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One-Pot Synthesis of Diarylmethylidenefluorenes and Phenanthrenes by Palladium-Catalyzed Multiple C–H Bond Functionalization

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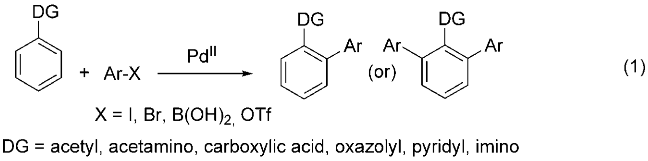
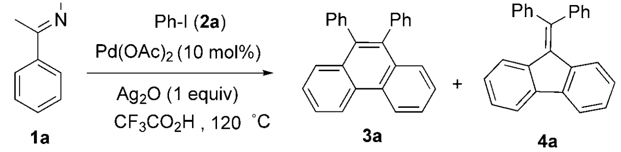
Transition-metal-catalyzed C–H bond functionalization has become a most challenging method for organic synthesis[1] in view of the large bond energy and the inertness of C–H bond. The sp^2 and sp^3 C–H bond activation and subsequent C–C bond formation reaction catalyzed by ruthenium, rhodium, palladium, iridium, and other metal complexes with or without directing groups have been demonstrated.[2] In this context, we were particularly attracted by the Pd^{II}-catalyzed directing-group-assisted *ortho*-functionalization of aromatic C–H bond. Various directing groups have been employed for the palladium-catalyzed arylation of *ortho* aromatic C–H bonds leading to mono or diarylated products [Eq. (1)].[3a–f]



Apart from the above directing groups, only a few examples are known using oximes as a directing group for the activation of aromatic or olefinic C–H bonds. Thus, Sanford and several other groups reported oxime-directed transformation of *ortho*-aromatic or olefinic C–H bonds to C–O, C–X, and C–N bonds catalyzed by palladium complexes.[4] Very recently, we reported a Pd-catalyzed synthesis of fluoren-9-one derivatives from aldoxime ether and aryl iodides involving two distinct steps of C–H activation and oxidative Heck-type cyclization in one pot.[5]

Devising C–H bond activation reactions that achieve multiple C–C bond formation in one operation has attracted considerable attention in metal-catalyzed organic synthesis,[6] but there are only few methods known that can construct complex molecules. Shi and co-workers reported the synthesis of highly functionalized carbazoles by Pd^{II}-catalyzed multiple C–H activation of acetanilide with arenes.[7] Very recently, Lautens et al. reported a palladium-catalyzed synthesis of tetrasubstituted helical alkenes by means of a norbornene-mediated multiple C–H bond activation of aryl iodide with bromoalkyl aryl alkynes.[8] Our continued efforts in metal-catalyzed C–H bond activation and cyclization reactions[9] prompted us to explore the reaction of aromatic ketoxime ethers with aryl iodides. Herein, we wish to report a rapid construction of diarylmethylidenefluorene and phenanthrene derivatives from these two reagents through a palladium-catalyzed multiple C–H bond functionalization strategy.

When we switched benzaldoxime ether to acetophenone oxime ether in the Pd-catalyzed C–H activation reaction with iodobenzene,[5] the reaction gave a diarylmethylidenefluorene and a phenanthrene derivative instead of the fluoren-9-one product. Thus, treatment of oxime ether **1a** and aryl iodide **2a** with 10 mol% of $Pd(OAc)_2$ and one equivalent of Ag_2O in trifluoroacetic acid at 120 °C for 15 h gave a mixture of diphenylphenanthrene (**3a**) and diphenylmethylidenefluorene (**4a**) in a 78:22 ratio in 78% combined yield (Scheme 1). Although products **3a** and **4a** could not be separated, the crystal structures of both compounds were determined by X-ray diffraction. The stoichiometry of these two



Scheme 1. The formation of diphenylmethylidenefluorene and diphenylphenanthrene.

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products shows that the catalytic reaction requires a molecule of oxime ether **1a** and three molecules of aryl iodide **2a** for the formation of each **3a** or **4a** molecule. To the best of our knowledge, this is the first example of multiple C–H functionalization, C–C bond formation, and a cyclization in one pot. It is worth noting that other directing groups generally gave only mono- or diarylated products at the *ortho*-position [Eq. (1)].

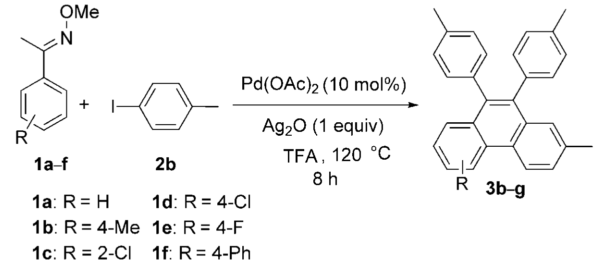
Under similar conditions, **1a** also reacted with 4-iodotoluene (**2b**) smoothly, but gave only the corresponding phenanthrene **3b** in 76% yield (entry 1, Table 1). There was no methylidenefluorene species observed. Similarly, various acetophenone oxime ethers **1b–f** reacted with **2b** to afford substituted 9,10-ditolylphenanthrenes **3c–g** (Table 1). Thus, treatment of 4-methyl acetophenone oxime ether **1b** with **2b** gave **3c** in 69% yield (entry 2). Both 2- and 4-chloroacetophenone oxime ethers (**1c**) and (**1d**) reacted smoothly with **2b** to give **3d** and **3e** in 74 and 71% yields, respectively (entries 3 and 4). In a similar manner, 4-fluoro- and 4-phenylacetophenone oxime ethers (**1e** and **1f**) performed well with **2b** to give **3f** and **3g**, respectively, in good yields (entries 5, 6).

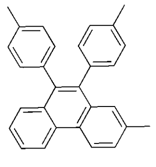
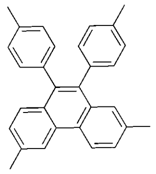
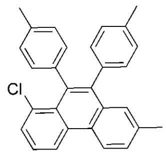
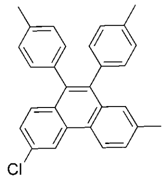
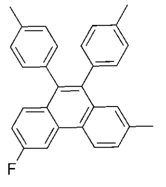
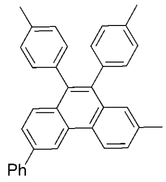
To our surprise, 3-iodotoluene (**2c**) reacted with **1d** under the present reaction conditions to afford the corresponding methylidenefluorene species **4b** in 58% yield (Table 2, entry 1), instead of the expected phenanthrene derivative. When aryl iodide **2** contained a strong electron-donating group, like 4-iodoanisole, it was inactive for the multiple C–H functionalization giving no desired compound **3** or **4**. In addition, 2-iodotoluene also did not undergo the reaction with **1d** to provide phenanthrene or methylidenefluorene product. The steric repulsion of methyl group at *ortho*-position likely accounts for the failure of the reaction.

This Pd-catalyzed formation of methylidenefluorene derivative was successfully extended to a range of aryl iodides with an electron-withdrawing substituent (**2d–f**) with oxime ethers **1a**. As shown in Table 2, ethyl 4-iodobenzoate (**2d**) afforded **4c** in 80% yield (entry 2), 4-nitroiodobenzene (**2e**) provided **4d** in 76% yield (entry 3) and 4-bromoiodobenzene (**2e**) gave a chemoselective product **4e** in which the C–Br bonds remain intact in 70% yield (entry 4). In a similar manner, aromatic oxime ether with different substituents on the phenyl ring (**1b–f**) also reacted with **2d** to give the corresponding diphenylmethylidenefluorenes derivatives **4f–j** in good yields (entries 4–9). However, the present reaction is limited by the use of acetophenone-type oxime ether. If the methyl group in acetophenone was changed to ethyl group or other longer-chain alkyl group, no similar type of methylidenefluorene or phenanthrene product was found.

A plausible mechanism to account for the present palladium-catalyzed formation of product **4a** from aromatic ketoxime ether **1a** and iodobenzene **2a** is proposed in (Scheme 2). The initial several steps are similar to the palladium-catalyzed synthesis of fluoren-9-one derivatives from the substituted benzaldehyde oxime ethers with aryl halides until the reaction steps after intermediate **9**.[5] Protonation of **9** followed by demethoxyamination gives **10** and Pd^{II}. Two consecutive arylation of the vinyl C–H bonds in **10** by aryl iodide then proceed to give product **4a**.

Table 1. Synthesis of diphenylphenanthrene derivatives.[a]

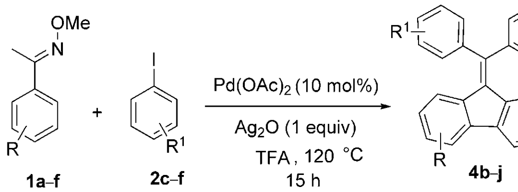


	1	2	Product 3		Yield [%][b]
1	**1a**	**2b**		**3b**	76
2	**1b**	**2b**		**3c**	69
3	**1c**	**2b**		**3d**	74
4	**1d**	**2b**		**3e**	71
5	**1e**	**2b**		**3f**	62
6	**1f**	**2b**		**3g**	58

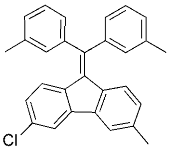
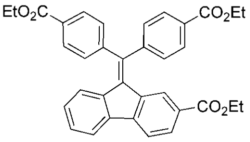
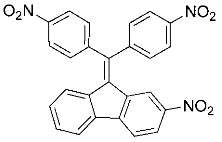
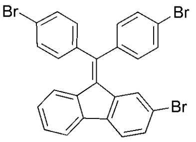
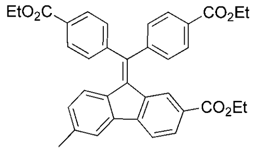
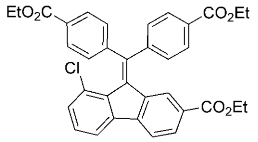
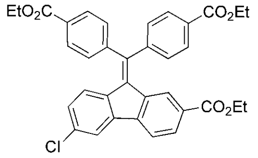
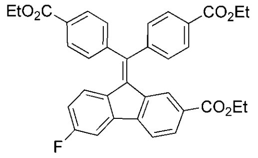
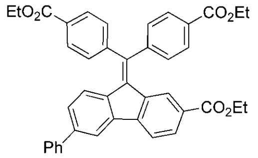
[a] Unless otherwise mentioned, all reactions were carried out using oxime ethers **1** (1.0 mmol), aryl iodide **2** (5–6 equiv), $Pd(OAc)_2$ (10 mol%), Ag_2O (1.0 mmol) and CF_3CO_2H (2.0 mL) at 120°C for 8 h. [b] Isolated yields.

To support the proposed mechanism, we tried to isolate intermediate **5** shown in Scheme 2. Thus, heating **1a** in the presence of one equivalent of $Pd(OAc)_2$ and Ag_2O in tri-

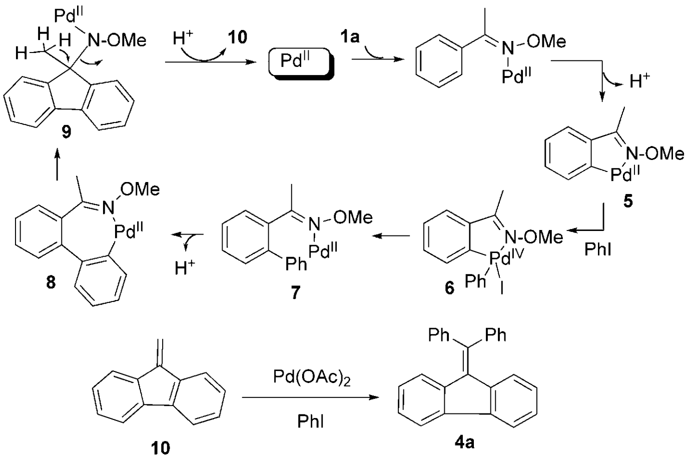
Table 2. Synthesis of diphenylphenanthrene derivatives.[a]



2c: R^1=3-Me **2e**: R^1=4-NO_2
2d: R^1=4-CO_2Et **2f**: R^1=4-Br

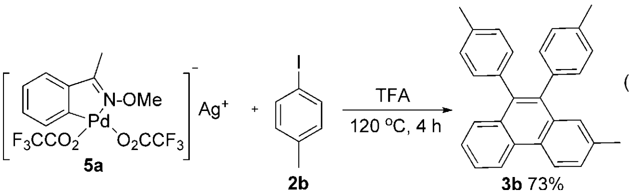
	1	2	Product 4		Yield [%][b]
1	**1d**	**2c**		**4b**	58
2	**1a**	**2d**		**4c**	80
3	**1a**	**2e**		**4d**	76
4	**1a**	**2f**		**4e**	70
5	**1b**	**2d**		**4f**	72
6	**1c**	**2d**		**4g**	66
7	**1d**	**2d**		**4h**	73
8	**1e**	**2d**		**4i**	65
9	**1f**	**2d**		**4j**	63

[a] Unless otherwise mentioned, all reactions were carried out using oxime ethers **1** (1.0 mmol), aryl iodide **2** (5–6 equiv), $Pd(OAc)_2$ (10 mol%), Ag_2O (1.0 mmol) and CF_3CO_2H (2.0 mL) at 120°C for 15 h. [b] Isolated yields.

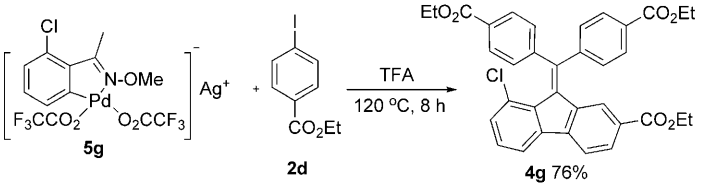


Scheme 2. Proposed mechanism for the formation of product **4**.

fluoroacetic acid (TFA) led to the isolation of an anionic palladacycle **5a** in 93% yield. Similarly, we isolated intermediate **5g** from **1c**. These complexes were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy. In addition, the structure of **5a** was determined by single-crystal X-ray diffraction. Interestingly, the reaction of **5a** with 4-iodotoluene (**2b**) in TFA at 120°C for 4 h gave **3b** in 73% yield [Eq. (2)]. On the other hand, treatment of **5g** with 4-iodobenzoate (**2d**) in TFA for 8 h gave **4g** in 76% yield [Eq. (3)].

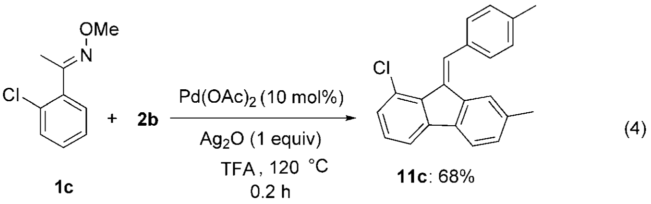


(2)

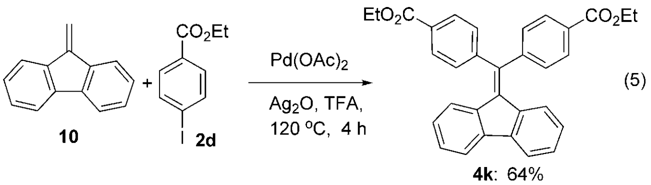


(3)

We were unable to detect or isolate intermediate **10** in the reaction. However, when **1c** and **2b** was heated under standard conditions for 0.2 h, we observed intermediate **11c** in 68% isolated yield [Eq. (4)].

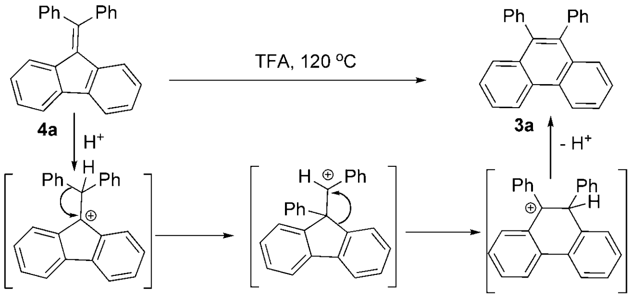


To further prove that compound **10** is an intermediate in the present catalytic reaction, **10** was synthesized by a reported method[10] and was examined under standard conditions. When **10** was heated with **2d** in the presence of 10 mol% of palladium acetate and one equivalent of Ag_2O in TFA at 120°C for 4 h, product **4k** was obtained in 64% yield [Eq. (5)]



The mechanism for the arylation of **10** is not clear. One possible route is through two C–H activations of the vinyl protons of intermediate **10** by Pd^{II} to give alkenylpalladium(II),[11] followed by oxidative addition of PhI to the alkenylpalladium(II) species, and subsequent reductive elimination of the resulting Pd^{IV} species. Alternatively, the arylation may take place by the Mizoroki–Heck reaction, which requires the presence of a Pd^0 species for the oxidative addition of aryl iodide. A drawback of this mechanism is that the reaction is performed in the presence of high concentration of silver ion that is known to oxidize Pd^0 to Pd^{II} readily. The observation of two distinct products **3** and **4** that depend greatly on the aryl iodide used from the present Pd-catalyzed reaction is extremely intriguing in terms of the mechanism of the reaction. We suspect that product **3** is from an acid-catalyzed rearrangement of the corresponding compound **4**. This notion is supported by the fact that further heating of **4a** in TFA at 120°C for 5 h led to complete conversion of **4a** to **3a**. A possible pathway for the rearrangement is presented in (Scheme 3). It is worth noting that six-membered-ring product **3** is more stable than the corresponding five-membered-ring product **4** because the latter has less aromatic resonance stabilization energy, but has relative high angle strain due to the small average angle of 108° for the sp^2 carbons in the five-membered ring.

While the role of silver oxide in the present catalytic reaction is not entirely clear, we think it can remove iodide from palladium complex **6** to facilitate reductive elimination to give **7**, is an oxidizing agent to oxidize Pd^0 to Pd^{II}, and is a base to remove protons released from the reaction. The removal of iodide ligand from Pd^{IV} to facilitate reductive elimination was reported previously.[12] In addition, the use of Ag^+ as an oxidant for the oxidation of Pd^0 species is known.[13]



Scheme 3. Possible pathway for the rearrangement of **4a** to **3a**.

In conclusion, we have successfully developed a palladium-catalyzed multiple C–H functionalization of aromatic ketoxime ethers with aryl iodides to afford diarylmethylidenefluorenes or phenanthrenes in good to excellent yields. The reaction requires one molecule of ketoxime ether and three molecules of aryl iodide for each molecule of products formed. Multiple C–H activation, C–C bond formation and extensive bond rearrangement and breaking are involved in the reaction. Several experimental evidences were provided to support the proposed multiple C–H functionalization pathways. The detailed mechanistic investigations are in progress.

Experimental Section

General procedure for the palladium-catalyzed synthesis of diarylmethylidenefluorenes or phenanthrenes: A 15 mL screw-cap seal tube initially fitted with septum containing $Pd(OAc)_2$ (22 mg, 0.01 mmol) and silver(I) oxide (231 mg, 1.00 mmol) was evacuated and purged with nitrogen gas three times. Then trifluoroacetic acid (2.0 mL), acetophenone oxime ether **1** (1.00 mmol) and aryl iodide (5–6 equiv) were added to the system and the reaction mixture was stirred at 120°C for 8–15 h. The mixture was filtered through a short Celite pad and the Celite pad was washed with dichloromethane several times. The filtrate was concentrated by vacuum and the residue was purified on a silica gel column using hexane/EtOAc as eluent to afford the desired product **3** or **4**.

Acknowledgements

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Keywords: C–H activation · C–H functionalization · methylidenefluorene · palladium · phenanthrene

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