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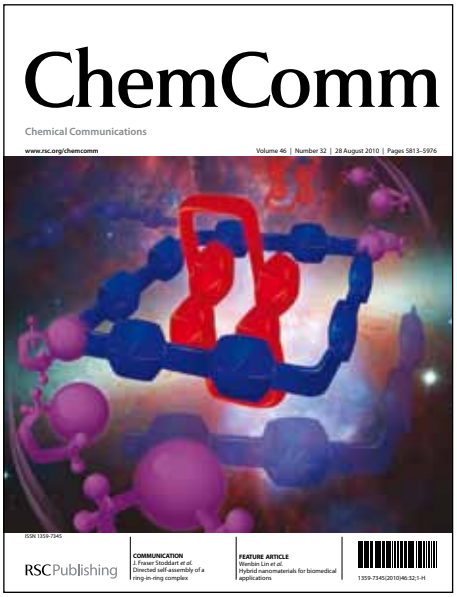

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Pd-Catalyzed Double C–H Bond Activations of Diaryl Ketones for the Synthesis of Fluorenones

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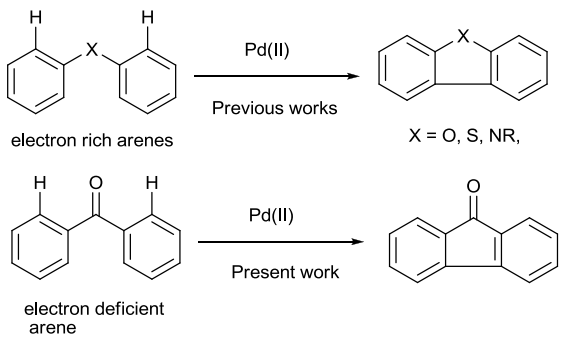
An efficient synthesis of fluorenones from diaryl ketones by Pd-catalyzed oxidative cyclization is described. A possible mechanism involving a carbonyl group assisted *ortho*-C–H activation and cyclometalation followed by a second C–H activation to form a six-membered palladacycle and reductive elimination is proposed.

Transition–metal–catalyzed oxidative C–H coupling is an attractive method for the synthesis of biaryls. Utilization of no pre-functionalized two C–H bonds as the coupling partners for the biaryl synthesis avoids the steps for installation of pre-activated functional groups. In recent years, a number of effective intermolecular oxidative C–H couplings have been developed.[1] By contrast, intramolecular C–C bond formations through oxidative C–H couplings are not widely examined. In an early example, synthesis of dibenzofurans from diaryl ethers were attained by oxidative C–C bond formation using stoichiometric or catalytic amount of Pd complexes.[2] Afterwards, various research groups extended this methodology to the synthesis of carbazole and indole derivatives from diaryl amines and enaminones.[3] This strategy was also used to form five-, six-, seven- and eight-member rings by intramolecular oxidative cyclization.[4] However, so far this type of reactions has only been applied to electron rich substrates. With this contrast, we wish to explore the possibility of oxidative cyclization of electron deficient diaryl ketones to form fluorenone derivatives (Scheme 1).

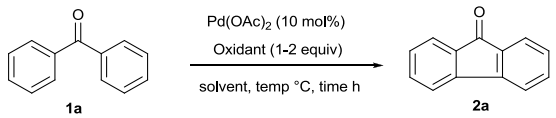


Scheme 1

The fluorenone structure is an important moiety in many natural products, drugs and organic light emitting materials.[5] Various synthetic methods towards the synthesis of fluorenones including oxidation of fluorenol, Friedal–Craft cyclization of biaryl carboxylic acids, Pschorr cyclization reaction and transition–metal–catalyzed cyclization of 2-haloarylketones and cyclocarbonylation reaction of *ortho*-halobiaryls are known.[6] Our group has developed a convenient method to access a variety of fluorenone derivatives from *O*-methyl aryl aldoxime ethers and aryl iodides or from simple arenes using Pd-catalyzed multiple C–H activation reactions.[7] Apart from us, other research groups also applied the C–H activation methodologies to fluorenone synthesis.[8] As a continuation of our earlier success of *ortho*-C–H functionalization of aryl ketones,[9] we wish to report an effective method for the synthesis of fluorenones from diaryl ketones via Pd-catalyzed oxidative cyclization.

The attempt to transform diaryl ketones to the corresponding fluorenones was initiated by heating benzophenone **1a** in the presence of a Pd(II) catalyst. Since the combination of $Pd(OAc)_2$ and Ag_2O is known to be an effective catalyst system for *ortho*-C–H functionalization of ketones,[9] we employed this system for the oxidative cyclization of benzophenone (**1a**) to screen solvents for this transformation. Heating **1a** in CH_3COOH at 130 °C for 12 h with $Pd(OAc)_2$ (10 mol%) and Ag_2O (1 equiv) gave fluorenone **2a** in 15% yield (Table 1, entry 1). When trifluoroacetic acid (TFA) was used as the solvent, the yield of **2a** was increased in 60% yield (entry 2). The choice of solvent is crucial for this transformation. Other solvents including pivalic acid (PivOH), 1,2-dichloroethane (DCE), toluene, 1,4-dioxane, *n*-butanol, DMF and DMSO were all not effective except PivOH which gave fluorenone **2a** in 34% yield (entries 3-9). We then focused on the oxidant for this transformation. Several other oxidants $K_2S_2O_8$, oxone, $Cu(OAc)_2$, benzoquinone and oxygen (O_2) were used as the oxidant for the transformation and no desired product **2a** was observed (entries 10-14). Later, we examined the reaction time of the reaction in entry 2. As the reaction time was extended to 24 h using Ag_2O as an oxidant, the yield of **2a** was increased to 85% (entry 15). Other silver salts such as AgOAc, Ag_2CO_3 are also effective in this transformation to produce **2a** in 70 and 74% respectively (entries 16-17). When the amount of Ag_2O was increased to 1.5 equiv, the yield of **2a** was increased to 93%. Without an oxidant, only 6% of product **2a** was observed. These results reveal the importance of Ag_2O in this transformation (entry 20). Finally, in the absence of $Pd(OAc)_2$, Ag_2O alone gave no reaction product **2a** (entry 21).

Table 1 Optimization studies for Pd-catalyzed oxidative cyclization of diaryl ketone[a]

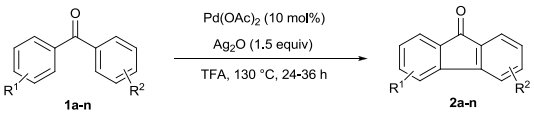


Entry	Oxidant/equiv	Solvent	Time h/Temp ºC	Yield (%)[b]
1	Ag_2O/1	AcOH	12/130	15
2	Ag_2O/1	TFA	12/130	60
3	Ag_2O/1	PivOH	12/130	34
4	Ag_2O/1	DCE	12/130	-
5	Ag_2O/1	toluene	12/130	-
6	Ag_2O/1	dioxane	12/130	-
7	Ag_2O/1	butanol	12/130	-
8	Ag_2O/1	DMF	12/130	-
9	Ag_2O/1	DMSO	12/130	-
10	$K_2S_2O_8$/2	TFA	12/130	-
11	Oxone/2	TFA	12/130	-
12	$Cu(OAc)_2$/2	TFA	12/130	-
13	O_2	TFA	12/130	-
14	BQ	TFA	12/130	-
15	Ag_2O/1	TFA	24/130	85
16	AgOAc/2	TFA	24/130	70
17	Ag_2CO_3/1	TFA	24/130	74
18	Ag_2O/2	TFA	24/130	96
19	Ag_2O/1.5	TFA	24/130	93
20	-	TFA	24/130	6
21[c]	Ag_2O/1.5	TFA	24/130	-
22	Ag_2O/1.5	TFA	24/120	81

[a]All reactions were carried out using benzophenone **1a** (1.0 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (1-2 equiv) and solvent (2.0 mL) at 130 ºC for 12-24 h. [b]Yields of **2a** were measured by ^1H NMR, using mesitylene as an internal standard. [c] No $Pd(OAc)_2$ was used.

With the optimized reaction conditions in hand, we next examined the scope of diaryl ketones for the formation of fluorenone derivatives (Table 2). Thus, by using the reaction conditions $Pd(OAc)_2$ (10 mol %), Ag_2O (1.5 equiv) in trifluoroacetic acid for 24-36 h at 130 ºC, simple benzophenone **1a** afforded fluorenone **2a** in 88% isolated yield (Table 2, entry 1). The product was carefully characterized by ^1H, ^{13}C and mass spectral data. Phenyl(*p*-tolyl)methanone **1b** and phenyl(*m*-tolyl)methanone **1c** gave the corresponding fluorenone derivatives **2b** and **2c** in 86 and 81% yield, respectively (entries 2-3). For 3-methyl benzophenone, the reaction proceeded in an excellent regioselective manner providing only one regioisomer **2c**. This presumably is due to the steric effect of methyl substituent (entry 3) preventing C–H bond activation at the carbon ortho to the keto and the methyl group. Similarly, 4-OMe-substituted benzophenone **1d** offered the corresponding fluorenone derivative product **2d** in 83% yield (entry 4). Electron-withdrawing halogens like 4-Cl, 4-F substituted

Table 2 Optimization studies for Pd-catalyzed oxidative cyclization of diaryl ketone[a]



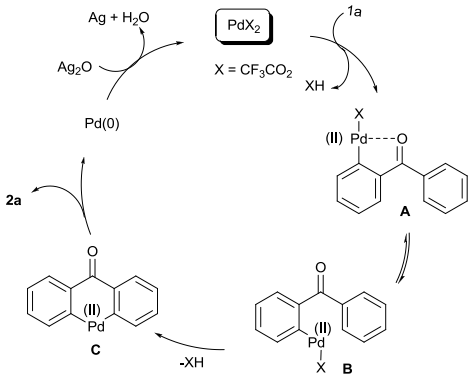
Entry	Diaryl Ketone **1**	Time h	Product **2**	Yield (%)[b]
1	**1a**	24	**2a**	88
2	**1b**	24	**2b**	86
3	**1c**	24	**2c**	81
4	**1d**: R^1 = OMe	24	**2d**: R^1 = OMe	83
5	**1e**: R^1 = Cl	30	**2e**: R^1 = Cl	71
6	**1f**: R^1 = F	30	**2f**: R^1 = F	63
7	**1g**: R^1 = $C(CH_3)_3$	36	**2g**: R^1 = $C(CH_3)_3$	91
8	**1h**: R^1 = Ph	36	**2h**: R^1 = Ph	90
9	**1i**: R^1 = R^2 = Me		**2i**: R^1 = R^2 = Me	88
10	**1j**: R^1 = R^2 = OMe	24	**2j**: R^1 = R^2 = OMe	74
11	**1k**	36	**2k**	79
12	**1l**	36	**2l**	72
13	**1m**: R^1 = 2-F; R^2 = H	30	**2m**: R^1 = 2-F; R^2 = H	68
14	**1n**: R^1 = 2-F; R^2 = Me	30	**2n**: R^1 = 2-F; R^2 = Me	76
15	**1o**: R^1 = 3-F; R^2 = H	30	**2o**: R^1 = 3-F; R^2 = H	71

[a] All reactions were carried out using diaryl ketone **1** (1.0 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2O (1.5 equiv) and TFA (2.0 mL) at 130 ºC for 24-36 h. [b] Isolated yield.

benzophenones **1e** and **1f** also reacted smoothly, but with extended reaction time to produce the corresponding fluorenone derivatives **2e** and **2f** in 71 and 63% yields, respectively (entries 5 and 6). 4-*tert*-Butyl, 4-phenyl substituted benzophenone **1g** and **1h** afforded fluorenone derivatives **2g** and **2h** in 91 and 90% yield, respectively. Di(*p*-tolyl)methanone (**1i**) and bis(4-methoxyphenyl)methanone (**1j**) were also treated under the standard reaction conditions to give fluorenones **2i** and **2j** in 88 and 74% yield respectively. 2-Naphthyl benzophenone **1k** was also transformed to benzofluorenone **2k** in 79% under the standared reaction conditions. In this reaction, there are two C–H activation sites at C2 and C6 of **1k**. However, the activation

occurs only at C6, owing to to the steric effect of the fused aromatic ring. Similarly, 1-benzoyl naphthalene **1l** underwent the transformation to afford benzoanthracenone **2l** in 72% yield (entry 12). There are two possible C–H functionalization sites at C2 and C8 for substrate **1l**, but the C8 functionalized product **2l** was observed exclusively. The regioselectivity is surprising, but the reason for the observed selectivity is not clear. The product structure was assigned based on comparison of the NMR data with those reported previously.[10] The oxidative cyclization of 2-F and 3-F substituted benzophenones **1m-1o** also proceeded smoothly to give the corresponding fluorenones **2m-2o** in good yields (entries 13-15).

Based on our observation and earlier literatures,[1-4],[9] a possible mechanism for this fluorenone formation is outlined in Scheme 2. Initially, the ketone group of **1a** is coordinated to Pd(II) and the consecutive *ortho*-C–H bond activation leads to the formation of palladacycle **A** which is expected to be in equilibrium with its palladium aryl σ-complex **B**. A second C–H bond activation in **B** takes place to form the six membered palladium complex **C** and its reductive elimination gives the fluorenone product and Pd(0) species. Oxidization of the Pd(0) species by Ag_2O to Pd(II) restarts the next catalytic cycle.



Scheme 2

In summary, we have developed an efficient approach to the synthesis of fluorenones by Pd-catalyzed oxidative cyclization of diaryl ketones. This simple method offers an alternative and complimentary way to other fluorenone synthesis.

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Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental procedures, compound characterizations, and the copies of ^{1}H NMR and ^{13}C NMR spectra.]. See DOI: 10.1039/b000000x/

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