Synthesis of 2-CF_3-Tetrahydroquinoline and Quinoline Derivatives from CF_3-*N*-Aryl-aldimine

Benoît Crousse,* Jean-Pierre Bégué, and Danièle Bonnet-Delpon

Biocis UPRES A CNRS 8076, Centre d'Etudes Pharmaceutiques, Rue J.B. Clément, 92296 Châtenay-Malabry, France

benoit.crousse@cep.u-psud.fr

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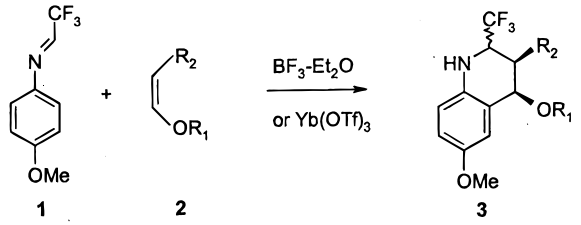
Introduction

Various tetrahydroquinoline derivatives bearing simple or complex substituents are used as pharmaceutical agents.[1] Besides pharmaceutical applications, tetrahydroquinoline derivatives are also useful as pesticides, antioxidants, and corrosion inhibitors.[2]

Among different ways for constructing tetrahydroquinolines, aza-Diels−Alder reaction between *N*-arylimines and dienophiles is an established route to these compounds.[3] However, this reaction requires a Lewis acid catalyst such as $BF_3{\cdot}Et_2O$ and lanthanide salts. It is usually limited to arylaldimines, and it is much less efficient with alkyl aldimines.[4] In fluorinated series, the only example of an aza-Diels−Alder reaction reported concerns a cationic dipolar reaction, where a preformed aryliminium salt is required.[5] Despite this, considering the extraordinary potential of fluoroalkyl-containing biologically relevant molecules,[6] we have studied the aza-Diels−Alder reaction with the (*E*)-α-CF_3-*N*-aryl-aldimine **1**. We have already reported that **1** could react as heterodiene of vinyl enol ethers to give tetrahydroquinolines in the presence of Lewis acids (Scheme 1).[7] We then extended this reaction to other dienophiles to prepare different patterns of 2-CF_3-tetrahydroquinolines. We report here full details of this study and the preparation of new functionalized 2-CF_3-quinolines.

Scheme 1



Results and Discussion

Aza-Diels−Alder Reaction with Vinyl Enol Ethers. The imine **1** is prepared from trifluoroacetaldehyde and *p*-anisidine.[8] The aza-Diels−Alder reaction was first carried out between **1** and the vinyl ether **2a** (Scheme 1, Table 1) under conditions of Povarov[4] (10 mol % of $BF_3{\cdot}Et_2O$). When the reaction was performed in solvents such as dichloromethane, ether, or THF, the yield of the cycloadduct was low. However, when toluene was used as solvent at −78 °C, the tetrahydroquinoline **3a** was obtained in 56% yield with good regio- and stereoselectivities. In the crude product, only traces of the other stereoisomer could be detected. The *cis* configuration was determined by ^1H NMR; large coupling constants between H-4 and H-3ax (10.7 Hz) and H-2 and H-3ax (11.6 Hz) indicate their *trans* diaxial relationship and hence the *cis* relationship between OEt and CF_3 (Scheme 2).

The reaction was then extended to other enol ethers (Table 1). Under the same conditions, butyl enol ether **2b** exhibited a reactivity similar to that of **2a**. With cyclic enol ethers, cycloaddition was efficient; the reaction with the 2,3-dihydrofuran **2c** afforded the tetrahydroquinoline **3c** (84%) as a mixture of *cis* and *trans* isomers in a ratio of 90/10 (*cis*/*trans*), which were separated by SiO_2 column chromatography. Similar results were obtained with the 3,4-dihydro-*2H*-pyran **2d**; however, 1 equiv of catalyst was required to obtain 86% of the tetrahydroquinoline **3d** in a 64/36 ratio (*cis*/*trans*). Configurations were assigned by comparison of NMR data (coupling constants) with those of nonfluorinated parent compounds.[9,10d]

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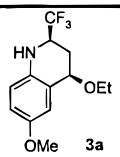
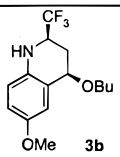
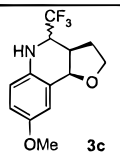
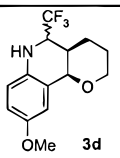
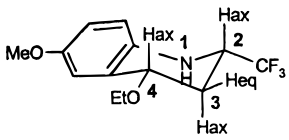
Table 1. Syntheses of Tetrahydroquinoline Derivatives (10 mol % $BF_3{\cdot}Et_2O$)

Entry	2	t	3	*cis/trans*	yield (%)[a]
1	**2a**	20 min	 **3a**	>98/2	56
2	 **2b**	30 min	 **3b**	>98/2	60
3	 **2c**	70 min	 **3c**	90/10	84
4	 **2d**	2h	 **3d**	64/36	86[b]

[a] Isolated yield. [b] 1 equiv of Lewis Acid was required.

Scheme 2



3a

H2ax-H3ax = 11.6 Hz

H3ax-H4ax = 10.7 Hz

Lanthanide triflates have been used to activate imines[10] and promote Diels−Alder reactions. We explored the reaction under 5 mol % of $Yb(OTf)_3$ in acetonitrile at room temperature. The results were roughly similar to those obtained with $BF_3{\cdot}Et_2O$ (Table 2). Tetrahydroquinolines **3a**,**b** were isolated in good yield and with a good diastereoselectivity (*cis* configuration). Lack of stereoselectivity was observed with **2c** and **2d**; tetrahydroquinolines **3c**,**d** were obtained as a 70/30 mixture of *cis* and *trans* isomers.

If we compare these results to those described with nonfluorinated alkyl aldimines,[4] it seems that the CF_3 group favors this aza-Diels−Alder cycloaddition reaction.[11] This could be explained by its electron-withdrawing character, which lowers the LUMO level of the molecule.[11,12] However, concomitantly the CF_3 group also significantly reduces the basicity of carbonyl and imine groups and hence the strength of complexation with a Lewis acid. This suggests that with the imine **1** a concerted mechanism rather than a two-step electrophilic process is favored. This could also explain the high stereoselectivity of the reaction; stabilizing secondary orbital interactions between the alkoxy group and the heterodiene in the six-membered ring transition state favor an *endo* approach of enol ethers as usually observed in Diels−Alder reaction.[13] This high stereoselectivity is not observed with nonfluorinated aldimines, when a two-step process is generally postulated.[10c,14] In the peculiar case of cyclic enol ethers, steric hindrance due to methylene groups could oppose these stabilizing orbital interactions. Despite this activating effect of the CF_3 group, the presence of Lewis acid is required for the success of the reaction. We observed that without Lewis acid, no reaction occurred even under heating.

Table 2. Syntheses of Tetrahydroquinoline Derivatives (5 mol % $Yb(OTf)_3$)

entry	2	t	3	*cis/trans*	yield (%)[a]
1	**2a**	15 min	**3a**	>98/2	56
2	**2b**	40 min	**3b**	>98/2	67
3	**2c**	30 min	**3c**	70/30	74
4	**2d**	6 h	**3d**	70/30	87

[a] Isolated yield.

Reaction with Other Dienophiles. We then explored this reaction with terminal vinylsulfide and with other unsaturated compounds that are expected to be less reactive in this reaction: enamide, vinylcarbamate, and styrene (Table 3).

Reactions were performed under the same conditions as for enol ethers under $BF_3{\cdot}Et_2O$ catalysis. The vinyl sulfide **2e** was a good heterodienophile in this [4 + 2] cycloaddition reaction, which led to the tetrahydroquinoline **3e** in 86% yield. With the enamide **2f** and the vinylcarbamate **2g**,[15] which are less electron-rich, reaction required a higher temperature (−20 °C) and tetrahydroquinolines **3f** and **3g** were also obtained in good yields, 70% and 82%, respectively. Even styrene smoothly reacted with imine **1** to afford the corresponding tetrahydroquinoline **3h** in high yield. In all cases, only one regio- and stereoisomer was obtained. The *cis* configuration between substituents was determined by measurement of H−H coupling constants in NMR spectra. These results seem to confirm a concerted process previously postulated.

When $Yb(OTf)_3$ was used as catalyst, the reaction was successful with **2e** and led selectively to the tetrahydroquinoline **3e** in 84% yield (*cis*/*trans*: >98/2). However, with less electron-rich **2f**, **2g**, and **2h**, no reaction was observed. Starting material was recovered.

Reaction with Dienes. CF_3-*N*-tosyl-imines are known to react as dienophiles with dienes.[16] We have thus investigated the reactivity of the imine **1** toward dienes.

At first, the reaction was performed between imine **1** and cyclopentadiene under $BF_3{\cdot}Et_2O$ or $Yb(OTf)_3$ catalysis (Scheme 3).

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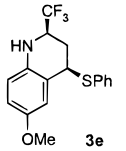
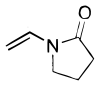
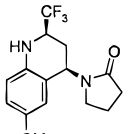
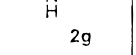
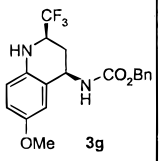
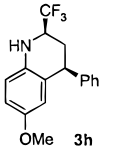
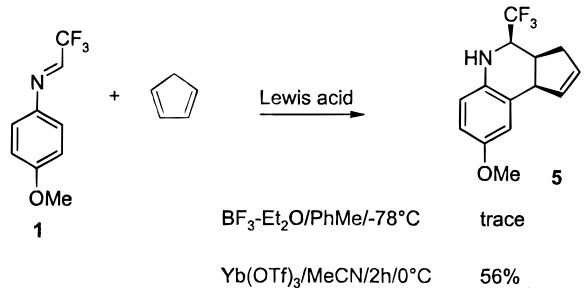
Table 3. Syntheses of Tetrahydroquinoline Derivatives (10 mol % BF_3·Et_2O)

Entry	2	t	3	*cis/trans*	Yield (%)[a]
1	 **2e**	2h	 **3e**	>98/2	86
2	 **2f**	1h	 **3f**	>98/2	70[b]
3	 **2g**	1h	 **3g**	>98/2	82[b]
4	 **2h**	1h	 **3h**	>98/2	90[b]

[a] Isolated yield. [b] −78 to −20 °C.

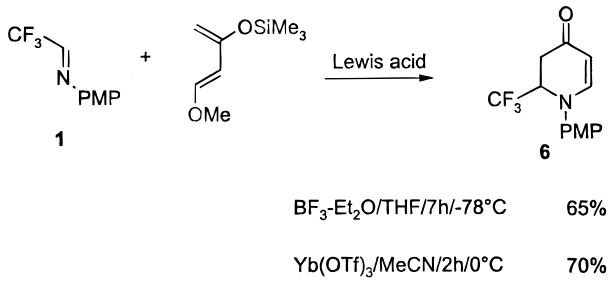
Scheme 3



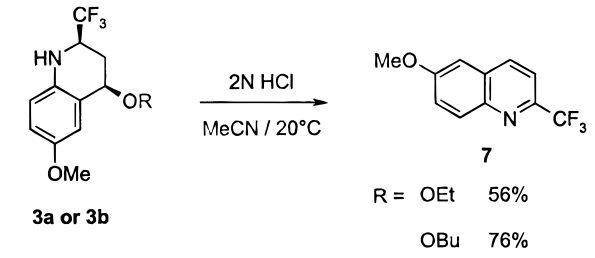
The use of BF_3·Et_2O (1 equiv or 10 mol %) afforded the tetrahydroquinoline **5** in a trace amount, and no other cycloadduct was obtained. In the presence of $Yb(OTf)_3$ (5 mol %), compound **5** (*cis* configuration) could be isolated at room temperature in a 56% yield. In this reaction, the imine **1** acted as an azadiene and reacted with one of the double bonds of cyclopentadiene. The striking efficiency of $Yb(OTf)_3$ compared to that of BF_3·Et_2O has not been elucidated. Examples of an aza-Diels−Alder reaction in which cyclopentadiene acts as dienophile have been reported with $InCl_3$.[17]

Conversely, when the imine **1** was treated with 1-methoxy-3-(trimethylsiloxy)buta-1,3-diene (Danishefsky's diene) in the presence of 1 equiv of BF_3·Et_2O or 5 mol % of $Yb(OTf)_3$, it reacted as a dienophile and afforded smoothly the corresponding tetrahydropyridine **6** as the sole regioisomer (Scheme 4). This type of cycloaddition with Danishefsky's diene had already been reported in cycloaddition reaction with the CF_2H parent of the imine **1**.[18]

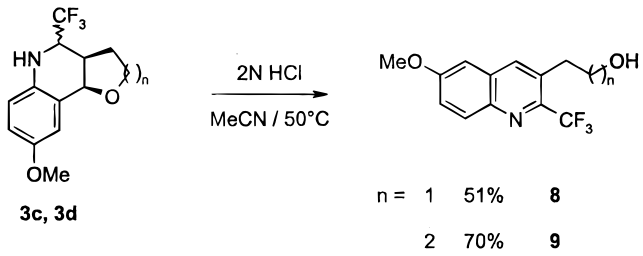
Scheme 4



Scheme 5



Scheme 6



Preparation of Quinolines. Because of their potential biological activity, considerable interest has been directed toward the synthesis of fluorinated quinolines,[19] e.g., mefloquine has been developed as a highly effective antimalarial drug.[20] We thus studied the conversion of tetrahydroquinolines, stemming from vinyl ethers, into quinolines. Under acidic conditions (2 N HCl in MeCN),[10a] **3a** and **3b** provided the quinoline **7** in 56% and 76%, respectively (Scheme 5).

With the tetrahydroquinolines **3c** and **3d**, quinolines **8** (51%) and **9** (70%), with a functionalized substituent in C-3, could be obtained (Scheme 6).

In conclusion, we have reported a route to new CF_3-substituted tetrahydroquinolines and quinolines. We have shown that the imine **1** exhibits a high reactivity in aza-Diels−Alder reactions catalyzed by Lewis acids (BF_3·Et_2O, $Yb(OTf)_3$). With substituted olefins, **1** acts as heterodiene involving the unsaturation of the aryl group. Tetrahydroquinolines are obtained in good yields with electron-rich and electron-poor olefins. Unlike what was

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observed in nonfluorinated series, the reaction is highly stereoselective, strongly suggesting a concerted process. With dienes, **1** reacts either as heterodiene or as dienophile depending on the structure of the diene. CF_3-substituted tetrahydroquinolines could be converted in acidic medium into corresponding quinolines. These compounds are under biological assays for potential antiparasitic activity.

Experimental Section

Structures of compounds were determinated by COSY, hmqc, and hmbc experiments and by NOE measurements. Elemental analyses were performed by the Service de Microanalyses of the Centre d'Etudes Pharmaceutiques, Châtenay-Malabry. All reactions were performed in an oven-dried apparatus under an inert atmosphere of argon.

Typical Procedure for the Synthesis of Substituted Tetrahydroquinolines. With BF_3·Et_2O. To a solution of **1** (306 mg, 1.5 mmol) in dry toluene (5 mL) was added, at −78 °C, BF_3·Et_2O (0.02 mL, 0.15 mmol). After the mixture stirred for 10 min, **2a** (166 mg, 2.26 mmol) in dry toluene (1 mL) was added. The reaction mixture was stirred for 20 min, then saturated aqueous $NaHCO_3$ (10 mL) was added, and the product was extracted with ether (3 × 10 mL). After the usual workup, chromatography on silica gel (petroleum ether/ethyl acetate, 20%) afforded 232 mg (56%) of **3a**.

With $Yb(OTf)_3$. To a solution of $Yb(OTf)_3$ (31 mg, 0.05 mmol) in MeCN (1 mL) was added imine **1** (203 mg, 1.0 mmol) and **2a** (0.108 mg, 1.5 mmol) in MeCN (1.5 mL) at room temperature. The reaction mixture was stirred for 15 min, then a saturated aqueous $NaHCO_3$ solution (10 mL) was added, and the product was extracted with ether (10 mL × 3). After usual workup, chromatography on silica gel afforded 154 mg (56%) of **3a**.

4-Ethoxy-6-methoxy-2-trifluoromethyl-1,2,3,4-tetrahydroquinoline (3a). Mp: 99 °C (petroleum ether); white solid. ^{1}H NMR: δ 1.31 (t, CH_3, J = 7.0 Hz, 3H); 1.97 (ddd, H-3ax, J = 12.1, 11.6, 10.7 Hz, 1H); 2.48 (ddd, H-3eq, J = 12.2, 5.5, 2.2 Hz, 1H); 3.60 (qd, 1H, OCH_2CH$_3$, J = 9.0, 7.0 Hz); 3.70 (s, NH, 1H); 3.76 (s, OCH_3, 3H); 3.77 (qd, OCH_2CH$_3$, J = 9.0, 7.0 Hz, 1H); 3.91 (dqd, H-2, J = 11.6, 6.9, 3.2 Hz, 1H); 4.66 (dd, H-4, J = 10.7, 5.5 Hz, 1H); 6.55 (d, H-8, J = 8.8 Hz, 1H); 6.70 (dd, H-7, J = 8.8, 2.2 Hz, 1H); 6.96 (d, H-5, J = 2.9 Hz, 1H). ^{13}C NMR: δ 15.5, 27.3, 53.2 (q, $^2J_{C-F}$ = 30 Hz), 55.7, 64.0, 72.3, 111.8, 115.0, 116.3, 124.3, 125.5 (q, $^1J_{C-F}$ = 278 Hz), 135.8, 153.3. ^{19}F NMR: δ −78.4 (d, J = 6.9 Hz). Anal. Calcd for $C_{13}H_{16}O_2NF_3$: C, 56.72; H, 5.85; N, 5.08. Found: C, 56.58; H, 6.01; N, 4.95.

4-Butyl-6-methoxy- 2-trifluoromethyl-1,2,3,4-tetrahydroquinoline (3b). Mp: 85 °C (petroleum ether); white solid. ^{1}H NMR: δ 0.96 (t, CH_3, J = 7.3 Hz, 3H); 1.47−1.66 (m, CH_2CH_2-CH_3, 4H); 1.95 (dt, H-3ax, J = 12.0, 10.7 Hz, 1H); 2.49 (ddd, H-3eq, J = 12.2, 5.4, 3.2 Hz, 1H); 3.54 (dt, OCH_2, J = 9.0, 6.6 Hz, 1H); 3.70 (s, NH, 1H); 3.72 (dt, OCH_2, J = 9.0, 6.6 Hz, 1H); 3.75 (s, OCH_3, 3H); 3.91 (dqd, H-2, J = 11.7, 6.5, 3.2 Hz, 1H); 4.64 (dd, H-4, J = 11.6, 6.6, 3.2 Hz, 1H); 6.55 (d, H-8, J = 8.6 Hz, 1H); 6.69 (dd, H-7, J = 8.6, 2.9 Hz, 1H); 6.96 (d, H-5, J = 2.9 Hz, 1H). ^{13}C NMR: δ 13.9, 19.5, 27.2, 32.2, 53.3 (q, $^2J_{C-F}$ = 30.2 Hz), 55.7, 68.5, 72.5, 111.7, 114.9, 116.3, 124.4, 125.5 (q, $^1J_{C-F}$ = 278 Hz), 135.8, 153.2. ^{19}F NMR: δ −78.4 (d, J = 6.5 Hz). Anal. Calcd for $C_{15}H_{20}O_2NF_3$: C, 59.25; H, 6.64; N, 4.61. Found: C, 59.25; H, 6.82; N, 4.50.

8-Methoxy-4-trifluoromethyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-*c*]quinoline (3c). *cis*-3c. Mp: 154 °C (petroleum ether); white solid. ^{1}H NMR: δ 1.99 (m, H-3, 1H); 2.22 (m, H-3, 1H); 2.84 (m, H-3a, 1H); 3.67 (s, NH, 1H); 3.75 (s, OCH_3, 3H); 3.81 (td, H-2, J = 9.0, 4.0 Hz, 1H); 3.87 (td, H-2, J = 8.0, 7.4 Hz, 1H); 4.01 (qdd, H-4, J = 7.0, 2.4, 1.5 Hz, 1H); 5.2 (d, H-9b, J = 7.5 Hz, 1H); 6.58 (d, H-6, J = 9.0 Hz, 1H); 6.72 (dd, H-7, J = 9.0, 2.9 Hz, 1H); 6.89 (d, H-9, J = 3.0 Hz, 1H). ^{13}C NMR: δ 24.1, 37.2, 54.7 (q, $^2J_{C-F}$ = 29.4 Hz), 55.6, 66.8, 75.3, 113.1, 116.1, 116.7, 123.1, 125.3 (q, $^1J_{C-F}$ = 278.2 Hz), 135.8, 153.9. ^{19}F NMR: δ −76.1 (d, J = 7.0 Hz). Anal. Calcd for $C_{13}H_{14}O_2NF_3$: C, 57.09; H, 5.16; N, 5.12. Found: C, 56.89; H, 5.28; N, 4.98.

***trans*-3c.** Mp: 98 °C (petroleum ether); white solid. ^{1}H NMR: δ 2.12 (dq, H-3, J = 13.0, 7.0 Hz, 1H); 2.27 (dtd, H-3, J = 13.0, 8.0, 5.0 Hz, 1H); 2.7 (dq, H-3a J = 8.3, 6.6 Hz, 1H); 3.56 (qd, H-4, J = 7.0, 6.6 Hz, 1H); 3.75 (s, OCH_3, 3H); 3.85 (td, H-2, J = 8.0, 7.2 Hz, 1H); 3.93 (td, H-2, J = 8.5, 5.0 Hz, 1H); 3.95 (s, NH, 1H); 4.77 (d, H-9b, J = 6.5 Hz, 1H); 6.58 (d, H-6, J = 9.0 Hz, 1H); 6.74 (dd, H-7, J = 9.0, 3.0 Hz, 1H); 6.9 (d, H-9, J = 2.9 Hz, 1H). ^{13}C NMR: δ 29.2, 35.9, 54.8 (q, $^2J_{C-F}$ = 28 Hz), 55.7, 65.6, 73.9, 113.5, 116.4, 115.8, 121.0, 125.5 (q, $^1J_{C-F}$ = 278 Hz), 135.0, 153.0. ^{19}F NMR: δ −75.9 (d, J = 7.0 Hz). Anal. Calcd for $C_{13}H_{14}O_2NF_3$: C, 57.09; H, 5.16; N, 5.12. Found: C, 56.97; H, 5.24; N, 5.04.

9-Methoxy-5-trifluoromethyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline (3d). *cis*-3d. Mp: 164 °C (petroleum ether/ether: 30%); white solid. ^{1}H NMR: δ 1.52−1.85 (m, H-3, H-4, 4H); 2.46 (m, H-4a, 1H); 3.44 (td, H-2ax, J = 12.0, 2.2 Hz, 1H); 3.62 (ddt, H-2eq, J = 11.5, 4.4, 1.6 Hz, 1H), 3.74 (s, NH, 1H); 3.76 (s, OCH_3, 3H); 3.87 (qd, H-5, J = 7.4, 2.3 Hz, 1H); 5.09 (d, H-10b, J = 5.5 Hz, 1H); 6.6 (d, H-7, J = 8.7 Hz, 1H); 6.73 (dd, H-8, J = 8.7, 2.8 Hz, 1H); 6.98 (d, H-10, J = 2.9 Hz, 1H). ^{13}C NMR: δ 18.6, 24.7, 32.0, 55.7, 57.1 (q, $^2J_{C-F}$ = 29.6 Hz), 60.6, 71.1, 111.6, 115.3, 116.8, 121.6, 125.3 (q, $^1J_{C-F}$ = 280.4 Hz), 136.6, 153.8. ^{19}F NMR: δ −74.1 (d, J = 7.5 Hz). Anal. Calcd for $C_{14}H_{16}O_2NF_3$: C, 58.52; H, 5.62; N, 4.88. Found: C, 58.66; H, 5.80; N, 4.79.

***trans*-3d.** Mp: 106 °C (petroleum ether/ether, 30%); white solid. ^{1}H NMR: δ 1.6−1.9 (m, H-3, H-4, 4H); 2.28 (m, H-4a, 1H); 3.75 (s × 2, OCH_3 and NH, 4H); 3.80 (m, H-2, 2H); 3.90 (qd, H-5, J = 6.8, 6.6 Hz, 1H); 4.6 (br, H-10b, 1H); 6.56 (d, H-7, J = 8.6 Hz, 1H); 6.74 (dd, H-8, J = 8.6, 2.9 Hz, 1H); 6.85 (d, H-10, J = 2.9 Hz, 1H). ^{13}C NMR: δ 23.3, 24.6, 31.8, 54.4 (q, $^2J_{C-F}$ = 29.4 Hz), 55.8, 65.4, 72.0, 110.3, 113.3, 115.8, 120.4, 125.0 (q, $^1J_{C-F}$ = 280.2 Hz), 135.9, 152.9. ^{19}F NMR: δ −75.6 (d, J = 6.8 Hz). Anal. Calcd for $C_{14}H_{16}O_2NF_3$: C, 58.52; H, 5.62; N, 4.88. Found: C, 58.52; H, 5.73; N, 4.80.

6-Methoxy-4-thiophenyl-2-trifluoromethyl-1,2,3,4-tetrahydroquinoline (3e). Mp: 112 °C (petroleum ether/ether, 30%); yellow solid. ^{1}H NMR: δ 2.15 (td, H-3, J = 12.9, 11.5 Hz, 1H); 2.46 (ddd, H-3, J = 13.0, 5.7, 3.0 Hz, 1H); 3.75 (s, OCH_3, 3H); 3.80 (s, NH, 1H); 3.82 (m, H-2, 1H); 4.46 (dd, H-4, J = 11.5, 5.7 Hz, 1H); 6.57 (d, H-8, J = 8.7 Hz, 1H); 6.71 (dd, H-7, J = 8.7, 2.3 Hz, 1H); 7.25−7.33 (m, H-5 and *Ph*, 4H); 7.44 (m, *Ph*, 2H). ^{13}C NMR: δ 30.2, 44.1, 54.1 (q, $^2J_{C-F}$ = 30.2 Hz), 55.8, 113.7, 115.3, 116.9, 122.2, 127.7, 129.2, 130.8 (q, $^1J_{C-F}$ = 300 Hz), 132.5, 136.5, 153.2, 175.8. ^{19}F NMR: δ −79.1 (d, J = 6.4 Hz). Anal. Calcd for $C_{17}H_{16}ONSF_3$: C, 60.16; H, 4.76; N, 4.13. Found: C, 60.14; H, 4.86; N, 4.05.

6-Methoxy-4-pyrrolidin-(2′-one)-2-trifluoromethyl-1,2,3,4-tetrahydroquinoline (3f). Mp: 178 °C (petroleum ether/AcOEt, 20%); white solid. ^{1}H NMR: δ 1.94−2.26 (m, H-3 and CH_2CH$_2$-CO, 4H); 2.50 (m, CH_2CO, 2H); 3.22 (m, CH_2N, 2H); 3.71 (s, OCH_3, 3H); 3.82 (s, NH, 1H); 3.98 (m, H-2, 1H); 5.60 (dd, H-4, J = 11.6, 6.0 Hz, 1H); 6.42 (d, H-5, J = 2.5 Hz, 1H); 6.61 (d, H-8, J = 8.7 Hz, 1H); 6.71 (dd, H-7, J = 8.9, 2.7 Hz, 1H). ^{13}C NMR: δ 18.1, 25.0, 31.1, 42.1, 46.7, 53.6 (q, $^2J_{C-F}$ = 30.6 Hz), 55.6, 111.6, 114.5, 117.1, 120.3, 125.0 (q, $^1J_{C-F}$ = 279.3 Hz), 137.1, 153.3, 175.8. ^{19}F NMR: δ −78.7 (d, J = 5.7 Hz). Anal. Calcd for $C_{15}H_{17}O_2N_2F_3$: C, 57.32; H, 5.45; N, 8.91. Found: C, 57.10; H, 5.31; N, 8.70.

6-Methoxy-4-carbamic Acid Benzyl Ester-2-trifluoromethyl-1,2,3,4-tetrahydroquinoline (3g). Mp: 148 °C (petroleum ether/AcOEt, 20%); white solid. ^{1}H NMR: δ 1.87 (dt, H-3ax, J = 12.6, 11.0 Hz, 1H); 2.52 (ddd, H-3eq, J = 12.7, 5.6, 3.2 Hz, 1H); 3.76 (s, NH, 1H); 3.7 (s, OCH_3, 3H); 3.95 (dqd, H-2, J = 13.2, 6.5, 3.2 Hz, 1H); 4.97 (d, NH, J = 9.3 Hz, 1H); 5.07 (dt, H-4, J = 10.3, 5.6 Hz, 1H); 5.18 (s, OCH_2Ph, 2H); 6.56 (d, H-8, J = 8.7 Hz, 1H); 6.70 (dd, H-7, J = 8.6, 3.0 Hz, 1H); 6.75 (d, H-5, J = 3.2 Hz, 1H); 7.38 (m, *Ph*, 5H). ^{13}C NMR: δ 29.0, 46.7, 53.1 (q, $^2J_{C-F}$ = 30.6 Hz), 55.7, 67.0, 111.7, 115.1, 116.6, 123.7, 125.1 (q, $^1J_{C-F}$ = 280 Hz), 128.1, 128.2, 128.5, 136.1, 136.2, 153.2, 156.2. ^{19}F NMR: δ −78.2 (d, J = 6.6 Hz). Anal. Calcd for $C_{19}H_{19}O_3N_2F_3$: C, 59.97; H, 5.04; N, 7.37. Found: C, 59.97; H, 5.07; N, 7.32.

6-Methoxy-4-phenyl-2-trifluoromethyl-1,2,3,4-tetrahydroquinoline (3h). Mp: 160 °C (petroleum ether); white solid. ^{1}H NMR: δ 2.16 (td, H-3ax, J = 12.7, 12.0 Hz, 1H); 2.38 (ddd, H-3eq, J = 12.7, 5.3, 3.1 Hz, 1H); 3.57 (s, OCH_3, 3H); 3.9 (s, NH, 1H), 4.02 (m, H-2, 1H); 4.13 (dd, H-4, J = 12.6, 5.1 Hz, 1H); 6.18 (m, H-8, 1H); 6.63 (m, H-5, H-7, 2H); 7.18−7.4 (m, *Ph*, 5H).

^{13}C NMR: δ 31.4, 43.0, 54.4 (q, $^2J_{C-F}$ = 30 Hz), 55.6, 113.5, 115.0, 116.2, 125.3 (q, $^1J_{C-F}$ = 278 Hz), 126.3, 127.1, 128.7, 128.8, 136.6, 143.7, 152.9. ^{19}F NMR: δ −78.7 (d, J = 6.7 Hz). Anal. Calcd for $C_{17}H_{16}ONF_3$: C, 66.43; H, 5.26; N, 4.56. Found: C, 66.44; H, 5.37; N, 4.50.

8-Methoxy-4-trifluoromethyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (5). Mp: 123 °C (petroleum ether/ether, 30%); brown solid. ^{1}H NMR: δ 2.33 (ddd, H-3, J = 16.5, 9.0, 2.8, 1H); 2.72 (dd, H-3, J = 16.5, 8.7 Hz, 1H); 3.00 (qd, H-3a, J = 9.0, 2.9 Hz, 1H); 3.59 (s, NH, 1H); 3.74 (s, O*CH*$_3$, 3H); 3.93 (qd, H-4, J = 7.5, 3.0 Hz, 1H); 4.01 (d, H-9b, J = 9.0 Hz, 1H); 5.76 (dtd, H-2, J = 5.8, 2.9, 1.3 Hz, 1H); 5.88 (ddt, H-1, J = 5.9, 2.9, 1.3 Hz, 1H); 6.60 (m, H-6, H-7, H-9, 3H). ^{13}C NMR: δ 31.2, 38.0, 46.2, 55.6, 55.8 (q, $^2J_{C-F}$ = 29 Hz), 112.8, 113.8, 117.5, 125.7 (q, $^1J_{C-F}$ = 279.5 Hz), 126.4, 131.0, 132.7, 136.3, 153.7. ^{19}F NMR: δ −74.6 (d, J = 7.5 Hz). Anal. Calcd for $C_{14}H_{14}ONF_3$: C, 62.44; H, 5.24; N, 5.20. Found: C, 62.46; H, 5.37; N, 5.08.

2-Trifluoromethyl-1-*p*-methoxyphenyl-2,3-dihydro-1*H*-pyridin-4-one (6). To a solution of imine **1** (203 mg, 1.0 mmol) and BF_3·Et_2O (1.0 mmol, 0.12 mL) in THF (8 mL) was added at −78 °C 2-[(trimethylsilyl)oxy]-1,3-butadiene (258 mg, 1.5 mmol). After 7 h of stirring, the reaction mixture was quenched with water (15 mL) and extracted with ether (3 × 10 mL). The extracts were dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography gave **6** (176 mg, 65%) as a brown oil. ^{1}H NMR: δ 2.77 (d, H-3, J = 17.4 Hz, 1H); 3.14 (dd, H-3, J = 17.4, 7.5 Hz, 1H); 3.82 (s, O*CH*$_3$, 3H); 4.48 (quint, H-2, J = 7.5 Hz, 1H); 5.22 (d, H-5, J = 8.1 Hz, 1H); 6.92 (m, *Ph*, 2H); 7.14 (m, *Ph*, 2H); 7.26 (d, H-6, J = 8.1 Hz, 1H). ^{13}C: δ 34.4, 55.4, 59.8 (q, $^2J_{C-F}$ = 29.2 Hz), 101.4, 114.9, 123.5, 125.9 (q, $^1J_{C-F}$ = 286.4 Hz), 138.1, 149.8, 157.8, 188.2. ^{19}F NMR: δ −72.7 (d, J = 7.5 Hz). Anal. Calcd for $C_{13}H_{12}O_2NF_3$: C, 57.56; H, 4.46; N, 5.16. Found: C, 57.62; H, 4.60; N, 5.21.

General Procedure for the Synthesis of Substituted Quinolines. Tetrahydroquinoline (0.9 mmol) (**3a**−**d**) was added to a solution of 2 N HCl (2 mL) in acetonitrile, and the mixture was stirred at room temperature or at reflux. The reaction was followed by GC and TLC. The mixture was quenched with a saturated solution of Na_2CO_3 and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (petroleum ether/AcOEt, 40%) to give analytically pure quinoline derivatives **7**−**9**.

6-Methoxy-2-trifluoromethyl-quinoline (7). Mp: 59 °C (petroleum ether) (lit.[19d] 54.5−57 °C), colorless solid. ^{1}H NMR: δ 3.95 (s, 3H, O*CH*$_3$); 7.11 (d, H-5, J = 2.7 Hz, 1H); 7.45 (dd, H-7, J = 9.3, 2.7 Hz, 1H); 7.68 (d, H-8, J = 8.6 Hz, 1H); 8.1 (d, H-4, J = 9.3 Hz, 1H); 8.21 (d, H-3, J = 8.6 Hz, 1H). ^{13}C NMR: δ 55.6, 104.7, 117.1, 121.8 (q, $^1J_{C-F}$ = 280 Hz), 124.0, 130.3, 131.5, 136.4, 143.3, 145.1, 159.3. ^{19}F NMR: −67.4 (s). Anal. Calcd for $C_{11}H_8ONF_3$: C, 58.10; H, 3.52; N, 6.16. Found: C, 57.98; H, 3.53; N, 6.09.

3-(2′-Hydroxy)ethyl-2-trifluoromethyl-6-methoxy-quinoline (8). Mp: 103 °C (petroleum ether/ether, 30%). ^{1}H NMR: δ 1.80 (s, OH, 1H); 3.18 (t, H-2, J = 6.4 Hz, 2H); 3.93 (s, O*CH*$_3$, 3H); 3.97 (t, H-1, J = 6.4 Hz, 2H); 7.04 (d, H-5, J = 2.7 Hz, 1H); 7.38 (dd, H-7, J = 9.2, 2.7 Hz, 1H); 8.03 (d, H-8, J = 9.2 Hz, 1H); 8.10 (s, H-4, 1H). ^{13}C NMR: δ 34.4, 55.6, 62.4, 104.1, 122.3 (q, $^1J_{C-F}$ = 274 Hz), 123.4, 129.3, 130.2, 131.1, 138.2, 141.2, 143.6 (q, $^2J_{C-F}$ = 31.7 Hz), 159.5. ^{19}F NMR: δ −63.6 (s). Anal. Calcd for $C_{13}H_{12}O_2NF_3$: C, 57.56; H, 4.46; N, 5.16. Found: C, 57.67; H, 4.40; N, 5.07.

3-(3′-Hydroxy)propyl-2-trifluoromethyl-6-methoxy-quinoline (9). Brown oil. ^{1}H NMR: δ 1.96 (m, H-2, 2H); 2.30 (s, OH, 1H); 3.01 (t, H-3, J = 7.5 Hz, 2H); 3.76 (t, H-1, J = 6.4 Hz, 2H); 3.91 (s, O*CH*$_3$, 3H); 7.01 (d, H-5, J = 2.7 Hz, 1H); 7.35 (dd, H-7, J = 9.3, 2.7 Hz, 1H); 8.00 (s, H-4, 1H); 8.02 (d, H-8, J = 9.3 Hz, 1H). ^{13}C NMR: δ 27.5, 33.8, 55.6, 61.9, 104.0, 122.4 (q, $^1J_{C-F}$ = 273.5 Hz), 123.2, 130.5, 131.1, 132.6, 137.1, 141.1, 143.6 (q, $^2J_{C-F}$ = 33.1 Hz), 159.4. ^{19}F NMR: δ −63.8 (s). Anal. Calcd for $C_{14}H_{14}O_2NF_3$: C, 58.94; H, 4.94; N, 4.91. Found: C, 59.20; H, 5.06; N, 5.12.

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