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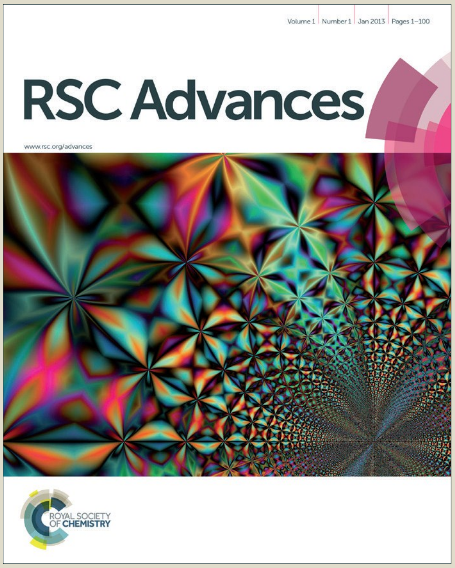

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COMMUNICATION

Palladium-Copper Catalyzed C(sp^3)-C(sp^2) Bond C-H Activation Cross-Coupling Reaction: Selective Arylation to Synthesis 9-Aryl-9*H*-Xanthene and 9,9-Diaryl-Xanthene Derivatives

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Guodong Shen,* Lingyu Zhao, Yichen Wang, Wenfang Xia, Mingsen Yang and Tongxin Zhang*

A novel and efficient palladium-copper cooperatively catalyzed C(sp^3)-C(sp^2) bond C-H activation cross-coupling reaction has been developed. A series of 9-aryl-9*H*-xanthenes and 9,9-diaryl-xanthenes are selectively synthesized in moderate to good yields by controlling the reaction time and temperature by applying this palladium-copper co-catalysts.

Xanthene derivatives are an important class of molecules and heterocyclic scaffolds in biological, medicinal and food areas.[1] For example (Figure 1), Erythrosine **(A)**, known as Red No. 3, is primarily used for food coloring, commonly used in sweets.[2] Mangostin **(B)** has exhibited excellent biological properties including antioxidant,[3] anti-bacterial,[4] anti-inflammatory[5] and anticancer activities.[6] Uridine derivative **(C)** is antiarrhythmic agent[7] and also can be used to treat a number of supraventricular tachycardia that do not improve with vagal maneuvers.[8] Adenosine derivative **(D)** can be used for the treatment of liver, cerebrovascular, cardiovascular and other diseases.[9] Furthermore, some xanthenes have been used as dyes, fluorescent materials and laser technologies for their useful spectroscopic properties.[10]

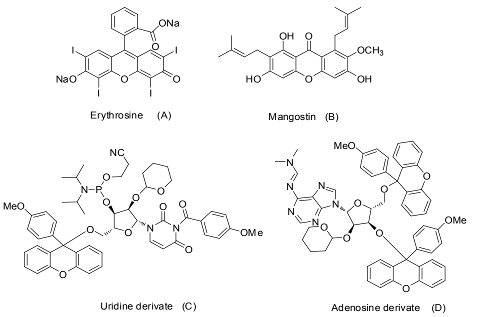
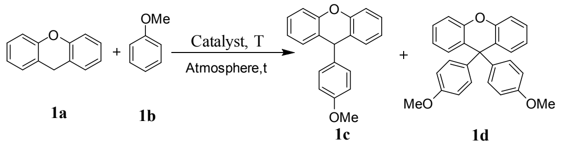


Fig. 1 Some useful xanthene derivatives.

Based on the broad spectrum of applications of the xanthene, a lot of methodologies for synthesizing xanthene derivatives have been investigated, especially some methods to synthesis of 9-substituted xanthenes. Using scandium triflate-catalyzed one-pot domino approach[11] and Brønsted acid (TfOH or MsOH) catalyzed oxidative coupling reactions[12] are some of good examples. However, these methods are not able to provide effective ways to selectively synthesize 9-aryl-9*H*-xanthenes and 9,9-diaryl-xanthenes.

Palladium and copper catalyzed C-H activation and cross-coupling (sp^2-C and sp^3-C) reactions are of paramount importance in the synthesis of organic molecules.[12] Numerous C-H activation and cross-coupling systems,[13] especially the cooperative palladium-copper co-catalysed systems[14] have been applied in the preparation of pharmaceuticals, agrochemicals and advanced materials on both laboratory and industrial scales. In the past decades, palladium and copper catalyzed C-X (X = C, N, O, S, etc.) bond formation reactions have drawn considerable attention for their efficiency.[15] However, there is rare report about the versatile and selective synthesis of 9-aryl-9*H*-xanthenes and 9,9-diaryl-xanthenes using the metal catalyzed cross-coupling reaction.[16] Herein, as a part of our effort, we report an efficient method for the synthesis of 9-aryl-9*H*- and 9, 9-diaryl-xanthene derivatives *via* the palladium-copper co-catalyzed C(sp^3)-C(sp^2) bond cross-coupling reaction in high selectivity by controlling the reaction time and temperature.

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst		T(°C)	t(h)	**1c** (%)[b]	**1d** (%)[b]
1	Cu(OTf)$_2$	N$_2$	140	15	5	0
2	Cu(OTf)$_2$	N$_2$	150	15	6	0
3	Pd(OAc)$_2$	N$_2$	140	15	4	0

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[a] School of Chemistry and Chemical Engineering, School of Pharmacy, Liaocheng University, Liaocheng 252000, Shandong, PR China.
E-mail: shenguodong33@163.com; xintongzhang123@163.com
Tel & Fax: (+86)-635-8239680

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4	Pd(OAc)$_2$/Cu(OTf)$_2$	N$_2$	130	15	25	5
5	Pd(OAc)$_2$/Cu(OTf)$_2$	N$_2$	140	15	21	11
6	Pd(OAc)$_2$/Cu(OTf)$_2$	N$_2$	130	2.5	35	trace
7	Pd(OAc)$_2$/Cu(OTf)$_2$	Air	130	2.5	85	trace
8	Pd(OAc)$_2$/Cu(OTf)$_2$	Air	120	2.5	40	0
9	Pd(OAc)$_2$	Air	130	2.5	13	0
10	Cu(OTf)$_2$	Air	130	2.5	41	0
11	Pd(OAc)$_2$/Cu(OTf)$_2$	O$_2$	130	2.5	34^c	0
12	Pd(OAc)$_2$/TfOH	Air	130	2.5	10	0
13	Pd(OAc)$_2$/Cu(OTf)$_2$	Air	145	24	<1	80
14	PdCl$_2$/Cu(OTf)$_2$	Air	130	2.5	80	5
15	Pd(dppf)Cl$_2$/Cu(OTf)$_2$	Air	130	2.5	45	trace
16	Pd(OAc)$_2$/Cu(OAc)$_2$	Air	130	2.5	0	0
17	Pd(OAc)$_2$/CuI	Air	130	2.5	0	0
18	Pd(OAc)$_2$	Air	145	24	<5	0
19	Cu(OTf)$_2$	Air	145	24	<5	0
20	Pd(OAc)$_2$/Cu(OTf)$_2$	N$_2$	145	24	24	15

[a] Reaction conditions: Pd catalyst (0.025 mmol), Cu catalyst (0.05 mmol), xanthene **1a** (0.5 mmol) in anisole (1.5 mL) under N$_2$/air/O$_2$ atmosphere.

[b] Isolated yield after flash chromatography based on **1a**.

[c] 35% of xanthone was isolated based on **1a**.

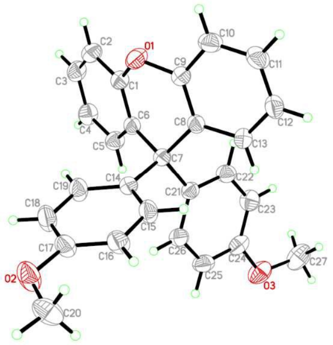

Fig. 2 X-ray Crystallographic Structure of **1d**.

Initially, xanthene **1a** and anisole **1b** were selected as the model substrates to identify and optimize the reaction parameters including transition metal catalysts, reaction temperature and reaction time. When the reaction was carried out with Cu(OTf)$_2$ (10 mol%) under N$_2$ atmosphere at 140 ^{o}C, the desired 9-(4-methoxyphenyl)-9*H*-xanthene **1c** could be detected in 5% yield after 15 hours (Table 1, entry 1). Raising the reaction temperature (150 °C) did not improve the yield of the desired compounds (Table 1, entry 2). Only using Pd(OAc)$_2$ to repeat this reaction did not generate the good yield either (Table 1, entry 3). After extensive studies we found that the yield of **1c** could be improved significantly by using the co-catalyst system of Pd(OAc)$_2$ and Cu(OTf)$_2$. A new compound **1d** was observed at the same time using this co-catalyst system (Table 1, entries 4-5). The structure of **1d** was unambiguously elucidated by X-ray crystallography (Figure 2). When we reduced the reaction time to 2.5 hours, only compound **1c** was obtained in high selectivity (Table 1, entry 6). Further extensive study was made to improve the reaction yield after we reached the good selectivity. We finally found that the reaction yield was greatly improved if the reaction was carried out in the open air (Table 1, entry 7). However, the reaction at lower temperature (120 °C) and using either Pd(OAc)$_2$ or Cu(OTf)$_2$ alone decreased the reaction yield obviously (Table 1, entries 8-10). We also conducted the reaction under oxygen balloon and found that the xanthene can be oxidized to the xanthone (Table 1, entry 11). We used TfOH instead of Cu(OTf)$_2$ and the reaction gave the low yield (Table 1, entry 12). To our delight, when the reaction temperature was raised to 145 ^{o}C and the reaction time was extended to 24 h, **1d** was obtained in 80% yield (Table 1, entry 13). Some other palladium and copper salts such as PdCl$_2$, Pd(dppf)Cl$_2$, Cu(OAc)$_2 \cdot$H$_2$O and CuI were also studied (Table 1, entries 14-17), the catalyst system of Pd(OAc)$_2$ and Cu(OTf)$_2$ provided the best result. We also carried out some control experiments for the second arylation to synthesis of 9,9-diaryl-xanthenes, from the result we can see the Pd/Cu co-catalysts still important for the reaction (Table 1, entries 18-20). Obviously, the entries 7 and 13 are the best conditions.

With the optimized conditions in hand, the scope of substrates was further investigated (Table 2). From the experimental results we could conclude that the reaction yields were mainly influenced by the electronic effect and steric hindrance of aromatics **b**. The aromatics **b** must have the electron-donating groups such as -OMe, -OH, -SMe, -NH$_2$ etc. The reaction time for mono- and bis-arylation is mainly determined by the TLC detection, when the starting material was consumed completely, then the reaction was stopped, and the best yield was got. The reactions of xanthene **1a** with anisole **1b**, ethoxybenzene **2b**, oxydibenzene **3b** or 1, 2-dimethoxybenzene **4b** could generate mono-substituted xanthenes (**1c**, **2c**, **3c** and **4c**) or di-substituted xanthenes (**1d**, **2d**, **3d** and **4d**) selectively by controlling the reaction time and temperature. However, when 1-methoxy-2-methylbenzene **5b**, 1-bromo-2-methoxybenzene **6b** and methyl(phenyl)sulfane **7b** were used, the yields of **5c**, **6c** and **7c** were not high, increasing the reaction temperature and extending the reaction time could not improve the yield obviously. Phenol **8b** was used to run the reaction at 130 ^{o}C for 2.5 h, we did not detect the product 4-(9*H*-xanthen-9-*yl*)phenol **8c** by TLC, but 4,4'-(9*H*-xanthene-9,9-diyl)diphenol **8d** was afforded at 140 ^{o}C for 24 h continually (for crystal structure of **8d**, see Supporting Information). Aniline **9b** and *o*-toluidine **10b** could proceed the reaction and the anticipated products **9c** and **10c** were obtained. Because of the steric hindrance of 1,3,5-trimethoxybenzene **11b**, we could not obtain bis-substituted

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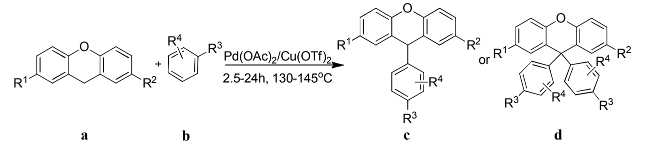
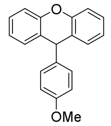
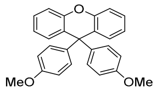
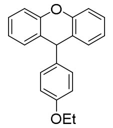
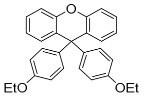
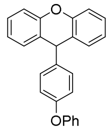
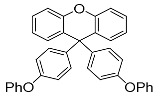
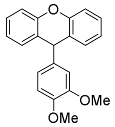
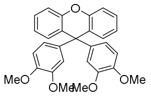
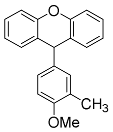
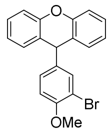
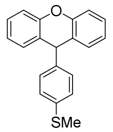
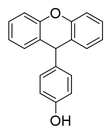
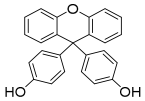
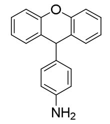
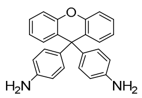
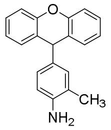
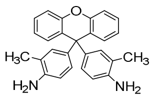
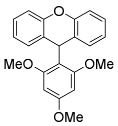
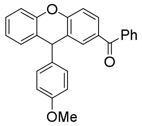
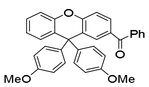
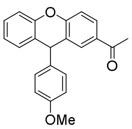
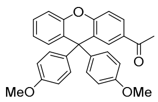
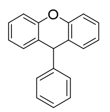
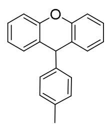
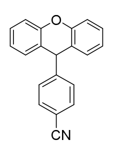
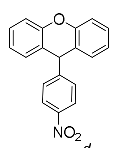
Table 2 Scope of the Palladium-Copper Catalyzed C(sp3)-C(sp2) Bond Cross-Coupling Reaction[a,b]



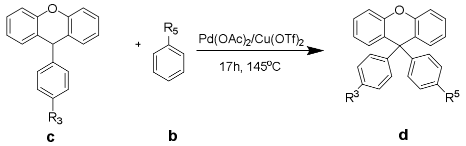
 **1c**, 85% 2.5 h, 130°C	 **1d**, 80% 17 h, 145°C	 **2c**, 75% 4 h (2.5h, 61%), 130°C	 **2d**, 66% 17 h, 145°C
 **3c**, 60% 6 h, 130°C	 **3d**, 55% 24 h, 145°C	 **4c**, 71% 5 h, 130°C	 **4d**, 65% [c] 17 h, 145°C
 **5c**, 32% 10 h, 130°C	 **6c**, 25% 18 h, 145°C	 **7c**, 32% 24 h, 145°C	 **8c**, /[c,d] 2.5 h, 130°C
 **8d**, 76%[c] 24h, 140°C	 **9c**, 35% 5h, 140°C	 **9d**, 55% 24h, 140°C	 **10c**, 34% 15 h, 140°C
 **10d**, 61% 36 h, 140°C	 **11c**, 45%[c] 3 h, 130°C	 **12c**, 85% 5.5 h, 130°C	 **12d**, 75% 17 h, 145°C
 **13c**, 66% 3 h, 130°C	 **13d**, 61% 17 h, 145°C	 **14c, /**[d,e] 2.5 h, 130°C	 **15c, /**[d,e] 2.5 h (10 h), 130°C
 **16c, /**[d] 2.5 h, 130°C	 **17c, /**[d] 2.5 h (10 h), 130°C		

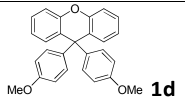
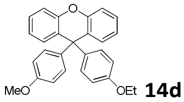
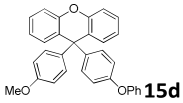
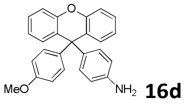
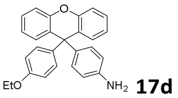
[a] Reaction conditions: Palladium acetate (0.025 mmol), Copper(II) trifluoromethanesulfonate (0.05 mmol), xanthenes **a** (0.5 mmol) in aromatics **b** as solvent (1.5 mL).
[b] Isolated yield after flash chromatography based on **a**.
[c] 0.5g **b** was added.
[d] No product was detected by TLC.
[e] A seal tube was used.

products. The substituted-xanthene derivatives bearing -COPh and -COMe groups were able to react with anisole **1b** to afford the corresponding products in moderate yields (**12c**, **12d**, **13c**, and **13d**). Benzene **12b** and toluend **13b** could not proceed the reaction. Benzonitrile **14b** and nitrobenzene **15b** with electron poor functional groups were not detected the corresponding products. Furthermore, our method can also be successfully applied to synthesize the 9,9-diaryl-xanthenes with different aromatic functional groups. As shown in Table 3, the reaction of 9-aryl-9*H*-xanthenes **c** with aromatics **b** could afford the anticipated 9,9-diaryl-xanthenes **d** in moderate yields (Table 3, entries 1-5). The yields for the 3,4-di-(differently)-substituted xanthenes were not high and it may due to the formation of isomers.

9*H*-Fluorene **4a** also can reacted with anisole **1b** under the reaction condition, but only bis-substituted products 9,9-bis(4-methoxyphenyl)-9*H*-fluorene **17d** was isolated in 51% yield (Scheme 1).

Table 3 Palladium-Copper Catalyzed C(sp^3)-C(sp^2) Bond Cross-Coupling Reaction of 9-Aryl-9*H*-Xanthenes **c** with Phenoxy or Anilino Substrates[a]



Entry	c	b	Product	Yield (%)[b]
1	**1c**	**1b**	 **1d**	62
2	**1c**	**2b**	 **14d**	48
3	**1c**	**3b**	 **15d**	55
4	**1c**	**8b**	 **16d**	52
5	**2c**	**8b**	 **17d**	40
6	**1a**	**1b+2b**[c]	**1d+2d+14d**	53(3:2:4)

[a] Reaction conditions: Palladium acetate (0.025 mmol), Copper(II) trifluoromethanesulfonate (0.05 mmol), 9-(4-

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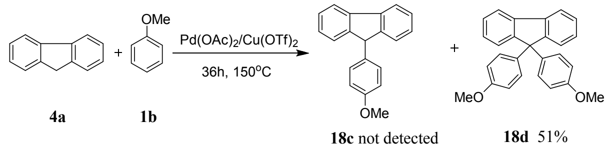
methoxyphenyl)-9*H*-xanthene **1c** (0.5 mmol) in aromatics **b** (1.5 mL) as solvent for 17 h under air.

[b] Isolated yield after flash chromatography based on **c**.

[c] 0.5 mL **1b** and 0.5 mL **2b** was used.



Scheme 1 Reaction of 9*H*-fluorene **4a** with anisole **1b**.

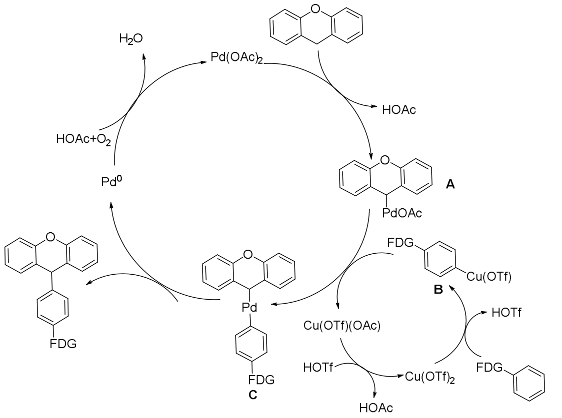


Fig. 3 Plausible mechanism of the reaction.

In the process of our experiment, xanthone was isolated in low yield under the optimal condition (Table 1, entry 7). To gain some insight of the reaction mechanism we used the xanthone to run the reaction and product **1c** was not detected.[17] Therefore, we speculate that the reaction did not proceed the intermediate of xanthone. Then a plausible mechanism which accounts for the palladium-copper cooperatively catalyzed C(sp^3)-C(sp^2) coupling reaction is shown in Figure 3. Firstly, aromatics bearing electron-donating functional groups and xanthenes can be reacted with the metal catalyst Cu($OTf)_2$ and Pd($OAc)_2$ respectively.[18] The obtained intermediates **A** and **B** proceeded the cross-coupling reaction to get the intermediate **C**, which then translated to the final product after the reductive elimination reaction.

In summary, we have developed a novel and efficient palladium-copper cooperatively catalyzed C(sp^3)-C(sp^2) C-H activation and cross-coupling reaction to synthesize 9-aryl-9*H*-xanthene and 9,9-diaryl-xanthene derivatives which are very important to chemical and pharmaceutical industry. The newly-developed co-catalyst system demonstrated moderate yield and good selectivity. We will use this protocol to expand our further research to more aromatics with other functional groups which might be potentially applicable in the pharmaceutical and biochemical areas.

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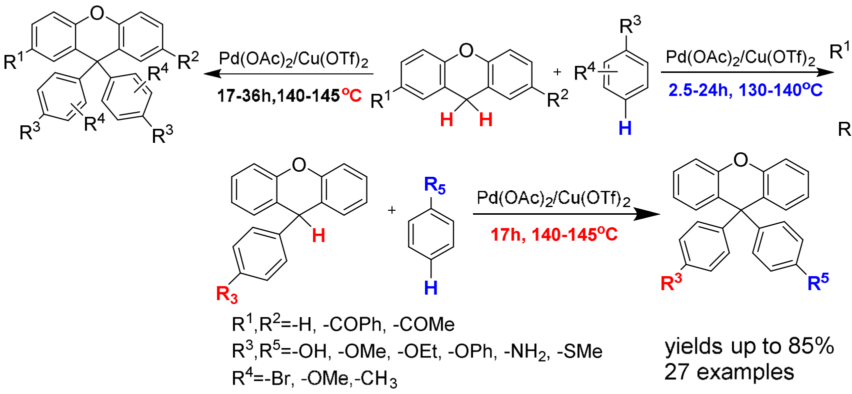
Palladium-Copper Catalyzed $C(sp^3)$-$C(sp^2)$ Bond C-H Activation Cross-Coupling Reaction: Selective Arylation to Synthesis 9-Aryl-9*H*-Xanthene and 9,9-Diaryl-Xanthene Derivatives

Guodong Shen,* Lingyu Zhao, Yichen Wang, Wenfang Xia, Mingsen Yang, Tongxin Zhang*

School of Chemistry and Chemical Engineering, School of Pharmacy, Liaocheng University, Liaocheng 252000, Shandong, PR China



A novel and efficient palladium-copper cooperatively catalyzed $C(sp^3)$-$C(sp^2)$ bond C-H activation cross-coupling reaction has been developed. A series of 9-aryl-9*H*-xanthenes and 9,9-diaryl-xanthenes are selectively synthesized in moderate to good yields by controlling the reaction time and temperature by applying this palladium-copper co-catalysts.