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Rhodium(III)-Catalyzed Oxidative Annulation of Amidines with Alkynes *via* Sequential C—H Bond Activation

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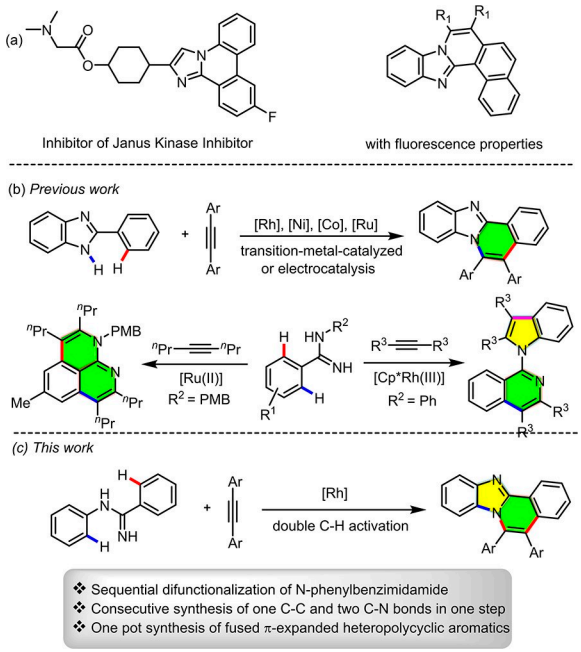
In this paper, a rhodium-catalyzed sequential two-fold *ortho*-C–H functionalization of *N*-phenylbenzimidamide with internal alkyne is reported. The double C–H activations proved viable in a one-pot fashion with the assistance of C=N and C–N bonds, providing a series of benzimidazoisoquinolines with high levels of positional selectivity control. The operationally simple transformation showed high functional group compatibility and featured the cleavage of C–H bonds located on different a moiety of the *N*-phenylbenzimidamide substrates. Detailed mechanistic studies provided strong support for C–H bond cleavage on the *N*-phenyl ring to be preferential compared with C–H bond cleavage on C-phenyl ring. As a multifunctional catalytic platform, the rhodium catalyst conducted two independent and compatible catalytic cycles in one pot.

Introduction

Nitrogen-containing heterocyclic compounds are ubiquitous features in a plethora of natural products, synthetic compounds with conspicuous biological activities,[1] and functional properties.[2] Among them, π-conjugated polycyclic heteroaryl scaffolds have received special attention owing to their photoluminescence properties,[3] electrochemical properties,[4] and pharmaceutically activities[5] (Scheme 1a). Benzimidazoisoquinolines, as classical π-conjugated polycyclic heteroaryl compounds, are widely found in biologically active molecules,[6] and can be potentially utilized as fluorescent labels due to the aggregation-induced emission (AIE) phenomenon.[7] Due to its importance, there exists a continued imperative demand for the highly efficient and selective construction of benzimidazoisoquinoline derivatives.

Traditionally, synthesis of benzimidazoisoquinolines has thus far largely relied on oxidative C–H/N–H annulation of phenylbenzimidazole with alkyne[8] or multistep methods[9] (Scheme 1b). As a paradigm, Miura and co-workers[10] successively demonstrated chelation-assisted C–H activation to synthesize imidazoisoquinoline from 2-phenyl-1H-benzimidazole and alkyne, wherein an additive (1,2,3,4-tetraphenylcyclopentadiene) was required. Following this pioneering work, cobalt(III)-catalyzed or nickel-catalyzed C–H activation of substituted (benz)imidazoles were independently reported by Sen[11] and Chatani.[12] Very recently, the group of Ackermann developed the ruthenium-catalyzed dehydrogenative annulation reaction of imidazoles with alkynes through an electrochemical C–H/N–H annulation.[13] While these strategies are of solid reliability and have been frequently used, the multiple C–H bond activations for the rapid construction of benzimidazoisoquinolines from readily available substrates is quite promising, in which several new bonds were formed in a single operation.



Scheme 1. Representative examples of benzimidazoisoquinolines synthesis.

Amidine has been used as a flexible reaction partner for direct C–H activation reaction with alkynes,[14] which include: 1) the C=N-aided monoannulation of amidines with alkynes to easily fabricate isoquinoline, 2) the incorporation of two alkyne units into specific substrates to generate indole-functionalized

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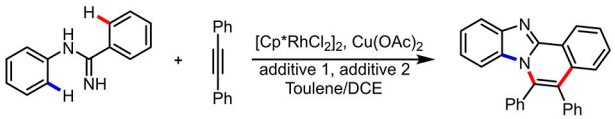
isoquinoline[15] and 1H-benzo[de][1,8]naphthyridine derivate,[16] 3) the fourfold C–H activation of amidines with alkynes, leading to π-conjugated polycyclic heteroaryl scaffolds, 4) ortho-alkenylation of aromatic amidines with alkynes,[17] and others. However, the twofold annulation of amidines with alkynes to furnish benzimidazoisoquinolines has generally remained undeveloped. One of the reasons for this is the absence of a general and reliable catalytic system for simultaneous activation of C–H bonds at different positions. It was observed that the *o*–C(sp^2)–H bond of *N*-phenyl ring is specifically activated under identical conditions rather than *C*- phenyl ring of amidine.[14a,15,18] Thus, it offers the possibility to exploit double C–H bond activation conducted by sequential difunctionalization of *N*-phenylbenzimidamide in one pot. Herein, we reported Rh-catalyzed oxidative C–H/N–H annulation of amidines with alkynes to assemble benzimidazoisoquinoline skeletons. In this cascade reaction, one C–C and two C–N bonds are rapidly formed to build the molecular complexity. Moreover, this protocol also features easily accessible starting materials and mild reaction conditions.

Results and Discussion

To begin our studies, we chose *N*-phenylbenzimidamide **1a** and diphenylacetylene **2a** as the model substrates. Inspired by our previous work,[19] the reaction was performed in the presence of 2.5 mol% $[Cp^*RhCl_2]_2$ and 1.0 equiv. of Na_2CO_3 in toluene/DCE at the temperature of 80 °C. The results are summarized in Table 1. Gratifyingly, the desired product 5,6-diphenylbenzo[4,5]imidazo[2,1-a]isoquinoline **3aa** was obtained in 40% yield after 48 h (Table 1, entry 1). Inspired by this initial result, we checked the effect of various additives like NaF, $(CH_3)_4NOH{\cdot}5H_2O$, CH_3COONa, and NBu_4F (entries 2–5). The results showed that NBu_4F was proven to be the better choice, affording **3aa** in 46% yield (entry 5). A slight improvement of the yield was observed upon increasing the loading of NBu_4F to 2 equiv, whereas an obvious decrease was detected on increasing the amounts of NBu_4F to 3 or 4 equiv. (entries 7 and 8). The reaction gave a lower yield (45%) when DCE was employed as a single solvent, while no desired product was obtained in toluene (entries 9 and 10). Further optimization was performed using different silver salts such as $AgSbF_6$, AgOTf, $AgBF_4$, and Ag_2CO_3, but in all these cases, no product was observed (entries 11–14). The yield was improved to 55% with the assistance of pivalic acid, and byproduct 1-aminoisoquinoline **3a** was obtained in 29% yield (entry 15). Notably, when the reaction was conducted without NBu_4F, the yield decreased to 25%, which suggested that NBu_4F played an important role in the reaction (entries 15 versus 16). To our delight, a further increase in the yield was achieved by post-treatment of the reaction mixture to CF_3CH_2OH and PIFA, then stirred for 4 h, delivering a satisfactory yield of **3aa** in 75% yield (entry 17). We have elaborated the reaction between **1a** and **2a**, and the result demonstrated that the starting material **2a** remained in 10% yield before the PIFA treatment. A control experiment demonstrated that no product was formed in the absence of $[Cp^*RhCl_2]_2$ (entry 18), and further investigation revealed that decreasing the reaction temperature to 40 °C afforded a trace amount of inseparable mixture (entry 19).

Table 1. Optimization of Reaction Conditions.[a]

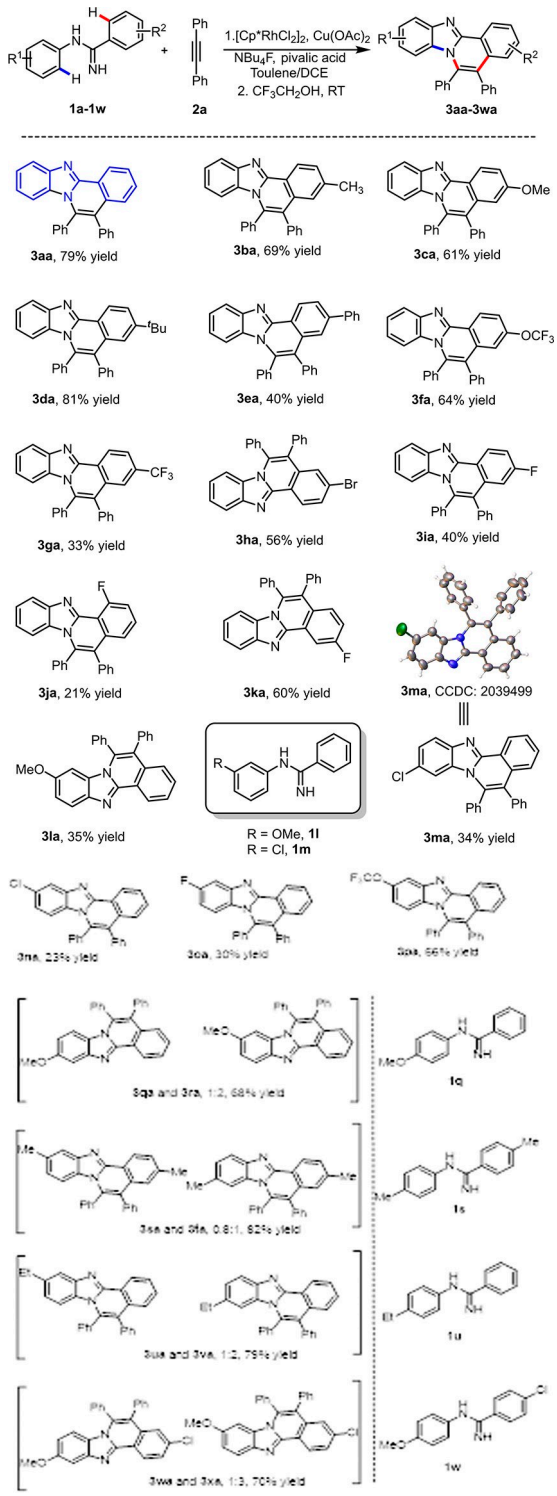


1a 2a 3aa

Entry	Catalyst	Additive 1	Additive 2	Yield[b]
1	$[Cp^*RhCl_2]_2$	Na_2CO_3	–	40
2	$[Cp^*RhCl_2]_2$	NaF	–	34
3	$[Cp^*RhCl_2]_2$	$(CH_3)_4NOH.5H_2O$	–	45
4	$[Cp^*RhCl_2]_2$	CH_3COONa	–	36
5	$[Cp^*RhCl_2]_2$	NBu_4F (1 equiv)	–	46
6	$[Cp^*RhCl_2]_2$	NBu_4F (2 equiv)	–	50
7	$[Cp^*RhCl_2]_2$	NBu_4F (3 equiv)	–	27
8	$[Cp^*RhCl_2]_2$	NBu_4F (4 equiv)	–	N.D.
9[c]	$[Cp^*RhCl_2]_2$	NBu_4F (2 equiv)	–	45
10[d]	$[Cp^*RhCl_2]_2$	NBu_4F (2 equiv)	–	N.D.
11	$[Cp^*RhCl_2]_2$	NBu_4F (2 equiv)	$AgSbF_6$	N.D.
12	$[Cp^*RhCl_2]_2$	NBu_4F (2 equiv)	AgOTf	N.D.
13	$[Cp^*RhCl_2]_2$	NBu_4F (2 equiv)	$AgBF_4$	N.D.
14	$[Cp^*RhCl_2]_2$	NBu_4F (2 equiv)	Ag_2CO_3	N.D.
15	$[Cp^*RhCl_2]_2$	NBu_4F (2 equiv)	pivalic acid	55
16	$[Cp^*RhCl_2]_2$	–	pivalic acid	25
17[e]	$[Cp^*RhCl_2]_2$	NBu_4F (2 equiv)	pivalic acid	75
18	–	NBu_4F (2 equiv)	pivalic acid	N.D.
19[e,f]	$[Cp^*RhCl_2]_2$	NBu_4F (2 equiv)	pivalic acid	trace

[a] Reaction conditions: $[Cp^*RhCl_2]_2$ (2.5%), alkyne **2a** (0.125 mmol, 22.8 mg), amidine **1a** (1.5 equiv), $Cu(OAc)_2$ (2 equiv), additive 1 (x equiv), additive 2 (20%), toluene/DCE (v/v = 1:4, 4 mL), 80 °C, 48 h. [b] Isolated yield. [c] DCE (3 mL). [d] Toluene (3 mL). [e] PIFA (1 equiv) and CF_3CH_2OH (2 ml) were added after reaction for 80 °C. [f] 40 °C.

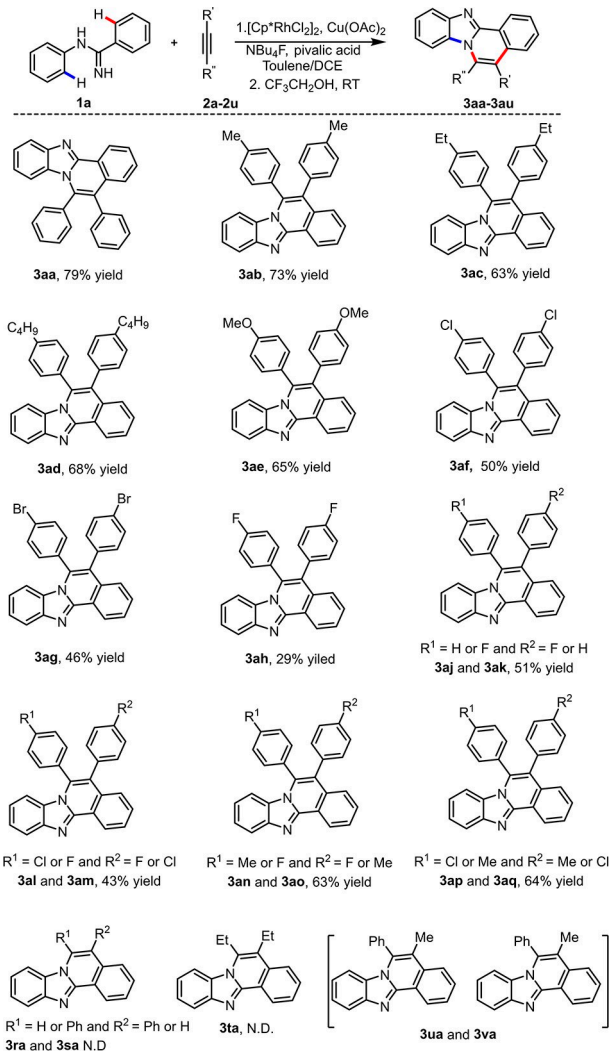
With the optimal reaction conditions in hand, we started to investigate the scope of the cascade between amidines **1a–1p** and alkyne **2a**. As summarized in Scheme 2, we were pleased to find that a range of amidines, regardless of the electronic nature and the positions, could be successfully employed in the reaction. The desired products **3aa–3pa** were furnished with a yield up to 81%, wherein the structures of **3ja** and **3ma** were verified unambiguously by X-ray crystallography (CCDC: 2039498 and 2039499, see the Supporting Information). Moreover, amidine bearing a *meta* moiety on C-phenyl ring was adopted to this protocol, as expected, the C–H bond with less steric hindrance was selectively transferred to the target product **3ka**. Furthermore, 2-fluoro-N-phenylbenzimidamide **1j** was attempted in the reaction and underwent the reaction, albeit with 21% yield. We next turned our attention to the substitutions on the *N*-phenyl ring. When the reaction was extended to N-(3-chlorophenyl)benzimidamide **1l** and N-(3-methoxyphenyl) benzimidamide **1m**, products **3la** and **3ma** were exclusive obtained in similarly yields. This phenomenon indicated that the second C–H activation on *N*-phenyl favored the pathway in a less hindered manner. Notably, the electronic nature of the 4-position substituted *N*-phenyl moiety in amidine has a distinguished effect on the reaction efficiency (Scheme 2). The opposite is in the case that substrates with electron-donating groups delivered two regioisomers in higher yields



Scheme 2. Reaction scope of amidines.

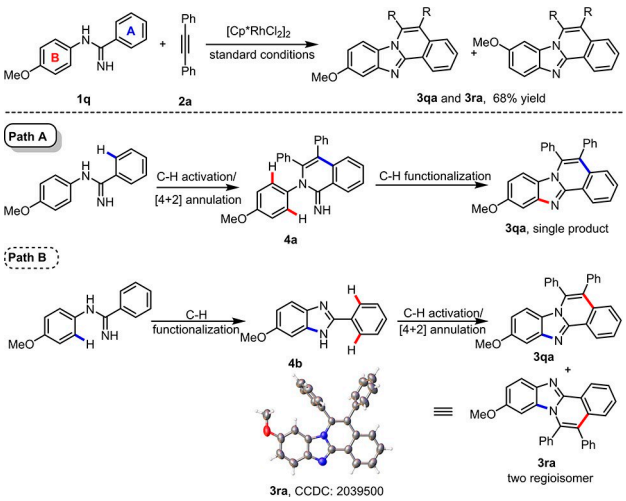
(**3 qa**–**3 xa**), while amidines bearing electron-withdrawing groups gave products in lower yields (**3 na** and **3 oa**).

Having identified the optimal template, we next focused our attention on the substrate scope with respect to alkynes. As shown in Scheme 3, electron-neutral, electron-donating, or electron-withdrawing substituents were generally well-tolerated, furnishing the desired products **3 aa**–**3 aq** in reasonable yields. Alkyl, halogen, and methoxy functionalities were compatible with the reaction conditions. Especially, a variety of alkynes with electron-donating groups at the *para*-positions on the aromatic ring reacted smoothly with **1 a** to construct the corresponding products (**3 ab**–**3 ae**) in good yields (63 %–73 %). The methyl substituent at the *ortho*-position of the phenyl ring failed to provide the desired product, which may be attributed to steric effects. The electron-withdrawing substituents were also tolerated in this protocol but furnished the products in absolutely lower yields (**3 af**–**3 ah**). The cascade reactions of asymmetrically disubstituted alkynes proceeded smoothly, and two possible regioisomers were achieved in moderate yields. However, terminal alkynes could not react with **1 a** under the standard reaction conditions. When 3-hexyne was employed, no desired product was obtained. Moreover, the reaction of **1 a** with a terminal alkyne such as phenylacetylene under the standard conditions failed to afford the desired product, whereas homocoupling product 1,4-diphenylbuta-1,3-diyne was obtained as a major product.

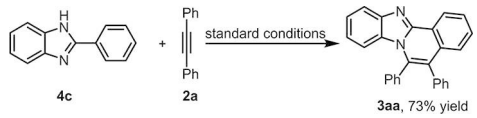


Scheme 3. Scope of alkynes.

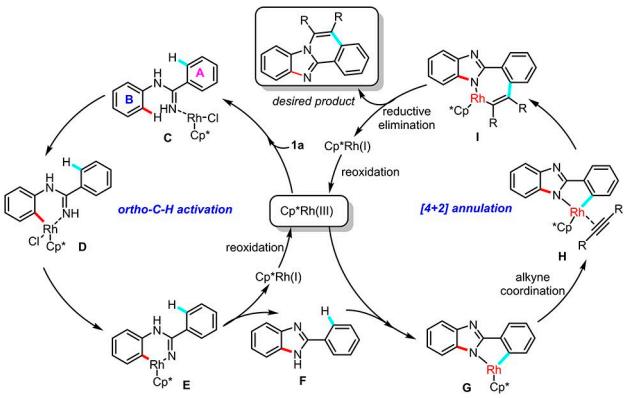
To elucidate the reaction mechanism, the reaction of amidine **1q** and **2a** was re-analyzed, and two possible paths are proposed (Scheme 4). For **path A**, C–H functionalization occurs preferentially at the C–H bond on ring **A**, and subsequent C–H functionalization on ring **B** gives **3qa**. As a more reasonable alternative **Path B**, the reaction of **1q** readily generates 6-methoxy-2-phenyl-1H-benzo[d]imidazole **4b**, which then undergoes C–H activation/[4+2] annulation to form **3qa** and **3ra**. In addition, the reaction towards to amidines **1s**, **1u**, and **1w** bearing electron-donating group at 4-position also delivered strong support for C−H bond cleavage on *N*-phenyl ring is preferential than C–H bond on C-phenyl ring. This would be premature to provide an explanation of the reactivity and selectivity. To develop a better understanding of the reaction mechanism, we performed an additional study. Treatment of **4c** with **2a** afforded the desired product **3aa** in 73% yield under standard conditions (Scheme 5). The reaction may be carried out according to **path A**, or it may be conducted simultaneously with two possible paths.



Scheme 4. Proposed mechanism.



Scheme 5. Control experiment.



Scheme 6. Proposed mechanism

On the basis of the above mechanistic studies and previous reports,[20] we proposed a plausible mechanism as depicted in Scheme 6. As a multifunctional catalytic platform, the rhodium catalyst conducted two independent and compatible catalytic cycles in one pot. The catalytic cycle was commenced by coordination of amidine to Cp*Rh(III) to form intermediate **C**, which undergoes C–H activation and release of HCl to provide intermediate **D**. Sequential release of a second HCl from **D** offers rhodacycle **E**. Finally, reductive elimination of **E** releases the intermediate **F** and regenerates the rhodium(I) species Cp*Rh(I). Next, (benz)imidazole-assisted C–H rhodiumation towards to C-phenyl ring was achieved. The cyclometalated rhodium complex **G** undergoes ligand coordination and alkyne insertion to give intermediate **I**. Then, the desired product and Cp*Rh(I) were released simultaneously *via* reductive elimination of **I**. Finally, reoxidation of Cp*Rh(I) regenerates catalytically competent Cp*Rh(III) again.

Conclusion

In summary, we have reported on the twofold *ortho*-C–H functionalization between *N*-phenylbenzimidamide and alkynes by a single Cp*Rh(III) catalyst that enables the synthesis of benzimidazoisoquinolines in moderate to good yields. The cascade strategy is believed to proceed through sequential C–H bond activation/[4+2]annulation. The catalytic system proved broadly applicable with wide scope and good functional group tolerability, thus reflecting the robustness of the C–H activation regime. This approach eliminates the need to isolate/store prefunctionalized starting materials, and occurred with remarkable site selectivity. Detailed mechanistic studies provided strong support for C–H bond cleavage on *N*-phenyl ring is preferential than C–H bond on C-phenyl ring. Current efforts are focused on the further exploration of multiple C–H activation of amidine for novel C–C bond formation in our laboratory.

Experimental Section

A mixture of $[Cp^*RhCl_2]_2$ (2.5%, 2 mg), alkyne (0.125 mmol), amidine (1.5 equiv), $Cu(OAc)_2$ (2 equiv, 49.9 mg) NBu_4F (2 equiv), pivalic acid (20%) and toluene/DCE (v/v = 1:4, 4 mL) was stirred at 80 °C for 48 h. After cooling the reaction to room temperature, PIFA (1 equiv) and CF_3CH_2OH (2 ml) were added, and then the mixture was stirred for 4 hours. After that, the solvent was removed under vacuum and the residue was purified by silica gel chromatography using ethyl acetate/petroleum ether (1:10-1:4) to afford desired products.

Deposition Numbers 2039498 (for **3ja**), 2039499 (for **3ma**), and 2039500 (for **3ra**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszen-

trum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Amidine · Alkynes · C–H activation · Cascade reactions · Dual catalysis

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