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Rhodium-catalyzed oxidative C–H/C–H cross-coupling of aniline with heteroarene: *N*-nitroso group enabled mild conditions

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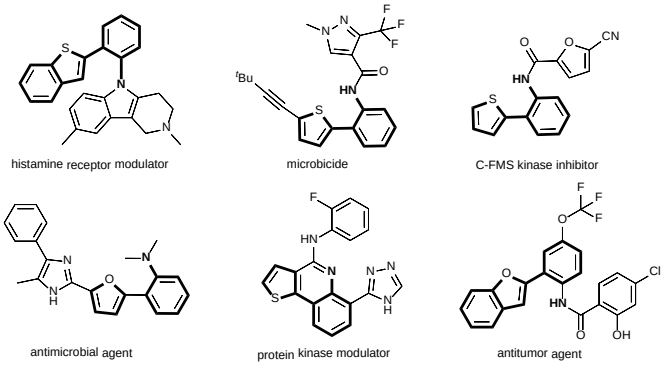
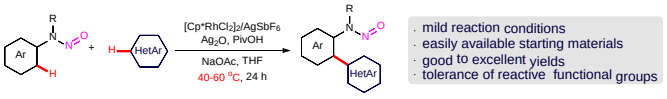
The development of transition metal-catalyzed oxidative C–H/C–H cross-coupling between two (hetero)arenes to forge aryl-heteroaryl motifs under mild conditions is an appealing, yet challenging task. Herein, we disclose a rhodium-catalyzed oxidative C–H/C–H cross-coupling reaction of a *N*-nitrosoaniline with a heteroarene under mild conditions. The judicious choice of the *N*-nitroso group as a directing group enables heightened reactivity. The coupled products could be transformed expediently to (2-aminophenyl)heteroaryl skeletons.

Aryl-heteroaryl motifs are highly valuable scaffolds widely existed in organic functional materials, pharmaceuticals, agrochemicals, organic synthetic intermediates, ligands and natural products.[1] Therefore, their synthesis has attracted much attention in the organic synthesis community. Among various synthetic approaches to aryl-heteroaryl motifs, transition metal-catalyzed oxidative C–H/C–H cross-coupling reactions between two (hetero)arenes are regarded as one of the most straightforward approaches to aryl-heteroaryl motifs in terms of step- and atom-economy.[2] Over the past decade, various oxidative C–H/C–H cross-coupling reactions between two (hetero)arenes have been reported for the efficient synthesis of aryl-heteroaryl scaffolds, as exemplified by the pioneering works of Miura, Glorius, Zhang, Su, and You et al.[3-7] Despite significant advance, the vast majority of these established reactions need relatively harsh reaction conditions, and particularly elevated temperatures (often above 120 °C) owing to high dissociation energies of the cleavage of heteroarene C–H bonds, which may be incompatible with some sensitive functional groups. Thus, it is highly desirable to develop an innovative strategy to realize this type of cross-coupling reactions under mild conditions.



Scheme 1. Pharmaceutical and biologically active molecules containing the (2-aminophenyl)heteroaryl motifs.

(2-Aminophenyl)heteroaryls are an important class of aryl-heteroaryl motifs (Scheme 1).[8] We recently demonstrated rhodium-catalyzed oxidative C–H/C–H cross-coupling reactions of aromatic amines with heteroarenes to rapidly construct (2-aminophenyl)heteroaryl frameworks using the pivaloyl group as the directing group.[9] However, this reaction is nagged by harsh reaction conditions, such as extremely high temperature (160 °C), which limits the synthetic utility of this strategy to a certain extent. Recently, the *N*-nitroso moiety proves to be a versatile directing group for mild C–H functionalization because of its moderate coordination effect.[10] As a part of our ongoing efforts in the construction of aryl-heteroaryl motifs, we herein wish to disclose a rhodium-catalyzed oxidative C–H/C–H cross-coupling of a *N*-nitrosoaniline with a heteroarene under mild condition. In contrast with our previous work, using the *N*-nitroso group as the directing group enables heightened reactivity. As a result, the reaction temperature is reduced from 160 °C to 60 °C (even 40 °C and room temperature) (Scheme 2).



Scheme 2. *N*-Nitroso group enabled mild oxidative C–H/C–H cross-coupling of aniline with heteroarene.

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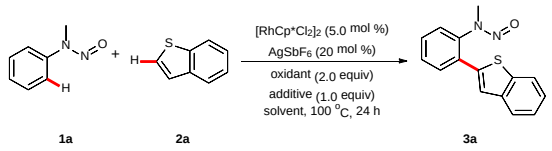
Table 1. Optimization of the reaction conditions[a]

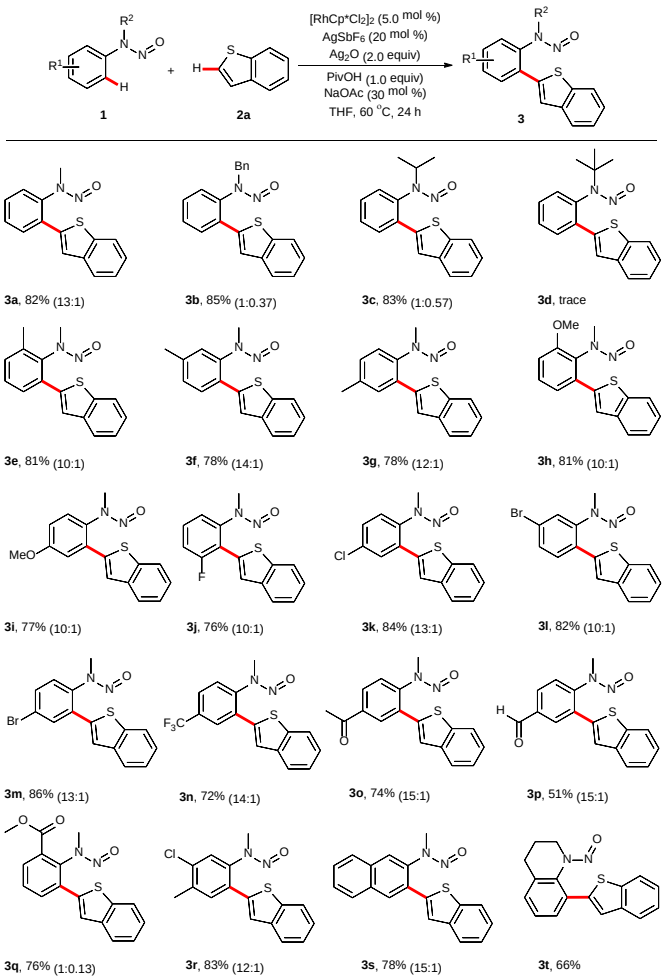


Entry	Oxidant	Additive	Solvent	Yield[b] (%)
1	Ag_2CO_3	PivOH	toluene/1.0	14
2	AgOAc	PivOH	toluene/1.0	11
3	Ag_2O	PivOH	toluene/1.0	23
4	$Cu(OAc)_2$	PivOH	toluene/1.0	8
5	Ag_2O	PivOH	DCE/1.0	43
6	Ag_2O	PivOH	DMF/1.0	16
7	Ag_2O	PivOH	dioxane/1.0	52
8	Ag_2O	PivOH	MeOH/1.0	43
9	Ag_2O	PivOH	THF/1.0	71
10	Ag_2O	PivOH	THF/0.5	75
11	Ag_2O	PivOH/NaOAc	THF/0.5	84
12[c]	Ag_2O	PivOH/NaOAc	THF/0.5	82
13[d]	Ag_2O	PivOH/NaOAc	THF/0.5	51
14[e]	Ag_2O	PivOH/NaOAc	THF/0.5	24

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.6 mmol, 3.0 equiv), $[Cp^*RhCl_2]_2$ (5.0 mol %), $AgSbF_6$ (20 mol %), oxidant (2.0 equiv), acid (1.0 equiv), and base (30 mol %) at 100 °C for 24 h under an N_2 atmosphere. [b] Isolated yield. [c] At 60 °C. [d] At 40 °C. [e] At room temperature for 36 h.

Our investigation commenced with the reaction between *N*-methyl-*N*-phenylnitrous amide **1a** and benzothiophene **2a** (For detailed optimization, see Table S1, ESI†). Initially, the reaction was performed in toluene (1 mL) at 100 °C for 24 h in the presence of $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), PivOH (1.0 equiv), and Ag salt (2.0 equiv) as the oxidant (Table 1, entries 1-3). Gratifyingly, the coupled product *N*-(2-(benzo[*b*]thiophen-2-yl)phenyl)-*N*-methylnitrous amide **3a** was obtained in 23% yield by using Ag_2O as the oxidant (Table 1, entry 3). Replacing Ag_2O with $Cu(OAc)_2$, **3a** was delivered in only 8% yield (Table 1, entry 4). After the solvents were examined, THF proved to be superior to toluene, DCE, DMF, dioxane and MeOH (Table 1, entries 3 and 5-9). Reducing the dosage of THF to 0.5 mL, **3a** could be afforded in 75% yield (Table 1, entry 10). The addition of 30 mol % of NaOAc could further improve the yield to 84% (Table 1, entry 11). Furthermore, an equal yield of **3a** could be obtained when running the reaction mixture of **1a** and **2a** at 60 °C (Table 1, entry 12). In addition, we were surprised to find that the cross-coupling reaction could occur at 40 °C and even room temperature, albeit in reduced yields (Table 1, entries 13 and 14). Finally, we established the optimal catalytic system composed of $[RhCp^*Cl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2O (2.0 equiv), PivOH (1.0 equiv), and NaOAc (30 mol %) in 0.5 mL of THF at 60 °C for 24 h. In addition, we performed the reaction of *N*-phenylpivalamide instead of *N*-nitrosoaniline with **2a** under the standard conditions, and the coupled product **3u** was obtained in only 32% yield (ESI†, Part IV).

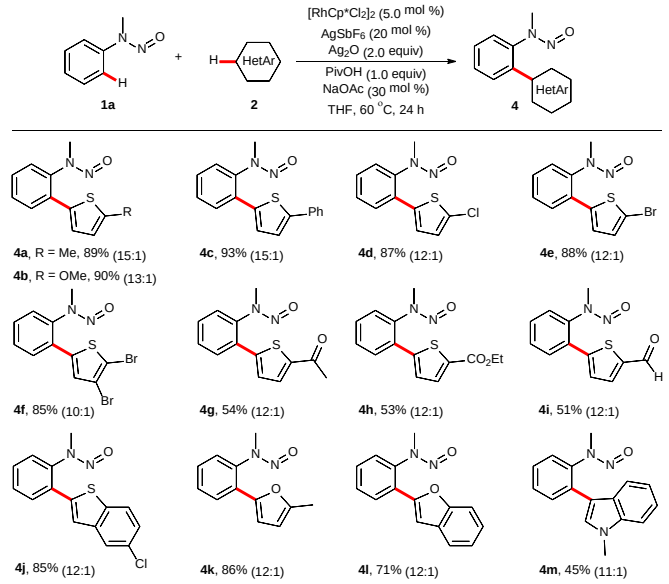
Table 2. Scope of *N*-nitrosoanilines[a,b,c]



[a] Reaction were performed with **1** (0.2 mmol, 1.0 equiv), and **2a** (0.6 mmol, 3.0 equiv) in THF (0.5 mL) at 60 °C for 24 h under an N_2 atmosphere. [b] Isolated yield. [c] The ratio of the *syn* to *anti* isomers relative to N–N bond, determined by the ^1H NMR spectrum.

With the optimal conditions in hand, the scope of *N*-nitrosoanilines was firstly examined. As shown in Table 2, various *N*-alkyl-substituted substrates could smoothly react with benzothiophene **2a**, delivering the corresponding products in good yields (Table 2, **3a**-**3c**). Due to steric hindrance effect, *N*-(*tert*-butyl)-*N*-phenylnitrous amide was not tolerated and only a trace amount of **3d** was detected. *N*-Methyl-*N*-phenylnitrous amides bearing an electron-donating group on the benzene ring could react with **2a** in good yields (Table 2, **3e-3i**). This protocol was also compatible with a variety of electron-withdrawing groups such as halide (F, Cl and Br), CF_3, acyl, formyl, and ester (Table 2, **3j**-**3q**). The *N*-methyl-*N*-phenylnitrous amide possessing two substituent groups could be engaged in this arylation, delivering **3r** in 83% yield. *N*-Methyl-*N*-(naphthalen-2-yl)nitrous amide provided the coupled product at the C3 position (Table 2, **3s**). Moreover, 1-nitroso-1,2,3,4-tetrahydroquinoline participated in this coupling reaction in 66% yield (Table 2, **3t**).

Table 3. Scope of heteroarenes[a,b,c]

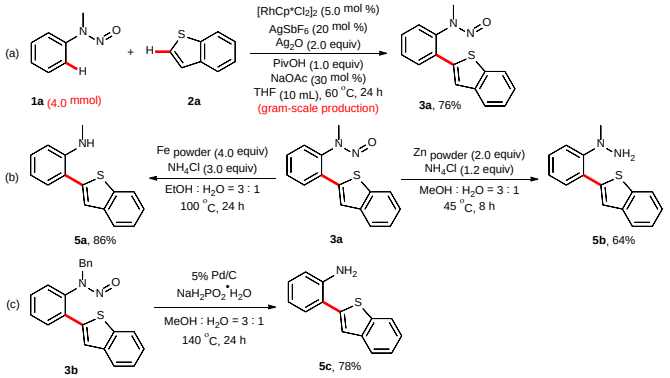


[a] Reaction were performed with **1a** (0.2 mmol, 1.0 equiv), and **2** (0.6 mmol, 3.0 equiv) in THF (0.5 mL) at 60 °C for 24 h under an N_2 atmosphere. [b] Isolated yield. [c] The ratio of the *syn* to *anti* isomers relative to N–N bond, determined by the ^{1}H NMR spectrum.

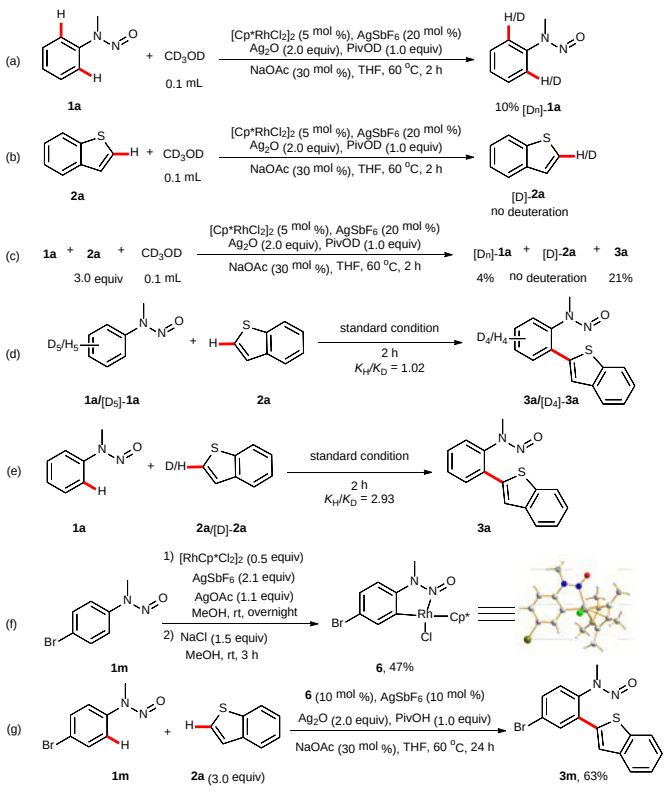
Next, we employed **1a** as the coupling partner to investigate the scope of heteroarenes (Table 3). To our delight, various thiophene derivatives possessing a wide range of functional groups such as methyl, methoxy, chloro, bromo, acyl, ester, and formyl were compatible with this protocol (Table 3, **4a-4i**). 5-Chlorobenzothiophene was engaged in this reaction (Table 3, **4j**). 2,5-Substituted thiophene such as 2-bromo-5-methylthiophene (**2o**) and 2,5-dichlorothiophene (**2p**) did not give the desired product except for the recovery of starting materials. This methodology could also be extended to furan and indole derivatives (Table 3, **4k-4m**), but 3-substituted indoles, such as 1-(1*H*-indol-3-yl)ethan-1-one (**2q**), 1-benzyl-1*H*-indole-3-carbaldehyde (**2r**), and methyl 1-benzyl-1*H*-indole-3-carboxylate (**2s**), failed to deliver the desired products.

To further highlight the synthetic utility of our strategy, we illustrated the scalability of the reaction. Under the standard conditions, **3a** could be obtained without problem on a gram scale in 76 % yield (Scheme 3, (a)). Furthermore, the *N*-nitroso group could be removed from the coupled product **3a** or be converted into amino, delivering 2-(benzo[*b*]thiophen-2-yl)-*N*-methylaniline **5a** and 1-(2-(benzo[*b*]thiophen-2-yl)phenyl)-1-methylhydrazine **5b** in 86% and 64% yields, respectively (Scheme 3, (b)).[10d,11a] Notably, treatment of **3b** with Pd/C and $NaH_2PO_2 \bullet H_2O$, the nitroso and benzyl groups could be removed in one pot, affording 2- (benzo[*b*]thiophen-2-yl)aniline **5c** in 78% yield (Scheme 3, (c)).[11b]

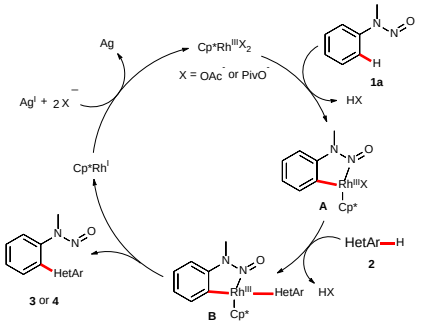
To gain some insights into the reaction mechanism, hydrogen/deuterium exchange experiments were performed (Scheme 4, (a)-(c)). Under the standard conditions, *N*-methyl-*N*-phenylnitrous amide **1a** reacted with CD_3OD (0.1 mL) in either the absence or present of **2a** for 2 h, the H/D exchange ratios of **1a** were 10% and 4%, respectively (Scheme 4, (a) and (c)), suggesting that the cleavage of the C−H bond of **1a** was a reversible process. Treatment of **2a** with CD_3OD (0.1 mL) in either the presence or absence of **1a** did not led to any deuterated [D]-**2a** (Scheme 4, (b) and (c)), suggesting that the C−H metalation of **2a** is an irreversible process. Then, the kinetic isotope effect (KIE) experiments for both coupling partners were investigated (Scheme 4, (d) and (e)). Two parallel competition reactions between **1a** and [D_5]-**1a** with **2a** did not give a significant KIE value (k_H/k_D = 1.02) (Scheme 4, (d)). A significant KIE value of 2.93 was observed for **2a** and [D]-**2a** with **1a** (Scheme 4, (e)). These above results reveal that the C−H cleavage of **2a** might be related to the rate-determining step.[12] Subsequently, we prepared the cyclometalated rhodium complex **6** according to the previous work by Zhu and coworkers (Scheme 4, (f)).[10a,13] When running the reaction of **1m** and **2a** in the presence of 10 mol % of **6**, the coupled product **3m** could be afforded in 63% yield (Scheme 4, (g)), indicating that the complex **6** could be a possible intermediate.



Scheme 3. Gram-scale reaction and the conversion of **3a** and **3b**.



Scheme 4. Mechanistic study.



Scheme 5. Plausible mechanistic pathway.

Based on the above observations and previous works on Rh(III)-catalyzed C(sp^2)–H heteroarylation,[3] a plausible mechanistic pathway is proposed (Scheme 5). First, the cyclorhodium intermediate **A** is formed through the coordination of *N*-methyl-*N*-phenylnitrous amide **1a** with the Cp*Rh(III) species and the subsequent *ortho*-C−H bond activation of arene. Next, the resulting intermediate **A** reacts with heteroarene **2** to produce the intermediate **B**, which further undergoes a reductive elimination to release the desired product **3** or **4**. Finally, the resulting Cp*Rh(I) species is reoxidized to the Cp*Rh(III) species by Ag salt to furnish the catalytic cycle.

In summary, we have disclosed a rhodium-catalyzed oxidative C–H/C–H cross-coupling reaction of a *N*-nitrosoaniline with a heteroarene to construct (2-aminophenyl)heteroaryl scaffolds. The protocol features mild reaction conditions, broad substrate scope and good tolerance of sensitive functional groups. The coupled products could be easily transformed to various (2-aminophenyl)heteroaryl derivatives. Further investigation to extend the application of this methodology is in progress.

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Conflicts of interest

There are no conflicts to declare.

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13 CCDC 1838256 (**6**) contains the supplementary crystallographic data for this communication.