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SYNTHESIS OF BENZYLISOQUINOLINE DERIVATIVES POSSESSING ELECTRON-WITHDRAWING SUBSTITUENTS ON THE BENZENE RING OF THE ISOQUINOLINE SKELETON

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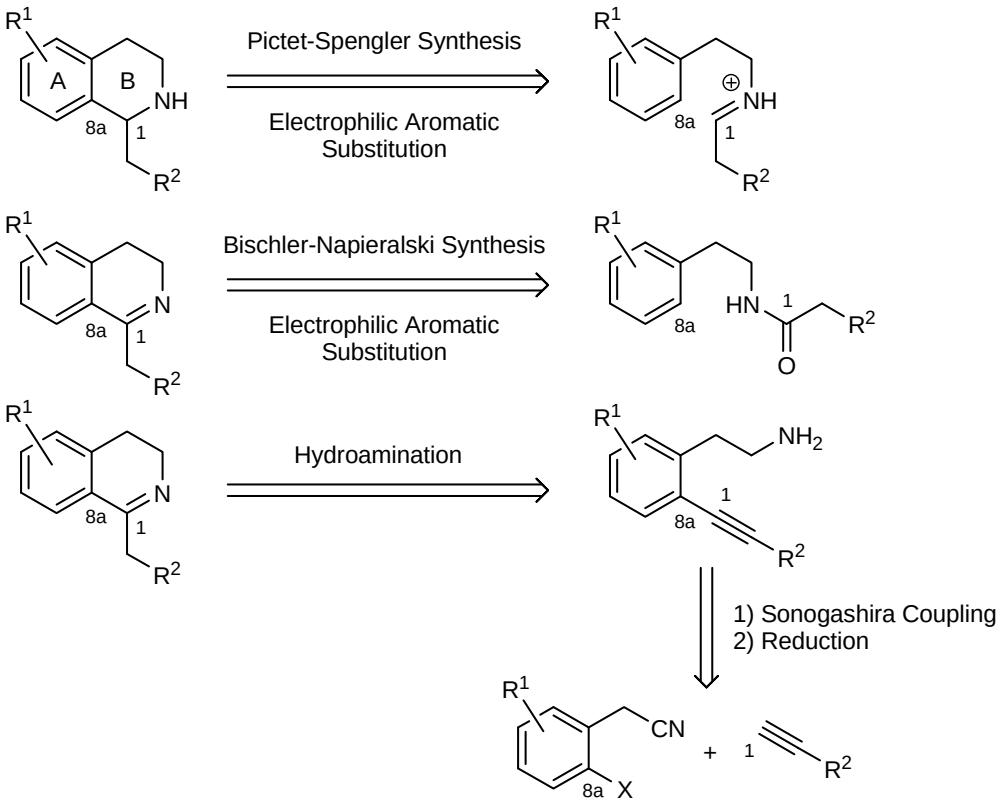
Dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday.

Abstract – 3,4-Dihydrobenzylisoquinolines and 1,2,3,4-tetrahydrobenzyl-isoquinolines possessing electron withdrawing substituents on the benzene ring of the isoquinoline framework are easily accessible by a synthetic approach that takes advantage of a Sonogashira coupling to build up the C1-C8a bond of the isoquinoline skeleton and a Ti-catalyzed intramolecular hydroamination of an alkyne to close the heterocyclic ring.

INTRODUCTION

Benzylisoquinoline alkaloids and related synthetic derivatives represent a class of compounds with a wide range of interesting pharmaceutical properties, including analgesic, sedative, narcotic, anesthetic, antitussive, spasmolytic, and sympathomimetic activity.[1,2] Consequently, the isolation, the therapeutic use, and the synthesis of corresponding molecules have attracted much attention during the past 200 years.[3] The most important synthetic approaches towards benzylisoquinoline derivatives are based on the Pictet-Spengler, Bischler-Napieralski, or Pommeranz-Fritsch synthesis.[4] Since all these methods rely on a typical electrophilic aromatic substitution reaction for the formation of the C1-C8a (or the C4-C4a) bond of the benzylisoquinoline skeleton (Scheme 1), best results are obtained with substrates possessing an electron-rich benzene ring. In this case, benzylisoquinoline derivatives possessing an electron-rich aromatic A-ring are formed. Not surprisingly, benzylisoquinolines with an electron-poor A-ring which may show improved pharmaceutical properties are rare in the literature.[5] However, 3,4-dihydrobenzylisoquinoline building blocks can also be obtained by Ti-catalyzed intramolecular hydroamination reactions of suitable aminoalkynes (Scheme 1).[6-8] The major advantage of this synthetic approach is the fact that in this case, the C1-C8a bond can easily be formed by a Sonogashira coupling[9]

between a suitable, *ortho*-functionalized aryl halide and a terminal alkyne. Correspondingly, the typical electrophilic aromatic substitution reaction which is usually employed for the formation of the C1-C8a bond can be avoided. Since the Pd-catalyzed Sonogashira coupling is facilitated by electron-withdrawing substituents (R^1) located at the benzene ring of the aryl halide, the Sonogashira coupling/hydroamination approach is somehow complementary to the common electrophilic substitution approach and should be particularly useful for the synthesis of benzylisoquinoline derivatives possessing an electron-poor benzene ring as part of the isoquinoline unit. To demonstrate this possibility, we planned to convert a number of (2-bromophenyl)acetonitriles bearing electron-withdrawing substituents R^1 into corresponding 3,4-dihydrobenzylisoquinoline building blocks. From these reactive intermediates, biologically interesting norlaudanosine or papaverine analogues should be easily accessible by either reduction[10] or dehydrogenation.[11] In addition, an alternative oxidation of the benzylic position of the side chain would give access to 1-benzoyl-3,4-dihydroquinolines, a class of new antitumor agents.[12]

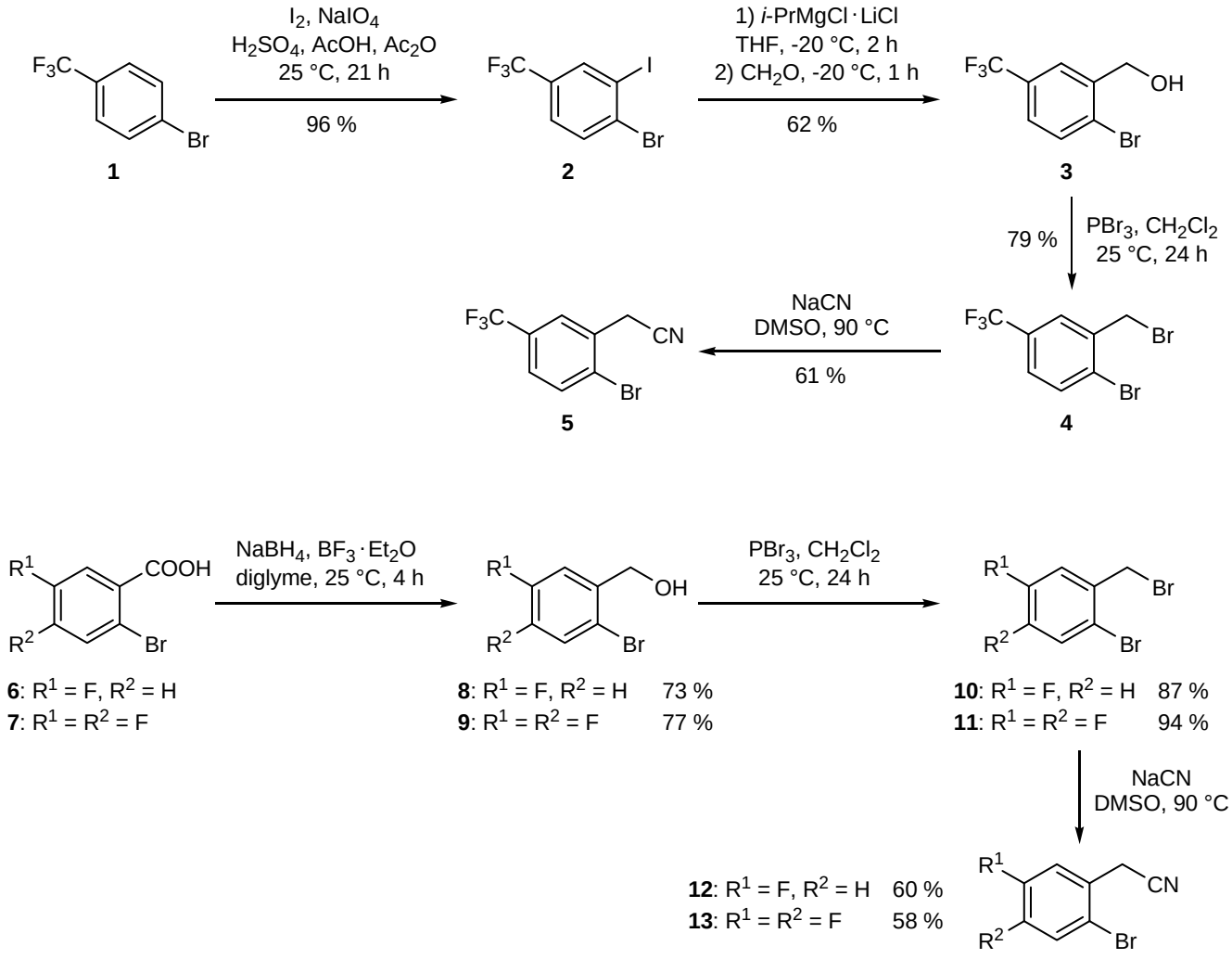


Scheme 1. Retrosynthesis of the benzylisoquinoline skeleton

RESULTS AND DISCUSSION

The synthesis of the trifluoromethyl- or fluoro-substituted (2-bromophenyl)acetonitriles **5**, **12** and **13** was accomplished as depicted in Scheme 2. Regioselective iodination of commercially available 4-bromotrifluorotoluene **1** under oxidative conditions[13] gave 1-bromo-2-iodo-4-trifluoromethylbenzene (**2**) in 96% yield. Subsequently, a selective I/Mg exchange reaction of **2** using Knochel´s mixed Mg/Li

reagent *i*-PrMgCl·LiCl[14] and trapping of the formed arylmagnesium compound with monomeric formaldehyde[15] gave the benzylic alcohol **3** in 62% yield. The final introduction of the missing cyano group was then achieved in two steps using standard procedures. Initial reaction of **3** with PBr_3 gave the corresponding dibromide **4** in 79% and a subsequent nucleophilic substitution performed with sodium cyanide in DMSO gave access to the desired (2-bromophenyl)acetonitrile **5** in 61% yield.

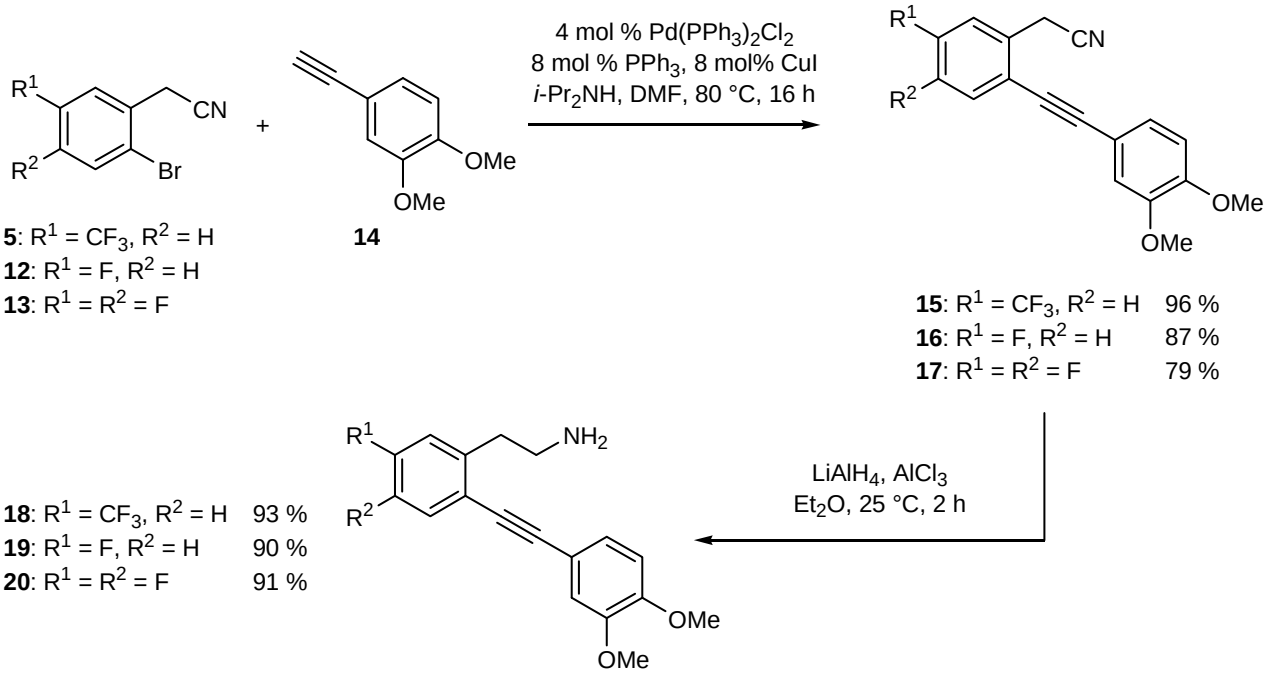


Scheme 2. Synthesis of (2-bromophenyl)acetonitriles **5**, **12** and **13**

The fluoro- and difluoro-substituted (2-bromophenyl)acetonitriles **12** and **13** were easily accessible in three steps from commercially available carboxylic acids **6** and **7**. Simple reductions to the benzylic alcohols **8** and **9** using $NaBH_4$ in the presence of $BF_3{\cdot}Et_2O$[16] took place in 73% and 77% yield, respectively. The same transformation could also be achieved with $LiAlH_4$ but in this case, the yields were below 60%. As described above, the desired acetonitriles **12** and **13** were obtained from the alcohols **8** and **9** using standard procedures in two steps via the dibromides **10** and **11**.

With (2-bromophenyl)acetonitriles **5**, **12** and **13** in hand, attention was now directed towards the synthesis of aminoalkynes **18**-**20**, as shown in Scheme 3. The substrates **5**, **12** and **13** were reacted with alkyne **14**[7]

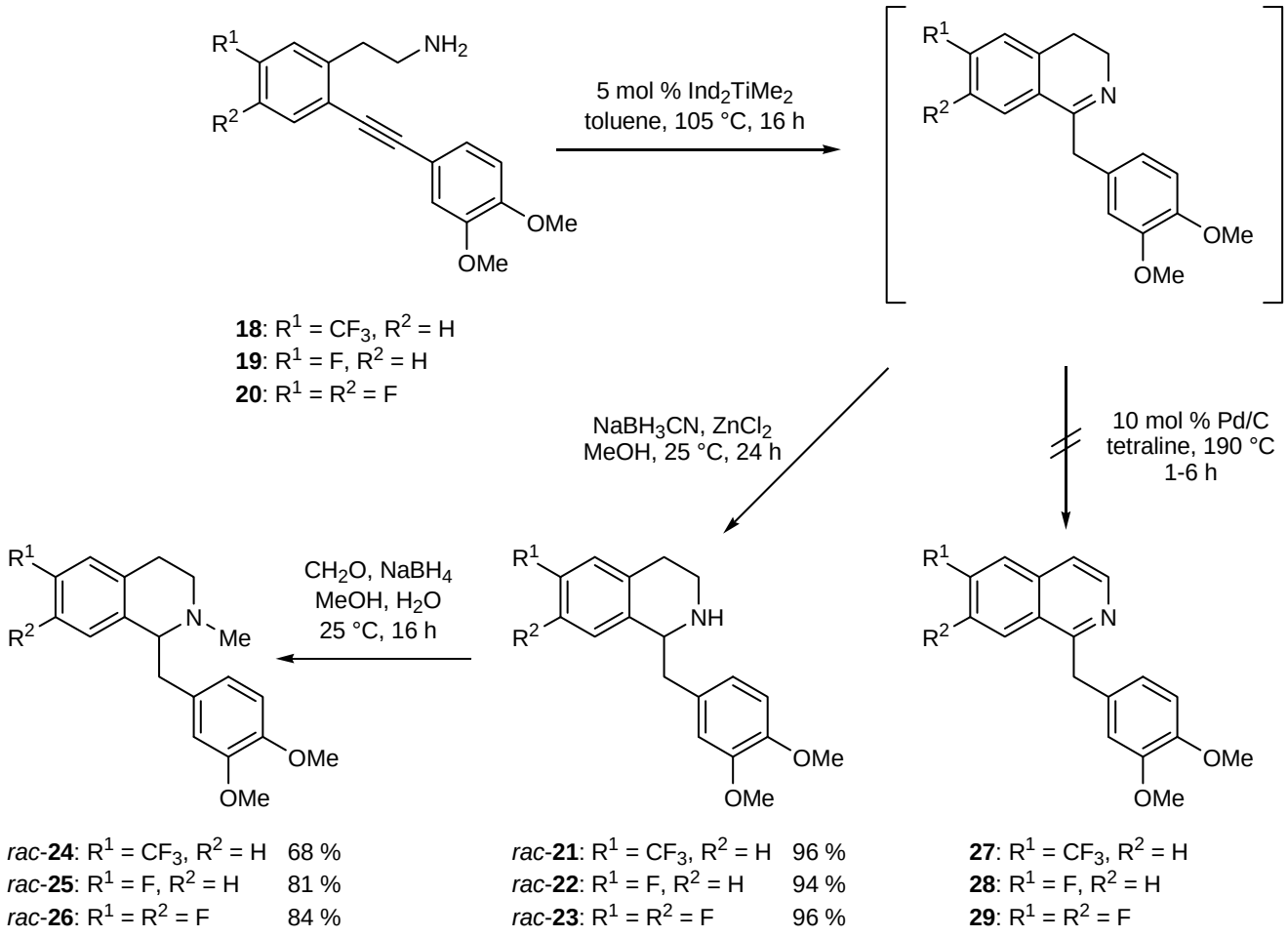
under Sonogashira coupling conditions. Using 4 mol% $Pd(PPh_3)_2Cl_2$, 8 mol% PPh_3, and 8 mol% CuI as the catalyst system, a mixture of *i*-Pr_2NH and DMF was found to be the best solvent for the cross coupling reactions. Under optimized conditions, the alkynes **15**, **16**, and **17** were obtained in 96%, 87%, and 79% yield, respectively. In this context, it is particular important to mention that the best yield for this formation of the C1-C8a bond was observed with substrate **5** which has the strongest electron-acceptor (the CF_3-group) bound to the benzene ring. This fact strongly supports the idea that our synthetic approach is particularly suitable for the synthesis of electron-acceptor substituted benzylisoquinoline derivatives. Subsequent reductions of the cyano groups present in the alkynes **15**-**17** with $LiAlH_4$ in the presence of $AlCl_3$ gave accesss to the desired aminoalkynes **18**-**20** in excellent yields (90-93%).



Scheme 3. Synthesis of aminoalkynes **18**-**20**

The aminoalkynes **18**-**20** were then subjected to intramolecular hydroamination reactions at 105 °C in toluene in the presence of 5 mol% Ind_2TiMe_2 (Ind = indenyl).[17] After a reaction time of 16 h (not minimized), the initially formed 3,4-dihydrobenzylisoquinolines (Scheme 4) were directly reduced by the addition of $NaBH_3CN$, $ZnCl_2$, and methanol to the crude reaction mixtures. After stirring at room temperature for 24 h, the racemic norlaudanosine analogues *rac*-**21**-**23** were finally isolated by chromatography in pure form. The efficiency of the two-step process is clearly underlined by the excellent yields (≥ 94%) obtained for all products. For future applications, it is also important to keep in mind that corresponding reductions can be performed enantioselectively with high ee values following Noyori´s protocol.[7,18] Furthermore, the norlaudanosine derivatives are suitable starting materials for

further transformations to more complex 1,2,3,4-tetrahydrobenzylisoquinolines, e.g. of the berberine- or the laudanosine type.[1-3,7] To verify this idea, *rac*-**21**-**23** were simply converted into the laudanosine analogues *rac*-**24**-**26** by reductive amination (CH_2O, $NaBH_4$) in 68%, 81%, and 84% yield, respectively.



Scheme 4. Synthesis of laudanosine and norlaudanosine analogues from aminoalkynes

Alternatively, it was tried to combine the initial hydroamination reaction with a subsequent dehydrogenation[11] to obtain isoquinolines of the papaverine type (**27**-**29**). For that purpose, tetraline was added together with a dehydrogenation catalyst (10 mol% Pd/C) to the crude reaction mixtures obtained from the hydroamination reactions. Unfortunately, heating of these mixtures to 190 °C for 1-6 hours always resulted in the formation of several products as determined by GC. As a consequence, the papaverines **27**-**29** could not be isolated in pure form yet. Interestingly, GC-MS analysis suggested that under the reaction conditions the desired aromatization is accompanied by a loss of one or more F-atoms probably caused by Pd-catalyzed C-F activation. However, alternative protocols for the dehydrogenation of the 3,4-dihydroisoquinolines are presently under investigation in our laboratories.

In summary, we have presented a highly flexible method for the synthesis of 1,2,3,4-tetrahydroisoquinolines possessing electron-withdrawing substituents on the benzene ring of the isoquinoline skeleton. The key-steps of the synthesis are a Sonogashira coupling of a (2-bromophenyl)acetonitrile and a terminal alkyne as well as an intramolecular hydroamination reaction that forms a 3,4-dihydroisoquinoline system. This key-intermediate can directly be reduced to biologically interesting 1,2,3,4-tetrahydroisoquinolines. An alternative dehydrogenation of the 3,4-dihydroisoquinolines that would result in the formation of electron-acceptor substituted papaverine analogues has failed so far. For future studies, it is also planned to oxidize the benzylic position of the side chain of the electron-acceptor substituted 3,4-dihydroisoquinolines to get access to corresponding α-ketoimines, a class of new antitumor agents.[12] Further synthetic studies employing other aryl bromides and other terminal alkynes for the Sonogashira coupling are presently underway in our laboratories. This will lead to the formation of a library of electron-acceptor substituted benzylisoquinoline derivatives for pharmaceutical studies.

EXPERIMENTAL

All reactions were performed under an inert atmosphere of argon in oven dried Duran glassware. Toluene was distilled from molten sodium under argon or purchased (toluene extra dry with molecular sieves) from Acros Organics. CH_2Cl_2 and triethylamine were distilled from calcium hydride. All other reagents were purchased from commercial sources and were used without further purification. Unless otherwise noted, yields refer to isolated yields of pure compounds as gauged by thin layer chromatography (TLC), ^{1}H and ^{13}C NMR. All products were characterized by ^{1}H NMR, ^{13}C NMR, infrared (IR) spectroscopy, and mass spectrometry (MS). Additional characterization data were obtained by CHN elemental analysis and/or high-resolution mass spectrometry (HRMS). NMR spectra were recorded on the following spectrometers: Bruker Avance DPX 300, Bruker Avance DRX 500. All ^{1}H NMR spectra are reported in δ units ppm downfield from tetramethylsilane internal standard. All ^{13}C NMR spectra are reported in δ units ppm relative to the central line of the triplet for $CDCl_3$ at 77.0 ppm. Infrared spectra were recorded on a Bruker Vector 22 or a Bruker Tensor 27 spectrometer using an attenuated total reflection (ATR) method. Mass spectra were recorded on a JEOL JMS-700, a Finnigan TSQ 700 or a Finnigan MAT 95 spectrometer (EI) with an ionization potential of 70 eV or a Waters Micromass Q-Tof Premier spectrometer (ESI, 8 eV). Elemental analyses were carried out on an Elementar Vario EL or a Fisons Instruments 1108 machine. Melting points are uncorrected. PE: light petroleum ether, b.p. 40-60 °C. MTBE: methyl *tert*-butyl ether.

Preparation of a solution of monomeric formaldehyde in THF: A mixture of dry paraformaldehyde

(3.00 g, dried for two days in a dry oven under vacuum at 80 °C), THF (100 mL) and a few drops of $BF_3{\cdot}Et_2O$ was refluxed at 70 °C for 2 h. Then, the mixture was slowly distilled and collected in a two-necked flask cooled to –70 °C. The concentration of the solution is approximately 0.8 mol/L.

1-Bromo-2-iodo-4-trifluoromethylbenzene (2): Concentrated H_2SO_4 (75.0 mL) was added dropwise to a solution of $NaIO_4$ (12.83 g, 60.0 mmol) and I_2 (15.23 g, 60.0 mmol) in a 2:1 mixture of AcOH and Ac_2O (75 mL) at 5-10 °C. Then, 4-bromotrifluorotoluene **1** (11.25 g, 50.0 mmol) was added dropwise at the same temperature. After this had been stirred at 25 °C for 21 h, the mixture was poured into ice-water containing Na_2SO_3. After extraction with CH_2Cl_2 (3 × 50 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (SiO_2, PE) gave aryl halide **2** (16.92 g, 48.2 mmol, 96%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (br d, J = 8.2 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 1 H), 8.09 (br s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 101.4 (C), 122.6 (CF_3, q, J = 273 Hz), 126.1 (CH, q, J = 4 Hz), 130.6 (C, q, J = 34 Hz), 133.0 (CH), 134.1 (C), 137.0 (CH, q, J = 4 Hz) ppm. IR (neat): $\tilde{\upsilon}$ = 1591, 1459, 1377, 1317, 1257, 1173, 1132, 1102, 1074, 1012, 893, 825, 800, 705 cm^{-1}. MS (EI): *m/z* (%) = 352 (100) [M^+ (^{81}Br)], 350 (99) [M^+ (^{79}Br)], 333 (6), 331 (5), 225 (19), 223 (19), 144 (29). *Anal.* Calcd for $C_7H_3BrF_3I$: C, 23.96; H, 0.86. Found: C, 23.81; H, 0.90.

(2-Bromo-5-trifluoromethylphenyl)methanol (3): At –20 °C, a solution of *i*-PrMgCl·LiCl in THF (12.5 mL, c = 2.0 mol/L, 25.0 mmol) was slowly added to a solution of **2** (8.75 g, 25.0 mmol) in THF (12.5 mL). After the mixture had been stirred at –20 °C for 2 h, a solution of monomeric formaldehyde in THF (35.0 mL, $c \approx$ 0.8 mol/L, 28.0 mmol) was added. Then, the mixture was stirred for additional 1 h and water (50 mL) was subsequently added. After extraction with Et_2O (5 × 30 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (SiO_2, PE/EtOAc, 9:1) gave alcohol **3** (3.95 g, 15.5 mmol, 62%) as a colorless solid, mp 66-67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (br s, 1 H), 4.78 (s, 2 H), 7.40 (dd, J = 1.9, 8.3 Hz, 1 H), 7.65 (d, J = 8.3 Hz, 1 H), 7.79 (d, J = 1.3 Hz, 1 H). ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 64.3 (CH_2), 123.8 (CF_3, q, J = 272 Hz), 125.1 (CH, q, J = 4 Hz), 125.5 (CH, q, J = 4 Hz), 125.7 (C), 130.1 (C, q, J = 33 Hz), 132.9 (CH), 140.8 (C) ppm. IR (KBr): $\tilde{\upsilon}$ = 3300, 2913, 1605, 1583, 1474, 1413, 1372, 1330, 1257, 1184, 1120, 1083, 1057, 1023, 897, 834, 829, 745, 716 cm^{-1}. MS (EI): *m/z* (%) = 256 (36) [M^+ (^{81}Br)], 254 (34) [M^+ (^{79}Br)], 237 (15), 235 (13), 175 (100), 145 (41), 127 (52), 113 (7). HRMS: calcd. ($C_8H_6O^{79}BrF_3$) 253.9554; found 253.9559. *Anal.* Calcd for $C_8H_6OBrF_3$: C, 37.68; H, 2.37. Found: C, 37.49; H, 2.41.

1-Bromo-2-bromomethyl-4-trifluoromethylbenzene (4): PBr_3 (677 mg, 2.50 mmol) was added dropwise to a solution of alcohol **3** (1.27 g, 5.00 mmol) in CH_2Cl_2 (25 mL). After the solution had been stirred at 25 °C for 24 h, saturated aqueous Na_2CO_3 solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE), dibromide **4** (1.25 g, 3.93 mmol, 79%) was isolated as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.61 (s, 2 H), 7.42 (dd, J = 1.0, 8.4 Hz, 1 H), 7.70-7.74 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 32.0 (CH_2), 123.4 (CF_3, q, J = 272 Hz), 126.6 (CH, q, J = 4 Hz), 127.9 (CH, q, J = 4 Hz), 128.3 (C), 130.5 (C, q, J = 33 Hz), 134.0 (CH), 138.1 (C) ppm. IR (neat): $\tilde{\upsilon}$ = 2934, 1780, 1605, 1580, 1479, 1440, 1409, 1333, 1276, 1220, 1198, 1173, 1131, 1081, 1032, 949, 908, 829, 748, 728 cm^{-1}. MS (EI): *m/z* (%) = 320 (8) [M^+ (^{81}Br/^{81}Br)], 318 (16) [M^+ (^{81}Br/^{79}Br)], 316 (10) [M^+ (^{79}Br/^{79}Br)], 285 (17), 239 (100), 237 (100), 158 (42), 151 (12), 113 (8). HRMS: calcd. ($C_8H_5{}^{79}Br_2F_3$) 315.8710; found 315.8703. *Anal.* Calcd for $C_8H_5Br_2F_3$: C, 30.22; H, 1.59. Found: C, 30.68; H, 1.76.

(2-Bromo-5-trifluoromethylphenyl)acetonitrile (5): A solution of NaCN (490 mg, 10.0 mmol) in DMSO (2.5 mL) was heated to 90 °C. The oil bath was removed and dibromide **4** (1.59 g, 5.00 mmol) was slowly added. After the mixture had been allowed to reach 50 °C, water (25 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 40 mL) and the combined organic layers were dried with $MgSO_4$. After concentration under vacuum and purification by flash chromatography (SiO_2, PE/EtOAc, 95:5), nitrile **5** (810 mg, 3.07 mmol, 61%) was isolated as a colorless solid, mp 61-62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 2 H), 7.50 (dd, J = 1.5, 8.3 Hz, 1 H), 7.76 (d, J = 8.7 Hz, 1 H), 7.78 (s, 1 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 25.0 (CH_2), 116.0 (C), 123.3 (CF_3, q, J = 273 Hz), 126.5 (CH, q, J = 4 Hz), 126.7 (CH, q, J = 4 Hz), 127.6 (C), 130.8 (C, q, J = 33 Hz), 131.2 (C), 133.8 (CH) ppm. IR (KBr): $\tilde{\upsilon}$ = 3080, 2914, 2252, 1607, 1476, 1425, 1403, 1331, 1322, 1286, 1263, 1187, 1167, 1129, 1085, 1032, 937, 877, 839, 747, 715 cm^{-1}. MS (EI): *m/z* (%) = 265 (75) [M^+ (^{81}Br)], 263 (78) [M^+ (^{79}Br)], 246 (9), 244 (11), 184 (100), 183 (21), 157 (13), 134 (11), 114 (6). HRMS: calcd. ($C_9H_5N^{79}BrF_3$) 262.9557; found 262.9533. *Anal.* Calcd for $C_9H_5NBrF_3$: C, 40.94; H, 1.91; N, 5.30. Found: C, 40.71; H, 1.96; N, 5.20.

(2-Bromo-5-fluorophenyl)methanol (8): 2-Bromo-5-fluorobenzoic acid **6** (7.00 g, 32.0 mmol) was added in portions to a stirred suspension of $NaBH_4$ (1.09 g, 28.8 mmol) in dry diglyme (40 mL). Then, a solution of freshly distilled $BF_3{\cdot}Et_2O$ (4.80 mL, 38.4 mmol) in diglyme (10 mL) was added over a period of 1 h. After this had been stirred at rt for 4 h (TLC control) the reaction mixture was poured on ice. The precipitate was suction filtered and dried under vacuum to give alcohol **8** (4.80 g, 23.3 mmol, 73%) as a colorless solid, mp 92 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.02 (t, J = 5.5 Hz, 1 H), 4.65 (d, J = 4.8 Hz,

2 H), 6.81 (dt, *J* = 3.1, 8.4 Hz, 1 H), 7.19 (dd, *J* = 3.3, 8.8 Hz, 1 H), 7.41 (dd, *J* = 5.3, 8.8 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 64.5 (CH_2), 115.6 (CH, d, *J* = 24 Hz), 115.7 (C), 115.8 (CH, d, *J* = 23 Hz), 133.6 (CH, d, *J* = 8 Hz), 142.0 (C, d, *J* = 7 Hz), 162.3 (CF, d, *J* = 247 Hz) ppm. IR (neat): $\tilde{\upsilon}$ = 3272, 3180, 2357, 2338, 1580, 1464, 1439, 1410, 1361, 1266, 1219, 1149, 1106, 1065, 1025, 984, 950, 874, 809 cm^{-1}. MS (EI): *m/z* (%) = 206 (44) [M^+ (^{81}Br)], 204 (47) [M^+ (^{79}Br)], 175 (15), 125 (100), 123 (18), 97 (89), 96 (64), 95 (55), 94 (26), 77 (74), 75 (56). HRMS: calcd. (C_7H_6BrFO) 203.9586; found 203.9586. *Anal.* Calcd for C_7H_6BrFO: C, 41.01; H, 2.95; Br, 38.97. Found: C, 41.15; H, 3.10; Br, 38.99.

(2-Bromo-4,5-difluorophenyl)methanol (9): 2-Bromo-4,5-difluorobenzoic acid **7** (2.00 g, 8.4 mmol) was added in portions to a stirred suspension of $NaBH_4$ (287 mg, 7.6 mmol) in dry diglyme (6.0 ml). Then, a solution of freshly distilled $BF_3{\cdot}Et_2O$ (1.30 mL, 10.1 mmol) in dry diglyme (3.8 mL) was added over a period of 0.5 h. After this had been stirred at room temperature for 4 h the mixture was poured on ice. The precipitate was suction filtered and dried under vacuum to give alcohol **9** (1.50 g, 6.5 mmol, 77%) as a colorless solid, mp 70-71 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (t, *J* = 5.8 Hz, 1 H), 4.68 (d, *J* = 5.3 Hz, 2 H), 7.34-7.42 (m, 2 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 63.9 (CH_2), 114.9 (C, dd, *J* = 4, 8 Hz), 117.0 (CH, d, *J* = 19 Hz), 121.3 (CH, d, *J* = 20 Hz), 136.8 (C, dd, *J* = 4, 5 Hz), 149.3 (CF, dd, *J* = 13, 251 Hz), 149.8 (CF, dd, *J* = 12, 249 Hz) ppm. IR (neat): $\tilde{\upsilon}$ = 3303, 3061, 2917, 1614, 1600, 1494, 1474, 1443, 1399, 1362, 1293, 1219, 1185, 1138, 1066, 981, 881, 809 cm^{-1}. MS (EI): *m/z* (%) = 224 (72) [M^+ (^{81}Br)], 222 (72) [M^+ (^{79}Br)], 207 (11), 203 (10), 193 (12), 162 (10), 143 (100), 141 (22), 126 (14), 125 (14), 115 (69), 114 (72), 113 (37), 112 (20), 95 (27), 63 (18). HRMS: calcd. ($C_7H_5O^{79}BrF_2$) 221.9492; found 221.9491. *Anal.* Calcd for $C_7H_5OBrF_2$: C, 37.70; H, 2.26. Found: C, 37.75; H, 2.39.

1-Bromo-2-bromomethyl-4-fluorobenzene (10): PBr_3 (1.90 g, 7.05 mmol) was added dropwise to a solution of alcohol **8** (2.89 g, 14.1 mmol) in CH_2Cl_2 (55 mL). After the mixture had been stirred at 25 °C for 24 h, saturated aqueous Na_2CO_3 solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE), dibromide **10** (3.29 g, 12.2 mmol, 87%) was isolated as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.53 (s, 1 H), 6.90 (dt, *J* = 3.0, 8.3 Hz, 1 H), 7.18 (dd, *J* = 3.0, 9.0 Hz, 1 H), 7.51 (dd, *J* = 5.3, 8.8 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 32.4 (CH_2), 117.3 (CH, d, *J* = 22 Hz), 118.1 (CH, d, *J* = 24 Hz), 118.4 (C, d, *J* = 3 Hz), 134.5 (CH, d, *J* = 8 Hz), 138.8 (C, d, *J* = 8 Hz), 161.8 (CF, d, *J* = 248 Hz) ppm. IR (neat): $\tilde{\upsilon}$ = 3072, 2976, 1603, 1580, 1473, 1439, 1408, 1271, 1237, 1214, 1157, 1126, 1100, 1032, 960, 871, 813, 739, 713 cm^{-1}. MS (EI): *m/z* (%) = 270 (6) [M^+ (^{81}Br/^{81}Br)], 268 (14) [M^+ (^{81}Br/^{79}Br)], 266 (7) [M^+ (^{79}Br/^{79}Br)], 189 (83), 188 (13), 187 (100), 108 (25), 107 (24), 81 (13). HRMS: calcd. ($C_7H_5{}^{79}Br_2F$) 265.8742; found 265.8742.

1-Bromo-2-bromomethyl-4,5-difluorobenzene (11): PBr_3 (1.49 g, 5.50 mmol) was added dropwise to a solution of alcohol **9** (2.45 g, 11.0 mmol) in CH_2Cl_2 (55 mL). After the mixture had been stirred at 25 °C for 24 h, saturated aqueous Na_2CO_3 solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE), dibromide **11** was isolated as a colorless oil (2.96 g, 10.3 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (s, 2 H), 7.32 (dd, *J* = 7.9, 10.4 Hz, 1 H), 7.42 (dd, *J* = 7.4, 9.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 31.7 (CH_2), 117.9 (C, dd, *J* = 4, 8 Hz), 119.5 (CH, d, *J* = 18 Hz), 122.2 (CH, d, *J* = 20 Hz), 133.9 (C, dd, *J* = 4, 5 Hz), 149.6 (CF, dd, *J* = 13, 250 Hz), 150.0 (CF, dd, *J* = 14, 255 Hz) ppm. IR (neat): $\tilde{\upsilon}$ = 3051, 2977, 2590, 1736, 1602, 1499, 1441, 1395, 1306, 1289, 1218, 1193, 1152, 1115, 994, 883, 815, 737, 703 cm^{-1}. MS (EI): *m/z* (%) = 288 (7) [M^+ (^{81}Br/^{81}Br)], 286 (11) [M^+ (^{81}Br/^{79}Br)], 284 (6) [M^+ (^{79}Br/^{79}Br)], 207 (97), 205 (100), 126 (33), 125 (19), 113 (8). HRMS: calcd. ($C_7H_4{}^{79}Br_2F_2$) 283.8648; found 283.8633. *Anal.* Calcd for $C_7H_4Br_2F_2$: C, 29.41; H, 1.41. Found: C, 29.31; H, 1.46.

(2-Bromo-5-fluorophenyl)acetonitrile (12): A solution of NaCN (1.76 g, 36.0 mmol) in DMSO (10 mL) was heated to 90 °C. The oil bath was removed and dibromide **10** (4.82 g, 18.0 mmol) was slowly added. After the mixture had been allowed to reach 50 °C, water (100 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 200 mL) and the combined organic layers were dried with $MgSO_4$. After concentration under vacuum and purification by flash chromatography (SiO_2, PE/EtOAc, 9:1), nitrile **12** (2.30 g, 10.75 mmol, 60%) was isolated as a colorless solid, mp 57-58 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.83 (s, 2 H), 6.97 (dt, *J* = 2.9, 8.4 Hz, 1 H), 7.30 (dd, *J* = 3.0, 8.7 Hz, 1 H), 7.57 (dd, *J* = 5.4, 8.7 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 24.9 (CH_2), 116.3 (C), 117.0 (CH, d, *J* = 24 Hz), 117.1 (CH, d, *J* = 22 Hz), 117.6 (C, d, *J* = 3 Hz), 131.9 (C, d, *J* = 7 Hz), 134.3 (CH, *J* = 8 Hz), 162.0 (CF, d, *J* = 249 Hz) ppm. IR (neat): $\tilde{\upsilon}$ = 3096, 3075, 2939, 2916, 2264, 2247, 1898, 1727, 1608, 1576, 1465, 1416, 1398, 1321, 1266, 1212, 1151, 1102, 1030, 965, 934, 926, 851, 815, 741 cm^{-1}. MS (EI): *m/z* (%) = 215 (71) [M^+ (^{81}Br)], 213 (76) [M^+ (^{79}Br)], 135 (17), 134 (100), 133 (45), 132 (22), 108 (17), 107 (69), 106 (17), 94 (5). HRMS: calcd. ($C_8H_5N^{79}BrF$) 212.9589; found 212.9590. *Anal.* Calcd for C_8H_5NBrF: C, 44.89; H, 2.35; N, 6.54; Br, 37.33. Found: C, 44.99; H, 2.48; N, 6.42; Br, 37.08.

(2-Bromo-4,5-difluorophenyl)acetonitrile (13): A solution of NaCN (980 mg, 20.0 mmol) in DMSO (5.0 mL) was heated to 90 °C. The oil bath was removed and dibromide **11** (2.86 g, 10.0 mmol) was slowly added. After the mixture had been allowed to reach 50 °C, water (25 mL) was added. The mixture was extracted with CH_2Cl_2 (5 × 40 mL) and the combined organic layers were dried with $MgSO_4$. After concentration under vacuum and purification by flash chromatography (SiO_2, PE/EtOAc, 9:1), nitrile **13**

(1.34 g, 5.78 mmol, 58%) was isolated as a colorless solid, mp 53-54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 2 H), 7.41 (dd, *J* = 7.7, 10.1 Hz, 1 H), 7.47 (dd, *J* = 7.3, 9.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 24.3 (CH_2), 116.1 (C), 117.1 (C, dd, *J* = 4, 7 Hz), 118.5 (CH, d, *J* = 20 Hz), 122.2 (CH, d, *J* = 20 Hz), 126.8 (C, dd, *J* = 4, 6 Hz), 149.8 (CF, dd, *J* = 11, 252 Hz), 149.9 (CF, dd, *J* = 12, 255 Hz) ppm. IR (KBr): $\tilde{\upsilon}$ = 3055, 2972, 2939, 2257, 1719, 1602, 1586, 1502, 1412, 1399, 1286, 1206, 1177, 1149, 993, 915, 887, 859, 805, 756 cm^{-1}. MS (EI): *m/z* (%) = 233 (96) [M^+ (^{81}Br)], 231 (97) [M^+ (^{79}Br)], 152 (100), 125 (47), 113 (7). HRMS: calcd. ($C_8H_4N^{79}BrF_2$) 230.9495; found 230.9488. *Anal.* Calcd for $C_8H_4NBrF_2$: C, 41.41; H, 1.74; N, 6.04. Found: C, 42.14; H, 1.97; N, 5.87.

[2-(3,4-Dimethoxyphenylethynyl)-5-trifluoromethylphenyl]acetonitrile (15): $Pd(PPh_3)_2Cl_2$ (85 mg, 0.12 mmol, 4 mol%), CuI (46 mg, 0.24 mmol, 8 mol%), PPh_3 (63 mg, 0.24 mmol, 8 mol%) and a 3:1 mixture of *i*-Pr_2NH/DMF (12.0 mL) were placed in a round-bottomed flask. After the addition of aryl bromide **5** (789 mg, 3.00 mmol), the mixture was stirred at 25 °C for 1 h and alkyne **14** (486 mg, 3.00 mmol) was then added. After the mixture had been stirred at 80 °C for additional 16 h, saturated aqueous NH_4Cl solution was added. The mixture was extracted with MTBE (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE/EtOAc, 9:1), alkyne **15** (994 mg, 2.88 mmol, 96%) was isolated as a colorless solid, mp 79-80 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 6 H), 4.01 (s, 2 H), 6.87 (d, *J* = 8.3 Hz, 1 H), 7.06 (d, *J* = 1.9 Hz, 1 H), 7.20 (dd, *J* = 1.9, 8.3 Hz, 1 H), 7.60 (d, *J* = 8.1 Hz, 1 H), 7.67 (d, *J* = 8.1 Hz, 1 H), 7.74 (s, 1 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 22.9 (CH_2), 56.0 (CH_3), 56.0 (CH_3), 83.6 (C), 98.7 (C), 111.1 (CH), 113.8 (C), 114.2 (CH), 116.6 (C), 123.5 (CF_3, q, *J* = 272 Hz), 125.1 (CH, q, *J* = 4 Hz), 125.4 (CH), 127.0 (C), 130.4 (C, q, *J* = 33 Hz), 132.3 (C), 132.5 (CH), 149.9 (C), 150.4 (C) ppm. IR(KBr): $\tilde{\upsilon}$ = 3079, 2972, 2942, 2915, 2842, 2249, 2208, 1600, 1578, 1518, 1499, 1463, 1442, 1426, 1320, 1273, 1251, 1229, 1165, 1137, 1105, 1075, 1020, 871, 834, 817 cm^{-1}. MS (EI): *m/z* (%) = 345 (100) [M^+], 330 (6), 302 (8), 275 (13), 259 (4), 258 (3), 190 (6), 173 (3), 151 (5). HRMS: calcd. ($C_{19}H_{14}NO_2F_3$) 345.0977; found 345.1010. *Anal.* Calcd for $C_{19}H_{14}NO_2F_3$: C, 66.09; H, 4.09; N, 4.06. Found: C, 65.91; H, 4.16; N, 4.03.

[2-(3,4-Dimethoxyphenylethynyl)-5-fluorophenyl]acetonitrile (16): $Pd(PPh_3)_2Cl_2$ (62 mg, 0.09 mmol, 4 mol%), CuI (34 mg, 0.18 mmol, 8 mol%), PPh_3 (46 mg, 0.18 mmol, 8 mol%), *i*-Pr_2NH (10 mL) and DMF (8 mL) were placed in a round-bottomed flask. After the addition of aryl bromide **12** (942 g, 4.40 mmol), the mixture was stirred at 25 °C for 1 h and alkyne **14** (714 mg, 4.40 mmol) was then added. After the mixture had been stirred at 80 °C for additional 16 h, saturated aqueous NH_4Cl solution was added. The mixture was extracted with MTBE (3 × 50 mL). The combined organic layers were dried with

$MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE/EtOAc, 5:1), alkyne **16** (1.12 g, 3.81 mmol, 87%) was isolated as a colorless solid, mp 117-118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.91 (s, 6 H), 3.96 (s, 2 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 7.02-7.07 (m, 2 H), 7.15 (dd, *J* = 1.8, 8.3 Hz, 1 H), 7.23 (dd, *J* = 2.4, 8.9 Hz, 1 H), 7.53 (dd, *J* = 5.6, 8.5 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 22.8 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 83.6 (C), 95.6 (C), 111.1 (CH), 114.1 (CH), 114.4 (C), 115.4 (CH, d, *J* = 22 Hz), 115.7 (CH, d, *J* = 24 Hz), 116.8 (C), 119.1 (C, d, *J* = 4 Hz), 125.0 (CH), 133.9 (C, d, *J* = 8 Hz), 134.0 (CH, d, *J* = 9 Hz), 148.8 (C), 150.0 (C), 162.3 (CF, d, *J* = 251 Hz). IR (neat): $\tilde{\upsilon}$ = 3106, 3014, 2997, 2940, 2915, 2839, 2247, 2211, 1608, 1579, 1516, 1492, 1468, 1457, 1439, 1426, 1411, 1335, 1279, 1251, 1232, 1203, 1151, 1130, 1081, 1023, 969, 939, 929, 883, 849, 819, 798, 764, 731 cm^{-1}. MS (EI): *m/z* (%) = 295 (100) [M^+], 280 (16), 252 (27), 225 (18), 222 (7), 209 (13), 208 (20), 182 (12), 158 (5). HRMS: calcd. ($C_{18}H_{14}NO_2F$) 295.1009; found 295.1008. *Anal.* Calcd for $C_{18}H_{14}NO_2F$: C, 73.21; H, 4.78; N, 4.74. Found: C, 73.11; H, 4.82; N, 4.74.

[2-(3,4-Dimethoxyphenylethynyl)-4,5-difluorophenyl]acetonitrile (17): $Pd(PPh_3)_2Cl_2$ (155 mg, 0.22 mmol, 4 mol%), CuI (84 mg, 0.44 mmol, 8 mol%), PPh_3 (115 mg, 0.44 mmol, 8 mol%), *i*-Pr_2NH (5.5 mL) and DMF (5.5 mL) were placed in a round-bottomed flask. After the addition of aryl bromide **13** (1.28 g, 5.52 mmol), the mixture was stirred at 25 °C for 1 h and alkyne **14** (900 mg, 5.55 mmol) was then added. After the mixture had been stirred at 80 °C for additional 16 h, saturated aqueous NH_4Cl solution was added. The mixture was extracted with MTBE (3 × 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE/EtOAc, 5:1), alkyne **17** (1.36 g, 4.34 mmol, 79%) was isolated as a colorless solid, mp 113-114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 8 H), 6.86 (d, *J* = 8.5 Hz, 1 H), 7.03 (d, *J* = 1.9 Hz, 1 H), 7.15 (dd, *J* = 1.8, 8.2 Hz, 1 H), 7.33 (dd, *J* = 7.7, 10.5 Hz, 1 H), 7.37 (dd, *J* = 7.7, 10.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 22.3 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 82.7 (C), 96.6 (C), 111.1 (CH), 113.9 (C), 114.1 (CH), 116.7 (C), 117.6 (CH, d, *J* = 20 Hz), 119.9 (C, dd, *J* = 4, 8 Hz), 120.9 (CH, d, *J* = 19 Hz), 125.2 (CH), 128.6 (C, dd, *J* = 4, 6 Hz), 149.7 (CF, dd, *J* = 13, 251 Hz), 148.9 (C), 150.3 (C), 150.1 (CF, dd, *J* = 13, 254 Hz) ppm. IR (KBr): $\tilde{\upsilon}$ = 3000, 2966, 2939, 2839, 2257, 2214, 1600, 1578, 1517, 1466, 1445, 1424, 1413, 1346, 1320, 1251, 1224, 1173, 1137, 1023, 882, 869, 815, 754 cm^{-1}. MS (EI): *m/z* (%) = 313 (100) [M^+], 298 (10), 270 (10), 243 (12), 226 (12), 212 (5), 200 (5), 162 (11), 151 (10), 113 (6), 91 (6). HRMS: calcd. ($C_{18}H_{13}NO_2F_2$) 313.0914; found 313.0930. *Anal.* Calcd for $C_{18}H_{13}NO_2F_2$: C, 69.01; H, 4.18; N, 4.47. Found: C, 68.79; H, 4.24; N, 4.41.

2-[2-(3,4-Dimethoxyphenylethynyl)-5-trifluoromethylphenyl]ethylamine (18): A solution of $AlCl_3$ (339 mg, 3.00 mmol) in Et_2O (4.5 mL) was rapidly added to a suspension of $LiAlH_4$ (114 mg, 3.00 mmol)

in Et_2O (3.0 mL) and the mixture was stirred at 25 °C for 30 min. Then, a solution of nitrile **15** (1.04 g, 3.00 mmol) in Et_2O (6.0 mL) was slowly added. After the mixture had been stirred at 25 °C for additional 2 h, water was added dropwise to decompose the excess of $LiAlH_4$ and aqueous KOH (5.0 mL, *c* = 5 mol/L) was then added. The colloidal mixture was extracted with Et_2O (10 × 30 mL) and the combined organic layers were dried with $MgSO_4$. After concentration under vacuum and purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 9:1:0.01), aminoalkyne **18** (980 mg, 2.81 mmol, 93%) was isolated as a yellow solid, mp 81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (br s, 2 H), 3.07-3.11 (m, 4 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 6.84 (d, *J* = 8.3 Hz, 1 H), 7.02 (d, *J* = 1.7 Hz, 1 H), 7.15 (dd , *J* = 1.9, 8.3 Hz, 1H), 7.40-7.50 (m, 2 H), 7.60 (d, *J* = 7.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 38.3 (CH_2), 42.2 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 85.3 (C), 95.6 (C), 111.1 (CH), 114.2 (CH), 114.7 (C), 123.1 (CH, q, *J* = 4 Hz), 123.9 (CF_3, q, *J* = 272 Hz), 125.1 (CH), 126.0 (CH, q, *J* = 4 Hz), 127.1 (C), 129.7 (C, q, *J* = 33 Hz), 132.5 (CH), 141.8 (C), 148.8 (C), 150.0 (C) ppm. IR (KBr): $\tilde{\upsilon}$ = 3386, 2999, 2946, 2838, 2206, 1615, 1598, 1577, 1518, 1471, 1456, 1441, 1412, 1327, 1256, 1229, 1173, 1125, 1020, 860, 844, 833, 815, 807 cm^{-1}. MS (EI): *m/z* (%) = 349 (100) [M^+], 334 (16), 330 (21), 318 (26), 273 (8), 233 (16), 212 (27), 198 (22), 166 (20), 162 (16), 151 (54), 113 (12), 86 (17). HRMS: calcd. ($C_{19}H_{18}NO_2F_3$) 349.1290; found 349.1270. *Anal.* Calcd for $C_{19}H_{18}NO_2F_3$: C, 65.32; H, 5.19; N, 4.01. Found: C, 65.31; H, 5.46; N, 4.28.

2-[2-(3,4-Dimethoxyphenylethynyl)-5-fluorophenyl]ethylamine (19): A solution of $AlCl_3$ (467 mg, 3.50 mmol) in Et_2O (4.5 mL) was rapidly added to a suspension of $LiAlH_4$ (133 mg, 3.50 mmol) in Et_2O (3.5 mL) and the mixture was stirred at 25 °C for 30 min. Then, a solution of nitrile **16** (1.03 g, 3.50 mmol) in Et_2O (7.0 mL) was slowly added. After the mixture had been stirred at 25 °C for 2 h, water was added dropwise to decompose the excess of $LiAlH_4$ and aqueous KOH (5.0 mL, *c* = 5 mol/L) was subsequently added. The colloidal mixture was extracted with Et_2O (10 × 30 mL) and the combined organic layers were dried with $MgSO_4$. After concentration under vacuum and purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 9:1:0.01), aminoalkyne **19** (1.94 g, 3.15 mmol, 90%) was isolated as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (br s, 2H), 2.99 (t, *J* = 6.7 Hz, 2 H), 3.07 (t, *J* = 6.4 Hz, 2 H), 3.91 (s, 6 H), 6.84 (d, *J* = 8.2 Hz, 1 H), 6.91 (dt, *J* = 8.4, 2.5 Hz, 1 H), 6.96 (dd, *J* = 9.5, 2.4 Hz, 1 H), 7.01 (d, *J* = 1.5 Hz, 1 H), 7.11 (dd, *J* = 8.1, 1.6 Hz, 1 H), 7.49 (dd, *J* = 8.4, 5.9 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 39.0 (CH_2), 42.5 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 85.6 (C), 92.7 (C), 111.1 (CH), 113.4 (CH, d, *J* = 22 Hz), 114.1 (CH), 115.4 (C), 116.2 (CH, d, *J* = 22 Hz), 119.3 (C, d, *J* = 3 Hz), 124.8 (CH), 133.9 (CH, d, *J* = 9 Hz), 144.3 (C, d, *J* = 7 Hz), 148.7 (C), 149.6 (C), 162.2 (CF, d, *J* = 250 Hz) ppm. IR (neat): $\tilde{\upsilon}$ = 3056, 3933, 2838, 2773, 2364, 1602, 1580, 1516, 1444, 1367, 1328, 1253, 1235, 1131, 1069, 1027, 817, 763, 735, 701 cm^{-1}. MS (EI): *m/z* (%) = 299 (96) [M^+], 298 (47), 283 (11),

270 (22), 269 (10), 268 (24), 255 (12), 223 (13), 207 (11), 196 (16), 183 (37), 166 (31), 162 (34), 161 (11), 151 (100), 148 (35), 138 (16). HRMS: calcd. ($C_{18}H_{18}NO_2F$) 299.1322; found 299.1322.

2-[2-(3,4-Dimethoxyphenylethynyl)-4,5-difluorophenyl]ethylamine (20): A solution of $AlCl_3$ (467 mg, 3.50 mmol) in Et_2O (4.5 mL) was rapidly added to a suspension of $LiAlH_4$ (133 mg, 3.50 mmol) in Et_2O (3.5 mL) and the mixture was stirred at 25 °C for 30 min. Then, a solution of nitrile **17** (1.10 g, 3.50 mmol) in Et_2O (7.0 mL) was slowly added. After the mixture had been stirred at 25 °C for 2 h, water was added dropwise to decompose the excess of $LiAlH_4$ and aqueous KOH (5 mL, *c* = 5 mol/L) was subsequently added. The colloidal mixture was extracted with Et_2O (10 × 30 mL) and the combined organic layers were dried with $MgSO_4$. After concentration under vacuum and purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 9:1:0.01), aminoalkyne **20** (1.01 g, 3.18 mmol, 91%) was isolated as a yellow solid, mp 60-61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (br s, 2 H), 2.95 (t, *J* = 6.4 Hz, 2 H), 3.05 (t, *J* = 6.1 Hz, 2 H), 3.91 (s, 6 H), 6.84 (d, *J* = 8,3 Hz, 1 H), 7.00 (d, *J* = 1.7 Hz, 1 H), 7.05 (dd, *J* = 8.0, 11.0 Hz, 1 H), 7.12 (dd, *J* = 1.9, 8.3 Hz, 1 H), 7.31 (dd, *J* = 7.9, 10.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 38.3 (CH_2), 42.5 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 84.6 (C), 93.5 (C), 111.1 (CH), 114.1 (CH), 114.9 (C), 118.0 (CH, d, *J* = 18 Hz), 119.7 (C, dd, *J* = 4, 7 Hz), 120.6 (CH, d, *J* = 19 Hz), 124.9 (CH), 139.0 (C, dd, *J* = 4, 5 Hz), 148.4 (CF, dd, *J* = 13, 247 Hz), 148.8 (C), 149.9 (C), 149.9 (CF, dd, *J* = 13, 251 Hz) ppm. IR (KBr): $\tilde{\upsilon}$ = 3441, 3040, 3012, 2935, 2834, 2794, 1609, 1591, 1517, 1461, 1417, 1329, 1303, 1259, 1241, 1208, 1155, 1137, 1102, 1029, 861, 807, 766 cm^{-1}. MS (EI): *m/z* (%) = 317 (100) [M^+], 302 (12), 288 (27), 286 (21), 243 (10), 241 (11), 225 (12), 214 (16), 201 (36), 180 (21), 175 (12), 166 (21), 151 (75), 138 (8), 113 (6). HRMS: calcd. ($C_{18}H_{17}NO_2F_2$) 317.1227; found 317.1234. *Anal.* Calcd for $C_{18}H_{17}NO_2F_2$: C, 68.13; H, 5.40; N, 4.41. Found: C, 67.89; H, 5.47; N, 4.36.

1-(3,4-Dimethoxybenzyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (*rac*-21): In a Schlenk tube, a mixture of aminoalkyne **18** (175 mg, 0.50 mmol) and Ind_2TiMe_2 (9 mg, 0.025 mmol, 5 mol%) in toluene (0.25 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to rt and a mixture of $NaBH_3CN$ (63 mg, 1.00 mmol) and $ZnCl_2$ (68 mg, 0.50 mmol) in MeOH (5.0 mL) was added. After this had been stirred at 25 °C for 24 h, saturated aqueous NH_4Cl solution (25 mL) was added and the mixture was extracted with MTBE (5 × 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 20:1:0.01), 1,2,3,4-tetrahydroisoquinoline *rac*-**21** (169 mg, 0.48 mmol, 96%) was isolated as a yellow solid, mp 92-94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (br s, 1 H), 2.80-2.96 (m, 4 H), 3.19-3.26 (m, 2 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 4.21 (dd, *J* = 3.2, 9.5 Hz, 1 H), 6.71 (d, *J* = 1.7 Hz, 1 H), 6.79 (dd, *J* = 1.7, 8.1 Hz, 1 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 7.33-7.43 (m, 3 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ =

29.9 (CH_2), 40.5 (CH_2), 41.8 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 57.1 (CH), 111.2 (CH), 112.1 (CH), 121.3 (CH), 122.2 (CH, q, J = 4 Hz), 124.2 (CF_3, q, J = 272 Hz), 126.1 (CH, q, J = 4 Hz), 126.6 (CH), 128.3 (C, q, J = 32 Hz), 130.7 (C), 136.2 (C), 142.5 (C), 147.7 (C), 148.9 (C) ppm. IR: $\tilde{\upsilon}$ = 3443, 2936, 2835, 1621, 1590, 1516, 1466, 1425, 1338, 1323, 1266, 1237, 1160, 1126, 1077, 1030, 828, 813, 764 cm^{-1}. MS (EI): *m/z* (%) = 351 (1) [M^+], 350 (3), 349 (4), 334 (4), 332 (11), 214 (6), 201 (94), 200 (100), 198 (23), 185 (22), 173 (7), 151 (35), 131 (11), 113 (7), 107 (7). HRMS: calcd. ($C_{19}H_{20}NO_2F_3$) 351.1446; found 351.1401. *Anal.* Calcd for $C_{19}H_{20}NO_2F_3$: C, 64.95; H, 5.74; N, 3.99. Found: C, 64.68; H, 5.80; N, 4.01.

1-(3,4-Dimethoxybenzyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline (*rac*-22): In a Schlenk tube, a mixture of aminoalkyne **19** (209 mg, 0.70 mmol) and Ind_2TiMe_2 (11 mg, 0.04 mmol, 5 mol%) in toluene (0.10 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to rt and a mixture of $NaBH_3CN$ (88 mg, 1.40 mmol) and $ZnCl_2$ (95 mg, 0.70 mmol) in MeOH (5 mL) was added. After this had been stirred at 25 °C for 24 h, saturated aqueous NH_4Cl solution (25 mL) was added and the mixture was extracted with MTBE (5 × 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 20:1:0.01), 1,2,3,4-tetrahydroisoquinoline *rac*-**22** (198 mg, 0.66 mmol, 94%) was isolated as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88-1.96 (br s, 1 H), 2.70-2.92 (m, 4 H), 3.16-3.22 (m, 2 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.14 (dd, J = 9.6, 3.6 Hz, 1 H), 6.74 (d, J = 1.6 Hz, 1 H), 6.84 (m, 4 H), 7.18 (dd, J = 8.5, 5.8 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 30.5 (CH_2), 41.0 (CH_2), 42.5 (CH_2), 56.3 (CH_3), 56.3 (CH_3), 111.8 (CH), 112.8 (CH), 113.1 (CH, d, J = 21 Hz), 115.8 (CH, d, J = 20 Hz), 121.8 (CH), 128.1 (CH, d, J = 8 Hz), 131.6 (C), 134.7 (C, d, J = 3 Hz), 138.0 (C, d, J = 7. Hz), 148.2 (C), 149.4 (C), 161.5 (CF, d, J = 244 Hz) ppm. IR (neat): $\tilde{\upsilon}$ = 3000, 2933, 2834, 2360, 2341, 1612, 1589, 1514, 1497, 1463, 1450, 1418, 1330, 1261, 1239, 1027, 935, 914, 857, 810, 763 cm^{-1}. MS (ESI, CH_2Cl_2): *m/z* (%) = 302 (30) [M^+ + H], 151 (5), 150 (100), 147 (5). HRMS (ESI, CH_2Cl_2): calcd. ($C_{18}H_{20}NO_2F$ + H) 302.1556; found 302.1555.

1-(3,4-Dimethoxybenzyl)-6,7-difluoro-1,2,3,4-tetrahydroisoquinoline (*rac*-23): In a Schlenk tube, a mixture of aminoalkyne **20** (159 mg, 0.50 mmol) and Ind_2TiMe_2 (9 mg, 0.025 mmol, 5 mol%) in toluene (0.25 mL) was stirred at 105 °C for 16 h. The resulting dark brown solution was cooled to rt and a mixture of $NaBH_3CN$ (63 mg, 1.00 mmol) and $ZnCl_2$ (68 mg, 0.50 mmol) in MeOH (5 mL) was added. After this had been stirred at 25 °C for 24 h, saturated aqueous NH_4Cl solution (25 mL) was added and the mixture was extracted with MTBE (5 × 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 20:1:0.01), 1,2,3,4-tetrahydroisoquinoline *rac*-**23** (154 mg, 0.48 mmol, 96%) was isolated as a yellow

solid, mp 60-61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (br s, 1 H), 2.63-2.93 (m, 4 H), 3.10-3.24 (m, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.08 (dd, *J* = 3.3, 9.5 Hz, 1 H), 6.74 (d, *J* = 1.7 Hz, 1 H), 6.78 (dd, *J* = 1.7, 8.1 Hz, 1 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 6.89 (dd, *J* = 8.5, 10.6 Hz, 1 H), 7.03 (dd, *J* = 8.3, 11.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 29.3 (CH_2), 40.7 (CH_2), 41.9 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 56.7 (CH), 111.4 (CH), 112.3 (CH), 114.6 (CH, dd, *J* = 2, 16 Hz), 117.3 (CH, dd, *J* = 3, 14 Hz), 121.3 (CH), 130.7 (C), 131.9 (C, dd, *J* = 4, 5 Hz), 135.0 (C, t, *J* = 4 Hz), 147.8 (C), 148.3 (CF, dd, *J* = 12, 248 Hz), 148.5 (CF, dd, *J* = 12, 248 Hz), 149.0 (C) ppm. IR (KBr): $\tilde{\upsilon}$ = 3007, 2944, 2840, 2211, 1598, 1578, 1517, 1465, 1442, 1407, 1342, 1283, 1266, 1247, 1221, 1189, 1174, 1134, 1023, 882, 863, 808, 765 cm^{-1}. MS (EI): *m/z* (%) = 319 (2) [M$^+$], 318 (2), 317 (3), 316 (3), 302 (4), 267 (5), 236 (4), 212 (4), 182 (18), 169 (41), 168 (100), 166 (15), 153 (16), 151 (17), 141 (7), 113 (6). HRMS: calcd. ($C_{18}H_{19}NO_2F_2$) 319.1384; found 319.1399. *Anal.* Calcd for $C_{18}H_{19}NO_2F_2$: C, 67.70; H, 6.00; N, 4.39. Found: C, 67.48; H, 6.10; N, 4.48.

1-(3,4-Dimethoxybenzyl)-2-methyl-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline (*rac*-24): Aqueous CH_2O (0.5 mL, *c* = 37%, 6.7 mmol) was added to a solution of *rac*-**21** (88 mg, 0.25 mmol) in MeOH (1.5 mL). After this mixture had been stirred at rt for 3 h, $NaBH_4$ (95 mg, 2.50 mmol) was slowly added. Subsequently, the reaction mixture was stirred at 25 °C for additional 16 h. Then, saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 95:5:1), *rac*-**24** (62 mg, 0.17 mmol, 68%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 2.62-2.95 (m, 4 H), 3.07-3.23 (m, 2 H), 3.72 (s, 3 H), 3.82 (t, *J* = 6.0 Hz, 1 H), 3.85 (s, 3 H), 6.45 (d, *J* = 1.8 Hz, 1 H), 6.63 (dd, *J* = 2.0, 8.7 Hz, 1 H), 6.76 (d, *J* = 8.3 Hz, 1 H), 6.82 (d, *J* = 8.1 Hz, 1 H), 7.26 (d, *J* = 7.9 Hz, 1 H), 7.32 (br s, 1 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 26.3 (CH_2), 40.4 (CH_2), 42.8 (CH_3), 47.0 (CH_2), 55.6 (CH_3), 55.8 (CH_3), 65.0 (CH), 110.9 (CH), 112.8 (CH), 121.7 (CH), 121.8 (CH, q, *J* = 4 Hz), 124.2 (CF_3, q, *J* = 272 Hz), 125.5 (CH, q, *J* = 4 Hz), 128.2 (C, q, *J* = 32 Hz), 128.5 (CH), 131.5 (C), 135.4 (C), 141.7 (C), 147.4 (C), 148.4 (C) ppm. IR (neat): $\tilde{\upsilon}$ = 2937, 2836, 2787, 1661, 1590, 1516, 1465, 1428, 1324, 1265, 1239, 1159, 1077, 1030, 976, 896, 803, 764, 738 cm^{-1}. MS (EI): *m/z* (%) = 363 (5) [M$^+$ – 2 H], 348 (4), 346 (4), 215 (46), 214 (100), 212 (22), 199 (16), 195 (7), 151 (15), 144 (4). HRMS: calcd. ($C_{20}H_{22}NO_2F_3$ – 2 H) 363.1446; found 363.1481.

1-(3,4-Dimethoxybenzyl)-6-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline (*rac*-25): Aqueous CH_2O (0.5 mL, *c* = 37%, 6.7 mmol) was added to a solution of *rac*-**22** (75 mg, 0.25 mmol) in MeOH (2.0 mL). After this mixture had been stirred at rt for 3 h, $NaBH_4$ (95 mg, 2.50 mmol) was slowly added.

Subsequently, the reaction mixture was stirred at 25 °C for additional 16 h. Then, saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 30 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 95:5:1), *rac*-**25** (64 mg, 0.20 mmol, 81%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.52 (s, 3 H), 2.91-2.56 (m, 4 H), 3.19-3.04 (m, 2 H), 3.73-3.76 m (1 H), 3.76 (s, 3 H), 3.85 (s, 3 H), 6.51 (d, *J* = 1.7 Hz, 1 H), 6.61-6.78 (m, 5 H) ppm. ^{13}C NMR (126 MHz, DEPT, $CDCl_3$): δ = 26.4 (CH_2), 40.5 (CH_2), 42.8 (CH_3), 46.7 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 64.6 (CH), 110.9 (CH), 112.2 (CH, d, *J* = 21 Hz), 112.9 (CH), 114.8 (CH, d, *J* = 20 Hz), 121.7 (CH), 129.5 (CH, d, *J* = 8 Hz), 132.0 (C), 133.2 (C), 136.6 (C, d, *J* = 7 Hz), 147.3 (C), 148.4 (C), 161.0 (CF, d, *J* = 244 Hz) ppm. IR (neat): $\tilde{\upsilon}$ = 2934, 2834, 2787, 2359, 1613, 1590, 1514, 1496, 1464, 1417, 1374, 1260, 1235, 1155, 1139, 1029, 864, 808, 764 cm^{-1}. MS (ESI, CH_2Cl_2): *m/z* (%) = 316 (38) [M^+ + H], 164 (100). HRMS (ESI, CH_2Cl_2): calcd. ($C_{19}H_{22}NO_2F$ + H) 316.1713; found 316.1710.

1-(3,4-Dimethoxybenzyl)-6,7-difluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline (*rac*-26): Aqueous CH_2O (0.5 mL, *c* = 37%, 6.7 mmol) was added to a solution of *rac*-**23** (80 mg, 0.25 mmol) in MeOH (1.5 mL). After this mixture had been stirred at rt for 3 h, $NaBH_4$ (95 mg, 2.5 mmol) was slowly added. Subsequently, the reaction mixture was stirred at 25 °C for additional 16 h. Then, saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 95:5:1), *rac*-**26** (70 mg, 0.21 mmol, 84%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 2.53-2.65 (m, 1 H), 2.67-2.86 (m, 3 H), 3.02-3.18 (m, 2 H), 3.69 (t, *J* = 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 6.49 (dd, *J* = 8.2, 11.2 Hz, 1 H), 6.57 (d, *J* = 1.9 Hz, 1 H), 6.61 (dd, *J* = 1.7, 8.1 Hz, 1 H), 6.76 (d, *J* = 8.1 Hz, 1 H), 6.84 (dd, *J* = 8.1, 10.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 25.5 (CH_2), 40.3 (CH_2), 42.6 (CH_3), 46.6 (CH_2), 55.8 (CH_3), 55.8 (CH_3), 64.5 (CH), 111.0 (CH), 112.8 (CH), 116.3 (CH, d, *J* = 17 Hz), 116.7 (CH, d, *J* = 16 Hz), 121.7 (CH), 130.9 (C, dd, *J* = 4, 6 Hz), 131.6 (C), 134.0 (C, t, *J* = 4 Hz), 147.5 (C), 147.9 (CF, dd, *J* = 18, 250 Hz), 148.5 (CF, dd, *J* = 16, 249 Hz), 148.5 (C) ppm. IR (neat): $\tilde{\upsilon}$ = 2936, 2836, 2798, 1608, 1591, 1516, 1465, 1417, 1375, 1315, 1264, 1238, 1212, 1157, 1140, 1085, 1030, 881, 807, 764 cm^{-1}. MS (EI): *m/z* (%) = 333 (5) [M^+], 332 (6), 316 (9), 201 (7), 198 (9), 183 (100), 182 (100), 180 (93), 167 (84), 151 (40), 139 (22), 133 (10), 127 (13), 119 (16), 107 (13), 106 (14). HRMS: calcd. ($C_{19}H_{21}NO_2F_2$) 333.1540; found 333.1523.

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