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Traceless Directing Strategy: Efficient Synthesis of N-Alkyl Indoles via Redox-Neutral C−H Activation

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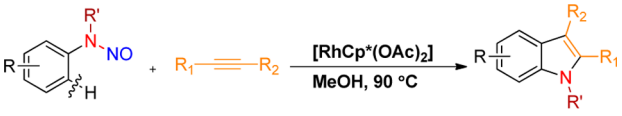
ABSTRACT



internal oxidant
without any additives
simple procedure
insensitive to air and moisture
traceless directing strategy

C-H activation and N-N cleavage
broad substrate scope
high regioselectivity
useful N-alkyl indole product
up to 97% yield

A general protocol for the synthesis of N-alkyl indoles has been developed via a redox neutral C−H activation strategy using a traceless nitroso directing group. A broad scope of substituted N-alkyl indoles has been prepared in good to excellent yields using a very simple Rh catalyst system in the absence of an external oxidant or any other additive. Good to excellent regioselectivity has been achieved for asymmetrically disubstituted acetylenes.

Indoles are an important class of aromatic heterocycles with respect to alkaloids, peptides, and proteins.[1] The biochemical functions of indole-containing molecules and the chemical versatility of this unique heterocycle have spurred intensive efforts to develop relevant synthetic methods.[2] Recently, the C−H activation and cyclization method has emerged as a new strategy to assemble this [6,5] nitrogen-containing heteroaromatic ring system.[3] Two general approaches have been developed: oxidative cyclization of enamines, imines, and oximes and directed transition-metal-catalyzed C−H annulation using internal alkynes (Scheme 1).[4,5] In particular, Hartwig et al. reported a significant redox-neutral cyclization of *O*-acetyl oximes (Scheme 1c), in which the OAc-protected oxime served as a directing group and an internal oxidant.[6] The starting diarylketones were prepared in two steps using preactivated reaction partners (aryl bromides). Herein, we describe an alternative redox-neutral indole synthesis using the C−H annulation approach with a traceless directing

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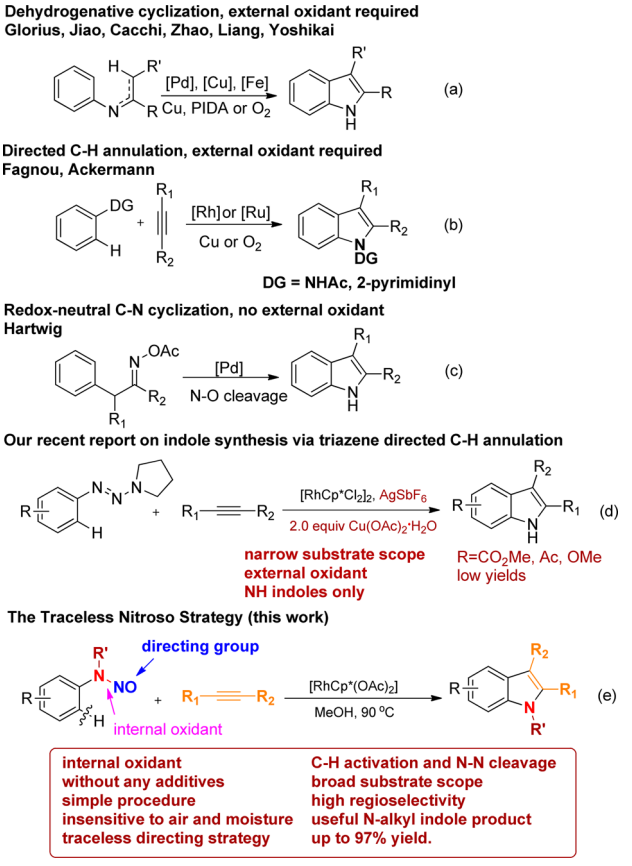
group under very simple reaction conditions. This is the first N-alkyl indole synthesis via directed C−H activation.

We recently reported the first Rh(III)-catalyzed indole synthesis using a removable triazene directing group and stoichiometric $Cu(OAc)_2$ as an oxidant.[5f,7] However, this reaction only worked for electron-neutral aryl triazenes. Electron-deficient and -rich substrates afforded poor yields (Scheme 1d). Subsequently, we decided to expand the substrate scope of our triazene method. More importantly, we wanted to eliminate the need for 2 equiv of $Cu(OAc)_2$ in order to turn over the Rh catalyst, which resulted in poor atom economy and was notoriously difficult to work with on large scales. Almost all redox-neutral C−H activation reactions have employed a N−O bond as the internal oxidant for Rh turnover.[6,8] Experimentally, the N2−N3 bond of the triazene did not have enough oxidative potential to convert Rh(I) to Rh(III).[5f] In the absence of an external oxidant, the reaction afforded only ~5% of the indole product. We envisioned that a more electron-extracting N−NO bond might be a sufficient internal oxidant. An additional benefit of this design was that it would allow for the installation of an alkyl group on the nitrogen attached to the arene, leading to N-alkyl indole products.

Although the corresponding N-nitroso group for directed oxidative Heck reactions was recently reported by Zhu,[9] no information has been found regarding the use of N−NO for Rh(I) oxidation. We decided to pursue this designer traceless directing strategy (TDS) for indole synthesis, in which the N-nitroso group kills two birds with one stone by serving as both a directing group for the C−H activation and an internal oxidant (via N−N cleavage, Scheme 1e).

Scheme 1. Indoles Synthesis via C−H Functionalization



Our initial investigation was performed by examining *N*-methyl-*N*-phenylnitrous amide **1a** and diphenylacetylene **2a** in the presence of $[RhCp^*(CH_3CN)_3][SbF_6]_2$ and KOAc in MeOH under air. Gratifyingly, the indole product **3a** was obtained in 38% GC-MS yield (Table 1, entry 1; for a comprehensive investigation of the conditions, see Supporting Information). This result demonstrated that the Rh catalyst was indeed recycled by the nitroso directing group through internal oxidation. The acetate counterion was critical for efficient Rh insertion, as other salts failed to promote the reaction. This suggested a concerted metalation−deprotonation (CMD) mechanism for the C−H activation. MeOH was essential for decent conversion (Table 1, entries 1−7). We reasoned that the particularly high conversions observed for $Cu(OAc)_2$ and AgOAc were due to the more facile OAc exchange with chloride. We then examined $[RhCp^*(OAc)_2]$ in lieu of $[RhCp^*Cl_2]_2$ and the acetate additive. We were delighted to find that this complex

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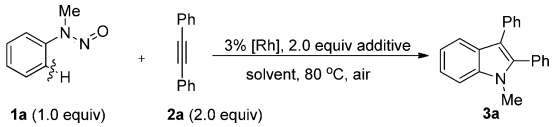
was equally effective in the absence of an additive. We obtained a 90% isolated yield under very simple conditions: 8 mol % [RhCp*(OAc)$_2$] in methanol in a sealed tube at 90 °C. The reaction allowed the use of reagent grade methanol without purification. The yields of these reactions were unaffected when performed in air. No predegassing was required.

Table 1. Investigation of Reaction Parameters for the Indole Synthesis[a]



1a (1.0 equiv) **2a** (2.0 equiv) **3a**

entry	solvent	catalyst	additive	conv (%)
1	MeOH	[RhCp*L$_3$][SbF$_6$]$_2$	KOAc	38
2	DMF	[RhCp*L$_3$][SbF$_6$]$_2$	KOAc	–
3	DCE	[RhCp*L$_3$][SbF$_6$]$_2$	KOAc	15
4	CH_3CN	[RhCp*L$_3$][SbF$_6$]$_2$	KOAc	11
5	toluene	[RhCp*L$_3$][SbF$_6$]$_2$	KOAc	–
6	*t*-AmOH	[RhCp*L$_3$][SbF$_6$]$_2$	KOAc	–
7	THF	[RhCp*L$_3$][SbF$_6$]$_2$	KOAc	8
8[b,c]	DCE	[RhCp*Cl$_2$]$_2$	Cu(OAc)$_2$	72
9[d]	MeOH	[RhCp*Cl$_2$]$_2$	$CuCl_2$	–
10	MeOH	[RhCp*Cl$_2$]$_2$	NaOAc	57
11[e,e]	MeOH	[RhCp*Cl$_2$]$_2$	AgOAc	94
12	MeOH	[RhCp*Cl$_2$]$_2$	–	<5
13[d,f]	MeOH	[RhCp*(OAc)$_2$]	–	76
14[b,g]	MeOH	[RhCp*(OAc)$_2$]	–	90

[a] Reactions were performed on a 0.3 mmol scale; isolated yields. [b] The reaction was carried out at 110 °C. [c] Under O_2. [d] 5% catalyst. [e] 60 °C. [f] 75 °C. [g] 8% catalyst. Note: L = CH_3CN, for entries 8–14; 1.3 equiv of aryne was used.

The scope and limitations of the indole synthesis were carefully examined, and the results are summarized in Table 1. The aryl group tolerated both electron-rich and electron-deficient substituents. Good to excellent yields were obtained for these reactions. It was noteworthy that the yields for ester substituted aryl nitrous amides were particularly high (Figure 1, product **3j**–**3l**, **3r**–**3t**). Reactions with the analogous substrates using our previous triazene protocol were ineffective. Similarly, a 77% yield was obtained for a methoxyarene (Figure 1, **3g**), whereas a similar substrate quickly decomposed with little indole formation (< 20%) in the analogous triazene reaction.

Substrates bearing two methoxyl groups, a substitution pattern widely found in indole motifs,[10] also worked well (Figure 1, **3u**). Halogens did not interfere with this reaction. Various N-alkyl groups were examined, and the yields using secondary alkyls and aryls were somewhat

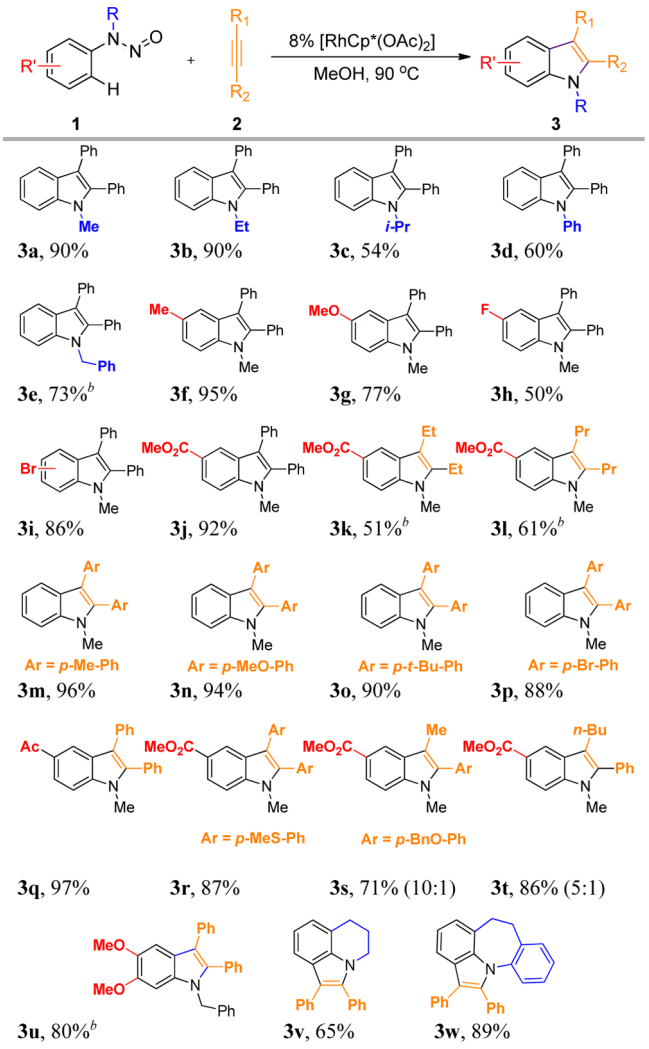


Figure 1. Substrates scope. [a] Reactions were performed on a 0.3 mmol scale; isolated yields. [b] The reaction was carried out at 110 °C.

decreased due to steric reasons (Figure 1, products **3c** and **3d**). Internal diarylalkynes were well tolerated regardless of the electronic nature of their substituents. For alkyl aryl acetylenes, good to excellent regioselectivity was observed (Figure 1, products **3s**–**t**). Intramolecularly tethered nitroso substrates (Figure 1, **3v**–**w**) underwent smooth indole formation to yield fused tricyclic frameworks that are common in natural products.[11] The benzyl substituted indole product was deprotected to give the free NH using *t*-BuOK in DMSO at room temperature (93% yield),[12] further broadening the synthetic capability of these products. No indole products were observed for terminal

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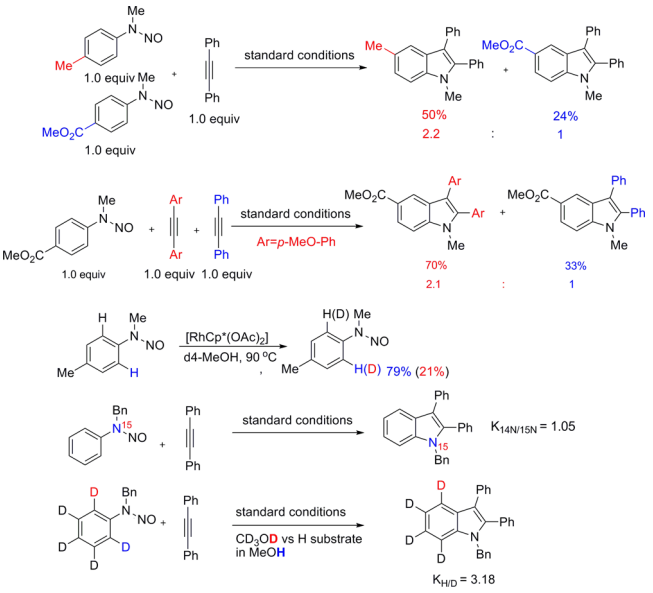
Scheme 2. Competition and Isotope Experiments



and electron-deficient alkynes under standard reaction conditions.

Competition experiments were performed using substrates with different electronic characteristics (Scheme 2). The *p*-tolyl substrate reacted 2.2 times faster than the corresponding *p*-CO_2Me analogue. This result suggested that the C−H insertion was slightly asynchronous, with the Ar−Rh interaction being more important than the pK_a of the *ortho*-C−H bond.[5e] Analogously, a reaction using electron-rich di-*p*-methoxyphenyl acetylenes was almost twice as fast as the diphenylacetylene reaction. The C−H activation step was reversible, as indicated by the 25% H/D scrambling in the nitroso starting material. The measured $K_{^{14}N/^{15}N}$ was 1.05, while the value of $K_{H/D}$ is 3.18, indicating that C−H activation is the rate-determining step and the internal oxidation is rather fast. The KIE values were calculated by dividing the yields of the isotopic products after 2.5 h (approximation to initial rate ratios).

The detailed reaction mechanism remains illusive at this stage. We believe the C−H activation step proceeds via the CMD mechanism, supported by a strong OAc effect.[3l,13] The resulting aryl Rh binds to the alkyne and prompts a 1,2-cis-addition, as suggested by related examples.[14] It remains unclear to us which step goes first, the reductive elimination or the N−N cleavage to regenerate Rh(III). Based on the mechanism of our previous indole synthesis using triazene as the directly group, a ring contraction of the seven-membered metallacycle,[5f] likely assisted by the nitroso group, might eventually lead to the formation of indole. Detailed mechanistic studies are currently underway to elucidate the full catalytic cycle.

In summary, we have developed a novel synthesis of N-alkyl indoles via redox-neutral C−H activation and annulation using a traceless nitroso directing group. This protocol features a simple operational procedure, no external oxidant or additive, a wide substrate scope, and robust reaction conditions. Good to excellent regioselectivity was accomplished for asymmetrically disubtituted internal acetylenes. The N-nitroso functionality serves as both a directing group for C−H activation and an internal oxidant for catalyst turnover.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.