无金属条件下通过与醚的自由基偶联反应实现 N-氧化物的 C-2 烷基化反应

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摘要 在无金属条件下通过自由基偶联反应, 实现了醚类与 N-氧化物的 C-2 烷基化反应, 反应条件温和, 只需加入氧化剂二叔丁基过氧化物(DTBP)就能够以中等至高产率获得各种所需产物。

关键词 喹啉-N-氧化物; 醚; 烷基化; 自由基偶联

Metal-Free C-2 Alkylation of N-Oxides with Ethers via Radical Cross-Coupling Reactions

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Abstract The C-2 alkylation of ethers and N-oxides was achieved via free radical coupling reaction under metal-free conditions. The reaction conditions are mild, and the desired products can be obtained in medium to high yields with the addition of the oxidant di-*tert*-butyl peroxide (DTBP).

Keywords quinoline N-oxides; ethers; alkylation; radical cross coupling

1 Introduction

Quinoline-containing cyclic compounds are important nitrogen-containing heteroaromatics and are prevalent key structural motifs in bioactive natural products, synthetic drugs and materials.^[1-9] Consequently, the development of mild and efficient methods for their construction is a hot topic in organic synthesis and pharmaceutical chemistry.^[10-13] In view of the abundance and accessibility of quinoline N-oxides, the direct C-2 functionalization of quinoline N-oxides is an attractive alternative compared with these reported methods.^[14-17] Recently, an environ-

mental-friendly method for the clean preparation of various quinolin-2-yl substituted ureas from the reaction of quinoline N-oxides and carbodiimides was presented by He's group.^[18] The first example of a metal and reductant-free deoxygenative sulfonylation of quinoline N-oxides with sodium sulfonates was also realized by this group. In this reaction, sodium sulfonates play dual roles of an oxidant and activating reagent.^[19] Cui's group showed an approach to polyheterocycles bearing furoquinoline and C-2-male-imide-substituted quinoline *via* tandem reactions between quinoline N-oxides and maleimides.^[20] The cross-dehydrogenative coupling of quinoline N-oxides with 1,3-azoles

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was also developed by Cui and coworkers. The desired products were isolated in good to excellent yields.^[21] Hartwig's group found that *N*-heterocyclic trifluoromethyl ethers could be efficiently synthesized via the reaction of *N*-oxides with trifluoromethyl or higher perfluoroalkyl triflate.^[22] The reactions of quinoline *N*-oxide with other substrates such as terminal alkyne,^[23] alcohols,^[24] H-phosphonates^[25] and so on^[26–30] were also reported in recent years.

On the other hand, the direct functionalization of C(sp³)—H bond has attracted wide research interest both in academic laboratories and chemical industries.^[31–38] Among these reactions, the functionalization of C(sp³)—H bonds adjacent to oxygen of alcohols was particularly powerful.^[39–43] For examples, in 2013, Cui's group described a strategy for the direct alkylation of quinoline *N*-oxides with ethers. Quinoline-containing heterocyclic molecules in moderate to excellent yields could be obtained.^[44] Li's group described a Fe-catalyzed cross-dehydrogenative-coupling reaction of ketone esters with ether for C—C bond formation.^[45] Ethers such as 1,4-dioxane were also good substrates to react with carboxylic acids^[46] and 2-hydroxyacetophenone.^[47] The cross-coupling of pyridine *N*-oxides and ethers was described by Wang group.^[48] However, new versatile and practical methods for the functionalization of C(sp³)—H bond are still highly desired. In line with our interest in C—H bond activation and functionalization of heterocyclic compounds.^[49–55] Herein, we describe the cross coupling reaction of quinoline *N*-oxide and C(sp³)—H bonds adjacent to oxygen of ether.

1 Results and discussion

At the beginning of our investigation, the reaction of quinoline 1-oxide with 1,4-dioxane was chosen as a model reaction. The results are summarized in Table 1. It was found that the reaction could generate the corresponding product in 65% yield when *tert*-butyl hydroperoxide (TBHP, 5.0~6.0 mol/L in decane) was used as oxidant (Table 1, Entry 1). However, TBHP (70% in H₂O) did not work in the model reaction (Table 1, Entry 2). Di-*tert*-butyl peroxide (DTBP) was the most effective oxidant for this reaction and the desired product could be isolated in 73% yield (Table 1, Entry 3). Other oxidants such as dicumyl peroxide (DCP), *tert*-butyl peroxybenzoate (TBPB), 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ), K₂S₂O₈, Na₂S₂O₈ and (NH₄)₂S₂O₈ were less effective (Table 1, Entries 4~9). When the equivalent of 1,4-dioxane was doubled, the yield of the desired product was elevated to 89% (Table 1, Entry 10). We next turned our attention to investigate the effect of additives on the reaction. To our disappointment, all the additives we examined led to slower reactions (Table 1, Entries 11~14).

Under the optimized reaction conditions, the scope of quinoline *N*-oxides and ethers was examined and the results were summarized in Table 2. To our delight, substituted quinoline *N*-oxides with a wide range of synthetically val-

uable functional groups underwent a coupling reaction to form the desired products in good to excellent yields (**3a**~**3g**). Either electron-donating or electron-withdrawing

Table 1 Optimization of the reaction conditions^a

Entry	Oxidant (3 equiv.)	Additives (1 equiv.)	Yield/%
1	TBHP	—	65
2 ^b	TBHP	—	Trace
3	DTBP	—	73
4	DCP	—	Trace
5	TBPB	—	12
6	DDQ	—	Trace
7	K ₂ S ₂ O ₈	—	Trace
8	Na ₂ S ₂ O ₈	—	Trace
9	(NH ₄) ₂ S ₂ O ₈	—	Trace
10 ^c	DTBP	—	89
11 ^c	DTBP	K ₂ CO ₃	40
12 ^c	DTBP	<i>t</i> -BuOK	21
13 ^c	DTBP	Na ₂ CO ₃	61
14 ^c	DTBP	DBU	62

^a Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mL), oxidant (3.0 equiv.), additives (1 equiv.), 100 °C, 24 h. ^b TBHP (70% in H₂O). ^c **2a** (2.0 mL).

groups are well tolerated in this system. It should be noted that 6-fluoroquinoline 1-oxide also reacted smoothly with dioxane and provided the desired product with 81% yield (**3e**). The reaction of *N*-oxides with various ethers was also investigated (**3h**~**3r**). It can be seen that tetrahydro-2*H*-pyran, tetrahydrofuran and tetrahydrothiophene all underwent a coupling reaction smoothly with *N*-oxides. To our disappointment, chain ethers, such as *tert*-butyl methyl ether and ether were not compatible in this transformation. The same excellent results were also obtained when this method was performed at a gram scale using quinolin *N*-oxide as substrate (Scheme 1). This example clearly demonstrates the preparative utility of this newly developed method.

Scheme 1 A gram-scale preparation of **3a**

A control experiment was designed and performed to acquire some insight into mechanism of the coupling reaction. When 2 equiv. of TEMPO were added as the radical scavengers under standard conditions, the coupling reaction was suppressed, suggesting that a free-radical pathway was involved in the catalytic cycle (Scheme 2).

Table 2 Reaction scope^a

^a Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 mL), DTBP (3.0 equiv), 100 °C, 24 h.

Scheme 2 Investigation of mechanism

On the basis of above-mentioned experiment results and previous reports,^[56–58] a proposed reaction mechanism was described in Scheme 3. Firstly, *tert*-butoxy radical (**A**) was generated via homolytic cleavage of dibutylperoxide (DTBP). Then the reaction of **A** with dioxane occurred to afford the radical **B**. Next the radical **D** was generated from the addition reaction of radical **B** with quinoline *N*-oxide. Finally, the intermediate **D** followed by deprotonation to afford the desired product **E**. It is worth noting that intermediate **C** which was generated from the reaction of TEMPO with radical **B** has been confirmed by HRMS.

2 Conclusions

In conclusion, we have demonstrated an inexpensive method for the metal-free C-2 alkylation of *N*-oxides with

Scheme 3 Proposed mechanism

ethers. A series of desired products were obtained in good to excellent yields. The developed transformation could also be performed in gram-scale which made this reaction have

good potential in synthetic chemistry. Mechanism investigation revealed that a radical process was involved in this procedure. Further investigation of the reaction mechanism and its applications are underway in our laboratory.

3 Experimental

2.1 Instruments and reagents

NMR spectra were recorded at 500 MHz for protons on a BRUKER AVANCE III HD spectrometers. ^1H NMR chemical shifts (δ) are relative to TMS ($\delta=0.0$). Chemical shifts for ^{13}C NMR spectra are reported from tetramethylsilane with the solvent as the internal standard. All major chemicals and solvents were obtained from commercial sources and used without further purification.

2.2 Synthesis of 2-(1,4-dioxan-2-yl)quinoline 1-oxide (3)

A sealable reaction tube equipped with a magnetic stirrer bar was charged with quinoline *N*-oxide (0.2 mmol), 1,4-dioxane (2 mL) and DTBP (3.0 equiv.). The reaction vessel was carried out 100 °C. After completion, it was diluted with ethyl acetate, and washed with water. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel to afford the corresponding product **3**.

2-(1,4-Dioxan-2-yl)quinoline 1-oxide (**3a**)^[59]: ^1H NMR (500 MHz, CDCl_3) δ : 8.74 (d, $J=8.8$ Hz, 1H), 7.86 (d, $J=8.1$ Hz, 1H), 7.82~7.74 (m, 2H), 7.67~7.60 (m, 2H), 5.56 (dd, $J=9.5$, 2.7 Hz, 1H), 4.60 (dd, $J=11.1$, 2.7 Hz, 1H), 4.11~3.97 (m, 2H), 3.93~3.84 (m, 1H), 3.77 (ddd, $J=11.7$, 10.3, 4.1 Hz, 1H), 3.33 (dd, $J=11.1$, 9.5 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 145.4, 141.3, 130.5, 129.5, 128.5, 128.1, 125.7, 119.4, 119.3, 73.0, 68.0, 67.3, 66.6.

2-(1,4-Dioxan-2-yl)-6-methylquinoline 1-oxide (**3b**)^[59]: ^1H NMR (500 MHz, CDCl_3) δ : 8.61 (d, $J=8.8$ Hz, 1H), 7.68 (d, $J=8.7$ Hz, 1H), 7.63~7.54 (m, 3H), 5.55 (dd, $J=9.5$, 2.6 Hz, 1H), 4.58 (dd, $J=11.1$, 2.6 Hz, 1H), 4.03 (dt, $J=10.8$, 5.4 Hz, 2H), 3.87 (dd, $J=11.3$, 1.8 Hz, 1H), 3.77 (ddd, $J=11.7$, 10.4, 4.1 Hz, 1H), 3.34 (s, 1H), 2.55 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 144.6, 139.9, 138.7, 132.6, 129.7, 126.99, 125.2, 119.3, 119.2, 73.0, 68.2, 67.33, 7.57, 21.4.

2-(1,4-Dioxan-2-yl)-3-methylquinoline 1-oxide (**3c**): ^1H NMR (500 MHz, CDCl_3) δ : 8.67 (d, $J=8.7$ Hz, 1H), 7.78~7.64 (m, 2H), 7.58 (t, $J=7.1$ Hz, 1H), 7.50 (s, 1H), 6.11 (dd, $J=10.1$, 2.9 Hz, 1H), 4.16 (dd, $J=11.2$, 2.8 Hz, 1H), 4.03~3.92 (m, 2H), 3.89~3.72 (m, 3H), 2.71 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 144.7, 139.9, 131.9, 129.7, 128.9, 128.6, 127.2, 127.1, 119.9, 74.6, 67.3, 66.50, 66.0, 20.5. HRMS calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3\text{N}$ [$\text{M}+\text{H}$]⁺ 246.11281, found 246.11247.

2-(1,4-Dioxan-2-yl)-6-methoxyquinoline 1-oxide (**3d**): ^1H NMR (500 MHz, CDCl_3) δ : 8.63 (d, $J=9.5$ Hz, 1H), 7.66 (d, $J=8.8$ Hz, 1H), 7.58 (d, $J=8.7$ Hz, 1H), 7.38 (dd, $J=9.5$, 2.6 Hz, 1H), 7.10 (d, $J=2.6$ Hz, 1H), 5.53 (dd, $J=9.5$, 2.6 Hz, 1H), 4.56 (dd, $J=11.1$, 2.6 Hz, 1H), 4.07~3.98 (m, 2H), 3.94 (s, 3H), 3.89~3.84 (m, 1H), 3.80~3.73 (m,

1H), 3.32 (dd, $J=11.0$, 9.6 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 159.3, 143.4, 137.1, 130.9, 124.6, 122.6, 121.2, 119.8, 105.9, 72.9, 68.3, 67.3, 66.6, 55.7. HRMS calcd for $\text{C}_{14}\text{H}_{16}\text{O}_4\text{N}$ [$\text{M}+\text{H}$]⁺ 262.10739, found 262.10738.

2-(1,4-Dioxan-2-yl)-6-fluoroquinoline 1-oxide (**3e**): ^1H NMR (500 MHz, CDCl_3) δ : 8.15 (d, $J=8.6$ Hz, 1H), 8.07 (dd, $J=13.2$, 8.0 Hz, 3H), 7.98 (d, $J=9.3$ Hz, 1H), 7.51 (t, $J=7.4$ Hz, 1H), 7.45 (t, $J=7.6$ Hz, 2H), 7.34 (dd, $J=9.3$, 2.7 Hz, 1H), 7.01 (d, $J=2.7$ Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 162.8, 160.8, 145.0, 138.5, 130.7, 130.6, 124.9, 124.8, 122.6, 122.5, 120.6, 120.4, 120.2, 111.7, 111.5, 72.9, 67.9, 67.3, 66.6. HRMS calcd for $\text{C}_{13}\text{H}_{13}\text{O}_3\text{NF}$ [$\text{M}+\text{H}$]⁺ 250.08759, found 250.08740.

6-Chloro-2-(1,4-dioxan-2-yl)quinoline 1-oxide (**3f**): ^1H NMR (500 MHz, CDCl_3) δ : 8.68 (d, $J=9.3$ Hz, 1H), 7.85 (d, $J=2.1$ Hz, 1H), 7.73~7.64 (m, 3H), 5.51 (dd, $J=9.5$, 2.7 Hz, 1H), 4.56 (dd, $J=11.1$, 2.6 Hz, 1H), 4.08~3.98 (m, 2H), 3.92~3.84 (m, 1H), 3.77 (ddd, $J=11.8$, 9.5, 4.9 Hz, 1H), 3.31 (dd, $J=11.1$, 9.5 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 145.7, 139.9, 134.7, 131.1, 130.2, 126.8, 124.3, 121.5, 120.6, 72.9, 67.9, 67.3, 66.6. HRMS calcd for $\text{C}_{13}\text{H}_{13}\text{O}_3\text{NCl}$ [$\text{M}+\text{H}$]⁺ 266.05801, found 266.05785.

2-(1,4-Dioxan-2-yl)-6-(methoxycarbonyl)quinoline 1-oxide (**3g**): ^1H NMR (500 MHz, CDCl_3) δ : 8.77 (d, $J=9.1$ Hz, 1H), 8.61 (d, $J=1.5$ Hz, 1H), 8.34 (dd, $J=9.1$, 1.7 Hz, 1H), 7.86 (d, $J=8.8$ Hz, 1H), 7.71 (d, $J=8.7$ Hz, 1H), 5.54 (dd, $J=9.4$, 2.6 Hz, 1H), 4.59 (dd, $J=11.1$, 2.6 Hz, 1H), 4.06~4.02 (m, 2H), 4.01 (s, 3H), 3.90 (dd, $J=11.4$, 6.9 Hz, 1H), 3.77 (ddd, $J=11.8$, 9.4, 5.1 Hz, 1H), 3.33 (dd, $J=11.0$, 9.5 Hz, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 165.9, 147.4, 143.1, 130.9, 130.2, 129.9, 128.9, 126.2, 120.3, 120.1, 73.0, 67.8, 67.3, 66.6, 52.7. HRMS calcd for $\text{C}_{15}\text{H}_{16}\text{O}_5\text{N}$ [$\text{M}+\text{H}$]⁺ 290.10257, found 290.10230.

6-Methyl-2-(tetrahydrofuran-2-yl)quinoline 1-oxide (**3h**): ^1H NMR (500 MHz, CDCl_3) δ : 8.62 (d, $J=8.9$ Hz, 1H), 7.61 (dt, $J=19.7$, 8.8 Hz, 4H), 5.59 (dd, $J=7.7$, 5.8 Hz, 1H), 4.17 (dd, $J=14.3$, 6.9 Hz, 1H), 4.10~3.97 (m, 1H), 2.88~2.76 (m, 1H), 2.54 (s, 3H), 2.13~2.00 (m, 1H), 1.99~1.85 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 150.1, 140.1, 138.2, 132.5, 129.5, 126.9, 125.2, 119.061, 118.5, 76.0, 69.3, 30.9, 25.8, 21.4. HRMS calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{N}$ [$\text{M}+\text{H}$]⁺ 230.11797, found 230.11756.

6-Chloro-2-(tetrahydrofuran-2-yl)quinoline 1-oxide (**3i**): ^1H NMR (500 MHz, CDCl_3) δ : 8.69 (d, $J=9.3$ Hz, 1H), 7.85 (d, $J=2.1$ Hz, 1H), 7.75~7.59 (m, 3H), 5.55 (dd, $J=7.8$, 5.8 Hz, 1H), 4.21~4.12 (m, 1H), 4.04 (dd, $J=14.9$, 6.7 Hz, 1H), 2.87~2.74 (m, 1H), 2.16~2.01 (m, 1H), 1.99~1.85 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 151.2, 140.1, 134.3, 130.9, 130.1, 126.7, 124.3, 121.2, 119.9, 75.9, 69.4, 30.8, 25.8. HRMS calcd for $\text{C}_{13}\text{H}_{13}\text{O}_2\text{NCl}$ [$\text{M}+\text{H}$]⁺ 250.06287, found 250.06293.

6-Methoxy-2-(tetrahydrofuran-2-yl)quinoline 1-oxide (**3j**)^[59]: ^1H NMR (500 MHz, CDCl_3) δ : 8.64 (d, $J=9.5$ Hz, 1H), 7.64 (d, $J=8.7$ Hz, 1H), 7.55 (d, $J=8.7$ Hz, 1H), 7.37 (dd, $J=9.5$, 2.7 Hz, 1H), 7.11 (d, $J=2.6$ Hz, 1H), 5.57 (dd, $J=7.7$, 5.8 Hz, 1H), 4.17 (dd, $J=13.7$, 7.4 Hz, 1H), 4.10~3.99 (m, 1H), 3.94 (s, 3H), 2.85~2.76 (m, 1H), 2.14~2.00

(m, 1H), 1.99~1.86 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 159.0, 148.8, 137.3, 130.7, 124.6, 122.4, 120.9, 119.0, 105.9, 75.9, 69.3, 55.67, 30.9, 25.8.

6-Fluoro-2-(tetrahydrofuran-2-yl)quinoline 1-oxide (**3k**): ^1H NMR (500 MHz, CDCl_3) δ : 8.76 (dd, $J=9.2$, 5.2 Hz, 1H), 7.66 (dd, $J=28.5$, 8.8 Hz, 2H), 7.56~7.43 (m, 2H), 5.56 (dd, $J=7.5$, 5.9 Hz, 1H), 4.17 (dd, $J=13.7$, 7.3 Hz, 1H), 4.10~3.98 (m, 1H), 2.90~2.74 (m, 1H), 2.14~2.01 (m, 1H), 1.99~1.85 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 162.6, 160.6, 150.4, 138.7, 130.4, 130.3, 124.7, 124.6, 122.4, 122.3, 120.1, 119.9, 119.8, 111.6, 111.4, 75.9, 69.3, 30.9, 25.8. HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{NF}$ $[\text{M} + \text{H}]^+$ 234.09282, found 234.09248.

2-(Tetrahydrofuran-2-yl)quinoline 1-oxide (**3l**): ^1H NMR (500 MHz, CDCl_3) δ : 8.75 (d, $J=8.8$ Hz, 1H), 7.87 (d, $J=8.1$ Hz, 1H), 7.81~7.74 (m, 2H), 7.63 (dd, $J=8.0$, 5.7 Hz, 2H), 5.61 (dd, $J=7.7$, 5.8 Hz, 1H), 4.18 (dd, $J=13.9$, 7.2 Hz, 1H), 4.13~4.00 (m, 1H), 2.89~2.77 (m, 1H), 2.15~2.00 (m, 1H), 1.94 (dq, $J=11.7$, 7.9 Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 151.2, 141.5, 130.4, 129.3, 128.1, 128.0, 125.9, 119.3, 118.5, 76.1, 69.4, 30.9, 25.8. HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{N}$ $[\text{M} + \text{H}]^+$ 216.10213, found 216.10191.

6-(Methoxycarbonyl)-2-(tetrahydro-2H-pyran-2-yl)quinoline 1-oxide (**3m**): ^1H NMR (500 MHz, CDCl_3) δ : 8.79 (d, $J=9.1$ Hz, 1H), 8.60 (d, $J=1.7$ Hz, 1H), 8.32 (dd, $J=9.1$, 1.8 Hz, 1H), 7.84 (d, $J=8.8$ Hz, 1H), 7.71 (d, $J=8.7$ Hz, 1H), 5.22 (dd, $J=10.8$, 1.9 Hz, 1H), 4.27~4.17 (m, 1H), 4.00 (s, 3H), 3.73 (td, $J=11.8$, 2.4 Hz, 1H), 2.50 (d, $J=13.3$ Hz, 1H), 1.97 (dd, $J=10.5$, 3.1 Hz, 1H), 1.90~1.70 (m, 2H), 1.70~1.59 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 165.9, 151.8, 143.1, 130.9, 129.8, 129.7, 128.7, 126.3, 120.2, 120.1, 74.6, 69.1, 52.6, 28.9, 26.0, 23.4. HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{O}_4\text{N}$ $[\text{M} + \text{H}]^+$ 288.12317, found 288.12303.

2-(Tetrahydro-2H-pyran-2-yl)quinoline 1-oxide (**3n**): ^1H NMR (500 MHz, CDCl_3) δ : 8.76 (d, $J=8.8$ Hz, 1H), 7.85 (d, $J=8.0$ Hz, 1H), 7.76 (dd, $J=12.2$, 4.9 Hz, 2H), 7.67~7.59 (m, 2H), 5.25 (dd, $J=10.8$, 1.9 Hz, 1H), 4.25~4.16 (m, 1H), 3.74 (td, $J=11.8$, 2.4 Hz, 1H), 2.50 (d, $J=13.2$ Hz, 1H), 1.97 (dd, $J=10.4$, 3.1 Hz, 1H), 1.87~1.70 (m, 3H), 1.68~1.63 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 149.9, 141.4, 130.3, 129.3, 128.1, 128.0, 125.9, 119.6, 119.1, 74.6, 69.1, 29.1, 26.1, 23.4. HRMS calcd for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{N}$ $[\text{M} + \text{H}]^+$ 230.11784, found 230.11756.

6-Chloro-2-(tetrahydro-2H-pyran-2-yl)quinoline 1-oxide (**3o**): ^1H NMR (500 MHz, CDCl_3) δ : 8.69 (d, $J=9.3$ Hz, 1H), 7.83 (d, $J=2.2$ Hz, 1H), 7.67 (q, $J=2.1$ Hz, 3H), 5.20 (dd, $J=10.8$, 2.0 Hz, 1H), 4.27~4.17 (m, 1H), 3.72 (td, $J=11.8$, 2.4 Hz, 1H), 2.47 (d, $J=13.2$ Hz, 1H), 2.00~1.93 (m, 1H), 1.89~1.69 (m, 3H), 1.68~1.62 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ : 150.2, 139.9, 134.3, 130.9, 129.9, 126.7, 124.7, 121.6, 120.4, 74.4, 69.1, 28.9, 26.0, 23.3. HRMS calcd for $\text{C}_{14}\text{H}_{15}\text{O}_2\text{NCl}$ $[\text{M} + \text{H}]^+$ 264.07861, found 264.07858.

2-(Tetrahydrothiophen-2-yl)quinoline 1-oxide (**3p**): ^1H NMR (500 MHz, CDCl_3) δ : 8.77 (d, $J=8.8$ Hz, 1H), 7.84

(d, $J=8.0$ Hz, 1H), 7.81~7.68 (m, 3H), 7.61 (ddd, $J=8.1$, 7.0, 1.1 Hz, 1H), 5.51~5.39 (m, 1H), 3.15~2.99 (m, 2H), 2.64~2.49 (m, 1H), 2.23~2.08 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 150.1, 141.7, 130.4, 129.1, 128.2, 127.9, 125.1, 120.1, 119.9, 46.0, 35.2, 32.8, 30.7. HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{ONS}$ $[\text{M} + \text{H}]^+$ 232.07901, found 232.07906.

6-Chloro-2-(tetrahydrothiophen-2-yl)quinoline 1-oxide (**3q**): ^1H NMR (500 MHz, CDCl_3) δ : 8.71 (d, $J=9.3$ Hz, 1H), 7.82 (d, $J=2.2$ Hz, 1H), 7.76 (d, $J=8.8$ Hz, 1H), 7.67 (dd, $J=9.3$, 2.2 Hz, 1H), 7.61 (d, $J=8.8$ Hz, 1H), 5.49~5.28 (m, 1H), 3.12~3.00 (m, 2H), 2.59~2.45 (m, 1H), 2.24~2.10 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 150.4, 140.2, 134.4, 131.1, 129.8, 126.6, 123.9, 121.8, 121.4, 45.9, 35.2, 32.8, 30.7. HRMS calcd for $\text{C}_{13}\text{H}_{13}\text{ONClS}$ $[\text{M} + \text{H}]^+$ 266.04016, found 266.04009.

6-(Methoxycarbonyl)-2-(tetrahydrothiophen-2-yl)quinoline 1-oxide (**3r**): ^1H NMR (500 MHz, CDCl_3) δ : 8.81 (d, $J=9.1$ Hz, 1H), 8.59 (d, $J=1.6$ Hz, 1H), 8.32 (dd, $J=9.1$, 1.8 Hz, 1H), 7.81 (s, 2H), 5.42 (dd, $J=6.8$, 5.6 Hz, 1H), 4.00 (s, 3H), 3.08 (ddd, $J=16.3$, 7.9, 4.0 Hz, 2H), 2.57 (ddd, $J=12.6$, 7.3, 4.2 Hz, 1H), 2.26~2.11 (m, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ : 165.9, 152.1, 143.3, 130.9, 129.9, 129.8, 128.5, 125.8, 121.0, 120.5, 52.6, 46.0, 35.1, 32.9, 30.7. HRMS calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3\text{NS}$ $[\text{M} + \text{H}]^+$ 290.08453, found 290.08454.

Supporting Information ^1H NMR and ^{13}C NMR spectra of compounds **3a**~**3r**. The Supporting Information is available free of charge via the Internet at <http://sioc-journal.cn>.

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