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Rh(III)-Catalyzed Selective Coupling of *N*-Methoxy-1*H*-indole-1-carboxamides and Aryl Boronic Acids

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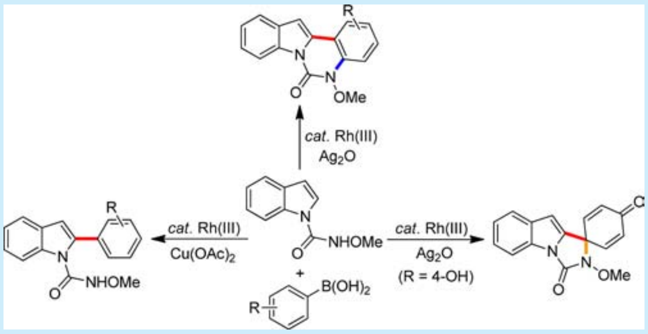
Supporting Information

ABSTRACT: A Rh(III)-catalyzed selective coupling of *N*-methoxy-1*H*-indole-1-carboxamide and aryl boronic acids is reported. The coupling is mild and efficient toward diverse product formation, with selective C−C and C−C/C−N bond formation. Kinetic isotope effects studies were conducted to reveal a mechanism of C−H activation and electrophilic addition.

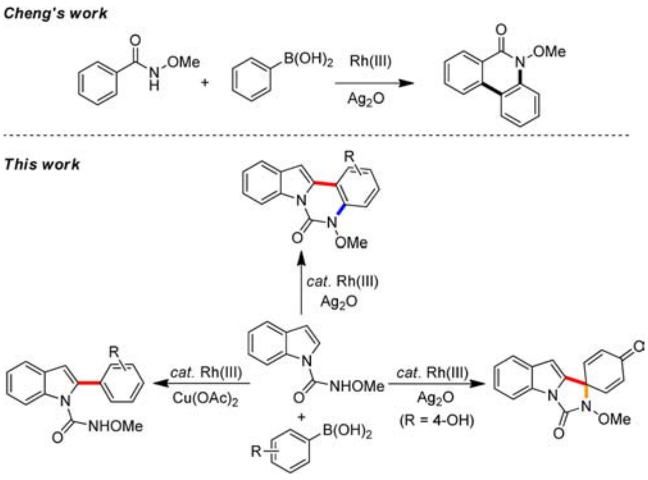


The indole framework is a structural motif commonly found in pharmaceutical drugs and natural products.[1] Consequently, great efforts have been devoted to the synthesis and chemical modification of indoles, especially involving transition-metal catalysis.[2] In the past few years, transition-metal-catalyzed directing-group assisted C−H functionalization has emerged as a distinct and powerful method for the construction of C−C, C−N, C−O, and C−X bonds.[3]

Recently, Rh(III)-catalyzed C−H functionalization has advanced significantly for the rapid assembly of various complex molecular structures, particularly in the fields of medicinal chemistry.[4] Alkynes,[5] alkenes,[6] allenes,[7] organic azides,[8] and diazo copounds[9] are frequently used as coupling partners in Rh(III)-catalyzed C−H functionalization. However, very few examples of Rh(III)-catalyzed C−H functionalization and late-stage coupling using organoboron reagents have been reported. Recently, Miura developed a Rh(III)-catalyzed oxidative coupling of aryl boronic acids and alkynes for the synthesis of naphthalenes and anthracenes.[10] More recently, Cheng reported an excellent Rh(III)-catalyzed dual oxidative coupling of *N*-methoxybenzamides and aryl boronic acids for facile access to phenanthridinones (Scheme 1).[11]

To the best of our knowledge, the Rh(III)-catalyzed coupling of indoles and aryl boronic acids giving divergent outcomes remains unreported.[12,13] Continuing our interest in Rh(III)-catalyzed C−H functionalization for biologically interesting small molecule synthesis,[14] herein, we wish to report a Rh(III)-catalyzed selective coupling of *N*-methoxy-1*H*-indole-1-carboxamides and aryl boronic acids, for arylation, [4 + 2] cyclization, and [4 + 1] cyclization respectively (Scheme 1).

Scheme 1. Rh(III)-Catalyzed Arylboronic Acids Involved Coupling



We commenced our study by investigating the coupling of *N*-methoxy-1*H*-indole-1-carboxamide **1a** and phenyl boronic with $[Cp^{*}RhCl_2]_2$ as the catalyst (Table 1). Control reactions showed that $[Cp^{*}RhCl_2]_2$ was essential in this reaction (entry 1), and the equivalent addition of $Cu(OAc)_2$ gave a phenylation product **3a** in 94% yield (entry 2). This encouraged us to further optimize the reaction conditions. When $K_2S_2O_8$ was used as an oxidant, no product was observed (entry 3). The use of AgOAc led to a mixture of **3a** and the [4 + 2] cyclization product **4a** (entry 4, **3a**, 56%; **4a**, 13%). This unpredicted result prompted us to further examine various silver salts, and we found that Ag_2CO_3 was inferior giving **4a** as the sole product only in 11% yield (entry 5). When Ag_2O was used as the

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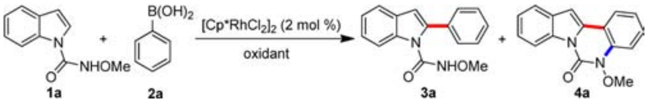
Table 1. Model Reaction Optimization[a]



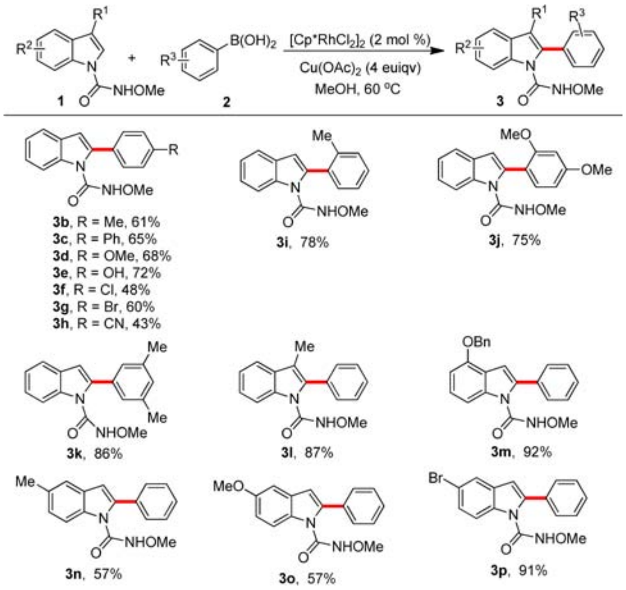
entry	oxidant	solvent	temp (°C)	product/yield (%)[b]
1	none	MeOH	60	–
2	$Cu(OAc)_2$	MeOH	60	**3a**/94
3	$K_2S_2O_8$[c]	MeOH	60	–
4	AgOAc	MeOH	60	**3a**/56, **4a**/13
5	Ag_2CO_3	MeOH	60	**4a**/11
6	Ag_2O[d]	MeOH	60	**3a**/93
7	Ag_2O	MeOH	60	**4a**/76
8	Ag_2O/O_2[c,e]	MeOH	60	**4a**/73
9	Ag_2O	CH_3CN	60	**4a**/58
10	Ag_2O	*t*BuOH	60	–
11	Ag_2O	MeOH	30	–
12	Ag_2O	MeOH	80	**4a**/75

[a]The reaction was carried out with **1** (0.2 mmol), **2a** (0.4 mmol), and oxidant (4 equiv) in solvent (2 mL) at indicated temperature for 12 h unless otherwise noted. [b]Yields of isolated product. [c]2 equiv of oxidant were used. [d]Reaction for 1 h. [e]Balloon of O_2 gas was used.

oxidant, the reaction furnished **3a** in 93% yield within 1 h (entry 6) and **4a** in 76% yield with a prolonged reaction time of 12 h (entry 7). This proved that **4a** was generated from **3a**. Next, a combination of Ag_2O (2 equiv) and oxygen (balloon gas) was tested to furnish **4a** in a slightly lower yield (entry 8, 73%). A survey of the solvent showed that *t*BuOH and CH_3CN were not optimal (entries 9−10). This indicated that further optimization revealed that decreasing the reaction temperature to 30 °C led to starting material recovery (entry 11), while increasing the temperature to 80 °C gave **4a** in 75% yield (entry 12).

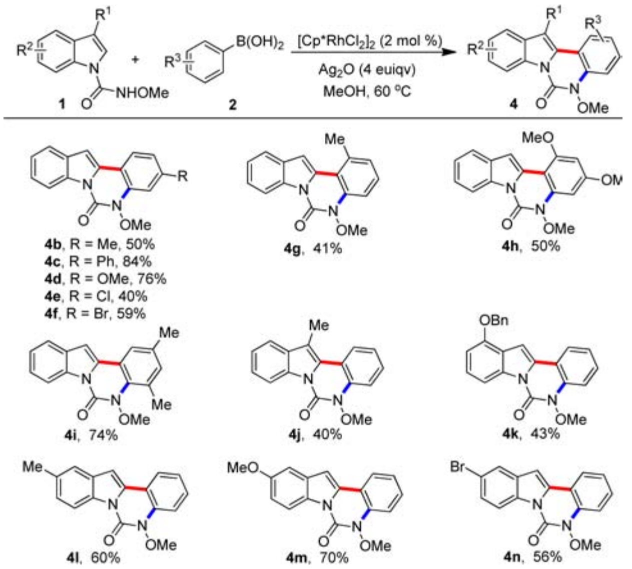
Next we proceeded to study the scope of Rh(III)-catalyzed coupling of indoles with various aryl boronic acids using $Cu(OAc)_2$ as the oxidant. As depicted in Table 2, various aryl boronic acids regardless of electron-donating or -withdrawing groups on the aromatic ring reacted smoothly in this coupling to furnish the 2-arylated indole products in good yields (Table 2, **3b**−**3i**, 48%−86%), with valuable functional group tolerance. Thus, the presence of a methyl, phenyl, methoxy, hydroxy, chloro, bromo, and cyano group offered ample opportunity for further derivatization. The electron-withdrawing group substituted aryl boronic acids (**3e** and **3f**) showed less efficiency than that of electron-donating group substituted aryl boronic acids in this coupling, probably due to their weaker nucleophilicity. Variation of indoles showed that differentially substituted indoles were also applicable in this transformation to produce the corresponding 2-phenylated products in moderate to excellent yields (Table 2, **3j**−**3n**, 57%−92%). Notably, this Rh(III)-catalyzed C−C coupling of indoles with aryl boronic acids for arylation is simple and proceeds under mild reaction conditions with a broad substrate scope.[15]

Table 2. Rh(III)-Catalyzed Coupling of Indoles with Various Aryl Boronic Acids for Arylation[a]



[a]The reaction was carried out with **1** (0.2 mmol), **2** (0.4 mmol), and $Cu(OAc)_2$ (0.8 mmol) in MeOH (2 mL) at 60 °C for 3 h to be completed.

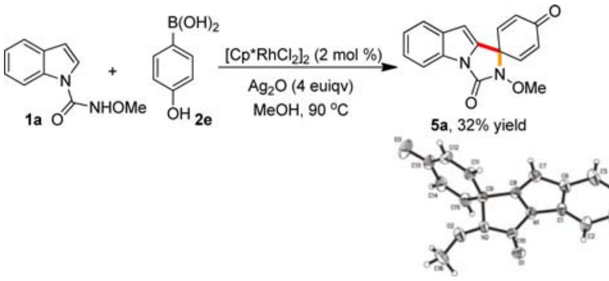
Table 3. Rh(III)-Catalyzed Coupling of Indoles with Various Aryl Boronic Acids for [4 + 2] Cyclization[a]



[a]The reaction was carried out with **1** (0.2 mmol), **2** (0.4 mmol), and Ag_2O (0.8 mmol) in MeOH (2 mL) at 60 °C for 12 h to be completed.

The scope of this Rh(III)-catalyzed coupling using Ag_2O as the oxidant was also investigated. As shown in Table 3, a broad range of indoles and aryl boronic acids were amenable to the reaction. Functionalized boronic acids with methyl, phenyl, methoxy, chloro, bromo substitution and polysubstituted boronic acids were compatible with the oxidative coupling system to deliver the cyclized 5-methoxyindolo[1,2-*c*]quinazolin-6(5*H*)-ones in moderate to good yields (Table 3, **4b**−**4i**, 40%−84%). The slightly lower yield of **4d** and **4e** is likely due to the electron-withdrawing nature and steric hindrance of the starting boronic acids. The generality of indoles was also demonstrated. Structurally and electronically varied indoles were explored and found applicable in this coupling furnishing the corresponding cyclized heterocycles in moderate to good yield (Table 3, **4j**−**4n**, 40%−70%). Compared to classical syntheses of indolo[1,2-*c*]quinazolin-6(5*H*)-ones,[16] this transformation represents a simple and direct approach toward this biologically interesting type of heterocycle from readily available starting materials under mild reaction conditions.[17]

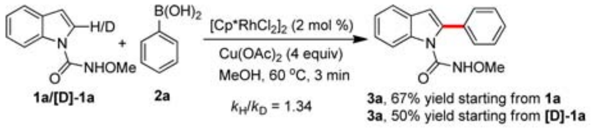
Interestingly, when 4-hydroxyphenylboronic acid **2e** was subjected to this reaction with **1a**, by elevating the reaction temperature to 90 °C, unexpected spiro-cyclohexadienone **5a** was exclusively obtained as the [4 + 1] cyclization form (eq 1),



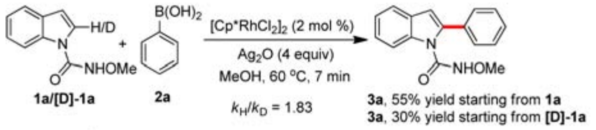
(1)

and the slightly low yield was due to the decomposition of starting materials. This unpredicted result of dearomtization of the phenol ring indicated that this C−C/C−N coupling probably occurred via an electrophilic addition process.[18,19] Furthermore, the structure of **5a** was unambiguously confirmed by X-ray analysis.

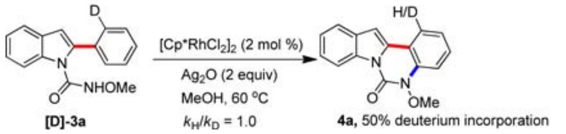
To gain insight into the reaction mechanism, a kinetic effect study was conducted to probe the mechanism.[20] When Cu(OAc)$_2$ was used as the oxidant, a KIE value of 1.34 was obtained for the coupling reaction (eq 2). This revealed a small,



(2)



(3)

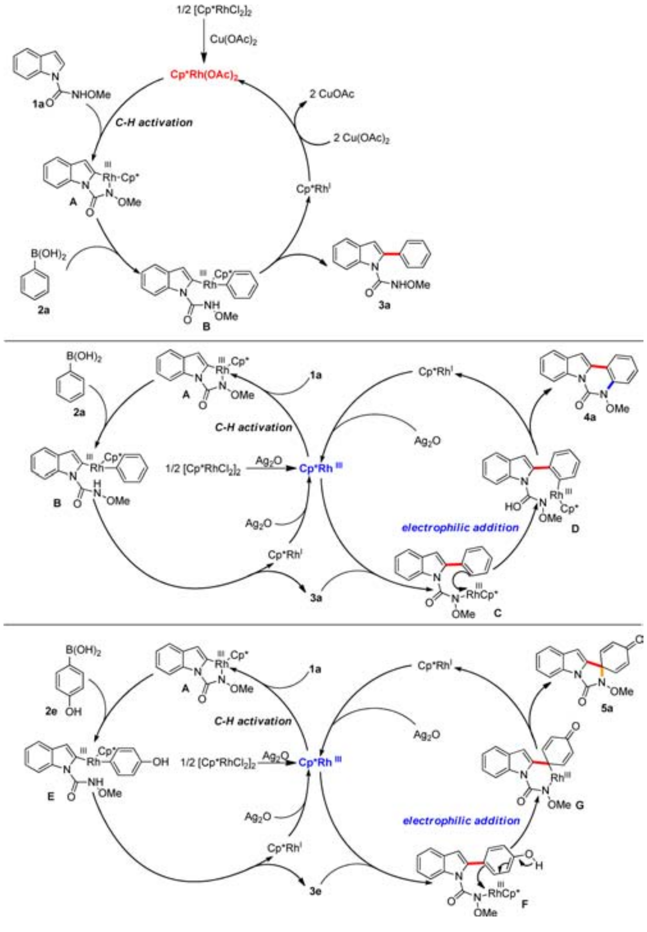


(4)

perhaps secondary isotope effect, suggesting that C−H bond cleavage occurs as part of the reaction, but cannot be part of the rate-determining step. When Ag$_2$O was used as the oxidant for **3a** synthesis, a KIE value of 1.83 was obtained (eq 3), suggesting a C−H bond cleavage was occurring during the rate-determining step. Notably, when [**D**]-**3a** was synthesized and subjected to the [Cp*RhCl$_2$]$_2$/Ag$_2$O oxidative system to obtain **4a**, a KIE value of 1.0 was observed which excluded C−H bond cleavage as the rate-determing step for the C−N bond formation from **3a** to **4a** (eq 4), suggesting an intramolecular electrophilic addition was occurring, which is evidenced by the dearomatization of **2e**. Therefore, this selective coupling is mechanically unique in comparison to the Rh(III)-catalyzed traditional coupling of arylboronic acids.[11]

Based on these experiments, a plausible set of mechanisms are proposed in Scheme 2 to explain these selective couplings. When Cu(OAc)$_2$ is used as the oxidant, the dimeric [Cp*RhCl$_2$]$_2$ changes to Cp*Rh(OAc)$_2$. Cp*Rh(OAc)$_2$ is then captured by **1a** to form the rhodacycle **A** via *N*-metalation and a turnover limiting C−H activation. Transmetalation of **A** with **2a** would lead to **B**, and reductive elimination furnished the C−C coupling product **3a** and a Rh(I) species. Reoxidation of Rh(I) to Cp*Rh(OAc)$_2$ by Cu(OAc)$_2$ would enable the catalytic cycle to proceed. With respect to the C−C/C−N coupling, the initial [Cp*RhCl$_2$]$_2$ could undergo chloride ligand removal by Ag$^+$ to form Cp*Rh(III). A similar *N*-metalation/C−H activation would generate rhodacycle **A**. Transmetalation would furnish **3a** and a Rh(I) species which could be reoxidized to Cp*Rh(III) by Ag$_2$O. At this stage, another *N*-metalation can occur on **3a** in the presence of Cp*Rh(III) to form intermediate **C**, and an intramolecular electrophilic addition of **C** would lead to the seven-membered rhodacycle **D**. Reductive elimination would afford the [4 + 2] cyclization product **4a** and the Rh(I) species. Reoxidation of Rh(I) to Cp*Rh(III) by Ag$_2$O would enable the catalytic cycle. Regarding the [4 + 1] cyclization, the mechanism is similar to that of the [4 + 2] cyclization, except that the intramolecular electrophilic addition takes place on the *para*-position of the phenol ring (**F** to **G**) to furnish the dearomatized spirocyclohexadienone product.

Scheme 2. Proposed Mechanism



In conclusion, we have demonstrated a Rh(III)-catalyzed selective coupling of *N*-methoxy-1*H*-indole-1-carboxamides and aryl boronic acids, for divergent product formation. Kinetic isotope effect studies were conducted to reveal a mechanism of C−H activation and electrophilic addition. Further applications of this method in pharmaceuticals is in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization for products, copies of H and C NMR spectra, and cif file for compound **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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