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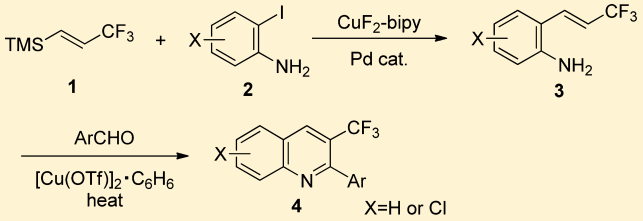
Synthesis of 2-Aryl-3-trifluoromethylquinolines Using (*E*)-Trimethyl(3,3,3-trifluoroprop-1-enyl)silane

Masaaki Omote, Miyuu Tanaka, Miki Tanaka, Akari Ikeda, Atsushi Tarui, Kazuyuki Sato, and Akira Ando*

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1 Nagaotoge-cho, Hirakata 573-0101, Japan

Supporting Information

ABSTRACT: The Hiyama cross-coupling reaction of (*E*)-trimethyl(3,3,3-trifluoroprop-1-enyl)silane (**1**) with 2-iodoaniline (**2**) proceeded without any protection of the amino group. The coordination of copper(II) fluoride to 2,2′-bipyridyl provided the fluoride source required to trigger this reaction, affording (*E*)-2-(3,3,3-trifluoroprop-1-enyl)aniline (**3**). In the presence of a stoichiometric amount of $[Cu(OTf)]_2{\cdot}C_6H_6$, the treatment of **3** with an aryl aldehyde at 200 °C provided the 2-aryl-3-trifluoromethylquinoline (**4**) via the oxidative cyclization of an in situ-generated imine substructure.

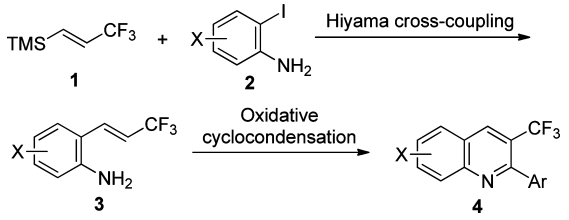


INTRODUCTION

Trifluoromethylated quinolines have recently been the subject of considerable levels of attention because of the important roles they play in pharmaceutical, agrochemical, and high-performance materials.[1,2] A wide variety of different synthetic methods have been reported for the construction of 2- and 4-trifluoromethylquinolines, including the direct trifluoromethylation of 2- and 4-halogenoquinolines[3] and the cyclocondensation of aniline derivatives with trifluoromethyl ketones.[4,5] In contrast, synthetic studies toward the development of methods providing access to 3-trifluoromethylquinolines remain scarce. The main difficulty associated with the construction of the 3-trifluoromethylquinoline core is the lack of a useful synthetic protocol that is compatible with the use of common aniline derivatives. Direct trifluoromethylation reactions have recently been established involving the cross-coupling of 3-quinolineboronic acid, but the chemical yields of the 3-trifluoromethylquinoline products were relatively low.[6] Furthermore, the synthesis of 2-substituted 3-trifluoromethylquinolines according to these methods becomes incredibly difficult because of the steric hindrance provided by the trifluoromethyl group, and only a few reports have been published in this particular area.[1d,7] The difficulties associated with the construction of 3-trifluoromethylquinolines have limited their use in the synthesis of several promising therapeutic targets.[1,2] With these issues in mind, we envisaged that the development of an efficient synthetic protocol involving the use of aniline derivatives would provide facile access to a wide range of 3-trifluoromethylquinolines and complement the existing library of trifluoromethylquinolines already available for the synthesis of potential therapeutic agents.

We recently reported the use of (*E*)-trimethyl(3,3,3-trifluoroprop-1-enyl)silane (**1**) for the 3,3,3-trifluoropropenylation of aryl iodide according to the Hiyama cross-coupling reaction to afford *β*-trifluoromethylstyrene derivatives, demonstrating that **1** was a useful 3,3,3-trifluoropropenylation reagent for aryl iodides.[8] During the course of that particular study, the Hiyama cross-coupling reaction of **1** was found to be applicable to 2-iodoaniline (**2**) when the reaction was conducted in the presence of copper(II) fluoride coordinated by 2,2′-bipyridine (bipy) as a source of fluoride anions. The reaction afforded (*E*)-2-(3,3,3-trifluoroprop-1-enyl)anilines (**3**) in quantitative yields without the need to protect the amino group in **2** (Scheme 1). The structure of **3** was critical to the success of the subsequent oxidative cyclocondensation reaction because the 3,3,3-trifluoroprop-1-enyl chain of **3** was perfectly aligned to participate in the cyclocondensation reaction. The oxidative cyclization reaction itself proceeded smoothly in the presence of $[Cu(OTf)]_2{\cdot}C_6H_6$ to give a series of 2-aryl-3-trifluoromethylquinolines (**4**). Herein, we wish to report the synthesis of **4** via the Hiyama cross-coupling reaction of **1** with **2** followed by an oxidative cyclocondensation reaction.

Scheme 1. Synthetic Approach for the Construction of 2-Aryl-3-trifluoromethylquinolines



RESULTS AND DISCUSSION

To begin our study, we screened a variety of different reaction conditions for the Hiyama cross-coupling reaction of **1** and **2**

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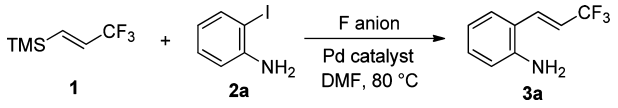
(Table 1). It is noteworthy that procedures for the protection and deprotection of the amino group were omitted from the screening process to simplify the overall transformation. When the reaction was carried out under the optimized conditions developed in our previous report, which involved the use of cesium fluoride and $Pd_2(dba)_3$ in DMF at a temperature of 80 °C (Table 1, entry 1), none of the desired product was observed. The failure of this reaction was attributed to the irreversible chelation of the nitrogen atom of the aniline to the palladium. The evaluation of several other reagents as fluoride sources under the same conditions also proved unsuccessful (Table 1, entries 2–5). During our search for suitable conditions, we discovered that copper(II) fluoride had a tendency toward accelerating the reaction when used in conjunction with an appropriate ligand. For example, although the use of copper(II) fluoride alone did not provide any of the desired product (Table 1, entry 6), the coordinative interaction of 1,10-phenanthroline (1,10-phen) with copper(II) fluoride began to initiate the reaction to afford a coupling product (**3a**) in a 13% yield (Table 1, entry 7). Pleasingly, the use of bipy as a ligand instead of 1,10-phen provided a significant enhancement in the yield of the reaction to give **3a** in a 61% yield over a shorter reaction time (Table 1, entry 8). The extension of the reaction time led to an increase in the yield of **3a** to 90%, and these conditions were determined to be optimal (Table 1, entry 9). Although it remains unclear why the combination of copper(II) fluoride and bipy had such a significant impact on the success of the reaction, we hypothesized that three significant effects resulted from this combination: (1) an increase in the solubility of copper(II) fluoride resulting from its coordination with bipy; (2) the enhanced feasibility of chelation between copper and the nitrogen atom of the aniline in **2** as a consequence of their good affinity, eliminating the detrimental effect of the chelation of the nitrogen atom with palladium; and (3) the viable generation of the fluoride anions necessary for C–Si bond dissociation through the chelation process. These hypotheses have been partially supported by the fact that the yield for the reaction was substantially reduced when *N*-Boc-protected **2a** was used (Table 1, entry 10) because the chelation between the nitrogen atom of the aniline and the copper would have been weakened by the Boc-substitution. Another palladium source, allylpalladium(II) chloride dimer, also participated in the reaction efficiently to give **3a** in the same yield. On the basis of these optimization experiments, we effectively developed an efficient Hiyama cross-coupling reaction of **1** with **2a** to afford **3a** without the need for any tedious protection and deprotection steps of the aniline.

Table 1. Optimization of Conditions for the Hiyama Cross-Coupling Reaction of 1 with 2a

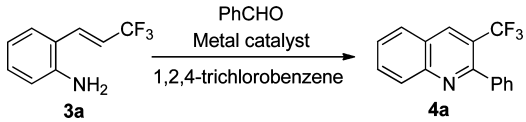


entry	catalyst (mol %)	F anion (equiv)	time (h)	**3a** yield (%)[a]
1	$Pd_2(dba)_3$(1.5)/ P(mesityl)$_3$ (15)	CsF (2)	19	
2	$Pd(dppe)_2$ (5)	TBAF (2)	15	
3	$Pd(dppe)_2$ (5)	KF (2)	19	
4	$Pd(dppe)_2$ (5)	ZnF_2 (2)/2,2′-bipy (2)	24	
5	$Pd(dppe)_2$ (5)	AgF (2)/2,2′-bipy (2)	23	
6	$Pd(dppe)_2$ (5)	CuF_2 (2)	20	
7	$Pd(dppe)_2$ (5)	CuF_2 (2)/1,10-phen (2)	20	13
8	$Pd(dppe)_2$ (5)	CuF_2 (2)/2,2′-bipy (2)	6	61
9	$Pd(dppe)_2$ (5)	CuF_2 (2)/2,2′-bipy (2)	19	90 (81)[c]
10[b]	$Pd(dppe)_2$ (5)	CuF_2 (2)/2,2′-bipy (2)	16	16
11	$[Pd(allyl)Cl]_2$ (5)	CuF_2 (2)/2,2′-bipy (2)	20	91

[a]NMR yields, which were calculated by ^{19}F NMR integration of products **3a** relative to the internal standard of ethyl 2,2,2-trifluoroacetate. [b]The *N*-Boc substrate was used. [c]The values in parentheses indicate the isolated yields of **3a**.

With an optimized procedure in hand for the Hiyama cross-coupling reaction, we proceeded to investigate the oxidative cyclocondensation of **3a** to **4a**. In 1988, Baine et al.[9] reported the convenient synthesis of 2-aryl-3-methoxycarbonylquinolines via the thermal electrocyclic rearrangement of methyl 3-(2-benzylideneamino)phenylacrylates. Although this reaction required high-temperature conditions of 200 °C to facilitate the electrocyclic rearrangement, it was simple and environmentally friendly because it only produced a small amount of waste. From a structural perspective, the *N*-benzylidene-2-alkenylaniline substructure employed in the reaction would be readily derived from **3a**, suggesting that the reaction would operate through **3a**. At the beginning of the current study, **3a** was subjected to the same condition reported by Baine et al.,[9] and a mixture of **3a** and benzaldehyde in 1,2,4-trichlorobenzene was heated to a temperature of 200 °C. The reaction proceeded to give the desired product **4a**, albeit in a low yield of 33%, following an even longer reaction time than that reported by Baine et al.[9] (Table 2, entry 1). The low yield observed in this particular case was attributed to the electron-deficient nature of the 3,3,3-trifluoromethylpropenyl group, which could interfere with the electrocyclic rearrangement. Changing the solvent to triglyme did not provide any improvement in the yield of the reaction (Table 2, entry 2). The addition of a stoichiometric amount of copper(I) iodide also failed to provide any

Table 2. Screening Process To Identify the Optimal Reaction Conditions for the Oxidative Cyclocondensation of 3a



entry	catalyst (mol %)	temp (°C)	time (h)	**4a** yield (%)[a]
1		200	48	33
2[b]		200	48	24
3	CuI (1)	200	22	27
4	$[Cu(OTf)]_2{\cdot}PhCH_3$ (1)	180	1	49
5	$[Cu(OTf)]_2{\cdot}PhCH_3$ (1)	150	30	9
6	$[Cu(OTf)]_2{\cdot}PhCH_3$(0.1)	180	9	18
7	$[Cu(OTf)]_2{\cdot}PhCH_3$ (1)	200	2	81
8	$[Cu(OTf)]_2{\cdot}C_6H_6$(1)	200	2	82 (78)[c]

[a]NMR yields, which were calculated by ^{19}F NMR integration of products **3a** relative to the internal standard of ethyl 2,2,2-trifluoroacetate. [b]Triglyme was used as a solvent. [c]The values in parentheses indicate the isolated yields of **3a**.

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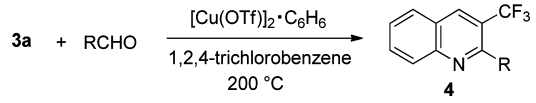
discernible improvement in the yield of the reaction, although the reaction profile became much cleaner with the generation of byproducts being significantly suppressed.

These results suggested that a copper(I) salt could be used as a competent catalyst for the reaction. The use of $[Cu(OTf)]_2 \cdot PhCH_3$, which had superior solubility in the solvent, had a significant impact on the reaction, with **4a** being isolated in a 49% yield when the mixture was heated for 1 h at 180 °C (Table 2, entry 4). An attempt to conduct the reaction under the same conditions, but at a lower temperature of 150 °C or using $[Cu(OTf)]_2 \cdot PhCH_3$ as a catalyst, led to a reduction in the yields of **4a** to 9 and 18%, respectively. The optimal conditions for the transformation were determined according to the experiments shown in Table 2, entries 7 and 8. Interestingly, no discernible difference was observed between the use of the toluene and benzene complexes of copper(I) triflate. Although the precise role of the copper(I) salt remained unclear from a mechanistic perspective, the salt clearly provided a significant level of activation to the reaction, even under a heavily deoxygenated atmosphere. With this in mind, we hypothesized that the copper(I) salt may be actively involved in promoting both the cyclization of the benzylidene aniline intermediate and the subsequent dehydrogenation reaction.

With the optimal conditions in hand, we proceeded to explore the scope of the reaction toward the aldehyde component. A series of different aldehydes were subjected to the optimal reaction conditions (Table 3). The use of aryl aldehydes bearing electron-donating groups at their *para*-position appeared to accelerate the reaction (Table 3, entries 1 and 3). In contrast, the use of aryl aldehydes bearing *ortho*-substituents had an adverse impact on the reaction because of the steric hindrance provided by the substituents, and extended reaction times were required to provide **4** in good yield (Table 3, entries 2 and 4). When aryl aldehydes bearing electron-withdrawing groups at the *ortho*-, *meta*-, or *para*-positions were subjected to the optimal conditions, the products **4** were isolated in relatively lower yields (Table 3, entries 5–8). Pleasingly, the optimal conditions were tolerant of polycyclic and heteroaromatic aldehydes, with naphthaldehyde and 2-furylaldehyde proceeding smoothly through the reaction (Table 3, entries 9 and 10). Unfortunately, aliphatic aldehydes were found to be unsuitable for this reaction (Table 3, entries 11 and 12). In the case of aliphatic aldehydes, the reactions became messy and many byproducts were observed probably due to the concomitant aldol-type reaction.

Table 3. Investigation of the Scope of the Oxidative Cyclocondensation of 3a with a Variety of Different Aldehydes

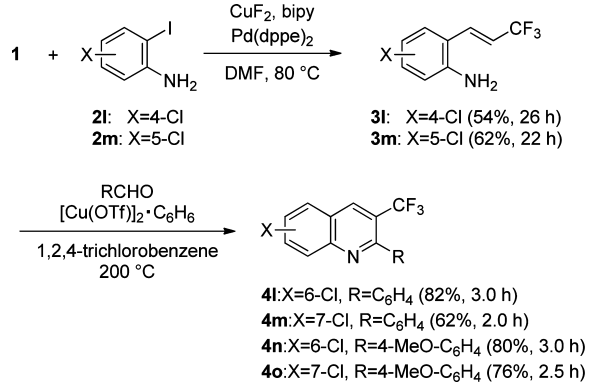


entry[a]	R	time (h)	4	yield (%)[b,c]
1	4-Me−C_6H_4	1.0	**4b**	76 (74)
2	2-Me−C_6H_4	3.0	**4c**	74 (68)
3	4-MeO−C_6H_4	2.0	**4d**	88 (65)
4	2-MeO−C_6H_4	3.5	**4e**	82 (78)
5	4-Cl−C_6H_4	2.0	**4f**	69 (63)
6	3-Cl−C_6H_4	1.5	**4g**	56 (44)
7	2-Cl−C_6H_4	2.0	**4h**	67 (47)
8	4-Br−C_6H_4	2.5	**4i**	64 (52)
9	2-naphthyl	2.0	**4j**	69 (50)
10	2-furyl	1.5	**4k**	44 (37)
11	2-phenylethyl	2.0		
12	benzyl	2.0		

[a]Reaction was conducted with **3a** (0.2 mmol) and $[Cu(OTf)]_2 \cdot C_6H_6$ (0.2 mmol). [b]NMR yields, which were calculated by ^{19}F NMR integration of products **4** relative to the internal standard of ethyl 2,2,2-trifluoroacetate. [c]The values in parentheses indicate the isolated yields of **4**.

With the optimized conditions in hand for the sequential synthesis of several different classes of 2-aryl-3-trifluoromethylquinolines, we proceeded to expand upon the utility of this reaction to deliver other 2-aryl-3-trifluoromethylquinolines functionalized at a benzene ring. To date, direct functionalization of quinolines was attained regioselectively at the 5- or 8-position; however, it becomes quite difficult to functionalize quinolines at the 6- or 7-position regioselectively.[10,11] In this view, we proceeded to apply our reaction to the synthesis of a series of 6- and 7-chloro-3-trifluoromethylquinolines (Scheme 2). These compounds were particularly interesting because they could be further derivatized through the functionalization of the chlorine atom. The first Hiyama cross-coupling reactions with **2l** and **2m** were performed according to the conditions used in Table 1, entry 9. Both of the reactions proceeded efficiently to give **3l** and **3m** in good yields. These compounds were subsequently cyclized according to the optimized condition with benzaldehyde and 4-methoxybenzaldehyde to give the desired products **4l–o** in good yields.

Scheme 2. Construction of 2-Aryl-3-trifluoromethylquinolines via a Sequential Hiyama Cross-Coupling[a,b] and Oxidative Cyclocondensation[b,c] Reaction Process To Give the Corresponding 6- and 7-Chloro-3-trifluoromethylquinolines



[a]Reaction was performed in the condition according to entry 9 in Table 1. [b]Isolated yield. [c]Reaction was conducted with **3** (0.2 mmol) and $[Cu(OTf)]_2 \cdot C_6H_6$ (0.2 mmol).

CONCLUSION

In conclusion, we have successfully synthesized a series of 2-aryl-3-trifluoromethylquinolines according to a sequential Hiyama cross-coupling and oxidative cyclocondensation reaction process. This process provides facile access to the 2-aryl-3-trifluoromethylquinoline core, which would otherwise be difficult to access according to existing techniques. We hope this synthetic process will provide chemists with the opportunity to synthesize a new library of 3-trifluoromethyl-

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quinolines, which may make an important contribution to future drug discovery projects.

EXPERIMENTAL SECTION

General Information. All experiments were carried out under an argon atmosphere in flame-dried glassware using standard inert techniques for introducing reagents and solvents, unless otherwise noted. *N,N*-Dimethylformamide (DMF) was distilled over calcium hydride and stored in a bottle with activated molecular sieves (4 Å). All commercially available materials were used as received without further purification. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a commercial measurement device at 400 and 600 MHz. An ^{19}F NMR spectrum was recorded at room temperature on a commercial measurement device at 90 and 600 MHz. Chemical shifts of ^{1}H NMR and ^{13}C NMR are reported in parts per million from tetramethylsilane (TMS), used as an internal standard. Chemical shifts of ^{19}F NMR are reported in parts per million from ethyl 2,2,2-trifluoroacetate, used as an internal standard. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, br = broad, brd = broad-doublet, m = multiplet), and coupling constants (Hz). High-resolution mass spectroscopy (HRMS) experiments were performed with a double-focusing mass spectrometer with EI. Melting points are not corrected.

Typical Procedure for Hiyama Cross-Coupling Reaction. In a glovebox purged with argon gas, bis[1,2-bis(diphenylphosphino)-ethane]palladium(0) (0.010 mmol), CuF_2 (0.4 mmol), and 2,2′-bipyridyl (0.4 mmol) were placed in a flask. To the flask were added anhydrous DMF (1.2 mL), 2-iodoaniline **2a** (0.2 mmol), and **1** (0.4 mmol), and the mixture was stirred at 80 °C. After the reaction mixture was stirred for about 20 h, it was poured into ice water. The mixture was extracted with Et_2O, and the organic layer was dried over anhydrous $MgSO_4$. After the solid was filtered, the solvent was removed in vacuo, and the residue was purified by silica gel column chromatography to give **3**.

*(E)-2-(3,3,3-Trifluoroprop-1-en-1-yl)aniline (**3a**).*[12] The title product (**3a**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 81% yield (30.3 mg). A colorless solid: mp 48−49 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 3.81 (2H, br), 6.14 (1H, qd, J = 6.4, 15.9 Hz), 6.72 (1H, dd, J = 1.3, 7.9 Hz), 6.80 (1H, dt, J = 1.2, 7.3 Hz), 7.18 (1H, dt, J = 1.5, 7.6 Hz), 7.25 (1H, qd, J = 2.1, 15.8 Hz), 7.29 (1H, dd, J = 1.5, 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.2 (q, J = 33.4 Hz), 116.7, 119.2, 119.4, 123.5 (q, J = 268.5 Hz), 127.9, 130.8, 133.3 (q, J = 6.7 Hz), 144.7; ^{19}F NMR (90 MHz, $CDCl_3$) δ 12.13 (3F, d, J = 4.7 Hz); MS m/z 187 (M^+); HRMS calcd for $C_9H_8F_3N$ 187.061 (M^+), found 187.061.

*(E)-4-chloro-2-(3,3,3-trifluoroprop-1-en-1-yl)aniline (**3l**).* The title product (**3l**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 54% yield (23.9 mg). A colorless solid: mp 43−44 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 3.88 (2H, br), 6.11 (1H, qd, J = 6.4, 15.9 Hz), 6.72 (1H, d, J = 1.8 Hz), 6.76 (1H, dd, J = 1.5, 8.6 Hz), 7.16 (1H, qd, J = 1.9, 15.9 Hz), 7.20 (1H, d, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.3, 117.0 (q, J = 33.3 Hz), 117.7, 119.3, 123.3 (q, J = 267.7 Hz), 129.0, 132.3 (q, J = 7.5 Hz), 136.4, 145.6; ^{19}F NMR (90 MHz, $CDCl_3$) δ 12.03 (3F, d, J = 6.2 Hz); MS m/z 221 (M^+); HRMS calcd for $C_9H_7ClF_3N$ 221.022 (M^+), found 221.022.

*(E)-5-chloro-2-(3,3,3-trifluoroprop-1-en-1-yl)aniline (**3m**).* The title product (**3m**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 62% yield (27.4 mg). A colorless solid: mp = 48−50 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 3.81 (2H, br), 6.14 (1H, qd, J = 6.4, 15.8 Hz), 6.66 (1H, d, J = 8.5 Hz), 7.13 (1H, dd, J = 2.4, 8.9 Hz), 7.17 (1H, dd, J = 2.2, 16.5 Hz), 7.26 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 117.8 (q, J = 34.2 Hz), 117.9, 120.6, 123.2 (q, J = 268.5 Hz), 123.9, 127.3, 130.6, 132.1 (q, J = 6.6 Hz), 143.2; ^{19}F NMR (90 MHz, $CDCl_3$) δ 11.89 (3F, d, J = 6.2 Hz); MS m/z 221 (M^+); HRMS calcd for $C_9H_7ClF_3N$ 221.022 (M^+), found 221.023.

Typical Procedure for Oxidative Cyclocondensation of 3 to 4. In a glovebox purged with argon gas, the copper(I) triflate benzene complex (0.2 mmol) was placed in a flask. To the flask were added **3** (0.2 mmol), aryl aldehyde (0.2 mmol), and 1,2,4-trichlorobenzene (2.0 mL), and the mixture was stirred at 200 °C. After the flask was stirred for the appropriate time listed in Table 3, the reaction mixture was poured into ice water. If precipitate emerged, it was removed through a pad of Celite. The whole mixture was extracted with Et_2O, and the organic layer was dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated in vacuo, and the residue was purified by silica gel column chromatography to give **4**.

*2-Phenyl-3-(trifluoromethyl)quinoline (**4a**).* The title product (**4a**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 78% yield (42.6 mg). A colorless solid: mp = 82−83 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 7.45−7.52 (3H, m), 7.54−7.61 (2H, m), 7.63−7.71 (1H, m), 7.84−7.90 (1H, m), 7.97 (1H, d, J = 7.9 Hz), 8.21 (1H, d, J = 8.5 Hz), 8.61 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.8 (q, J = 31.7 Hz), 123.6 (q, J = 272.7 Hz), 125.3, 127.7, 127.9, 128.2, 128.7 (q, J = 1.6 Hz), 128.7, 129.5, 132.0, 135.8 (q, J = 5.0 Hz), 139.6, 148.3, 157.2; ^{19}F NMR (90 MHz, $CDCl_3$) δ 18.11 (3F, s); MS m/z 273 (M^+); HRMS calcd for $C_{16}H_{10}F_3N$ 273.077 (M^+), found 273.076.

*2-(p-Tolyl)-3-(trifluoromethyl)quinoline (**4b**).* The title product (**4b**) was purified by column chromatography (hexane 100%) and was obtained in 74% yield (42.5 mg). A colorless oil;: ^{1}H NMR ($CDCl_3$) δ 2.44 (3H, s), 7.29 (2H, d, J = 8.0 Hz), 7.48 (2H, d, J = 7.9 Hz), 7.63−7.68 (1H, m), 7.83−7.89 (1H, m), 7.96 (1H, d, J = 8.0 Hz), 8.20 (1H, d, J = 8.5 Hz), 8.59 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 122.8 (q, J = 30.8 Hz), 123.6 (q, J = 272.7 Hz), 125.2, 127.6, 128.2, 128.6 (q, J = 1.7 Hz), 128.6, 129.5, 131.9, 135.8 (q, J = 5.8 Hz), 136.8, 138.6, 148.4, 157.6; ^{19}F NMR (90 MHz, $CDCl_3$) δ 18.09 (3F, s); MS m/z 287 (M^+); HRMS calcd for $C_{17}H_{12}F_3N$ 287.092 (M^+), found 287.092.

*2-(o-Tolyl)-3-(trifluoromethyl)quinoline (**4c**).* The title product (**4c**) was purified by column chromatography (AcOEt/hexane = 5:95) and was obtained in 84% yield (186 mg). A colorless solid: mp = 90−92 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 2.09 (3H, s), 7.26−7.40 (4H, m), 7.66−7.91 (1H, m), 7.85−7.91 (1H, m), 7.99 (1H, d, J = 7.7 Hz), 8.21 (1H, d, J = 8.6 Hz), 8.62 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 123.2 (q, J = 30.9 Hz), 123.4 (q, J = 272.6 Hz), 125.0, 125.3, 127.8, 128.3, 128.6 (q, J = 1.6 Hz), 128.7, 129.5, 130.0, 131.9, 135.5 (q, J = 5.0 Hz), 136.1, 138.4, 148.4, 157.4; ^{19}F NMR (90 MHz, $CDCl_3$) δ 15.71 (3F, s); MS m/z 287 (M^+); HRMS calcd for $C_{17}H_{12}F_3N$ 287.092 (M^+), found 287.092.

*2-(4-Methoxyphenyl)-3-(trifluoromethyl)quinoline (**4d**).* The title product (**4d**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 65% yield (39.4 mg). A colorless solid: mp = 103−104 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 7.02 (2H, d, J = 8.9 Hz), 7.55 (2H, d, J = 8.8 Hz), 7.63−7.68 (1H, m), 7.84−7.89 (1H, m), 7.96 (1H, d, J = 7.9 Hz), 8.20 (1H, d, J = 8.2 Hz), 8.59 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 113.5, 122.8 (q, J = 31.7 Hz), 123.8 (q, J = 271.9 Hz), 125.2, 127.5, 128.2, 129.5, 130.1 (q, J = 1.7 Hz), 131.9, 132.2, 135.9 (q, J = 5.8 Hz), 148.4, 156.9, 160.1; ^{19}F NMR (90 MHz, $CDCl_3$) δ 18.13 (3F, s); MS m/z 303 (M^+); HRMS calcd for $C_{17}H_{12}F_3NO$ 303.087 (M^+), found 303.088.

*2-(2-Methoxyphenyl)-3-(trifluoromethyl)quinoline (**4e**).* The title product (**4e**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 78% yield (47.3 mg). A colorless solid: mp = 115−118 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 3.86 (3H, s), 7.00−7.19 (3H, m), 7.39 (1H, t, J = 7.9 Hz), 7.67 (1H, t, J = 7.4 Hz), 7.87 (1H, t, J = 7.6 Hz), 7.97 (1H, d, J = 8.0 Hz), 8.22 (1H, d, J = 8.6 Hz), 8.60 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 114.3, 114.8, 121.2, 122.8 (q, J = 30.9 Hz), 123.5 (q, J = 272.7 Hz), 125.3, 127.7, 128.2, 129.0, 129.6, 132.0, 135.8 (q, J = 5.0 Hz), 140.8, 148.3, 156.9, 159.1; ^{19}F NMR (90 MHz, $CDCl_3$) δ 15.18 (3F, s); MS m/z 303 (M^+); HRMS calcd for $C_{17}H_{12}F_3NO$ 303.087 (M^+), found 303.087.

*2-(4-Chlorophenyl)-3-(trifluoromethyl)quinoline (**4f**).* The title product (**4f**) was purified by column chromatography (AcOEt/hexane

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= 1:9) and was obtained in 63% yield (38.7 mg). A colorless solid: mp = 118−120 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 7.47 (2H, d, J = 8.5 Hz), 7.53 (2H, d, J = 8.6 Hz), 7.68 (1H, t, J = 7.7 Hz), 7.88 (1H, t, J = 8.3 Hz), 7.97 (1H, d, J = 8.2 Hz), 8.20 (1H, d, J = 8.5 Hz), 8.61 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.7 (q, J = 31.7 Hz), 123.6 (q, J = 271.9 Hz), 125.3, 128.0, 128.2, 129.5, 130.1, 132.2, 135.0, 136.0 (q, J = 5.0 Hz), 138.0, 148.4, 155.9; ^{19}F NMR (90 MHz, $CDCl_3$) δ 1818 (3F, s); MS m/z 307 (M^+); HRMS calcd for $C_{16}H_9ClF_3N$ 307.038 (M^+), found 307.037.

*2-(3-Chlorophenyl)-3-(trifluoromethyl)quinoline (**4g**).* The title product (**4g**) was purified by column chromatography (AcOEt/hexane = 5:95) and was obtained in 44% yield (27.0 mg). A colorless solid: mp = 82−83 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 7.38−7.51 (3H, m), 7.59 (1H, s), 7.70 (1H, t, J = 8.0 Hz), 7.90 (1H, t, J = 8.2, Hz), 7.99 (1H, d, J = 8.0 Hz), 8.21 (1H, d, J = 8.3 Hz), 8.63 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.6 (q, J = 31.7 Hz), 123.4 (q, J = 272.6 Hz), 125.4, 126.9 (q, J = 1.7 Hz), 128.1, 128.3, 128.9, 129.0 (q, J = 1.7 Hz), 129.2, 129.5, 132.3, 134.0, 136.0 (q, J = 5.0 Hz), 141.1, 148.3, 155.5; ^{19}F NMR (90 MHz, $CDCl_3$) δ 18.15 (3F, s); MS m/z 307 (M^+); HRMS calcd for $C_{16}H_9ClF_3N$ 307.038 (M^+), found 307.038.

*2-(2-Chlorophenyl)-3-(trifluoroethyl)quinoline (**4h**).* The title product (**4h**) was purified by column chromatography (hexane 100%) and was obtained in 47% yield (28.9 mg). A colorless solid: mp = 87−89 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 7.33−7.46 (3H, m), 7.51 (1H, d, J = 7.3 Hz), 7.70 (1H, m), 7.89 (1H, m), 8.00 (1H, d, J = 8.2 Hz), 8.23 (1H, d, J = 8.6 Hz), 8.62 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.1 (q, J = 31.6 Hz), 123.2 (q, J = 271.8 Hz), 125.6, 126.2, 128.1, 128.3, 129.4, 129.6, 130.0, 130.2, 132.1, 133.2, 135.6 (q, J = 5.0 Hz), 137.7, 148.3, 154.6; ^{19}F NMR (90 MHz, $CDCl_3$) δ 15.64 (3F, s); MS m/z 307 (M^+); HRMS calcd for $C_{16}H_9ClF_3N$ 307.038 (M^+), found 307.037.

*2-(4-Bromophenyl)-3-(trifluoromethyl)quinoline (**4i**).* The title product (**4i**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 52% yield (36.6 mg). A colorless solid: mp = 113−115 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 7.47 (2H, d, J = 8.3 Hz), 7.63 (2H, d, J = 8.5 Hz), 7.67−7.72 (1H, m), 7.86−7.92 (1H, m), 7.98 (1H, d, J = 8.3 Hz), 3275.9 (1H, J = 8.6 Hz), 8.62 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.6 (q, J = 31.7 Hz), 123.3, 123.6 (q, J = 272.7 Hz), 125.3, 128.0, 128.3, 129.5, 130.4 (q, J = 1.7 Hz), 131.2, 132.2, 136.0 (q, J = 5.8 Hz), 138.4, 148.3, 155.9; ^{19}F NMR (90 MHz, $CDCl_3$) δ 18.20 (3F, s); MS m/z 352 (M^+); HRMS calcd for $C_{16}H_9BrF_3N$ 350.987 (M^+), found 350.988.

*2-(Naphthalen-2-yl)-3-(trifluoromethyl)quinoline (**4j**).* The title product (**4j**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 50% yield (32.3 mg). A colorless solid: mp = 94−97 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 7.50−7.58 (2H, m), 7.64−7.74 (2H, m), 7.84−8.03 (5H, m), 8.07 (1H, s), 8.24 (1H, d, J = 9.2 Hz), 8.65 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.0 (q, J = 31.7 Hz), 123.7 (q, J = 272.6 Hz), 125.3, 126.3, 126.6, 127.7, 127.8, 128.2, 128.3, 128.5, 129.6, 132.0, 132.8, 133.3, 135.9 (q, J = 5.8 Hz), 137.0, 148.4, 157.1; ^{19}F NMR (90 MHz, $CDCl_3$) δ 18.24 (3F, s); MS m/z 323 (M^+); HRMS calcd for $C_{20}H_{12}F_3N$ 323.092 (M^+), found 323.092.

*2-(Furan-2-yl)-3-(trifluoromethyl)quinoline (**4k**).* The title product (**4k**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 37% yield (19.5 mg). A colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.61 (1H, dd, J = 1.8, 3.4 Hz), 7.25 (1H, d, J = 3.3 Hz), 7.62 (1H, t, J = 7.7 Hz), 7.70 (1H, d, J = 1.2 Hz), 7.82−7.88 (1H, m), 7.91 (1H, d, J = 8.2 Hz), 8.19 (1H, d, J = 8.5 Hz), 8.59 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.9, 113.4 (q, J = 2.5 Hz), 120.5 (q, J = 32.5 Hz), 123.5 (q, J = 271.8 Hz), 125.0, 127.7, 128.2, 129.3, 132.1, 136.5, (q, J = 6.7 Hz), 144.6, 145.5, 148.4, 151.0; ^{19}F NMR (90 MHz, $CDCl_3$) δ 15.45 (3F, s); MS m/z 263 (M^+); HRMS calcd for $C_{14}H_8F_3NO$ 263.056 (M^+), found 263.056.

*6-Chloro-2-phenyl-3-(trifluoromethyl)quinoline (**4l**).* The title product (**4l**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 82% yield (50.3 mg). A colorless solid: mp = 82−83 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 7.44−7.63 (5H, m), 7.80 (1H, dd, J = 2.4, 8.9 Hz), 8.96 (1H, d, J = 2.2 Hz), 8.15 (1H, d, J = 8.9 Hz), 8.52 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.4 (q, J = 272.7 Hz), 123.7 (q, J = 32.5 Hz), 125.9, 126.8, 128.0, 128.6, 128.9, 131.1, 133.0, 133.6, 134.9 (q, J = 5.9 Hz), 139.1, 146.7, 157.4; ^{19}F NMR (90 MHz, $CDCl_3$) δ 17.91 (3F, s); MS m/z 307 (M^+); HRMS calcd for $C_{16}H_9ClF_3N$ 307.038 (M^+), found 307.038.

*7-Chloro-2-phenyl-3-(trifluoromethyl)quinoline (**4m**).* The title product (**4m**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 62% yield (38.1 mg). A colorless solid: mp = 87−88 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 7.47−7.59 (5H, m), 7.63 (1H, dd, J = 2.2, 8.9 Hz), 7.91 (1H, d, J = 8.5 Hz), 8.22 (1H, d, J = 1.8 Hz), 8.58 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.0 (q, J = 31.7 Hz), 123.4 (q, J = 272.6 Hz), 123.6, 128.0, 128.6, 128.6, 128.9, 128.9, 129.4, 135.7 (q, J = 5.0 Hz), 138.2, 139.1, 148.6, 158.3; ^{19}F NMR (90 MHz, $CDCl_3$) δ 18.04 (3F, s); MS m/z 307 (M^+); HRMS calcd for $C_{16}H_9ClF_3N$ 307.038 (M^+), found 307.038.

*6-Chloro-2-(4-methoxyphenyl)-3-(trifluoromethyl)quinoline (**4n**).* The title product (**4n**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 80% yield (53.9 mg). A colorless solid: mp = 127−129 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 7.02 (2H, d, J = 8.8 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.79 (1H, dd, J = 2.4, 9.2 Hz), 7.94 (1H, d, J = 2.2 Hz), 8.13 (1H, d, J = 8.8 Hz), 8.50 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 113.6, 123.5 (q, J = 272.7 Hz), 123.7 (q, J = 31.7 Hz), 125.7, 126.7, 130.1, 131.0, 131.7, 132.9, 133.4, 135.0 (q, J = 5.0 Hz), 146.8, 157.1, 160.2; ^{19}F NMR (90 MHz, $CDCl_3$) δ 17.94 (3F, s); MS m/z 337 (M^+); HRMS calcd for $C_{17}H_{11}ClF_3NO$ 337.048 (M^+), found 337.047.

*7-Chloro-2-(4-methoxyphenyl)-3-(trifluoromethyl)quinoline (**4o**).* The title product (**4o**) was purified by column chromatography (AcOEt/hexane = 1:9) and was obtained in 76% yield (51.2 mg). A colorless solid: mp = 113−114 °C (recrystallized from dichloromethane and hexane); ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 7.02 (2H, d = 8.9 Hz), 7.54 (2H, d, J = 8.5 Hz), 7.57−7.62 (1H, m), 7.88 (1H, d, J = 8.5 Hz), 8.19 (1H, s), 8.56 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 113.6, 123.0 (q, J = 31.7 Hz), 123.5, 123.6 (q, J = 271.8 Hz), 128.5, 128.7, 129.3, 130.1 (q, d = 1.7 Hz), 131.8, 135.7 (q, J = 5.8 Hz), 138.1, 148.8, 158.0, 160.3; ^{19}F NMR (90 MHz, $CDCl_3$) δ 18.09 (3F, s); MS m/z 337 (M^+); HRMS calcd for $C_{17}H_{11}ClF_3NO$ 337.048 (M^+), found 337.047.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C spectra for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: aando@pharm.setsunan.ac.jp. Tel: +81-72-866-3140. Fax: +81-72-850-7020.

Notes

The authors declare no competing financial interest.

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