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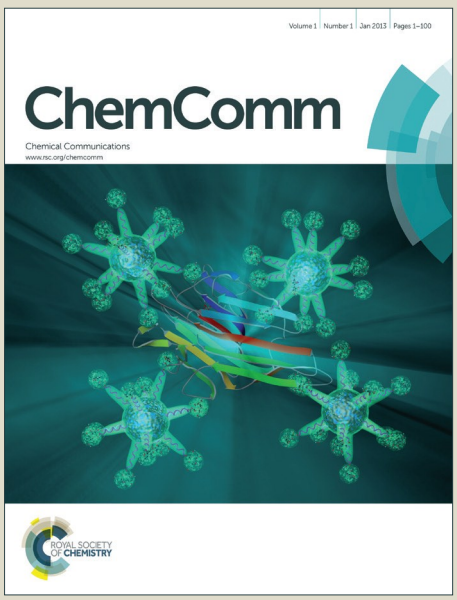

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Rhodium(III)-catalyzed C–H activation and intermolecular annulation with terminal alkynes: from indoles to carbazoles

Jinlong Jia, [a,b+] Jingjing Shi,[a+] Jie Zhou,[a,c] Xuelei Liu,[a] Yanling Song,[b] H. Eric Xu*[a,d] and Wei Yi*[a]

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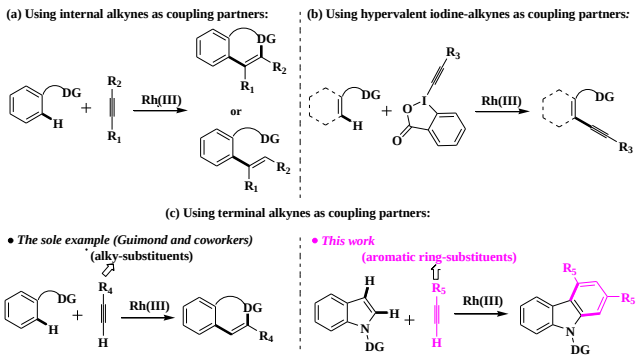
Herein we disclose the first example of Rh(III)-catalyzed intermolecular annulation of indoles with terminal alkynes to give highly efficient one-pot access to privileged carbazoles. The mild reaction features moderate to good yields, exclusive regioselectivity, broad substrate scope, and excellent functional group tolerance.

For many decades, the direct functionalization of inert C–H bonds ubiquitous in organic molecules has attracted widespread attention from synthetic chemists since it allows for efficient construction of structurally diverse building blocks in a step- and atom-economical manner.[1] As a consequence, significant progress has been made in this hot area of research.[2] In general, to achieve direct C–H functionalization, the introduction of a proper transition metal catalyst was critical for the activation of inert C–H bond. Among those transition metals, recently developed Rh(III) catalysts played a particularly prominent role.[3] Indeed, they could complement other reported metal catalysts in the field of C–H functionalization in terms of activity, selectivity, substrate scope and functional group tolerance, and so far, a tremendously large number of key structural motifs have been efficiently constructed by employing a Rh(III)-catalyzed and directing group (DG)-assisted C–H activation strategy.

However, by reviewing these developed Rh(III)-catalyzed C–H activation reactions, one common feature was found that almost all the reactions used internal alkynes as coupling partners, which gave rise exclusively to disubstituted alkenes (Scheme 1a).[4] To overcome this drawback, very recently Li,[5a,b] Glouris,[5c] Loh[5d,e,f] and Chang[5g] have independently developed a profound Rh(III)-catalyzed C–H functionalization for direct construction of versatile disubstituted alkynes by using prefunctionalized hypervalent iodine-alkynes as powerful alkynylating reagents (Scheme 1b). Despite these remarkable advances, it would be ideal and more straightforward to use ubiquitous terminal alkynes as coupling partners in view of economy and utility. However, such a useful coupling in the Rh(III) catalysis remains a great challenge, largely because of the lack of solutions to the problem associated with relatively acidic terminal protons and thus easily homocoupling of terminal alkynes under commonly used oxidative conditions.[6]

To address the challenge, In 2011, Guimond and coworkers pioneered a Rh(III)-catalyzed redox-neutral C–H activation/cyclization of benzamides with terminal alkynes giving access to monosubstituted isoquinolones (Scheme 1c, left).[7] However, this reported protocol was only compatible with alkyl-substituted terminal alkynes. Moreover, to the best of our knowledge, no further example that employed terminal alkynes as coupling partners in the Rh(III)-catalyzed C-H functionalization has been reported to date. Obviously, more efforts are urgently needed to search and develop new Rh(III)-catalyzed C–H functionalization of (hetero)arenes by using terminal alkynes especially aromatic ring-substituted terminal alkynes as coupling partners.



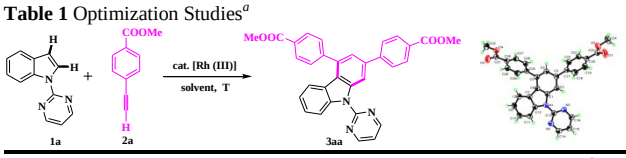
Scheme 1. Rh(III)-Catalyzed C–H Functionalization with Alkynes

Motivated by this and in continuation of our interest in the Rh(III)-catalyzed C-H functionalization,[8] herein we report an unprecedented Rh(III)-catalyzed intermolecular annulation of indoles with terminal alkynes as a highly versatile and economical alternative for one-pot cascade synthesis of carbazole scaffold (Scheme 1c, right), a privileged core structural motif widely found in natural products, organic materials and biologically active compounds.[9] Notably, this transformation represented the first example of Rh(III)-catalyzed C–H functionalization of (hetero)arenes with aromatic ring-substituted terminal alkynes.

On the basis of literature precedent,[10] we envisioned that the rational design of a simple and mild Rh(III) catalytic system with the assistance of a suitable DG might be able to reduce even avoid the undesired homocoupling of terminal alkynes. To test the hypothesis and considering the importance of indole skeleton in natural products and medicinal chemistry,[11] therefore, we commenced our study with the reaction of *N*-functionalized indoles bearing the corresponding DG [*N*-H, *N*-Me, *N*-Boc, *N*-$(CH_3)_2NCO$, or *N*-2-pyrimidyl] (0.1 mmol) and methyl 4-ethynylbenzoate **2a** in several well-known Rh(III) catalysis for the reaction development (see ESI†). To our great surprise, the carbazole **3aa** was formed after 12 h in 51% yield by employing *N*-2-pyrimidyl group as the DG and using $[Cp^*Rh(MeCN)_3](SbF_6)_2$ complex as the catalyst (Table 1, entry 1). The molecular structure of **3aa** was confirmed by the single crystal X-ray analysis (CCDC 1036782). Based on this encouraging finding, next we chosen $[Cp^*Rh(MeCN)_3](SbF_6)_2$ as the catalyst, and *N*-2-pyrimidyl indole **1a** (0.1 mmol) and **2a** (2.2 equiv) as model substrates for this reaction optimization

including solvent (entries 1-5), reaction temperature (entries 5-7), catalyst loading (entries 6 and 8), and concentration (entries 6 and 9-10). Through an intensive investigation, we ultimately obtained the best reagent blend consisting of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (10 mol%), **1a** (0.1 mmol) and **2a** (2.2 equiv) in dioxane (2.0 mL), which operated at 80 °C under air to give the desired product **3aa** with an impressive isolated yield of 85% (entry 6). It was important to note that a self-dimerizated product[6c] of **2a** was not detected under the optimized conditions, which illustrated the remarkable robustness of this Rh(III)-catalyzed system.

Table 1 Optimization Studies[a]

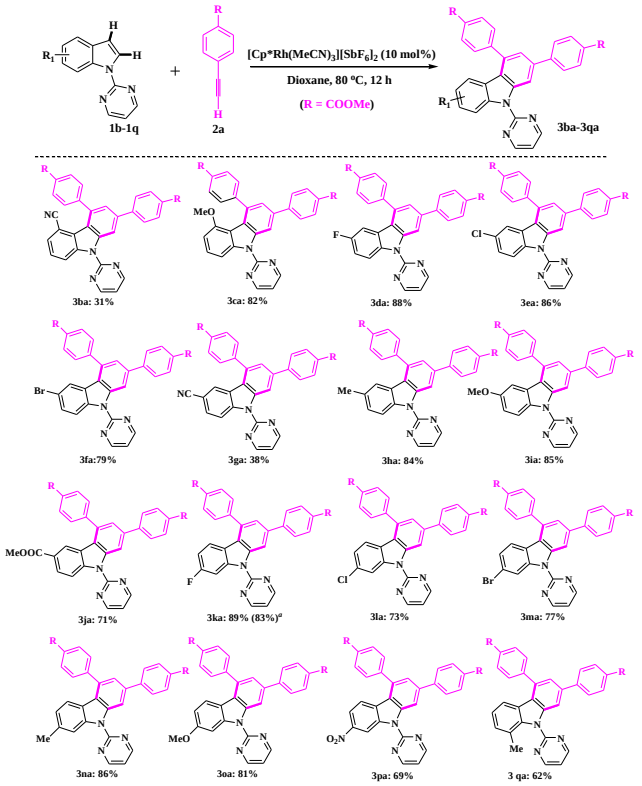


Entry	Catalyst system (mol %)	Solvent	T (°C)	Yield[b] (%)
1	$[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$(10)	THF	100	51
2	$[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$ (10)	DCE	100	22
3	$[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$ (10)	EtOH	100	32
4	$[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$ (10)	CH_3CN	100	25
5	$[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$ (10)	Dioxane	100	84
6	$[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$ (10)	Dioxane	80	85
7[c]	$[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$ (10)	Dioxane	r.t.	42
8	$[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$ (5)	Dioxane	80	48
9[d]	$[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$ (10)	Dioxane	80	72
10[e]	$[Cp^*Rh^{III}(MeCN)_3](SbF_6)_2$ (10)	Dioxane	80	61

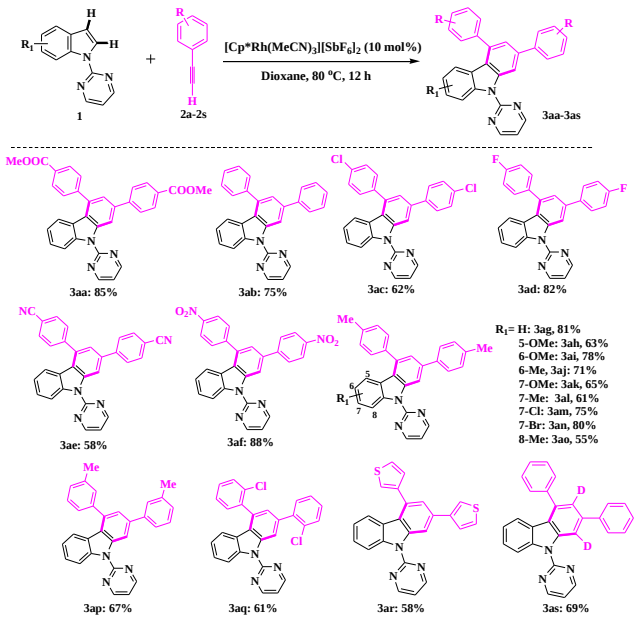
[a]Reaction conditions: **1a** (0.10 mmol, 1.0 equiv), **2a** (0.22 mmol, 2.2 equiv), Rh catalyst (X mol%), solvent (2.0 mL), 12 h, under air. [b]Isolated yields. [c]For 24 h. [d]Dioxane (1.0 mL). [e]Dioxane (0.5 mL).

Having the optimized conditions in hand, we first examined the substrate scope of this reaction with respect to indoles (Scheme 2). To our delight, both electro-donating and -withdrawing groups were well tolerated in delivering the desired carbazoles with moderate to good yields [62-89%, except **3ba** (31%) and **3ga** (38%), the reason for the low yields was due to their bad solubility in dioxane]. Importantly, the reaction also showed good compatibility with a wide range of valuable functional groups such as cyano (**3ba** and **3ga**), methoxy (**3ca**, **3ia** and **3oa**), fluoro (**3da** and **3ka**), chloro (**3ea** and **3la**), bromo (**3fa** and **3ma**), ester (**3ja**), methyl (**3ha**, **3na** and **3qa**), and nitro (**3pa**) substituents. Tolerance to the chloro, bromo, cyano, and ester functional groups was especially noteworthy since they have been frequently used as key intermediates for further synthetic transformations. Moreover, the position of the substituent on indole moiety showed no obvious influence on the reaction outcome, and substitutions at the C4- (**3ba-3ca**), C5- (**3da-3ja**), C6- (**3ka-3pa**), and C7- (**3qa**) positions were all well tolerated with the developed Rh(III) system. Finally, the preparation of **3ka** on 2.0 mmol scale with decent yield (83%) further demonstrated the versatility of this reaction.

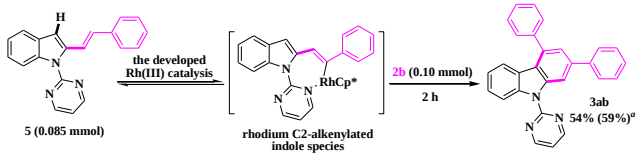
Subsequently, we evaluated the substrate scope with respect to terminal alkynes (Scheme 3). In general, the reaction was well compatible with various substituents either at the *para*- (**3aa-3ao**), *meta*- (**3ap**), or *ortho*- (**3aq**) postion on the benzene rings of terminal alkynes, including electron-donating and -withdrawing groups, and all providing the corresponding carbazoles in generally good yields. Different substituted indoles were also tested and the reaction gave the desired products regardless of the electronic properties of the substituents (**3ag-3ao**). Interestingly, the heteroaromatic alkynes also served as suitable substrates as exemplified by the synthesis of **3ar**. Removal of the pyrimidyl group on product **3aj** was easily achieved by treatment with EtONa in anhydrous DMSO to provide valuable free-NH carbazole **4** in good yield.[12] Of note, the reaction also took place with $[D_1]$-phenylacetylene to provide the $[D_2]$-product **3as** in 69% yield where the relatively acidic terminal-D had not involved in the catalytic reaction, which hinted at the reaction mechanism.



Scheme 2 Scope of indoles. Reaction conditions: **1b-1q** (0.10 mmol, 1.0 equiv), **2a** (0.22 mmol, 2.2 equiv), Rh catalyst (0.01 mmol, 10 mol%), dioxane (2.0 mL), 12 h, under air. Isolated yields. [a]Performed on a 2.0 mmol scale.

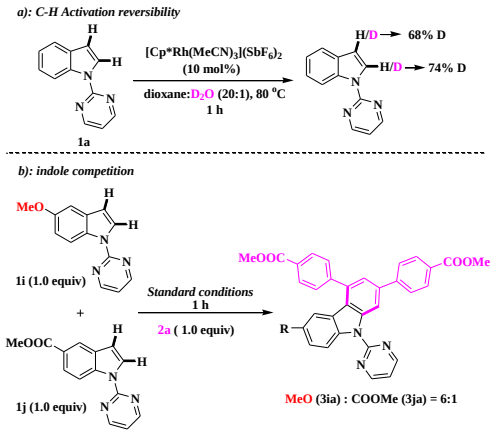


Scheme 3 Scope of terminal alkynes. Reaction conditions: **1** (0.10 mmol, 1.0 equiv), **2a-2s** (0.22 mmol, 2.2 equiv), Rh catalyst (0.01 mmol, 10 mol%), dioxane (2.0 mL), 12 h, under air. Isolated yields.



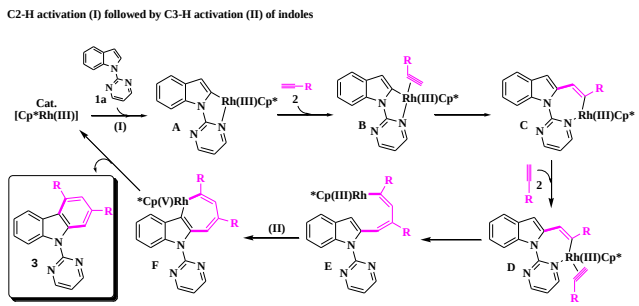
Scheme 4 Mechanistic investigation. [a]Isolated yield of **3ab**; 59% of **5** was recovered after reaction.

Motivated by the aforementioned results, we speculated that rhodium C2-alkenylated indole species might be a key intermediate in the catalytic cycle (Scheme 4). Thus, C2-alkenylated indole **5** was prepared and was designated as a substrate to provide insight into the reaction mechanism. To our delight, the reaction of **5** and **2b** for 2 h in the developed Rh(III) catalysis occurred to give the predicted product **3ab** in 54% isolated yield, which confirmed our speculation.



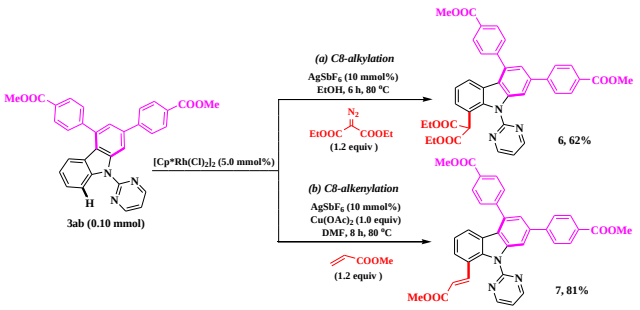
Scheme 5 Mechanistic experiments.

To obtain better insight into the reaction mechanism, additional experiments were conducted (Scheme 5). First, the reversibility of the C−H activation step was defined by running the reaction in dioxane/D_2O in the absence of terminal alkynes (Scheme 5a). As shown in Scheme 5a, significant deuteration of **1a** was observed at the C2 and C3-positions of indole core (for C2−H, 74% H/D scrambling; for C3−H, 68% H/D scrambling), revealing that the C2−H and C3−H bonds metalation steps were largely reversible. Moreover, the competition experiment between differently substituted indoles was carried out to delineate the action mode of the reaction (Scheme 5b). The results demonstrated that electron-rich indoles were preferentially converted (e.g. **3ia**/**3ja** = 6:1), suggesting that the dual C−H activation might be *via* an internal electrophilic substitution (IES)-type mechanism.[8f,14]



Scheme 6 Proposed mechanism.

On the basis of these observations, a plausible reaction mechanism is proposed in Scheme 6. First, the coordination of C2-position of *N*-2-pyrimidyl indole **1a** to a [Cp*Rh(III)] species is the key step for the regioselective C2−H bond cleavage of indole to form a five-membered rhodacycle **A**.[8a,c,d,13] This rhodacycle can coordinate one equivalent of terminal alkyne **2** to afford **B**. Subsequently, insertion of alkyne **2** into the Rh−C bond gives a seven-membered rhodacycle **C**, followed by the coordination and the regionselective alkyne insertion once again to give **D** and **E**, respectively. Then intermedicate **E** undergoes further coordination with the C3-position of indole core to provide the seven-membered rhodacycle **F**. Reductive elimination[15] of **F** delivers the desired carbazoles **3** and the active Rh(III) catalyst.



Scheme 7 Derivatization of **3ab** *via* Rh(III)-Catalyzed C8–H Functionalization.

Due to the privileged structural features and biological activities of carbazole derivatives,[9c,d,e] we finally attempted to develop the direct C–H functionalization of the obtained carbazoles. As illustrated in Scheme 7, product **3ab** respectively underwent Rh(III)-catalyzed alkylation[16d] and alkenylation to generate the corresponding C8-functionalized products in good yields. Since methods for direct C–H activation of the carbazole core are quite rare,[16] the presented synthetic transformations would open a new avenue to practical intermolecular C–H functionalization of carbazoles.

In summary, we have developed a new, mild and efficient Rh(III)-catalyzed intermolecular annulation of indoles with terminal alkynes for one-pot cascade synthesis of privileged carbazoles by using the readily installable and removable pyrimidyl group as a DG. This transformation could proceed smoothly in a very simple catalytic system under air atmosphere with features of moderate to good yields, exclusive regioselectivity, broad substrate scope, and excellent functional group tolerance. Through the experimental investigation, a possible reaction mechanism was rationally derived. Synthetic application of the obtained carbazoles has also been demonstrated by subsequent derivatization reactions *via* Rh(III)-catalyzed regioselective C8–H functionalization. Taken together these results, we believe the new and versatile protocol will inspire the use of terminal alkynes as coupling partners for direct and highly efficient construction of other important structural motifs *via* Rh(III)-catalyzed direct C–H functionalization, and further studies on the scope, mechanism and application of this catalytic reaction are in progress.

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[a]*VARI/SIMM Center, Center for Structure and Function of Drug Targets, CAS-Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, P.R. China.*

E-mail: yiwei.simm@simm.ac.cn, eric.xu@simm.ac.cn;
Fax: +86-21-20231000-1715; Tel: 86-21-20231000-1715
[b]*College of Pharmaceutical and Biological Engineering, Shenyang University of Chemical Technology, Shenyang 110142, P.R. China*
[c]*School of Chemistry and Chemical Engineering, Sun Yat-sen University, Guangzhou 510275, P.R. China*
[d]*Laboratory of Structural Sciences, Program on Structural Biology and Drug Discovery, Van Andel Research Institute, Grand Rapids, Michigan 49503, USA*
[+] *J. Jia and J. Shi contributed equally to this work.*

†Electronic Supplementary Information (ESI) available: Detailed experimental procedure and characterization of new compounds (H^1 and C^{13} NMR spectra) and CIF of **3aa** (CCDC 1036782). See DOI: 10.1039/b000000x/

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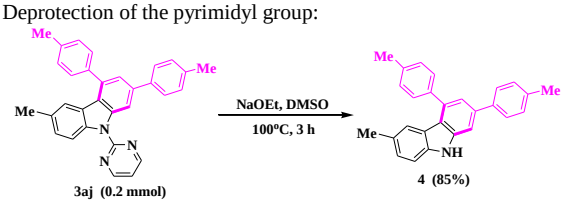

3aj (0.2 mmol) 4 (85%)

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