Regioselective Arylation of Quinoline N-Oxides (C8), Indolines (C7) and N-tert-Butylbenzamide with Arylboronic Acids

Shiv Shankar Gupta, Rakesh Kumar, and Upendra Sharma*

Natural Product Chemistry and Process Development Division and AcSIR, CSIR-IHBT, Palampur 176061, India

Supporting Information

ABSTRACT: Herein, we disclose Ru(II)-catalyzed regioselective distal C(sp²)−H arylation of quinoline N-oxide with arylboronic acids to 8-arylquinolines. In the developed method, the Ru(II)-catalyst shows dual activity, that is, distal C−H activation of quinoline N-oxides followed by in situ deoxygenation of arylated quinoline N-oxide in the same pot. The current catalytic method features use of Ru metal as the catalyst and arylboronic acids as the arylation source under mild reaction conditions. Use of the Rh(III)-catalyst in place of Ru(II) under the same conditions afforded 8-arylquinoline N-oxides with excellent regioselectivity. Furthermore, the developed Ru(II) catalytic system is also extended for the C(sp²)−H arylation of indolines, N-tert-butylbenzamide, and 6-(5H)-phenanthridinone. Formation of the quinoline N-oxide coordinated ruthenium adduct is found to be the key reaction intermediate, which has been characterized by single crystal X-ray diffraction and NMR spectroscopy.

INTRODUCTION

N-heterocyclic aromatic scaffolds are often encountered in a wide range of compounds including natural products, pharmaceuticals, agrochemicals, and ligands. Quinoline, a prominent structural scaffold, is found in a wide range of natural products and capable of showing diverse type of therapeutic activity. Among them the 8-arylated quinoline moiety has its own importance as it is often found in bioactive compounds (Scheme 1). Therefore, functionalization of the quinoline scaffold to corresponding 8-arylquinolines is highly desirable, in order to produce bioactive compounds synthetically.

Scheme 1. Selected Example of Bioactive 8-Arylquinoline Scaffolds

Transition metal-catalyzed regioselective C−H functionalization has emerged as an ideal strategy for the synthesis of therapeutically active quinoline scaffolds. In this direction, N-oxide has been explored as an excellent directing group for the selective functionalization of quinolines. Although, C8 functionalization of quinoline N-oxides is not explored much, various methods have been developed for C2 functionalization. Among them, few reports are available on C8 arylation of quinolines (Scheme 2). In 2011, first Rh(II)(NHC)-catalyzed direct C8 arylation of quinolines through C−H functionalization with aryl bromide as a coupling partner has been reported by the Chang group. Later, Pd(II)-catalyzed C8 arylation of quinoline N-oxide has been reported with aryl halide as a coupling partner by the Larionov group.

Scheme 2. Regioselective C8 Functionalization of Quinoline N-Oxide

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with aryl diazonium salt as an arylating source. In addition to these reports, the Liu group reported C8 arylation of quinoline N-oxide by using potassium aryl trifluoroborate as a coupling partner with a limited substrate scope and low yields. In spite of all these examples, cheaper metal, i.e., ruthenium has never been explored for C8 functionalization of quinoline N-oxides. Arylboronic acid is also most predominantly available and a cost-effective choice for arylation. Herein, we disclosed Ru(II)-catalyzed distal sp3(C8−H) arylation with arylboronic acids under mild reaction conditions (Scheme 2). During the compilation of this work, similar transformation was also reported by the Chang group, but the current methodology is not limited only for quinoline N-oxide, it is also applicable for the arylation of indolines, 6-(SH)-phenanthridinone and N-tert-butylbenzamide substrates. Additionally, use of the Rh(III) catalyst in place of Ru(II), afforded an arylated product with N-oxide which provides opportunity for further derivatization (Scheme 2).

**RESULT AND DISCUSSION**

Initially, quinoline N-oxide (1a) and arylboronic acid (2a) were reacted in the presence of [RuCl2(η5-cymene)]2 (5 mol %), AgSbF6 (20 mol %), Cu(OTf)2 (20 mol %), Ag2CO3 (2.5 equiv), and dimethoxyethane (DME) as solvent at 100 °C. Therefore, we screened different silver additives and oxidants, in order to reduce undesired quinoline and we found that the combination of AgOTf, Cu(OTf)2, and Ag2O were appreciable to afford the arylated product with N-oxide which provides opportunity for further derivatization (Scheme 2).

Table 1. Optimization Study for Ru-Catalyzed C(8)−H Arylation

| entry | variation from standard condition | 3a yield (%) | 4a yield (%) |
|-------|----------------------------------|--------------|-------------|
| 1     | none                             | 70           | 30          |
| 2     | triphenylboroxine instead of 2a   | 70           | 30          |
| 3     | phenyltrimethoxysilane, triphenylborane, and tetraphenyltin instead of 2a | up to 40% yield | | |
| 4     | DME as solvent along with AgSbF6 & Cu(OTf)2 salt and Ag2CO3 as oxidant | 70% yield | 30% yield |
| 5     | 1,4-dioxane instead of THF        | 40           | 40          |
| 6     | Ag2CO3 instead of Ag2O           | 40           | 40          |
| 7     | Cu(OTf)2 instead of Ag2O         | 25           | 10          |
| 8     | Mn2O instead of Ag2O             | 10           | 10          |
| 9     | AgOTf and Cu(OTf)2 instead of Tf2O | 70           | 30          |
| 10    | Cu(OTf)2 instead of Tf2O         | 45           | 55          |
| 11    | AgOTf instead of Tf2O            | ND           | ND          |
| 12    | at 100 °C                        | 45           | 35          |
| 13f   | [RhCp*Cl2]2 instead of RuCl2(η5-cymene) | 92            | (90)% yield |

*Table 1, entry 9*) Further optimization study shows that triflic anhydride (25 mol %) is also significant to carry out the reaction, which replaced costlier metal triflate salt, that is, AgOTf and Cu(OTf)2 without affecting the reaction yield (Table 1, entry 1). Additionally, triphenylboronic (1 equiv) was found to be of approximately equal potency (entry 2). Solvent screening indicated tetrahydrofuran (THF) as a solvent of choice (entry 1, 4−5). Oxidant screening have shown Ag2O as the best one, while Ag2CO3, Cu2O, and Mn2O have shown inferior result than Ag2O (Table 1, entry 6−8). Alone Cu(OTf)2 as an additive with oxidant Ag2O gave 45% product yield (Table 1, entry 10). AgOTf instead of Tf2O was not able to give the product (Table 1, entry 11). Moreover, heat energy analysis indicated that the forward reaction is compatible broadly throughout 30−100 °C, but traces of the side product was also observed at 100 °C (Table 1, entry 12). Notably, we got rid of the undesired side reaction by performing the reaction at 40 °C instead of 100 °C. We have also tried other arylating agents such as trimethoxyphenylisilane (1 equiv AgF added additionally in order to make silane more reactive), triphenylborane, and tetraphenyltin, which afforded low to moderate yield of the desired product (Table 1, entry 3). We finalized the standard condition as 3 equiv phenylboronic acid, 5 mol % [RuCl2(η5-cymene)]2, 25 mol % triflic anhydride, 2.5 equiv Ag2O, and THF as the solvent at 40 °C to afford 70% arylated product along with quinoline as a byproduct.

With the best optimized condition, substrate scopes with various arylboronic acids as well as quinoline N-oxide have been studied (Table 2). The reaction of C-2-substituted quinoline N-oxide 1b and 1c with 2a afforded the corresponding C8 arylated products (3b−3c) in a good yield. On the other hand, electron deficient quinoline N-oxide (1d and 1i) as well as polyaromatic quinoline N-oxide (1j) provided up to 28% desired product yield (3d, 3i−3j). Variation of methyl at 4-position and 6-position gave a product yield of 32 and 28%, respectively (3e & 3f), while 6-bromo quinoline N-oxide afforded 24% of the product yield (3h). Electron-rich quinoline N-oxide (1g) rings were able to give the product in 35% yield (3g). Next, differentially substituted arylboronic acids were tested with 1a under optimal reaction conditions. Electron-rich arylating sources like 4-alkylphenylboronic acid, 3,5-dimethylphenylboronic acid, 4-methylphenylboronic acid, and 4-methoxyphenylboronic acid were able to afford the corresponding arylated product in moderate to good yield (3k, 3l, 3m, 3o), while the electron-deficient arylating source like 4-nitrophenoxyboronic acid gave no product. This indicates that nucleophilicity of the arylating source is significant; more nucleophilic arylating sources are good and vice-versa. Additionally, 4-chloro and 4-bromophenylboronic acids gave 52 and 35% yield, respectively (3p and 3q), while 4-phenyl and 4-formylphenylboronic acid afforded 25 and 22% of product yield (3n and 3r).

In order to investigate the standardized condition scope with other metal catalysts, we replaced Ru(II) metal with its isoelectronic species Rh(III) (Table 1, entry 13), which gave 90% isolated yield of 8-phenylquinoline N-oxide instead of the deoxygenated product (3a). With these re-optimized reaction conditions substrate scope was studied (Table 3). Halogenated quinoline N-oxide gave a good yield of the desired product (5b), and additionally electron-rich quinoline rings were twice better as compare to the electron-deficient ones (5c and 5d). Moreover, 4-nitrophenoxyboronic acid was not compatible,
possibly due to weaker nucleophilic arylating agent (5i). Besides this, 2-fluorophenylboronic acid was not able to give the product (5j), and it may be due to the steric factor as well as the fluoro group which is also the electron withdrawing group inductively, deteriorating its reactivity. Further, variation of meta and para-substituted phenylboronic acid gave up to 66% of the corresponding arylated product with N-oxide (5e–5h).

Indoline scaffolds are also one of the most important bioactive structural moieties which are widely present in vinblastine, strychnine, and (-)-physostigmine.9 There were also few reports for derivatization of the indoline scaffold in order to get more valuable bioactive products.10 Therefore, we have tried to explore our arylation methodology for this important heterocyclic scaffolds with pyrimidine as the directing part, which can be removed easily by heating it at 110 °C in dimethyl sulfoxide solvent.11 Interestingly, we got 90% corresponding C-7 arylated indoline product (7a) under slightly varied reaction conditions, that is, at 100 °C with an oxygen atmosphere. Subsequently, electronically different substituents at para and meta-position of phenylboronic acids were found to be well tolerated under revised reaction conditions and afforded a good yield of arylated products (7b–7f). We have also tried heteroarylation, as well as methylation by utilizing their corresponding boronic acid on indolines but it was found to be incompatible (7g–7h). Consequently, we have also explored arylation of benzo[h]quinoline and 6-(SH)-phenanthridinone with 2a, which afforded 55 and 20% yield, respectively, at 100 °C with no oxygen atmosphere (Table 4, entry 8 and 9). In the same direction, the weak coordinating directing group-containing scaffold, that is, N-tert-butylbenzamide was reacted with 2a, which gave 65% arylation on the ortho position of the amide group (10). These results show broad applicability of our developed methodology.

### Table 2. Substrate Scope of Ru-Catalyzed C–H Arylation

| R1 | R2 | R3 | Yield |
|----|----|----|-------|
| H  | Me | N   | 60%   |
| CN | H  | N   | 65%   |
| Ph | H  | N   | 60%   |
| N  | OMe| N   | 60%   |
| Br | H  | N   | 25%   |
| 3e | 32%|
| 3f | 28%|
| 3g | 35%|
| 3h | 24%|

*Reaction condition: 1 (0.4 mmol), 2 (1.2 mmol), [Ru(p-cymene)Cl2]2 (5 mol %), Ag2O (2.5 equiv), Tf2O (25 mol %), dry THF (2.0 mL), 40 °C, 16 h.

### Table 3. Scope of Rh(III)-Catalyzed C–H Arylation

| R1 | R2 | R3 | Yield |
|----|----|----|-------|
| H  | Me | N   | 60%   |
| CN | H  | N   | 65%   |
| Ph | H  | N   | 60%   |
| N  | OMe| N   | 60%   |
| Br | H  | N   | 25%   |
| 3e | 32%|
| 3f | 28%|
| 3g | 35%|
| 3h | 24%|

*Reaction condition: 1 (0.4 mmol), 2 (1.2 mmol), [Cp*RhCl2]2 (5 mol %), Ag2O (2.5 equiv), Tf2O (25 mol %), dry THF (2.0 mL), 40 °C, 16 h.

### Table 4. Scope of Ru(II)-Catalyzed Arylation of Indolines and Other Substrates

| R1 | R2 | R3 | Yield |
|----|----|----|-------|
| H  | Me | N   | 60%   |
| CN | H  | N   | 65%   |
| Ph | H  | N   | 60%   |
| N  | OMe| N   | 60%   |
| Br | H  | N   | 25%   |
| 5a | 90%|
| 5b | 75%|
| 5c | 60%|
| 5d | 31%|
| 5e | 65%|
| 5f | 50%|
| 5g | 51%|
| 5h | 26%|
| 5i | 0% |
| 5j | 0% |

*Reaction condition: 6 (0.4 mmol), 2 (1.2 mmol), [Ru(p-cymene)Cl2]2 (5 mol %), Ag2O (2.5 equiv), Tf2O (25 mol %), dry THF (2.0 mL), 100 °C, 20 h, O2 atmosphere for indoline substrates only.
In order to anticipate the mechanistic pathway, we have carried out control experiments. A parallel experiment showed that $K_{\text{H}}/K_{\text{D}} = 1.40$ (Scheme 3), which implies that the C–H bond cleavage might not be the rate limiting step.

**Scheme 3. Parallel Experiment for KIE.**

We have also tried to synthesize the ruthenacycle intermediate by the previously reported method but we got quinoline oxygen coordinated ruthenium adduct $\text{Ru1}$, which have been characterized by NMR and single crystal X-ray diffraction technique (Scheme 4a). Further, $\text{Ru1}$ is utilized in place of an active ruthenium catalyst, which afforded the desired product in 50% yield (Scheme 4b).

**Scheme 4. Synthesis of the Ruthenium Adduct and Its Utility as an Catalyst.**

No product was observed by reacting quinoline with $2a$, which confirmed the necessity of N-oxide as a directing part in the quinoline moiety (Scheme 5a). In order to confirm the role of Ru as a deoxygenating agent, we have performed a preliminary experiment, one with the Ru(II) metal and second with the Rh(III) metal in the absence of $2a$, which afforded 35% yield of $4a$ in the first case, while $1a$ was intact in the second case (Scheme 5b,c). In the same consequence, we have added 1 mol % of the Ru catalyst under Rh-catalyzed reaction conditions, which gave 48% arylated product $3a$ (Scheme 5d).

These experiments strongly recommend the role of the Ru(II) metal as a deoxygenating agent along with catalytic activity in the same pot.

Further studies have shown that there is stronger bond dissociation energy in case of the Ru–O bond as compared to that of the Rh–O bond, therefore, it can act as a driving force for the deoxygenation process in case of Ru-catalyzed reaction conditions.

On the basis of these preliminary experiments, we proposed the probable catalytic cycle (Scheme 6). The reaction may proceed through the intermediacy of $\text{Ru1}$ species, which may be formed through lewis acid (ruthenium metal) and lewis base (N-oxide) interaction, followed by $\text{C(8)}–\text{H}$ activation leading to complex $B$, which can undergo transmetallation with arylboronic acid to afford complex $C$, which may oxidized to their higher valent metal complex $D$, in order to facilitate easy reductive elimination to afford product with N-oxide $5a$, which can be easily deoxygenated by the ruthenium catalyst in the same pot to afford the traceless product $3a$. Further, complex $E$ can be oxidized to their active Ru species to continue the catalytic cycle.
CONCLUSIONS

In conclusion, we have developed a new methodology for C8 arylation of quinoline N-oxide, with by utilizing Ru(II)-catalyst to afford deoxygenated arylated product in one pot. Moreover, we have also explored the Rh(III) catalyst, which afforded an arylated product with N-oxide. Additionally, we have also extended this methodology for other class of important heterocyclic scaffolds, indolines. Besides this, 6-(pH)-phenanthridinone and N-tert-butylbenzamide were also utilized for arylation. The role of the Ru metal as a deoxygenating agent was well explored which might be applied in future for other important application.

EXPERIMENTAL SECTION

General Information. All the reactions were carried out in screw cap reaction vials under an air atmosphere. All the solvents were bought from Aldrich in sure-seal bottle and used as such. Chemicals were bought from Sigma-Aldrich, Alfa Aesar, and TCI. For column chromatography, silica gel (230–400 mesh) and silica gel C18 from Merck was used. A gradient elution using n-hexane/ethyl acetate and MeOH/H2O was performed based on Merck aluminum TLC sheets (silica gel 60F254) and silica gel C18 on TLC plates.

Analytical Information. The melting points were recorded on a Börseñt Electrothermometer 9100. All isolated compounds are characterized by 1H NMR, 13C NMR, IR, and high-resolution mass spectrometry (HRMS). Mass spectra were recorded on water Q-ToF-Micro Micromass, high-resolution 6560 Ion Mobility Q-TOF LC/MS (Agilent, Santa Clara, USA). IR was analyzed by Shimadzu IR Prestige-21 with a ZnSe ATR accessory. Copies of 1H, 13C NMR, and 19F NMR are provided in Supporting Information. Nuclear magnetic resonance spectra were recorded either on a Bruker-Avance 600 or 300 and 565 (19F NMR) MHz instrument. All 1H NMR experiments were reported in units ppm and were measured relative to the signals for residual chloroform (7.26 ppm) and methanol (3.31 and 4.78) in the deuterated solvents. All 13C NMR spectra were reported in ppm relative to deuterated chloroform (77.23 ppm) and methanol (49.15 ppm) and were obtained with 1H decoupling.

General Procedure for the Preparation of Quinoline N-Oxides. All the solid reactants, m-CPBA (4 mmol) and quinoline (2 mmol) were added in a Schlenk tube and put under vacuum for 2 h, then CH2Cl2 (4 mL) was added at 0 °C. The reaction was allowed to stir at room temperature for 12 h. On completion, the reaction mixture was extracted with ethyl acetate and the organic extract was dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (230–400 mesh size) with n-hexane/etherOAc as an eluent to yield desired N-oxides.

General Procedure Preparation of Ru1. Under an argon atmosphere, to an oven-dried reaction vial equipped with a magnetic stirring bar was added a solution of [p-cymene]RuCl2 (60 mg, 0.1 mmol) in CH2Cl2 (1 mL), quinoline N-oxide (21.75 mg, 0.15 mmol), silver trifluoroacetate (44.17 mg, 0.2 mmol), and Li2CO3 (14.80 mg, 0.2 mmol). The reaction mixture was stirred at 25 °C for 12 h. An additional portion of silver trifluoroacetate (44.17 mg, 0.2 mmol) was added and the reaction mixture was further stirred at 25 °C for 12 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. n-Hexane (1 mL) was added to the oily residue and the mixture was stirred for 16 h to form a yellow-green precipitant. After filtration, the filtrate was removed and the residue was dissolved in CH2Cl2 (2 mL), doped with n-hexane (3 mL), and the mixture was shaken to precipitate out the dark green chunk, which was removed by filtration through a pad of Celite. Slow evaporation of the filtrate at 25 °C provided the crude product as an orange crystal, which was further purified by recrystallization in CH2Cl2/n-hexane. Orange crystal (36.4 mg, 60%). 1H NMR (600 MHz, CDCl3): δ 8.54–8.58 (m, 2H), 8.14 (d, J = 8.4 Hz, 1H), 7.90–7.93 (m, 2H), 7.69–7.72 (m, 1H), 7.24–7.26 (m, 1H), 2.98–3.04 (m, 1H), 2.29 (s, 3H), 1.33 (d, J = 7.2 Hz, 6H).13C NMR (150 MHz, CDCl3): δ 162.5, 143.4, 140.9, 135.4, 132.4, 129.8, 129.1, 128.4, 120.0, 119.1 114.92 (q, JCF = 289.5 Hz), 99.7, 95.6, 79.8, 31.2, 22.5, 18.3. 19F NMR (565 MHz, CDCl3): δ −75.28.

General Procedure for C8 Arylation of Quinoline N-Oxides with Arylboronic Acids. To an oven-dried screw cap reaction vial charged with a Spinkine magnetic stirbar, the starting material (0.4 mmol), arylboronic acid (1.2 mmol), [Ru(p-cymene)]Cl2 (5 mol%), and silver oxide (2.5 equiv) were weighed, whereas liquid trifluoromethanesulfonate anhydride (25 mol%) were added by a micropipette and dry THF was added by a laboratory syringe, respectively. The reaction vial was closed with a screw cap and allowed to stir at 40 °C for 16 h. After completion, the reaction mixture was allowed to cool, filtered through a silica plug, and washed with CH2Cl2, followed by workup with aqueous NaHCO3 solution and CH2Cl2. The collected CH2Cl2 fraction of the crude reaction mixture was evaporated under reduced pressure. The residue was purified by flash chromatography using silica gel (230–400 mesh size) and n-hexane/etherOAc as an eluent. Note, [Rh Cp*Cl2]2 was used instead of the Ru catalyst in order to get the arylated product with N-oxide.

Characterization Data. 8-Phenylquinoline (Table 2, Entry 3a). It was obtained as a light yellow liquid. Yield = 49.3 mg (60%). Isolated from flash chromatography (5% EtOAc/n-hexane). 1H NMR (600 MHz, CDCl3): δ 8.96–8.97 (m, 1H), 8.21 (dd, J = 7.8, 1.8 Hz, 1H), 7.84 (dd, J = 8.4, 1.2 Hz, 1H), 7.61–7.72 (m, 2H), 7.60–7.63 (m, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.41–7.44 (m, 2H). 13C{1H} NMR (150 MHz, CDCl3): δ 150.4, 146.2, 141.1, 139.7, 136.4, 130.7, 130.5, 128.9, 128.1, 127.7, 127.5, 126.4, 121.1. HRMS (ESI-TOF) m/z: calcd for C16H13ClN [M + H]+, 206.0964; found, 206.0969.

7-Chloro-2-methyl-8-phenylquinoline (Table 2, Entry 3b). It was obtained as a light pale solid. Yield = 66.0 mg (65%). mp 125–127 °C. Isolated from flash chromatography (5% EtOAc/n-hexane). 1H NMR (600 MHz, CDCl3): δ 8.19 (d, J = 8.4 Hz, 1H), 7.84 (dd, J = 8.4 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.44–7.46 (m, 2H), 7.40 (d, J = 7.2 Hz, 1H), 3.73 (d, J = 8.4 Hz, 1H), 3.70–3.71 (m, 2H), 2.54 (s, 3H). 13C{1H} NMR (150 MHz, CDCl3): δ 161.1, 147.9, 139.4, 138.0, 137.3, 135.2, 131.7, 129.2, 128.4, 128.2, 128.0, 126.6, 122.9, 24.88. IR (ZnSe) vmax (cm−1): 1654, 1170, 1033, 763, 630. HRMS (ESI-TOF) m/z: calcd for C16H13ClN [M + H]+, 254.0731; found, 254.0732.

2,8-Diphenylquinoline (Table 2, Entry 3c). It was obtained as a light yellow viscous liquid. Yield = 67.5 mg (60%). Isolated from flash chromatography (5% EtOAc/n-hexane). 1H NMR (600 MHz, CDCl3): δ 8.27 (d, J = 8.4 Hz,
7.35 (dd, 7.8 Hz, 2H), 7.60 (m, 1H), 7.59 (m, 1H), 7.51 (t, J = 8.4 Hz, 1H), 7.48–7.50 (m, 1H).

13C{1H} NMR (150 MHz, CDCl3): δ 153.4, 148.0, 145.1, 143.1, 138.2, 137.5, 130.5, 128.4, 128.2, 127.7, 123.6, 122.3, 122.6. IR (ZnSe) νmax (cm⁻¹): 3237, 1481, 1442, 1193.

HRMS (ESI-TOF) m/z: calc for C19H18NO2 [M + H]^+: 291.1381; found, 291.1381.

5-Phenylbenzo[b]quinoline (Table 2, Entry 3)  

It was obtained as a brownish yellow solid. Yield = 28.6 (28%). mp 100–102 °C. Isolated from flash chromatography (5% EtOAc/n-hexane).

1H NMR (600 MHz, CDCl3): δ 9.04 (dd, J = 8.4, 1.2 Hz, 1H), 9.00 (dd, J = 8.4, 1.8 Hz, 1H), 8.66 (dd, J = 8.4, 1.8 Hz, 1H), 8.01 (s, 1H), 7.96–7.98 (m, 1H), 7.76 (dd, J = 8.4, 1.2 Hz, 2H), 7.67–7.73 (m, 2H), 7.59 (dd, J = 8.4, 2.4 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.43–7.46 (m, 1H).

13C{1H} NMR (150 MHz, CDCl3): δ 149.56, 146.86, 139.85, 139.47, 131.59, 131.33, 130.96, 130.70, 129.65, 128.95, 128.14, 127.66, 127.59, 127.12, 125.94, 122.57, 121.28. HRMS (ESI-TOF) m/z: calc for C19H16N [M + H]^+: 256.1121; found, 256.1124.

8-(3,5-Dimethylphenyl)quinoline (Table 3, Entry 2)  

It was obtained as a greenish viscous semisolid. Yield = 42.0 (45%). Isolated from flash chromatography (5% EtOAc/n-hexane).

1H NMR (600 MHz, CDCl3): δ 8.98 (dd, J = 4.2, 1.8 Hz, 1H), 8.20 (dd, J = 8.4, 1.8 Hz, 1H), 7.81 (dd, J = 8.4, 1.2 Hz, 1H), 7.70 (dd, J = 7.2, 1.8 Hz, 1H), 7.57–7.60 (m, 1H), 7.43 (dd, J = 8.4, 4.2 Hz, 1H), 7.27 (br s, 2H), 7.05 (s, 1H), 2.43 (s, 6H).

13C{1H} NMR (150 MHz, CDCl3): δ 150.4, 146.3, 141.5, 139.6, 137.5, 136.4, 130.4, 129.3, 128.8, 128.5, 127.4, 126.4, 121.0, 21.6. IR (ZnSe) νmax (cm⁻¹): 3059, 1722, 1604, 1481, 1265, 1193, 1028, 854, 783. HRMS (ESI-TOF) m/z: calc for C22H22N [M + H]^+: 324.1277; found, 324.1279.

8-(p-Tolyl)quinoline (Table 3, Entry 3)  

It was obtained as a yellow viscous liquid. Yield = 45.6 mg (52%). Isolated from flash chromatography (5% EtOAc/n-hexane).

1H NMR (600 MHz, CDCl3): δ 8.96 (dd, J = 4.2, 1.8 Hz, 1H), 8.19–8.21 (m, 1H), 7.81–7.82 (m, 1H), 7.73 (dd, J = 7.2, 1.2 Hz, 1H), 7.59–7.61 (m, 3H), 7.41 (dd, J = 8.4, 4.2 Hz, 1H), 7.32 (dd, J = 7.8 Hz, 2H).

13C{1H} NMR (150 MHz, CDCl3): δ 150.6, 146.5, 141.3, 137.4, 137.0, 136.6, 130.4, 130.8, 129.3, 128.3, 127.6, 126.6, 121.3, 21.6. HRMS (ESI-TOF) m/z: calc for C22H22N [M + H]^+: 324.1211; found, 220.1119.

8-(4-Pentylphenyl)quinoline (Table 3, Entry 3m)  

It was obtained as a yellow phenylquinoline. Yield = 66.1 mg (60%). Isolated from flash chromatography (5% EtOAc/n-hexane).

1H NMR (600 MHz, CDCl3): δ 8.96 (dd, J = 4.2, 1.8 Hz, 1H), 8.20 (dd, J = 4.2, 1.8 Hz, 1H), 7.81 (dd, J = 7.8, 1.2 Hz, 1H), 7.74 (dd, J = 7.2, 1.2 Hz, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.58–7.61 (m, 1H), 7.41 (dd, J = 7.8, 4.2 Hz, 1H), 7.32 (dd, J = 7.8 Hz, 2H), 2.69 (t, J = 7.8 Hz, 2H), 1.68–1.73 (m, 2H), 1.39–1.41 (m, 4H), 0.92–0.94 (m, 3H).

13C{1H} NMR (150 MHz, CDCl3): δ 150.2, 146.1, 142.1, 140.9, 136.8, 136.3, 130.5, 130.3, 128.8, 128.1, 127.3, 126.3, 120.9, 35.8, 31.7, 31.1, 22.6, 14.1. IR (ZnSe) νmax (cm⁻¹): 2926, 1571, 823, 792, 756. HRMS (ESI-TOF) m/z: calc for C30H22N [M + H]^+: 276.1745; found, 276.1746.

8-[1(1′)Biphenyl-4-yl]quinoline (Table 3, Entry 3n)  

It was obtained as a white solid. Yield = 28.1 mg (25%). mp 155–157 °C. Isolated from flash chromatography (5% EtOAc/n-hexane).

1H NMR (300 MHz, CDCl3): δ 8.99 (dd, J = 4.2, 1.8 Hz, 1H), 8.23 (dd, J = 8.4, 1.8 Hz, 1H), 7.61–7.87 (m, 1H), 7.51–7.52 (m, 2H), 7.49–7.50 (m, 2H).

13C{1H} NMR (150 MHz, CDCl3): δ 150.2, 146.1, 142.1, 140.9, 136.8, 136.3, 130.5, 130.3, 128.8, 128.1, 127.3, 126.3, 120.9, 35.8, 31.7, 31.1, 22.6, 14.1. IR (ZnSe) νmax (cm⁻¹): 2926, 1571, 823, 792, 756. HRMS (ESI-TOF) m/z: calc for C30H22N [M + H]^+: 276.1745; found, 276.1746.

ACS Omega 2020, 5, 904–913
8-(4-Methoxyphenyl)quinoline (Table 1, Entry 3a) It was obtained as a white solid. Yield was 49.9 mg (52%).

1H NMR (600 MHz, CDCl3): δ 8.96 (dd, J = 4.2, 1.8 Hz, 1H), 8.22 (dd, J = 8.4, 1.8 Hz, 1H), 7.85–7.86 (m, 1H), 7.72 (dd, J = 7.2, 1.2 Hz, 1H), 7.65 (dd, J = 8.4 Hz, 2H), 7.60–7.63 (m, 1H), 7.47 (dd, J = 8.4 Hz, 2H), 7.44 (m, 1H). 13C NMR (150 MHz, CDCl3): δ 150.3, 145.8, 139.6, 137.9, 136.3, 133.4, 131.8, 130.1, 128.7, 128.2, 126.2, 126.1. IR (ZnSe) νmax (cm⁻¹): 1658, 1593, 1489, 1087, 817, 729. HRMS (ESI-TOF) m/z: calc’d for C16H13NO [M + H]+, 240.0575; found, 240.0574.

8-(4-Chloroquinoline (Table 1, Entry 3b). It was obtained as a yellowish brown semisolid. Yield = 33.0 mg (66%).

1H NMR (600 MHz, CDCl3): δ 8.36 (d, J = 6.0 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 8.4, 1.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.53 (dd, J = 7.2, 1.2 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.46 (q, J = 4.2 Hz, 1H). 13C NMR (150 MHz, CDCl3): δ 192.4, 150.7, 146.2, 145.9, 139.7, 136.6, 135.4, 131.5, 130.6, 129.6, 128.9, 126.4, 126.1. IR (ZnSe) νmax (cm⁻¹): 3051, 2922, 1660, 1593, 1489, 1463, 1381, 1087, 962, 817, 763, 729. HRMS (ESI-TOF) m/z: calc’d for C16H12NO [M + H]+, 234.0913; found, 234.0911.

8-Fluoroquinoline N-Oxide (Table 3, Entry 5a). It was obtained as a yellow semisolid. Yield = 79.7 mg (90%).

1H NMR (600 MHz, CDCl3): δ 8.79 (d, J = 5.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.4, 1.8 Hz, 1H), 7.61 (t, J = 7.2, 1.2 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.36–7.39 (m, 2H), 7.32–7.34 (m, 3H), 7.27–7.30 (m, 1H). 13C NMR (150 MHz, CDCl3): δ 142.8, 139.2, 137.2, 136.5, 134.4, 132.1, 128.5, 128.2, 127.8, 127.0, 126.4, 126.3, 121.3. HRMS (ESI-TOF) m/z: calc’d for C16H12NO [M + H]+, 222.0913; found, 222.0916.

6-Fluoro-8-phenylquinoline N-oxyde (Table 3, Entry 5b). It was obtained as a yellowish viscous semisolid. Yield = 71.7 mg (75%).

Isolated from flash chromatography (90% EtOAc/n-hexane). 1H NMR (600 MHz, CDCl3): δ 8.31 (d, J = 6.0 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.50 (dd, J = 7.8, 3.0 Hz, 1H), 7.35–7.40 (m, 3H), 7.30–7.32 (m, 4H). 13C NMR (150 MHz, CDCl3): δ 161.0, 159.4, 141.7, 139.9, 136.6, 133.3, 127.9, 127.2, 126.8, 125.6, 124.0, 122.4, 111.6. IR (ZnSe) νmax (cm⁻¹): 3055, 1511, 1325, 1276, 1159, 904, 763, 696, 638. HRMS (ESI-TOF) calc’d for C16H10FNO [M + H]+, 240.0819; found, 240.0815.

8-Fluoroquinoline N-Oxide (Table 3, Entry 5c). It was obtained as a yellow solid. Yield = 66.3 mg (66%).

1H NMR (600 MHz, CDCl3): δ 8.36 (d, J = 6.0 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 8.4, 1.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.53 (dd, J = 7.2, 1.8 Hz, 1H), 7.25–7.29 (m, 3H), 6.92 (d, J = 8.4 Hz, 2H), 3.86 (s, 3H). 13C NMR (150 MHz, CDCl3): δ 158.3, 139.5, 137.2, 136.3, 135.2, 134.6, 132.3, 129.4, 128.3, 127.8, 126.2, 121.2, 112.5, 55.4. IR (ZnSe) νmax (cm⁻¹): 3379, 2854, 1514, 1286, 1103, 1031, 823, 792, 758. HRMS (ESI-TOF) calc’d for C16H12NO2 [M + H]+, 267.0764; found, 267.0769.

8-Fluoroquinoline N-Oxide (Table 3, Entry 6a). It was obtained as a yellow solid. Yield = 64.9 mg (50%).

1H NMR (600 MHz, CDCl3): δ 8.36 (d, J = 6.0 Hz, 1H), 7.85–7.86 (m, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.59 (m, 1H), 7.50 (dd, J = 7.2, 1.2 Hz, 1H), 7.26–7.29 (m, 1H), 6.97 (s, 1H), 6.94 (s, 2H), 2.36 (s, 6H). 13C NMR (150 MHz, CDCl3): δ 150.1, 142.8, 139.4, 137.1, 136.8, 136.3, 134.3, 132.1, 132.4, 128.0, 127.5, 126.1, 121.2, 21.6. IR (ZnSe) νmax (cm⁻¹): 2920, 2852, 1656, 1598, 1413, 1219, 1031, 819, 756. HRMS (ESI-TOF) m/z: calc’d for C16H12NO2 [M + H]+, 252.1019; found, 252.1015.
CH₂Cl₂, followed by workup with aqueous NaHCO₃ solution and CH₂Cl₂. The collected CH₂Cl₂ fraction of the crude reaction mixture was evaporated under reduced pressure. The residue was purifed by flash chromatography using silica gel (230–400 mesh size) and n-hexane/EtOAc as the eluent. 1H and 13C NMR spectra were recorded in CDCl₃.

**Characterization Data.** 7-Phenyl-1-(pyrimidin-2-yl)-indoline (Table 4, Entry 7a).

- **7-(3,5-Dimethyl)phenyl-1-(pyrimidin-2-yl)-indoline (Table 4, Entry 7d).** It was obtained as a white solid. Yield = 41.8 mg (35%), mp 169–170 °C. Isolated from flash chromatography (5% EtOAc/n-hexane). 1H NMR (300 MHz, CDCl₃): δ 7.98 (d, J = 4.8 Hz, 2H), 7.6 (s, 4H), 7.3 (m, 1H), 7.22–7.25 (m, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.45 (t, J = 4.8 Hz, 1H), 4.47 (t, J = 8.1 Hz, 2H), 3.19 (m, 1H). 13C NMR (75 MHz, CDCl₃): δ 157.6, 156.8, 147.5, 141.3, 140.0, 135.5, 132.0, 128.7, 126.8, 127.5, 124.9, 124.1, 112.5, 109.6, 52.2, 29.5. IR (ZnSe) νmax (cm⁻¹): 2916, 2280, 1552, 1452, 1402, 766, 771, 738. HRMS (ESI-TOF) m/z: calc for C₂₀H₂₀N₃ [M + H]+, 302.1625; found, 302.1649.

- **7-(3,5-Bis(trifluoromethyl)phenyl)-1-(pyrimidin-2-yl)-indoline (Table 4, Entry 7f).** It was obtained as a yellow solid. Yield = 101.5 mg (62%), mp 78–79 °C. Isolated from flash chromatography (5% EtOAc/n-hexane). 1H NMR (300 MHz, CDCl₃): δ 7.94 (d, J = 4.8 Hz, 2H), 7.78 (s, 2H), 7.61 (s, 1H), 7.33 (dd, J = 7.2, 6.0 Hz, 1H), 7.26–7.28 (m, 1H), 7.14–7.17 (m, 1H), 6.43 (t, J = 4.8 Hz, 1H), 4.48–4.51 (m, 2H), 3.22 (t, J = 7.8 Hz, 2H). 13C NMR (75 MHz, CDCl₃): δ 158.9, 156.7, 144.8, 141.4, 135.7, 131.6 (q, JCF = 33.0 Hz), 128.6, 127.3, 127.1, 125.2, 124.15, 123.43 (q, JCF = 291.0 Hz), 119.54 (q, JCF = 4.5 Hz), 112.46, 52.29, 29.43. 19F NMR (565 MHz, CDCl₃): δ −62.87. IR (ZnSe) νmax (cm⁻¹): 1575, 1548, 1465, 1450, 1381, 1276, 1165, 1114, 1091, 798, 682. HRMS (ESI-TOF) m/z: calc for C₂₀H₁₈F₆N₃ [M + H]+, 410.1086; found, 410.1086.

**10-Phenylbenz[h]quinoline (Table 4, Entry 8).** It was obtained as a light yellow solid. Yield = 56.2 mg (55%). Isolated from flash chromatography (5% EtOAc/n-hexane). 1H NMR (600 MHz, CDCl₃): δ 8.45 (dd, J = 4.2, 1.8 Hz, 1H), 8.09 (dd, J = 8.4, 1.8 Hz, 1H), 7.94 (dd, J = 7.8, 1.2 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.69–7.71 (m, 2H), 7.58 (dd, J = 7.2, 1.8 Hz), 7.42–7.44 (m, 2H), 7.37–7.40 (m, 3H), 7.33 (dd, J = 7.8, 4.2 Hz, 1H). 13C NMR (150 MHz, CDCl₃): δ 146.99, 144.95, 146.6, 141.8, 135.3, 135.1, 131.6, 132.9, 128.9, 128.4, 128.1, 127.5, 127.4, 127.2, 126.0, 125.8. HRMS (ESI-TOF) m/z: calc for C₁₉H₁₄F₃N₂ [M + H]+, 256.1121; found, 256.1132.

**7-Phenylphenanthridin-6(5H)-one (Table 4, Entry 9).** It was obtained as a light yellow solid. Yield = 21.7 mg (20%). mp 265–266 °C. Isolated from flash chromatography (5% EtOAc/n-hexane). 1H NMR (300 MHz, CDCl₃): δ 11.24 (br s, 1H, NH), 8.36 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 8.1 Hz, 1H), 8.20.
N-(tert-Butyl)-[1,1’-biphenyl]-2-carboxamide (Table 4, Entry 10). It was obtained as a whitish brown solid. Yield = 65.9 mg (65%), mp 97–100 °C. Isolated from manual column chromatography by using reverse phase C-18 silica gel (75% MeOH/H2O). 1H NMR (600 MHz, CDCl3): δ 7.27 (d, J = 7.8 Hz, 1H), 7.39–7.46 (m, 7H), 7.33 (d, J = 7.8 Hz, 1H), 7.46 (m, 7H), 7.33 (d, J = 7.8 Hz, 1H), 5.00 (br s, 1H, NH), 1.10 (s, 9H). 13C NMR (150 MHz, CDCl3): δ 140.6, 139.5, 136.9, 130.1, 129.9, 129.1, 129.0, 128.7, 127.8, 51.5, 28.3. HRMS (ESI-TOF) m/z: calcd for C37H30NO [M + H]+, 524.1539; found, 524.1544.

Parallel Reaction for KIE Study. In two different screw capped vials with a Spinnvane triangular-shaped stirbar separately placed quinoline N-oxide (1a) (0.1 mmol) and C8-aq-quinoline N-oxide (1a-d1), (0.1 mmol) were reacted with arylboronic acid (0.1 mmol) and (0.1 mmol) and Ag2O (2.5 equiv), and dry THF were added. The reaction was stirred at 40 °C for 5 h. Both the reactions mixtures were filtered through a silica plug and extracted with aqueous NaHCO3 and CH2Cl2. The organic phase was dried over Na2SO4 and removed under reduced pressure. Further, it has been isolated by flash chromatography and the analysis was performed on the basis of the isolated yield (Scheme 3).

Ru1 as an Intermediate (Scheme 4). To a screw capped vial with a Spinnvane triangular-shaped stirbar quinoline N-oxide (0.1 mmol), arylboronic acid (3 equiv), [Ru(p-cymene)Cl2] (5 mol %), TfO (25 mol %), and Ag2O (2.5 equiv) in dry THF were added. The reaction was stirred at 40 °C for 16 h. After completion, the reaction was filtered through a silica plug and washed with aqueous NaHCO3 and CH2Cl2. The organic phase was dried over Na2SO4 and removed under reduced pressure for 1H NMR analysis by using 1,1,2,2-tetrachloroethane as an internal standard, which have shown 50% yield.

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References
(1) Tan, R.; Jia, P.; Rao, Y.; Jia, W.; Hadzovic, A.; Yu, Q.; Li, X.; Song, D. Platinum Complexes Supported by Novel Tetradentate Ligands with Quinoline Functionalities for Tandem C–Cl Activation and Dearomatization. Organometallics 2008, 27, 6614–6622.
(2) Properzi, R.; Marcantoni, E. Construction of Heterocyclic Structures by Trivalent Cerium Salts Promoted Bond Forming Reactions. Chem. Soc. Rev. 2014, 43, 779–791.
(3) Kumar, S.; Bawa, S.; Gupta, H. Biological Activities of Quinoline Derivatives. Mini-Rev. Med. Chem. 2009, 9, 1648–1654.
(4) Macdonald, D.; Perrier, H.; Liu, S.; Laliberté, F.; Rasori, K.; Robichaud, A.; Masson, P.; Huang, Z. Hunting the Emesis and Efficacy Targets of PDE4 Inhibitors: Identification of the Photoaffinity Probe 8-(3-Azidoephenoxy)-4-(4-iodo-1H-1-imidazolyl) methylquinoline (APIIMQ). J. Med. Chem. 2000, 43, 3820–3823.
(5) Huang, C. Q.; Wilcoxen, K.; McCarthy, J. R.; Haddad, M.; Webb, T. R.; Gu, J.; Xie, Y.-F.; Grigoriadis, D. E.; Chen, C. Synthesis and SAR of 8-Aryquinolines as Potent Corticotropin-Releasing Factor1 (CRF1) Receptor Antagonists. Bioorg. Med. Chem. Lett. 2003, 13, 3375–3379.
(6) Rossiter, S.; Peron, J.-M.; Whiffeld, P. J.; Jones, K. Synthesis and Anthelmintic Properties of Aryquinolines with Activity Against Drug-Resistant Nematodes. Bioorg. Med. Chem. Lett. 2005, 15, 4806–4808.
(7) Crabtree, R. H.; Lei, A. Introduction: CH Activation. Chem. Rev. 2011, 117, 8481–8482.
(8) Sharma, R.; Sharma, U. Distant C-H Activation/Dearomatization. Organometallics 2017, 36, 4806–4808.
(9) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavalier, M.; Fagnou, K. Palladium-Catalyzed Direct Arylation of Azirines and Azole-N-Oxides: Reaction Development, Scope, and Applications in Synthesis. J. Am. Chem. Soc. 2009, 131, 3291–3306.
(10) Yan, G.; Borah, A. J.; Yang, M. Transition-Metal-Catalyzed Site-Selective C-H Functionalization of Quinolines beyond C2 Selectivity. ACS Catal. 2015, 5, 5031–5040.
(11) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavalier, M.; Fagnou, K. Palladium-Catalyzed Direct Arylation of Azirines and Azole-N-Oxides: Reaction Development, Scope, and Applications in Synthesis. J. Am. Chem. Soc. 2009, 131, 3291–3306.
(12) Yan, G.; Borah, A. J.; Yang, M. Recent Advances in Catalytic Functionalization of N-Oxide Compounds via C-H Bond Activation. Adv. Synth. Catal. 2014, 356, 2375–2394.
(13) Zhang, L.; Wang, Y. Recent Developments in the Chemistry of Heteroaromatic N-Oxides. Synthesis 2015, 47, 289–305.
(14) Kwak, J.; Kim, M.; Chang, S. Rh(III)-Catalyzed Direct and Selective Arylation of Quinolines at the 8-Position. J. Am. Chem. Soc. 2011, 133, 3780–3783.
(15) Sharma, U.; Park, Y.; Chang, S. Rh(III)-Catalyzed Traceless Coupling of Quinoline N-Oxides with Internal Diarylalkynes. J. Org. Chem. 2014, 79, 9899–9906.
(16) Stephens, D. E.; Laky-Bettia, J.; Atesin, A. C.; Atesin, T. A.; Chavez, G.; Arman, H. D.; Laronion, O. V. Palladium-Catalyzed C8-Selective C-H Arylation of Quinoline N-Oxides: Insights into the Electronic, Steric, and Solvation Effects on the Site Selectivity by Mechanistic and DFT Computational Studies. ACS Catal. 2015, 5, 167–175.
(17) Shin, K.; Park, S.-W.; Chang, S. C–C Activation on Arylidrazonan Salts Leading to the External Oxidant-Free Approach. J. Am. Chem. Soc. 2015, 137, 8584–8592.
(18) Sharma, R.; Kumar, R.; Kumar, L.; Sharma, U. RhIII-Catalyzed Dehydrogenative Coupling of Quinoline N-Oxides with Alkenes: N-Oxide as Traceless Directing Group for Remote C–C Activation. Eur. J. Org. Chem. 2015, 2015, 7519–7528.
(19) Chen, X.; Cui, X.; Wu, Y. "One-Pot" Approach to 8-Acylated 2-Quinolinones via Palladium-Catalyzed Regioselective
Acylation of Quinoline N-Oxides. Org. Lett. 2016, 18, 2411–2414. (g) Chen, X.; Cui, X.; Wu, Y. C8-Selective Acylation of Quinoline N-Oxides with α-Oxocarboxylic Acids via Palladium-Catalyzed Regioselective C-H Bond Activation. Org. Lett. 2016, 18, 3722–3725. (h) Wang, B.; Li, C.; Liu, H. Cp*Rh(III)-Catalyzed Directed C–H Methylation and Arylation of Quinoline N-Oxides at the C-8 Position. Adv. Synth. Catal. 2017, 359, 3029–3034. (i) Sharma, R.; Kumar, J.; Kumar, R.; Sharma, U. Rhodium-Catalyzed Remote C8-Alkylation of Quinolines with Activated and Unactivated Olefins: Mechanistic Study and Total Synthesis of EP4 Agonist. Adv. Synth. Catal. 2017, 359, 3022–3028. (j) Ghosh, B.; Biswas, A.; Chakraborty, S.; Samanta, R. RhIII-Catalyzed Direct C8-Arylation of QuinolineN-Oxides using Diazonaphthalen-2(1H)-ones: A Practical Approach towards 8-aza BINOL. Chem.—Asian J. 2018, 13, 2388–2392. (k) Sharma, R.; Kumar, R.; Kumar, R.; Upadhyay, P.; Sahal, D.; Sharma, U. Rh(III)-Catalyzed C(8)-H Functionalization of Quinolines via Simultaneous C-C and C-O Bond Formation: Direct Synthesis of Quinoline Derivatives with Antiplasmodial Potential. J. Org. Chem. 2018, 83, 12702–12710. (l) Dhiman, A. K.; Gupta, S. S.; Sharma, R.; Kumar, R.; Sharma, U. Rh (III)-Catalyzed C(8) –H Activation of Quinoline N-Oxides: Regioselective C–Br and C–N Bond Formation. J. Org. Chem. 2019, 84, 12871. (m) Sharma, R.; Kumar, R.; Sharma, U. Rh(O2)3-Catalyzed C8-Olefination of Quinoline N-Oxides with Activated and Unactivated Olefins. J. Org. Chem. 2019, 84, 2786–2797.

(7) (a) Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. Palladium-Catalyzed Alkenylation of Quinoline-N-oxides via C–H Activation under External-Oxidant-Free Conditions. J. Am. Chem. Soc. 2009, 131, 13888–13889. (b) Wu, Z.; Pi, C.; Cui, X.; Bai, J.; Wu, Y. Direct C2-Alkylation of QuinolineN-Oxides with EthynylPalladium-Catalyzed Dehydrogenative Cross-Coupling Reaction. Adv. Synth. Catal. 2013, 355, 1971–1976. (c) Li, G.; Jia, C.; Sun, K. Copper-Catalyzed Intermolecular Dehydrogenative Amidation/Amination of Quinoline N-oxides with Lactams/Cyclazines. Org. Lett. 2013, 15, 5198–5201. (d) Bering, L.; Antontchik, A. P. Regioselective Metal-Free Cross-Coupling of Quinoline N-oxides with Boronic Acids. Org. Lett. 2015, 17, 3134–3137. (e) Kumar, R.; Kumar, R.; Dhiman, A. K.; Sharma, U. Regioselective Metal-Free C2–H Arylation of Quinoline N-Oxides with Aryldiazonium Salts/Anilines under Ambient Conditions. Asian J. Org. Chem. 2017, 6, 1043–1053. (f) Xie, L.-Y.; Peng, S.; Jiang, L.-L.; Peng, X.; Xia, W.; Yu, X.; Wang, X.-X.; Cao, Z.; He, W.-M. AgBF4-Catalyzed Deoxygenative C2-Amination of Quinoline N-oxides with Isothiocyanates. Org. Chem. Front. 2019, 6, 167–171. (g) Kim, J.; Kim, S.; Kim, D.; Chang, S. Ru-Catalyzed Deoxygenative Regioselective C8–H Arylation of Quinoline N-Oxides. J. Org. Chem. 2019, 84, 13150.

(9) (a) Kuehne, M. E.; Bornmann, W. G.; Markö, I.; Qin, Y.; Leboulluec, K. L.; Frasier, D. A.; Xu, F.; Mulamba, T.; Ensiger, C. L.; Borman, L. S.; Huot, A. E.; Exon, C.; Bizzarro, F. T.; Cheung, J. B.; Borman, L. S.; Huot, A. E.; Exon, C.; Bizzarro, F. T.; Cheung, J. B.; Bane, S. L. Syntheses and Biological Evaluation of Vinblastine Congeners. Org. Biomol. Chem. 2003, 1, 2120–2136. (b) Zhang, H.; Boonsombat, J.; Padwa, A. Total Synthesis of α-[4 + 2]-Cycloaddition/Rearrangement Cascade. Org. Lett. 2007, 9, 279–282. (c) Bui, T.; Stry, S.; Barbas, C. F.; III Thiourea-Catalyzed Highly ENantio- and Diastereoselective Additions of Oxindoles to Nitroolefins: Application to the Formal Synthesis of (+)-Phystostigmine. J. Am. Chem. Soc. 2009, 131, 8758–8759. (10) (a) Siddiqui, M. A.; Snieckus, V. Concise Syntheses of the Amaryllidaceae Alkaloids Ungerimine and Hippadine via the Suzuki Aryl-Aryl Cross Coupling Reaction. Tetrahedron Lett. 1990, 31, 1523–1526. (b) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. Pd(II)-Catalyzed meta-C–H Olefination, Arylation, and Acetoxylation of Indoles Using a U-Shaped Template. J. Am. Chem. Soc. 2014, 136, 10807–10813. (c) Han, S. H.; Choi, M.; Jeong, T.; Sharma, S.; Mishra, N. K.; Park, J.; Oh, J. S.; Kim, W. J.; Lee, J. S.; Kim, I. S. Rhodium-Catalyzed C-H Arylation of Indoles with Allylic Alcohols: Direct Access to β-Aryl Carbonyl Compounds. J. Org. Chem. 2015, 80, 11092–11099. (d) Bose, A.; Mal, P. Using weak interactions to control C-H mono-nitration of indolines. Chem. Commun. 2017, 53, 11368–11371. (e) De, P. B.; Pradhan, S.; Banerjee, S.; Punniyamurthy, T. Expedient cobalt(ii)-catalyzed site-selective C7-arylation of indolines with arylboronic acids. Chem. Commun. 2018, 54, 2494–2497. (f) Luo, H.; Xie, Q.; Sun, K.; Deng, J.; Xu, L.; Wang, K.; Luo, X. Rh(III)-catalyzed C–7 arylation of indoles with arylsilanes via C–H activation. RSC Adv. 2019, 9, 18191–18195.