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Chemical Communications
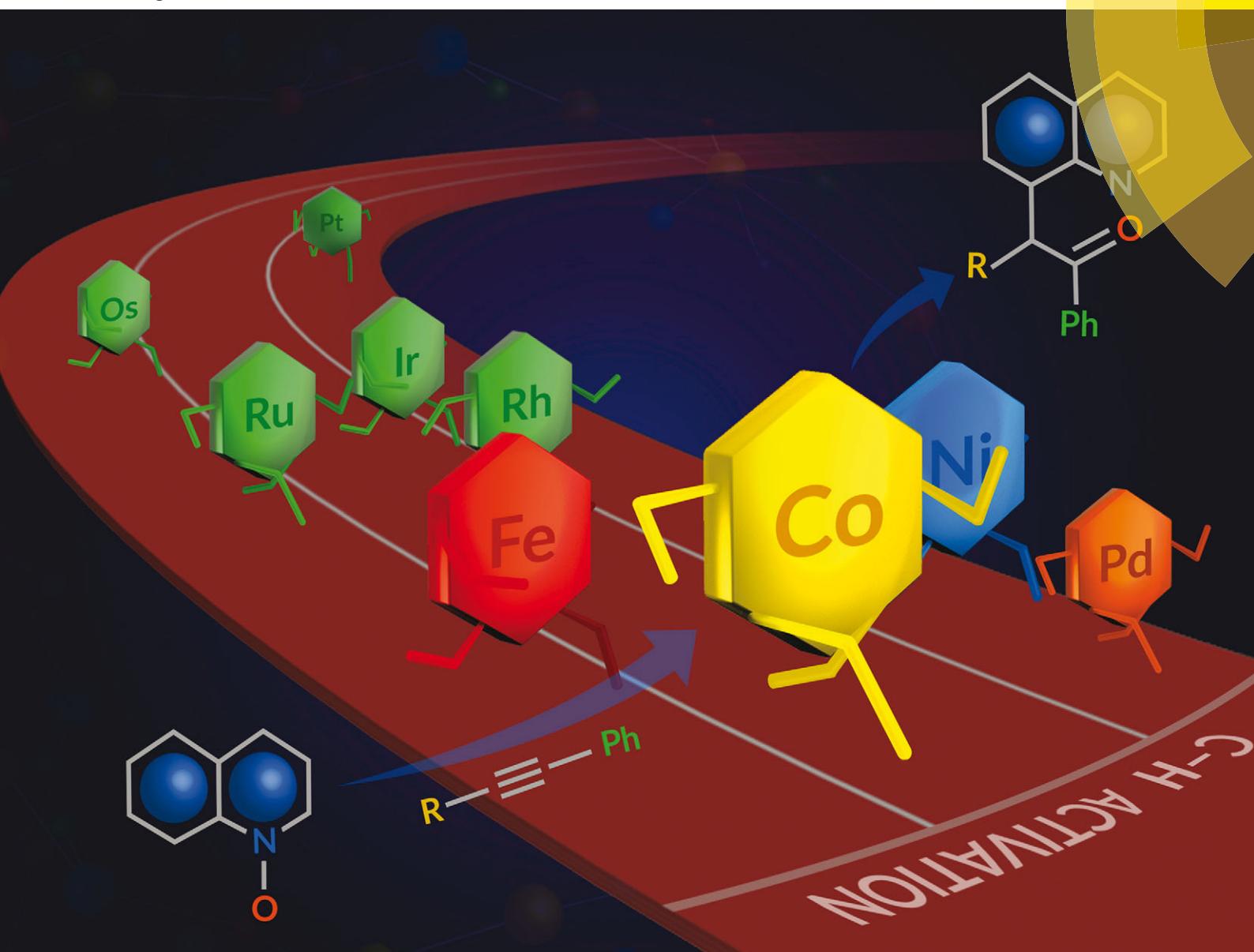
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**COMMUNICATION**
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Cobalt(III) catalyzed C-8 selective C–H and C–O coupling of quinoline
*N*-oxide with internal alkynes *via* C–H activation and oxygen atom transfer

175 YEARS

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## Cobalt(III) catalyzed C-8 selective C−H and C−O coupling of quinoline *N*-oxide with internal alkynes *via* C−H activation and oxygen atom transfer†

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**An efficient, scalable, atom-economical, regio-selective air stable Cp\*Co(III) catalyzed C−H and C−O coupling *via* a C−H activation/ oxygen atom transfer reaction of quinoline *N*-oxide and an internal alkyne is reported. Such a catalytic transformation is witnessed for the first time with a cobalt catalyst and using *N*-oxide as a traceless directing group, in contrast to the existing literature. The developed synthetic methodology is straightforward and possesses various functional group tolerances, including heterocycles.**

Quinolines are versatile heterocycles that are widely used as 'parental' compounds to integrate molecules with medicinal benefits, natural products and agrochemicals with applications in materials chemistry.[1–3] Site selective functionalizations of quinoline at various positions are important, but the majority of the literature deals with C–2(H) bond functionalization.[4] The elegant work by Chang[5] and Sawamura[6] showed that the nitrogen in quinoline can be used as a directing group for C-8 selective functionalization. Chang and others further developed a system based on quinoline-*N*-oxide for C-8 selective functionalization, where oxygen is used as a traceless directing group for various C–C and C–X bond formations using group VII noble metal catalysts such as Rh(III) and Ir(III).[7] Since the first report by Fagnou[8k] and later development by others, of the utilization of N–O/N–N as a directing group as well as an internal oxidant for C–H bond functionalization, examples have been reported based on this redox-neutral concept as it does not require any external oxidant and produces only environmentally friendly side products (ROH, H₂O, *etc.*).[8] Very recently, Li[9] and Chang[10] have independently developed a Rh(III) catalytic system to advance this redox-neutral process for C-8 selective functionalization of quinoline *via* sequential C–H activation/oxygen atom transfer

(OAT) with internal alkynes. Though many new catalytic C–H bond functionalizations have been exemplified in the last decade using relatively expensive noble metal catalysts,[11] the challenge still remains to effect the same or new transformations by utilizing relatively cheap, abundant first row transition metal catalysts.[12] The continuing theme of our research efforts to develop C–H bond functionalizations using first row transition metal catalysts[13] has led us to investigate the novel reaction of the C(8)–H bond functionalization of quinoline. Herein, we report the Cp\*Co(III)[14] catalyzed C(8)–H bond functionalization of quinoline with internal alkynes, in the absence of additives and using quinoline-*N*-oxide as a traceless directing group.[15] This elegant methodology has many advantages; as it does not require any directing groups, external oxidants or deprotection of *N*-oxide, it provides 100% atom efficiency (Scheme 1). We have also shown that the Co(III) catalyst efficiency and reactivity for the C(8)–H bond functionalization of quinoline are better than those for Ir(III) and Rh(III) catalysts.[9,10]

A summary of the results for the optimization is presented in Table S1 (ESI†).[16] We began our investigation using quinoline-*N*-oxide **1a**, as a model substrate, and diphenylacetylene **2a** in the presence of Cp\*Co(CO)I₂ (10 mol%) and NaOAc (20 mol%) in dioxane at 80 °C for 24 h; this did not give the expected product **3a**. A solvent dependency study for the same reaction was carried out (Table S1, entries 2–8, ESI†) and we found that the reaction proceeded more efficiently in TFE (trifluoroethanol) compared to other solvents, with an isolated yield for **3a** of 80% (Table S1, entry 2, ESI†). An improved yield for **3a** was obtained when we employed NaOPiv (Table S1, entry 14, ESI†) compared to other

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Scheme 1  Co(III) catalyzed C−H activation/oxygen atom transfer process.

carboxylates (Table S1, entries 9–14, ESI†). There was no significant improvement in the formation of **3a** from changing other reaction parameters such as temperature, catalyst loading or ionization with silver salt (Table S1, entries 15–17, ESI†). Further, control experiments revealed that both the [Co] catalyst and NaOPiv are mandatory for a smooth reaction with a high yield of **3a** (Table S1, entries 18 and 19, ESI†). The reactions were ineffective when they were performed at 50 °C or ambient temperature (Table S1, entries 20–22, ESI†). The transformation of **1a** with alkyne **2a** does not proceed forward when using other cobalt sources of Co(III) or Co(II) such as Co(acac)₃ or CoCl₂ (Table S1, entries 23 and 24, ESI†). Replacing the Co(III) catalyst (in our optimized conditions) with Rh(III)/Ir(III)/Ru(II) resulted in a poor yield or no reaction occurring (Table S1, entries 26 and 27, ESI†). However, a reported catalytic system based on Rh(III) gave a good yield under different conditions;[9,10] but the reaction was inefficient when aliphatic alkynes were employed as the substrate under the reported Rh(III) catalytic conditions.

Our further screening revealed that a high yield of **3a** was obtained when the alkyne **2a** was used as the limiting factor (Table S1, entries 28 and 29, ESI†).

With the best optimized conditions in hand, we further extended the scope of the reaction by exercising various substituted quinoline-N-oxides with **2a** to access diverse functionalized quinoline derivatives (Table 1). For example, substituent groups such as bromo, aryl, heteroaryl, alkenyl, alkynyl or unsaturated esters on the C(3)-position of the heteroarene are amenable and produce a good yield (**3b–i**). Compound **3c** was further confirmed using X-ray crystallography.[17] Sensitive functional groups, such as ketones and nitro groups, remain intact even after the C–H activation and OAT process (**3j–k**). Mono- and disubstituted quinoline-N-oxides, at various positions, gave good yields (**3l–q**). Substituents at the C-7 position suffer from only respectable yields, which is likely due to steric and electronic reasons (**3r**). The reaction is not limited only to quinoline and can be extended to other heterocycles, in good yields (**3s–t**).

A gram-scale reaction was performed with the objective of evaluating the feasibility of this catalytic process for **1a** (1.068 g, 6 mmol) and **2a** (0.957 g, 6.5 mmol) using 5 mol% of [Cp*Co(CO)I₂] and 15 mol% of NaOPiv in trifluoroethanol at 100 °C for 36 h, which produced **3a** in 94% (1.839 g) yield (Scheme S1, ESI†). To further demonstrate the generality and practicality of this sequential C–H activation/OAT reaction, we examined an array of alkynes **2** (Table 2). A wide range of symmetrical alkynes could readily undergo the reaction with quinoline-N-oxide **1a** with a good to high reactivity and selectivity (**4a–d**). When a symmetrical aliphatic alkyne such as 4-octyne was employed under the optimized reaction conditions, the reaction gave a 70% yield of **4e** with Co(III), whereas the Ir(III) catalyst failed to promote such a reaction and Rh(III) gave a 15% yield under our optimized conditions. On the other hand, the reported Rh(III) catalytic system did not provide any product formation with 4-octyne (**4e**, Table 2). Thus, this emphasizes the unique reactivity of Co(III) over the other group 9 metals and its importance and applicability with a wide variety of internal alkynes. This change in the order of reactivity of Co(III) vs. Rh(III)

**Table 1** Scope of quinoline-N-oxide **1**[a]
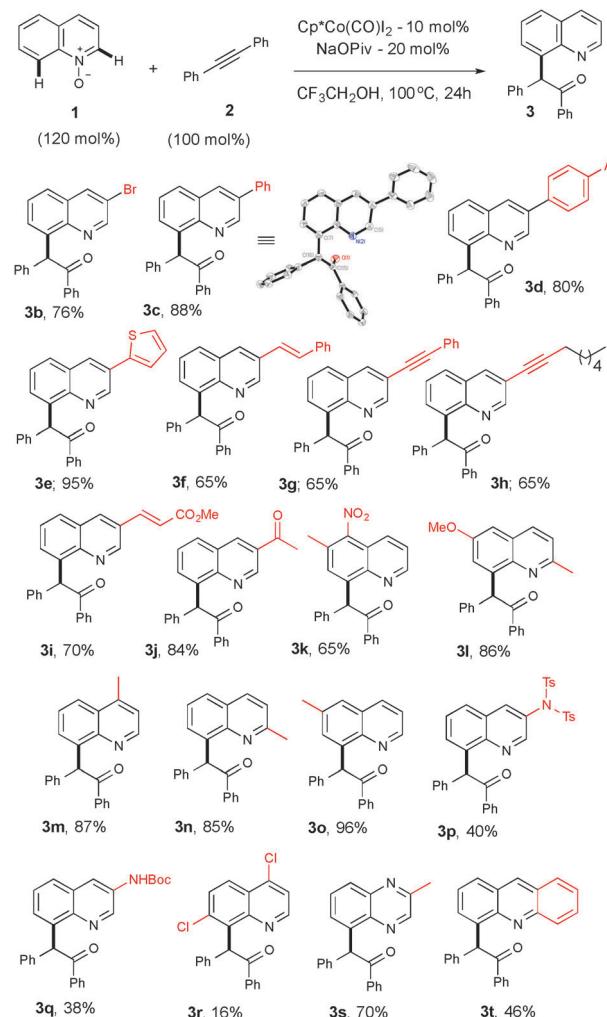


[a] Reaction conditions: all reactions were performed under an Ar atm using **1** (0.36 mmol), **2a** (0.3 mmol), [Cp*Co(CO)I₂] (0.03 mmol) and NaOPiv (0.06 mmol) in CF₃CH₂OH (1 mL) at 100 °C (oil bath temperature) for 24 h.

for 4-octyne can be explained through charge transfer stabilization energy (Table S3, ESI†).[16]

To further evaluate the regioselectivity, a number of unsymmetrical internal alkynes were investigated from the arsenal (Table 2, **4f–o**). To our delight, all of the unsymmetrical internal alkynes reacted with **1a** smoothly to provide a single regioisomer with excellent control over regioselectivity in good yield (**4f–m**). Electronically biased unsymmetrical biarylacetylene gave a mixture of regioselective products, including heteroarylacetylene, in good yields (**4n–o**). Further, biarylacetophenone **3a** was put forth for cascade C–H bond functionalization using the reported procedure[18] and gave a tetracyclic compound as a single diastereomer in moderate yield (Scheme S2, ESI†). To understand the high reactivity and selectivity of the C–H activation/OAT process, we conducted a series of preliminary experiments in order to understand the mechanism. Deuterium-labelled experiments were carried out under the optimized reaction conditions to examine the

**Table 2** Scope of alkynes **2**[a]





**Scheme 2** Proposed mechanism.
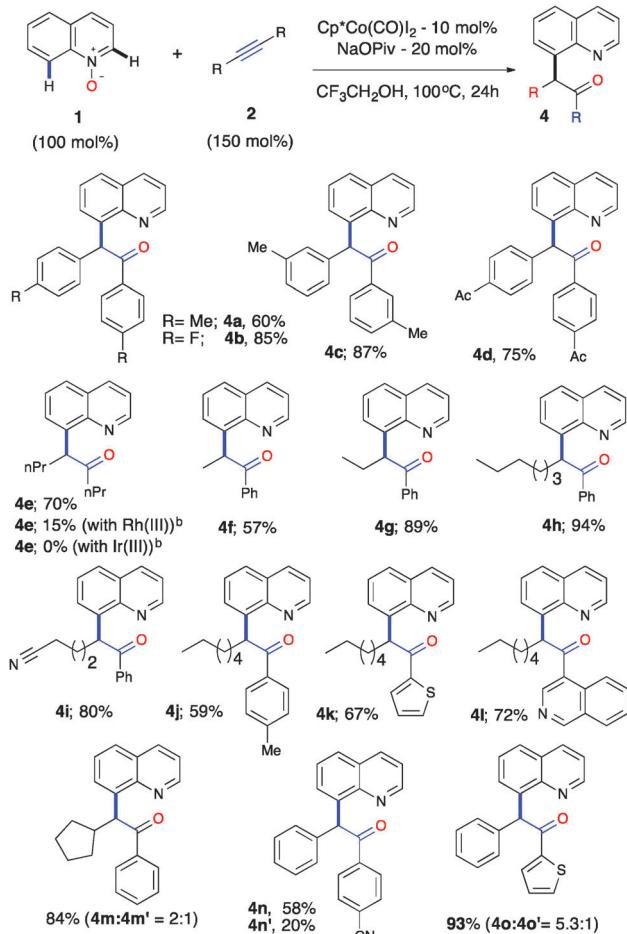
[a] Reaction conditions: all reactions were performed under an Ar atm using **1** (0.3 mmol), **2a** (0.45 mmol), [Cp*Co(CO)I₂] (0.03 mmol) and NaOPiv (0.06 mmol) in CF₃CH₂OH (1 mL) at 100 °C (oil bath temperature) for 24 h. [b] No reaction was obtained with the reported Rh(III) catalytic system as in ref. 9 and 10.

incorporation of deuterium on the C(8)–H position of quinoline N-oxide (Scheme S3a–c, ESI†). It was revealed that no deuterium was detected on the C(8) position, with or without **2a**, in the presence of Co(III), this suggests that the C–H bond cleavage could be irreversible in nature. To confirm this further, competitive experiments were conducted with electronically variant alkynes and quinoline N-oxides, which resulted in no selectivity (Scheme S3d and e, ESI†). C(8)-alkenylquinoline-N-oxide **5** was exposed to our reaction conditions which resulted in no formation of the oxygen transfer product, suggesting that the C–H activation and OAT are cascade processes in nature, ruling out the possibility of a C(8)-alkenyl intermediate (Scheme S3f, ESI†).

Based on our preliminary studies and the relevant reports on Rh(III),[19] a plausible mechanism has been drawn (Scheme 2). Cationic complex **I** undergoes an irreversible cyclometallation followed by alkyne coordination and migratory insertion between the Co and C atoms, leading to the alkenyl cobaltacyclic intermediate **V**. It further undergoes reductive elimination to the Co(I) intermediate **VI**, which will further proceed via oxidative addition
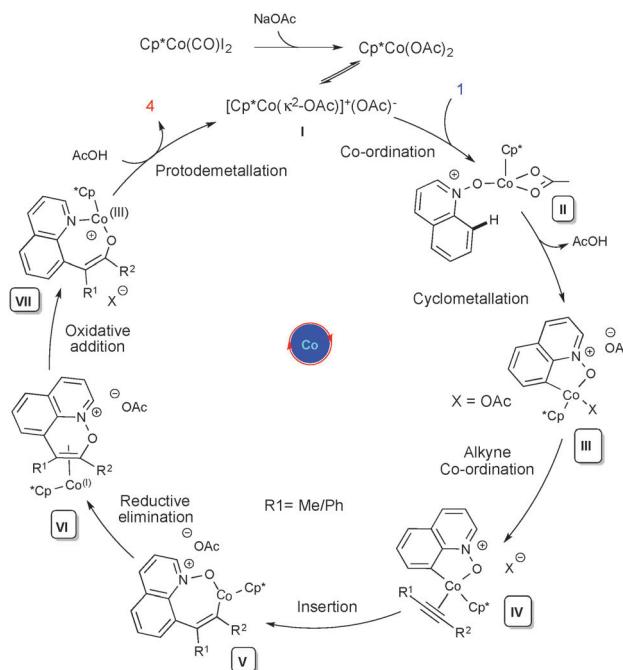
between the N and O atoms, leading to intermediate **VII**. This then undergoes protodemetallation leading to C-8 functionalized quinoline **3**/**4** and the regeneration of the active catalyst. The proposed mechanism is further supported by DFT calculations performed using the Gaussian 09 program and the DFT method B3LYP.[16]

In conclusion, we have developed a cobalt catalyzed C–H and C–O coupling of quinoline-N-oxide with internal alkynes via a C–H activation/OAT process, which is reported for the first time. We have shown that various substituted quinoline-N-oxide structures can be coupled with symmetrical (diaryl-, dialkylacetylene) and unsymmetrical internal alkynes (alkylarylacetylene) with excellent control over the regioselectivity. DFT calculations showed that regioselective product formation could be achieved with unsymmetrical alkynes due to better conjugation with the alkenyl intermediate and the phenyl group.[16] Preliminary studies have revealed that the reaction likely undergoes irreversible cyclometallation. We have also shown that the Co(III) catalyst displayed a better reactivity with aliphatic alkynes compared to its congeners from group 9, metals such as Rh(III) and Ir(III).

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