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Rh(III)-Catalyzed Tandem Acylmethylation/Nitroso Migration/Cyclization of *N*-Nitrosoanilines with Sulfoxonium Ylides in One Pot: Approach to 3-Nitrosoindoles

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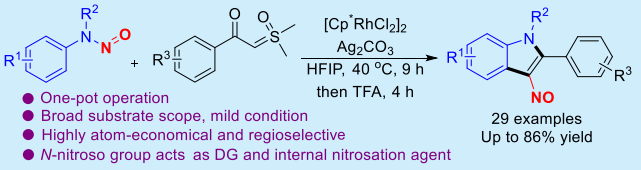
Supporting Information

ABSTRACT: A novel synthesis of 3-nitrosoindoles starting from easily available *N*-nitrosoanilines and sulfoxonium ylides via Rh(III)-catalyzed acylmethylation and trifluoroacetic acid (TFA)-mediated nitroso transfer/cyclization cascade reaction in one pot has been developed. The *N*-nitroso group plays a dual role as a versatile directing group and internal nitrosation reagent. Rh(III)-catalyzed C−H activation/C−C bond formation and TFA-mediated N−N bond cleavage/formation of two C−N bonds are involved in this reaction. This process is scalable and avoids external oxidation. DMSO and H_2O are produced as byproducts. Moreover, further chemical transformations of the desired products enhance its synthetic value.



C−H bond activation (CHA), allowing construction of special skeletons, has become powerful in organic synthesis and has led to improvement of the atom and step economy.[1] In this regime, directing groups (DGs) are required to control the regioselectivity. However, they always leave a chemical trace in the products, which limits the structural diversity.[2] Some strategies have been developed to solve this problem.[3] For example, we pioneered a traceless N−O oxidizing DG in redox coupling of quinoline *N*-oxides with olefins.[4] The N−O group was a fully cleavable DG and internal oxidant that allowed convenient removal after the C−H functionalization. To date, this strategy has been broadly extended to O−O,[3b] N−O,[4a,5] and N−N[6] groups as oxidizing and traceless DGs. Incorporation of the DG into a product via CHA/DG migration is an alternative strategy to realize a highly atom-economical process and reuse of the DG.[7] Li and co-workers described their elegant work on acylmethylation of quinoline *N*-oxides with alkynes by CHA and subsequent O atom transfer with 100% atom economy.[8] Recently, Wang and colleagues reported the enaminylation of *N*-pyrimidinylindoles with ketenimines catalyzed by cobalt(III) and subsequent base-promoted migration of the pyrimidine group as a DG.[9]

One other hand, the *N*-nitroso group has played an important role in the development of a series of significant reactions, especially because of its ability to serve as a versatile DG for CHA[6e,10] and the polar nature of the N−NO bond.[11] In 2012, Zhu and co-workers first disclosed the Rh(III)-catalyzed *N*-nitroso-directed aryl *ortho*-olefination of *N*-nitrosoanilines with methyl acrylates.[10a] Later, Zhu and others realized the coupling reactions of *N*-nitrosoanilines with toluene,[12] alkynes,[13] diazo compounds,[14] and NCTS[15] under redox-neutral conditions. In these reactions, the nitroso group was liberated as waste through N−NO bond cleavage. The nitroso group could undergo intramolecular migration of "NO^+" to the *para* position of the phenyl ring in the presence of a strong acid (Fischer−Hepp rearrangement).[11a] We assumed that the *N*-nitroso group could be employed as a DG to realize regioselective C−H functionalization, followed by production of "NO^+" through N−NO bond cleavage and introduction of the NO group in the final products. To verify this hypothesis in the context of our continuing interest in clean transition-metal-catalyzed C−H bond functionalization, we have developed a novel Rh(III)-catalyzed cascade reaction of *N*-nitrosoanilines and sulfoxonium ylides to access 3-nitroso-2-phenylindoles, in which the *N*-nitroso group works as not only a DG but also an internal nitrosation agent. Acylmethylation and TFA-mediated nitroso transfer/cyclization tandem reactions are involved in a one-pot manner. Interestingly, the products are important building blocks for the synthesis of bioactive molecules and functional materials through further chemical transformations.[16]

We initiated our investigation by screening the reaction parameters using the coupling of *N*-nitrosoaniline (**1a**) and benzoyl sulfoxonium ylide (**2a**) as a model reaction (Table 1). Through the extensive survey of various reaction parameters, the desired 3-nitroso-2-phenylindole **4aa** was obtained in 86% yield from the reaction of **1a** with **2a** at 40 °C for 9 h using $[Cp^*RhCl_2]_2$ (5 mol %)/Ag_2CO_3 (20 mol %) as a catalyst combination and HFIP as the solvent followed by addition of TFA (2.5 equiv) and continued reaction for 4 h (Table 1, entry 1).[17] The structure of **4aa** was confirmed by single-crystal X-ray diffraction analysis (see the Supporting Information for more details). In the absence of either $[Cp^*RhCl_2]_2$ or

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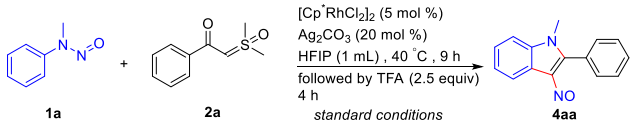
Table 1. Screening of Reaction Parameters[a]



entry	variation from the standard conditions	yield (%)[b]
1	none	86
2	without $[Cp^*RhCl_2]_2$	NR
3	without Ag_2CO_3	NR
4	$Cp^*Co(CO)I_2$ instead of $[Cp^*RhCl_2]_2$	NR
5	$[RuCl_2(p\text{-cymene})]_2$ instead of $[Cp^*RhCl_2]_2$	NR
6	$[Cp^*IrCl_2]_2$ instead of $[Cp^*RhCl_2]_2$	NR
7	$Pd(OAc)_2$ instead of $[Cp^*RhCl_2]_2$	NR
8	MeOH, MeCN, acetone, DCE, 1,4-dioxane, or DMSO instead of HFIP	NR
9	PivOH (1 equiv), AcOH (1 equiv), PhCOOH (1 equiv), or TsOH (1 equiv) instead of TFA	NR
10	HCl instead of TFA	32
11	decreasing the loading of TFA to 2.0 equiv	75
12	increasing the loading of TFA to 3.0 equiv	73

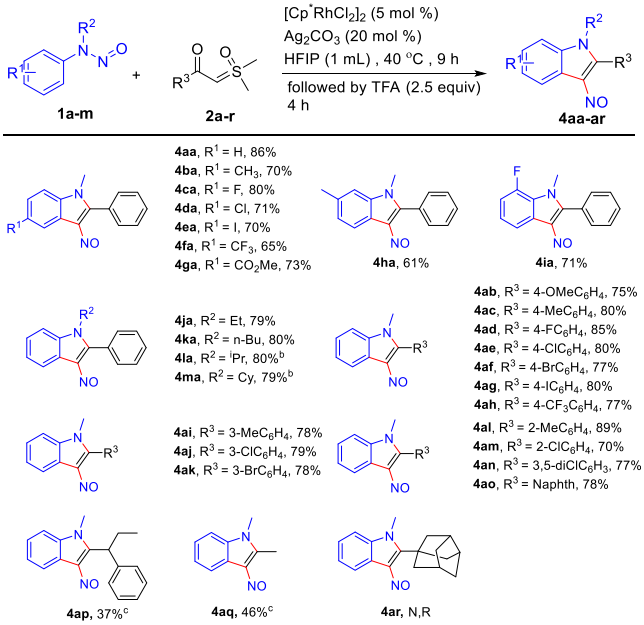
[a]Standard conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), Ag_2CO_3 (20 mol %), HFIP (1 mL), 9 h, 40 °C, then TFA (2.5 equiv), 4 h. Abbreviations: HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol; TFA = trifluoroacetic acid. [b]Isolated yields.

Ag_2CO_3 (Table 1, entries 2 and 3), the reaction did not work well, indicating that the cationic Rh(III) complex was likely to be involved in the catalytic cycle. Under otherwise identical conditions, it was proved that $Cp^*Co(Co)I_2$, $[Ru(p\text{-cymene})Cl_2]_2$, $[Cp^*IrCl_2]_2$, or $Pd(OAc)_2$ instead of $[Cp^*RhCl_2]_2$ was detrimental (Table 1, entries 4–7). Subsequent screening of reaction parameters revealed that switching the solvent to MeOH, MeCN, acetone, DCE, 1,4-dioxane, or DMSO completely shut down this transformation (Table 1, entry 8). Further screening of various protonic acids (PivOH, AcOH, PhCOOH, TsOH, and HCl) showed that strongly acidic conditions were conducive to achieve the conversion, and investigation of a series of representative acids proved TFA to be the optimal acid additive (Table 1, entries 9 and 10). In addition, either decreasing or increasing the loading of TFA led to a decrease in the yield of **4aa** (Table 1, entries 11 and 12).

With the optimal conditions established, the scope of *N*-nitrosoanilines was first examined, as shown in Scheme 1. To our delight, it was perfectly tolerable to introduce both electron-donating (Me) and electron-withdrawing groups (F, Cl, I, CF_3, and CO_2Me) at the *para* position of the *N*-nitrosoaniline, affording the corresponding products (**4ba–ga**) in good yields (65–80%). These results showed that the electron density on the phenyl ring of the *N*-nitrosoaniline has no significant effect on this transformation. When the *meta* substituent was alkyl (Me), the reaction occurred exclusively at the less hindered site, showing good regioselectivity. *o*-F-substituted *N*-nitrosoaniline **1i** allowed the generation of the corresponding product in a good yield of 71%. In addition, various *N*-alkyl groups (e.g., ethyl, *n*-butyl, isopropyl, and cyclohexyl) were examined, and good yields were obtained (**4ja–ma**), which exemplified the versatility of the reaction. However, the reaction did not proceed when phenyl or benzyl groups were utilized, perhaps because of the competitive multiple-acylmethylation side reaction.

Next, we examined the scope of sulfoxonium ylides. When R^3 was an aryl group, a variety of electron-donating or

Scheme 1. Scope of *N*-Nitrosoanilines and Sulfoxonium Ylides[a]



[a]Reaction conditions: **1a–m** (0.1 mmol), **2a–r** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), Ag_2CO_3 (20 mol %), HFIP (1 mL), 9 h, 40 °C, then TFA (2.5 equiv), 4 h. Isolated yields are shown. [b]Reaction time: from 9 to 12 h. [c]Reaction time: from 9 to 17 h.

electron-withdrawing groups on the phenyl ring were well-tolerated in this transformation, affording the corresponding products (**4ab–ah**) in good yields (75–86%). These results revealed that the electron density of R^3 did not significantly influence the efficiency of the reaction. In addition, substitutions at the 2- or 3-position of the benzene ring were suitable for this reaction, delivering the corresponding products (**4ai–am**) in good yields (70–89%). Moreover, a disubstituted benzoyl sulfoxonium ylide, 3,5-dichlorophenyl sulfoxonium ylide, was coupled with **1a** to provide the corresponding 3-nitrosoindole **4an** in 77% yield. In addition, the 1-naphthalene-substituted substrate **2o** still showed good reactivity, and 78% yield of the coupling product **4ao** was obtained. Alkyl-substituted sulfoxonium ylides were also suitable for this catalytic system (**4ap** and **4aq**), whereas the sulfoxonium ylide with a sterically hindered group failed to form the cyclized product (**4ar**).

To further highlight the synthetic value of this strategy, we carried out some follow-up reactions. For example, the reaction of **1a** and **2a** was carried out on a 3 mmol scale to give **4aa** in 75% yield (0.53 g) (Scheme 2, a). Furthermore, 3-nitrosoindole **4aa** was easily reduced to 3-aminoindole **5aa** in 86% yield (Scheme 2, b).[18] The 3-aminoindole framework is a structural motif that is ubiquitous in many synthetic intermediates[19] and biologically active molecules.[20] In addition, 3-nitrosoindole **4aa** was also easily transformed into **6aa** and **7aa** in 46% and 86% yield, respectively (Scheme 2, c and d).[16c] Heteroarenes (e.g., **6aa**) have been widely used in the preparation of various LED polymers[21] and high-spin organic polymers,[22] and 2-aminobenzonitriles, represented by product **7aa**, have been reported to have anti-inflammatory properties and serve as DPP-IV inhibitors.[23]

To clarify the reaction mechanism, we carried out a series of control experiments (Scheme 3). The desired product **4aa** was

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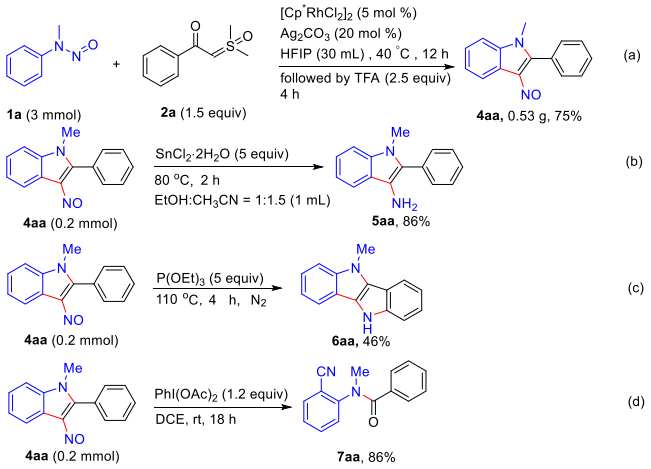
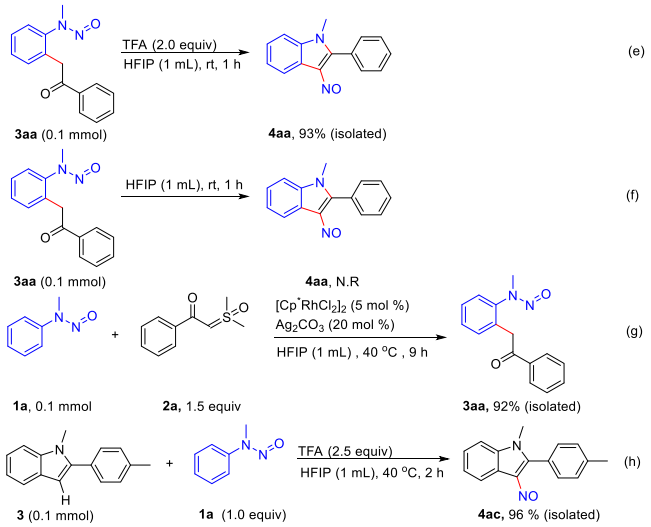
Scheme 2. Scaled-Up Reaction and Conversion of 4aa



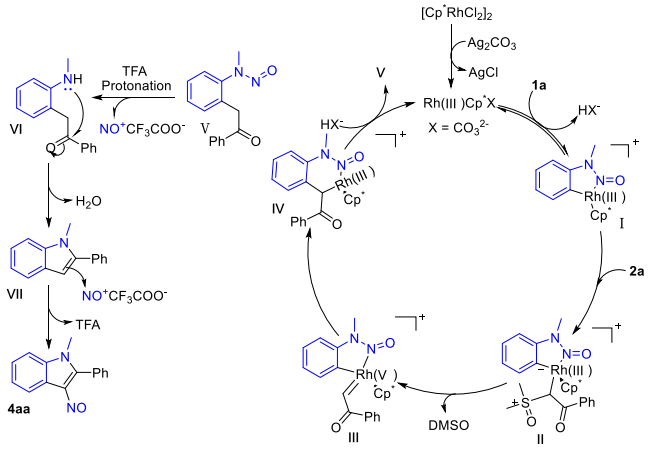
Scheme 3. Control Experiments



solely obtained in 93% isolated yield by treatment of **3aa** with TFA (Scheme 3, e), and cyclization could not happen without any additives (Scheme 3, f). Furthermore, only **3aa** was obtained in the absence of TFA (Scheme 3, g), which further implies that TFA is crucial for the conversion of intermediate **3aa** to **4aa**. In order to understand the transformation process from intermediate **3aa** to the target product, the reaction of **3** and **1a** was carried out under TFA conditions to give **4ac** in 96% yield (Scheme 3, h). These results supported 2-phenylindole **3** as an important intermediate, and the final step was an acid-promoted cyclization reaction combined with nucleophilic attack of 2-phenylindole (at the electron-rich 3-position of 2-phenylindole) on the nitrosyl N atom.

On the basis of the previous literature[11a,16c] and the results obtained, a plausible mechanistic pathway is proposed in Scheme 4. First, the cationic active species Cp*Rh(III) is generated through treatment $[Cp^*RhCl_2]_2$ with Ag_2CO_3 and then coordinates with the *N*-nitrosoaniline and subsequently undergoes *ortho* C−H activation of the arene to generate cyclorhodium intermediate **I**. Coordination of the sulfoxonium ylide with intermediate **I** generates Rh(III) intermediate **II**, which in turn gives the reactive carbene species **III** by *α*-elimination of DMSO. Migratory insertion of the Rh−Ar bond and protonolysis releases acylmethylated intermediate **V** and

Scheme 4. Proposed Reaction Mechanism



Rh(III) for the next catalytic cycle. Subsequently, the *N*-nitroso group is protonated with TFA to release NO^+, and then nucleophilic addition and dehydration afford intermediate **VII**. Finally, electrophilic substitution of NO^+ at electron-rich C3 of **VII** results in nitroso compound **4aa**.

In conclusion, we have developed a novel synthesis of 3-nitrosoindoles from easily available *N*-nitrosoanilines and sulfoxonium ylides via Rh(III)-catalyzed acylmethylation and TFA-mediated nitroso transfer/cyclization multistep cascades in one pot. The protocol is useful to prepare various substituted 3-nitrosoindoles because of its high atom economy, mild reaction conditions, and good functional group tolerance. Moreover, further chemical transformations of the desired products enhance its synthetic value.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03768.

Experimental procedures, characterization data, crystallographic data for **4aa**, and NMR spectra (PDF)

Accession Codes

CCDC 1918585 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(17) For more details, see Table S1 in the Supporting Information.

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