladium-catalyzed cyclization of 2′-halo-diarylmethanes for the synthesis of fluorene derivatives. Solvent screens were first performed with 2′-bromo-diphenylmethane in the presence of 3 mol% $Pd(OA)_2$, 6 mol% of PCy_3, 3.0 equiv. of K_2CO_3 and 1.0 equiv. of PivOH at 120 °C. The results were outlined in Table 1; DMF (Table 1, entry 1) and toluene (Table 1, entry 2) gave inferior results in the reaction. The optimal solvent was THF (Table 1, entry 4) and gave the product fluorene in 96% yield (determined by ^{1}H NMR analysis) which was better than 1,4-dioxane (Table 1, entry 3). The influence of the base was also examined (Table 1). It was revealed that both Cs_2CO_3 and Na_2CO_3 were ineffective (Table 1, entries 6 and 7) for this cyclization reaction. PivOCs provided a comparable result to K_2CO_3/PivOH and a slightly higher yield (98%) could be obtained (Table 1, entry 8). However, the reaction was obviously sluggish at lower temperature (Table 1, entries 10 and 11). We reasoned that the elevated reaction temperature could facilitate the C–H activation processes. The optimum reaction conditions thus far being developed employed 1.0 equiv. of 2′-bromo-diphenylmethane (**1a**) (0.5 mmol), 3 mol% of $Pd(OAc)_2$, 6 mol% of PCy_3, and 3.0 equiv. of PivOCs in THF (2 mL) at 120 °C for 12 h. This procedure provided fluorene (**2a**) in 90% isolated yield.

Table 1 Optimization of conditions for palladium catalyzed direct arylation *via* C–H activation[a]



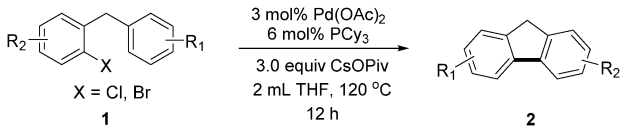
Entry	Base	Solvent[d]	T (°C)	Yield[b] (%)
1	K_2CO_3/PivOH	DMF	120	48
2	K_2CO_3/PivOH	Toluene	120	31
3	K_2CO_3/PivOH	1,4-Dioxane	120	85
4	K_2CO_3/PivOH	THF	120	96
5	K_3PO_4/PivOH	THF	120	51
6	Cs_2CO_3/PivOH	THF	120	Trace
7	Na_2CO_3/PivOH	THF	120	25
8	PivOCs	THF	120	98 (90[c])
9	PivOK	THF	120	81
10	PivOCs	THF	100	94
11	PivOCs	THF	80	54

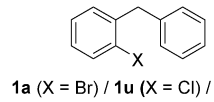
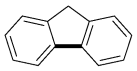
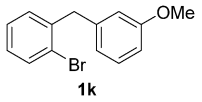
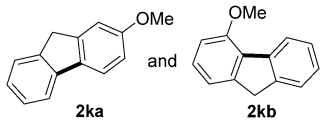
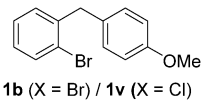
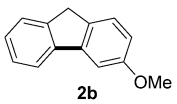
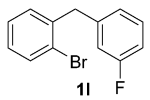
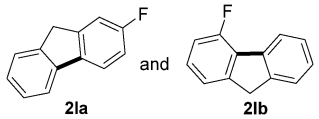
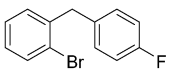
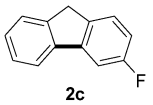
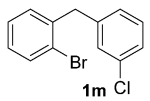
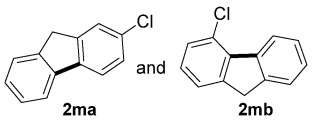
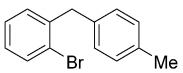
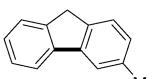
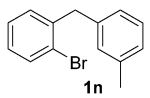
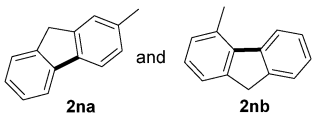
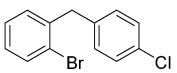
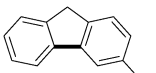
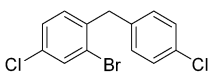
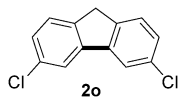
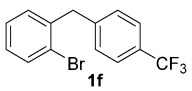
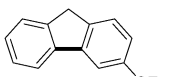
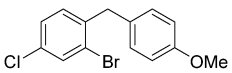
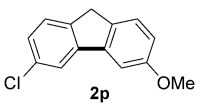
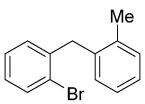
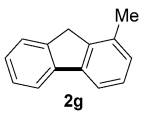
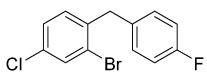
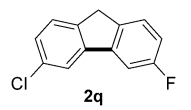
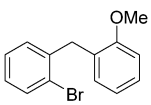
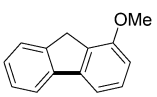
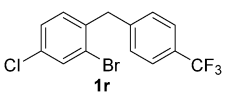
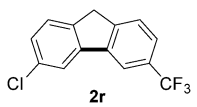
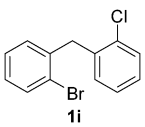
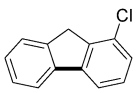
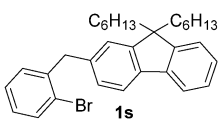
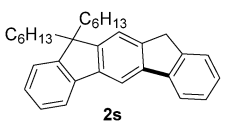
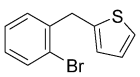
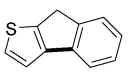
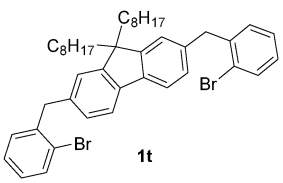
[a] Reaction conditions: **1** (0.5 mmol, 1.0 equiv.), 3 mol% of $Pd(OAc)_2$, 6 mol% of PCy_3, base (1.5 mmol, 3.0 equiv.), PivOH (0.3 mmol, 1.0 equiv.), solvent (2 mL). [b] Yields were determined by ^{1}H NMR. [c] Isolated yield. [d] DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

The scope of the cyclization with 2′-halo-diarylmethanes was outlined in Table 2. All the employed substrates bearing either electron-withdrawing groups such as –F (**1c**, **1l**, **1w**), –Cl (**1e**, **1i**, **1m**), and –CF_3 (**1f**) or electron-donating groups such as –Me (**1d**, **1g**, **1n**) and –OMe (**1b**, **1h**, **1k**, **1v**) were well tolerated and proceeded smoothly to afford their corresponding products in good to excellent yields. This reaction was also effective for 2-(2-bromobenzyl) thiophene (**1j**) and produced the desired fluorene (**2j**) in moderate yield (Table 2, entry 10). These experimental results indicated that there was only a weak electronic effect and steric effect for the transformation in the reaction. However, for 2′-bromo-3″-substituted-diphenyl methanes (**1k**, **1l**, **1m**, **1n**), the electronic effect and steric effect had a great influence on selectivity for this transformation. 2′-Bromo-3″-methoxy-diphenyl methane (**1k**) and 2′-bromo-3″-methyl-diphenyl methane (**1n**) gave more 2-substituted fluorene than 4-substituted fluorene (Table 2, entries 11 and 14). In contrast, 2′-bromo-3″-fluoro-diphenyl methane (**1l**) and 2′-bromo-3″-chloro-diphenyl methane (**1m**) afforded more 4-substituted fluorine unexpectedly (Table 2, entries 12 and 13). The selectivity was improved by increasing the steric hindrance of the substituent at the 3″-position. For example, **2s** could be synthesized with high efficiency and high selectivity by the cyclization of **1s** (Table 2, entry 19). A more challenging double annulation of this palladium method was also attempted using **1t** as a substrate and an enhanced π-conjugation compound **2t** was synthesized conveniently (Table 2, entry 20). They were useful molecules in organic electronic materials. The reactivity of aryl C–Cl is generally considered to be inferior in coupling reaction and use of aryl chlorides is rare despite the fact that aryl chlorides are more readily available and less expensive. In subsequent studies, we were glad to discover that aryl C–Cl (**1u**, **1v**, **1w**) also reacted smoothly to afford their corresponding products in good to excellent yields (Table 2, entries 1–3). Interestingly, the C–Cl bond was tolerated in the substrates of 2′-bromo-diarylmethanes (**1e**, **1i**, **1m**, **1o**, **1p**, **1q**, **1r**), and more significantly, the preservation of C–Cl bonds offered the opportunity for further functionalizations. More wonderfully, 2′-iodo-diphenylmethane (**1y**) was also well tolerated and afforded fluorene (**2a**) in 83% yield (Table 2, entry 1) which indicated that no catalyst poisoning occurred in our reaction system.

In summary, a facile protocol for the synthesis of fluorene derivatives has been developed through palladium-catalyzed cyclization of 2′-halo-diarylmethanes *via* activation of aryl C–H bonds. The reactions occurred smoothly and allowed both electron-rich and electron-deficient substrates to convert into their corresponding fluorenes in good to excellent yields. Studies revealed that this Pd-catalyzed cyclization was also available for the substrates of 2′-chloro-diarylmethanes and no catalyst poisoning occurred for 2′-iodo-diphenylmethane in our reaction system. This approach could afford a diversity of fluorene-based molecular architectures and therefore would provide more opportunity for research on the properties of material molecules. Further investigation on the application of this chemistry is currently underway in our laboratory.

Table 2 Synthesis of fluorenes by palladium-catalyzed C(sp^2)–H activation[a]



Entry	Substrate	Product	Yield (%)	Entry	Substrate	Product	Yield (%)
1	 **1a** (X = Br) / **1u** (X = Cl) / **1y** (X = I)	 **2a**	90/85/83	11	 **1k**	 **2ka** and **2kb**	94 **2ka**/**2kb** = 5.4 : 4.6
2	 **1b** (X = Br) / **1v** (X = Cl)	 **2b**	90/64	12	 **1l**	 **2la** and **2lb**	84 **2la**/**2lb** = 1 : 9
3	 **1c** (X = Br) / **1w** (X = Cl)	 **2c**	94/90	13[c]	 **1m**	 **2ma** and **2mb**	87 **2ma**/**2mb** = 2.8 : 5
4[b]	 **1d**	 **2d**	64	14[c]	 **1n**	 **2na** and **2nb**	78 **2na**/**2nb** = 2.3 : 1
5	 **1e**	 **2e**	91	15	 **1o**	 **2o**	81
6	 **1f**	 **2f**	99	16	 **1p**	 **2p**	88
7[b]	 **1g**	 **2g**	56	17	 **1q**	 **2q**	84
8	 **1h**	 **2h**	93	18	 **1r**	 **2r**	89
9	 **1i**	 **2i**	93	19	 **1s**	 **2s**	99
10	 **1j**	 **2j**	65	20	 **1t**	**2t**	99

[a] Reaction was conducted with **1** (0.50 mmol), $Pd(OAc)_2$ (3 mol%), PCy_3 (6 mol%), PivOCs (3.0 equiv.) and THF (2 mL) at 120 °C for 12 h. Isolated yield. [b] Yields were determined by ^1H NMR. A mixture of the cyclization product and the hydrodebromination byproduct. [c] A mixture of two regioisomers (the ratio of the products was determined by ^1H NMR).

Experimental section

To an oven dried sealed tube containing PivOCs (1.5 mmol, 349.0 mg) and $Pd(OAc)_2$ (0.015 mmol, 3.4 mg), PCy_3 (0.030 mmol, 8.4 mg) was added in a glove box under an argon atmosphere. 1-Benzyl-2-bromobenzene (0.50 mmol, 124.0 mg) and THF (2.0 mL) were injected into the reaction tube *via* a syringe. The mixture was allowed to stir at room temperature for 5 minutes

and then heated to 120 °C with vigorous stirring for 12 hours. After being quenched by saturated NH_4Cl solution, the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined, dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. Column chromatography on silica gel (petroleum ether) afforded the desired product.

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Notes and references

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