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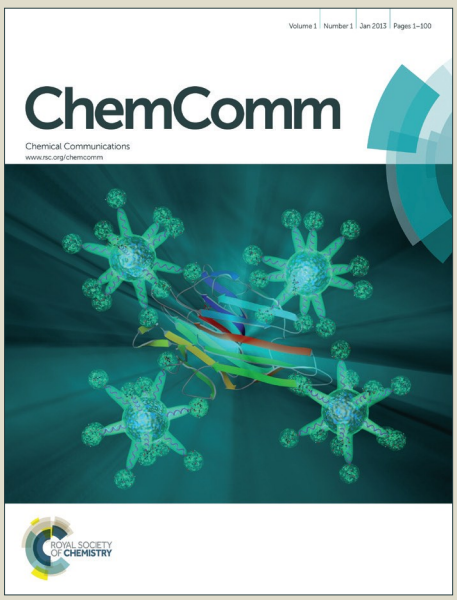

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Rh(III)-catalyzed chemoselective C–H functionalizations of tertiary aniline *N*-oxides with alkynes

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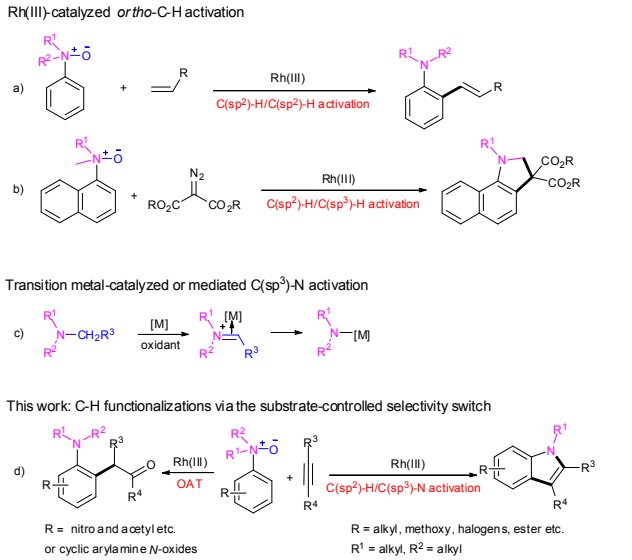
In this work, we report novel Rh(III)-catalyzed chemoselective functionalizations of tertiary aniline *N*-oxides with alkynes, including an annulation via the sequential C(sp^2)–H and C(sp^3)–N activations for the formation of *N*-alkylindoles and an O-atom transfer (OAT) process for the synthesis of acetophenones.

Tertiary anilines are important building blocks in organic synthesis and widely exist in natural products, pharmaceuticals and material molecules.[1] Thus, the transformations of tertiary anilines are a lasting hot topic in organic chemistry. Because of electron-donor characteristics and steric hindrance, *ortho*-selective aromatic C–H functionalization of tertiary anilines remains a tremendous challenge. To resolve this problem, our group recently developed a Rh(III)-catalyzed *ortho*-C–H activation strategy[2,3] using tertiary aniline *N*-oxides as both the internal oxidant and the traceless directing group for the synthesis of 2-alkenylated tertiary anilines (Scheme 1a).[4] Later, with this strategy, Zhou and co-workers reported a Rh(III)-catalyzed regioselective annulation reaction of 1-naphthylamine *N*-oxides with diazo compounds via C(sp^2)–H/C(sp^3)–H activation to afford various 1*H*-benzo[*g*]indoline derivatives (Scheme 1b).[5] As far as we know, this traceless internal oxidant/directing strategy is only applied in the coupling reactions with olefins and diazo compounds so far, and it is thus highly valuable to develop new transition metal-catalyzed *ortho*-C–H activation/functionalizations of tertiary aniline *N*-oxides to further demonstrate the synthetic utility of this strategy.

Meanwhile, transition metal-catalyzed activation of the C–N bond has been attracting great interest since 2010.[6] Since tertiary anilines are a kind of important *N*-containing compounds, cleaving the C–N bonds of tertiary anilines and utilizing the generated nitrogen and carbon sources in organic synthesis are of great significance. However, owing to the high C–N bond dissociation energy, the C–N bond activation of tertiary anilines, especially C(sp^3)–N bonds, is still a significant challenge and remains less developed (Scheme 1c).[7] We envision that the C(sp^3)–N bond activation could be integrated with the Rh(III)-catalyzed *ortho*-C–H activation of tertiary aniline *N*-oxides to form valuable heterocyclic compounds using alkynes as the coupling partner.



Scheme 1. Evolution of Rh(III)-catalyzed C–H functionalizations of tertiary aniline *N*-oxides.

It is known that *N*-oxides can undergo an O-atom transfer (OAT) to alkynes through transition metal catalysis.[8] Recently, the groups of Li,[9a] Chang,[9b,9c] Lu,[9d] Sundararaju,[9e] and Ackermann[9f] successfully combined an OAT process and a Rh(III)- or Co(III)-catalyzed *N*-oxide assisted aromatic C–H activation of quinoline *N*-oxides and arylnitrones with alkynes to afford substituted acetophenones. A Rh(III)-catalyzed OAT from tertiary aniline *N*-oxides to diazomalonates was reported by Zhou and co-workers in 2015.[5] Herein, we would like to disclose Rh(III)-catalyzed chemoselective C–H functionalizations of tertiary aniline *N*-oxides with alkynes, including an annulation *via* the sequential C(sp^2)–H and C(sp^3)–N activations to provide *N*-alkylindole derivatives[10,11] and an OAT process to deliver acetophenone derivatives (Scheme 1d).

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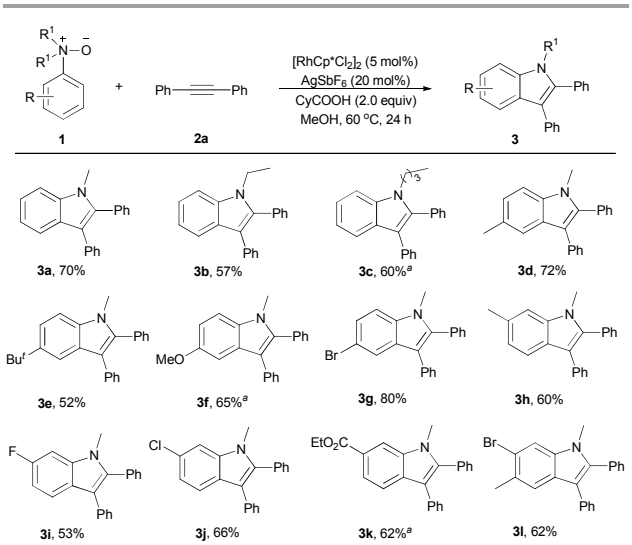
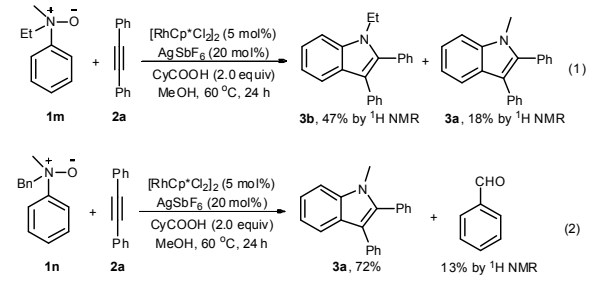
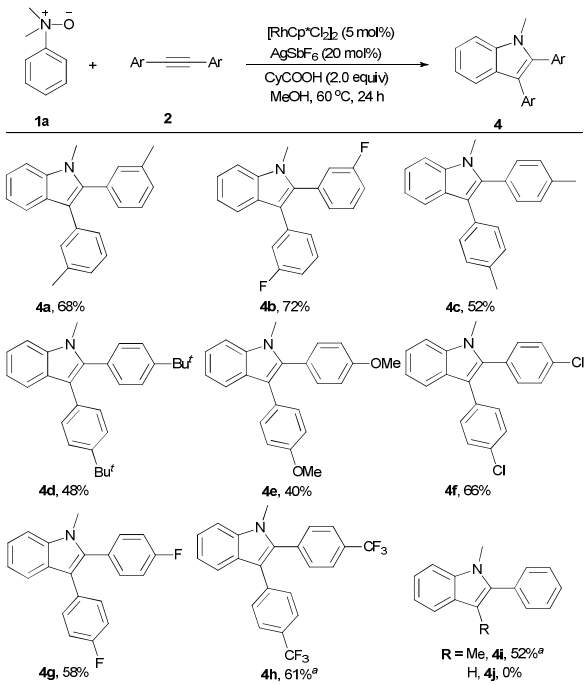
Our study commenced with the annulation of *N,N*-dimethylaniline *N*-oxide **1a** and diphenylacetylene **2a** as the model reaction (For details, see Table S1 in ESI). Initially, using 5.0 mol% of $[Cp^*RhCl_2]_2$ (Cp^* = pentamethylcyclopentadienyl) and 20 mol% of $AgSbF_6$ as the catalyst, and 2.0 equiv of PivOH as the additive in methanol at 60 °C for 24 h, a 60% yield of the desired *N*-methylindole derivative **3a** along with a 25% yield of the OAT product **3a'** as a by-product was obtained (Table S1, entry 1). Other solvents such as 1,4-dioxane, DMF, DCE and *t*-AmOH were less effective for the formation of **3a** (Table S1, entries 2-5). Next, various acid and base additives were investigated. CyCOOH proved to be superior to PivOH, HOAc, CF_3COOH, AdCOOH, $Cu(OAc)_2$ and CsOPiv, and **3a** was obtained in a 70% yield (Table S1, entries 1 and 6-11). The yields of **3a** were decreased when $AgPF_6$, AgOPiv, and AgOAc were used instead of $AgSbF_6$ (Table S1, entries 12-14). It is noteworthy that **3a** could be obtained in a 44% yield in the absence of Ag^+ salt (Table S1, entry 15). Increasing the loading of $AgSbF_6$ to 40 mol% from 20 mol% led to a comparable yield of **3a** (Table S1, entries 9 and 16). Furthermore, the reaction of **1a** with 1.0 equiv of **2a** in the presence of 1.2 equiv of $AgSbF_6$ gave the **3a** in a 61% yield. (Table S1, entry 17). Using *N,N*-dimethylaniline or *N*-methylaniline instead of the *N*-oxide **1a** as the substrate, no desired product was formed (Table S1, entry 18), which suggests the key role of the N–O bond for the transformation. Thus, we established the catalytic system comprising $[Cp^*RhCl_2]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%) and CyCOOH (2.0 equiv) in MeOH under an N_2 atmosphere at 60 °C for 24 h.



Scheme 2 The scope of tertiary aniline *N*-oxides. Reaction conditions: **1** (0.50 mmol, 2.0 equiv), **2a** (0.25 mmol), $[RhCp^*Cl_2]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%) and CyCOOH (2.0 equiv) in MeOH (1.0 mL) at 60 °C for 24 h under an N_2 atmosphere. Isolated yields are given. [a] $AgSbF_6$ (40 mol%) and 110 °C were used.

With the optimal conditions in hand, we next explored the scope of tertiary aniline *N*-oxides. As summarized in Scheme 2, various *N,N*-dialkyl aniline *N*-oxides could react with diphenylacetylene to afford the corresponding *N*-alkylindoles (**3a**-**3c**). Moreover, both the electron-donating (Me, Bu^t, and MeO) and electron-withdrawing groups (F, Cl, Br, and CO_2Et) on the phenyl ring of aniline *N*-oxides were compatible with this protocol, delivering the desired products in satisfactory yields (**3d**-**3k**). 3,4-Disubstituted *N,N*-dimethylaniline *N*-oxide could also undergo the annulation in a 62% yield (**3l**). Furthermore, *N*-ethyl-*N*-methylaniline *N*-oxide reacted with **2a** to produce *N*-ethyl and *N*-methyl substituted indoles **3b** and **3a** in 47% and 18% yields, respectively (eq. 1). When *N*-benzyl-*N*-methylaniline *N*-oxide was treated with **2a**, a 72% yield of **3a** and a 13% yield of benzaldehyde were obtained without the formation of *N*-benzyl substituted indole (eq. 2). These observations indicate an order of reactivity of C(benzyl)−N > C(methyl)−N > C(ethyl)−N, which provides a significant hint for the selective cleavage of the C(alkyl)–N bonds.





Scheme 3 The scope of alkynes. Reaction conditions: **1a** (0.50 mmol, 2.0 equiv), **2** (0.25 mmol), $[RhCp^*Cl_2]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%) and CyCOOH (2.0 equiv) in MeOH (1.0 mL) at 60 °C for 24 h under an N_2 atmosphere. Isolated yields are given. [a] $AgSbF_6$ (40 mol%) and 110 °C were used.

Next, we examined the scope of the internal alkynes. A variety of diarylacetylenes containing the common functional groups such as Me, MeO, Bu^t, X (X = F, Cl), and CF_3 could smoothly undergo the annulation process with *N,N*-dimethylaniline *N*-oxide **1a** to form the indole derivatives (Scheme 3, **4a**-**4h**). In addition, the unsymmetrical prop-1-yn-1-ylbenzene was compatible with the protocol, affording the desired product with an exclusive regioselectivity in a moderate yield (Scheme 3, **4i**). When the

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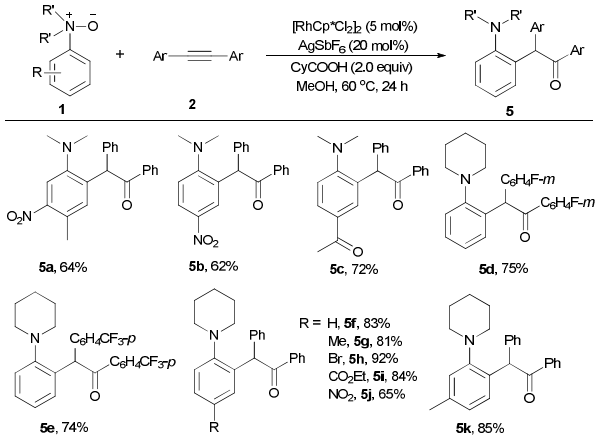
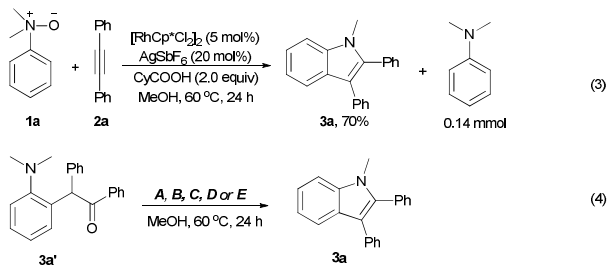
reaction of *N,N*-dimethylaniline *N*-oxide **1a** with terminal phenylacetylene, no desired product was detected (Scheme 3, **4j**).

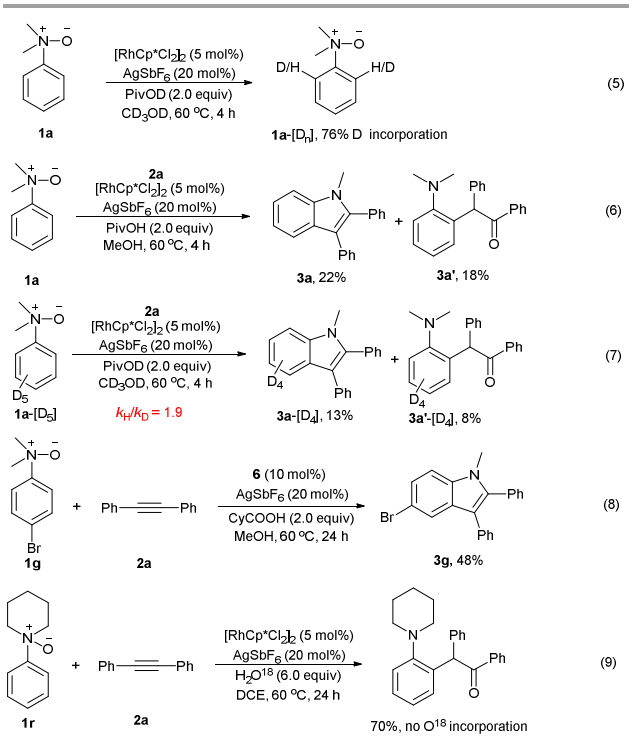


Scheme 4 Rh(III)-catalyzed O-atom transfer reactions of tertiary aniline *N*-oxides with alkynes. Reaction conditions: **1** (0.50 mmol, 2.0 equiv), **2** (0.25 mmol), $[RhCp^*Cl_2]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%) and CyCOOH (2.0 equiv) in MeOH (1.0 mL) at 60 °C for 24 h under an N_2 atmosphere. Isolated yields are given.

Interestingly, when the *N,N*-dimethylaniline *N*-oxides with the strong electron-withdrawing nitro and acetyl groups on the phenyl ring were treated with diphenylacetylene under the standard conditions, the OAT products rather than *N*-methylindoles were formed exclusively (Scheme 4, **5a**-**5c**). In addition, cyclic arylamine *N*-oxides could also participate in the OAT reaction. For example, various 1−arylpiperidine *N*−oxides containing both the electron-donating and electron-withdrawing groups coupled with diphenylacetylene to afford the OAT products in good to excellent yields (Scheme 4, **5f**-**5k**).



To gain some preliminary insights into the reaction mechanism, further experiments were carried out. First, 0.14 mmol of *N,N*-dimethylaniline was isolated from the reaction of **1a** and **2a** under the standard conditions, indicating that *N,N*-dimethylaniline *N*-oxide **1a** also serves as an oxidant in the annulation (eq. 3). Next, a series of control experiments on the conversion of the OAT product **3a'** into *N*-methylindole **3a** were performed. The results showed that the isolated **3a'** could not be converted into **3a** without $AgSbF_6$ (eq. 4, **A**, **B**, **D**). Treatment of **3a'** in the presence of $AgSbF_6$ in MeOH afforded **3a** in a 14% yield (eq. 4, **C**). Under the standard conditions, a 10% yield of **3a** was obtained (eq. 4, **E**). Thus, although the details of the indole formation is not entirely clear at the present stage, the pathway involving the generation of the OAT product and the subsequent cyclization seems less favored.



The H/D exchange experiments implied that the *ortho*-C–H bond cleavage was a reversible process (eq. 5). A KIE value of 1.9 was observed in an intermolecular competition reaction between **1a** and **1a**-$[D_5]$ with **2a** (eq. 6 and eq. 7), demonstrating that the C–H bond cleavage might be related with the rate-determining step.[12] Moreover, the five-membered cyclometalated Rh(III) complex **6** could serve as the catalyst in the reaction of **1g** with **2a** to give the desired product **3g** in a 48% yield (eq. 8). This result indicate the possible intermediacy of a rhodacycle species in the catalytic cycle. An O^{18} labeling experiment was performed, and no O^{18} incorporation was observed in the product, showing that the *N*-oxide group is likely the source of O atom in the formation of acetophenones (eq. 9).[9a]

Based on the the above observations, a plausible mechanistic pathway of the formation of *N*-alkylindoles is proposed in Scheme 5. First, the *N*-oxide-assisted C−H activation reaction of **1a** with the [Rh(III)Cp*] species affords the cyclometalated Rh(III) species **IM1**, which further reacts with alkyne **2a** to form the intermediate **IM2** via a migratory insertion process. Next, the reaction encounters two possible pathways. In *path a*, **IM2** undergoes a methyl $C(sp^3)$–Rh bond formation to give the intermediate **IM3**. After an intramolecular rearrangement, **IM3** is converted to **IM4**, which may also be generated from a Polonovski-type reaction of **IM2**.[5] **IM4** undergoes the C=N bond cleavage,[7c-7f] leading to the intermediate **IM5** with the release of one molecule of formaldehyde. Furthermore, a reductive elimination results in **3a** and [Rh(I)Cp*] species. Finally, the generated [Rh(I)Cp*] species is reoxidized to

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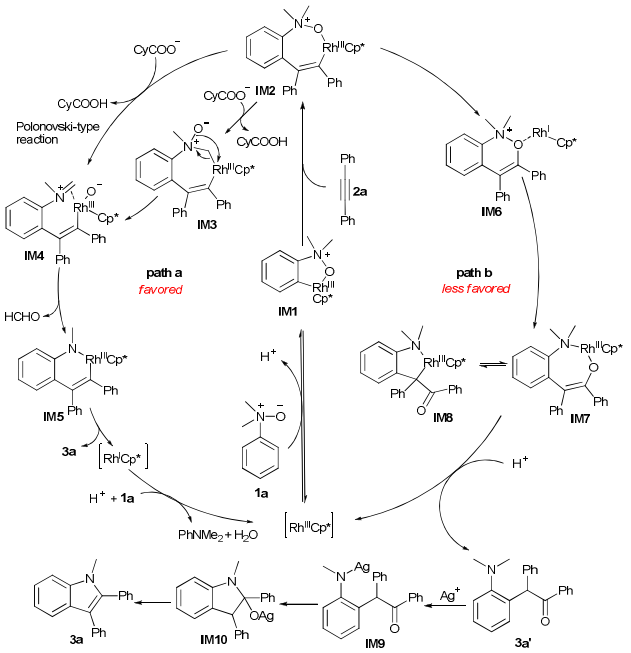
the [Rh(III)Cp*] species by **1a** to complete the catalytic cycle. In another route (*path b*), the reductive elimination of **IM2** affords the intermediate **IM6**, which is further transformed into **IM7** or **IM8** via an oxidative addition.[9d] After a protonation, the OAT product **3a'** is generated. In the presence of Ag^+, the C(sp^3)–N bond cleavage of **3a'** gives **IM9**.[13] Further intramolecular nucleophilic addition and β-hydride elimination produce the indole **3a**.



Scheme 5 Plausible mechanism for the formation of *N*-alkylindole.

In conclusion, we have addressed for the first time a Rh(III)-catalyzed regioselective annulation of tertiary aniline *N*-oxides with alkynes *via* the sequential C(sp^2)–H and C(sp^3)–N activation, which provides a novel method to prepare *N*-alkylindoles. Using *N*-oxide as a traceless directing group, this annulation proceeds well under the mild reaction conditions and does not need metal oxidants. The *N,N*-dimethylaniline *N*-oxides with the strong electron-withdrawing nitro and acetyl groups on the phenyl ring and cyclic arylamine *N*-oxides encounter a selectivity switch to afford the OAT products rather than the indole derivatives under the same conditions. Further investigation to verify the mechanism of this methodology is in progress.

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