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Rhodium(III)-Catalyzed Oxidative C−H/C−H Cross-Coupling of Heteroarenes and Masked Benzylamines

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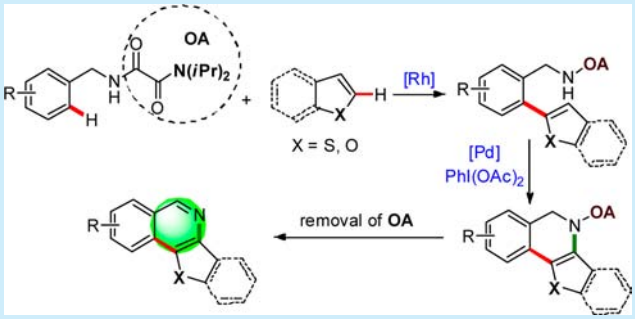
Supporting Information

ABSTRACT: The first example of oxidative C−H/C−H cross-coupling of oxalyl amide-protected benzylamines and various heteroarenes in the presence of a rhodium(III) catalyst has been developed. The route provides a means of synthesizing *ortho*-heteroarylated benzylamines. The methodology presents broad substrate scope, great functional group tolerance, and good to excellent yields in the synthesis of substituted benzylamines. The study also reveals that the thienoisoquinoline derivatives can be accessed through the intramolecular amination of thiophenyl-substituted benzylamines with palladium(II).



Thiophenyl-substituted arenes are an important class of building blocks in various natural products, drugs, organic solar cells, organic charge-transporting molecules, and organic light-emitting diode dyes.[1] For example, various well-known drugs such as raloxifene, canagliflozin, suprofen, zileuton, and tiaprofenic acid contain thiophene moieties as important functional groups. Thiophene scaffolds are usually important structures of various functional materials (Figure 1, **I**).[2a,b] Thus, the use of thiophene derivatives as starting materials to construct thiophenyl-containing arenes is a straightforward route and is in great demand.

In recent years, oxidative C−H/C−H cross-couplings of arenes and heteroarenes have attracted much attention, providing a straightforward route to furnish various bi(hetero)-aryls from heteroarenes.[3] For example, the *ortho*-selective thiophenation of arenes by C−H/C−H cross-coupling assisted by directing groups of pyridines and quinoline,[4] pyrimidines and thiazole,[5] oxime ethers,[6] amides,[7] azobenzenes,[8] and carboxylic acids[9] has been independently developed by the groups of Miura, You, Glorius, and Kambe (Scheme 1A). These discoveries have greatly enriched the approaches to synthesis of bi(hetero)aryls. However, to the best of our knowledge, there is still no example of oxidative C−H/C−H cross-couplings of benzylamines and heteroarenes.

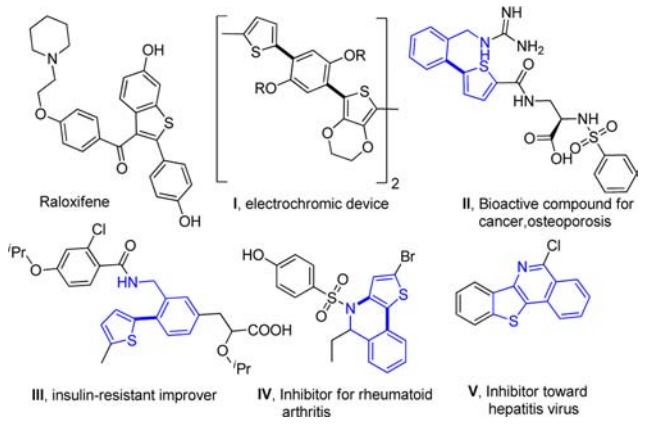
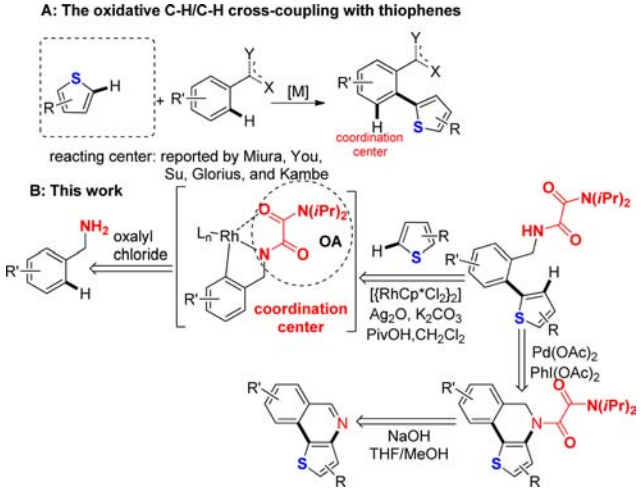


Figure 1. Examples of significant functional molecules containing thiophenes.

Scheme 1. Transition-Metal-Catalyzed C−H Functionalization



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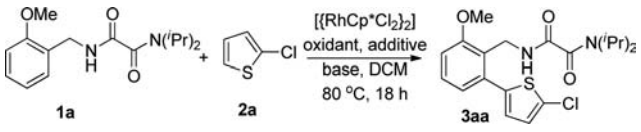
Benzylamines are important synthetic units in biologically active parts of pharmaceuticals and in materials chemistry (Figure 1, **II**–**V**).[2c−f] To date, only a few synthetic methods for constructing thiophenyl-substituted benzylamines have been developed.[10] One of the general approaches is the transition-metal-catalyzed cross-coupling of prefunctionalized benzylamines with thiophenes. Because of the multiple steps required to prepare the prefunctionalized starting materials, there has been a lack of structural diversity in terms of *o*-thiophenyl-substituted benzylamines, which has significantly hindered exploration of the bioactivities of these compounds. Thus, the development of a highly regioselective practical C−H activation to synthesize *o*-thiophenylbenzylamines from readily available thiophenes and benzylamine derivatives is challenging and in great demand.

Herein we report the first accomplishment of oxidative C−H/C−H cross-coupling of benzylamine derivatives and thiophenes in the presence of $[\{RhCp^*Cl_2\}_2]$ (Cp^* = C_5Me_5) as catalyst with oxalyl amide (OA) as a directing group (Scheme 1B). In this way, various *o*-thiophenyl-substituted benzylamine derivatives have been obtained. These reactions all proceed well under mild conditions and tolerate various functional groups. Furthermore, the introduced thiophenyl substituents have been successfully used to form thienoisoquinoline derivatives through intramolecular amination.

We first explored the C−H/C−H cross-coupling of 2-methoxybenzylamine derivative **1a** and 2-chlorothiophene (**2a**). After screening of the reaction conditions (Table 1), it turned out that Ag_2O was the best oxidant (entries 1−7). Additives such as PivOH, 1-AdOH, and AcOH had great promoting effects (entries 8−11). Further scanning revealed that the reaction gave better yields when it was performed under basic conditions (entries 12−16). Several other *ortho*-directing groups were also tested under the optimized reaction conditions, and oxalyl amide was identified as the best directing group for further development (see the Supporting Information).[11] Notably, there have been few examples of oxidative C−H/C−H cross-couplings being performed at temperatures below 100 °C.

Having established the most promising conditions, we next investigated the substrate scope in terms of benzylamines and thiophenes (Scheme 2). Generally, reactions of benzylamines

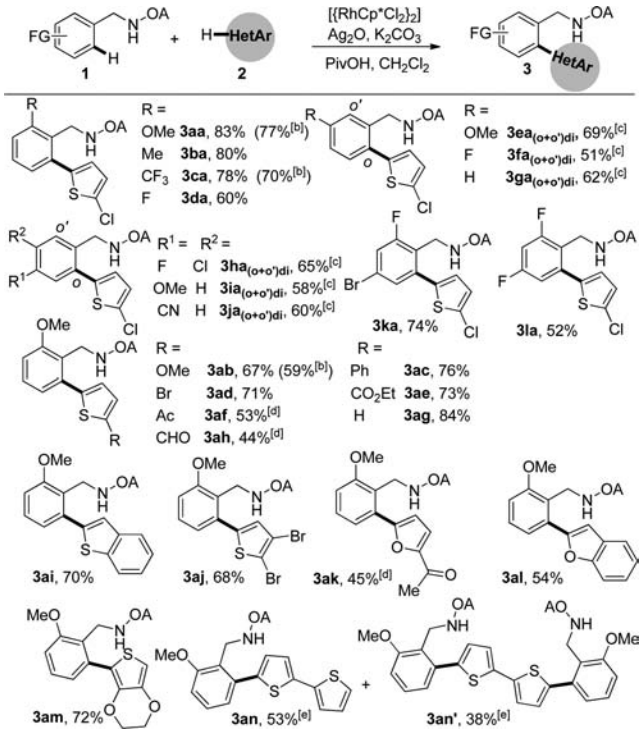
Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant	additive	base	yield (%)[b]
1	Ag_2O	–	–	39
2[c]	$AgSbF_6$	–	–	6
3	Ag_2CO_3	–	–	25
4	AgOAc	–	–	8
5	$Cu(OAc)_2$	–	–	5
6	BQ	–	–	NR
7	TEMPO/O_2	–	–	NR
8	Ag_2O	PivOH	–	74
9	Ag_2O	1-AdOH	–	65
10	Ag_2O	HOAc	–	51
11	Ag_2O	Ac-Gly-OH	–	47
12	Ag_2O	PivOH	K_2CO_3	87 (83[d])
13	Ag_2O	PivOH	Na_2CO_3	63
14	Ag_2O	PivOH	$KHCO_3$	68
15	Ag_2O	PivOH	K_3PO_4	82
16	Ag_2O	PivOH	K_2HPO_4	78

[a]Reactions were carried out using **1a** (0.1 mmol), **2a** (0.15 mmol), $[\{RhCp^*Cl_2\}_2]$ (5.0 mol %), oxidant (0.15 mmol), and DCM (0.5 mL) at 80 °C for 18 h in a 15 mL sealed tube. [b]Yields were determined by LC using acetophenone as an internal standard. [c]20.0 mol % $AgSbF_6$. [d]Isolated yield.

Scheme 2. Scope of Benzylamines and Heteroarenes[a]



[a]Conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[\{RhCp^*Cl_2\}_2]$ (5 mol %), Ag_2O (0.3 mmol), PivOH (0.06 mmol), K_2CO_3 (0.4 mmol), CH_2Cl_2 (0.8 mL), 80 °C, 18 h. Isolated yields are shown. [b]The solvent was DCE. [c]0.6 mmol of **2a**. [d]36 h. [e]**1a** (0.4 mmol), **2** (0.2 mmol), $[\{RhCp^*Cl_2\}_2]$ (10 mol %), Ag_2O (0.6 mmol), PivOH (0.12 mmol), K_2CO_3 (0.8 mmol), CH_2Cl_2 (1.5 mL), 80 °C, 36 h.

bearing both electron-donating and electron-withdrawing substituents, such as methoxy, methyl, fluoro, chloro, bromo, trifluoromethyl, and nitrile, at the *ortho*, *meta*, or *para* position proceeded smoothly, affording the *ortho*-heteroarylated products in moderate to good yields (**3aa**−**la**) Interestingly, the *meta*-substituted derivatives gave the diheteroarylated products in good yields, along with less than 5% yield of the monoheteroarylated products (**3ea**−**ga**). When we tested the *para*-substituted benzylamines, only the diheteroarylated products were observed (**3ia** and **3ja**). This transformation also proceeded well with polysubstituted benzylamines (**3ga**, **3ka**, and **3la**). This directed *ortho* C−H/C−H coupling reaction also tolerated various thiophenes and furans (**3ab**−**an**). Aldehyde, ketone, ester, and bromo functional groups were all compatible, resulting in the corresponding products in good yields. Interestingly, 2,2′-bithiophene also served as a good coupling partner, giving the products **3an** and **3an′**, which could be easily separated by chromatography on silica gel.

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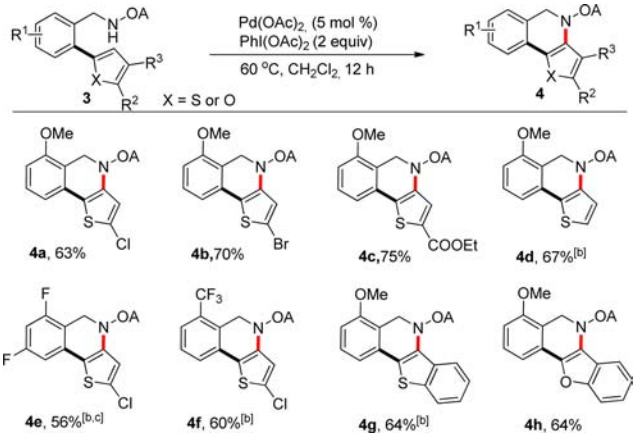
Thienoisoquinoline derivatives are an important class of synthetic units because they are constituents of many pharmaceuticals and biologically active materials. For example, thienoisoquinoline−phenylsulfonamides are used as nuclear factor-κB inhibitors.[2d] Thieno[c]isoquinolines have been incorporated in light-emitting device materials.[12] We discovered that thienoisoquinoline derivatives could be accessed through intramolecular amination. Various thiophenes were tolerated in this intramolecular amination (Scheme 3, **4a**−**g**),

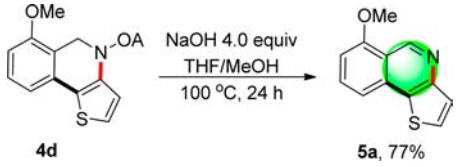
Scheme 3. Synthesis of Thienoisoquinoline Derivatives[a]



[a]Conditions: **3** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), $PhI(OAc)_2$ (0.4 mmol), CH_2Cl_2 (4.0 mL), 60 °C, 12 h. Isolated yields are shown. [b]18 h. [c]70 °C.

affording the corresponding products in moderate to good yields. Notably, the directing group could be easily removed under basic conditions, affording **5a** in 77% yield (Scheme 4).

Scheme 4. Removal of the Oxalyl Amide Directing Group



Several deuterium-labeling experiments were performed to gain insight into the reaction pathway.[3b,5a,6,7c] The reversibility of the C−H activation was explored (for detailed information, see the Supporting Information). Ag_2O proved to be indispensable, implying that it is required to activate the catalyst precursor. Unsurprisingly, pivalic acid greatly enhanced the C−H activation. Analogous deuteration results were observed with benzo[b]thiophene, but deuterated benzo[b]-thiophene was obtained in a lower yield than that of **1a** (see the Supporting Information). We next subjected **1a** and **2i** to deuterium-labeling experiments (see the Supporting Information). As expected, **1a** (63% D) and **2i** (9% D) were obtained (Scheme 5). These results suggested that oxidative C−H/C−H cross-coupling might ensue following cyclometalation of the oxalyl amide-protected benzylamines.

In conclusion, we have developed a new approach to prepare *ortho*-heteroarylated benzylamines under mild conditions through oxidative C−H/C−H cross-coupling in the presence of $[\{RhCp^*Cl_2\}_2]$ ($Cp^* = C_5Me_5$) as the catalyst with oxalyl amide as a directing group. This methodology presents broad

Scheme 5. Deuterium-Labeling Experiments

substrate scope, great functional group tolerance, and good to excellent yields in the synthesis of substituted benzylamines. Furthermore, thienoisoquinoline derivatives could be accessed through intramolecular amination of thiophenyl-substituted benzylamines with palladium(II). This provides a convenient approach for constructing thienoisoquinoline derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02773.

Optimization of the reaction conditions, detailed experimental procedures, deuterium experiments, characterization data of the products, and ^1H, ^{13}C, and ^{19}F NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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