

Article

TMSBr-Promoted Cascade Cyclization of *ortho*-Propynol Phenyl Azides for the Synthesis of 4-Bromo Quinolines and Its Applications

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Abstract: Difficult-to-access 4-bromo quinolines are constructed directly from easily prepared *ortho*-propynol phenyl azides using TMSBr as acid-promoter. The cascade transformation performs smoothly to generate desired products in moderate to excellent yields with good functional groups compatibility. Notably, TMSBr not only acted as an acid-promoter to initiate the reaction, and also as a nucleophile. In addition, 4-bromo quinolines as key intermediates could further undergo the coupling reactions or nucleophilic reactions to provide a variety of functionalized compounds with molecular diversity at C4 position of quinolines.

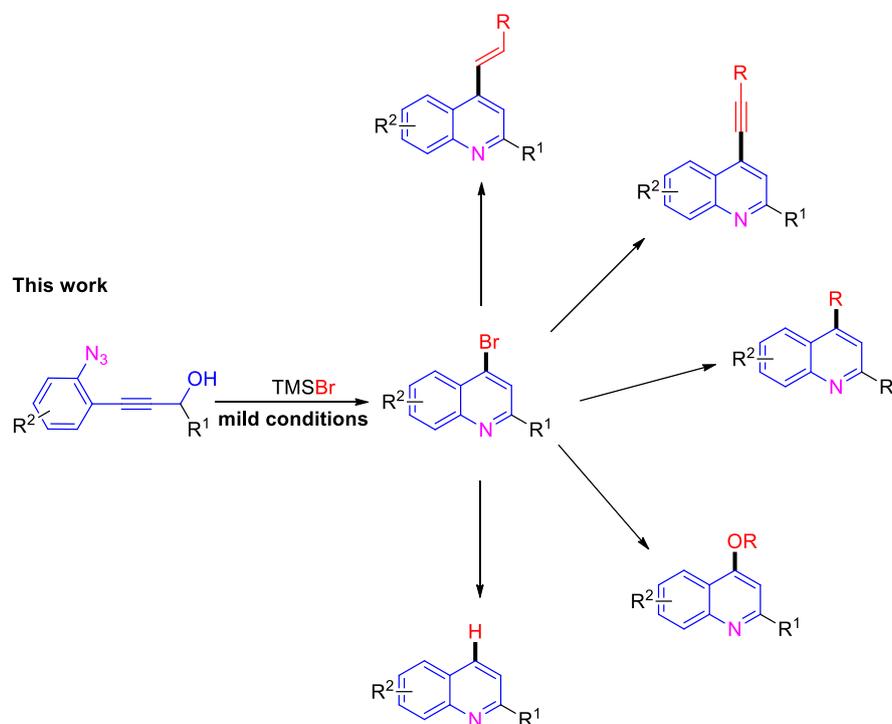
Keywords: TMSBr; propargylic alcohols; azides; cascade cyclization; 4-bromo quinolines

1. Introduction

Quinolines are distinctive and significant frameworks which are widely existed in numerous pharmaceuticals, pesticide molecules, bioactive molecules, and natural products [1–8]. Moreover, such compounds using as ligands play crucial role in synthetic and catalysis chemistry [9–13]. Consequently, developing general and flexible approach towards these heterocycles has attracted much attention among synthetic chemists. Until now, despite significant achievements having been made in the construction of functionalized quinolines [14–22], methods for the direct synthesis of 4-halo quinolines are still limited [23–26]. 4-halo quinolines have been widely used as key synthetic intermediates for the construction of various bioactive molecules or drugs [27–29]. Therefore, the development of an efficient and versatile strategy towards 4-halo quinolines is highly desirable, especially through a cascade cyclization, because of the merits of efficiency and atomic economy.

Based on its distinctive bifunctional group characteristics, the cascade reaction of propynols is an important tactic in organic synthesis, which exerts a significant role in the construction of functionalized carbo- or heterocyclic compounds [30–34]. In the past few years, our group had developed various efficient methods to construct functionalized heterocyclics through the cascade cyclization of propargylic alcohols in the presence of acid-promoter [35–44]. For example, we recently reported an efficient approach for the construction of 4-chloro quinolines via the cyclization of *ortho*-propynol phenyl azides with TMSCl as acid-promoter [45]. Taking into consideration that the coupling reaction of chloro-substituted compounds is more difficult than bromo- or iodo-substituted compounds, the further development of universal approach for the construction of 4-bromo quinolines is still desirable and necessary. Herein, we report a general TMSBr-promoted the cascade cyclization

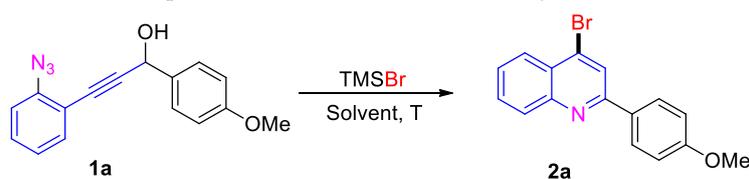
of *ortho*-propynol phenyl azides for constructing 4-bromo quinolines, which can further undergo the coupling reactions or nucleophilic reactions to provide a variety of functionalized compounds with molecular diversity at C4 position of quinolines (Scheme 1). Compared to the Shvartsberg's method [26], our developed strategy has the merits of good functional groups compatibility, easy preparation of the starting material, and simple operation.



Scheme 1. Our strategy for the construction of 4-bromo quinolines and its applications.

2. Results and Discussion

Initially, the reaction conditions were optimized for cascade cyclization of *ortho*-propynol phenyl azides **1a** in the presence of TMSBr. Various solvents, temperatures, and TMSBr loading were investigated, and all cases were shown in Table 1. To our delight, with 2.5 equiv of TMSBr in different solvents—such as MeCN, CH_3NO_2 , DCE, 1,4-dioxane, HOAc, and DCM—all reactions proceeded smoothly and cleanly to produce expected product 4-bromo-2-(4-methoxyphenyl)quinoline **2a** (Table 1, entries 1–5); CH_3NO_2 as solvent was most suitable for this transformation (73% yield). Encouraged by this preliminary result, further efforts were then directed toward improving the yield of desired product **2a** while suppressing the classical Meyer–Schuster rearrangement side reaction. Our studies on the loading of TMSBr with CH_3NO_2 as solvent showed that 3.5 equiv of TMSBr was the most efficient for this cascade transformation and could improve the yield of product **2a** to 81% (Table 1, entries 6–8). Subsequently, the examination of the reaction temperature indicated that the choice of reaction temperature was also an important in this transformation (entries 9, 10). Furthermore, no better yield was obtained when hydrobromic acid (HBr, 48 wt % in H_2O) was used instead of TMSBr as the acid promoter (entry 11). Therefore, we establish the reaction conditions as optimum: 0.2 mmol of 2-propynol phenyl azides, 3.5 equiv of TMSBr in CH_3NO_2 were stirred at 60 °C.

Table 1. Optimization of the reaction for the synthesis of **2a** ^a.

Entry	Solvent	TMSBr (x Equiv)	T [°C]	Yield [%]
1	DCE	2.5	60	45
2	MeCN	2.5	60	39
3	CH ₂ Cl ₂	2.5	40	15
4	MeNO ₂	2.5	60	73
5	HOAc	2.5	60	36
6	MeNO ₂	3.5	60	81
7	MeNO ₂	3.0	60	78
8	MeNO ₂	2.0	60	67
9	MeNO ₂	3.5	80	82
10	MeNO ₂	3.5	rt	69
11 ^b	MeNO ₂	3.5	60	75

^a Unless otherwise noted, all reactions were performed with 0.2 mmol of **1a** in solvent (2.0 mL) for 1.0 h. ^b hydrobromic acid instead of TMSBr was used.

Then, we investigated the generality of the reaction with diverse substituted propynols **1** using TMSBr as acid-promoter and nucleophile, and the results are presented in Figure 1. Various substituents R¹ and R² on the aryl ring were well-tolerated under the optimal conditions, efficiently generating the corresponding products 4-bromo quinolines in favorable yields (up to 91% yield). Firstly, we investigated the influence of substituent electronic effects on this reaction, and the results indicated that substrates containing electron-donor groups (OMe, Me) gave better transformation than those containing electron-poor groups (F, Cl, Br). This might be due to the fact that the reaction involved the carbocation intermediate (Intermediate **B**, see Scheme 4); and the electron-rich groups were good for the stabilization of carbocation intermediate. The corresponding products 4-bromo quinolines give the better yields compared to the synthesis of 4-chloro quinolines bearing the electron-withdrawing groups. Substrates bearing *ortho*-position substituent provided slightly lower yields (**2j–2k**), indicating that the steric effect showed clear influence on this reaction. Importantly, the functionalities of halogen atoms such as fluorine, chlorine, and bromine were also tolerated for this transformation producing the target products. Such halogenated products could be converted into a variety of functionalized quinolines through cross-coupling reactions. Substrates containing two or three substituents attached to the benzene ring smoothly, and the target compounds were generated in good to excellent yields. Notably, the substrates with naphthyl or styryl group (**1m** and **1o**) were also compatible to generate the target products in good yields (**2k–2m**). Then we examined the effect of a substituent (R²) on another aromatic ring on this transformation. Both electron-rich and electron-poor substituents were performed smoothly to produce the target compounds in 76–89% yields (**2m–2s**). It was noteworthy that the strong electron-deficient groups (CN and CF₃) in R² also proceeded well in this reaction and provided the target products in good yields. Unfortunately, no target product **2t** was generated when alkyl-substituted substrate **1t** was performed under the optimal conditions. Having successfully accomplished the direct formation of 4-bromo-quinolines, this cascade reaction was further extended to the construction of 4-iodo quinolines by using 2-propynol phenyl azides as starting materials with TMSI in CH₃NO₂ at 60 °C for 1.0 h under these circumstances. Some selected substrates (**1a**, **1b**, **1n**) were tolerated smoothly to the corresponding 4-iodo quinolines in moderate yields.

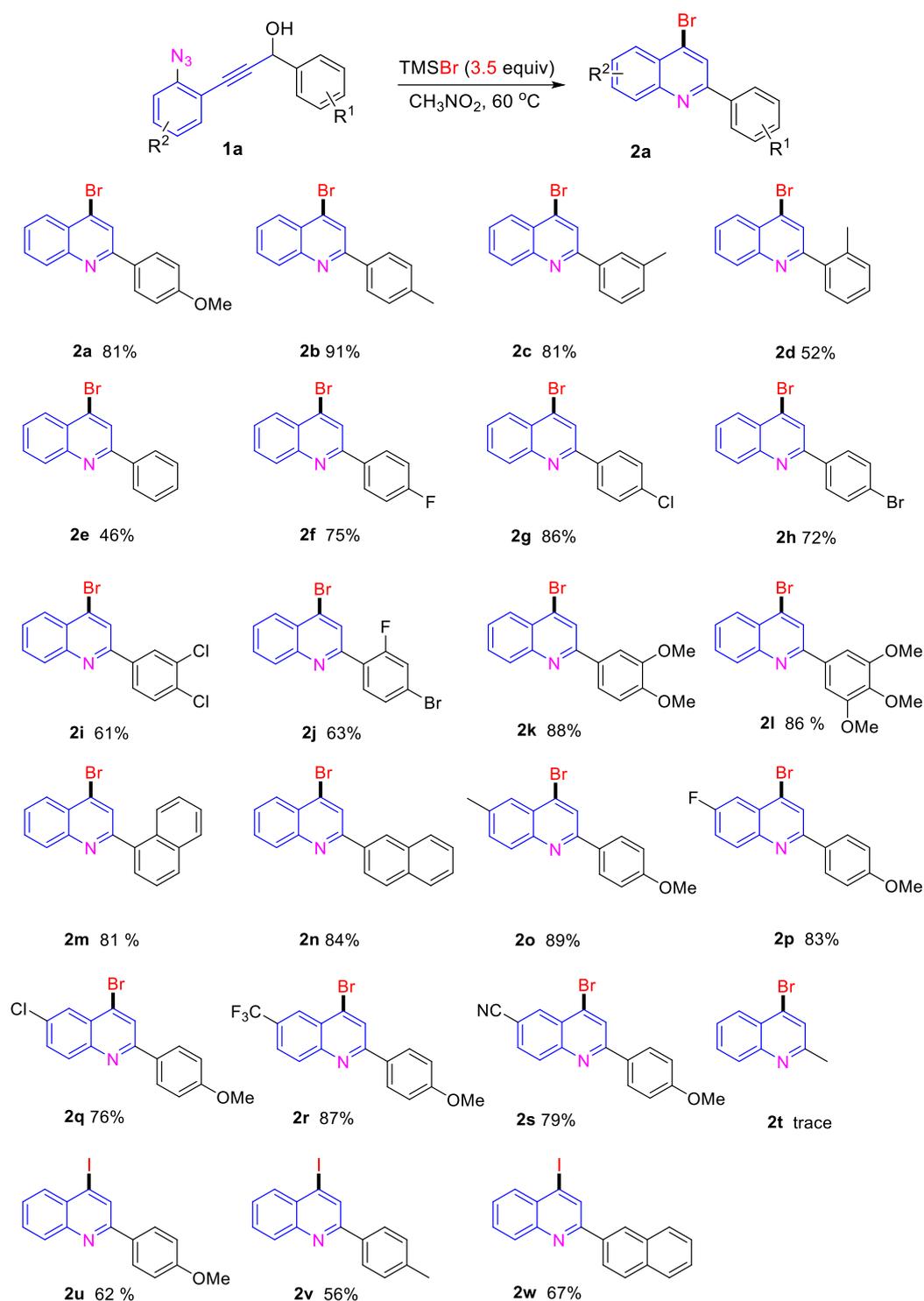
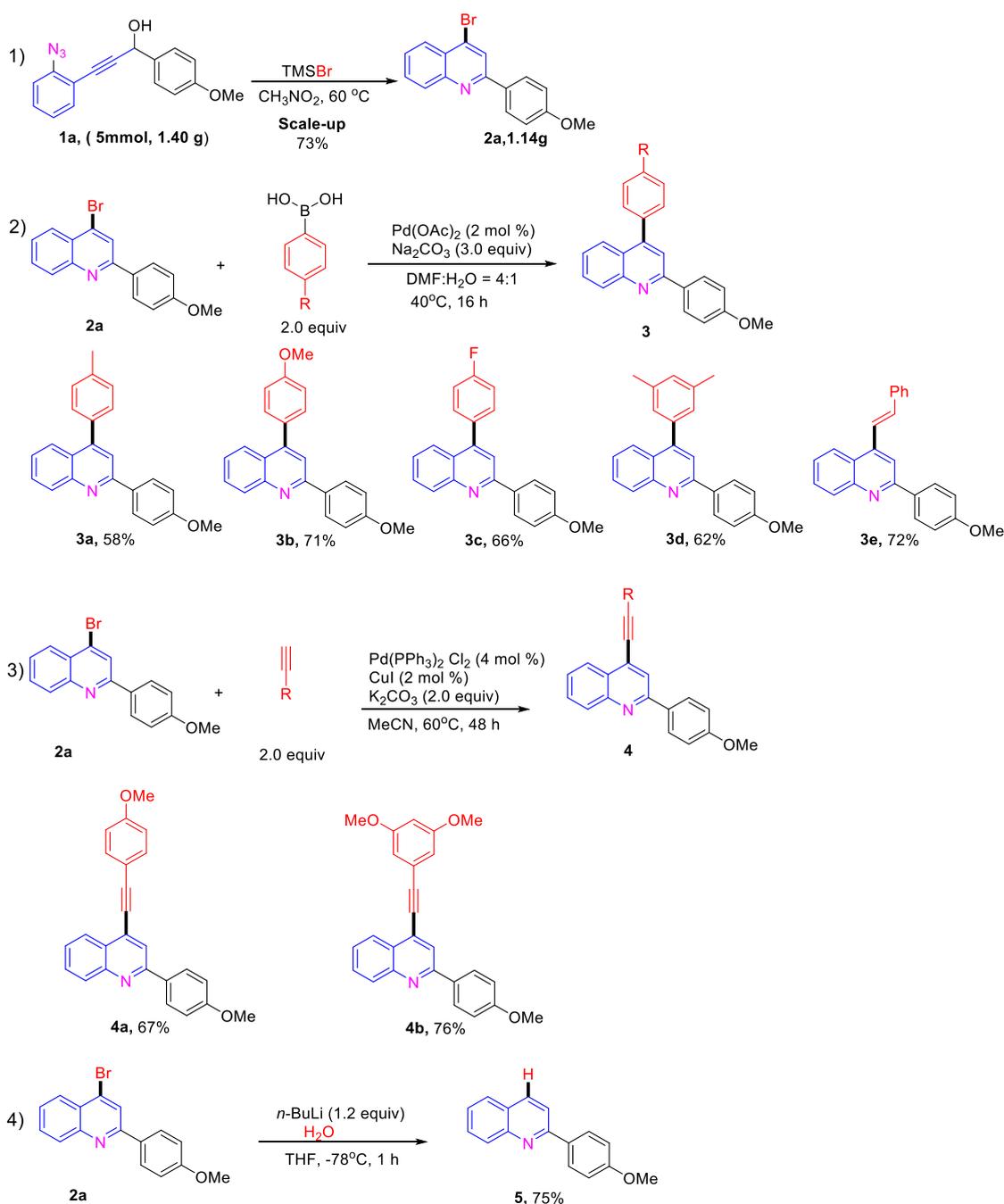


Figure 1. Transformation of *ortho*-propynol phenyl azides **1** to 4-bromo quinolines **2**^a. ^a Unless otherwise noted, all reactions were performed with **1** (0.2 mmol) in CH₃NO₂ (2.0 mL) at 60 °C for 1 h. Isolated yield.

Furthermore, the synthetic utility of this TMSBr-promoted reaction of *ortho*-propynol azides was demonstrated by a gram-scale synthesis (Scheme 2-1). The yield of product **2a** was not obviously affected when a gram-scale (5 mmol, 1.40g) experiment of **1a** was performed under similar reaction conditions. Importantly, a bromine atom at the 4-position of obtained product quinolines moiety is useful and easily substituted by various functional hydrocarbon and heteroatomic groups, which persuades

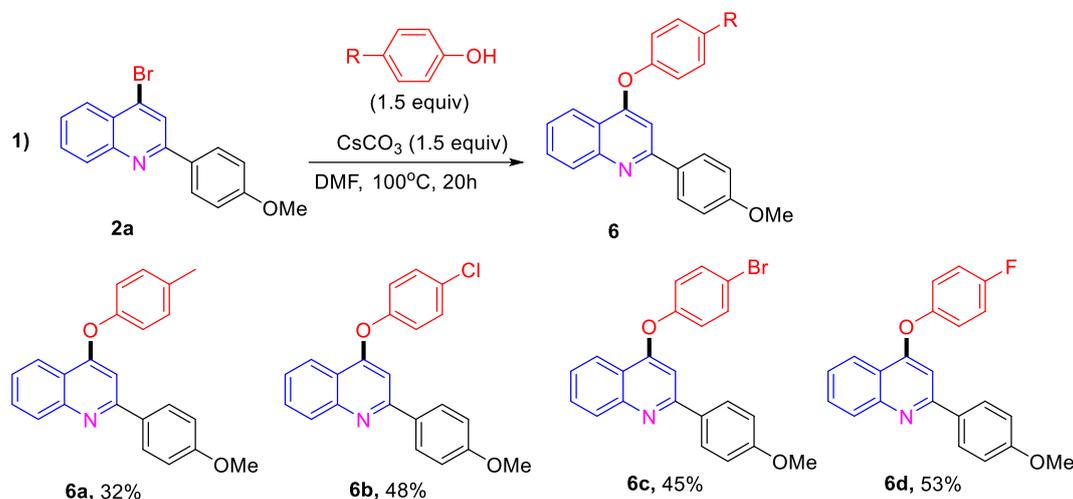
us to exploit synthetic transformation of 4-bromo quinolones [46–48]. As representative examples, the Suzuki coupling reaction of **2a** with arylboronic acids to 4-aryl quinolines **3a–3d** in good yield was achieved (Scheme 2-2) [46]. Notably, the corresponding product 4-vinyl quinoline **3e** was also generated when the reaction of **2a** with *E*-phenylethenylboronic acid. Furthermore, the Sonogashira coupling of **2a** with arylacetylene could smoothly proceed to produce the target products **4a–4b** in good yields (Scheme 2-3) [47]. More importantly, the classical reduction reaction of **2a** to the corresponding quinoline **5** was also investigated (Scheme 2-4). These results clearly demonstrate the usefulness of our obtained product 4-bromo quinolines as synthetic intermediates.



Scheme 2. Functionality elaboration of 4-bromo-quinolines.

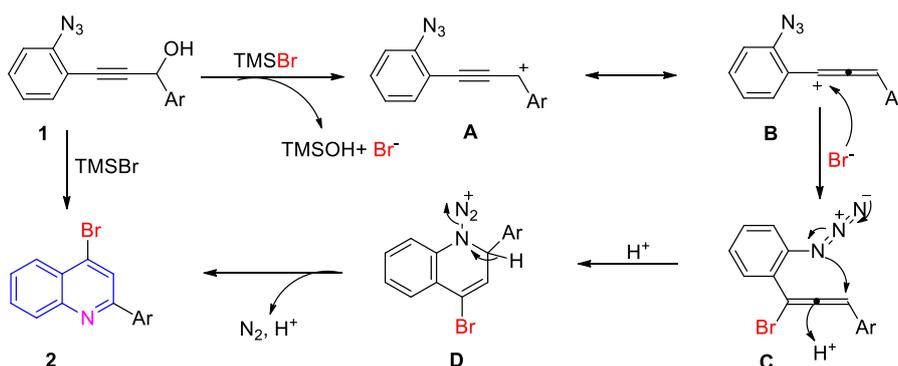
As we all known, 4-aryloxy quinolines are significant structure frameworks which are existed widely in various bioactive molecules and natural products [49–52]. In this context, the synthesis of

4-aryloxy quinolines from 4-bromo quinolines is attractive because of the clean conversion and the mild reaction conditions. Therefore, the scope of the reactions was also investigated by varying the phenols. Some representative substituted 4-aryloxy quinolines **6a–6d** were generated in acceptable yields by choosing the appropriate nucleophilic reagents (Scheme 3).



Scheme 3. Transformation of 4-bromo quinoline **2a** to 4-aryloxy quinolines **6**.

On the basis of the above experimental results and literature reports [45,53,54], we propose a plausible reaction mechanism for this reaction (Scheme 4). Firstly, a proargylic carbocation intermediate **A** was formed through the TMSBr-promoted the dehydration of propargylic alcohols **1**. Intermediate **A** could easily undergo tautomerization to generate allenic carbocation intermediate **B**, which could be attracted by nucleophile halide anion (Br^-) to produce intermediate **C**. Subsequently, the 6-endo-trig cyclization of intermediate **C** in the presence of proton forms intermediate **D**. Finally, the target product **2** was generated through the aromatization of the intermediate **D** with the generation of a nitrogen gas and a proton.



Scheme 4. Proposed reaction mechanism.

3. Materials and Methods

3.1. General Remarks

1H -NMR spectra were recorded on 400 MHz in $CDCl_3$ and ^{13}C -NMR spectra were recorded on 100 MHz in $CDCl_3$. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), q (quartet), or m (multiplet). High-resolution mass spectrometry (HRMS) was performed on a TOF/Q-TOF mass spectrometer. Copies of the 1H -NMR and ^{13}C -NMR spectra are provided in

the Supporting Information. Commercially available reagents were used without further purification. All solvents were dried under standard method.

3.2. General Procedure for the Construction of 4-Bromo Quinolines 2

To a seal tube was added *ortho*-propynol phenyl azides (**1**) (0.2 mmol), TMSBr (0.7 mmol), in CH₃NO₂ at 60 °C. After 1.0 h, as monitored by TLC, the reaction mixture was concentrated in vacuum and purified by column chromatography to generate 4-bromo quinolines **2**.

4-Bromo-2-(4-Methoxyphenyl)quinoline (**2a**)

The title compound was prepared according to the 0.5, 130.8, 134.5, 148.7, 156.7, 161.1. general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2a** (81%) [45]. ¹H-NMR (400 MHz, CDCl₃): δ 3.79 (s, 3 H), 6.95 (dd, *J* = 2.0, 6.8 Hz, 2 H), 7.47–7.51 (m, 1 H), 7.63–7.67 (m, 1 H), 8.01–8.07 (m, 5 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.4, 122.4, 126.3, 126.5, 127.0, 128.9, 129.8, 13.

4-Bromo-2-(*p*-tolyl)quinoline (**2b**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2b** (91%). ¹H-NMR (400 MHz, CDCl₃): δ 2.34 (s, 3 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.48–7.52 (m, 1 H), 7.64–7.68 (m, 1 H), 7.95 (d, *J* = 8.0 Hz, 2 H), 8.04–8.08 (m, 3 H). ¹³C-NMR (100 MHz, CDCl₃): δ 21.3, 122.7, 126.5, 127.2, 127.4, 129.6, 130.0, 130.4, 134.5, 135.5, 139.9, 148.7, 157.1. HRMS (ESI, *m/z*): calcd for C₁₆H₁₂BrN: M + H = 298.0226; found: 298.0229.

4-Bromo-2-(*m*-tolyl)quinoline (**2c**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2c** (81%). ¹H-NMR (400 MHz, CDCl₃): δ 2.39 (s, 3 H), 7.21 (d, *J* = 7.2 Hz, 1 H), 7.33 (t, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.2 Hz, 1 H), 7.68 (t, *J* = 7.6 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.89 (s, 1 H), 8.07–8.10 (m, 3 H). ¹³C-NMR (100 MHz, CDCl₃): δ 21.5, 123.0, 124.6, 126.5, 126.6, 127.4, 128.2, 128.8, 130.0, 130.5, 130.6, 134.5, 138.3, 138.6, 148.7, 157.4. HRMS (ESI, *m/z*): calcd for C₁₆H₁₂BrN: M + H = 298.0226; found: 298.0229.

4-Bromo-2-(*o*-tolyl)quinoline (**2d**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2d** (52%). ¹H-NMR (400 MHz, CDCl₃): δ 2.35 (s, 3 H), 7.20–7.29 (m, 3 H), 7.41 (d, *J* = 6.8 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.70 (t, *J* = 7.6 Hz, 1 H), 7.78 (s, 1 H), 8.06–8.16 (m, 2 H). ¹³C-NMR (100 MHz, CDCl₃): δ 20.3, 126.1, 126.1, 126.3, 126.6, 127.6, 128.9, 129.6, 130.0, 130.5, 131.1, 133.9, 136.1, 139.4, 148.4, 160.0. HRMS (ESI, *m/z*): calcd for C₁₆H₁₂BrN: M + H = 298.0226; found: 298.0227.

4-Bromo-2-phenylquinoline (**2e**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2e** (46%). ¹H-NMR (400 MHz, CDCl₃): δ 7.40–7.48 (m, 3 H), 7.54–7.56 (m, 1 H), 7.67–7.71 (m, 1 H), 8.05–8.11 (m, 5 H). ¹³C-NMR (100 MHz, CDCl₃): δ 122.9, 126.5, 126.7, 127.5, 127.5, 128.9, 129.8, 130.1, 130.5, 134.6, 138.4, 148.8, 157.2. HRMS (ESI, *m/z*): calcd for C₁₅H₁₀BrN: M + H = 284.0069; found: 284.0071.

4-Bromo-2-(4-fluorophenyl)quinoline (**2f**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2f** (75%). ¹H-NMR (400 MHz, CDCl₃): δ 7.11–7.18 (m, 2 H), 7.52–7.56 (m, 1 H), 7.67–7.71 (m, 1 H), 8.05–8.11 (m, 5 H).

^{13}C -NMR (100 MHz, CDCl_3): δ 115.8, 116.0, 122.5, 126.6, 127.5, 129.4, 129.5, 130.0, 130.7, 134.5, 134.8, 148.7, 156.0, 162.8, 165.3. HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_9\text{BrFN}$: $M + H = 301.9975$; found: 301.9973.

4-Bromo-2-(4-chlorophenyl)quinoline (2g)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2g** (86%). ^1H -NMR (400 MHz, CDCl_3): δ 7.41 (d, $J = 8.4$ Hz, 2 H), 7.52–7.56 (m, 1 H), 7.67–7.71 (m, 1 H), 7.99–8.10 (m, 5 H). ^{13}C -NMR (100 MHz, CDCl_3): δ 122.5, 126.6, 126.7, 127.7, 128.7, 129.1, 130.0, 130.7, 134.8, 136.0, 136.7, 148.7, 155.8. HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_9\text{BrClN}$: $M + H = 317.9680$; found: 317.9682.

4-Bromo-2-(4-bromophenyl)quinoline (2h)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2h** (72%). ^1H -NMR (400 MHz, CDCl_3): δ 7.54–7.57 (m, 3 H), 7.68 (t, $J = 8.4$ Hz, 1 H), 7.94 (d, $J = 8.4$ Hz, 2 H), 8.04–8.10 (m, 3 H). ^{13}C -NMR (100 MHz, CDCl_3): δ 122.4, 124.5, 126.6, 126.7, 127.7, 129.0, 130.1, 130.7, 132.0, 134.8, 137.2, 148.7, 155.9. HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_9\text{Br}_2\text{N}$: $M + H = 361.9175$; found: 361.9179.

4-Bromo-2-(3,4-dichlorophenyl)quinoline (2i)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2i** (61%). ^1H -NMR (400 MHz, CDCl_3): δ 7.50 (d, $J = 8.4$ Hz, 1 H), 7.54–7.58 (m, 1 H), 7.69–7.73 (m, 1 H), 7.87–7.90 (m, 1 H), 8.02–8.11 (m, 3 H), 8.21 (d, $J = 2.0$ Hz, 1 H). ^{13}C -NMR (100 MHz, CDCl_3): δ 122.2, 126.4, 126.6, 126.8, 128.0, 129.3, 130.1, 130.8, 130.9, 133.3, 134.1, 135.0, 138.1, 148.6, 154.4. HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_8\text{BrCl}_2\text{N}$: $M + H = 351.9290$; found: 351.9291.

4-Bromo-2-(4-bromo-2-fluorophenyl)quinoline (2j)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2j** (63%). ^1H -NMR (400 MHz, CDCl_3): δ 7.34 (dd, $J = 1.6, 6.8$ Hz, 1 H), 7.40 (dd, $J = 1.6, 8.4$ Hz, 1 H), 7.59 (t, $J = 7.2$ Hz, 1 H), 7.72 (t, $J = 7.2$ Hz, 1 H), 7.97 (t, $J = 7.6$ Hz, 1 H), 8.07–8.14 (m, 3 H). ^{13}C -NMR (100 MHz, CDCl_3): δ 119.8, 120.0, 124.1, 124.2, 125.8, 125.9, 126.7, 126.9, 128.1, 128.2, 128.2, 130.0, 130.7, 132.5, 132.6, 134.4, 148.6, 152.6, 159.1, 161.8. HRMS (ESI, m/z): calcd for $\text{C}_{15}\text{H}_8\text{Br}_2\text{FN}$: $M + H = 379.9080$; found: 379.9084.

4-Bromo-2-(3,4-dimethoxyphenyl)quinoline (2k)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2k** (88%). ^1H -NMR (400 MHz, CDCl_3): δ 3.87 (s, 3 H), 3.97 (s, 3 H), 6.89 (d, $J = 8.4$ Hz, 1 H), 7.48–7.56 (m, 2 H), 7.64–7.68 (m, 1 H), 7.75 (d, $J = 2.0$ Hz, 1 H), 8.05–8.08 (m, 3 H). ^{13}C -NMR (100 MHz, CDCl_3): δ 55.9, 56.0, 110.2, 111.0, 120.3, 122.5, 126.4, 126.5, 127.1, 129.8, 130.5, 131.0, 134.5, 148.6, 149.4, 150.7, 156.6. HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{14}\text{BrNO}_2$: $M + H = 344.0281$; found: 344.0283.

4-Bromo-2-(3,4,5-trimethoxyphenyl)quinoline (2l)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2l** (86%). ^1H -NMR (400 MHz, CDCl_3): δ 3.85 (s, 3 H), 3.93 (s, 6 H), 7.29 (s, 2 H), 7.53 (t, $J = 7.2$ Hz, 1 H), 7.69 (t, $J = 7.6$ Hz, 1 H), 8.04 (s, 1 H), 8.07–8.10 (m, 2 H). ^{13}C -NMR (100 MHz, CDCl_3): δ 56.3, 60.9, 104.8, 122.7, 126.5, 127.5, 129.9, 130.6, 133.8, 134.6, 139.8, 148.5, 153.6, 156.7. HRMS (ESI, m/z): calcd for $\text{C}_{18}\text{H}_{16}\text{BrNO}_3$: $M + H = 374.0386$; found: 374.0382.

4-Bromo-2-(naphthalen-1-yl)quinoline (2m)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2m** (81%). ¹H-NMR (400 MHz, CDCl₃): δ 7.41–7.48 (m, 2 H), 7.51–7.55 (m, 1 H), 7.61–7.66 (m, 2 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.86–7.91 (m, 2 H), 7.96 (s, 1 H), 8.05 (d, *J* = 8.0 Hz, 1 H), 8.19 (dd, *J* = 8.8 Hz, 2 H). ¹³C-NMR (100 MHz, CDCl₃): δ 125.3, 126.1, 126.6, 126.7, 126.9, 127.0, 127.9, 128.0, 128.5, 129.6, 129.9, 130.8, 131.0, 133.9, 134.4, 137.1, 148.4, 159.1. HRMS (ESI, *m/z*): calcd for C₁₉H₁₂BrN: M + H = 334.0226; found: 334.0227.

4-Bromo-2-(naphthalen-2-yl)quinoline (**2n**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2n** (84%). ¹H-NMR (400 MHz, CDCl₃): δ 7.42–7.46 (m, 2 H), 7.50–7.54 (m, 1 H), 7.66–7.70 (m, 1 H), 7.78–7.81 (m, 1 H), 7.88 (dd, *J* = 2.8, 5.6 Hz, 2 H), 8.08–8.11 (m, 2 H), 8.22–8.24 (m, 2 H), 8.47 (d, *J* = 0.8 Hz, 1 H). ¹³C-NMR (100 MHz, CDCl₃): δ 123.0, 124.7, 126.4, 126.6, 126.7, 126.9, 127.3, 127.5, 127.7, 128.7, 128.8, 130.1, 130.6, 133.3, 134.0, 134.6, 135.6, 148.8, 156.9. HRMS (ESI, *m/z*): calcd for C₁₉H₁₂BrN: M + H = 334.0226; found: 334.0227.

4-Bromo-2-(4-methoxyphenyl)-6-methylquinoline (**2o**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2o** (89%). ¹H-NMR (400 MHz, CDCl₃): δ 2.48 (s, 3 H), 3.79 (s, 3 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 7.47 (dd, *J* = 1.6, 8.4 Hz, 1 H), 7.80 (s, 1 H), 7.91 (d, *J* = 8.8 Hz, 1 H), 7.98–8.00 (m, 3 H). ¹³C-NMR (100 MHz, CDCl₃): δ 21.7, 55.3, 114.2, 122.4, 125.3, 126.2, 128.7, 129.6, 131.1, 132.6, 133.7, 137.2, 147.3, 155.8, 160.9. HRMS (ESI, *m/z*): calcd for C₁₇H₁₄BrNO: M + H = 328.0332; found: 328.0331.

4-Bromo-6-fluoro-2-(4-methoxyphenyl)quinoline (**2p**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2p** (83%). ¹H-NMR (400 MHz, CDCl₃): δ 3.81 (s, 3 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 7.39–7.44 (m, 1 H), 7.70 (dd, *J* = 2.8, 9.6 Hz, 1 H), 7.99–8.05 (m, 4 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.4, 110.2, 110.4, 114.3, 120.5, 120.7, 123.0, 127.2, 127.3, 128.8, 130.6, 132.4, 132.5, 133.3, 133.4, 145.8, 156.1, 156.2, 159.7, 161.2, 162.2. HRMS (ESI, *m/z*): calcd for C₁₆H₁₁BrFNO: M + H = 332.0081; found: 332.0081.

4-Bromo-6-chloro-2-(4-methoxyphenyl)quinoline (**2q**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2q** (76%). ¹H-NMR (400 MHz, CDCl₃): δ 3.80 (s, 3 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 7.57 (dd, *J* = 2.4, 8.8 Hz, 1 H), 7.94–8.05 (m, 5 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.4, 114.3, 123.1, 125.5, 127.0, 128.8, 130.4, 131.4, 131.5, 133.0, 133.1, 147.1, 156.9, 161.3. HRMS (ESI, *m/z*): calcd for C₁₆H₁₁BrClNO: M + H = 347.9785; found: 347.9787.

4-Bromo-2-(4-methoxyphenyl)-6-(trifluoromethyl)quinoline (**2r**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2r** (87%). ¹H-NMR (400 MHz, CDCl₃): δ 3.80 (s, 3 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 7.79 (d, *J* = 8.8 Hz, 1 H), 8.03 (d, *J* = 8.4 Hz, 2 H), 8.10 (d, *J* = 8.4 Hz, 2 H), 8.34 (s, 1 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.4, 114.4, 123.4, 124.6, 124.7, 125.5, 126.1, 126.1, 129.1, 130.0, 131.0, 135.0, 149.7, 158.6, 161.7. HRMS (ESI, *m/z*): calcd for C₁₇H₁₁BrF₃NO: M + H = 382.0049; found: 382.0045.

4-Bromo-2-(4-methoxyphenyl)quinoline-6-carbonitrile (**2s**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2s** (79%). ¹H-NMR (400 MHz, CDCl₃): δ 3.83 (s, 3 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 7.79 (dd, *J* = 1.6, 8.4 Hz, 1 H), 8.08 (dd,

$J = 5.6, 8.8$ Hz, 3 H), 8.16 (s, 1 H), 8.47 (d, $J = 1.2$ Hz, 1 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 55.5, 110.4, 114.5, 118.5, 123.8, 126.0, 129.3, 129.7, 131.2, 131.3, 132.9, 134.5, 149.9, 159.4, 162.0. HRMS (ESI, m/z): calcd for $\text{C}_{17}\text{H}_{11}\text{BrN}_2\text{O}$: $M + H = 339.0128$; found: 339.0128.

4-Iodo-2-(4-methoxyphenyl)quinoline (**2u**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2u** (62%) [45]. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.89 (s, 3 H), 7.03–7.05 (m, 2 H), 7.54–7.58 (m, 1 H), 7.70–7.74 (m, 1 H), 7.98 (d, $J = 8.4$ Hz, 1 H), 8.05 (d, $J = 8.4$ Hz, 1 H), 8.09–8.12 (m, 2 H), 8.42 (s, 1 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 66.4, 112.5, 114.3, 127.4, 128.9, 128.9, 130.1, 130.1, 130.5, 130.6, 131.4, 147.8, 156.7, 161.1.

4-Iodo-2-(*p*-tolyl)quinoline (**2v**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2v** (56%). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 2.44 (s, 3 H), 7.33 (d, $J = 8.0$ Hz, 2 H), 7.60 (t, $J = 7.2$ Hz, 1 H), 7.72–7.76 (m, 1 H), 7.99–8.08 (m, 4 H), 8.45 (s, 1 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 21.3, 112.5, 127.4, 127.6, 129.0, 129.7, 130.2, 130.4, 130.5, 131.4, 135.2, 139.9, 147.8, 157.0. HRMS (ESI, m/z): calcd for $\text{C}_{16}\text{H}_{12}\text{IN}$: $M + H = 346.0087$; found: 346.0092.

4-Iodo-2-(naphthalen-2-yl)quinoline (**2w**)

The title compound was prepared according to the general procedure and purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **2w** (67%). $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.54–7.57 (m, 2 H), 7.60–7.64 (m, 1 H), 7.75–7.80 (m, 1 H), 7.90–7.92 (m, 1 H), 7.99–8.05 (m, 3 H), 8.14 (d, $J = 8.4$ Hz, 1 H), 8.32–8.35 (m, 1 H), 8.59 (s, 1 H), 8.63 (s, 1 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 112.6, 124.8, 126.5, 126.9, 127.3, 127.7, 127.9, 128.7, 128.8, 129.2, 130.3, 130.6, 130.7, 131.5, 133.4, 134.0, 135.3, 147.9, 156.9. HRMS (ESI, m/z): calcd for $\text{C}_{19}\text{H}_{12}\text{IN}$: $M + H = 382.0087$; found: 382.0089.

2-(4-Methoxyphenyl)-4-(*p*-tolyl)quinoline (**3a**)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **3a** (58%) [55]. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.38 (s, 3 H), 3.78 (s, 3 H), 6.95 (d, $J = 8.4$ Hz, 2 H), 7.26 (d, $J = 8.0$ Hz, 2 H), 7.32–7.37 (m, 3 H), 7.59–7.63 (m, 1 H), 7.66 (s, 1 H), 7.81 (d, $J = 8.4$ Hz, 1 H), 8.05–8.12 (m, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 21.3, 55.3, 114.2, 118.8, 125.6, 125.7, 125.8, 128.9, 129.2, 129.3, 129.4, 129.8, 132.3, 135.6, 138.2, 148.8, 149.0, 156.4, 160.8.

2,4-bis(4-Methoxyphenyl)quinoline (**3b**)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **3b** (71%) [55]. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.79 (s, 3 H), 3.81 (s, 3 H), 6.97 (dd, $J = 8.8, 13.2$ Hz, 4 H), 7.33–7.37 (m, 1 H), 7.41 (d, $J = 8.8$ Hz, 2 H), 7.59–7.63 (m, 1 H), 7.66 (s, 1 H), 7.82 (d, $J = 8.4$ Hz, 1 H), 8.06–8.12 (m, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 55.3, 55.4, 114.0, 114.2, 118.8, 125.6, 125.7, 125.8, 128.9, 129.3, 129.8, 130.7, 132.3, 148.6, 148.9, 156.4, 159.8, 160.8.

4-(4-Fluorophenyl)-2-(4-methoxyphenyl)quinoline (**3c**)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **3c** (66%) [55]. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 3.80 (s, 3 H), 6.96 (d, $J = 8.8$ Hz, 2 H), 7.13–7.18 (m, 2 H), 7.35–7.39 (m, 1 H), 7.43–7.46 (m, 2 H), 7.61–7.65 (m, 2 H), 7.73 (d, $J = 8.4$ Hz, 1 H), 8.06–8.13 (m, 3 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 55.4, 114.2, 115.5, 115.7, 118.9, 125.3, 125.5, 126.0, 128.9, 128.5, 130.0, 131.2, 131.3, 132.0, 134.4, 134.5, 147.9, 148.8, 156.4, 160.9, 161.6, 164.1.

4-(3,5-Dimethylphenyl)-2-(4-methoxyphenyl)quinoline (**3d**)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **3d** (62%). ¹H-NMR (400 MHz, CDCl₃): δ 2.34 (s, 6 H), 3.79 (s, 3 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 7.05–7.08 (m, 3 H), 7.33–7.37 (m, 1 H), 7.59–7.63 (m, 1 H), 7.67 (s, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 8.06–8.12 (m, 3 H). ¹³C-NMR (100 MHz, CDCl₃): δ 21.3, 55.3, 114.2, 118.7, 125.6, 125.7, 125.8, 127.3, 128.9, 129.3, 129.8, 129.9, 132.2, 138.1, 138.4, 148.7, 149.3, 156.4, 160.8. HRMS (ESI, *m/z*): calcd for: C₂₄H₂₁NO: M + H = 340.1696; found: M + H = 340.1692.

(*E*)-2-(4-Methoxyphenyl)-4-styrylquinoline (**3e**)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **3e** (72%) [56]. ¹H-NMR (400 MHz, CDCl₃): δ 3.83 (s, 3 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 7.27–7.39 (m, 4 H), 7.44–7.49 (m, 1 H), 7.58 (d, *J* = 7.2 Hz, 2 H), 7.63–7.67 (m, 1 H), 7.77 (d, *J* = 16.0 Hz, 1 H), 7.95 (s, 1 H), 8.08–8.12 (m, 4 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.4, 114.2, 114.7, 123.3, 123.6, 125.2, 125.9, 127.1, 128.7, 128.8, 128.9, 129.4, 130.2, 132.4, 134.9, 136.7, 143.5, 148.8, 156.8, 160.8.

2-(4-Methoxyphenyl)-4-((4-methoxyphenyl)ethynyl)quinoline (**4a**)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **4a** (67%) [45]. ¹H-NMR (400 MHz, CDCl₃): δ 3.86 (s, 3 H), 3.89 (s, 3 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 7.05 (d, *J* = 8.8 Hz, 2 H), 7.55–7.59 (m, 1 H), 7.63 (d, *J* = 8.8 Hz, 2 H), 7.71–7.75 (m, 1 H), 8.00 (s, 1 H), 8.13–8.16 (m, 3 H), 8.33 (d, *J* = 7.6 Hz, 1 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.4, 84.5, 98.2, 114.2, 114.4, 120.9, 125.7, 126.3, 126.3, 128.8, 129.8, 129.9, 130.5, 131.8, 133.5, 148.2, 156.4, 160.4, 160.9.

4-((3,5-Dimethoxyphenyl)ethynyl)-2-(4-methoxyphenyl)quinoline (**4b**)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **4b** (76%). ¹H-NMR (400 MHz, CDCl₃): δ 3.78 (s, 6 H), 3.82 (s, 3 H), 6.48 (t, *J* = 2.0 Hz, 1 H), 6.76 (d, *J* = 2.4 Hz, 2 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 7.67 (t, *J* = 8.0 Hz, 1 H), 7.96 (s, 1 H), 8.07–8.10 (m, 3 H), 8.25 (d, *J* = 8.0 Hz, 1 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.5, 85.0, 97.8, 102.6, 109.7, 114.3, 121.3, 123.6, 125.6, 126.3, 126.5, 128.8, 129.9, 130.0, 130.0, 131.7, 148.2, 156.4, 160.7, 161.0. HRMS (ESI, *m/z*): calcd for: C₂₆H₂₁NO₃: M + H = 396.1594; found: 396.1596.

2-(4-Methoxyphenyl)quinoline (**5**)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **5** (75%) [57]. ¹H-NMR (400 MHz, CDCl₃): δ 3.79 (s, 3 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 7.38–7.42 (m, 1 H), 7.59–7.64 (m, 1 H), 7.70–7.75 (m, 2 H), 8.04–8.09 (m, 4 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.4, 114.2, 118.5, 125.8, 126.9, 127.4, 128.9, 129.5, 129.5, 132.2, 136.6, 148.3, 156.9, 160.8.

2-(4-Methoxyphenyl)-4-(*p*-tolylloxy)quinoline (**6a**)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **6a** (32%). ¹H-NMR (400 MHz, CDCl₃): δ 2.35 (s, 3 H), 3.77 (s, 3 H), 6.88–6.90 (m, 3 H), 7.04 (d, *J* = 8.4 Hz, 2 H), 7.18–7.21 (m, 2 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 8.8 Hz, 2 H), 8.04 (d, *J* = 8.8 Hz, 1 H), 8.25 (d, *J* = 8.0 Hz, 1 H). ¹³C-NMR (100 MHz, CDCl₃): δ 20.9, 55.4, 101.7, 114.0, 120.4, 120.7, 121.7, 125.4, 128.8, 129.1, 130.2, 130.7, 132.5, 135.1, 149.8, 152.3, 158.1, 160.7, 162.5. HRMS (ESI, *m/z*): calcd for: C₂₃H₁₉NO₂: M + H = 342.1489; found: 342.1495.

4-(4-Chlorophenoxy)-2-(4-methoxyphenyl)quinoline (**6b**)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **6b** (48%). ¹H-NMR (400 MHz, CDCl₃): δ 3.77 (s, 3 H), 6.89–6.92 (m, 3 H), 7.09 (d, *J* = 8.8 Hz, 2 H), 7.36 (d, *J* = 9.2 Hz, 2 H), 7.45 (t, *J* = 7.2 Hz, 1 H), 7.65–7.70 (m, 1 H), 7.86 (d, *J* = 8.8 Hz, 2 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 8.19 (d, *J* = 7.6 Hz, 1 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.5, 110.4, 114.5, 118.5, 123.8, 126.0, 129.3, 129.7, 131.2, 131.3, 132.9, 134.5, 149.9, 159.4, 162.0. HRMS (ESI, *m/z*): calcd for: C₂₂H₁₆ClNO₂: M + H = 362.0942; found: 362.0948.

4-(4-Bromophenoxy)-2-(4-methoxyphenyl)quinoline (6c)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **6c** (45%). ¹H-NMR (400 MHz, CDCl₃): δ 3.77 (s, 3 H), 6.89–6.93 (m, 3 H), 7.04 (d, *J* = 8.8 Hz, 2 H), 7.45 (t, *J* = 7.2 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 7.67 (t, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 2 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.4, 102.3, 114.1, 118.2, 120.2, 121.5, 122.5, 125.7, 128.8, 129.2, 130.4, 132.1, 133.3, 149.8, 153.9, 158.1, 160.9, 161.7. HRMS (ESI, *m/z*): calcd for: C₂₂H₁₆BrNO₂: M + H = 406.0437; found: 406.0431.

4-(4-Fluorophenoxy)-2-(4-methoxyphenyl)quinoline (6d)

The title compound was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to give a product **6d** (53%). ¹H-NMR (400 MHz, CDCl₃): δ 3.77 (s, 3 H), 6.89–6.93 (m, 3 H), 7.04 (d, *J* = 8.8 Hz, 2 H), 7.45 (t, *J* = 7.2 Hz, 1 H), 7.51 (d, *J* = 8.8 Hz, 2 H), 7.67 (t, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 2 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H). ¹³C-NMR (100 MHz, CDCl₃): δ 55.4, 102.3, 114.1, 118.2, 120.2, 121.5, 122.5, 125.7, 128.8, 129.2, 130.4, 132.1, 133.3, 149.8, 153.9, 158.1, 160.9, 161.7. HRMS (ESI, *m/z*): calcd for: C₂₂H₁₆FNO₂: M + H = 346.1238; found: 346.1234.

4. Conclusions

In summary, we have developed an efficient and general approach for the synthesis of 4-bromo or 4-iodo quinolines through the TMSBr promoted the cascade cyclization of *ortho*-propynol phenyl azides. It is noteworthy that the obtained products 4-halo quinolines could be used as key intermediate for the construction of various bioactive molecules, natural products, and drugs. A variety of 4-halo quinolines were obtained in moderate to excellent yields under mild conditions. This process does not require the use of metal catalysts, additional oxidants; water and nitrogen gas are generated as the only side products.

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