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Palladium-Catalyzed Site-Selective Benzocylization of Aromatic Acids with *o*-Fluoro-Substituted Diaryliodonium Salts toward 3,4-Benzocoumarins

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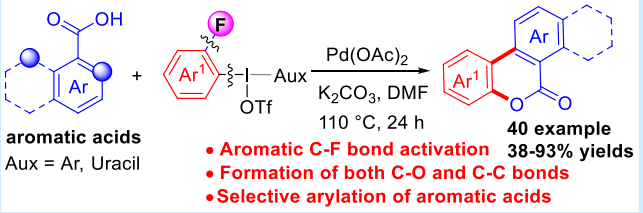
ABSTRACT: By using 2-fluoro-substituted diaryliodonium salts, a novel benzocylization has been accomplished for the synthesis of 3,4-benzocoumarin derivatives via a cascade of *ortho*-arylation and defluorination in the presence of palladium catalysts. The reaction exhibits a broad compatibility of readily available aromatic acids with an excellent level of site-selectivity. Mechanistic investigations revealed a unique reactivity of carboxylic acid directed arylation by followed nucleophilic substitution of aromatic fluoride in the present system.



Coumarin is a widespread structural motif with the benzopyrone congener that possesses a variety of biological properties and peculiar physicochemical features.[1] In particular, the extension of coumarin π-systems has been extensively investigated due to their possible applications in terms of energy and electron transfer systems as well as pharmaceutical agents, thereby significantly accelerating the development of synthetic methodologies.[2] As a consequence, a number of benzocoumarins have been discovered with emphasis on their photochemistry, and the optical property of benzocoumarins was altered by the number and position of attached aromatic rings (Scheme 1a).[3] As comprehensively summarized by Ahn and Gryko in a review article, the most frequently employed approaches toward the π-expanded coumarin skeleton mainly rely on the classical strategies such as Pechmann reaction, Knoevenagel condensation, or metal-catalyzed cyclizations.[4] However, the scope with respect to the substrates reported for each method is notably limited and often focuses on phenolics or aromatic aldehydes. With this rationale, synthetic endeavors by utilizing feedstock chemicals of arylcarboxylic acids are necessary in the development of synthetic approaches for direct access to benzocoumarin derivatives.

Recently, transition-metal-catalyzed coupling reactions have been demonstrated as a powerful tool for the incorporation of an aromatic unit. In sharp contrast, palladium-catalyzed efficient formation of multiple carbon−carbon bonds in one pot proved to be much more challenging, probably owing to the bonding angle and steric constraints; only a few examples have been disclosed so far.[5] In this regard, the research group of Itami conceptualized a one-step annulative π-extension (APEX) reaction of polycyclic aromatics for rapid production of various π-extended aromatics, in which extra oxidants and additives were generally necessary.[6] Alternatively, diaryliodonium salts in high oxidation states can play dual roles in the reactions as both arylating reagents and oxidants, allowing diarylations in an extremely efficient manner.[7] Meanwhile, the incorporation of fluoroaryl motifs into the diaryliodonium salts has resulted in novel synthetic methodologies as well as pharmacological studies.[8] In connection with our interest in exploring dual activation with diaryliodonium salts (Scheme 1b),[9] we herein described an unprecedented benzocylization of aromatic acids via palladium-catalyzed C−I and vicinal C−F bond activations in the synthesis of 3,4-benzocoumarins, in which the reactive site of aromatic acids was selective at the *ortho*-position of the carboxylic acid with the formation of both C−O and C−C bonds (Scheme 1c). Of note, activation of aromatic C−F bonds by transition-metal complexes is very attractive but a difficult topic due to the strong bonding energy of C−F bonds.[10] Reported reactions involving metal-catalyzed C−F activation were generally focused on perfluoroaromatic systems or several fluorinated nitrobenzenes.[11] The functionalization of the C−F bond adjacent to readily removable cationic aryl iodide moieties with the highly electron-deficient nature is, to the best of our knowledge, unknown. It is noteworthy that the 3,4-benzocoumarin framework is conserved in many active pharmaceutical agents in the treatment of various diseases such as cancer and neovascular age-related

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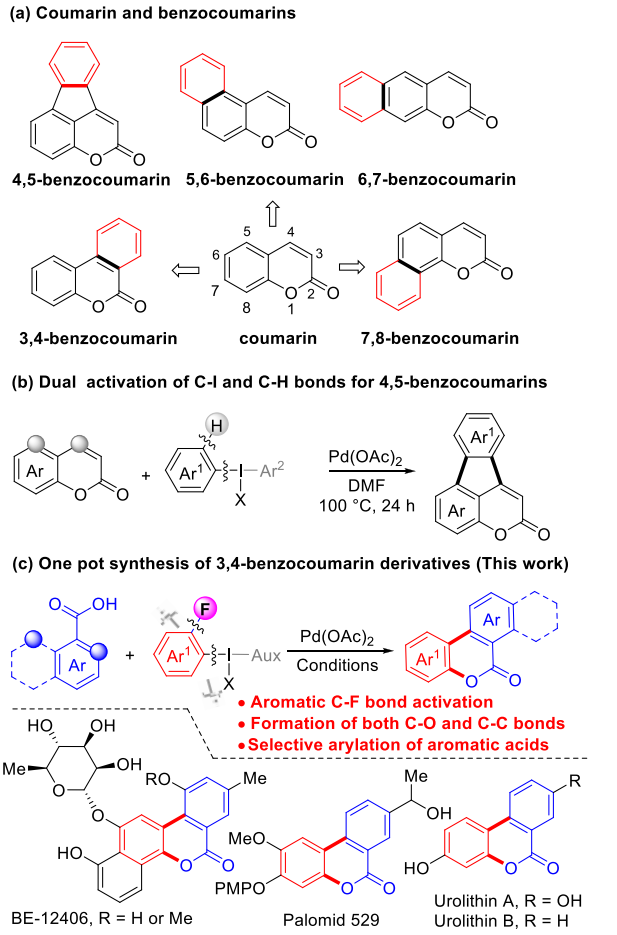
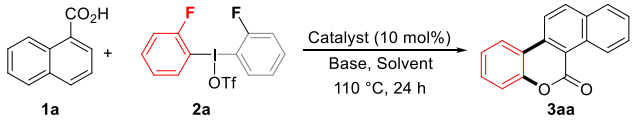
Scheme 1. Benzocoumarins and Novel Reactivity Pattern of *Ortho*-Functionalized Diaryliodonium Salts



macular degeneration and in prolonging lifespan (Scheme 1c).[12]

To begin our studies, we chose 1-naphthoic acid (**1a**) as the model substrate, the reaction was performed with 1.5 equiv of 2-fluoro-substituted diaryliodonium salts (**2a**) in the presence of $Pd(OAc)_2$ (10 mol %) as catalyst and 1.5 equiv of K_3PO_4 in DMF at the temperature of 110 °C. To our delight, 3,4-naphthocoumarin (**3aa**) was obtained in 65% yield after 24 h (Table 1, entry 1). However, no desired product was observed with total recovery of **1a** when K_2HPO_4 was employed as the base. We then examined the influence of various bases such as K_2CO_3, Na_2CO_3, Cs_2CO_3, NaOMe, KOH and even the organic base of dimethylaminopyridine (DMAP) on the reaction (Table 1, entries 3−8) and were pleased to find that K_2CO_3 can increase the yield of **3aa** to 72% (Table 1, entry 3). However, DMAP was proved to be ineffective (Table 1, entry 8). Then, we increased the amount with 3.0 equiv of **2a**, and **3aa** was obtained in an isolated yield of 78% (Table 1, entry 9). TEMPO as a radical scavenger was used to trap aryl radicals in the reaction, in which **3aa** were still furnished in 70% yield. As a result, the reaction did not generate free radicals as the reactive intermediates. The reaction on a 1 mmol scale gave **3aa** in a comparable yield of 75%. In order to investigate the solvent effect, polar solvents were preferentially employed with a consideration of avoiding aryl ester formation by *O*-arylation.[13] The solvents of dimethyl sulfoxide (DMSO), 1,4-dioxane, *N*-methyl-2-pyrrolidione (NMP), and *tert*-butyl

Table 1. Screening of Reaction Conditions for Palladium-Catalyzed Benzocyclization of 1-Naphthoic Acid[a]



entry	solvent	base	catalyst	yield of **3aa**[b] (%)
1	DMF	K_3PO_4	$Pd(OAc)_2$	65
2	DMF	K_2HPO_4	$Pd(OAc)_2$	0
3	DMF	K_2CO_3	$Pd(OAc)_2$	72
4	DMF	Na_2CO_3	$Pd(OAc)_2$	50
5	DMF	Cs_2CO_3	$Pd(OAc)_2$	53
6	DMF	NaOMe	$Pd(OAc)_2$	6
7	DMF	KOH	$Pd(OAc)_2$	31
8	DMF	DMAP	$Pd(OAc)_2$	0
9[c−e]	DMF	K_2CO_3	$Pd(OAc)_2$	78 (70, 75)
10	DMSO	K_2CO_3	$Pd(OAc)_2$	0
11	dioxane	K_2CO_3	$Pd(OAc)_2$	30
12	NMP	K_2CO_3	$Pd(OAc)_2$	30
13	*t*-BuOH	K_2CO_3	$Pd(OAc)_2$	11
14	DMF	K_2CO_3	$Pd(TFA)_2$	50
15	DMF	K_2CO_3	$Pd(dba)_2$	0
16	DMF	K_2CO_3	$[Pd(PPh)_3]_2Cl_2$	0

[a]Reaction conditions unless specifically noted: **1a** (0.4 mmol), **2a** (0.6 mmol), base (1 equiv), and catalyst (10 mol %) in solvent (4 mL) at 110 °C for 24 h. [b]Isolated yields were obtained after purification with column chromatography. [c]3 equiv of **2a** was used. [d]TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl, 10 equiv) was used as a radical scavenger; **3aa** was obtained in 70% yield. [e]The reaction on 1 mmol scale gave **3aa** in 75% yield.

alcohol were screened, and no better yield was achieved (Table 1, entries 10−13). We also examined the palladium catalysts, it was found that $Pd(OAc)_2$ was the best choice (Table 1, entries 14−16).

With the optimized reaction conditions in hand, we started to investigate the structural diversity of various substituted aromatic carboxylic acids toward a wide range of coumarin-cored polyaromatics by assessing the substitution effect (Scheme 2). First, substrates of substituted 1-naphthoic acids with a broad range of substituents on the naphthalene unit were examined under the standard conditions. As shown in Scheme 2, electron-neutral, -donating, or -withdrawing substituents were generally well-tolerated, affording the desired products **3ab**−**3ag** in moderate to good yields of 45−91%, and **3ae** bearing bromine is a useful synthon by further cross coupling reaction in the synthesis of functional materials. One notable feature is that the diarylation exhibits excellent regioselectivity with naphthoic acid derivatives (1-naphthoic acids possess more reactive site at α-position in the reported palladium-catalyzed protocols).[14] We next turned our attention to the heterocyclic framework of aromatic acids; fortunately, the reactions proceeded smoothly to afford the desired products of **3ah** in 45% yield and **3ai** in 50% yield, respectively. It is worth mentioning that coumarin-cored polyaromatics formed by palladium-catalyzed annulative fusion successfully reacted with pyrene-1-carbocylic acid or 1-anthroic acid to give **3aj** or **3ak** in good yield (**3aj**, 67% yield; **3ak**, 63% yield), which could be used for π-extended material design. Furthermore, simple benzoic acid was employed in this procedure, it was pleased to find that 3,4-benzocoumarin (**3al**) was furnished in 53% yield.[15] We therefore studied the

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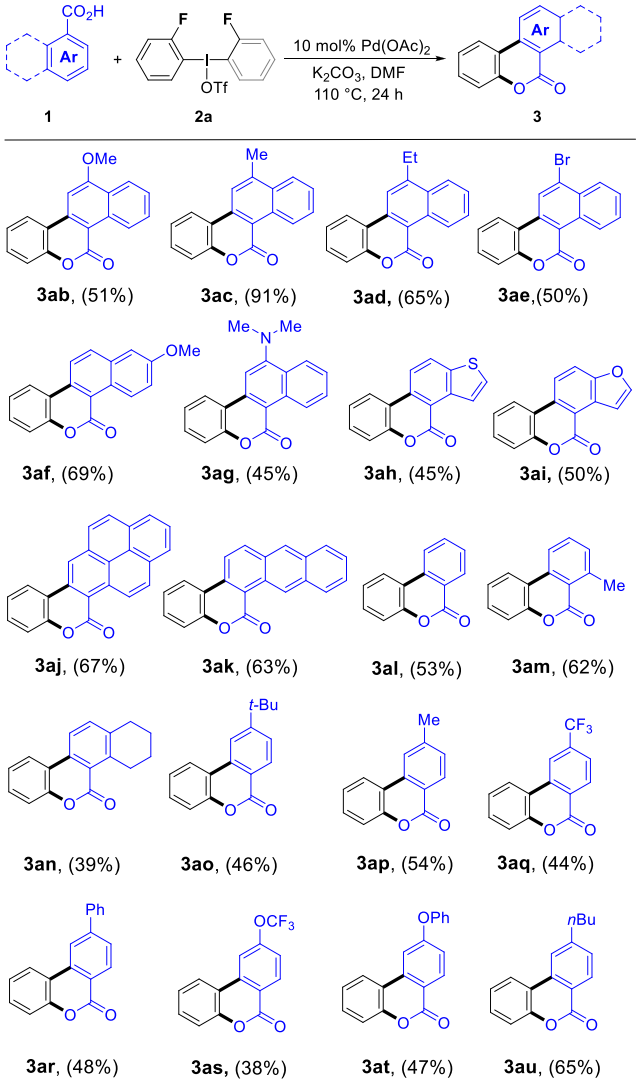
Scheme 2. Scope of Palladium-Catalyzed Benzocyclization of Aromatic Acid with 2a[a,b]

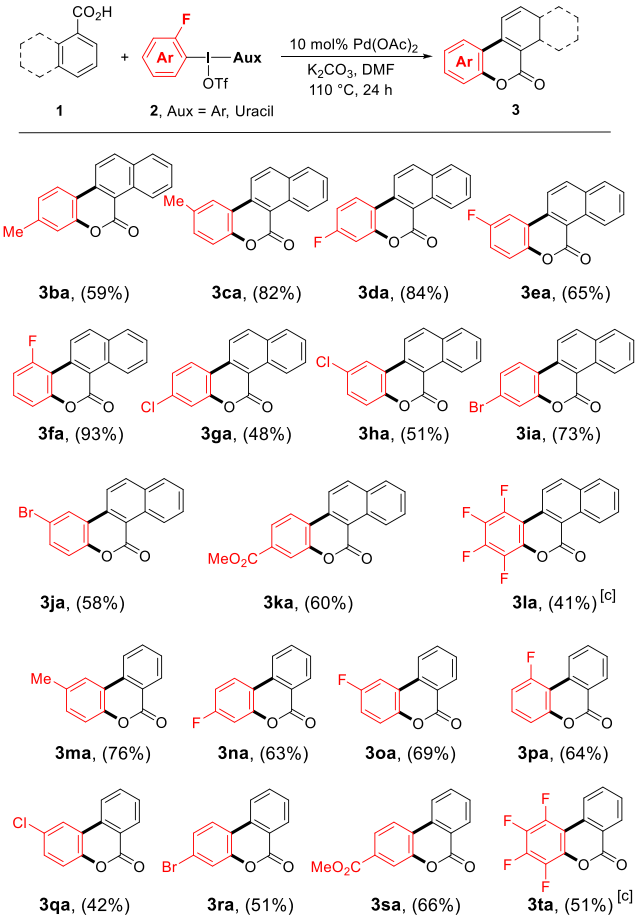


[a]Reaction conditions: **1** (0.4 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (10 mol %), and K_2CO_3 (0.4 mmol) in 4 mL of DMF at 110 °C for 24 h. [b]Isolated yields were obtained after purification with column chromatography.

reactivity of a range of substituted aryl carboxylic acids, and the desired products **3am**−**3au** bearing various functional groups such as alkyl, trifluoromethyl, trifluoromethoxy, phenyl, and phenoxyl were afforded in 38−65% yields in which the alkyl groups were responsible for addressing the key issue of low solubility of these coumarin-based polyaromatics in common organic solvents.

Next, we turned our attention to the scope of diaryliodonium salts as the reaction partner in this protocol of dual activation with C−F bond cleavage. A family of *ortho*-fluorinated iodonium salts was prepared by classic synthetic approaches.[13] As shown in Scheme 3, by using 1-naphthoic acid or benzoic acid, a wide range of symmetrical 2-fluoro-substituted diaryliodonium triflates with various substituents were readily converted to the corresponding products, and **3ba**−**3ta** were furnished in yields of 42−93% with excellent regioselectivity. Notably, functional groups including chlorine, bromine, and ester groups were readily tolerated; these

Scheme 3. Scope of Fluoro-Substituted Diaryliodonium Salts in Benzocyclization of 1-Naphthoic Acid and Benzoic Acid[a,b]



[a]Reaction conditions: **1** (0.4 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (10 mol %), and K_2CO_3 (0.4 mmol) in 4 mL of DMF at 110 °C for 24 h. [b]Isolated yields were obtained after purification with column chromatography. [c]Unsymmetrical aryluracil iodonium salt (**2l**) was used.

products possess a useful feature with respect to further synthetic manipulations. Moreover, an unsymmetrical aryluracil iodonium salt (**2l**) bearing a pentafluorophenyl motif was readily prepared with a modified literature procedure.[16] Compound **2l** was subjected the reaction with 1-naphthoic acid or benzoic acid under the standard conditions. Surprisingly, the 3,4-benzotetrafluorocoumarins were exclusively formed in 41% (**3la**) and 51% (**3ta**) yields, respectively.

Fortunately, 3,4-benzocoumarin **3ka** was successfully determined by single-crystal X-ray diffraction analysis. As presented in Figure 1, crystallographic studies of **3ka** suggested the unambiguous structure possessing fairly planar conformation in which the six-membered lactone ring was cyclized by a carbon−carbon bond and a carbon−oxygen bond. Furthermore, the regioselective formation of C−C bond originated from the cleavage of the C−I bond of the diaryliodonium salt followed by a C−O bond formation from defluorination, which suggested the carboxylic acid was the directing group. As a result, substituted 1-naphthoic acids were fused with a phenyl ring with two chemical bonds by C−H functionalization as well as the C−F bond activation, thereby leading to the highly efficient construction of benzocoumarin framework.

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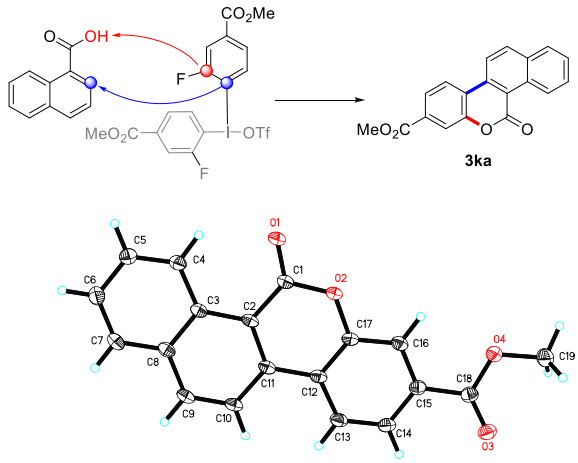
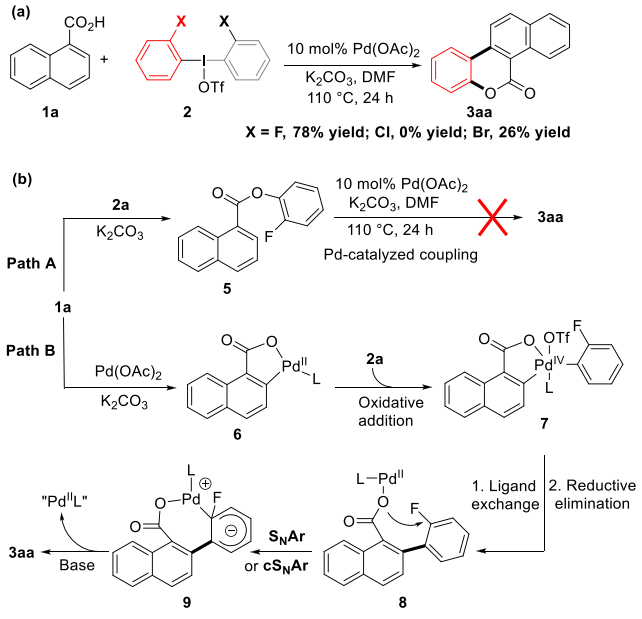


Figure 1. Bond formation and X-ray-derived structural views of **3ka** (carbon atoms in this view are depicted with ellipsoids at the 30% probability level).

To further evaluate the reaction mechanism experimentally, 2 chloro- and 2-bromodiaryliodonium salts were also incorporated in the reaction to compare their reactivity. As shown in Scheme 4a, the bromo-substituted iodonium salt led

Scheme 4. Comparison between Aromatic C−F, C−Cl, and C−Br Bonds and the Proposed Mechanism



to **3aa** in 26% yield, while the chloro substrate resulted in no reactivity. To further understand the forming order of the C−O bond and C−C bond, *O*-arylation of 1-naphthoic acid was easily achieved with generation of **5** according to Olofsson's procedure.[17] We performed the reaction of **5** under the standard conditions; however, no desired product of **3aa** was observed. We therefore proposed a catalytic mechanism as described in Scheme 4b. The reaction was initiated by acid-assisted formation of a palladacycle intermediate (**6**) with C−H activation. Oxidation of **6** afforded the Pd(IV) complex (**7**) with **2a**. Then a ligand exchange with subsequently reductive elimination gave intermediate **8**, which is consistent with the site-selectivity. Finally, palladium-assisted intramolecular nucleophilic substitution (S_NAr type) of **8** with C−F bond activation led to Meisenheimer complex **9** in accordance with the literature.[10a,11a,b] Intermediate **9** in the presence of bases afforded the desired product **3aa** with regeneration of a palladium catalytic species. An alternative pathway might proceed by a concerted nucleophilic aromatic substitution reaction (cS_NAr) rather than the classical two-step mechanism of traditional S_NAr.[18]

In summary, we have developed a one-pot protocol for synthesis of 3,4-benzocoumarin derivatives from readily accessible substituted 1-naphthoic or benzoic acids. The reaction proceeded in the presence of palladium catalysts with good functional group tolerance in which two chemical bonds were formed in a cascade of *ortho*-arylation and nucleophilic substitution of aryl fluoride in a single operation. Given the current availability of a large number of aromatic acids as feedstock substrates, we view the current method to be a highly useful platform for efficiently accessing to the benzocoumarin pharmacophores as well as optoelectronic materials. Further investigation of the detailed reaction mechanism and optimization of reaction conditions to achieve a broader scope is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01577.

Experimental procedures, characterization data and spectra of new compounds (PDF)

Accession Codes

CCDC 2000929 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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