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Rhodium(III)-Catalyzed *N*-Nitroso-Directed C–H Addition to Ethyl 2-Oxoacetate for Cycloaddition/Fragmentation Synthesis of Indazoles

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Abstract: Rh^{III}-catalyzed *N*-nitroso-directed C–H addition to ethyl 2-oxoacetate allows subsequent construction of indazoles, a privileged heterocycle scaffold in synthetic chemistry, through the exploitation of reactivity between the directing group and installed group. The formal [2+2] cycloaddition/fragmentation reaction pathway identified herein, a unique reactivity pattern hitherto elusive for the *N*-nitroso group, emphasizes the importance of forward reactivity analysis in the development of useful C–H functionalization-based synthetic tools. The synthetic utility of the protocol is demonstrated with the synthesis of a tricyclic-fused ring system. The diversity of covalent linkages available for the nitroso group should enable the extension of the genre of reactivity reported herein to the synthesis of other types of heterocycles.

Transition-metal-catalyzed C–H functionalization represents a promising strategy for expediting the synthesis of sophisticated chemical architectures. The functionalization typically relies on a directing group for the streamlining of a target reaction course.[1,2] Indeed, an effective directing group can provide proximity-driven high reactivity and selectivity. However, a high-efficiency reaction does not automatically translate to a synthetically useful tool. An equally important requirement is the ability to elaborate the directing groups and/or installed groups into desired functionalities. In this regard, transformable groups have been vigorously pursued for the improvement of versatility and practicality of C–H functionalization reactions.[3,4] The majority of transformations reported thus far are individually targeted at either the directing groups or installed groups for the generation of distinct appendages.[3] The creation of distinct molecular skeletons is synthetically more demanding and typically proceeds at the C–H functionalization stage.[4] The convenience of such a cascade reaction-based skeleton generation approach comes at the price of limited available experimental parameter space and therefore diminished chance for success because of the requirement for the robustness of catalytic species under subsequent cyclization conditions.

We are interested in the creation of distinct molecular skeletons after the C–H functionalization step. In particular, we anticipate that such a directed intermolecular C–H functionalization for the intramolecular cyclization strategy allows for the exploration of synergy between a directing group and an installed group at an expanded experimental parameter space and should therefore increase the likelihood of discovering new reactivity patterns. Intramolecular cyclization has been routinely used for the construction of heterocycles (e.g., indole)[5] but frequently involves cumbersome preassembly of substrate frameworks. The C–H functionalization-based strategy offers a handy tool for expeditious heterocycle synthesis, and forward reactivity analysis[6] is essential to the success of this integrated approach.

We have recently launched a program on the utilization of nitroso (*C*-, *N*-, *O*-, or *S*-linked) groups for directed C–H functionalization.[7] The initially explored *N*-nitroso group system proves to be effective for C–C and C–N couplings. The achievement of C–N coupling is exclusively built upon the reactivity of the N–N bond. The creation of a distinct molecular skeleton mandates the identification of a distinct path of reactivity between the *N*-nitroso group and installed group. In line with this, we have decided to explore the N=O bond as a synthetic handle, inspired by a previously documented [2+2] cycloaddition of a *C*-nitroso group and ketene.[8] Described herein is a Rh^{III}-catalyzed *N*-nitroso-directed C–H addition to ethyl 2-oxoacetate for the synthesis of 3-hydroxyindazoles, a privileged heterocycle scaffold in synthetic chemistry.[9] Significantly, 3-hydroxyindazoles are generated through a formal intramolecular [2+2] cycloaddition/fragmentation pathway, a hitherto synthetically elusive reactivity pattern for the *N*-nitroso group.[10]

Reaction development was initiated with the screening of experimental conditions for the achievement of *N*-nitroso-directed C–H addition (with *N*-methyl-*N*-nitrosoaniline, **1a**, as the model substrate) to the aldehyde carbonyl group of ethyl 2-oxoacetate (**2**). Although directing group (e.g., pyridinyl, quinolinyl, oxime, azo, amide, carboxyl) approaches have recently been demonstrated for such a transformation,[11] they suffer from the requirement to use a harsh reaction conditions (e.g., high reaction temperature), a synthetically restrictive directing

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group, or a pre-purified cationic metal catalyst. Our transformable *N*-nitroso group enables Rh^{III}-catalyzed synthesis of target molecule **3a** in 96% isolated yield at 50 °C. An optimal catalytic system includes 2.5 mol% $[RhCl_2Cp^*]_2$/10 mol% (Cp^* = 1,2,3,4,5-pentamethylcyclopentadienyl) $AgSbF_6$ as the catalyst precursor, 10 mol% NaOAc as the base and proton shuttle, and dichloroethane as the solvent. The reaction can be scaled up to 10 mmol (~2.5 g **3a**) level without sacrificing the product yield.

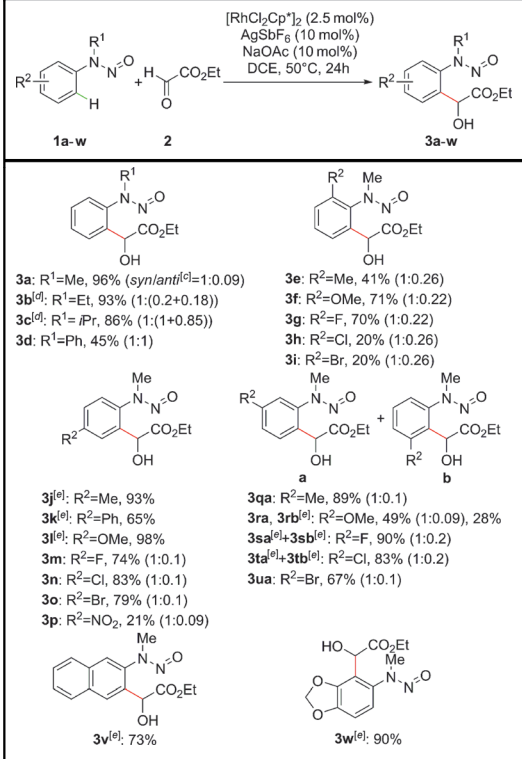
An investigation of the reactivity of *N*-nitrosoaniline derivatives identifies exclusive *N*-nitroso-directed *ortho* selectivity and compatibility of a broad range of substitution patterns (**1a–w**, Table 1). The existence of *syn* and *anti* isomers[7] in the C–H functionalization products reported herein due to thermodynamically restricted N–N bond rotation does not affect their synthetic utility because further elaboration of the transformable *N*-nitroso group is typically mandated and allows for the generation of identical synthetic targets. The yield is observed to be inversely correlated with the steric bulkiness of the N-substituent (**1a–d**). The *ortho*-substituted *N*-nitrosoanilines (**1e–i**) generally exhibit a lower reactivity than the *para*-substituted counterparts (**1j**, **1l–o**). The reaction is favored for an electron-donating group (**1j**, **1l**) over an electron-withdrawing group (**1p**). For a *meta*-substituted *N*-nitrosoaniline, the degree of regioselectivity is governed by the substituent (**1q–u**). The reaction proceeds in a regiocontrolled manner for the two examined disubstituted *N*-nitrosoanilines (**1v**, **1w**); however, a diverged site selectivity is displayed. The critical directing role of *N*-nitroso group is demonstrated by the absence of reaction between *N*-methylaniline and **2**.

Mechanistic experiments indicate the intermediacy of a five-membered rhodacycle[7] in the catalytic cycle and C–H activation as the turnover-limiting step (kinetic isotope effect value of 2.0). A catalytic mechanism involving *N*-nitroso-directed electrophilic C–H activation/*ortho*-rhodation (with the assistance of OAc^-), migratory insertion of the aldehyde carbonyl group, and proto-demetalation for product release and catalyst turnover, is therefore proposed.

With C–H functionalization products **3a–w** in hand, we then set out to explore the N=O bond as a synthetic handle for the creation of a heterocycle scaffold. The [2+2] cycloaddition reactivity of the *C*-nitroso N=O bond toward the ketene,[8] coupled with ketene generation from an α proton-bearing ester[12] and remarkable stability of N–N bond[10] under basic conditions, highlights a hypothetically viable mechanistic course. The use of *t*BuOK (2 equiv) in dichloromethane proved effective in delivering 1-methyl-1*H*-indazol-3-ol (**4a**, as confirmed by single-crystal analysis, Table 2) from **3a** at RT, through a formal [2+2] cycloaddition/fragmentation process. The synthetic potential of such a distinct enabling methodology is illustrated by a broad substrate scope (**3a–w**, Table 2), regardless of sterics and electronics. This represents a significant advantage over previously documented methodologies that involve either the preinstallation of synthetically demanding groups (e.g., halogens)[9b–h] or imposition of undesired auxiliaries (aryl substituents at N2)[9i,11a] on the products.

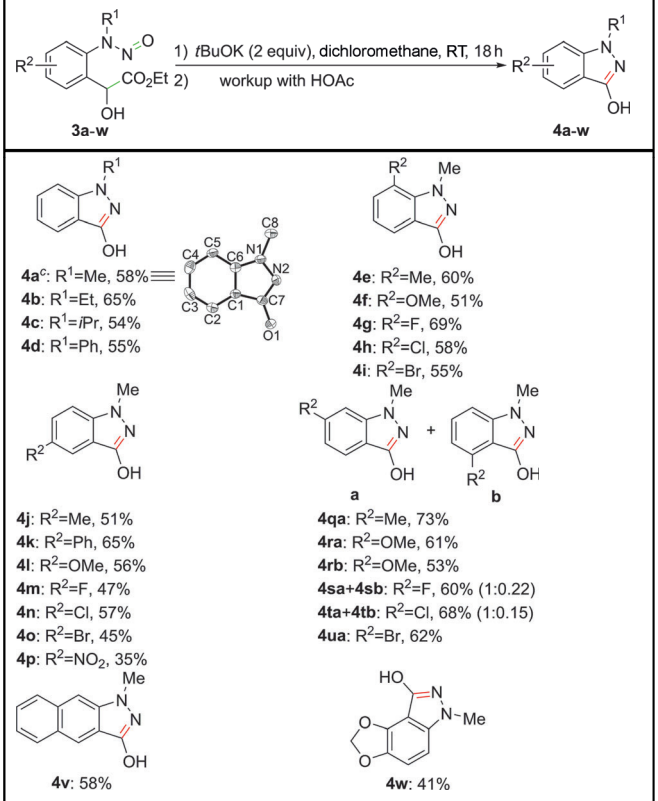
Initial attempted ^1H NMR spectroscopic characterization of the **3a** to **4a** reaction course directly under basic conditions provides no informative signals, as a result of the low solubility of ionic species involved in the transformation. Acidification with HOAc (with inevitable presence of adventitious H_2O), a reagent that **3a** does not react with (Scheme 1, middle left, top panel), allows the conversion process to be monitored (Scheme 1, top panel) and, together with other pertinent observations, suggests a ketene as a key intermediate for the [2+2] cycloaddition/fragmentation process: 1) the transformation features a fast detachment of the EtO^- fragment from deprotonated **3a** (no ^1H NMR spectroscopic signals observed for **3a** after merely 20 min; detachment of EtO^-, as confirmed by a change in the ^1H NMR spectroscopic chemical shift and splitting pattern of its methylene protons), presumably to generate ketene **3a-K** (as revealed by the observation of its nucleophilic addition-afforded hydration product,[12a] **3a-det**), and a slow conversion of **3a-K** to **3a-CA-FO** (decrease of **3a-det** and increase of **4a** with the elapse of time, but with their combined amount approximately constant and equivalent to that of EtO^- (Scheme 1, bottom left, top panel); consistent with the initial production of **3a-K** and EtO^- and subsequent exclusive transformation of **3a-K** to **3a-CA-FO**). 2) Only a trace amount of **4a** can be generated from **3a-det** (ruling out hydrolyzed species,

Table 1. Substrate scope for Rh^{III}-catalyzed *N*-nitroso-directed C–H addition to ethyl 2-oxoacetate.[a,b]

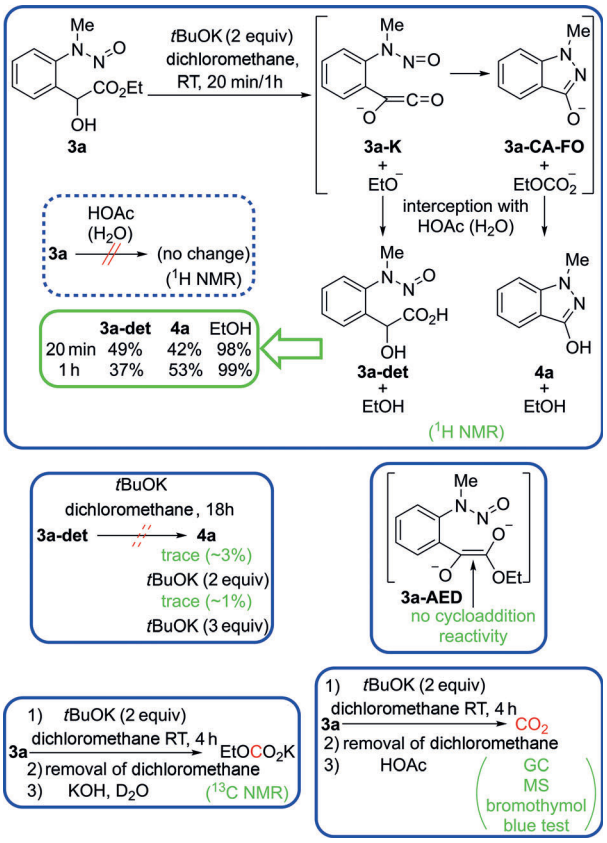


[a] Reaction conditions: *N*-nitrosamine **1a–w** (0.4 mmol), ethyl 2-oxoacetate **2** (0.8 mmol), dichloroethane (DCE; 2 mL). [b] Isolated yields. [c] Isomers due to restricted N–N bond rotation; *syn*: *N*-alkyl (except for **3d**, *N*-phenyl) *cis* to nitroso oxygen atom; *anti*: *N*-alkyl (except for **3d**, *N*-phenyl) *trans* to the nitroso oxygen atom. [d] Further splitting of NMR spectroscopic signals observed for *anti*-like isomers due to, presumably, additional restricted bond rotation. [e] *syn* isomer.

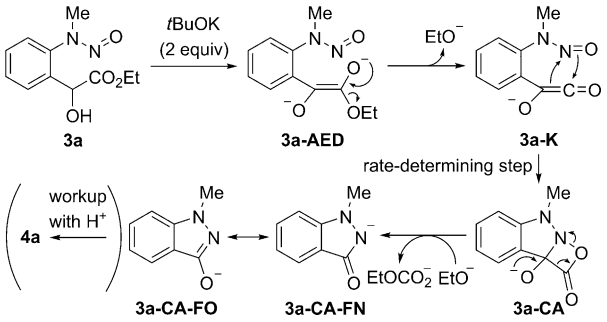
Table 2. Substrate scope for the synthesis of 3-hydroxyindazoles.[a,b]



[a] Reaction conditions: **3a–w** (0.2 mmol), *t*BuOK (0.4 mmol), dichloroethane (2 mL), HOAC (0.2 mL). [b] Isolated yields. [c] CCDC-1015964 (thermal ellipsoid plot drawn at the 30% probability level and hydrogen atoms omitted for clarity) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



Scheme 1. Evidence for ketene as a reactive intermediate and entrapment of ring fragmentation to afford the side product CO_2.



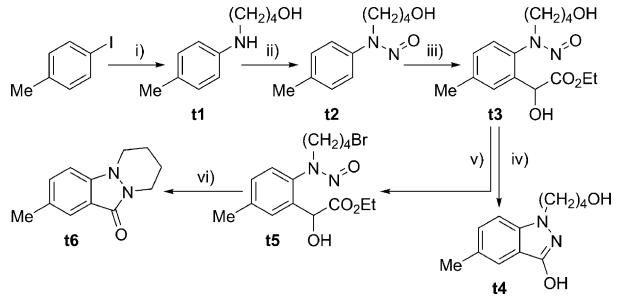
Scheme 2. Proposed formal [2+2] cycloaddition/fragmentation mechanism.

if any, due to the presence of adventitious water, as a viable participant in the transformation) (Scheme 1, middle left panel). 3) Alkoxy enediolate,[13] **3a-AED**, is unlikely to be a direct participant in the [2+2] cycloaddition (from orbital symmetry, sterics, and electronics perspectives)[12a] and indeed, no cycloaddition reactivity has been documented for such a type of species (Scheme 1, middle right panel).

The following mechanism can therefore be envisioned for the transformation (Scheme 2): double deprotonation of **3a** (consistent with the optimal condition, 2 equiv of *t*BuOK) to afford alkoxy enediolate (**3a-AED**),[13] elimination of EtO^- to generate ketene (**3a-K**), intramolecular cycloaddition of ketene and N=O bond with the formation of **3a-CA** (rate-determining step, as indicated by the lack of cyclic adduct by ^1H NMR spectrosopy, vide supra), ring-strain-release fragmentation[8,12a,14,15] furnishing **3a-CA-FN**/**3a-CA-FO** (as a resonance-stabilized species) with the concomitant loss of CO_2 (CO_2 entrapped by EtO^-, with $EtOCO_2K$ as the product, as characterized by ^{13}C NMR spectroscopy (Scheme 1, bottom left panel)).[16] The entrapment of CO_2 is also evidenced by the absence of CO_2 in the gas phase of the reaction mixture, and its appearance upon the addition of HOAc (release of CO_2 by the reaction between $EtOCO_2K$ and HOAc)[17] (as probed by gas chromatography, or GC, mass spectrometry, or MS, and bromothymol blue test (Scheme 1, bottom right panel).

A salient feature of the cycloaddition/fragmentation mechanism formulated above is predicted nucleophilic reactivity for N2 driven by the ring fragmentation. In corroboration of this proposal, MeI can serve as an electrophilic trap and furnishes an N2-methylated product. Significantly, this represents an umpolung reactivity as compared to the original nitroso nitrogen atom[10] and this reactivity is not experimentally observed for **4a** under the *t*BuOK conditions employed herein.

The synthetic utility of the C–H functionalization based protocol developed herein is demonstrated on the synthesis of



Scheme 3. Synthesis of a tricyclic fused ring system. Reaction conditions: i) ref. [18a], 1-iodo-4-methylbenzene (1 mmol), 4-aminobutan-1-ol (1.5 mmol), CuI (0.05 mmol) Cs_2CO_3 (2 mmol), 2-isobutyrylcyclohexanone (0.2 mmol), DMF (0.5 mmol), RT, 16 h; 99%; ii) **t1** (0.025 mmol), $NaNO_2$ (0.025 mmol), HCl (conc., 3.7 mL, 0.12 mol), ice (10 g), 0 °C, 2 h; 96%; iii) **t2** (0.4 mmol), ethyl 2-oxoacetate (0.8 mmol), [$RuCl_2Cp^*$] (0.01 mmol), AgSbF6 (0.04 mmol), NaOAc (0.04 mmol), dichloroethane (2 mL), 50 °C, 24 h; 88%; iv) **t3** (0.4 mmol), *t*BuOK (1.2 mmol), dichloromethane (2 mL), RT, 18 h, workup with HOAc (0.4 mL); 32%; v) ref. [18a], **t3** (1.56 mmol), CBr_4 (1.72 mmol), PPh_3 (1.72 mmol), dichloromethane (6 mL), RT, 6 h; 77%; vi) **t5** (1 mmol), *t*BuOK (2 mmol) THF (6 mL), 60 °C, 4 h; 25%.

a tricyclic fused ring system (Scheme 3), a natural product analogue of nigellicine, nigellidine, and nigeglanine.[9a] The synthesis is enabled by virtue of the functional-group tolerance at both C–H functionalization (hydroxyl, **t2** to **t3**) and subsequent cycloaddition/fragmentation (hydroxyl, **t3** to **t4**, and bromo, **t5** to **t6**) stages and features a one-step generation of two rings through a cascade sequence (**t5** to **t6**).

In summary, a directed intermolecular C–H functionalization for intramolecular cycloaddition/fragmentation synthesis of heterocycle strategy has been developed. Rh^{III}-catalyzed *N*-nitroso-directed C–H addition to ethyl 2-oxoacetate has enabled access to indazoles through the exploitation of a distinct path of reactivity between the directing group and installed group. The unique reaction pathway identified herein emphasizes forward reactivity analysis as an essential guide to the C–H functionalization-based synthetic strategy. Given the diversity of covalent linkages available for the nitroso group, we anticipate that this genre of reactivity can be extended to the synthesis of other types of heterocycles.

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Keywords: C–H functionalization · cycloaddition/fragmentation · directing groups · installed groups · rhodium

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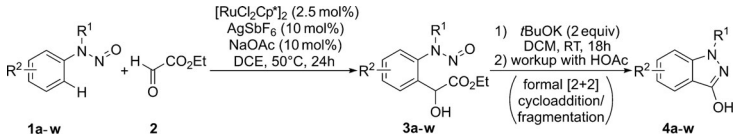
Rhodium(III)-Catalyzed *N*-Nitroso-Directed C–H Addition to Ethyl 2-Oxoacetate for Cycloaddition/Fragmentation Synthesis of Indazoles



Go cyclo! Herein Rh^{III}-catalyzed *N*-nitroso-directed C–H addition to ethyl 2-oxoacetate for the formal [2+2] cycloaddition/fragmentation synthesis of indazoles is reported (see scheme; Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl). The unique reactivity pattern identified herein emphasizes the importance of forward reactivity analysis in the development of useful C–H functionalization-based synthetic tools.