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# Rh(III)-Catalyzed Decarboxylative *ortho*-Heteroarylation of Aromatic Carboxylic Acids by Using the Carboxylic Acid as a Traceless Directing Group

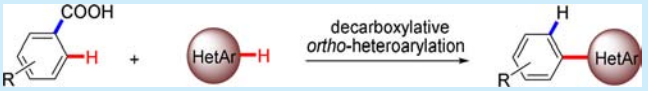
Xurong Qin,[†,‡] Denan Sun,[†] Qiulin You,[†] Yangyang Cheng,[†] Jingbo Lan,*[,†] and Jingsong You*[,†]

[†]Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Medical School, Sichuan University, 29 Wangjiang Road, Chengdu 610064, China

[‡]College of Pharmaceutical Science, Southwest University, 2 Tiansheng Road, Chongqing 400716, China

Supporting Information

**ABSTRACT:** Highly selective decarboxylative *ortho*-heteroarylation of aromatic carboxylic acids with various heteroarenes has been developed through Rh(III)-catalyzed two-fold C−H activation, which exhibits a wide substrate scope of both aromatic carboxylic acids and heteroarenes. The use of naturally occurring carboxylic acid as the directing group avoids troublesome extra steps for installation and removal of an external directing group.




Aryl−heteroaryl scaffolds are highly important structural motifs frequently found in natural products, pharmaceuticals, and functional materials (Figure 1).[1] From the step- and atom-economic perspective, transition-metal-catalyzed oxidative C−H/C−H cross-coupling between a simple arene and a heteroarene is one of the most attractive approaches to access these bi(hetero)aryl moieties, which obviates tedious and wasteful prefunctionalization of coupling partners in C−H/C−X or C−X/C−M coupling reactions.[2] Although the realm has undergone rapid growth with a number of impressive examples over the past few years,[3] two major barriers make this pathway greatly challenging and impose severe limitations on synthetic applications: (1) a troublesome regioselectivity issue with the substituted arene partner and (2) a required large excess of arene (usually as solvent or cosolvent) due to the generally low reactivity of C−H bonds. Recently, methods involving directing groups for the selective cleavage of the proximal aromatic C−H bond have been considered as an efficient strategy to overcome these difficulties.[4] The groups of Miura,[4a,e] Glorius,[4d] Kambe,[4c] and You[4b] have independently disclosed that several nitrogen-containing directing groups including pyridyl, pyrimidinyl, pyrazolyl, and amides enable *ortho*-selective heteroarylation of arenes via two-fold C−H activation (Scheme 1).

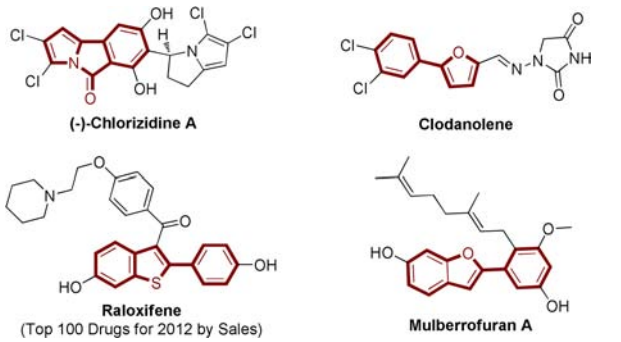
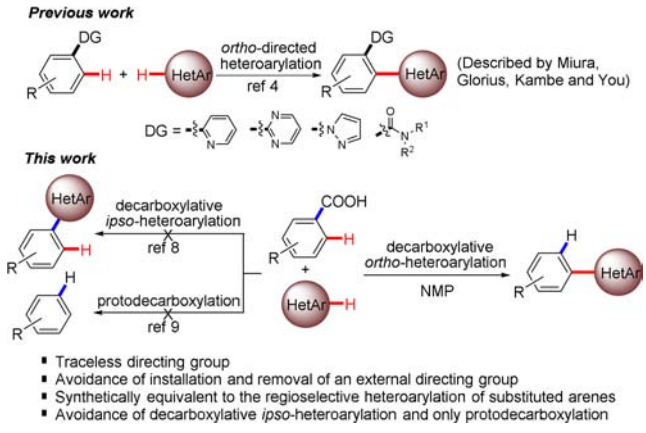



**Figure 1.** Selected molecules containing aryl−heteroaryl scaffolds.

**Scheme 1. Direct *ortho*-Heteroarylation of Aromatic Carboxylic Acids via Transition-Metal-Catalyzed Oxidative C−H/C−H Cross-Coupling**




In principle, the most ideal directing group should be an intrinsic part of the substrate, which avoids extra and cumbersome steps for installation and detachment (even nonremovability) of an external directing group. Aromatic carboxylic acids are prevalent in natural and synthetic products. The direct use of the naturally occurring carboxylic acid as the directing group instead of the mostly used amide and oxazoline can obviate the extra derivatization step of the carboxylate group.[5] Another substantial advantage is that the carboxylate

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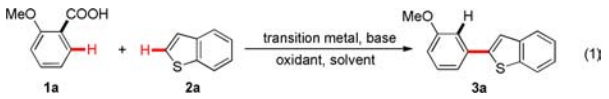
group could be tracelessly removed by protodecarboxylation to produce decarboxylative *ortho*-functionalized products. Both *ortho*- and *para*-substituted aromatic carboxylic acids could be transformed into the "formal" *meta*-substituted species via a decarboxylative *ortho*-functionalization, which is otherwise more difficult to reach in the presence of the *ortho*/*para*-orientation of substituents.[6]

Although a number of successful examples of transition-metal-catalyzed carboxyl-directed *ortho*-C−H functionalizations of anenes have been explored,[7] the oxidative *ortho*-C−H heteroarylation of aromatic carboxylic acids with heteroarenes through double C−H activation still remains scarce (Scheme 1).[7b] To perform the *ortho*-selective heteroarylation process, a series of fundamental challenges should be surmounted: (1) Can less thermodynamically stable cyclometalated intermediates formed by the weakly coordinating carboxylate group cleave the C−H bond of heteroarene coupling partner?[5a] (2) Can decarboxylative *ipso*-heteroarylation of aromatic carboxylic acids be prevented?[8] (3) Can protodecarboxylation of the starting aromatic carboxylic acids be restrained?[9] (4) Can homocoupling[10] and decomposition of heteroarenes be suppressed and eliminated? As a part of our program focusing on oxidative C−H/C−H cross-coupling of two (hetero)arenes, we describe the solution to these challenges and disclose the rhodium-catalyzed decarboxylative *ortho*-heteroarylation of aromatic carboxylic acids. During the submission of this paper, Su et al. reported Rh(III)-catalyzed decarboxylative C−H arylation of thiophenes.[7b] However, only thiophenes, benzothiophenes, and benzofuran were employed as the coupling partners in their work.

Allured by the success of palladium catalysis, we initially investigated the palladium-catalyzed oxidative C−H/C−H cross-coupling reaction between 2-methoxybenzoic acid (**1a**) with benzothiophene (**2a**) (eq 1). To our disappointment, the

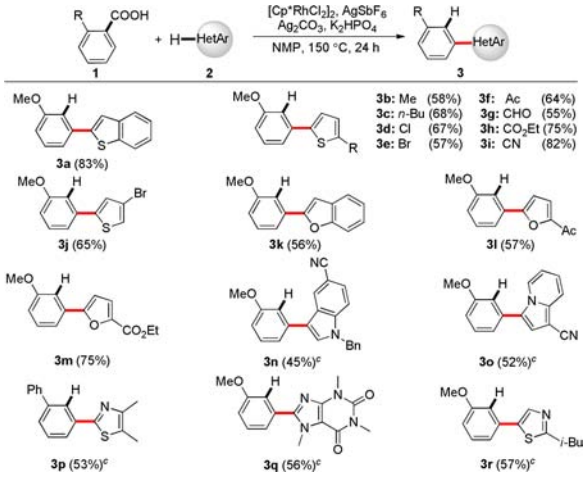



reaction was very complicated and no obvious product was observed (Table S1, entries 1−7). Subsequently, encouraged by our recent results of Rh(III)-catalyzed oxidative C−H/C−H cross-couplings of pyridyl- or pyrimidinyl-containing (hetero)-arenes with heteroarenes,[4b,11] we resorted to the rhodium catalytic systems. The coupling reaction of **1a** with **2a** led to the desired product **3a** in 35% yield with concomitant protodecarboxylation in the presence of $[Cp^*RhCl_2]_2$ by using $Ag_2CO_3$ as the oxidant (Table S1, entry 8). In view of the importance of the decarboxylative *ortho*-heteroarylated products, the reaction conditions were further optimized. After screening several parameters (Tables S2−S5), the reaction proceeded well and gave **3a** in 83% yield when $[Cp^*RhCl_2]_2$ (2.5 mol %) was used in combination with $AgSbF_6$ (10 mol %), $K_2HPO_4$ (2.0 equiv), and $Ag_2CO_3$ (3.0 equiv) in *N*-methyl-2-pyrrolidone (NMP) at 150 °C for 24 h (Table S5, entry 4).

Under the optimized reaction conditions, a broad range of thiophenes reacted smoothly with 2-methoxybenzoic acid to afford the *meta*-heteroarylated products (Scheme 2, **3a**−**j**). More importantly, this protocol was compatible with the presence of synthetically important functional groups such as fluoro, chloro, bromo, aldehyde, ketone, ester, and cyano (Scheme 2, **3d**−**j**). Other electron-rich heteroarenes such as furans, indoles, and indolizines also reacted with 2-methoxybenzoic acid to produce the *meta*-heteroarylated products in synthetically useful yields (Scheme 2, **3k**−**o**). Moreover, electron-deficient heteroarenes such as caffeine and thiazoles could undergo decarboxylative *ortho*-coupling with benzoic acids at the C2 site of azoles (Scheme 2, **3p**,**q**). The 2-substituted thiazole selectively underwent the cross-coupling at the C5 position to form 5-arylthiazole (Scheme 2, **3r**).

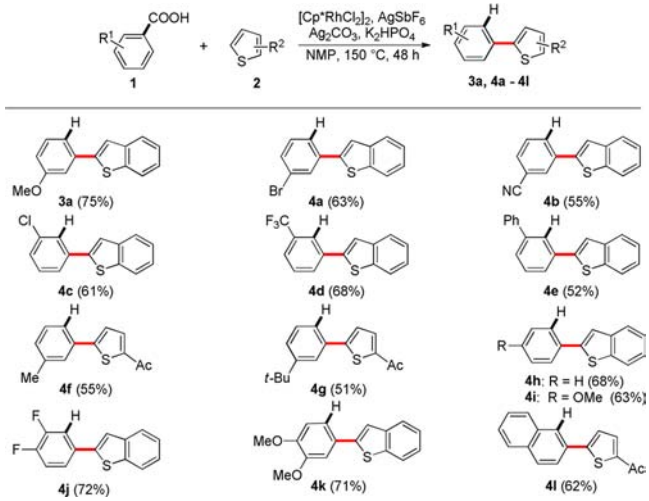
The scope of aromatic carboxylic acids was next examined (Scheme 3). The *ortho*- or *para*-substituted benzoic acids bearing both electron-donating and electron-withdrawing groups regioselectively afforded the *meta*-heteroarylated products in moderate to good yields (Scheme 3, **3a**, **4a**−**g**). When a *meta*-substituted benzoic acid was used, the heteroarylation

**Scheme 2. Scope of Heteroarenes**[a,b]




[a]Reaction conditions: aromatic carboxylic acid (0.25 mmol), heteroarene (3.0 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), $Ag_2CO_3$ (3.0 equiv), $K_2HPO_4$ (2.0 equiv), 4 Å MS (100 mg), and NMP (1.0 mL) at 150 °C for 24 h under a $N_2$ atmosphere. [b]Isolated yields. [c]$[Cp^*RhCl_2]_2$ (5.0 mol %) and $AgSbF_6$ (20 mol %) at 160 °C for 48 h.

**Scheme 3. Scope of Aromatic Carboxylic Acids**[a,b]




[a]Reaction conditions: aromatic carboxylic acid (0.25 mmol), heteroarene (3.0 equiv), $[Cp^*RhCl_2]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), $Ag_2CO_3$ (3.0 equiv), $K_2HPO_4$ (2.0 equiv), 4 Å MS (100 mg), and NMP (1.0 mL) at 150 °C for 48 h under a $N_2$ atmosphere. [b]Isolated yields.



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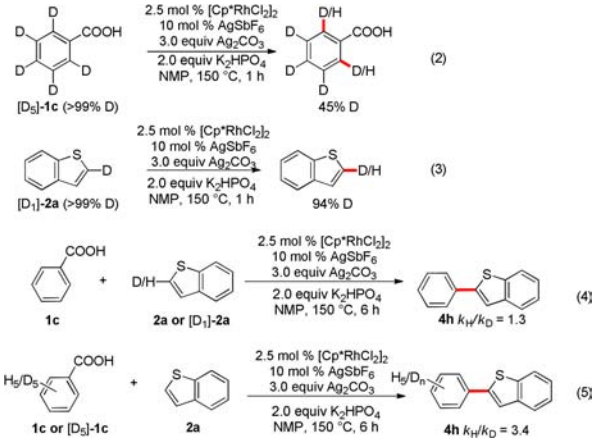
occurred at the less hindered site, exclusively providing the *para*-heteroarylation isomer (Scheme 3, **4i**). The coupling of 2,3- and 3,4-disubstituted benzoic acids with benzothiophene gave the 3,4-disubstituted aryl benzothiophenes in good yields (Scheme 3, **4j**,**k**). In addition, $\alpha$-naphthoic acid was amenable to the *ortho*-heteroarylation at the $\beta$-position in 62% yield (Scheme 3, **4l**).

To gain insight into the mechanism, a series of deuteration experiments was conducted. First, the exposure of the deuterated [$D_5$]-**1c** to the rhodium catalytic system in the presence of $K_2HPO_4$ for 1 h gave a loss of 55% deuterium (eq 2), whereas the H/D exchange ratio of [$D_1$]-**2a** was only 6%




(eq 3). These observations suggested that the cross-coupling reaction might initiate from the cyclometalation of benzoic acids.[4a,b,12] Next, kinetic isotope effects (KIE) for both coupling partners were studied with regard to the C−H/D bonds. An intermolecular competition reaction between benzothiophene **2a** and its deuterated derivative did not give a significant KIE value ($k_H/k_D$ = 1.3) (eq 4), indicating that the C−H bond cleavage of **2a** could not be the rate-determining step. However, a significant KIE of 3.4 was determined for benzoic acid **1c** (eq 5). These results suggested that the C−H bond breaking of **1c** might be the rate-limiting step.[13]

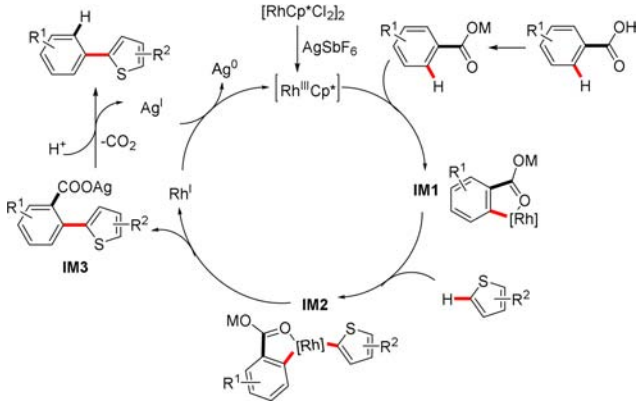
Subsequently, the competition experiments among electronically differentiated 4-methoxybenzoic acid, 4-bromobenzoic acid, and 4-cyanobenzoic acid indicated that the reactivity of electron-rich benzoic acid is higher than that of electron-deficient benzoic acid (Table S6). Thus, the cyclometalation might proceed via an electrophilic C−H bond activation.[14]

Finally, the influence of [$Cp^*RhCl_2$]$_2$ and silver salt on the decarboxylation step was investigated. In the absence of [$Cp^*RhCl_2$]$_2$, 2-(benzothiophen-2-yl)-6-methoxybenzoic acid (**3a′**) could smoothly decarboxylate to afford the desired product **3a** in 82% yield (eq 6). In sharp contrast, a trace


amount of decarboxylated product **3a** was observed without silver salt (eq 7). These observations suggested that the decarboxylation step could be mediated by silver salt rather than [$Cp^*RhCl_2$]$_2$.[15]

Although the detailed mechanism is not clear, a plausible pathway could involve (1) coordination of the carboxylate oxygen atom to Cp*Rh(III) to give a rhodium(III) carboxylate and a subsequent electrophilic *ortho*-C−H bond activation of arene; (2) the resulting rhodacycle intermediate **IM1** reacting with a heteroarene partner to give the critical heteroaryl−rhodacycle intermediate **IM2**; and (3) reductive elimination and subsequent protodecarboxylation giving the decarboxylative *ortho*-heteroarylated product (Scheme 4).

**Scheme 4. Plausible Mechanism for *ortho*-Heteroarylation of Aromatic Carboxylic Acids by Using the Carboxylic Acid as a Traceless Directing Group**




In summary, we have developed a highly regioselective Rh(III)-catalyzed decarboxylative *ortho*-heteroarylation of aromatic carboxylic acids with various heteroarenes (e.g., thiophenes, furans, indoles, indolizines, azoles, and xanthines) by using the carboxylic acid as a traceless directing group. This process offers an efficient alternative synthesis of the formal *meta*-substituted adducts from *ortho*- and *para*-substituted aromatic carboxylic acids and the *para*-heteroarylated adducts from *meta*-substituted substrates. The current catalytic system efficiently restrains homocoupling of heteroarene substrates. Furthermore, the use of naturally occurring carboxylic acid as the directing group avoids troublesome extra steps for installation and removal of an external directing group.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Authors

*E-mail: jingbolan@scu.edu.cn.
*E-mail: jsyou@scu.edu.cn.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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