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Rhodium(III)-Catalyzed Indole Synthesis Using N−N Bond as an Internal Oxidant

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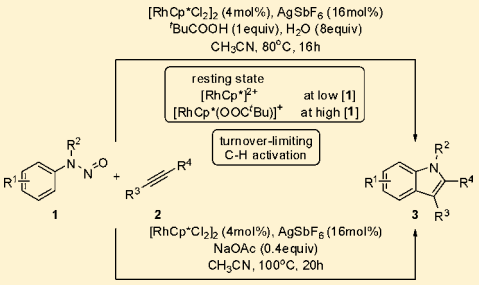
Supporting Information

ABSTRACT: We report herein a Rh(III)-catalyzed cyclization of *N*-nitrosoanilines with alkynes for streamlined synthesis of indoles. The synthetic protocol features a distinct internal oxidant, N−N bond, as a reactive handle for catalyst turnover, as well as a hitherto tantalizingly elusive intermolecular redox-neutral manifold, predicated upon C−H activation, for the formation of a five-membered azaheterocycle. The compatibility of seemingly dichotomous acidic and basic conditions ensures reaction versatility for multifarious synthetic contexts. The tolerance of an array of auxiliary functional groups potentially permits predefined, programmable substitution patterns to be incorporated into the indole scaffold. Comprehensive mechanistic studies, under acidic condition, support $[RhCp^*]^{2+}$ as generally the catalyst resting state (switchable to $[RhCp^*(OOC^tBu)]^+$ under certain circumstance) and C−H activation as the turnover-limiting step. Given the variety of covalent linkages available for the nitroso group, this labile functionality is likely to be harnessed as a generic handle for strikingly diverse coupling reactions.



INTRODUCTION

Transition-metal-catalyzed C−H functionalization has emerged as a powerful tool for the synthesis of structurally diverse organic molecules.[1] The participation of C−H bonds, in general as nucleophiles, allows access to two distinct redox manifolds: oxidative coupling (between two nucleophiles)[2] and redox-neutral coupling (between an electrophile and a nucleophile,[1a,3] including the formal insertion of highly active, electrophilic carbene/nitrene/oxo species[4]). Oxidative coupling provides a conceptually straightforward and synthetically versatile way of generating C−C and C−heteroatom bonds. The versatility stems from the ready availability of a plethora of C- and heteroatom-centered nucleophiles as well as their coordination reactivity leading to the efficient release of target product along the desired course (e.g., reductive elimination). Nevertheless, despite its great synthetic potential, the generally required use of an external oxidant for catalyst turnover represents a significant drawback because of undesired waste byproduct (especially late metal-based) and off-cycle side reaction. Redox-neutral coupling offers an appealing mechanistically complementary pathway for catalyst turnover through either a stepwise (oxidative addition/reductive elimination or vice versa) or concerted (simultaneous bond cleavage/bond formation) fashion. However, the synthetic utility of this external oxidant-free strategy is plagued by the limited repertoire of compatible electrophiles, especially heteroatom-based umpolung synthons (therefore primarily used for C−C coupling).[5] Only recently has the flexibility of the transformation been significantly improved in other synthetic contexts (e.g., for C−N coupling).[3] Illustrative is the demonstration of synthesis of azaheterocycles, ubiquitous structural elements[6,7] in nature and medicinal chemistry, using electrophilic nitrogen source with pendant oxygen functionality. In these internal oxidant protocols, N−O bonds have been recruited as a critical handle for both C−N cyclization and catalyst turnover.

We have recently initiated a program on the exploitation of nitroso (depending on the covalent linkage, categorized as *C*-, *N*-, *O*-, and *S*-nitroso) group as C−H activation directing group for further functionalization. The heightened reactivity endowed by the localized high-lying filled orbitals of *N*-nitroso group has already translated to a Rh(III)-based versatile synthetic protocol for *ortho* C−H olefination.[8] We envisioned that the extension of this reactivity profile to the coupling with alkyne would bypass otherwise efficient β-H elimination and render the lability of nitroso group to be further utilized for C−N bond formation. Herein we wish to disclose a Rh(III)-catalyzed cyclization of *N*-nitrosoanilines with alkynes for streamlined synthesis of indoles, under both acidic and basic conditions. The synthetic protocol features a distinct internal oxidant, N−N bond, as a reactive handle for catalyst turnover, as well as a hitherto tantalizingly elusive intermolecular redox-neutral manifold, predicated upon C−H activation, for the formation of a five-membered azaheterocycle.[6,7] Noteworthy is the tolerance of a broad range of auxiliary functional groups, thus potentially permitting predefined, programmable substitution patterns to be incorporated into the indole scaffold.

Received: August 17, 2013
Published: October 7, 2013

dx.doi.org/10.1021/ja408541c | J. Am. Chem. Soc. 2013, 135, 16625−16631

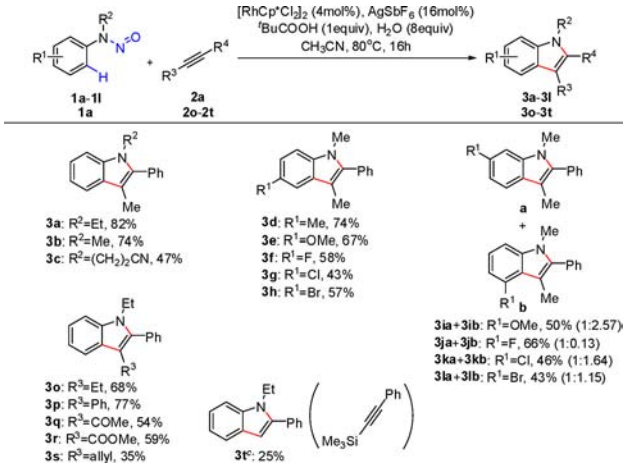
Comprehensive mechanistic studies on the deuterium labeling, kinetic isotope effect (KIE), electronic effect, intermediate interception, cyclization pathway, ^{15}N labeling, kinetic profile, and resting state have allowed the key set of catalytic elementary steps to be delineated.

RESULTS AND DISCUSSION

Reaction Development under Acidic Condition. We commenced our investigations by examining Rh(III)-catalyzed coupling of *N*-nitrosanilines and alkynes under acidic condition. In particular, experimental parameters (with $[RhCp^*Cl_2]_2$/$4AgSbF_6$ as the catalyst precursor, **1a** and **2a** as the model substrates) were screened targeting cyclized indole derivative (**3a**) (Supplementary Table S1). Reactions performed with an array of acids (HOAc, CF_3COOH, H_3PO_4, ^{t}BuCOOH) in protic solvents (^{t}BuCH$_2$OH, ^{t}AmOH) prove promising but fail to offer a yield beyond 50%. A switch of solvent to CH_3CN (Supplementary Table S1) allows the identification of a standard acidic condition (Supplementary Table S2), featuring 1 equiv of ^{t}BuCOOH and 8 equiv of H_2O, as the experimental setting of choice. With the omission of either ^{t}BuCOOH or both ^{t}BuCOOH and H_2O or with pure H_2O as the solvent, a significantly diminished yield is observed. The yield is also negatively influenced by a decrease of ^{t}BuCOOH, but an increase of ^{t}BuCOOH provides no beneficial impact. Further variation of H_2O and temperature proves to be futile. Replacement of ^{t}BuCOOH with HOAc under otherwise identical condition leads to attenuation of the catalytic activity.

Substrate Scope under Acidic Condition. With the optimized reaction condition in hand, we then embarked on an exploration of the substrate scope of the transformation. The scope of *N*-nitrosoanilines was first examined by the adoption of **2a** as the coupling partner (Table 1). The versatility of the

Table 1. Substrate Scope under Acidic Condition[a,b]



[a]Conditions: *N*-nitrosoaniline (1 equiv), alkyne (1.5 equiv), CH_3CN (2 mL). [b]Isolated yields. [c]The structure of the alkyne substrate is in the parentheses.

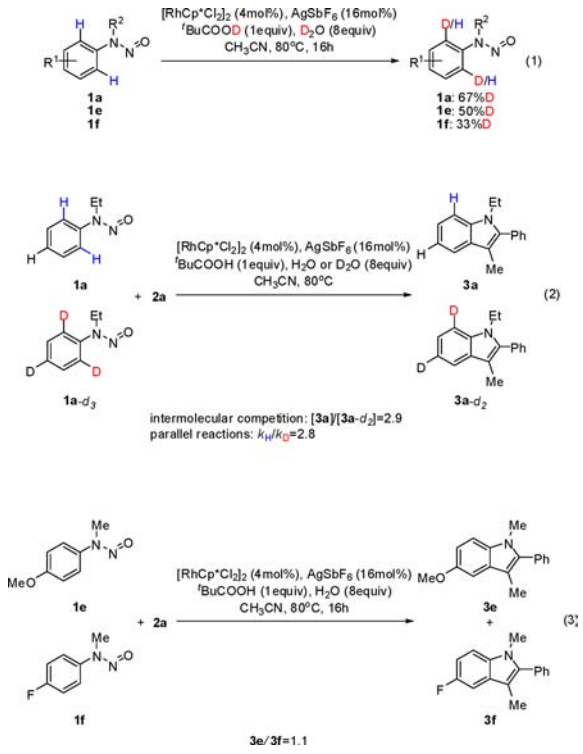
reaction is exemplified by the tolerance of varied *N*-alkyl substituents (**1b**, **1c**) and associated distal capping functionality (CN group). Both electron-rich (Me, **1d**; OMe, **1e**) and electron-poor (halogen, **1f**, **1g**, **1h**) *para*-substituted *N*-nitrosoanilines participate in good yields. The survival of the Br substituent represents a distinct feature of a rhodium-based synthetic protocol. The reaction is also effective for *meta*-substitution (OMe, **1i**; halogen, **1j**, **1k**, **1l**); however, the regioselectivity is generally, except for **1j**, not observed (**1i**, **1k**, **1l**). An *ortho*-substituent (Me, OMe, F) residing in close proximity significantly retards the transformation, delivering the product in low yield. The alkyne scope was next examined using **1a** as the coupling partner. A diversity of alkynes proves to be efficient participants for the transformation. Variation of the substituent in **2a** from a Me group to a bulkier Et (**2o**) or Ph (**2p**) group is tolerated. Electron-withdrawing substituents, ketone (COMe, **2q**) and ester (COOMe, **2r**), are also compatible with the reaction. Alkenyl group (**2s**) is not as reactive as alkyne and remains intact after the transformation. Trimethylsilyl substitution (**2t**) enables the synthetic equivalent incorporation of an otherwise incompatible terminal alkyne.[9] The reaction also proceeds, albeit less efficiently at the current stage, for an internal alkyne bearing two alkyl groups (^{n}Pr), two ester groups (COOEt), or one alkyl group (Me) and one ester group (COOEt). Importantly, the compatibility of a variety of transformable groups (CN, halogen, ketone, ester, alkenyl) potentially permits innumerable substitution patterns to be programmed into the indole scaffold.

Classic and Emerging Indole Synthetic Methodologies. Indoles have been privileged targets of interest for organic and medicinal chemistry for the past century.[6,7] Despite the availability of a plethora of classic protocols, new synthetic methods are constantly being evolved for the practical access of ever increasingly expanded chemical space. The venerable Fischer reaction and related sigmatropic rearrangement methods (e.g., those developed by Gassman, Bartoli, Thyagarajan, Julia, Buchwald, Odom, Ackermann, Eilbracht) effectively afford ring-closure products through pericyclic electron and bond redistribution processes. A key disadvantage of these methods is the general involvement of multiple reaction steps (even via Japp-Klingemann reaction) for the preparation of requisite substrates. The benzophenone strategy partially overcomes this limitation, but at the expense of atom economy and therefore transformation efficiency. The alkyne hydroamination approach, especially early metal-based, suffers from narrow substrate scope, and the alkene hydroformylation process operates under harsh reaction condition. The reductive cyclization methods (e.g., those developed by Leimgruber-Batcho, Reissert, Cadogan-Sundberg, Fürstner) limit the use of substrates that are compatible with the stringent reducing condition. Myriad other methods (e.g., those developed by Nenitzescu, Kanematsu, Hemetsberger, van Leusen, Madelung-Houlihan) require the participation of either synthetically demanding substrates or operationally challenging reagents. The Mori-Ban method and related variants (e.g., those developed by Larock, Cacchi, Castro) provide conceptually alternative, late metal-derived routes to the versatile incorporation of diversified functional groups, but a tedious step for the preinstallation of halides, pseudohalides, or other moieties presents a serious stumbling block for their broad utility. Direct C−H functionalization promises a shortened synthetic sequence and has recently been explored for the more straightforward assembly of an indole skeleton. However, the typically adopted oxidative cross-dehydrogenative coupling methods translate to the inevitable undesired use of synthetically restrictive, often late metal-based and environmentally toxic external oxidants for catalyst turnover, whereas the internal oxidant-derived strategy has thus far been demonstrated only on a palladium-catalyzed intramolecular reaction manifold that requires the cumbersome preassembly of

dx.doi.org/10.1021/ja408541c | J. Am. Chem. Soc. 2013, 135, 16625−16631

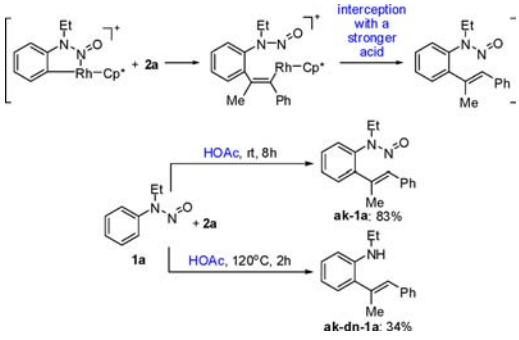
substrate frameworks. The N−N bond-based internal oxidant strategy described herein provides a robust solution to the issues associated with the aforementioned methods, featuring facile substrate preparation (one-step reaction from anilines, affording stable *N*-nitrosoanilines; commercially available alkynes), mild synthetic condition, broad reaction scope, and superior atom economy.

C−H Activation, KIE, and Electronic Effect. The high efficacy of the catalytic system prompts a detailed inspection of its mode of action. The exclusive incorporation of deuterium (**1a**, **1e**, **1f**) *ortho* to the *N*-nitroso group on exposure to ^{t}BuCOOD/D_2O (eq 1), as well as a pronounced KIE value (2.9 determined from intermolecular competition reaction and 2.8 determined from two parallel reactions, eq 2),[10] supports an initial reversible, *N*-nitroso-directed turnover-limiting C−H activation step. The lack of electronic preference in the competition experiment (competition reaction of **1e** and **1f** with **2a**) (eq 3) suggests the operation of a concerted metalation-deprotonation (CMD, presumably through initial weakening of C−H bond by agnostic interaction[11]) pathway (with no buildup of charge in the transition state).

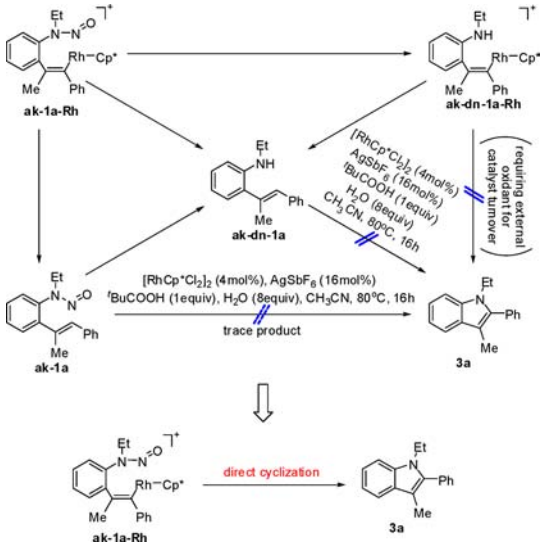


Migratory Insertion of Alkyne and Direct Cyclization of Alkenylrhodium. The C−H activation delivers an arylrhodium species primed for subsequent migratory insertion of alkyne. The feasibility of this step can be validated by the proto-demetalation interception of presumed alkenylrhodium species. A forcing, pure HOAc condition indeed favors the formation of, besides **3a**, two otherwise elusive alkenylated products (**ak-1a**, **ak-dn-1a**[12]) at a convenient rate (Scheme 1). However, under our weaker acidic synthetic condition, additional experiments and analysis rule out the occurrence of either proto-demetalation (cleavage of the coordination bond between Rh(III) and alkenyl carbon with H^+) or proto-denitrosation (cleavage of the N−N bond with H^+) process for alkenylrhodium (**ak-1a-Rh**) prior to the cyclization step (Scheme 2): only trace amount of **3a** is formed from **ak-1a**;

Scheme 1. Interception of Alkenylrhodium under a More Forcing Acidic Condition

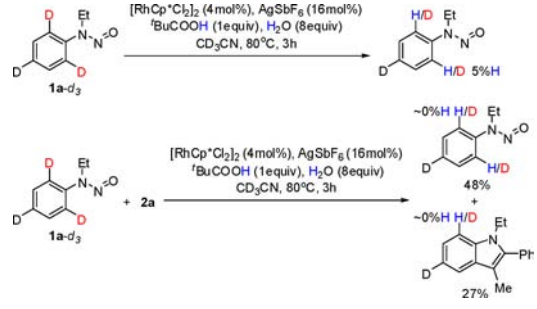


Scheme 2. Proposal of Direct Cyclization Pathway for Alkenylrhodium (without Either Proto-Demetalation or Proto-Denitrosation) Based on Reactivity Studies and Analysis of Hypothetically Possible Intermediates



no **3a** is generated from either **ak-dn-1a** or **dn-1a** (Supplementary eq S12); cyclization of hypothetical **ak-dn-1a-Rh** requires an external oxidant for catalyst turnover. Therefore, direct cyclization of **ak-1a-Rh** is proposed as the catalytically viable pathway. The irreversibility of migratory insertion step is inferred by reaction of deuterated **1a** (**1a**-d_3) in the absence and presence of **2a** (Scheme 3). Deuterium loss is identified only in the absence of **2a**; in the presence of such a coupling partner, no loss in either **1a**-d_3 or **3a**-d_2 is observed.

Scheme 3. Irreversibility of Migratory Insertion of Alkyne

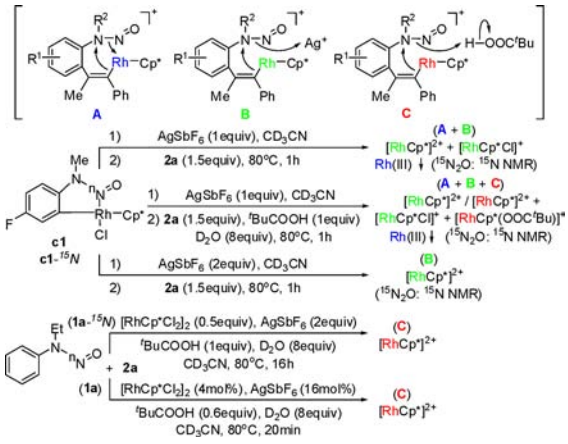


dx.doi.org/10.1021/ja408541c | J. Am. Chem. Soc. 2013, 135, 16625−16631

Mechanistic Course of Direct Cyclization Pathway. With the establishment of direct cyclization pathway for alkenylrhodium, the delineation of the working mode of this critical process is important for the elaboration of a reaction condition that facilitates the high-efficiency regeneration of catalytically competent Rh(III) species. A stepwise reductive elimination/oxidative addition (or vice versa) sequence[3] is unlikely to be operative for catalyst turnover as it involves inherently impractical proto-demetalation of $[RhCp^*(NO)]^+$ (cleavage of the strong coordination bond between Rh(III) and NO^- with H^+).[13] The external oxidant mechanism, a process referring to the intermolecular reoxidation of released Rh(I) (in the form of RhCp*) with the N−N bond still bound to the indole nitrogen, is also not feasible because (1) reductive elimination typically proceeds with the participation of two anionic (or covalent) ligands, affording a neutral coupling product; the *N*-nitroso moiety is a neutral (or dative) ligand and therefore not an effective reactive partner, and (2) this mechanistic course demands a challenging intermolecular reaction channel among three species (electron transfer from RhCp* to the N−N bond, affording the indole derivative, NO^-, and $[RhCp^*]^{2+}$, and reaction between thus formed NO^- and an electrophile) and/or the aforementioned proto-demetalation of $[RhCp^*(NO)]^+$. Instead, a concerted N−N bond cleavage/C−N bond formation cyclization process is envisaged, which will extrude, putatively, a NO^- fragment susceptible to synergistic electrophilic attack.

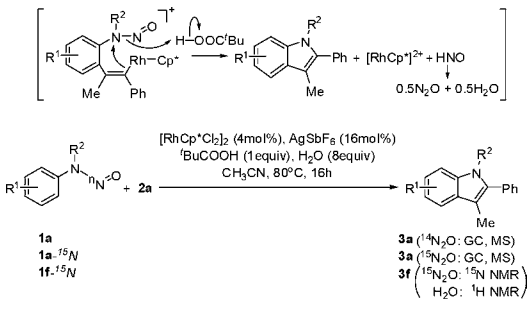
The competition outcome of three hypothetically possible pathways ($[RhCp^*]^{2+}$, **A**; Ag^+, **B**; H^+, from ^{t}BuCOOH, **C**) could have significant implications for the catalytic reaction (**A**: loss of catalytically competent Rh(III) species;[14] **B**: regeneration of $[RhCp^*]^{2+}$, release of catalytically deleterious counterion Cl^- and partial formation of $[RhCp^*Cl]^+$; **C**: regeneration of $[RhCp^*]^{2+}$) (Scheme 4). Pathway **A** is conceivably accessible

Scheme 4. Proposal of H^+ Abstraction Pathway for NO^- Based on Reactivity Studies of Hypothetically Possible Pathways



when the accumulation of alkenylrhodium species is comparatively expedient and competing pathways are of limited efficiency (Scheme 4, Supplementary eqs S15, S17, S18, and S20). The participation of stoichiometric amount of rhodacycle **c1**,[8] in the presence of metathesis-generated AgCl or with additional ^{t}BuCOOH/H_2O, ensures the operation of such an intramolecular pathway (with ensued detrimental loss of catalytically competent Rh(III) species, as evidenced by reduced integration area of total Cp* peak on ^{1}H NMR; occurrence of thermal decomposition of $[RhCp^*(NO)]^+$, proposed on the basis of the lack of identifiable ^{15}N NMR signal associated with either linear NO^+ or bent NO^- coordinated species, for the reaction involving **c1**-^{15}N). The reactivity exhibited by AgCl and ^{t}BuCOOH/H_2O elicits the involvement of pathway **B** (production of N_2O;[15,16] partial formation of $[RhCp^*Cl]^+$, as verified by its quantitative metathesis reactivity with $AgSbF_6$ through ^{1}H NMR; N_2O and $^{15}N_2O$ confirmed by ^{15}N NMR,[17] gas chromatography, or GC, and mass spectrometry, or MS, vide infra) and pathway **C** (production of N_2O and expectedly, H_2O; $[RhCp^*(OOC^tBu)]^+$, if any, not convertible to $[RhCp^*]^{2+}$ through an attempted metathesis reaction with $AgSbF_6$), respectively. The engagement of excess $AgSbF_6$, with an abundant pool of freely available Ag^+, completely blocks pathway **A** (Supplementary eqs S21 and S23). All of the above reactions proceed essentially to completion within 1 h, affording **3a** alongside liberated N_2O. In general, the mixtures afforded by the above stoichiometric reactions contain catalytically competent species for effecting the indole synthesis (Supplementary eqs S16, S19, and S22). When the turnover-limiting C−H activation step retards the accumulation of alkenylrhodium species, pathway **A** is also readily eliminated. Thus, pathway **C** (70% contribution) is favored over pathway **B** (30% contribution) (pathway contribution determined assuming that each reaction event from pathway **B** corresponds to the release of one counterion Cl^- and each reaction event from both pathway **B** and pathway **C** corresponds to the regeneration of one $[RhCp^*]^{2+}$; contribution from pathway **B** therefore calculated by the division of combined concentrations of Cl^- and $[RhCp^*Cl]^+$ over the total concentrations of $[RhCp^*]^{2+}$ and $[RhCp^*Cl]^+$, Supplementary Figure S30, utilizing the equilibrium constant of the reaction involving $[RhCp^*]^{2+}$, Cl^-, and $[RhCp^*Cl]^+$, Supplementary Figure S16) for a reaction between **1f** and **2a** (stoichiometric condition; ^{t}BuCOOH to AgCl ratio, 1:2) (Supplementary eqs S24−S26), and the replacement of **1f** with **1a**-^{15}N already leaves pathway **C** as the only venue of choice (Supplementary eq S27). The much higher ^{t}BuCOOH to AgCl ratio (6:1) under catalytic condition should warrant pathway **C** as the prevailing, if not exclusive, operative mechanism for our synthetic protocol (Supplementary eq S28). The general kinetic predominance of $[RhCp^*]^{2+}$ (vide infra), quantitative preservation of catalytically competent Rh(III) species (Supplementary Figure S35), and accumulation of N_2O and H_2O over the reaction (from a well established dimerization and subsequent decomposition reaction course for the transient HNO species[16]) (Scheme 5) provide strong

Scheme 5. Evidence for the H^+ Abstraction Pathway for NO^- Based on the Detection of N_2O and H_2O



dx.doi.org/10.1021/ja408541c | J. Am. Chem. Soc. 2013, 135, 16625−16631

circumstantial evidence for the validity of such a proposal. The N−N bond as the formal locus of reduction supports its role as an internal oxidant in the catalytic cycle. Monitoring with ^{15}N NMR reveals no detectable discrete complex formed between metal and NO^-, as the sole signal associated with $^{15}N_2O$ disappears (confirmation of gaseous nature) upon solvent evaporation. A working hypothesis can therefore be conceived for the cyclization process: nucleophilic attack of alkenylrhodium on electrophilic amino nitrogen with concomitant abstraction of NO^- by H^+.

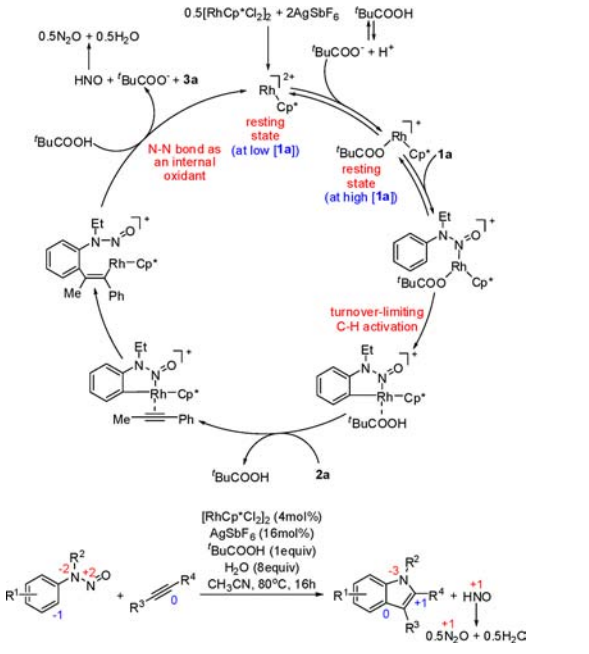
Effect of Counterion on Catalytic Activity. Even though the predominance of the H^+ pathway for NO^- abstraction ensures efficient regeneration of $[RhCp^*]^{2+}$, the presence of Cl^- (slightly released from AgCl) might inhibit the formation of catalytically competent $[RhCp^*(OOC^tBu)]^+$. Consistent with this conjecture, removal of AgCl significantly enhances the catalytic activity, allowing the completion of reaction essentially within 1 h, as monitored by NMR (Supplementary eq S32) (albeit not necessarily implicating the improvement of final yield, Supplementary eq S33). A prominent feature observed during the course of this transformation is the expedient accumulation and even dominance of $[RhCp^*(OOC^tBu)]^+$. Taken together, the above stoichiometric and catalytic reactions have established two empirical rules: (1) NO^- abstraction with an electrophile other than $[RhCp^*]^{2+}$ is of utmost importance for precluding the loss of catalytically competent species. (2) NO^- abstraction should not release a counterion (e.g., Cl^-) that is detrimental to the catalytic activity. The inhibition role of Cl^- is further highlighted by the low product yields (50% and 28%, respectively) offered by $[RhCp^*Cl_2]_2/3AgSbF_6$ (furnishing $[RhCp^*]^{2+}$ and $[RhCp^*Cl]^+$) and $[RhCp^*Cl_2]_2/2AgSbF_6$ (furnishing $[RhCp^*Cl]_2^{2+}$) systems.

Kinetic Profile, Catalyst Resting State, and Catalytic Cycle. Kinetic studies provide key insight into the plausible sequence of elementary steps in the catalytic cycle. The reaction is first order in Rh_t (total of rhodium species) (as observed analogously in the *N*-nitroso-directed arene *ortho*-olefination reaction[8]), first order in *N*-nitrosoaniline derivative (**1a**), zero order in alkyne (**2a**), non-integer order in ^{t}BuCOOH, and first order in H_2O (eq 4). Under typical catalytic condition, the

$$\text{rate} = k\cdot[Rh_t]^1\cdot[\mathbf{1a}]^1\cdot[\mathbf{2a}]^0\cdot[^t\text{BuCOOH}]^{ni}\cdot[H_2O]^1 \qquad (4)$$

catalyst resting state is identified to be $[RhCp^*]^{2+}$. Taken together, the following catalytic cycle is proposed (Scheme 6): generation of $[RhCp^*]^{2+}$ as the catalyst resting state, reversible coordination of ^{t}BuCOO$^-$ and *N*-nitrosoaniline derivative, turnover-limiting C−H activation to form an arylrhodium intermediate via a ^{t}BuCOO$^-$-assisted CMD pathway, migratory insertion of alkyne to form an alkenylrhodium intermediate, concerted N−N bond cleavage/C−N bond formation with the concomitant abstraction of NO^- by H^+ (N_2O and H_2O as the thermodynamic sink to drive the reaction forward), and regeneration of $[RhCp^*]^{2+}$ (N−N bond as the formal locus of reduction, and therefore as an internal oxidant; for the formal oxidation states designated for the key elements involved in the redox-neutral process, see the equation presented at the bottom of Scheme 6). The non-integer order kinetics observed for ^{t}BuCOOH can be rationalized by the generation of maximum $[RhCp^*(OOC^tBu)]^+$, as experimentally observed, only at its medium concentration (Supplementary Figures S61−S63). The first order kinetics in

Scheme 6. Proposed Catalytic Cycle and Overall Reaction Showing the Internal Oxidant Role of N−N Bond (Formal Oxidation States Designated for the Key Elements Involved in the Redox-Neutral Process)

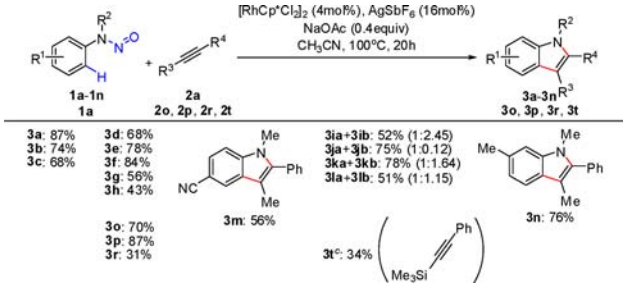


H_2O is derived from its contribution to the ionization of ^{t}BuCOOH and formation of $[RhCp^*(OOC^tBu)]^+$ (Supplementary Figures S64 and S65). Of particular note in the kinetic studies, inter alia, is a positive correlation between reaction rate and $[RhCp^*(OOC^tBu)]^+$ concentration. In fact, the catalyst resting state can even be switched to $[RhCp^*(OOC^tBu)]^+$ under certain circumstance (e.g., at high concentration of *N*-nitrosoaniline derivative, attributable to its role as a base and abstraction of H^+ from ^{t}BuCOOH) (Supplementary Figures S66 and S67). The first order kinetics for **1a** is apparently derived from its coordination to the $[RhCp^*(OOC^tBu)]^+$ prior to the C−H activation. The zero order kinetics for **2a** can be accounted for by either its coordination to the rhodacycle after the C−H activation or its initial competitive inhibitory off-cycle coordination to $[RhCp^*(OOC^tBu)]^+$ and subsequent participation in the C−H activation (facilitating C−H activation through the displacement of ^{t}BuCOOH).

Reaction under Basic Condition. Recognizing the pivotal role played by ^{t}BuCOO$^-$/^{t}BuCOOH in C−H activation and NO^- abstraction under acidic condition, we envisioned that a suitable base could likewise act as a proton shuttle. Extensive screening reveals that substoichiometric NaOAc (0.4 equiv) is sufficient for the transformation (Supplementary Tables S3 and S4). The reactions generally mirror those conducted under acidic condition, with two notable exceptions (Table 2): compatibility of *para*-substituted electron-withdrawing CN group (**1m**) and regioselective transformation from a *meta*-substituted (Me) electron-rich *N*-nitrosoaniline derivative (**1n**). A pronounced KIE value (2.1 determined from intermolecular competition reaction and 2.0 determined from two parallel reactions) and a higher reactivity for electron-rich *N*-nitrosoaniline derivative suggest electrophilic C−H activation as the turnover-limiting step.

dx.doi.org/10.1021/ja408541c | J. Am. Chem. Soc. 2013, 135, 16625−16631

Table 2. Substrate Scope under Basic Condition[a,b]



[a]Conditions: *N*-nitrosoaniline (1 equiv), alkyne (1.5 equiv), CH_3CN (2 mL). [b]Isolated yields. [c]The structure of the alkyne substrate is in the parentheses.

CONCLUSION

In summary, a C−H activation-based intermolecular redox-neutral strategy for indole synthesis has been developed. Our N−N bond-based internal oxidant approach offers a valuable complement to the thus far exclusively used N−O variant for the synthesis of azaheterocycles. The compatibility of seemingly dichotomous acidic and basic conditions as well as tolerance of an array of auxiliary functional groups ensures reaction versatility and structure tunability for multifarious synthetic contexts. Comprehensive mechanistic studies, under acidic condition, support $[RhCp^*]^{2+}$ as generally the catalyst resting state (switchable to $[RhCp^*(OOC^tBu)]^+$ under certain circumstance) and C−H activation as the turnover-limiting step. Given the diversity of accessible covalent linkages for the nitroso group, this labile functionality is likely to serve as a generic synthetic handle for strikingly diverse coupling reactions.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, mechanistic studies, and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

J.Z. gratefully acknowledges support from the National Natural Science Foundation of China (21274058) and the National Basic Research Program of China (2013CB922101, 2011CB935801).

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