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Synthesis of 4-Perfluoroalkylquinolines

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Abstract

4-($C_{n-1}F_{2n-1}$)-Substituted quinolines (n = 2-4) are obtained by the reaction of 2-(C_nF_{2n+1})-substituted anilines **1** with lithium enolate of acetaldehyde. A similar treatment of **1** with lithium enolates of methyl ketones, the treatment of **1** with lithium phenylacetylide or cyclization of ketimines derived from **1** and aryl methyl ketones furnish the corresponding 2-aryl-4-perfluoroalkylquinolines. The reaction of **1** with lithiated carbonitriles RCH(Li)CN (R = H, alkyl) provides an easy access to 2-amino-4-perfluoroalkyl-3-R-quinolines.

The activated trifluoromethyl group, such as in **1** (R^f = F, Scheme 1), its para isomer or analogs, has already found a solid place in organic synthesis as a valuable synthon for various functionalities and heterocyclic systems [1]. It is believed that the first step of these base-mediated one-pot transformations is ionization followed by elimination of fluoride ion, as illustrated by the formation of an intermediate product **2** from **1**. Then the intermediate **2** undergoes aromatization by the addition reaction with a nucleophile. The subsequent steps depend on the nature of the nucleophilic species and may include a similar elimination/addition pathway and/or cyclization with the involvement of the ortho amino group. An example of the latter pathway is illustrated by the cyclization of **3** to 4-fluoroquinoline (**4**, R^f = F) [2]. Similar approaches to 2-substituted and 2,3-disubstituted 4-fluoroquinolines have been described [2,3].

Recently we have shown for the first time that base-mediated transformations of higher ortho- and para-perfluoroalkyl-substituted anilines permit regioselective modifications at the benzylic CF_2 position of the perfluoroalkyl group [4]. Preliminary results have also strongly suggested that the ortho amino/C_nF_{2n+1} functionality of **1** may serve as a general synthon for the construction of quinolines containing a $C_{n-1}F_{2n-1}$ group at the 4-position. Several successful approaches involving inter- and intramolecular cyclizations are discussed in this paper. The new synthetic routes to 4-

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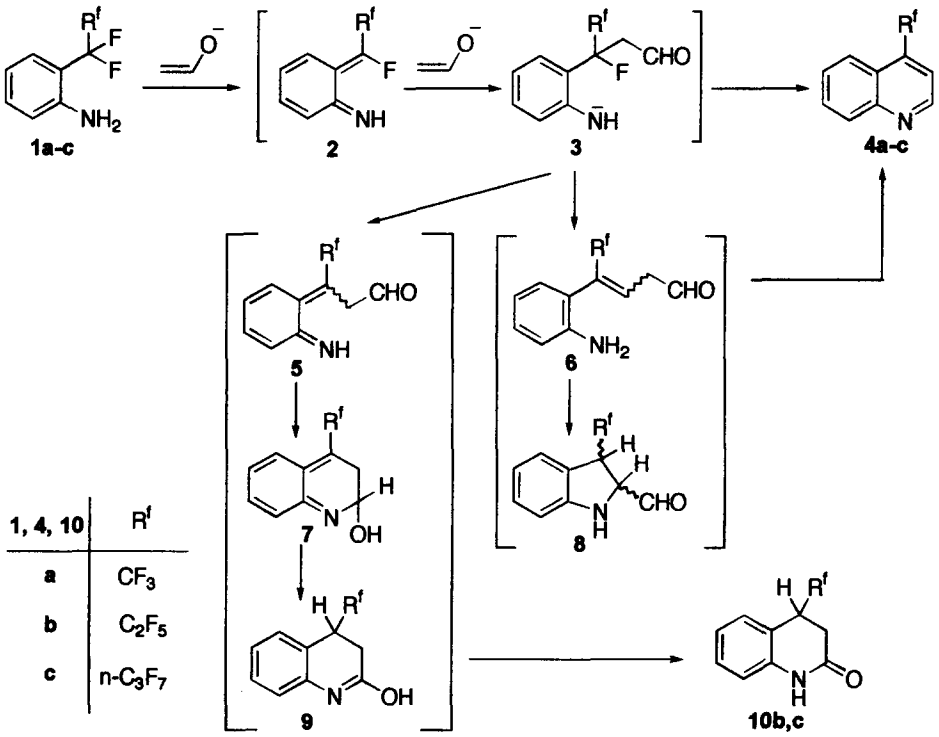
perfluoroalkylquinolines are more versatile than the Friedländer reactions of 2-perfluoroacylanilines or their diethyl acetals reported by us recently [5]. We are aware of no other reports on the synthesis of 4-perfluoroalkylquinolines.

This work has been strongly encouraged by the ready accessibility of substrates **1**. Their preparation involves Ullmann coupling of 2-iodoaniline with a perfluoroalkyl iodide [6] or a direct perfluoroalkylation of aniline with the perfluoroalkyl iodide under reductive conditions that involve the intermediacy of a perfluoroalkyl radical [7].

Results and Discussion

The treatment of **1** (1 equiv) with lithium enolate of acetaldehyde (5 equiv) gave the corresponding 4-perfluoroalkylquinoline **4** in yields of 40-55 % (Scheme 1). A smaller amount of the lithium reagent resulted in an annoying aldol condensation of acetaldehyde and the presence of anilines **1** in crude mixtures.

Scheme 1

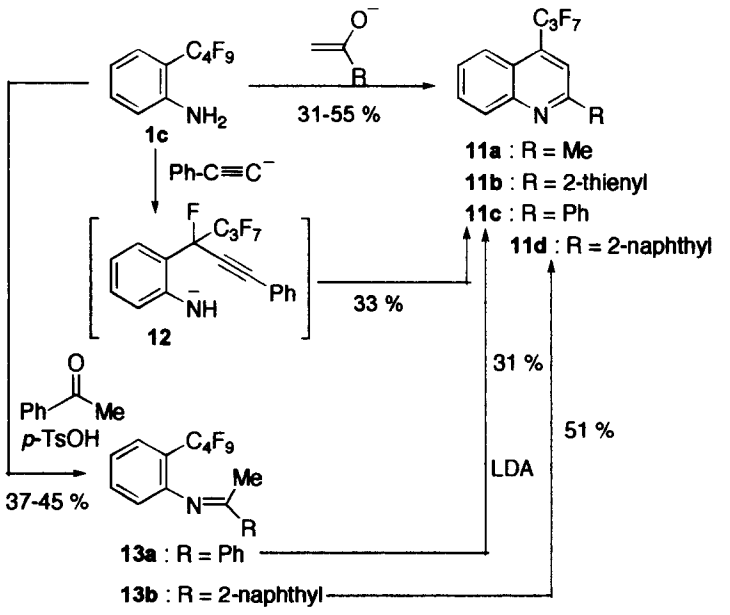


1, 4, 10	R^f
a	CF_3
b	C_2F_5
c	n-C_3F_7

Despite the modest yields of **4** these products were easily purified by silica gel chromatography because they eluted first. The ^{1}H NMR spectra of **4** were typical for 4-substituted quinolines [8] and the presence of a $C_{n-1}F_{2n-1}$ group (vs. C_nF_{2n+1} in **1**) was evident from the ^{19}F NMR spectra. Each CF_2 group and the terminal CF_3 group gave a narrow multiplet or a broad singlet due to the relatively low values of coupling constants ($J < 12$ Hz), as also observed for **1**. In two cases the crude mixtures were analyzed in more detail. A GC-MS analysis showed the presence of **4** as a major product and suggested the presence of three additional isomeric products. Two of the three additional products were poorly separated on a GC column. Following separation by silica gel chromatography it was shown by both HRMS and elemental analysis that, indeed, the two inseparable products (obtained as a mixture) and the other product are isomeric. On the basis of spectral analysis, the mixture (total yields of 17-22 %) was assigned tentative structures **6** and/or **8**, and the third product was shown to be a dihydroquinoline **10** (yields of 10-13 %). A unified mechanism to **4**, **6/8**, and **10** involving the same intermediate adduct **3** is suggested in Scheme 1.

Substitution of lithium enolates of methyl ketones for the acetaldehyde enolate provides an easy access to 2-substituted 4-perfluoroalkylquinolines, as illustrated in Scheme 2 by the synthesis of **11a-c** from **1c**. Again, as with **4** the use of an excess of a ketone enolate inhibits self-condensation of the ketone, which facilitates separation work. Under such optimized conditions the quinolines **11** were the only major products in the crude mixtures. The material balance consisted of tar and several low molecular weight by-products, each of which formed in low yield, as observed by GC analysis.

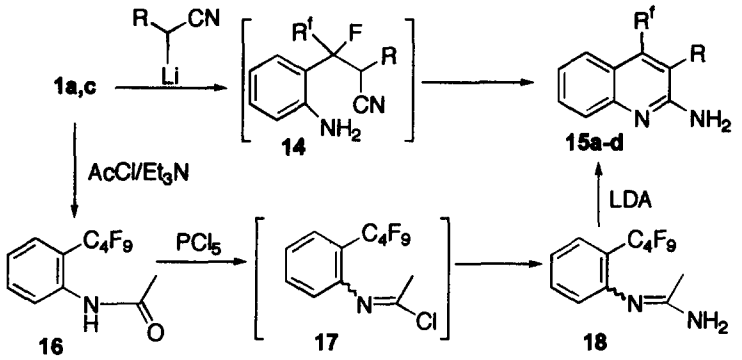
Scheme 2



Two additional preparations of a phenyl derivative **11c**, namely (i) by the reaction of **1c** with lithium phenylacetylide that apparently involves the intermediary of an adduct **12** and (ii) by LDA-mediated intramolecular cyclization of ketimine **13a** derived from **1c** and acetophenone are also presented in Scheme 2. These two additional approaches offer no advantage over the reaction of **1c** with lithium enolate of acetophenone. By contrast, the naphthylquinoline **11d** that could not be prepared by an attempted reaction of **1c** with lithium enolate of acetonaphthone, was easily obtained by intramolecular cyclization of the ketimine **13b**.

The reactions of **1** (1 equiv) with lithiated acetonitrile (5 equiv, see above) yield 2-amino-4-perfluoroalkylquinolines **15**, and 2,3,4-trisubstituted quinolines **15** are obtained by the use of lithium derivatives of higher carbonitriles (Scheme 3). These reactions apparently involve cyclization of an intermediate adduct **14**. They are relatively efficient as the yields of analytically pure products **15** are in the range of 45-56 %.

Scheme 3



15	R^f	R
a	CF_3	H
b	C_3F_7	H
c	C_3F_7	Et
d	C_3F_7	CH_2NMe_2

An alternative synthesis of 2-amino-4-heptafluoropropylquinoline (**15b**) by LDA-mediated cyclization of amidine **18** is also given in Scheme 3. Compound **18** was obtained in an overall yield of 71 % by acetylation of **1c** followed by one-pot transformations of the resulting acetyl derivative **16** into chloro imine **17** and amination of **17**. The LDA-mediated cyclization of **18** to quinoline **15b** is highly unusual because the CF_3 analog of **18** is cyclized to a quinazoline in the presence of a lithium alkylamide [9]. Although the configuration of **18** (*Z* or *E*) was not established, the stereochemistry is irrelevant because similar compounds are configurationally unstable under the cyclization conditions [10]. The strikingly different outcomes for similar reactions of **18** and its CF_3

analog are apparently due to different stereoelectronic effects in the corresponding intermediate products that undergo electrocyclization. We have shown previously that all fluorine atoms are eliminated from the CF_3 group and this group becomes a diaminomethylene functionality that is involved in the intramolecular cyclization [11]. By contrast, the corresponding intermediate product derived from **18** must be substituted with a strongly electron-withdrawing perfluoropropyl group.

In summary, we have described several novel synthetic routes to 4-perfluoroalkylquinolines. This new chemistry complements the Friedländer approach reported by us recently [5].

Experimental Section

General. THF was distilled from sodium benzophenone ketyl immediately before use. Crude mixtures were analyzed, and mass spectra of pure components were obtained on a GC-MS instrument equipped with an on-column injector, a poly(dimethylsiloxane)-coated capillary column, and a mass selective detector operating at 70 eV. Products were separated on a chromatotron with a silica gel coated rotor. All yields correspond to analytically pure products. Melting points (Pyrex capillary) are not corrected. ^{1}H NMR (300 MHz) and ^{19}F NMR (282 MHz) spectra were taken in $CDCl_3$ solutions with TMS and C_6F_6 as the respective internal references. Proton-proton coupling constants smaller than 2 Hz are not reported. 2-Perfluoroalkylanilines **1a-c** were synthesized as described previously [6]. Lithium enolate of acetaldehyde was generated by the reaction of *n*-BuLi with THF. A modified procedure was used [2]. Lithium enolates of acetone, 2-acetylthiophene, and acetophenone were generated by a slow addition of a solution of the corresponding carbonyl compound (5 mmol) in THF (3 mL) to a solution of LDA (7.5 mmol) in THF (20 mL) at -50 °C [2,12]. Lithium phenylacetylide was generated by the reaction of phenylacetylene (0.51 g, 5 mmol) with *n*-BuLi (5.1 mmol) under otherwise similar conditions.

Reactions of 1a-c with Lithium Enolates and Cyclization of 13a,b. Published procedures for the reactions of 2-trifluoromethylaniline (**1**, R = F) and for cyclizations of CF_3-substituted ketimines were followed without modifications [2]. Products were purified by chromatography on silica gel eluting with hexanes (**4a-c** and **11a-c**) or hexanes/ether (19:1, **10b,c**).

4-Trifluoromethylquinoline (4a): yield 46 %; an oil; ^{1}H NMR δ 7.71 (m, 2H), 7.84 (t, J = 7 Hz, 1H), 8.16 (d, J = 7 Hz, 1H), 8.23 (d, J = 8 Hz, 1H), 9.05 (d, J = 4 Hz, 1H); ^{19}F NMR δ 100.3 (s); MS *m/z* 197 (100, M^+); HRMS exact mass calcd for $C_{10}H_6F_3N$ 197.0452, found 197.0452.

4-Pentafluoroethylquinoline (4b): yield 40 %; an oil; ^{1}H NMR δ 7.63 (m, 2H), 7.77 (t, J = 8 Hz, 1H), 8.16 (d, J = 8 Hz, 1H), 8.20 (d, J = 8 Hz, 1H), 9.02 (d, J = 4 Hz, 1H); ^{19}F NMR δ 51.3 (2F), 78.6 (3F); MS *m/z* 178 (100), 247 (70, M^+); HRMS exact mass calcd for $C_{11}H_6F_5N$ 247.0420, found 247.0420.

4-Heptafluoropropylquinoline (4c): yield 55 %; an oil; ^{1}H NMR δ 7.67 (m, 2H), 7.81 (t, J = 8 Hz, 1H), 8.18 (d, J = 8 Hz, 1H), 8.24 (d, J = 8 Hz, 1H), 9.07 (d, J = 4 Hz, 1H); ^{19}F NMR δ 37.1

(2F), 54.2 (2F), 81.9 (3F); MS *m/z* 178 (100), 297 (80, M^+); HRMS exact mass calcd for $C_{12}H_6F_7N$ 297.0388, found 297.0402.

4-Pentafluoroethyl-3,4-dihydroquinolin-(1*H*)-2-one (10b): yield 13 %; mp 159-161 °C (from ether); ^{1}H NMR δ 2.92 (dd, J_{AB} = 17.0 Hz, J_{AX} = 7.2 Hz, 1H, 3-H_A), 3.03 (d, J_{AB} = 17.0 Hz, 1H, 3-H_B), 3.68 (dt, J_{XF} = 15.8 Hz, J_{AX} = 7.2 Hz, J_{BX} = 0.0 Hz, 1H, 4-H_X), 6.91 (d, J = 8 Hz, 1H), 7.06 (t, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 1H), 7.32 (t, J = 8 Hz, 1H), 9.11 (br s, exchangable with D_2O, 1H); ^{19}F NMR δ 42.0 (dd, J_{AB} = 273 Hz, J_{HF} = 15.8 Hz, 1F of CF_2), 43.4 (dd, J_{AB} = 273 Hz, J_{HF} = 15.8 Hz, 1F of CF_2), 80.6 (3F); MS *m/z* 146 (100), 265 (50, M^+). Anal. Calcd for $C_{11}H_8F_5NO$: C, 49.81; H, 3.02; N, 5.28. Found: C, 49.84; H, 2.89; N, 5.21.

4-Heptafluoropropyl-3,4-dihydroquinolin-(1*H*)-2-one (10c): yield 10 %; mp 149-151 °C (from ether); ^{1}H NMR δ 2.92 (dd, J_{AB} = 17.0 Hz, J_{AX} = 7.2 Hz, 1H, 3-H_A), 3.05 (d, J_{AB} = 17.0 Hz, 1H, 3-H_B), 3.78 (m, 1H, 4-H_X), 6.86 (d, J = 8 Hz, 1H), 7.06 (t, J = 8 Hz, 1H), 7.25 (d, J = 8 Hz, 1H), 7.32 (t, J = 8 Hz, 1H), 8.40 (br s, exchangable with D_2O, 1H); ^{19}F NMR δ 37.7 (2F), 44.5 (br d, J = 280 Hz, 1F of CF_2), 48.1 (br d, J = 280 Hz, 1F of CF_2), 81.2 (3F); MS *m/z* 146 (100), 315 (40, M^+). Anal. Calcd for $C_{12}H_8F_7NO$: C, 45.73; H, 2.56; N, 4.44. Found: C, 45.69; H, 2.37; N, 4.39.

4-Heptafluoropropyl-2-methylquinoline (11a): yield 31 %; an oil; ^{1}H NMR δ 2.82 (s, 3H), 7.53 (s, 1H), 7.59 (t, J = 8 Hz, 1H), 7.76 (t, J = 8 Hz, 1H), 8.12 (d, J = 8 Hz, 2H); ^{19}F NMR δ 37.0 (2F), 54.0 (2F), 81.9 (3F); MS *m/z* 192 (100), 311 (40, M^+); HRMS exact mass calcd for $C_{13}H_8F_7N$ 311.0545, found 311.0551.

4-Heptafluoropropyl-2-(2-thienyl)quinoline (11b): yield 38 %; mp 46-48 °C; (from pentanes); ^{1}H NMR δ 7.19 (t, J = 4.4 Hz, 1H), 7.52 (d, J = 5.2 Hz, 1H), 7.59 (t, J = 8 Hz, 1H), 7.77 (m, 2H), 8.01 (s, 1H), 8.11 (d, J = 8 Hz, 1H), 8.19 (d, J = 8 Hz, 1H); ^{19}F NMR δ 37.2 (2F), 54.1 (2F), 81.9 (3F); MS *m/z* 260 (60), 379 (100, M^+); HRMS exact mass calcd for $C_{16}H_8F_7NS$ 379.0266, found 379.0247.

4-Heptafluoropropyl-2-phenylquinoline (11c): yield 40 % from **1c** and lithium enolate of acetophenone, 33 % from **1c** and lithium phenylacetylide, and 31 % by cyclization of **13a**; mp 64-65 °C (from EtOH/H_2O); ^{1}H NMR δ 7.55 (m, 3H), 7.64 (t, J = 8 Hz, 1H), 7.81 (t, J = 8 Hz, 1H), 8.12 (s, 1H), 8.19 (m, 3H), 8.28 (d, J = 8 Hz, 1H); ^{19}F NMR δ 37.1 (2F), 54.2 (2F), 82.0 (3F); MS *m/z* 254 (80), 373 (100, M^+). Anal. Calcd for $C_{18}H_{10}F_7N$: C, 57.92; H, 2.70; N, 3.75. Found: C, 57.85; H, 2.64; N, 3.65.

4-Heptafluoropropyl-2-(2-naphthyl)quinoline (11d): yield 51 % by cyclization of **13b**; mp 117-118 °C (from hexanes); ^{1}H NMR δ 7.55 (m, 2H), 7.64 (t, J = 8 Hz, 1H), 7.91 (m, 2H), 8.01 (d, J = 8 Hz, 2H), 8.19 (d, J = 8 Hz, 1H), 8.27 (s, 1H), 8.32 (d, J = 8 Hz, 1H), 8.38 (d, J = 8 Hz, 1H), 8.62 (s, 1H); ^{19}F NMR δ 37.1 (2F), 54.2 (2F), 82.0 (3F); MS *m/z* 152 (60), 423 (100, M^+). HRMS exact mass calcd for $C_{22}H_{12}F_7N$ 423.0858, found 423.0851.

Ketimines 13a and 13b. A solution of aniline **1c** (3.1 g, 10 mmol), acetophenone or methyl 2-naphthylketone (15 mmol), and a catalytic amount of p-toluenesulfonic acid in xylenes (50 mL) was

heated under reflux for 48 h with azeotropic removal of water. Workup and purification were conducted as described previously [11].

2-Nonafluorobutyl-*N*-(1-phenylethylidene)aniline (13a): yield 41 %; an oily mixture of *E* and *Z* diastereomers, *E*/*Z* = 2:1 (a tentative assignment); ^{1}H NMR for the major isomer, δ 2.13 (s, Me), 6.72 (d, J = 8 Hz, 6-H of the aniline), 7.1-8.0 (m, the remaining aromatic protons); ^{1}H NMR for the minor isomer, δ 1.85 (s, Me), 6.82 (d, J = 8 Hz, 6-H of the aniline), 7.1-8.0 (m, the remaining aromatic protons); MS *m/z* 398 (100), 413 (70, M^+); HRMS exact mass calcd for $C_{18}H_{12}F_9N$ 413.0826, found 413.0818.

***N*-[1-(2-Naphthyl)ethylidene]-2-nonafluorobutylaniline (13b)**: yield 45 % of a single isomer; an oil; ^{1}H NMR δ 2.35 (s, 3H), 6.77 (d, J = 8 Hz, 1H), 7.21 (t, J = 8 Hz, 1H), 7.55 (m, 4H), 7.90 (m, 3H), 8.16 (d, J = 8 Hz, 1H), 8.32 (s, 1H); ^{19}F NMR δ 35.9 (2F), 40.0 (2F), 54.9 (2F), 80.8 (3F); MS *m/z* 448 (100), 463 (50, M^+); HRMS exact mass calcd for $C_{22}H_{14}F_9N$ 463.0983, found 463.1013.

Synthesis of Quinolines 15a-d: General Procedure. A stirred solution of LDA (10 mmol) in THF (25 mL) was treated dropwise at -50 °C with a solution of a carbonitrile RCH_2CN (10 mmol) in THF (2 mL). The resultant mixture was stirred for 1 h and then treated dropwise at -70 °C with a solution of **1a-c** (2 mmol) in THF (2 mL). After the addition was completed the mixture was allowed to reach 23 °C within 1 h, stirred at °C for 30 min, and then quenched with water (0.25 mL). Standard workup was followed by chromatography eluting with pentanes/ether (1:1).

2-Amino-4-(trifluoromethyl)quinoline (15a, from **1a** and MeCN): yield 45 %; an oil; ^{1}H NMR δ 5.09 (br s, exchangeble with D_2O, 2H), 7.04 (s, 1H), 7.32 (t, J = 8 Hz, 1H), 7.60 (t, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 1H), 7.88 (d, J = 8 Hz, 1H); ^{19}F NMR δ 99.6 (s); MS *m/z* 212 (100, M^+); HRMS exact mass calcd for $C_{10}H_7F_3N_2$ 212.0561, found 212.0553.

2-Amino-4-(heptafluoropropyl)quinoline (15b, from **1c** and MeCN): yield 48 %; an oil; ^{1}H NMR δ 5.01 (br s, exchangeble with D_2O, 2H), 7.00 (s, 1H), 7.34 (t, J = 8 Hz, 1H), 7.62 (t, J = 8 Hz, 1H), 7.75 (d, J = 8 Hz, 1H), 7.95 (d, J = 8 Hz, 1H); ^{19}F NMR δ 37.1 (m, 2F), 53.8 (m, 2F), 81.9 (m, 3F); MS *m/z* 166 (90), 193 (70), 312 (100, M^+); HRMS exact mass calcd for $C_{12}H_7F_7N_2$ 312.0497, found 312.0484.

2-Amino-3-ethyl-4-(heptafluoropropyl)quionoline (15c, from **1c** and *n*-PrCN): yield 51 %; an oil; ^{1}H NMR δ 1.35 (t, J = 7 Hz, 3H), 2.77 (q, J = 7 Hz, 2H), 5.06 (br s, exchangeable with D_2O, 2H), 7.30 (t, J = 8 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.97 (d, J = 8 Hz, 1H); ^{19}F NMR δ 37.9 (m, 2F), 63.1 (m, 2F), 81.6 (m, 3F); MS *m/z* 221 (100), 340 (70, M^+); HRMS exact mass calcd for $C_{14}H_{11}F_7N_2$ 340.0810, found 340.0805.

2-Amino-3-(dimethylaminomethyl)-4-(heptafluoropropyl)quinoline (15d, from **1c** and $Me_2NCH_2CH_2CN$): yield 56 %; mp 87-88 °C (from hexanes/ether); ^{1}H NMR δ 2.29 (s, 6H), 3.67 (s, 2H), 6.7 (br, exchangeable with D_2O, 2H), 7.28 (t, J = 8 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.69 (d, J = 8 Hz, 1H), 7.97 (d, J = 8 Hz, 1H); ^{19}F NMR δ 38.5 (m, 2F), 65.5 (m, 2F), 81.7 (m, 3F); MS *m/z* 58 (100), 369 (70, M^+); HRMS exact mass calcd for $C_{15}H_{14}F_7N_3$ 369.1076, found 369.1058.

***N*-Acetyl-2-(nonafluorobutyl)aniline (16).** This compound was synthesized from **1d** and AcCl and purified by using a published general procedure [11a]: yield 88 %; mp 51-53 °C (from EtOH); ^{1}H NMR δ 2.17 (s, 3H), 7.28 (d, J = 8 Hz, 1H), 7.56 (m, 3H), 8.10 (br s, exchangeable with D_2O, 1H); ^{19}F NMR δ 36.0 (2F), 39.4 (2F), 55.2 (2F), 80.9 (3F); MS *m/z* 142 (100), 311(30), 353 (10, M^+); HRMS exact mass calcd for $C_{12}H_8F_9NO$ 353.0462, found 353.0445.

***N'*-[2-(Nonafluorobutyl)phenyl]ethanimidamide (18).** The treatment of **16** with PCl_5 and a subsequent reaction of the crude imidoyl chloride **17** with ammonia were conducted as described previously for a CF_3-analog of **16** [9]. Amidine **18** was purified by chromatography on silica gel eluting with hexanes/ether (2:1): yield 81 % of a single isomer; mp 74-76 °C (from hexanes/ether); ^{1}H NMR δ 2.09 (s, 3H), 4.35 (br s, exchangeable with D_2O, 2H), 6.9-7.5 (m, 4H); ^{19}F NMR δ 35.9 (2F), 40.0 (2F), 54.4 (2F), 80.8 (3F); MS *m/z* 143 (100), 163 (50), 352 (30, M^+); HRMS exact mass calcd for $C_{12}H_9F_9N_2$ 352.0622, found 352.0610.

Cyclization of 18. A solution of **18** (0.35 g, 1 mmol) and LDA (5 mmol) in THF (20 mL) was heated to 50 °C for 8 h under a nitrogen atmosphere. A standard workup [9] was followed by chromatrography on silica gel eluting with hexanes/ether (5:1) to give 0.14 g (44 %) of **15 b.**

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References and Notes

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[12] LTMP or LHMDS could be substituted for LDA but the use of NaH or *n*-BuLi resulted in considerably lower yields of the subsequent cyclization reactions.