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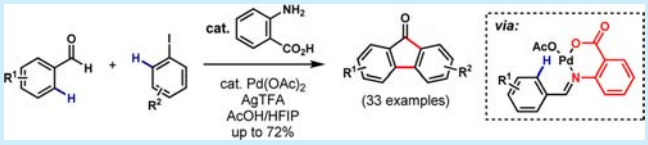
Synthesis of Fluorenones from Benzaldehydes and Aryl Iodides: Dual C−H Functionalizations Using a Transient Directing Group

Xiao-Yang Chen,[†] Seyma Ozturk,[†] and Erik J. Sorensen*[,†]

[†]Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

Supporting Information

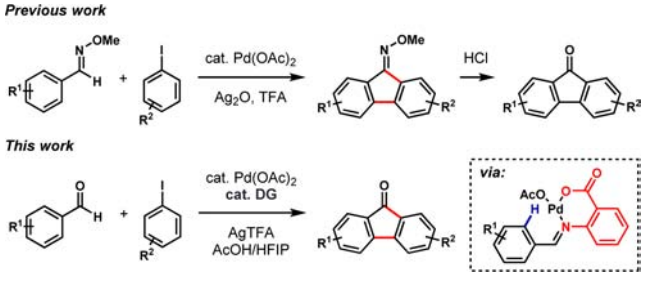
ABSTRACT: The first synthesis of substituted fluorenones directly from benzaldehydes and aryl iodides via a Pd(II)-catalyzed C(sp^2)−H functionalization cascade is reported. Featuring anthranilic acid as an inexpensive transient directing group, the process is compatible with a variety of benzaldehydes and aryl iodides. A three-step synthesis of the antiviral drug Tilorone was completed in an excellent overall yield (40%), demonstrating the utility of this method.



The prevalence of fluorenone-containing natural products, biologically active molecules, and pharmaceutically important agents has underscored the importance of general synthetic methods for their efficient construction.[1] Traditional strategies, such as the Friedel−Crafts cyclization of biarylcarboxylic acids[2] and the oxidation of fluorenes,[3] usually require multistep syntheses of the substrates and are limited to electron-rich arenes. Recent C−H functionalization[4] approaches involve intramolecular cyclization of biarylaldehydes, imines, carboxylic acids, or diaryl ketone derivatives,[5] as well as directed *ortho* C−H arylation of benzonitriles, benzyl amines, benzamides, or benzoic acids with subsequent cyclization.[6] However, the possibility of utilizing abundant, synthetically versatile but weakly coordinating benzaldehydes as the substrates remains enigmatic, due to their susceptibility toward oxidation and the competing metal insertion into formyl C−H bonds. To address this issue, the laboratories of Cheng and Shi used benzaldehyde oxime ethers with aryl iodides, aryl boronic acids, or arenes as the coupling reagent to obtain fluorenones via a Pd-catalyzed C−H functionalization cascade (Scheme 1).[7] Nevertheless, the practicability of these methods was undermined by the additional steps required for the stochiometric installation and removal of the oxime directing group (DG).

Our laboratory recently constructed the key hydrofluorenone skeleton in Hirsutellone B through a double cyclization cascade.[8]

Scheme 1. Synthesis of Fluorenones via a Transient-Directing-Group-Enabled C−H Functionalization Cascade



As part of our efforts to expand our repertoire for synthesizing fluorenone-containing natural products, we were intrigued by the possibility of using benzaldehydes and aryl iodides as simple starting materials to directly access substituted fluorenones via a C−H functionalization cascade. For such an approach to work without initial substrate modifications, we realized that an appropriate, transient directing group (TDG) could enable the process by reversibly binding and directing the C−H functionalizations. This strategy has been exploited in several Rh catalyzed C−H functionalization reactions;[9] however, successful utilization of Pd is a more recent advent, with the first example of Pd(II)-catalyzed C(sp^3)−H arylation of 2-methyl benzaldehydes and aliphatic ketones featuring amino acids as the TDG reported by Yu and co-workers.[10] Subsequently, the laboratories of Hu and Ge reported similar reactions with 2-methyl benzaldehydes and aliphatic aldehydes as the substrates using acetylhydrazide and *β*-alanine as the TDG, respectively.[11] In 2016, Dong and co-workers also described a Pd(II)-catalyzed *γ*-C(sp^3)−H arylation of free primary amines with a DG generated *in situ* from 8-formylquinoline.[12] The substrate scope of the reaction was expanded very recently by the laboratories of Yu, Ge, and Murakami using 2-hydroxynicotinaldehyde, glyoxylic acid, and 3,5-di-*tert*-butylsalicylaldehyde as the catalytic TDG, respectively.[13]

Inspired by these contributions, we reasoned that a similar strategy could be employed to arylate the *ortho* C−H bond of benzaldehydes[14] and that fluorenone frameworks could arise in the wake of a second C−H functionalization and a terminal, oxidative Heck reaction[15] (Scheme 1). With this idea in mind, we commenced our studies by treating benzaldehyde with an excess of iodoanisole in the presence of Pd catalysts, TDGs, and silver salts in various solvent systems under an air atmosphere at 120 °C. After an extensive screening effort, the desired fluorenone was formed in 45% yield after a 36 h reaction that employed 10 mol % of $Pd(OAc)_2$ as the catalyst, 2 equiv of AgTFA as the oxidant, 40 mol % of anthranilic acid (DG1) as the TDG, and 9:1 AcOH/

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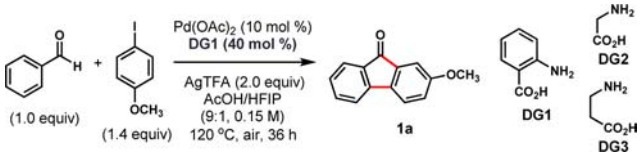
HIFP (0.15 M) as the solvent (Table 1, entry 1). A series of control experiments were subsequently conducted to elucidate

Table 1. Control Experiments for Fluorenone Syntheses[a]



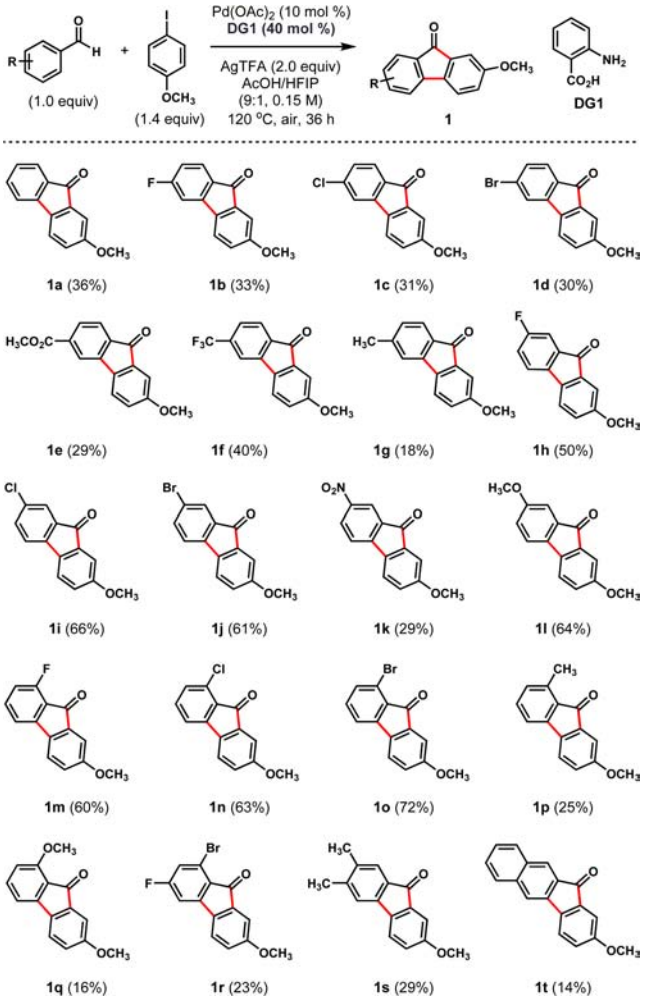
entry	variation from the standard condition	yield of **1a** (%)[b]
1	none	45 (36%)[c]
2	no $Pd(OAc)_2$	0
3	no DG1	0
4	DG2 instead of DG1	trace
5	DG3 instead of DG1	9
6	20 mol % DG1	30
7	60 mol % DG1	37
8	at 100 °C	15
9	$Pd(TFA)_2$ instead of $Pd(OAc)_2$	35
10	$PdCl_2$ instead of $Pd(OAc)_2$	29
11	AgOAc instead of AgTFA	24
12	AgF instead of AgTFA	20
13	in AcOH	38
14	in AcOH/H_2O (9:1)	27
15	in AcOH/HFIP (3:1)	39
16	in AcOH/HFIP (1:3)	30
17	with 5 equiv of H_2O	39
18	0.1 M instead of 0.15 M	43
19	under argon	45

[a]The reaction was performed with benzaldehyde (0.1 mmol), iodoanisole (0.14 mmol), $Pd(OAc)_2$ (0.01 mmol), DG1 (0.04 mmol), and AgTFA (0.2 mmol) in 9:1 AcOH/HFIP (0.667 mL) under air at 120 °C for 36 h. [b]Determined by ^1H NMR using CH_2Br_2 as the internal standard. [c]Isolated yield (based on a 0.3 mmol-scale reaction).

the role of each additive. Not surprisingly, no reaction was observed in the absence of either $Pd(OAc)_2$ or DG**1** (Table 1, entries 2 and 3). Attempts to replace the TDG with either DG**2** or DG**3** resulted in a significant loss of reactivity (Table 1, entries 4 and 5). The reaction was only slightly affected upon reducing or increasing the loading of TDG (Table 1, entries 6 and 7); however, lowering the reaction temperature to 100 °C had a detrimental effect (Table 1, entry 8). Inferior reaction performance was also observed when other Pd catalysts or silver salts were used (Table 1, entries 9−12). Attempts to use AcOH or AcOH/H_2O (9:1) as the solvent, or changes in the ratio of AcOH to HFIP, were all accompanied by poorer reaction performance (Table 1, entries 13−16). Addition of 5 equiv of H_2O or a lower concentration of benzaldehyde did not further increase the yield (Table 1, entries 17 and 18). The reaction was not improved when performed under argon, suggesting that it is not sensitive to moisture or air (Table 1, entry 19).

With the optimized conditions in hand, the scope of the benzaldehydes was next investigated to examine the utility of this method. To our delight, various *para* electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) (e.g., halides, ester, trifluoromethyl, and methyl groups) in the aldehyde component were all tolerated, affording the desired products in moderate yields (Scheme 2, **1a**−**1g**). When we changed the placement of the substituent groups from the *para* to the *meta* position, we observed a significant improvement in the efficiency

Scheme 2. Scope of the Benzaldehydes



of the reaction (Scheme 2, **1h**−**1j**). *m*-Anisaldehyde reacted with *p*-iodoanisole to give the desired fluorenone **1l** in 64% yield, and interestingly, it was also possible to produce an unsymmetrical, disubstituted fluorenone **1k** by pairing *m*-nitrobenzaldehyde with *p*-iodoanisole (Scheme 2). The reaction is also tolerant of various *ortho* functional groups in the aldehyde component (Scheme 2, **1m**−**1q**), as well as substrates possessing two EWGs or EDGs (Scheme 2, **1s**, **1r**). 2-Naphthaldehyde can also be transformed to **1t**, although the yield is modest with this substrate (Scheme 2). It is noteworthy that the fluorenones **1r** and **1t** are formed in a regioselective fashion; directed functionalizations of *ortho*-C−H bonds can thus be selective in substrates containing two *ortho*-C−H bonds (Scheme 2).

Having shown that direct syntheses of fluorenones from diverse aldehydes are possible, we evaluated the couplings of structurally diverse aryl iodides with the particular aldehyde, 2-bromobenzaldehyde, due to its excellent performance in our initial studies. As shown in Scheme 3, a variety of substituted aryl iodides are transformed to fluorenone products, although the substrates bearing donor alkyl groups in the *para* position display significantly higher efficiencies in relation to the less electron-rich aryl iodides (e.g., Scheme 3, **2g**−**2i** vs **2b**−**2f**). Comparable yields were obtained when *meta*-substituted aryl iodides were employed; however, mixtures of regioisomeric fluorenones were formed (Scheme 3, **2k**−**2m**).

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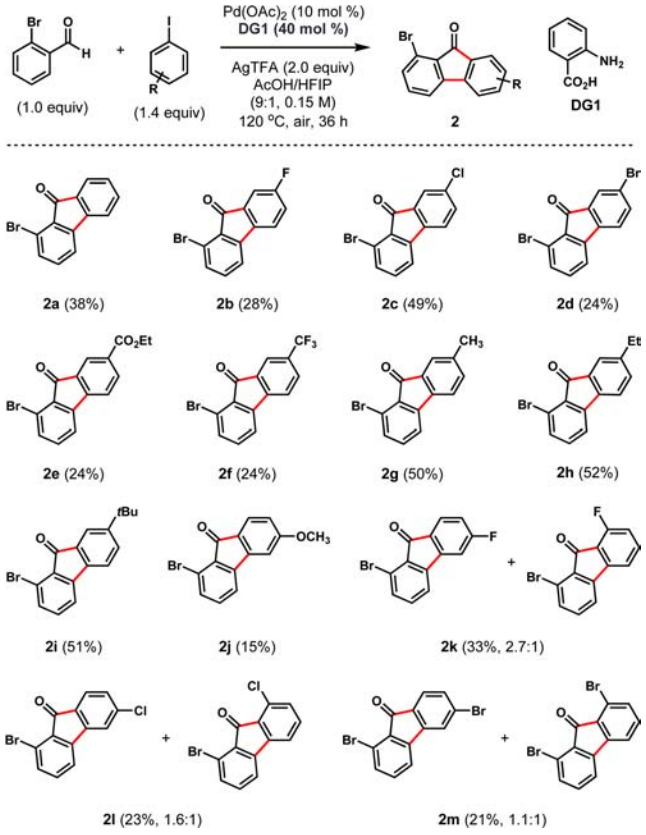
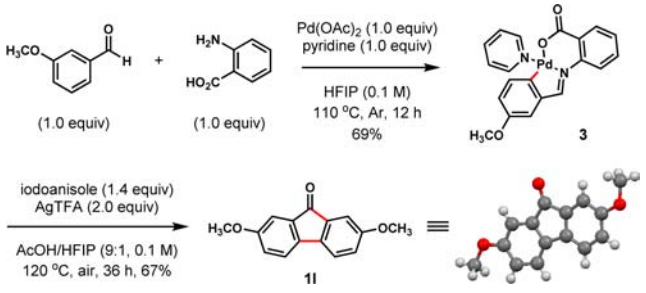
Scheme 3. Scope of the Aryl Iodides



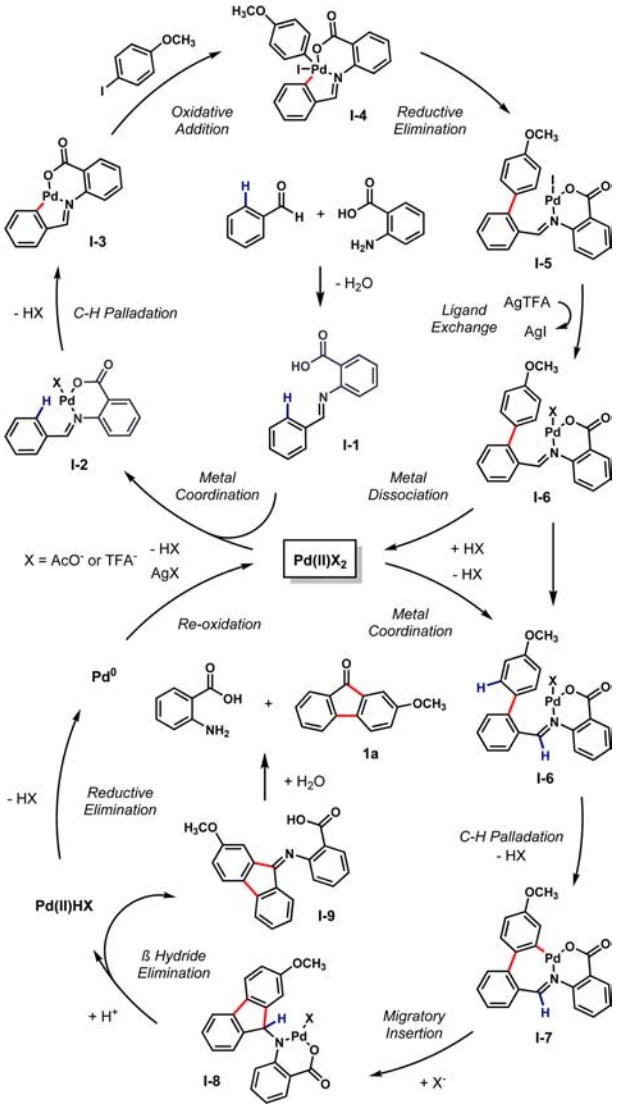
In our efforts to gain insight into the mechanism of this process, we isolated the cyclopalladated complex **3** from the reaction of *m*-anisaldehyde with stoichiometric amounts of $Pd(OAc)_2$, DG1, and pyridine.[16] Upon treatment with iodoanisole and AgTFA, this intermediate was successfully transformed into fluorenone **1l** in a satisfactory overall yield; the structure of **1l** was unambiguously confirmed by X-ray crystallography (Scheme 4).

Scheme 4. Isolation of Palladacycle 3 and Its Oxidation



A putative mechanism for this fluorenone synthesis method is outlined in Scheme 5. We propose that the reaction begins with the transient formation of **I-1** from benzaldehyde and anthranilic acid (DG1). After deprotonation and metal complexation, an intramolecular C−H palladation occurs with the loss of one molecule of AcOH, possibly via a concerted metalation−deprotonation process.[17] Oxidative addition of palladacycle **I-3** with iodoanisole subsequently produces the putative Pd(IV) intermediate **I-4**,[18] which undergoes reductive elimination to generate the arylated species **I-5**. A ligand exchange promoted by AgTFA restores the TFA (or acetate) bound Pd species, and the

Scheme 5. Mechanistic Rationalization



resulting intermediate **I-6** enters the second catalytic cycle. After a second C−H palladation to give the transient seven-membered palladacycle **I-7**, a ring-contracting, intramolecular migratory insertion into the coordinated imine function would generate the second C−C bond and intermediate **I-8**.[19] Finally, a β-hydride elimination would produce imine **I-9** and extrude the Pd catalyst from the anthranilate ligand, which can be returned to the reaction after a simple hydrolysis of the imine function; this final imine hydrolysis step would also generate the fluorenone product **1a**. The hydride-bound Pd species would also be converted into the active Pd(II) catalyst after reductive elimination and reoxidation by Ag(I).[20]

To highlight the utility of this new method, we executed a short synthesis of Tilorone, an orally active, broad-spectrum antiviral drug.[21] As depicted in Scheme 6, **1l** was first prepared under the standard conditions in 64% yield. A high-yielding cleavage of the two methyl ethers with HBr in AcOH afforded compound **4** and set the stage for a final, twofold substitution reaction with the free base derived from 2-chloro-*N*,*N*-diethylethylamine hydrochloride, which produced Tilorone in 72% yield. In relation to the previously reported approaches,[22] this synthesis uses cheaper starting materials and requires only three steps.

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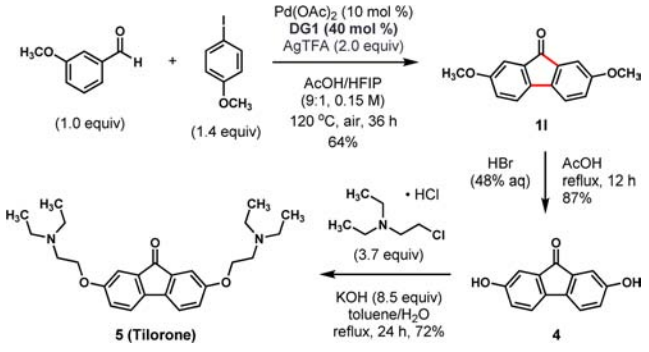
Scheme 6. Three-Step Synthesis of Tilorone



In summary, an efficient method was developed to directly construct fluorenones from readily available benzaldehydes and aryl iodides. Key to this new method is the use of anthranilic acid as an inexpensive TDG, which effectively orchestrates two, Pd-mediated C−H functionalizations as a prelude to two C−C bond formations. Given the importance of fluorenone scaffolds in medicinal chemistry, we envision that this reaction holds great potential to become a cost-effective combi-block method for synthesizing diverse fluorenone-containing compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00161.

Crystallographic data (CIF)

Experimental procedures, spectral data, X-ray data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ejs@princeton.edu.

ORCID

Xiao-Yang Chen: 0000-0003-3449-4136

Erik J. Sorensen: 0000-0002-9967-6347

Notes

The authors declare no competing financial interest.

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