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Convenient synthesis of fluorinated quinoline, 1,2-dihydroquinoline, and 1,2,3,4-tetrahydroquinoline derivatives

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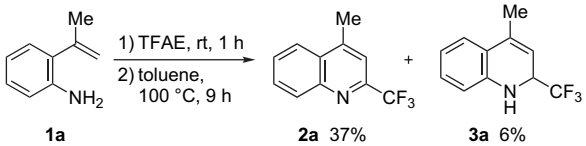
Abstract—A convenient synthetic method for 2-polyfluoroalkylated quinoline systems through the efficient generation of perfluoroalkylated imine from *o*-vinylanilines with perfluorinated hemiacetals or aldehyde hydrates was developed. In most cases, the major products are 2-polyfluoroalkyl-1,2-dihydroquinoline derivatives **3**, which can be converted to either quinolines or 1,2,3,4-tetrahydroquinolines.

1. Introduction

The use of fluorinated heterocyclic compounds as bioactive or functional molecules has been increasing recently.[1] In a number of fluorinated heterocycles, 2-trifluoromethylquinoline moiety is widely found in development of drugs such as antimalarials,[2] PDE4 inhibitors,[3] DPP-IV inhibitors,[4] and other bioactive molecules.[5] Furthermore, 2-trifluoromethyl-1,2-dihydroquinoline derivatives have selective COX-2 inhibitory activity.[6] For the synthesis of 2-trifluoromethylquinoline compounds, the use of fluorinated building blocks, e.g., trifluoroacetate derivatives,[7] trifluoromethylated 1,3-diketones,[8] trifluoromethylimidoyl chloride,[9] and trifluoroacetaldehyde, has been reported, but most of these methods have several problems from a viewpoint of convenience and/or industrial use. Among such fluorinated building blocks, trifluoroacetaldehyde ethyl hemiacetal (TFAE) is a cheap and useful trifluoroacetaldehyde equivalent.[10–12] However, direct use of TFAE for 2-trifluoromethylquinoline synthesis would not be easy due to the strong −I effects of trifluoromethyl group, which make the generation of trifluoromethylated imines difficult.[13] Indeed, synthesis of 2-trifluoromethylquinoline derivatives from isolated trifluoromethylated anils has been known, but direct synthesis from trifluoroacetaldehyde hydrate or hemiacetals has not been reported.[14,15] In this paper, we would like to report a convenient synthesis of 2-polyfluoroalkylated quinolines through the direct in situ formation of polyfluoroalkylated anils from fluorinated aldehyde hydrate/hemiacetals and aniline derivatives using chlorotrimethylsilane (TMSCl) as the industrially usable dehydrating reagent.

2. Results and discussion

It has been reported that thermal 6π-cyclization reaction of *o*-vinyl anils, which are prepared from *o*-vinylanilines and benzaldehyde derivatives, followed by air oxidation gives rise to the corresponding quinoline compounds.[16] This reaction requires high reaction temperature for the smooth reaction, although excellent yields are generally observed. Furthermore, the consecutive imine formation, cyclization, and oxidation steps can be conducted in one pot. As an extension of this procedure, we examined the reaction of *o*-isopropenylaniline **1a** with TFAE. Thus, as shown in Scheme 1, the reaction of **1a** with TFAE (2.2 equiv) was carried out at 100 °C for 9 h in toluene to give 2-trifluoromethylquinoline **2a** (37% yield) and 2-trifluoromethyl-1,2-dihydroquinoline **3a** (6% yield) with the recovery of **1a**. Under the similar conditions, addition of pyridine as a base to the reaction mixture reduced the yield of **2a** to a trace amount. Although it was reported that the reactions of *o*-vinylanilines with less reactive ketones are catalyzed by iodine[17] or Lewis acids,[18] the use of Lewis acids, such as $BF_3 \cdot OEt_2$, ZnI_2, $Yb(OTf)_3$, $Sc(OTf)_3$, and $In(OTf)_3$, did not give any desired products in this reaction.



1a **2a** 37% **3a** 6%

Scheme 1.

Keywords: Fluorinated heterocycles; Quinoline; 1,2-Dihydroquinoline; Trifluoroacetaldehyde ethyl hemiacetal.
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We found that addition of TMSCl as an additive and the use of pyridine as the solvent remarkably promoted the formation of the desired products **2a/3a** (Table 1). A mixture of **1a** and TFAE (1.1 equiv), premixed at room temperature for 1 h, was treated with TMSCl (1.5 equiv) at 100 °C for 9 h in toluene to give quinoline **2a** (36% yield) and 1,2-dihydroquinoline **3a** (17% yield). In toluene, the improvement of the product yields was not realized by increasing the molar equivalent of TMSCl (3.0 equiv) or by the use of 2.2 equiv of TFAE and 3.0 equiv of TMSCl under the similar conditions (entries 2 and 3). On the other hand, using pyridine as the solvent, the desired quinoline derivatives **2a/3a** were obtained in high yields (**2a** 9% yield and **3a** 89% yield, entry 4). As shown in entry 5, the reaction rate was also increased under the concentrated conditions (0.2 M of **1a** in pyridine) without loss of the isolated yields of **2a** (8% yield) and **3a** (87% yield). However, under the concentrated conditions, the reaction using 1.1 equiv of TFAE and 2.2 equiv of TMSCl gave poor result (**2a** 7% yield and **3a** 57% yield, entry 6). In the absence of TMSCl in pyridine or in the presence of pyridine hydrochloride, no desired products **2a/3a** were obtained with the recovery of **1a** (92%, entry 7). These results indicate that the concentration of substrate **1a** and the molar ratio of **1a**, TFAE, and TMSCl plays an important role to obtain the products in good yield (see, entry 6). Furthermore, reaction solvents altered the product selectivity. Thus, while quinoline **2a** was favorably formed in toluene, the reaction in pyridine produced 1,2-dihydroquinoline **3a** as the major product.

Next, the reactions of various *o*-vinylanilines **1** were examined under the optimal conditions for **1a**. The results are summarized in Table 2. As shown in entry 1, the reactivity of non-substituted substrate **1b** decreased notably, and the reaction of **1b** using 4.4 equiv of TFAE and 6.0 equiv of TMSCl at 120 °C for 23 h gave a mixture of **2b/3b** in only 38% (**2b/3b**=1:9.6). As in the case of α-methyl derivative **1a**, α-phenyl derivative **1c** was also a good substrate giving rise to a mixture of **2c** and **3c** in 87% yield with excellent selectivity (**2c/3c**=1:>20, entry 2). On the other hand, the reaction of *trans*-β-phenyl derivative **1d** with 4.4 equiv of TFAE and 6.0 equiv of TMSCl gave imine **4d** as a stable product in 82% yield without the formation of any cyclized products (entry 3). As shown in Scheme 2, a remarkable difference in the reactivity between *E*/*Z* isomer of α-phenyl-β-methyl derivative **1e** having trisubstituted olefin moiety was observed. The reaction of an *E*/*Z* mixture of **1e** (1:1) was conducted at 100 °C for 10 h to give a mixture of **2e** and **3e** in 57% yield (**2e/3e**=1:7.3). Under the same conditions, pure (*E*)-**1e** was converted to a mixture of **2e/3e** in 81% yield (**2e/3e**=1:6.9), while (*Z*)-**1e** gave a mixture of the cyclized products in only 7% yield. Thus, (*E*)-isomer, (*E*)-**1e**, is more reactive than (*Z*)-isomer. Although a certain limitation regarding the substituent types would be involved, the present reaction provides a convenient preparative method for 3,4-disubstituted 2-trifluoromethylquinoline systems. The reaction of secondary aniline **1f** required longer reaction time (72 h) than that of primary aniline **1a**, obtaining *N*-benzyl-1,2-dihydroquinoline **3f** in 52% yield (Table 2, entry 4).

Product ratio (**2** vs **3**) was strongly influenced by the electronic nature of the substituent(s) on the aryl group. The reaction of 2-isopropenyl-4,5-dimethoxyaniline **1g**, having electron-donating group proceeded smoothly to give only quinoline form **2g** in 63% yield with small amount of teromeric products (entry 5).

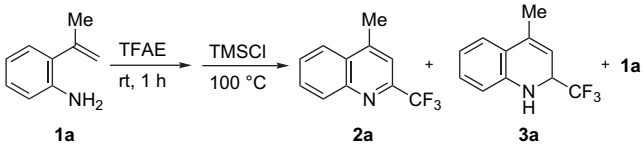
In contrast, the reaction of 5-chloro-2-isopropenylaniline **1h** having electron-withdrawing group provided only 1,2-dihydroquinoline form **3h** in 83% yield without the formation of the quinoline product (entry 6). The reaction of 3-isopropenyl-2-naphthalenamine **1i** with TFAE was also examined to give a complex mixture due to the decomposition of substrate and/or products (entry 7).

Next, we applied the present TMSCl/pyridine system to the reaction of **1a** with other fluorinated hemiacetals (Table 3). Treatment of **1a** with 2.2 equiv of pentafluoropropanal hydrate and 4.0 equiv of TMSCl gave a mixture of 2-pentafluoroethyl quinoline **2j** and dihydroquinoline **3j** in 47% yield (**2j/3j**=1:10, entry 1). On using 1.5 equiv of pentafluoropropanal hydrate, the yield of **2j/3j** was improved to 89% (entry 2). The reaction of **1a** and chlorodifluoroacetaldehyde ethyl hemiacetal (2.2 equiv) with TMSCl (3.0 equiv) efficiently proceeded to give a mixture of the products **2k/3k** in 70% yield in a ratio of 1:12.

As shown above, since in most cases 1,2-dihydroquinoline derivatives **3** were obtained as the major products, we examined the conversion of **3** to quinolines **2** or 1,2,3,4-tetrahydroquinolines **5** (Scheme 3). Air oxidation of **3a** at room temperature for 2 days provided quinoline **2a** in 98% yield.[16] Moreover, hydrogenation reaction of **3a** catalyzed by palladium on carbon proceeded smoothly to give *cis*-4-methyl-2-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline *cis*-**5a** in quantitative yield with perfect diastereoselectivity.

Concerning the reaction mechanism, we assume that TMSCl promotes the imine formation step through O-silylation reaction of *N*,*O*-hemiacetal intermediate **A** under basic condition leading to imine **4** (Scheme 4). The cyclization process should involve electrocyclic ring-closing of 6π system followed by 1,5-H shift to provide 1,2-dihydroquinoline derivative **3**.[16] It should be noted that TMSCl possibly promotes not only the imine formation, but also this electrocyclic

Table 1. Survey of reaction conditions for cyclization of **1a** with TFAE

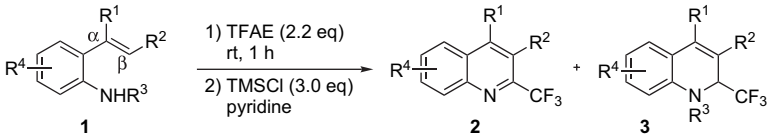


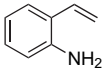
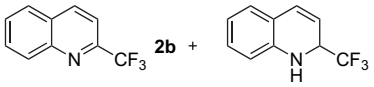
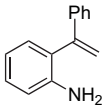
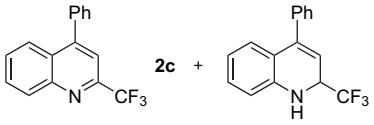
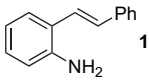
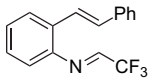
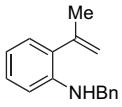
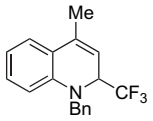
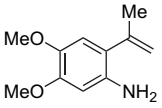
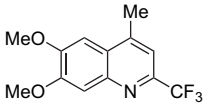
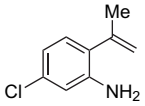
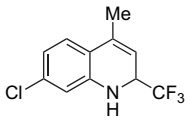
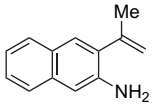
1a **2a** **3a**

Entry	TFAE (equiv)	TMSCl (equiv)	Solvent (Concn of **1a**, M)	Time (h)	Yield[a] (%)	
					2a	**3a**
1	1.1	1.5	Toluene (0.1)	9	36	17
2	1.1	3.0	Toluene (0.1)	9	50	—
3	2.2	3.0	Toluene (0.1)	9	36	18
4	2.2	3.0	Pyridine (0.1)	9	9	89
5	2.2	3.0	Pyridine (0.2)	6	8	87
6	1.1	2.2	Pyridine (0.2)	9	7	57
7[b]	2.2	None	Pyridine (0.2)	9	0	0

[a] Isolated yield.
[b] Compound **1a** of 92% was recovered.

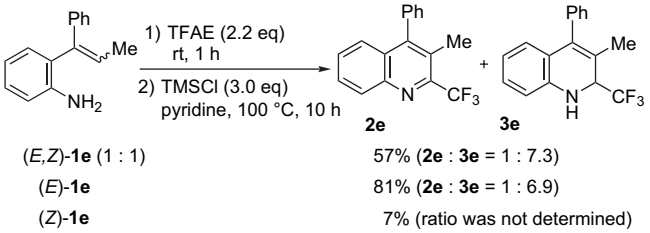
Table 2. Reactions of various *o*-isopropenylanilines **1** with TFAE



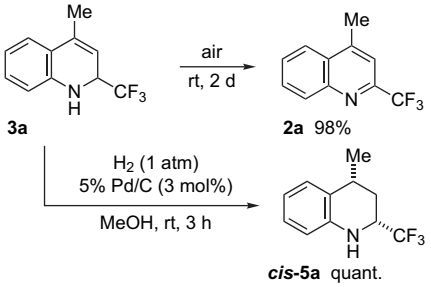
Entry	1	Temp (°C)	Time (h)	2–4	Yield[a] (%)	Ratio[b] (**2**/**3**)
1[c]	 **1b**	120	23	 **2b** + **3b**	38	1:9.6
2	 **1c**	100	7	 **2c** + **3c**	87	1:>20
3	 **1d**	100	5	 **4d**	82	—
4	 **1f**	100	72	 **3f**	52	**3f** only
5[d]	 **1g**	100	6	 **2g**	63	**2g** only
6	 **1h**	100	10	 **3h**	83	**3h** only
7	 **1i**	100	12	—	Complex	—

[a] Isolated yield.
[b] Based on ^{19}F NMR of a crude mixture.
[c] TFAE (4.4 equiv) and TMSCl (6.0 equiv) were used.
[d] Small amount of teromeric products was obtained.

process as a Lewis acid catalyst. By considering this electrocyclic cyclization process requiring conformational control of imine intermediate **4** to be *cisoid* form, the observed substituent effect on the reactivity can be explained. For example, as in the cases of **1a** and **1c** (R^1=Me and Ph), introduction of α-substituent facilitated the cyclization reaction as compared with non-substituted substrate **1b** (R^1=H) (Table 2, entry 1 vs entry 2). This would be due to the destabilization of the *transoid* form **4** by the steric repulsion between R^1 (R^1=Me or Ph) and bulky trifluoromethylimine moiety, whereas such a steric repulsion should be significantly diminished in the case of non-substituted substrate **1b** (R^1=H).

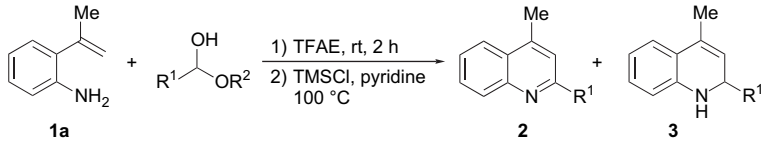


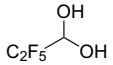
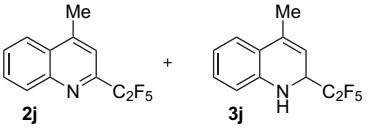
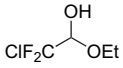
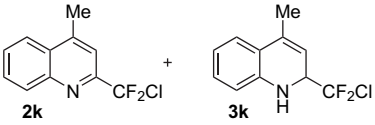
Scheme 2.



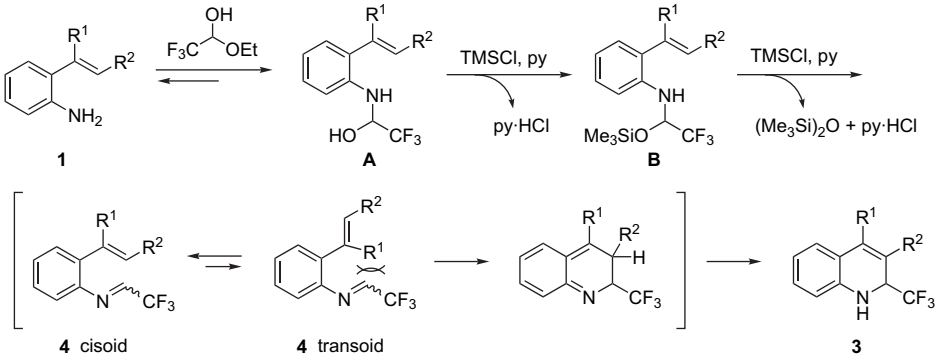
Scheme 3.

Table 3. Reaction of *o*-isopropenylaniline **1a** with aldehyde hydrate or hemiacetal



Entry	$R^1CH(OH)OR^2$		TMSCl (equiv)	Time (h)	Products (**2** and **3**)	Yield[a] (%)	Ratio[b] (**2**/**3**)
1		2.2	4.0	16	 **2j** + **3j**	47	1:10
2		1.5	4.0	16		89	1:9.8
3		2.2	3.0	14	 **2k** + **3k**	70	1:12

[a] Isolated yield.
[b] Based on ^{19}F NMR of a crude mixture.



Scheme 4.

3. Conclusion

We have developed a convenient preparative method for 2-polyfluoroalkyl quinoline systems through an efficient generation of perfluoroalkylated imine from *o*-vinylanilines with perfluorinated hemiacetals or aldehyde hydrates, in particular TFAE as a stable and cheap fluorinating building block. Furthermore, in most cases the major product is 2-polyfluoroalkyl-1,2-dihydroquinoline derivative **3**, which can be converted to either quinolines or 1,2,3,4-tetrahydroquinolines.

4. Experimental

4.1. General

All reactions were carried out under Ar atmosphere. ^1H and ^{13}C NMR spectra were taken on a Bruker dpx400 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^1H NMR and $CDCl_3$ (77.01 ppm) for ^{13}C NMR as an internal standard. ^{19}F NMR spectra were taken on a Bruker dpx400 spectrometer or a Varian Mercury 300 spectrometer, and chemical shifts were reported in parts per million using benzotrifluoride (0 ppm) as a standard. Infrared (IR) spectra were recorded on a JASCO FT/IR-620 infrared spectrophotometer. Mass spectra (MS) were obtained on a Micromass LCT (ESI) or Micromass AutoSpec (EI). Medium pressure liquid chromatography (MPLC) was performed using prepacked column (KUSANO prepacked column Si-10, 40×300 mm i.d., silica gel, 50 μm) with UV detector.

4.2. Preparation of *o*-vinylanilines (1)

2-Isopropenylaniline **1a** is available commercially. 2-Vinylaniline **1b**,[19] 2-(1-phenylvinyl)aniline **1c**,[20] 2-[(*E*)-2-phenylethenyl]aniline **1d**,[21] *N*-benzyl-2-isopropenylaniline **1f**,[22] and 2-isopropenyl-4,5-dimethoxyaniline **1g**[23] were prepared by the reported procedure.

4.2.1. 2-(1-Phenyl-1-propenyl)aniline (1e). To a solution of 2-aminobenzophenone (1.97 g, 10 mmol) in THF (50 mL), EtMgBr (0.87 M in THF, 35 mL, 31 mmol) was added at −78 °C. After being stirred at room temperature for 30 min, the reaction mixture was quenched by saturated aqueous solution of NH_4Cl and filtered through Celite pad. After the filtrate was extracted with EtOAc (50 mL×3), the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified with silica gel column chromatography (hexane/EtOAc= 10:1) to give 1-(2-aminophenyl)-1-phenyl-1-propanol

(2.01 g, 8.8 mmol, 88% yield) as yellow crystals. Mp 102 °C. IR (neat, ν cm^{-1}): 3388, 2970, 2935, 1614, 1493, 1454, 1161, 748. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 0.81 (3H, t, J=7.3 Hz), 2.06 (1H, dq, J=13.7, 7.3 Hz), 2.20 (1H, dq, J=13.7, 7.3 Hz), 3.66 (3H, br, NH_2+OH), 6.49 (1H, br d, J=7.9 Hz), 6.77 (1H, t, J=7.5 Hz), 7.02 (1H, t, J=7.5 Hz), 7.09–7.16 (1H, m), 7.17–7.24 (2H, m), 7.27 (2H, d, J=7.8 Hz), 7.33 (1H, d, J=7.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 7.9, 34.8, 78.4, 118.6, 118.7, 125.8, 126.6, 126.6, 127.9, 128.3, 131.7, 144.5, 145.8. ESI-MS (*m*/*z*): 228 $[M+H]^+$, 210 $[(M-OH)+H]^+$. HRMS Calcd for $C_{15}H_{18}NO$ $[M+H]^+$: 228.1388. Found: 228.1371. The above carbinol (1.93 g, 8.5 mmol) was treated with solid NH_4Cl (1.36 g, 25.5 mmol) for 20 min at 180 °C. The reaction mixture was cooled to ambient temperature and purified with silica gel column chromatography (hexane/EtOAc=40:1) to give the *E*/*Z* mixture of 2-(1-phenyl-1-propenyl)aniline (1.30 g, 6.2 mmol, 73% yield, *E*/*Z*=1:1). The *E*/*Z* mixture was separated by MPLC (hexane/EtOAc=20:1) to give (*Z*)-**1e** (593 mg, 2.83 mmol) as the less polar isomer and (*E*)-**1e** (599 mg, 2.86 mmol) as the more polar isomer. The stereochemistry of **1e** was confirmed by X-ray crystallographic analysis of (*E*)-**1e**.[24] Isomer (*Z*)-**1e**: colorless oil. IR (neat, ν cm^{-1}): 3467, 3377, 3018, 2848, 1612, 1493, 1452, 1298, 845. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.74 (3H, d, J=6.9 Hz), 3.88 (2H, br, NH), 6.41 (1H, q, J=6.9 Hz), 6.80–6.90 (2H, m), 7.04 (1H, dd, J=7.5, 1.5 Hz), 7.17–7.38 (6H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 15.5, 115.8, 118.8, 125.4, 126.0, 126.2, 127.0, 128.3, 128.4, 130.9, 138.7, 140.8. ESI-MS (*m*/*z*): 210 $[M+H]^+$. HRMS Calcd for $C_{15}H_{16}N$ $[M+H]^+$: 210.1283. Found: 210.1286. Isomer (*E*)-**1e**: colorless crystals. Mp 67.8 °C. IR (KBr, ν cm^{-1}): 3465, 2796, 1614, 1493, 1450, 1298, 850. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.00 (3H, br d, J=7.1 Hz), 3.60 (2H, s, NH), 6.04 (1H, q, J=7.1 Hz), 6.69 (1H, d, J=7.7 Hz), 6.80–6.89 (1H, m), 7.12–7.21 (2H, m), 7.30–7.48 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 15.5, 115.8, 118.3, 127.1, 128.3, 128.4, 129.3, 130.2, 131.0, 139.5, 140.1, 144.0. ESI-MS (*m*/*z*): 210 $[M+H]^+$. HRMS Calcd for $C_{15}H_{16}N$ $[M+H]^+$: 210.1283. Found: 210.1288.

4.2.2. 5-Chloro-2-isopropenylaniline (1i). To a solution of methyl 2-amino-4-chlorobenzoate[22] (0.81 g, 4.36 mmol) in Et_2O (20 mL), MeMgBr (0.96 M in THF, 21 mL, 20 mmol) was added at −78 °C. After being stirred for 24 h at room temperature, the reaction mixture was quenched by saturated aqueous solution of NH_4Cl, and filtered through Celite pad. After the filtrate was extracted with EtOAc (30 mL×3), the organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified with silica gel column chromatography (hexane/EtOAc=10:1) to give 2-(2-amino-4-chlorophenyl)-2-propanol (553 mg, 2.98 mmol, 68% yield) as brown oil. IR (neat, ν cm^{-1}): 3365, 2976, 2931, 1612, 1493, 1417, 1142, 1109, 908. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.59 (6H, s), 4.01 (3H, br, NH_2+OH), 6.55 (1H, d, J=2.1 Hz), 6.61 (1H, dd, J=8.3, 2.1 Hz), 6.97 (1H, d, J=8.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 29.1, 73.7, 116.6, 117.2, 126.8, 129.0, 133.3, 146.8. ESI-MS (*m*/*z*): 186 $[M+H]^+$. HRMS Calcd for $C_9H_{13}ClNO$ $[M+H]^+$: 186.0663. Found: 186.0686. In a similar manner for the preparation of **1e**, reaction of the above carbinol (278 mg, 1.5 mmol) with NH_4Cl (262 mg, 4.5 mmol) for 30 min at 160 °C and the subsequent purification by silica gel column chromatography (hexane/EtOAc=40:1) gave 5-chloro-2-isopropenylaniline **1i** (177 mg, 1.05 mmol, 70% yield) as a colorless oil. IR (neat, ν cm^{-1}): 3475, 3384, 3080, 2970, 1612, 1491, 1417, 1110, 899. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.05 (3H, s), 3.95 (2H, br, NH), 5.06 (1H, s), 5.31 (1H, s), 6.69 (1H, s), 6.71 (1H, d, J=7.9 Hz), 6.95 (1H, d, J=7.9 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 23.7, 115.0, 115.8, 118.0, 127.5, 129.2, 133.1, 142.4, 144.0. EIMS (*m*/*z*): 168 $[M+H]^+$. Anal. Calcd for $C_9H_{10}ClN$: C, 64.48; H, 6.01; N, 8.36. Found: C, 64.68; H, 6.16; N, 7.96.

4.2.3. 3-Isopropenyl-2-naphthalenamine (1j). After a mixture of 2-(3-amino-2-naphthyl)-2-propanol[25] (300 mg, 1.49 mmol) and NH_4Cl (250 mg, 4.5 mmol) was stirred for 1.5 h at 160 °C, purification of the resulting mixture by silica gel column chromatography (hexane/EtOAc=20:1) gave 3-isopropenyl-2-naphthalenamine **1j** (193.2 mg, 1.05 mmol, 67% yield). Yellow crystals. Mp 37.0 °C. IR (KBr, ν cm^{-1}): 3467, 3377, 3053, 2968, 1633, 1504, 1215, 893, 864. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.09 (3H, s), 3.95 (2H, br, NH), 5.06 (1H, br s), 5.29 (1H, br s), 7.10–7.18 (1H, m), 7.23–7.29 (1H, m), 7.44 (1H, s), 7.49 (1H, d, J=8.2 Hz), 7.58 (1H, d, J=8.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 24.1, 108.9, 116.0, 122.5, 125.3, 126.0, 127.1, 127.5, 127.8, 132.5, 134.0, 141.5, 143.4. ESI-MS (*m*/*z*): 184 $[M+H]^+$. HRMS Calcd for $C_{13}H_{14}N$ $[M+H]^+$: 184.1126. Found: 184.1140.

4.3. Typical procedure for cyclization reaction of *o*-vinylanilines with TFAE: 4-methyl-2-(trifluoromethyl)quinoline (2a) and 4-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (3a)

Under Ar atmosphere, a mixture of 2-isopropenylaniline (66.7 mg, 0.50 mmol) and TFAE (128 μL, 1.09 mmol) was stirred for 1 h at room temperature. To the reaction mixture, chlorotrimethylsilane (190 μL, 1.5 mmol) and dehydrated pyridine (2.5 mL) were added at room temperature. After being stirred for 6 h at 100 °C, the reaction mixture was quenched by H_2O (4 mL), and extracted with Et_2O (3 mL×3). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and purified by silica gel column chromatography (hexane/EtOAc=50:1 to 10:1) to give a mixture of 4-methyl-2-(trifluoromethyl)-quinoline **2a** and 4-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline **3a**. Further purification by MPLC (hexane/EtOAc=20:1) gave **3a** (retention time=24.4 min, 91.9 mg, 0.43 mmol, 87% yield) and **2a** (retention time=26.4 min, 8.6 mg, 0.05 mmol, 8% yield). 4-Methyl-2-(trifluoromethyl)quinoline **2a**: colorless crystals. Mp 55.2 °C. IR (KBr, ν cm^{-1}): 3067, 2954, 1714, 1597, 1151. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.78 (3H, s), 7.56 (1H, s), 7.67–7.70 (1H, m), 7.79–7.83 (1H, m), 8.04 (1H, d, J=8.3 Hz), 8.21 (1H, d, J=8.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 19.4, 117.8, 122.1 (q, J=275.3 Hz), 124.2, 128.7, 129.2, 130.8, 131.1, 147.3, 147.4, 148.0 (q, J=34.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −4.9 (3F, s). ESI-MS (*m*/*z*): 212 $[M+H]^+$. HRMS Calcd for $C_{11}H_9F_3N$: 212.0687. Found: 212.0696 $[M+H]^+$. 4-Methyl-2-(trifluoromethyl)-1,2-dihydroquinoline **3a**: colorless oil. IR (neat, ν cm^{-1}): 3410, 3059, 2923, 1607, 1256, 1121,

750. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.08 (3H, s), 4.15 (1H, br s, NH), 4.64–4.73 (1H, m), 5.41 (1H, br d, J=3.8 Hz), 6.50 (1H, br d, J=8.0 Hz), 6.68–6.74 (1H, m), 7.01–7.08 (1H, m), 7.12 (1H, br d, J=7.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 18.8, 54.7 (q, J=31.0 Hz), 110.9, 112.7, 118.3, 120.0, 124.2, 124.2 (q, J=285.0 Hz), 129.4, 135.8, 141.7. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −13.0 (3F, d, J=7.2 Hz). ESI-MS (m/z): 214 $[M+H]^+$. HRMS Calcd for $C_{11}H_{11}F_3N$ $[M+H]^+$: 214.0844. Found: 214.0847.

4.3.1. 2-(Trifluoromethyl)quinoline (2b) and 2-(trifluoromethyl)-1,2-dihydroquinoline (3b). Compounds **2b/3b** were obtained as an inseparable mixture (a ratio was 1:9.6). The structure of **2b** was confirmed by comparison of spectrum data from a commercially available sample. 2-(Trifluoromethyl)-1,2-dihydroquinoline **3b**: colorless oil. IR (neat, ν cm^{-1}): 3689, 3051, 2927, 1649, 1606, 1491, 1255, 1167, 1132, 1120, 840, 748. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.14 (1H, br s), 4.73–4.81 (1H, m), 5.48 (1H, dd, J=9.9, 4.6 Hz), 6.48 (1H, d, J=7.9 Hz), 6.62 (1H, J=9.9 Hz), 6.66 (1H, t, J=7.4 Hz), 6.92 (1H, br d, J=7.4 Hz), 7.03 (1H, t, J=7.9 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 54.8 (q, J=31.2 Hz), 112.6, 113.6, 118.5, 124.0 (q, J=284.8 Hz), 129.7, 130.5, 141.5. ^{19}F NMR (282 MHz, $CDCl_3$, δ ppm): −18.1 (3F, d, J=7.9 Hz). ESI-MS (m/z): 200 $[M+H]^+$. HRMS Calcd for $C_{10}H_9F_3N$: 200.0687. Found: 200.0676 $[M+H]^+$.

4.3.2. 4-Phenyl-2-(trifluoromethyl)quinoline (2c) and 4-phenyl-2-(trifluoromethyl)-1,2-dihydroquinoline (3c). 4-Phenyl-2-(trifluoromethyl)quinoline **2c**: colorless crystals. Mp 59.8 °C. IR (KBr, ν cm^{-1}): 3062, 2777, 1589, 1468, 1383, 1263, 1187, 1136, 1093, 887. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.50–7.59 (6H, m), 7.59–7.67 (1H, m), 7.69 (1H, s), 8.00 (1H, d, J=8.4 Hz), 8.31 (1H, d, J=8.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 117.4, 122.1 (q, J=275.5 Hz), 126.3, 127.8, 129.0, 129.2, 129.4, 129.9, 130.9, 131.0, 137.6, 148.0 (q, J=34.4 Hz), 148.2, 151.3. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −4.7 (3F, s). ESI-MS (m/z): 274 $[M+H]^+$. HRMS Calcd for $C_{16}H_{11}F_3N$ $[M+H]^+$: 274.0844. Found: 274.0839. Anal. Calcd for $C_{16}H_{10}F_3N$: C, 70.33; H, 3.69; N, 5.13. Found: C, 70.26; H, 3.96; N, 4.89. 4-Phenyl-2-(trifluoromethyl)-1,2-dihydroquinoline **3c**: colorless oil. IR (neat, ν cm^{-1}): 3410, 3057, 3028, 1604, 1487, 1313, 1257, 1165, 1122, 864. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.27 (1H, br s, NH), 4.83 (1H, qd, J=7.0, 4.9 Hz), 5.54 (1H, d, J=4.9 Hz), 6.59 (1H, d, J=7.9 Hz), 6.62–6.68 (1H, m), 6.91 (1H, br d, J=7.7 Hz), 7.04–7.12 (1H, m), 7.34–7.48 (5H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 54.7 (q, J=31.1 Hz), 112.6, 113.1, 118.4, 119.6, 124.3 (q, J=285.2 Hz), 126.7, 127.9, 128.3, 128.8, 129.7, 138.5, 142.1, 142.5. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −17.5 (3F, d, J=7.0 Hz). ESI-MS (m/z): 276 $[M+H]^+$. HRMS Calcd for $C_{16}H_{13}F_3N$ $[M+H]^+$: 276.1000. Found: 276.0990.

4.3.3. 2-[(*E*)-2-Phenylethenyl]-*N*-(2,2,2-trifluoroethylidene)aniline (4d). Colorless crystals. Mp 27.0 °C. IR (KBr, ν cm^{-1}): 2742, 2360, 1643, 1357, 1284, 1165, 964. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 6.98 (1H, dd, J=7.9, 1.0 Hz), 7.12 (1H, d, J=16.4 Hz), 7.27–7.41 (4H, m), 7.46–7.57 (3H, m), 7.76 (1H, br d, J=7.7 Hz), 7.81 (1H, q, J=3.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 117.8, 118.9 (q, J=271.6 Hz), 123.7, 126.1, 126.8, 127.9, 128.4, 128.6, 128.7, 131.0, 132.2, 137.3, 145.4, 147.2 (q, J=38.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −8.21 (3F, d, J=3.5 Hz). ESI-MS (m/z): 276 $[M+H]^+$, 196 $[M-C_2HF_3+3H]^+$. HRMS Calcd for $C_{16}H_{13}F_3N$ $[M+H]^+$: 276.1000. Found: 276.0992.

4.3.4. 3-Methyl-4-phenyl-2-(trifluoromethyl)quinoline (2e) and 3-methyl-4-phenyl-2-(trifluoromethyl)-1,2-dihydroquinoline (3e). 3-Methyl-4-phenyl-2-(trifluoromethyl)-quinoline **2e**: colorless crystals. Mp 93.7 °C. IR (KBr, ν cm^{-1}): 3028, 2935, 1572, 1489, 1373, 1178, 1125, 1039, 766, 704. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.35 (3H, q, J=1.7 Hz), 7.22–7.28 (2H, m), 7.40 (1H, d, J=8.5 Hz), 7.46–7.60 (4H, m), 7.69–7.76 (1H, m), 8.22 (1H, d, J=8.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 15.5, 122.3 (q, J=276.5 Hz), 125.9, 126.1, 128.3, 128.4, 128.6, 128.8, 129.1, 129.4, 130.0, 136.4, 144.7, 146.6 (q, J=32.2 Hz), 150.1. ^{19}F NMR (282 MHz, $CDCl_3$, δ ppm): −2.5 (3F, s). ESI-MS (m/z): 288. HRMS Calcd for $C_{17}H_{13}F_3N$ $[M+H]^+$: 288.1000. Found: 288.1012. 3-Methyl-4-phenyl-2-(trifluoromethyl)-1,2-dihydroquinoline **3e**: colorless oil. IR (neat, ν cm^{-1}): 3406, 3055, 3026, 2914, 2856, 1604, 1489, 1251, 1161, 1124. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.77 (3H, s), 4.43 (1H, q, J=7.4 Hz), 6.51 (1H, dd, J=7.8, 1.4 Hz), 6.57 (1H, br d, J=7.5 Hz), 6.61 (1H, d, J=7.8 Hz), 7.01 (1H, td, J=7.5, 1.4 Hz), 7.06–7.14 (1H, m), 7.22–7.14 (1H, m), 7.33–7.50 (3H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 19.8, 58.5 (q, J=29.3 Hz), 112.5, 118.5, 119.4, 122.4, 125.2 (q, J=290.2 Hz), 126.6, 127.3, 128.3, 128.4, 128.5, 129.1, 130.2, 137.8, 137.9, 140.6. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −14.5 (3F, d, J=7.4 Hz). ESI-MS (m/z): 290. HRMS Calcd for $C_{17}H_{15}F_3N$ $[M+H]^+$: 290.1157. Found: 290.1162.

4.3.5. 1-Benzyl-4-methyl-3-phenyl-2-(trifluoromethyl)-1,2-dihydroquinoline (3f). Colorless crystals. Mp 82.1 °C. IR (KBr, ν cm^{-1}): 3021, 2921, 1658, 1602, 1495, 1157, 1124, 858. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.12 (3H, s), 4.32–4.42 (1H, m), 4.44 (1H, d, J=15.8 Hz), 4.86 (1H, d, J=15.8 Hz), 5.47 (1H, d, J=6.0 Hz), 6.65 (1H, d, J=8.2 Hz), 6.72 (1H, t, J=8.2 Hz), 7.04–7.10 (1H, m), 7.16–7.32 (6H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 19.0, 54.5, 58.7 (q, J=29.6 Hz), 112.0, 112.7, 117.8, 123.0, 124.3, 125.4 (q, J=291.0 Hz), 127.3, 127.4, 128.7, 129.2, 136.1, 137.0, 143.0. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −14.0 (d, J=6.9 Hz). ESI-MS (m/z): 304 $[M+H]^+$. HRMS Calcd for $C_{18}H_{17}F_3N$ $[M+H]^+$: 304.1313. Found: 304.1306.

4.3.6. 6,7-Dimethoxy-4-methyl-2-(trifluoromethyl)quinoline (2g). Colorless crystals. Mp 99.0 °C. IR (KBr, ν cm^{-1}): 2968, 1622, 1496, 1248, 1122, 919. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.69 (3H, s), 4.02 (3H, s), 4.04 (3H, s), 7.13 (1H, s), 7.43 (1H, s), 7.94 (1H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 19.4, 56.1, 56.3, 101.1, 108.8, 116.0, 121.9 (q, J=274.8 Hz), 124.6, 144.2, 144.3, 145.4 (q, J=34.0 Hz), 151.1, 153.1. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −4.5 (3F, s). ESI-MS (m/z): 272 $[M+H]^+$. HRMS Calcd for $C_{13}H_{13}F_3NO_2$ $[M+H]^+$: 272.0898. Found: 272.0877.

4.3.7. 7-Chloro-4-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline (3h). Colorless oil. IR (neat, ν cm^{-1}): 3419,

3059, 2979, 2924, 1602, 1257, 1126, 810. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.06 (3H, s), 4.21 (1H, br s, NH), 4.62–4.70 (1H, m), 5.39 (1H, br d, J=4.4 Hz), 6.50 (1H, d, J=2.0 Hz), 6.66 (1H, dd, J=8.2, 2.0 Hz), 7.01 (1H, d, J=8.2 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 19.1, 54.9 (q, J=31.2 Hz), 111.4, 112.9, 118.7, 119.0, 124.4 (q, J=289.3 Hz), 125.8, 135.2, 135.6, 143.1. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −13.0 (3F, d, J=7.2 Hz). ESI-MS (m/z): 246 $[M+H]^+$. HRMS Calcd for $C_{11}H_{18}ClF_3N$ $[M+H]^+$: 246.0297. Found: 246.0285.

4.3.8. 4-Methyl-2-(1,1,2,2,2-pentafluoroethyl)quinoline (2j) and 4-methyl-2-(1,1,2,2,2-pentafluoroethyl)-1,2-dihydroquinoline (3j). 4-Methyl-2-(1,1,2,2,2-pentafluoroethyl)quinoline **2j**: colorless crystals. Mp 73.1 °C. IR (KBr, ν cm^{-1}): 2960, 2920, 1593, 1383, 1330, 1198, 1144, 1109, 1028, 766. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.80 (3H, s), 7.58 (1H, s), 7.67–7.71 (1H, m), 7.79–7.83 (1H, m), 8.07 (1H, br td, J=8.3 Hz), 8.23 (1H, d, J=8.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 19.1, 118.4, 123.8, 128.4, 128.7, 130.3, 130.9, 146.7, 147.1. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −54.1 (2F, s), −20.0 (3F, s). ESI-MS (m/z): 262 $[M+H]^+$. HRMS Calcd for $C_{12}H_9F_5N$ $[M+H]^+$: 262.0655. Found: 262.0655. 4-Methyl-2-(1,1,2,2,2-pentafluoroethyl)-1,2-dihydroquinoline **3j**: colorless oil. IR (neat, ν cm^{-1}): 3419, 3060, 2979, 2925, 1657, 1608, 1491, 1315, 1205, 1119, 1032, 1007, 833, 748. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.08 (br s, 3H), 4.76–4.84 (1H, m), 5.39 (1H, d, J=4.9 Hz), 6.50 (1H, d, J=7.9 Hz), 6.68–6.73 (1H, m), 7.02–7.07 (1H, m), 7.10 (1H, d, J=7.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 18.9, 53.8 (t, J=23.7 Hz), 110.4, 112.7, 118.4, 120.2, 124.2, 129.4, 136.1, 141.8. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −65.0 (1F, dd, J=270, 13.0 Hz), −63.0 (1F, dd, J=270, 10.5 Hz), −18.1 (3F, s). ESI-MS (m/z): 264 $[M+H]^+$. HRMS Calcd for $C_{12}H_{11}F_5N$ $[M+H]^+$: 264.0812. Found: 264.0799.

4.3.9. 2-[Chloro(difluoro)methyl]-4-methylquinoline (2k) and 2-[chloro(difluoro)methyl]-4-methyl-1,2-dihydroquinoline (3k). 2-[Chloro(difluoro)methyl]-4-methylquinoline **2k**: colorless crystals. Mp 52.5 °C. IR (KBr, ν cm^{-1}): 2924, 1637, 1593, 1219, 1134, 1092, 957, 874, 764. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.80 (3H, s), 7.58 (1H, s), 7.68 (1H, br t, J=8.5 Hz), 7.81 (1H, dd, J=8.5, 8.2 Hz), 8.05 (1H, br td, J=8.2 Hz), 8.221 (1H, d, J=8.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 19.1, 116.7, 124.7 (t, J=308.1 Hz), 128.2, 128.6, 130.4, 130.7, 146.7, 147.1. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −7.51 (2F, s). ESI-MS (m/z): 228 $[M+H]^+$. HRMS Calcd for $C_{11}H_9ClF_2N$ $[M+H]^+$: 228.0392. Found: 228.0376. 2-[Chloro(difluoro)-methyl]-4-methyl-1,2-dihydroquinoline **3k**: due to the rapid decomposition, analyses by IR and mass spectroscopies have not been carried out. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.10 (3H, s), 4.70–4.76 (1H, m), 5.48 (1H, d, J=4.6 Hz), 6.52 (1H, d, J=7.9 Hz), 6.70–6.73 (1H, m), 7.05–7.09 (1H, m), 7.13 (1H, d, J=7.7 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 18.9, 60.0 (t, J=26.5 Hz), 111.9, 112.6, 118.2, 120.0, 124.2, 126.6, 129.4, 136.0, 141.6. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −11.7 (1F, dd, J=160, 9.1 Hz), −11.2 (1F, dd, J=160, 7.6 Hz).

4.3.10. Air oxidation reaction of 1,2-dihydroquinoline (3a). After the treatment of 4-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline **3a** (8.6 mg, 0.04 mmol) with air at room temperature for 2 days, the resulting mixture was purified by MPLC (hexane/EtOAc=20:1) to give 4-methyl-2-(trifluoromethyl)quinoline **2a** (26.4 min, 8.3 mg, 0.04 mmol, 98% yield).

4.3.11. Hydrogenation reaction of 1,2-dihydroquinoline: (2*R,4*R**)-4-methyl-2-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (5a).** To a suspension of 5% Pd/C containing 50% w/w H_2O (42 mg, 0.01 mmol, 3 mol %) in MeOH (1.0 mL), a solution of 4-methyl-2-(trifluoromethyl)-1,2-dihydroquinoline **3a** (71.7 mg, 0.34 mmol) in MeOH (1.0 mL) was added. After being stirred at room temperature for 3 h under H_2 atmosphere (1 atm), the reaction mixture was filtered through Celite pad. The filtrate was concentrated under reduced pressure, and purified by column chromatography on silica gel (hexane/EtOAc=50:1) to give (2*R**,4*R**)-4-methyl-2-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline **5a** (73.1 mg, 0.34 mmol, 100% yield) as a single product. Colorless crystals. Mp 42.3 °C. IR (KBr, ν cm^{-1}): 3396, 3058, 2964, 2973, 1610, 1489, 1279, 1140. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.43 (3H, d, J=6.8 Hz), 1.75 (1H, q, J=12.1 Hz), 2.22 (1H, dt, J=12.1, 4.3 Hz), 2.97–3.04 (1H, m), 3.93–3.99 (1H, m), 4.02 (1H, br s, NH), 6.61 (1H, d, J=7.9 Hz), 6.79–6.84 (1H, m), 7.05–7.10 (1H, m), 7.19 (1H, d, J=7.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$, δ ppm): 19.5, 29.2, 30.5, 53.9 (q, J=30.2 Hz), 115.0, 118.9, 125.5 (q, J=279.6 Hz), 126.1, 126.3, 127.2, 129.6, 142.2. ^{19}F NMR (376 MHz, $CDCl_3$, δ ppm): −4.27 (3F, d, J=6.4 Hz). ESI-MS (m/z): 216 $[M+H]^+$. HRMS Calcd for $C_{11}H_{13}F_3N$ $[M+H]^+$: 216.1000. Found: 216.0979.

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