JOC Article

Trifluoromethoxy Substituted Anilines: Metalation as the Key Step for Structural Elaboration

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Trifluoromethoxy-substituted anilines undergo hydrogen/lithium permutation ("metalation") with optional site selectivity depending on the *N*-protective group employed. *N*-*tert*-Butoxycarbonyl-2- and −4-(trifluoromethoxy)aniline react with *tert*-butyllithium at the nitrogen-adjacent 6- and 2-position affording, after electrophilic trapping, products **1**−**6**. In contrast, deprotonation of the *para* isomer occurs at the oxygen-neighboring 3-position, giving rise to the acid **12**, when the amino group is carrying two trimethylsilyl groups. *sec*-Butyllithium attacks 3-trifluoromethoxy-*N*-mono(trimethylsilyl)aniline at the 2-position, but 3-trifluoromethoxy-*N*,*N*-bis(trimethylsilyl)aniline at the 4-position to provide respectively the acids **10** and **11** after carboxylation. The synthesis of two new benzodiazepines illustrates (**19** and **22**) the preparative potential of the aniline functionalization mediated by organometallic reagents.

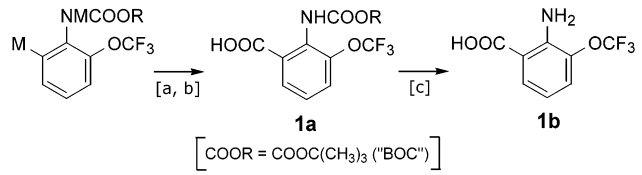
Introduction

Although readily accessible by three different methods,[1−5] aryl trifluoromethyl ethers have so far been only scarcely investigated. We have recently published a series of articles,[6−9] wherein we disclose how organometallic intermediates can be generated from (trifluoromethoxy)benzene and fluoro-, bromo-, or methoxy-substituted congeners to convert them into a variety of functionalized derivatives. We have now extended this work to amino-substituted (trifluoromethoxy)arenes, anilines being particularly versatile and attractive building blocks and starting materials for important classes of heterocycles as well.

Results and Discussion

The *N*-*tert*-butoxycarbonyl (BOC)-protected[10−12] 2-(trifluoromethoxy)aniline underwent smooth deprotonation, first of the NH bond and then, more slowly, of the 6-position adjacent to the nitrogen substituent. Carboxylation and neutralization afforded the *N*-BOC-protected anthranilic acid **1a** (78%) and, after acid treatment, the unprotected compound **1b** (93%) (Scheme 1).

SCHEME 1[a]



[a] Reagents: [a] M = H + $LiC(CH_3)_3$ (2.0 equiv). [b] M = Li + (1) CO_2; (2) H_2O. [c] F_3CCOOH.

In the same way, the *N*-BOC-protected 4-(trifluoromethoxy)aniline gave the acids **2a** (81%) and **2b** (96%). To demonstrate the universality of the procedure, the organometallic intermediate was trapped with various other electrophiles. The aldehyde **3** (86%) was obtained upon treatment with *N*,*N*-dimethylformamide, the lactone **4** (75%), and the alcohol **5** (81%) with formaldehyde and oxirane, respectively, and the methylated compound **6** (66%) with dimethyl sulfate (Scheme 2).

No new product was identified when *N*-BOC-3-(trifluoromethoxy)aniline was submitted to the same reaction sequence. As the metalation of the position flanked by both activating groups should occur with particular ease, we tentatively assume that the *ortho*-lithiated intermediate, once formed, immediately decomposes by single electron transfer, thus setting free a radical **7** that becomes stabilized by hydrogen transfer from the solvent.

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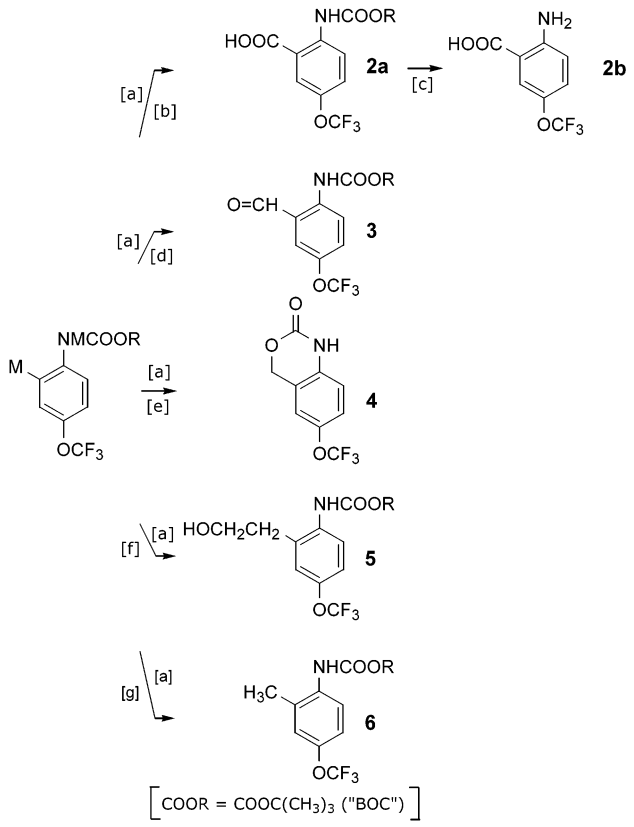
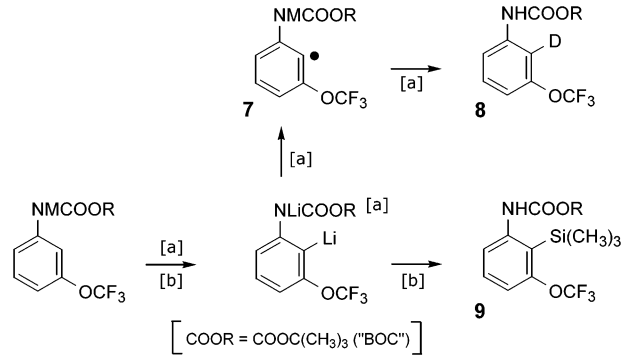
SCHEME 2[a]



[a] Reagents: [a] M = H + $LiC(CH_3)_3$ (2.0 equiv). [b] M = Li + (1) CO_2; (2) H_2O. [c] F_3CCOOH. [d] M = Li + (1) O=CH−$N(CH_3)_2$; (2) H_2O. [e] M = Li + (1) CH_2O; (2) H_2O. [f] M = Li + (1) $(CH_2)_2O$; (2) H_2O. [g] M = Li + $(H_3CO)_2SO_2$.

In fact, when the reaction was repeated in perdeuteriotetrahydrofuran as the solvent, large amounts (up to 55%) of the labeled isotopomer **8** were found. However, high yields of the silane **9** (78%) could be isolated if the organometallic intermediate was generated with lithium diisopropylamide and trapped *in situ* with chlorotrimethylsilane (Scheme 3).

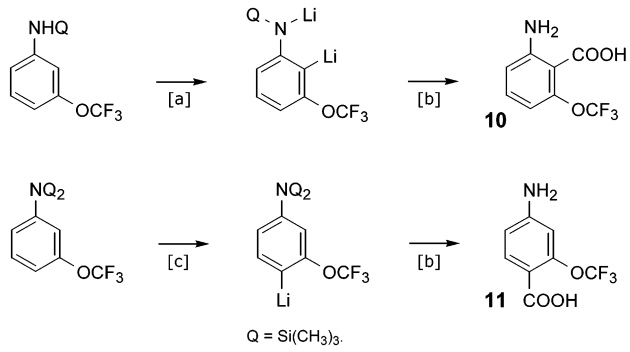
SCHEME 3[a]



[a] Reagents: [a] (1) $LiC(CH_3)_3$ (2.0 equiv) in tetrahydrofuran-d_8 at −75 °C; (2) H_2O. [b] (1) $LiN(^iC_3H_7)_2$ (2 equiv) and $ClSi(CH_3)_3$ in tetrahydrofuran at −75 °C; (2) H_2O.

Clean metalation and subsequent functionalization of the *meta*-isomeric aniline was achieved (33% of acid **10**) after prior monoprotection of the amino function, whereas

SCHEME 4[a]

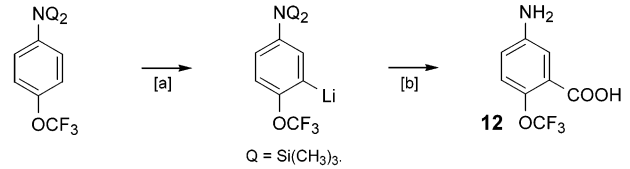


[a] Reagents: [a] $LiC(CH_3)_3$ (2.0 equiv). [b] (1) CO_2; (2) H_2O. [c] $LiCH(CH_3)C_2H_5$ + *N*,*N*,*N*′,*N*″*N*″-pentamethyldiethylenetriamine (PMDTA, 1.0 equiv).

the target of deprotonation and carboxylation became the 4-position (69% of acid **11**), when both amino hydrogens were replaced by a trimethylsilyl group (Scheme 4). An example of neighboring group assistance in arene metalation by a 2-[(*N*-lithio-*N*-trimethylsilyl)amino]ethyl group has been reported[13] and also the regiochemical redirection of the organometallic reagent by a bulky bis(trialkylsilyl)amino substituent to a sterically less shielded position has been recognized previously.[12,14]

Nitrogen substituents promote *ortho* metalations not by their inductive effect but rather by their coordinative power.[15,16] When the latter is weakened or completely suppressed by silylation, other groups may exert a superior action. Thus, 4-trifluoromethoxy-*N*,*N*-bis(trimethylsilyl)aniline gave the acid **12** (48%) when it was consecutively treated with *sec*-butyllithium and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine, dry ice, and water (Scheme 5).

SCHEME 5[a]



[a] Reagents: [a] $LiCH(CH_3)C_2H_5$ + *N*,*N*,*N*′,*N*″*N*″-pentamethyldiethylenetriamine (PMDTA, 2.0 equiv). [b] (1) CO_2; (2) H_2O.

In contrast, all attempts to convert 2-(trifluoromethoxy)aniline into the 3-amino-2-(trifluoromethoxy)benzoic acid (**13**) failed. Whatever combination of metalation reagent and protective groups tried, either no metalation occurred at all or it took place at the nitrogen-adjacent position exclusively (Scheme 6).

Thus, we had to explore a round-about way, which, as it turned out, became the most difficult and time-consuming part of the entire work. 3-Bromo-2-(trifluoromethoxy)benzoic acid,[7] readily accessible in 63% yield by consecutive lithiation, bromination,[6] another lithiation

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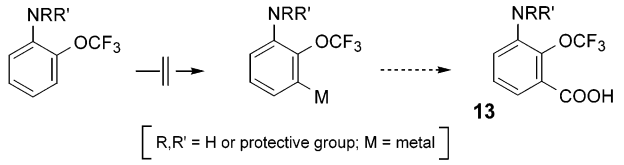
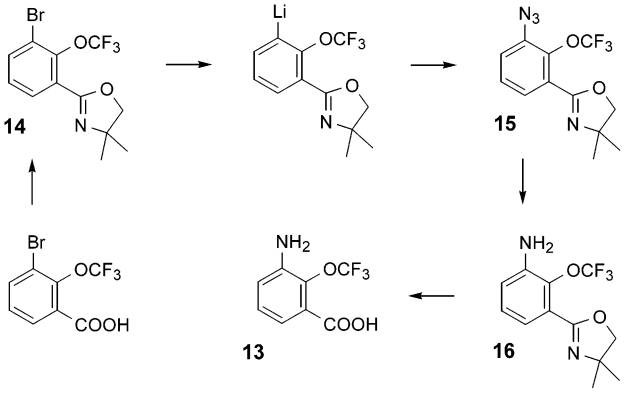
SCHEME 6



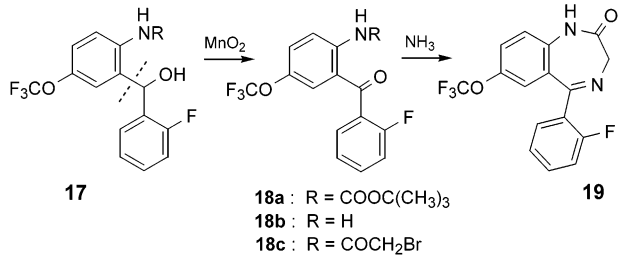
(performed at −95 °C rather than −100 °C[7]) and carboxylation of (trifluoromethoxy)benzene was condensed with 2-amino-2-methyl-1-propanol to afford the oxazoline **14** (63 or 43%, respectively, depending on whether the Gschwend protocol[17] or another standard procedure[18] was applied). The latter compound was subjected to a halogen/metal permutation with butyllithium in toluene before being treated with benzenesulfonyl azide. Reduction and deprotonation of the resulting azido compound **15** gave the anilinooxazoline **16** (35% over-all) and deprotonation of the latter intermediate afforded the targeted acid **13** (56%) (Scheme 7).

SCHEME 7

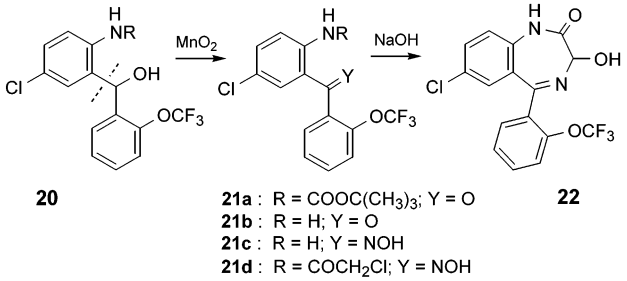


Two benzodiazepines were synthesized following established lines[19−21] to demonstrate the practical utility of the methods described above. Reaction of the *N*,*O*-dilithiated *N*-BOC-4-(trifluoromethoxy)aniline with 2-fluorobenzaldehyde afforded the benzhydrol **17** (61%), which was oxidized to the ketone **18a** (82%). Removal of the BOC group (to 91% of the amino compound **18b**) and α-bromoacetylation (to 86% of the amide **18c**) followed by condensation and cyclization with ammonia eventually produced the seven-membered heterocycle **19** (92%) (Scheme 8). Similarly, the *N*,*O*-dilithiated *N*-BOC-4-chloroaniline was allowed to combine with 2-(trifluoromethoxy)benzaldehyde[6] and the resulting benzhydrol **20** (53%) was dehydrated (to 75% of ketone **21a**), deprotected to the aminoketone **21b** (89%), and converted into the oxime **21c** (94%) and the latter α-chloroacetylated to give the amide **21d** (90%). After cyclization in alkaline medium, the benzodiazepine **22** (86%) was isolated (Scheme 9).

SCHEME 8



SCHEME 9



Experimental Section

Generalities: For laboratory routine and abbreviations, see recent publications[22−23] from this laboratory. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, all samples being dissolved in deuteriochloroform.

1. Starting Materials. *tert*-Butyl *N*-[2-(Trifluoromethoxy)phenyl]carbamate. A solution of 2-(trifluoromethoxy)-aniline (36 g, 0.20 mol) and di-*tert*-butyl dicarbonate (44 g, 0.20 mol) in toluene (0.20 L) was heated to 100 °C for 2 h. Upon distillation, a colorless liquid was collected; bp 102−104 °C/5 mmHg; n^{20}_D 1.4572; yield 54 g (98%). ^{1}H NMR: δ 8.21 (d, J = 8.0 Hz, 1 H), 7.2 (m, 2H), 7.04 (t, J = 8.2 Hz, 1 H), 6.8 (s, br, 1 H), 1.56 (s, 9 H). MS: *m*/*z* (%) 203 (22), 177 (100), 108 (45). Anal. Calcd for $C_{12}H_{14}F_3NO_3$ (277.24): C 51.99, H 5.09. Found: C 5.91, H 5.32.

***tert*-Butyl *N*-[3-(Trifluoromethoxy)phenyl]carbamate.** Analogously prepared from 3-(trifluoromethoxy)aniline (0.20 mol); isolated after evaporation of the solvent and crystallization of the residue as colorless needles; mp 81−83 °C (from hexanes); yield 55 g (99%). ^{1}H NMR: δ 7.42 (s, 1 H), 7.29 (t, J = 8.3 Hz, 1 H), 7.19 (d, J = 8.4 Hz, 1 H), 6.90 (d, J = 8.4 Hz, 1 H), 6.6 (s, br, 1H), 1.54 (s, 9 H). MS: *m*/*z* (%) 295 (100, $M^+ + NH_4$), 278 (27, $M^+ + 1$), 239 (24), 177 (26). Anal. Calcd for $C_{12}H_{14}F_3NO_3$ (277.24): C 51.99, H 5.09, Found: C 51.97, H 5.10.

***tert*-Butyl *N*-[4-(Trifluoromethoxy)phenyl]carbamate.** Prepared from 4-(trifluoromethoxy)aniline (0.20 mol) and isolated as described in the preceding paragraph; colorless needles; mp 104−105 °C (from hexanes); yield 55 g (99%). ^{1}H NMR: δ 8.01 (s, 1 H), 7.39 (d, J = 9.0 Hz, 2 H), 7.12 (d, J = 8.9 Hz, 2 H), 1.48 (s, 9 H). MS: *m*/*z* (%) 203 (16), 177 (100), 108 (56). Anal. Calcd for $C_{12}H_{14}F_3NO_3$ (277.24): C 51.99, H 5.09. Found: C 52.02, H 4.96.

3-Trifluoromethoxy-*N*-(trimethylsilyl)aniline. 3-(Trifluoromethoxy)aniline (8.9 g, 50 mmol) and chlorotrimethylsilane (6.3 mL, 5.4 g, 50 mmol) were added consecutively to butyllithium (50 mmol) in tetrahydrofuran (30 mL) and hexanes (32 mL). Direct distillation gave a colorless liquid; bp 80−81 °C/4 mmHg; n^{20}_D 1.4572; yield 12.1 g (97%). ^{1}H NMR: δ 7.04 (t, J = 7.9 Hz, 1 H), 6.50 (dd, J = 8.3 Hz, 2.1, 2 H), 6.42 (s, br, 1 H), 0.23 (s, 9 H). MS: *m*/*z* (%) 249 (M^+, 55), 306 (100),

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236 (22). Anal. Calcd for $C_{10}H_{14}F_3NSiO$ (249.31): C 48.18, H 5.66. Found: C 48.05, H 5.57.

3-Trifluoromethoxy-*N*,*N*-bis(trimethylsilyl)aniline. Butyllithium (0.10 mol) in hexane (65 mL) and chlorotrimethylsilane (13 mL, 11 g, 0.10 mol) were added consecutively to 3-(trifluoromethoxy)aniline (8.9 g, 50 mmol) in tetrahydrofuran (0.10 L) at −75 °C. Upon immediate distillation a colorless liquid was obtained; bp 89−90 °C/6 mmHg; n^{20}_D 1.4460; yield 15.8 g (98%). ^{1}H NMR: δ 7.13 (t, J = 7.8 Hz, 1 H), 6.57 (dd, J = 8.2, 2.2 Hz, 2 H), 6.49 (s, br, 1 H), 0.28 (s, 18 H). MS: *m*/*z* (%) 321 (M^+ − 1, 100), 246 (23), 175 (54). Anal. Calcd for $C_{13}H_{22}F_3NSi_2O$ (321.49): C 48.57, H 6.90. Found: C 48.48, H 6.59.

4-Trifluoromethoxy-*N*,*N*-bis(trimethylsilyl)aniline. Analogously prepared from 4-(trifluoromethoxy)aniline (8.9 g, 50 mmol) and isolated as described in the preceding paragraph; colorless liquid; bp 90−91 °C/6 mmHg; n^{20}_D 1.4461; yield 15.9 g (99%). ^{1}H NMR: δ 7.07 (d, J = 8.6 Hz, 2 H), 6.89 (d, J = 8.9 Hz, 2 H), 0.10 (s, 18 H). MS: *m*/*z* (%) 321 (M^+, 46), 306 (100), 236 (22). Anal. Calcd for $C_{13}H_{22}F_3NSi_2O$ (321.49): C 48.57, H 6.90. Found: C 48.55, H 6.62.

2. Functionalization of (Trifluoromethoxy)aniline Derivatives. 2-[(*tert*-Butoxycarbonyl)amino]-3-(trifluoromethoxy)benzoic Acid (1a). At −75 °C, *tert*-butyllithium (50 mmol) in pentanes (35 mL) was added to *tert*-butyl *N*-[2-(trifluoromethoxy)phenyl]carbamate (6.9 g, 25 mmol) dissolved in tetrahydrofuran (50 mL). After 2 h at −50 °C, the homogeneous mixture was poured on an excess of freshly crushed carbon dioxide. At 25 °C, water (50 mL) was added. The aqueous phase was separated, washed with diethyl ether (15 mL), acidified (to pH 1), and extracted with diethyl ether. The combined organic layers were dried and evaporated. The residue was crystallized from a 1:5 (v/v) mixture of diethyl ether and hexanes; colorless needles; mp 135−136 °C; yield 6.3 g (78%). ^{1}H NMR: δ 7.93 (dd, J = 8.0, 1.4 Hz, 1 H), 7.76 (s, br, 1 H), 7.51 (d, br, J = 8.2 Hz, 1 H), 7.27 (t, J = 7.8 Hz, 1 H), 1.50 (s, 9 H). ^{13}C NMR: δ 170.5, 153.0, 143.2, 131.9, 129.4, 125.9, 125.1, 125.0, 120.4 (q, J = 259.6 Hz), 81.8, 28.0 (3 C). MS: *m*/*z* (%) 278 (26), 239 (51), 222 (100). Anal. Calcd for $C_{13}H_{14}F_3NO_5$ (321.26): C 48.60, H 4.39. Found: C 48.52, H 4.32.

2-Amino-3-(trifluoromethoxy)benzoic Acid (1b). A solution of carbamate **1a** (4.8 g, 15 mmol) and trifluoroacetic acid (1.5 mL, 2.3 g, 20 mmol) in dichloromethane (30 mL) was kept for 2 h at 25 °C. Evaporation and crystallization from water afforded colorless needles; mp 99−101 °C; yield 3.1 g (93%). ^{1}H NMR: δ 7.90 (d, J = 8.2 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 6.66 (t, J = 8.0 Hz, 1 H), 6.2 (s, br, 2 H). ^{13}C NMR: δ 172.7, 144.1, 136.5, 130.5, 126.2, 120.8 (q, J = 258.1 Hz), 114.9, 111.2. MS: *m*/*z* (%) 221 (M^+, 100), 203 (85), 134 (25), 106 (40). Anal. Calcd for $C_8H_6F_3NO_3$ (221.14): C 43.45, H 2.73. Found: C 43.50, H 2.93.

2-[(*tert*-Butyloxycarbonyl)amino]-5-(trifluoromethoxy)benzoic Acid (2a). As described for the *ortho* isomer (see the preparation of acid **1a**) *tert*-butyl *N*-[4-(trifluoromethoxy)-phenyl]carbamate (6.9 g, 25 mmol) was treated consecutively with *tert*-butyllithium and dry ice. Workup by extraction and crystallization from a 1:5 (v/v) mixture of ethyl acetate and hexanes gave colorless needles; mp 181−183 °C; yield 6.5 g (81%). ^{1}H NMR: δ 10.12 (s, br, 1H), 8.58 (d, J = 8.3 Hz, 1 H), 7.93 (s, br, 1 H), 7.34 (d, br, J = 8.2 Hz, 1 H), 1.52 (s, 9 H). ^{13}C NMR (D_3CCOCD_3): δ 168.0, 152.2, 141.7, 136.6, 127.4, 123.6, 120.3 (q, J = 260.1 Hz), 119.8, 115.3, 80.4, 27.4 (3 C). MS: *m*/*z* (%) 339 (100, $M^+ + NH_4$), 322 (58%, $M^+ + 1$), 283 (61), 221 (48). Anal. Calcd for $C_{13}H_{14}F_3NO_5$ (321.14): C 48.60, H 4.39. Found: C 48.44, H 4.29.

2-Amino-5-(trifluoromethoxy)benzoic Acid (2b). A solution of acid **2a** (6.4 g, 20 mmol) in dichloromethane (40 mL) was incubated with trifluoroacetic acid (1.9 mL, 2.9 g, 25 mmol) for 2 h at 25 °C. Evaporation of the solvent and crystallization from water afforded colorless needles; mp 137−138 °C; yield 4.3 g (96%). ^{1}H NMR: δ 7.79 (d, J = 2.4 Hz, 1 H), 7.20 (dd, J = 9.0, 2.6 Hz, 1 H), 6.66 (d, J = 9.0 Hz, 1 H). ^{13}C NMR: δ 171.6, 149.8, 138.8, 129.0, 124.4, 120.4 (q, J = 262.0 Hz), 117.7, 108.9. MS: *m*/*z* (%) 221 (M^+, 100), 203 (81), 176 (15), 134 (19), 106 (34). Anal. Calcd for $C_8H_6F_3NO_3$ (221.14): C 43.45, H 2.73. Found: C 43.29, H 2.92.

***tert*-Butyl *N*-[2-Formyl-4-(trifluoromethoxy)phenyl]-carbamate (3).** In the same way, a reaction employing *N*,*N*-dimethylformamide (1.6 mL, 1.5 g, 25 mmol) was accomplished. After crystallization from a 1:5 (v/v) mixture of ethyl acetate and hexanes, colorless needles were collected; mp 102−104 °C; yield 6.6 g (86%). ^{1}H NMR: δ 9.88 (s, 1 H), 8.54 (d, J = 9.3 Hz, 1 H), 7.49 (d, J = 2.2 Hz, 1 H), 7.43 (dd, J = 9.3, 2.3 Hz, 1 H), 1.55 (s, 9 H). ^{13}C NMR: δ 193.5, 152.6, 142.7, 140.5, 128.9, 127.5, 121.5, 120.4 (q, J = 268.0 Hz), 120.0, 81.4, 28.1. MS: *m*/*z* (%) 323 (100, $M^+ + NH_4$), 306 (94, $M^+ + 1$), 305 (43, M^+), 205 (79), 177 (25). Anal. Calcd for $C_{13}H_{14}F_3NO_4$ (305.26): C 51.15, H 4.63. Found: C 51.03, H 4.42.

1,4-Dihydro-6-trifluoromethoxy-2*H*-3,1-benzoxazin-2-one (4). A strictly analogous reaction was performed as described in the preceding paragraph except that oxirane was replaced by dry paraformaldehyde (3.0 g, 0.10 mol). After crystallization from ethyl acetate, colorless platelets were collected; mp 182−184 °C; yield 1.7 g (75%). ^{1}H NMR: δ 7.6 (s, br, 1H), 7.15 (d, J = 8.6 Hz, 1 H), 7.02 (s, 1 H), 6.82 (d, J = 8.7 Hz, 1 H), 5.31 (s, 2 H). ^{13}C NMR: δ 144.7, 134.2, 122.3, 120.4 (q, J = 258.9 Hz), 119.1, 117.5, 115.4, 115.1, 68.1. MS: *m*/*z* (%) 233 (99, M^+), 216 (17), 189 (100), 162 (19). Anal. Calcd for $C_9H_6F_3NO_3$ (233.15): C 46.37, H 2.59. Found: C 46.24, H 2.55.

***tert*-Butyl *N*-[2-(Hydroxyethyl)-4-(trifluoromethoxy)-phenyl]carbamate (5).** A solution of *tert*-butyl *N*-[4-(trifluoromethoxy)phenyl]carbamate (6.9 g, 25 mmol) was treated consecutively with *tert*-butyllithium (for the conditions, see the preparation of acid **1a**) and with oxirane (1.3 mL, 1.1 g, 25 mmol). After neutralization and crystallization from ethanol, colorless prisms were obtained; mp 110−111 °C; yield 6.5 g (81%). ^{1}H NMR: δ 7.80 (s, br, 1 H), 7.74 (d, J = 8.6 Hz, 1 H), 7.07 (dd, J = 8.7, 2.0 Hz, 1 H), 3.91 (t, J = 5.5 Hz, 2 H), 2.82 (t, J = 5.6 Hz, 2 H), 2.1 (s, br, 1 H), 1.50 (s, 9 H). ^{13}C NMR: δ 153.7, 145.1, 136.0, 132.8, 124.0, 122.6, 120.4 (q, J = 256.4 Hz), 119.7, 80.4, 64.0, 34.6, 28.3 (3 C). MS: *m*/*z* (%) 339 (100, $M^+ + NH_4$), 292 (95, $M^+ + 1$), 283 (82), 266 (79), 221 (76). Anal. Calcd for $C_{14}H_{18}F_3NO_4$ (321.30): C 52.34, H 5.65. Found: C 52.27, H 5.58.

***tert*-Butyl *N*-[2-methyl-3-(trifluoromethoxy)phenyl]-carbamate (6).** The reaction was initially conducted as described in the preceding paragraph, oxirane being replaced by dimethyl sulfate (2.4 mL, 3.2 g, 25 mmol). Evaporation of the mixture and crystallization of the residue from ethanol gave colorless platelets; mp 95−96 °C; yield 4.8 g (66%). ^{1}H NMR: δ 7.88 (d, J = 8.7 Hz, 1 H), 7.02 (d, J = 8.8 Hz, 1 H), 7.00 (s, 1 H), 2.32 (s, 1 H), 1.53 (s, 9 H). ^{13}C NMR: δ 152.9, 144.7, 135.0, 129.1, 122.8, 121.9, 120.4 (q, J = 256.1 Hz), 119.3, 80.8, 28.2 (3 C), 17.7. MS: *m*/*z* (%) 309 (100, $M^+ + NH_4$), 292 (84, $M^+ + 1$), 253 (65), 236 (46), 191 (65). Anal. Calcd for $C_{13}H_{16}F_3NO_3$ (291.27): C 53.62, H 5.54. Found: C 53.61, H 5.25.

[2-(*tert*-Butylcarbonyl)amino-6-(trifluoromethoxy)phenyl]trimethylsilane (9). At −75 °C, diisopropylamine (2.8 mL, 2.0 g, 20 mmol), *tert*-butyl *N*-[3-(trifluoromethoxy)phenyl]-carbamate (2.8 g, 10 mmol), and chlorotrimethylsilane (1.3 mL, 1.1 g, 10 mmol) were added consecutively to butyllithium (20 mmol) in tetrahydrofuran (30 mL) and hexanes (12 mL). When the mixture had attained ambient temperature, the volatiles were evaporated and the residue distilled to afford a ocherous mass, which rapidly solidified; colorless cubes after crystallization from hexanes; mp 64−66 °C; bp 120−122 °C/3 mmHg; yield 2.73 g (78%). ^{1}H NMR: δ 7.64 (d, J = 8.3 Hz, 1 H), 7.35 (t, J = 8.3 Hz, 1 H), 6.99 (d, J = 8.3 Hz, 1 H), 6.62 (s, br, 1 H), 1.51 (s, 9 H), 0.40 (s, 9 H). ^{13}C NMR: δ 154.5, 153.1, 143.9, 131.0, 128.9, 121.0, 120.3 (q, J = 257.8 Hz), 114.3, 80.6, 28.3 (3 C), 1.3 (3 C). Anal. Calcd for $C_{15}H_{22}F_3NO_3Si$ (349.43): C 51.56, H 6.35. Found: C 51.37, H 6.18.

2-Amino-6-(trifluoromethoxy)benzoic Acid (10). A solution prepared with 3-trifluoromethoxy-*N*-(trimethylsilyl)-aniline (6.2 g, 25 mmol) and *tert*-butyllithium (50 mmol) in pentanes (35 mL) and tetrahydrofuran (50 mL) was kept for 2 h at −75 °C before being poured on an excess of freshly crushed dry ice. The product was taken up in water (50 mL). The aqueous phase was washed with diethyl ether (15 mL), acidified (to pH 2), and extracted with diethyl ether (3 × 30 mL). The residue left behind upon evaporation of the combined organic layers was crystallized from hexanes providing colorless needles; mp 115−117 °C; yield 1.8 g (33%). ^{1}H NMR: δ 7.25 (t, J = 8.2 Hz, 1 H), 6.65 (dd, J = 8.4, 0.8 Hz, 1 H), 6.59 (dd, J = 8.1, 0.9 Hz, 1 H). ^{13}C NMR: δ 171.4, 152.1, 149.8, 133.8, 120.3 (q, J = 258.0 Hz), 115.7, 110.1, 104.9. MS: *m*/*z* (%) 239 (100, $M^+ + NH_4$), 222 (52, $M^+ + 1$), 203 (8). Anal. Calcd for $C_8H_6F_3NO_3$ (221.14): C 43.45, H 2.73. Found: C 43.48, H 2.78.

4-Amino-2-(trifluoromethoxy)benzoic Acid (11). Solutions of 3-trifluoromethoxy-*N*,*N*-bis(trimethylsilyl)aniline (4.8 g, 15 mmol) and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (3.0 mL, 2.6 g, 15 mmol) in tetrahydrofuran (30 mL) and *sec*-butyllithium (15 mmol) in hexanes (10 mL) were mixed and kept for 6 h at −75 °C. The carboxylation, neutralization, and extraction was carried out as described in the preceding paragraph to give, after crystallization from water, colorless prisms; mp 164−165 °C; yield 2.3 g (69%). ^{1}H NMR: δ 7.93 (d, J = 8.6 Hz, 1 H), 6.59 (dd, J = 8.4, 2.2 Hz, 1 H), 7.54 (s, 1 H). ^{13}C NMR: δ 166.1, 152.5, 149.8, 134.0, 120.3 (q, J = 256.5 Hz), 112.5, 111.9, 107.3. MS: *m*/*z* (%) 239 (100, $M^+ + NH_4$), 222 (89, $M^+ + 1$), 204 (44), 169 (21). Anal. Calcd for $C_8H_6F_3NO_3$ (221.14): C 43.45, H 2.73. Found: C 43.31, H 2.75.

5-Amino-2-(trifluoromethoxy)benzoic Acid (12). Analogously 4-trifluoromethoxy-*N*,*N*-bis(trimethylsilyl)aniline (4.8 g, 15 mmol) was converted into the acid **12**, which was isolated as colorless prisms by crystallization from water; mp 201−203 °C; yield 1.6 g (48%). ^{1}H NMR: δ 7.20 (d, J = 2.6 Hz, 1 H), 7.02 (d, J = 8.5 Hz, 1 H), 6.79 (dd, J = 8.6, 2.6 Hz, 1 H). ^{13}C NMR: δ 171.2, 151.3, 131.1, 128.4, 126.4, 122.9, 121.5, 120.3 (q, J = 258.9 Hz). MS: *m*/*z* (%) 239 (100, $M^+ + NH_4$), 221 (50, M^+), 204 (5). Anal. Calcd for $C_8H_6F_3NO_3$ (221.14): C 43.45, H 2.73. Found: C 43.54, H 2.82.

2-[3-Bromo-2-(trifluoromethoxy)phenyl]-4,5-dihydro-4,4-dimethyloxazole (14). Thionyl chloride (4.8 mL, 7.9 g, 66 mmol) was added to a suspension of 3-bromo-2-(trifluoromethoxy)benzoic acid[7] (14 g, 50 mmol) in toluene (0.10 L). The mixture was heated under reflux for 2 h before the volatiles were evaporated under reduced pressure. The residue and 2-amino-2-methyl-1-propanol (9.1 mL, 8.5 g, 95 mmol) were conjointly dissolved in dichloromethane (0.10 L). After being kept for 12 h at 25 °C, the suspension was washed with a saturated aqueous solution of sodium carbonate (2 × 50 mL), dried, and evaporated. The residue was crystallized from a 1:5 (v/v) mixture of ethyl acetate and hexanes (0.10 L) to give **3-bromo-*N*-(2-hydroxy-1,1-dimethylethyl)-2-(trifluoromethoxy)benzamide** as colorless platelets; mp 122−123 °C; yield 14.8 g (83%). ^{1}H NMR: δ 7.75 (d, J = 7.9 Hz, 2 H), 7.29 (t, J = 8.2 Hz, 1 H), 6.27 (s, br, 1 H), 3.68 (s, 2 H), 1.40 (s, 6 H). Anal. Calcd for $C_{12}H_{13}BrF_3NO_3$ (356.14): C 40.47, H 3.68. Found: C 40.71, H 3.47. This solid (14 g, 40 mmol) was dissolved in excess thionyl chloride (20 mL) and kept for 1 h at 25 °C. The mixture was poured on ice (0.20 kg), alkalized to pH 11 with a 5.0 M aqueous solution of sodium hydroxide (0.20 L), and extracted with dichloromethane (3 × 0.10 L). The combined organic layers were washed with brine (0.10 L), dried, and evaporated. Upon distillation a colorless liquid was collected; bp 70−72 °C/0.2 mmHg; n^{20}_D 1.4986; yield 10.3 g (76%). ^{1}H NMR: δ 7.80 (dd, J = 7.9, 1.8 Hz, 1 H), 7.74 (dd, J = 8.2, 1.5 Hz, 1 H), 7.23 (t, J = 8.0 Hz, 1 H), 4.13 (s, 2 H), 1.38 (s, 6 H). ^{13}C NMR: δ 159.3, 144.3, 136.3, 130.5, 128.2, 125.9, 120.4 (q, J = 260.5 Hz), 118.8, 79.5, 67.8, 28.1. MS: *m*/*z* (%) 338 (64, M^+), 322 (100), 284 (51). Anal. Calcd for $C_{12}H_{11}BrF_3NO_2$ (338.12): C 42.63, H 3.28. Found: C 42.79, H 3.17.

2-[3-Azido-2-(trifluoromethoxy)phenyl]-4,5-dihydro-4,4-dimethyloxazole (15). The oxazoline **14** (14 g, 40 mmol) and, 5 min later, a solution of benzenesulfonyl azide (8.1 g, 44 mmol) in toluene (50 mL) were added to butyllithium (40 mmol) in toluene (0.20 L) and hexanes (27 mL). The sticky mass was allowed to reach 25 °C and stirred for 1 h. A 2.0 M aqueous solution of sodium hydroxide (0.20 L) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL). The residue left behind upon evaporation of the combined organic layers was purified by chromatography on silica gel (0.40 L, 0.22 kg) with a 1:3 (v/v) mixture of ethyl acetate and hexanes. The azide **15** was obtained after evaporation of the volatiles as colorless liquid; yield 7.71 g (64%). IR (film): 2972 (C−H), 2126 (N_3), 1654 (C=N). ^{1}H NMR: δ 7.63 (dd, J = 7.7, 1.9 Hz, 1 H), 7.36 (t, J = 7.9 Hz, 1 H), 7.28 (dd, J = 8.0, 1.6 Hz, 1 H), 4.12 (s, 2 H), 1.38 (s, 6 H). MS: *m*/*z* (%) 301 (100, M^+), 260 (38).

2-[3-Amino-2-(trifluoromethoxy)phenyl]-4,5-dihydro-4,4-dimethyloxazole (16). The azide **15** (6.0 g, 20 mmol) was dissolved in methanol (0.10 L) and treated with sodium borohydride (3.8 g, 0.10 mol) in four portions. After 2 h, the volatiles were removed by evaporation and the residue was suspended in diethyl ether (20 mL) and filtered through a pad of Celite. Washing with more diethyl ether (2 × 20 mL) and distillation afforded a colorless liquid; bp 126−129 °C/0.2 mmHg; 2.96 g (54%); n^{20}_D 1.5052. ^{1}H NMR: δ 7.17 (dd, J = 7.8, 1.7 Hz, 1 H), 7.09 (t, J = 7.9 Hz, 1 H), 6.87 (dd, J = 8.2, 1.8 Hz, 1 H), 4.09 (s, 2 H), 1.36 (s, 6 H). ^{13}C NMR: δ 160.0, 140.9, 131.9, 131.3, 127.5, 120.8 (q, J = 259.2 Hz), 119.8, 119.2, 79.1, 67.5, 27.9. Anal. Calcd for $C_{12}H_{13}F_3N_2O_2$ (274.24): C 52.56, H 4.78. Found: C 52.24, H 4.68.

3-Amino-2-(trifluoromethoxy)benzoic Acid (13). The anilinooxazoline **16** (0.82 g, 3.0 mmol) dissolved in 5.0 M aqueous hydrochloric acid (20 mL) was heated under reflux for 12 h. The mixture was alkalized to pH 12 with a 5.0 M aqueous solution of sodium hydroxide (40 mL) and washed with diethyl ether (2 × 10 mL). The aqueous phase was acidified with concentrated hydrochloric acid to pH 2 and evaporated to dryness. The remaining solid was triturated with hot acetonitrile (3 × 20 mL) and insoluble salts were removed by filtration. The residue obtained after evaporation of the volatiles was crystallized from chloroform (5.0 mL) to give the acid **13** as colorless needles; mp 105−106 °C; yield 0.37 g (56%). ^{1}H NMR: δ 7.38 (dd, J = 7.7, 1.6 Hz, 1 H), 7.16 (t, J = 8.0 Hz, 1 H), 7.03 (dd, J = 8.1, 1.6 Hz, 1 H), 6.50 (s, 3 H). ^{13}C NMR: δ 170.1, 141.0, 134.2, 127.6, 125.6, 121.8, 121.4, 120.9 (q, J = 259.2 Hz). MS: *m*/*z* (%) 256 (3, $M^+ + 2\ NH_4^+$), 239 (100, $M^+ + NH_4^+$), 221 (31, M^+). Anal. Calcd for $C_8H_6F_3NO_3$ (221.13): C 43.45, H 2.73. Found: C 43.37, H 2.66.

3. Trifluoromethoxy Substituted Diazepams. *tert*-Butyl *N*-[2-(α-2-Fluorophenyl-α-hydroxymethyl)-4-(trifluoromethoxy)phenyl]carbamate (17). Solutions of *tert*-butyl *N*-[4-(trifluoromethoxy)phenyl]carbamate (28 g, 0.10 mol) in tetrahydrofuran (0.20 L) and *tert*-butyllithium (0.20 mol) in pentanes (0.13 L) were mixed and kept for 2 h at −50 °C before being treated with 2-fluorobenzaldehyde (11 mL, 12 g, 0.10 mol). At 25 °C, water (0.10 L) was added. The organic layer was decanted, dried, and evaporated. Colorless cubes formed upon crystallization of the residue from hexanes; mp 117−118 °C; yield 24.3 g (61%). ^{1}H NMR: δ 7.84 (d, J = 9.0 Hz, 1 H), 7.64 (s, br, 1 H), 7.47 (td, J = 7.6, 1.5 Hz, 1 H), 7.4 (m, 1 H), 7.22 (td, J = 7.6, 1.4 Hz, 1 H), 7.16 (dd, J = 9.0, 1.9 Hz, 1 H), 7.07 (ddd, J = 9.1, 8.1, 1.0 Hz, 1 H), 6.93 (s, 1 H), 6.16 (s, 1 H), 3.04 (s, br, 1 H), 1.50 (s, 9 H). ^{13}C NMR: δ 161.2, 155.6, 153.4, 144.8, 134.2 (d, J = 254.1 Hz), 130.0 (d, J = 8.8 Hz), 127.7, 124.5 (d J = 3.2 Hz), 123.7, 121.7 (d, J = 40.1 Hz), 121.3, 120.9, 120.4 (q, J = 261.0 Hz), 115.7 (d, J = 21.6 Hz), 80.8, 69.9, 28.3 (3 C). MS: *m*/*z* (%) 419 (9, $M^+ + NH_4$), 381 (16), 295 (100), 278 (97). Anal. Calcd for $C_{19}H_{19}F_4NO_4$ (401.36): C 56.85, H 4.77. Found: C 57.26, H 4.80.

***tert*-Butyl *N*-[2-(2-Fluorobenzoyl)-4-(trifluoromethoxy)-phenyl]carbamate (18a).** Commercial manganese dioxide

(22 g, 0.25 mol) was added to the alcohol **17** (20 g, 50 mmol) in ethyl acetate (0.30 L). The slurry was stirred for 20 h at 25 °C, then filtered. The clear solution was evaporated and the residue crystallized from pentanes to give colorless needles; mp 77−78 °C; yield 16.4 g (82%). ^{1}H NMR: δ 10.47 (s, 1 H), 8.57 (d, J = 9.2 Hz, 1 H), 7.6 (m, 1 H), 7.47 (t, J = 7.3 Hz, 1 H), 7.41 (dd, J = 9.1, 2.2 Hz, 1 H), 7.3 (m, 2 H), 7.18 (d, J = 9.1 Hz, 1 H), 1.55 (s, 9 H). ^{13}C NMR: δ 195.2, 159.6 (d, J = 255.2 Hz), 152.8, 142.1, 140.7, 133.6 (d, J = 9.5 Hz), 130.3, 128.0, 126.8 (d, J = 14.3 Hz), 126.1, 124.4 (d, J = 3.6 Hz), 122.6, 120.8, 120.4 (d, J = 258.4 Hz), 116.5 (d, J = 22.0 Hz), 81.2, 28.2 (3 C). MS: m/z (%) 417 (100, $M^+ + NH_4$), 400 (86, $M^+ + 1$), 344 (73), 299 (77).

2-Amino-5-(trifluoromethoxy)phenyl 2-Fluorophenyl Ketone (18b). Carbamate **18a** (16 g, 40 mmol) and trifluoroacetic acid (3.8 mL, 5.7 g, 50 mmol) were dissolved in dichloromethane (80 mL) and kept for 2 h at 25 °C. When the solvent was evaporated and the residue crystallized from hexanes (at −75 °C), pale yellow microneedles were obtained; mp 55−56 °C; yield 10.9 g (91%). ^{1}H NMR: δ 7.5 (m, 1 H), 7.42 (td, J = 7.2, 1.6 Hz, 1 H), 7.27 (td, J = 7.4, 0.9 Hz, 1 H), 7.2 (m, 3 H), 6.71 (d, J = 9.2 Hz, 1 H), 6.43 (s, br, 2 H). ^{13}C NMR: δ 194.3, 159.0 (d, J = 251.9 Hz), 149.7, 138.3, 132.4 (d, J = 9.0 Hz), 129.8, 128.9, 127.2 (d, J = 15.7 Hz), 126.6, 124.3 (d, J = 3.8 Hz), 120.4 (q, J = 257.6 Hz), 117.9, 117.5, 116.2 (d, J = 21.7 Hz). MS: m/z (%) 299 (100, M^+), 280 (12), 204 (7), 177 (3), 123 (31). Anal. Calcd for $C_{14}H_9F_4O_2$ (299.23): C 56.20, H 3.03. Found: C 56.23, H 3.19.

***N*-[2-(2-Fluorobenzoyl)-4-(trifluoromethoxy)phenyl]-α-bromoacetamide (18c).** The aminobenzophenone **18b** (7.5 g, 25 mmol) was dissolved in ethyl acetate (50 mL) and treated with bromoacetyl bromide (2.2 mL, 5.0 g, 25 mmol). After 2 h at 25 °C, the homogeneous mixture was washed with a 1.0 M aqueous solution (50 mL) of sodium hydroxide. The organic layer was decanted, dried, and evaporated. Crystallization from hexanes afforded colorless needles; mp 96−97 °C; yield 9.0 g (86%). ^{1}H NMR: δ 8.77 (d, J = 9.2 Hz, 1 H), 7.6 (m, 1 H), 7.54 (td, J = 7.4, 1.8 Hz, 1 H), 7.48 (dd, J = 9.2, 1.5 Hz, 1 H), 7.4 (m, 1 H), 7.32 (td, J = 7.6, 1.0 Hz, 1 H), 7.20 (ddd, J = 9.3, 8.4, 1.0 Hz, 1 H), 4.05 (s, 2 H). ^{13}C NMR: δ 195.4, 165.4, 160.7 (d, J = 253.3 Hz), 143.9, 138.5, 134.2 (d, J = 8.0 Hz), 130.6, 127.8, 126.3 (d, J = 14.3 Hz), 126.1, 124.7 (d, J = 3.2 Hz), 124.5, 122.6, 120.5 (q, J = 258.1 Hz), 116.6 (d, J = 22.2 Hz), 29.3. MS: m/z (%) 421 (52, $M^+ + 1$), 340 (7), 298 (24), 228 (100), 214 (36), 177 (10), 123 (35). Anal. Calcd for $C_{16}H_{10}BrF_4NO_3$ (420.16): C 45.74, H 2.40. Found: C 45.92, H 2.44.

5-(2-Fluorophenyl)-1,3-dihydro-7-trifluoromethoxy-2*H*-1,4-benzodiazepin-2-one (19). At 0 °C, gaseous ammonia was introduced for 45 min into a solution containing acetamide **18c** (4.2 g, 10 mmol) in methanol (20 mL). After having been heated to reflux for 2 h, the mixture was evaporated. The oily residue crystallized from a 1:9 (v/v) mixture of diethyl ether and hexanes as colorless needles; mp 165 166 °C; 3.2 g (92%). ^{1}H NMR: δ 9.12 (s, br, 1 H), 7.65 (td, J = 7.5, 1.7 Hz, 1 H), 7.5 (m, 1 H), 7.39 (d, J = 8.1 Hz, 1 H), 7.3 (m, 1 H), 7.22 (d, J = 8.9 Hz, 1 H), 7.1 (m, 2 H), 4.42 (s, br, 2 H). ^{13}C NMR: δ 171.1, 166.4, 159.5 (d, J = 252.5 Hz), 144.5, 136.1, 132.4 (d, J = 9.5 Hz), 131.4, 129.2, 127.0 (d, J = 12.8 Hz), 124.8, 124.4 (d, J = 3.2 Hz), 120.2 (q, J = 259.6 Hz), 116.3 (d, J = 21.5 Hz), 56.6. MS: m/z (%) 338 (60, M^+), 337 (62), 310 (98), 299 (100), 282 (45), 123 (18). Anal. Calcd for $C_{16}H_{10}F_4N_2O_2$ (338.26): C 56.81, H 2.96. Found: C 56.65, H 3.06.

***tert*-Butyl *N*-[4-Chloro-2-[α-hydroxy-α-2-(trifluoromethoxy)phenyl]]carbamate (20).** At −75 °C, *tert*-butyl *N*-(4-chlorophenyl)carbamate[24] (23 g, 0.10 mol) in tetrahydrofuran (0.20 L) was treated with *tert*-butyllithium (0.20 L) in pentanes (0.13 L). After the addition of 2-(trifluoromethoxy)benzaldehyde (19 g, 0.10 mol), the mixture was kept 1 h more at −75 °C before being washed with brine (0.10 L). The organic phase was dried and evaporated. The residue crystallized from hexanes in the form of colorless cubes; mp 115−116 °C; yield 22.1 g (53%). ^{1}H NMR: δ 7.6 (m, 2 H), 7.4 (m, 2 H), 7.3 (m, 2 H), 7.09 (d, J = 2.4 Hz, 1 H), 6.17 (d, J = 3.4 Hz, 1 H), 3.21 (s, br, 1 H), 1.50 (s, 9 H). ^{13}C NMR: δ 158.3, 146.2, 134.7, 134.3, 133.2, 129.6, 129.4, 128.7, 128.2, 128.1, 126.9, 124.4, 120.4 (q, J = 263.4 Hz), 119.6, 80.9, 68.2, 28.2 (3 C). MS: m/z (%) 435 (13, $M^+ + NH_4$), 381 (19), 344 (44), 281 (100), 127 (39). Anal. Calcd for $C_{19}H_{19}ClF_3NO_4$ (417.81): C 54.62, H 4.58. Found: C 54.55, H 4.63.

***tert*-Butyl *N*-[4-Chloro-2-[2-(trifluoromethoxy)phen-yl-]]carbamate (21a).** Commercial manganese dioxide (22 g, 0.25 mol) was added to alcohol **20** (21 g, 50 mmol) dissolved in ethyl acetate (0.30 L). The slurry was stirred for 20 h at 25 °C, then filtered. The clear solution was evaporated. Crystallization of the residue from pentanes gave colorless needles; mp 102−104 °C; yield 15.6 g (75%). ^{1}H NMR: δ 8.52 (d, J = 9.2 Hz, 1 H), 7.60 (ddd, J = 9.2, 6.5, 2.8 Hz, 1 H), 7.50 (dd, J = 9.1, 2.6 Hz, 1 H), 7.4 (m, 3 H), 7.28 (d, J = 2.6 Hz, 1 H), 1.54 (s, 9 H). ^{13}C NMR: δ 195.9, 152.8, 141.0, 138.2, 135.2, 133.0, 132.5, 132.2, 129.7, 126.8, 125.7, 122.4, 121.2, 120.7, 120.5 (q, J = 262.1 Hz), 81.2, 28.2 (3 C). MS: m/z (%) 415 (4, M^+), 315 (100), 230 (20), 189 (9), 154 (13). Anal. Calcd for $C_{19}H_{17}ClF_3NO_4$ (415.80): C 54.88, H 4.12. Found: C 54.87, H 4.32.

2-Amino-4-chlorophenyl 2-(Trifluoromethoxy)phenyl Ketone (21b). The carbamate **21a** (15 g, 35 mmol) and trifluoroacetic acid (3.8 mL, 5.7 g, 50 mmol) were dissolved in dichloromethane (70 mL) and kept for 2 h at 25 °C. Upon distillation, a yellow oil was collected; bp 183−185 °C/3 mmHg; n_D^{20} 1.5915; yield 9.8 g (89%). ^{1}H NMR: δ 7.5 (m, 1 H), 7.4 (m, 3 H), 7.21 (dd, J = 8.9, 2.5 Hz, 1 H), 7.14 (d, J = 2.4 Hz, 1 H), 6.66 (d, J = 8.8 Hz, 1 H), 6.4 (s, br, 2 H). ^{13}C NMR: δ 194.7, 149.7, 145.6, 135.1, 133.3, 132.9, 131.3, 129.2, 126.7, 121.0, 120.3 (q, J = 259.3 Hz), 119.9, 118.5, 118.2. MS: m/z (%) 315 (100, M^+), 246 (14), 230 (13), 189 (9), 154 (15). Anal. Calcd for $C_{14}H_9ClF_3NO_2$ (315.16): C 53.26, H 2.88. Found: C 53.13, H 2.83.

2-Amino-4-chlorophenyl 2-(Trifluoromethoxy)phenyl Ketone Oxime (21c). Hydroxylamine hydrochloride (8.6 g, 9.12 mol) was added to a solution of ketone **21b** (7.9 g, 25 mmol) and pyridine (25 mL) in ethanol (25 mL). The suspension was heated to reflux for 60 h under stirring. After filtration, the volatiles were evaporated to leave behind a colorless crude product; yield 7.8 g (94%). ^{1}H NMR: δ 7.53 (td, J = 7.6, 1.8 Hz, 1 H), 7.4 (m, 2 H), 7.28 (dd, J = 7.8, 1.7 Hz, 1 H), 7.09 (dd, J = 8.2, 2.1 Hz, 1 H), 6.68 (d, J = 8.3 Hz, 1 H), 6.60 (d, J = 2.2 Hz, 1 H), 4.70 (s, br, 2 H). MS: m/z (%) =331 (65, $M^+ + 1$), 316 (100), 246 (11), 230 (16), 189 (10), 154 (12).

***N*-[4-Chloro-2-(α-hydroxyimino-α-2-(trifluoromethoxy)-phenyl]-α-chloroacetamide (21d).** The (hydroxyimino)benzophenone **21c** (5.0 g, 15 mmol) and chloroacetyl chloride (1.2 mL, 1.8 g, 15 mmol) were conjointly dissolved in ethyl acetate (30 mL). The homogeneous mixture was allowed to stand for 2 h at 25 °C before being shaken with a 2.0 M aqueous solution (30 mL) of sodium hydroxide. The organic layer was decanted, dried, and evaporated. Upon crystallization of the residue from ethanol, pale yellow needles were obtained; mp 146−149 °C; yield 5.5 g (90%). ^{1}H NMR: δ 11.37 (s, br, 1 H), 8.67 (d, J = 9.0 Hz, 1 H), 7.65 (td, J = 7.8, 1.9 Hz, 1 H), 7.5 (m, 3 H), 7.25 (dd, J = 8.1, 1.9 Hz, 1 H), 4.03 (s, 2 H). ^{13}C NMR: δ 165.6, 163.7, 161.8, 145.9, 136.2, 132.2 (2 C), 131.2, 129.6, 129.0, 127.0, 123.3, 121.9, 120.7 (q, J = 259.8 Hz), 120.5, 43.7. MS: m/z (%) 407 (6, M^+), 391 (43), 373 (55), 341 (80), 312 (100). Anal. Calcd for $C_{16}H_{11}Cl_2F_3N_2O_3$ (407.18): C 47.20, H 2.72. Found: C 46.88, H 2.90.

7-Chloro-1,3-dihydro-3-hydroxy-5-[2-(trifluoromethoxy)phenyl]-2*H*-1,4-benzodiazepin-2-one (22). The acetamide **21d** (4.1 g, 10 mmol) and sodium hydroxide (0.80 g, 20 mmol) were conjointly dissolved in 50% aqueous dioxane (20 mL). The homogeneous mixture was kept for 20 h at 25 °C before being acidified (to pH 2) with concentrated hydrochloric acid. The precipitate formed was removed by filtration and

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recrystallized from 85% aqueous dioxane to afford colorless needles; mp 223−224 °C (repr.); yield 3.2 g (86%). ^{1}H NMR: δ 8.62 (s br, 1 H), 7.5 (m, 2 H), 7.4 (m, 3 H), 7.12 (d, J = 8.6 Hz, 1 H), 6.94 (d, J = 2.3 Hz, 1 H), 4.75 (s, br, 1 H), 4.72 (s, 1 H). ^{13}C NMR: δ 165.5, 147.1, 142.8, 138.2, 134.0, 131.9, 131.7, 130.8, 129.2, 127.0, 126.4, 126.1, 123.1, 120.9, 120.3 (q, J = 260.5 Hz), 67.5. MS: m/z (%) 371 (34, $M^+ + 1$), 246 (14), 230 (13), 189 (9), 154 (15). Anal. Calcd for $C_{16}H_{10}ClF_3N_2O_3$ (370.72): C 51.84, H 2.72. Found: C 51.78, H 2.98.

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