C–H Activation

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Rhodium(III)-Catalyzed C–C and C–O Coupling of Quinoline *N*-Oxides with Alkynes: Combination of C–H Activation with O-Atom Transfer**

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Abstract: *[Cp*Rh^{III}]-catalyzed C–H activation of arenes assisted by an oxidizing N–O or N–N directing group has allowed the construction of a number of hetercycles. In contrast, a polar N–O bond is well-known to undergo O-atom transfer (OAT) to alkynes. Despite the liability of N–O bonds in both C–H activation and OAT, these two important areas evolved separately. In this report, [Cp*Rh^{III}] catalysts integrate both areas in an efficient redox-neutral coupling of quinoline N-oxides with alkynes to afford α-(8-quinolyl)acetophenones. In this process the N–O bond acts as both a directing group for C–H activation and as an O-atom donor.*

Metal-catalyzed activation of C–H bonds has been widely recognized as a step-economic and waste-reducing strategy in the formation of C–C, C–O, and C–N bonds, and a tremendously large number of synthetic methods have been established.[1] Among the transition metals, rhodium(III) catalysts play a particularly prominent role. Initially developed in 2007 under oxidative conditions,[2] C–H activation catalyzed by stable [Cp*Rh^{III}] complexes has recently garnered increasing attention.[3,4] Although a number of synthetic methods have been developed based on rhodium(III)-catalyzed oxidative C–H activation,[3c,d,5] it would be ideal to adopt a redox-economic process. To reach this goal, Fagnou and co-workers pioneered the design of a built-in oxidizing N–O directing group (DG) in redox-neutral coupling of *N*-methoxybenzamides with alkynes.[6] This strategy was broadly extended using other N–O and N–N DGs,[7] and to other metal catalysts (Scheme 1b).[8] In fact, earlier examples of redox-neutral C–H activation by N–O cleavage has been reported by palladium catalysis.[9] Despite the progress, in almost all such intermolecular coupling systems only one heteroatom was incorporated into the product as a result of N–O or N–N cleavage,[7–9] with the liberation of a small molecule (water, alcohol, carboxylic acid, and amide).

In contrast, the N–O bond in pyridine/quinoline/tertiary amine *N*-oxides can readily undergo O-atom transfer (OAT) to alkynes to afford an α-oxo carbenoid when catalyzed by gold,[10] iridium(III), and ruthenium(II) complexes[11] (Scheme 1a). Thus this strategy has allowed facile construction of various C–C, C–O, and C–N bonds. Although polar N–O bonds can participate in both C–H activation and OAT, these two areas were developed separately and there has been no report which integrates C–H activation with OAT. We noted that C–H activation of quinoline *N*-oxides has been reported mostly at the more acidic 2-position,[9a,12] and in rare cases at the 8-position.[13] We think that quinoline *N*-oxide may make a good substrate for this purpose when coupled with an alkyne. As a proof of concept, we now report the C–C and C–O coupling of quinoline *N*-oxides with alkynes by C–H activation and subsequent OAT with 100% atom economy (Scheme 1c).

We initiated our studies with the screening of the reaction conditions in the coupling of quinoline *N*-oxide (**1a**) with diphenylacetylene (**2a**; Table 1). No reaction took place when [{RhCp*Cl$_2$}$_2$] (5 mol%) was employed as the sole catalyst in DCE (entry 1). Introduction of $AgSbF_6$ initiated a coupling, from which the product **3aa** was isolated in 32% yield (entry 2) and was fully characterized as an α,α-diarylacetophenone. The yield of the isolated product was significantly enhanced when $Zn(OTf)_2$ was introduced as an additive (entry 4). The reaction experienced significant solvent effects and a dramatic enhancement of the efficiency was achieved when 1,4-dioxane was used, and **3aa** was isolated in high yield (entries 7 and 9). Lowering the catalyst loading to 4 mol% had no negative effect (entry 10). However, either omission of the acid additive or further lowering of the catalyst loading gave slightly lower yields (entries 11 and 12). In contrast, no desired product was detected when the iridium congener was employed as a catalyst, and is indicative of the specific role of rhodium.

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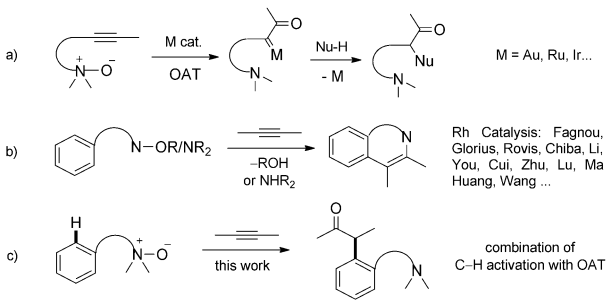
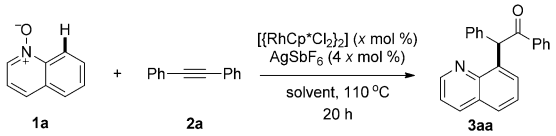


Scheme 1. Combination of C–H activation with OAT.

Table 1: Optimization studies.[a]



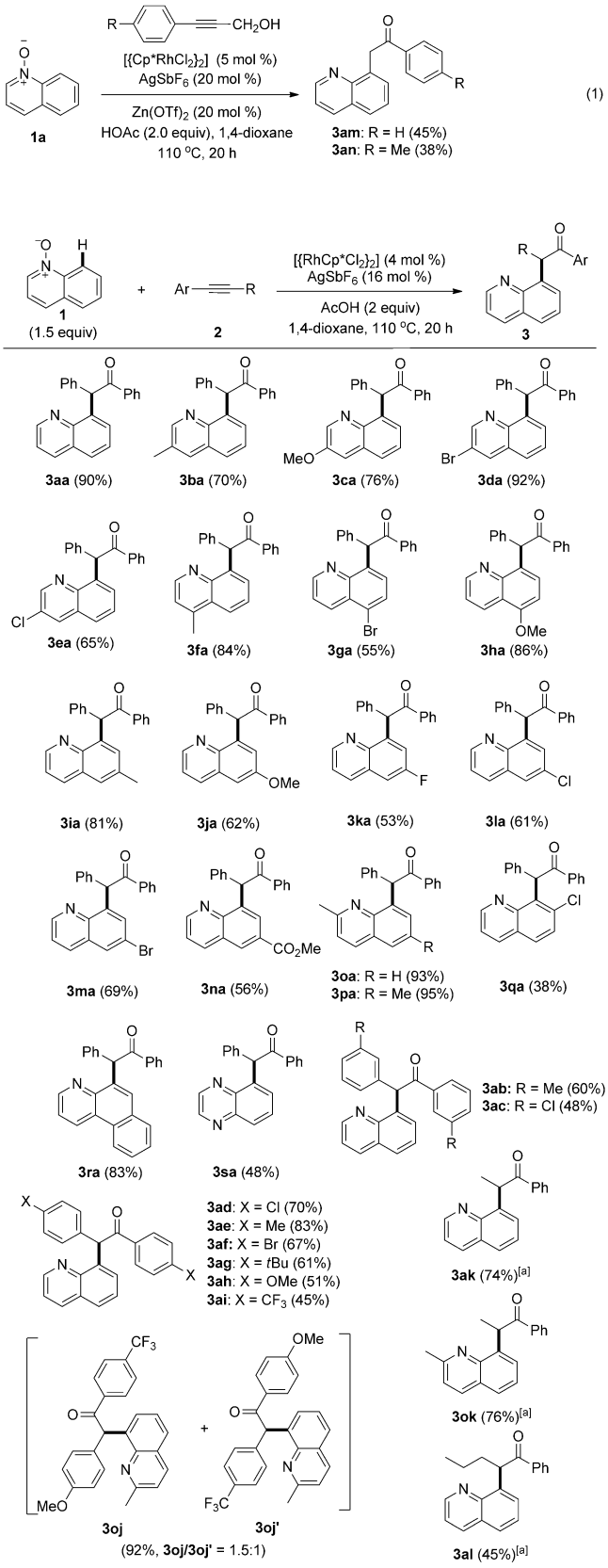
Entry	x	Additive [equiv]	Solvent	Yield [%][b]
1[c]	5	AcOH (2)	DCE	n.d.
2	5	AcOH (2)	DCE	32
3	5	PivOH (2)	DCE	38
4	5	PivOH (2) $Zn(OTf)_2$ (0.2)	DCE	81
5	5	PivOH (2)	MeOH	30
6	5	PivOH (2)	DMSO	16
7	5	PivOH (2)	1,4-dioxane	91
8	5	PivOH (2)	CH_2Cl_2	28
9	5	AcOH (2)	1,4-dioxane	90
10	4	AcOH (2)	1,4-dioxane	90
11	3	AcOH (2)	1,4-dioxane	78
12	4	–	1,4-dioxane	80

[a] Reaction conditions: quinoline *N*-oxide (0.3 mmol), diphenylacetylene (0.2 mmol), acid additive (0.4 mmol), [{RhCp*Cl_2}$_2$] (3–5 mol%), $AgSbF_6$ (12–20 mol%), solvent (3 mL), 110°C, 20 h, sealed tube under Ar. [b] Yield of the isolated product after column chromatography. [c] No $AgSbF_6$ was used. DCE = 1,2-dichloroethane, Cp* = C_5Me_5, DMSO = dimethylsulfoxide, Piv = pivaloyl, Tf = trifluoromethanesulfonyl.

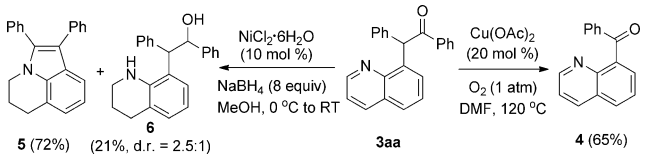
By using the optimized reaction conditions, the scope of this system was next examined (Scheme 2). It was found that variation of electron-donating, electron-withdrawing, and halogen groups at the different positions of the quinoline ring is well tolerated in the coupling with PhC≡CPh, and the coupled products were isolated in 38–95% yield. Interestingly, no steric influence at the 2-position was found as **3oa, 3pa**, and **3ok** were isolated in high yields. In contrast, the reaction seems sensitive to steric perturbation at the 7-position given the low yield of **3qa**. The *N*-oxide is not limited to a quinoline system, as **3ra** (83%) and **3sa** (48%) were both isolated in moderate to high yields.

The scope of the alkyne substrate was next examined in the coupling with **1a**. Symmetric diarylacetylenes (**3ab–ai**) bearing substituents all coupled smoothly in moderate to high yields. The coupling of an electronically biased diarylalkyne afforded two regioisomeric products, **3oj** and **3oj′**, in a 1.5:1 ratio (^{1}H NMR and GC-MS). Subjection of 1-phenyl-1-propyne to the optimal reaction conditions met with failure. Gratifyingly, additional introduction of $Zn(OTf)_2$ (20 mol%) regained the catalytic efficiency and this coupling occurred with exclusive regioselectivity (**3ak–al**). Although essentially no desired coupling was observed for terminal alkynes, such as phenylacetylene, an alternative approach using propargyl alcohols can be utilized. Thus α-arylacetophenone was isolated in moderate yield when the the corresponding propargyl alcohol was employed [**3am** and **3an**; Eq. (1)]. However, extension to PhC≡CTMS or dialkyl-substituted alkynes all met with failure, which is indicative of the limitation of the method.

The synthetic utility of **3aa** has been demonstrated. Copper(II)-catalyzed aerobic oxidative C–C cleavage[14] of



Scheme 2. Scope of C–H activation/O-atom transfer. Reaction conditions: *N*-oxide (0.3 mmol), alkyne (0.2 mmol), [{RhCp*Cl_2}$_2$] (4 mol%), $AgSbF_6$ (16 mol%), AcOH (0.4 mmol), 1,4-dioxane (3 mL), 110°C, 20 h. Yield is that of the isolated product. [a] $Zn(OTf)_2$ (0.04 mmol) was also added.



Scheme 3. Transformations of a coupled product.

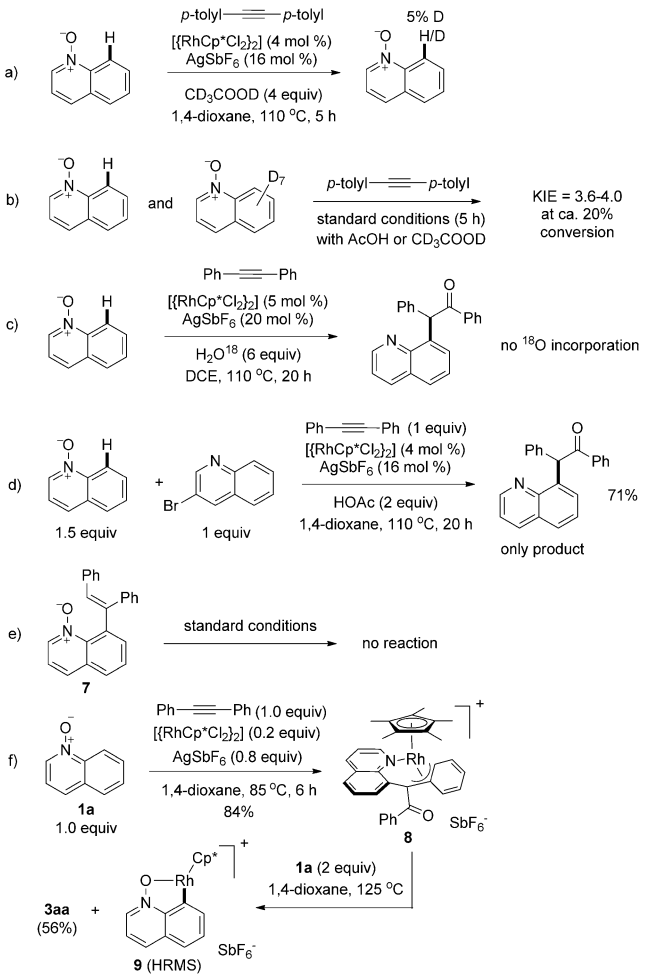
3aa afforded the diaryl ketone **4** in good yield (Scheme 3), together with benzoic acid. Nickel-catalyzed reductive annulation affords a condensed indole (**5**; 72% yield) and a small amount of a diastereomeric mixture of alcohol-functionalized tetrahydroquinolines (**6**). Fused indoles such as **5** are known as an important scaffold in many biologically active natural products and pharmaceuticals.[15]

Extensive mechanistic studies have been carried out. To probe the relevancy of C–H activation, **1a** and di(*p*-tolyl)-acetylene were reacted under the catalytic conditions in the presence of [D_4]acetic acid (Scheme 4a). NMR analysis of the recovered quinoline *N*-oxide revealed 5% deuteration at the 8-position (at ca. 20% conversion). This observation pinpointed a largely irreversible C8–H activation. We also attempted but failed to isolate any rhodacyclic intermediate from a stoichiometric reaction between **1a** and [{RhCp*Cl_2}$_2$] in the presence of various bases, possibly because the ring strain renders the cyclometalation thermodynamically uphill. Additional KIE studies by intermolecular competition in the presence of AcOH or CD_3COOD (4 equiv) consistently gave a relatively large k_H/k_D value (3.6–4.0), thus suggesting that C–H cleavage is probably involved in the rate-limiting step (Scheme 4b).

To explore the O-atom transfer process, the coupling between **1a** and **1b** was conducted in the presence of H_2O^{18} (6 equiv; Scheme 4c). GC-MS and HRMS analysis of the isolated product revealed no ^{18}O incorporation. Therefore, water is not involved and the OAT is very likely intramolecular. To establish the sequencing of the OAT and the C–H activation, the coupling of **1a** and **2a** was performed in the presence of 3-bromoquinoline, a potential competing intermediate (Scheme 4d). Both ^1H NMR and GC-MS analyses of the reaction product established **3aa** as the sole product with no incorporation of the 3-bromoquinoline. This result indicates the unlikelihood of a direct OAT to alkynes which generates a quinoline and a rhodium α-oxo carbene. In addition, unassisted insertion of the C8–H of a simple quinoline into a rhodium(III) α-oxo carbene is also quite unlikely.[16] Consequently, the C–H activation occurs prior to the OAT.

To further understand whether the C–H activation leads to a C8 olefination intermediate by hydroarylation,[13a,17] the olefin **7** was prepared[13a] and was subjected to the standard reaction conditions (Scheme 4e). Essentially no conversion was observed. Therefore the intermediacy of this olefin can be ruled out.

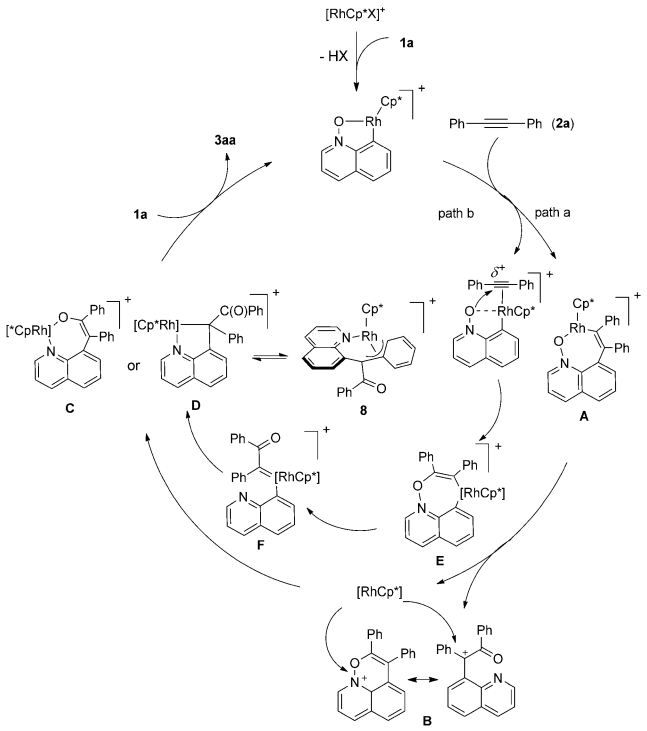
Despite the failure in isolation of a cyclometalated intermediate, the reaction of **1a** ad **2a** under a higher catalyst loading (1,4-dioxane, 85 °C) led to the formation of a rhodium(III) η^3-benzyl complex (**8**) in high yield (Scheme 4f, under these reaction conditions, essentially no catalytic



Scheme 4. Mechanistic studies.

coupling occurred). The complex **8** was fully characterized (see the Supporting Information for details), including by X-ray crystallography (CCDC 1009768). The complex **8** also proved to be the resting state of the catalyst in the absence of AcOH (Table 1, entry 12) and exhibited comparable efficiency for the coupling of **1a** and **2a**. Thus it is a likely intermediate (or a direct precursor by η^1 slippage). The isolation of **8** seems to suggest that subsequent release of the coupled product (likely by an incoming **1a**) is a slower step. Indeed, heating a suspension of **8** and quinoline *N*-oxide (2 equiv) in 1,4-dioxane at a higher temperature (125 °C) afforded **3aa** in 56% GC yield (Scheme 4f), and HRMS analysis of the organometallic products pointed to the formation of the rhodacyle **9** or its adduct (*m*/*z* 382.0682). Thus **3aa** is likely released with concurrent C–H activation assisted by the *N*-oxide, and probably constitutes the rate-limiting step.

On the basis of our mechanistic studies, two possible pathways have been proposed (Scheme 5). In path a, cyclometalation of **1a** is followed by alkyne coordination and Rh–C migratory insertion to afford the seven-member rhodacyclic intermediate **A**. Subsequent reductive elimination of a C–O bond generates a cationic heterocyclic



Scheme 5. Proposed mechanisms.

intermediate (**B**) together with a rhodium(I) species. Oxidative addition of **B** at the O or C terminus generates an O- or C-bound enolate (**C** or **D**), respectively. Tautomerization or slippage produces the isolable η^3-benzyl intermdiate **8**. The coupled product **3aa** is released by cyclometalation of an incoming quinoline *N*-oxide,[18] thus completing the catalytic cycle. Alternatively, in path b, the alkyne is activated toward intramolecular nucleophilic attack by the (ligated or unbound) *N*-oxide to afford the metal alkenyl intermediate **E**. Elimination of the quinoline nitrogen atom generates a metal α-oxo carbene[10] (**F**), which is prone to migratory insertion to afford the same intermediate **8**. Although the observed regioselectivity of the coupling of 1-phenyl-1-propyne agrees with this mechanism (electronic effect) and with that in gold-catalyzed OAT reactions,[19] the observed regioselectivity for **3oj** and **3oj′** in this eletronically biased push-pull alkyne argues against this mechanism. If path b is operative, the *N*-oxide oxygen atom should preferentially attack a positively polarized alkynyl carbon atom, and consequently **3oj′** would be the major product. Therefore, path a is preferred.[20]

In summary, we have developed a rhodium(III)-catalyzed redox-neutral coupling of quinoline *N*-oxide with internal alkynes, thus leading to the synthesis of substituted acetophenones. This system represents the first example which combines C–H activation and OAT. A broad scope of both coupling partners has been established. A series of mechanistic studies have been performed and an unusual rhodium(III) η^3-benzyl intermediate has been isolated from the catalytic conditions and a $Rh^{III}/Rh^{I}/Rh^{III}$ mechanism is proposed. The combination of different important areas in catalysis may allow opportunities to expand the scope of and applications of C–H activation toward construction of complex structures.

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[20] An intramolecular version of this coupling was attempted using the *N*-oxide **10**, but only the benzofuran **11** was isolated. This result suggests that path a is likely to be operational. We reasoned that the tethering effect of the newly formed five-membered ring in the rhodacyclic intermediate renders C–O reductive elimination conformationally infeasible. Instead, a competitive protonolysis occurred followed by C=C isomerization.