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Synthesis of Fluorenone Derivatives through Pd-Catalyzed Dehydrogenative Cyclization

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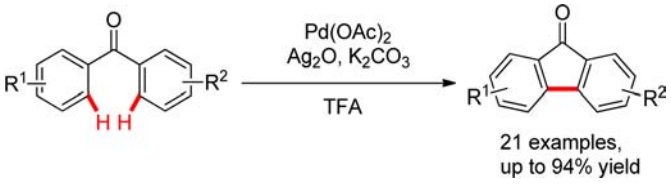
ABSTRACT



Palladium-catalyzed dual C−H functionalization of benzophenones to form fluorenones by oxidative dehydrogenative cyclization is reported. This method provides a concise and effective route toward the synthesis of fluorenone derivatives, which shows outstanding functional group compatibility.

The fluorenone chemical scaffold is considered a privileged structure that constitutes the central core of a variety of compounds exhibiting extraordinary biological and pharmaceutical activities as well as optical and electronic properties.[1] Traditionally, the strategies toward syntheses of fluorenone derivatives include Friedel−Crafts acylation (Scheme 1, route a),[2] palladium-catalyzed C−H functionalization employing aryl halides (route b),[3] carbonylation (route c),[4] and decarboxylation (route d).[5] However, most of the above methods involve multistep procedures and need prefunctionalization. From the point view of atom- and process-economical chemistry, the most concise route with reduced waste and in fewer steps is straightforward dehydrogenative coupling by dual C−H functionalization of benzophenone derivatives (Scheme 1), which are inexpensive and readily available.[6]

During the past several decades, transition-metal-catalyzed dehydrogenative coupling to construct dibenzofurans,[7] carbazoles,[7b,8] xanthones,[9] and fluorenes[10] have been well developed. However, methods to build fluorenones remains an outstanding challenge because of the structural and electronic features of benzophenones.[11]

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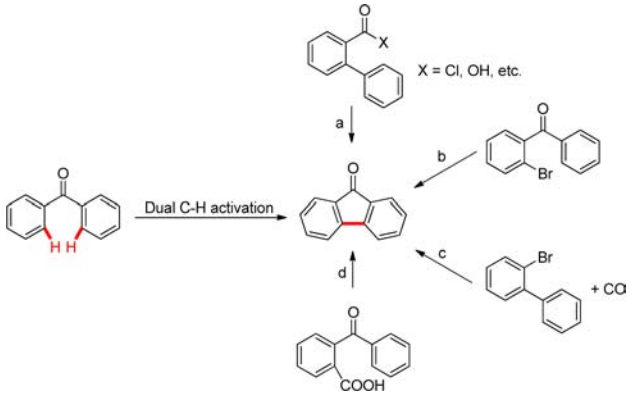
Scheme 1. Strategies toward Syntheses of Fluorenones



Owing to the synthetic importance of the fluorenone and our continuous interests in transition-metal-catalyzed oxidative couplings, herein we deliver the first palladium-catalyzed dual C−H functionalization of benzophenones to form fluorenone derivatives.

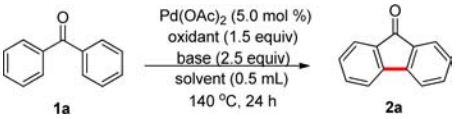
We initiated our research by using benzophenone (**1a**) as the standard substrate. The combination of $Pd(OAc)_2$, K_2CO_3, and Ag_2O in trifluoroacetic acid (TFA) at 140 °C gave the desired cyclization product fluorenone (**2a**) in 85% isolated yield within 24 h (Table 1, entry 1). Other oxidants (entries 2 and 3), bases (entry 4), or solvents (entries 5 and 6) decreased the yield. Employment of CF_3COOAg and CF_3COOK resulted in a slightly lower yield (entry 7). Modifying the quantity of oxidant, base, concentration, reaction temperature, and time also showed lower efficiency in terms of chemical yields, respectively (entries 8−12).[12] Notably, essentially no reaction occurred in the absence of palladium catalyst (entry 13), which indicated that an acid-promoted Nazarov cyclization reaction was unlikely.

With the above optimized conditions, the oxidative cyclization of a variety of benzophenone derivatives was examined (Scheme 2). Benzophenones substituted with 4- or/and 3-methyl groups afforded the corresponding fluorenones in good to excellent yields (**2b**−**f**). Diphenyl-substituted product was obtained in a moderate yield (**2g**). A bulky substituent such as a *tert*-butyl group showed little influence (**2h**). However, a 2-substituted benzophenone resulted in a moderate yield (**2i**). In general, benzophenones bearing electron-rich substituents worked better than those bearing electron-deficient substituents. Both 4-methoxybenzophenone and 4,4′-dimethoxybenzophenone afforded the desired products in good yields (**2j** and **2k**). Surprisingly, 4-hydroxybenzophenone could also form the corresponding 3-hydroxyfluorenone in 84% yield under the oxidative dehydrogenative conditions (**2n**). Understandably, 2-hydroxy-4-methoxybenzophenone

(11) During preparation of our manuscript, similar research was reported: Gandeepan, P.; Hung, C.-H.; Cheng, C.-H. *Chem. Commun.* **2012**, *48*, 9379.

(12) For a more detailed condition screening table, see the Supporting Information.

Table 1. Pd-Catalyzed Oxidative Dehydrogenative Dual C−H Functionalization of Benzophenone[a]



entry	oxidant	base	solvent	yield[b] (%)
1	Ag_2O	K_2CO_3	TFA	91 (85)
2	Ag_2CO_3	K_2CO_3	TFA	68
3	AgOAc	K_2CO_3	TFA	83
4	Ag_2O	Cs_2CO_3	TFA	86
5	Ag_2O	K_2CO_3	HOAc	30
6	Ag_2O	K_2CO_3	EtCOOH	trace
7[c]	CF_3COOAg	CF_3COOK	TFA	66
8[d]	Ag_2O	K_2CO_3	TFA	77
9[e]	Ag_2O	K_2CO_3	TFA	54
10[f]	Ag_2O	K_2CO_3	TFA	80
11[g]	Ag_2O	K_2CO_3	TFA	72
12[h]	Ag_2O	K_2CO_3	TFA	85
13[i]	Ag_2O	K_2CO_3	TFA	0

[a] The reactions were conducted with 0.20 mmol of **1a**, unless otherwise noted. [b] GC yields were given using dodecane as the internal standard, and isolated yield was shown in parentheses. [c] 3.0 equiv of CF_3COOAg and 5.0 equiv of CF_3COOK were employed. [d] 1.0 equiv of Ag_2O was used. [e] 10 mol % of K_2CO_3 was used. [f] 1.0 mL of trifluoroacetic acid was used. [g] The reaction was conducted in 120 °C. [h] The reaction was conducted within 20 h. [i] The reaction was performed in the absence of a palladium catalyst.

and 2-fluoro-4′-methoxybenzophenone resulted in low yields of oxidative cyclization products (**2o** and **2p**). Notably, benzophenones bearing halogen substituents could be tolerated well, which provided opportunities for further functionalization (**2l**, **2m**, and **2q**−**s**). However, benzophenones substituted with strong electron-withdrawing groups, such as trifluoromethyl (**2t**), nitro, and cyano, were not suitable substrates for the reaction. On the other hand, when 2-benzoylnaphthalene was employed as the substrate, the cyclization product was obtained uneventfully (**2u**). However, other than benzophenone, benzophenone imine, oxime, and hydrazone did not produce the desired cyclization products at all.

To gain some preliminary insight into the reaction mechanism, and to exclude the possibility of the reaction taking place through a Nazarov cyclization pathway, isotope-labeled experiments were conducted. The intramolecular and intermolecular kinetic isotopic effects (KIE) provided the evidence that C−H cleavage of phenyl rings was involved in the rate-determining step (eqs 1−3). Furthermore, the different intramolecular KIE values of 2-D-4-fluoro-4′-methylbenzophenone (**1x**) and 2-D-4-methyl-4′-fluorobenzophenone (**1y**) indicated the possibility that the concerted metalation−deprotonation (CMD) process rather than the electrophilic substitution was involved in the rate-determining step.

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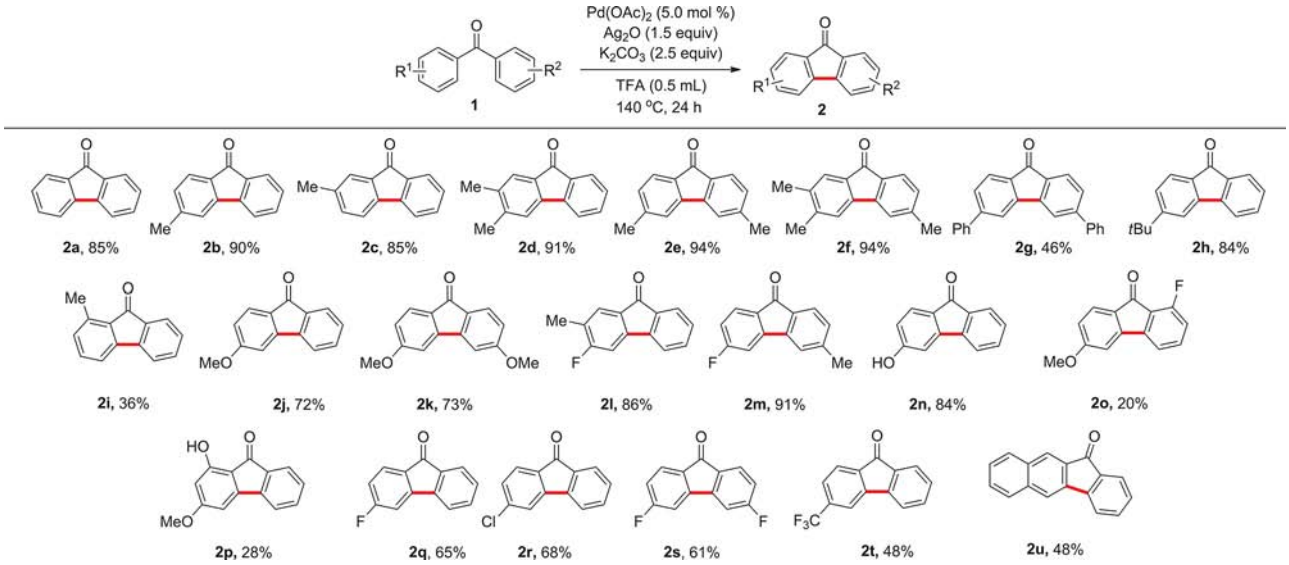
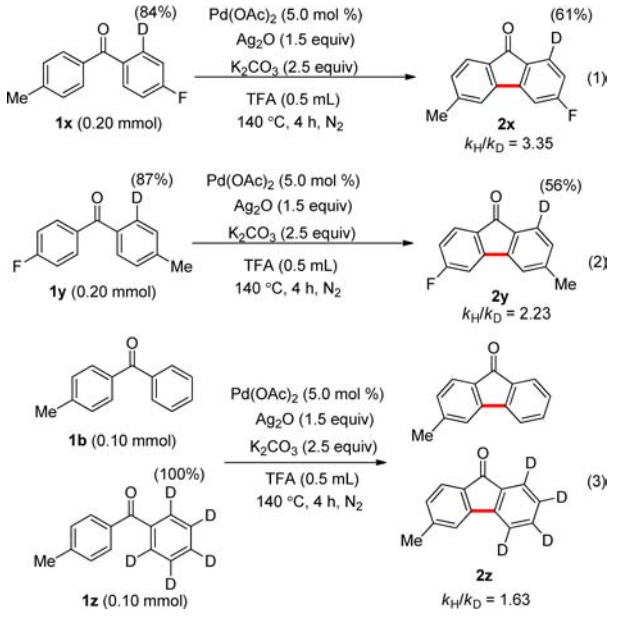
Scheme 2. Pd-Catalyzed Oxidative Dehydrogenative Cyclization of Benzophenone Derivatives[a]

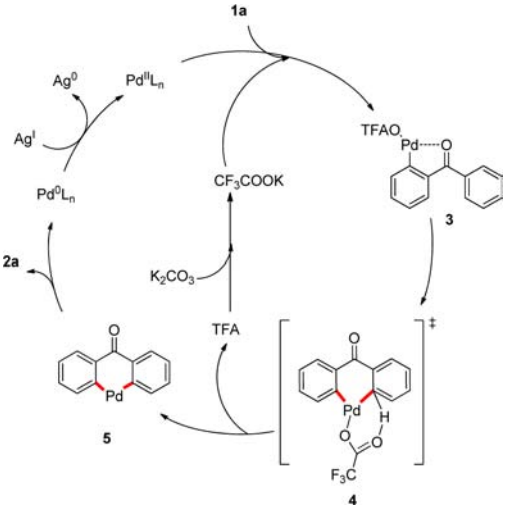


[a] The reactions were conducted with 0.20 mmol of **1**, and isolated yields are given unless otherwise noted.



On the basis of the above results and previous studies, a plausible mechanism is proposed in Scheme 3. The reaction was initiated by fast electrophilic palladation of **1a** with $Pd(OTFA)_2$, which was formed in situ by the reaction of $Pd(OAc)_2$ with TFA, thus generating a five-membered palladacycle intermediate **3** with a carbonyl group as a directing group. Further, the intramolecular C−H cleavage took place via a CMD process (transition state **4**) to generate intermediate **5**, which was considered as the rate-determining step.[13] The subsequent reductive elimination produced the fluorenone **2a** and generated a Pd(0) species, which was oxidized by Ag(I) to regenerate a Pd(II) species to finish the catalytic cycle.

Scheme 3. Plausible Mechanism for Pd-Catalyzed Oxidative Dehydrogenative Cyclization of Benzophenone



In summary, we have developed the first palladium-catalyzed dual C−H functionalization of benzophenones to form fluorenones by oxidative dehydrogenative cyclization. This method provides a concise and effective route toward the synthesis of fluorenone derivatives, which shows outstanding functional group compatibility. Further studies on extending this transformation to the synthesis of biologically active compounds and surveying the detailed mechanism are currently underway and will be reported in due course.

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Supporting Information Available. Experimental procedures as well as spectral data for cyclization products and mechanistic study experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.