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Authors	Ke Jiang, Cheng Pan, Limin Wang, Hao-Yang Wang and Jianwei Han
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ORCID® iDs	Jianwei Han - https://orcid.org/0000-0002-8354-5684

Ortho-Ester-Substituted Diaryliodonium Salts Enabled Regioselective Cyclization of Naphthols toward 3,4-Benzocoumarins

Ke Jiang[1], Cheng Pan[1], Limin Wang[1], Hao-Yang Wang,*[2] and Jianwei Han*[1]

Address: [1]Key Laboratory for Advanced Materials and Feringa Nobel Prize Scientist Joint Research Center, Department of Fine Chemistry and Institute of Fine Chemicals, School of Chemistry and Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, P. R. China

Email: Jianwei Han* – jianweihan@ecust.edu.cn;

[2]National Center for Organic Mass Spectrometry in Shanghai, Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China.

Email: Hao-Yang Wang* – haoyangwang@sioc.ac.cn

* Corresponding author

Abstract

Cyclic annulation involving diaryliodonium salts is an efficient tool for the construction of two or more chemical bonds in a one-pot process. *Ortho*-functionalized diaryliodonium salts have showcased distinct reactivity in the exploration of benzocyclization or arylocyclization. With this strategy of ortho-ester substituted diaryliodonium salts, herein, we utilized a copper catalyst to activate the C-I bonds of diaryliodonium salts in the generation of aryl radicals, thus resulting in an annulation

reaction with naphthols and substituted phenols. This approach yielded a diverse array of 3,4-benzocoumarin derivatives bearing various substituents.

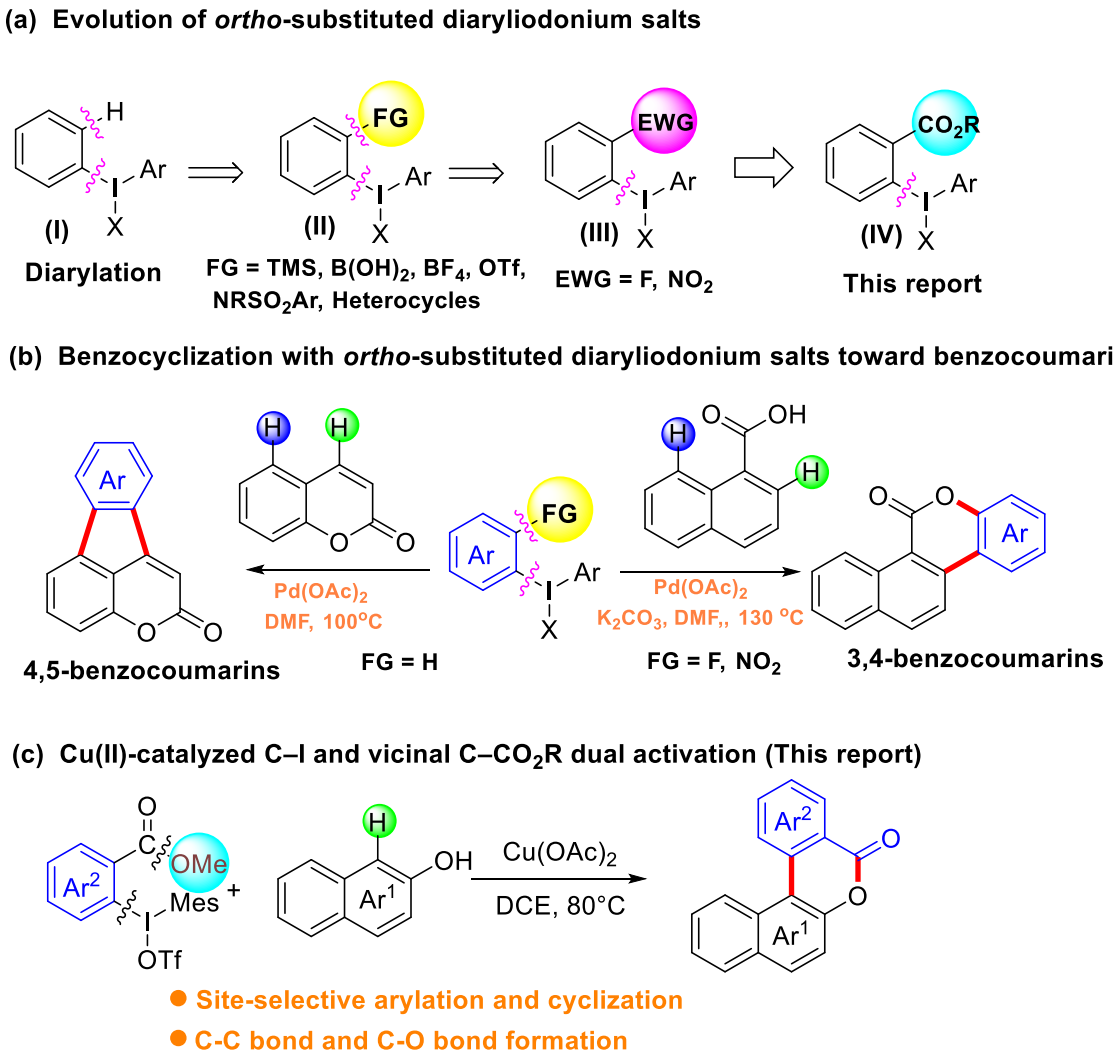
Keywords

Diaryliodonium salts; Annulation; Arylocyclization; Naphthol; 3,4-Benzocoumarin.

Introduction

Diaryliodonium salts as electrophilic reagents have attracted significant attention in the field of organic synthesis owing to their efficiency and selectivity.[1] Particularly, they have been employed in benzocyclization and arylocyclization reactions, enabling intramolecular cyclization by forming aromatic or heterocyclic ring as a part of cyclic structures.[2] In these reactions, the dual activation of C-I bond and vicinal C-H bonds/functional groups features a distinct advantage, facilitating the formation of two or more chemical bonds in a step-economic manner.[3] In a prior study, we reported a palladium-catalyzed activation of both C-I bond and the adjacent C-H bond of diaryliodonium salts in the formation of 4,5-benzocoumarin derivatives efficiently, expanding the benzocoumarin family (Scheme 1, (b)).[4] Recently, ortho-functionalized diaryliodonium salts, due to their coordinating and electrophilic effects, have exhibited unique reactivity and chemoselectivity.[5] As such, a wide range of functional groups including trimethylsilyl group, boronic acid, trifluoroborate moiety, trifluoromethanesulfonate, aryl sulfonamides, heterocycles, have been incorporated into the ortho-position of diaryliodonium structures.[6] Ortho-trimethylsilyl or boronic acid substituted diaryliodonium salts can serve as aryne precursors. Ortho-trifluoroborate substituted diaryliodonium salts furnished iodonium zwitterions as bifunctional reagents.[7] Additionally, ortho-trifluoromethanesulfonate, N-sulfonyl, or tosylmethylene-substituted diaryliodonium salts can undergo intramolecular aryl migrations.[8] More recently, we explored the reactivity of ortho-functionalized

diaryliodonium salts containing electron-withdrawing groups (EWGs) such as fluorine and nitro groups.[9] These ortho-substituted diaryliodonium salts proceeded the selective benzocyclizations with aromatic acids, leading to 3,4-benzocourmain skeletons in the presence of palladium catalysts (Scheme 1, (b)). Furthermore, Olofsson and colleagues described an unprecedented reaction pathway using ortho-fluoro-substituted diaryliodonium salts bearing strong electron-withdrawing groups, leading to novel diarylations of N-, O-, and S-nucleophiles.[10] Building on our great interest in ortho-functionalized diaryliodonium salts and their dual activation capabilities, we sought to incorporate carboxylic ester groups into the structures of ortho-substituted diaryliodonium salts to explore their properties and reactivity. Our previous investigations demonstrated the ability of diaryliodonium salts for selective mono-arylation of 2-naphthols.[11] In this context, we embark on a strategy to modify the neighboring position of the diaryliodonium salt with ester group, presenting a novel copper-catalyzed regioselective benzocyclization of naphthols and substituted phenols. This method represents an efficient approach to access 3,4-benzocoumarin derivatives (Scheme 1, (c)).



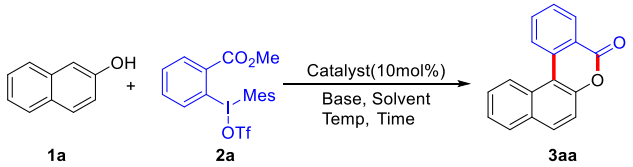
Scheme 1. Arylations of Aromatics and Reaction Patterns of ortho-Functionalized Diaryliodonium Salts

Results and Discussion

To begin the study, we used 2-naphthol (**1a**) and 1.1 equivalent of o-methylformate-diaryliodonium salts (**2a**) as template substrates. The reaction was performed in the presence of 10 mol% $Cu(OTf)_2$ and 1.0 equivalent of K_2CO_3 in DCE at the temperature of 80 °C. To our delight, the reaction afforded 3,4-benzocoumarin (**3aa**) in a 27% yield (Table 1, entry 1). The structure of **3aa** was confirmed through NMR and mass spectra analysis. Subsequently, we embarked on screen various bases such as Na_2CO_3, Cs_2CO_3, KOH, NaO^tBu, LiHMDS, and DMAP (Table 1, entries 2-7).

Regrettably, none of these bases led to improved yields. However, it was pleased to find that the reaction yield was increased to 50% in the absence of any base (Table 1, entry 8). Further investigation involved assessing the influence of various solvents including dimethyl sulfoxide (DMSO), N,N-Dimethylformamide (DMF), toluene , acetic acid (AcOH) and water (Table 1, entries 9-13). However, polar solvents of AcOH and H_2O were proved to be unsuitable for this reaction. For catalysts, we found that $Cu(OAc)_2$ gave the best results (Table 1, entries 15-18). Finally, the reaction temperature and time were optimized, **3aa** was produced in 61% yield at the temperature of 80 °C after 3 hours (Table 1, entries 9,14).

Table 1. Optimization of Reaction Conditions.[a]



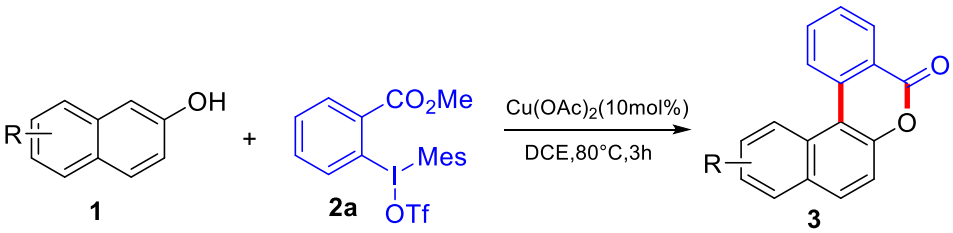
Entry	Solvent	Base	Catalyst	**3aa** (%)[b]
1	DCE	K_2CO_3	$Cu(OTf)_2$	27
2	DCE	Na_2CO_3	$Cu(OTf)_2$	25
3	DCE	Cs_2CO_3	$Cu(OTf)_2$	16
4	DCE	KOH	$Cu(OTf)_2$	24
5	DCE	DMAP	$Cu(OTf)_2$	26
6	DCE	NaO^tBu	$Cu(OTf)_2$	35
7	DCE	LiHMDS	$Cu(OTf)_2$	30
8	DCE	/	$Cu(OTf)_2$	50
9[c,d]	DMSO	/	$Cu(OTf)_2$	45(40)
10	DMF	/	$Cu(OTf)_2$	23
11	Toluene	/	$Cu(OTf)_2$	10
12	AcOH	/	$Cu(OTf)_2$	0
13	H_2O	/	$Cu(OTf)_2$	0
14[e]	DCE	/	$Cu(OTf)_2$	48
15	DCE	/	$Cu(OAc)_2$	61
16	DCE	/	$Pd(OAc)_2$	22
17	DCE	/	$PdCl_2$	40
18	DCE	/	AgOAc	20

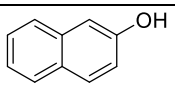
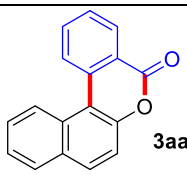
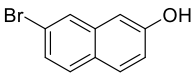
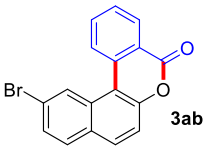
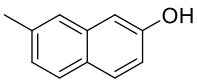
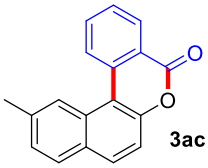
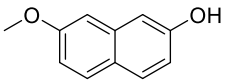
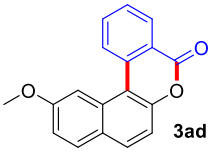
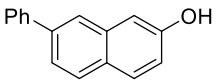
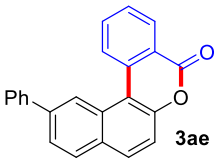
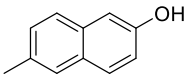
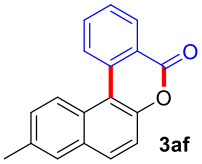
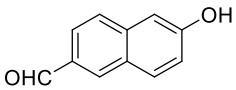
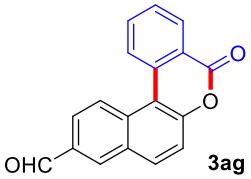
[a]Reaction conditions: **1a** (0.3 mmol, 1 equiv.), **2a** (0.33 mmol, 1.1 equiv.), base (0.3 mmol; 1 equiv.), catalyst (10 mol%), solvent (2 mL), 80 ^oC, 3 hours. [b]Isolated yields were obtained after purification with column chromatography. [c]The reaction

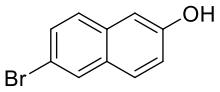
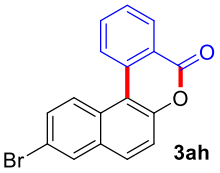
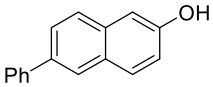
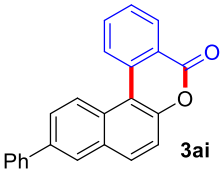
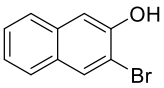
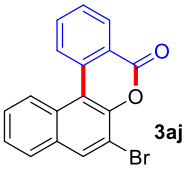
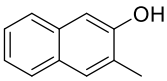
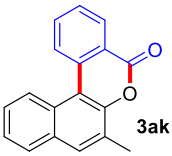
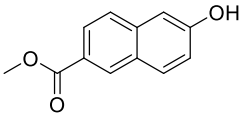
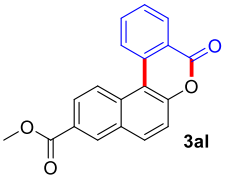
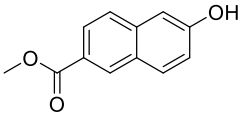
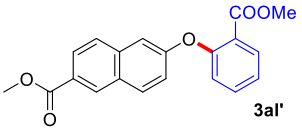
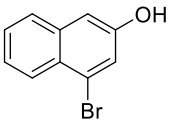
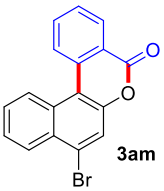
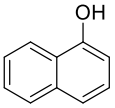
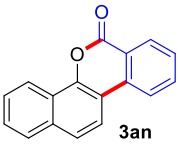
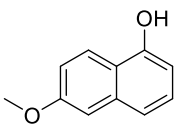
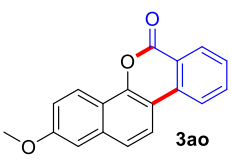
temperature was 110 °C. [d]The reaction temperature was 130 °C. [e]The reaction temperature was 80 °C. [f]The reaction was quenched after 12 hours.

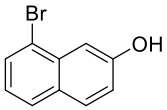
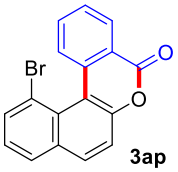
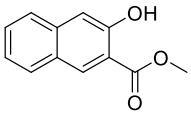
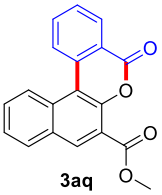
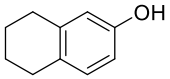
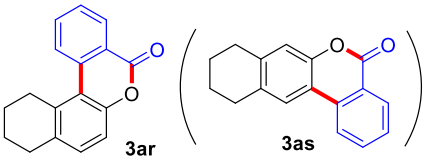
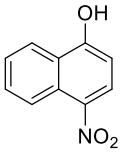
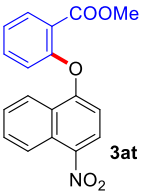
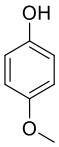
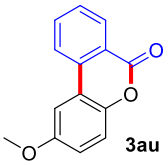
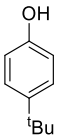
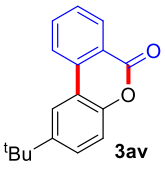
With the optimized reaction conditions in hand, we started to explore the substrate scope of the cyclization to construct a variety of 3,4-benzocoumarin derivatives. Our investigations commenced with naphthol (**1**), and the results are presented in Table 2. Various substituted naphthols with a broad range of substituents on the naphthalene unit were well tolerated in the reaction, affording the corresponding products **3aa**–**3aq** in generally moderate to good yields (22–83%) (Table 2, entries 1-18). These substituents included halogen (Br), methyl, phenyl, aldehyde, ester, methoxy, and tert-butyl groups, all of which were compatible with the reaction conditions. Notably, compounds **3ab**, **3ah**, **3aj**, **3am** and **3ap** bearing bromine are very useful modules for the synthesis of functional materials via cross-coupling reactions. Next, we extended our investigation to 1-naphthol in this reaction, and found that the arylation of 1-naphthol was achieved selectively at the C-2 position. The cascade cyclization resulted in the corresponding products **3an** and **3ao** in in yields of 49% and 40%, respectively (Table 2, entries 15 and 16). When 5,6,7,8-tetrahydro-2-naphthol was subjected to the reaction, we obtained products **3ar** and **3as** as a mixture (40% and 10% yield, respectively, Table 2, entries 19). However, when naphthol bearing a strong electron-withdrawing group (such as a nitro group) in the para position, the corresponding product could not be obtained, but gave a O-arylated product of **3at** (Table 2, entry 20). Apart from naphthol, we also tested substituted phenols under the standard conditions, the corresponding products of **3au** and **3av** were produced in 34% and 39% yields, respectively, in which methoxyl and tert-butyl group were located in the para position of the hydroxyl group (Table 2, entries 21 and 22).

Table 2. Scope of Naphthols and Phenols for 3,4-Benzocoumarins [a,b]



Entry	1	Product	Yield (%)[b]
1		 3aa	61
2		 3ab	63
3		 3ac	80
4		 3ad	77
5		 3ae	26
6		 3af	31
7		 3ag	28

8		 3ah	54
9		 3ai	25
10		 3aj	22
11		 3ak	49
12		 3al	48
13		 3al'	20
14		 3am	83
15		 3an	49
16		 3ao	40

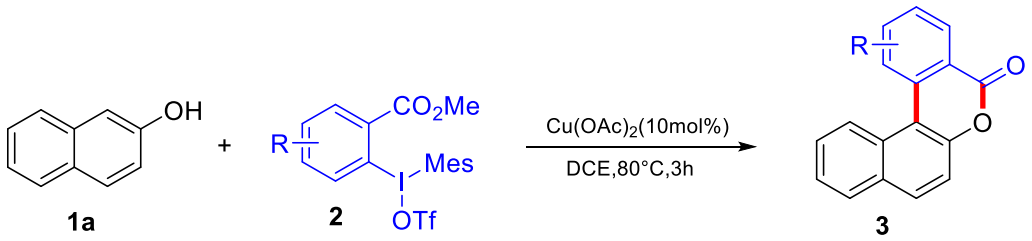
17		 **3ap**	25
18		 **3aq**	43
19		 **3ar** **3as**	45 (10)
20		 **3at**	51
21		 **3au**	34
22		 **3av**	39

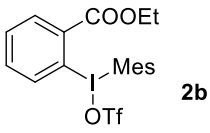
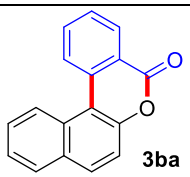
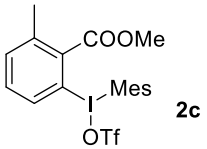
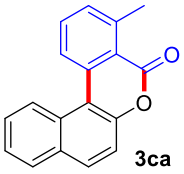
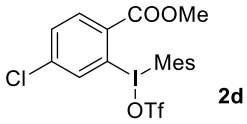
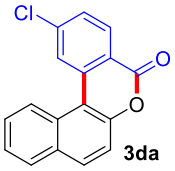
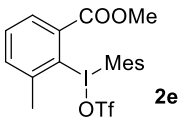
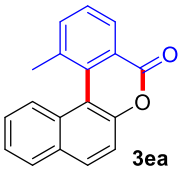
[a]Reaction conditions: **1** (0.3 mmol, 1 equiv.), **2a** (0.33 mmol, 1.1 equiv.), $Cu(OAc)_2$ (10 mol%), DCE (2 mL), 80 °C, 3 hours. [b]Isolated yields were obtained after purification with column chromatography. Mes = 2,4,6-trimethylphenyl, OTf = trifluoromethansulfonate.

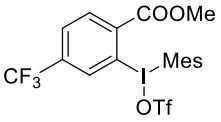
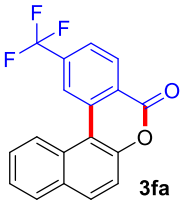
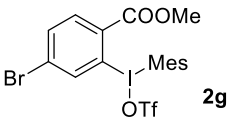
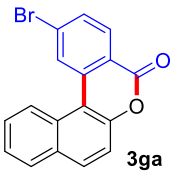
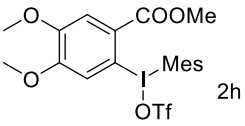
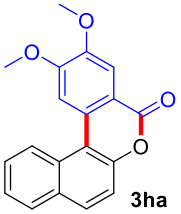
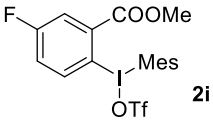
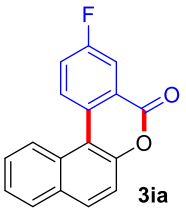
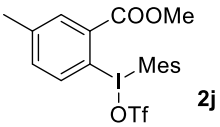
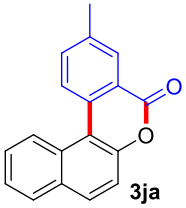
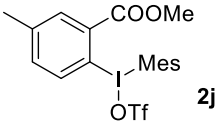
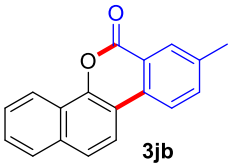
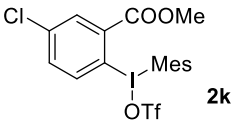
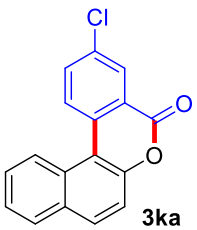
We subsequently turned our attention to explore the effect of structural diversity of the ortho-ester-substituted diaryliodonium salts. Firstly, a family of substituted diaryliodonium salts were synthesized in a one-pot procedure. These ortho-substituted diaryliodonium salts were isolated as stable solids, whose structures were

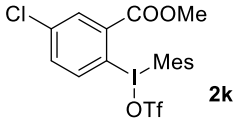
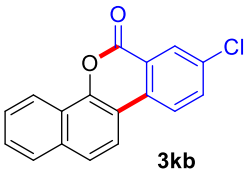
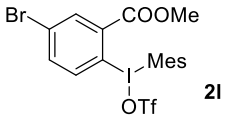
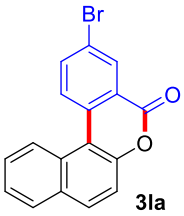
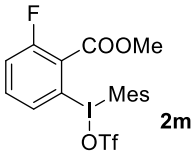
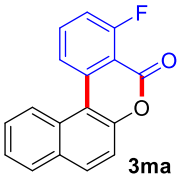
fully characterized by NMR spectra. As shown in Table 3, we utilized 2-naphthol and 1-naphthol as template substrates to react with various unsymmetrical 2-ester-substituted diaryliodonium salts. Remarkably, iodonium salts **2** proved to be versatile in this reaction, regardless of the electronic nature and position of the substituents. The desired 3,4-benzocoumarin products **3ba**–**3ma** were obtained in the yields of 21–59%. Notably, substituents such as halogens (F, Cl, and Br), methyl, methoxy, and trifluoromethyl groups at the ortho-, meta-, or para-positions of the ester group were all well-tolerated (Table 3).

Table 3. Scope of N-substituted pyrroles 1.[a]



Entry	2	Product	Yield (%)[b]
1	 **2b**	 **3ba**	55
2	 **2c**	 **3ca**	32
3	 **2d**	 **3da**	50
4	 **2e**	 **3ea**	46

5	 **2f**	 **3fa**	49
6	 **2g**	 **3ga**	55
7	 2h	 **3ha**	43
8	 **2i**	 **3ia**	21
9	 **2j**	 **3ja**	59
10	 **2j**	 **3jb**	28
11	 **2k**	 **3ka**	37

12	 **2k**	 **3kb**	45
13	 **2l**	 **3la**	35
14	 **2m**	 **3ma**	50

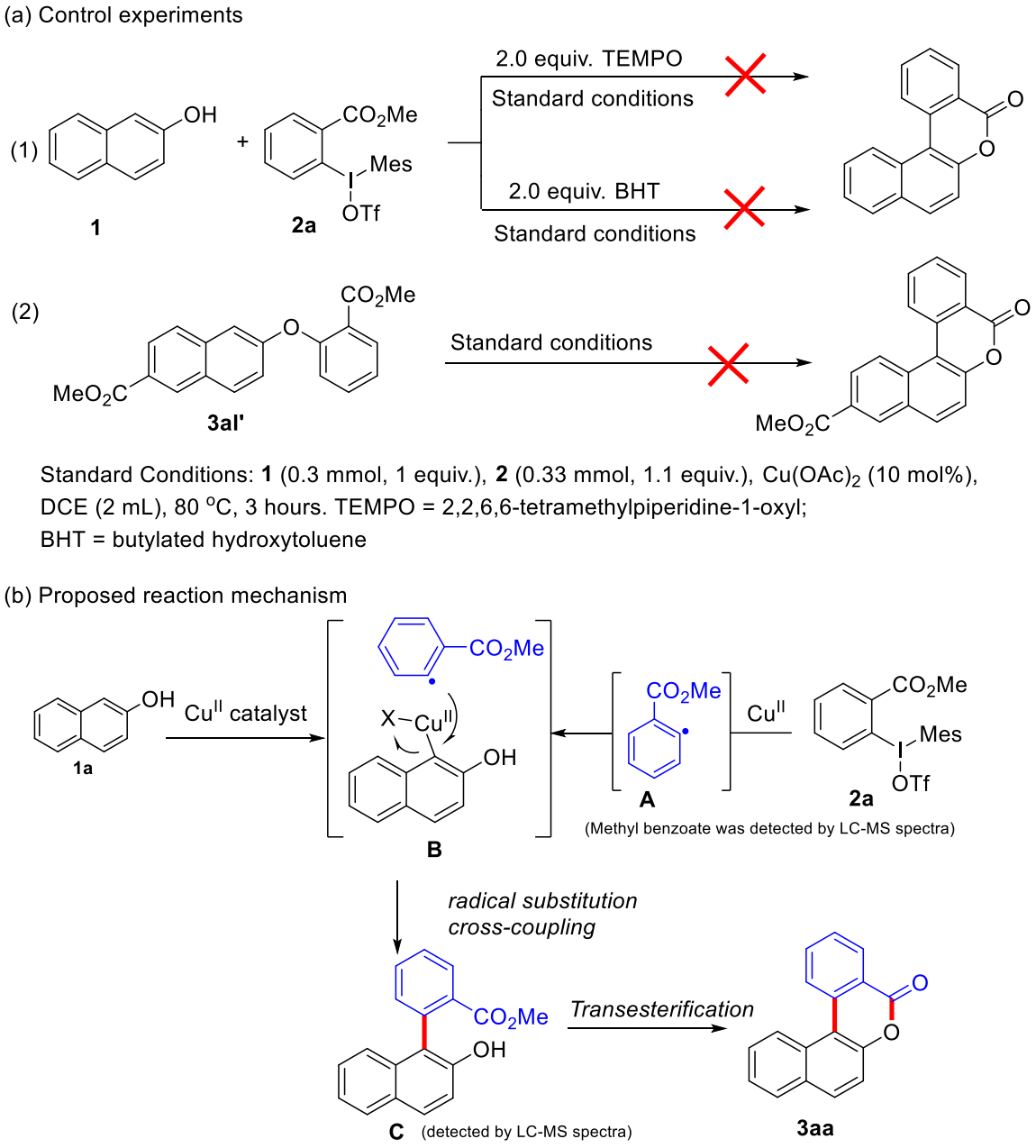
[a]Reaction conditions: **1** (0.3 mmol, 1 equiv.), **2** (0.33 mmol, 1.1 equiv.), $Cu(OAc)_2$ (10 mol%), DCE (2 mL), 80 °C, 3 hours. [b]Isolated yields were obtained after purification with column chromatography. Mes = 2,4,6-trimethylphenyl, OTf = trifluoromethansulfonate.

To gain further insights into the reaction mechanism, we conducted control experiments. Given the utility of diaryliodonium salts in radical chemistry, we introduced 2 equivalents of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 2 equivalents of butylated hydroxytoluene (BHT) into the template reaction. Remarkably, we observed that the desired product was not formed, suggesting a radical pathway. Subsequently, we investigated the bond-formation sequence in the benzocyclization reaction. A possible intermediate of **3al'** was prepared and tested in the reaction under the standard conditions, however, product **3aa** was not obtained.

Based on these experimental evidences, we proposed a plausible reaction mechanism (Scheme 2b). The reaction begins with the formation of the radical intermediate **A** from the diaryliodonium salt **2a**. Naphthol **1a** forms intermediate **B** with **A** after the participation with Cu(II) catalyst. Intermediate **B** generates **C** by

radical substitution. The final intramolecular transesterification yields the benzocoumarin product **3aa**.

Scheme 2. Mechanism study.



Conclusion

In summary, we have employed ortho-ester-substituted diaryliodonium salts in a cascade cyclization, the cyclization features a copper-catalyzed activation strategy

involving the cleavage of C-I bond and esterification. The resulting cascade of selective arylation/intramolecular cyclization facilitated the synthesis of 3,4-benzocoumarin derivatives. The protocol enables the efficient formation of two chemical bonds in one pot, representing a valuable tool for the synthesis of polycyclic benzocoumarins. Furthermore, the strategy of ortho-functionalization of diaryliodonium salts as bifunctional reagents is introduced to transfer the arenes, showcasing significant potential for the discovery of practical synthetic methodologies for constructing polyaromatic molecules. Our ongoing research endeavours are dedicated to explore the detailed reaction mechanism with the ultimate aim of broadening the scope and applicability of this approach.

Supporting Information

Supporting Information File 1

Experimental procedures, LC-MS spectra and characterizations data of all products, copies of ^{1}H, ^{13}C, ^{19}F NMR spectra of all compounds.

Acknowledgements

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