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COMMUNICATION

Rhodium(III)-Catalyzed Indole Synthesis at Room Temperature Using the Transient Oxidizing Directing Group Strategy

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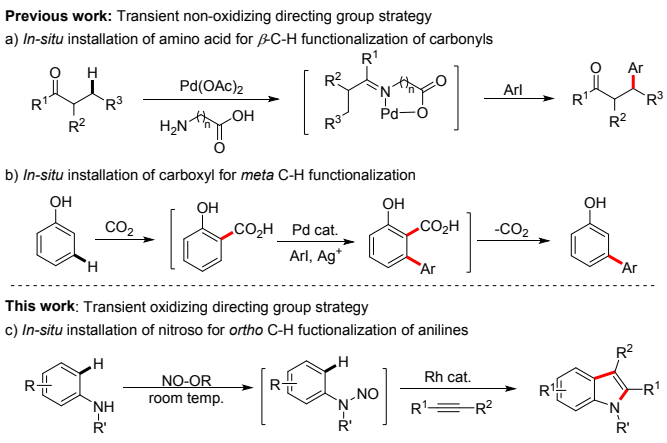
The Rh-catalyzed reaction of *N*-alkyl anilines with internal alkynes at room temperature has been developed using *in-situ* generated *N*-nitroso group as a transient oxidizing directing group. Due to mild reaction conditions, this method enabled syntheses of a broad range of *N*-alkyl indoles,including even two indole-based medicinal compounds. Our work disclosed the feasibility of the transient oxidizing directing group strategy in C-H functionalization reactions, which possesses a potential to enhance overall step-economy and impart new reactivity pattern to substrates.

Due to the prevalence of indole structural motifs in natural products, pharmaceuticals and agrochemicals,[1] the efficient method for indole synthesis has always been a target sought after by chemists.[2,3] Among the established metal-catalyzed methods, both the intermolecular annulation of *ortho*-halo-substituted anilines with internal alkynes[3] and the cross-coupling of *ortho*-alkynylanilines with electrophiles[4] represent powerful tools for the construction of 2,3-disubstituted indole scaffolds. To bypass the pre-functionalization of substrates, a variety of direct C-H functionalization approaches towards indole synthesis have been developed during the past decade.[2] These methods mainly focus on the directing group-assisted *ortho*-C-H functionalization reactions of *N*-substituted aniline derivatives with alkyne partners,[5,6] the intramolecular dehydrogenative annulation reactions of *N*-aryl enamines, azides, imines and *ortho*-alkenylanilines.[7] Notably, the traceless oxidizing directing group strategy for C-H activation has been developed[8] and successfully applied to syntheses of *N*-unprotected indoles without the need for external oxidants.[6] Despite undisputed advance, these C-H functionalization reactions largely relied on the preinstalled specific directing groups on the nitrogen atoms of anilines, and occurred at the elevated temperatures. Both installation and removal or conversion of directing groups require additional chemical manipulations, especially when the directing groups are not expected in the targeted molecules. Thus far, the examples for the synthesis of indole from commercially available *N*-unprotected or *N*-alkyl anilines via C-H bond activation have been very scarce.[9]

The concept of transient directing group has recently emerged as an effective strategy for fascinating *regio*-selective C-H functionalization method.[10-12] In this context, the *regio*-selective C-H bond functionalization of aldehydes, ketones and amines have been achieved, in which imine was generated *in-situ* as a traceless directing group via reversible aldehyde-amine or ketone-amine condensation (Scheme 1a).[11] And the *in-situ* installation of carboxyl group enabled interesting *meta*-C-H functionalization of substituted arenes[12] (Scheme 1b), demonstrating that carboxyl group is a versatile traceless directing group for C-H activation.[10d, 13] In spite of these elegant studies, to date, the transient directing groups have been limited to non-oxidizing functionalities. Inspired by the success in the development of the traceless oxidizing directing group strategy,[6,8] we envisioned whether an appropriate oxidant could *in-situ* install a transient oxidizing directing group which



Scheme 1 Transient directing group strategy for C-H functionalization.

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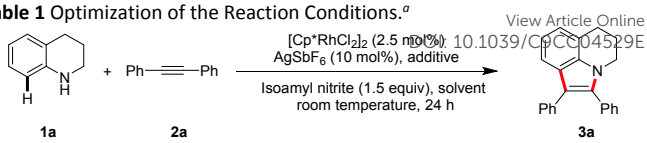
could trigger the targeted C-H bond activation/functionalization while generate the product via reductive cleavage of its oxidizing bond. This transient oxidizing directing group strategy would enhance the overall step economy and impart new reactivity pattern to substrate. Herein, we report a Rh-catalyzed room temperature reaction of readily available *N*-alkyl anilines with internal alkynes, which produces indoles via *in-situ* installation of *N*-nitroso group on *N*-alkyl anilines (Scheme 1c). Our work exemplifies that the transient oxidizing directing group strategy is viable for the regioselective C-H functionalization.

To implement the transient oxidizing directing group strategy for this Rh-catalyzed indole synthesis reaction, we need to prevent overoxidation of *N*-alkyl anilines in the *N*-nitrosylation with nitrite ester. [14a-b] Recently, the reaction of nitrite ester with aniline and internal alkyne has been reported to produce 2,5-dihydrooxazole very fast, [14c] which did not involve *N*-nitrosoaniline intermediate. In addition, the reaction of aniline with nitrite ester tends to produce overoxidized product, namely *N*-nitroso *N*-alkyl nitroaniline, even at room temperature.[14a] Our strategy to suppress competitive overoxidizing side reactions is the identification of the active Rh-catalyst system that enables fast C-H functionalization reaction under mild conditions.

With these considerations in mind, we initiated our investigations by examining Rh(III)-catalyzed coupling of 1,2,3,4-tetrahydroquinoline (**1a**) with diphenylacetylene (**2a**) using isoamyl nitrite as an oxidant (Table 1). Previously reported Rh-catalyzed C-H functionalization reactions involving internal alkynes in which substrates bearing oxidizing directing groups[6] (e.g. *N*-nitrosoanilines)[6b, 6d] generally occurred at the elevated temperatures. However, we sought after room temperature conditions to avoid over-oxidization of anilines by isoamyl nitrite. Gratifyingly, the desired indole product **3a** could be obtained in 40% yield from the reaction of **1a** with **2a** conducted at room temperature for 24 h using $[Cp^*RhCl_2]_2$ (2.5 mol%)/$AgSbF_6$ (10 mol%) as a precatalyst and dichloromethane as solvent (entry 1). Screenings of reaction parameters revealed that switch of solvent to CH_3CN or *t*-AmylOH completely shut down this transformation (entries 2-3). In the case of CH_3CN, the solvent molecules might coordinate to Rh center, thus leaving no spare coordination site for substrate molecules. Similarly, cationic $Cp^*Rh(CH_3CN)_3[SbF_6]_2$ was observed to have a negative effect (entry 4). Although previous report revealed that acetate salts had a beneficial effect on the Rh-catalyzed reaction of *N*-nitrosoanilines with internal alkynes,[6d] the use of NaOAc as additive proved to be futile (entry 5). Delightfully, further screenings revealed that decent yields were accessible by identifying suitable carboxylic acid as an additive. For instance, we found that adding pivalic acid remarkably improved the yield (entry 6) and reducing the amount of acid from 1.0 equiv. to 0.5 equiv. led to a slight decrease in reaction yield (entry 7). Next, we turned our attention to aryl carboxylic acids bearing various substituents (entries 8-12) and found out that the addition of 4-*tert*-butylbenzoic acid delivered the best result, furnishing the desired product **3a** in 83% isolated yield

Table 1 Optimization of the Reaction Conditions.[a]



1a 2a 3a

Entry	Solvent	Additive	Yield (%)[b]
1	DCM	-	40
2	CH_3CN	-	0
3	tert-amyl alcohol	-	0
4[c]	DCM	-	24
5	DCM	NaOAc (1.0 equiv)	7
6	DCM	PivOH (1.0 equiv)	70
7	DCM	PivOH (0.5 equiv)	68
8[d]	DCM	benzoic acid	57
9[d]	DCM	2,4,6-trimenthylbenzoic acid	40
10[d]	DCM	*p*-^{t}BuPhCO$_2$H	83
11[d]	DCM	*m*-NO2-PhCO$_2$H	38
12[d]	DCM	*p*-OMe-PhCO$_2$H	31
13[e]	DCM	*p*-^{t}BuPhCO$_2$H	40

[a]Reaction Conditions: **1a** (0.2 mmol),**2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol, 2.5 mol%), $AgSbF_6$ (0.02 mmol, 10 mol%), additive (0.5-1.0 equiv.),isoamyl nitrite (0.3 mmol), N_2 and solvent (1.0 mL) at room temperature for 24 h. [b]Yield of isolated product. [c]$Cp^*Rh(CH_3CN)_3[SbF_6]_2$ (0.01mmol, 5 mol%) was used.[d]aryl carboxylic acids(0.5 equive) was used. [e]*t*-butyl nitrite (0.3 mmol) was used as oxidant.

(entry 10). However, other aryl carboxylic acids failed to enhance the reaction to a comparable degree. Finally, the use of *t*-butyl nitrite as an alternative to isoamyl nitrite was less effective (entry 13).

With the optimized reaction conditions in hand, we evaluated the substrate scope with respect to *N*-substituted anilines (Table 2). As illustrated, anilines with various groups at the nitrogen atom participated in this transformation smoothly (**3b**-**3i**). Notably, both allylic substituent and an alkyl nitrile group could be tolerated to give **3h** and **3i** in 72% and 55% yields, respectively. Interestingly, diphenyl amine (**3f**) show a similar reactivity to *N*-alkyl anilines. Once again, cyclic anilines proved to be suitable substrates for easy construction of important fused tricyclic indoles (**3a, 3j-3n**). Furthermore, a variety of electronically diverse functionalities (**3m-3y**) including halogen substituents on the phenyl rings of anilines were well tolerated to give desired indole products in excellent yields regardless of the substituted positions. It is worth mentioning that an excellent regioselectivity was observed when *meta*-substituted anilineswere employed. In most cases, these anilines (**3z, 3aa, 3ac-3ah**) underwent reaction exclusively at positions *para* to the substituents, probably due to the effects of steric hindrance. One exception is the *meta*-fluorine substituented product (**3ab**), which furnished the product at the position *ortho* to fluorine atom (confirmed by single crystal X-ray diffraction).[15] This difference in selectivity might originate from the small atomic radius of fluorine, which renders the electronic effect overriding steric effect in C-H functionalization steps.

We then turned our attention to the substrate scope of internal alkynes (Table 3). To our delight, the reaction proved to be general for a variety of symmetric diarylacetylenes (**4a-4j**).

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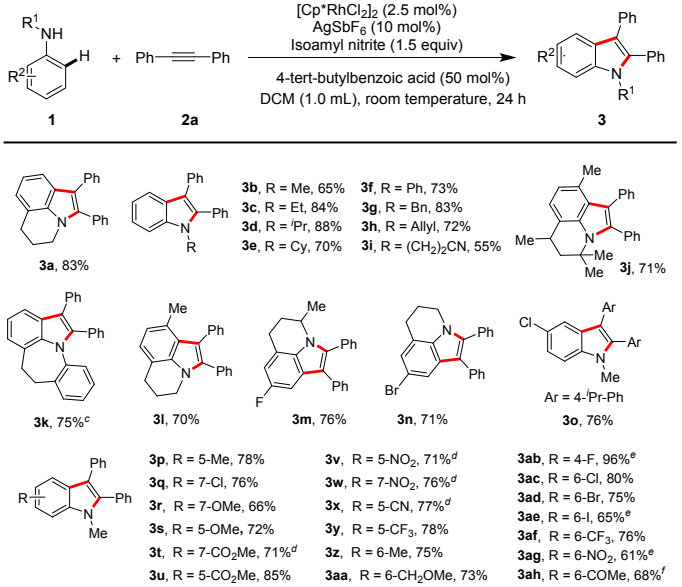
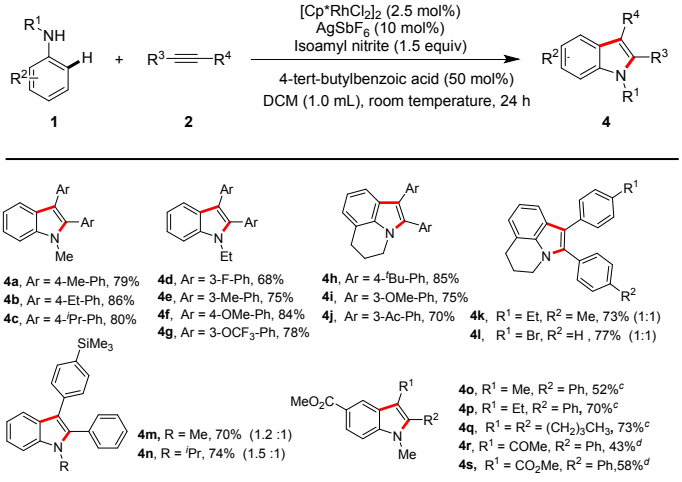
Table 2 Scope of *N*-substituted anilines.[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol, 2.5 mol%), $AgSbF_6$ (0.02 mmol, 10 mol%), 4-tert-butylbenzoic acid (50 mol%), isoamyl nitrite (0.3 mmol), N_2 and DCM (1.0 mL) at room temperature for 24 h. [b]Yield of isolated product. [c]The reaction was carried out at 80 °C in DCE (1.0 mL). [d]The reaction was carried out at 50 °C in DCE (1.0 mL). [e]PivOH (1.0 equiv) was used as additive. [f]The reaction was carried out at 80 °C in DCM (1.0 mL) with PivOH (1.0 equiv) as an additive instead of 4-tert-butylbenzoic acid.

Table 3 Scope of internal alkynes.[a, b]



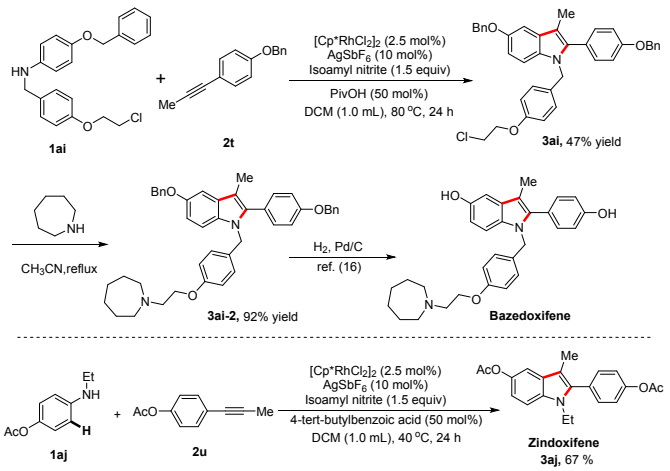
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol, 2.5 mol%), $AgSbF_6$ (0.02 mmol, 10 mol%), 4-*tert*-butylbenzoic acid (50 mol%), isoamyl nitrite (0.3 mmol), N_2 and DCM (1.0 mL) at room temperature for 24 h. [b]Yield of isolated product.[c]The reaction was carried out at 80 °C with PivOH (1.0 equiv) instead of 4-*tert*-butylbenzoic acid. [d]The reaction was carried out at 60 °C for 48 h with PivOH (1.0 equiv) instead of 4-*tert*-butylbenzoic acid.

For unsymmetrical diarylacetylenes (**4k-4n**), the reaction delivered approximate 1:1 ratio isomers due to the unbiased characters of the two phenyl groups. On the contrary, unsymmetrical alkyl aryl acetylenes (**4o, 4p**) exhibited excellent regioselectivity for the indole products with aryl group at C-2 positions (confirmed by X-ray crystallography analysis).[15]

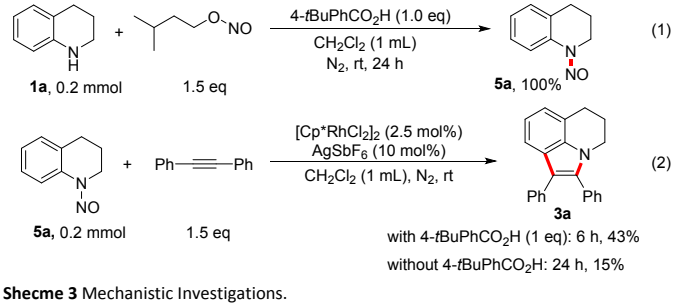
Additionally, the reaction with dialkylacetylene (**4q**) also proceeded smoothly. Notably, the internal alkynes bearing electron-deficient groups were effective in this transformation (**4r, 4s**), which generated C-2 arylated indoles exclusively.[15] The high regioselectivity displayed in this protocol is seldom observed in previously reported annulation reactions, thus providing a complement to indole synthesis.

Our protocol also enables facile syntheses of two indole-based medicinal compounds, namely, bazedoxifene[16],and zindoxifene[17]. As shown in scheme 2, both the immediate precursor to marketed bazedoxifene and zindoxifene could be prepared in good yields from readily available starting materials, demonstrating the merit of our protocol in organic synthesis. Compared with previous procedures, our protocol offers a more concise pathway to syntheses of these molecules.

To check whether this Rh-catalyzed reaction involves *in-situ* installation of nitroso directing groups, the reaction of 1,2,3,4-tetrahydroquinoline (**1a**) with isoamyl nitrite was carried out in the presence of 4-*tert*-butylbenzoic acid in CH_2Cl_2 at room temperature for 6 hours (eq.1 Scheme 3), in which proceeded *N*-nitroso 1,2,3,4-tetrahydroquinoline **5a** was obtained in quantitative yield. Moreover, **5a** was observed to react with diphenylacetylene at room temperature for 6 hours with $[Cp^*RhCl_2]_2/AgSbF_6$ as a precatalyst, dichloromethane as solvent and 4-*tert*-butylbenzoic acid as an additive to form 2,3-diphenyl indole (**3a**) in 43% yield. In the absence of 4-*tert*-butylbenzoic acid, however, the same reaction run for even 24 hours gave **3a** in only 15% yield (eq.2 Scheme 3), which might shed light on the key role of benzoic acid in enhancement of catalyst activity.



Scheme 2 Synthesis of Bazedoxifene and Zindoxifene.



Shecme 3 Mechanistic Investigations.

In conclusion, the Rh(III)-catalyzed reactions of diverse *N*-alkyl anilines with internal alkynes have been developed for facile synthesis of indoles at room temperature. The mild reaction conditions were ascribed to the reasonable combination of catalyst, acid additive and solvent. Our work demonstrated that the transient oxidizing directing group strategy is promising for the development of C-H functionalizations with unfunctionalized substrates. Application of this intriguing strategy to other useful C-H transformation is currently underway in our laboratory.

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Conflicts of interest

The authors declare no competing financial interest.

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15 CCDC 1905948 (**3ab**), 1905949 (**3aj**), 1905951 (**4p**), and 1906495 (**4r**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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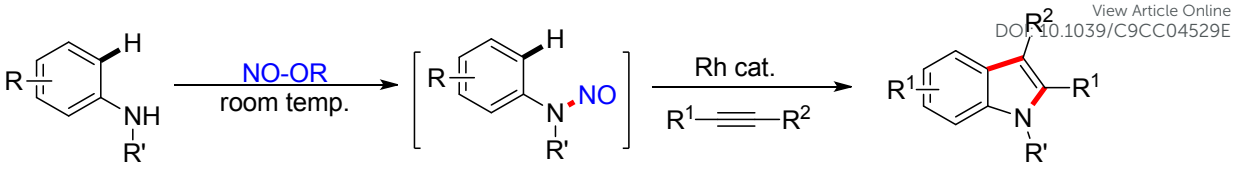

- Transient oxidizing directing group
- *ortho*-C-H accessible to reaction
- Room temperature reaction

55 examples, up to 96% yield