Heterocycle Synthesis

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A [4+1] Cyclative Capture Approach to 3*H*-Indole-*N*-oxides at Room Temperature by Rhodium(III)-Catalyzed C–H Activation

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Abstract: *The rhodium(III)-catalyzed [3+2] C–H cyclization of aniline derivatives and internal alkynes represents a useful contribution to straightforward synthesis of indoles. However, there is no report on the more challenging synthesis of pharmaceutically important N-hydroxyindoles and 3H-indole-N-oxides. Reported herein is the first rhodium(III)-catalyzed [4+1] C–H oxidative cyclization of nitrones with diazo compounds to access 3H-indole-N-oxides. More significantly, this reaction proceeds at room temperature and has been extended to the synthesis of N-hydroxyindoles and N-hydroxyindolines.*

Indoles are among the most abundant structural components of bioactive natural products, pharmaceuticals, and agrochemicals.[1] Among them, 3*H*-indole-*N*-oxides, and *N*-hydroxyindoles have recently received considerable attention owing to their proven promising biological properties and previously demonstrated usefulness as synthetic building blocks (Figure 1).[2,3] Despite great significance, only very limited methods were developed for the synthesis of these two unique structural motifs. The first synthesis of *N*-hydroxyindoles was attributed to Mousseron-Canet and Boca in 1967.[4] In addition, *N*-hydroxyindoles were also accessed by either intramolecular reductive cyclization of nitrobenzenes or by oxidation of indolines.[5]

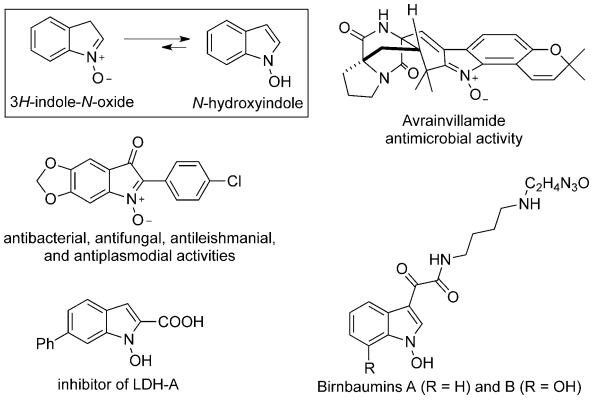
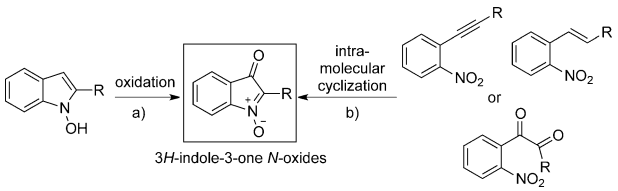


Figure 1. Representative biologically active 3*H*-indole-*N*-oxides and *N*-hydroxyindoles.

In stark contrast to *N*-hydroxyindoles, their tautomeric 3*H*-indole-*N*-oxides are kinetically labile and much more unstable. 3*H*-indole-*N*-oxides are typically formed by either oxidation of *N*-hydroxy-2-substituted indoles (Scheme 1a)[6] or intramolecular reductive annulation of an *ortho*-substituted nitrobenzene precursor (Scheme 1b).[7] However, their parent heterocycles must be prepared in advance and a multi-step preparation of the *ortho*-substituted nitrobenzene precursor is also required. Moreover, these methods are generally limited to synthesis of 3*H*-indole-3-one *N*-oxides. Therefore, the development of catalytic, mild, and efficient methods (especially for intermolecular reactions) to directly access various 3*H*-indole-*N*-oxides, is highly desirable and of prime synthetic value.



Scheme 1. Previous approaches to 3*H*-indole-*N*-oxides.

Metal-catalyzed C–H activation has advantages over traditional protocols in that no substrate preactivation is necessary.[8] The rhodium(III) fragment has stood out as one of the most frequently used catalysts for the activation of a large array of C–H bonds,[9] and a number of novel C–H activation strategies have been explored for the synthesis of heterocycles. Particularly, the [3+2] C–H cyclization of aniline derivatives and alkynes represents a useful contribution to straightforward and efficient synthesis of indoles by either rhodium(III)- or other transition-metal-catalyzed C–H activation (Scheme 2a).[10] Despite the significant advance made in the construction of indole skeletons, there is no report on the more challenging synthesis of pharmaceutically important *N*-hydroxyindoles and 3*H*-indole-*N*-oxides, presumably because of the problematic preferential cleavage of the N–O bond.[11,12]

In contrast, rhodium(II)-catalyzed C(sp^3)–H insertion of metal carbenoids is a powerful method for constructing C–C bonds.[13] However, intermolecular aromatic C(sp^2)–H insertion has limited precedent in the literature. Until recently, a significant breakthrough has been made by Yu and coworkers,[14a] who developed the first rhodium(III)-catalyzed chelation-assisted insertion of aromatic C(sp^2)–H bonds into diazo compounds. Mechanistically, the reaction is likely to follow a pathway involving a chelation-assisted C(sp^2)–H metalation, which is followed by metal–carbene formation,

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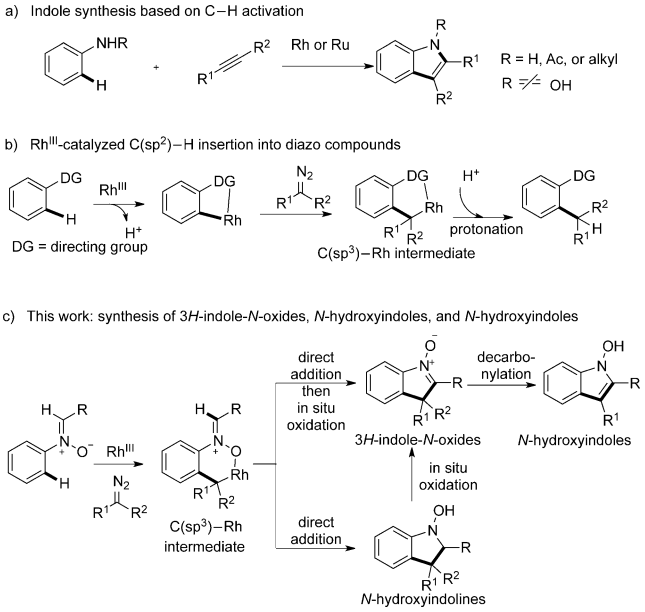


Scheme 2. Rhodium(III)-catalyzed C–H functionalization.

migratory insertion, and subsequent protonation of the resulting C(sp^3)–Rh species (Scheme 2b).

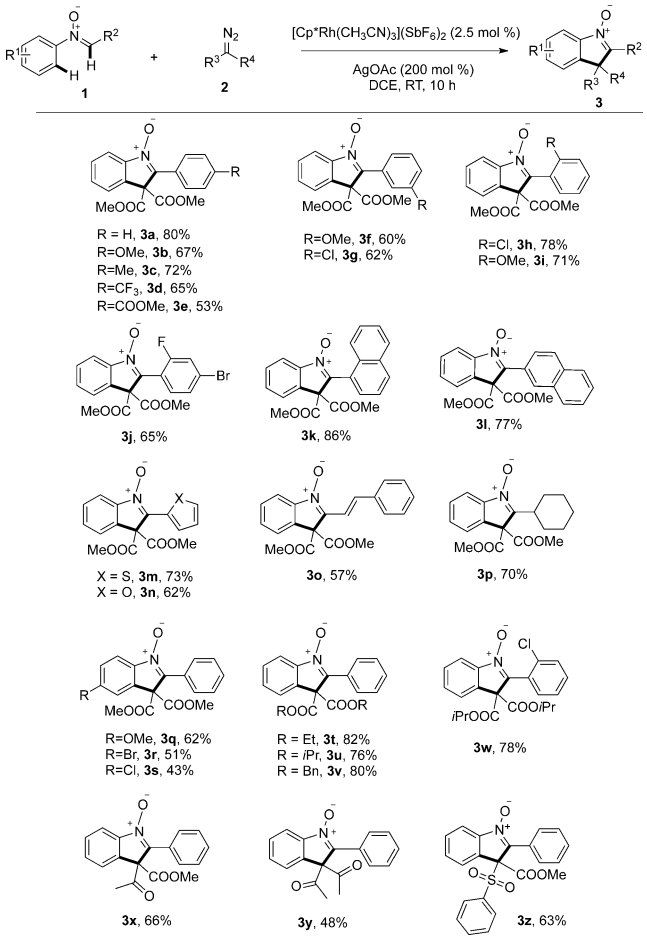
In this context and in connection with the challenges associated with the synthesis of 3*H*-indole-*N*-oxides, we wondered whether a catalytic *ortho*-C(sp^2)–H functionalization of nitrones with diazo compounds might be possible, thus leading to a C(sp^3)–Rh intermediate, which upon intramolecular addition to the C=N bond and in situ oxidation would provide 3*H*-indole-*N*-oxides, if the protonation step is inhibited (Scheme 2c). Furthermore, nitrones could be easily accessible from readily available nitroarenes and aldehydes in a single step. Herein, we introduce nitrone as a directing group to trigger a new [4+1] cyclative capture approach wherein diazo compounds undergo migratory insertion and subsequent intramolecular addition to the polarized C=N bond and in situ oxidation to afford 3*H*-indole-*N*-oxides. More significantly, this reaction proceeds at room temperature and has been extended to the synthesis of *N*-hydroxyindoles and *N*-hydroxyindolines. However, the following challenges have to be solved:

1) The N–O bond is easily cleaved in rhodium(III)-catalyzed transformations,[11,12] especially for the N–O bond of *N*-oxides.[14l,15,16] For example, the N–O cleavage of arylamine *N*-oxides has been uncovered under a rhodium-(III)-catalyzed system the groups of You, Li, Chang and ourselves.[14l,15] Moreover, very recently, the N–O cleavage of nitrones has also been reported when coupling with alkynes under a rhodium(III) system.[16]
2) Although rhodium(III)-catalyzed C(sp^2)–H insertion of diazo compounds has been developed,[14] the coupling with diazo compounds under oxidative conditions has not been achieved. The diazo compound and external oxidant need to be compatible.
3) Even though the C(sp^2)–Rh intermediate have been reported to be able to undergo a Grignard-type addition to polarized double bond,[17] the addition of a C(sp^3)–Rh species to a C=N bond is still unsolved, presumably because of the problematic preferential β-hydride elimination[14e,18] and protonation.[14]
4) The stability of 3*H*-indole-*N*-oxide is generally low and it is liable to undergo thermal isomerization and photoisomerization.[19] Therefore, relatively mild reaction conditions are necessary.

The initial experiments were performed with nitrone (**1a**) and diazomalonate (**2a**) in the presence of 2.5 mol% [{Cp*$RhCl_2$}$_2$], 10 mol% $AgSbF_6$, and 100 mol% $Cu(OAc)_2$ as the oxidant at 60°C in 1,2-dichloroethane, thus providing the desired product **3a** in only trace amounts (see entry 1 in Table S1 in the Supporting Information; for structures see Scheme 3). Replacement of the oxidant $Cu(OAc)_2$ with Ag_2CO_3 gave a slightly improved yield of 7% (entry 2). Pleasingly, the situation changed significantly when AgOAc was used as the oxidant (Table S1, entry 3). The prepared rhodium(III) precursor [Cp*$Rh(CH_3CN)_3$]$(SbF_6)_2$ led to a slightly improved yield (Table S1, entry 4). Further investigations revealed that milder reaction conditions (room temperature) could be successfully applied and an improved yield of 62% was obtained (Table S1, entry 5). Increasing the amount of oxidant gave an improved coupling efficiency (80%; Table S1, entry 6). After a screen of solvents (Table S1, entries 6–9), DCE was proven to be optimal. The structure of the product **3a** was confirmed by X-ray crystallographic analysis.[20]

With the optimal reaction conditions in hand, we sought to further explore the reaction scope for nitrones (Scheme 3). It was found that the electronic and steric effects of the substituents at the phenylimino moiety of nitrones did not play key roles. Various substrates bearing electron-donating (**3b**,**c**, **3f**, and **3i**) and electron-withdrawing (**3d**,**e**,**g**,**h**,**j**) groups at *ortho*- (**3h** and **3i**), *meta*- (**3f** and **3g**), and *para*- (**3b**–**e**) positions were readily converted into the corresponding products in good yields. The nitrones containing a 1-naphthyl and 2-naphthyl group at the α-position underwent the cyclization to afford the 3*H*-indole-*N*-oxides **3k** (86%) and **3l** (77%), respectively. The cyclizations of substrates bearing 2-thienyl (**3m**) and 2-furyl (**3n**) groups proceed with high efficiency. Particularly remarkable is the participation of nitrones bearing an alkenyl and alkyl group in this reaction, despite the instability of C-alkyl nitrones,[16] thus providing the corresponding 2-alkenyl- and 2-alkyl-substituted 3*H*-indole-*N*-oxides **3o** (57%) and **3p** (70%). 3*H*-indole-*N*-oxides bearing electron-donating (**3q**) and electron-withdrawing (**3r** and **3s**) substituents at the 6-position could also be synthesized in good yields. The scope of the diazo compounds was subsequently investigated and various α-diazomalonates (**3t**–**w**) participated in the reaction smoothly to afford the corresponding products in high yields. Besides α-diazomalonates, α-diazoacetylacetate (**3x**), α-diazodiketones (**3y**), and α-diazosulfonylacetate (**3z**) were tolerated in the present cyclization reaction.

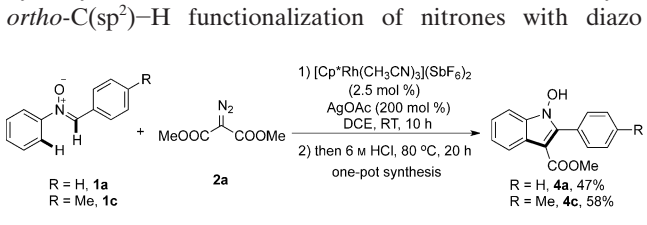
Considering that there are limited approaches[5] to *N*-hydroxyindoles which also display very important pharmacological properties,[2] and that these methods generally require a multistep preparation of *ortho*-substituted nitrobenzene



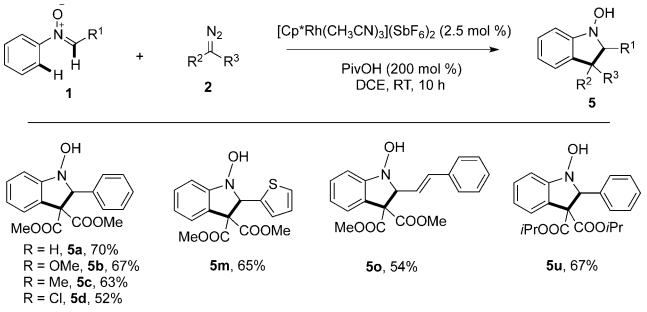
Scheme 3. Rhodium/(III)-catalyzed synthesis of 3*H*-indole-*N*-oxides. Reactions were carried out on a 0.2 mmol scale. Yields of the isolated products are given. Cp* = C_5Me_5, DCE = 1,2-dichloroethane.

precursor,[5] we wondered if we could utilize the present transformations for the synthesis of *N*-hydroxyindoles. To our delight, we successfully developed a one-pot protocol wherein the rhodium(III)-catalyzed annulation of nitrones and diazo compounds was combined with decarbonylation to deliver *N*-hydroxyindoles in good yields (Scheme 4).

Encouraged by the successful results in the synthesis of 3*H*-indole-*N*-oxides and *N*-hydroxyindoles, we turned our attention to the synthesis of biologically active products by using the current [4+1] cyclization strategy. To date, synthetic approaches to *N*-hydroxyindolines are generally limited to *N*-oxidation of indolines. However, their parent heterocycle indolines must be prepared in advance and this method suffers from the preferential overoxidation to form *N*-hydroxyindoles. In this context, we envisioned that a catalytic *ortho*-C(sp^2)–H functionalization of nitrones with diazo compounds, followed by a direct intramolecular nucleophilic attack of the C(sp^3)–Rh intermediate on the C=N bond, might provide a possibility to access *N*-hydroxyindoline products, if the external oxidant was obviated. Pleasingly, we found that the *N*-hydroxyindole **5a** (Scheme 5) could be formed in 10% yield when removing the oxidant under the standard reaction conditions. Further optimization led to 70% yield when 2 equivalents of PivOH were added. As shown in Scheme 5, by using this procedure, a variety of *N*-hydroxyindolines (**5a**–**u**) were obtained in good yields.



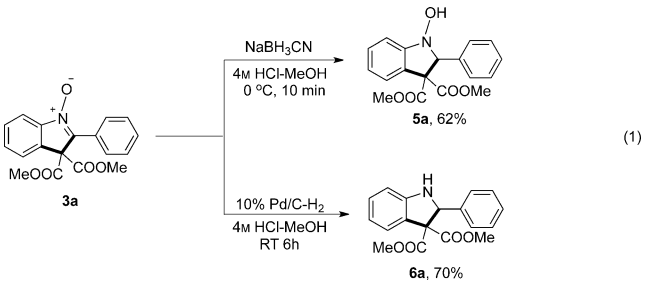
Scheme 4. One-pot synthesis of *N*-hydroxyindoles from nitrones and diazo compounds.



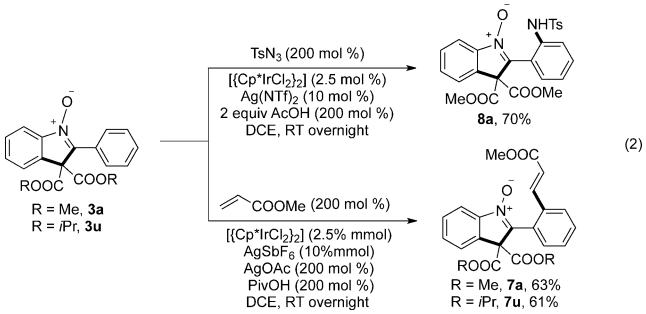
Scheme 5. Rhodium(III)-catalyzed synthesis of *N*-hydroxyindolines from nitrones and diazo compounds. Reactions were carried out on a 0.2 mmol scale. Yields of the isolated products are given.

To further demonstrate the synthetic utility of the 3*H*-indole-*N*-oxides, four additional transformations with our products were carried out. First, the 3*H*-indole-*N*-oxide **3a** was easily reduced to yield either the free indoline **6a** or *N*-hydroxyindoline **5a** in high yield [Eq. (1)]. Moreover, compared with the parent heterocycles, 3*H*-indole-*N*-oxides exhibit different reactivities and regioselectivities. For example, the 3*H*-indole-*N*-oxides **3a** and **3u** were smoothly alkenylated at the C2 phenyl group with acrylate at room temperature to give **7a** and **7u**, respectively, in good yields by rhodium-catalyzed C–H activation using the *N*-oxide as a directing group [Eq. (2); Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl]. Moreover, an iridium(III)-catalyzed amidation with TsN_3 proceeded smoothly at room temperature to give product **8a** in 70% yield.

To further investigate the mechanism, a series of experiments were carried out. First, a H/D exchange was observed when the nitrone **1b** was subjected to the standard reaction conditions in the absence of **2a**, and is indicative of the reversibility of the *ortho*-C(sp^2)–H bond-cleavage process [Eq. (3)]. However, no deuterium incorporation was observed in the re-isolated **1b** when the reaction was carried



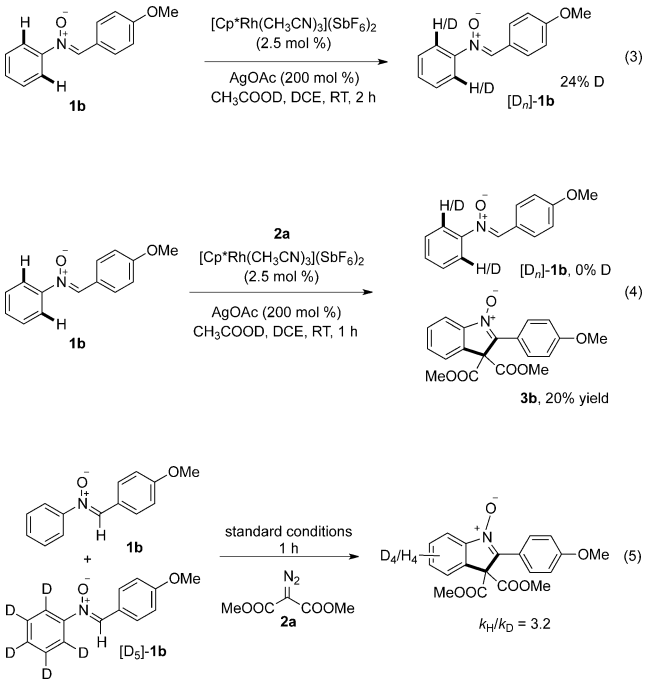
(1)

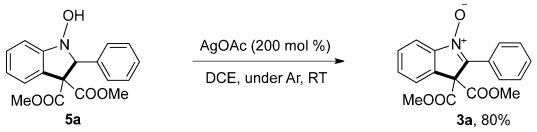


(2)

out in the presence of **2a**, thus indicating that the coupling process is much faster than the deuteration [Eq. (4)]. Additionally, a notable primary kinetic isotope effect ($k_H/k_D = 3.2$) was observed in two parallel experiments, thus suggesting that the C–H bond cleavage might be involved in the rate-determining step [Eq. (5)].[21] To further understand the reaction process, we treated **5a** with AgOAc in DCE under an argon atmosphere at room temperature and **3a** was formed in 80% yield [Eq. (6)]. Considering that **5a** could be obtained in the absence of an oxidant and that **5a** could be directly oxidized by AgOAc to give **3a**, both results indicate the plausible intermediacy of **5a**, thus ruling out the possibility of a Rh^I/Rh^{III} catalytic cycle involved in the addition of $C(sp^3)$-Rh species to C=N bond and subsequent β-hydride elimination.

On the basis of our preliminarily mechanistic experiments and literature precedence, we propose the coordination of the substrate **1a** to the rhodium(III) catalyst as the key step for the directed C–H activation to form a five-membered rhodacycle (see Scheme S1). Next a rhodium(III) carbene is generated by dediazoniation of the diazo compound, and a subsequent intramolecular 1,2-migratory insertion of the aryl group affords a rhodacyclic intermediate. An intra-





(6)

molecular addition of the $C(sp^3)$–Rh species to the C=N bond and protonation occurs successively with the formation of **5a** and with the regeneration of Rh^{III} catalyst. Finally, the oxidation of **5a** with AgOAc gives **3a**.

In summary, we have developed the first rhodium(III)-catalyzed regioselective synthesis of 3*H*-indole-*N*-oxides from nitrones and diazo compounds. Mechanistic studies support a pathway involving a directed C–H activation, metal-carbene formation, migratory insertion, Grignard-type addition, and in situ oxidation. More significantly, this reaction proceeds at room temperature and has been extended to the synthesis of *N*-hydroxyindoles and *N*-hydroxyindolines.

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Keywords: C–H activation · cyclizations · diazo compounds · heterocycles · rhodium

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