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Domino Oxidative [Pd]-Catalysis: One-Pot Synthesis of Fluorenones Starting from Simple Benzylamines and Iodo Arenes

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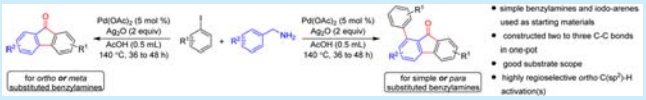
Supporting Information

ABSTRACT: A domino [Pd]-catalysis for the efficient synthesis of fluorenones is presented. The overall reaction proceeds through the formation of a five membered Pd(II)-cycle via a highly regioselective *ortho* C(sp^2)-H activation(s) of simple benzylamine that combines with external iodo arenes to give *ortho* arylated products. Significantly, the reaction further activates the C(sp^3)-H and C(sp^2)-H (intramolecular oxidative Heck coupling) bonds to give tricyclic imine systems. Then the usual water workup affords the fused tricyclic ketones (fluorenones). Remarkably, this one-pot operation enabled the effective construction of two C−C to three C−C bonds



Transition-metal-catalyzed *ortho* C−H activation[1] of aromatic compounds has emerged as one of the most powerful methods in the realm of organic synthesis. Indeed, these activated aromatic compounds are proven to be effective and enable the formation of various bonds [i.e., C−C, C−O, C−N, C−S, and C−X (X = halogen)] in a highly regioselective manner, and have also been applied in the synthesis of natural products as well as pharmaceutically important molecules.[2] Most likely, the C−H group is the most important and abundant moiety, which enhances the scope of synthetic transformations in the field of organic chemistry. A range of *ortho* directing functional groups has been successfully employed for C−H activation.[3] Despite the number of reports on C−H activations, *ortho* C−H activations followed by cyclization catalyzed solely by the metal-catalyst are comparatively rare. In particular, the intramolecular activation of C(sp^2/sp^3)−H bonds after the usual intermolecular *ortho* C−H activations, in a domino one-pot fashion to accomplish cyclic products, is quite a challenging task, particularly for those with β-hydrogen to the [Pd]-species.

Fluorenones[4] belong to an important class of organic compounds, as they are present in some natural products and compounds of biological relevance[5] and also found in electronic and optical materials.[6] Their initial synthesis was based on classical methods.[7−9] Notably, the Larock research group disclosed the synthesis of fluorenones via [Pd]-catalyzed C−H bond activation.[10] Recently, the Cheng report deals with oxime directed [Pd]-catalyzed dual C−H activation,[4a] while Shi et al. revealed a different protocol.[5] The Daugulis research group developed a sequential one-pot process.[4c]

Although [Pd]-catalyzed *ortho* C−H activation of *N*,*N*-dialkylbenzylamines is well established, the *ortho* palladation of benzylamines containing a free NH-group is uncommon. This may be because the *ortho* palladation of benzylamines in strong acid is retarded due to deactivation (protonation) of the directing amino group. Significantly, Daugulis et al. reported [Pd]-catalyzed direct *ortho* arylations of benzylamines.[11] In continuation of our ongoing research interest in transition-metal catalyzed one-pot transformations,[12] we anticipated that fluorenones could be achived in one-pot by coupling simple benzylamines with iodoarenes. Herein, we present an efficient and novel strategy for fluorenones through domino[13] one-pot highly regioselective *ortho*-arylation (mono- or diarylation) and subsequent intramolecular coupling using simple benzylamines and iodo arenes, in the presence of a [Pd]-catalyst. We envisioned that after *ortho*-arylations, the reaction would further propagate to furnish the cyclic imine intermediate that facilitates the activation of C(sp^3)−H and C(sp^2)−H (intramolecular oxidative Heck coupling) bonds. Finally, the typical water workup would furnish fluorenones as the end products of the reaction sequence.

We initially examined the reaction with the oxidant Ag_2O and solvent CH_3COOH with 1:4 and 1:2 ratios of benzylamine[14] **1a** and 4-iodoanisole **2d**, respectively. As expected, the diarylated product **3ad** was obtained albeit in very poor yield (Table 1, entries 1 to 2). Since it was well established that the [Pd]-catalysis of directing a free amine group will be retarded by the acid medium probably through protonation, we thus thought that loading more equivalents of benzylamine **1a** would be good to increase the yield. To our delight, as anticipated, a gradual increase of equivalents of benzylamine **1a** showed pronounced results (Table 1, entries 3 to 5). Increasing the concentration of reaction showed further increment of the yield (Table 1, entry 6). Notably, longer reaction times gave the product **3ad** in very good yield (Table 1, entry 7). However, all variations such as with different oxidizing agents and solvents or solvent mixtures were not very effective (Table 1, entries 8 to 19).

With the optimized reaction conditions in hand (Table 1, entry 7), to check the scope and generality of the method, we explored the reaction with other (simple or *para* substituted) benzylamines **1a**−**e** and iodo arenes **2a**−**f**. Most importantly the reaction showed a broad substrate scope and furnished the fluorenones **3aa**−**df** in moderate to very good yields (Table 2).

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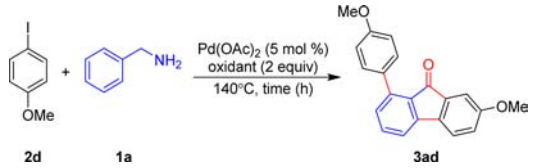
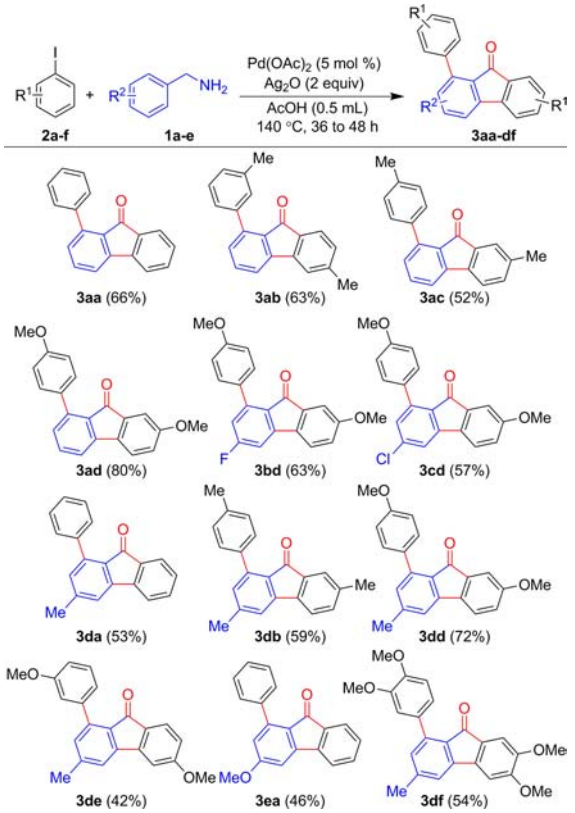
Table 1. Optimization Studies for the Formation of Fluorenone 3ad[a]



entry	oxidant	solvent (mL)	1a/2d ratio	time (h)	yield 3ad (%)[b]
1	Ag_2O	AcOH (1.0)	1/4	24	11
2	Ag_2O	AcOH (1.0)	1/2	24	17
3	Ag_2O	AcOH (1.0)	1/1	24	24
4	Ag_2O	AcOH (1.0)	3/1	24	36
5	Ag_2O	AcOH (1.0)	5/1	40	59
6	Ag_2O	AcOH (0.5)	5/1	24	52
7	Ag_2O	AcOH (0.5)	5/1	40	80
8	Ag_2CO_3	AcOH (1.0)	5/1	24	26
9	AgOAc	AcOH (1.0)	5/1	24	34
10	AgOAc	AcOH (0.5)	5/1	24	43
11	$K_2S_2O_8$	AcOH (0.5)	5/1	40	*g*
12	Ag_2O	TFA (0.5)	5/1	24	*g*
13[c]		AcOH (0.5)	5/1	40	*g*
14[d]	Ag_2O	AcOH (0.5)	5/1	24	*g*
15	Ag_2O	DMF (0.5)	5/1	24	*g*
16[e]	Ag_2O	DMF (0.25) + AcOH (0.25)	5/1	40	40
17[f]	Ag_2O		5/1	24	5%
18	BQ	AcOH (0.5)	5/1	24	*g*
19	$Cu(OAc)_2$	AcOH (0.5)	5/1	24	10

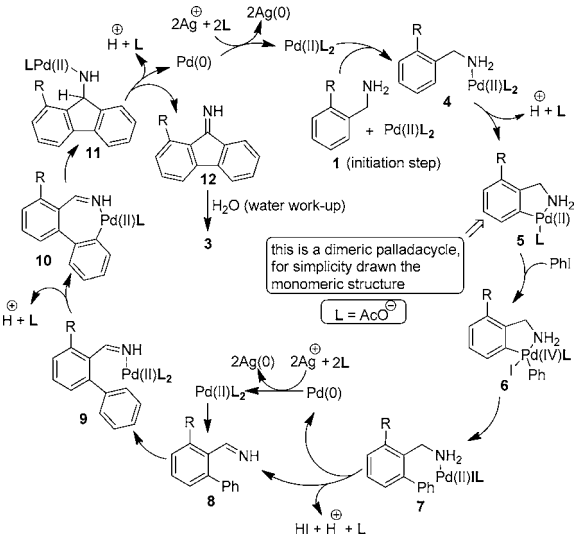
[a]Unless otherwise mentioned, all the reactions were carried out by using 100 mg (0.43 mmol) of aryl iodide **2d** and 5 mol % of $Pd(OAc)_2$. [b]Isolated yields of chromatographically pure products. [c]Reaction was carried out without oxidant. [d]Reaction carried out without palladium acetate. [e]Reaction carried out in mixture of acetic acid and DMF in 1:1 ratio. [f]Reaction was carried out without solvent. [g]No significant spot was observed on TLC for isolation; neither the starting material was recovered nor any product was isolated.

Table 2. Scope and Generality of Formation of Aryl Fluorenones 3aa–df[a,b,c]



[a]Aryl iodides **2a–f** (0.43 mmol), benzylamines **1a–e** (2.15 mmol, 5.0 equiv), Ag_2O (199.5 mg, 2.0 equiv), acetic acid (0.5 mL), 140 °C, 36 to 48 h. [b]Yields in the parentheses are isolated yields of chromatographically pure products. [c]The first alphabet letter for the compounds **3** refers to the benzylamine, while the second letter indicates the iodo arene.

Scheme 1. Plausible Mechanism for the Formation of Fluorenones 3



Interestingly, this method was amenable to different benzylamines **1a–e** and iodo arenes **2a–f** ranging from electron deactivating to electron rich functional groups on the aromatic rings (Table 2). However, the reaction was unsuccessful either with iodo arenes or benzylamines having strong electron withdrawing groups such as esters and nitro groups; even after many trials under several conditions (i.e., neither the starting materials nor the products were isolated). In fact, these observations were in good agreement with that reported by Daugulis and co-workers. This may be probably due to the more nucleophilic nature of the free amine functionality unlike the work with directing the oxime group by the research group of Cheng. Also, the reaction was unsuccessful with 1-bromo-2-iodo benzene. This might be due to the *ortho* bromo substituent that would exert steric hindrance to the flat tricyclic product. Though, use of excess of benzylamine did not furnish the expected mono-arylation product. Only in two cases (**3de**, **3df**) was the formation of mono-arylated fluorenones identified, albeit in negligible yields (4 to 5%). This may occur because the [Pd]-species might not depart from the system after the mono-arylation and still be intact with the nitrogen atom via chelation (see the plausible mechanism of Scheme 1). Subsequently, it would prefer to form a second five-membered cycle in order to establish the second arylation. Presumably, the second five-membered palladacycle formations would be more feasible owing to favorable steric repulsions caused by the first mono-arylated ring on the adjacent [Pd]-moiety.

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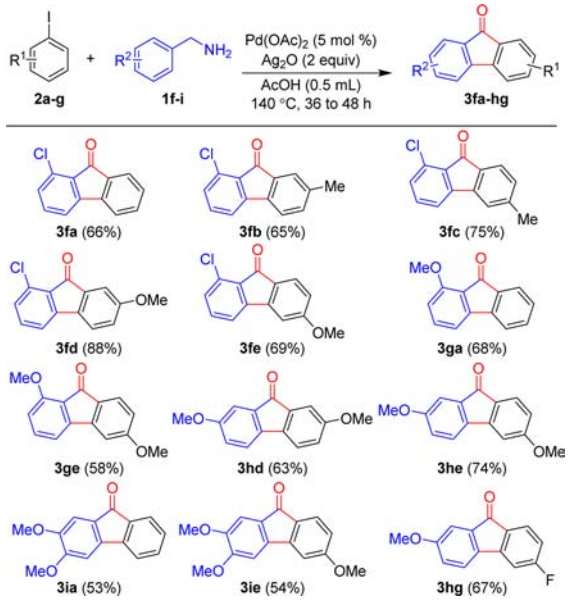
Further to check the scope and limitations of the method, we employed the reaction with other sterically constrained benzylamines **1f–i** as well. As anticipated, the reaction was impeded after mono *ortho* C(sp^2)-H activation for *ortho* and *meta*-substituted benzylamines **1f–i**. In the case of *ortho*-substituted benzylamines **1f–g**, there is only one *ortho* C(sp^2)-H group available for arylation, hence, mono-arylated fluorenones were formed **3fa–ge**. Though, in the case of *meta*-substituted benzylamines **1h–i**, two *ortho* C(sp^2)-H groups are available, the reaction stopped at mono *ortho* arylation because of steric thwart and gave the corresponding mono arylated fluorenones **3hd–hg** (Table 3). As discussed in the section related to Table 2,

Table 3. Scope and Generality of Formation of Fluorenones 3fa–hg[a,b,c]



[a]Aryl iodides **2a–g** (0.43 mmol), benzylamines **1f–j** (4.3 mmol, 10 equiv), Ag_2O (199.5 mg, 2.0 equiv), acetic acid (0.5 mL), 140 °C, 36 to 48 h. [b]Yields in the parentheses are isolated yields of chromatographically pure products. [c]The first alphabet letter for the compounds **3** refers to the benzylamine, while the second letter indicates the iodo arene.

the reaction was still unsuccessful with iodo arenes or benzylamines with strong electron withdrawing groups (esters and nitro groups). On the other hand, we also attempted to isolate the tricyclic imine intermediate by direct loading of the concentrated crude reaction mixture to the short silicagel column purged with triethylamine. Even then, we were able to isolate solely the fluorenone, but not the imine, showing the high reactive nature to form stable ketones.

In addition to the spectroscopic evidence, the structure of fluorenones **3** was confirmed by the single crystal X-ray diffraction analysis of **3ad** and **3hd** (see Supporting Information).

To account for the catalytic path of the reaction, the possible mechanism would proceeded via the formation of five-membered palladacycle[15] **5** through directing group assistance. Now the palladacycle **5** combines with the external iodo arene **2** to give *ortho* arylated products **7** via the insertion intermediate **6**. Further, the arylated product **7** continues through C(sp^3)-H activation to give the imine intermediate **8**. The subsequent C(sp^2)-H activations lead to the formation of tricyclic imine **12**

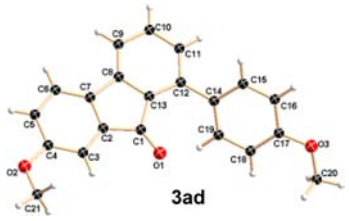
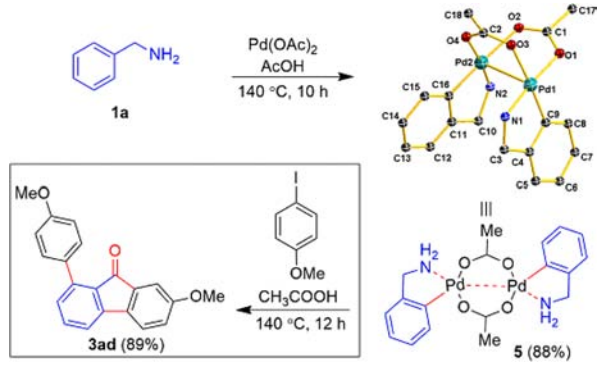


Figure 1. X-ray crystal structure of aryl fluorenone **3ad**. Thermal ellipsoids are drawn at the 50% probability level.

via the intermediates **9**, **10** and **11**. Finally, the water workup[16] of **12** gives fluorenones **3** (Scheme 1). For simplicity, the mechanism is shown on a restricted mono-arylation between the *ortho* substituted benzylamines **1** and simple iodo benzene **2a** (Scheme 1). We presume that the reaction sequence would proceed through biarylation followed oxidation to imine and oxidative Heck coupling. This could be clearly realized based on the Daugulis report, wherein only biraylation was observed without oxidation of the amine group.[11]

The possible formation of a palladacycle through the directing group assistance was further demonstrated by the isolation of dimeric five-membered Pd(II)-cycle **5** by direct treatment of $Pd(OAc)_2$ with benzylamine **1a** in CH_3COOH (yield 88%). The structure was established from ^1H- and ^{13}C NMR data. It was further confirmed by the single crystal X-ray diffraction analysis. In addition, treatment of **5** with iodo arene **2d**, gave the fluorenone **3ad** in 89% yield (Scheme 2).

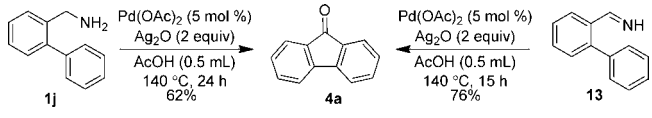
Scheme 2. Formation of Fluorenone 3ah via the Isolation of Five-Membered Palladacycle[a]



[a]Thermal ellipsoids are drawn at the 50% probability level for the crystal structure of intermediate palladium complex **5**.

Besides the reaction on palladacycle **5**, to confirm the final cyclization from amine through imine followed by fluorenone formation, the [Pd]-catalyzed cyclization was conducted on amine **1j** and imine **13**. As anticipated, the reaction afforded the fluorenone **4a** (Scheme 3). On the one hand, the reaction with aryl aldimine without $Pd(OAc)_2$ gave back the biphenyl aldehyde without any Friedel–Crafts cyclization, presumably due to the intervening effect of the acetic acid medium. This proves the

Scheme 3. Formation of Fluorenone 4a from 1j and 13



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importance of the [Pd]-catalyst for oxidative cyclization. On the other hand, it is noteworthy that the reaction with aldimine derived from simple benzaldehyde gave back simple benzaldehyde with or without the [Pd]-catalyst. This might occur because the sp^3-hybridized nitrogen atom is more nucleophilic, chelating [Pd]-catalyst better than the sp^2-hybridized imine nitrogen.

In summary, we have disclosed a novel domino [Pd]-catalysis for the efficient synthesis of fluorenones. The overall reaction proceeds through the formation of a five-membered Pd(II)-cycle and subsequent *ortho* C(sp^2)-H activation(s) with external iodo arenes in a highly regioselective manner. Significantly, the reaction was not stopped after the usual *ortho* arylation(s); instead, it further continued to C(sp^3)-H and C(sp^2)-H activations to give the fused tricyclic ketones after a normal water workup procedure, and enabled the effective construction of two C−C to three C−C bonds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03077.

Characterization of 7-methoxy-1-(4-methoxyphenyl)-9H-fluoren-9-one (CIF)

Characterization of 2,7-dimethoxy-9H-fluoren-9-one (CIF)

Experimental details, characterization data for new compounds PDF

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

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