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# Redox-Neutral Couplings between Amides and Alkynes via Cobalt(III)-Catalyzed C−H Activation

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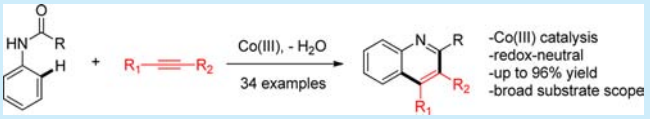
Supporting Information

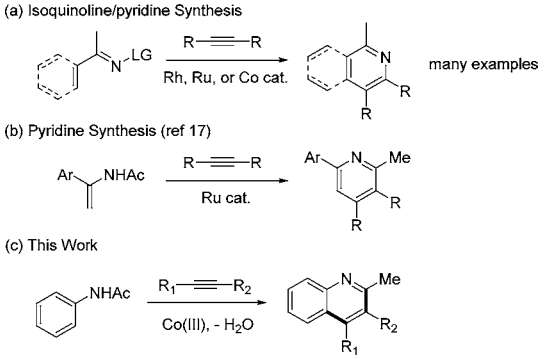
**ABSTRACT:** C−H activation assisted by a bifunctional directing group has allowed the construction of heterocycles. This is ideally catalyzed by earth-abundant and eco-friendly transition metals. We report Co(III)-catalyzed redox-neutral coupling between arenes and alkynes using an NH amide as an electrophilic directing group. The redox-neutral C−H activation/coupling afforded quinolines with water as the sole byproduct.




The past decades have witnessed significant progress in metal-catalyzed C−H bond activation as an advantageous strategy in the construction of complex molecules.[1] The ubiquity of C−H bonds and highly atom- and step-economic transformations in C−H activation have attracted increasing attention in utilizing arenes as direct substrates. The activation of unreactive arene C−H bonds typically requires the assistance of a proximal directing group.[1,2] However, in most cases, the directing group (DG) only exhibited a ligating effect or acted as a simple nucleophile in postcoupling transformations. Thus, the DG was carried over to the final product with limited functional diversity. To overcome this limitation, functionalizable DGs with nucleophlicity, electrophilicity, and redox property have been designed.[3] Electrophilic DGs are bifunctional in that they consist of a nucleophilic coordinating site and an electrophilic center. This discrepancy has been reconciled in recent work by Cheng,[4] Glorius,[5] Shi,[6] and others[7] in Rh(III)-catalyzed C−H activation. However, reports in this regard remain limited, particularly in the context of heterocycle synthesis.[8]

Recently, cost-effective Cp*Co(III) complexes have been increasingly employed as highly efficient catalysts for the C−H activation of arenes, as in the reports by Kanai,[9] Glorius,[10] Ackermann,[11] Ellman,[12] Daugulis,[13] Chang,[14] and others,[15] where the DGs are single-functional and Co(III)-catalyzed annulation reactions are rare.[9e,11c,15c] We reasoned that bifunctional DGs with low electrophilicity can be viable in facilitating cyclization reactions when the electrophilicity is enhanced by Lewis acidic metals. With Lewis acidity higher than that of their Rh(III) and Ir(III) congeners, Cp*Co(III) catalysts are expected to meet the criteria by activating both C−H bonds and the bifunctional DG. Amides are readily available DGs, and the bifunctionality of amides has been established in C−H activation systems, leading to annulation.[6,9b,16,17] In particular, Wang, Yu, and co-workers recently reported the synthesis of pyridines via [4 + 2] annulation between enamides and alkynes (Scheme 1).[17] On the other hand, while access to isoquinolines has been extensively explored in Rh- and Ru-catalyzed C−H activation,[18] examples of quinoline synthesis via a C−H activation pathway are very limited,[19] especially under redox-neutral conditions. We now report Co(III)-catalyzed, redox-neutral couplings between amides and alkynes, leading to efficient synthesis of quinolines.

**Scheme 1. C−H Activation for the Synthesis of Heterocycles**




We initiated our studies with the development of a synthetic method to access quinolines. Traditional quinoline syntheses such as the Doebner−Von Miller, Skraup, Combes, Knorr, and Friedlander methods typically suffered from harsh conditions, necessity of using toxic and corrosive reagents, and a limited substrate scope.[20] We began our quinoline synthesis using acetanilide (**1a**) and diphenylacetylene (**2a**) as model substrates (Table 1). When the reaction was conducted in DCE using $[Cp^*CoCl_2]_2/AgSbF_6$ (4 mol %/20 mol %) as the catalyst at 130 °C, the desired quinoline **3aa** was isolated in only 35% yield as a result of dehydrative annulation (entry 1). The silver additive had a significant impact on the reaction efficiency. Switching the additive to $AgNTf_2$ improved the yield to 43% (entry 2), but essentially no product was detected when other additives such as AgOAc, AgOTf, and AgOPiv were used (entries 4−6). Solvent screening revealed that DCE was the most efficient medium (entries 7 and 8). The amount of the silver additive had a significant effect on the reaction efficiency. While moderate yield was observed using 0.5 equiv of $AgNTf_2$, the yield was

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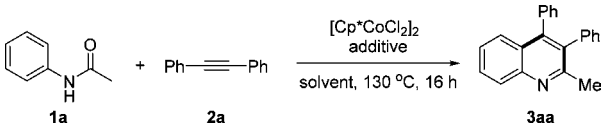
**Table 1. Screening of Reaction Conditions**[a]



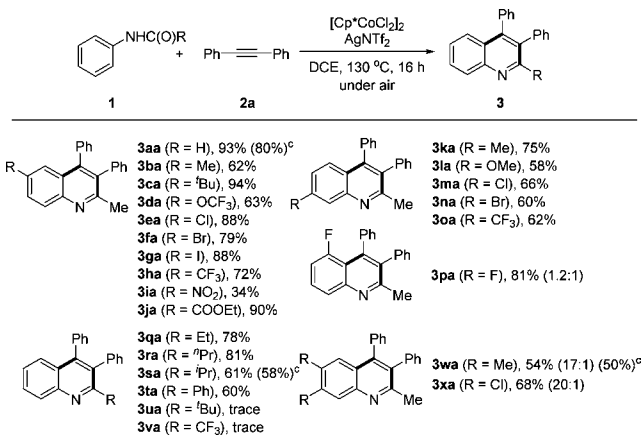

| entry | cat. (mol %) | additive (mol %) | solvent | yield[b] (%) |
|---|---|---|---|---|
| 1 | $[Cp^*CoCl_2]_2$ (4) | $AgNTf_2$ (20) | DCE | <5 |
| 2 | $[Cp^*CoCl_2]_2$ (4) | $AgSbF_6$ (20) | DCE | 35 |
| 3 | $[Cp^*CoCl_2]_2$ (4) | $AgNTf_2$ (20) | DCE | 43 |
| 4 | $[Cp^*CoCl_2]_2$ (4) | AgOAc (20) | DCE | <5 |
| 5 | $[Cp^*CoCl_2]_2$ (4) | AgOTf (20) | DCE | <5 |
| 6 | $[Cp^*CoCl_2]_2$ (4) | AgOPiv (20) | DCE | <5 |
| 7 | $[Cp^*CoCl_2]_2$ (4) | $AgNTf_2$ (20) | dioxane | <5 |
| 8 | $[Cp^*CoCl_2]_2$ (4) | $AgNTf_2$ (20) | PhCl | <5 |
| 9 | $[Cp^*CoCl_2]_2$ (4) | $AgNTf_2$ (50) | DCE | 51 |
| 10 | $[Cp^*CoCl_2]_2$ (4) | $AgNTf_2$ (100) | DCE | 80 |
| 11 | $[Cp^*CoCl_2]_2$ (6) | $AgNTf_2$ (100) | DCE | 93 |
| 12 | $[Cp^*CoCl_2]_2$ (8) | $AgNTf_2$ (100) | DCE | 90 |

[a]Reaction conditions: acetanilide **1a** (0.2 mmol), **2a** (0.24 mmol), solvent (4 mL), 130 °C, 16 h, sealed tube under air. [b]Isolated yield after chromatography.

dramatically improved when 6 mol % of $[Cp^*CoCl_2]_2$ and $AgNTf_2$ (1 equiv) was used (entry 11), where a stoichiometric amount of $AgNTf_2$ likely serves as both a halide scavenger (catalyst activation) and a Lewis acid (activation of the carbonyl group). Notably, no extrusion of air was necessary. Furthermore, when the scale of the reaction was enlarged to 1 mmol with a reduced catalyst loading (3 mol %), product **3aa** was isolated in moderate yield (60%). In comparison, essentially no desired reaction was observed when the Ru-catalyzed conditions that proved optimal for the coupling between enamides and alkynes were employed.[17]

With the establishment of the optimized conditions, the scope and generality of the reactions were next evaluated (Scheme 2). It was found that a range of acetanilide bearing various electron-donating, -withdrawing, and halogen substituents at the *para* positions all coupled smoothly with **2a**, and the quinoline products were isolated in 34−94% yields. A *para*-nitro group,

**Scheme 2. Scope of Amide Substrates**[a,b]

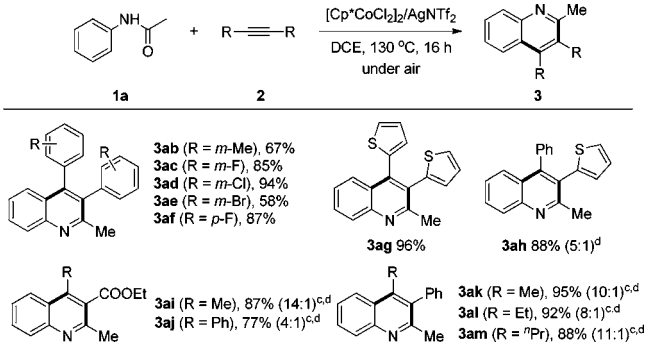



[a]Reaction conditions: amide (0.2 mmol), alkyne (0.24 mmol), $[Cp^*CoCl_2]_2$ (6 mol %), $AgNTf_2$ (1.0 equiv), DCE (4.0 mL), 130 °C, 16 h, sealed tube under air. [b]Isolated yield. [c]With 4 mol % of catalyst.

which is often problematic in C−H activation systems, is also compatible, albeit with lower yield (**3ia**). Various *meta* substituents such as methyl (**3ka**), methoxy (**3la**), chloro (**3ma**), bromo (**3na**), and $CF_3$ (**3oa**) groups were fully tolerated, and in these cases, C−H activation occurred at the less-hindered position. In contrast to the high selectivity, the coupling of *N*-(3-fluorophenyl)acetamide afforded a mixture of regioisomeric products (**3pa** and **3pa′**) in 1.2:1 ratio and in 81% total yield as a result of the reduced steric bulk of the fluoro group. The C−H activation reaction is not limited to a monosubstituted arene, and 2,3-disubstituted acetanilides also reacted under optimized conditions to afford the desired products (**3wa** and **3xa**) in good yields and high regioselectivity (>17:1). Meanwhile, amides bearing other acyl groups (**3qa**, **3ra**, **3sa**, and **3ta**) also coupled efficiently to provide the quinolines in 60−81% yields. In contrast, pivaloyl (**3ua**) and trifluoroacetyl (**3va**) amides failed to undergo any coupling, indicating that the electronic and steric effects of the acyl group played an important role.

We next investigated the scope of the alkyne in the coupling with **1a** (Scheme 3). Symmetrically substituted diarylacetylenes

**Scheme 3. Scope of Alkyne Substrates**[a,b]




[a]Reaction conditions: acetanilide (0.2 mmol), alkynes (0.24 mmol), $[Cp^*CoCl_2]_2$ (6 mol %), $AgNTf_2$ (1 equiv), DCE (4 mL), 130 °C, 16 h, sealed tube under air. [b]Isolated yield. [c]Alkyne (0.3 mmol) was used. [d]Only the major isomer was shown.

bearing halogen or methyl groups at the *para* and *meta* positions gave the desired products **3ab**−**3af** in 58−94% yield. The alkynes can also be extended to heteroaryl substitution with di(2-thienyl)acetylene with excellent yield (**3ag**, 96%). In addition, unsymmetrical alkynes displayed good to high reactivity and moderate to high regioselectivity. Of note, couplings for alkyl- and aryl-disubstituted alkynes gave excellent yields (**3ak**−**3am**, 88−95%) and high regioselectivities (8−11:1), while other unsymmetrical alkynes offered high reactivity but lower regioselectivity.

To demonstrate the synthetic utility, a derivatization reaction was carried out for a quinoline product. Treatment of quinoline **3aa** with *m*-CPBA led to the quantitative formation of the corresponding quinoline *N*-oxide. A functionalized acetophenone (**4**) was isolated in high yield via a Rh(III)-catalyzed C−H activation with subsequent O-atom transfer (Scheme 4).[21]

To shed light on the mechanism, the kinetic isotope effect was studied by two side-by-side reactions using **1a** and **1a**-$d_5$ under the standard conditions, from which a $k_H/k_D$ value of 3.4 was obtained on the basis of $^1$H NMR analysis (Scheme 5). In addition, the competitive coupling of an equimolar mixture of **1a** and **1a**-$d_5$ with diphenylacetylene gave a consistent value of $k_H/k_D$ = 5.3. These results indicated that C−H activation is likely



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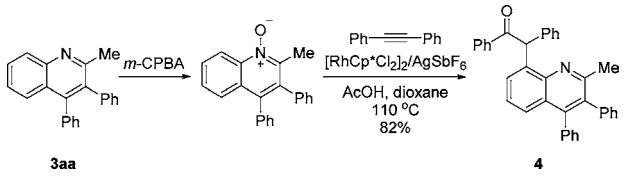
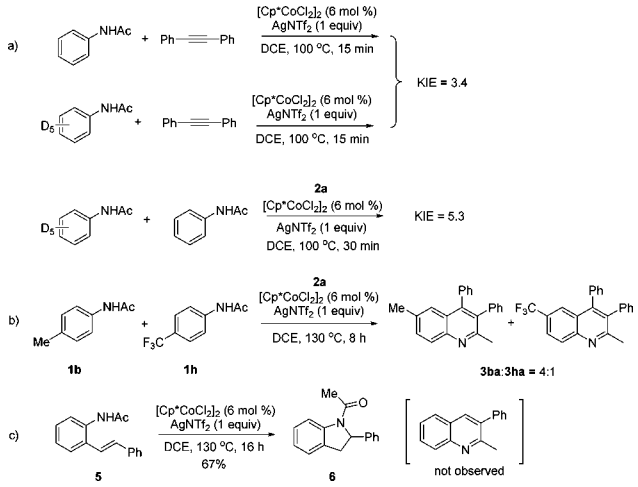
**Scheme 4. Transformations of a Coupled Product**



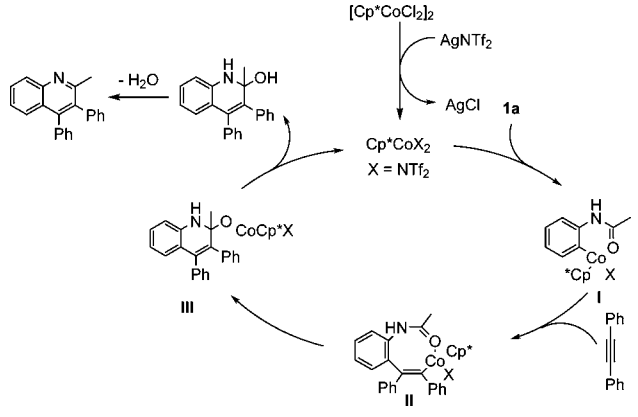

**Scheme 5. Mechanistic Studies**




involved in the turnover-limiting step. To further investigate the electronic preference of the reaction, competitive coupling of **1b** and **1h** differing in electronic effects was performed, and the coupling was favored for the more electron-rich substrate (**1b**). Furthermore, to probe if the annulation proceeded with the intermediacy of an olefin, styrene **5** was prepared and subjected to the standard reaction conditions. No desired product was observed; instead, an indoline was generated in good yield (Scheme 5). This indicates that the reaction did not proceed via initial full hydroarylation and subsequent cyclization.

On the basis of our mechanistic experiments and previous reports,[14a] a plausible catalytic cycle is depicted in Scheme 6. The active cationic Co(III) catalyst is generated upon treatment of $[Cp^*CoCl_2]_2$ with $AgNTf_2$. Cobalt-mediated C−H bond activation of acetanilide affords a six-membered metallacyclic intermediate **I**.[14a] Alkyne coordination and migratory insertion of the aryl group generates a Co(III) alkenyl species **II**. The Co−C bond of **II** undergoes migratory insertion into the carbonyl group, forming a Co(III) alkoxide species **III**. This migratory insertion is favored by the enhanced electrophilicity of the amide carbonyl assisted by the stoichiometric amount of $AgNTf_2$. Protonolysis of the Co−O bond produces a tertiary alcohol and regenerates the active catalyst, and the final product was released upon dehydration of the tertiary alcohol.

**Scheme 6. Proposed Mechanism**




In conclusion, we have developed Cp*Co(III)-catalyzed redox-neutral annulative couplings for the synthesis of quinolines between amides and alkynes via a C−H activation pathway. The reactions proceeded with high functional compatibility. Amides bearing various functional groups are viable substrates, and a wide range of aryl-, hetero-, and ester-substituted alkynes have been established as efficient coupling partners in the reactions. The coupling system represents a rare synthesis of quinolines via a C−H activation process. This efficient and concise protocol to access important quinoline scaffolds may find applications in the synthesis of complex products.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03629.

General experimental procedures, characterization details, and $^1H$ and $^{13}C$ NMR spectra of new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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