A New Color of the Synthetic Chameleon Methoxyallene: Synthesis of Trifluoromethyl-Substituted Pyridinol Derivatives: An Unusual Reaction Mechanism, a Remarkable Crystal Packing, and First Palladium-Catalyzed Coupling Reactions

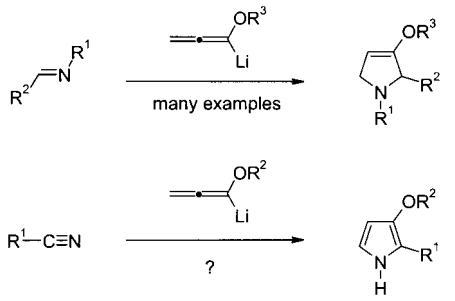
Oliver Flögel, Jyotirmayee Dash, Irene Brüdgam, Hans Hartl, and Hans-Ulrich Reißig*[a]

Abstract: Addition of lithiated methoxyallene to pivalonitrile afforded after aqueous workup the expected iminoallene **1** in excellent yield. Treatment of this intermediate with silver nitrate accomplished the desired cyclization to the electron-rich pyrrole derivative **2** in moderate yield. Surprisingly, trifluoroacetic acid converted iminoallene **1** to a mixture of enamide **3** and trifluoromethyl-substituted pyridinol **4** (together with its tautomer **5**). A plausible mechanism proposed for this intriguing transformation involves addition of trifluoroacetate to the central allene carbon atom of an allenyl iminium intermediate as crucial step. Enamide **3** is converted to pyridinol **4** by an intramolecular aldol-type process. A practical direct synthesis of trifluoromethyl-substituted pyridinols **4**, **10**, **11**, and **12** starting from typical nitriles and methoxyallene was established. Pyridinol **10** shows an interesting crystal packing with three molecules in the elementary cell and a remarkable helical supramolecular arrangement. Trifluoromethyl-substituted pyridinol **4** was converted to the corresponding pyridyl nonaflate **13**, which is an excellent precursor for palladium-catalyzed reactions leading to pyridine derivatives **14**–**16** in good to excellent yields. The new synthesis of trifluoromethyl-substituted pyridines disclosed here demonstrates a novel reactivity pattern of lithiated methoxyallene which is incorporated into the products as the unusual tripolar synthon **B**.

Keywords: allenes · cyclization · palladium · pyridines · supramolecular chemistry

Introduction

We recently reported that the addition of lithiated alkoxyallenes to various imines is a very smooth and highly flexible route towards many dihydropyrrole derivatives.[1] This [3+2] cyclization path to functionalized pyrroles was applied to a relatively short and perfectly stereoselective synthesis of the uncommon γ-amino acid (−)-detoxinine,[2] to a synthesis of the pyrrolidinol derivative anisomycin,[3] and (by use of 3-alkyl-substituted 1-alkoxyallene derivatives) to a synthesis of (−)-preussin.[4] In addition, a variety of other highly substituted pyrrole derivatives have been synthesized.[5] Inspired by this broad scope of the allene/imine combination, we tried to extend the alkoxyallene methodology to the corresponding C–N triple-bond systems. Nitriles as electrophilic partners of lithiated alkoxyallenes should provide primary adducts which, after cyclization, could directly furnish electron-rich pyrroles (Scheme 1) that are potentially interesting aromatic π systems.[6] This turned out to be feasible, but synthetically not very useful. However, during the search for a suitable cyclization protocol we detected an entirely unexpected and mechanistically intriguing formation of new highly functionalized trifluoromethyl-substituted pyridine derivatives. These results impressively demonstrate the chameleon-like character of lithiated alkoxyallenes as versatile



Scheme 1.

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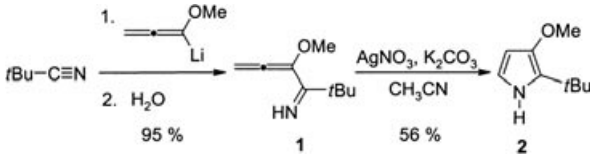
synthetic building blocks, which has again led us in a new direction.[7]

Results

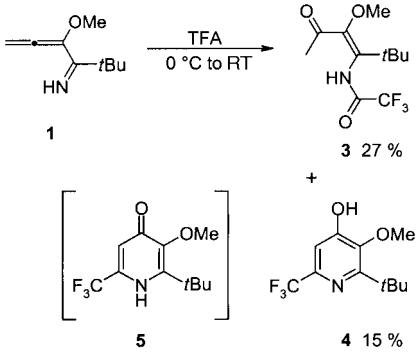
Formation and reactions of iminoallene derivatives: As anticipated lithiated methoxyallene added to a nitrile such as pivalonitrile, and after aqueous workup followed by careful distillation, iminoallene **1** was obtained analytically pure in excellent yield (Scheme 2). Similar adducts could be isolated



Scheme 2.

in modest yields and purities from other nitriles; however, these compounds proved to be considerably more sensitive to hydrolysis or oxidation than *tert*-butyl-substituted **1**.[5a] The desired cyclization of **1** could be achieved by catalysis with silver nitrate in the presence of potassium carbonate, which is often the method of choice for cyclizations of allenyl amines and alcohols,[8] and it provided the expected 2-*tert*-butyl-3-methoxypyrrole (**2**) in moderate yield. This electron-rich pyrrole is sensitive to oxygen and decomposes rather rapidly. Other nitrile–allene adducts delivered the corresponding pyrroles only in much inferior yields and with lower purity.[5a]

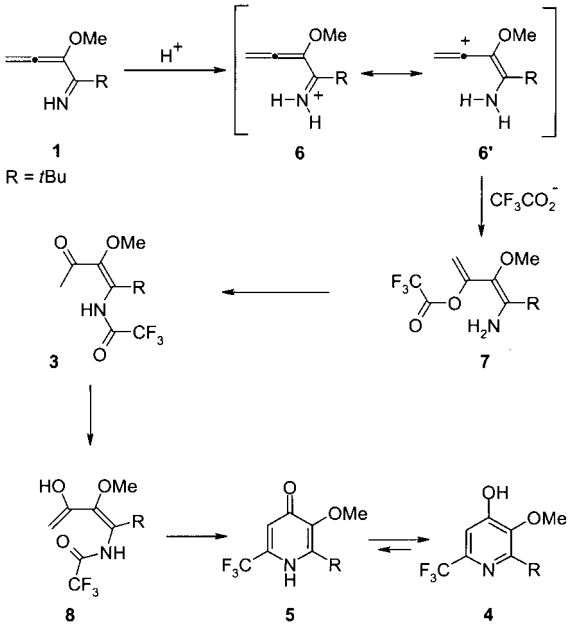
We also observed that **1** was completely converted to **2** on storing a sample in deuterochloroform for seven days. After distillation **2** was obtained in 64% yield. Since we suspected that this process occurred by proton/deuteron catalysis, we studied the reaction of **1** in the presence of acid. Quite unexpectedly, treatment of iminoallene **1** with trifluoroacetic acid in deuterochloroform provided two new compounds. After 20 min at 0 °C we could already observe enamide **3** together with pyridinol **4** (Scheme 3). These two products were isolated after stirring the solution for 16 h at room temperature in 27 and 15% yield, respectively. Enamide **3**



Scheme 3.

was formed as one of the possible two diastereomers, whereas pyridinol **4** exists in solution together with its pyridinone tautomer **5** (ratio in $CDCl_3$ ca. 60:40); in CD_3OD only the signals of pyridinol **4** were detected.

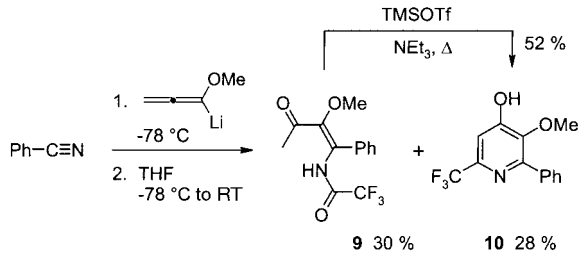
A mechanism to explain these puzzling results is presented in Scheme 4. Although we do not have real proof of any



Scheme 4.

of these steps, the overall mechanism seems plausible. In the first step iminoallene **1** is protonated to give iminium ion **6**, which can also be represented by mesomer **6′**. Protonation therefore results in electrophilic character of the central carbon atom of the allene moiety. Apparently, even a weak nucleophile such as trifluoroacetate is able to add (in equilibrium?) to this center to generate the next intermediate **7** with an alkenyl trifluoroacetate as key functional group. This unit is a fairly strong acylating agent, and it transfers the trifluoroacetyl group to the geometrically well positioned amino group to finally lead to the isolated enamide **3**.[9] The formation of the second product, pyridinol **4**, is easily explained by an acid-catalyzed formation of enol **8** and its intramolecular aldol condensation, which furnishes pyridinone **5** and its tautomer **4**. We are not aware of pyridine syntheses which employ three components in a similar manner.[10]

Having found these surprising transformations of iminoallene **1** we checked the possibility of forming enamide and pyridine derivatives without isolation of the imine intermediate. Treatment of benzonitrile with lithiated methoxyallene and subsequent addition of an excess of trifluoroacetic acid led to a mixture of the expected enamide **9** and its condensation product, pyridinol **10** (Scheme 5). The two compounds could easily be separated by column chromatography and were isolated in good overall yield. For **10** we did not observe its pyridinone tautomer in the NMR spectrum.

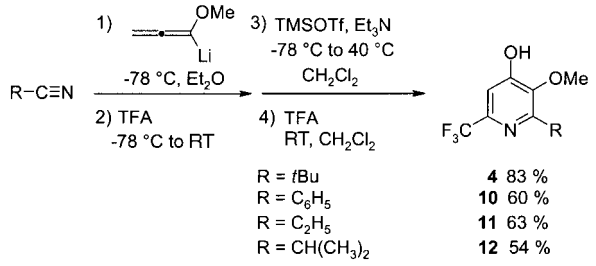


Scheme 5.

With these compounds we could also establish a method for complete conversion of enamide **9** to pyridine derivative **10**. Treatment of **9** with trimethylsilyl triflate in the presence of triethylamine under reflux in dichloromethane provided the desired pyridinol **10** in 52 % yield.[11]

The question now arises why enamides **3** and **9** did not completely undergo cyclization in the presence of trifluoroacetic acid. Possibly, the enamides isolated are actually the *Z* isomers and not the *E* isomers depicted in the schemes above. However, only the *E* isomers can directly undergo aldol condensation to give pyridine derivatives, whereas the *Z* enamides must change configuration before cyclization. Perhaps this latter process is too slow with trifluoroacetic acid, but induced under forcing conditions with trimethylsilyl triflate and triethylamine.

Direct synthesis of trifluoromethyl-substituted pyridine derivatives: The next task was the development of a direct protocol for conversion of nitriles to trifluoromethyl-substituted pyridinols which combines all reactions described above. For this purpose the nitriles were treated with lithiated methoxyallene and then with trifluoroacetic acid. The crude product obtained was subsequently refluxed with trimethylsilyl triflate in the presence of triethylamine and, after acidic workup, pyridine derivatives **4**, **10**, **11**, and **12** were obtained in moderate to very good yields (Scheme 6).



Scheme 6.

These first examples demonstrate that nitriles with alkyl groups (primary, secondary, tertiary) and with aryl substituents are suitable substrates for this three-component multistep process.[12] We are currently exploring the scope and limitations of this unique reaction leading to pyridine derivatives with so far unknown substitution patterns.[13]

Crystal structure of 10: From pyridinol derivative **10** we were able to obtain suitable single crystals for an X-ray crystal structure analysis, which not only proved the constitution of the compound but also showed an interesting arrangement of the molecules in the unit cell. The compound crystallizes triclinic in the centrosymmetric space group $P\bar{1}$. The crystal structure is built up by three crystallographically independent molecules A, B, and C with almost identical bond lengths and angles (Figure 1, Table 1). These molecules are connected by strong O–H···N hydrogen bonds with O–N distances of 2.787(2), 2.667(2), and 2.756(2) Å to form

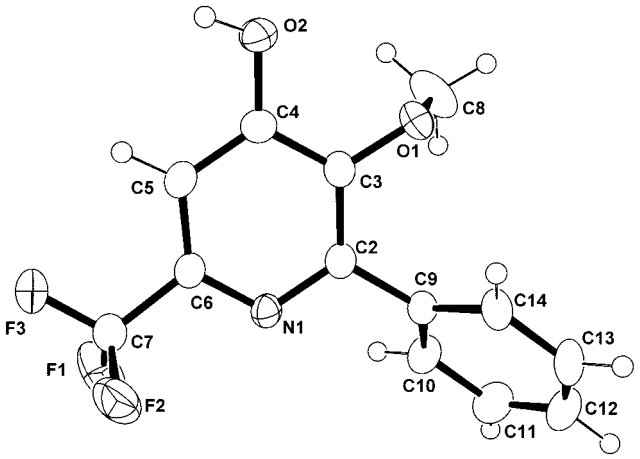


Figure 1. Structure of **10** (ORTEP plot; 50 % probability level).

Table 1. Bond lengths [Å] for the three crystallographically independent molecules of **10**.

Bond	Molecule A	Molecule B	Molecule C
N1–C6	1.3363(19)	1.340(2)	1.334(2)
N1–C2	1.3559(19)	1.358(2)	1.3523(19)
C2–C3	1.393(2)	1.392(2)	1.397(2)
C2–C9	1.483(2)	1.488(2)	1.490(2)
C3–O1	1.3732(18)	1.3675(19)	1.3620(19)
C3–C4	1.397(2)	1.403(2)	1.393(2)
C4–O2	1.3376(18)	1.3358(19)	1.3422(18)
C4–C5	1.400(2)	1.396(2)	1.392(2)
C5–C6	1.376(2)	1.370(2)	1.371(2)
C5–H5	0.955(17)	0.958(17)	0.953(17)
C6–C7	1.504(2)	1.505(2)	1.506(2)
C7–F3	1.321(2)	1.324(2)	1.335(2)
C7–F1	1.328(2)	1.325(2)	1.336(2)
C7–F2	1.329(2)	1.328(2)	1.339(2)
C8–O1	1.424(2)	1.402(3)	1.454(3)
C8–H82	0.97(3)	0.97(3)	0.96(3)
C8–H81	1.03(3)	1.04(3)	1.01(3)
C8–H83	0.98(3)	0.88(3)	1.15(5)
C9–C10	1.391(2)	1.389(2)	1.389(2)
C9–C14	1.394(2)	1.392(2)	1.394(2)
C10–C11	1.379(2)	1.383(3)	1.384(3)
C10–H10	0.943(18)	0.967(18)	0.946(19)
C11–C12	1.379(3)	1.377(3)	1.381(3)
C11–H11	0.95(2)	0.95(2)	0.98(2)
C12–C13	1.379(3)	1.382(3)	1.373(3)
C12–H12	0.96(2)	0.96(2)	0.98(2)
C13–C14	1.380(3)	1.381(2)	1.381(3)
C13–H13	0.956(19)	0.96(2)	1.02(2)
C14–H14	0.953(19)	0.985(18)	0.94(2)
O2–H2	0.93(2)	0.90(2)	0.87(3)

helical chains with the approximate symmetry of a threefold screw axis in the direction of the *c* axis. The O–H···N hydrogen bonds are almost linear, with bond angles of 173(2), 173(2), and 176(2)° (Figure 1), whereby the hydrogen atoms are clearly located at the oxygen atoms. The only significant differences between the three molecules are the dihedral angles of the C–CF_3 and C–OCH_3 moieties and the C–C bond linking the phenyl and the pyridyl rings. The interplanar angles between the best planes of the pyridyl and phenyl rings are 58.05(6)° in molecule A, 69.17(5)° in B, and 46.76(8)° in C. The helical chains are arranged as pairs of enantiomers with left- and right-hand screw in an approximately hexagonal rod packing parallel to the *c* axis (Figure 2).

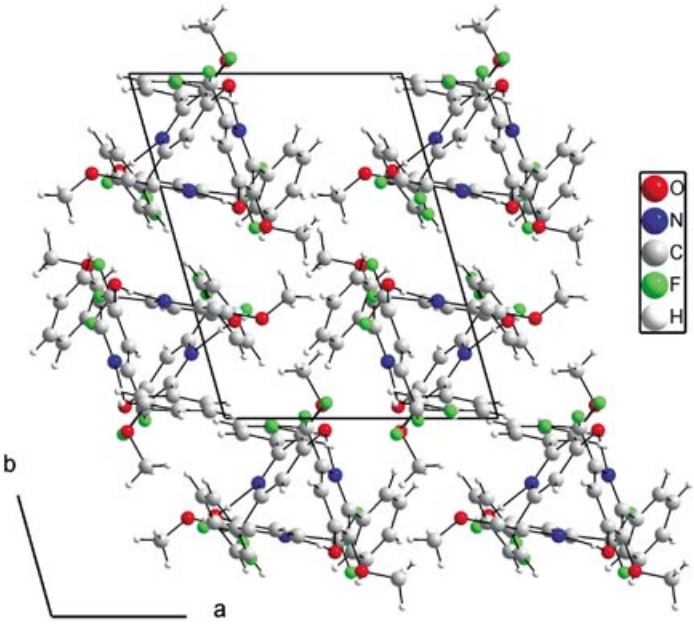
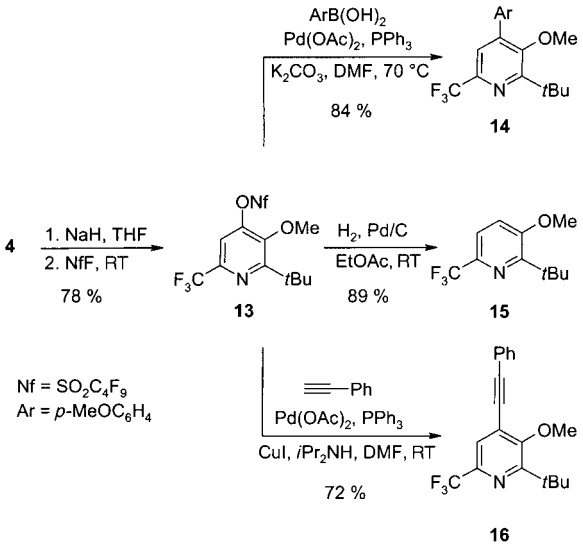


Figure 2. Packing of **10** along the *c* axis.

Palladium-catalyzed coupling reactions: Heterocycles bearing trifluoromethyl (or perfluoroalkyl) groups are of interest as substituents of biologically active compounds for use as pharmaceuticals or as crop-protection agents.[14] Although methods leading to 2- or 6-trifluoromethyl-substituted pyridine derivatives have been reported[15] the pyridinols presented here should offer many and unique possibilities for subsequent synthetic manipulation. The 4-hydroxy group allows alkylation or arylation, and demethylation at the 3-methoxy substituent should provide brenzcatechin-analogous pyridine derivatives.[16] These building blocks are not only of interest because they may be connected as substituents for potential biologically active compounds, but they may also serve as novel elements of supramolecular constructions. Here we present our first results employing typical palladium-catalyzed reactions which replace the 4-hydroxy group of **4** by different substituents.

For this purpose pyridinol **4** was deprotonated with sodium hydride in THF and then quenched with nonafluorobutane-1-sulfonyl fluoride (NfF), which provided the desired pyridyl nonaflate **13** in good yield (Scheme 7).[17] Reductive removal of this excellent leaving group occurred under standard conditions with hydrogen in the presence of Pd/C to



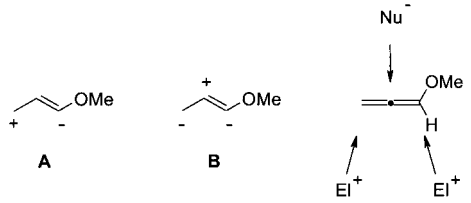
Scheme 7.

smoothly furnish 2-*tert*-butyl-3-methoxy-6-trifluoromethylpyridine (**15**).[18] As expected **13** is an excellent substrate for palladium-catalyzed C–C bond forming processes. Suzuki coupling[19] with *para*-methoxyphenylboronic acid in the presence of 5 mol% of palladium(II) acetate afforded the desired 4-anisyl-substituted pyridine derivative **14** in 84% yield. With phenylacetylene in the presence of palladium(II) acetate, nonaflate **13** provided the Sonogashira coupling[20] product **16** in 72% yield. These first examples demonstrate that a broad range of subsequent transformations, in particular, palladium-catalyzed reactions, are possible with our serendipitously discovered trifluoromethyl-substituted pyridinol derivatives. Many interesting pyridine derivatives with extended π systems are conceivable, for example, new donor–acceptor-substituted π systems, but the palladium chemistry may also be very suitable for introducing these trifluoromethyl-substituted pyridinyl substituents into targets which should be studied for their biological activity.

Conclusion

We have demonstrated that the reaction of lithiated alkoxyallenes with nitriles does not only lead to the expected electron-rich pyrrole derivatives (Scheme 2) but it also opens the way to a completely unexpected and unique pyridine synthesis. By subsequent treatment of the intermediates with trifluoroacetic acid and then with trimethylsilyl triflate, 6-trifluoromethyl-substituted pyridinols **4**, **10**, **11**, and **12** were obtained in good overall yield. Compound **10** shows an interesting helical arrangement of the molecules in the crystal (Figure 2). A practical direct synthesis of these unusually substituted pyridine derivatives from nitriles and the me-

thoxyallene could be established (Scheme 6). The resulting pyridinols are very versatile building blocks that are of interest for introduction into potentially biological active compounds and also as construction elements of supramolecular arrangements. As first examples of their subsequent transformations a few typical palladium-catalyzed transformations were performed and led to coupling products such as **14** and **16**. The synthetic chameleon methoxyallene has again presented a new color: whereas the equivalence of lithiated methoxyallene with 1,3-zwitterions **A** is well established[7] the introduction of this C_3 building block into the trifluoromethyl-substituted pyridines in a unique three-component reaction demonstrates its equivalence to the new tripolar synthon **B**. As illustrated in Scheme 8 the methoxyallene unit is attacked by an electrophile at C-1, a nucleophile at C-2, and a second electrophile at C-3, which involves a formal umpolung of reactivity at all three carbon atoms.[21]



Scheme 8.

Experimental Section

General methods: Unless otherwise stated all reactions were performed under argon atmosphere in flame-dried flasks by adding the components by syringe. All solvents were dried by standard procedures. IR spectra were measured with a Perkin Elmer FT-IR spectrometer Nicolet 5 SXC or Nicolet 205. ^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments (WH 270, AC 250, AC 500). Proton chemical shifts are reported in ppm relative to TMS ($\delta = 0.00$ ppm) or $CHCl_3$ ($\delta = 7.26$ ppm). Higher order NMR spectra were approximately interpreted as first-order spectra if possible. ^{13}C chemical shifts are reported relative to $CDCl_3$ ($\delta = 77.0$ ppm). Neutral aluminum oxide (activity III, Fluka/Merck) or silica gel (0.040–0.063 mm, Fluka) were used for column chromatography. Nucleosil 50-5 (Macherey & Nagel) was used for HPLC. Melting points are uncorrected.

X-ray crystallography: Single-crystal X-ray data were collected on a Brooker-XPS diffractometer (CCD area detector, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, graphite monochromator), empirical absorption correction using symmetry-equivalent reflections (SADABS),[22] structure solution and refinement by SHELXS-97[23] and SHELXL-97[24] in the WINGX system (Table 2).[25] The hydrogen atoms were located by difference Fourier syntheses. CCDC-234635 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.uk).

4-Methoxy-2,2-dimethyl-4,5-hexadien-3-imine (1): A solution of methoxyallene (0.50 mL, 420 mg, 6.00 mmol) in diethyl ether (8 mL) was treated at −40 °C with *n*-butyllithium (2.00 mL, 2.5 M in hexane, 5.00 mmol) and the mixture was stirred for 15 min. At −78 °C pivalonitrile (0.20 mL, 150 mg, 1.81 mmol) was added, and the mixture was stirred for 4 h at this temperature and then quenched with water (60 mL). After extraction with diethyl ether (3 × 10 mL), drying with $MgSO_4$, and evaporation of the solvent the crude product was purified by careful distillation at room temperature/0.04 mbar. In the dry ice trap of a Büchi kugelrohr oven **1** (262 mg, 95 %, purity > 95 %) was condensed as pale yellow liquid.

Table 2. Crystal data and structure refinement for **10**.

recrystallized from	hexane/ethyl acetate
empirical formula	$C_{13}H_{10}F_3NO_2$
formula weight	269.2
T [K]	173(2)
λ [Å]	0.71073
crystal system, space group	triclinic, $P\bar{1}$
a [Å]	10.009(3)
b [Å]	14.057(4)
c [Å]	15.292(5)
α [°]	113.61(1)
β [°]	100.61(1)
γ [°]	99.67(1)
V [Å^3]	1866.6(10)
Z	6
ρ_{calcd} [Mg m^{-3}]	1.437
absorption coefficient [mm^{-1}]	0.127
effective transmission min./max.	5.82
$F(000)$	828
crystal size [mm]	0.3 × 0.1 × 0.03
θ range for data collection [°]	1.64–30.56
limiting indices	$-14 \le h \le 14$, $-19 \le k \le 16$, $-20 \le l \le 21$
collected/unique reflections	23138/11194 [R(int) = 0.0291]
completeness to $\theta = 30.56°$ [%]	97.8
refinement method	full-matrix least-squares on F^2
data/restraints/parameters	11194/0/634
goodness-of-fit on F^2	1.014
final R indices [$I > 2\sigma(I)$]	$R1 = 0.0463$, $wR2 = 0.1105$
R indices (all data)	$R1 = 0.0911$, $wR2 = 0.1281$
largest diff. peak/hole [e A^{-3}]	0.463/−0.353

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 5.77$ (s, 2H, 6-H), 3.47 (s, 3H, OMe), 1.27 ppm (s, 9H, $C(CH_3)_3$), the signal for NH could not be detected; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 202.7$ (s, C-5), 177.3 (s, C-3), 127.5 (s, C-4), 93.3 (t, C-6), 55.2 (q, OMe), 38.5, 28.3 ppm (s, q, $C(CH_3)_3$), the intensity of the C-4 signal at 127.5 ppm is extremely low; its presence was confirmed by addition of chromium(III) tris(acetylacetonate);[26] IR (neat): $\tilde{\nu} = 3270$ (=N–H), 2955–2835 (C–H), 1940 (C=C=C), 1685 (C=N), 1600 cm^{-1} (C=C); MS (80 eV, EI): *m/z* (%): 153 (56) $[M]^+$, 138 (97) $[M-CH_3]^+$, 123 (20) $[M-C_2H_6]^+$, 96 (28) $[M-C_4H_9]^+$, 57 (100) $[C_4H_9]^+$; HRMS (80 eV): calcd for $C_9H_{15}NO$ 153.11536; found 153.11578.

2-*tert*-Butyl-3-methoxypyrrole (2): Iminoallene **1** was prepared from pivalonitrile (166 mg, 2.00 mmol) as described above, but not purified. The crude addition product (285 mg, max. 2.00 mmol) was dissolved in acetonitrile (10 mL), and silver nitrate (68 mg, 0.40 mmol) and potassium carbonate (550 mg, 3.98 mmol) were added. The resulting mixture was stirred with exclusion of light for 17 h at room temperature, then filtered through a short pad of celite (elution with ethyl acetate), and the filtrate was concentrated by evaporation. Purification of the residue by chromatography on aluminum oxide (*n*-hexane/ethyl acetate 10/1, 1 % triethylamine added) provided **2** (172 mg; 56 %) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.66$ (s_{br}, 1H, NH), 6.38, 5.97 (2t, $J = 3.0$ Hz, 1 H each, 5-H, 4-H), 3.72 (s, 3H, OMe), 1.31 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 154.4$, 123.3 (2 s, C-3, C-2), 111.5, 98.1 (2 d, C-5, C-4), 59.0 (q, OMe), 31.3, 29.4 ppm (s, q, $C(CH_3)_3$); IR (neat): $\tilde{\nu} = 3400$ (N–H), 3130–3000 (=C–H), 2955–2825 (C–H), 1575 cm^{-1} (C=C); MS (80 eV, EI): *m/z* (%): 153 (31) $[M]^+$, 138 (100) $[M-CH_3]^+$, 123 (26) $[M-C_2H_6]^+$, 108 (7) $[M-C_3H_9]^+$; HRMS (80 eV) calcd for $C_9H_{15}NO$: 153.11536; found: 153.11488.

Cyclization of 1 to 2 in deuterochloroform: Crude iminoallene **1** (294 mg, max. 1.81 mmol) was dissolved in $CDCl_3$ (1 mL) and stored for seven days at room temperature. The solvent was evaporated, and the resulting pyrrole **2** purified by distillation (60 °C, 0.05 mbar). Yield: 178 mg (64 %) of **2** as a yellow oil.

Treatment of iminoallene 1 with TFA: Compound **1** (273 mg, max. 1.81 mmol, crude product) was dissolved in $CDCl_3$ (2 mL) under an argon atmosphere. At 0 °C trifluoroacetic acid (0.15 mL, 222 mg, 1.95 mmol) was added and the solution was stirred for 15 min. After 16 h at room temperature the solvent was evaporated and the reddish residue

was treated with *n*-hexane (50 mL), stirred for 1 h, and filtered, and the filtrate was again evaporated. Purification by HPLC (silica gel, *n*-hexane/*i*PrOH 95/5) provided **3** (131 mg; 27%) as a colorless solid (m.p. 104–108°C), and **4** (67 mg; 15%) as a yellowish oil.

N-[1-(*tert*-Butyl)-2-methoxy-3-oxo-1-buten-1-yl]-2,2,2-trifluoroacetamide (**3**): ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.06$ (s_{br}, 1H, NH), 3.56 (s, 3H, OMe), 2.30 (s, 3H, 4′-H), 1.25 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 200.4$ (s, C-3′), 156.6 (q, $^2J_{C,F} = 37$ Hz, C-1), 151.9 (s, C-2′), 130.1 (s, C-1′), 115.8 (q, $^1J_{C,F} = 288$ Hz, C-2), 58.9 (q, OMe), 36.4, 28.2 (s, q, $C(CH_3)_3$), 27.2 ppm (q, C-4′); IR (KBr): $\tilde{\nu} = 3285$ (N–H), 2975–2945 (C–H), 1725, 1700 (C=O), 1630 cm^{-1} (C=C); MS (80 eV, EI): *m/z* (%): 267 (2) $[M]^+$, 252 (1) $[M-CH_3]^+$, 224 (100) $[M-C_2H_3O]^+$, 210 (2) $[M-C_4H_9]^+$, 194 (11) $[M-C_3H_5O_2]^+$, 69 (11) $[CF_3]^+$, 57 (10) $[C_4H_9]^+$, 43 (14) $[C_2H_3O]^+$; elemental analysis calcd (%) for $C_{11}H_{16}F_3NO_3$ (267.3): C 49.44, H 6.03, N 5.24; found: C 49.44, H 5.94, N 5.16.

2-*tert*-Butyl-3-methoxy-6-(trifluoromethyl)-4-pyridinol (**4**) and 2-*tert*-butyl-3-methoxy-6-(trifluoromethyl)-4(1*H*)-pyridone (**5**): In $CDCl_3$ at 243 K a ratio of **4**:**5** of approximately 60:40 was observed.

Signals of pyridinol **4**: ^{1}H NMR (500 MHz, $CDCl_3$, 243 K): $\delta = 10.9$ (s_{br}, 1H, OH), 7.23 (s, 1H, 5-H), 3.95 (s, 3H, OMe), 1.40 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$, 243 K): $\delta = 162.1$ (s, C-2), 157.1 (s, C-4), 145.2 (s, C-3), 140.9 (q, $^2J_{C,F} = 34$ Hz, C-6), 121.4 (q, $^1J_{C,F} = 273$ Hz, CF_3), 114.9 (d, C-5), 60.0 (q, OMe), 37.8, 28.9 ppm (s, q, $C(CH_3)_3$).

Signals of pyridone **5**: ^{1}H NMR (500 MHz, $CDCl_3$, 243 K): $\delta = 8.73$ (s_{br}, 1H, NH), 7.01 (s, 1H, 5-H), 4.04 (s, 3H, OMe), 1.52 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 174.7$ (s, C-4), 150.2 (s, C-2), 148.9 (s, C-3), 133.4 (q, $^2J_{C,F} = 36$ Hz, C-6), 120.4 (q, $^1J_{C,F} = 273$ Hz, CF_3), 59.2 (q, OMe), 35.7, 27.5 ppm (s, q, $C(CH_3)_3$).

In CD_3OD at room temperature we observed only the signals of **4**: ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.08$ (s, 1H, 5-H), 3.87 (s, 3H, OMe), 1.34 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125.8 MHz, CD_3OD): $\delta = 163.2$ (s, C-2), 158.7 (s, C-4), 146.7 (s, C-3), 142.5 (q, $^2J_{C,F} = 34$ Hz, C-6), 122.9 (q, $^1J_{C,F} = 273$ Hz, CF_3), 109.1 (d, C-5), 60.4 (q, OMe), 38.9, 29.7 ppm (s, q, $C(CH_3)_3$).

IR (neat): $\tilde{\nu} = 3405$ (O–H), 3285 (N–H), 2990–2900 (C–H), 1610 cm^{-1} (C=O); MS (80 eV, EI): *m/z* (%): 249 (39) $[M]^+$, 234 (100) $[M-CH_3]^+$, 218 (22) $[M-OMe]^+$, 192 (8) $[M-C_4H_9]^+$, 69 (2) $[CF_3]^+$, 57 (5) $[C_4H_9]^+$; elemental analysis calcd (%) for $C_{11}H_{14}F_3NO_2$ (249.2): C 53.01, H 5.66, N 5.62; found: C 53.09, H 5.57, N 5.37.

Reaction of benzonitrile followed by treatment with trifluoroacetic acid: Methoxyallene (0.55 mL, 462 mg, 6.60 mmol) was dissolved in diethyl ether (10 mL) and treated at −40°C with *n*-butyllithium (2.20 mL, 2.5 M in hexane, 5.50 mmol). After 15 min of stirring at −50 to −40°C the solution was cooled to −78°C and a solution of benzonitrile (0.20 mL, 202 mg, 1.96 mmol) in diethyl ether (5 mL) was added. After 4 h at −78°C trifluoroacetic acid (1.00 mL, 1.48 g, 13.0 mmol) was added and the solution was allowed to warm to room temperature over 16 h and then quenched with saturated $NaHCO_3$ solution (20 mL). Extraction with diethyl ether (3×20 mL), drying with $MgSO_4$, and evaporation provided the crude products. Purification by column chromatography (silica gel, *n*-hexane/ethyl acetate 8/1) afforded **9** (158 mg; 30%) as a yellowish solid (m.p. 132–133°C) and **10** (159 mg; 28%) as a yellow oil.

N-[2-Methoxy-3-oxo-1-phenyl-1-buten-1-yl]-2,2,2-trifluoroacetamide (**9**): ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 12.19$ (s_{br}, 1H, NH), 7.43 (m_c, 5H, Ph), 3.23 (s, 3H, OMe), 2.41 ppm (s, 3H, 4′-H); ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 203.0$ (s, C-3′), 155.3 (q, $^2J_{C,F} = 38$ Hz, C-1), 140.4, 138.8 (2s, *ipso*-Ph, C-2′), 129.6, 128.3, 128.2 (3d, Ph), 115.3 (q, $^1J_{C,F} = 289$ Hz, C-2), 60.5 (q, OMe), 27.4 ppm (q, C-4′), the C-1′ signal was hidden by the signals of the aryl group; IR (neat): $\tilde{\nu} = 3250$ (N–H), 3060–3000 (=C–H), 2940–2840 (C–H), 1750 (C=O), 1610, 1590 cm^{-1} (C=C); MS (80 eV, EI): *m/z* (%): 287 (37) $[M]^+$, 268 (1) $[M-F]^+$, 244 (100) $[M-C_2H_3O]^+$, 229 (17) $[M-C_3H_6O]^+$, 77 (19) $[C_6H_5]^+$; HRMS (80 eV) calcd for $C_{13}H_{12}F_3NO_3$: 287.07693; found 287.07744.

3-Methoxy-2-phenyl-6-(trifluoromethyl)-4-pyridinol (**10**): ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.95$–7.88, 7.50–7.40 (2m, 5H, Ph), 7.22 (s, 1H, 5-H), 3.55 ppm (s, 3H, OMe), the OH signal could not be detected; ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 158.0$, 151.6, 144.4 (3s, C-2, C-3, C-4), 143.5 (q, $^2J_{C,F} = 34$ Hz, C-6), 135.7 (s, *ipso*-Ph), 129.3, 128.8, 128.4 (3d, Ph), 121.2 (q, $^1J_{C,F} = 274$ Hz, CF_3), 108.5 (d, C-5), 60.6 ppm (q, OMe); ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.86$–7.82, 7.45–7.37 (2m, 5H, Ph), 7.21 (s, 1H, 5-H), 3.60 ppm (s, 3H, OMe); ^{13}C NMR (125.8 MHz, CD_3OD): $\delta = 160.2$, 154.1, 146.1 (3s, C-2, C-3, C-4), 144.7 (q, $^2J_{C,F} = 34$ Hz, C-6), 135.7 (s, *ipso*-Ph), 130.1, 130.0, 129.1 (3d, Ph), 122.9 (q, $^1J_{CF} = 273$ Hz, CF_3), 109.8 (d, C-5), 60.8 ppm (q, OMe); IR (neat): $\tilde{\nu} = 3410$ (O–H), 3065–3015 (=C–H), 2940–2845 (C–H), 1605 cm^{-1} (C=C); MS (80 eV, EI): *m/z* (%): 269 (100) $[M]^+$, 250 (27) $[M-F]^+$, 77 (16) $[C_6H_5]^+$, 69 (3) $[CF_3]^+$; elemental analysis calcd (%) for $C_{13}H_{10}F_3NO_2$ (269.2): C 58.00, H 3.74, N 5.20; found: C 58.01, H 3.72, N 5.08.

Conversion of enamide 9 to pyridinol 10: Enamide **9** (112 mg, 0.39 mmol) was dissolved in dichloromethane (15 mL) and treated at −78°C with triethylamine (0.72 mL, 518 mg, 5.09 mmol) and trimethylsilyl triflate (1.08 mL, 1.32 g, 5.97 mmol). After 30 min the cooling bath was removed and the solution allowed to warm to room temperature over 16 h. The mixture was heated under reflux for three days and then quenched at room temperature with saturated NH_4Cl solution (20 mL). Extraction with dichloromethane (3×20 mL), drying with $MgSO_4$, and evaporation provided the crude product. Purification by column chromatography (silica gel, *n*-hexane/ethyl acetate 8/1) furnished **10** (55 mg; 52%) as a pale yellow solid. For analytical details, see above.

Direct synthesis of pyridines from nitriles, general procedure: Methoxyallene was dissolved in diethyl ether (10 mL), and *n*-butyllithium (BuLi) was added at −40°C. After 15 min at −50 to −40°C the solution was cooled to −78°C, and the corresponding nitrile, dissolved in diethyl ether (2.5 mL/1.00 mmol), was added. After stirring for 4 h at this temperature trifluoroacetic acid (TFA, for amounts see individual experiments) was added and the mixture was warmed overnight to room temperature. Then saturated aqueous $NaHCO_3$ solution (10 mL/1.00 mmol of nitrile) was added, and the mixture was extracted with dichloromethane (3× 10 mL/1.00 mmol). The combined organic phases were dried with $MgSO_4$ and then evaporated. The resulting crude product mixture was dissolved in dichloromethane (7.5 mL/1.00 mmol), and at −78°C triethylamine and trimethylsilyl triflate (TMS triflate) were added. After 30 min the cooling bath was removed, and the reaction flask was allowed to warm to room temperature overnight. Then it was heated under reflux for 3 d and quenched with saturated NH_4Cl solution (10 mL/1.00 mmol). After extraction with dichloromethane (3×25 mL/1.00 mmol) the combined organic phases were dried with $MgSO_4$ and evaporated. The resulting crude product was dissolved in dichloromethane (20 mL/1.00 mmol) and treated first with TFA (ca. 1 equivalent) and then with water (20 mL/1.00 mmol). Extraction with dichloromethane (3×20 mL/1.00 mmol), drying with $MgSO_4$, and evaporation provided the corresponding pyridine.

2-*tert*-Butyl-3-methoxy-6-(trifluoromethyl)-4-pyridinol (4): According to the general procedure, pivalonitrile (0.22 mL, 165 mg, 1.99 mmol), methoxyallene (0.55 mL, 462 mg, 6.60 mmol), *n*BuLi (2.20 mL, 2.5 M in hexane, 5.50 mmol), TFA (1.00 mL, 1.48 g, 13.0 mmol), TEA (1.12 mL, 806 mg, 7.97 mmol), TMS triflate (1.93 mL, 2.22 g, 9.99 mmol), and TFA (0.15 mL, 222 mg, 1.95 mmol) provided crude **4**, which was purified by HPLC (silica, hexane/*i*PrOH 95/5) to yield **4** (410 mg; 83%) as a pale yellow oil.

3-Methoxy-2-phenyl-6-(trifluoromethyl)-4-pyridinol (10): According to the general procedure, benzonitrile (0.20 mL, 202 mg, 1.96 mmol), methoxyallene (0.55 mL, 462 mg, 6.60 mmol), *n*BuLi (2.20 mL, 2.5 M in hexane, 5.50 mmol), TFA (1.00 mL, 1.48 g, 13.0 mmol), TEA (1.12 mL, 806 mg, 7.97 mmol), TMS triflate (1.93 mL, 2.22 g, 9.99 mmol), and TFA (0.15 mL, 222 mg, 1.95 mmol) provided crude **10**, which was purified by column chromatography with silica gel (gradient elution: *n*-hexane/ethyl acetate 8/1 to 4/1) to yield **10** (323 mg; 60%) as a yellowish solid (m.p. 132–133°C).

2-Ethyl-3-methoxy-6-trifluoromethyl-4-pyridinol (11): According to the general procedure, propionitrile (0.14 mL, 108 mg, 1.96 mmol), methoxyallene (0.55 mL, 462 mg, 6.60 mmol), *n*BuLi (2.20 mL, 2.5 M in hexane, 5.50 mmol), TFA (1.00 mL, 1.48 g, 13.0 mmol), TEA (1.12 mL, 806 mg, 7.97 mmol), TMS triflate (1.93 mL, 2.22 g, 9.99 mmol), and TFA (0.15 mL, 222 mg, 1.95 mmol) provided crude **11**, which was purified by column chromatography on silica gel (hexane/ethyl acetate 4/1). Yield: 273 mg (63%) of **11** as a colorless solid (m.p. 102–103°C). ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.06$ (s, 1H, 5-H), 3.85 (s, 3H, OMe), 2.79, 1.21 ppm (q, t, $J = 7.5$ Hz, 2H, 3H, CH_2CH_3); ^{13}C NMR (125.8 MHz, CD_3OD): $\delta = 159.5$, 145.8 (2s, C-2, C-3, C-4)*, 143.7 (q, $^2J_{C,F} = 36$ Hz,

C-6), 122.8 (q, $^1J_{C,F}=273$ Hz, CF_3), 109.6 (d, C-5), 61.1 (q, OMe), 26.0 (t, CH_2), 13.7 ppm (q, CH_3), * only two signals could be unambiguously detected for three carbon atoms; IR (KBr): $\tilde{\nu}=3395$ (br, O–H), 2980–2885 (C–H), 1610 cm^{-1} (C=C); MS (80 eV, EI): *m/z* (%): 221 (100) $[M]^+$, 206 (58) $[M-CH_3]^+$, 203 (55) $[M-H_2O]^+$, 191 (31) $[M-C_2H_6]^+$, 69 (9) $[CF_3]^+$; elemental analysis calcd (%) for $C_9H_{10}F_3NO_2$ (221.2): C 48.87, H 4.56, N 6.33; found: C 48.60, H 4.54, N 6.13.

3-Methoxy-2-isopropyl-6-(trifluoromethyl)-4-pyridinol (12): According to the general procedure, isobutyronitrile (0.18 mL, 137 mg, 1.98 mmol), methoxyallene (0.55 mL, 462 mg, 6.60 mmol), *n*BuLi (2.20 mL, 2.5 M in hexane, 5.50 mmol), TFA (1.00 mL, 1.48 g, 13.0 mmol), TEA (1.12 mL, 806 mg, 7.97 mmol), TMS triflate (1.93 mL, 2.22 g, 9.99 mmol), and TFA (0.15 mL, 222 mg, 1.95 mmol) provided crude **12**, which was purified by HPLC (silica gel, *n*-hexane/*i*PrOH 95/5) to yield **12** (252 mg; 54%) as a colorless oil.

^{1}H NMR (250 MHz, CD_3OD): $\delta=7.04$ (s, 1H, 5-H), 3.83 (s, 3H, OMe), 3.42, 1.21 ppm (sept, d, $J=6.8$ Hz, 1H, 6H, $CH(CH_3)_2$); ^{13}C NMR (62.9 MHz, CD_3OD): $\delta=162.8$, 158.8, 144.8 (3 s, C-2, C-3, C-4), 144.3 (q, $^2J_{C,F}=34$ Hz, C-6), 123.0 (q, $^1J_{C,F}=273$ Hz, CF_3), 108.8 (d, C-5), 61.2 (q, OMe), 30.3, 21.9 ppm (d, q, $CH(CH_3)_2$); IR (neat): $\tilde{\nu}=3360$ (br, O–H), 3090 (=C–H), 2970–2840 (C–H), 1610 cm^{-1} (C=C); MS (80 eV, EI): *m/z* (%): 235 (70) $[M]^+$, 220 (100) $[M-CH_3]^+$, 204 (23) $[M-OMe]^+$, 192 (9) $[M-C_3H_7]^+$, 69 (21) $[CF_3]^+$, 43 (32) $[C_3H_7]^+$; HRMS (80 eV) calcd for $C_{10}H_{12}F_3NO_2$: 235.08202; found: 235.08355.

2-*tert*-Butyl-3-methoxy-6-trifluoromethylpyridin-4-yl nonaflate (13): NaH (128 mg, 60% in mineral oil, 3.2 mmol) was added to a solution of pyridinol **4** (400 mg, 1.60 mmol) in THF (10 mL) under an argon atmosphere. Nonafluorobutanesulfonyl fluoride (0.83 mL, 4.8 mmol) was added dropwise at room temperature. The mixture was stirred for 3 h and quenched by slow addition of water (15 mL). It was extracted with ethyl acetate (3×10 mL), dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (*n*-hexane) to afford **13** (663 mg; 78%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.42$ (s, 1H, 5-H), 3.98 (s, 3H, OMe), 1.41 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=166.4$ (s, C-2), 149.5, 149.4 (2 s, C-3, C-4), 142.0 (q, $^2J_{C,F}=37$ Hz, C-6), 120.6 (q, $^1J_{C,F}=275$ Hz, CF_3), 113.1 (d, C-5), 62.0 (q, OMe), 39.1, 28.8 ppm (s, q, $C(CH_3)_3$); ^{19}F NMR (470.6 MHz, $CDCl_3$): $\delta=-67.8$ (s, 3 F, CF_3), −80.5 (s, 3 F, F-4), −109.1 (s, 2 F, F-3), −120.6 (s, 2 F, F-2), −125.7 ppm (s, 2 F, F-1); IR (neat): $\tilde{\nu}=2960$–2870 (C–H), 1590, 1575 (C=C), 1435, 1350 cm^{-1} (SO); elemental analysis calcd (%) for $C_{15}H_{13}F_{12}NSO_4$ (531.3): C 33.91, H 2.47, N 2.64; found: C 34.06, H 2.57, N 2.63.

2-*tert*-Butyl-3-methoxy-4-(4-methoxyphenyl)-6-trifluoromethylpyridine (14): A mixture of nonaflate **13** (200 mg, 0.376 mmol), 4-methoxyphenylboronic acid (68 mg, 0.45 mmol), $Pd(OAc)_2$ (4.2 mg, 0.019 mmol), PPh_3 (19.7 mg, 0.075 mmol), and K_2CO_3 (51 mg, 0.38 mmol) in DMF (2.8 mL) was heated to 70 °C for 5 h under an argon atmosphere. The mixture was allowed to cool to room temperature, diluted with water (4 mL), and extracted with diethyl ether (3×5 mL). The combined organic phase was washed with water and brine, dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (pentane/ethyl acetate 10/1) to afford **14** (107 mg; 84%) as a colorless solid (m.p. 93–95 °C). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.53$–7.51 (m, 2H, Ar), 7.45 (s, 1H, 5-H), 7.02–6.98 (m, 2H, 4-Ar), 3.87, 3.36 (2 s, 3 H each, OMe), 1.46 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=162.8$, 160.1, 155.2 (3 s, C-2, C-3, *ipso*-Ar), 142.1 (s, C-4), 140.8 (q, $^2J_{CF}=35$ Hz, C-6), 129.8 (d, Ar), 128.6 (s, *ipso*-Ar), 120.8 (d, C-5), 114.4 (d, Ar), 60.3, 55.4 (2 q, OMe), 38.4, 29.4 ppm (s, q, $C(CH_3)_3$), the CF_3 signal could not unambiguously be assigned; IR (KBr): $\tilde{\nu}=3000$ (=C–H), 2980–2835 (C–H), 1610, 1515 cm^{-1} (C=C); MS (80 eV, EI): *m/z* (%): 339 (53) $[M]^+$, 338 (100) $[M-H]^+$, 324 (69) $[M-CH_3]^+$, 308 (19) $[M-OCH_3]^+$; elemental analysis calcd (%) for $C_{18}H_{20}F_3NO_2$ (339.4): C 63.71, H 5.94, N 4.13; found: C 63.29, H 5.49, N 3.60.

2-*tert*-Butyl-3-methoxy-6-trifluoromethylpyridine (15): A mixture of nonaflate **13** (100 mg, 0.188 mmol) and palladium (ca. 10 mg, 10% on charcoal) in ethyl acetate (1 mL) was stirred for two days under an atmosphere of hydrogen. Filtration of the reaction mixture through a short pad of silical gel with pentane/ethyl acetate (10/1) afforded **15** (39 mg; 89%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.48$, 7.15 (2 d, $J=8.4$ Hz, 2H, 4-H, 5-H), 3.89 (s, 3H, OMe), 1.40 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=158.2$, 156.3 (2 s, C-2, C-3), 137.8 (q, $^2J_{C,F}=35$ Hz, C-6), 122.1 (q, $^1J_{C,F}=273$ Hz, CF_3), 119.1, 117.2 (2 d, C-4, C-5), 55.2 (q, OMe), 38.2, 28.3 ppm (s, q, $C(CH_3)_3$); IR (neat): $\tilde{\nu}=3090$, 2955–2850 (C–H), 1665–1590 cm^{-1} (C=C); MS (80 eV, EI): *m/z* (%): 233 (29) $[M]^+$, 218 (100) $[M-CH_3]^+$, 214 (5) $[M-F]^+$, 202 (4) $[M-OCH_3]^+$, 198 (24) $[M-CH_3-HF]^+$, 57 (44) $[C_4H_9]^+$; HRMS calcd for $C_{11}H_{14}F_3NO$: 233.10344; found: 233.10275.

2-*tert*-Butyl-3-methoxy-4-phenylethynyl-6-trifluoromethylpyridine (16): A reaction flask containing nonaflate **13** (100 mg, 0.188 mmol), $Pd(OAc)_2$ (2.1 mg, 0.0094 mmol), PPh_3 (9.9 mg, 0.038 mmol), and CuI (1.8 mg, 0.0094 mmol) was degassed and filled with argon. DMF (0.86 mL) and diisopropylamine (0.43 mL) were added followed by phenylacetylene (23 mg, 0.23 mmol). After stirring at room temperature under an argon atmosphere for 17 h, the mixture was diluted with water (2 mL) and extracted with diethyl ether (3×5 mL). The combined organic solution was washed with water and brine, dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (pentane) to afford **16** (45 mg; 72%) as a colorless solid (m.p. 72–73 °C). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.61$ (s, 1H, 5-H), 7.58–7.56, 7.43–7.37 (2 m, 2H, 3H, Ph), 4.19 (s, 3H, OMe), 1.43 ppm (s, 9H, $C(CH_3)_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=162.7$ (s, C-2), 157.8 (s, C-3), 140.2 (q, $^2J_{C,F}=35$ Hz, C-6), 131.6 (d, Ph), 129.6 (d, C-5), 128.7 (d, Ph), 124.3 (s, C-4), 122.8 (d, Ph), 122.1 (s, *ipso*-Ph), 121.6 (q, $^1J_{C,F}=274$ Hz, CF_3), 99.3, 83.7 (2 s, C≡C), 61.1 (q, OMe), 38.5, 29.1 ppm (s, q, $(C(CH_3)_3$); IR (KBr): $\tilde{\nu}=3010$–2990 (=C–H), 2960 (C–H), 2225–2205 (C≡C), 1600, 1590, 1580 cm^{-1} (C=C); MS (80 eV, EI): *m/z* (%): 333 (42) $[M]^+$, 332 (19) $[M-H]^+$, 318 (28) $[M-CH_3]^+$, 302 (8) $[M-OCH_3]^+$; elemental analysis calcd (%) for $C_{19}H_{18}F_3NO$ (333.3): C 68.46, H 5.44, N 4.20; found: C 68.16, H 5.22, N 4.12.

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