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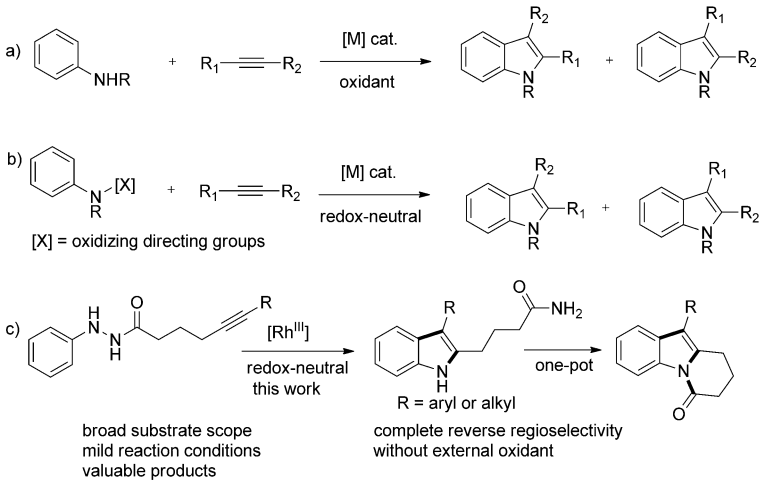
Rhodium(III)-Catalyzed Intramolecular Redox-Neutral Annulation of Tethered Alkynes: Formal Total Synthesis of (±)-Goniomitine

Bing Zhou,* Juanjuan Du, Yaxi Yang, and Yuanchao Li*[a]

Abstract: A Rh^{III}-catalyzed intramolecular redox-neutral atom-economic annulation of a tethered alkyne has been developed to efficiently construct 2-amidealkyl indoles with completely reversed regioselectivity by a C–H activation pathway. Furthermore, using the Rh^{III}-catalyzed C–H activation/annulation as a key step, a one-pot synthesis of pyrido[1,2-a]indoles has also been developed and applied to a highly efficient formal total synthesis of (±)-goniomitine.

Indoles are ubiquitous structural motifs in natural products, marketed drugs, and other functional molecules.[1] Therefore, there is a continued interest in the development of new methods to selectively access indole derivatives.[2] Among them, transition-metal-catalyzed oxidative C–H/N–H cyclization has emerged as a powerful and distinct approach to this structural moiety due to its high efficiency, selectivity, and easy availability (Scheme 1a).[3] This method has opened up a new avenue in indole synthesis.[4] However, stoichiometric amounts of metal oxidants, such as Cu^{II} and Ag^{I} salts, are generally required, thus generating undesired waste and limiting the substrate scope as well.[5] Recently, an oxidizing–directing-group strategy has emerged as an attractive alternative, allowing annulation reactions under redox-neutral reaction conditions and also showing the clear advantages of high selectivity, functional-group tolerance as well as an improved level of reactivity (Scheme 1b).[6,7]

Despite remarkable progress, there remain some major challenges: 1) The reactions with arylalkyl acetylenes give only 2-aryl-3-alkyl substituted indoles and no 2-alkyl-3-aryl substituted indoles could be formed.[5a–e,7] 2) An additional issue is the poor regioselectivities (ca. 1:1 to 2:1) when unsymmetrical dialkyl or diaryl acetylenes were employed.[5a,b] Recognizing these limitations and with our continued interest in Rh^{III}-catalyzed C–H functionalization,[8] we became interested in the intramolecular annulation reaction of an alkyne-tethered phenylhydrazine (Scheme 1c). The successful development of this method would not only overcome the mentioned restrictions, but also give a redox-neutral and regioselective synthesis of 2-amidealkyl-substituted indoles, which could be readily converted into pyrido[1,2-*a*]indole scaffolds that are found in a variety of biologically active natural products[9–16] including *Strychnos*,[9] *Kopsia*,[10] *Melodinus henryi*,[11a] *Gonioma Malagasy*,[12] Hunteria eburnean,[13] Aspidosperma,[14] *Vinca minor* L,[15] and Alstonia angustofolia[16] alkaloid families (Figure 1). Herein, we successfully develop this Rh^{III}-catalyzed intramolecular annulation of arylhydrazines with a tethered alkyne by C–H activation. This methodology was used to finish the formal total synthesis of goniomitine.



Scheme 1. Indole synthesis by C–H activation.

We initially evaluated the reaction of substrate **1a** with $[RhCl_2(Cp^*)]_2$ ($Cp^* = 1,2,3,4,5$-pentamethylcyclopentadienyl) under different conditions (see Table S1 in the Supporting Information). When **1a** was treated with $[RhCl_2(Cp^*)]_2$ (2.5 mol%) and CsOAc (20 mol%) in MeOH at 70 °C for 12 h, no product

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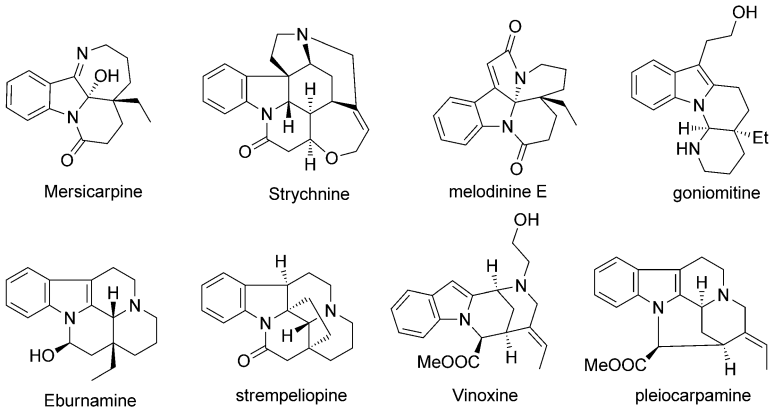
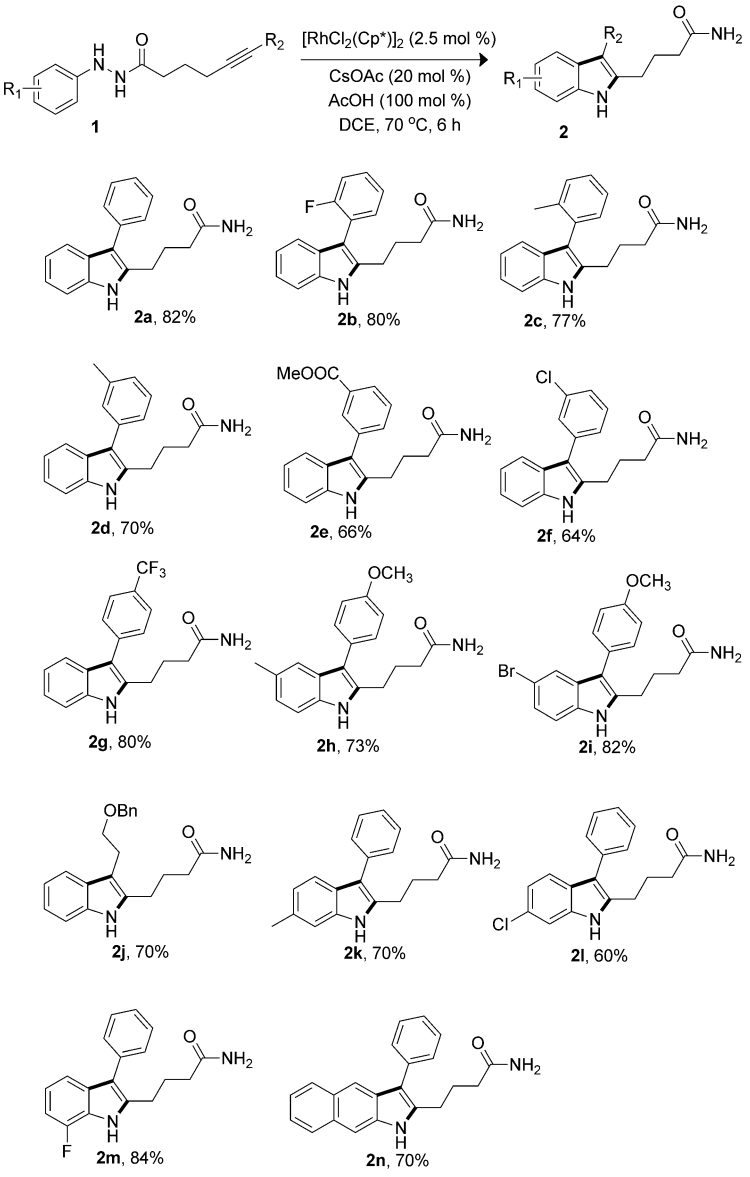


Figure 1. Representative biologically active natural products bearing a pyrido[1,2-*a*]indole core.

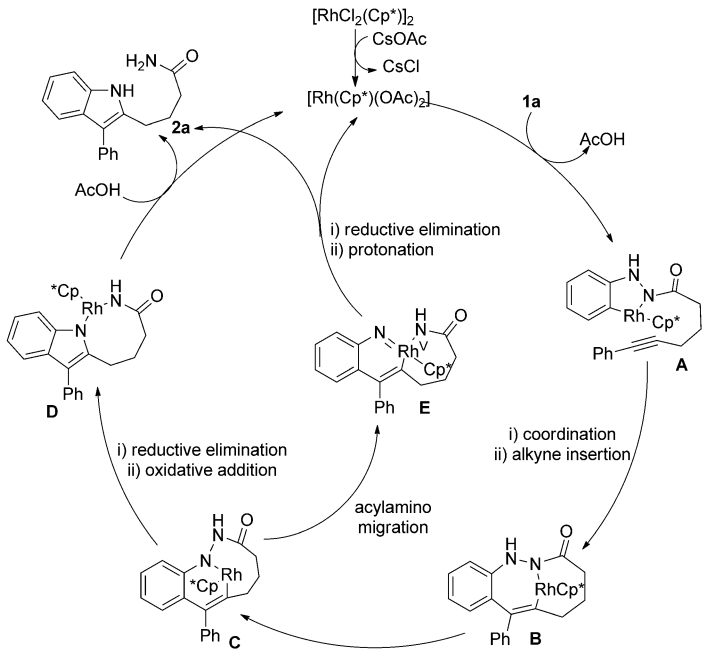
was detected. However, when one equivalent of AcOH was added, 30% of product **2a** was obtained (for the structure, see Scheme 2). Other acids, such as PivOH and dichloroacetic acid, did not improve the yield of **2a**. Next, we tested various solvents, such as PhMe, THF, CH_3CN, 1,4-dioxane, and 1,2-dichloroethane. DCE as the solvent proved to be optimal, improving the yield of **2a** to 82%. The use of other acetate salts, such as NaOAc, AgOAc, and KOAc decreased the yield of **2a** and other metal catalysts like $[RuCl_2(p\text{-cymene})]_2$ and $[IrCl_2(Cp^*)]_2$ failed to provide the product **2a**.

Next the optimized conditions were used to survey the scope of the reaction with various substrates (Scheme 2). Diverse functional groups were tolerated on the *ortho*, *meta*, and *para* positions of the ethynylphenyl substituent, including electron-donating (**2c**, **2d**, **2h**, **2i**) and -withdrawing (**2b**, **2e**, **2f**, **2g**) groups, all providing their corresponding products in >60% yield. Remarkably, in this methodology, the alkyl-substituted (or ethoxybenzyl-substituted) alkyne produced only one regioisomer, indole **2j**. This regioselectivity is superior to other reported intermolecular versions in which a 1.2:1 regioselectivity was observed.[5b,17] Furthermore, the phenylhydrazine substituent also tolerated either electron-donating or -withdrawing substitutions at its *para* (**2h**–**i**), *meta* (**2k**–**l**), and *ortho* (**2m**) positions. *Meta*-substituted derivatives underwent this annulation reaction only at the sterically more accessible C–H bond (**2k**, **2l**). Naphthalene-2-ylhydrazine substrate was well tolerated, yielding **2n** and demonstrating the versatility of this annulation. Notably, the reversed regioselectivity of this method,[18] producing 2-alkyl-3-aryl indoles, provides a good complement to previously reported methods that form 2-aryl-3-alkyl-indoles[5a–e,7] and offers great potential for indole synthesis.

To probe the reaction mechanism, an intermolecular competition experiment between protio and deuteron **1a** was carried out [Eq. (1)] and an observed KIE value of 1.0 indicated that C–H bond cleavage might not be involved in the rate-limiting step.[19] On the basis of the above-mentioned results, a tentative mechanism for the Rh-catalyzed annulation reaction is proposed (Scheme 3). First, a Rh^{III}-catalyzed *ortho*-directed C–H bond cleavage occurs to form intermediate **A**, followed by coordination and alkyne insertion to give seven-membered rhodacycle **B**. Then a rearrangement presumably occurs to provide



Scheme 2. Substrate scope: Conditions: **1** (0.2 mmol), $[RhCl_2(Cp^*)]_2$ (0.005 mmol), CsOAc (0.04 mmol), AcOH (0.2 mmol), and DCE (1 mL) at 70 °C for 6 h under an argon atmosphere. Yield of isolated product.



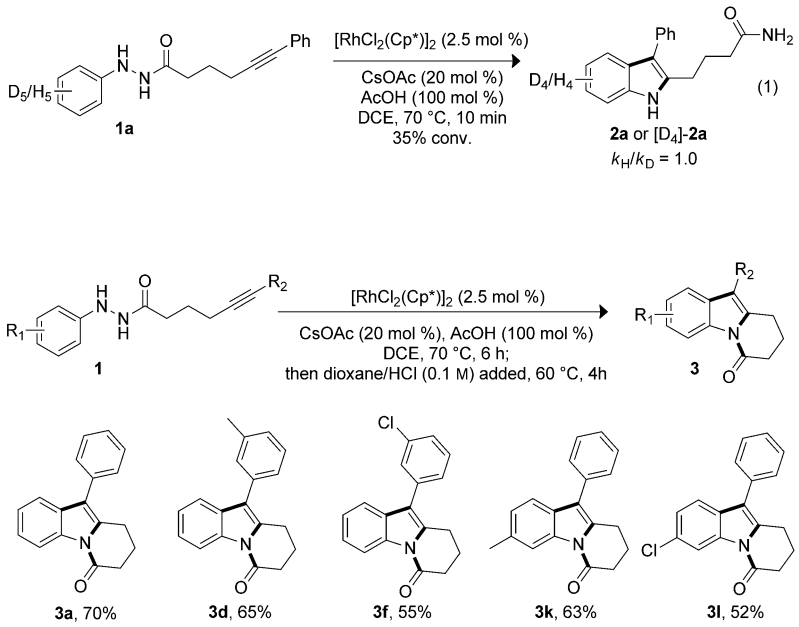
Scheme 3. Proposed mechanism.

a more stable six-membered rhodacycle **C**, which undergoes reductive elimination and oxidative addition to form intermediate **D**. Protonation of **D** yields the desired indole **2a** and regenerates the Rh^{III} catalyst. Alternatively, **C** could undergo an acylamino migration to give a cyclic Rh^{V} nitrene intermediate **E**,[20] followed by a reductive elimination and protonation to deliver indole **2a** and Rh^{III} catalyst.

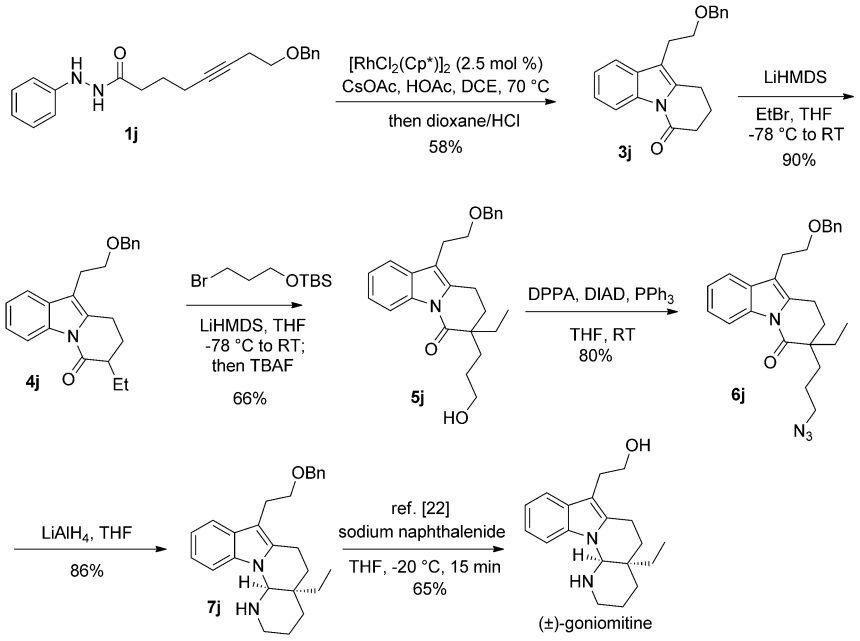
The synthetic utility of the intramolecular redox-neutral annulation reaction was exemplified by a successful one-pot synthesis of pyrido[1,2-*a*]indoles **3**[9–16] directly from alkynes **1** (Scheme 4).[21] For example, treatment of alkynes **1** under our optimized reaction conditions, and subsequent treatment with dioxane/HCl (0.1 M) in one-pot gave the desired pyrido[1,2-*a*]indoles **3** in good yields.

Utility of our methodology is further demonstrated by its application in a seven-step formal total synthesis of (±)-goniomitine (Scheme 5). Thus, annulation of **1j** under our optimized reaction conditions and subsequent treatment with dioxane/HCl in one-pot afforded the pyrido-[1,2-*a*]indole **3j** in 58% yield. Treatment of **3j** with lithium hexamethyldisilazide (LiHMDS) and ethyl bromide afforded **4j** in 90% yield. Addition of the propanol group to the same carbon was accomplished by treatment of **4j** with LHMDS and (3-bromopropoxy)(*tert*-butyl)-dimethylsilane, and a subsequent deprotection with tetra-*n*-butylammonium fluoride (TBAF) yielding the alcohol **5j** in 66% yield. Mitsunobu reaction of **5j** provided azide **6j**, and subsequent reduction of **6j** with $LiAlH_4$ gave **7j** in good yield. Finally, deprotection of **7j** afforded (±)-goniomitine.[22] Thus, the formal total synthesis of racemic goniomitine was completed in seven steps from phenylhydrazine **1j**.

In summary, we have developed a mild and efficient Rh^{III}-catalyzed redox-neutral C–H activation/intramolecular annulation of alkyne-tethered arylhydrazines to prepare 2-amidealkyl indoles. This reaction does not require any external oxidant and features high reverse regioselectivity, which offers a good complement to previous methods. Furthermore, using the Rh^{III}-catalyzed C–H activation/annulation as a key step, a one-pot synthesis of pyrido[1,2-*a*]indoles has also been developed and applied to a highly efficient formal total synthesis of (±)-goniomitine. Considering the valuable structure of the products, we expect this intramolecular annulation reaction to gain broad synthetic utility.



Scheme 4. One-pot synthesis of pyrido[1,2-*a*]indoles **3** from arylhydrazines **1**.



Scheme 5. Formal total synthesis of (±)-goniomitine. DIAD = diisopropyl azodicarboxylate; DPPA = diphenylphosphoryl azide.

Acknowledgements

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Keywords: C–H activation · goniomitine · indoles · redox-neutral · total synthesis

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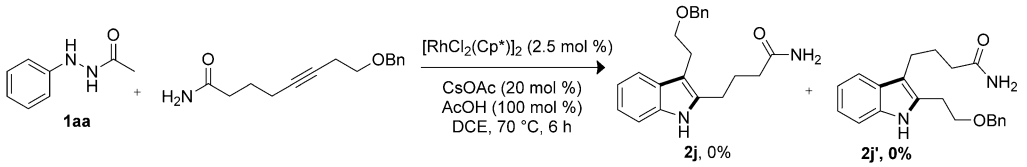

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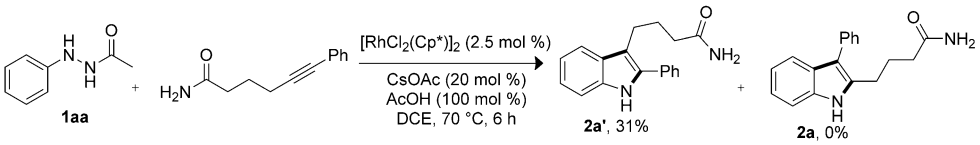
[18] For comparison, the intermolecular reaction of **1aa** with 6-phenylhex-5-ynamide only gave 2-aryl-substituted indoles:



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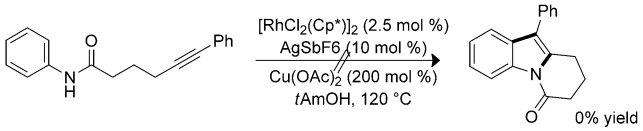

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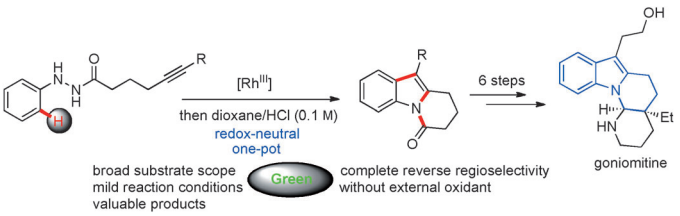
Rhodium(III)-Catalyzed Intramolecular Redox-Neutral Annulation of Tethered Alkynes: Formal Total Synthesis of (±)-Goniomitine



C–H activation: A Rh^{III}-catalyzed intramolecular redox-neutral atom-economic annulation of a tethered alkyne has been developed to efficiently construct 2-amidealkyl indoles with completely reversed regioselectivity by a C–H activation pathway (see scheme). A one-pot synthesis of pyrido[1,2-a]indoles has also been developed and applied to a highly efficient formal total synthesis of (±)-goniomitine.