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Co(III)-Catalyzed, Internal and Terminal Alkyne-Compatible Synthesis of Indoles

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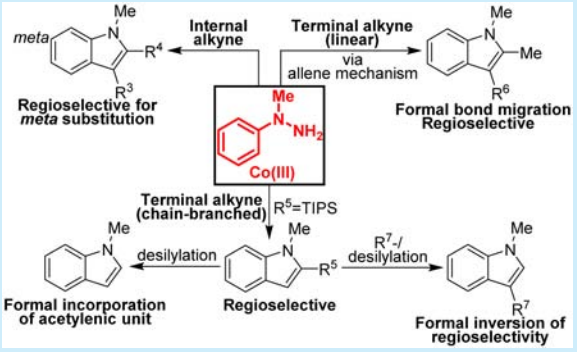
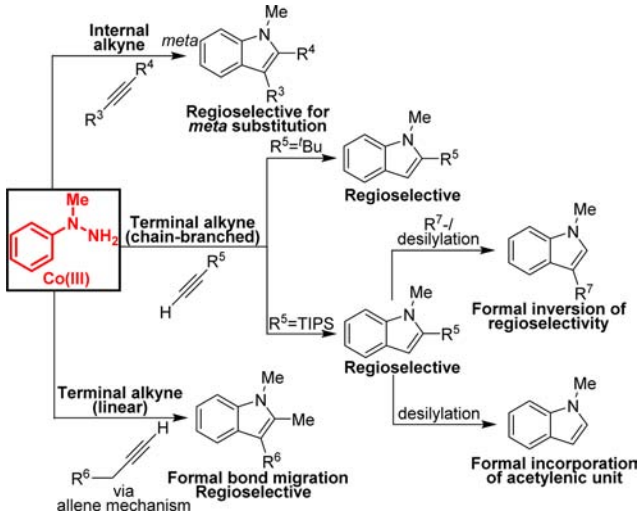
Supporting Information

ABSTRACT: A Co(III)-catalyzed, internal and terminal alkyne-compatible indole synthesis protocol is reported herein. The *N*-amino (hydrazine) group imparts distinct, diverse reactivity patterns for directed C−H functionalization/cyclization reactions. Notable synthetic features include regioselectivity for a *meta*-substituted arylhydrazine, regioselectivity for a chain-branched terminal alkyne, formal incorporation of an acetylenic unit through C2-desilylation on a C2-silylated indole derivative, formal inversion of regioselectivity through consecutive C3-derivatization and C2-desilylation processes, and formal bond migration for a linear-chain terminal alkyne.



Transition-metal-catalyzed C−H functionalization has received widespread attention for its emerging applications in diverse synthetic contexts.[1] Method development in this nascent field has been dedicated, to a great extent, to the construction of heterocyclic scaffolds.[2] An important and persistent theme in this respect is the search for distinct reactivity patterns that allow translation into unique substitution patterns and therefore access to expanded structural space. Herein we report a Co(III)-catalyzed, internal and terminal alkyne-compatible synthetic protocol for the construction of the indole skeleton (Scheme 1). In particular, an *N*-amino (hydrazine) group,[3] free from an end protecting group, has been used in combination with a Co(III) catalytic system for redox-neutral directed C−H functionalization/cyclization reactions, allowing the generation of a broad range of substitution patterns for the cyclic framework. This represents an important contribution to the indole synthetic schemes since none of the recently disclosed Co(III) catalytic protocols demonstrated compatibility with terminal alkynes.[4] Indeed, terminal alkynes are notoriously difficult to accommodate into C−H functionalization reactions, largely because of the existence of competing alternative reaction pathways (e.g., Glaser−Hay-type homocoupling[5]). Only recently have there been several reports describing the synthesis of heterocycles via a C−H activation pathway using terminal alkynes as the coupling partner.[6] However, these methods suffer from one or more of the following drawbacks: required use of a high reaction temperature, retention of an undesired bulky group in the final product, and generation of costly waste products from external oxidants. For the indole skeleton, only an isolated case was described,[7] and no general applicability was demonstrated. We have recently uncovered an *N*-amino directing group for C−H functionalization and applied that group in a Rh(III) catalytic system for the synthesis of indoles.[3] In spite of the heightened reactivity imparted by the *N*-amino group, the method developed therein is not versatile enough to be terminal alkyne-compatible. Cobalt is an earth-abundant, low-

Scheme 1. Co(III)-Catalyzed, Internal and Terminal Alkyne-Compatible Synthesis of Indoles: The *N*-Amino Directing Group Imparts Distinct, Diverse Reactivity Patterns for C−H Functionalization/Cyclization Reactions, Which Translates into Unique Substitution Patterns and Expanded Structural Space for the Indole Skeleton



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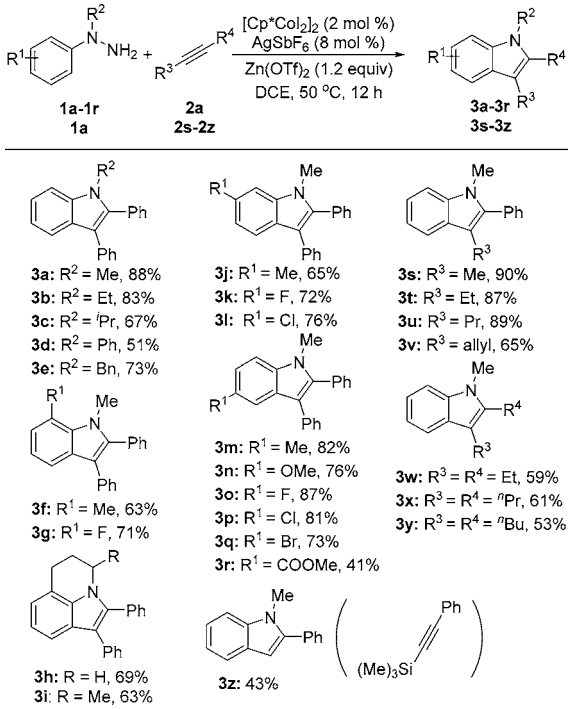
cost, nontoxic species and has recently demonstrated, in several transformations, unique reactivity that is elusive for other transition metals.[8] For example, the lower electronegativity of cobalt relative to its heavier congener can in principle translate into a higher nucleophilicity for the covalently bound C atom; the higher nucleophilicity can in turn offer faster C−heteroatom bond formation kinetics, thus overriding alternative competing reaction pathways. The results communicated herein provide further proof that an expanded substrate scope can indeed be achieved through the use of this first-row transition metal.

For the synthetic system developed herein, the reaction involving an internal alkyne affords a single regioisomer for a *meta*-substituted arylhydrazine (C−H coupling site *para* instead of *ortho* to the *meta* group). Significantly, in the transformations involving terminal alkynes, two distinct reaction pathways have been observed, depending on whether or not chain branching exists on the neighboring atom of the C≡C bond. In the presence of chain branching, bond position remains the same. In the absence of chain branching, a formal bond migration occurs, which proceeds through initial isomerization of the terminal alkyne to an allene and subsequent kinetically favored, selective incorporation of the allene moiety into the indole framework. The regioselectivity is superior for both types of terminal alkynes, allowing the generation of a single type of regioisomer. The chain-branched, bulky silyl group at C2 of the as-synthesized indole can be easily removed, thus enabling the synthetic equivalent of incorporating an acetylenic unit. Furthermore, the occupation of C2 by the bulky silyl unit allows selective functionalization at C3, and its subsequent removal affords a single type of indole derivative with formal inverse regioselectivity.

We commenced our investigations by examining the reaction between an arylhydrazine and an internal alkyne. This reaction is expected to be synthetically less challenging, and the optimized reaction conditions obtained for internal alkynes could serve as a guide for the selection of conditions for terminal alkynes. With $[Cp^*CoI_2]_2$ (2 mol %)/$AgSbF_6$ (8 mol %) as the catalyst precursor, **1a** and **2a** could indeed, with the assistance of KOAc (2 equiv), react at 60 °C in a variety of solvents to form the target indole derivative **3a** (see the Supporting Information). A promising 33% yield was achieved in DCE, which provided a starting point for further optimization of the conditions. Thus, a change in additive from KOAc to other species allowed an increase of yield, and in the presence of $Zn(OTf)_2$ the yield was boosted to 85%. An examination of the amount of $Zn(OTf)_2$ revealed that the yield remained essentially constant for 1.2 equiv and above. A slight adjustment of the reaction temperature to 50 °C gave us the optimized reaction conditions and 88% yield. A control experiment performed in the presence of either $AgSbF_6$ or $Zn(OTf)_2$ ruled out catalytic reactivity associated with these additives.

With the optimized reaction condition in hand, we next examined the substrate scope for both arylhydrazines and internal alkynes (Scheme 2). The reaction yield is inversely correlated with the bulkiness of the alkyl group (**1a**, methyl; **1b**, ethyl; **1c**, isopropyl) on the N atom, reflecting the operation of a steric effect. As expected, the reaction proceeded even more sluggishly for a phenyl-substituted substrate (**1d**). Insertion of a methylene bridging group between the N atom and the phenyl ring allowed partial recovery of the reactivity (**1e**). The *ortho* substitution on the phenyl ring (**1f**, methyl; **1g**, fluoro) resulted

Scheme 2. Substrate Scope of Internal Alkynes[a,b,c]



[a]Conditions: arylhydrazine substrate (0.4 mmol), alkyne (1.5 equiv), DCE (2.0 mL). [b]Isolated yields are shown. [c]The compound in parentheses is the alkyne substrate for **3z**.

in a slightly higher yield for an electronically deficient substrate. The reaction proceeded well for substrates bearing a cyclic substituent (closure at the N atom and *ortho* C atom, **1h** and **1i**). In the case of *meta* substitution, the Co(III) system reported herein exhibited superior regioselectivity compared with the Rh(III) system,[3,9] allowing the generation of a single type of isomer not only for **1j** (methyl) but also for **1k** (fluoro) and **1l** (chloro). Although the exact mechanism for the regioselectivity has yet to be elucidated, the applicability of both electronically rich and deficient substrates, in combination with the fact that C−C coupling occurs at the remote site, suggests that most likely the steric effect plays a dictating role here. Examination of a variety of *para*-substituted substrates revealed broad compatibility of both electronically rich and deficient substrates. The internal alkyne scope was next investigated using phenyl/alkyl-disubstituted asymmetric alkynes (**1s**, methyl; **1t**, ethyl; **1u**, propyl) as the test substrates. All of the reactions proceeded well, allowing single types of regioisomers to be obtained in yields comparable to that from phenyl/phenyl-disubstituted alkyne. The C≡C bond is the site of coupling in the presence of a potentially competing C═C bond (**1v**), although the product was furnished in a slightly diminished yield. Alkyl/alkyl-disubstituted symmetric alkynes (**1w**, ethyl; **1x**, propyl; **1y**, butyl) are also competent substrates for the transformation. A phenyl/silyl-disubstituted alkyne (**1z**) could act as a synthetically equivalent surrogate substrate for the terminal alkyne phenylacetylene.

Importantly, the reaction can be scaled up to the multigram scale with a very low catalyst loading (0.2 mol %) (eq S1), highlighting the superior reactivity imparted by the *N*-amino group.

Switching the substrates from internal alkynes to terminal alkynes will inevitably generate the issue of competing side

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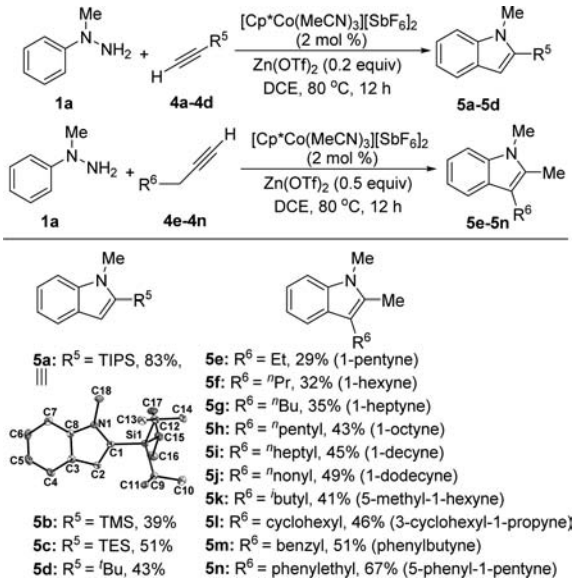
reactions, as terminal alkynes are more prone to alternative reaction pathways. This implies that in order to gain access to indoles in a synthetically productive manner, the indole synthesis reaction pathway should be favored kinetically. We have discovered previously that the counterion (Cl^-) in the Rh(III) system can partially inhibit its catalytic activity.[9] In accordance with this, although $[Cp^*CoI_2]_2$, $[Cp^*Co(CO)I_2]_2$, and $[Cp^*CoCl_2]_2$, with the assistance of $AgSbF_6$, allowed the generation of the target product **5a** (whose structure was confirmed with single-crystal X-ray diffraction analysis) via a model reaction between **1a** and triisopropylsilyl (TIPS)-substituted terminal alkyne (**4a**), they invariably gave a low yield (<30%). Replacement of the catalyst precursor with a cationic Co(III) species, $[Cp^*Co(MeCN)_3][SbF_6]_2$, resulted in a significant increase in the yield (56%). Adjustment of the amount of $Zn(OTf)_2$ to 0.2 equiv increased the yield to 76%. Further tuning of the temperature to 80 °C provided an 83% yield (Scheme 3).

Scheme 3. Substrate Scope of Terminal Alkynes[a,b,c]



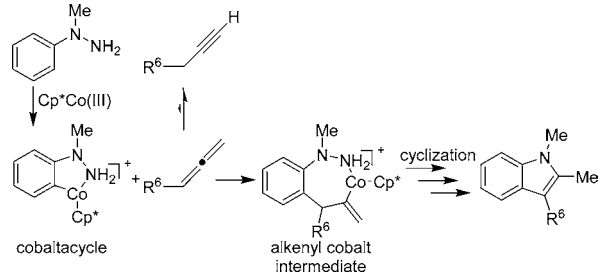
[a]Conditions: **1a** (0.4 mmol), alkyne (1.5 equiv), DCE (2.0 mL). [b]Isolated yields are shown. [c]Compounds in the parentheses are the alkyne substrates.

With these reaction conditions in hand, we next examined the substrate scope of terminal alkynes. A decrease of the bulkiness in the silyl group resulted in a seemingly surprising lower yield (**4b**, trimethylsilyl (TMS); **4c**, triethylsilyl (TES)). The yield in fact correlates well with the availability of the alkyne substrate in the reaction mixture. The availability is dictated by the boiling point/volatility. The reaction also proceeded smoothly for a *tert*-butyl-substituted terminal alkyne (**4d**). Further expansion of the substrate scope to an alkyl-group-substituted terminal alkyne (**4e**, pentyne) provided an intriguing bond-migrated product. Systematic testing with a variety of alkynes (**4f**–**n**) showed the same reactivity pattern as long as there was no chain branching at the neighboring atom of the C≡C bond. Again, the reaction yield also generally correlated with the availability of the substrate.

Several experiments were then conducted to examine the C–H activation process. A competition reaction was performed to evaluate the electronic preference for the transformation (see the Supporting Information). A one-pot reaction between **1n**/**1r** and **2a** revealed preferred reaction for the substrate bearing an electron-withdrawing group (product distribution: **3n**/**3r** = 0.55), suggesting that concerted metalation–deprotonation is responsible for the C–H activation process. Two kinetic isotope effect (KIE) experiments were performed with the participation of **1a** and **1a**-d_3 (deuteration at two *ortho* positions and one *para* position of the *N*-amino group). A high KIE value was observed for the coupling with both internal alkyne (**2a**, k_H/k_D = 2.6) and terminal alkyne (**4a**, k_H/k_D = 3.2), suggesting the participation of C–H bond cleavage in the turnover-limiting step, as also observed in other Co(III)-based catalytic systems,[4] for both of the transformations.

The bond migration for the reaction involving a linear-chain terminal alkyne is proposed to proceed through an initial alkyne-to-allene isomerization (promoted by the Co(III) catalyst[10]), subsequent carbocobaltation of the allene (on a five-membered cobaltacycle formed via C–H cobaltation)[3,4a,9] on the internal C=C bond (via an alkenylcobalt intermediate instead of a π-allylcobalt intermediate[11]), followed by the final cyclization process (Scheme 4). Supporting lines of evidence

Scheme 4. Bond Migration Mechanism for a Reaction Involving a Linear-Chain Terminal Alkyne



for this mechanistic proposal include the following: (1) The reaction involving an internal 2-alkyne gave a mixture of regioisomers (eq S2), ruling out the initial isomerization from 1-alkyne to 2-alkyne. (2) Replacement of the terminal alkyne with the same amount of the corresponding allene provided a single identical regioisomer, albeit in a significantly reduced yield (eq S3), consistent with participation of the allene in the carbocobaltation and cyclization processes; along with this finding is also the identification of many side products on the TLC plate. The reaction can be rationalized (Scheme 4) by (1) constant release of minute amounts of allene from the terminal alkyne (for thermodynamic stability reasons[12]) and (2) dominance of allene in the carbocobaltation and cyclization processes because of its higher reactivity (the presence of only a minute amount ensures its preferred reactivity along a single pathway). Indeed, arrival at a thermodynamic equilibrium between the alkyne and allene typically requires strongly basic conditions,[12] and no such equilibrium was identified on a large scale for the reaction system reported herein (eq S4).

As a further demonstration of the synthetic utility of this *N*-amino-directed C–H functionalization protocol, several organic transformations on the TIPS-substituted indole derivative **5a** were performed (Scheme 5). TIPS at C2 can be readily removed by tetrabutylammonium fluoride, affording an indole derivative that incorporates a formal acetylenic unit.[13] Acyloxylation can proceed at C3 with retention of the TIPS group.[14] A sulfenyl group can also be installed at C3 without affecting the TIPS group.[15] Desilylation can then be executed

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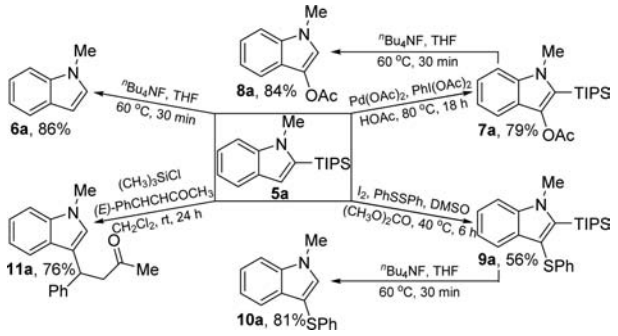
Scheme 5. Synthetic Transformations Performed on a C2-Silylated Indole Derivative



on both the acyloxylated and sulfenylated indole derivatives. For a Michael addition reaction performed herein, desilylation occurs simultaneously with the conjugate addition process.[16] These three types of desilylated products offer an intriguing formal inversion of regioselectivity for a nominal terminal alkyne bearing an acyloxy group, a sulfenyl group, and a ketone-containing group, respectively.

In summary, a Co(III)-catalyzed, internal and terminal alkyne-compatible C−H functionalization protocol has been developed for the synthesis of indoles. The protocol takes advantage of the high reactivity imparted by the *N*-amino directing group and the unique catalytic activity associated with the Co(III) system. Alkynes can be regioselectively incorporated into the indole skeleton, allowing the generation of a broad range of substitution patterns and pointing toward the vast synthetic possibilities that have yet to be uncovered for this first-row transition metal.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01805.

Experimental procedures and characterization of the products (PDF)

Copies of the ^{1}H and ^{13}C NMR spectra of selected products (PDF)

Crystallographic data for **5a** (CIF)

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Notes

The authors declare no competing financial interest.

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