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Palladium-catalyzed one-pot Suzuki coupling followed by arylpalladium addition to aldehyde: a convenient route to fluoren-9-one derivatives

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ABSTRACT

Various fluoren-9-one derivatives were prepared efficiently by a one-pot reaction involving sequential Suzuki coupling of 2-bromophenyl boronic acid with 2-bromocarboxaldehyde followed by intramolecular arylpalladium addition to aldehyde.

The importance of fluoren-9-one, found in many biologically active products, has been emphasized in organic chemistry. It consists of essential structural backbone of various pharmaceuticals.[1] Also number of natural products have been found containing fluoren-9-one as the core structure. Examples of such natural products include dengibsin, dengibsinin, dendroflorin, and kinobscurinone showing a range of biological activities.[2] Utility of fluoren-9-one derivatives as photosensitizers in organic photoconductor devices and their electrical and optical properties are also important.[3] Therefore methodologies for the preparation of fluoren-9-one moiety have attracted much attention from both academia and industry.

Several methods for the preparation of fluoren-9-ones have been developed among which the useful syntheses include Friedel–Crafts ring closure of biarylcarboxylic acid and its derivatives,[4] remote aromatic metalation,[5] oxidation of fluorenes,[6] intramolecular Diels–Alder reaction of conjugated enyne or diarylacetylene systems,[7] ring contraction,[8] etc.

Over the past decades Pd-catalyzed cross-coupling reactions have become powerful tools for C–C bond formation to synthesize a wide variety of organic compounds ranging from small molecules to macromolecules. There are some synthetic protocols available involving Pd-catalyzed coupling reactions leading to fluoren-9-one moiety such as Pd-catalyzed cyclization of *o*-iodobenzophenone,[9] cyclocarbonylation of *o*-halobiaryls,[10] arylation followed by oxidative Heck cyclization of aromatic aldoxime ether[11] have been reported. Larock and co-workers have synthesized fluoren-9-one starting from 2-haloarenecarboxaldehyde via Pd-catalyzed annulation of arynes.[12] Our continued efforts in palladium-catalyzed cyclization reactions on substrates derived from β-bromovinyl aldehydes to develop the carbocycles and heterocycles[13] have driven us to develop a facile and efficient Pd-catalyzed synthesis of functionalized fluoren-9-one derivatives starting from various 2-bromocarboxaldehydes along with 2-bromophenyl boronic acid with two distinct sequential steps, Suzuki coupling followed by arylpalladium addition to aldehyde, in one-pot.

We initially focused on the reaction between commercially available 2-bromobenzaldehyde **(1a)** and 2-bromophenyl boronic acid (**2**) for the preparation of fluoren-9-one (**4a**). Toward this we carried out Suzuki coupling[14] between **1a** and **2** in presence of $Pd(PPh_3)_4$ as catalyst, Et_3N as base in DMF at 90 °C for 2 h where the 2′-bromobiphenyl-2-carbaldehyde (**3**) was obtained as the only isolable product in good yield. It was expected to undergo the intramolecular arylpalladation[12,15] to aldehyde on subjecting to Pd(0)-catalytic condition to construct the fluoren-9-one (**4a**). Thus when this intermediate **3** was heated at somewhat higher temperature (120 °C) in presence of $Pd(OAc)_2$ as catalyst, Na_2CO_3 as base, PPh_3 as ligand in DMF for 13–14 h, it gave fluoren-9-one (**4a**) accordingly (Scheme 1). We then envisioned that these two steps can be carried out sequentially using one catalytic system in one-pot without isolating the intermediate.

With this idea in mind, we carried out a survey of Pd-catalysts, bases, solvents, and temperature to get the optimal condition for the preparation of fluoren-9-one in one-pot (summarized in Table 1). Initially we performed the reaction in presence of $Pd(PPh_3)_4$

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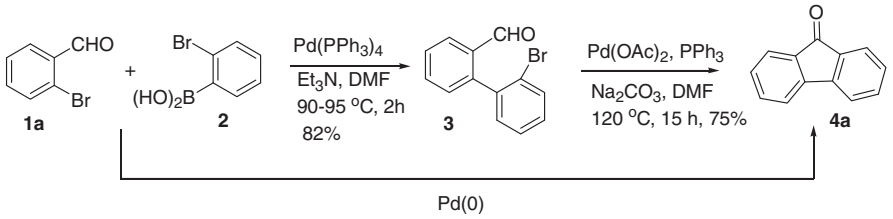
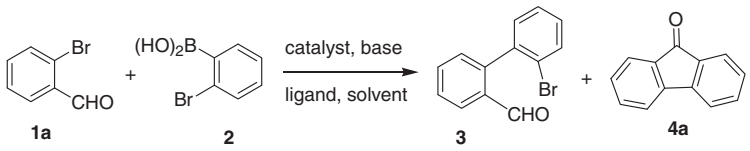


Scheme 1. Synthesis of fluoren-9-one.

Table 1
Optimization studies[a]

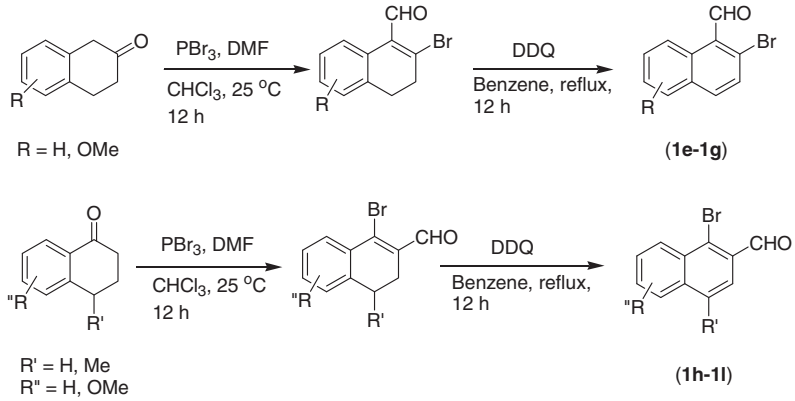


Entry	Catalyst	Ligand	Base	Solvent	Temp (°C)	Yield%[c]	
						3	**4a**
1	$Pd(PPh_3)_4$	—	Et_3N	DMF	120	79	Tr
2	$Pd(PPh_3)_4$	—	NaOAc	DMF	120	78	Tr
3	$Pd(PPh_3)_4$	—	Na_2CO_3	DMA	130	73	<10
4	$Pd(OAc)_2$	PPh_3	Na_2CO_3	DMF	100	67	15
5	$Pd(OAc)_2$	PPh_3	Na_2CO_3	DMF	120	10	65
6	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	120	10	68
7	$Pd(OAc)_2$	PPh_3	NaOAc	DMF	120	—	80
8	$Pd(OAc)_2$	PPh_3	NaOAc	Toluene[b]	110	50	20
9	$Pd(OAc)_2$	PPh_3	Et_3N	DMF	120	50	30
10	$Pd(PPh_3)_2Cl_2$	—	NaOAc	DMF	120	<5	75

[a] Reagents and conditions: *o*-bromobenzaldehyde (1 mmol), 2-bromophenyl boronic acid (1.2 mmol), catalyst (10 mol %), base (4 mmol), ligand (0.5 mmol), and solvent (6 mL) at the indicated temperature for 15–16 h under N_2.
[b] Reaction was run in a two-necked round-bottomed flask with a reflux condenser.
[c] Yields refer to the isolated yield after purification. Tr = traces.

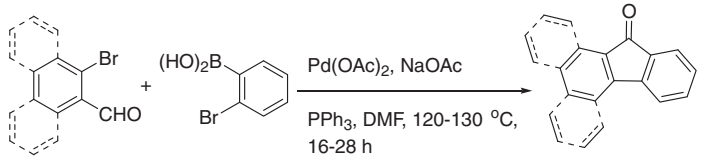
as catalyst, Et_3N as the base in dry DMF under N_2 at 120 °C for 16 h where the intermediate 2′-bromobiphenyl-2-carbaldehyde (**3**) was obtained in 79% yield accompanied by the traces amount of desired fluoren-9-one (**4a**) (Table 1, entry 1). Changing the bases and solvents with $Pd(PPh_3)_4$ did not effect this transformation appreciably (entries 2, 3). On carrying out the reaction in presence $Pd(OAc)_2$, PPh_3, Na_2CO_3 in DMF at 120 °C, **4a** was formed in 65% yield at 120 °C (entry 5). Using NaOAc as a base improved the yield of **4a** to 80% (entry 7). However using toluene as a solvent gave poor yield (20%) (entry 8). Therefore after a thorough screening with different combination of catalyst, base, solvent, and temperature, the 'optimal' condition was found when the substrates **1a** (1 mmol) and **2** (1.2 mmol) were heated in presence of $Pd(OAc)_2$ (10 mol %), PPh_3 (0.5 mmol), NaOAc (4 mmol) in DMF (6 mL) at 120 °C for 15–16 h under N_2.[16] Performing the reaction with $Pd(OAc)_2$ less than 10 mol % under the same reaction condition leads to decrease in yield of fluoren-9-one. With 5 mol % $Pd(OAc)_2$ only 30% fluoren-9-one (**4a**) along with 43% intermediate (**3**) was isolated. However in none of the cases the biphenyl formed due to oxidative homocoupling product from boronic acid was found.

With the optimum reaction condition we successfully extended our methodology to other substituted 2-bromocarboxaldehydes (**1a–1l**). Among them *o*-bromonaphthalenecarboxaldehydes (**1e–1l**) were synthesized from their corresponding tetralone



Scheme 2. Preparation of *o*-bromonaphthalenecarboxaldehydes.

Table 2
Synthesis of fluoren-9-one derivatives[a]



(**1a-1l**) **2** (**4a-4l**)

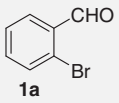
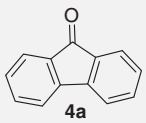
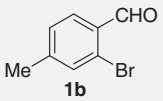
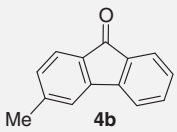
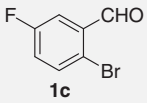
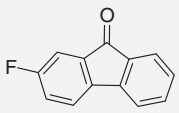
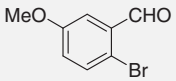
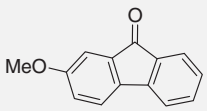
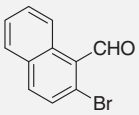
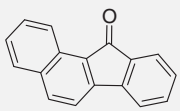
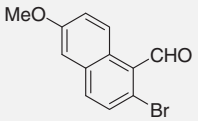
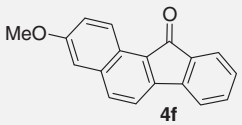
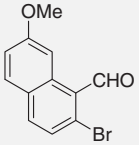
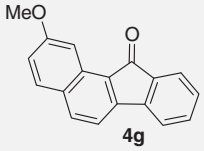
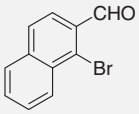
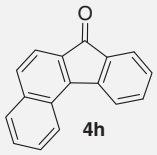
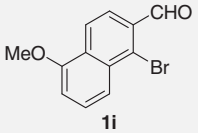
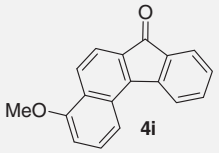
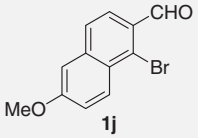
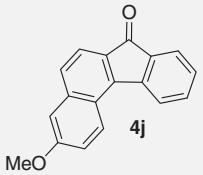
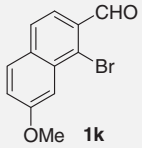
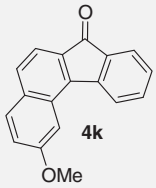
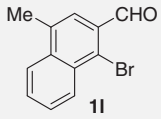
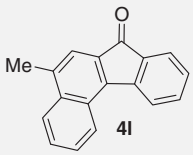
Entry	Substrate	Product	Yield%[b]
1	 **1a**	 **4a**	80
2	 **1b**	 **4b**	79
3	 **1c**	 **4c**	86
4	 **1d**	 **4d**	76
5	 **1e**	 **4e**	67
6	 **1f**	 **4f**	68
7	 **1g**	 **4g**	66
8	 **1h**	 **4h**	53[c]
9	 **1i**	 **4i**	53[c]
10	 **1j**	 **4j**	52[c]

Table 2 (*continued*)

Entry	Substrate	Product	Yield%[b]
11	 **1k**	 **4k**	51[c]
12	 **1l**	 **4l**	54[c]

[a] Reagent and conditions: All the reactions were carried out under the following conditions unless otherwise specified: 2-bromocarboxaldehyde (1 mmol), 2-bromophenyl boronic acid (1.2 mmol), $Pd(OAc)_2$ (10 mol %), PPh_3 (0.5 mmol), NaOAc (4 mmol), DMF (6 mL), at 120 °C for 15–16 h.

[b] Yields refer to the isolated yield after purification.

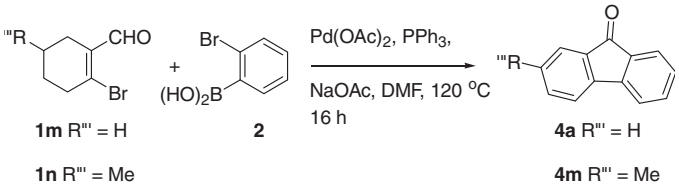
[c] These reactions were run at 130 °C and needed 28 h to reach completion.

derivatives in an excellent yield using Vilsmeier–Haack type reaction[17] followed by aromatization with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Scheme 2).

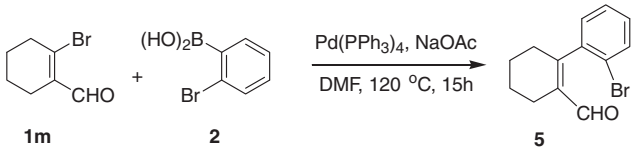
Several fluoren-9-one derivatives (**4a–4l**) were successfully prepared from the reaction of various 2-bromoarenecarboxaldehydes (**1a–1l**) with 2-bromophenyl boronic acid (**2**) under optimized reaction condition (Table 2). With the substituted *o*-bromobenzaldehydes (**1a–1d**) and 2-bromonaphthalen-1-carboxaldehydes (**1e–1g**), fluoren-9-one derivatives were isolated in moderate to good yield. However the 1-bromonaphthalen-2-carboxaldehydes (**1h–1l**) gave comparatively lower yield which may be due to the location of bromine at the sterically hindered 1-position of naphthalene and for this reason they required rather higher temperature (130 °C) and prolonged reaction time (28 h) for the completion of reaction.

A number of cyclic β-bromovinyl aldehydes (prepared from Vilsmeier–Haack[17] type reaction from their cyclic-keto derivatives) were also subjected to the similar reaction condition where only 2-bromocyclohex-1-enecarbaldehyde derivatives (**1m–1n**) gave fluoren-9-ones (**4a**, **4m**) instead of 1,2,3,4-tetrahydro-fluoren-9-ones which underwent Pd(0)-catalyzed dehydrogenation in the reaction medium (Scheme 3).

In order to investigate the step at which dehydrogenation occurred, we carried out the reaction of 2-bromocyclohex-1-enecarbaldehyde (**1m**) with 2-bromophenyl boronic acid (**2**) using the



Scheme 3. Synthesis of fluoren-9-one derivatives from 2-bromocyclohex-1-enecarbaldehydes.



Scheme 4. Isolation of intermediate 2-(2-bromophenyl)-cyclohex-1-enecarbaldehyde.

experimental condition stated in Table 1, entry 2 (Scheme 4) where we isolated 2-(2-bromophenyl)-cyclohex-1-enecarbaldehyde (**5**) which confirmed that the dehydrogenation occurred during the cyclization step. With 5, 7, and 8-membered cyclic β-bromovinylaldehydes, after Suzuki coupling the formed intermediate underwent a complete decomposition under this reaction condition.

In conclusion we have successfully developed a simple and effective one-pot synthesis of fluoren-9-one derivatives which involves the Suzuki coupling of 2-bromophenyl boronic acid with various 2-bromocarboxaldehydes followed by arylpalladium addition to aldehyde. To our knowledge this method is the first report for the synthesis of fluoren-9-one using one-pot Suzuki coupling followed by arylpalladation to aldehyde. It provides an efficient synthesis of various fluoren-9-one and condensed fluoren-9-one derivatives in moderate to good yield from the readily available starting materials.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.062.

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16. *General procedure for the one-pot Pd-catalyzed synthesis of fluoren-9-ones*: The 2-bromocarboxaldehyde (1 mmol), 2-bromophenyl boronic acid (1.2 mmol), dry NaOAc (4 mmol), and PPh_3 (0.5 mmol) were placed in a two-necked round-bottomed flask, flushed with N_2 and DMF (6 mL) was added to it. After degasification, $Pd(OAc)_2$ (10 mol %) catalyst was added and the mixture was heated at 120–130 °C for 16–28 h. The mixture was allowed to cool, diluted with water, and extracted with ethyl acetate (3×15 mL). The solvent was evaporated in vacuo after drying over Na_2SO_4 to give the crude product which was purified by silica gel (60–120 mesh) column chromatography using petroleum ether/ethyl acetate (50:1) as the eluent.
Spectral data of representative compounds: *2-fluoro-fluoren-9-one* (**4c**):[18] From 2-bromo-5-fluoro-benzaldehyde (**1c**) (0.1 g, 0.49 mmol) and 2-bromophenyl boronic acid (**2**) (0.12 g, 0.59 mmol) with $Pd(OAc)_2$ (10 mol %), NaOAc (1.9 mmol) and PPh_3 (0.25 mmol) in DMF (5 mL) at 120 °C for 15 h, product **4c** was obtained as yellow solid in 86% yield (0.083 g); mp 113–115 °C (lit. mp 117 °C); IR (KBr): 1718, 1601, 1458, 1268 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.13 (1H, dt, $J = 2.4, 8.2$), 7.23–7.24 (1H, m), 7.27–7.33 (1H, m), 7.42–7.46 (3H, m), 7.62 (1H, d. $J = 7.2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.8 (d, $J = 24$), 120.0, 120.8 (d, $J = 23$), 121.5 (d, $J = 8$), 124.5, 128.7, 134.3, 134.9, 136.3 (d, $J = 7$), 140..1, 143.8, 163.5 (d, $J = 248$), 192.4. Elemental analysis: found: C, 78.62; H, 3.65. $C_{13}H_7FO$ requires C, 78.78; H, 3.56. HRMS (ESI, 70 eV): $m/z = 199.0554$ [M^++H] (calcd mass for $C_{13}H_8FO$: 199.0559 [M^++H]).
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