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HFIP mediated transition metal-free synthesis of C4-aryl-substituted quinolines

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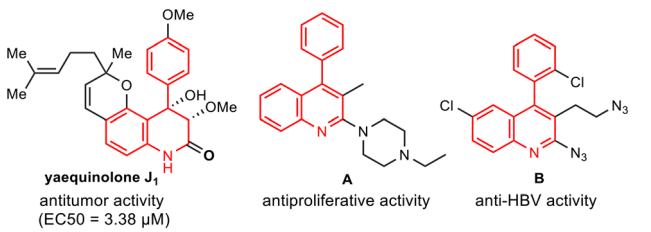
A transition metal-free method for C4-arylated quinolines synthesis from propargylic chloride and aniline was developed using 1,1,1,3,3,3,-hexafluoroisopropanol (HFIP). During the *N*-alkylation process, overalkylation was effectively resolved by hydrogen bonding interaction in HFIP. The cyclized intermediates were oxidized to quinolines under ambient air without additional oxidants. A cosolvent system was found to expand the substrate scope to include unstable electron-rich propargyl substrates by preventing acid-induced decomposition.

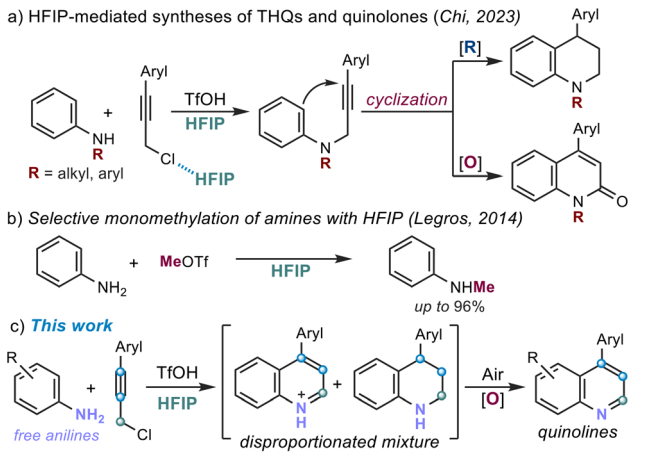
Quinolines and their derivatives are widely found in natural products and biologically active drug candidates. In particular, 4-aryl quinolines have been identified in compounds exhibiting antiproliferative, anti-HBV, and anti-tumor activities (Scheme 1).[1]

Due to the significant therapeutic potential of 4-aryl quinolines, various synthetic methods have been developed. Among those, one of the most well-established and widely employed strategies for synthesizing 4-aryl quinolines involves transition metal-catalyzed reactions.[2] However, these transition metals are costly and pose toxicity concerns that limit their use in pharmaceutical applications.[3] Consequently, alternative strategies have been developed to synthesize 4-aryl quinolines without the use of transition metals, for example, by reacting alkynes and anilines in DMSO with various oxidants.[4] Our group has also developed a strategy to access 4-arylated tetrahydroquinolines (THQs) and quinolones directly from propargylic chlorides and *N*-substituted anilines (Scheme 2a).[5] In this process, HFIP was found to be crucial for the activation of the C–Cl bond, facilitating C–N bond formation with poorly nucleophilic anilines. After the cyclization, the resulting disproportionated mixture is then converted into either THQs or quinolones, depending on the use of a proper reductant or oxidant.

In previous studies, the use of free aniline was avoided due to concerns on overalkylation. HFIP is known not only to activate C–X,[6] C–O,[7] C–H,[8] and C=N[9] bonds, but also to suppress overalkylation through hydrogen bonding with primary amines.[10] This was exemplified by the Legros group, where



Scheme 1 Bioactive natural products with 4-aryl quinolines.



Scheme 2 (a) HFIP-mediated syntheses of THQs and quinolones. (b) Selective monomethylation of amines with HFIP. (c) HFIP-mediated synthesis of quinolines.

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HFIP enabled the selective monomethylation of anilines under mild conditions (Scheme 2b).[11] Building upon these insights, it was hypothesized that HFIP could effectively mitigate the overalkylation observed in prior studies. Herein, we demonstrate the synthesis of C4-aryl-substituted quinolines from propargylic chlorides and free anilines, confirming the ability of HFIP to resolve overalkylation.

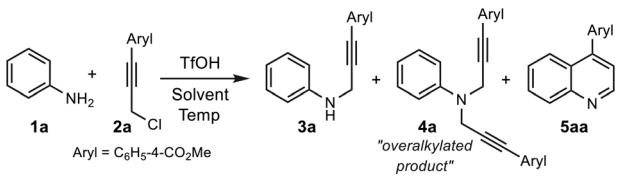
In the preliminary investigation, aniline (**1a**) and propargylic chloride **2a** were selected as model substrates to evaluate the effects of different solvents and temperatures. Initially, the HFIP system was tested at 80 °C with 1 equiv. of aniline. Under these conditions, the desired quinoline product, **5aa**, was obtained along with an *N*-alkylated intermediate and a trace amount of overalkylated byproduct **4a** (Table 1, entry 1). When the reaction was conducted in MeCN, formation of **5aa** was not observed, while the production of the overalkylated byproduct increased (Table 1, entry 2), suggesting that HFIP suppresses the overalkylation of the nitrogen. Increasing the amount of **1a** to 3 equiv. slightly improved the yield of **5aa**, although compounds **3a** and **4a** remained present (Table 1, entry 3). Subjecting 3 equiv. of **1a** in MeCN, only resulted in further accumulation of **3a** (Table 1, entry 4), indicating that HFIP plays a critical role in the cyclization step. In contrast to the results at 80 °C, full conversion to **5aa** was observed with no overalkylated byproducts at 120 °C (Table 1, entry 5).

To investigate the ability of HFIP to suppress overalkylation, additional experiments were conducted using the overalkylated byproduct **4a** (Table 2). Upon reaction of separately prepared **4a** with aniline in HFIP at 120 °C, quinoline **5aa** was obtained in 36% yield (Table 2, entry 1). In contrast, no quinoline formation was observed in the absence of aniline or at 80 °C (Table 2, entries 2 and 3). To further elucidate the conversion pathway of **4a** to **5aa**, a kinetic study was performed. The quinolinium intermediate **5aa′** grew rapidly, followed by the formation of quinoline **5aa** and *N*-alkylated intermediate **3a** (see SI). This transformation was only observed under the conditions of 120 °C in the presence of aniline, suggesting that **4a** undergoes cyclization to form **5aa′** at elevated temperature, which then reacts with aniline *via* nucleophilic attack to produce both quinoline **5aa** and *N*-alkylated intermediate **3a**. These findings suggest that HFIP exerts a dual function by first suppressing overalkylation *via* hydrogen bonding and then enabling the conversion of the overalkylated byproduct into quinoline.

To further optimize the reaction conditions, a screening was performed to evaluate the effects of temperature and the amounts of aniline, Brønsted acids, and oxidants (see SI). A key factor in the optimization process was the variation in reactivity of propargylic chlorides depending on their electron density. In the previous studies, electron-deficient propargyl chlorides degraded slowly under the acidic reaction conditions, while the analogs with increased electron density were found to undergo rapid decomposition. Thus, the reaction conditions were optimized accordingly depending on the electron densities of the propargylic chlorides. For electron-deficient substrates, elevated temperatures (120 °C) and catalytic amounts (1.0 or 0.1 equiv.) of TfOH were critical for accelerating the reaction. In contrast, for electron-rich substrates, decomposition was effectively suppressed by employing toluene as a cosolvent with HFIP. These results highlight the necessity of tuning reaction conditions based on the electronic nature of the propargylic chloride to achieve both efficient conversion and minimal decomposition.

The optimized conditions were applied to a variety of propargylic chlorides, using *p*-toluidine (**1b**) as the nitrogen source. This choice was made based on the expectation that the electron-rich aromatic ring of *p*-toluidine would enhance the rate of the Friedel–Crafts reaction, potentially leading to slightly higher yields (Scheme 3). Electron-deficient propargylic chlorides **2a–o** were subjected to condition A. Propargylic chlorides substituted with diverse electron-withdrawing groups at the *para* position were first evaluated. Methyl ester substituted propargylic chloride **2a** afforded quinoline **5ba** in a good yield (**5ba**, 64%). Halogenated propargylic chlorides **2b–2e** not particularly efficient substrates, resulting

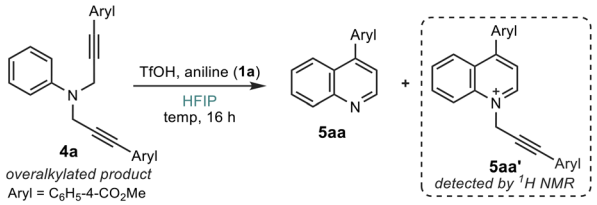
Table 1 Overalkylation test with anilines[a]



Entry	**1a** (equiv.)	Solvent	Temp (°C)	Ratio of **3a** : **4a** : **5aa**[b]
1	1	HFIP	80	25 : 2 : 28
2	1	MeCN	80	19 : 9 : 0
3	3	HFIP	80	28 : 2 : 33
4	3	MeCN	80	62 : 6 : 0
5	**3**	**HFIP**	**120**	**0 : 0 : 60**

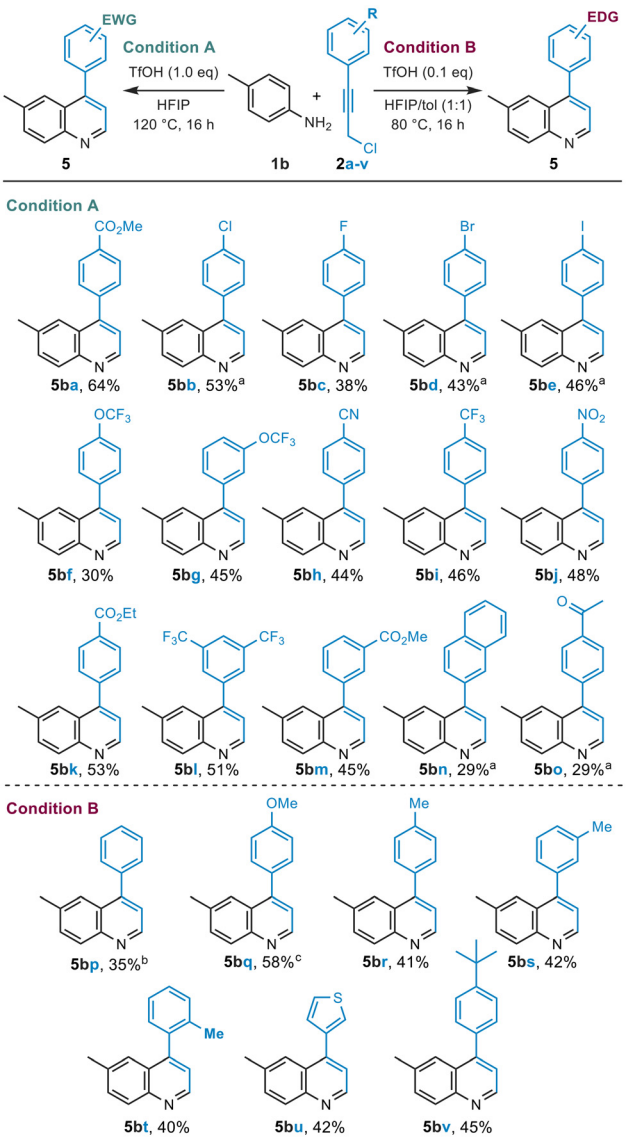
[a] Reaction conditions: **1a** (1 or 3 equiv.), **2a** (0.10 mmol), TfOH (0.1 equiv.), and solvent (0.20 mL) at designated temperature for 20 h. [b] NMR yield determined by using CH_2Br_2 as an internal standard.

Table 2 Conversion of **4a** to quinoline[a]



Entry	**1a** (equiv)	Temp (°C)	Yield (%) of **5aa**[b]
1	**3**	**120**	**36**
2	0	120	N.D.
3	3	80	N.D.

[a] Reaction conditions: **1a** (each equiv.), **4a** (0.10 mmol), TfOH (0.1 equiv.), and HFIP (0.20 mL) at designated temperature for 20 h. [b] NMR yield determined by using CH_2Br_2 as an internal standard.



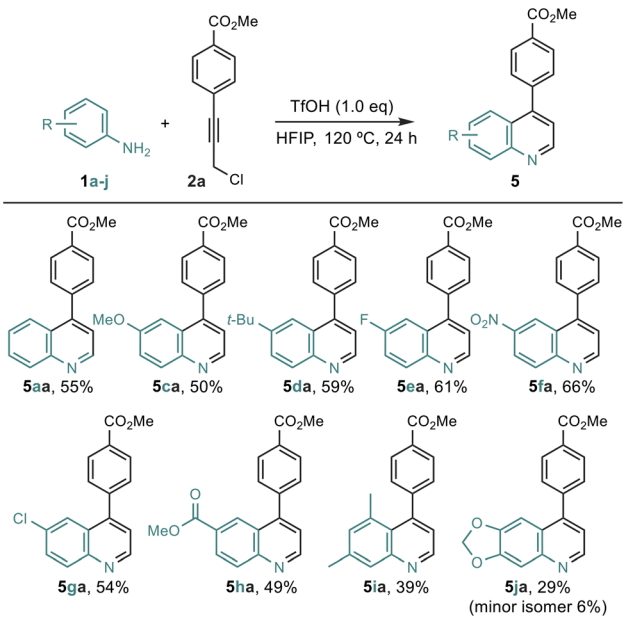
Scheme 3 Scope of propargylic chlorides. Condition A: **1b** (3.0 equiv.), **2** (0.25 mmol), TfOH (1.0 equiv.), and HFIP (0.50 mL) at 120 °C for 16 h; condition B: **1b** (3.0 equiv.), **2** (0.25 mmol), TfOH (0.1 equiv.), and HFIP/toluene (1 : 1 mixture, 0.50 mL) at 80 °C for 16 h. Isolated yield. [a]0.1 equiv. of TfOH was used. [b]Only HFIP was used as the solvent. [c]Reaction performed at 120 °C with HFIP (1.0 equiv.) in toluene (0.5 mL).

in somewhat low yields (**5bb–5be**, 38–46%). The *para*-substituted trifluoromethoxy propargylic chloride **2f** produced quinoline **5bf** in a reduced yield of 30%, likely due to the unique properties of the trifluoromethoxy group. While the trifluoromethoxy group introduced an inductive effect through the oxygen-substituted trifluoromethyl group rendering the aromatic ring electron-deficient, the repulsion between the lone pairs on fluorine and the π-electrons of the aromatic ring increased the electron density specifically at the *para* position.[12] The decreased stability of propargylic chloride **2f** is likely ascribed to increased electron density at the *para* position, which leads to rapid decomposition and consequently a lower yield compared to other electron-deficient substrates. In contrast, propargylic chloride **2g** bearing a trifluoromethoxy group at the *meta* position was unaffected by such destabilizing interactions and behaved like other electron-deficient substrates, affording quinoline **5bg** in 45% yield.

Electron-withdrawing propargylic chlorides, **2h–2k** featuring nitrile, trifluoromethyl, nitro or ethyl ester groups, delivered the desired quinolines in acceptable yields of 44% to 53% (**5bh–5bk**). The electron-deficient nature of 3,5-trifluoromethyl-substituted propargylic chloride **2l** required the use of 1 equiv. of TfOH, affording quinoline **5bl** in 51% yield. For substrate **2m**, bearing methyl ester groups at the *meta* position, a fair yield of 45% was obtained. Propargylic chlorides **2n** and **2o**, substituted with a 2-naphthyl group and a *para*-methyl ketone, respectively, both afforded a 29% yield. For the 2-naphthyl derivative **2n**, it required high temperature to fully convert the *N*-alkylation intermediate, but this promoted decomposition. For **2o**, while *para*-methyl ketone substituents have shown good yields in previous studies, the presence of free aniline in this reaction led to imine formation resulting in reduced yields.

Electron-rich propargylic chlorides **2p–2v** were evaluated under condition B. Compared to other electron-rich propargylic chlorides, the lower electron density of propargylic chloride **2p** led to sluggish cyclization of the *N*-alkylated intermediate when toluene was employed. Consequently, the reaction with **2p** was carried out in HFIP without any cosolvent. Although the *N*-alkylated intermediate was fully consumed, decomposition of propargylic chloride resulted in a low yield (35%) of quinoline **5bp**. For propargylic chloride **2q** bearing a *para*-substituted OMe group, decomposition was effectively suppressed by employing only 1 equiv. of HFIP. Under the reaction conditions at 120 °C, quinoline **5bq** was afforded in a good yield of 58%. Propargylic chlorides **2r–2t**, with methyl substituents at the *para*-, *meta*-, and *ortho*-positions respectively, yielded the corresponding quinolines in 40–42% yields, indicating that steric effects at these positions exert minimal influence on the reactivity (**5br–5bt**). Quinoline **5bu** was smoothly obtained in a moderate yield of 42% from **2u**, which contains a thiophene substituent known for its versatility in various reactions. For **2v**, substituted with a bulky *tert*-butyl group at the *para* position, quinoline **5bv** was produced in 45% yield.

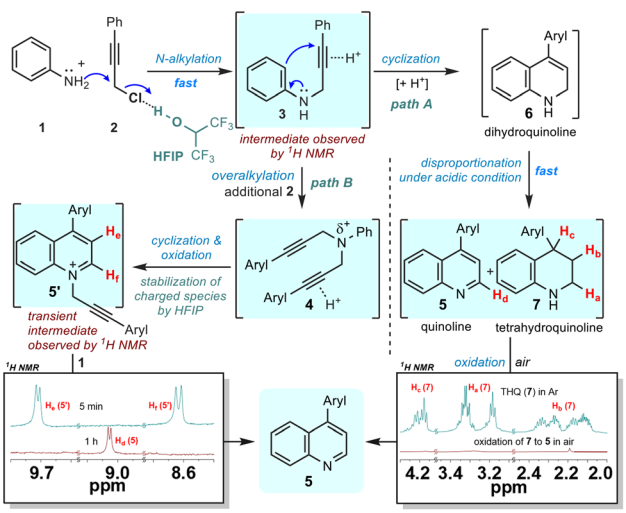
To further expand the substrate scope, functionalized anilines were also investigated (Scheme 4). Several anilines were tested with methyl ester substituted propargylic chloride **2a**. Electron-neutral aniline **1a**, along with electron-rich anilines **1c** and **1d**, substituted with methoxy and *tert*-butyl groups at the *para* position, provided the corresponding quinolines in good yields (**5aa–5da**, 50–59%). Interestingly, electron-deficient anilines **1e** and **1f**, substituted at the *para* position with fluorine or nitro groups, afforded quinolines **5ea** and **5fa** in good yields of 61% and 66%, respectively. Anilines with moderate electron-withdrawing groups, such as chloro **1g** and methyl ester **1h** substituents, delivered quinolines in fair yields (**5ga–5ha**, 49–54%). In contrast, 3,5-dimethyl-substituted aniline **1i** exhibited reduced yield (**5ia**, 39%), likely due to steric



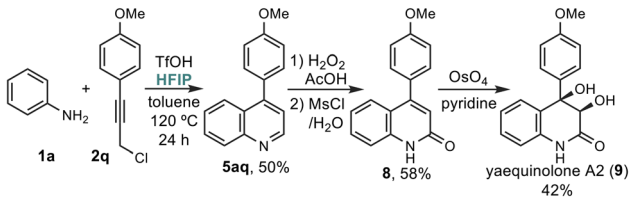
Scheme 4 Scope of anilines. Reaction conditions: **1** (0.75 mmol), **2a** (0.25 mmol), TfOH (1.0 equiv.), and HFIP (0.50 mL) at 120 °C for 24 h. Isolated yield.

hindrance at the *meta* positions impacting the reaction. Aniline derivative **1j**, containing a 1,3-dihydrofuran moiety at the 3,4-positions, which is a structural motif commonly found in pharmaceuticals, was converted to quinoline **5ja** in 29% yield, with a 6% isomer observed by NMR spectroscopy.

A plausible reaction mechanism has been proposed (Scheme 5). The process begins with HFIP-mediated activation of the C–Cl bond in propargylic chloride, enabling nucleophilic attack by aniline to form *N*-alkylated intermediate **3**. This intermediate diverges into two pathways: cyclization to dihydroquinoline **6** (path A) or additional propargylation to form



Scheme 5 Plausible mechanism.



Scheme 6 Total synthesis of yaequinolone A2.

intermediate **4** (path B). In path A, **6** undergoes acid-mediated disproportionation to give quinoline **5** and THQ **7**, and the THQ is further oxidized to quinoline **5** by molecular oxygen in air. In Path B, intermediate **4** cyclizes to form quinolinium **5′**, stabilized by HFIP. Nucleophilic attack of **5′** by aniline yields quinoline **5** along with regeneration of the intermediate **3**. Kinetic studies with **4** as the substrate confirmed the formation of **5′** at early stages, followed by quinoline production (see SI).

For further demonstration, this methodology was applied to the total synthesis of C4-aryl quinoline derivative yaequinolone A2 known for its antibacterial activity (Scheme 6).[13] In previous studies, the synthesis of structurally similar aflaquinolone F required an additional oxidation step starting from THQ **5aq**.[5] In contrast, the current method facilitated the direct one-pot conversion of quinoline **5aq** to quinolone **8**,[14] followed by vicinal dihydroxylation to furnish yaequinolone A2 (**9**) in only three steps.

Conclusions

In summary, A method for synthesizing C4-aryl quinolines from propargylic chlorides and anilines was developed, minimizing the use of excess oxidants and effectively suppressing overalkylation. The reaction was facilitated by HFIP, which played a pivotal role in activating the C–Cl bond, stabilizing cationic intermediates, and promoting air-mediated oxidation of tetrahydroquinolines without the need for additional oxidants. Moderate to good yields of C4-aryl quinolines were obtained through the use of a cosolvent system, including those derived from electron-rich substrates that were previously incompatible due to their instability. The method's utility was further demonstrated by the efficient three-step total synthesis of yaequinolone A2.

Author contributions

H. M. C. conceived and supervised the project. T. K. K. conducted the experimental analyses. The paper was written through the contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included in this published article and its SI.

SI containing experimental details and characterization data of the new compounds as well as copies of ^{1}H and ^{13}C NMR spectra with HRMS data of all new compounds are available. See DOI: **https://doi.org/10.1039/d5ob01182e**.

Acknowledgements

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