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Palladium Catalyzed C−I and Vicinal C−H Dual Activation of Diaryliodonium Salts for Diarylation: Synthesis of 4,5-Benzocoumarins

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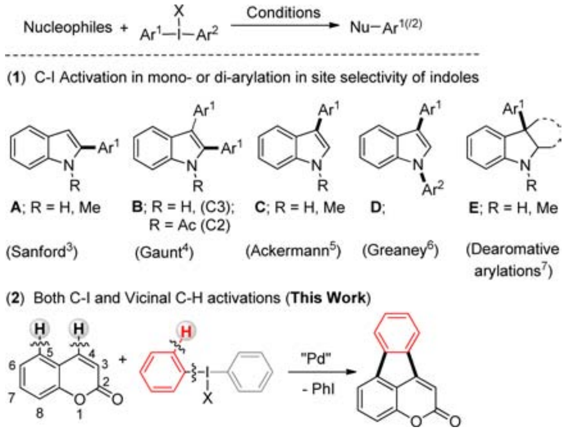
Ⓢ *Supporting Information*

ABSTRACT: With a strategy that makes use of palladium activation of both C−I and vicinal C−H bonds of diaryliodonium salts, an unprecedented approach in diarylation of coumarins was reported. As such, a wide range of 4,5-benzocoumarins with potential fluorescence properties have been synthesized in good yields. A series of experiments suggested that the formation of two carbon−carbon bonds proceeded in a synergetic manner.

Diaryliodonium salts (Ar_2IX), owing to their favorable safety profile, ease of handling, and air and moisture stability, are particularly attractive arylating reagents in organic synthesis.[1] In recent years, a growing interest has been focused on the exploration of their unique reactivities that facilitate novel reaction pathways.[2] An outstanding example is the site-selective arylation of indoles with iodonium salts. By using Ar_2IX, the research groups of Sanford,[3] Gaunt,[4] Ackermann,[5] and Greaney[6] reported arylations at the C2, C3, and/or N-positions selectively of indoles depending on the reaction conditions employed (**A**−**D**, (**1**), Scheme 1). Additionally, dearomative arylations of 3-substituted indoles were achieved by several research groups with iodonium salts (**E**, (**1**), Scheme 1).[7] Besides indoles, the highly electron-deficient nature of Ar_2IX with the excellent leaving ability of aryl iodide enables efficient arylation of various nucleophiles including arenes, alkenes, amides and so on.[1,8] However, in nearly all iodonium arylation reactions to date, the reactivity pattern is limited to only C−I bond activation in the catalytic reaction pathways.[9] Although, transition-metal-catalyzed C−H functionalization of coumarins to synthesize 4-arylcoumarins is well documented,[10] Pd-catalyzed dual or multiple functionalization of coumarin derivatives with coupling substrates has been rarely studied.

Scheme 1. Metal Catalyzed Activations of Diaryliodonium Salts in Arylations



Palladium catalyzed C−H bond activation assisted by hypervalent iodine oxidants to generate C−C bonds directly (termed cross-dehydrogenative coupling reactions) has achieved much progress.[11] Loh and co-workers demonstrated that diphenyliodonium salts could be employed as superior oxidants in the iron-catalyzed oxidative C−H functionalization of activated alkenes.[12] In this context, we therefore hypothesized that diaryliodonium salts could play dual roles in the reaction as both powerful arylation reagents and also the oxidants, thereby leading to the construction of multiple carbon−carbon bonds in an extremely efficient manner. In connection with our continuous interest in developing multiarylations with diaryliodoniums in one operation,[13] we herein reported an unprecedented diarylation of coumarins (2*H*-chromen-2-ones) via simultaneous C−I and vicinal C−H bond activations of diaryliodonium salts for the synthesis of 4,5-benzocoumarins as a new π-expanded coumarin framework[14] ((**2**), Scheme 1).

We began our study using diphenyliodonium triflate (**2a**), coumarin (**1a**) by examining the metal catalysts, solvents, and

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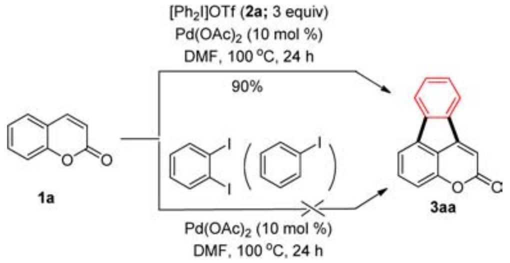
reaction temperature. We were pleased to find that 10 mol % palladium acetate catalyzed the formation of the diarylation product in DMF (dimethylformamide) at 100 °C; **3aa** was obtained in 90% isolated yield with excess diphenyliodonium salts **2a** (3 equiv) after 24 h (see the Supporting Information). The solvent has a determinative effect on the reactivity; an amide scaffold embedding in the solvent structures is necessary according to the solvents screened. It is a remarkable fact that when iodobenzene or 1,2-diiodobenzene was used in replacement of diphenyliodoniums, no reaction occurred under the standard conditions (Scheme 2).

Scheme 2. Diarylation of Coumarin 1a

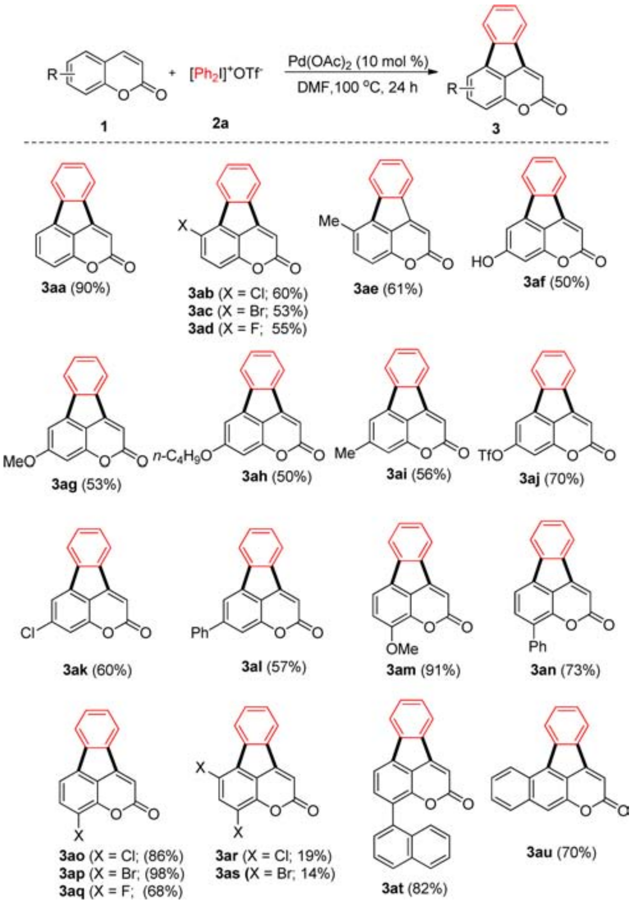


We subsequently examined the structural diversity of various coumarin derivatives by assessing the substitution effect on the coumarin motif. As shown in Scheme 3, substituents including halogens, alkoxy, phenyl, and methyl groups regardless of substituted positions on the aromatic ring of the coumarin nucleus (6-, 7-, or 8-position) are well tolerated in the diarylation. Gratifyingly, the reaction is compatible with bromo and OTf substituents, which allows further functionalizations by using conventional coupling processes. Moreover, coumarins with double substituents on the aromatic ring of **1** also reacted well, albeit in very low yields (19% of **3ar** and 14% of **3as**, Scheme 3). Interestingly, the coumarin derivative **1f** bearing a free hydroxyl group furnished the desired product **3af** in 50% yield without formation of *O*-phenyled products.[15] **3ah** bearing an alkyl chain was prepared in 50% yield with consideration of the solubility in organic solvents which is crucial in material science. Four π-expanded frameworks of **3al**, **3an**, **3at**, and **3au** were readily synthesized in good yields from corresponding substrates with this procedure (Scheme 3).

X-ray diffraction analysis was performed on the product **3aq** whose structure drawing is presented in Figure 1. The results showed cyclization of the phenyl ring to the coumarin framework by forming a five-membered ring with two carbon−carbon bonds. The three-dimensional structure of 4,5-benzocoumarin has demonstrated that the molecule is fairly planar (right, Figure 1).

Next, various diaryliodonium salts were investigated as aryl-transfer partners. As shown in Table 1, both symmetrical and unsymmtrical diaryliodonium salts bearing a wide variety of functionalities, for examples, halogens, methyl, and electron-donating groups such as methoxyl- or an electron-withdrawing group of a trifluoromethyl substituent on the aromatic ring, worked well in the reaction to provide the corresponding 4,5-benzocoumarins. The structure of **3ba** was confirmed by 2D-NMR analyses (see the Supporting Information). It indicated that the carbon site of the C−I bond attacked the 4-position of **1a**. Steric factors severely affected the reactivity, and almost no reaction took place with bis(2,4,6-trimethylphenyl)iodonium triflate **2j** as an arylating reagent. Unsymmetrical aryl-mesityl iodonium reagents in the diarylation of **1a** readily transferred a broad range of *meta*- and *para*-substituted aryl rings to the desired products (Table 1, entries 10−13). It is noteworthy to mention that when the unsymmetrical salt of [(4-MeOC$_6$H$_4$)-(4-NO$_2$C$_6$H$_4$)I]OTf was used in this protocol, **3fa** was formed in 84% yield exclusively (Table 1, entry 14).

Scheme 3. Scope of Diverse Coumarins in Diarylation[a,b]



[a]Unless otherwise specified, reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol, 3.0 equiv), Pd(OAc)$_2$ (0.05 mmol), and DMF (2.0 mL) at 100 °C for 24 h. [b]Isolated yield.

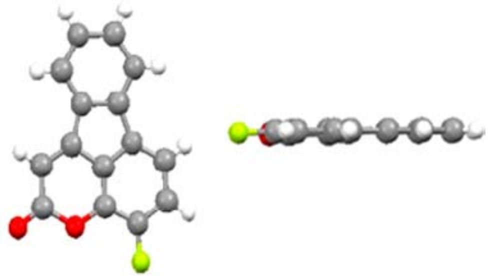


Figure 1. X-ray derived structural views of **3aq**.

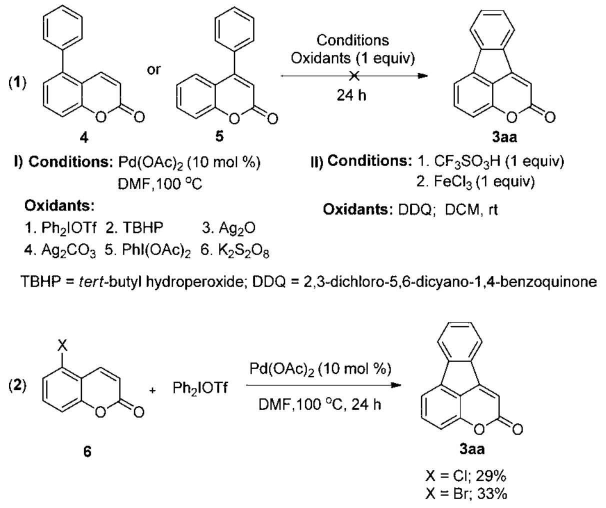
To gain further insight into the mechanism, we prepared monophenylated coumarin derivatives **4** and **5** (Scheme 4). Palladium-catalyzed intramolecular aryl−aryl dehydrogenative coupling reactions of **4** and **5** were conducted in the presence of a variety of oxidants (I of (**1**), Scheme 4). No desired product of **3aa** was formed in these reactions. Moreover, we performed the oxidative aromatic couplings (Scholl reaction) of **4** and **5** mediated by a strong Brønsted acid of TfOH or a

Table 1. Scope of Diverse Iodonium Salts in Arylation[a]

entry	Ar^1(Ar^2)	X	product	yield[b] (%)
1	(4-BrC$_6$H$_4$)$_2$	OTf	**3ba**	58
2	(4-FC$_6$H$_4$)$_2$	OTf	**3ca**	65
3	(4-ClC$_6$H$_4$)$_2$	OTf	**3da**	72
4	(4-^{t}BuC$_6$H$_4$)$_2$	OTf	**3ea**	88
5	(4-MeOC$_6$H$_4$)$_2$	OTf	**3fa**	95
6	(4-MeC$_6$H$_4$)$_2$	OTf	**3ga**	87
7	(3-MeC$_6$H$_4$)$_2$	OTf	**3ha**	90
8	(4-CF$_3$C$_6$H$_4$)$_2$	BF$_4$	**3ia**	88
9	(Mesityl)$_2$	OTf	**3ja**	0
10	3-MeC$_6$H$_4$(Mesityl)	OTf	**3ha**	53
11	4-BrC$_6$H$_4$(Mesityl)	OTf	**3ba**	54
12	4-ClC$_6$H$_4$(Mesityl)	OTf	**3da**	30
13	4-MeC$_6$H$_4$(Mesityl)	OTf	**3ga**	62
14	4-MeOC$_6$H$_4$(4-NO$_2$C$_6$H$_4$)	OTs	**3fa**	84

[a] Unless otherwise specified, reaction conditions: **1a** (0.5 mmol), iodonium salt (1.5 mmol, 3.0 equiv), Pd(OAc)$_2$ (0.05 mmol) and DMF (2.0 mL) at 100 °C for 24 h. [b] Isolated yield.

Scheme 4. Palladium Catalyzed Coupling Reactions of 4, 5, and 6



Lewis acid of FeCl$_3$ with additional oxidants of DDQ; however, no reaction occurred in these cases (II of (**1**), Scheme 4). These results implied that the cleavage of C−I/C−H bonds and formation of C−C bonds proceeded in a simultaneous manner. In contrast, when 5-halogen (Cl and Br) substituted coumarins **6** were subjected to the standard conditions, **3aa** was obtained in 29% and 33% yields, respectively. Although it is premature to draw a conclusive mechanism at this stage, the results disclosed above suggested a possible pathway involving double Pd(II/IV) cycles.[16] We therefore proposed a catalytic mechanism as shown in Figure 2. The reaction is initiated by cleavage of the hypervalent iodine−aryl bond to generate palladium species **7**. On the other hand, iodonium species could act as Lewis acids in association with an activation of the carbonyl group of coumarin (**1a**).[17] Oxidative attack at C4 with a synergetic activation of the vicinal C−H bond of coumarin **1a** formed arylpalladacycle **8** in strongly coordinating solvent such as DMF.[18] Reductive elimination forges one aryl−aryl bond. Second oxidative addition of **9** with the assistance of [Ph$_2$I]OTf gave palladium(IV) complex **10**, another reductive elimination regenerate the catalyst (**7**) with the formation of two carbon−carbon bonds of **3aa**.

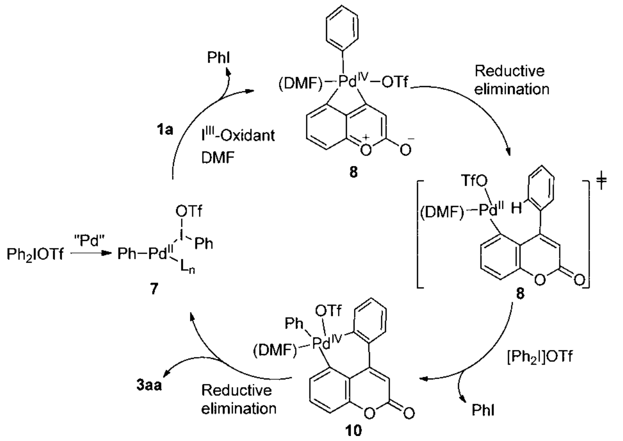


Figure 2. Proposed mechanism for Pd(OAc)$_2$ catalyzed diarylation of coumarin.

In summary, we have developed a palladium-catalyzed diarylation of coumarins by using diaryliodonium salts in the synthesis of 4,5-benzocoumarin derivatives. This method features simultaneous C−I and vicinal C−H bond activations of diaryliodonium salts. More importantly, the advantages of the present reaction system are as follows: (1) no ligands, (2) no assisted groups, (3) no additional oxidants, and (4) direct formation of two C−C bonds. The application of this method in preparation of the relevant pigments is being actively explored. Further studies on the mechanism of this reaction are also underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02938.

Conditions optimization, experimental details and characterization data (PDF)
Crystallographic data for the **3aq** (CIF)

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Notes

The authors declare no competing financial interest.

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