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Rhodium(III)-Catalyzed Redox-Neutral C–H Annulation of Arylnitrones and Alkynes for the Synthesis of Indole Derivatives

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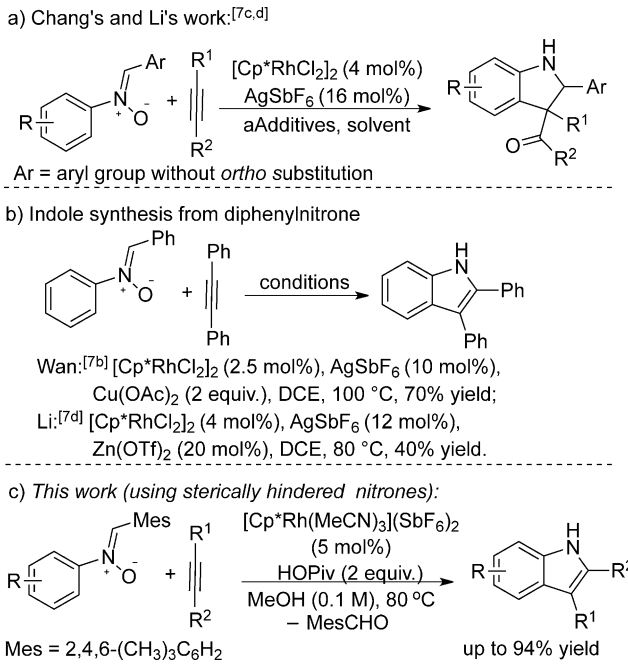
Abstract: By using a nitrone as the oxidizing directing group, a mild, practical and efficient rhodium(III)-catalyzed C–H functionalization for the synthesis of indole derivatives has been developed. This reaction obviates the need for an external oxidant and shows good functional group tolerance. The employment of a sterically hindered Mes group on the carbon center of the nitrone is crucial to produce indoles in high yield.

Keywords: alkynes; annulation; C–H activation; nitrones; oxidizing directing group; rhodium

Transition metal-catalyzed directed C–H functionalization represents an atom- and step-economical approach for complex molecules from less functionalized substrates.[1] Despite the notable advances, stoichiometric amounts of external oxidants are generally required for catalyst regeneration. To circumvent the use of external oxidants, an attractive redox-neutral strategy employing an oxidizing directing group, which acts as both directing group and internal oxidant, has been applied in this field.[2] In recent years, diverse oxidizing directing groups have been developed, which typically contain an oxidizing N–O,[3] N–N,[4] or N–S bond.[5] Further development of novel oxidizing directing groups with desired synthetic features is still in demand.

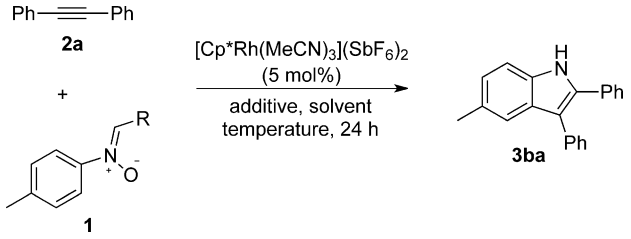
In a search for innovative oxidizing directing groups that enable novel transformations to deliver valuable structures under mild conditions, we turned our attention to nitrones. Nitrones are easily accessible and can be viewed as promising compounds due to their diversity in chemical properties and synthetic utility.[6] Being the *N*-oxide of an imine, we envisioned that the nitrone moiety may serve as an internal oxidant by the cleavage of the N–O bond during the C–H functionalization, which will open new aspects of nitrones by acting as an oxidizing directing group.[7a,b] It should be noted that during the preparation of this manuscript, an attractive cyclization of arylnitrones with alkynes to indolines catalyzed by Rh(III) under external oxidant-free conditions was reported independently by Chang's and Li's groups (Scheme 1a).[7c,d] It would be intriguing to explore other transfromations by the use of nitrones as an oxidizing directing group.

Indole represents a privileged structural framework widely existing in natural products, biologically active molecules and pharmaceuticals, which has attracted broad and continued interest in the development of synthetic approaches for this motif.[8,9] Of the many



Scheme 1. C–H activation using a nitrone as the oxidizing directing group.

Table 1. Optimization of reaction conditions for the synthesis of indoles.[a]



Entry	R	Additive (equiv.)	Solvent	Yield [%][b]
1[c]	Ph	CsOAc (0.5)	DCE	NR
2	Ph	–	DCE	6
3	Ph	HOPiv (1)	DCE	30
4	2-thienyl	HOPiv (1)	DCE	32
5	CH=CHPh	HOPiv (1)	DCE	55
6	Mes	HOPiv (1)	DCE	56
7	cyclohexyl	HOPiv (1)	DCE	<5
8	Mes	HOPiv (1)	MeOH	78
9[d]	Mes	HOPiv (1)	MeOH	49
10[e]	Mes	HOPiv (1)	MeOH	69
11[f]	Mes	HOPiv (1)	MeOH	65
12[g]	Mes	HOPiv (2)	MeOH	88 (85)[h]

[a] *Reaction conditions:* **1** (0.14 mmol), **2a** (0.1 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%) and additives in solvent (0.5 mL) at 80 °C for 24 h under air. Mes = 2,4,6-trimethylphenyl.
[b] Yield determined by ^1H NMR.
[c] 2.5 mol% of $[Cp^*RhCl_2]_2$ were used as the catalyst.
[d] Reaction was run at 50 °C.
[e] 20 mg of 4 Å MS were added.
[f] 5 equiv. of water were added.
[g] MeOH (1 mL).
[h] Isolated yield is shown in parentheses.

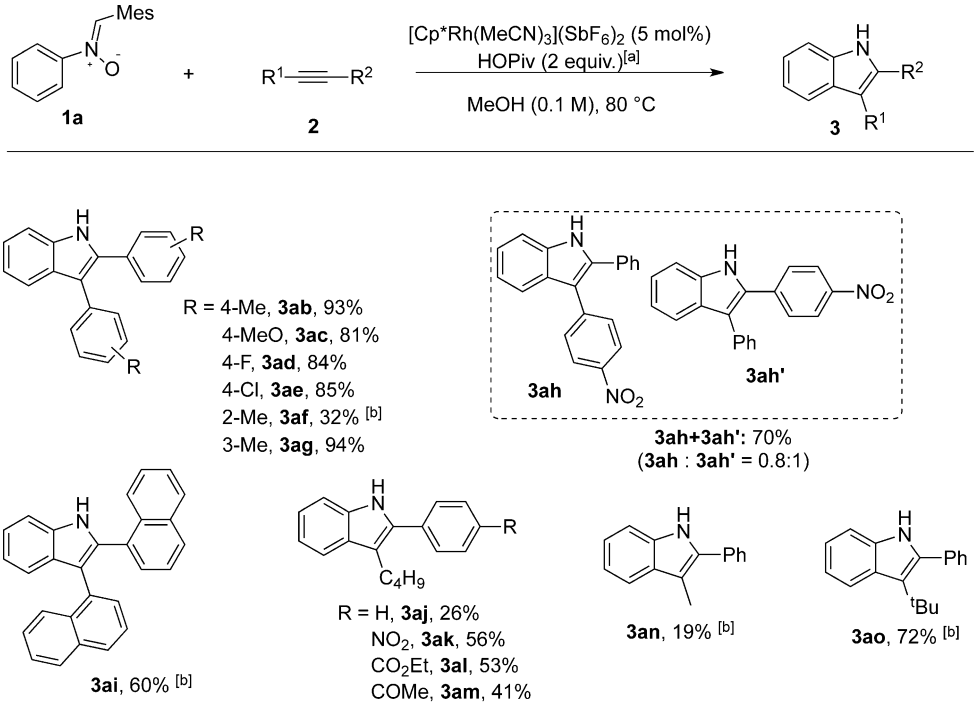
approaches developed, the transition metal-catalyzed C–H functionalization provides a straightforward and efficient way to produce indole derivatives.[10] Though several directing groups, including oxidizing directing groups,[4,11] were designed to construct this structural moiety, the nitrone has been rarely exploited in such transformations. Wan's group[7b] and Li's group[7d] demonstrated that the C–H functionalization of *C,N*-diphenylnitrone with diphenylacetylene could furnish 2,3-diphenylindole (Scheme 1b). However, this kind of reaction has not been well studied. Herein, we disclose our development of a mild Rh(III)-catalyzed C–H functionalization of *N*-aryl-*C*-mesitylnitrone with internal alkynes for the synthesis of indoles (Scheme 1c). Compared to Chang's and Li's indoline synthesis, the employment of a sterically hindered Mes group on the carbon center of nitrones led to a markedly different coupling and mechanistic experiments were conducted to verify the different reaction pathways.

Initially, the reaction of *N*-(4-methylphenyl)-*C*-phenylnitrone and diphenylacetylene (**2a**) was investigated, and the representative data using $[Cp^*Rh(MeCN)_3](SbF_6)_2$ as the catalyst are shown in Table 1. With HOPiv as the additive, the desired indole product **3ba** was produced in 30% NMR yield (Table 1, entry 3).[12] Subsequently, nitrones bearing different substituents on the carbon center were screened. Fortunately, a significantly improved yield was observed with *N*-(4-methylphenyl)-*C*-mesitylnitrone as the substrate, although other analogous nitrones were found to be less effective (Table 1, entries 4–7). Simply changing the solvent from dichloroethane to methanol significantly increased the yield to 78% (Table 1, entry 8). Lowering the reaction temperature gave an inferior result (Table 1, entry 9). When the reaction was performed in the presence of 4 Å molecular sieves or water (5 equiv.), the yield of indole was decreased (Table 1, entries 10 and 11). The optimized conditions were ultimately identified as: 5 mol% of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ and HOPiv (2 equiv.) in MeOH (0.1 M) at 80 °C (Table 1, entry 12). No reaction occurred in the absence of a rhodium catalyst.

With the optimized conditions in hand, we first examined the reaction scope of the internal alkynes (Scheme 2). Symmetric diarylacetylenes bearing various substituents at the *para* or *meta* positions were compatible with the reaction conditions, furnishing the corresponding indoles in high yields (81–94%). A relatively low yield was obtained for *ortho*-methyl-substitued diarylacetylene (**3af**, 32%). Notably, 1,2-di(naphthalene-1-yl)ethyne was also tolerated to give a moderate yield of the desired product (**3ai**, 60% yield). Moreover, an unsymmetrical diarylacetylene also reacted smoothly, affording a mixture of two regioisomers (**3ah** and **3ah′**). The aryl-alkyl disubstituted alkynes seemed to be less effective (**3aj** and **3an**) unless an electron-withdrawing group was present on the aryl ring (**3ak**–**3am**). It is interesting to note that a good yield of desired indole product **3ao** was observed when phenyl-*tert*-butylacetylene was employed. Nevertheless, dialkylalkynes and terminal alkynes gave poor results.

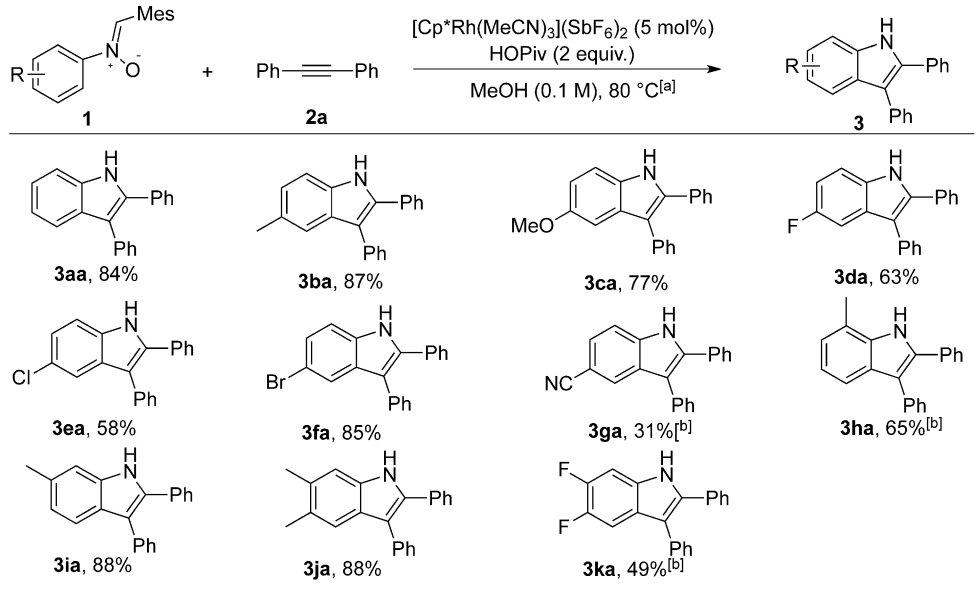
A variety of readily available nitrones bearing various *N*-aryl substituents was next assessed (Scheme 3). Nitrones containing F, Cl, Br, CH_3 and OMe groups on the *N*-aryl moiety were well tolerated, giving the desired products in moderate to good yields. The *para*-cyano-substituted and *ortho*-methyl-substituted *N*-phenyl-*C*-mesitylnitrones seemed to be less effective, and the desired products **3ga** and **3ha** were obtained in moderate yields with higher catalyst loading at 100 °C. When *meta*-methyl-substituted *N*-phenyl-*C*-mesitylnitrone was employed, the arene rhodation took place at the less hindered site selectively (**3ia**).

Further experiments were then carried out to gain more insights into the reaction mechanism. When the reaction of **1b** was conducted in CD_3OD in the absence of alkyne, **1b** was partially decomposed, and



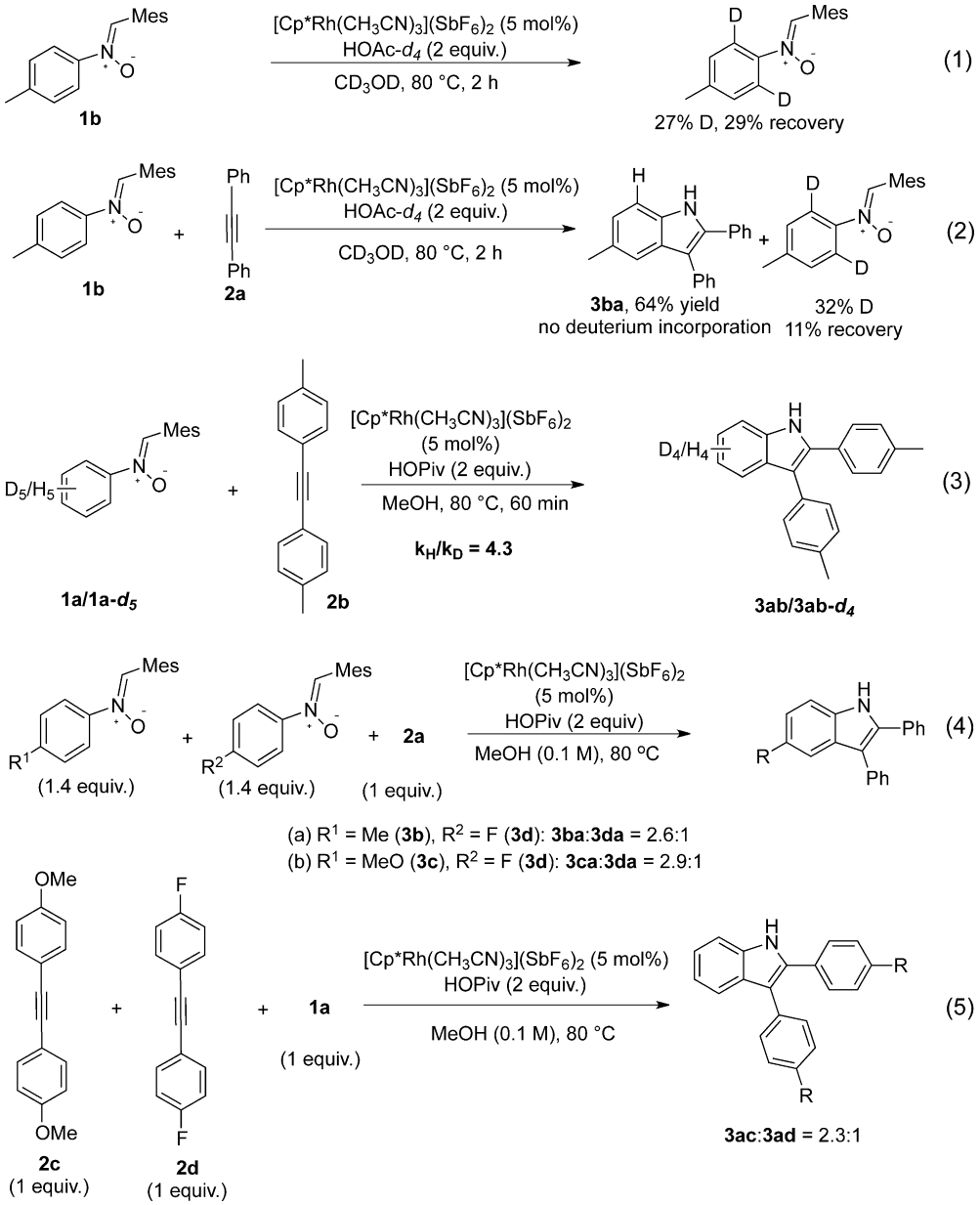
[a] *Reaction conditions:* **1a** (0.28 mmol), **2** (0.2 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%) and HOPiv (2 equiv.) in MeOH (0.1 M) at 80 "C for 24 h under air; isolated yield is reported.
[b] Reaction was run at 100 °C using 10 mol% of catalyst.

Scheme 2. Scope of alkyne substrates.



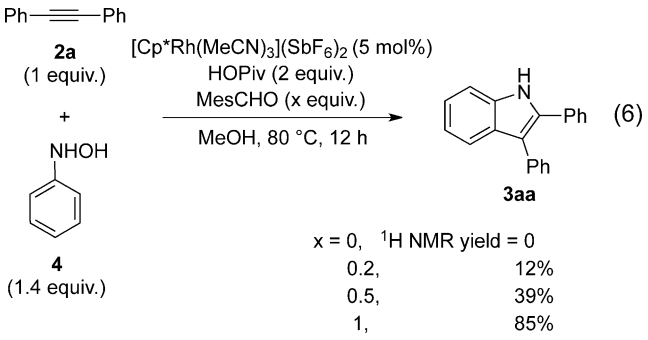
[a] *Reaction conditions:* **1** (0.28 mmol), **2a** (0.2 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%) and HOPiv (2 equiv.) in MeOH (0.1 M) at 80 °C for 24 h under air; isolated yield is reported.
[b] Reaction was run at 100 °C using 10 mol% of catalyst.

Scheme 3. Scope of nitrone substrates.



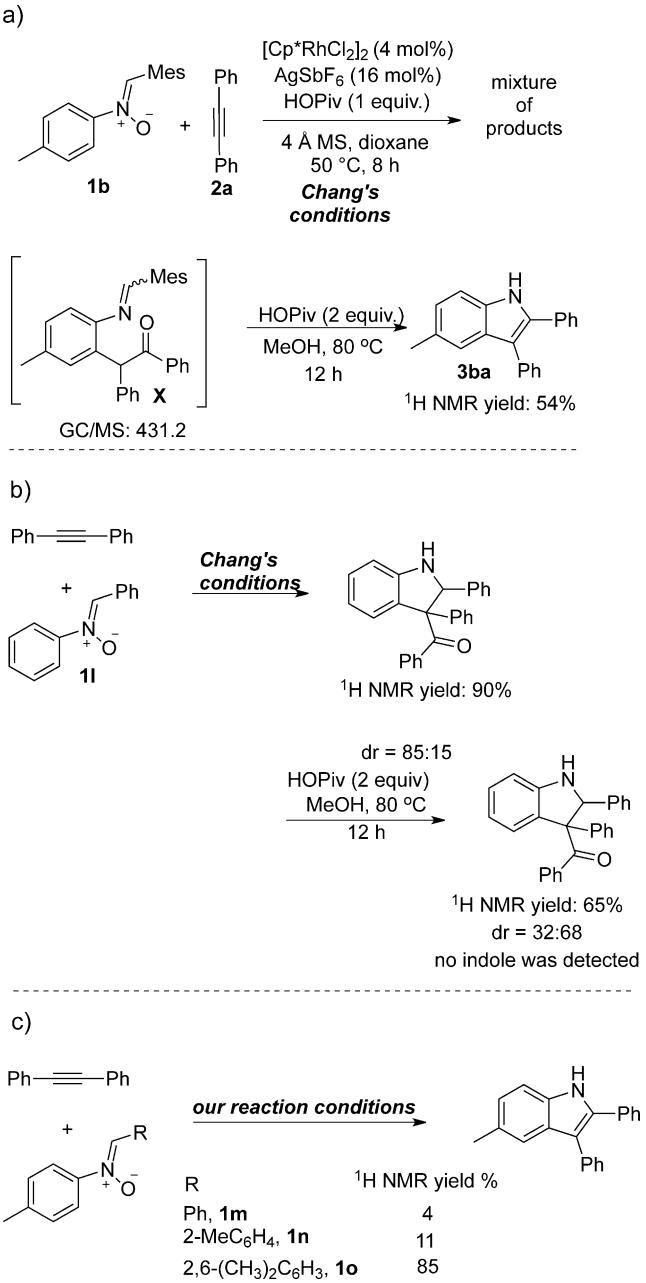
27% deuterium incorporation was observed at the *ortho*-positions of recovered **1b** [Eq. (1)]. If the same reaction was performed in the presence of **2a**, **3ba** was obtained smoothly. No deuterium incorporation was found in **3ba** while 32% deuterium incorporation was detected in unreacted **1b** [Eq. (2)]. These results imply that the C–H activation might be reversible under the reaction conditions. Furthermore, a primary KIE value of 4.3 was observed in the intermolecular isotopic study [Eq. (3)], indicating that the C–H bond cleavage process was most likely involved in the rate-determining step. Competition experiments showed that electron-rich arenes are preferentially functionalized [Eq. (4)], hence rendering an electrophilic activation manifold more likely to be operative. Additionally, a competition experiment between diphenylacetylene derivatives **2c** and **2d** revealed that the product formation favors indole **3ac** derived from the more electron-rich alkyne [Eq. (5)], which is consistent with the reported Rh-catalyzed annulation of arenes with alkynes.[13]

Under the standard conditions, indole **3aa** could also be efficiently accessed by using *in situ* formed nitrone from commercially available *N*-phenylhydroxylamine **4** and mesitaldehyde [Eq. (6)]. Since the reaction of nitrone **1a** with **2a** produced a good yield of mesitaldehyde besides the desired indole product,[14] we wondered whether a catalytic amount of mesitaldehyde could promote the reaction of **4** and **2a**. However, lowering the amount of mesitaldehyde significantly decreased the yield of indole due to the instability of **4** under the reaction conditions.



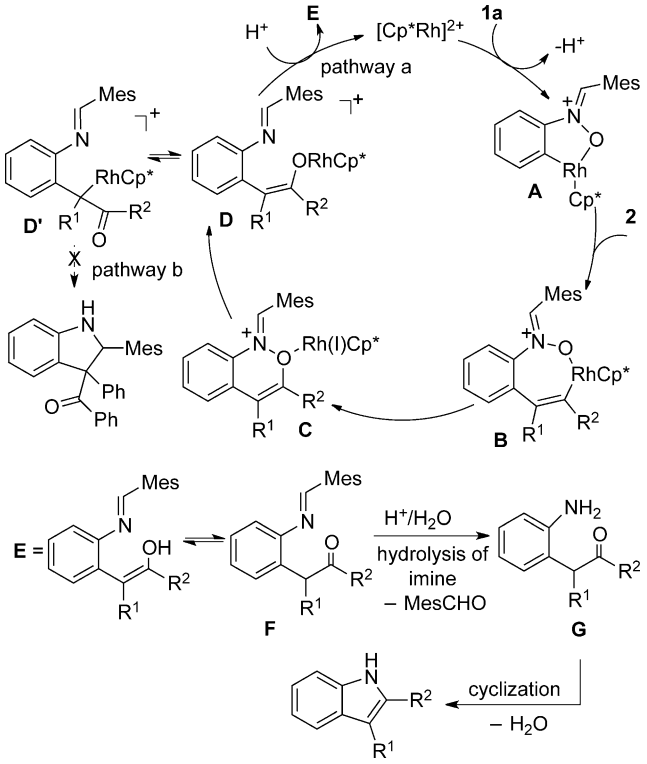
According to Chang's work, the rhodium(III)-catalyzed cyclization of *C*-phenyl-substituted nitrones and alkynes in dry 1,4-dioxane containing molecular sieves leads to the construction of indolines (Scheme 1a).[7c] In contrast, our work revealed that with a similar catalytic system the reaction of *C*-mestiyl-substituted nitrones with alkynes in methanol under air delivered indoles exclusively (Scheme 1c). The different results observed between these two works prompted us to investigate the factors that influence the reaction outcome. When *C,N*-diphenylnitrone was subjected to our reaction conditions, only a trace of indole was obtained and no detectable indoline was observed. When *C*-mestiyl-substituted nitrone **1b** was subjected to Chang's reaction conditions, no trace of indole or indoline product was detected. These experiments indicate that the appropriate choice of substituents and reaction conditions is critical for high chemoselectivity.

For the reaction of **1b** with alkyne under Chang's conditions, the main products were impossible to be isolated because they decomposed on neutral alumina or silica gel column affording indole and mesitaldehyde. When the crude products obtained from this reaction were treated with HOPiv in methanol, a 54% yield of indole could be produced (Scheme 4a). In contrast, indoline could not be transformed to indole under the same conditions (Scheme 4b). From these experiments together with MS, IR and ^{1}H NMR data, we suspected that the imine compound **X** might be one of the products formed in the reaction of **1b** with **2a** under Chang's conditions, and **X** might be the intermediate for the formation of the indole. The origin of the different reactivity of **1b** and **1l** could be ascribed to the different substituents on the carbon center of the nitrones. Guided by the assumption that a bulky substituent on the carbon center of nitrones may favour the formation of indoles, substrates **1m**–**1o** were exposed to our reaction conditions (Scheme 4c). As expected, while phenyl- and *o*-tolyl-subsitiuted nitrones (**1m** and **1n**) gave low yields of indole, 2,6-dimethylphenyl-subsitiuted nitrone **1o** could be converted to the indole in good yield (85%).



Scheme 4. Investigation of the factors that influence the reaction outcome.

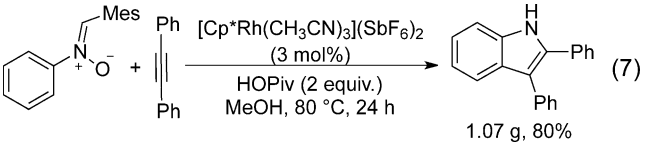
On the basis of the results obtained above and the precedent literature,[7,15] a proposed reaction mechanism is put forward in Scheme 5. Coordination of nitrone to the cationic rhodium followed by a reversible C–H cleavage generates rhodacycle **A**. Subsequent insertion of alkyne yields a seven-membered intermediate **B**, which is believed to undergo reductive elimination to form intermediate **C** together with Rh(I).[15] The resulting Rh(I) could be oxidized by the N–O bond in intermediate **C** *via* oxidative addition affording Rh(III) enolate **D**, which upon protonolysis provides enolate intermediate **E** and regenerates



Scheme 5. Proposed reaction mechanism.

Rh(III) to complete the catalytic cycle. Enolate intermediate **E** is in equilibrium with keto intermediate **F**, which can be transformed to indole facilely after imine hydrolysis and intramolecular cyclization.[16] According to Chang's and Li's indoline synthesis,[7c,d] an alternative pathway from Rh(III) enolate **D** is also shown in Scheme 4 (pathway b). Tautomerization of the O-bond enolate **D** produces the C-bond enolate **D′**, which undergoes nucleophilic addition of the C–Rh bond to give an intramolecular imine affording the indoline product. No indoline was detected when the mesityl-substituted nitrone **1a** was used as the substrate, probably due to the bulky substitution on the imine in intermediate **D′** sterically inhibited the cyclization. Although substitution on the carbon center of the nitrones is believed to be crucial for chemoselectivity, the reaction conditions could influence the reaction outcome. The fact that a trace of water was beneficial for the indole synthesis (Table 1, entries 9 and 10) is consistent with the proposed mechamism (from **F** to **G** to indole). In Chang's indoline synthesis, the addition of molecular sieves may prevent the imine intermediate (the analogue of **D** or **D′**) from hydrolysis, thus lead to a high yield of indoline product. The mechanism proposed here for the synthesis of indole is similar to the one in Li's paper except that Lewis acid was added in Li's work to facilitate the hydrolysis of imine **F** thus favouring the formation of indole.

Finally, a relatively large-scale reaction was conducted. Under the standard conditions, the desired indole product could be produced conveniently on a gram scale without any obvious decrease in yield [Eq. (7)].



(7)

In summary, by using the nitrone as the oxidizing directing group, a mild, practical and efficient Rh(III)-catalyzed C–H functionalization for the synthesis of indole derivatives was developed. This redox neutral strategy circumvents the use of external oxidants. Moreover, a step-economic process using commercially available *N*-phenylhydroxylamine as the precursor of the nitrone was demonstrated. More detailed investigations to explore new transformation properties of nitrones for C–H bond activation are in progress.

Experimental Section

Representative Procedure

Without any particular precautions to exclude oxygen or moisture, the *N*-aryl-*C*-mesitylnitrone **1** (1.4 equiv.), the alkyne **2** (1 equiv.), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%) and HOPiv (2 equiv.) were weighed into a 10-mL tube with a stir bar. MeOH (0.1 M) was then added. The reaction mixture was stirred at 80 °C and monitored by TLC. Afterwards, it was diluted with EtOAc and transferred to a round-bottom flask. Silica gel was added to the flask and volatiles were evaporated under reduced pressure. The purification was performed by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to give the desired indole product **3**.

Acknowledgements

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