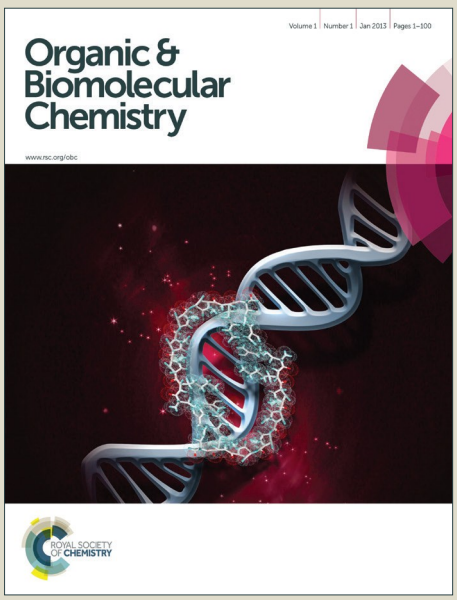
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Y. Kuninobu, M. Nishi and M. Kanai, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB01325B.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

View Article Online
DOI: 10.1039/C6OB01325B

Organic & Biomolecular Chemistry

PAPER

Received 00th January 20xx,

Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

5-Position-selective C-H Trifluoromethylation of 8-Aminoquinoline Derivatives

Yoichiro Kuninobu,*[a,b] Mitsumi Nishi[a,b] and Motomu Kanai*[a,b]

We developed a copper-catalyzed 5-position-selective C-H trifluoromethylation of 8-aminoquinoline derivatives. The reaction proceeded with high functional group tolerance under mild conditions. In the case of quinolines with an amide, carbamate, urea, or sulfonamide group at the 8-position of quinoline moieties, a radical scavenger experiment indicated that the reaction proceeded via a radical pathway. The protecting group of an 8-amidoquinoline derivative could be removed by hydrolysis. On the other hand, the trifluoromethylation of 8-aminoquinolines was also promoted by other Lewis acids as well as the copper catalyst and proceeded even in the presence of the radical scavenger. These results indicated that the trifluoromethylation of 8-aminoquinolines proceeded via a Friedel-Crafts-type reaction. Interestingly, the copper salt works as either a catalyst for the formation of a CF_3 radical or as a Lewis acid to promote a Friedel-Crafts-type reaction, depending on the substrate.

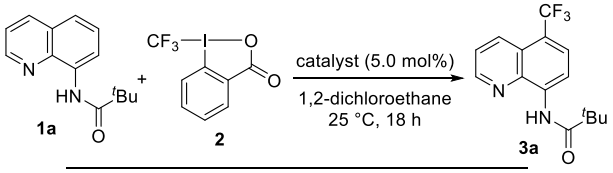
Introduction

Trifluoromethyl groups play important roles in many drugs,[1] agrochemicals,[2] and organic functional materials.[3] Several trifluoromethylation reactions have been reported; e.g., cross-coupling reactions.[4] Regioselective C-H trifluoromethylation reactions, however, are considered to be more efficient methods for introducing trifluoromethyl group(s) into organic molecules. In the case of 6-membered heteroaromatic compounds, such as pyridine and quinoline derivatives, the regioselectivity is difficult to control, and mixtures of regioisomers are usually formed.[5] To overcome this problem, we recently focused on developing a regioselective C-H trifluoromethylation of 6-membered heteroaromatic compounds, and succeeded in promoting highly regioselective C-H trifluoromethylation and its related reactions at the 2-,[6] 4-,[7] and benzylic-positions[8] of 6-membered heteroaromatic compounds. In the case of aromatic substrates, *ortho*-selective C-H trifluoromethylation was achieved using a directing group.[9] Examples of C-H trifluoromethylation at the remote position of aromatic compounds, however, remain rare. We report herein a 5-position-selective C-H trifluoromethylation of 8-aminoquinoline derivatives under copper catalysis. The copper catalyst worked as either a catalyst to generate a trifluoromethyl radical or as a Lewis acid to promote Friedel-Crafts-type C-H trifluoromethylation.

Results and discussion

Treatment of *N*-(8-quinolinyl)pivalamide (**1a**) with Togni reagent **2** in the presence of a copper catalyst, CuCl, at 25 ºC gave 5-trifluoromethylated quinoline derivative **3a** in 41% yield and 58% of **1a** was recovered (98% yield based on conversion, Table 1, entry 1).[10-12] In this reaction, no 7-trifluoromethylated quinoline derivative formed as a byproduct. Trifluorometylation did not occur without a copper catalyst

Table 1 Investigation of several catalysts[a]



entry	catalyst	yield/%[b]
1	CuCl	37 (41) [98]
2	none	0
3[c]	CuCl	40
4	CuBr	13
5	CuI	36
6	$CuCl_2$	10
7	$CuBr_2$	16
8	$FeCl_2$	33
9	$Mg(OTf)_2$	0
10[d]	$Mg(OTf)_2$	<1
11	$AlCl_3$	0
12[d]	$AlCl_3$	8
13	$La(OTf)_3$	0
14[d]	$La(OTf)_3$	<1

[a] **2** (1.0 equiv). [b] ^{1}H NMR yield. Isolated yield is described in parentheses. ^{1}H NMR yield base on conversion is described in square brackets. [c] 20 mol%. [d] 80 ºC.

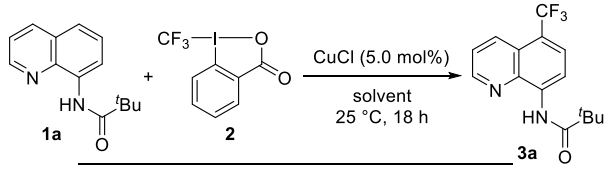
[a] *Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: kuninobu@mol.f.u-tokyo.ac.jp; kanai@mol.f.u-tokyo.ac.jp*
[b] *ERATO, Japan Science and Technology Agency (JST), Kanai Life Science Catalysis Project, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.*

† Electronic Supplementary Information (ESI) available: General experimental procedure and characterization data for trifluoromethylated products. See DOI: 10.1039/x0xx00000x

(Table 1, entry 2). The yield of **3a** was not improved by increasing the amount of CuCl (Table 1, entry 3). The reaction also proceeded using several copper salts, such as CuBr, CuI, $CuCl_2$, and $CuBr_2$, and $FeCl_2$ catalyst (Table 1, entries 4-8), but the use of several other metal salts, such as $Mg(OTf)_2$, $AlCl_3$, and $La(OTf)_3$, did not promote the trifluoromethylation reaction at 25 and 80 ºC (Table 1, entries 9-14).

Next, we investigated several solvents (Table 2). Nonpolar solvents, such as c-hexane and toluene, did not provide desired product **3a** (entries 1 and 2). 1,2-Dichroloethane gave the highest yield (entry 3). Other solvents were not effective to improve the yield of **3a** (entries 4-12).

Table 2 Investigation of several solvents[a]

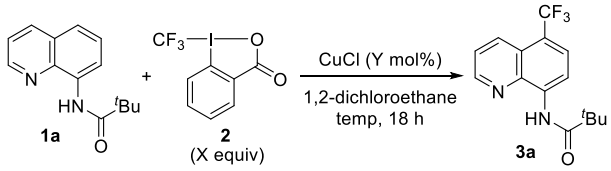


entry	solvent	yield/%[b]
1	*c*-hexane	0
2	toluene	<1
3	$ClCH_2CH_2Cl$	37 (41) [98]
4	THF	6
5	HFIP	29
6	EtOH	9
7	AcOEt	16
8	acetone	4
9	MeCN	9
10	DMA	8
11	DMF	15
12	DMSO	11

[a] **2** (1.0 equiv). [b] ^{1}H NMR yield. Isolated yield is described in parentheses. ^{1}H NMR yield base on conversion is described in square brackets.

To improve the yield of **3a**, several reaction conditions were surveyed (Table 3). The yield of **3a** was not increased at lower (0 ºC) and higher (50 ºC, 100 ºC) temperatures (entries 1-4). A longer reaction time did not lead to a significant improvement of the yield (entry 5). A divided addition of Togni reagent **2** and addition of an excess amount of **2** were ineffective to improve the yield of **3a** (entries 6 and 7). The trifluoromethylation did not proceed well when using 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (28%), 5-(trifluoromethyl) dibenzothiophenium tetrafluoroborate (0%), or 5-(trifluoromethyl)dibenzothiophenium trifluoromethanesulfonate (0%) as trifluoromethylation reagents.

Table 3 Investigation of reaction conditions

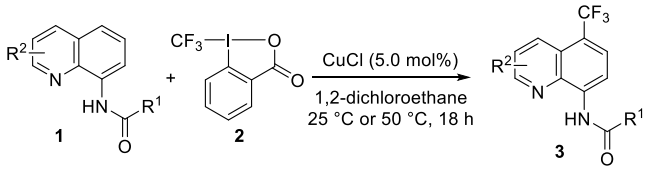


entry	X	Y	temp/°C	yield/%[a]
1	1.0	5	0	4
2	1.0	5	25	37 (41) [98]
3	1.0	5	50	34
4	1.0	5	100	34
5[b]	1.0	5	25	43
6[c]	1.0	5	25	32
7	2.0	5	25	29

[a] ^{1}H NMR yield. Isolated yield is described in parentheses. ^{1}H NMR yield base on conversion is described in square brackets. [b] 36 h. [c] **2** (0.33 equiv, 6 h) was added three times.

We next investigated the substrate scope of quinoline derivatives with an amide, carbamate, urea, or sulfonamide group at the 8-position (Table 4). Trifluoromethylated products **3b**-**3g** were regioselectively obtained using 8-amidoquinolines with a tertiary, secondary, or primary alkyl group on the amide. The trifluoromethylation reaction produced desired products **3h**-**3l** in the case of 8-amidoquinolines with an aryl group on the amide. We then investigated a substituent on the quinoline moiety of 8-amidoquinolines. The trifluoromethylation reaction proceeded with high regioselectivity and trifluoromethylated products **3m**-**3q** were afforded with high functional group tolerance. Trifluoromethylated product **3r** was also produced using 5-amidoquinoline, whereas the yield of **3r** was low. Quinoline derivatives with a carbamate or urea moiety gave the corresponding trifluoromethylated products **3s**-**3u**. 8-Sulfonamidoquinolines act as MetAP,[13] NF-KB,[14] and hepcidin[15] inhibitors. Trifluoromethylated 8-sulfonamidoquinolines **3v** and **3w** were obtained by trifluoromethylation.

Table 4 Investigation of quinoline derivatives with a 8-amide-, 8-carbamate, 8-urea-, or 8-sulfonamide group[a]



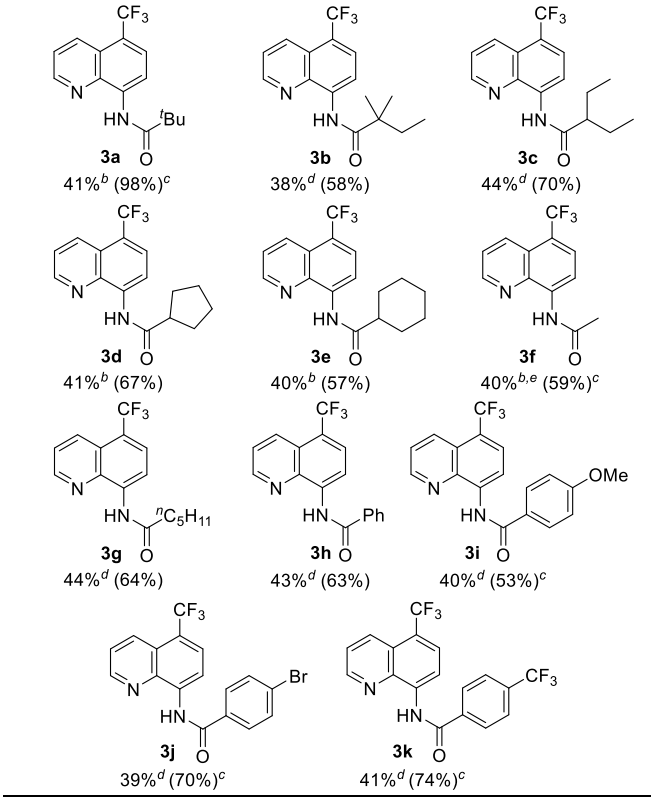
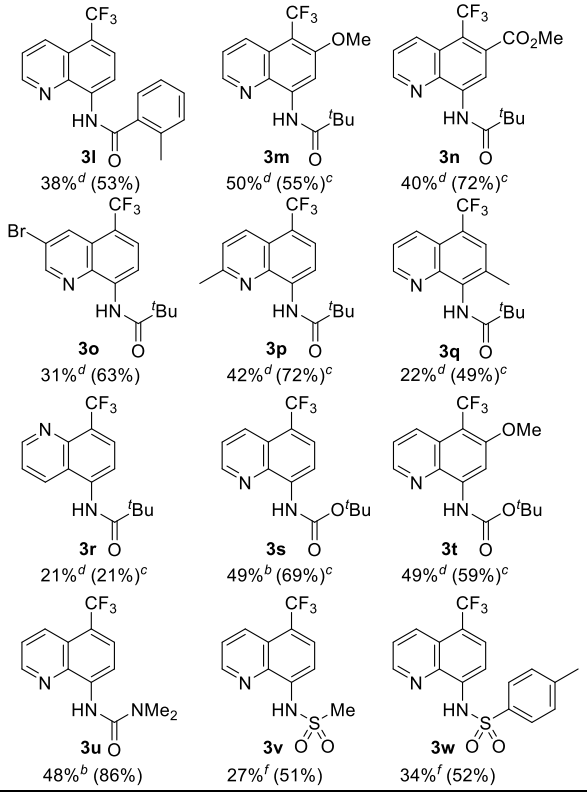


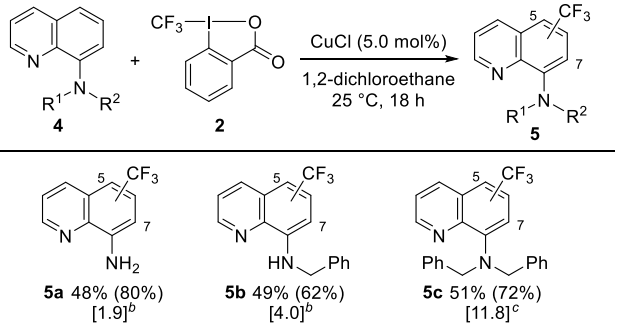
Table 4 (Continued)



[a] **2** (1.0 equiv). Isolated yields are shown. Isolated yields based on conversion are described in parentheses unless otherwise noted. [b] 25 ºC. [c] ^{1}H NMR yield based on conversion. [d] 50 ºC. [e] **1f** (0.33 equiv, 6 h) was added three times. [f] 80 ºC.

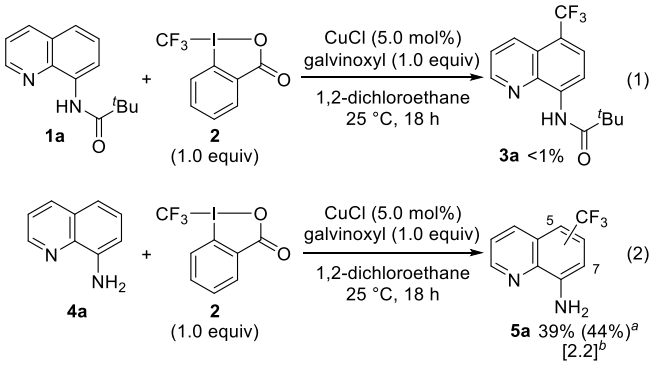
We then investigated 8-aminoquinoline derivatives (Table 5). In the case of 8-aminoquinoline (**4a**), the trifluoromethylation reaction proceeded and trifluoromethylated product **5a** was obtained in 48% yield, whereas the C-5 selectivity was only 1.9. In this reaction, other Lewis acids, such as $FeCl_2$, $Fe(OTf)_3$, $Mg(OTf)_2$, $ZnCl_2$, $SnCl_2$, $AlCl_3$, $Al(OTf)_3$, $La(OTf)_3$, $Nd(OTf)_3$, $Eu(OTf)_3$, $Gd(OTf)_3$, $Dy(OTf)_3$, and $Yb(OTf)_3$, also promoted the reaction, in sharp contrast to the trifluoromethylation of quinolines with an amide, carbamate, urea, or sulfonamide group at the 8-position (Table 4). In addition, trifluoromethylated product **5a** was obtained in moderate yield whereas the trifluoromethylation of **4a** did not proceed in a recently reported reaction.[10] The C-5 selectivity in trifluoromethylated products **5b** and **5c** was improved by introducing benzyl group(s) on the nitrogen atom of 8-aminoquinoline.

Table 5 Investigation of 8-aminoquinoline derivatives[a]



[a] **2** (1.0 equiv). Isolated combined yields are shown. ^{1}H NMR yields based on conversion are described in parentheses. [b] The ^{1}H NMR ratio of 5-CF_3 product / 7-CF_3 product. [c] The ratio of 5-CF_3 product / 7-CF_3 product.

Several Lewis acids promoted the trifluoromethylation of 8-aminoquinolines, whereas trifluoromethylation did not proceed when using Lewis acids in the case of quinoline derivatives with an amide, carbamate, urea, or sulfonamide group at the 8-position. These results indicate that the reaction mechanisms differ depending on the substrate. To elucidate whether the trifluoromethylation reaction proceeds via a radical mechanism, we performed the following two experiments in the presence of a radical scavenger, galvinoxyl (Scheme 1). In the case of 8-amidoquinoline **1a**, the trifluoromethylation reaction did not proceed (Scheme 1, eq. 1). This result indicates that trifluoromethylation of 8-amidoquinolines proceeds via a radical pathway. On the other hand, trifluoromethylation of 8-aminoquinoline **8** gave trifluoromethylated product **5a** in 39% yield, even in the presence of galvinoxyl (Scheme 1, eq. 2). In addition, the trifluoromethylation reaction was promoted by several Lewis acids as well as CuCl. These results indicate that trifluoromethylation of 8-aminoquinolines proceeded via a Friedel-Crafts-type reaction.



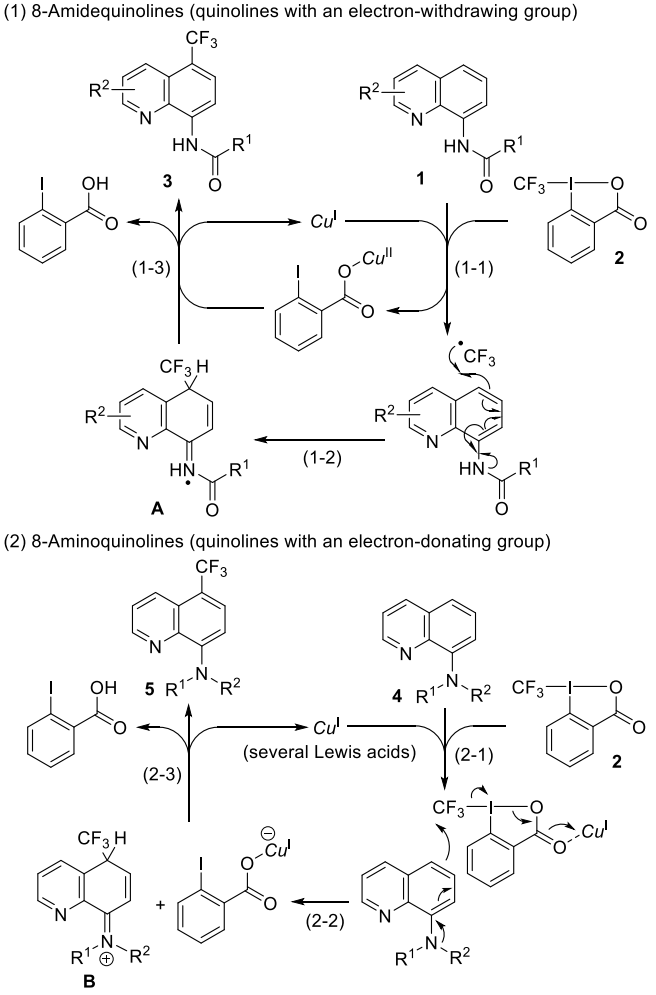
[a] Isolated combined yields are shown. ^{1}H NMR yield based on conversion is described in the parenthesis. [b] The ratio of 5-CF_3 product / 7-CF_3 product.

Scheme 1 Radical scavenger experiments.

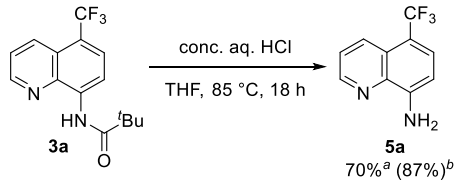
Based on the radical scavenger experiments, we propose one of the following two pathways depending on the substrate (Scheme 2): [1] in the case of 8-amidoquinolines (quinolines with an electron-withdrawing group), (1-1) formation of a CF_3 radical from Togni reagent **2** and CuCl; (1-2) addition of a CF_3 radical to 8-amidoquinoline **1** to give intermediate **A**; and (1-3) elimination of a hydrogen radical from intermediate **A** to give trifluoromethylated product **3**; and [2] in the case of 8-aminoquinolines (quinolines with an electron-donating group), (2-1) Togni reagent **2** is electrophilically activated by the CuCl (Lewis acid); (2-2) nucleophilic attack of 8-aminoquinoline **4** to the CF_3 group of the activated Togni reagent to give

intermediate **B**; and (2-3) deprotonation of intermediate **B** to give trifluoromethylated product **5** and regenerate the copper catalyst. This reaction was also promoted by several Lewis acids.

Finally, we investigated the deprotection of trifluoromethylated product **3a** (Scheme 3). Treatment of trifluoromethylated *N*-(8-quinolinyl)pivalamide **3a** with concentrated HCl in THF at 85 ºC for 18 h gave trifluoromethylated 8-aminoquinoline **5a** in 70% yield.



Scheme 2 Proposed mechanisms of 4-position-selective C-H trifluoromethylation.



[a] Isolated yield. [b] ^{1}H NMR yield based on conversion.

Scheme 3 Deprotection of product **3a**.

Conclusions

In summary, we successfully developed a copper-catalyzed 5-position-selective C-H trifluoromethylation of 8-aminoquinoline derivatives. The reaction proceeded with high functional group tolerance under mild conditions. In the case of quinolines with an amide, carbamate, urea, or sulfonamide group at the 8-position of quinoline moieties, trifluoromethylation proceeded with high regioselectivity and the acyl-protecting group could be removed by hydrolysis. The results of radical scavenger experiments indicate that trifluoromethylation proceeded via a radical pathway. On the other hand, trifluoromethylation of 8-aminoquinolines could also be promoted by other Lewis acids, and the trifluoromethylation reaction proceeded even in the presence of a radical scavenger. These results indicate that trifluoromethylation of 8-aminoquinolines proceeded via a Friedel-Crafts-type reaction. Interestingly, the copper salt can work as either a catalyst for the formation of a CF_3 radical or as a Lewis acid to promote a Friedel-Crafts-type reaction, depending on the substrate. We expect that the present results will advance organofluorine chemistry.

Experimental

All reactions were carried out in a dry and degassed solvent under an argon atmosphere. All reagents were purchased from commercial sources and used without further purification unless otherwise noted. Quinolylamides **1a**-**1d**,[16a] **1e**,[16b] **1f**,[16a] **1g**,[16c] **1h**,[16d] **1i**,[16e] **1j**,[16f] **1k**,[16g] **1l**,[16d] and **1m-1r**, carbamates **1s**[17a] and **1t**,[17b] urea **1u**, sulfonamides **1v**[18a] and **1w**,[18b] and *N*-benzylquinolylamines **4b**[19] and **4c**,[20] were prepared from 8-aminoquinoline according to the literature methods and identified by comparing the spectroscopic data with those of reported data. Trifluoromethylated products **5a** are known compounds.[6] 1-Trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (**2**) (contains 60% diatomaceous earth) and 8-aminoquinoline (**4a**) were purchased from Tokyo Kasei Kogyo Co. Copper(I) chloride, was purchased from Wako Co. 1,2-Dichloroethane was purchased from Sigma Aldrich Co and degassed before use. Column chromatography was performed with silica gel (230-400 mesh ASTM). Recycling preparative HPLC (LC-9210NEXT; column, JAIGEL-1H and JAIGEL-2H; solvent, $CHCl_3$) was used for isolation of trifluoromethylated products **5b** (as mixtures of 5- and 7- regioisomers) after removing metal wastes through a short pad of silica gel. NMR spectra were recorded on 500 MHz (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) and 400 MHz (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, 368 MHz for ^{19}F NMR) spectrometers. Proton and carbon chemical shifts are reported relative to the solvent used as an internal reference. Fluorine chemical shifts are reported relative to trifluoroacetic acid (δ -76.55 ppm) as an external reference. Infrared (IR) spectra were recorded on Fourier transform infrared spectrophotometer. ESI-MS spectra were measured on a spectrometer for HRMS.

Typical procedure for copper-catalyzed trifluoromethylation of 8-quinolinylamide 1.

A mixture of CuCl (0.6 mg, 6.3 μmol, 5.0 mol%) and 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (**2**, 99.8 mg, 0.125 mmol, 1.0 equiv) was added to a solution of 8-quinolinylamide

1a (28.6 mg, 0.125 mmol, 1.0 equiv) in 1,2-dichloroethane (1.25 mL) in a sealed tube. The mixture was then stirred at 25 ºC for 18 h. The product was isolated by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give **3a** (15.2 mg, 41% yield).

***N*-(5-(Trifluoromethyl)quinolin-8-yl)pivalamide (3a).** 41% yield; white solid; R_f = 0.50 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 M Hz, $CDCl_3$) δ 1.43 (s, 9H), 7.60 (dd, *J* = 9.0, 4.0 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 8.50 (dt, *J* = 9.0, 1.8 Hz, 1H), 8.81 (d, *J* = 8.5 Hz, 1H), 8.89 (dd, *J* = 4.0, 1.8 Hz, 1H), 10.4 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 40.5, 113.8, 119.2 (q, *J* = 31.0 Hz), 122.7, 124.2, 124.3 (q, *J* = 273 Hz), 126.6 (q, *J* = 5.6 Hz), 133.2 (q, *J* = 1.9 Hz), 138.2, 138.5, 146.6, 177.6; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.3; IR (KBr, ν / cm^{-1}) 3369, 3345, 2965, 1672, 1524, 1397, 1382, 1318, 1222, 1203, 1168, 1148, 1138, 1099, 957, 848, 791, 680; HRMS (ESI^+) Calcd for $C_{15}H_{15}F_3N_2NaO$ ($[M+Na]^+$) 319.1034, Found 319.1042.

2,2-Dimethyl-*N*-(5-(trifluoromethyl)quinolin-8-yl)butanamide (3b). 38% yield; white solid; R_f = 0.50 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.2 Hz, 3H), 1.39 (s, 6H), 1.77 (q, *J* = 7.2 Hz, 2H), 7.60 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.83 (d, *J* = 8.1 Hz, 1H), 8.90 (d, *J* = 4.0 Hz, 1H), 10.4 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.3, 25.0, 34.1, 44.2, 113.8, 119.2 (q, *J* = 31.0 Hz), 122.7, 124.2, 124.3 (q, *J* = 273 Hz), 126.6 (q, *J* = 5.6 Hz), 133.2 (q, *J* = 1.9 Hz), 138.2, 138.6, 148.6, 177.1; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.3; IR (KBr, ν / cm^{-1}) 3356, 2970, 1682, 1523, 1505, 1477, 1457, 1386, 1328, 1218, 1177, 1143, 1108, 958, 862, 788, 697; HRMS (ESI^+) Calcd for $C_{16}H_{17}F_3N_2NaO$ ($[M+Na]^+$) 333.1191, Found 333.1180.

2-Ethyl-*N*-(5-(trifluoromethyl)quinolin-8-yl)butanamide (3c). 44% yield; white solid; R_f = 0.45 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.2 Hz, 6H), 1.60-1.75 (m, 2H), 1.76-1.91 (m, 2H), 2.31-2.44 (m, 1H), 7.60 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 8.48-8.60 (m, 1H), 8.86 (d, *J* = 8.5 Hz, 1H), 8.89 (dd, *J* = 4.5, 1.8 Hz, 1H), 10.0 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 25.8, 52.7, 114.1, 119.4 (q, *J* = 31.0 Hz), 124., 124.3 (q, *J* = 273 Hz), 122.7, 126.6 (q, *J* = 5.6 Hz), 133.2 (q, *J* = 1.9 Hz), 138.0, 138.2, 148.6, 175.2; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.4; IR (KBr, ν / cm^{-1}) 3335, 2969, 1685, 1529, 1501, 1462, 1395, 1332, 1322, 1226, 1176, 1144, 1106, 963, 847, 789, 691; HRMS (ESI^+) Calcd for $C_{16}H_{17}F_3N_2NaO$ ($[M+Na]^+$) 333.1191, Found 333.1190.

***N*-(5-(Trifluoromethyl)quinolin-8-yl)cyclopentanecarboxamide (3d).** 41% yield; white solid; R_f = 0.50 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60-1.80 (m, 2H), 1.80-1.93 (m, 2H), 1.95-2.25 (m, 4H), 2.92-3.07 (m, 1H), 7.59 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.81 (d, *J* = 8.1 Hz, 1H), 8.88 (d, *J* = 4.5 Hz, 1H), 10.0 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 30.5, 47.4, 113.9, 119.2 (q, *J* = 31.0 Hz), 122.7, 124.2, 124.3 (q, *J* = 273 Hz), 126.6 (q, *J* = 5.6 Hz), 133.2, 138.16, 138.19, 148.5, 175.5; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.3; IR (KBr, ν / cm^{-1}) 3344, 2954, 2871, 1698, 1521, 1392, 1321, 1223, 1140, 1111, 845, 789, 649; HRMS (ESI^+) Calcd for $C_{16}H_{15}F_3N_2NaO$ ($[M+Na]^+$) 331.1034, Found 331.1032.

***N*-(5-(Trifluoromethyl)quinolin-8-yl)cyclohexanecarboxamide (3e).** 40% yield; white solid; R_f = 0.44 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.51 (m, 3H), 1.55-1.82 (m, 3H), 1.85-1.97 (m, 2H), 2.04-2.16 (m, 2H), 2.44-2.56 (m, 1H), 7.60 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.81 (d, *J* = 8.1 Hz, 1H), 8.89 (d, *J* = 4.0 Hz, 1H), 10.1 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.66, 25.70, 29.6, 46.9, 114.0, 119.2 (q, *J* = 31.0 Hz), 122.7, 124.2, 124.3 (q, *J* = 273 Hz), 126.6 (q, *J* = 5.6 Hz), 133.2, 138.1, 138.2, 148.5, 175.2; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.3; IR (KBr, ν / cm^{-1}) 3353, 2936, 2854, 1695, 1523, 1457, 1393, 1320, 1213, 1169, 1142, 1115, 961, 846, 786, 646; HRMS (ESI^+) Calcd for $C_{17}H_{17}F_3N_2NaO$ ($[M+Na]^+$) 345.1191, Found 345.1178.

***N*-(5-(Trifluoromethyl)quinolin-8-yl)acetamide (3f).** 40% yield; white solid; R_f = 0.13 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.60 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 8.51 (dt, *J* = 8.5, 1.4 Hz, 1H), 8.79 (d, *J* = 8.1 Hz, 1H), 8.88 (dd, *J* = 4.1, 1.4 Hz, 1H), 9.98 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 114.0, 119.5 (q, *J* = 31.0 Hz), 122.8, 124.22 (q, *J* = 273 Hz), 124.23, 126.6 (q, *J* = 5.6 Hz), 133.2 (q, *J* = 1.9 Hz), 137.95, 138.00, 148.5, 169.1; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.4; IR (KBr, ν / cm^{-1}) 3357, 3078, 1681, 1582, 1541, 1505, 1392, 1330, 1268, 1227, 1136, 1104, 1080, 1037, 967, 858, 794, 737, 634; HRMS (ESI^+) Calcd for $C_{12}H_9F_3N_2NaO$ ($[M+Na]^+$) 277.0565, Found 277.0563.

***N*-(5-(Trifluoromethyl)quinolin-8-yl)hexamide (3g).** 44% yield; pale yellow solid; R_f = 0.45 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 6.7 Hz, 3H), 1.28-1.48 (m, 4H), 1.72-1.90 (m, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 7.60 (dd, *J* = 9.0, 4.0 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 8.50 (d, *J* = 9.0 Hz, 1H), 8.81 (d, *J* = 8.1 Hz, 1H), 8.88 (d, *J* = 4.0 Hz, 1H), 9.99 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.4, 25.2, 31.4, 38.2, 114.0, 119.3 (q, *J* = 31.9 Hz), 122.8, 124.2, 124.2 (q, *J* = 273 Hz), 126.6 (q, *J* = 5.6 Hz), 133.2 (q, *J* = 1.9 Hz), 138.0, 138.1, 148.5, 172.3; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.4; IR (KBr, ν / cm^{-1}) 3328, 2955, 2939, 2868, 1697, 1580, 1527, 1394, 1325, 1221, 1201, 1179, 1145, 1098, 966, 790, 696; HRMS (ESI^+) Calcd for $C_{16}H_{17}F_3N_2NaO$ ($[M+Na]^+$) 333.1191, Found 333.1179.

***N*-(5-(Trifluoromethyl)quinolin-8-yl)benzamide (3h).** 43% yield; white solid; R_f = 0.40 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.65 (m, 4H), 7.98 (d, *J* = 8.5 Hz, 1H), 8.02-8.12 (m, 2H), 8.48-8.57 (m, 1H), 8.94 (dd, *J* = 4.0, 1.3 Hz, 1H), 8.97 (d, *J* = 8.1 Hz, 1H), 10.9 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.2, 119.7 (q, *J* = 31.0 Hz), 122.9, 123.5 (q, *J* = 272 Hz), 124.3, 126.6 (q, *J* = 5.6 Hz), 127.4, 128.9, 132.3, 133.3 (q, *J* = 1.9 Hz), 134.6, 138.1, 138.6, 148.7, 165.7; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.4; IR (KBr, ν / cm^{-1}) 3373, 3086, 1680, 1579, 1533, 1506, 1492, 1390, 1329, 1263, 1220, 1175, 1145, 1092, 953, 867, 789, 705, 689; HRMS (ESI^+) Calcd for $C_{17}H_{11}F_3N_2NaO$ ($[M+Na]^+$) 339.0721, Found 339.0722.

4-Methoxy-*N*-(5-(trifluoromethyl)quinolin-8-yl)benzamide (3i). 40% yield; white solid; R_f = 0.25 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.62 (dd, *J* = 8.5, 4.1 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 8.50-8.62 (m, 1H), 8.91-9.00 (m, 2H), 10.9 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 114.0, 114.1,

119.3 (q, *J* = 31.0 Hz), 122.8, 124.27 (q, *J* = 272 Hz), 124.30, 126.7 (q, *J* = 5.6 Hz), 126.8, 129.3, 133.2 (q, *J* = 1.9 Hz), 138.3, 138.5, 148.6, 162.8, 165.2; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.3; IR (KBr, ν / cm^{-1}) 3364, 2942, 1670, 1607, 1578, 1532, 1512, 1389, 1329, 1268, 1218, 1176, 1138, 1095, 1021, 953, 849, 790, 760, 652; HRMS (ESI^+) Calcd for $C_{18}H_{13}F_3N_2NaO_2$ ($[M+Na]^+$) 369.0827, Found 369.0825.

4-Bromo-*N*-(5-(trifluoromethyl)quinolin-8-yl)benzamide (3j). 39% yield; pale yellow solid; R_f = 0.48 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.90-7.84 (m, 3H), 8.54 (d, *J* = 8.5 Hz, 1H), 8.86-9.00 (m, 2H), 10.9 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.3, 120.0 (q, *J* = 31.0 Hz), 123.0, 124.1 (q, *J* = 273 Hz), 124.3, 126.6 (q, *J* = 5.6 Hz), 127.1, 128.9, 132.2, 133.3 (q, *J* = 1.9 Hz), 133.4, 137.8, 138.5, 148.8, 164.6; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.4; IR (KBr, ν / cm^{-1}) 3339, 3121, 3050, 2925, 1686, 1593, 1580, 1541, 1502, 1486, 1390, 1332, 1311, 1221, 1135, 1102, 1010, 952, 858, 842, 792, 741, 665; HRMS (ESI^+) Calcd for $C_{17}H_{10}BrF_3N_2NaO$ ($[M+Na]^+$) 416.9826, Found 416.9825.

4-Trifluoromethyl-*N*-(5-(trifluoromethyl)quinolin-8-yl)benzamide (3k). 41% yield; white solid; R_f = 0.48 (hexane/ethyl acetate = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.6, 4.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.99 (d, *J* = 8.6 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 2H), 8.56 (d, *J* = 8.6 Hz, 1H), 8.90-8.97 (m, 2H), 11.0 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.5, 120.3 (q, *J* = 31.1 Hz), 123.0, 123.6 (q, *J* = 272 Hz), 124.1 (q, *J* = 273 Hz), 124.3, 126.0 (q, *J* = 3.6 Hz), 126.6 (q, *J* = 5.6 Hz), 127.8, 133.4, 133.9 (q, *J* = 32.4 Hz), 137.6, 137.8, 138.5, 148.9, 164.3; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.4, -63.6; IR (KBr, ν / cm^{-1}) 3344, 3122, 2924, 1680, 1582, 1550, 1514, 1503, 1396, 1329, 1308, 1223, 1199, 1169, 1150, 1113, 1070, 1034, 1014, 953, 903, 861, 795, 767, 685; HRMS (ESI^+) Calcd for $C_{18}H_{10}F_6N_2NaO$ ($[M+Na]^+$) 407.0595, Found 407.0592.

2-Methyl-*N*-(5-(trifluoromethyl)quinolin-8-yl)benzamide (3l). 38% yield; pale yellow solid; R_f = 0.43 (hexane/ethyl acetate = 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61 (s, 3H), 7.31-7.38 (m, 2H), 7.41-7.46 (m, 1H), 7.61 (dd, *J* = 8.6, 4.0 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 8.53 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.86 (dd, *J* = 4.0, 1.2 Hz, 1H), 8.97 (d, *J* = 8.0 Hz, 1H), 10.4 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 114.1, 119.8 (q, *J* = 31.0 Hz), 122.9, 124.2 (q, *J* = 273 Hz), 124.3, 126.1, 126.6 (q, *J* = 5.6 Hz), 127.3, 130.7, 131.5, 133.2, 136.0, 136.9, 138.2, 138.4, 148.7, 168.4; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.4; IR (KBr, ν / cm^{-1}) 3326, 2957, 2855, 1676, 1603, 1578, 1537, 1499, 1459, 1394, 1331, 1319, 1221, 1174, 1135, 1102, 952, 849, 794, 745, 688; HRMS (ESI^+) Calcd for $C_{18}H_{13}F_3N_2NaO$ ($[M+Na]^+$) 353.0878, Found 353.0864.

***N*-(6-Methoxy-5-(trifluoromethyl)quinolin-8-yl)pivalamide (3m).** 50% yield; white solid; R_f = 0.48 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 4.05 (s, 3H), 7.50 (dd, *J* = 8.9, 4.0 Hz, 1H), 8.54 (dt, *J* = 8.9, 1.3 Hz, 1H), 8.69 (dd, *J* = 4.0, 1.3 Hz, 1H), 8.82 (s, 1H), 10.5 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 40.6, 56.8, 103.5, 103.6 (q, *J* = 30.0 Hz), 123.2, 125.1 (q, *J* = 274 Hz), 126.2, 132.6 (q, *J* = 5.6 Hz), 133.9, 139.3, 145.9, 158.2 (q, *J* = 1.9 Hz), 178.1; ^{19}F NMR (368 MHz, $CDCl_3$) δ -52.7; IR (KBr, ν / cm^{-1}) 3359, 2960, 2876, 1682, 1624, 1577, 1525, 1489, 1465, 1410, 1396, 1292, 1211, 1099, 1081, 992, 934, 861, 780, 686; HRMS (ESI^+) Calcd for $C_{16}H_{17}F_3N_2NaO_2$ ($[M+Na]^+$) 349.1140, Found 349.1134.

***N*-(6-Methoxycarbonyl-5-(trifluoromethyl)quinolin-8-yl)pivalamide (3n).** 40% yield; colorless solid; R_f = 0.40 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 3.95 (s, 3H), 7.64 (dd, *J* = 9.0, 4.0 Hz, 1H), 8.57 (dt, *J* = 9.0, 1.3 Hz, 1H), 8.86 (s, 1H), 8.92 (dd, *J* = 4.0, 1.3 Hz, 1H), 10.4 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.5, 40.5, 53.1, 113.0, 115.7 (q, *J* = 31.0 Hz), 123.3, 123.7 (q, *J* = 274 Hz), 124.4, 133.5 (q, *J* = 3.7 Hz), 134.1 138.2, 138.3, 149.4 168.4, 177.7; ^{19}F NMR (368 MHz, $CDCl_3$) δ -54.8; IR (KBr, ν / cm^{-1}) 3359, 2961, 1745, 1692, 1576, 1527, 1489, 1409, 1387, 1346, 1287, 1256, 1165, 1124, 1008, 958, 792; HRMS (ESI^+) Calcd for $C_{17}H_{17}F_3N_2NaO_3$ ($[M+Na]^+$) 377.1089, Found 377.1086.

***N*-(3-Bromo-5-(trifluoromethyl)quinolin-8-yl)pivalamide (3o).** 31% yield; pale yellow solid; R_f = 0.55 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 7.92 (t, *J* = 8.5 Hz, 1H), 8.63 (d, *J* = 1.8 Hz, 1H), 8.83 (d, *J* = 8.5 Hz, 1H), 8.90 (d, *J* = 1.8 Hz, 1H), 10.2 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 40.5, 114.3, 118.5 (q, *J* = 32.0 Hz), 119.7, 123.9 (q, *J* = 273 Hz), 125.1, 127.9 (q, *J* = 5.6 Hz), 134.7 (q, *J* = 1.9 Hz), 136.6, 138.4, 149.9, 177.6; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.4; IR (KBr, ν / cm^{-1}) 3376, 2963, 2928, 1692, 1568, 1516, 1477, 1447, 1397, 1385, 1327, 1313, 1222, 1161, 1111, 970, 891, 862, 850, 802, 677, 659; HRMS (ESI^+) Calcd for $C_{15}H_{14}BrF_3N_2NaO$ ($[M+Na]^+$) 397.0139, Found 397.0147.

***N*-(2-Methyl-5-(trifluoromethyl)quinolin-8-yl)pivalamide (3p).** 42% yield; white solid; R_f = 0.48 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.77 (s, 3H), 7.46 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 8.37 (d, *J* = 9.0 Hz, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 10.5 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 27.6, 40.5, 113.8, 119.1 (q, *J* = 31.0 Hz), 122.3, 123.5, 124.4 (q, *J* = 273 Hz), 125.5 (q, *J* = 5.6 Hz), 133.2 (q, *J* = 1.9 Hz), 137.5, 138.0, 157.7, 177.5; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.3; IR (KBr, ν / cm^{-1}) 3343, 2973, 2872, 1685, 1612, 1575, 1523, 1479, 1457, 1387, 1332, 1300, 1227, 1209, 1185, 1164, 1141, 1112, 1094, 956, 854, 708; HRMS (ESI^+) Calcd for $C_{16}H_{17}F_3N_2NaO$ ($[M+Na]^+$) 333.1191, Found 333.1183.

***N*-(7-Methyl-5-(trifluoromethyl)quinolin-8-yl)pivalamide (3q).** 22% yield; colorless solid; R_f = 0.38 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.45 (s, 3H), 7.50 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.81 (s, 1H), 8.44 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.88 (dd, *J* = .0, 1.3 Hz, 1H), 9.25 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 27.7, 40.1, 121.7, 121.8 (q, *J* = 31.0 Hz), 122.5, 124.2 (q, *J* = 273 Hz), 129.3 (q, *J* = 5.6 Hz), 131.0, 132.6 (q, *J* = 1.9 Hz), 135.7, 142.4, 149.4, 177.2; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.3; IR (KBr, ν / cm^{-1}) 3366, 2970, 1692, 1508, 1495, 1395, 1344, 1230, 1187, 1146, 1129, 1113, 1055, 948, 899, 822, 706, 660; HRMS (ESI^+) Calcd for $C_{16}H_{17}F_3N_2NaO$ ($[M+Na]^+$) 333.1191, Found 333.1205.

***N*-(8-(Trifluoromethyl)quinolin-5-yl)pivalamide (3r).** 21% yield; white solid; R_f = 0.70 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 7.53 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.88 (brs, 1H), 8.01-8.09 (m, 2H), 8.13 (dd, *J* = 8.6, 1.8 Hz, 1H), 9.08 (dd, *J* = 4.0, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7, 40.1, 119.0, 121.6, 122.5, 123.9 (q, *J* = 273 Hz), 124.7 (q, *J* = 30.0 Hz),

128.3 (q, *J* = 6.0 Hz), 129.3, 136.4, 145.2, 151.0, 177.1; ^{19}F NMR (368 MHz, $CDCl_3$) δ -60.7; IR (KBr, ν / cm^{-1}) 3442, 2972, 1690, 1598, 1520, 1497, 1400, 1362, 1331, 1308, 1238, 1153, 1122, 1113, 964, 828, 788; HRMS (ESI^+) Calcd for $C_{15}H_{15}F_3N_2NaO$ ($[M+Na]^+$) 319.1034, Found 319.1047.

***tert*-Butyl(5-(trifluoromethyl)quinolin-8-yl)carbamate (3s).** 49% yield; white solid; R_f = 0.53 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 7.57 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 8.43 (d, *J* = 8.5 Hz, 1H), 7.81 (dt, *J* = 8.5, 1.8 Hz, 1H), 7.81 (dd, *J* = 4.0, 1.8 Hz, 1H), 9.24 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 81.1, 112.0, 118.2 (q, *J* = 31.0 Hz), 122.7, 124.3, 124.4 (q, *J* = 273 Hz), 126.5 (q, *J* = 5.6 Hz), 133.0 (q, *J* = 1.9 Hz), 138.0, 138.9, 148.4, 152.5; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.2; IR (KBr, ν / cm^{-1}) 3351, 2990, 2925, 1722, 1581, 1533, 1499, 1456, 1394, 1373, 1335, 1318, 1254, 1213, 1165, 1140, 1125, 1113, 1009, 842, 684; HRMS (ESI^+) Calcd for $C_{15}H_{15}F_3N_2NaO_2$ ($[M+Na]^+$) 335.0983, Found 335.0974.

***tert*-Butyl(6-methoxy-5-(trifluoromethyl)quinolin-8-yl)carbamate (3t).** 49% yield; pale yellow solid; R_f = 0.48 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 9H), 4.06 (s, 3H), 7.50 (dd, *J* = 9.0, 4.0 Hz, 1H), 8.38 (s, 1H), 8.52 (dt, *J* = 9.0, 1.4 Hz, 1H), 8.69 (dd, *J* = 4.0, 1.4 Hz, 1H), 9.30 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 56.9, 81.2, 101.7, 102.6 (q, *J* = 30.0 Hz), 123.2, 125.2 (q, *J* = 274 Hz), 126.3, 132.5 (q, *J* = 5..6 Hz), 133.4, 140.1, 145.6, 152.5, 158.3; ^{19}F NMR (368 MHz, $CDCl_3$) δ -52.5; IR (KBr, ν / cm^{-1}) 3350, 2979, 2937, 1727, 1624, 1581, 1534, 1494, 1466, 1413, 1392, 1367, 1291, 1250, 1222, 1168, 1097, 1082, 1011, 780, 691; HRMS (ESI^+) Calcd for $C_{16}H_{17}F_3N_2NaO_3$ ($[M+Na]^+$) 365.1089, Found 365.1079.

1,1-Dimethyl-3-(5-(trifluoromethyl)quinolin-8-yl)urea (3u). 48% yield; pale yellow solid; R_f = 0.35 (hexane/ethyl acetate = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (s, 6H), 7.56 (dd, *J* = 8.9, 4.5 Hz, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 8.59 (d, *J* = 8.5 Hz, 1H), 8.48 (dd, *J* = 8.5, 1.8 Hz, 1H), 8.83 (dd, *J* = 4.5, 1.8 Hz, 1H), 9.60 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.4, 112.1, 117.4 (q, *J* = 31.0 Hz), 122.6, 124.3, 124.5 (q, *J* = 272 Hz), 126.8 (q, *J* = 5.6 Hz), 133.2 (q, *J* = 1.9 Hz), 138.2, 139.6, 148.1, 155.0; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.1; IR (KBr, ν / cm^{-1}) 3364, 2921, 1669, 1581, 1548, 1504, 1394, 1335, 1316, 1223, 1173, 1140, 1106, 1086, 1007, 951, 866, 791; HRMS (ESI^+) Calcd for $C_{13}H_{12}F_3N_3NaO$ ($[M+Na]^+$) 306.0830, Found 306.0826.

***N*-(5-(Trifluoromethyl)quinolin-8-yl)-methanesulfonamide (3v).** 27% yield; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (s, 3H), 7.65 (dd, *J* = 9.0, 4.5 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 8.53 (dt, *J* = 9.0, 1.4 Hz, 1H), 8.91 (dd, *J* = 4.5, 1.4 Hz, 1H), 9.24 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8, 111.5, 120.3 (q, *J* = 31.0 Hz), 123.4, 124.0 (q, *J* = 273 Hz), 124.7, 126.1 (q, *J* = 5.6 Hz), 133.3 (q, *J* = 1.9 Hz), 137.9, 138.1, 149.3; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.5; IR (KBr, ν / cm^{-1}) 3434, 3303, 1579, 1510, 1482, 1368, 1323, 1149, 1121, 1105, 1073, 1038, 976, 880, 822, 799, 733; HRMS (ESI^+) Calcd for $C_{11}H_9F_3N_2NaO_2S$ ($[M+Na]^+$) 313.0234, Found 313.0233.

***N*-(5-(Trifluoromethyl)quinolin-8-yl)-*p*-toluenesulfonamide (3w).** 34% yield; colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.57 (dd, *J* = 8.6, 4.0 Hz, 1H), 7.75-7.82 (m, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 8.43 (d, *J* = 8.6 Hz, 1H), 8.85 (dd, *J* = 4.0, 1.2 Hz, 1H), 9.25 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 111.4, 119.8 (q, *J* = 31.0 Hz), 123.2, 124.0 (q, *J* = 273 Hz), 124.5, 125.9 (q, *J* = 5.6 Hz), 127.2, 129.8, 133.1 (q, *J* = 1.9 Hz), 136.0, 137.5, 138.0, 144.3, 149.0; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.5; IR (KBr, ν / cm^{-1}) 3435, 3270, 2923, 1580, 1509, 1478, 1378, 1317, 1167, 1113, 876, 734, 662; HRMS (ESI^+) Calcd for $C_{17}H_{13}F_3N_2NaO_2S$ ($[M+Na]^+$) 389.0547, Found 389.0559.

Typical procedure for copper-catalyzed trifluoromethylation of 8-aminoquinoline derivatives 4.

A mixture of A mixture CuCl (0.6 mg, 6.25 μmol, 5.0 mol%) and 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (**2**, 99.8 mg, 0.125 mmol, 1.0 equiv) was added to a solution of 8-quinolinylamine (**4a**, 28.6 mg, 0.125 mmol, 1.0 equiv) in 1,2-dichloroethane (1.25 mL) in a sealed tube. The mixture was then stirred at 25 ºC for 18 h. The product was isolated from starting material and other byproducts by column chromatography on silica gel or recycling preparative HPLC to give regioisomers (12.7 mg, 48% yield).

***N*-(Trifluoromethylquinolin-8-yl)benzylamine (5b).** 49% yield (5- and 7-position isomers); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (5-position isomer) 4.60 (d, *J* = 5.4 Hz, 2H), 6.55 (d, *J* = 8.5 Hz, 1H), 7.09 (brs, 1H), 7.30-7.48 (m, 5H), 7.51 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 8.56 (dt, *J* = 8.5,1.8 Hz, 1H), 8.77 (dd, *J* = 4.0, 1.8 Hz, 1H); (7-position isomer) 4.72 (s, 2H), 7.14 (d, *J* = 9.0 Hz, 1H), 7.30-7.48 (m, 7H), 7.60 (d, *J* = 9.0 Hz, 1H) , 8.07 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.74 (dd, *J* = 4.5, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (5-position isomer) 47.2, 102.1, 111.6 (q, *J* = 31.0 Hz), 122.6, 125.2 (q, *J* = 272 Hz), 124.9, 127.2 (q, *J* = 5.6 Hz), 127.3, 127.4, 128.7, 132.8 (q, *J* = 1.9 Hz), 137.7, 138.2, 147.2, 147.4; (7-position isomer) 51.5, 109.1 (q, *J* = 31.0 Hz), 115.0, 123.0, 125.3 (q, *J* = 272 Hz), 124.8 (q, *J* = 5.6 Hz), 128.1, 128.6, 129.6, 136.0, 139.6, 140.2, 144.8 (q, *J* = 1.9 Hz), 147.4, 147.7; ^{19}F NMR (368 MHz, $CDCl_3$) δ (5-position isomer) -58.6; (7-position isomer) -55.2; IR (neat, ν / cm^{-1}) 3394, 3065, 3032, 2926, 2856, 1613, 1577, 1525, 1503, 1454, 1388, 1359, 1318, 1263, 1223, 1178, 1143, 1103, 1263, 1223, 1178, 1143, 1103, 1031, 948, 816, 792, 735, 697; HRMS (ESI^+) Calcd for $C_{17}H_{13}F_3N_2Na$ ($[M+Na]^+$) 325.0928, Found 325.0924.

***N*-(5-Trifluoromethylquinolin-8-yl)dibenzylamine (5c).** 47% yield; yellow oil; R_f = 0.50 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 4H), 7.18-7.36 (m, 10H), 6.84 (d, *J* = 8.1 Hz, 1H), 7.48 (dd, *J* = 9.0, 4.0 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 8.43 (d, *J* = 9.0, 1.8 Hz, 1H), 8.90 (dd, *J* = 4.0, 1.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 56.6, 114.5, 116.7 (q, *J* = 31.0 Hz), 121.8, 124.8 (q, *J* = 272 Hz), 125.7 (q, *J* = 5.6 Hz), 126.1, 127.0, 128.0, 128.3, 132.7 (q, *J* = 1.9 Hz), 138.3, 142.2, 147.3, 150.6; ^{19}F NMR (368 MHz, $CDCl_3$) δ -59.0; IR (neat, ν / cm^{-1}) 3086, 3063, 3029, 2929, 2852, 1726, 1605, 1567, 1508, 1495, 1453, 1365, 1324, 1219, 1180, 1096, 1074, 1044, 1029, 1008, 956, 918, 821, 791, 735, 699; HRMS (ESI^+) Calcd for $C_{24}H_{19}F_3N_2Na$ ($[M+Na]^+$) 415.1398, Found 415.1392.

Trifluoromethylation of lamidoquinoline 1a in the presence of a radical scavenger.

A mixture of $CuCl_2$ (0.60 mg, 6.25 μmol, 5.0 mol%), 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (**2**, 99.8 mg, 0.125 mmol,

1.0 equiv), and galvinoxy free radical (52.7 mg, 0.125 mmol, 1.0 equiv) was added to a solution of *N*-(8-quinolinyl)pivalamide (**1a**, 28.6 mg, 0.125 mmol, 1.0 equiv) in 1,2-dichloroethane (1.25 mL) in a sealed tube. The mixture is then stirred at 25 ºC for 18 h. Trifluoromethylated product **3a** was not detected by ^{1}H NMR.

Deprotection of trifluoromethylated product 3a.[21]

To a solution of *N*-(5-(trifluoromethyl)quinolin-8-yl)pivalamide (**3a**, 59.2 mg, 0.200 mmol) in THF (1.0 mL), conc. HCl (0.50 mL) was added and the mixture was refluxed for 18 h. The mixture was cooled to room temperature and then aq. $NaHCO_3$ (10.0 mL) and ethyl acetate (10.0 mL) were added, and the mixture was extracted with ethyl acetate (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was isolated by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give **5a** (29.7mg, 70% yield).

Acknowledgements

This work was supported in part by ERATO from JST, Grant-in-Aid for Scientific Research (B) and Grant-in-Aid for Challenging Exploratory Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and Yakugaku Shinkoukai.

Notes and references

1 (*a*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*b*) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432.

2 (*a*) P. Jeschke, *ChemBioChem*, 2004, **5**, 570; (*b*) F. Giornal, S. Pazenok, L. Rodefeld, N. Lui, J. P. Vors, F. R. Leroux, *J. Fluorine Chem.*, 2013, **152**, 2.

3 M. Schlosser, *Angew. Chem. Int. Ed.*, 2006, **45**, 5432.

4 Stoichiometric reactions: (*a*) G. G. Dubinina, H. Furutachi and D. A. Vicic, *J. Am. Chem. Soc.*, 2008, **130**, 8600; (*b*) C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu and J.-C. Xiao, *Angew. Chem. Int. Ed.*, 2011, **50**, 1896; (*c*) H. Morimoto, T. Tsubogo, N. D. Litvinas and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2011, **50**, 3793; (*d*) P. Novák, A. Lishchynskyi and V. V. Grushin, *Angew. Chem. Int. Ed.*, 2012, **51**, 7767; (*e*) J.-J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z.-J. Liu, X. Lu, L. Liu and Y. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 8436; (*f*) M. G. Mormino, P. S. Fier, and J. F. Hartwig, *Org. Lett.*, 2014, **16**, 1744. Catalytic reactions: (*g*) Y. Ye and M. S. Sanford, *J. Am. Chem. Soc.*, 2012, **134**, 9034; (*h*) M. Chen and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2013, **52**, 11628.

5 (*a*) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond and P. S. Baran, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 14411; (*b*) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature*, 2012, **492**, 95; (*c*) E. Mejía and A. Togni, *ACS Catal.*, 2012, **2**, 521; (*d*) F. O'hara, D. G. Blackmond, and P. S. Baran, *J. Am. Chem. Soc.*, 2013, **135**, 12122.

6 T. Nishida, H. Ida, Y. Kuninobu and M. Kanai, *Nat. Commun.*, 2014, **5**, 3387.

7 M. Nagase, Y. Kuninobu and M. Kanai, *J. Am. Chem. Soc.*, 2016, **138**, 6103.

8 Y. Kuninobu, M. Nagase and M. Kanai, *Angew. Chem. Int. Ed.*, 2015, **54**, 10263.

9 (*a*) X. Wang, L. Truesdale and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3648; (b) A. Hafner and S. Bräse, *Angew. Chem. Int. Ed.*, 2012, **51**, 3713; (c) L.-S. Zhang, K. Chen, G. Chen, B.-J. Li, S. Luo, Q.-Y. Guo, J.-B. Wei and Z.-J. Shi, *Org. Lett.*, 2013, **15**, 10.

10 During the preparation of this manuscript, the similar trifluoromethylation reaction has been reported: Z. Wu, Y. He, C. Ma, X. Zhou, X. Liu, Y. Li, T. Hu, P. Wen and G. Huang, *Asian J. Org. Chem.*, **2016**, *5*, 724.

11 The reaction was not inhibited by product **3a** or 2-iodobenzoic acid, which was formed as a byproduct from Togni reagent **2**.

12 The desired product **3a** was obtained in 32% yield in 1.0 mmol scale whereas the yield was slightly decreased compared with that in a smaller scale (0.125 mmol, 41%).

13 M. Huang, S.-X. Xie, Z.-Q. Ma, R. P. Hanzlik and Q.-Z. Ye, *Biochem. Biophys. Res. Commun.*, 2006, **339**, 506.

14 Y. Xie, G. Gong, Y. Liu, S. Deng, A. Rinderspacher, L. Branden and D. W. Landry, *Tetrahedron Lett.*, 2008, **49**, 2320.

15 B. Wilm, B. Susanna, D. Franz, F. Felix, G. P. Otto, C. V. Anthony, C. S. Martin, D. Tara, S. Mark, R. M. Peter, Y. C. John, D. Graham, B. Susan and E. A. Antonius, Appl. (2012), WO 2012110603 A1 20120823.

16 (*a*) L. Zhu, R. Qiu, X. Cao, S. Xiao, X. Xu, C.-T. Au and S.-F. Yin, *Org. Lett.*, 2015, **17**, 5528; (*b*) V. G. Zaitsev, D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2005, **127**, 13154; (*c*) Y. Ano, M. Tobisu and N. Chatani, *J. Am. Chem. Soc.*, 2011, **131**, 12986; (*d*) F.-R. Gou, X.-C. Wang, P.-F. Huo, H.-P. Bi, Z.-H. Guan and Y.-M. Liang, *Org. Lett.*, 2009, **11**, 5726; (*e*) Y. Ano, M. Tobisu and N. Chatani, *Org. Lett.*, 2012, **14**, 354; (*f*) D. Shabashov and O. Daugulis, *J. Am. Chem. Soc.*, 2010, **132**, 3965; (*g*) M. Rouffet, C. A. F. de Oliveira, Y. Udi, A. Agrawal, I. Sagi, J. A. McCammon and S. M. Cohen, *J. Am. Chem. Soc.*, 2010, **132**, 8232.

17 (*a*) K. Chen, X. Li, S.-Q. Zhang and B.-F. Shi, *Chem. Commun.*, 2016, **52**, 1915; (*b*) G. Xue, J. S. Bradshaw, N. K. Dalley, P. B. Savage, K. E. Krakowiak, R. M. Izatt, L. Prodi, M. Montalti and N. Zaccheroni, *Tetrahedron*, 2001, **57**, 7623.

18 (*a*) B. Macías, I. García, M. V. Villa, J. Borrás, A. Castiñeiras, and F. Sanz, *Polyhedron*, 2002, **21**, 1229; (*b*) J. A. Jacobsen, J. L. Fullagar, M. T. Miller and S. M. Coben, *J. Med. Chem.*, 2011, **54**, 591.

19 A. Horikawa and K. Yokota, JP2000109462 (A).

20 X. Ling, Y. Xiong, R. Huang, X. Zhang, S. Zhang and C. Chen, *J. Org. Chem.*, 2013, **78**, 5218.

21 H.-W. Liang, K. Jiang, W. Ding, Y. Yuan, L. Shuai, Y.-C. Chen and Y. Wei, *Chem. Commun.*, 2015, **51**, 16928.

View Article Online
DOI: 10.1039/C6OB01325B

A rare example of C-H trifluoromethylation at the remote position of 8-aminoquinoline derivatives was realized by a CuCl catalyst/Togni reagent system.