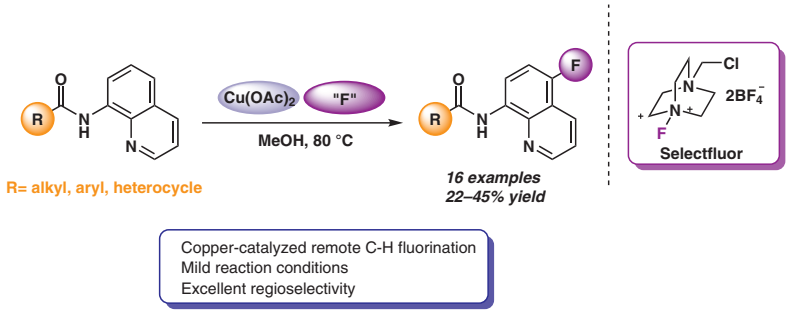
Synlett S.-S. Luo et al. Letter

Copper-Catalyzed Direct C-5 Fluorination of 8-Aminoquinolines by Remote C–H Activation

Si-Si Luo[a]
Lan-Jun Su[a]
Yue Jiang[a]
Xiao-Bao Li[b]
Zheng-Hui Li[a]
Huan Sun*[a]
Ji-Kai Liu*[a]

[a] School of Pharmaceutical Sciences, South-Central University for Nationalities, Wuhan, 430074, P. R. of China
sunh15@163.com
jkliu@mail.kib.ac.cn
[b] Department of Civil and Environmental Engineering, Northwestern University, Evanston, IL, 60060, USA



Received: 02.02.2018
Accepted after revision: 06.04.2018
Published online: 16.05.2018
DOI: 10.1055/s-0037-1610130; Art ID: st-2018-w0070-l

Abstract A convenient method was developed for direct regioselective fluorination of 8-aminoquinolines at the C-5 position by copper-catalyzed remote C–H activation using Selectfluor as the electrophile fluorinating reagent. With this method, diverse fluorinated quinoline derivatives were facilely obtained under mild conditions with moderate yields.

Key words fluorination, copper-catalyzed, 8-aminoquinolines, Selectfluor, remote C–H activation

The quinolines are among the most abundant and important nitrogen-containing heterocycles found in natural products, pharmaceuticals, and functional materials.[1] The distinctive fluorescence characteristics of quinoline[2] lead to the extensive application of quinolines in pH indicators, fluorescent probes, and colorants.[3] Quinoline was demonstrated as a critical core in antitumoral, antifungal, anti-asthmatic, and immune-depressing activities.[4] In the past decade, directed inert C–H functionalization offered spanew insight on rapidly increasing molecular complexity of quinoline (Figure 1). Aminoquinoline is a representative of strong bident chelating DGs to facilitate diverse C–H functionalizations pioneered by Daugulis.[5] Recent work illustrated that the electronic property of the quinoline rings could deeply influence the directing ability.[6] Therefore, functionalization of the quinoline core to enrich the structural motifs diversity is of great importance and value. Generally, the modification mainly focuses on C-2, C-3, C-4, C-8 position via Minisci reaction or metal-catalyzed C–C coupling.[7,8] The modification of C-5 position was not accessible until Stahl reported the first chlorination example in 2013.[9] Since then, more attention has been devoted to C-5 position. Various transition metals (copper, iron, nickel, cobalt,

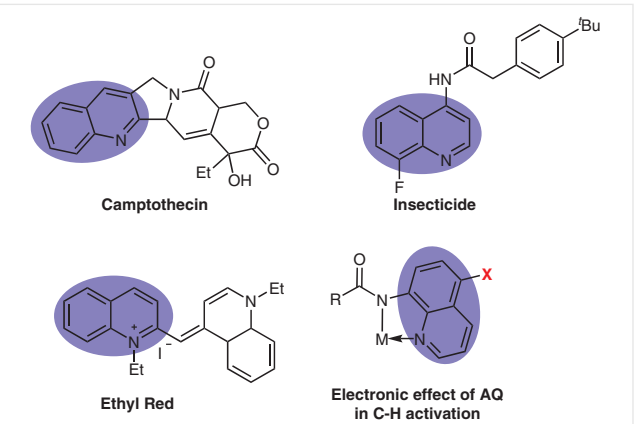
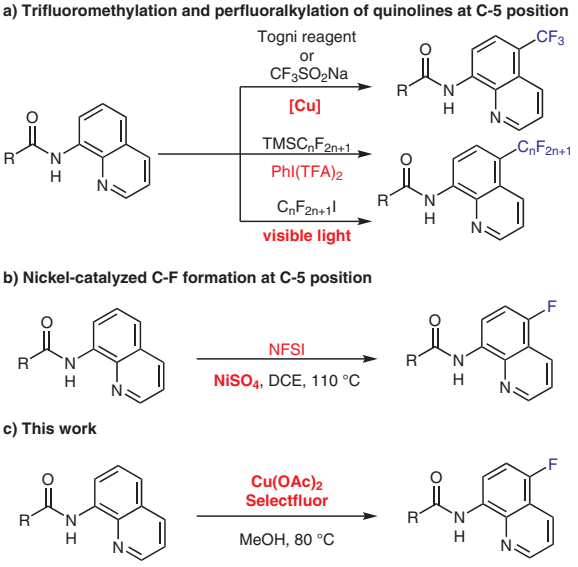


Figure 1 Selective molecules containing quinoline scaffolds

etc.) can be used to facilitate the C–H transformations including halogenation,[10] nitration,[11] sulfonylation,[12] azidation,[13] alkylation,[14] phosphonation,[15] etc. and to enormously enhance the structure diversity of quinolines.

Fluorine-containing functional group is another important class of building blocks of quinoline, which has been constantly applied in drug design, agrochemicals, and organic functional materials, due to their unique physical, chemical, and biological properties.[16] Consequently, intensive research has been directed toward the development of methods for effective incorporation of fluorine-containing functional groups to quinoline.[17] For these developed methods for fluorine introduction, transition-metal-catalyzed C–H functionalization is an indispensable strategy, with which C_{sp2}–H bond and even inert C_{sp3}–H bond can be smoothly converted into the corresponding C–CF_3, C–F, or C–CHF_2.[18] However, the reaction site was mostly limited to the *ortho*- or β- position of the directing group via an organometallic intermediate. Generally, the remote inert C–H bond remained untouched and inaccessible without the di-

recting auxiliary. Accordingly, the direct incorporation of fluorinated groups to the quinolines at C-5 position was relatively rare. Trifluoromethylation was firstly achieved at C-5 position using CuCl as the catalyst.[19] Afterwards, perfluoralkylated quinoline was obtained through a radical-based approach under visible-light-induced or oxidant atmosphere (Scheme 1, a).[20] In spite of these successes of C-5 fluorination, the direct C–F bond formation at the C-5 position was scarce, except for an unique example using nickel as the catalyst and NFSI as the fluorine source, which, however, was limited by the relative high reaction temperature and substrate compatibility (Scheme 1, b).[21] Due to such limitations in existing approaches, a methodology that allows a more effective selective fluorination at C-5 position is necessary. Here, we reported a copper-catalyzed 5-position-selective C–H fluorination of 8-aminoquinolines with broad functional group tolerance under mild conditions (Scheme 1, c).



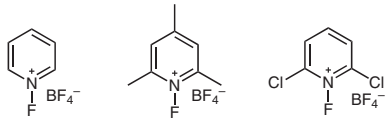
Scheme 1 Incorporation of fluorinate-containing functional groups to C-5 position of quinolines

8-Aminoquinoline derivative **1a** was chosen as the model substrate for reaction conditions development (Table 1). A variety of transition metals were attempted and Selectfluor was used as the fluorine source at 80 °C. Among the transition metals, $Cu(OAc)_2$demonstrated the highest activity, giving 30% yield. CoF_2, $Ni(OAc)_2$ also accelerated the reaction smoothly but at lower yield compared to $Cu(OAc)_2$, however, when $NiCl_2$ was used, the chlorination product at C-5 position was obtained as byproduct.

Diverse electrophile fluorinating reagent, such as NFSI, 1-fluoro-pyridine salts, were also investigated. Among these reagents, Selectfluor offered the most satisfying yield. Moreover, the screening of reaction solvents indicated that

Table 1 Screening Reaction Conditions for Fluorination of 8-Aminoquinoline[a]

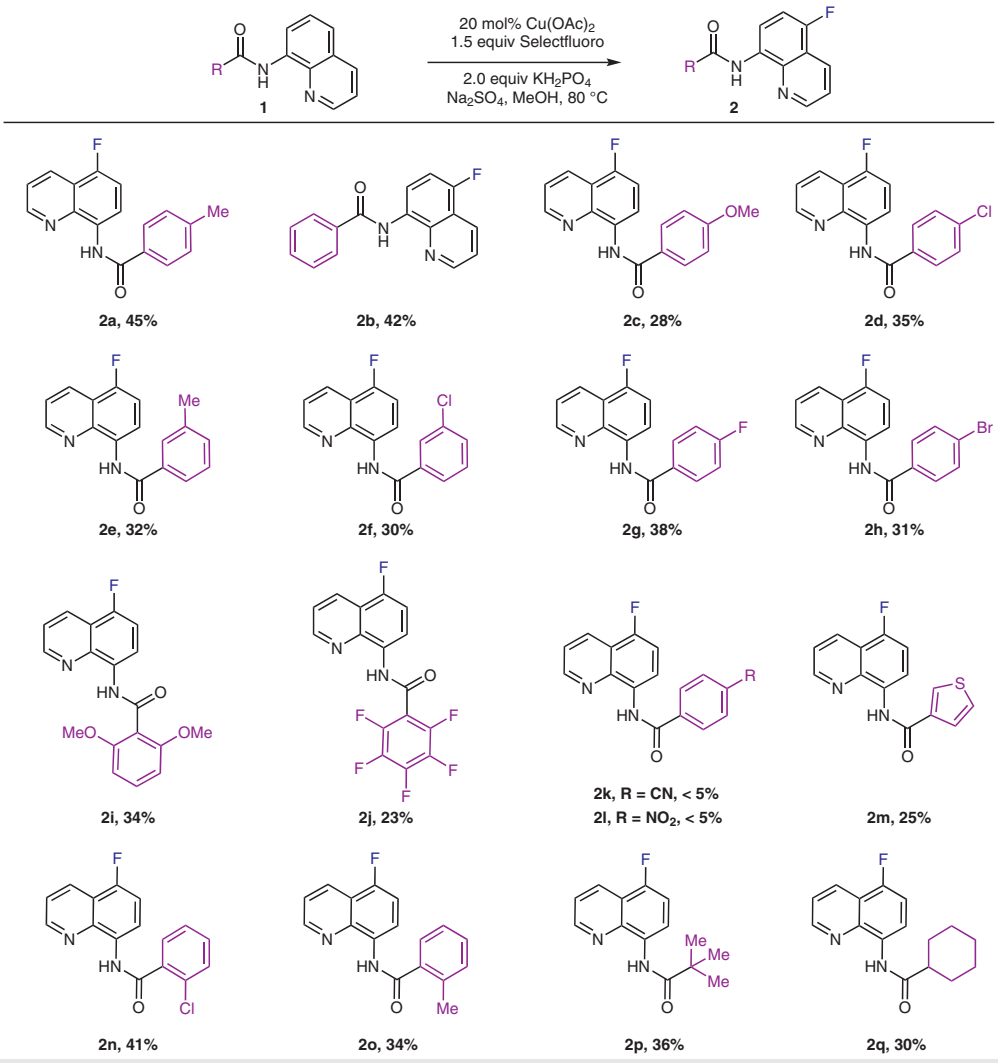
Entry	Catalyst	'F'	Additive	Solvent	Yield (%)[b]
1	$Ni(OAc)_2$	Selectfluor	–	MeOH	22
2	$Cu(OAc)_2$	Selectfluor	–	MeOH	30
3	CoF_2	Selectfluor	–	MeOH	23
4	$NiCl_2$	Selectfluor	–	MeOH	20
5	$Mn(OAc)_2$	Selectfluor	–	MeOH	NR
6	$Cu(OAc)_2$	NFSI	–	MeOH	trace
7	$Cu(OAc)_2$	A	–	MeOH	trace
8	$Cu(OAc)_2$	B	–	MeOH	trace
9	$Cu(OAc)_2$	C	–	MeOH	22
10	$Cu(OAc)_2$	Selectfluor	–	DCE	NR
11	$Cu(OAc)_2$	Selectfluor	–	CH_3CN	NR
12	$Cu(OAc)_2$	Selectfluor	–	DMF	trace
13	$Cu(OAc)_2$	Selectfluor	KH_2PO_4	MeOH	35
14	$Cu(OAc)_2$	Selectfluor	KH_2PO_4 Na_2SO4	MeOH	45



[a] Reaction conditions: **1a** (0.1 mmol), 'F' source (0.15 mmol, 1.5 equiv), transition-metal catalyst (0.02 mmol, 0.2 equiv), additive (0.2 mmol, 2.0 equiv), solvent (1 mL), 80 °C, 12 h.
[b] Isolated yield.

MeOH was most appropriate, compared with DCE, MeCN, DMF, etc. Increasing the amount of Selectfluor and reaction temperature did not make a great difference. Further, bases and additives were well studied and optimized with KH_2PO_4, Na_2SO_4 selected for high yield.

With the optimized conditions in hand, we then examined the scope of functional group tolerance. As shown in Scheme 2, a variety of 8-aminoquinoline derivatives were smoothly converted into the desired fluorinated product with moderate yields. Aromatic substrates with a broad substitution pattern and of different electronic nature were well tolerated. Halogen, no matter bromide or chloride, did not interfere the transition-metal-catalyzed process. Arenes bearing *para*-, *meta*-, or disubstituted groups afforded the desired fluorinated product successfully. Steric hindrance from the *ortho* substitution showed little impact on the fluorination. Substrates with strong electron-withdrawing groups, such as NO_2 and CN, showed unsatisfying

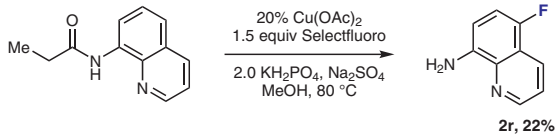


Scheme 2 Substrate scope for the fluorination of quinoline at C-5 position

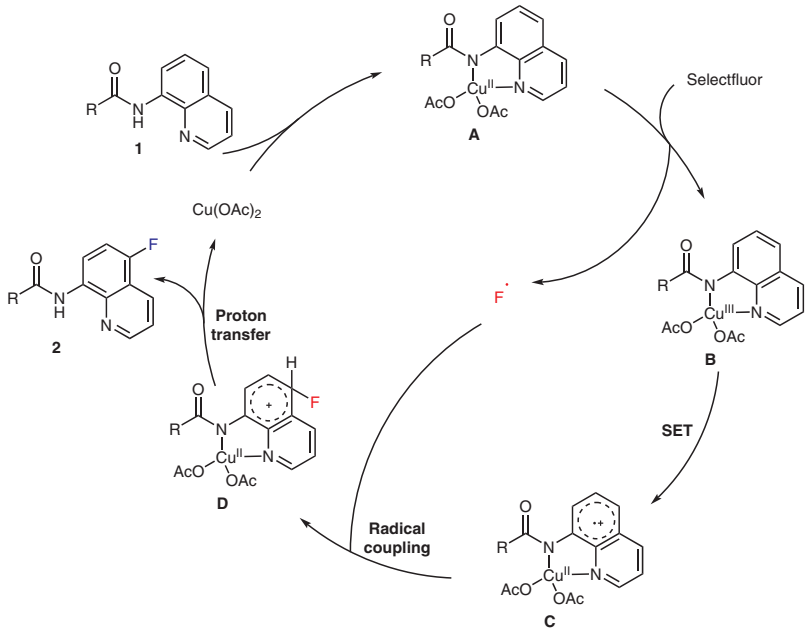
yields. Heterocycles and alkyl substrates, on the other hand, demonstrated well tolerance under the fluorinated conditions.

As previous reported, hydrolysis of amide bond always requires harsh conditions, such as strong bases or acids and high temperature.[21] However, under our fluorination conditions, hydrolysis of the amide bond occurred simultaneously to afford the fluorinated 8-amino quinoline, which offers more opportunities for further transformation (Scheme 3). However, considering the difluorinated product as byproduct, further reaction modification was necessary and underway.

Based on the related reports,[19,21] the plausible mechanism that involves a single-electron transfer (SET) approach was proposed (Scheme 4). Initially, the coordination of substrate **1** with Cu(II) generated the five-membered organometallic heterocycle **A**, which was then oxidized to Cu(III) in the presence of Selectfluor, accompanied by fluorine radical formation. Subsequently, a SET approach happened to afford the cationic quinoline radical intermediate **C**. The C-5 position of intermediate **C** was attacked by fluorine radical to generate intermediate **D**. A concerted proton transfer/demetallation step provided the final fluorination product and released the $Cu(OAc)_2$ for a new catalytic cycle.



Scheme 3 Hydrolysis of amide bond to afford the fluorinated 8-amino quinoline



Scheme 4 Proposed mechanism

In conclusion, we successfully developed an efficient and practical method for the direct C-5 fluorination of quinoline scaffolds by making use of cheap and readily available $Cu(OAc)_2$ as the catalyst and Selectfluor as the efficient fluorine source.[22] An excellent regioselectivity and good functional group tolerance were demonstrated. For this transformation, a single-electron transfer approach was proposed, and further mechanistic studies are underway in our group.

Funding Information

The authors gratefully acknowledge funding from National Natural Science Foundation of China (81561148013, 31560010, 21502239), Key Projects of Technological Innovation of Hubei Province (No. 2016ACA138), Hubei Provincial Natural Science Foundation of China (2018CFB222), "the Fundamental Research Funds for the Central Universities", South-Central University for Nationalities (CZQ17008).

Acknowledgment

Analytical data were obtained from Analytical & Measuring Center, School of Pharmaceutical Sciences, South-Central University for Nationalities.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610130.

Primary Data

for this article are available online at https://doi.org/10.1055/s-0037-1610130 and can be cited using the following DOI: 10.4125/pd0098th.

References and Notes

(1) (a) Singh, S.; Kaur, G.; Mangla, V.; Gupta, M. K. *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 492. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223.
(2) Hamer, F. M. *J. Chem. Soc., Trans.* **1921**, *119*, 1432.
(3) (a) Adhikari, S.; Mandal, S.; Ghosh, A.; Das, P.; Das, D. *J. Org. Chem.* **2015**, *80*, 8530. (b) Niu, W.; Fan, L.; Nan, M.; Li, Z.; Lu, D.; Wong, M.; Shuang, S.; Dong, C. *Anal. Chem.* **2015**, *87*, 2788.
(4) (a) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245. (b) Hussaini, S. M. A. *Expert Opin. Ther. Pat.* **2016**, *26*, 1201. (c) Kumar, S.; Bawa, S.; Gupta, H. *Mini-Rev. Med. Chem.* **2009**, *9*, 1648.
(5) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.
(6) Sun, H.; Zhang, Y.; Chen, P.; Wu, Y.-D.; Zhang, X.; Huang, Y. *Adv. Synth. Catal.* **2016**, *358*, 1946.
(7) For selected reviews, see: (a) Iwai, T.; Sawamura, M. *ACS Catal.* **2015**, *5*, 5031. (b) Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. *RSC Adv.* **2014**, *4*, 24463. (c) Stephens, D. E.; Larionov, O. V. *Tetrahedron* **2015**, *71*, 8683. (d) Ramann, G. A.; Cowen, B. J. *Molecules* **2016**, *21*, 986.
(8) For represented examples, see: (a) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926. (b) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2010**, *49*, 1275. (c) Chen, Q.; du Jourdin, X. M.; Knochel, P. *J. Am. Chem. Soc.* **2013**, *135*, 4958. (d) Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 3780.

(9) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797.
(10) (a) Xu, J.; Zhu, X.; Zhou, G.; Ying, B.; Ye, P.; Su, L.; Shen, C.; Zhang, P. *Org. Biomol. Chem.* **2016**, *14*, 3016. (b) Khan, B.; Kant, R.; Koley, D. *Adv. Synth. Catal.* **2016**, *358*, 2352. (c) Qiao, H.; Sun, S.; Yang, F.; Zhu, Y.; Kang, J.; Wu, Y.; Wu, Y. *Adv. Synth. Catal.* **2017**, *359*, 1976.
(11) Whiteoak, C. J.; Planas, O.; Company, A.; Ribas, X. *Adv. Synth. Catal.* **2016**, *358*, 1679.
(12) Liang, H. W.; Jiang, K.; Ding, W.; Yuan, Y.; Shuai, L.; Chen, Y. C.; Wei, Y. *Chem. Commun.* **2015**, *51*, 16928.
(13) Dou, Y. D.; Xie, Z. D.; Shen, C.; Zhang, P. F.; Zhu, Q. *ChemCatChem* **2016**, *8*, 3570.
(14) Du, C.; Li, P.-X.; Zhu, X.; Suo, J.-F.; Niu, J.-L.; Song, M.-P. *Angew. Chem. Int. Ed.* **2016**, *55*, 13571.
(15) Sun, M. M.; Sun, S. Y.; Qiao, H. J.; Yang, F.; Zhu, Y.; Kang, J. X.; Wu, Y. S.; Wu, Y. J. *Org. Chem. Front.* **2016**, *3*, 1646.
(16) (a) Schlosser, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5432. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470.
(17) (a) Chu, L.; Qing, F.-L. *Acc. Chem. Res.* **2014**, *47*, 1513. (b) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661.
(18) For selected examples, see: (a) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160. (b) Li, Y.; Wu, Y.; Li, S.-G.; Wang, X.-S. *Adv. Synth. Catal.* **2014**, *356*, 1412. (c) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (d) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520.
(19) (a) Kuninobu, Y.; Nishi, M.; Kanai, M. *Org. Biomol. Chem.* **2016**, *14*, 8092. (b) Wu, Z.; He, Y.; Ma, C.; Zhou, X.; Liu, X.; Li, Y.; Hu, T.; Wen, P.; Huang, G. *Asian J. Org. Chem.* **2016**, *5*, 724. (c) Jin, L.-K.; Lu, G.-P.; Cai, C. *Org. Chem. Front.* **2016**, *3*, 1309. (d) Shen, C.; Xu, J.; Ying, B.; Zhang, P. *ChemCatChem* **2016**, *8*, 3560.
(20) (a) Chen, H.; Li, P. H.; Wang, M.; Wang, L. *Org. Lett.* **2016**, *18*, 4794. (b) Xu, J.; Qiao, L.; Ying, B.; Zhu, X.; Shen, C.; Zhang, P. *Org. Chem. Front.* **2017**, *4*, 1116. (c) Arockiam, P.; Guillemard, L. *Adv. Synth. Catal.* **2017**, *359*, 2571.
(21) Ding, J.; Zhang, Y.; Li, J. *Org. Chem. Front.* **2017**, *4*, 1528.
(22) **Fluorinated Product 2a–t, General Procedure**
8-Aminoquinoline derivatives **1** (0.1 mmol, 1.0 equiv), $Cu(OAc)_2$ (0.02 mmol, 0.2 equiv), Selectfluor (0.15 mmol, 1.5 equiv), KH_2PO_4 (0.2 mmol, 2.0 equiv), and Na_2SO_4 (50 mg) were weighed into an oven-dried Schlenk tube, and MeOH (1 mL) was added. The reaction vessel was capped and vacuum-flushed with N_2 three times. The reaction was stirred under N_2 atmosphere at 80 °C, and the progress of the fluorination was monitored by TLC. Upon complete consumption of **1**, the reaction was cooled to room temperature. Volatile solvent and reagents were removed by rotary evaporation, and the residue was purified by silica gel flash chromatography using PE/EtOAc (100:1 to 20:1) to afford fluorinated product **2**.

N-(5-Fluoroquinolin-8-yl)-4-methylbenzamide (2a)
45% yield, white solid. ^{1}H NMR (600 MHz, chloroform-*d*): δ = 10.52 (s, 1 H), 8.94–8.85 (m, 2 H), 8.47 (dd, *J* = 8.4, 1.7 Hz, 1 H), 8.01–7.94 (m, 2 H), 7.56 (dd, *J* = 8.4, 4.2 Hz, 1 H), 7.40–7.33 (m, 2 H), 7.30–7.27 (m, 1 H), 2.46 (s, 3 H). ^{13}C NMR (151 MHz, chloroform-*d*): δ = 165.48 , 153.87 (d, *J* = 250.7 Hz), 149.22, 142.55, 139.09 (d, J = 3.0 Hz), 132.28, 131.35 (d, *J* = 3.0 Hz), 129.98 (d, *J* = 3.0 Hz), 129.62, 127.37, 121.87 (d, *J* = 3.0 Hz), 119.00 (d, *J* = 3.0 Hz), 116.09 (d, *J* = 7.6 Hz), 110.72 (d, *J* = 19.6 Hz), 21.71. ^{19}F NMR (565 MHz, chloroform-*d*): δ = –129.22. HRMS (ESI): *m/z* calcd for $C_{17}H_{14}ON_2F$ $[M + H]^+$: 281.1090; found: 281.1086.

4-Fluoro-N-(5-fluoroquinolin-8-yl)benzamide (2g)
38% yield, white solid. ^{1}H NMR (600 MHz, chloroform-*d*): δ = 10.50 (s, 1 H), 8.91 (dd, *J* = 4.2, 1.6 Hz, 1 H), 8.87 (dd, *J* = 8.6, 5.3 Hz, 1 H), 8.48 (dd, *J* = 8.4, 1.7 Hz, 1 H), 8.12–8.06 (m, 2 H), 7.57 (dd, *J* = 8.4, 4.2 Hz, 1 H), 7.30–7.23 (m, 3 H). ^{13}C NMR (151 MHz, chloroform-*d*): δ = 165.83, 164.23, 164.16, 153.89 (d, *J* = 252.2 Hz), 149.16, 138.92 (d, *J* = 3.0 Hz), 131.16 (d, *J* = 3.0 Hz), 130.96 (d, *J* = 4.5 Hz), 129.95 (d, *J* = 4.5 Hz), 129.64 (d, *J* = 9.1 Hz), 121.82 (d, *J* = 1.5 Hz), 118.90 (d, *J* = 18.1 Hz), 116.07 (d, *J* = 9.1 Hz), 115.97 (d, *J* = 22.6 Hz), 110.59 (d, *J* = 19.6 Hz). ^{19}F NMR (565 MHz, chloroform-*d*): δ = –107.51, –128.74. HRMS (ESI): *m/z* calcd for $C_{16}H_{11}ON_2F_2$ $[M + H]^+$: 285.0839; found: 285.0833.

N-(5-Fluoroquinolin-8-yl)-2,6-dimethoxybenzamide (2i)
34% yield, white solid. ^{1}H NMR (600 MHz, chloroform-*d*): δ = 10.10 (s, 1 H), 8.99 (dd, *J* = 7.6, 1.3 Hz, 1 H), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.18 (dd, *J* = 8.2, 1.7 Hz, 1 H), 7.61 (t, *J* = 7.9 Hz, 1 H), 7.56 (dd, *J* = 8.3, 1.4 Hz, 1 H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1 H), 7.14 (dd, *J* = 11.2, 9.1 Hz, 1 H), 6.64 (dd, *J* = 9.2, 3.3 Hz, 1 H), 4.01 (d, *J* = 1.9 Hz, 3 H), 3.83 (s, 3 H). ^{13}C NMR (151 MHz, chloroform-*d*): δ = 162.92 (d, *J* = 3.0 Hz), 153.18 (d, *J* = 3.0 Hz), 150.80 (d, *J* = 241.6 Hz), 148.35, 145.77 (d, *J* = 12.1 Hz) 138.60, 136.44, 134.76, 128.10, 127.60, 121.97, 121.73, 117.79 (d, *J* = 21.1 Hz), 117.01, 106.10 (d, *J* = 7.6 Hz), 62.32 (d, *J* = 4.5 Hz), 56.49. ^{19}F NMR (565 MHz, chloroform-*d*): δ = –139.30, –139.33. HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_3N_2F$ $[M + H]^+$: 327.1145; found: 327.1140.

2,3,4,5,6-Pentafluoro-N-(5-fluoroquinolin-8-yl)benzamide (2j)
23% yield, white solid. ^{1}H NMR (600 MHz, chloroform-*d*): δ = 10.19 (s, 1 H), 8.87 (ddd, *J* = 4.7, 3.0, 1.7 Hz, 1 H), 8.83 (ddd, *J* = 8.9, 5.3, 3.8 Hz, 1 H), 8.48 (ddd, *J* = 8.4, 4.2, 1.7 Hz, 1 H), 7.58 (ddd, *J* = 8.5, 4.2, 2.9 Hz, 1 H), 7.32–7.27 (m, 1 H). ^{13}C NMR (151 MHz, chloroform-*d*): δ = 155.23, 154.61 (d, *J* = 253.7 Hz), 149.49, 145.35 (m), 143.66 (m), 141.81 (m), 138.65 (m), 136.98 (m), 130.07 (m), 122.08, 118.90 (dd, *J* = 18.4, 3.6 Hz), 116.99 (d, *J* = 9.1 Hz), 116.94 (m), 110.51(dd, *J* = 19.6, 2.8 Hz). ^{19}F NMR (565 MHz, chloroform-*d*): δ = –126.79, –139.92 (d, *J* = 19.0 Hz), –149.94 (d, *J* = 20.9 Hz), –149.99, –159.64 (t, *J* = 19.2 Hz). HRMS (ESI): *m/z* calcd for $C_{16}H_7ON_2F_6$ $[M + H]^+$: 357.0463; found: 357.0457.