DOI: 10.1002/chem.201102996

Pd-Catalyzed Multiple C–H Functionalization to Construct Biologically Active Compounds from Aryl Aldoxime Ethers with Arenes

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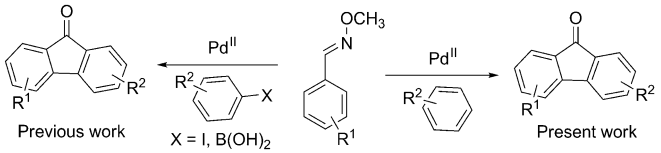
Fluorenones are an important structural scaffold found in many natural products,[1] some antitumor drugs,[2] and compounds for organic electronics.[3] In addition, fluorenone derivatives are known to show various pharmaceutical properties that allows them to act as DNA G-Quadruplex-selective binders or stabilizers, virus and enzyme inhibitors and receptors.[4]

Several major synthetic methods for the preparation of fluorenone derivatives have been reported including the oxidation of fluorenol and fluorenes,[5a–b] Friedel–Crafts-type cyclizations of biarylcarboxylic acid derivatives,[5c] C–C bond formation under Pschorr cyclization reaction of 2-haloarylketones to give fluorenones,[5d] transition-metal-catalyzed cyclization of 2-haloarylketones,[5e] and the cyclocarbonylation reaction of *ortho*-halobiaryls and benzyne.[5f–g] Pd-catalyzed directing-group-assisted C–H bond activation is a promising and efficient methodology for the synthesis of fluorenone derivatives (Scheme 1). First, Larock and co-workers reported the synthesis of fluorenones from 2-iodophenyl(2-phenyl-benzylidene)amine by using a palladium migration method.[6] In 2008, Daugulis reported the synthesis of fluorenones from simple aromatic amides and aryl halides.[7]



Scheme 1. Complementary method for the synthesis of fluorenones.

We also reported the synthesis of functionalized fluorenones from *O*-methyl benzaldehyde oxime ethers and aryl halides catalyzed by a palladium complex[8] Later, Shi et al. developed a Pd-catalyzed synthesis of fluorenones from *O*-methyl benzaldehyde oxime ethers and aryl boronic acids.[9]

The regioselective coupling of two arenes through C–H bond activation in both arenes to give biaryls or other related products has become very attractive recently.[10] Directing groups such as anilides, pyridines, pyridine N-oxide, *O*-phenyl carbamates, and imines have been used for this type of biaryl synthesis.[11] Our continuous interest in metal-catalyzed C–H bond activation and cyclization reactions[12] prompted us to explore the reaction of Pd-catalyzed *ortho*-directed multiple C–H bond activation of aromatic aldoxime ether with arenes. Herein, we disclose a complementary method for the synthesis of fluorenone derivatives by using this reaction. This reaction involves the formation of biaryls as the intermediates and requires a three-step C–H bond activation, however avoids the use of aryl halides or boronic acids and expensive metal oxidant.

Initially, we chose benzaldehyde oxime ether (**1a**, 0.70 mmol) and benzene (**2a**, 2.0 mL) as model substrates for the optimization studies. Oxime ether **1a** was easily prepared from the corresponding benzaldehyde and *O*-methyl hydroxylamine hydrochloride. First, the reaction was carried out using $Pd(OAc)_2$ (10 mol%) as the catalyst in the presence of different silver salts such as Ag_2O, Ag_2CO_3, or AgOAc. However, no conversion was observed at 120°C for 36 h. Next, we tried other oxidants including $Cu(OAc)_2$, BQ, and $PhI(OAc)_2$, again no desired product was obtained. When we used oxone as the oxidant, the reaction afforded a mixture of fluorenone oxime ether **3A** in 15% and fluorenone **3a** in 22% isolated product yields. The mixture was then hydrolyzed to give **3a** in 32% yield. The replacement of oxone by potassium persulfate ($K_2S_2O_8$) afforded the desired product **3a** in 57% yield. As the catalyst loading was increased to 20 mol%, compound **3a** was obtained in 78% yield. If both the amount of trifluoroacetic acid (TFA) and oxidant increase, the yield of **3a** decreases, but biphenyl from oxidative coupling of benzene (**2a**) became the major product. Controlled experiments revealed that no product was observed in the absence of $Pd(OAc)_2$ or TFA.

With the optimized conditions in hand, we next examined the scope of the substrates. As shown in Table 1, the reaction of electron-donating aryl aldoxime ethers such as 4-methyl, 3-methyl and 4-*tert*-butyl benzaldehyde oxime ethers **1b–1d** with benzene proceeded smoothly to give the corresponding substituted fluorenone derivatives in good yields (Table 1, entries 2, 9, and 3). Interestingly, for substrate **1c**, there are two possible sites at C2 and C6 for C–H bond activation, but the reaction occurred only at C6, which is most likely due to the steric effect of methyl group at C3. The aromatic aldoxime ethers having an electron-withdraw-

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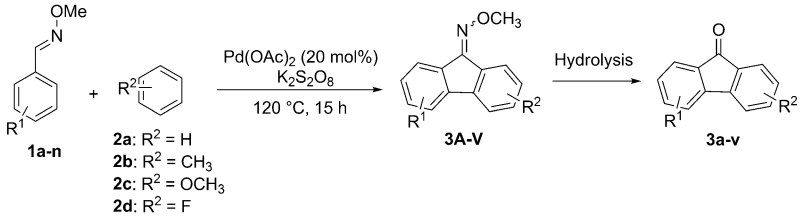
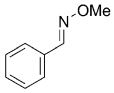
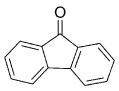
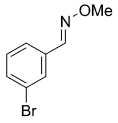
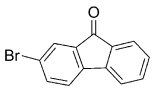
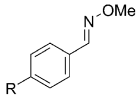
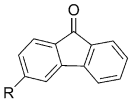
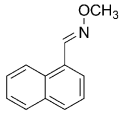
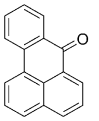
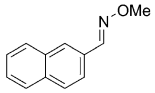
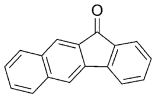
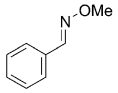
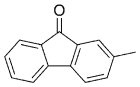
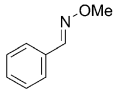
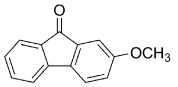
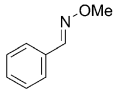
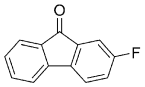
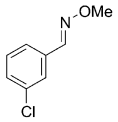
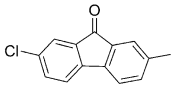
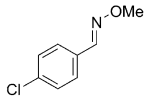
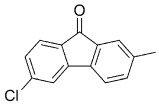
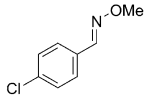
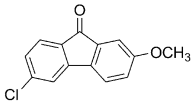
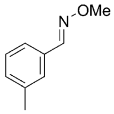
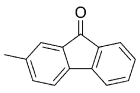
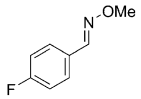
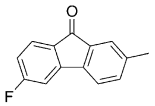
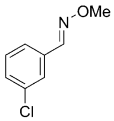
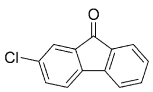
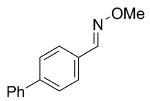
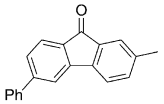
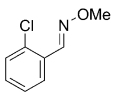
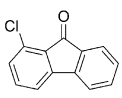
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201102996.

Table 1. Results of the reaction of aromatic aldoxime ethers with arenes.[a]



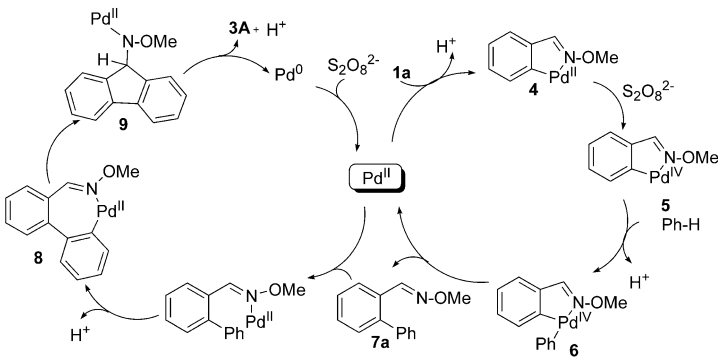
Entry	1	2	Product 3	Yield [%][b]	Entry	1	2	Product 3	Yield [%][b]
1		**1a** **2a**		**3a** 78	12		**1i** **2a**		**3i** **69**
					13		**1m** **2a**		**3m** **49**
2	R = Me	**1b** **2a**		**3b** 62	14		**1n** **2a**		**3n** **42**
3	R = *t*Bu	**1d** **2a**		**3d** 77	15		**1a** **2b**		**3o** **51**
4	R = Cl	**1e** **2a**		**3e** 82	16		**1a** **2c**		**3p** **65**
5	R = F	**1h** **2a**		**3h** 56[c]	17		**1a** **2d**		**3q** **39**
6	R = CF_3	**1j** **2a**		**3j** 74[c]	18		**1f** **2b**		**3r** **73**
7	R = Ph	**1k** **2a**		**3k** 71	19		**1e** **2b**		**3s** **85[d]**
8	R = NO_2	**1l** **2a**		**3l** 53	20		**1e** **2c**		**3t** **91[d]**
9		**1c** **2a**		**3c** 55[c]	21		**1h** **2b**		**3u** **64[c]**
10		**1f** **2a**		**3f** 63	22		**1k** **2b**		**3v** **69[d]**
11		**1g** **2a**		**3g** 71[c]					

[a] Unless otherwise mentioned, all reactions were carried out using aldoxime ethers **1** (0.7 mmol), arenes **2** (2 mL), $Pd(OAc)_2$ (20 mol%), $K_2S_2O_8$ (1.4 mmol) and TFA (7.0 mmol) at 120°C for 15 h. Following filtration, the filtrate was treated with an aqueous solution of HCl (8 mol L^{-1}, 2 mL), 100°C, 6–8 h. [b] Isolated product yields. [c] $Pd(OAc)_2$ (20 mol%), $K_2S_2O_8$ (2.8 mmol) and TFA (14.0 mmol) [d] $Pd(OAc)_2$ (20 mol%), $K_2S_2O_8$ (3.5 mmol) and TFA (21.0 mmol).

ing group appear compatible with the present catalytic reactions. Thus, the reaction of 4-chloro-, 3-chloro-, 2-chloro-, 3-bromo-, and 4-trifluoromethyl-benzaldehyde oxime ethers **1e–j** with **2a** afforded the corresponding fluorenones **3e–3j** in 82–74% yields (Table 1, entries 4, 10, 11, 12, and 6). 4-Phenyl and 4-nitro benzaldehyde oximes **1k–l** were also efficiently arylated under the reaction conditions (Table 1, entries 7 and 8) to give the expected products **3k–l** in good yields. The reaction of 1-naphthyl and 2-naphthyl oxime ethers with **2a** also proceeded smoothly to give benzoanthracenone and benzofluorenone, in moderate yields (Table 1, entries 13 and 14). There are two possible C–H bond functionalization sites at C2 and C8 for substrate **1m**, but the C8-functionalized product **3m** was observed exclusively.

Next, we investigated the arylation of benzaldehyde oxime ether **1a** with various arenes. Benzaldehyde oxime ether **1a** reacted nicely with toluene and anisole as the coupling partner to afford the regioselective fluoren-9-ones **3o** and **3p** in good yields (Table 1, entries 15 and 16). The transformation is highly site-selective at the 4-position and then at 3-position of arenes. No other regioisomeric product of **3o** and **3p** was observed indicating that the arylation step does not occur at C2- or C3-position of the substituted arene. The reaction of fluorobenzene **2d** having an electron-withdrawing fluoro group with **1a** was less efficient and gave fluorenone **3q** in a lower yield (Table 1, entry 17). Finally, the coupling of aldoxime ether **1e** having an electron-withdrawing 4-chloro group with **2b** and **2c** afforded the functionalized fluorenones **3r–3v** in excellent yields (Table 1, entries 18–22).

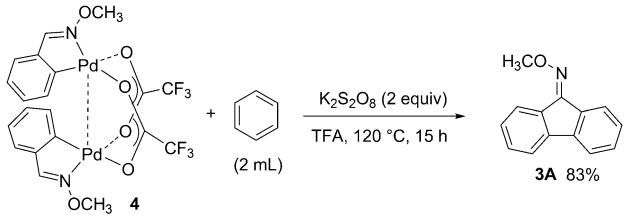
A plausible mechanism for the catalytic reaction of aldoxime ether **1a** with arene **2a** is proposed as shown in Scheme 2, which is based on previously reported chelation-assisted cross-couplings through C–H bond functionalization.[8,13] The catalytic reaction likely consists of two catalytic cycles. The first one involves the formation of palladacycle **4**, the oxidation of **4** by persulfate to give a Pd^{IV} intermediate **5** and arylation of **5** by benzene to afford **6**. Then, reductive elimination leads to *ortho*-arylated product **7a** and Pd^{II}. It is known that acetoxylation and arylation of palladacycle in the presence of strong oxidant were proposed to proceed via Pd^{IV}.[13] In the second cycle, **7a** is converted to fluorenone oxime ether **3A** catalyzed by the Pd complex with C–H bond activation and an insertion reaction as the key steps. During the reaction, the Pd^0 that is generated is reoxidized to the active Pd^{II} by potassium persulfate.



Scheme 2. Proposed mechanism (For clarity, some ligands on palladium intermediates are omitted). X = $OCOCF_3$.

The proposed mechanism is strongly supported by the isolation of a 5-membered palladacycle **4** (Scheme 2) and its reaction with arenes under various conditions. Complex **4** was prepared by the cyclometallation of **1a** with $Pd(OAc)_2$ (1 equiv) in TFA at 50 °C in 67% yield. The structure of **4** was confirmed by the single-crystal X-ray crystallographic analysis. Notably, the Pd complex is dimeric in nature with trifluoroacetate ligands bridging the two palladium metals. In addition, there is a weak interaction between the two palladium nuclei with a Pd–Pd distance of 2.882 Å.[11f,g]

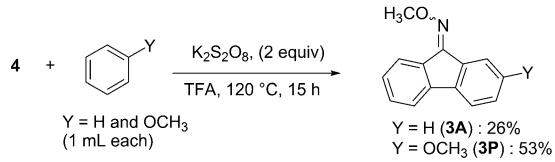
When complex **4** was treated with benzene and $K_2S_2O_8$ (2 equiv) in TFA at 120 °C for 15 h, the cyclization product **3a** was produced in 83% yield (Scheme 3). If the same reaction was carried out in the absence of $K_2S_2O_8$ and TFA, no desired product was observed. Similarly, no product **3A** was observed when **4** was treated with benzene and $K_2S_2O_8$ in the absence of TFA. These results show that both $K_2S_2O_8$ and TFA are required for the transformations of complex **4** to product **3A** via intermediate **6a**. In the above reaction (Scheme 3) or in the catalytic reactions (Table 1), no intermediate product **6** was found in the product mixture. However, if the catalytic reaction of **1a** with **2a** was allowed for only 25 min, product **6a** was isolated in 7%. Whereas, with a longer reaction time, this intermediate (**6a**) disappeared completely. These observations, coupled with the fact that **4** can be easily generated at low temperature, suggest that the arylation step, that is, the reaction of **4** with arene, is likely to be the rate limiting step in the present catalytic reaction.



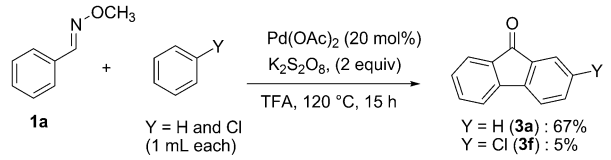
Scheme 3.

To further understand the nature of the catalytic reaction, we next examined competition experiments using **4** as the substrate. Treatment of **4** with 1:1 mixture of benzene and anisole afforded products **3A** and **3P** in a 1:2 ratio, indicating that the arylation is faster with electron-rich arene (Scheme 4). This is in agreement with the results shown in Table 1 that electron-rich arenes gave high yields of product **3** (Table 1, entries 15–17). Indeed, a catalytic competition experiment of **1a** with benzene and chlorobenzene (Scheme 5) also supports the relative trends.

In conclusion, we have developed a useful and convenient method for the synthesis of fluoren-9-one derivatives from



Scheme 4.



Scheme 5.

substituted benzaldehyde oxime ethers with simple arenes. In addition, this methodology provides synthesis of fluoren-9-one that avoids the use of aryl halides, aryl boronic acids, and expensive metal oxidants. The proposed mechanism is supported by the isolation of a dimeric cyclopalladacycle **4** and its reaction with arenes.

Experimental Section

General procedure for the synthesis of fluoren-9-one derivatives: A sealed tube (15 mL) (initially fitted with a septum) containing $Pd(OAc)_2$ (46 mg, 0.020 mmol) and potassium persulfate (560 mg, 2.00 mmol) was evacuated and purged with nitrogen gas three times. Arenes (4 mL), trifluoroacetic acid (1.18 g, 10.0 mmol), and aldoxime ether **1** (1.00 mmol) were added to the system and the reaction mixture was stirred at 120 °C for 12–15 h until complete consumption of **1** (based on TLC monitoring). Then, an aqueous solution of HCl (8 mol L^{-1}, 2 mL) was added to the tube for hydrolysis at 100 °C for 6–8 h. After completion of reaction, the mixture was cooled, diluted with dichloromethane, filtered and then concentrated. Separation on a silica gel column using *n*-hexane/EtOAc as eluent gave the corresponding pure fluoren-9-one product.

Acknowledgements

We thank the National Science Council of the Republic of China (NSC 99–2119-M-007–010) for support of this research.

Keywords: C–H activation · cyclization · fluorenone · oxime ether · palladium

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Received: September 23, 2011
Published online: December 6, 2011

