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COMMUNICATION

γ-Carboline synthesis enabled by Rh(III)-catalysed regioselective C-H annulation

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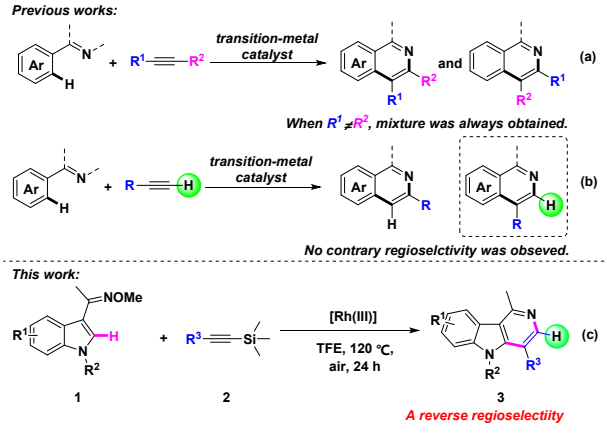
A redox-neutral Rh(III)-catalyzed C-H annulation of indolyl oximes was developed. Relying on the use of various alkynyl silanes as the terminal alkyne surrogates, the reaction exhibited a reverse regioselectivity, thus giving an exclusive and easy way for the synthesis of a wide range of substituent free γ-carbolines at C3 position with high efficiency. Deuterium-labelling experiments and kinetic analysis have preliminarily shed light on the working mode of this catalytic system.

γ-Carboline, as a very important class of alkaloid, frequently occurs in natural products, bioactive compounds and drugs.[1] To date, it has been found to exhibit a variety of bioactivities, including antiviral, antibacterial, antitumor activities and so on.[2] To satisfy the needs of preparing multifarious γ-carbolines in high-throughput screening and the research of structure-activity relationship (SAR), many successful synthetic methods[3] (for example, transition-metal catalysed coupling,[4] acid catalysed condensation[5] and photoinduced cyclization[6]) had been developed in the past few decades. However, some methods suffer tedious reaction steps, harsh reaction conditions, low efficiency and regioselectivity. With this regard, it is still highly desirable to develop novel strategies for the easy and rapid synthesis of diverse substituted γ-carboline scaffolds from readily available substrates.

Recently, the application of transition-metal catalysed direct C-H activation/cyclization in the synthesis of *N*-heterocycles has emerged as a facile strategy due to its high step-economy and atom-economy.[7] In these applications, nitrogen-contained groups always played a dual role, to be the directing group maintaining the chelation and to serve as the nitrogen source.[8] Meanwhile, numerous reaction partners had been employed to fulfil the annulations, delivering five or six membered *N*-heterocycles.[9] Among them, alkynes such as internal alkynes, terminal alkynes and other surrogates were identified as the most popular and ideal participants depending on their easy availability and versatile reactivity.[10] They often performed well and accomplished the annulations with high efficiency. However, in most cases, symmetric internal alkynes were adopted, avoiding to generate the mixture caused by the low regioselectivity which was following the use of asymmetric internal alkynes (Scheme 1a).[11] For terminal alkynes and their surrogates, as a kind of more challenged substrates in C-H activations, in the limited reports, 2,1-insertion occurred only (Scheme 1b).[12] To the best of our knowledge, no contrary regioselectivity has been observed in transition-metal catalysed C-H annulations. In this context, how to control and adjust the regioselectivity in the using of asymmetric internal alkynes and get the reverse regioselectivity in the using terminal alkynes leaves much room to do. Surprisingly, some pioneering works



Scheme 1 Transition-metal catalysed C-H annulations for the synthesis of *N*-heterocycles with alkynes

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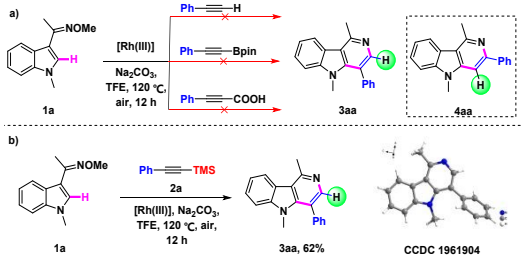
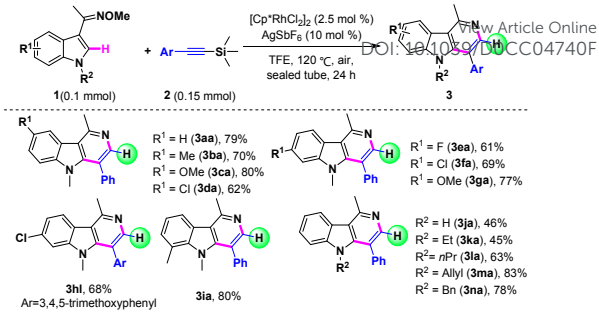


Scheme 2 Rh(III)-catalysed C-H annulations of indolyl oximes with terminal alkynes and surrogates



Scheme 3 Indolyl oximes scope in Rh (III)-catalysed regioselective C-H annulations

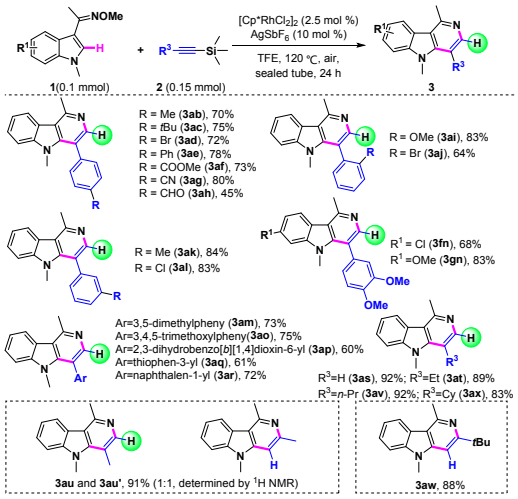
reported previously brought some enlightenments to face this challenge.[13] For instance, Ma and co-workers developed an efficient and selective synthesis of fully substituted allenes from arenes and tertiary propargylic carbonates *via* Rh-catalysed C-H activation in 2015.[14] In this approach, the excellent regioselectivity for the alkyne insertion was derived from *O*-coordination and the steric effect of tertiary carbon centre. In 2017, Glorius et al. reported a redox-neutral Mn(I)-catalysed C-H annulation for the synthesis of *N*-heterocycles, in which a traceless directing group on alkynes was employed to guide and control the high regioselectivity for unsymmetrical alkynes.[15]

Inspired by these pioneering works, we surmise that a suitable alkyne partner with steric factors or coordination sites might determine and change the regioselectivity in the related transition-metal catalysed C-H annulations, especially for the asymmetric alkynes. Based on this, to continue our interests on Rh-catalysis and the synthesis of *N*-heterocycles, herein, we disclose an efficient *γ*-carboline synthesis enabled by Rh(III)-catalysed C-H activation/cyclization of indolyl oximes under redox-neutral reaction conditions, in which, the contrary regioselectivity is obtained solely by the use of bulky alkynyl silanes as terminal alkyne surrogates (Scheme 1c).

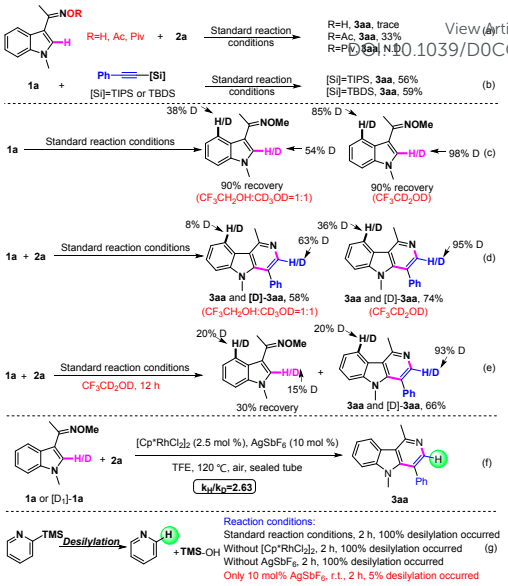
In Rh-catalysed chelation-directed C-H bond activations, the oxime moiety is a very charming directing group which always can accomplish the reductive elimination without external oxidants.[8, 16] Therefore, *N, O*-methyl/indolyl oxime (**1a**) was employed as the model substrate to perform the Rh(III)-catalysed C-H annulations for the synthesis of *γ*-carbolines. Four different terminal alkynes and surrogates were firstly subjected to the reactions with **1a** to probe the feasibility of our envision on how to control the regioselectivity. As shown in Scheme 2a, using $[Cp^*RhCl_2]_2/AgSbF_6$ as the catalyst, Na_2CO_3 as the additive, in trifluoroethanol (TFE), under air, at 120 °C for 12 h, phenylacetylene, alkynyl boronate ester and phenylpropiolic acid all failed to carry out the C-H annulation. No target product (**3aa** or **4aa**) was obtained, accompanying with the considerable amount of oxime remain and decomposition. To our surprise, when we used phenylalkynyl silane **2a** as the reaction partner, in striking contrast with previous reports, only one isomer **3aa** was isolated in 62% yield with a reverse regioselectivity (Scheme 2b), as confirmed by single-crystal X-ray analysis (see details in the ESI: section VI). Subsequently, we moved our attention to gain the best reaction efficiency depending on the extensive screening of reaction parameters (see details in ESI: section IV). For the potential compatible transition-metal catalysts, $[Cp^*RhCl_2]_2/AgSbF_6$ was deemed to be the only successful one rather than Ru, Co and Ir complex. Addition of base or acid was not helpful to improve the productivity. Increasing the reaction time to 24 h led a considerable promotion of conversion, and **3aa** was isolated in 79% yield. For organic solvents, HFIP (hexafluoro-2-propanol), as another fluorinated solvent, possessing unique and magic effects[17] in transition-metal catalysed C-H activations, also proved to be effective, giving **3aa** in similar yield with TFE. Control experiments showed that $[Cp^*RhCl_2]_2$ and $AgSbF_6$ were both necessary for this transformation. Notably, inert gas atmosphere is needless for this approach and the reaction proceeded smoothly under air in a sealed tube.

With the optimized reaction conditions established, the scope of indolyl oximes was then investigated (Scheme 3). Pleasingly, a wide range of different substituted indolyl oximes on the indole ring reacted with aromatic alkynyl silanes well, regardless of substituent locations, which delivered the corresponding substituent free *γ*-carbolines at C3 position in moderate to good yields (**3aa**-**3ia**). Fluoro indolyl oxime (**3ea**) and chloro indolyl oxime (**3da**, **3fa**, **3hl**) all participated the C-H annulations smoothly to produce the desired *γ*-carbolines in satisfied yields, providing a good chance for further modification. Apart from *N, O*-methyl/indolyl oximes, *N*-free indolyl oxime (**3ja**) other *N*-substituted indolyl oximes (**3ka**-**3na**) were also compatible for this transformation, but *N*-free indolyl oxime (**3ja**), *N*-ethyl indolyl oxime (**3ka**) and *N*-propyl indolyl oxime (**3la**) all gave lower conversions and yields relatively. Notably, for all tested indolyl oximes, only one regio-isomer was observed, and the high and reverse regioselectivity remained along with substituent variations.

Next, we probed the versatility and generality of this Rh(III)-catalysed C-H activation/cyclization with various alkynyl silanes (Scheme 4). For para-substituted phenyl alkynyl silanes, alkyl (**3ab**, **3ac**), bromo (**3ad**), phenyl (**3ae**), ester (**3af**), cyano (**3ag**), even overly sensitive formyl (**3ah**) were all well-tolerated, affording the desired product in 45-80% yields with high regioselectivity. Except for *para*-substituted phenyl alkynyl silanes, *ortho*-substituted (**3ai**, **3aj**) phenyl alkynyl silanes and *meta*-substituted (**3ak**, **3al**) phenyl alkynyl silanes were both feasible substrates, revealing that the substitution positions



Scheme 4 Alkynyl silanes scope in Rh(III)-catalysed regioselective C-H annulations



Scheme 5 Mechanistic studies

have no obvious impact on the reaction efficiency and selectivity. It is worth noting that the reaction of polymethyl-substituted (**3am**) phenyl alkynyl silane and polyalkoxy-substituted (**3fn**, **3gn**, **3ao** and **3ap**) phenyl alkynyl silanes proceeded efficiently to give the desired polysubstituted *γ*-carbolines which are important for the research of SAR in drug discovery.[1, 2] Moreover, we were delighted to find that thienyl alkynyl silane and naphthyl alkynyl silane could also furnish the **3aq** and **3ar** respectively in synthetically useful yields. To fully explore the scope of alkynyl silanes, several alkyl alkynyl silanes were examined as the reaction partners. Remarkably, as more challenged substrates for the current protocol, all of them performed the annulation well. Four desired products (**3as**, **3at**, **3av** and **3ax**) were obtained in excellent yields affording the consistent regioselectivity with phenyl alkynyl silanes. However, along with the change of steric-hindrance difference for alkyl group, the regioselectivity varied consequently (**3au** and **3au'**), and for *t*-butyl trimethylsilyl acetylene (**3aw**), the regioselectivity returned to normal probably due to the similar size between *t*-butyl and trimethylsilyl.

To delineate the working mode of the present catalytic system and the reason of reverse regioselectivity, several mechanistic studies were conducted. At first, under the standard reaction conditions, switching *O*-methyl/indolyl oxime (**1a**) into *O*-free/indolyl oxime resulted in extremely low reactivity and only trace amounts of **3aa** was observed. The substrates **1** with acetyl group or pivaloyl group were also tested, unfortunately, target *γ*-carboline was obtained in incredibly low yields because of the considerable side reactions (Scheme 5a). The introduction of bulkier alkynyl silanes (TIPS, TBDS) maintained the reverse regioselectivity despite slightly lower output, which indicated that the bulky alkylsilyl groups might be vital in achieving the contrary regioselectivity (Scheme 5b). Afterwards, several H/D exchange experiments of **1a** were carried out by the replacement of the solvent into isotopically labelled solvent. Without the reaction partner **2a**, the H/D scrambling difference demonstrated two potential reactive sites in C-H activation, and C2 position of indole was favourable at 120 °C, which was consistent with previous related literature reports[18] (Scheme 5c). Meanwhile, the H/D scrambling with **2a** implied a possibility of desilylation and subsequent H-abstraction from the solvent (Scheme 5d). The reaction of **1a** and **2a** in CF_3CD_2OD terminated at the early stage was conducted. It was found that the C-H cleavage could be reversible, and **3aa** was obtained in following competitive transformations (Scheme 5e). Moreover, two parallel independent kinetic experiments of **1a** and [D_1]-**1a** suggested an evident kinetic isotope effect (k_H/k_D=2.63), which indicated that the C-H bond cleavage might be the rate-determining step of the catalytic cycle (Scheme 5f). Additionally, an investigation with 2-trimethylsilyl pyridine to imitate the desilylation process was performed, indicating the anion SbF_6^- and trace amounts of water in the solvent possibly played the prominent role in this step (Scheme 5g).

In accordance with the above experimental observations, surveying the previous related reports,[10-15, 19, 20] the following reaction pathway for producing **3aa** is proposed (Scheme 6). A dissociation of $[Cp^*RhCl_2]_2$ occurs with $AgSbF_6$ initially, affording a cationic Rh(III) species. Then the rhodacycle intermediate **I** (A similar rhodacycle (CCDC 2023824) was captured by the reaction of stoichiometric amounts of $[Cp^*RhCl_2]_2$ with **1a** in the absence of $AgSbF_6$, see details in ESI: section V and VI) is generated through a competitive C-H cleavage at C2 position and C4 position of **1a**. Subsequent coordination of bulky alkynyl silanes **2a** to rhodium centre and a steric effect guided regioselective alkyne insertion delivers the seven-membered rhodacycle **II**. Next, intermediate **II** undergoes a redox-neutral

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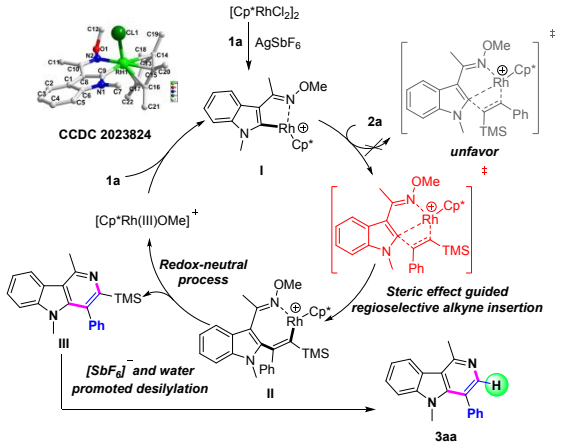

Scheme 6 A possible reaction pathway for producing **3aa**

process (see details in ESI: section V) to produce the cyclization product **III**, accompanying the regeneration of Rh catalyst *via N-O* cleavage. Finally, anion SbF_6^- and water in the solvent assisted desilylation occurs, and the following hydrogen abstraction from the protic solvent delivers the desired *γ*-carboline **3aa**.

In summary, we report here a regioselective Rh(III)-catalysed C-H activation/cyclization for the synthesis of potentially bioactive *γ*-carbolines. By virtue of combining indolyl oximes with alkynyl silanes, this protocol allows a broad substrate scope, high reaction efficiency, redox-neutral conditions and a unique reverse regioselectivity coached by the steric hinderance. We believe that it could facilitate the construction of *γ*-carboline molecular library for drug discovery and screening. Further studies to understand the complementary regioselectivity are underway.

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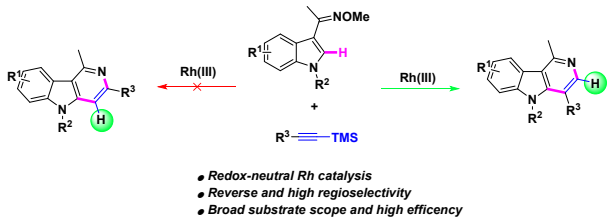

A Rh(III)-catalysed C-H annulation of indolyl oximes with alkynyl silanes was developed, delivering diverse *γ*-carbolines with unexpected reverse regioselectivity.