

Synthesis of Fluorenones from Aromatic Aldoxime Ethers and Aryl Halides by Palladium-Catalyzed Dual C–H Activation and Heck Cyclization**

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Recently, directing-group-assisted activation of *ortho* aromatic C–H bonds, and subsequent C–C bond formation by coupling with organic halides or organometallic reagents have been reported.^[1] A variety of directing groups, such as acetyl, acetamino, carboxylic acid, oxazolyl, pyridyl, and imino moieties have been used for C–H bond activation.^[2] Aside from the above functional groups, a few examples have been reported using oximes as directing groups for C–H bond activation. Thus, Bezoudnova and Ryabov reported the isolation of an *ortho*-palladated aryl oxime from benzaldehyde oximes and a palladium complex.^[3] Sanford and co-workers reported a palladium-catalyzed *O*-methyl oxime-directed activation of sp^2 and sp^3 C–H bonds, followed by oxygenation with ozone and $PhI(OAc)_2$.^[4a,b] In 2006, Che and co-workers reported the *ortho* amidation of *O*-methyl oxime by palladium-catalyzed C–H activation/nitrene insertion.^[4c] Very recently, we reported a rhodium-catalyzed chelation-assisted C–H activation of α,β -unsaturated ketoxime and the reaction with alkynes, which afforded substituted pyridine derivatives in good-to-excellent yields.^[5]

The oxidative Heck cyclization is a synthetically useful carbon–carbon bond-forming reaction catalyzed by transition-metal complexes.^[6] Moritani and Fujiwara first reported an intermolecular oxidative Heck cyclization reaction of benzene with activated olefins.^[7] In 2004, Stoltz and co-workers reported a palladium-catalyzed synthesis of functionalized benzofurans and dihydrobenzofurans by direct intramolecular oxidative Heck cyclization of allyl phenyl ether.^[8] Recently, Tanaka and co-workers developed a palladium-catalyzed Heck-type cyclization of oxime ethers that leads to the formation of 3-indolinone derivatives.^[9] In this context, an intermolecular version of Heck cyclization reactions of carbon–nitrogen double bonds is extremely limited. Our continued efforts in metal-catalyzed C–H bond activation and cyclization reactions^[10] prompted us to explore the reaction of aromatic aldoxime ethers with aryl iodides.

Herein, we report a new palladium-catalyzed synthesis of functionalized 9-fluorenone derivatives from aromatic aldoxime ethers and aryl iodides, with two distinct steps, C–H activation and oxidative Heck cyclization, in one pot.

Treatment of benzaldehyde oxime ether **1a** and iodobenzene (**2a**) with $Pd(OAc)_2$ (10 mol %) and Ag_2O (1 equivalent) in trifluoroacetic acid (TFA) at 120 °C for 36 h afforded a mixture of fluorenone oxime ether **3A** and fluorenone **3a** in a 78:22 ratio, in 95 % combined yield. The mixture was then hydrolyzed to give **3a** in 90 % yield (Table 1, entry 1).

The presence of a silver salt was crucial to the reaction. Various silver salts were examined to investigate the effect on the product yield. Among them, Ag_2O gave the best results, and afforded **3a** in 90 % yield. Other silver salts including $AgOAc$, Ag_2CO_3 , $Ag(O_2CCF_3)$ and $AgOTf$ are less effective, giving **3a** in 53, 36, 27, and 18 % yields, respectively. Replacing the silver salt with $NaOAc$ led to no formation of the expected product **3a**. The effect of solvents was also vital to the catalytic reaction. Reaction in TFA gave the best results, affording **3a** in 90 % yield. Acetic acid was also effective, giving **3a** in 53 % yield. Other solvents, such as 1,2-dichloroethane, dimethylsulfoxide, *N,N*-dimethylformamide, and toluene, were totally ineffective for the catalytic reaction.

Under similar reaction conditions to those for the reaction of **1a** with **2a**, various *para*-substituted aryl iodides **2b–d** were treated with aldoxime ether **1a**, to give the corresponding substituted fluorenone derivatives. 4-Iodotoluene (**2b**) afforded **3b** in 72 % yield (Table 1, entry 2). Electron-withdrawing aryl iodides, such as 4-nitroiodobenzene **2c** and ethyl 4-iodobenzoate **2d**, provided functionalized 9-fluorenones **3c** and **3d** in 84 and 86 % yields, respectively (Table 1, entries 3 and 4). *Meta*-substituted aryl iodides **2e** and **2f** also reacted smoothly with **1a**, in a highly regioselective fashion, to give **3e** and **3f**, respectively, in slightly lower yields (Table 1, entries 5 and 6). Both of these reactions demonstrate interesting *meta* substitution effects. There are two possible C–H bond activation sites, at C2 and C6 of 3-iodotoluene (**2e**) and 3-iodonitrobenzene (**2f**), but only the products resulting from C–H bond activation at C6 were formed. The steric effect of the *meta* substituent for the C–H bond activation at C2 likely accounts for the absence of the other regioisomer in both of these cases. 4-Methylbenzaldehyde oxime ether (**1b**) reacted with **2a** and **2b** to give **3e** and **3g** in 77 and 73 % yield, respectively (Table 1, entries 7 and 8). The present catalytic reaction is also compatible with nitro, chloro, and fluoro substituents on the aromatic ring of oxime ethers **1**. Thus, the reaction of 4-nitro-, 4-chloro-, and 4-fluorobenzaldehyde oxime ethers (**1c–e**) with **2a** gave substituted fluorenones

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Table 1: Results of the reaction of aromatic aldoxime ethers with aryl halides.^[a]

Entry	1 ^[b]	2	Product 3	Yield [%] ^[c]
1		2a		90
2		2b		72
3		2c		84
4		2d		86
5		2e		65
6		2f		63
7		2a		77
8		2b		73
9		2a		82
10		2a		78
11		2b		71
12		2d		80

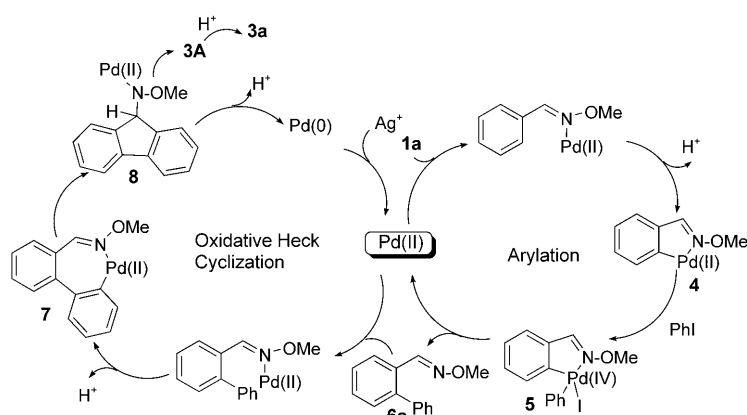
Table 1: (Continued)

Entry	1 ^[b]	2	Product 3	Yield [%] ^[c]
13		2a		72
14		2d		78
15		2a		74
16		2a		73
17		2a		79
18		2a		76

[a] Reaction conditions unless otherwise stated: aldoxime ether **1** (1.0 mmol), aryl iodide **2** (5–6 equiv), Pd(OAc)₂ (10 mol%), Ag₂O (1.0 mmol) and CF₃CO₂H (2.0 mL), 120°C, 36 h. Following filtration, the filtrate was treated with concentrated HCl (2.0 mL), 100°C, 8 h. [b] E/Z ratio ≥ 95:5. [c] Yield of isolated product.

3f, **3h**, and **3k** in 72–82 % yield (Table 1, entries 9, 10, and 13). The reaction of 4-chloro- and 4-fluorobenzaldehyde oxime ether with other aryl iodides also proceeded smoothly to give the corresponding substituted fluorenones in good yield (Table 1, entries 11, 12, and 14). Interestingly, the *ortho*-substituted substrate 2-fluorobenzaldehyde oxime ether **1f** also reacted smoothly with **2a** to give product **3m** in 74 % yield (Table 1, entry 15). For 3-bromobenzaldehyde oxime ether (**1g**), the reaction with **2a** proceeded in a regioselective manner, to give **3n** in 73 % yield (Table 1, entry 16). Oxime ether **1h**, bearing a phenyl substituent, is also compatible with the reaction with **2a**, providing **3o** in 79 % yield (Table 1, entry 17). Finally, the reaction of 2-naphthaldehyde oxime ether (**1i**) with **2a** afforded benzofluorenone **3p** in 76 % yield. In this reaction, there are two possible C–H bond activation sites at C2 and C6 of **1g**. However, activation occurs only at C6, most likely owing to the steric effect of the fused aromatic ring.

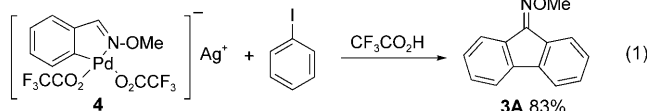
Based on known metal-catalyzed directing-group-assisted C–H bond activation and Heck cyclization reactions,^[1,4,7,8] a mechanism for the present palladium-catalyzed cyclization of aldoxime ether **1a** with iodobenzene **2a** has been proposed, involving two different catalytic cycles (Scheme 1). In the first cycle, coordination of **1a** to the Pd^{II} species is followed by an *ortho* C–H bond activation to form a five-membered palladacycle **4** and the release of a proton. Oxidative addition of



Scheme 1. Proposed mechanism for the reaction of benzaldoxime ethers with aryl iodides. Some ligands on palladium intermediates are omitted for clarity.

iodobenzene to **4** gives palladium(IV) intermediate **5**. Subsequent reductive elimination leads to *ortho*-arylated product **6a** and Pd^{II}. In the second catalytic cycle, the coordination of **6a** to palladium(II) followed by C–H bond activation gives seven-membered palladacycle **7**. Subsequent intramolecular insertion of the C=N group into the Pd–aryl bond to produce intermediate **8**,^[11] followed by β-H elimination affords compound **3A** and Pd⁰. The latter is reoxidized to Pd^{II} by silver ions in the solution.

The proposed mechanism is supported by the isolation of intermediate **4**. Heating of **1a** in the presence of one equivalent of Pd(OAc)₂ and Ag₂O in TFA led to the formation of the anionic palladacycle **4** in 77% yield. This complex was characterized by ¹H NMR, ¹³C NMR, and IR spectroscopy. In addition, the structure was further elucidated by single-crystal X-ray diffraction (Figure 1). The reaction of **4** with iodobenzene in TFA at 120°C for 3 h afforded the fluorenone oxime ether **3A** in 83% yield [Eq. (1)].



Further evidence supporting the proposed mechanism for the catalytic reaction was the isolation of 2-(4-nitrophenyl)-benzaldehyde *O*-methyl oxime (**6c**) in 52% yield from the reaction of **1a** and **2c**, under the standard catalytic reaction conditions shown in Table 1, except that the solution was heated for only six hours. To further prove that compound **6** is an intermediate in the catalytic reaction, **6a** was prepared separately,^[12] and examined under various conditions. Firstly, **6a** was treated with palladium acetate (10 mol %) and silver(I) oxide (1 equivalent) in TFA at 120°C for 18 h, affording Heck cyclization product **3A** in 87% yield [Eq. (2)]. The same reaction, carried out in the absence of silver oxide, afforded **3A** in 8% yield. Product **3A** was not formed by treatment of **6a** with one equivalent of silver oxide in the absence of palladium acetate in TFA. The above results

indicate that both palladium acetate and silver oxide are required for the conversion of intermediate **6** into product **3**, and also that silver(I) acts as an oxidant to regenerate the Pd^{II} active catalyst.

Whereas the role of silver oxide is not entirely clear, it seems to perform three separate functions in the present catalytic reaction. In addition to its status as an oxidant, oxidizing Pd⁰ to Pd^{II}, it acts as a halide scavenger, removing iodide from palladium(IV) complex **5**, facilitating reductive elimination.^[13] Thirdly, it acts as a base to remove protons released from the reaction. In addition, the use of Ag⁺ as an oxidant for the oxidation of Pd⁰ species is known.^[14]

In summary, we have successfully developed a new efficient palladium-catalyzed synthesis of 9-

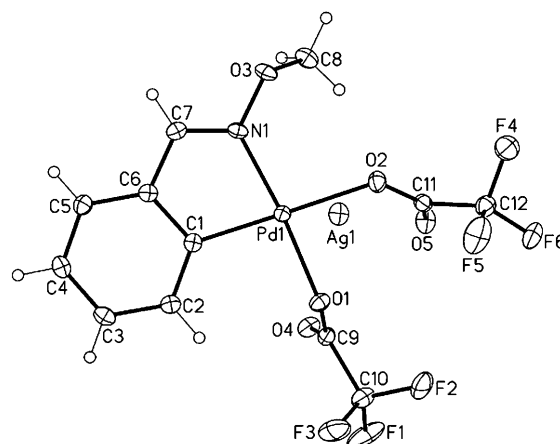
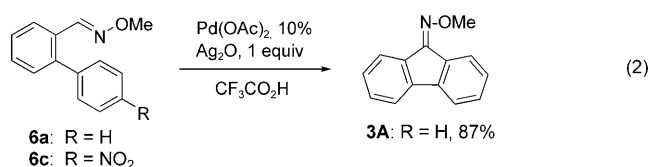


Figure 1. ORTEP representation of palladacycle **4**. Thermal ellipsoids are set at 50% probability.



fluorenone derivatives, from the reaction of substituted benzaldehyde oxime ethers with aryl halides. This transformation involves an unprecedented one-pot dual C–H activation and oxidative Heck cyclization. The proposed mechanism is strongly supported by the isolation of an anionic palladacycle **4** and an intermediate organic compound **6c**.

Experimental Section

General procedure for the palladium-catalyzed synthesis of 9-fluorenone derivatives: In a sealed tube under a N₂ atmosphere, trifluoroacetic acid (2.0 mL), aldoxime ether **1** (1.00 mmol), and aryl iodide **2** (5–6 equivalents) were added to Pd(OAc)₂ (22 mg, 0.010 mmol) and silver(I) oxide (231 mg, 1.00 mmol), and the reaction mixture was stirred at 120°C for 36 h. The mixture was filtered

through a short celite pad, which was washed with dichloromethane several times. The filtrate was concentrated in vacuo. Concentrated hydrochloric acid (2.0 mL) was added to the residue and the resultant mixture was kept at 100°C for 8 h. After completion of the reaction, the mixture was cooled, diluted with dichloromethane (80 mL), filtered to remove solids, and then concentrated in vacuo. Purification by column chromatograph on silica gel (eluent: hexane/EtOAc 9:1) gave the corresponding pure 9-fluorenone product **3a-p**.

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