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Rhodium(III)-Catalyzed Cross Coupling of Sulfoxonium Ylides and 1,3-Diynes to Produce Naphthol-Indole Derivatives: An Arene *ortho* C–H Activation/Annulation Cascade

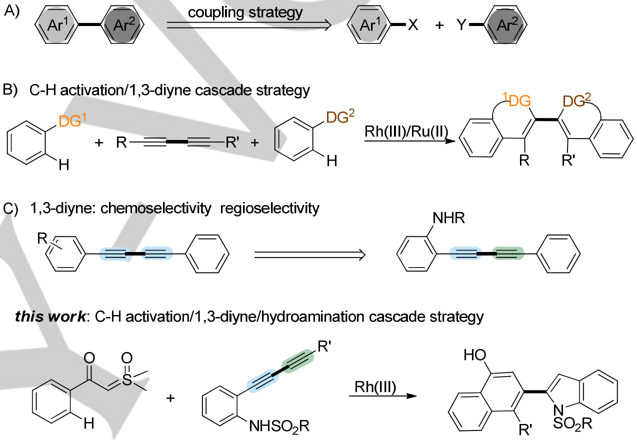
Ruixing Liu,[a] Yin Wei,[a] Min Shi*[a,b]

Abstract: Synthesis of naphthol-indoles starting from easily available 1,3-diynes and sulfoxonium ylides via Rh(III)-catalyzed C-H activation/hydroamination cascade process in a one pot manner has been developed. The reaction proceeds through a Rh(III)-catalyzed arene *ortho* C-H activation and silver-catalyzed hydroamination cascade to afford a variety of C2 position functionalized indoles in good yields with broad substrate scope and good functional group tolerance.

Biaryl scaffold plays important roles in numerous areas of organic chemistry.[1] For example, a variety of 2, 2-bipyridine derivatives are often used as ligands in transition metal-catalyzed chemical transformations. The synthetic methods on the construction of biaryl compounds basically utilize cross/homo coupling strategy, in which functionalized arenes are frequently employed as the coupling reaction partners (Scheme 1A).[2] Recently, the direct C-H functionalization of arenes has made this synthetic protocol more straightforward, obviating the need for prefunctionalization of one arene in the coupling reaction.[3] Besides the coupling of two aromatics, there is another strategy to construct these biaryl scaffolds, starting from diyne molecules. 1,3-Diynes have been thoroughly investigated since the discovery of the Glaser-Hay Reaction in 1869. They are easily available by a number of synthetic methods and can be widely used in the synthesis of arenes and heteroarenes. For example, an elegant C-H activation/1,3-diyne cascade strategy for the synthesis of bisheterocycles has been reported by Glorius and Volla, respectively (Scheme 1B).[4] Thus, the introduction of 1,3-diyne moiety can avoid the use of coupling strategy to construct C-C bond connecting two aryls, which could largely simplify the synthetic procedures.

However, utilizing 1,3-diynes in C-H activation instead of monoalkynes would face several challenges: (a) chemoselectivity between the two alkyne units (Scheme 1C); (b) regioselectivity of the migratory insertion process; and (c) selectivity between mono- and bifunctionalization. One of the solutions on above problems is to make the two alkyne units having significant discrepancy on the cyclization reactivity.

Indoles can be efficiently synthesized using ethynylaniline derivatives through intramolecular hydroamination upon metal or Lewis acid catalysis.[5] Therefore, we designed and synthesized 1,3-diynes tethering an amino group at the proximal position, rendering that the functionalized diynes can distinguish the two alkyne units to solve chemo- and regioselectivity in the next cascade reaction.



Scheme 1. Synthesis of adjacent biaromatics.

Sulfoxonium ylides have recently demonstrated a wide utility in C−H activation, because of their high flexibility, stability, and diverse reactivity.[6] Employment of sulfoxonium ylide as an arene substrate bearing a built-in directing group provides an efficient method to synthesize aromatic derivatives. In 2017, Li and co-workers reported [4+2] annulation of sulfoxonium ylides with alkynes for the rapid construction of substituted naphthols, in which sulfoxonium ylide functioned as a carbene-like directing group (DG), affording functionalized aromatic compounds.[7] Given the rapid assembly of otherwise hard-to-access skeletons, operational simplicity, and controllable selectivity, sulfoxonium ylides provide good sources in the synthesis of related fused carbocyclic scaffolds. Based on its unique property, Prabhu reported an example to synthesize furanone-fused naphthol derivatives by domino Rh(III)-catalyzed C−H activation, regioselective annulations, and lactonization.[6l]

Herein, we wish to report our findings on rhodium-catalyzed synthesis of naphthol-indoles through annulation of sulfoxonium ylides and diynes. Furthermore, by taking advantage of intramolecular hydroamination, we will also indicate that the functionalized 1,3-diynes have good chemo- and regioselectivity in this C-H activation/1,3-diyne/hydroamination cascade reaction (Scheme 1, *this work*).

The initial optimization of the reaction conditions was conducted with sulfoxonium ylide **1a** and diyne **2a** as substrates, and all of the results are summarized in Table 1. When the reaction of **1a** with **2a** was carried out in the presence of

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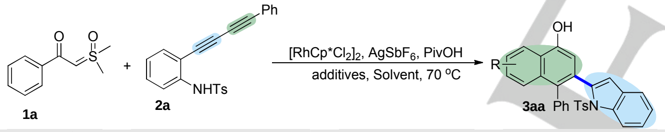
$[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (20 mol%), PivOH (2.0 equiv), and $Zn(OAc)_2$ (2.0 equiv) in DCE at 70 °C for 12 h, we were pleased to observe the formation of the corresponding naphthol-indole **3aa** in 67% yield (entry 1). Since the use of zinc salt was crucial in the reaction, we next examined several other zinc salts in the reaction (for the initial examination of the reaction, see Table S1 in the Supporting Information). On the examination of various zinc salts such as $Zn(OAc)_2$, $Zn(OTf)_2$, $Zn(NTf)_2$, it was found that the addition of $Zn(OTf)_2$ could afford **3aa** in 78% yield (entries 1-3). However, using $Zn(OTf)_2$ as an additive, the obtained product contained some impurities that were difficult to be separated from the desired product **3aa** (entry 3). The use of other zinc salts such as zinc oxide and chloride could not afford the corresponding product **3aa**, suggesting the crucial role of counterion in zinc salt (entries 4-5). In addition, zinc glycinate was proved to have similar effect as that of zinc acetate (entry 6), presumably due to that its counterion has the similar role as that of acetate. Other additives such as $Cu(OAc)_2$, $Cu(OTf)_2$, AgOAc AgOTf and NaOAc, which have been widely used in the previously reported C−H activation reactions, were inactive in this transformation, highlighting the crucial role of zinc acetate as the additive (entry 7). Moreover, Lewis acids as $In(OTf)_3$ and $Yb(OTf)_3$ are also totally invalid for this transformation (entry 7). This observation may be due to the highly coordinating ability between zinc acetate and oxygen atom in this transformation. The exploration of solvent effects revealed that the use of ethanol as solvent could give **3aa** in 95% yield, which was better than others including DCE, MeCN and TFE (entries 8-10).

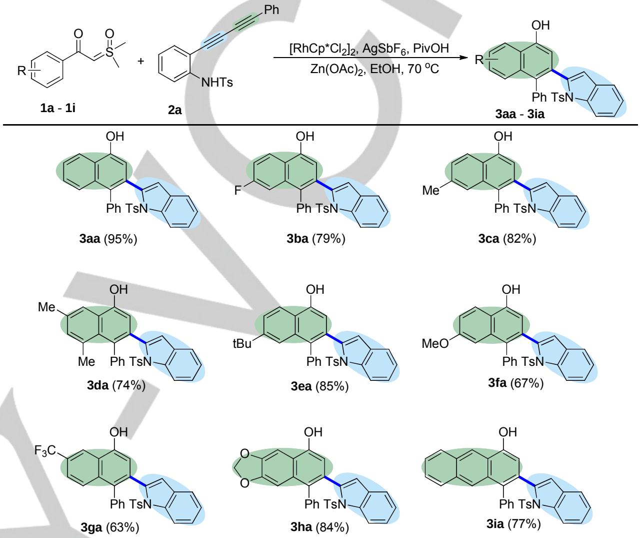
Table 1. Optimization of the reaction conditions for the synthesis of **3aa**.



entry[a]	additive	solvent	yield (%)[c]
1	$Zn(OAc)_2$	DCE	67
2	$Zn(OTf)_2$	DCE	78
3	$Zn(NTf)_2$	DCE	55
4	$ZnCl_2$	DCE	n.r.
5	ZnO	DCE	n.r.
6	$Zn(glycine)_2$	DCE	69
7	-/other[b]	DCE	n.r.
8	$Zn(OAc)_2$	TFE	n.r.
9	$Zn(OAc)_2$	EtOH	95
10	$Zn(OAc)_2$	MeCN	41

[a] Substrate **1a** (0.10 mmol), **2a** (0.15 mmol), PivOH (0.20 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (20 mol%), additives (2.0 equiv) were added. All the reactions were carried out in a 0.10 mmol scale in solvent (1.0 mL) at 70 °C for 12 h. [b] The other additives are $Cu(OAc)_2$, $Cu(OTf)_2$, AgOAc, AgOTf, NaOAc, $In(OTf)_3$ and $Yb(OTf)_3$. [c] Isolated yields.

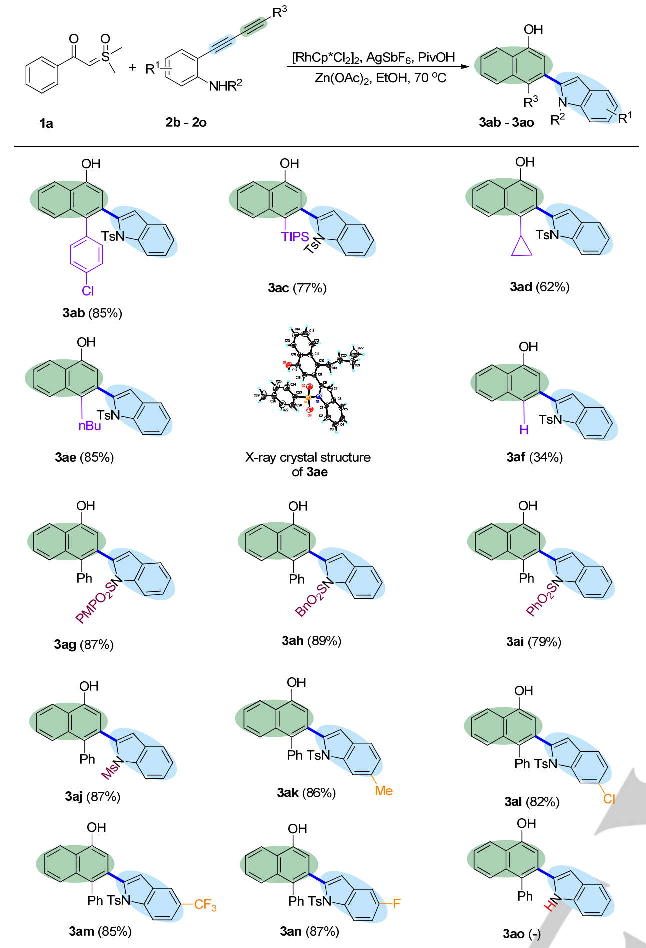
After determining the optimal reaction conditions, we subsequently investigated the generality of this protocol by using different sulfoxonium ylides to react with **2a** and the results are shown in Scheme 2. To our delight, a range of substituted sulfoxonium ylides containing either electron-donating or electron-withdrawing groups such as F, Me, ^{t}Bu, OMe and CF_3 could be all tolerated, giving the corresponding indole products **3ba**-**3ga** in good yields ranging from 63% to 85%. The other ring fused sulfoxonium ylides were also compatible under the standard reaction conditions, affording the desired indole derivatives **3ha** and **3ia** in 84% and 77% yields, respectively.



[a] Reaction condition: **1** (0.10 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (20 mol%), PivOH (0.20 mmol), $Zn(OAc)_2$ (0.20 mmol). All the reactions were carried out in a 0.10 mmol scale in EtOH (1.0 mL) at 70 °C for 12 h.

Scheme 2. Substrate scope for indoles..

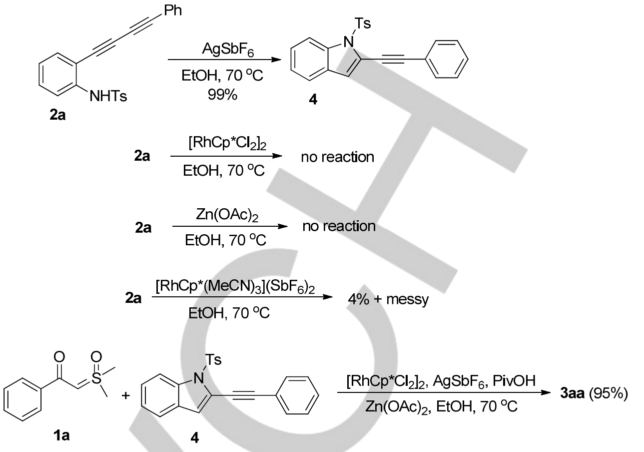
Next, we investigated the substrate scope of 1,3-diyne units in this reaction. The R^3 group on the 1,3-diyne terminal position could be extended to *para*-chlorobenzene, TIPS, cyclopropane and butyl groups, smoothly furnishing the corresponding products **3ab**-**3ae** in good yields ranging from 62% to 85%. The structure of **3ae** has been determined by X-ray diffraction. When R^3 is a TMS group, the silyl group was removed after the reaction, affording the corresponding product **3af** in 34% yield. We also examined the R^2 protecting groups on the amino moiety and found that a variety of sulfonyl groups likewise *para*-methoxybenzenesulfonyl group (**3ag**), benzylsulfonyl group (**3ah**), benzenesulfonyl group (**3ai**), and methanesulfonyl group (**3aj**) are compatible in this reaction, delivering the desired products in good yields. The diversified R^1 group such as methyl group, chlorine and fluorine atoms, and CF_3 group could be introduced into the aromatic ring of 1,3-diyne units, leading to the synthesis of functionalized indole derivatives in good yields with a simple operation. Unprotected aniline such as **2o** was not compatible for the reaction under the standard conditions (for product **3ao**).



[a] Reaction condition: **1a** (0.10 mmol), **2** (0.15 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (20 mol%), PivOH (0.20 mmol), $Zn(OAc)_2$ (0.20 mmol). All the reactions were carried out in 0.10 mmol scale in EtOH (1.0 mL) at 70 °C for 12 h.

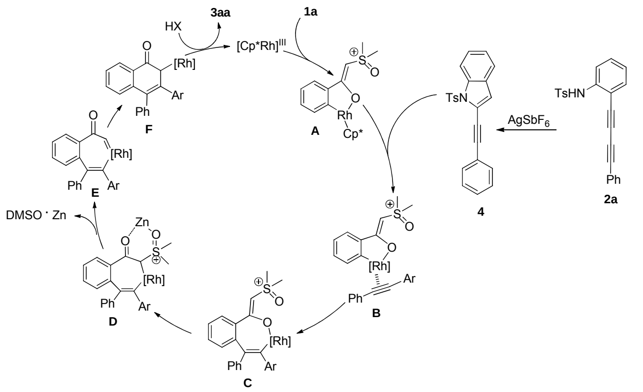
Scheme 3. Substrate scope of 1,3-diynes.

To get more mechanistic insights of this cascade annulation, a series of control experiments were carried out to investigate the reaction sequence. As shown in Scheme 4, using 1,3-diyne **2a** as substrate in the presence of $[Cp^*RhCl_2]_2$, $AgSbF_6$, or $Zn(OAc)_2$ or with cationic $Cp^*Rh(III)$ complex as a single catalyst, we found that only $AgSbF_6$ can catalyze the hydroamination of **2a** to form 2-alkynyl indole species **4** in 99% yield. The others all failed to afford the hydroamination product.[8] Finally, we also identified that using **4** instead of **2a** to react with **1a** under the standard conditions could give the desired product **3aa** in 95% yield. These experimental results suggested that the first step of this cascade transformation is a Ag-catalyzed cyclization of **2a** to produce the corresponding 2-alkynyl indole intermediate. Moreover, Zinc acetate may play a role on assisting the cyclization process in the second step of rhodium-catalyzed process.[6l, 9]



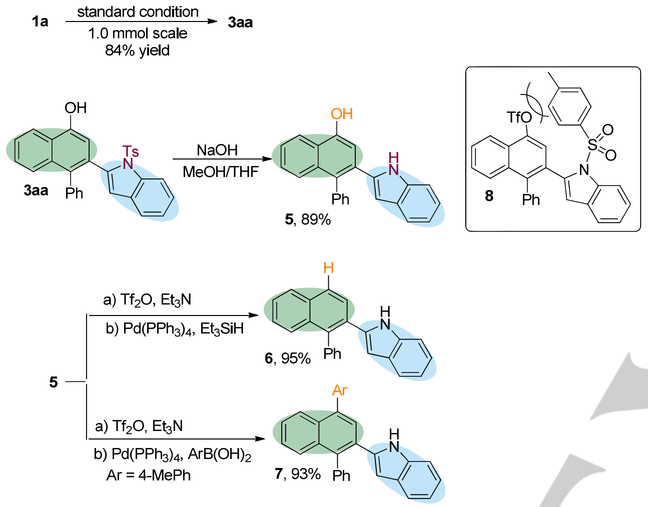
Scheme 4. Control Experiments

On the basis of the previous literature[7] and the above obtained experimental results, a plausible mechanistic pathway is proposed in Scheme 5. First, 1,3-diyne **2a** undergoes intramolecular hydroamination to generate 2-alkynyl indole intermediate **4** in the presence of $AgSbF_6$.[10] Meanwhile, the cationic $Cp^*Rh(III)$ complex is generated upon treatment of $[Cp^*RhCl_2]_2$ with $AgSbF_6$, which then coordinates with sulfoxonium ylide **1a** and subsequently undergoes an *ortho* arene C−H activation to generate rhodacyclic intermediate **A**. The coordination of rhodium complex **A** with **4** gives intermediate **B**, which goes through a migratory insertion to afford intermediate **C**. Then, another Rh(III) intermediate **D** can be formed through an intramolecular rearrangement, which in turn gives the reactive carbenoid species **E** by α-elimination of DMSO with the assistance of $Zn(OAc)_2$. Next, the migratory insertion of Rh−alkenyl bond into the resulting carbenoid moiety in intermediate **E** produces a Rh(III) alkyl species F, which undergoes protonolysis of Rh−C bond by HX to release the final product along with the regeneration of the active catalyst. The regioselectivity was determined on the step of coordination/insertion of intermediate **4**. The different steric hindrance of two groups on acetylene moiety is the key factors on this selectivity.



Scheme 5. Mechanistic paradigm

To briefly demonstrate the potential synthetic utility of these biaryl compounds, the production of **3aa** can be scaled to 1.0 mmol in 84% yield (see Supporting Information). Moreover, it could be converted to a detosylated indole **5** upon treatment with sodium hydroxide. The reaction of **5** with Tf$_2$O affords the triflated product, which can be reduced with Pd(PPh$_3$)$_4$/Et$_3$SiH catalytic system or couple with 4-methylphenylboronic acid using Pd(PPh$_3$)$_4$ as catalyst, affording the desired products **6** and **7** in high yields. Noteworthy, triflate **8** can not be used as coupling partner with other reactants under Pd catalysis presumably due to that the sterically bulk tosyl group in indole impaired the reactivity of its triflated derivative.



Scheme 6. Synthetic Application

In conclusion, we have developed a novel synthetic method for the rapid construction of naphthol-indole derivatives in good yields from easily prepared 1,3-diynes and sulfoxonium ylides via a Rh(III)-catalyzed C-H activation and silver-catalyzed hydroamination cascade process in a one pot manner. This synthetic protocol can provide a variety of C2 functionalized indole derivatives with a good functional group tolerance under mild reaction conditions. Further investigations on expanding the applications of this synthetic method are ongoing in our laboratory.

Acknowledgements

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Keywords: rhodium • silver • C-H activation • sulfoxonium ylides • naphthol-indole

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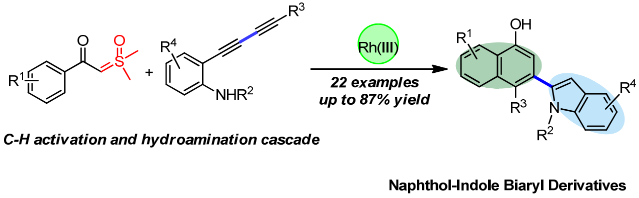
Synthesis of naphthol-indoles starting from easily available 1,3-diynes and sulfoxonium ylides via Rh(III)-catalyzed C-H activation/hydroamination cascade process in a one pot manner has been developed.



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