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One-Pot Synthesis of 3-Fluoro-4-(trifluoromethyl)quinolines from Pentafluoropropen-2-ol and Their Molecular Modification

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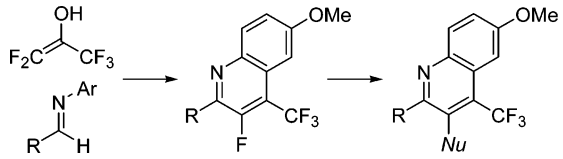

Pentafluoropropen-2-ol (PFP) was prepared by the reaction of hexafluoroacetone (HFA) with Mg/TMSCl. The one-pot tandem sequential reactions of PFP via Mannich addition with aldimines followed by Friedel−Crafts cyclization and aromatization afforded the title quinolines. A variety of corresponding 3-substituted quinolines were derived from the title quinoline by nucleophilic substitution of 3-fluorine with nucleophiles. A defluorinative transformation of the 4-trifluoromethyl group of the title quinoline with hydrazine afforded pyrazoloquinoline.

Introduction

Due to their unique bioactivities, quinolines often have been regarded as leading pharmaceutical compounds.[1−3] Among them, fluoroalkylated quinolines often exhibit interesting bioactivities, thus they have been developed as drugs, such as Mefloquine.[2,3] Because of less availability of fluorinated organic starting materials, full survey of the quantitative structure−activity relationship (QSAR) of fluoroalkylated quinolines has not been addressed systematically yet. Thus, development of a new synthetic method for fluorine-functionalized quinolines which possess functionalities necessary for both potential bioactivity and further functional group modification toward target molecules has remained a subject for active research.

From this viewpoint, it is useful to design fluorine-functionalized quinolines which can be diversely and systematically transformed to highly functionalized quinolines. One of the common structures feasible for the desired quinolines would be fluoroalkylated haloquinolines.[4] Halogen on an aromatic ring could be replaced with other functional groups, for instance, nucleophiles by nucleophilic substitution,[5] aryl and alkenyl groups by transition metal-catalyzed cross-coupling reactions,[6] metal species by halogen−metal exchange,[7] etc. In particular, it has been recognized recently that fluorine is the most useful halogen for nucleophilic substitution on an aromatic ring since fluorine activates α-carbon and greatly accelerates the initial addition step for the nucleophilic substitution.[8] Based on the background, it is interestingly to see the possibility of

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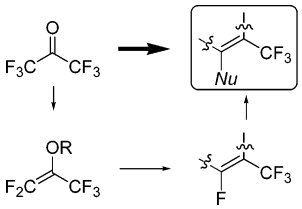
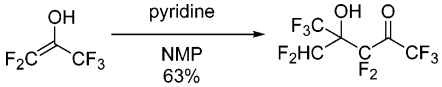
SCHEME 1. Transformation of CF_3 of HFA



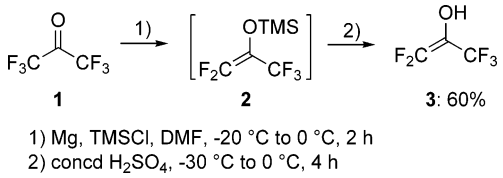
SCHEME 2. C−C Bond Formation of PFP at C-2



incorporation of hexafluoroacetone (HFA) into the functionalized quinoline skeleton where one of the trifluoromethyl groups of HFA is transformed into the substituted C3-carbon moiety of quinoline via successive defluorination reactions as shown in Scheme 1.

On this basis, one of the subjects of the research would be C−C bond formation of pentafluoropropen-2-ol (PFP) at the C2-carbon with aldimines which would lead subsequently to the skeleton of 3-fluoro-4-(trifluoromethyl)quinolines. The PFP is expected to be one of the very promising building blocks for trifluoromethylated compounds since the difluoromethylene carbon of PFP would be not only electrophilic but also nucleophilic due to an enol form of pentafluoroacetone.[9] And its hydroxyl group would be acidic enough to promote acid-catalyzed reactions since the pK_a of PFP was reported to be about 4.[10b] However, very few applications of PFP for the synthesis of fluorinated molecules have been reported.[11] So far, there has been only one report on the reaction of PFP at the C2-carbon (self-condensation of two molecules of PFP resulting in the formation of 4-hydroxy-4-difluoromethyloctafluoro-2-pentanone (Scheme 2)),[11f] presumably because PFP has been less available since it was prepared by acid hydrolysis from perfluoroisopropenyl phosphate or perfluoropropenyl ether intermediates, which were derived from perfluoroisobutene (PFIB), an extremely toxic and volatile alkene.[9,12] PFP could also be prepared from triethylsilyl pentafluoropropen-2-olate by acid-catalyzed desilylation. However, the preparation of the triethylsilyl enol ether from hexafluoroisopropanol (HFIP) requires rather expensive reagents: 2 equiv of *n*-butyllithium and triethylsilyl chloride (TESCl).[13] Thus, the development of a conventional preparation of PFP is also one of the objectives of the present study.

SCHEME 3. Synthesis of PFP



Reductive C−F bond activation of trifluoromethyl group attached to a π-system such as carbonyl, iminyl, alkenyl, and aromatic groups is quite easy since the π-system accepts two electrons from metal magnesium into its low LUMO so as to extrude a fluoride ion from the trifluoromethyl group.[14] This fact suggests that PFP **3** could be prepared by the well-known Mg-promoted defluorination of an available hexafluoroacetone (HFA) **1** followed by acid-catalyzed desilylation of trimethylsilyl pentafluoropropen-2-olate **2**.

Here, we describe three subjects: (1) a facile preparation of **2** and PFP **3** from HFA **1**, (2) one-pot synthesis of 3-fluoro-4-(trifluoromethyl)quinolines from **3** via tandem Mannich addition/Friedel−Crafts cyclization/aromatization sequence, and (3) defluorinative transformation of the 3-fluoroquinoline to 3-substituted quinolines.

Results and Discussion

Preparation of PFP. The Mg-promoted defluorination reaction is so moisture sensitive that a dry reaction condition is required. Thus, dried gaseous HFA **1** was generated by the reaction of commercially available HFA-trihydrate with concd H_2SO_4, and again dried through concd H_2SO_4.[15] Then, the dry HFA was bubbled into dimethylformamide (DMF) on cooling the solution at −20 °C. Defluorination of HFA **1** proceeded smoothly in the DMF (0.25 M) solution of Mg (4 equiv) and TMSCl (4 equiv) at −20 °C. The defluorination gave silyl enol ether **2** in 80% yield along with hexafluoroisopropanol (HFIP) and the trimer of HFA in 3% and 5% yields, respectively, which were determined by ^{19}F NMR (Scheme 3). The volatile products were separated from DMF solution by distillation under reduced pressure. Then, subsequent desilylation was repeated twice by distillation of **2** over concd H_2SO_4 and the product was distilled in vacuo at 0 °C and trapped into a glass tube cooled in liquid nitrogen. Consequently, the PFP **3** was obtained in 60% yield from HFA trihydrate, which contained trimethylsilylfluoride (TMSF) and a trace amount of HFIP as impurities. These impurities did not hinder subsequent Mannich reaction and provided almost the same results as those obtained with 95% pure PFP prepared from triethylsilyl pentafluoropropen-2-olate.[16]

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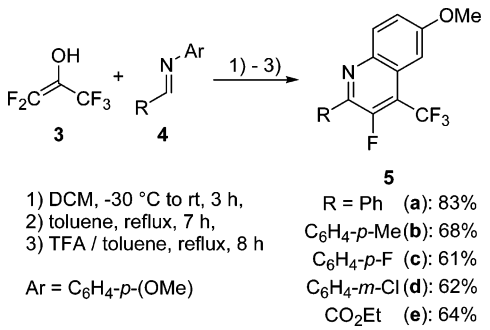
(16) The 95% pure PFP was prepared from triethylsilyl pentafluoropropen-2-olate.[13] The PFP with aldimine **4a** afforded the Mannich product quantatively (detemied by ^{19}F NMR analysis).

SCHEME 4. One-Pot Synthesis of 3-Fluoro-4-(trifluoromethyl)quinoline



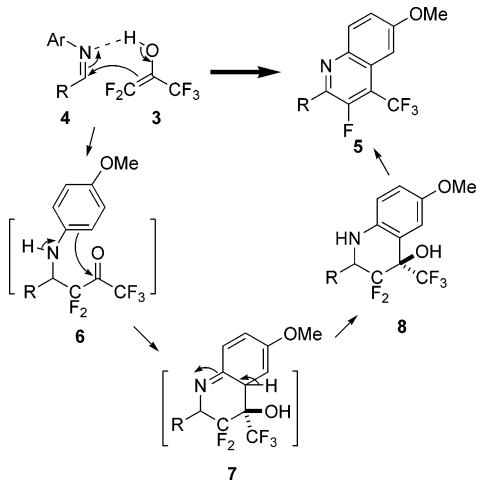
Thus, the PFP **3** was used without further purification for the following quinoline synthesis.[17]

Synthesis of Quinolines. The Mannich reaction of aldimines with silyl enol ether generally needs Lewis acid or Brønsted acid catalysts.[18] Interestingly, the reaction of the enol **3** with aldimines **4** did not need any acid catalyst. The C−C bond formation occurred spontaneously just by mixing the enol **3** with aldimines **4** in dichloromethane (DCM) and completed within 4 h at room temperature. However, intramolecular Friedel−Crafts cyclization of **6** to tetrahydroquinoline **8** via **7** required higher temperature for completion. Thus, DCM solvent was exchanged to toluene and the toluene solution was refluxed for 7 h. Aromatization of tetrahydroquinoine **8** via dehydration and dehydrofluorination successfully proceeded under trifluoroacetic acid (TFA) catalysis in refluxing toluene. Use of *p*-toluenesulfonic acid (TsOH), boron trifluoride diethyl etherate (BF_3•OEt_2), trifluoroacetic acid anhydride (TFAA), or TFAA/pyridine complex resulted in unsuccessful aromatization of tetrahydroquinoline **8**. Consequently, one-pot synthesis via three sequential reactions gave quinolines **5** from the PFP **3** and aromatic aldimines **4a**−**d** bearing an *N*-(4-methoxyphenyl) (PMP) group in reasonable yields: 83% (**5a**), 68% (**5b**), 61% (**5c**), and 62% (**5d**), respectively (Scheme 4).

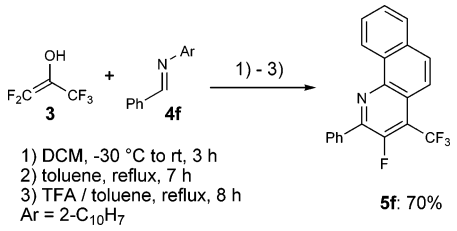
To widen the scope of the one-pot reaction, the reaction of PFP with alkyl aldimine (R = CH_3) was examined. Because the aldimine with R = CH_3 was difficult to isolate, the aldimine was used after preparation in situ for the present one-pot reaction.[19] However, the reaction did not give a desired quinoline with R = CH_3. Meanwhile, the reaction of PFP and aldimine **4e** of ethyl glyoxalate gave the quinoline **5e** in 64% yield.

A step-by-step ^{19}F NMR analysis of the intermediates suggested a mechanism of the one-pot quinoline synthesis (Scheme 5). First, Mannich adduct **6** would be formed. The intermediates **6** and its hydrate would be converted via intermediate **7** into tetrahydroquinoline **8** on heating at the reflux temperature of toluene. Subsequently, tetrahydroquinoline **8** would undergo acid-catalyzed dehydration and dehydrofluorination to be converted into quinoline **5a** as a final product (see details in the Experimental Section).

SCHEME 5. Plausible Reaction Mechanism



SCHEME 6. Application of the Reaction to Benzo[*h*]quinoline



Benzo[*h*]quinoline possesses an important skeleton for potential inhibiting activity.[3b] Thus, the same reaction of aldimine **4f** with an *N*-(2-naphthyl) group was examined. Benzo[*h*]-quinoline **5f** was obtained in 70% yield by the same one-pot procedure (Scheme 6).

Reaction of Quinoline. Replacements of the 3-fluorine of quinoline **5** with nucleophiles were examined. It is well-known that fluorine is the most reactive among halogens attached to an aromatic ring on being subjected to nucleophilic substitution. For instance, the enolate of ethyl cyanoacetate substitutes the fluorine of 3-chloro-5-fluorobromobenzene exclusively to give ethyl dihalophenylcyanoacetate.[21] Therefore, the fluorine atom on C3 of quinolines **5** must be reactive enough for nucleophilic substitution due to the additional activation by the 4-trifluoromethyl group and thus would be replaced with various nucleophiles.

Substitution of the 3-fluorine with the cyano group was conducted by the use of 0.5 equiv of tetrabutylammonium fluoride (TBAF) and 2 equiv of trimethylsilyl cyanide (TMSCN) at room temperature for 48 h (Table 1, entry 1). Although the S_NAr reaction in general requires high temperature, the cyanation of 3-fluoroquinoline **5a** occurred at room temperature. It is noteworthy that 0.5 equiv of TBAF is good enough to complete the substitution since the fluoride ion is regenerated from the substrate aromatic fluoride.[22] Results of the nucleophilic substitution of aryl fluoride **5a** by various nucleophiles are summarized in Table 1.

(17) Further purification was conducted by precise distillation for removal of TMSF, and desilylation in H_2SO_4 gave an 87% pure PFP with impurities of TMSF and HFIP on NMR in 26% yield.

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(19) (a) Nakajima, T.; Inada, T.; Igarashi, T.; Sekioka, T.; Shimizu, I. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1941−1949. (b) Oudeyer, S.; Dudot, B.; Royer, J. *Heterocycles* **2005**, *65*, 823−841. Although Mannich reactions of aldimine with R = CH_3 have been reported, they occurred on using the aldimine prepared in situ from aldehyde and aniline.

(20) X-ray crystallographic analyses of the structures of **8a** and **5a** are described in the Supporting Information.

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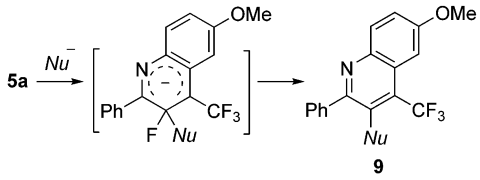
TABLE 1. Nucleophilc Substitutions of Aromatic Fluorine



entry	reagent	*Nu*	yield [%]
1	TMSCN	CN (**a**)	92
2		$OC(=CH_2)Ph$ (**b**)	71
3	NaOH	OH (**c**)	76
4	NaOEt	OEt (**d**)	99
5	KOCN	NH_2 (**e**)	70
6	NaSPh	SPh (**f**)	76
7	$NaBH_4$	H (**g**)	89

Similarly to the cyanation, all of the nucleophilic substitutions examined so far were successful: alkoxylation with silyl enol ether [CH_2═C(OTMS)Ph] in DMF (entry 2), hydroxylation with sodium hydroxide in DMF (entry 3), ethoxylation with sodium ethoxide in EtOH (entry 4), amination[23] with potassium cyanate (KOCN) in *N*-methyl-2-pyrrolidone (NMP) (entry 5), and sulfenylation with sodium thiophenoxide in DMF (entry 6). Replacement of 3-fluorine with hydrogen by the use of $NaBH_4$ in DMF (entry 7) also proceeded smoothly.[24] The quinoline **9g** is an interesting substrate since lithium−hydrogen exchange would occur easily at the ortho-position of the trifluoromethyl group by treatment with butyllithium (BuLi) and incorporation of electrophiles at the 3-carbon of quinoline **5** would provide various 3-substituted quinolines.[25]

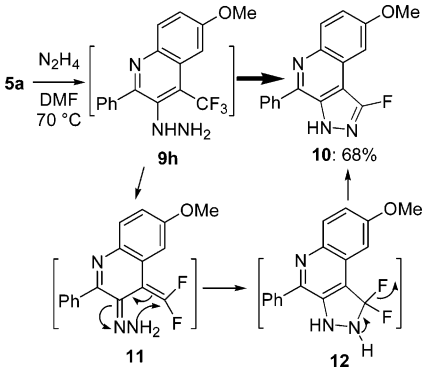
Meanwhile, nucleophilic iodination, bromination, or chlorination of the 3-fluorine has not been attained yet. The reactions with NaX, TMSX/TBAF, or ZnX_2 (X = I, Br, Cl) resulted only in recovery of starting quinoline **5a** and with CuX_2 (X = Br, Cl), BBr_3, and $AlBr_3$ gave no desired 3-haloquinoline.

The reaction of hydrazine with quinoline **5a** accompanied further substitution at the CF_3 group to give pyrazoloquinoline **10** (Scheme 7) in 68% yield. The base-catalyzed 1,4-dehydrofluorination from the *o*-trifluoromethyl group in 2-CF_3-substituted phenols, anilines, and benzylic compounds is quite facile, leading to the formation of *o*-quinone methide intermediates.[26] The successive dehydrofluorinations of **9h** via **11** and **12** resulted in pyrazole ring formation.

Conclusion

Pentafluoropropen-2-ol (PFP **3**) was prepared in 60% yield by reductive defluorination of HFA in the Mg/TMSCl/DMF system followed by acid-catalyzed desilylation of silyl enol ether

SCHEME 7. Nucleophilic Hydrazination



2. 3-Fluoro-4-(trifluoromethyl)quinolines **5** were synthesized in 83−61% yields by the one-pot sequential Mannich addition/Friedel−Crafts cyclization/aromatization reactions from PFP with aldimines. Quinoline **5** experienced further nucleophilic substitutions of 3-fluorine to give a variety of 3-substituted quinolines (**9**) in good yields. A series of 3-substituted-4-(trifluoromethyl)quinolines could be prepared from 3-fluoro-4-(trifluoromethyl)quinolines (**5**) via further transformation of the fluorine on the quinoline ring.

Experimental Section

General Procedure for the Preparation of Pentafluoropropen-2-ol (PFP) (3). Dry gaseous hexafluoroacetone (HFA) was generated by dropwise addition of HFA trihydrate (13.8 mL, 100 mmol) into concd H_2SO_4 (40 mL) at 90 °C over 1 h. Then, the gaseous HFA was dried again through concd H_2SO_4. The dry HFA gas was bubbled into the dimethylformamide (DMF) (400 mL) suspension of Mg (9.72 g, 400 mmol) and triethylsilyl chloride (TMSCl) (50.8 mL, 400 mmol) at −20 °C. After the solution was stirred for an additional 1 h, volatile products were distilled from the DMF solution at 80 °C into a glass tube cooled in liquid nitrogen under reduced pressure. Then, distilled PFP derivatives were combined with H_2SO_4 (10.2 mL) at −30 °C under an Ar atmosphere, and the solution was stirred for 0.5 h to decompose trimethylsilylated compounds. After the solution was stirred at 0 °C for an additional 1.5 h, PFP derivatives were distilled from H_2SO_4 at 0 °C. After mixing again with H_2SO_4 (10.2 mL) at −30 °C and stirring, PFP [7.1 g (58% purity), 60%] was distilled in vacuo and used for the next reactions.

1,1,3,3,3-Pentafluoropropen-2-ol (3). An authentic sample of **3** was prepared from triethylsilyl pentafluoropropen-2-olate by acid-catalyzed desilylation. Spectral data of **3** were analyzed for the authentic enol. PFP **3** from HFA was identifiable as the authentic sample by ^{19}F NMR spectra. ^1H NMR ($CDCl_3$) δ_H 3.97 (br, 1H). ^{19}F NMR ($CDCl_3$) δ_F 93.5 (dd, J = 25, 9 Hz, 3F), 66.9 (dq, J = 58, 9, 1F), 57.3 (dq, J = 58, 25 Hz, 1F). ^{13}C NMR($CDCl_3$) δ_C 153.9 (ddq, J = 295, 288, 3 Hz), 120.6 (qdd, J = 271, 9, 7 Hz), 107.3 (qdd, J = 39, 35, 25 Hz).

General Procedure for One-Pot Synthesis of Quinoline (5). A dichloromethane (DCM) (6 mL) solution of 58% pure PFP **3** (642 mg, 3 mmol) and aldimine was stirred at −30 °C for 0.5 h. Then, the mixture was stirred for 2.5 h at 0 °C. After removal of DCM under reduced pressure, the reaction mixture was dissolved in toluene (6 mL) and the toluene solution was refluxed for 7 h. Then, trifluoroacetic acid (TFA) (3 mL) was added into the toluene solution and the mixture was refluxed for 8 h more. After quenched by $NaHCO_3$ aq, DCM solution was washed with NaCl aq and dried with Mg_2SO_4. After removal of the solvent, quinoline was purified by silica gel column chromatography (with hexane:DCM = 5:1 eluent), and then recrystallized from hexane solution. The quinoline

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also could be purified by recrystallization from DCM solution and washed by diethyl ether (DEE).

3-Fluoro-6-methoxy-2-phenyl-4-(trifluoromethyl)quinoline (5a). White powder, 803 mg, 83% yield from 58% pure PFP (642 mg, 3 mmol of PFP). Mp 117.6−118.0 °C. IR (KBr) 1620. ^{1}H NMR ($CDCl_3$) δ_H 8.11−8.09 (m, 1H), 8.01−7.99 (m, 2H), 7.55−7.49 (m, 3H), 7.41−7.39 (m, 2H), 3.97 (s, 3H). ^{19}F NMR ($CDCl_3$) δ_F 106.1 (d, J = 32 Hz, 3F), 38.5 (q, J = 32 Hz, 1F). ^{13}C NMR ($CDCl_3$) δ_C 159.6, 153.2, 151.3, 146.8 (d, J = 17 Hz), 141.4 (d, J = 4 Hz), 134.9 (d, J = 5 Hz), 132.0, 129.7, 129.2, 128.6, 124.9, 123.2 (q, J = 276 Hz), 121.9, 117.5 (qd, J = 32, 8 Hz), 102.1 (m), 55.6. MS (EI) *m*/*e* 321 (M^+, 100), 306 (9), 278 (44). Anal. Calcd for $C_{17}H_{11}F_4NO$: C, 63.55; H, 3.45; N, 4.36. Found: C, 63.36; H, 3.42; N, 4.48.

3-Fluoro-6-methoxy-2-(4-methylphenyl)-4-(trifluoromethyl)-quinoline (5b). Yellowish green powder, 688 mg, 68% yield from 58% pure PFP (3 mmol). Mp 112.2−113.0 °C. IR (KBr) 1630. ^{1}H NMR ($CDCl_3$) δ_H 8.10−8.07 (m, 1H), 7.91 (dd, J = 8, 2 Hz, 2H), 7.40−7.38 (m, 2H), 7.34 (d, J = 8 Hz, 2H), 3.97 (s, 3H), 2.44 (s, 3H). ^{19}F NMR ($CDCl_3$) δ_F 106.2 (d, J = 32 Hz, 3F), 38.6 (q, J = 32 Hz, 1F). ^{13}C NMR ($CDCl_3$) δ_C 159.4, 153.2, 151.4, 146.8, 146.7, 141.4 (d, J = 4 Hz), 139.8, 132.1, 131.9, 129.2, 129.0 (d, J = 6 Hz), 124.6, 123.3 (q, J = 276 Hz), 121.7, 117.3 (qd, J = 31, 8 Hz), 102.1 (m), 55.5, 21.4. MS (EI) *m*/*e* 335 (M^+, 100), 320 (9), 292 (29). Anal. Calcd for $C_{18}H_{13}F_4NO$: C, 64.48; H, 3.91; N, 4.18. Found: C, 64.51; H, 3.92; N, 4.20.

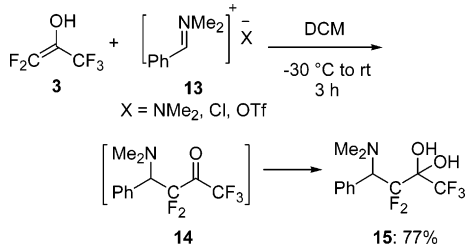
3-Fluoro-2-(4-fluorophenyl)-6-methoxy-4-(trifluoromethyl)-quinoline (5c). White powder, 619 mg, 61% yield from 58% pure PFP (3 mmol). Mp 152.5−154.4 °C. IR (KBr) 1630. ^{1}H NMR ($CDCl_3$) δ_H 8.08 (d, J = 9 Hz, 1H), 8.03−8.01 (m, 2H), 7.42−7.40 (m, 2H), 7.22 (t, J = 9 Hz, 2H), 3.98 (s, 3H). ^{19}F NMR ($CDCl_3$) δ_F 106.1 (d, J = 32 Hz, 3F), 50.7−50.6 (m, 1F), 38.2 (q, J = 32 Hz, 1F). ^{13}C NMR ($CDCl_3$) δ_C 164.5, 162.9, 159.7, 153.1, 151.2, 145.5 (d, J = 17 Hz), 141.3 (d, J = 5 Hz), 132.0, 131.3 (dd, J = 9, 6 Hz), 131.1 (t, J = 1 Hz), 124.9, 123.2 (q, J = 276 Hz), 122.0, 117.5 (qd, 31, 7), 115.6 (d, J = 22 Hz), 102.1 (m), 55.6. MS (EI) *m*/*e* 339 (M^+, 100), 324 (9), 296 (40). Anal. Calcd for $C_{17}H_{10}F_5NO$: C, 60.18; H, 2.97; N, 4.13. Found: C, 60.14; H, 2.91; N, 4.15.

2-(3-Chlorophenyl)-3-fluoro-6-methoxy-4-(trifluoromethyl)-quinoline (5d). White powder, 657 mg, 62% yield from 58% pure PFP (3 mmol). Mp 88.9−89.9 °C. IR (KBr) 1620. ^{1}H NMR ($CDCl_3$) δ_H 8.08 (d, J = 9 Hz, 1H), 8.04−8.02 (m, 1H), 7.92−7.89 (m, 1H), 7.48−7.40 (m, 4H), 3.98 (s, 3H). ^{19}F NMR ($CDCl_3$) δ_F 106.1 (d, J = 32 Hz, 3F), 38.2 (q, J = 32 Hz, 1F). ^{13}C NMR ($CDCl_3$) δ_C 159.9, 153.1, 151.2, 144.9 (d, J = 17 Hz), 141.4 (d, J = 5 Hz), 136.6 (d, J = 5 Hz), 134.6, 132.1, 129.7 (d, J = 5 Hz), 129.2 (d, J = 6 Hz), 127.3 (d, J = 6 Hz), 125.1, 123.2 (q, J = 276 Hz), 122.2, 117.6 (qd, J = 33, 7 Hz), 102.0 (m), 55.6. MS (EI) *m*/*e* 355 (M^+, 100), 312 (22). Anal. Calcd for $C_{17}H_{10}ClF_4NO$: C, 57.40; H, 2.83; N, 3.94. Found: C, 57.38; H, 2.77; N, 3.86.

Ethyl 3-Fluoro-6-methoxy-4-(trifluoromethyl)quinoline-2-carboxylate (5e). Yellowish ivory powder, 611 mg, 64% yield from 58% pure PFP (3 mmol). Mp 79.6−80.8 °C. IR (KBr) 1730, 1630. ^{1}H NMR ($CDCl_3$) δ_H 8.14 (d, J = 10 Hz, 1H), 7.41 (dd, J = 10, 3 Hz, 1H), 7.35−7.34 (m, 1H), 4.54 (q, J = 7 Hz, 2H), 3.96 (s, 3H), 1.46 (t, J = 7 Hz, 3H). ^{19}F NMR($CDCl_3$) δ_F 106.0 (d, J = 33 Hz, 3F), 38.8 (q, J = 33 Hz, 1F). ^{13}C NMR ($CDCl_3$) δ_C 162.7 (d, J = 6 Hz), 161.2, 153.5 (d, J = 2 Hz), 151.7 (d, J = 2 Hz), 140.6 (d, J = 4 Hz), 137.5 (d, J = 17 Hz), 132.9, 127.2, 122.9, 122.7 (q, J = 275 Hz), 118.2 (qd, J = 32, 7 Hz), 101.8 (m), 62.6, 55.7, 14.2. MS (EI) *m*/*e* 317 (M^+, 18), 245 (100). Anal. Calcd for $C_{14}H_{11}F_4NO_3$: C, 53.00; H, 3.49; N, 4.42. Found: C, 53.12; H, 3.47; N, 4.38.

3-Fluoro-2-phenyl-4-(trifluoromethyl)benzo[*h*]quinoline (5f). White powder, 794 mg, 70% yield from 58% pure PFP (3 mmol). Mp 119.6−120.5 °C. IR (KBr) No remarkable peak. ^{1}H NMR ($CDCl_3$) δ_H 9.36 (d, J = 8 Hz, 1H), 8.22 (d, J = 6 Hz, 2H), 8.07−8.04 (m, 1H), 7.95 (dd, J = 18, 8 Hz, 2H), 7.79−7.73 (m, 2H), 7.61−7.54 (m, 3H). ^{19}F NMR ($CDCl_3$) δ_F 107.5 (dd, J = 33, 2 Hz, 3F), 36.7 (q, J = 33 Hz, 1F). ^{13}C NMR ($CDCl_3$) δ_C 153.2 (d, J = 2 Hz), 151.4 (d, J = 2 Hz), 146.6 (d, J = 16 Hz), 142.9 (d, J = 5 Hz), 135.1 (d, J = 5 Hz), 132.5, 131.0, 130.5, 129.9, 129.5 (d, J = 6 Hz), 128.6, 128.5, 127.6 (d, J = 18 Hz), 124.9, 123.2 (q, J = 276 Hz), 122.1, 120.4 (m), 119.4 (qd, J = 32, 8 Hz). MS (EI) *m*/*e* 341 (M^+, 100). Anal. Calcd for $C_{20}H_{11}F_4N$: C, 70.38; H, 3.25; N, 4.10. Found: C, 70.45; H, 3.31; N, 4.15.

SCHEME 8. Reaction of PFP with Iminium Salt



Mechanism of the Quinoline Syntheses. A step-by-step ^{19}F NMR analysis of the intermediates suggested a mechanism of the one-pot quinoline synthesis (Scheme 5). First, Mannich adduct **6** would be formed although it was not isolated. The ^{19}F NMR chemical shifts of **6** [δ 87 ppm (d) for CF_3, δ 61 (d) and 35 (ddq) for CF_2] and its hydrate [δ 81 (dd) for CF_3, δ 48 (dq) and 34 (ddq) for CF_2] were similar to those of the authentic samples of the closely related ketone **14** [δ 87 (dd) for CF_3, δ 66 (d) and 42 (ddq) for CF_2] and its hydrate **15** [δ 81 (t) for CF_3, δ 50 (dq) and 38 (ddq) for CF_2], which were prepared by the reaction of PFP **3** with *N*,*N*-dimethyliminium salt **13** and were isolable (Scheme 8). On observing the ^{19}F NMR of the reaction solution of PFP **3** with **13**, peaks of PFP **3** [δ 94 (dd) for CF_3, δ 66 (dq) and 58 (dq) for CF_2] disappeared within 2 min completely and new peaks of **15** appeared immediately. Thus, ketone **14** would be formed, and then converted to its hydrate **15**. A trace amount of water involved in solvent and substrates (**3** and **13**) may hydrate the ketone **14**. In the case of the reaction of PFP **3** with aldimine **4a**, similar ^{19}F NMR peaks ascribed to **3**, ketone **6**, and its hydrate were observed, although the reaction required more than 30 min. The intermediates **6** and its hydrate would be converted via intermediate **7** into tetrahydroquinoline **8** on heating at the reflux temperature of toluene. The tetrahydroquinolines **8** were obtained as a mixture of diastereomers quantitatively from aldimine **4a**. One of the diastereomers, (2,4)-*cis*-**8a**,[20] was crystallized from DCM solution of **8** and its stereochemistry was confirmed by X-ray crystallographic analysis, while the other diastereomer, (2,4)-*trans*-**8b**, remained in a powder. Subsequently, tetrahydroquinoline **8** would undergo acid-catalyzed dehydration and dehydrofluorination to be converted into quinoline **5a** as a final product.

Synthesis of Tetrahydroquinoline 8. In the procedure of quinoline synthesis, the reaction was quenched without addition of TFA. After removal of solvent, tetrahydroquinoline **8** as a mixture of diastereomers (1.02 g, 94%) was purified by silica gel column chromatography (hexane:DCM = 3:1). The tetrahydroquinoline (*cis*-**8a**) was recrystallized from DCM solution as colorless crystal. And also, another diastereoisomer (*trans*-**8b**) was purified by silica gel column chromathography (hexane:DEE = 3:1).

***cis*-3,3-Difluoro-6-methoxy-2-phenyl-4-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-4-ol (8a).** White powder: colorless platelet crystal. Mp 174.5−178.7 °C. IR (KBr) 3400, 3250. ^{1}H NMR ($CDCl_3$) δ_H 7.56−7.55 (m, 2H), 7.44−7.41 (m, 3H), 7.13 (d, J = 2 Hz, 1H), 6.90 (dd, J = 9, 3 Hz, 1H), 6.61 (d, J = 9, 1H), 4.95 (dd, J = 28, 3 Hz, 1H), 4.04 (br, 1H), 3.79 (s, 3H), 3.04 (d, J = 3 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ_F 87.2 (dd, J = 16, 5 Hz, 3F), 41.9 (dd, J = 254, 28 Hz, 1F), 38.6 (dq, J = 254, 16 Hz, 1F). ^{13}C NMR [$(CD_3)_2CO$)] δ_C 206.2 (d, J = 1 Hz), 152.6 (d, J = 1 Hz), 139.2, 135.8, 130.5, 129.8, 128.9, 124.7 (q, J = 291 Hz), 119.1, 116.4, 116.0 (dd, J = 109, 5 Hz), 113.4, 75.7 (td, J = 28, 21 Hz), 59.9

(ddq, J = 28, 22, 3 Hz), 55.9. MS (EI) *m/e* 359 (M^+, 100), 344 (13), 290 (91). Anal. Calcd for $C_{17}H_{14}F_5NO_2$: C, 56.83; H, 3.93; N, 3.90. Found: C, 56.84; H, 3.85; N, 3.85.

***trans*-3,3-Difluoro-6-methoxy-2-phenyl-4-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-4-ol (8b).** Brown solid, 97% purity (determined by ^{19}F NMR). ^1H NMR ($CDCl_3$) δ_H 7.58−7.56 (m, 2H), 7.44−7.42 (m, 3H), 7.18 (d, J = 2 Hz, 1H), 6.92 (dd, J = 8, 2 Hz, 1H), 6.68 (d, J = 8 Hz, 1H), 4.69 (d, J = 23 Hz, 1H), 4.05 (br, 1H), 3.78 (s, 3H), 3.38 (br, 1H). ^{19}F NMR ($CDCl_3$) δ_F 91.5 (dd, J = 16, 12 Hz, 3F), 40.3 (dq, J = 253, 12 Hz, 1F), 34.3 (ddq, J = 253, 26, 16 Hz, 1F). ^{13}C NMR ($CDCl_3$) δ_C 153.1, 138.4, 133.1, 129.5, 129.4, 128.6, 124.4 (q, J = 290 Hz), 118.9, 118.7, 117.2, 117.1, 116.1 (d, J = 3 Hz), 115.4, 112.4, 74.0 (td, J = 28, 21 Hz), 58.2 (dd, J = 31, 20 Hz), 55.8. MS (EI) *m/e* 359 (M^+, 100), 344 (13), 321 (22), 290 (91).

4-(Dimethylamino)-1,1,1,3,3-pentafluoro-4-phenylbutan-2,2-diol (15). A DCM (3 mL) solution of 95% pure PFP (44 mg, 0.3 mmol of PFP), which was prepared by acid-catalyzed desilylation of triethylsilyl pentafluoropropen-2-olate, and diamine (80 mg, 0.45 mmol) was stirred for 0.5 h at −76 °C. After removal of solvent, hydrate **15** (70 mg, 77%) was purified by silica gel column chromathography (hexane:DCM = 1:1, then hexane:DEE = 1:1) and kugerlorh distillation. White powder. IR (KBr) 3320. ^1H NMR [$(CD_3)_2CO$)] δ_H 7.54−7.51 (m, 2H), 7.48−7.44 (m, 3H), 4.78 (d, J = 31 Hz, 1H), 2.32 (s, 6H). ^{19}F NMR [$(CD_3)_2CO$)] δ_F 83.6 (t, J = 12 Hz, 3F), 52.9 (dq, J = 263, 12 Hz, 1F), 40.3 (ddq, J = 263, 30, 12 Hz, 1F). ^{13}C NMR [$(CD_3)_2CO$] δ_C 132.1 (d, J = 3 Hz), 129.7, 129.1, 128.7, 123.1 (q, J = 274 Hz), 119.2(t, J = 260 Hz), 94.4(quint d, J = 31, 25 Hz), 68.2 (dd, J = 30, 4 Hz), 42.1. MS (EI) *m/e* 134 (M^+ − 165, 100). Anal. Calcd for $C_{12}H_{14}F_5NO_2$: C, 48.17; H, 4.72; N, 4.68. Found: C, 48.20; H, 4.75; N, 4.64.

6-Methoxy-2-phenyl-4-(trifluoromethyl)quinoline-3-carbonitrile (9a). A DMF (3 mL) solution of quinoline **5a** (96 mg, 0.3 mmol), trimethylsilylcyanide (TMSCN) (60 mg, 0.6 mmol), and a THF solution of tetrabutylammonium fluoride (TBAF) (0.15 mL, 0.15 mmol) were stirred at 0 °C for 1 h. After the mixture was stirred for 47 h at room temperature, the solvent was removed in vacuo. Then, quinoline **9a** (91 mg, 92%) was purified by silica gel column chromatography (hexane:DCM = 1:1). Yellow powder. Mp 174.2−177.3 °C. IR (KBr) 2240, 1620. ^1H NMR ($CDCl_3$) δ_H 8.17 (d, J = 10 Hz, 1H), 7.87−7.86 (m, 2H), 7.61 (dd, J = 2, 9 Hz, 1H), 7.64−7.55 (m, 3H), 7.46 (quant, J = 2 Hz, 1H), 4.01 (s, 3H). ^{19}F NMR ($CDCl_3$) δ_F 105.0 (s, 3F). ^{13}C NMR (CD−Cl_3) δ_C 159.9, 157.2, 145.8, 137.4 (q, J = 16 Hz), 137.3, 132.2, 130.1, 129.4, 128.6, 126.6, 122.6 (q, J = 278 Hz), 122.7, 115.1, 103.3 (q, J = 3 Hz), 102.1 (q, J = 4 Hz), 55.8. MS (EI) *m/e* 328 (M^+, 100), 313 (45), 285 (44), 216 (47). Anal. Calcd for $C_{18}H_{11}F_3N_2O$: C, 65.85; H, 3.38; N, 8.53. Found: C, 65.92; H, 3.20; N, 8.61.

6-Methoxy-2-phenyl-3-[(1-phenylethenyl)oxy]-4-(trifluoromethyl)quinoline (9b). A DMF (3 mL) solution of quinoline **5a** (96 mg, 0.3 mmol), CsF (46 mg, 0.3 mmol), silyl enol ether (1-phenyl-1-trimethylsiloxyethylene) (39 mg, 0.6 mmol) was stirred at 70 °C for 12 h. After filtration and removal of the solvent, quinoline **9b** (90 mg, 71%) was purified by silica gel column chromathograpy (hexane:DEE = 5:1) and followed by recrystallization from hexane/DEE eluent. White powder. Mp 126.5−128.2 °C. IR (KBr) 1630. ^1H NMR ($CDCl_3$) δ_H 8.14 (d, J = 9 Hz, 1H), 7.85−7.82 (m, 2H), 7.58−7.55 (m, 2H), 7.49−7.47 (m, 1H), 7.44 (dd, J = 9, 3 Hz, 1H), 7.36−7.31 (m, 6H), 4.65 (d, J = 4 Hz, 1H), 3.99 (s, 3H), 3.68 (d, J = 4 Hz, 1H). ^{19}F NMR ($CDCl_3$) δ_F 105.6 (s, 3F). ^{13}C NMR ($CDCl_3$) δ_C 160.2, 159.2, 153.1, 144.1, 142.4, 136.9, 134.3, 131.9, 128.9, 128.1, 128.1, 125.3, 125.1, 124.6 (q, J = 30 Hz), 123.6 (q, J = 277 Hz), 122.0, 102.5 (dd, J = 6, 4 Hz), 87.8, 55.6. MS (EI) *m/e* 421 (M^+, 17), 352 (28), 319 (32), 318 (30), 103 (100). Anal. Calcd for $C_{25}H_{18}F_3NO_2$: C, 71.25; H, 4.31; N, 3.32. Found: C, 71.28; H, 4.33; N, 3.28.

6-Methoxy-2-phenyl-4-(trifluoromethyl)quinolin-3-ol (9c). A DMF (3 mL) solution of quinoline **5a** (96 mg, 0.3 mmol), sodium hydride−60% oil suspension (120 mg, 3 mmol), and water (54 mg, 3 mmol) was stirred at 0 °C for 12 h. After being quenched by NH_4Cl aq, the DEE solution was washed with NaCl aq and dried with Mg_2SO_4. After removal of the solvent, quinoline **9c** (73 mg, 76%) was purified by silica gel column chromathography (hexane:DEE = 5:1). Yellow powder. Mp 120.8−122.8 °C. IR (KBr) 3580, 1620. ^1H NMR ($CDCl_3$) δ_H 8.00 (d, J = 9 Hz, 1H), 7.76 (dd, J = 7, 1 Hz, 1H), 7.48 (td, J = 7, 1 Hz, 2H), 7.43 (td, J = 7, 1 Hz, 1H), 7.35 (br, 1H), 7.28 (dd, J = 9, 2 Hz, 1H), 6.69 (br, 1H), 3.96 (s, 3H). ^{19}F NMR ($CDCl_3$) δ_F 107.4 (s, 3F). ^{13}C NMR ($CDCl_3$) δ_C 159.3, 149.2 (d, J = 3 Hz), 145.9, 139.1 (d, J = 3 Hz), 135.7, 131.6, 129.2, 128.9 (d, J = 5 Hz), 125.4, 124.9 (q, J = 276 Hz), 119.6, 113.5 (qd, J = 29, 11 Hz), 102.0 (q, J = 4 Hz), 55.5. MS (EI) *m/e* 319 (M^+, 100), 291 (22). Anal. Calcd for $C_{17}H_{12}F_3NO_2$: C, 63.95; H, 3.79; N, 4.39. Found: C, 63.95; H, 3.82; N, 4.50.

3-Ethoxy-6-methoxy-2-phenyl-4-(trifluoromethyl)quinoline (9d). An ethanol (7 mL) solution of quinoline **5a** (321 mg, 1.0 mmol) and a 20% ethanol solution of sodium ethoxide (0.68 mL, 2.0 mmol) was stirred at 78 °C for 5 h. After short silica gel column chromathography with DEE, quinoline **9d** (350 mg, 99%) was purified by Kugerlorh distillation. White powder. Mp 74.5−76.8 °C. IR (KBr) 1620. ^1H NMR ($CDCl_3$) δ_H 8.06 (d, J = 9 Hz, 1H), 7.98−7.96 (m, 2H), 7.52−7.48 (m, 2H), 7.48−7.43 (m, 2H), 7.35 (dd, J = 9, 3 Hz, 1H), 3.96 (s, 3H), 3.65 (q, J = 7 Hz, 2H), 1.18 (t, J = 7 Hz, 3H). ^{19}F NMR ($CDCl_3$) δ_F 106.5 (s, 3F). ^{13}C NMR ($CDCl_3$) δ_C 159.0, 153.2, 149.9 (q, J = 1.8 Hz), 141.4, 137.6, 131.8, 129.1, 129.0, 128.3, 125.2, 124.2 (q, J = 277 Hz), 123.8 (q, J = 29 Hz), 102.4 (q, J = 5 Hz), 71.3, 55.5, 15.1. MS (EI) *m/e* 347 (M^+, 100), 318 (62), 303 (18), 291 (30). Anal. Calcd for $C_{19}H_{16}F_3NO_2$: C, 65.70; H, 4.64; N, 4.03. Found: C, 65.79; H, 4.68; N, 3.96.

6-Methoxy-2-phenyl-4-(trifluoromethyl)quinolin-3-amine (9e). An *N*-methyl-2-pyrrolidone (NMP) (3 mL) solution of quinoline **5a** (96 mg, 0.3 mmol) and sodium cyanate (117 mg, 3 mmol) was stirred at 130 °C for 12 h. After being quenched by NH_4Cl aq, the DEE solution was washed with NaCl aq and dried with Mg_2SO_4. After removal of the solvent, quinoline **9e** (67 mg, 70%) was purified by silica gel column chromathography (hexane:DEE = 3:1). Yellowish powder. Mp 104.2−106.1 °C. IR (KBr) 3470, 1610; ^1H NMR ($CDCl_3$) δ_H 7.91 (d, J = 9 Hz, 1H), 7.64 (dt, J = 8, 2 Hz, 2H), 7.54 (tt, J = 8, 1 Hz, 2H), 7.49 (tt, J = 8, 1 Hz, 1H), 7.28 (t, J = 2 Hz, 1H), 7.14 (dd, J = 9, 2 Hz, 1H), 4.83 (br, 2H), 3.94 (s, 3H). ^{19}F NMR ($CDCl_3$) δ_F 107.6 (s, 3F). ^{13}C NMR ($CDCl_3$) δ_C 159.1, 149.7, 137.3, 137.3, 136.7, 131.5, 130.1, 129.2, 128.7, 127.6, 126.3 (q, J = 276 Hz), 125.8, 117.2, 107.6 (q, J = 29 Hz), 101.9 (q, J = 4 Hz), 55.3. MS (EI) *m/e* 318 (M^+, 100), 149. Anal. Calcd for $C_{17}H_{13}F_3N_2O$: C, 64.15; H, 4.12; N, 8.80. Found: C, 64.13; H, 4.19; N, 8.73.

6-Methoxy-2-phenyl-3-(phenylsulfenyl)-4-(trifluoromethyl)-quinoline (9f). A DMF (3 mL) solution of quinoline **5a** (96 mg, 0.3 mmol), sodium borohydride (227 mg, 6 mmol), and diphenyl disulfide (635 mg, 3 mmol) was stirred at 0 °C for 12 h. After being quenched by NH_4Cl aq, the DEE solution was washed with NaCl aq and dried with Mg_2SO_4. After removal of the solvent, quinoline **9f** (312 mg, 76%) was purified by silica gel column chromathography (hexane:DEE = 5:1). White powder. Mp 115.3−116.3 °C. IR (KBr) 1620. ^1H NMR ($CDCl_3$) δ_H 8.07 (d, J = 10 Hz, 1H), 7.58 (br, 1H), 7.45 (dd, J = 9, 2 Hz, 1H), 7.33−7.32 (m, 2H), 7.30−7.27 (m, 2H), 7.26−7.23 (m, 1H), 7.05−7.02 (m, 1H), 7.00−6.98 (m, 2H), 6.69−6.67 (m, 2H), 3.99 (s, 3H). ^{19}F NMR ($CDCl_3$) δ_F 109.1 (s, 3F). ^{13}C NMR ($CDCl_3$) δ_C 160.5, 159.1, 144.0, 140.3, 136.5, 136.2 (q, J = 29 Hz), 131.9, 129.7, 128.9, 128.7, 128.0, 127.7, 126.3, 124.8, 124.3 (q, J = 279 Hz), 123.2. MS (EI) *m/e* 411 (M^+, 100), 334 (55). Anal. Calcd for $C_{23}H_{16}F_3NOS$: C, 67.14; H, 3.92; N, 3.40. found: C, 67.19; H, 3.62; N, 3.44.

6-Methoxy-2-phenyl-4-(trifluoromethyl)quinoline (9g). A DMF (3 mL) solution of quinoline **5a** (96 mg, 0.3 mmol) and sodium borohydride (34 mg, 0.9 mmol) was stirred at 70 °C for 12 h. After being quenched by NH_4Cl aq, the DEE solution was washed with

NaCl aq and dried with Mg_2SO_4. After removal of the solvent, quinoline **9g** (81 mg, 89%) was purified by silica gel column chromathograpy (hexane:DCM = 5:1). White powder. Mp 120.8−121.6 °C. IR (KBr) 1630. ^{1}H NMR ($CDCl_3$) δ_H 8.17−8.11 (m, 4H), 7.54 (t, J = 8 Hz, 2H), 7.48 (t, J = 8 Hz, 1H), 7.45 (d, J = 9 Hz, 1H), 7.36 (s, 1H), 3.96 (s, 3H). ^{19}F NMR ($CDCl_3$) δ_F 99.5 (s, 3F). ^{13}C NMR ($CDCl_3$) δ_C 158.7, 154.0, 145.3, 138.5, 133.4 (q, J = 31 Hz), 132.0, 129.6, 128.9, 127.1, 123.7 (q, J = 275 Hz), 123.1, 116.1 (q, J = 5 Hz), 101.8 (d, J = 2 Hz), 55.6. MS (EI) *m*/*e* 303 (M^+, 100), 260 (49).

1-Fluoro-8-methoxy-4-phenyl-3*H*-pyrazolo[3,4-*c*]quinoline (10). A DMF (3 mL) solution of quinoline **5a** (96 mg, 0.3 mmol) and hydrazine (anhydrous) (188 μL, 6 mmol) was stirred at 70 °C for 12 h. After being quenched by NH_4Cl aq, the DEE solution was washed with NaCl aq and dried with Mg_2SO_4. After removal of the solvent, quinoline **10** (60 mg, 68%) was purified by silica gel column chromathography (hexane:DEE = 3:1). Yellowish ivory powder. Mp 246.3−250.0 °C. IR (KBr) 3350, 1630. ^{1}H NMR ($CDCl_3$) δ_H 9.90 (br, 1H), 8.19 (d, J = 9 Hz, 1H), 8.00−7.98 (m, 2H), 7.63−7.60 (m, 3H), 7.56 (t, J = 8 Hz, 1H), 7.33 (dd, J = 3, 9 Hz, 1H) 4.02 (s, 3H). ^{19}F NMR ($CDCl_3$) δ_F 32.5 (s). ^{13}C NMR [$(CD_3)_2SO$] δ_C 158.9, 158.9, 157.3, 143.3, 137.3, 136.4, 134.2, 131.4, 130.0, 129.1, 128.6, 120.8 (d, J = 4 Hz), 117.8, 106.6 (d, J = 22 Hz), 102.7 (d, J = 2 Hz), 55.8. MS (EI) *m*/*e* 293 (M^+, 100), 278 (25). Anal. Calcd for $C_{23}H_{12}FN_3O$: C, 69.62; H, 4.12; N, 14.33. Found: C, 69.58; H, 4.09; N, 14.28.

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Supporting Information Available: Spectral data for all previously unreported compounds **3**, **5**, **8**, **9**, **10**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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