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Synthesis of Quinoline *N*-Oxides by Cobalt-Catalyzed Annulation of Arylnitrones and Alkynes

Yue Liu,[a] Chen Wang,[b] Ningning Lv,[a] Zhanxiang Liu,[a] and Yuhong Zhang[a,c,*]

[a] Department of Chemistry, Zhejiang University, Hangzhou 310027, People's Republic of China
Fax: (+86)-571-8795-3244; e-mail: yhzhang@zju.edu.cn
[b] Zhejiang Key Laboratory of Alternative Technologies for Fine Chemicals Process, Shaoxing University, Shaoxing 312000, People's Republic of China
[c] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China

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Abstract: A new and straightforward protocol for the synthesis of quinoline *N*-oxides from the annulation of arylnitrones and alkynes is described. For the first time, a [4+2] cyclization of nitrone and alkynes has been achieved by cobalt catalysis *via* a nitrone-assisted dual C–H cleavage under relatively mild conditions.

Keywords: C–H activation; cobalt; heterocycles; nitrones; quinoline *N*-oxides

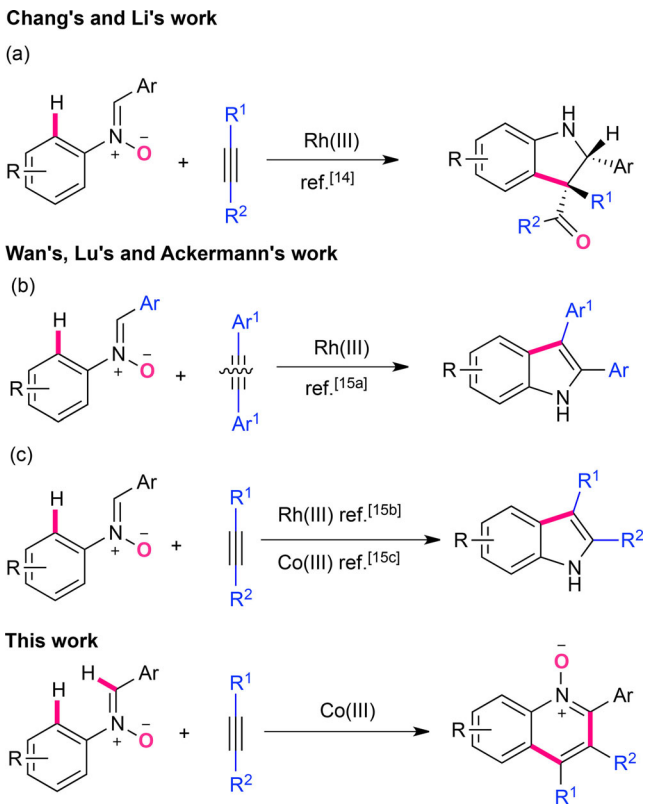
Introduction

Heterocycles are important motifs of natural products, pharmaceuticals, and functional materials. As a consequence, a great deal of effort has focused on developing new and efficient synthetic approaches to heterocycles.[1] In particular, there has been much interest in the discovery of transition metal-catalyzed C–H functionalizations for the synthesis of heterocycles that are less reliant on preactivation.[2] Many important nitrogen-containing heterocycles, including pyrroles,[3] pyridines,[4] indoles,[3a,5] and quinolines,[6,7] have been prepared through the direct functionalization of otherwise unreactive C−H bonds. Quinoline *N*-oxides constitute an important class of compounds that possess a range of physiological activities[8] and valuable coordination properties.[9] More importantly, quinoline *N*-oxides have been proven to be common precursors to prepare derivatives of quinolines due to the poor regioselectivity and reactivity of quinoline.[10] More recently, the *N*-oxide group of quinoline *N*-oxides was found to be able to function as a directing group as well as the source of oxygen for the synthesis of derivatives of quinolines.[11] However, a straightforward approach to quinoline *N*-oxides remains challenging, and the installation of the *N*-oxide group generally requires an additional oxidation step.[12] Due to its important application as a precursor of quinoline derivatives and the prevalence of this heterocycle in many molecules of interest, the direct formation of quinoline *N*-oxides is highly desirable.

Nitrones are important building blocks that are easily accessible, and their chelation properties in rhodium-catalyzed C–H activation reactions have been explored.[13] The elegant work by the groups of Chang and Li have demonstrated the dual role of nitrones as both directing group and oxygen source in the rhodium-catalyzed synthesis of indolines (Scheme 1a).[14] The rhodium(III)-catalyzed C–H annulation of nitrones with internal alkynes to furnish multi-substituted indoles was reported by Wan and Lu (Scheme 1b and c).[15a,b] The catalytic properties of low-cost cobalt for this annulation were explored by Ackermann and coworkers (Scheme 1c).[15c] In these transformations, the five-membered indole derivative is always formed through the nitrone-assisted C–H activation.

Results and Discussion

We recently reported an annulation of anilides and alkynes for the synthesis of quinolones[6c] by using the unique nucleophilic reactivity of a cobalt catalyst.[16] In our initial experiment, none of the expected cyclization product quinoline *N*-oxide was formed in the reaction of (*Z*)-*N*-benzylideneaniline oxide **1b** and diphenylacetylene **2a**, yet the indole product could be obtained the same as in Ackermann's report in low yield (Figure 1) (for more details see the Supporting Information) However, we did not focus on the indole product because it had been reported from a similar rhodium catalysis. We wondered whether we



Scheme 1. Annulation of nitrones with alkynes.

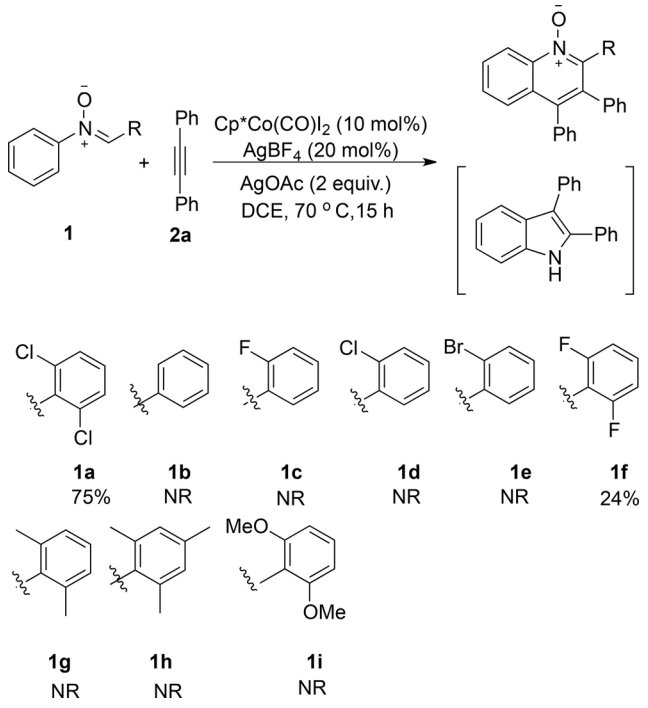
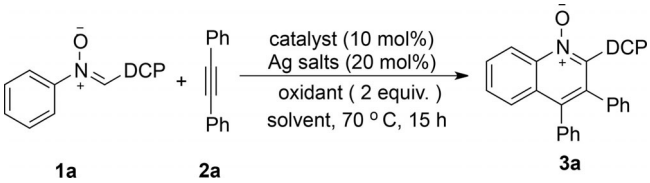


Figure 1. Screen of various nitrone substrates for the annulation.

could use the unique nucleophilic activity of the organocobalt species to realize the synthesis of different heterocycles. To probe this poor reactivity, we envisioned that introducing different substituents in the *ortho* position of aryl structure on the carbon center could enhance its reactivity. It was observed that the use of 2,6-dichlorophenyl (DCP) substrate afforded the six-membered annulation product of quinoline *N*-oxide (Figure 1).

Relying on the efficiency of phenylnitrone **1a**, we performed some studies on the reaction conditions as summarized in Table 1. Silver salts for activation of the cobalt catalyst were first tested by reacting of phenylnitrone **1a** with alkyne **2a** in DCE at 70 °C for 15 h in air. It was found that AgOTf and $AgNTf_2$ delivered the product **3a** in low yields (entries 1 and 2), but $AgPF_6$ was inactive (entry 3). The use of $AgSbF_6$ improved the yield to 65% (entry 4), and $AgBF_4$ afforded the best result (entry 5). Among the oxidants tested (entries 6–9), AgOAc showed the optimal efficiency to give the quinoline *N*-oxide in 75% yield. The solvent also influenced the reaction. Lower yields were obtained when the reaction was performed in DCM, TFE and $PhCF_3$ (entries 10–12), and DCE was

Table 1. Optimization of the reaction conditions.[a]



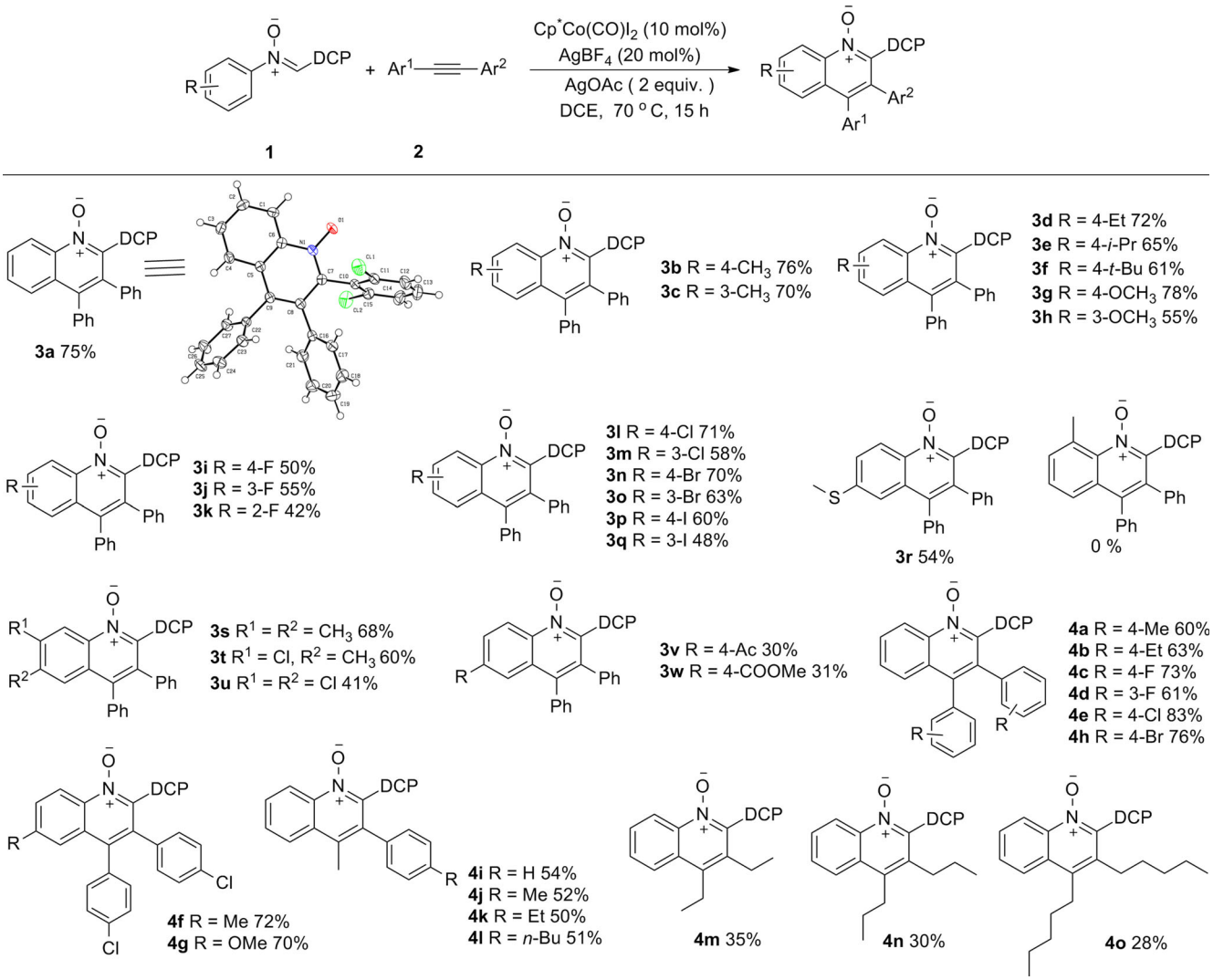
Entry	Catalyst	Additive	Oxidant	Yield of **3a** [%][b]
1	$Cp^*Co(CO)I_2$	AgOTf	AgOAc	42
2	$Cp^*Co(CO)I_2$	$AgNTf_2$	AgOAc	48
3	$Cp^*Co(CO)I_2$	$AgPF_6$	AgOAc	0
4	$Cp^*Co(CO)I_2$	$AgSbF_6$	AgOAc	65
5	$Cp^*Co(CO)I_2$	$AgBF_4$	AgOAc	75
6	$Cp^*Co(CO)I_2$	$AgBF_4$	$Cu(OAc)_2$	30
7	$Cp^*Co(CO)I_2$	$AgBF_4$	Ag_2CO_3	trace
8	$Cp^*Co(CO)I_2$	$AgBF_4$	CuO	trace
9	$Cp^*Co(CO)I_2$	$AgBF_4$	Ag_2O	trace
10	$Cp^*Co(CO)I_2$	$AgBF_4$	AgOAc	40[c]
11	$Cp^*Co(CO)I_2$	$AgBF_4$	AgOAc	28[d]
12	$Cp^*Co(CO)I_2$	$AgBF_4$	AgOAc	30[e]
13	$Cp^*Co(CO)I_2$	–	AgOAc	NR
14	–	$AgBF_4$	AgOAc	NR
15	$\{Cp^*RhCl_2\}_2$	$AgBF_4$	AgOAc	NR
16	$RuCl_2$(*p*-cymene)	$AgBF_4$	AgOAc	NR
17	$Pd(OAc)_2$	–	AgOAc	NR

[a] *Reaction conditions:* **1a** (0.3 mmol), **2a** (0.2 mmol), catalyst (10 mol%), $AgBF_4$ (20 mol%), oxidant (0.4 mmol) in solvent (1.0 mL) in air at 70 °C for 15 h.
[b] Yield of isolated product.
[c] DCM was used as solvent.
[d] TFE was used as solvent.
[e] $PhCF_3$ was used as solvent. DCP = 2,6-dichlorophenyl.

the best reaction medium. No reaction was observed in the absence of the cobalt catalyst or $AgBF_4$ (entries 13 and 14). Furthermore, the cobalt catalyst exhibits unique reactivity in this annulation reaction. Other catalysts, including $\{Cp^*RhCl_2\}_2$, $RuCl_2$(*p*-cymene), and $Pd(OAc)_2$, were inactive (entries 15–17).

With the optimized conditions in hand, we next investigated the scope of arylnitrones and alkynes in this annulation reaction and the results are summarized in Scheme 2. Substrates with electron-donating groups in the aryl ring were reactive toward diphenylethyne **2a** and gave the quinoline *N*-oxide products in good yields (Scheme 2, **3a**–**3h**). Synthetically versatile halogen substituents can be positioned at various points on the aryl motif to afford the corresponding quinoline *N*-oxides smoothly (Scheme 2, **3i**–**3q**). The methylthio group was tolerated to give the corresponding quinoline *N*-oxide in 54% yield (**3r**). Multisubstituted substrates participated in the reaction smoothly (**3s** and **3t**). However, the reactivity of substrates with steric hindrance decreased drastically. For example, when 2-methylphenylnitrone was used, the corresponding product was not observed. Electron-deficient arylnitrones showed less reactivity but worked to produce the expected quinoline *N*-oxide products in lower yields (Scheme 2, **3u**–**3w**). The structure of quinoline *N*-oxide **3a**[17] was further confirmed by X-ray crystallographic analysis (Scheme 2).

This annulation reaction proceeded smoothly using a variety of internal alkynes. A range of substituents is tolerated on the aryl moiety of alkynes such as methyl, ethyl, methoxy, fluoro, chloro and bromo groups (Scheme 2, **4a**–**4h**). After we had demonstrated the success of the annulation of arylalkynes, we were prompted to investigate the reactivity of alkylarylalkynes under similar reaction conditions since they may give two possible products from two possible annulation directions.[3a,18] To our surprise, a single regioisomeric product is observed with C–C bond for-

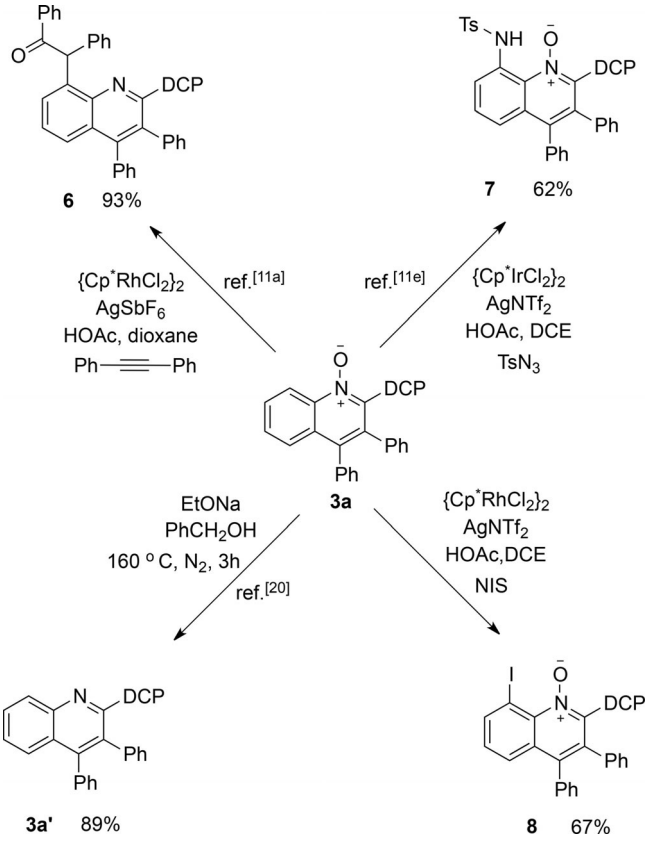


Scheme 2. Substrate scope of arylnitrones and alkynes.

mation between the *ortho*-position of phenylnitrone and the carbon of the alkynyl triple bond adjacent to the alkyl group (Scheme 2, **4i**–**4l**). This regioselectivity is consistent with the insertion of unsymmetrical alkynes into the Rh–C bond.[19] The examined dialkylalkynes only gave products in relatively lower yields (**4m**–**4o**).

Some derivatizations to demonstrate the synthetic utility of using an as-prepared quinoline *N*-oxide as precursors are presented in Scheme 3. For example, by using the N–O moiety as directing group, the rhodium-catalyzed C-8 alkylation was successfully achieved to give the quinoline **6** in high yield. Selective C-8 amination and iodination were performed from quinoline *N*-oxide **3a** under iridium catalysis and rhodium catalysis under mild reaction conditions to give compounds **7** and **8**. Quinoline *N*-oxide **3a** could be readily reduced to deliver the corresponding quinoline **3a′** using the $PhCH_2OH$/NaOEt system.[20]

In order to explore the possible reaction mechanism, a series of control experiments was carried out. 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 3.7 was obtained on the basis of ^{1}H NMR analysis. In addition, the competitive coupling of an equimolar mixture of **1a** and **1a**-d_5 with diphenylacetylene gave a consistent

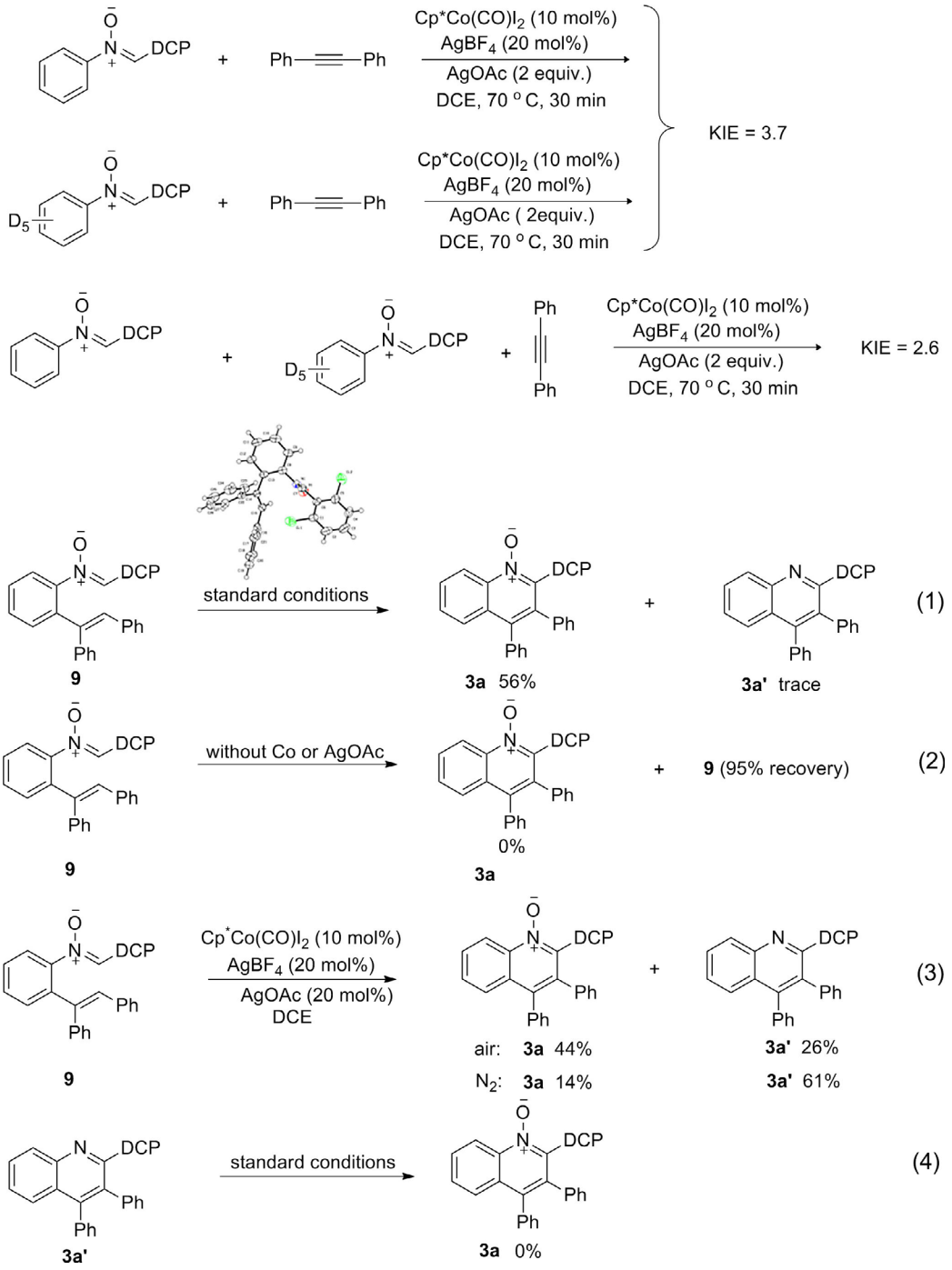


Scheme 3. Syntheic utility of quinoline *N*-oxide **3a**.

value of $k_H/k_D = 2.6$ (Scheme 4). These results indicated that C–H activation is likely involved in the rate-limiting step. After the reaction was performed for 1 h, two products were observed that were assigned as quinoline *N*-oxide product **3a** and alkenylated intermediate **9**. Treatment of the alkenylated intermediate **9** under the standard reaction conditions afforded the quinoline *N*-oxide product **3a** [Scheme 4, Eq. (1)]. The structure of alkenylated intermediate **9**[21] was confirmed by X-ray crystallographic analysis. Either cobalt catalyst or silver oxidant is needed for the annulation of alkenylated intermediate **9** [Scheme 4, Eq. (2)]. Air may be involved as oxidant to promote the reaction. For instance, more quinoline *N*-oxide **3a** was generated when the reaction was performed under air, and in contrast, more quinoline **3a′** was observed under nitrogen [Scheme 4, Eq. (3)]. The by-product quinoline **3a′** failed to form the quinoline *N*-oxide product **3a** under the standard reaction conditions, suggesting that quinoline *N*-oxide product **3a** is generated from the catalytic cycle rather than from the oxidation of quinoline **3a′** [Scheme 4, Eq. (4)].

To gain insights into the origin of the observed activity of arylnitrone **1**, theoretical calculations were conduct.[23] Since the concerted metalation–deprotonation of carboxylate-assisted transition metal-catalyzed C–H activation by Co catalysts[16] or other transition metals[24] has been well studied, here we focus on the alkyne insertion and nucleophilic attack steps (Figure 2). It should be note that in the transition state corresponding to the nucleophlic attack, the phenyl on the carbon atom of the imine might be *syn*- or *anti*- to the Cp*Co (Figure 3). Interestingly, it is found that the relative stabilities of the *syn*- and *anti*-transition states are related to the substituents on the phenyl. For the di-*ortho*-chloride-substituted phenyl, the *anti*-transition state is more favorable than the *syn*-one (***anti*-2Cl-TS-NA** 27.4 *vs.* ***syn*-2Cl-TS-NA** 32.2 kcal mol^{-1}). In contrast, for the non-substituted phenyl, the *syn*-transition state is more stable than the *anti*-one (***syn*-2H-TS-NA** 31.7 *vs* ***anti*-2H-TS-NA** 33.1 kcal mol^{-1}). As shown in Figure 2, the alkyne insertion step always has a lower energy barrier than the nucleophilic attack step and should not account for the observed activity. Comparing the nucleophilic attack steps for **2Cl-INT1** and **2H-INT1**, it can be seen that the energy demand of ***anti*-2Cl-TS-NA** is significantly lower than that of ***syn*-2H-TS-NA** (27.4 *vs.* 31.7 kcal mol^{-1}), meaning that the nucleophlic attack for the former is much faster than that for the latter. Therefore, these calculation results provide theoretical support that the nucleophlic attack step is responsible for the distinct activity between **2Cl-INT1** and **2H-INT1**.

On the basis of previous studies of cobalt chemistry[15c] and our experimental findings, a plausible reaction mechanism is proposed as shown in Scheme 5.



Scheme 4. Control experiments.

The first step is the formation of active cobalt catalyst **I** by the abstraction of iodide from the pre-catalyst Cp*Co(CO)I_2 by $AgBF_4$. The following cobalt-catalyzed C–H cleavage assisted by the nitrone group affords the cyclic cobalt intermediate **II**, which undergoes insertion with the alkyne to give the intermediate **III**. The protonation of intermediate **III** produces the alkenylated product **9**. The intramolecular nucleophilic attack of intermediate **III** into the C=N double bond of the nitrone forms the intermediate **IV**, which undergoes protonation to give the intermediate **V**. Oxidation of intermediate **V** gives the quinoline *N*-oxide product **3a**, and dehydration of **V** generates the by-product quinoline **3a′**.[22] In the process of formation of **IV** from **III**, the DCP group has a great influence on the intramolecular nucleophilic attack. The DCP group not only breaks the planarity between the aryl group and carbon-nitrogen double bonds but also

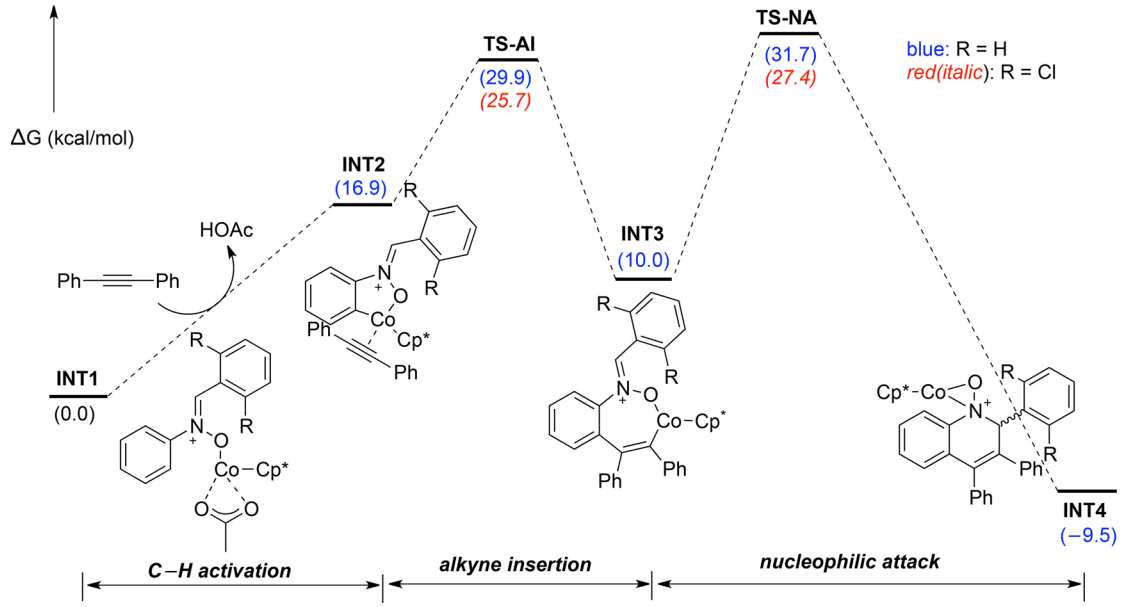


Figure 2. Energy profiles for the alkyne insertion and nucleophlic attack steps starting from Cp*Co(III)(κ^2-OAc)-**1a**/**1b** and 1,2-diphenylethyne.

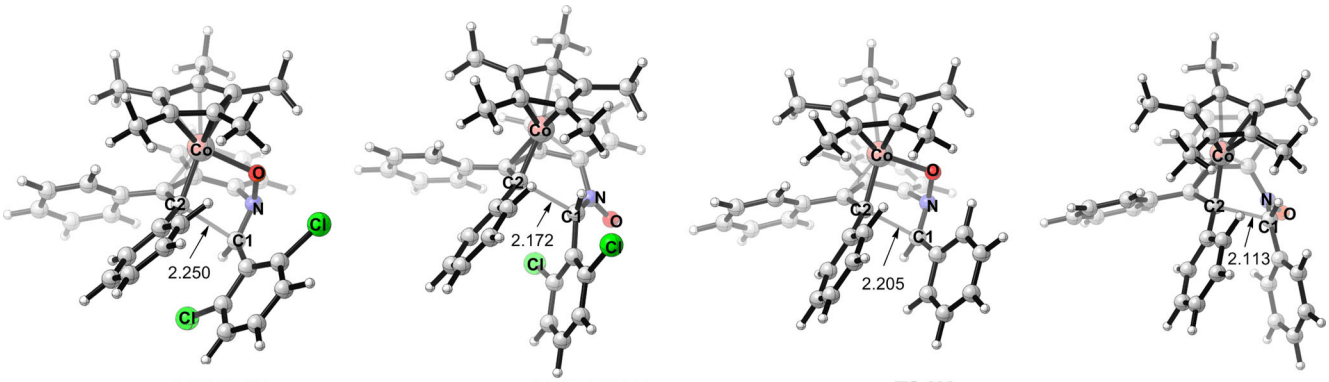


Figure 3. Optimized structures of the *syn*- or *anti*-transition states for the nucleophlic attack step. Energies are in kcal mol^{-1}. Bond distances are in Ångstrom units.

enhances the electrophilicity of the carbon-nitrogen double. Then the process of intramolecular nucleophilic attack could be carried out smoothly.

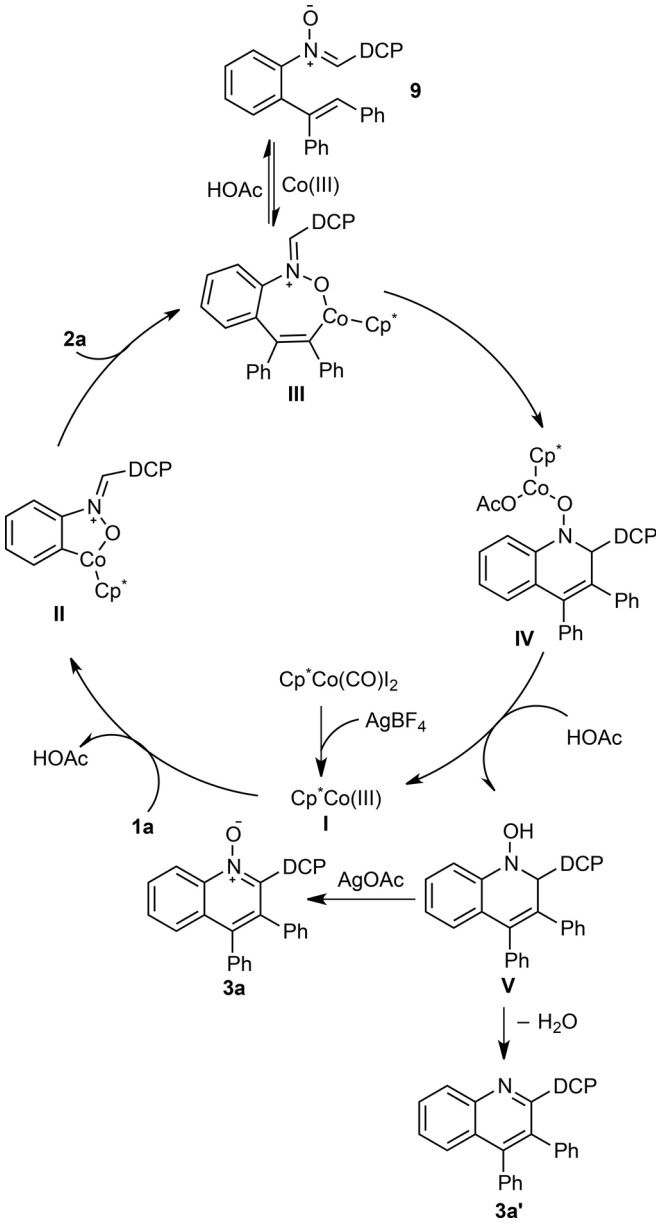
Conclusions

In summary, we have developed a straightforward cobalt-catalyzed method involving dual C–H activation for the synthesis of quinoline *N*-oxides from easily accessible substrates. The new reaction is highly selective and shows good functional group tolerance. The derivatizations by using as-prepared quinoline *N*-oxide as precursors are achieved for the synthesis of valuable quinoline derivatives. Further research on the development of novel nitrone-directed C–H activations is currently ongoing in our laboratory.

Experimental Section

General Procedure

To a test-tube with a stir bar were added diphenylacetylene (**2a**, 0.20 mmol), nitrone (**1a**, 0.30 mmol), Cp*Co(CO)I$_2$ (0.02 mmol), AgBF$_4$ (0.04 mmol) and AgOAc (0.4 mmol) in DCE (1.0 mL) under atmospheric conditions. The reaction mixture was stirred at 70 °C for 15 h, cooled to room temperature and the organic solvents were removed under re-



Scheme 5. Proposed reaction pathway.

duced pressure and the crude reaction mixture was purified by column chromatography on an alkaline aluminum oxide column with petroleum ether/EtOAc/CH_2Cl_2 as an eluent to give the desired product.

Acknowledgements

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Synthesis of Quinoline *N*-Oxides by Cobalt-Catalyzed Annulation of Arylnitrones and Alkynes

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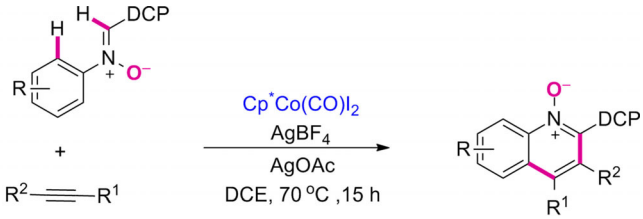
Yue Liu, Chen Wang, Ningning Lv, Zhanxiang Liu, Yuhong Zhang*



DCP=2,6-dichlorophenyl

√ **First example of selective conversion of arylnitrones to quinoline *N*-oxides**
√ **Dual C–H activation to achieve [4+2] annulation**
√ **Mild reaction conditions**