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Tandem Oxidative Radical Halogenated Addition of Alkynyl Imines: Regioselective Synthesis of 3-Haloquinolines

Dianpeng Chen,*[a] Jianming Li,[a] Peiying Cui[a] Yingying Shan,*[a] Yutong Zhao,[a] and Guanyinsheng Qiu*[b]

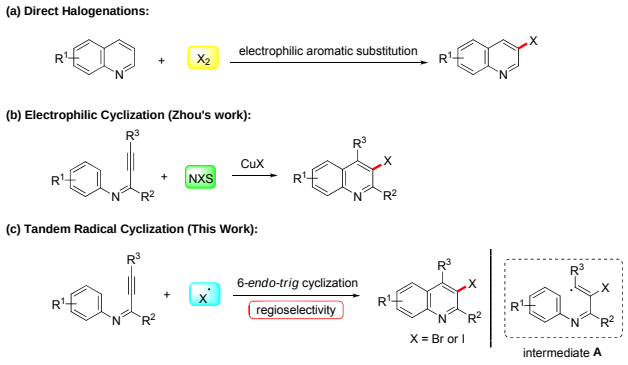
Abstract: A tandem oxidative radical halogenated addition of alkynyl imines for regioselective synthesis of 3-haloquinolines is described. Mechanism investigation suggests that the oxidation of halogen, 6-*endo-trig* cyclization and aromatization are involved in the process. Easily available starting materials, mild conditions, and a wide substrate scope make this approach potentially useful.

Introduction

Quinolines represent an important class of nitrogen-containing heterocycles that can be found in a wide range of interesting compounds, including natural products, pharmaceuticals, and functional materials.[1-3] In particular, 3-haloquinolines,[4] a member of the family of privileged scaffold, occupy a significant place in synthetic building blocks, due to the fact that halogen atom could provide a further avenue for structural elaboration.[5]

In view of the various applications, considerable research effort had been devoted to the development of efficient methods for the regioselective functionalization of quinolines (Scheme 1).[6] Classical methods for the synthesis of 3-haloquinolines were predominantly focused on direct halogenations *via* electrophilic aromatic substitution (Scheme 1a).[7] However, progress in this area frequently encountered the issue of over-halogenation and poor regioselectivity.[7d,7e] Another alternative strategy was electrophilic cyclization, which need halogen cations, for example NBS, I_2, and ICl *etc.* as electrophilic reagent (Scheme 1b).[4a,4d,8] For example, Zhou and co-workers reported an efficient protocol for the preparation 3-haloquinolines *via* electrophilic cyclization of alkynyl imines using the NXS/CuX system.[4a] Although these methods were efficient, the inferior of atom economy and poor tolerance of functional groups might limit the synthetic applications in some cases. Accordingly, developing new and regioselective approach for the preparation of 3-haloquinolines remained a formidable challenge.

On the other hand, tandem radical cyclization had been well-recognized as a versatile tool to construct various useful cyclic molecules.[9] In the past decade, its prosperous development had emerged as a very attractive branch of modern organic synthesis.[10] Considering our continuous interest in radical chemistry,[11] we would like to disclose our endeavor in the regioselective synthsis of 3-haloquinolines (Scheme 1c). In this process, it was hypothesized that the halogen radical,[12] deriving from the single electron oxidation of halogen anions, was added to the triple bond to form a vinyl radical intermediate **A**, which underwent 6-*endo-trig* cyclization to achieve final products.



Scheme 1. Proposal for the Synthesis of 3-haloquinolines.

Results and Discussion

Stimulated by this proposal, we chose (*Z*)-*N*-(1,3-diphenylprop-2-ynylidene)aniline (**1a**), an important dual-functionalized building block,[13] as the starting material, which could be readily prepared *via* the treatment of (*Z*)-*N*-phenylbenzimidoyl chloride with ethynylbenzene under Sonogashira conditions.[14] Based on our previous work about tandem oxidative radical halogenated addition,[15] an initial trial was occupied by the reaction of 0.2 mmol of **1a** and 1.0 equiv of *tetra*-*n*-butylammonium bromide (TBAB) in 2 mL of DCE:H_2O (1:1, v/v) at 80 °C in the presence of 1.0 equiv of $K_2S_2O_8$ as an oxidant. To our delight, the desired product of 3-bromo-2,4-diphenylquinoline (**3a**) was obtained in 32% isolated yield (Table 1, entry 1), and the NMR data was consistent with the literature reports.[4a]

Encouraged by this positive result, further optimization was then carried out. Considering the high activity of bromo radical, increase of $K_2S_2O_8$ and TBAB dosage was evaluated at first. As expected, the yield was improved apparently when both oxidant and bromo source were increased to 2.0 equiv, leading to the final product **3a** in 56% yield (Table 1, entry 2). However, increase of $K_2S_2O_8$ and TBAB dosage to 3.0 equiv did not gave a better result (Table 1, entry 3). Then we began to optimize the reaction with respect to different oxidants, bromo sources and solvents. Whereas subsequent screening of oxidants, such as H_2O_2, MnO_2 or DTBP (2-(*tert*-butylperoxy)-2-methylpropane), offered unsatisfactory results (Table

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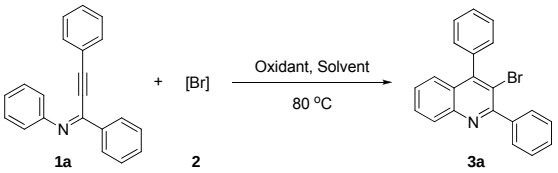
1, entries 4-6), Oxone ($2KHSO_5•KHSO_4•K_2SO_4$) was found to be an appropriate oxidant for this reaction that afforded the product in 82% yield (Table 1, entry 7). Replacing TBAB with halometallate gave similar yields (Table 1, entries 8-9), and NBS (*N*-Bromosuccinimide) showed poor reactivity (Table 1, entry 10). In addition, the effect of water-containing co-solvents was also explored. From the results, DCE : H_2O (v/v, 1 : 1) was the best choice (Table 1, entry 7), which was probably due to the improved solubility of bromide salt and oxidant in the co-solvent system. No improvements were observed when different co-solvents were screened (Table 1, entries 11-15). Thus, the optimized reaction conditions were chosen as follows: **1a** (0.2 mmol), Oxone (2.0 equiv), TBAB (2.0 equiv) in 2 mL of DCE : H_2O (v/v, 1 : 1) were stirred at 80 °C.

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



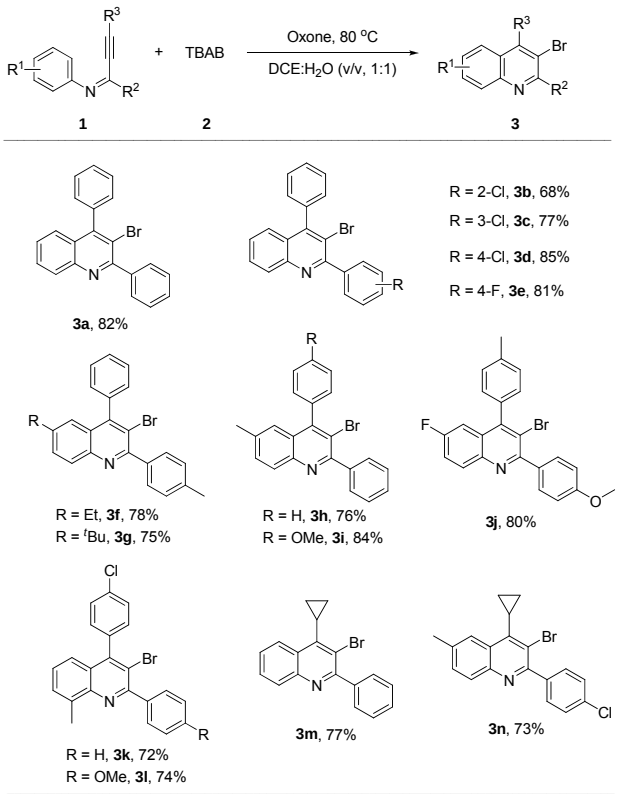
Entry	Oxidant (equiv)	[Br] (equiv)	Solvent	Yield[b]
1	$K_2S_2O_8$ (1.0)	TBAB (1.0)	DCE:H_2O (v/v, 1:1)	32
2	$K_2S_2O_8$ (2.0)	TBAB (2.0)	DCE:H_2O (v/v, 1:1)	56
3	$K_2S_2O_8$ (3.0)	TBAB (3.0)	DCE:H_2O (v/v, 1:1)	43
4	H_2O_2 (2.0)	TBAB (2.0)	DCE:H_2O (v/v, 1:1)	18
5	MnO_2 (2.0)	TBAB (2.0)	DCE:H_2O (v/v, 1:1)	Trace
6	DTBP (2.0)	TBAB (2.0)	DCE:H_2O (v/v, 1:1)	21
7	**Oxone (2.0)**	**TBAB (2.0)**	**DCE:H_2O (v/v, 1:1)**	**82**
8	Oxone (2.0)	KBr (2.0)	DCE:H_2O (v/v, 1:1)	80
9	Oxone (2.0)	$ZnBr_2$ (2.0)	DCE:H_2O (v/v, 1:1)	77
10	Oxone (2.0)	NBS (2.0)	DCE:H_2O (v/v, 1:1)	Trace
11	Oxone (2.0)	TBAB (2.0)	DCE	39
12	Oxone (2.0)	TBAB (2.0)	THF:H_2O (v/v, 1:1)	58
13	Oxone (2.0)	TBAB (2.0)	MeCN:H_2O (v/v, 1:1)	35
14	Oxone (2.0)	TBAB (2.0)	DMF:H_2O (v/v, 1:1)	13
15	Oxone (2.0)	TBAB (2.0)	MeOH:H_2O (v/v, 1:1)	Complex

[a] Conditions: **1a** (0.2 mmol), Oxone (2.0 equiv), TBAB (2.0 equiv) in 2 mL of DCE : H_2O (v/v, 1 : 1) were stirred at 80 °C. [b] Isolated yield based on **1a**.

With the optimized conditions in hand, the scope of this tandem oxidative radical brominative addition was investigated further. As shown in Table 2, various alkynyl imines could be tolerated. The R^1 group could be H (Table 2, **3a**-**3e**, **3m**), alkyl (Table 2, **3f**-**3i**, **3k**, **3l**, **3n**), or halogen (Table 2, **3j**), and the yields were satisfactory. The R^2 group could be phenyl groups optionally substituted with an electron-withdrawing (Table 2, **3b**-**3e**, **3n**) or an electron-donating group (Table 2, **3f**, **3g**, **3j**, **3l**). Unfortunately, we failed to obtain target products when R^2 was an alkyl group, indicating that the radical intermediate might be stabilized by aryl groups, which probably due to the relative short life time of bromo radical. Encouragingly, the reaction could proceed smoothly when R^3 was alkyl group, producing the corresponding product **3m** and **3n** in 77% and 73% yield, respectively.

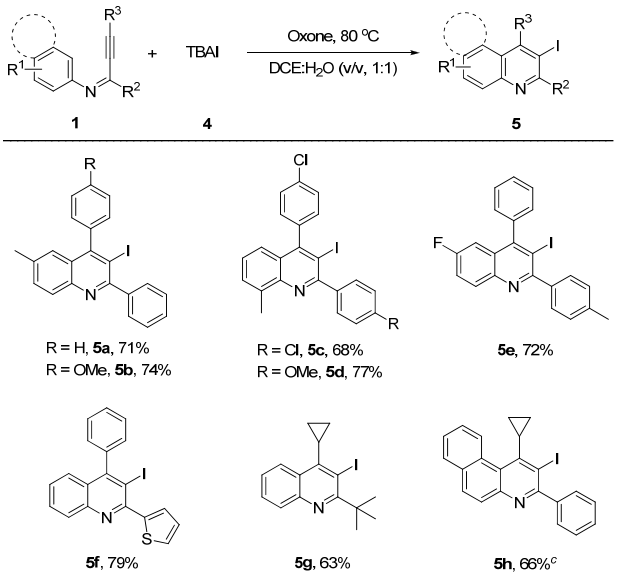
Then we turned our attention to explore the scope of tandem oxidative radical iodinated addition, which just needed to utilize TBAI (*tetra*-*n*-butylammonium iodide) as the iodo sources instead of TBAB under standard conditions. As shown in Table 3, a series of 3-iodoquinolines were achieved in good yields. To our delight, the reaction processed smoothly when R^2 was *tert*-butyl (Table 3, **5g**). We reasoned that the result was ascribed to relatively easy accessibility and high stability of iodo radical. Remarkably, this approach was also applicable to the synthesis of 2-iodobenzo[*f*]quinoline,[16] and produced the target molecule **5h** in 66% yield.

Table 2. Synthesis of 3-bromoquinolines[a][b]



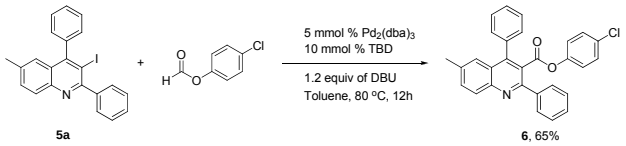
[a] Conditions: **1** (0.2 mmol), Oxone (2.0 equiv), TBAB (2.0 equiv) in 2 mL of DCE : H_2O (v/v, 1 : 1) were stirred at 80 °C. [b] Isolated yield based on **1**.

Table 3. Synthesis of 3-iodoquinolines[a][b]



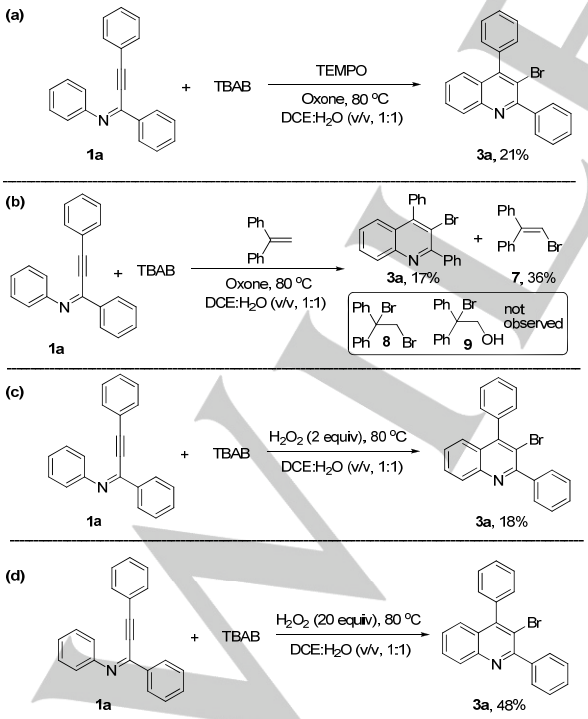
[a] Conditions: **1** (0.2 mmol), Oxone (2.0 equiv), TBAI (2.0 equiv) in 2 mL of DCE : H_2O (v/v, 1 : 1) were stirred at 80 °C. [b] Isolated yield based on **1**.[c] The substrate was (*Z*)-*N*-(3-cyclopropyl-1-phenylprop-2-ynylidene)naphthalen-2-amine.

The halogen substituent was a vital part of the products and could be used as a convenient chemical handle for other organic conversion. According to the literature about carbonylation,[17] we treated **5a** with 4-chlorophenyl formate in the presence of $Pd_2(dba)_3$, TBD (2,3,4,6,7,8-hexahydro-1*H*-pyrimido[1,2-*a*]pyrimidine) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in toluene at 80 °C. As envisaged, 4-chlorophenyl 6-methyl-2,4-diphenylquinoline-3-carboxylate **6** was obtained in 65% yield, which provided a transformation from halogen atoms to a synthetically useful carbonyl group (Scheme 2).



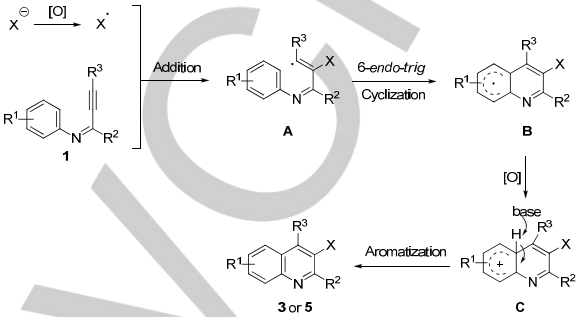
Scheme 2. The carbonylation of the product

To understand the reaction, control experiments were conducted as shown in Scheme 3. To clarify the radical process, the reactions with excessive radical scavengers (2,2,6,6-tetramethylpiperidinyloxyl and 1,1-diphenylethene) were carried out. The reaction was prominently retarded, but not completely prevented (Scheme 3a and 3b). Interestingly, 2-bromo-1,1-diphenylethene **7** was observed in 36% yield. Supposing the reaction underwent a bromo cation pathway, 1,1-diphenyl-based electrophilic addition products **8** and **9** should be detected. However, the addition products **8** and **9** were not observed. As we know, the combination of bromide and H_2O_2 served as a well-known alternative.[18] The control experiment using 2.0 equiv of H_2O_2 as replacement, as noted in entry 3 of Table 1, was also conducted, just providing the final **3a** in 18% (Scheme 3c). Further increase of H_2O_2 loading to 20 equiv gave rise to the final product **3a** in an improved yield as expected (Scheme 3d).



Scheme 3. Control experiments.

In light of the above results, a plausible mechanism was proposed in Scheme 4. In this process, halogen radical was produced by the oxidation of halogen anion, and added to the triple bond to form the intermediate **A**. Cyclic intermediate **B** was obtained *via* 6-*endo*-*trig* cyclization, which was oxidized to the intermediate **C**. In the presence of base, intermediate **C** experienced aromatization to furnish the final product **3** or **5**.



Scheme 4. Plausible mechanism.

Conclusions

In conclusion, we described a tandem oxidative radical halogenated addition of alkynyl imines for regioselective synthesis of 3-haloquinolines. In the transformation, halogen radical was produced by the oxidation of halogen anion. The reaction proceeded smoothly with good functional tolerance and efficiency. Further work toward expanding on this protocol was currently underway.

Experimental Section

General information: All reactions were carried out in oven-dried glassware sealed with rubber septa under nitrogen condition. All solvents were distilled under nitrogen atmosphere prior to use. Purification of products was conducted by flash chromatography on silica gel (200-300 mesh). NMR spectra were measured on a Bruker magnetic resonance spectrometer (^{1}H at 500 MHz, ^{13}C at 126 MHz). Chemical shifts are reported in ppm using tetramethylsilane as internal standard (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet). MS data were obtained on an Agilent 5975C inert 350 EI mass spectrometer (GC-MS). HRMS data were obtained on a VG ZAB-HS mass spectrometer, Brucker Apex IV FTMS spectrometer. Compounds described in the literature were characterized by the comparison of ^{1}H and/or ^{13}C NMR spectra to the previously reported data.

General procedure for 3-bromoquinolines: Alkynyl imine **1** (0.2 mmol), TBAB **2** (128 mg, 0.4 mmol), Oxone (246 mg 0.4 mmol) and solvent DCE : H_2O (v/v = 1:1, 2 mL) were added to a test tube. The mixture was stirred at 80 °C for 8 h, diluted with water (10 mL) and extracted with EtOAc (3×5 mL). The combined organic layer was dried over Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by column chromatography to afford the pure product **3**.

General procedure for 3-iodoquinolines: Alkynyl imine **1** (0.2 mmol), TBAI **4** (148 mg, 0.4 mmol), Oxone (246 mg 0.4 mmol) and solvent DCE : H_2O (v/v = 1:1, 2 mL) were added to a test tube. The mixture was stirred at 80 °C for 8 h, diluted with water (10 mL) and extracted with EtOAc (3×5 mL). The combined organic layer was dried over Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by column chromatography to afford the pure product **5**.

General procedure for ester 6: To a test tube sealing with 3-iodoquinoline **5a** (210 mg, 0.5 mmol) in toluene (5 mL) was added $Pd_2(dba)_3$ (22 mg, 0.025 mmol), TBD (2 mg, 0.0125 mmol) and DBU (91 mg, 0.6 mmol). The 4-chlorophenyl formate (234 mg, 1.5 mmol) was added at last, and the solution was stirred for 12 hours at 80 °C. Then the reaction was quenched with water (10 mL), extracted with DCM (3×5 mL), dried with anhydrous Na_2SO_4. After evaporation, chromatography on silica gel of the reaction mixture afforded desired ester **6**.

3-bromo-2,4-diphenylquinoline (3a): Amorphous solid, 59 mg, 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.76–7.71 (m, 3H), 7.59–7.55 (m, 2H), 7.54–7.49 (m, 3H), 7.48–7.46 (m, 1H), 7.45–7.41 (m, 2H), 7.37–7.34 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 149.8, 146.4, 140.9, 138.1, 129.6, 129.5, 129.4, 129.3, 128.7, 128.6, 128.5, 128.0, 127.9, 127.4, 126.4, 118.6; IR (neat) 2360, 1568, 912 cm^{-1}; HRMS (EI-TOF) calcd for $C_{21}H_{14}BrN$ 359.0310, found 359.0311.

3-bromo-2-(2-chlorophenyl)-4-phenylquinoline (3b): Pale yellow oil, 53 mg, 68% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.74 (m, 1H), 7.58–7.46 (m, 7H), 7.44–7.37 (m, 3H), 7.33 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 149.2, 146.4, 140.2, 137.6, 133.0, 130.3, 130.0, 129.9, 129.7, 129.6, 129.2, 128.7, 128.6, 128.5, 128.2, 126.9, 126.5, 119.5; IR (neat) 2359, 1551, 916 cm^{-1}; HRMS (EI-TOF) calcd for $C_{21}H_{13}BrClN$ 392.9920, found 392.9923.

3-bromo-2-(3-chlorophenyl)-4-phenylquinoline (3c): Pale yellow oil, 61 mg, 77% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 11.0, 4.0 Hz, 2H), 7.66–7.61 (m, 1H), 7.55 (m, 3H), 7.49–7.42 (m, 4H), 7.35 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 150.0, 146.3, 142.5, 137.9, 134.0, 130.1, 129.7, 129.5, 129.3, 129.2, 128.9, 128.6, 128.6, 128.1, 127.8, 127.7, 126.5, 118.1; IR (neat) 2358, 1549, 912 cm^{-1}; HRMS (EI-TOF) calcd for $C_{21}H_{13}BrClN$ 392.9920, found 392.9924.

3-bromo-2-(4-chlorophenyl)-4-phenylquinoline (3d): Pale yellow solid, 67 mg, 85% yield; Mp 87−89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 1H), 7.76–7.68 (m, 3H), 7.55 (m, 3H), 7.50–7.41 (m, 4H), 7.34 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 150.0, 146.4, 139.3, 138.0, 134.9, 131.0, 130.0, 129.6, 129.2, 128.6, 128.5, 128.3, 128.0, 127.6, 126.5, 118.2; IR (neat) 2360, 1611, 910 cm^{-1}; HRMS (EI-TOF) calcd for $C_{21}H_{13}BrClN$ 392.9920, found 392.9923.

3-bromo-2-(4-fluorophenyl)-4-phenylquinoline (3e): Pale yellow solid, 61 mg, 81% yield; Mp 81−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 1H), 7.78–7.71 (m, 3H), 7.56 (m, 3H), 7.48–7.40 (m, 2H), 7.37–7.32 (m, 2H), 7.21–7.16 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1 (*J* = 247 Hz), 157.9, 149.9, 146.4, 138.0, 137.0, 131.5 (*J* = 8 Hz), 129.8 (*J* = 50 Hz), 129.3, 128.6, 128.5, 128.0, 127.5, 126.5, 118.4, 115.0 (*J* = 21 Hz); IR (neat) 2359, 1612, 915 cm^{-1}; HRMS (EI-TOF) calcd for $C_{21}H_{13}BrFN$ 377.0215, found 377.0218.

3-bromo-6-ethyl-4-phenyl-2-*p*-tolylquinoline (3f): Amorphous solid, 63 mg, 78% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.59 (dd, *J* = 12.0, 4.0 Hz, 2H), 7.54 (dd, *J* = 9.0, 5.0 Hz, 2H), 7.38–7.33 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.15 (s, 1H), 2.70 (q, *J* = 8.0 Hz, 2H), 2.43 (s, 3H), 1.20 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 149.1, 143.6, 138.5, 138.4, 130.9, 129.4, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 127.9, 123.9, 118.7, 29.1, 21.4, 15.5; IR (neat) 2357, 1615, 908 cm^{-1}; HRMS (EI-TOF) calcd for $C_{24}H_{20}BrN$ 401.0779, found 401.0776.

3-bromo-6-*tert*-butyl-4-phenyl-2-p-tolylquinoline (3g): Amorphous solid, 64 mg, 75% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.82 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.60–7.51 (m, 3H), 7.36 (d, *J* = 7.0 Hz, 2H), 7.33–7.28 (m, 3H), 2.43 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3, 150.2, 149.5, 145.0, 138.5, 138.3, 129.4, 129.3, 129.0, 128.7, 128.6, 128.5, 128.4, 127.6, 121.3, 118.6, 35.1, 31.0, 21.4; IR (neat) 2357, 1609, 912 cm^{-1}; HRMS (EI-TOF) calcd for $C_{26}H_{24}BrN$ 429.1092, found 429.1091.

3-bromo-6-methyl-2,4-diphenylquinoline (3h): Pale yellow solid, 57 mg, 76% yield; Mp 79−81 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.76–7.69 (m, 2H), 7.61–7.52 (m, 4H), 7.52–7.46 (m, 3H), 7.37–7.32 (m, 2H), 7.15 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 149.1, 144.9, 140.9, 138.3, 137.5, 132.2, 129.5, 129.3, 129.2, 128.6, 128.5, 128.4, 128.0, 127.9, 125.1, 118.6, 21.8; IR (neat) 2360, 1513, 911 cm^{-1}; HRMS (EI-TOF) calcd for $C_{22}H_{16}BrN$ 373.0466, found 373.0469.

3-bromo-4-(4-methoxyphenyl)-6-methyl-2-phenylquinoline (3i): Yellow solid, 68 mg, 84% yield; Mp 86−88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.0 Hz, 1H), 7.74–7.68 (m, 2H), 7.55 (d, *J* = 9.0 Hz, 1H), 7.47 (m, 3H), 7.27 (d, *J* = 9.0 Hz, 2H), 7.22 (s, 1H), 7.09 (d, *J* = 9.0 Hz, 2H), 3.92 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 158.0, 148.9, 145.0, 141.1, 137.4, 132.1, 130.7, 130.5, 129.5, 129.3, 128.6, 128.3, 128.0, 125.2, 119.1, 114.0, 55.3, 21.9; IR (neat) 2358, 1526, 910 cm^{-1}; HRMS (EI-TOF) calcd for $C_{23}H_{18}BrNO$ 403.0572, found 403.0574.

3-bromo-6-fluoro-2-(4-methoxyphenyl)-4-*p*-tolylquinoline (3j): Yellow solid, 67mg, 80% yield; Mp 80−82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 9.0 Hz, 2H), 7.19–7.13 (m, 2H), 7.09 (s, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7 (*J* = 287 Hz), 160.3, 158.8, 146.2, 142.2, 131.8, 131.5, 130.4, 130.2, 129.6, 128.4, 122.0, 121.4 (*J* = 8 Hz), 115.2 (*J* = 21 Hz), 113.9, 113.7, 109.6, 55.4, 21.6; IR (neat) 3416, 1625, 1116 cm^{-1}; HRMS (EI-TOF) calcd for $C_{23}H_{17}BrFNO$ 421.0478, found 421.0477.

3-bromo-4-(4-chlorophenyl)-8-methyl-2-phenylquinoline (3k): Pale yellow oil, 59 mg, 72% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ

7.90–7.82 (m, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.55 (dd, *J* = 11.0, 7.0 Hz, 4H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 6.0 Hz, 3H), 2.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 149.9, 145.5, 139.7, 138.6, 137.8, 134.7, 131.5, 131.4, 130.0, 129.3, 128.5, 128.4, 128.0, 127.3, 124.4, 117.9, 18.1; IR (neat) 2356, 1612, 913 cm^{-1}; HRMS (EI-TOF) calcd for $C_{22}H_{15}BrClN$ 407.0076, found 407.0073.

3-bromo-4-(4-chlorophenyl)-2-(4-methoxyphenyl)-8-methylquinoline (3l): Yellow solid, 65 mg, 74% yield; Mp 66−68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 6.0 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.32 (q, *J* = 9.0 Hz, 2H), 7.26–7.21 (m, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 3.91 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 155.9, 149.8, 145.5, 139.8, 137.7, 134.7, 131.4, 130.8, 130.6, 129.9, 128.4, 128.0, 127.2, 124.6, 118.5, 113.9, 55.3, 18.1; IR (neat) 2362, 1608, 905 cm^{-1}; HRMS (EI-TOF) calcd for $C_{23}H_{17}BrClNO$ 437.0182, found 437.0185.

3-bromo-4-cyclopropyl-2-phenylquinoline (3m): Amorphous solid, 50 mg, 77% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, *J* = 9.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.74–7.68 (m, 1H), 7.65 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.61–7.55 (m, 1H), 7.47 (m, 3H), 2.13 (m, 1H), 1.45–1.39 (m, 2H), 0.92 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 148.1, 146.4, 141.2, 130.1, 129.4, 129.3, 129.1, 128.5, 128.0, 126.7, 124.6, 122.2, 15.0, 10.1; IR (neat) 2360, 1615, 916 cm^{-1}; HRMS (EI-TOF) calcd for $C_{18}H_{14}BrN$ 323.0310, found 323.0313.

3-bromo-2-(4-chlorophenyl)-4-cyclopropyl-6-methylquinoline (3n): Pale yellow oil, 54 mg, 73% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 18.0, 8.0 Hz, 3H), 7.45 (d, *J* = 8.0 Hz, 2H), 2.60 (s, 3H), 2.15–2.05 (m, 1H), 1.46–1.38 (m, 2H), 0.93–0.87 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.8, 147.9, 144.6, 137.1, 134.7, 132.0, 131.0, 129.5, 129.2, 128.2, 123.5, 121.8, 22.2, 14.9, 10.2; IR (neat) 2356, 1612, 913 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{15}BrClN$ 371.0076, found 371.0077.

3-iodo-6-methyl-2,4-diphenylquinoline (5a): Yellow solid, 60 mg, 71% yield; Mp 83−85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.0 Hz, 1H), 7.64 (d, *J* = 7.0 Hz, 2H), 7.59–7.52 (m, 4H), 7.50–7.43 (m, 3H), 7.28 (d, *J* = 7.0 Hz, 2H), 7.14 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 154.0, 145.5, 143.8, 142.4, 137.4, 132.4, 129.4, 129.2, 129.1, 128.7, 128.5, 128.4, 128.0, 127.4, 125.6, 98.6, 21.8; IR (neat) 2358, 1535, 1084 cm^{-1}; HRMS (EI-TOF) calcd for $C_{22}H_{16}IN$ 421.0327, found 421.0325.

3-iodo-4-(4-methoxyphenyl)-6-methyl-2-phenylquinoline (5b): Yellow solid, 67 mg, 74% yield; Mp 96−98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.0 Hz, 1H), 7.66–7.59 (m, 2H), 7.52 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.49–7.38 (m, 3H), 7.20 (t, *J* = 7.0 Hz, 3H), 7.06 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 159.6, 153.9, 145.6, 144.0, 137.3, 134.7, 132.4, 130.5, 129.4, 129.2, 128.5, 128.0, 127.8, 125.7, 114.1, 99.6, 55.4, 21.9; IR (neat) 2359, 1612, 910 cm^{-1}; HRMS (EI-TOF) calcd for $C_{23}H_{18}INO$ 451.0433, found 451.0431.

2,4-bis(4-chlorophenyl)-3-iodo-8-methylquinoline (5c): Yellow solid, 67 mg, 68% yield; Mp 85−87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 7.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.34–7.28 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 3H), 2.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 153.7, 146.0, 142.1, 140.9, 137.8, 134.7, 134.6, 131.3, 130.6, 130.4, 129.0, 128.0, 127.4, 127.3, 124.5, 97.6, 18.0; IR (neat) 2358, 1379, 1082 cm^{-1}; HRMS (EI-TOF) calcd for $C_{22}H_{14}Cl_2IN$ 488.9548, found 488.9546.

4-(4-chlorophenyl)-3-iodo-2-(4-methoxyphenyl)-8-methylquinoline (5d): Yellow solid, 75mg, 77% yield; Mp 82−84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.51–7.45 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 4.0 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 3.83 (s, 3H), 2.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 157.8, 153.8, 145.0, 141.3, 136.5, 134.0, 133.5, 130.3, 129.4, 129.1, 126.9, 126.8, 126.0, 124.0, 112.9, 97.5, 54.3, 17.0; IR (neat) 2359, 1508, 1026 cm^{-1}; HRMS (EI-TOF) calcd for $C_{23}H_{17}ClINO$ 485.0043, found 485.0041.

6-fluoro-3-iodo-4-phenyl-2-*p*-tolylquinoline (5e): Yellow solid, 63 mg, 72% yield; Mp 99−101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 9.0, 6.0 Hz, 1H), 7.61–7.53 (m, 5H), 7.51–7.45 (m, 1H), 7.34–7.27 (m, 4H), 7.03 (dd, *J* = 10.0, 3.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 160.7 (*J* = 248 Hz), 154.1 (*J* = 6 Hz), 144.1, 141.8, 140.6, 138.6, 131.9 (*J* = 10 Hz), 129.2, 129.0, 128.8, 128.7, 128.6, 127.9 (*J* = 8 Hz), 120.3 (*J* = 25 Hz), 110.3 (*J* = 22 Hz), 100.0, 21.5; IR (neat) 3416, 1512, 1184 cm^{-1}; HRMS (EI-TOF) calcd for $C_{22}H_{15}FIN$ 439.0233, found 439.0234.

3-iodo-4-phenyl-2-(thiophen-2-yl)quinoline (5f): Amorphous solid, 65 mg, 79% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 3.0 Hz, 1H), 7.71 (dd, *J* = 11.0, 4.0 Hz, 1H), 7.59–7.53 (m, 3H), 7.51 (d, *J* = 5.0 Hz, 1H), 7.36 (dd, *J* = 13.0, 7.0 Hz, 2H), 7.30–7.26 (m, 2H), 7.15 (dd, *J* = 5.0, 4.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 154.5, 146.8, 145.2, 142.5, 130.3, 130.1, 129.2, 129.1, 128.7, 128.5, 128.1, 127.4, 127.3, 126.9, 126.8, 97.3; IR (neat) 2358, 1526, 912 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{12}INS$ 412.9735, found 412.9731.

2-*tert*-butyl-4-cyclopropyl-3-iodoquinoline (5g): Amorphous solid, 44mg, 63% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 9.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 2.11–2.01 (m, 1H), 1.72 (s, 9H), 1.49–1.43 (m, 2H), 0.77 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 152.7, 145.5, 129.7, 128.9, 128.1, 125.8, 124.1, 99.4, 41.3, 30.1, 21.1, 12.9, 8.7; IR (neat) 2358, 1532, 935 cm^{-1}; HRMS (EI-TOF) calcd for $C_{16}H_{18}IN$ 351.0484, found 351.0487.

1-cyclopropyl-2-iodo-3-phenylbenzo[f]quinoline (5h): Yellow solid, 56 mg, 66% yield; Mp 103−105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (d, *J* = 7.0 Hz, 1H), 8.40 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 7.0 Hz, 1H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 7.0 Hz, 2H), 7.68–7.59 (m, 2H), 7.50 (dd, *J* = 15.0, 7.0 Hz, 3H), 2.22–2.07 (m, 1H), 1.49 (m, 2H), 0.88 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 152.0, 145.3, 144.2, 133.3, 131.6, 130.0, 128.4, 128.3, 127.7, 127.6, 127.5, 127.0, 126.6, 125.2, 121.9, 102.3, 20.0, 12.1; IR (neat) 2358, 11503, 909 cm^{-1}; HRMS (EI-TOF) calcd for $C_{22}H_{16}IN$ 421.0327, found 421.0325.

4-chlorophenyl 6-methyl-2,4-diphenylquinoline-3-carboxylate (6): Pale yellow oil, 58 mg, 65% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.0 Hz, 2H), 7.59 (q, *J* = 8.0 Hz, 6H), 7.44 (t, *J* = 9.0 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.51 (d, *J* = 10.0 Hz,

2H), 6.40 (d, *J* = 10.0 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 149.3, 143.2, 139.2, 133.6, 132.0, 131.3, 130.9, 130.8, 130.0, 129.8, 128.8, 128.7, 127.7, 127.6, 127.5, 127.1, 126.5, 125.3, 124.8, 120.3, 21.6; IR (neat) 3415, 1516, 1182 cm^{-1}; HRMS (EI-TOF) calcd for $C_{29}H_{20}ClNO_2$ 449.1183, found 449.1185.

(2-bromoethene-1,1-diyl)dibenzene (7): Amorphous solid, 19 mg, 36% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.0 Hz, 2H), 7.36 (d, *J* = 7.0 Hz, 1H), 7.29 (dd, J = 8.0, 6.0 Hz, 5H), 7.21 (dd, J = 6.0, 2.8 Hz, 2H), 6.77 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.9, 140.8, 139.1, 129.7, 128.5, 128.3, 128.2, 128.0, 127.7, 105.2; IR (neat) 2452, 1705, 920 cm^{-1}; HRMS (EI-TOF) calcd for $C_{14}H_{11}Br$ 258.0044, found 258.0054.

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Conflict of interest

The authors declare no conflict of interest.

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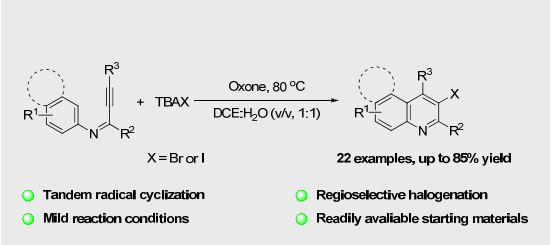

Regioselective halogenation*

Dianpeng Chen, Jianming Li, Peiying Cui, Yingying Shan,* Yutong Zhao, and Guanyinsheng Qiu**

Tandem Oxidative Radical Halogenated Addition of Alkynyl Imines: Regioselective Synthesis of 3-Haloquinolines

A tandem oxidative radical halogenated addition of alkynyl imines for regioselective synthesis of 3-haloquinolines was described. In this process, it is believed that the oxidation of halogen, 6-*endo-trig* cyclization and aromatization were involved in the process. With the advantages of simple operation, mild conditions and useful products, this protocol should be of great significance not only for laboratory synthesis but also helpful for industrial production.

*Halogen Radical