C–H Activation

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Palladium-Catalyzed Oxidative Double C–H Functionalization/Carbonylation for the Synthesis of Xanthones**

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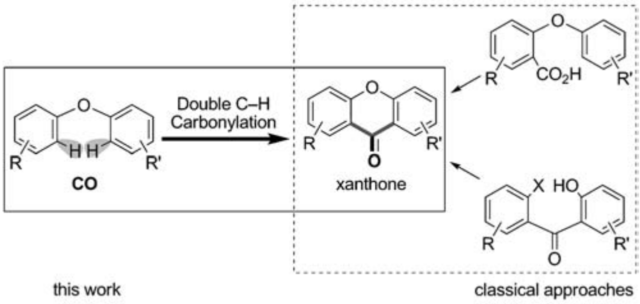
The chemical structure of xanthone constitutes the central core of a wide variety of naturally occurring and manmade compounds, which exhibit extraordinary biological and pharmaceutical properties (e.g. antibacterial, anti-inflammatory, anticancer, and antiviral).[1] The xanthone scaffold has even been described as "privileged structure", since members of this structural class are able to interact with different types of drug targets and attracted interests across a broad spectrum of sciences from chemistry and biology to medicine (Scheme 1).[2] Among the known synthetic routes to obtain the xanthone skeleton, the cyclodehydration of 2,2′-dihydroxybenzophenones and electrophilic cycloacylation of 2-aryloxybenzoic acids are the most popular methods (Scheme 1).[3] However, both methods involve multistep procedures under harsh reaction conditions, in which strong acids or toxic metals are often used.[4] Because of the important biological applications of xanthones, the development of an efficient and general synthetic route with reduced waste and in fewer steps is highly desirable.



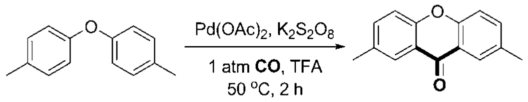
Scheme 1. Strategies towards syntheses of xanthones. X = OH, OMe.

The double C–H functionalization/carbonylation of simple diaryl ethers with CO would represent a very attractive and sustainable approach towards the syntheses of xanthone, because neither of the two C–H bonds need to be prefunctionalized, and diaryl ethers can be easily synthesized from basic chemicals (Scheme 1). Transition-metal-catalyzed carbonylation of aromatic halides with CO in the presence of various nucleophiles has undergone rapid development,[5] since the pioneering work of Heck and co-workers in 1974.[6] During the past decade, increased attention has been focused on Pd-catalyzed aromatic C–H functionalization/carbonylation.[7] Very recently, Pd-catalyzed direct transformation of two C–H bonds simultaneously has attracted more and more interest.[8] However, double C–H functionalization/carbonylation remains an outstanding challenge.

Owing to the synthetic importance of the xanthone structure and our continuous interests in the Pd-catalyzed oxidative coupling[8c] and carbonylation reactions,[7b] herein, we describe the first Pd-catalyzed double C–H functionalization/carbonylation of diaryl ethers to form biologically active xanthone derivatives.

The combination of Pd(OAc)$_2$ and $K_2S_2O_8$ in trifluoroacetic acid (TFA) at 50 °C gave the best result for the oxidative carbonylation of 4-tolyl ether (**1a**) under 1 atm CO (Table 1, entry 1). With these conditions, a 93 % yield of 2,7-

Table 1: Pd-catalyzed oxidative double C–H carbonylation of **1a**: effects of reaction parameters.[a]



1a **2a**

Entry	Variation from "standard conditions"	Yield[%][b]
1	none	93
2	PdCl$_2$, instead of Pd(OAc)$_2$	0
3	[Pd(dba)$_2$], instead of Pd(OAc)$_2$	17
4	MnO$_2$, instead of $K_2S_2O_8$	87
5	BQ, instead of $K_2S_2O_8$	90
6	$Na_2S_2O_8$, instead of $K_2S_2O_8$	47
7	Cu(OAc)$_2$, instead of $K_2S_2O_8$	34
8	O_2, instead of $K_2S_2O_8$	0
9	TFA/TFAA (9:1), instead of TFA	56
10	TFA/HOAc (1:9), instead of TFA	0
11	25 °C, instead of 50 °C	32
12	diphenyl ether, instead of **1a**	27

[a] Standard reaction conditions: **1a** (0.2 mmol), Pd(OAc)$_2$ (2.5 mol %), $K_2S_2O_8$ (2 equiv), 1 atm CO, TFA (1.0 mL), 50 °C, 2 h. [b] The yield was determined by GC, calibrated using biphenyl as internal standard. BQ = 1,4-benzoquinone, dba = dibenzylideneacetone, TFAA = trifluoroacetic anhydride.

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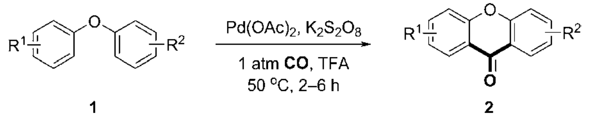
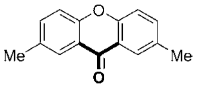
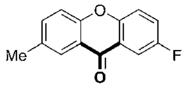
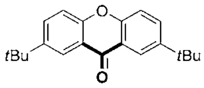
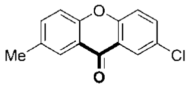
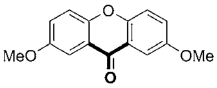
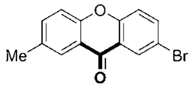
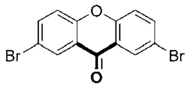
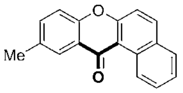
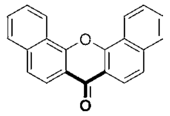
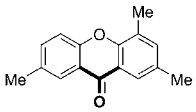
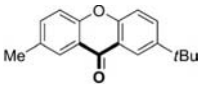
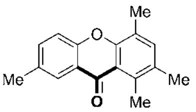
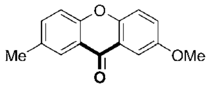
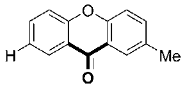
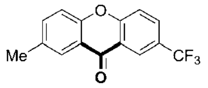
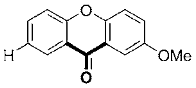
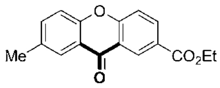
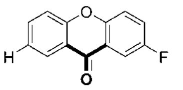
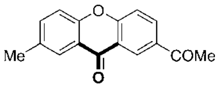
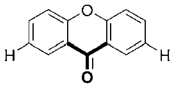
dimethyl xanthone (**2a**) was obtained within two hours. The choice of palladium catalyst was crucial for the reaction. When Pd$(OAc)_2$ was replaced by $PdCl_2$, essentially no reaction occurred (Table 1, entry 2). The use of $[Pd(dba)_2]$ as catalyst decreased the yield dramatically (Table 1, entry 3). As to oxidant, $K_2S_2O_8$ gave the highest yield for this oxidative reaction. MnO_2 and BQ were also effective and afforded **2a** in 87 and 90% yield, respectively (Table 1, entries 4 and 5). Other oxidants such as $Na_2S_2O_8$, $Cu(OAc)_2$, and O_2 showed less or no efficiency in terms of chemical yields (Table 1, entries 6–8). Addition of TFAA as co-solvent led to a decreased yield while a mixed solvent of HOAc and TFA led to no reaction (Table 1, entries 9 and 10). A lower reaction temperature resulted in a slower reaction, affording 32% yield of **2a** (Table 1, entry 11). Notably, when diphenyl ether was employed as the substrate, relatively low yield of the corresponding carbonylated product was obtained (Table 1, entry 12).

Table 2: Pd-catalyzed oxidative double C–H carbonylation of different diaryl ethers.[a]



Entry	**2**	Product	Yield [%][b]	Entry	**2**	Product	Yield [%][b]
1	**2a**		96	11	**2k**		76
2	**2b**		92	12	**2l**		63
3	**2c**		50	13	**2m**		70
4	**2d**		65	14	**2n**		70
5	**2e**		41	15	**2o**		89
6	**2f**		82	16	**2p**		71
7	**2g**		71	17	**2q**		52
8	**2h**		56	18	**2r**		46
9	**2i**		51	19	**2s**		34
10	**2j**		58	20	**2t**		27

[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (2.5 mol%), $K_2S_2O_8$ (2 equiv), 1 atm CO, TFA (1.0 mL), 50°C, 2–6 h. [b] Yield of isolated product.

With the above optimized conditions, the oxidative carbonylation of a range of symmetrical diaryl ethers was tested (Table 2). Diaryl ethers substituted with alkyl groups, such as methyl and *tert*-butyl, afforded the corresponding xanthones in excellent yields (Table 2, entries 1 and 2). The carbonylation of the aryl ether bearing methoxy groups produced the xanthone in 50% yield (Table 2, entry 3). To our delight, a Br substituent could be well tolerated in this oxidative reaction (Table 2, entry 4). Moreover, dinaphthyl ether could also be carbonylated to form the corresponding naphthyl xanthone (Table 2, entry 5).

Furthermore, we investigated the oxidative carbonylation of unsymmetrical diaryl ethers with CO (Table 2). In general, substrates bearing both electron-donating and -withdrawing substituents worked well under the optimized reaction conditions. The reaction of diaryl ethers containing *tert*-butyl and methoxy groups produced the xanthones **2f** and **2g** in 82% and 71% yield, respectively (Table 2, entries 6 and 7). Treatment of an ether bearing the strong electron-withdrawing group CF_3 with CO afforded **2h** in moderate yields (Table 2, entry 8). Surprisingly, ester and ketone groups were tolerated under these acidic conditions (Table 2, entries 9 and 10). Halo substituents, such as F, Cl, and Br, were all well-tolerated, which provided the possibility for further functionalization (Table 2, entries 11–13). In a similar manner, naphthyl xanthone **2n** was obtained in 70% yield (Table 2, entry 14). Multi-substituted ethers also reacted well in this carbonylation (Table 2, entries 15 and 16).

To further explore the scope of the reaction, various mono-substituted diaryl ethers were tested. Substrates with either electron-donating substituents such as Me, OMe, or electron-withdrawing substituent F reacted smoothly to give the desired products (Table 2, entries 17–19). Nonsubstituted diphenyl ether afforded xanthone in 27% yield (Table 2, entry 20).

To gain some preliminary insights into the reaction mechanism, we monitored the oxidative carbonylation of different substrates using React IR spectroscopy (Figure 1).

As shown in Figure 1, zero-order kinetics for the carbonylation of different substrates were observed, thus indicating that the first C–H functionalization of diaryl ether with Pd^{II} was not the rate-determining step. Furthermore, the carbonylation of **1a** was conducted under different pressures of CO (Figure 2). The kinetic profiles were overlaid, indicating that the insertion of CO was not rate-determining under the conditions. The reductive elimination of ArCOPdAr species has been reported to be a facile process;[9] therefore, we concluded that the second C–H fuctionalization might be the rate-determining step of this catalytic cycle.

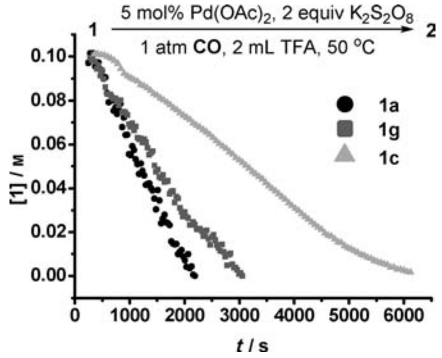


Figure 1. Kinetic plots of oxidative double C–H carbonylation of different substrates.

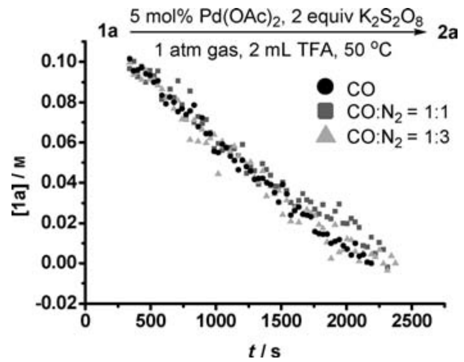
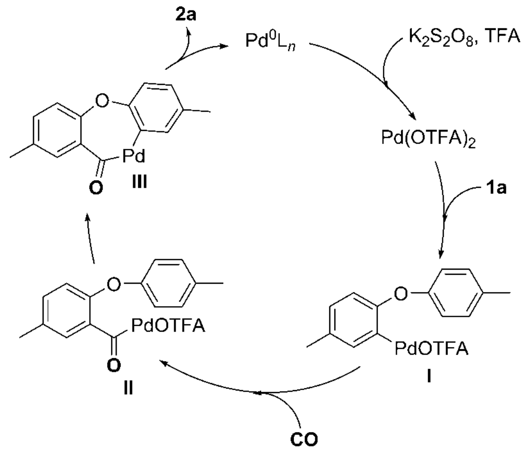


Figure 2. Kinetic profiles of oxidative double C–H carbonylation of **1a** with different CO pressures.

On the basis of above results and previous studies,[10] we propose a mechanism for this double C–H functionalization/carbonylation reaction (Scheme 2). Pd(OTFA)$_2$ is formed in situ by the reaction of Pd(OAc)$_2$ with TFA. Then, the fast electrophilic palladation of **1a** with Pd(OTFA)$_2$ affords the arylpalladium species **I**, which further reacts with CO to produce the intermediate **II**. The subsequent intramolecular C–H functionalization and reductive elimination of **III** gives the xanthone **2a** and generates the Pd^0 species. Pd(OTFA)$_2$ is then regenerated by oxidation with $K_2S_2O_8$ in the presence of TFA.

In conclusion, we have developed the first Pd-catalyzed double C–H functionalization/carbonylation of diaryl ethers to form xanthones. By using a simple catalytic system consisting of Pd(OAc)$_2$, $K_2S_2O_8$, and TFA, a variety of diaryl ethers could be directly carbonylated to xanthones in moderate to good yields. Moreover, various functional groups were tolerated under the optimized conditions. Notably, this transformation provides an effective and practical protocol towards the syntheses of bioactive xanthones. Preliminary mechanism studies revealed that the second C–H functionalization might be the rate-determining step. Further studies on substrate scope and mechanism are currently underway and will be reported in due course.



Scheme 2. Proposed reaction mechanism.

Experimental Section

General procedure: In an oven-dried Schlenk tube equipped with a stir bar, Pd(OAc)$_2$ (2.5 mol %), $K_2S_2O_8$ (2 equiv), and diaryl ether (0.2 mmol) were combined. A balloon filled with CO was connected to the Schlenk tube by the side tube and purged three times. Then, TFA (1.0 mL) was added to the tube through a syringe. The Schlenk tube was heated at 50 °C for 2–6 h (as indicated by TLC) and then cooled to room temperature. After the gas from the balloon was released carefully, the reaction was quenched by water and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuum. The desired products were obtained in the corresponding yields after purification by flash chromatography on silica gel with petroleum ether and ethyl acetate.

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