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Direct Access to Cobaltacycles via C−H Activation: *N*-Chloroamide-Enabled Room-Temperature Synthesis of Heterocycles

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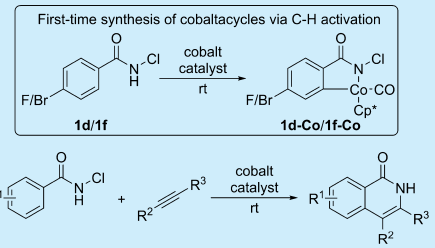
Supporting Information

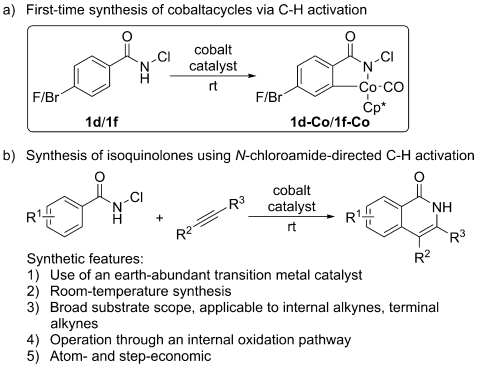
ABSTRACT: Cobaltacycle synthesis via C−H activation has been achieved for the first time, providing key mechanistic insight into cobalt catalytic chemistry. *N*-Chloroamides are used as a directing synthon for cobalt-catalyzed room-temperature C−H activation and construction of heterocycles. Alkynes as coupling partners allow convenient access to isoquinolones, a class of synthetically and pharmaceutically important compounds. The broad substrate scope enables a diverse range of substitution patterns to be incorporated into the heterocyclic scaffold.



Transition-metal-catalyzed directed C−H functionalization has witnessed tremendous progress as a handy tool for organic synthesis.[1] Reaction development traditionally relies on the use of second-row transition metal catalytic centers (e.g., palladium, rhodium)[2−5] to effect the desired transformations. Only recently have first-row transition metal complexes (e.g., cobalt)[6] established their utility in catalytic synthetic contexts. The unique electronic and steric properties associated with these complexes promise the achievement of distinct reactivity. Despite the synthetic progress, mechanistic understanding lags far behind because of challenges in the isolation of elusive intermediate species proposed in the catalytic cycle. Indeed, in contrast to abundant examples of five-membered palladacycles and rhodacycles,[7] to date no five-membered cobaltacycle has been directly accessed through C−H activation under bona fide catalysis-relevant experimental settings. Only one type of five-membered cobaltacycle[8] has been synthesized through indirect methods, starting from a catalysis-irrelevant aryl halide, involving a key step of either transmetalation or oxidative addition. Although this five-membered cobaltacycle has been demonstrated to be catalytically active,[8b] the ad hoc synthetic process offers no definitive proof for the occurrence of C−H activation. The ability to directly synthesize and isolate C−H-activated five-membered cobaltacycles is therefore still an urgent need to advance the understanding and expand the scope of cobalt-catalyzed C−H functionalization reactions.

We have a long-term interest in the development of novel C−H-activation-directing synthons for achieving hitherto-elusive mechanistic insight and synthetically useful reactivity. In search of a directing synthon that not only can stabilize the C−H-activated five-membered cobaltacycle but also allows for convenient entry into the desired reaction manifold, *N*-chloroamide[9] has emerged as our candidate of choice by virtue of its unique reactivity. The facile N−H deprotonation capability (e.g., even with KF as the base) can furnish an anionic ligand for expedient docking of the cobalt catalytic center, and the N−Cl oxidizing reactivity provides a potentially viable internal oxidation reaction pathway. Herein we report the first direct synthesis of cobaltacycles via C−H activation (Scheme 1a) and document *N*-chloroamide-enabled room-temperature (rt) construction of heterocycles (Scheme 1b). The cobalt catalytic chemistry allows efficient coupling of *N*-chlorobenzamides with alkynes to afford isoquinolones, a class of synthetically and pharmaceutically important compounds.[10] The N−Cl bond-based catalytic process described herein differs substantially from those documented in previous N−O bond-derived protocols, which are synthetically restrictive, as manifested by the requirement of rare metals (e.g., rhodium, ruthenium),[11,12] harsh reaction conditions (e.g., elevated

Scheme 1. First-Time Synthesis of Cobaltacycles via C−H Activation and *N*-Chloroamide-Enabled Room-Temperature Construction of Heterocycles



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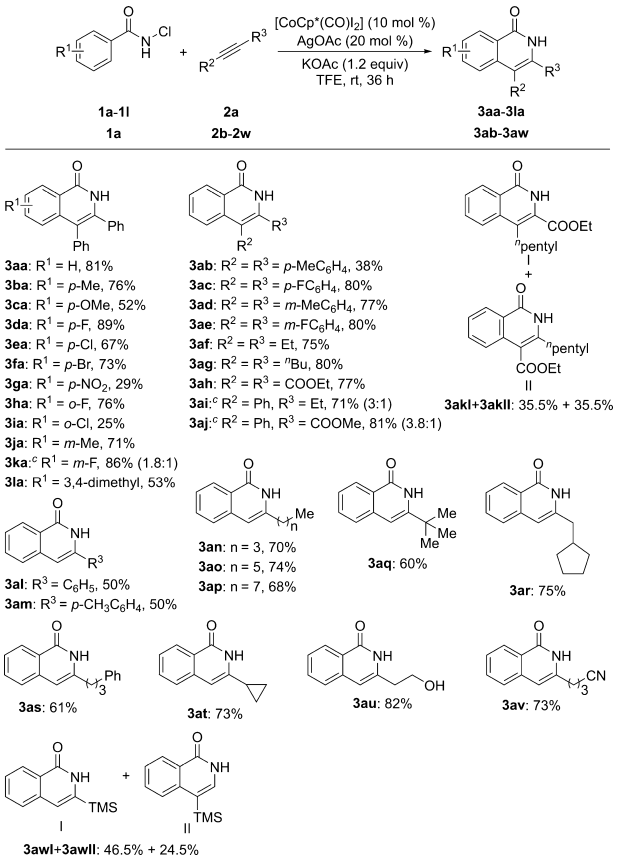
reaction temperature), and limited substrate scope (e.g., incompatibility with terminal alkynes).[13]

We commenced our investigation by identifying feasible synthetic conditions for the coupling between *N*-chloroamides and alkynes under cobalt catalysis. With *N*-chlorobenzamide (**1a**) and diphenylacetylene (**2a**) as the substrates and with $[CoCp^*(CO)I_2]$ (10 mol %) as the catalyst precursor, extensive screening revealed that a combination of AgOAc (20 mol %) and KOAc (1.2 equiv) in trifluoroethanol (TFE) can provide an optimum yield of 81% for 3,4-diphenylisoquinolin-1(2*H*)-one (**3aa**) after 36 h of rt reaction.

With the optimized reaction conditions established, the substrate scope of *N*-chlorobenzamides was first investigated by reaction with **2a** (Scheme 2). *N*-Chlorobenzamides bearing

Scheme 2. Substrate Scope of *N*-Chlorobenzamides and Alkynes[a,b]



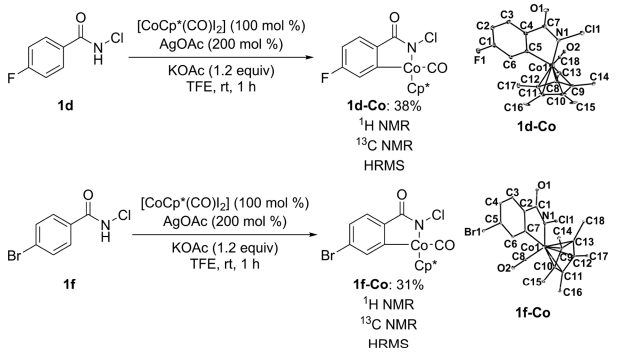
[a]Reaction conditions: **1a**–**l** (0.2 mmol), **2a**–**w** (0.24 mmol), TFE (1.0 mL). [b]Isolated yields are shown. [c]Only the major regioisomer is shown.

both electron-donating (**1b**, **1c**) and electron-withdrawing (**1d**–**g**) groups at the *para* position can react in high yield. *Ortho* substitution is also synthetically compatible (**1h**, **1i**), with a diminished product yield observed for a bulkier substituent. *Meta*-substituted *N*-chlorobenzamides show reactivity similar to that of the *para*-substituted ones, but the reactions can be complicated by varied regioselectivity patterns. The placement of a methyl group at the *meta* position (**1j**) results in exclusive reactivity at the sterically more accessible site, thus allowing the delivery of a single regioisomer as the product. However, the transformation is less selective for a *meta*-fluoro-substituted *N*-chlorobenzamide (**1k**). Disubstitution does not significantly retard the reactivity (**1l**).

The substrate scope for alkynes was then examined by reaction with **1a** (Scheme 2). Significantly, a broad range of substitution patterns can be tolerated for internal and terminal alkynes. Both electron-rich and electron-poor diarylalkynes (**2b**–**e**) are competent for the transformation. Dialkylalkynes (**2f**, **2g**) exhibit essentially identical reactivity as diarylalkynes. An internal alkyne bearing two electron-withdrawing ester groups (**2h**) can also react efficiently. The reactions for aryl/alkyl (**2i**) and aryl/ester (**2j**) unsymmetrical alkynes give a mixture of inseparable regioisomers, whereas the regioisomers derived from the alkyl/ester unsymmetrical alkyne (**2k**) can be individually isolated. The high reactivity imparted by *N*-chlorobenzamide also enables smooth reaction for terminal alkynes. The reactivity for aryl-substituted terminal alkynes (**2l**, **2m**) is slightly lower than that for alkyl- (**2n**–**s**) and cycloalkyl-substituted (**2t**) terminal alkynes. Functional groups can be incorporated, if desired, at the chain end of the alkyl-substituted terminal alkynes (**2u**, **2v**) for further synthetic manipulation. Alternatively, the synthetic compatibility of a silyl-substituted terminal alkyne (**2w**) and generation of two isolable regioisomeric products can provide silyl group as a versatile synthetic handle for diverse transformations.

Mechanistic studies allowed the first-time synthesis of cobaltacycles via C–H activation (Scheme 3). The reaction

Scheme 3. First-Time Synthesis of Cobaltacycles via C–H Activation



of **1d** or **1f** with $[CoCp^*(CO)I_2]$ afforded a C–H-activated five-membered cobaltacycle (**1d-Co** or **1f-Co**;[14] characterized with ^{1}H NMR, ^{13}C NMR, HRMS, and single-crystal X-ray diffraction) (Scheme 3). **1d-Co** not only can react as a stoichiometric reagent with **2a** (96% yield after 12 h) (Scheme 4, eq 1) but also can serve as an effective catalyst for the coupling between **1d** and **2a** (95% yield of **3da**) (Scheme 4, eq 2). The cobalt-catalyzed C–H activation leads to highly efficient *ortho* H/D and D/H scrambling when starting from **1a** and **1a**-d_5, respectively (Scheme 4, eqs 3 and 4). C–H activation is reversible, as evidenced by (1) *ortho* D/H scrambling in **3aa**-d_4 for a reaction between **1a**-d_5 and **2a** (Scheme 4, eq 5), and (2) the ability to convert **1d-Co** back to **1d** under HOAc (Scheme 4, eq 6). The high kinetic isotope effect (KIE) value of 4.0 observed for the reaction between **1a**/**1a**-d_5 and **2a** is consistent with a turnover-limiting C–H activation step (Scheme 4, eq 7). A competition reaction for *N*-chlorobenzamides with different electronic characters (**1b**, **1d**) with **2a** favors electron-poor **1d** (Scheme 4, eq 8), suggesting

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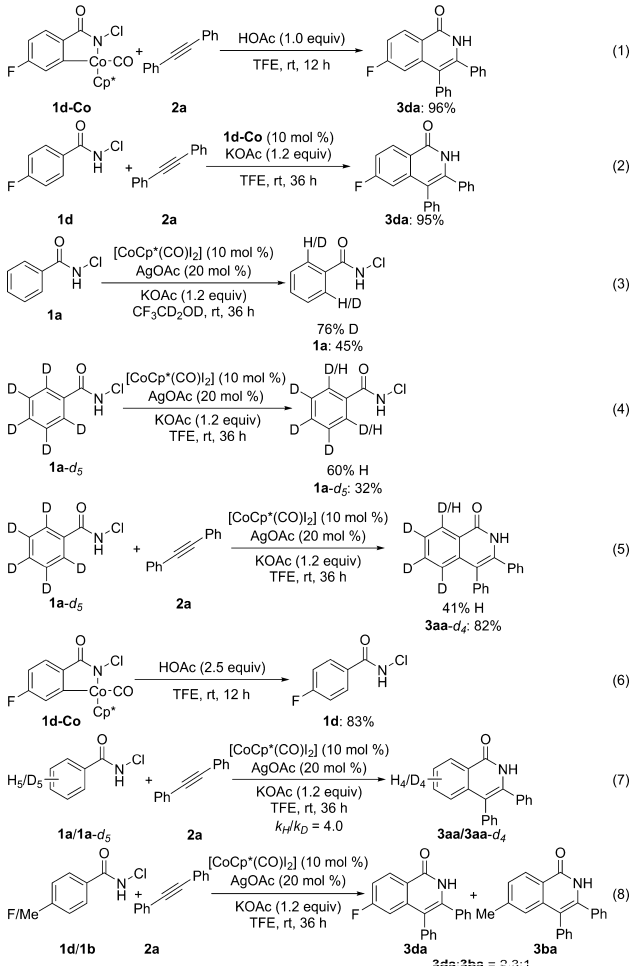
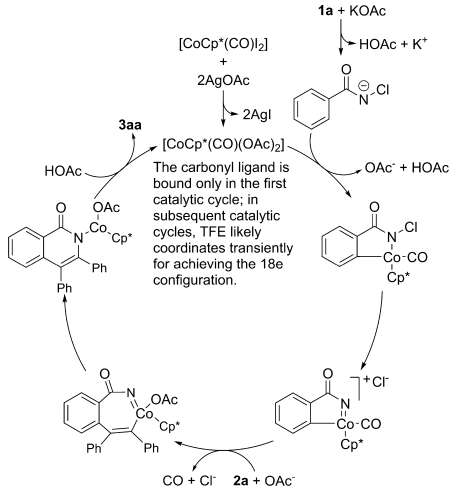
Scheme 4. Mechanistic Studies of Cobalt-Catalyzed Coupling of *N*-Chloroamides with Alkynes



that C−H activation occurs through a concerted metalation−deprotonation mechanism.

Taken together, these results indicate that mechanistically, Co^{III}-enabled turnover-limiting C−H activation occurs first, followed by Co^{III}-to-Co^{V} oxidation (high-valent Rh^{V} has been previously invoked in rhodium-catalyzed C−H functionalization reactions[15]). Subsequent consecutive alkyne migratory insertion and C−N reductive elimination provide the target product and allow the regeneration of Co^{III} (Scheme 5). The proposal of the Co^{III}-to-Co^{V} oxidation pathway is consistent with the high oxidizing reactivity of the N−Cl bond, as demonstrated by the ability to convert **1d-Co** into 4-fluorophthalimide (**1d-1**) (see the Supporting Information). Two bond cleavage sites can be conceived for the initiation of this reaction cascade, i.e., the N−Cl bond and the Co−(CO) bond. The formation of **1d-1** is consistent with the N−Cl bond as the reactivity launching site and the following reaction pathway: Co^{III}-to-Co^{V} oxidation by the N−Cl bond leading to destabilization of the carbonyl ligand (due to less efficient back-bonding to the π-acidic ligand from the electron-poor Co^{V} center), migratory insertion of the carbonyl ligand into the Co−C bond, and C−N reductive elimination. This proposal is further supported by the identification of 4-fluoro-2-iodobenzamide (**1d-2**) as a product when **1d-Co** is reacted with KI (see the Supporting Information). In this case, the carbonyl ligand

Scheme 5. Mechanistic Proposal for Cobalt-Catalyzed Coupling of *N*-Chloroamides with Alkynes



in the destabilized Co^{V} complex is substituted with I^{-}, and C−I reductive elimination proceeds subsequently.

In summary, the direct synthesis of cobaltacycles via C−H activation has been achieved for the first time, providing elusive mechanistic insight into cobalt-catalyzed C−H functionalization reactions. An *N*-chloroamide directing synthon strategy has been developed for cobalt-catalyzed rt construction of heterocycles. Alkynes as coupling partners allow efficient access to isoquinolones. The broad substrate scope offers the ability to incorporate a diverse range of substitution patterns into the heterocycle scaffold. The intriguing versatile reactivity identified herein will inspire the development of more transition-metal-catalyzed, synthetically unique transformations based on highly reactive C−H-activation-directing synthons.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02632.

Experimental procedures and product characterization (PDF)

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

Crystallographic data for **1d-Co** (CIF)

Crystallographic data for **1f-Co** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) CCDC 1555149 (**1d-Co**) and CCDC 1562390 (**1f-Co**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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