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ortho-Heteroarylation of Azobenzenes by Rh-Catalyzed Cross-Dehydrogenative Coupling: An Approach to Conjugated Biaryls

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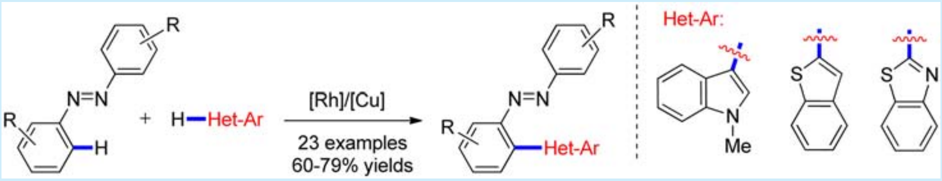
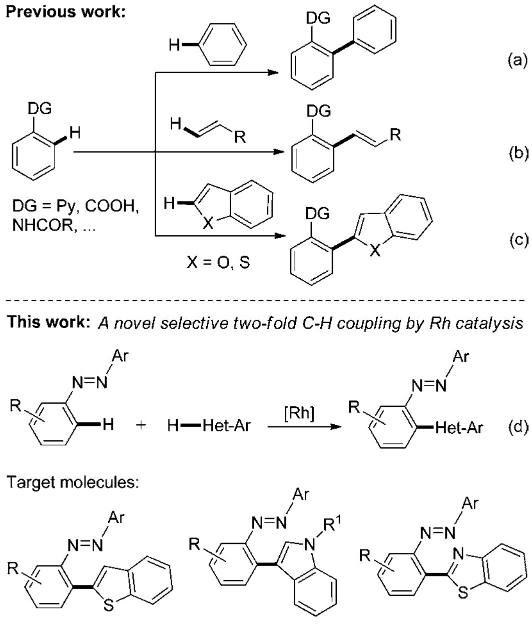
Supporting Information



ABSTRACT: A direct cross-dehydrogenative coupling strategy for *ortho*-C−H activation and functionalization of azobenzenes with heteroarenes in the presence of a Rh catalyst was developed. Excellent regioselectivity was achieved by azo-coordinated Rh to realize oxidative C−H/C−H cross-coupling, providing a series of π-conjugated biaryls in good yields.

Over the past decades, there has been an increasing effort to exploit diverse inert C−H bond activation and functionalization in organic synthesis.[1] Toward such challenging goals, the oxidative C−H/C−H coupling strategy developed by Li,[2a−c] Dong,[2d] and others[2e,f] enabled the generation of coupling partners without requiring prefunctionalization, which provides a concise approach to target organic molecules. Although remarkable progress in cross-dehydrogenative coupling (CDC) by transition metal catalysis has been achieved in recent years, regioselectivity control is one of the big problems. Several protocols, such as the use of excess arenes and electronically distinct coupling reagents,[3] have improved such selectivity more or less. Most recently, an alternative strategy involving the introduction of a directing group including pyridine, amide, or carbamate into the reactant could enhance the reactivity and regioselectivity of the oxidative C−H/C−H coupling reaction (Scheme 1).[4] Particularly, Rh-catalyzed CDC reactions have received much attention due to their availability, unique catalytic activity, and good group tolerance.[5] While Rh-catalyzed group-directed CDC reactions offered a reliable and used synthetic method, narrow substrate scope limited application in organic synthesis. Therefore, development of a new directing group to this chemistry, as well as the use of commercially available arenes as coupling partners, for the practical and concise synthesis of novel biaryls and other potentially active compounds, is highly desirable.

Scheme 1. Typical Strategies for C−H/C−H Coupling



Azobenzenes have been widely used as industrial dyes, indicators, etc. due to their conjugated π-system and unique properties.[6] Apart from these, azobenzenes with an effective unit of N═N as a directing group were investigated in C−H bond activation and functionalizations, providing alternative approaches to steric azo compounds and others with heteroaromatic rings.[6,7] Additionally, a larger number of heterocycles, such as indole,[8a−c] benzothiophene,[8d,g] and benzothiazole,[8h] as the potential coupling partners in oxidative C−H functionalization were explored in recent years. For some early examples, Glorious and co-workers pioneered related CDC reactions via Rh catalysis.[8d−g] However, regioselective functionalization of heteroaromatic compounds including those at the C2- or C3-position of indole and C2-position of benzothiophene remains a troublesome issue in organic synthesis. For indoles with rich electrons, they often suffer from decomposition or oxidative homocoupling under oxidative conditions.[9] Furthermore, a rare

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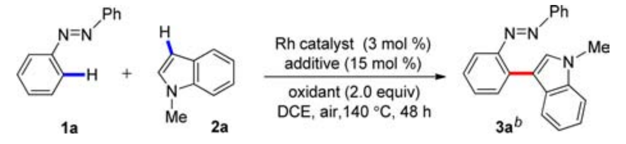
example of direct C3-position functionalization of indole with the CDC strategy was reported previously.[8b,c] Based on these understandings and our recent work on azo-group-directed C−H activation,[10] we disclose a novel Rh-catalyzed *ortho*-heteroarylation of azobenzenes with indole, benzothiophene, and benzothiazole, which provides an alternative approach to a series of π-conjugated biaryls.

Table 1. Optimization of the Reaction Conditions[a]

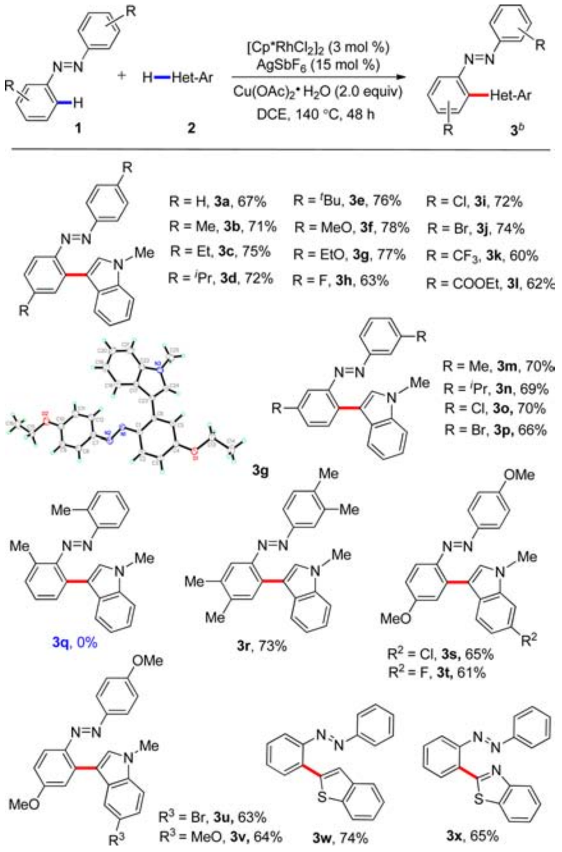


entry	Rh catalyst	additive	oxidant	yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2$	64
2	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	67
3	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	61[c]
4	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	58[d]
5	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	34[e]
6	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	37[f]
7	$[Cp^*RhCl_2]_2$	$AgBF_4$	$Cu(OAc)_2 \cdot H_2O$	trace
8	$[Cp^*RhCl_2]_2$	$AgPF_6$	$Cu(OAc)_2 \cdot H_2O$	11
9	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$PhI(OAc)_2$	nr
10	$Rh(Ph_3P)_3Cl$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	nr
11	$[Cp^*Rh(CH_3CN)_3]Y_2$		$Cu(OAc)_2 \cdot H_2O$	63
12	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	53[g]
13	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2 \cdot H_2O$	68[h]

[a]Reaction conditions: **1a** (0.30 mmol), **2a** (0.60 mmol), Rh catalyst (containing 6 mol % of Rh), additive (15 mol %), oxidant (2.0 equiv), 140 °C for 48 h. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl. [b]Isolated yield. [c]N_2. [d]HOAc (1.0 equiv). [e]1-Ad-COOH (1.0 equiv). [f]TFA (1.0 equiv). [g]At 130 °C. [h]At 150 °C. Y = SbF_6.

Our first effort toward the oxidative C−H/C−H coupling focused on the reaction of azobenzene (**1a**) with 1-methylindole (**2a**), as shown in Table 1. Early exploration demonstrated that there is an effective directing group in azobenzene for Rh-catalyzed C(sp^2)−H bond activation.[7a,10e,12] Presumably, the formed cyclic Rh intermediate is highly active due to its coordination with azo (N═N) for further transformation. It is known that $AgSbF_6$ is the most effective additive for Rh-catalyzed *ortho*-C−H functionalization.[7a,10e] At the beginning, a model reaction of **1a** with **2a** in the presence of $[Cp^*RhCl_2]_2$ (3 mol %), $AgSbF_6$ (15 mol %), and $Cu(OAc)_2$ (2.0 equiv) in DCE as the reaction medium at 140 °C for 48 h was examined, providing desired compound **3a** in 64% isolated yield (Table 1, entry 1). Meanwhile, no homocoupling of 1-methylindole or its C2 functionalization was observed during the reaction. Next, the feasibility of the reaction was investigated under various reaction conditions. A comparable result was obtained when $Cu(OAc)_2 \cdot H_2O$ was used instead of $Cu(OAc)_2$ as oxidant in the reaction (entry 2). The model CDC reaction carried out in inert atmosphere led to a slightly decreased yield of **3a** (entry 3). In addition, some common additives, such as HOAc (acetic acid), 1-Ad-COOH (1-adamantane carboxylic acid), and TFA, were screened, and they did not accelerate the CDC reaction (entries 4−6). The use of $AgBF_4$ and $AgPF_6$ gave poor results in the formation of **3a** (entries 7 and 8). Employment of $PhI(OAc)_2$ as oxidant or $Rh(Ph_3P)_3Cl$ as catalyst gave negative results (entries 9 and 10). It should be noted that the model reaction proceed well in the presence of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$, suggesting that coordinated anion SbF_6^- is very crucial for *ortho*-C−H functionalization of azobenzene (entry 11). Moreover, optimization of the reaction temperature did not enhance the yield of **3a** (entries 12 and 13). Finally, solvent screening revealed that DCE was the best choice (Table S1, Supporting Information). Therefore, the optimal catalytic system for this Rh-catalyzed oxidative C−H/C−H coupling reaction was obtained as follows: **1a** (0.30 mmol), **2a** (0.60 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), $AgSbF_6$ (15 mol %), and $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv) in DCE (2.0 mL) at 140 °C under air for 48 h.

Scheme 2. Scope of Azobenzene and Heteroarene[a]



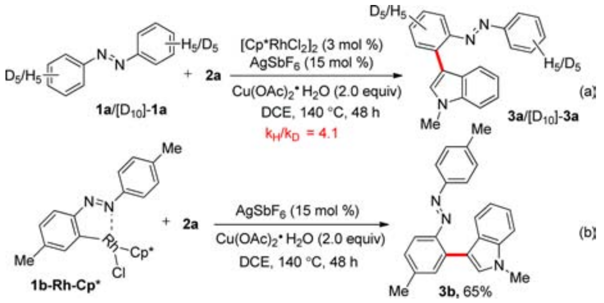
[a]Reaction conditions: **1** (0.30 mmol), **2** (0.60 mmol), $[Cp^*RhCl_2]_2$ (3 mol %), $AgSbF_6$ (15 mol %), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), DCE, 140 °C for 48 h. [b]Isolated yield.

Next, the generality of the CDC reaction of azobenzenes with indoles was investigated under optimal reaction conditions, and the results are listed in Scheme 2. The scope of azobenzenes was examined using **2a** as a coupling partner. It was found that azobenzenes with an electron-rich substituent at the *para*-position of the azo group, such as Me, Et, ^{i}Pr, ^{t}Bu, MeO, and OEt, proceeded well under the standard conditions, providing the corresponding products (**3b−g**) in 71−79% yields. Single-crystal X-ray analysis of **3g** confirmed its structure and demonstrated the high regioselectivity of the reaction.[11] Substrates with halogens, including F, Cl, and Br at the *para*-position of the azo group reacted with **2a** to afford the according products (**3h−j**) in moderate to good yields (63−74%). However, azobenzenes with a stronger electron-withdrawing group (CF_3 or COOEt) showed reactivity lower than that of azobenzenes with an electron-donating group (**3b−g** vs **3k−l**). In addition, reactions of **2a** with *meta*-substituted azobenzenes with Me, ^{i}Pr, Cl, or Br also generated 66−70% yields of the desired products (**3m−p**).

Unfortunately, the use of *ortho*-substituted azobenzenes failed in this reaction (**3q**). Further, the multisubstituted azobenzene was also an excellent substrate, forming an anticipated product **3r** in 73% yield. We continued our investigation on the scope of indoles and other heterocycles under optimized reaction conditions. For selected examples, indole derivatives containing F, Cl, Br, and MeO on the phenyl rings were also compatible for this oxidative coupling with (*E*)-1,2-bis(4-methoxyphenyl)-diazene and transformed into the corresponding products (**3s−v**) in 61−65% yields. Importantly, this CDC reaction was also extended to benzothiophene and benzothiazole with **1a** under the present reaction conditions, affording **3w** and **3x** in 74 and 65% yield, respectively.

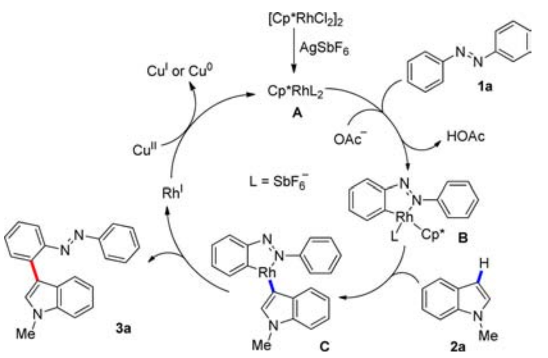
To gain insight into the reaction mechanism, some control experiments were conducted (Scheme 3). With D_2O (10 equiv) as an additive, **1a** was stirred under the given conditions for 0.5 h, and D-labeled azobenzene was determined by ^{1}H NMR, indicating that 86% of [D_2]-**1a** was observed (Figure S1 in Supporting Information). Meanwhile, the 3-position of H in **2a** was replaced by 73% D under the same reaction conditions (Figure S2). In addition, an obvious kinetic isotope effect (KIE, k_H/k_D = 4.1) was obtained from intermolecular competing experiments (Scheme 3a), implying that *ortho*-C−H activation of azobenzene by Rh^{III} initiates the CDC reaction. A similar KIE (k_H/k_D = 3.6) is also presented in Scheme S1. Based on this assumption, a complex of **1b** with Rh (**1b-Rh-Cp***) was then synthesized according to the reported procedure.[12] It was found that a reaction of obtained **1b-Rh-Cp*** with **2a** afforded **3b** in 65% yield under the optimal conditions (Scheme 3b).

Scheme 3. Mechanistic Study



Based on the previous reports[8g,h] and the preliminary mechanistic studies, a possible mechanism for the Rh-catalyzed CDC reaction is proposed in Scheme 4. The reaction was initiated by an anion exchange between [Cp*$RhCl_2$]$_2$ and $AgSbF_6$ to generate an active Rh complex **A**. The formed **A** reacted with **1a** to form intermediate **B** through *ortho*-C−H activation of **1a**. The obtained **B** underwent an insertion into the 3-position of the C−H bond of **2a** to afford **C**, which proceeded through a reductive elimination to deliver product **3a** along with the formation of Rh(I). Finally, Rh(I) was reoxidized to Rh(III) species by Cu(II) salt to complete the catalytic cycle.

Scheme 4. Proposed Reaction Mechanism



In conclusion, this communication describes a novel Rh-catalyzed CDC reaction for the *ortho*-heteroarylation of azobenzenes with indole, benzothiophene, and benzoxazole, which provides a direct and concise route to π-conjugated biaryls. The unique reactivity and selectivity observed in the CDC reaction prompted us to initiate further studies on the reaction mechanism, and the potential application in luminous materials is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01277.

Full experimental details and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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