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Novel Furo-pyridine Derivatives via Sonogashira Reactions of Functionalized Pyridines

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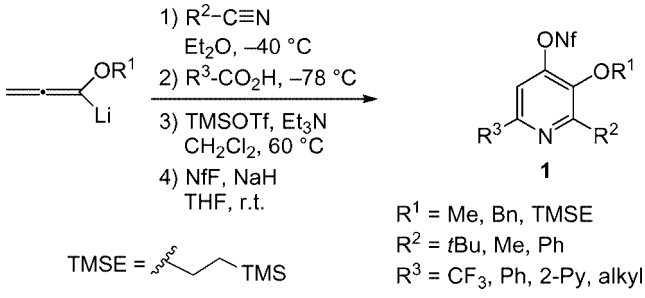
A series of 4-pyridyl nonaflates was coupled with several terminal alkynes to efficiently provide new 4-alkynyl-substituted 3-alkoxypyridine derivatives. Apt conditions were developed for their conversion into furo[2,3-*c*]pyridines. Sonogashira reactions of 4-alkoxy-substituted 3-pyridyl nonaflates allowed an access to regioisomeric furo[3,2-*c*]pyridines. For both types of alkynyl-substituted alkoxypyridines an alternative method for cyclization employing iodine monochloride furnished iodinated furo[2,3-*c*]- or furo[3,2-*c*]pyridines, which can undergo a second palladium-catalyzed step. Iodination of 4-hydroxypyridine derivative **24** with iodine afforded a pentasubstituted pyridine which after Sonogashira reaction immediately undergoes a cyclization to furo-pyridine **25**. Thus, three different types of furo-pyridines can be prepared starting from one precursor. Several compounds prepared are fluorescent and show strong Stokes shifts.

Introduction

In recent reports we described the flexible synthesis of 4-hydroxy-substituted pyridine derivatives by a novel three-component reaction employing lithiated alkoxyallenes, nitriles and carboxylic acids as precursors (Scheme 1).[1,2] This mechanistically unique process[1a] has a very broad scope[2] and the resulting pyridine derivatives are of high synthetic value. Their activation as 4-nonafluorobutanesulfonates[3] is easily achieved and the resulting pyridyl nonaflates **1** are most promising starting materials for palladium-catalyzed reactions. We have already demonstrated that Suzuki and Heck reactions can smoothly be performed affording highly substituted pyridine derivatives.[1,2] In this communication we want to present a series of Sonogashira reactions[4] which could be performed in a regioselective fashion at C-3, C-4, and C-5 position of the pyridine derivatives. Subsequent cyclizations of the alkyne moiety with a neighbouring hydroxy group smoothly provided a series of highly substituted furo-pyridine derivatives.



Scheme 1. General route to 2,6-disubstituted 4-pyridyl nonaflates.

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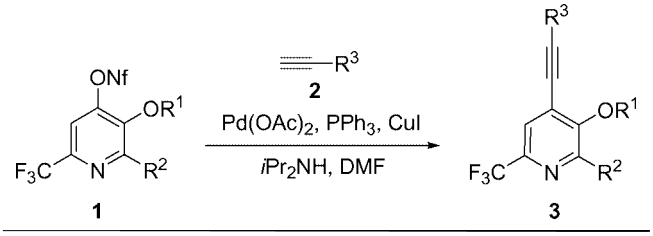
Results and Discussion

6-(Trifluoromethyl)pyridyl nonaflates **1a**–**1e** were treated with different monosubstituted alkynes **2** under standard conditions of Sonogashira couplings employing an excess of diisopropylamine as base. In general, the yields of the resulting disubstituted alkynes **3** are good to excellent

Table 1. Sonogashira couplings of 4-pyridyl nonaflates with different alkynes.

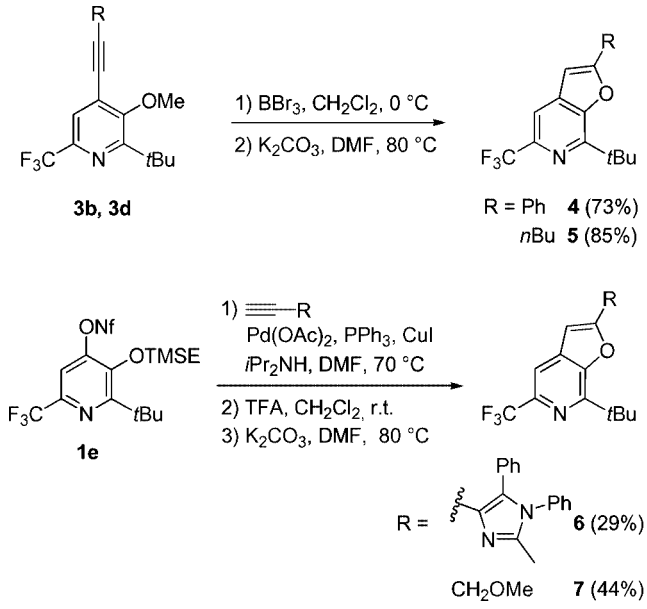


Precursor[a]	R^1	R^2	R^3	*t* [h]	*T* [°C]	**3**, % yield
1a	Me	Et	Ph	17	r.t.	**3a**, 72
1b	Me	*t*Bu	Ph	17	r.t.	**3b**, 72[1]
1c	Me	Ph	Ph	17	r.t.	**3c**, 75
1b	Me	*t*Bu	*n*Bu	7	70	**3d**, 61
1b	Me	*t*Bu	CMe_2OH	4	70	**3e**, 96
1d	Bn	*t*Bu	CH_2OMe	6	70	**3f**, 75
1d	Bn	*t*Bu	Ph	3	70	**3g**, 99
1e	TMSE	*t*Bu	Ph	3	70	**3h**, 78

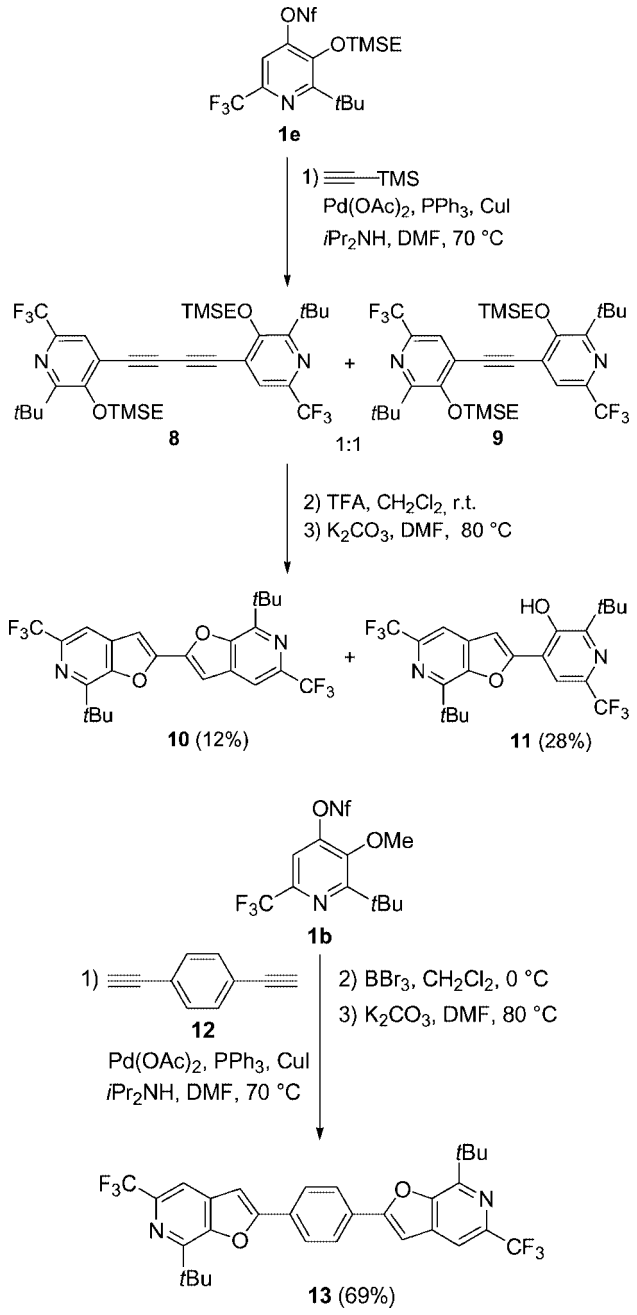
[a] Reaction conditions: 5–7 mol-% $Pd(OAc)_2$, 20–24 mol-% PPh_3, 5 mol-% CuI, 1.2 equiv. alkyne.

(Table 1). We initially performed the coupling at room temperature, but later shifted to 70 °C and shorter reaction times giving similar yields.

During an attempt to deprotect methoxy-substituted compound **3b** by subsequent treatment with boron tribromide and potassium carbonate we discovered the partial cyclization to furo[2,3-*c*]pyridine **4**. This transformation was optimized and hence starting with **3b** or **3d** products **4** or **5** were isolated in good yields (Scheme 2). Two other furo-pyridines **6** and **7** were obtained in a similar fashion.[5,6] In the first step 2-(trimethylsilyl)ethoxy-substituted pyridine **1e** was coupled with methyl propargyl ether or with an imidazolyl-substituted alkyne. The deprotection of the TMSE group succeeded under milder conditions (trifluoroacetic acid) and subsequent heating with potassium carbonate delivered products **6** and **7** in moderate overall yields. Remarkably, the imidazolyl-substituted alkyne introduced for the preparation of **6** also derives from a multicomponent reaction with lithiated alkoxyallenes as crucial building block.[7] Thus, product **6** contains two C_3 subunits arising from alkoxyallenes.[8]



Scheme 2. Conversion of 3-alkoxy-4-alkynylpyridines to furo[2,3-*c*]-pyridines.



Scheme 3. Sonogashira reactions of 4-pyridyl nonaflates with TMS acetylene and 1,4-diethynylbenzene.

The coupling of pyridyl nonaflate **1e** with (trimethylsilyl)-acetylene provided a mixture of bisalkyne **8** and dipyridyl-substituted alkyne **9**, which was directly converted into bis(furo-pyridine) derivative **10** (12%) and furo-pyridine derivative **11** (28%) (Scheme 3).[9] The related compound **13** with an inserted central benzene ring was rapidly prepared starting from nonaflate **1b** and 1,4-diethynylbenzene **12**. Here, boron tribromide has to be employed for deprotection of the methoxy groups. The X-ray analysis of bis(furo[2,3-*c*]-pyridyl)benzene derivative **13** proves the constitution and shows an *anti*-arrangement of the two furo-pyridine rings (Figure 1).[10]

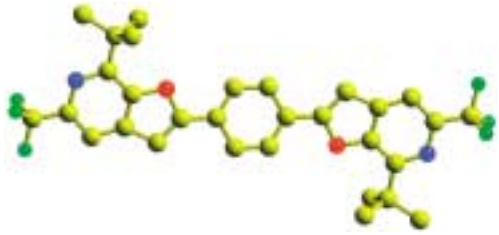
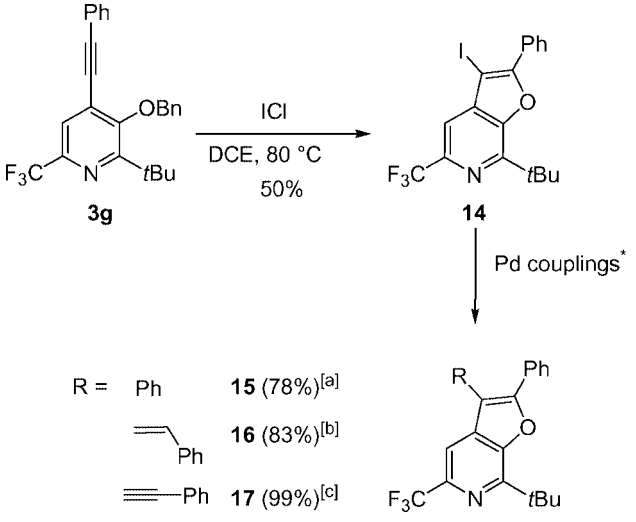


Figure 1. X-ray crystal structure of compound **13** (red: O, green: F, blue: N, yellow: C).

New options to extend the synthesized heterocyclic π-systems are offered by an alternative method for furan formation. Heating of benzyloxy-substituted pyridine derivative **3g** with iodine monochloride[11] at 80 °C furnished iodo-substituted furo-pyridine **14** in 50% yield (23% of **3g** were recovered). This compound was engaged in palladium-catalyzed reactions which provided the phenyl-, styryl-, and 2-phenylethynyl-substituted products **15**, **16**, and **17** in good to excellent yields (Scheme 4).

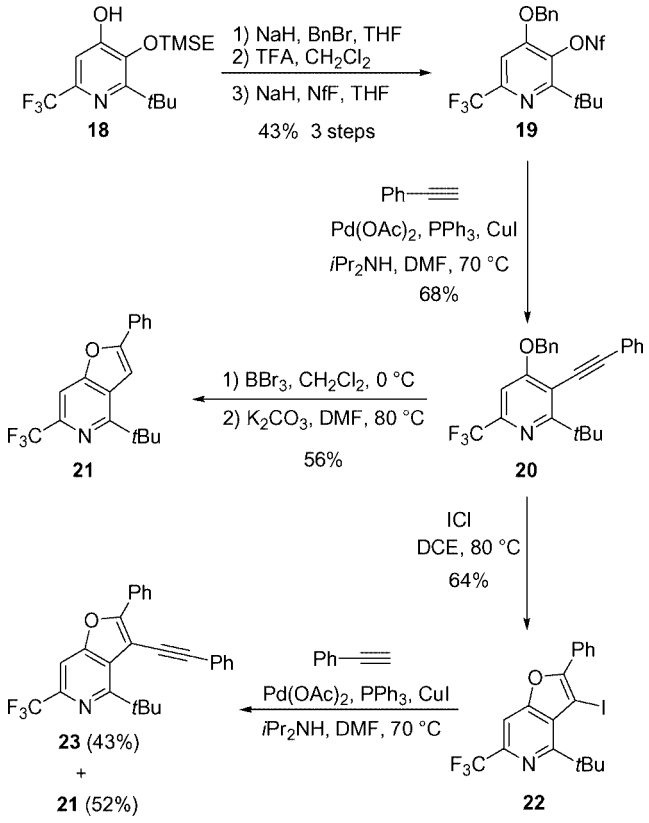


Scheme 4. ICl-promoted cyclization of 4-alkynyl-3-(benzyloxy)pyridine **3g** to iodo-substituted furo-pyridine derivative **14**; *Reaction conditions: a) $Pd(OAc)_2$, PPh_3, K_2CO_3, $PhB(OH)_2$, DMF, 70 °C, 4 h; b) $Pd(OAc)_2$, LiCl, styrene, Et_3N, DMF 70 °C, 5 h; c) $Pd(OAc)_2$, PPh_3, CuI, phenylacetylene, DMF, Et_3N, 70 °C, 3 h.

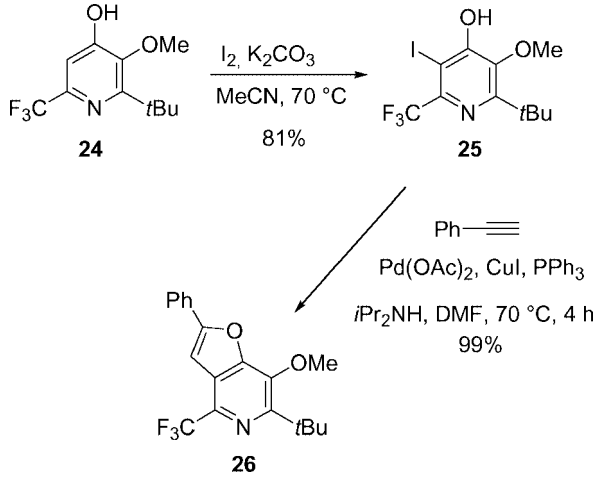
Starting from TMSE-substituted pyridinol derivatives such as **18** we could also easily approach regioisomeric furo[3,2-*c*]pyridines. *O*-Benzylation, deprotection of the TMSE group and nonaflation under standard conditions afforded 3-pyridyl nonaflate **19** in 43% overall yield (Scheme 5). Coupling with phenylacetylene to **20** and cyclization provided the desired furo[3,2-*c*]pyridine **21**. Alternatively, cyclization in the presence of iodine monochloride gave the iodinated heterocycle **22** in 64% yield (28% of **20** were recovered). Palladium-catalyzed reaction with phenylacetylene furnished alkyne **23** in 43% yield and as major component the deiodinated compound **21** (52%). Apparently, the coupling is fairly hindered in **22** due to the bulky *tert*-butyl group.

Additional options are offered by iodination of compounds such as **24** (Scheme 6), which provides the penta-substituted pyridine derivative **25** in very good yield. During Sonogashira reaction of **25** with phenylacetylene a spontaneous cyclization provided furo[2,3-*c*]pyridine **26** almost quantitatively. Thus, three similar furo-pyridines **4**, **21**, and **26** differing in the ring annulation position could be prepared.

The furo-pyridines prepared absorb in the region of 270 to 315 nm (Table 2) and several of these compounds are highly fluorescent. As expected the Stokes shift strongly depends on the substitution pattern.



Scheme 5. Synthesis of different furo[3,2-*c*]pyridine derivatives.



Scheme 6. Preparation of 5-iodopyridine derivative **25** and subsequent cyclization to furo[2,3-*c*]pyridine **26**.

Table 2. Absorption and emission of furo-pyridines.

	λ_{abs} [nm]	λ_{em} [nm]	Stokes Shift [nm]
4	300	340	40
6	310	390	80
10	315	355	40
11	270	465	195
15	300	375	75
16	280	415	135
17	270	390	120
21	305	340	35
26	310	370	60

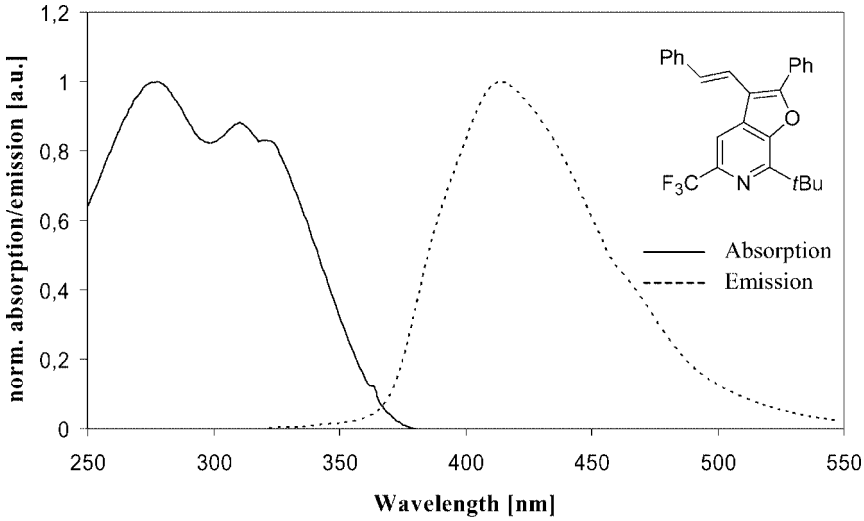


Figure 2. Absorption and emission spectra of compound **16**.

In Figure 2 we display the absorption and emission of stilbene-type compound **16** with a Stokes shift of 136 nm. The largest value was determined for compound **11** (195 nm).

Systematic investigations of the photophysical properties[12] of these furo-pyridines are required. Our highly modular synthesis of precursor pyridine derivatives by three-component cyclization followed by palladium-catalyzed reactions will be very helpful for this endeavour. Heterocycles fused to pyridine derivatives are also of interest in medicinal chemistry.[13] It should be emphasized that trifluoromethyl and *tert*-butyl groups, which are present at C-6 and C-2 position of most of our pyridine derivatives presented here, are no prerequisite as demonstrated in our reports describing the preparation of starting materials **1**.[1,2]

Conclusions

Our new approach to highly functionalized 4-pyridinol derivatives allows a highly flexible entry to alkynyl-substituted pyridine derivatives and to furo-pyridines. The key steps are efficient Sonogashira reactions of the corresponding pyridyl nonaflates and subsequent cyclizations to generate the furan ring. Of particular value is the fact that three different types of furo-pyridines can be prepared. Several of these compounds display interesting photophysical properties which require further investigations.

Experimental Section

General Methods: Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were added by syringes. Solvents were dried using standard procedures. Reagents were purchased and were used as received without further purification unless otherwise stated. Unless otherwise stated, products were purified by flash chromatography on silica gel (230–400 mesh, Merck or Fluka) or HPLC (Nucleosil 50–5). Unless otherwise stated, yields refer to analytical pure samples. NMR spectra were recorded on Bruker (AC 500) and JOEL (Eclipse 500) instruments. Chemical shifts are reported relative to TMS (^{1}H: δ = 0.00 ppm), $CDCl_3$ (^{13}C: δ = 77.0 ppm), or CD_3OD (^{1}H: δ = 3.31 ppm, ^{13}C: δ = 49.0 ppm). Integrals are in accordance with assignments; coupling constants are given in Hz. All ^{13}C-NMR spectra were proton-decoupled. For detailed peak assignments 2D spectra were measured (COSY, HMBC and HMQC). IR spectra were measured with an FT-IRD spectrometer Nicolet 5 SXC. UV/Vis spectra were measured with a UV/Vis spectrophotometer Scinco S-3150 PDA. Fluorescence spectra were measured with a spectrofluorometer Jasco FP-6500. For both techniques a concentration of 10^{-6} M in degassed CH_3CN (1 cm cuvette) at 25 °C was used. MS and HRMS analyses were performed with Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT CH7A (EI, 80 eV, 3 kV), CH5DF (FAB, 3 kV), Varian Ionspec QFT-7 (ESI-FT ICRMS) and Agilent 6210 (ESI-TOF) instruments. Elemental analyses were carried out with CHN-Analyzer 2400 (Perkin–Elmer). Melting points were measured with a Reichert apparatus Thermovar and are uncorrected. Single-crystal X-ray data were collected on a Bruker-XPS diffractometer (CCD area detector, Mo-K_α radiation, λ = 0.71073 Å, graphite monochromator), empirical absorption correction using symmetry-equivalent reflections (SADABS), structure solution and refinement by SHELXS-97 and SHELXL-97 in the WINGX System.[14,15] The hydrogen atoms were located by difference Fourier syntheses.

Typical Procedure for Sonogashira Coupling Reactions (Method A): A mixture of pyridyl nonaflate **1d** (295 mg, 0.49 mmol), $Pd(OAc)_2$ (8 mg, 0.03 mmol), PPh_3 (25 mg, 0.10 mmol), CuI (5 mg, 0.03 mmol), phenylacetylene (57 mg, 0.56 mmol) in DMF (2.0 mL) and diisopropylamine (1.0 mL) was heated to 70 °C for 3 h under an argon atmosphere. The mixture was cooled to room temperature, diluted with brine (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 40:1) to give 199 mg (99%) of **3-(benzyloxy)-2-*tert*-butyl-4-(phenylethynyl)-6-(trifluoromethyl)pyridine** (**3g**) as a colourless solid; m.p. 54–59 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 5.46 (s, 2 H, OCH_2), 7.28–7.55 (m, 10 H, Ph), 7.66 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 29.2, 38.6 [q, s, $C(CH_3)_3$], 75.0 (t, OCH_2), 83.7, 99.6 (2 s, C≡C), 121.6 (q, $^1J_{CF}$ = 273 Hz, CF_3), 121.8, 124.9 (2 s, C-4, *i*-Ph), 122.8 (dq, $^3J_{CF}$ = 2.8 Hz, C-5), 124.9, 127.4, 128.1, 128.6, 129.4, 131.7 (6 d, Ph), 140.3 (q, $^2J_{CF}$ = 35 Hz, C-6), 136.8,

156.9, 162.5 (3 s, C-2, C-3, *i*-Ph) ppm. IR (KBr): $\tilde{\nu}$ = 3090–3030 (=C–H), 2960–2870 (C–H), 2230–2205 (C≡C), 1600–1585 (C=C) cm^{-1}. MS (EI, 80 eV, 70 °C): *m*/*z* (%) = 409 (12) $[M]^+$, 394 (14) $[M - CH_3]^+$, 318 (2) $[M - C_7H_7]^+$, 91 (100) $[C_7H_7]^+$, 65 (4) $[C_6H_5]^+$. HRMS calcd. for $C_{25}H_{22}F_3NO$: 409.16535; found 409.16488.

2-Ethyl-3-methoxy-4-(phenylethynyl)-6-(trifluoromethyl)pyridine (3a): According to method A, pyridyl nonaflate **1a** (100 mg, 0.198 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), PPh_3 (10.2 mg, 0.039 mmol), CuI (1.9 mg, 0.01 mmol), phenylacetylene (30 mg, 0.29 mmol) in DMF (0.70 mL) and diisopropylamine (0.35 mL) provided the crude product. Column chromatography on silica gel (hexane/ethyl acetate, 40:1) afforded 43 mg (72%) of **3a** as a light yellow solid; m.p. 66–68 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.29, 2.91 (t, q, *J* = 7.5 Hz, 3 H, 2 H, Et), 4.14 (s, 3 H, OMe), 7.38–7.55 (m, 5 H, Ph), 7.59 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 12.8, 26.1 (q, t, Et), 61.2 (q, OMe), 83.2, 99.0 (2 s, C≡C), 121.5 (q, $^1J_{CF}$ = 274 Hz, CF_3), 121.9 (dq, $^3J_{CF}$ = 2.8 Hz, C-5), 122.4, 123.6, 128.7, 129.6, 131.7 (2 s, 3 d, C-4, Ph), 141.9 (q, $^2J_{CF}$ = 35.6 Hz, C-6), 156.2, 158.9 (2 s, C-2, C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3000–2870 (=C–H, C–H), 2220 (C≡C), 1600–1540 (C=C) cm^{-1}. MS (EI, 80 eV, 70 °C): *m*/*z* (%) = 305 (100) $[M]^+$, 276 (32) $[M - C_2H_5]^+$. $C_{17}H_{14}F_3NO$ (305.3): calcd. C 66.88, H 4.62, N 4.59; found C 66.72, H 4.39, N 4.40.

2-Phenyl-3-methoxy-4-(phenylethynyl)-6-(trifluoromethyl)pyridine (3c): According to method A, pyridyl nonaflate **1c** (100 mg, 0.181 mmol), $Pd(OAc)_2$ (2.0 mg, 0.009 mmol), PPh_3 (9.4 mg, 0.036 mmol), CuI (1.7 mg, 0.009 mmol), phenylacetylene (23 mg, 0.23 mmol) in DMF (0.8 mL) and diisopropylamine (0.4 mL) provided the crude product. Column chromatography on silica gel (hexane/ethyl acetate, 40:1) afforded 48 mg (75%) of **3c** as a colourless solid; m.p. 122 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.91 (s, 3 H, OMe), 7.39–7.50 (m, 6 H, Ph), 7.72 (s, 1 H, 5-H), 7.61–8.01 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 61.2 (q, OMe), 83.2, 99.0 (2 s, C≡C), 121.8 (dq, $^3J_{CF}$ = 2.9 Hz, C-5), 123.3 (q, $^1J_{CF}$ = 275 Hz, CF_3), 126.1, 128.4, 128.7, 129.4, 129.5, 129.7, 131.9, 136.2, 138.6 (2 s, 6 d, s, C-4, Ph), 142.6 (q, $^2J_{CF}$ = 35.5 Hz, C-6), 152.8, 156.5 (2 s, C-2, C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3000–2940 (=C–H, C–H), 2220 (C≡C), 1600–1580 (C=C) cm^{-1}. MS (EI, 80 eV, 80 °C): *m*/*z* (%) = 353 (100) $[M]^+$, 352 (64) $[M - H]^+$. HRMS calcd. for $C_{21}H_{14}F_3NO$: 353.10275; found 353.10377.

2-*tert*-Butyl-4-(hex-1-ynyl)-3-methoxy-6-(trifluoromethyl)pyridine (3d): According to method A, pyridyl nonaflate **1b** (100 mg, 0.188 mmol), $Pd(OAc)_2$ (2.5 mg, 0.013 mmol), PPh_3 (10 mg, 0.037 mmol), CuI (1.8 mg, 0.009 mmol), 1-hexyne (46 mg, 0.56 mmol) in DMF (0.8 mL) and diisopropylamine (0.4 mL) provided the crude product. Column chromatography on silica gel (hexane/ethyl acetate, 40:1) afforded 36 mg (61%) of **3d** as a light yellow oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, Me), 1.39 [s, 9 H, $C(CH_3)_3$], 1.43–1.53, 1.60–1.66 (2 m, 2 H each, CH_2), 2.49 (t, *J* = 7.5 Hz, 2 H, CH_2), 4.01 (s, 3 H, OMe), 7.47 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 13.6, 19.5, 22.1, 29.1 (q, 3 t, Bu), 30.4, 38.3 [q, s, $C(CH_3)_3$], 60.8 (q, OMe), 75.4, 101.5 (2 s, C≡C), 121.6 (q, $^1J_{CF}$ = 273.5 Hz, CF_3), 123.3 (dq, $^3J_{CF}$ = 2.9 Hz, C-5), 140.1 (q, $^2J_{CF}$ = 34.5 Hz, C-6), 125.3, 157.9, 162.4 (3 s, C-2, C-3, C-4) ppm. IR (KBr): $\tilde{\nu}$ = 2960–2870 (=C–H, C–H), 2230 (C≡C), 1590–1540 (C=C) cm^{-1}. MS (EI, 80 eV, 80 °C): *m*/*z* (%) = 313 (69) $[M]^+$, 298 (100) $[M - CH_3]^+$, 57 (17) $[C_4H_9]^+$. HRMS: calcd. for $C_{17}H_{22}F_3NO$: 313.16534; found 313.16488.

4-[2-*tert*-Butyl-3-methoxy-6-(trifluoromethyl)pyridin-4-yl]-2-methylbut-3-yn-2-ol (3e): According to method A, pyridyl nonaflate **1b** (1.63 g, 3.06 mmol), $Pd(OAc)_2$ (48 mg, 0.21 mmol), PPh_3 (159 mg, 0.61 mmol), CuI (29 mg, 0.15 mmol), 2-methylbut-3-yn-2-ol (309 mg, 3.67 mmol) in DMF (14 mL) and diisopropylamine (7 mL) provided the crude product. Column chromatography on silica gel (hexane/ethyl acetate, 10:1) afforded 924 mg (96%) of **3e** as a colourless solid; m.p. 56–58 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.37 [s, 9 H, $C(CH_3)_3$], 1.63 (s, 6 H, Me), 4.08 (s, 3 H, OMe), 7.48 (s, 1 H, 5-H) ppm; OH signal could not be detected. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 28.9, 38.3 [q, s, $C(CH_3)_3$], 31.0 (q, Me), 65.7 (s, C-2′), 60.9 (q, OMe), 76.7, 103.8 (2 s, C≡C), 121.4 (q, $^1J_{CF}$ = 274 Hz, CF_3), 122.9 (dq, $^3J_{CF}$ = 2.6 Hz, C-5), 140.1 (q, $^2J_{CF}$ = 35 Hz, C-6), 123.8, 157.8, 162.6 (3 s, C-2, C-3, C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3360 (O–H), 3080–3060 (=C–H), 2990–2865 (C–H), 2250–2225 (C≡C), 1600–1585 (C=C) cm^{-1}. $C_{16}H_{20}F_3NO_2$ (315.3): calcd. C 60.94, H 6.39, N 4.44; found C 60.93, H 6.43, N 4.46.

3-(Benzyloxy)-2-*tert*-butyl-4-(3-methoxyprop-1-ynyl)-6-(trifluoromethyl)pyridine (3f): According to method A, pyridyl nonaflate **1d** (412 mg, 0.68 mmol), $Pd(OAc)_2$ (8 mg, 0.04 mmol), PPh_3 (36 mg, 0.14 mmol), CuI (6 mg, 0.04 mmol), methyl propargyl ether (56 mg, 0.81 mmol) in DMF (3 mL) and diisopropylamine (1.5 mL) provided the crude product. Column chromatography on silica gel (hexane/ethyl acetate, 40:1) afforded 191 mg (75%) of **3f** as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.41 [s, 9 H, $C(CH_3)_3$], 3.35 (s, 3 H, OMe), 4.23, 5.37 (2 s, 2 H, 2 H, OCH_2), 7.33–7.53 (m, 5 H, Ph), 7.57 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 29.1, 38.5 [q, s, $C(CH_3)_3$], 58.0 (q, OMe), 60.2, 75.1 (2 t, OCH_2), 80.2, 95.9 (2 s, C≡C), 121.5 (q, $^1J_{CF}$ = 273 Hz, CF_3), 122.5 (s, C-4), 123.0 (dq, $^3J_{CF}$ = 2.8 Hz, C-5), 127.4, 128.2, 128.5 (3 d, Ph), 140.5 (q, $^2J_{CF}$ = 30 Hz, C-6), 136.6, 156.6, 162.9 (3 s, *i*-Ph, C-2, C-3) ppm. IR (film): $\tilde{\nu}$ = 3095–3030 (=C–H), 2960–2820 (C–H), 2235–2225 (C≡C), 1590–1540 (C=C) cm^{-1}. MS (EI, 80 eV, 80 °C): *m*/*z* (%) = 377 (1) $[M]^+$, 362 (1) $[M - CH_3]^+$, 346 (2) $[M - OCH_3]^+$, 91 (100) $[C_7H_7]^+$, 69 (21) $[CF_3]^+$, 57 (5) $[C_4H_9]^+$. HRMS calcd. for $C_{21}H_{22}F_3NO_2$: 377.16026; found 377.16144.

2-*tert*-Butyl-4-(phenylethynyl)-6-(trifluoromethyl)-3-[2-(trimethylsilyl)ethoxy]pyridine (3h): According to method A, pyridyl nonaflate **1e** (212 mg, 0.35 mmol), $Pd(OAc)_2$ (7 mg, 0.02 mmol), PPh_3 (18 mg, 0.07 mmol), CuI (4 mg, 0.02 mmol), phenylacetylene (42 mg, 0.42 mmol) in DMF (2.0 mL) and diisopropylamine (1.0 mL) provided the crude product. Column chromatography on silica gel (hexane/ethyl acetate, 40:1) afforded 115 mg (78%) of **3h** as a colourless solid; m.p. 61 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.02 (s, 9 H, TMS), 1.34 (t, *J* = 9.0 Hz, 2 H, CH_2), 1.44 [s, 9 H, $C(CH_3)_3$], 4.51 (t, *J* = 9.0 Hz, 2 H, OCH_2), 7.35–7.56 (m, 5 H, Ph), 7.60 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = –1.4 (q, TMS), 19.1 (t, CH_2), 29.2, 38.6 [q, s, $C(CH_3)_3$], 71.8 (t, OCH_2), 84.2, 98.5 (2 s, C≡C), 121.7 (q, $^1J_{CF}$ = 274 Hz, CF_3), 122.1, 124.3 (2 s, C-4, *i*-Ph), 122.8 (qd, $^3J_{CF}$ = 2.8 Hz, C-5), 128.6, 129.4, 131.6 (3 d, Ph), 139.8 (q, $^2J_{CF}$ = 37 Hz, C-6), 156.6, 162.6 (2 s, C-2, C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3090–3070 (=C–H), 3000–2870 (C–H), 2235–2210 (C≡C), 1600–1540 (C=C) cm^{-1}. MS (EI, 80 eV, 50 °C): *m*/*z* (%) = 419 (1) $[M]^+$, 404 (1) $[M - CH_3]^+$, 391 (32) $[M - C_2H_4]^+$, 101 (10) $[C_2H_4SiC_3H_9]^+$, 73 (100) $[C_3H_9Si]^+$, 69 (2) $[CF_3]^+$, 57 (6) $[C_4H_9]^+$. $C_{23}H_{28}F_3NOSi$ (419.6): calcd. C 65.84, H 6.73, N 3.34; found C 65.89, H 6.68, N 3.29.

Typical Procedure for the Preparation of Furo-pyridine Derivatives (Method B): To a solution of pyridine **3b** (200 mg, 0.60 mmol) in dichloromethane (6 mL) under argon atmosphere was added BBr_3 (1 M in CH_2Cl_2, 0.90 mL, 0.90 mmol) dropwise at 0 °C and warmed up to room temperature. The reaction mixture was monitored by TLC; upon completion, ice/water was added and the mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with water and brine, dried with Na_2SO_4 and

evaporated under reduced pressure. The residue was dissolved in DMF (5 mL) and K_2CO_3 (243 mg, 1.80 mmol) was added. After stirring at 80 °C for 12 h, the mixture was diluted with water (12 mL) and extracted with diethyl ether (3×10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. Column chromatography on silica gel (hexane/ethyl acetate, 10:1) afforded 139 mg (73%) of **7-*tert*-butyl-2-phenyl-5-(trifluoromethyl)furo[2,3-*c*]pyridine** (**4**) as a colourless solid; m.p. 88–89 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.61 [s, 9 H, $C(CH_3)_3$], 7.06 (s, 1 H, 3-H), 7.44–7.92 (m, 5 H, Ph), 7.77 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 29.0, 37.7 [q, s, $C(CH_3)_3$], 100.7 (d, C-3), 111.7 (dq, $^3J_{CF}$ = 2.7 Hz, C-4), 122.3 (q, $^1J_{CF}$ = 278 Hz, CF_3), 121.2, 125.7, 129.2, 130.1 (3 d, s, Ph), 140.2 (q, $^2J_{CF}$ = 34.4 Hz, C-5), 136.3, 150.4, 153.6, 159.0 (4s, C-2, C-3a, C-7, C-7a) ppm. IR (KBr): $\tilde{\nu}$ = 3120 (=C–H), 2970–2870 (C–H), 1600–1570 (C=C) cm^{-1}. MS (EI, 80 eV, 60 °C): *m*/*z* (%) = 319 (59) $[M]^+$, 304 (100) $[M - CH_3]^+$, 277 (64) $[M - C(CH_3)_2]^+$, 57 (9) $[C(CH_3)_3]^+$. HRMS: calcd. for $C_{18}H_{16}F_3NO$: 319.11841; found 319.11793.

2-Butyl-7-*tert*-butyl-5-(trifluoromethyl)furo[2,3-*c*]pyridine (5): According to method B, pyridine **3d** (156 mg, 0.50 mmol), BBr_3 (1 M in CH_2Cl_2, 0.75 mL, 0.75 mmol) in dichloromethane (4 mL) provided the crude product, which was treated with K_2CO_3 (203 mg, 1.50 mmol) in DMF (6 mL) at 80 °C for 12 h. Column chromatography on silica gel (hexane/ethyl acetate, 4:1) afforded 127 mg (85%) of **5** as a light yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.98 (t, *J* = 7.7 Hz, 3 H, Me), 1.55 [s, 9 H, $C(CH_3)_3$], 1.43–1.48, 1.75–1.82 (2 m, 2 H each, CH_2), 2.86 (t, *J* = 7.7 Hz, 2 H, CH_2), 6.47 (s, 1 H, 3-H), 7.68 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 13.7, 22.3, 28.3, 28.8 (q, 3 t, Bu), 29.6, 37.5 [q, s, $C(CH_3)_3$], 101.9 (d, C-3), 111.4 (dq, $^3J_{CF}$ = 2.6 Hz, C-4), 123.6 (q, $^1J_{CF}$ = 275 Hz, CF_3), 139.7 (q, $^2J_{CF}$ = 35.5 Hz, C-5), 136.3, 150.5, 152.9, 163.5 (4s, C-2, C-3a, C-7, C-7a) ppm. IR (film): $\tilde{\nu}$ = 3120 (=C–H), 2960–2870 (C–H), 1600–1590 (C=C) cm^{-1}. MS (EI, 80 eV, 30 °C): *m*/*z* (%) = 299 (37) $[M]^+$, 284 (100) $[M - CH_3]^+$, 257 (37) $[M - C(CH_3)_2]^+$, 57 (7) $[C(CH_3)_3]^+$. $C_{16}H_{20}F_3NO$ (299.3): calcd. C 64.20, H 6.73, N 4.68; found C 63.68, H 6.41, N 4.24.

Typical Procedure for the Preparation of Furo-pyridine Derivatives Starting from Pyridyl Nonaflates (Method C): A mixture of pyridyl nonaflate **1e** (365 mg, 0.59 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), PPh_3 (31 mg, 0.12 mmol), CuI (6 mg, 0.04 mmol), methyl propargyl ether (50 mg, 0.71 mmol) in DMF (2.6 mL) and diisopropylamine (1.3 mL) was heated to 70 °C for 3 h under an argon atmosphere. The mixture was cooled to room temperature, diluted with brine (10 mL) and extracted with diethyl ether (3×10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The crude product was dissolved in a 1:7 mixture of TFA and dichloromethane (4 mL). After stirring for 2 h at room temperature the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The resulting crude product was dissolved in DMF (2.7 mL) and K_2CO_3 (245 mg, 1.77 mmol) was added. After heating for 3 h at 80 °C, the mixture was quenched at room temperature with water (10 mL) and extracted with diethyl ether (3×10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. Column chromatography on silica gel (hexane/ethyl acetate, 10:1) afforded 75 mg (44%) of **7-*tert*-butyl-2-(methoxymethyl)-5-(trifluoromethyl)furo[2,3-*c*]pyridine** (**7**) as light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.53 [s, 9 H, $C(CH_3)_3$], 3.48 (s, 3 H, OMe), 4.63 (s, 2 H, OCH_2), 6.76 (s, 1 H, 3-H), 7.75 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 28.8, 37.5 [q, s, $C(CH_3)_3$], 58.8 (q, OMe), 67.0 (t, OCH_2), 104.8 (d, C-3), 112.0 (dq, $^3J_{CF}$ = 2.9 Hz, C-4), 122.3 (q, $^1J_{CF}$ = 273 Hz, CF_3), 135.3 (s, C-2), 140.0 (q, $^2J_{CF}$ = 34.4 Hz, C-5), 150.8, 153.8, 158.1 (3 s, C-3a, C-7, C-7a) ppm. IR (film): $\tilde{\nu}$ = 3120 (=C–H), 2975–2830 (C–H), 1610–1580 (C=C) cm^{-1}. MS (EI, 80 eV, 80 °C): *m*/*z* (%) = 287 (20) $[M]^+$, 272 (83) $[M - CH_3]^+$, 242 (9) $[M - C_2H_5O]^+$, 69 (10) $[CF_3]^+$, 57 (36) $[C_4H_9]^+$, 45 (45) $[C_2H_5O]^+$, 41 (100), 31 (6) $[OCH_3]^+$. HRMS calcd. for $C_{14}H_{16}F_3NO_2$: 287.11299; found 287.11331.

7-*tert*-Butyl-2-(2-methyl-1,5-diphenyl-1*H*-imidazol-4-yl)-5-(trifluoromethyl)furo[2,3-*c*]pyridine (6): According to method C, pyridyl nonaflate **1e** (311 mg, 0.504 mmol), $Pd(OAc)_2$ (8 mg, 0.035 mmol), PPh_3 (28 mg, 0.106 mmol), CuI (6 mg, 0.025 mmol), 4-ethynyl-2-methyl-1,5-diphenylimidazole (156 mg, 0.604 mmol) in DMF (2.4 mL) and diisopropylamine (1.2 mL), TFA/CH_2Cl_2 (4 mL, 1:7), K_2CO_3 (209 mg, 1.51 mmol) and DMF (3.0 mL) provided the crude product. Column chromatography on silica gel (hexane/ethyl acetate, 5:1) afforded 70 mg (29%) of **6** as a colourless solid; m.p. 241–243 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.14 [s, 9 H, $C(CH_3)_3$], 2.37 (s, 3 H, Me), 7.10 (s, 1 H, 3-H), 7.09–7.37 (m, 10 H, Ph), 7.72 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 14.1 (q, Me), 28.5, 37.0 [q, s, $C(CH_3)_3$], 100.9 (d, C-3), 111.4 (d, C-4), 122.3 (q, $^1J_{CF}$ = 275 Hz, CF_3), 139.7 (q, $^2J_{CF}$ = 34 Hz, C-5), 127.8, 128.1, 128.4, 128.5, 128.9, 129.4, 129.5, 130.9 (3 d, s, 3 d, s, Ph), 132.8, 135.8, 136.1 (3 s, C-3a, C-4′, C-5′), 146.6 (s, C-2′), 150.0, 153.1, 155.7 (3 s, C-2, C-7a, C-7) ppm. IR (KBr): $\tilde{\nu}$ = 3060–3010 (=C–H), 2985–2850 (C–H), 1635–1590 (C=C) cm^{-1}. HRMS: (ESI-TOF) calcd. for $C_{28}H_{25}F_3N_3O$ $[MH]^+$: 476.1965; found 476.1944. $C_{28}H_{24}F_3N_3O$ (475.5): calcd. C 70.72, H 5.09, N 8.84; found C 71.01, H 4.82, N 8.59.

7-*tert*-Butyl-2-{4-[7-*tert*-butyl-5-(trifluoromethyl)furo[2,3-*c*]pyridin-2-yl]phenyl}-5-(trifluoromethyl)furo[2,3-*c*]pyridine (13): According to method C, pyridyl nonaflate **1b** (120 mg, 0.226 mmol), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol), PPh_3 (11.8 mg, 0.045 mmol), CuI (1.9 mg, 0.01 mmol), 1,4-diethynylbenzene (**12**) (34 mg, 0.271 mmol) in DMF (1.0 mL) and diisopropylamine (0.50 mL), BBr_3 (1 M in CH_2Cl_2, 0.51 mL, 0.51 mmol) in dichloromethane (2 mL) provided the crude product, which was subjected with K_2CO_3 (135 mg, 1.00 mmol) in DMF (6 mL) at 80 °C for 12 h. Column chromatography on silica gel (hexane/ethyl acetate, 1:1) afforded 88 mg (69%) of **13** as a colourless solid; m.p. 302–304 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.63 [s, 18 H, $C(CH_3)_3$], 7.18 (s, 2 H, 3-H), 7.81 (s, 2 H, 4-H), 8.05 (s, 4 H, Ar) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 29.0, 37.7 [q, s, $C(CH_3)_3$], 101.8 (d, C-3), 111.9 (dq, $^3J_{CF}$ = 2.8 Hz, C-4), 122.3 (q, $^1J_{CF}$ = 243 Hz, CF_3), 126.3, 130.4 (d, s, Ar), 140.5 (q, $^2J_{CF}$ = 35 Hz, C-5), 136.3, 150.5, 153.9, 157.8 (4s, C-2, C-3a, C-7, C-7a) ppm. IR (KBr): $\tilde{\nu}$ = 3115 (=C–H), 2975–2870 (C–H), 1600–1585 (C=C) cm^{-1}. MS (EI, 80 eV, 60 °C): *m*/*z* (%) = 560 (100) $[M]^+$, 545 (80) $[M - CH_3]^+$, 541 (11) $[M - F]^+$, 503 (5) $[M - C(CH_3)_3]$, 57 (8) $[C(CH_3)_3]^+$. $C_{30}H_{26}F_6N_2O_2$ (560.5): calcd. C 64.28, H 4.68, N 5.00; found C 64.17, H 4.30, N 4.70.

7,7′-Di(*tert*-butyl)-5,5′-bis(trifluoromethyl)-2,2′-bifuro[2,3-*c*]pyridine (10) and 2-*tert*-Butyl-4-[7-*tert*-butyl-5-(trifluoromethyl)furo[2,3-*c*]pyridin-2-yl]-6-(trifluoromethyl)pyridin-3-ol (11): According to method C, pyridyl nonaflate **1e** (618 mg, 1.00 mmol), $Pd(OAc)_2$ (16 mg, 0.07 mmol), PPh_3 (60 mg, 0.23 mmol), CuI (10 mg, 0.05 mmol), trimethylsilylacetylene (118 mg, 1.20 mmol) in DMF (4.6 mL) and diisopropylamine (2.3 mL) provided the crude 1:1 mixture of **8** and **9** which was not separated. TFA/CH_2Cl_2 (4 mL, 1:7), K_2CO_3 (829 mg, 6.00 mmol) and DMF (5 mL) provided the crude product. Column chromatography on silica gel (hexane/ethyl acetate, 20:1→10:1) afforded 30 mg (12%) of **10** as a colourless solid and 65 mg (28%) of **11** as a light yellow solid.

Data for 10: M.p. 210–214 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.61 [s, 18 H, $C(CH_3)_3$], 7.36 (s, 2 H, 3-H), 7.85 (s, 2 H, 4-H) ppm.

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 28.8, 37.8 [q, s, $C(CH_3)_3$], 104.9 (d, C-3), 112.3 (dq, $^3J_{CF}$ = 2.4 Hz, C-4), 122.0 (q, $^1J_{CF}$ = 273 Hz, CF_3), 135.2 (s, C-2), 140.9 (q, $^2J_{CF}$ = 34.5 Hz, C-5), 148.9, 150.8, 154.5 (3 s, C-7, C-7a, C-3a) ppm. ^{19}F NMR ($CDCl_3$, 470 MHz): δ = –66.7 (s, CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 2980–2845 (=C–H, C–H), 1740–1580 (C=C) cm^{-1}. HRMS: (ESI-TOF) calcd. for $C_{24}H_{23}F_6N_2O_2$ $[MH]^+$: 485.1658; found 485.1635.

Data for 11: M.p. 126–129 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.53, 1.61 [2 s, 9 H each, $C(CH_3)_3$], 7.35 (br. s, 1 H, OH), 7.42 (s, 1 H, 3-H), 7.84 (s, 1 H, 4′-H), 7.86 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 28.5, 29.1, 37.7, 38.4 [2q, 2 s, $C(CH_3)_3$], 106.6 (d, C-3), 112.3, 116.4 (2 dq, both $^3J_{CF}$ = 2.8 Hz each, C-4), 121.7 (s, C-4′), 121.6, 122.0 (2q, $^1J_{CF}$ = 273, $^1J_{CF}$ = 274 Hz, CF_3), 135.2 (s, C-2), 138.8, 141.2 (2q, $^2J_{CF}$ = 34.6, $^2J_{CF}$ = 35.5 Hz, C-5, C-6′), 149.5, 149.9, 154.0, 154.1, 158.4 (5s, C-2′, C-7, C-4′, C-7a, C-3′) ppm. ^{19}F NMR ($CDCl_3$, 470 MHz): δ = –67.2, –66.7 (2 s, CF_3) ppm. IR (KBr): $\tilde{\nu}$ = 3615, 3530 (O–H, N–H), 2970–2850 (=C–H, C–H), 1725–1580 (C=C) cm^{-1}. HRMS: (ESI-TOF) calcd. for $C_{22}H_{23}F_6N_2O_2$ $[MH]^+$: 461.1658; found 461.1670.

7-*tert*-Butyl-3-iodo-2-phenyl-5-(trifluoromethyl)furo[2,3-*c*]pyridine (14): To a solution of pyridine **3g** (150 mg, 0.367 mmol) in 1,2-dichloroethane (2 mL) was added dropwise ICl (1.10 mL, 1 M in CH_2Cl_2, 1.10 mmol). After heating to 80 °C in a sealed tube for 1 d the reaction mixture was diluted with satd. aq. $Na_2S_2O_5$ solution (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 40:1) to give 82 mg (50%) of **14** as a colourless solid and 35 mg (23%) of **3g**; m.p. 176 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.58 [s, 9 H, $C(CH_3)_3$], 7.49–8.21 (m, 5 H, Ph), 7.64 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 28.9, 37.5 [q, s, $C(CH_3)_3$], 59.6 (s, C-3), 112.7 (dq, $^3J_{CF}$ = 2.7 Hz, C-4), 122.1 (q, $^1J_{CF}$ = 274 Hz, CF_3), 127.9, 128.8, 128.9, 130.5 (3 d, s, Ph), 140.0 (q, $^2J_{CF}$ = 30 Hz, C-5), 140.1, 150.0, 153.9, 155.9 (4s, C-2, C-3a, C-7, C-7a) ppm. IR (KBr): $\tilde{\nu}$ = 3060–3050 (=C–H), 2990–2865 (C–H), 1605–1530 (C=C) cm^{-1}. MS (EI, 80 eV, 100 °C): *m*/*z* (%) = 445 (100) $[M]^+$, 430 (97) $[M - CH_3]^+$, 318 (2) $[M - I]^+$, 126 (5) $[I]^+$, 77 (5) $[C_6H_5]^+$, 69 (11) $[CF_3]^+$, 57 (11) $[C_4H_9]^+$. HRMS: calcd. for $C_{18}H_{15}F_3INO$: 445.01505; found 445.01622. $C_{18}H_{15}F_3INO$ (445.2): calcd. C 48.56, H 3.40, N 3.15; found C 48.87, H 3.46, N 3.10.

7-*tert*-Butyl-2,3-diphenyl-5-(trifluoromethyl)furo[2,3-*c*]pyridine (15): A mixture of furo-pyridine **14** (35 mg, 0.078 mmol), $Pd(OAc)_2$ (1 mg, 0.005 mmol), PPh_3 (5 mg, 0.02 mmol), K_2CO_3 (11 mg, 0.078 mmol) and phenylboronic acid (11 mg, 0.094 mmol) in DMF (0.36 mL) was heated to 70 °C for 4 h under an argon atmosphere. The mixture was cooled to room temperature, diluted with brine (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 40:1) to give 24 mg (78%) of **15** as a colourless solid; m.p. 194 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.64 [s, 9 H, $C(CH_3)_3$], 7.35–7.71 (m, 10 H, Ph), 7.66 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 29.0, 37.6 [q, s, $C(CH_3)_3$], 110.8 (dq, $^3J_{CF}$ = 2.6 Hz, C-4), 117.1 (s, C-3), 122.2 (q, $^1J_{CF}$ = 274 Hz, CF_3), 127.4, 128.4, 128.7, 129.36, 129.43, 129.5, 129.7, 131.2 (6 d, 2 s, Ph), 140.6 (q, $^2J_{CF}$ = 34 Hz, C-5), 137.3, 153.5, 153.7, 156.4 (4s, C-7a, C-7, C-3a, C-2) ppm. IR (KBr): $\tilde{\nu}$ = 3115–3030 (=C–H), 2990–2850 (C–H), 1750–1690 (C=C) cm^{-1}. MS (EI, 80 eV, 120 °C): *m*/*z* (%) = 395 (32) $[M]^+$, 380 (78) $[M - CH_3]^+$, 77 (36) $[C_6H_5]^+$, 69 (18) $[CF_3]^+$, 57 (41) $[C_4H_9]^+$, 41 (100). HRMS calcd. for $C_{24}H_{20}F_3NO$: 395.14969; found 395.14922.

7-*tert*-Butyl-2-phenyl-3-(2-phenylethenyl)-5-(trifluoromethyl)-furo[2,3-*c*]pyridine (16): A mixture of furo-pyridine **14** (43 mg, 0.097 mmol), $Pd(OAc)_2$ (1.5 mg, 0.006 mmol), LiCl (20 mg, 0.485 mmol) and styrene (61 mg, 0.582 mmol) in DMF (0.44 mL) and Et_3N (0.22 mL) was heated to 70 °C for 5 h under an argon atmosphere. The mixture was cooled to room temperature and diluted with brine (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 40:1) to give 34 mg (83%) of **16** as a colourless solid; m.p. 123 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.62 [s, 9 H, $C(CH_3)_3$], 7.26, 7.31 (2 d, *J* = 16.6 Hz, 1 H each, HC=CH), 7.29–7.89 (m, 10 H, Ph), 8.08 (s, 1 H, 4-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 28.6, 37.6 [q, s, $C(CH_3)_3$], 111.5 (dq, $^3J_{CF}$ = 3 Hz, C-4), 114.1 (s, C-3), 118.1 (d, HC=), 122.3 (q, $^1J_{CF}$ = 274 Hz, CF_3), 126.5, 128.1, 128.2, 128.9, 129.1, 129.7, 129.9, 135.1 (6 d, 2 s, Ph), 132.9 (d, HC=), 140.3 (q, $^2J_{CF}$ = 34 Hz, C-5), 137.0, 149.9, 154.0, 155.4 (4s, C-7, C-7a, C-3a, C-2) ppm. IR (KBr): $\tilde{\nu}$ = 3110–3025 (=C–H), 2990–2865 (C–H), 1650–1600 (C=C) cm^{-1}. MS (EI, 80 eV, 50 °C): *m*/*z* (%) = 421 (100) $[M]^+$, 406 (53) $[M - CH_3]^+$, 77 (2) $[C_6H_5]^+$, 69 (1) $[CF_3]^+$. HRMS calcd. for $C_{26}H_{22}F_3NO$: 421.16534; found 421.16501.

7-*tert*-Butyl-2-phenyl-3-(phenylethynyl)-5-(trifluoromethyl)furo[2,3-*c*]-pyridine (17): A mixture of furo-pyridine **14** (30 mg, 0.067 mmol), $Pd(OAc)_2$ (1 mg, 0.005 mmol), PPh_3 (5 mg, 0.02 mmol), CuI (1 mg, 0.005 mmol) and phenylacetylene (8 mg, 0.08 mmol) in DMF (0.3 mL) and diisopropylamine (0.15 mL) was heated to 70 °C for 3 h under an argon atmosphere. The mixture was cooled to room temperature, diluted with brine (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 40:1) to give 28 mg (99%) of **17** as a colourless solid; m.p. 112 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.62 [s, 9 H, $C(CH_3)_3$], 7.40–7.65 (m, 8 H, Ph), 7.92 (s, 1 H, 4-H), 8.31–8.37 (m, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 28.9, 37.9 [q, s, $C(CH_3)_3$], 79.2, 97.9 (2 s, C≡C), 99.2 (s, C-3), 111.3 (dq, $^3J_{CF}$ = 3 Hz, C-4), 121.1 (q, $^1J_{CF}$ = 273 Hz, CF_3), 122.6, 126.6, 128.6, 128.9, 129.0, 130.6, 131.7, 133.5 (s, 6 d, s, Ph), 140.8 (q, $^2J_{CF}$ = 36 Hz, C-5), 137.4, 149.1, 153.8, 158.6 (4s, C-7, C-7a, C-3a, C-2) ppm. IR (KBr): $\tilde{\nu}$ = 3090–3030 (=C–H), 3000–2870 (C–H), 1610–1560 (C=C) cm^{-1}. $C_{26}H_{20}F_3NO$ (419.4): calcd. C 74.45, H 4.81, N 3.34; found C 74.35, H 4.59, N 3.25.

4-(Benzyloxy)-2-*tert*-butyl-6-(trifluoromethyl)pyridin-3-yl-1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate (19): To a solution of pyridinol **18** (2.53 g, 7.53 mmol) in THF (15 mL) were added NaH (904 mg, 60% in mineral oil, 22.6 mmol) and benzyl bromide (2.69 mL, 22.6 mmol) at room temperature and stirred for 3 d. The mixture was slowly diluted with water (15 mL) and extracted with diethyl ether (3 × 15 mL), dried with Na_2SO_4 and concentrated to dryness. The residue was diluted in dichloromethane (10 mL) and TFA (5 mL) was added. The reaction mixture was stirred at room temperature for 8 h and quenched with water (20 mL), extracted with dichloromethane (3 × 20 mL), dried with Na_2SO_4 and concentrated to dryness. The crude product was dissolved in THF (15 mL) and NaH (904 mg, 60% in mineral oil, 22.6 mmol) was added. After dropwise addition of nonafluorobutanesulfonyl fluoride (4.07 mL, 22.6 mmol) the mixture was stirred at room temperature for 3 d and quenched by slow addition of water (20 mL). It was extracted with ethyl acetate (3 × 20 mL), dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 40:1) to afford 1.97 g (43%) of **19** as a colourless solid; m.p. 90–92 °C. ^{1}H NMR

($CDCl_3$, 500 MHz): δ = 1.48 [s, 9 H, $C(CH_3)_3$], 5.24 (s, 2 H, OCH_2), 7.21 (s, 1 H, 5-H), 7.35–7.41 (m, 5 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 29.4, 38.7 [q, s, $C(CH_3)_3$], 72.2 (t, OCH_2), 105.1 (dq, $^3J_{CF}$ = 3 Hz, C-5), 120.7 (q, $^1J_{CF}$ = 275 Hz, CF_3), 128.1, 128.9, 129.1, 133.6 (3 d, s Ph), 146.2 (q, $^2J_{CF}$ = 35 Hz, C-6), 136.1, 157.5, 163.0 (3 s, C-2, C-3, C-4) ppm. ^{19}F NMR ($CDCl_3$, 470 MHz): δ = –68.2 (s, CF_3), –80.6 (m, 4′-F), –105.4 (m, 3′-F), –120.7 (m, 2′-F), –125.6 (m, 1′-F) ppm. IR (KBr): $\tilde{\nu}$ = 3105–3025 (=C–H), 3010–2850 (C–H), 1605–1560 (C=C) cm^{-1}. $C_{21}H_{17}F_{12}NO_4S$ (607.4): calcd. C 41.52, H 2.82, N 2.31, S 5.28; found C 41.49, H 2.52, N 2.31, S 5.04.

4-(Benzyloxy)-2-*tert*-butyl-3-(phenylethynyl)-6-(trifluoromethyl)pyridine (20): According to method A, pyridyl nonaflate **19** (278 mg, 0.458 mmol), $Pd(OAc)_2$ (7 mg, 0.032 mmol), PPh_3 (24 mg, 0.092 mmol), CuI (4 mg, 0.023 mmol), phenylacetylene (55 mg, 0.550 mmol) in DMF (2.2 mL) and diisopropylamine (1.1 mL) provided the crude product. Column chromatography on silica gel (hexane/ethyl acetate, 40:1) afforded 127 mg (68%) of **20** as a colourless solid; m.p. 120 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.62 [s, 9 H, $C(CH_3)_3$], 5.24 (s, 2 H, OCH_2), 7.14 (s, 1 H, 5-H), 7.37–7.56 (m, 10 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 29.0, 39.7 [q, s, $C(CH_3)_3$], 70.6 (t, OCH_2), 83.2, 104.2 (2 s, C≡C), 101.7 (dq, $^3J_{CF}$ = 3 Hz, C-5), 121.4 (q, $^1J_{CF}$ = 274 Hz, CF_3), 145.7 (q, $^2J_{CF}$ = 34 Hz, C-6), 123.3, 127.0, 128.2, 128.5, 128.7, 128.8, 131.1, 135.4 (s, 6 d, s, Ph), 110.1, 166.9, 171.2 (3 s, C-2, C-3, C-4) ppm. IR (KBr): $\tilde{\nu}$ = 3080–3010 (=C–H), 2985–2860 (C–H), 2210–2200 (C≡C), 1600–1545 (C=C) cm^{-1}. MS (EI, 80 eV, 150 °C): *m*/*z* (%) = 409 (19) $[M]^+$, 394 (6) $[M - CH_3]^+$, 318 (8) $[M - C_7H_7]^+$, 91 (100) $[C_7H_7]^+$, 69 (3) $[CF_3]^+$, 57 (8) $[C_4H_9]^+$. $C_{25}H_{22}F_3NO$ (409.4): calcd. C 73.34, H 5.42, N 3.42; found C 73.01, H 5.17, N 3.37.

4-*tert*-Butyl-2-phenyl-6-(trifluoromethyl)furo[3,2-*c*]pyridine (21): According to method B, pyridine **20** (120 mg, 0.29 mmol), BBr_3 (1 M in CH_2Cl_2, 0.88 mL, 0.88 mmol) in dichloromethane (3 mL) provided the crude product, which was treated with K_2CO_3 (122 mg, 0.88 mmol) in DMF (5 mL) at 80 °C for 12 h. Column chromatography on silica gel (hexane/ethyl acetate, 10:1) afforded 52 mg (56%) of **21** as a colourless solid; m.p. 94–95 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.54 [s, 9 H, $C(CH_3)_3$], 7.27 (s, 1 H, 3-H), 7.41–7.90 (m, 5 H, Ph), 7.70 (s, 1 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 29.8, 39.2 [q, s, $C(CH_3)_3$], 100.8 (d, C-3), 102.7 (dq, $^3J_{CF}$ = 3.3 Hz, C-7), 122.2 (q, $^1J_{CF}$ = 273 Hz, CF_3), 124.8 125.4, 129.0, 129.1, 129.7 (s, 3 d, s, C-3a, Ph), 141.3 (q, $^2J_{CF}$ = 34.8 Hz, C-6), 157.3, 159.8, 163.8 (3 s, C-2, C-4, C-7a) ppm. IR (KBr): $\tilde{\nu}$ = 3090–3040 (=C–H), 2990–2850 (C–H), 1605–1560 (C=C) cm^{-1}. MS (EI, 80 eV, 70 °C): *m*/*z* (%) = 319 (55) $[M]^+$, 304 (100) $[M - CH_3]^+$, 284 (24) $[M - CH_3 - HF]^+$, 77 (4) $[C_6H_5]^+$. HRMS calcd. for $C_{18}H_{16}F_3NO$: 319.11840; found 319.11808.

4-*tert*-Butyl-3-iodo-2-phenyl-6-(trifluoromethyl)furo[3,2-*c*]pyridine (22): To a solution of pyridine **20** (230 mg, 0.562 mmol) in 1,2-dichloroethane (2 mL) was added dropwise ICl (1.68 mL, 1 M in CH_2Cl_2, 1.68 mmol). After heating to 80 °C in a sealed tube for 1 d the reaction mixture was diluted with satd. aq. $Na_2S_2O_5$ solution (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 40:1) to give 159 mg (64%) of **22** as a colourless solid and 64 mg (28%) of **20**; m.p. 108–110 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.71 [s, 9 H, $C(CH_3)_3$], 7.50–7.94 (m, 5 H, Ph), 7.72 (s, 1 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 32.0, 39.6 [q, s, $C(CH_3)_3$], 59.0 (s, C-3), 103.3 (dq, $^3J_{CF}$ = 2.9 Hz, C-7), 106.4 (s, C-3a), 122.9 (q, $^1J_{CF}$ = 273 Hz, CF_3), 127.2, 128.4, 129.8, 130.3 (3 d, s, Ph), 140.8 (q, $^2J_{CF}$ = 35 Hz, C-6), 158.1, 160.4, 164.6 (3 s, C-2, C-4, C-7a) ppm. IR (KBr): $\tilde{\nu}$ = 3090–3060 (=C–H), 3005–2865 (C–H), 1605–1545 (C=C) cm^{-1}. MS (EI, 80 eV, 70 °C): *m*/*z* (%) = 445 (90) $[M]^+$, 430 (100) $[M - CH_3]^+$, 426 (7) $[M - F]^+$, 318 (19) $[M - I]^+$, 77 (22) $[C_6H_5]^+$, 69 (12) $[CF_3]^+$, 57 (29) $[C_4H_9]^+$. HRMS calcd. for $C_{18}H_{15}F_3INO$: 445.01505; found 445.01433. $C_{18}H_{15}F_3INO$ (445.2): calcd. C 48.56, H 3.40, N 3.15; found C 48.07, H 2.92, N 3.07.

4-*tert*-Butyl-2-phenyl-3-(phenylethynyl)-6-(trifluoromethyl)furo[3,2-*c*]-pyridine (23): A mixture of furo-pyridine **22** (62 mg, 0.139 mmol), $Pd(OAc)_2$ (2 mg, 0.010 mmol), PPh_3 (7 mg, 0.028 mmol), CuI (1 mg, 0.005 mmol) and phenylacetylene (17 mg, 0.167 mmol) in DMF (0.6 mL) and diisopropylamine (0.3 mL) was heated to 70 °C for 4 h under an argon atmosphere. The mixture was cooled to room temperature and diluted with brine (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 40:1) to give 25 mg (43%) of **23** as a colourless solid and 23 mg (52%) of **21**; m.p. 112 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.72 [s, 9 H, $C(CH_3)_3$], 7.48–8.39 (m, 10 H, Ph), 7.74 (s, 1 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 30.0, 39.4 [q, s, $C(CH_3)_3$], 84.3, 98.4, 98.5 (3 s, C-3, C≡C), 103.1 (dq, $^3J_{CF}$ = 3.9 Hz, C-7), 121.9 (q, $^1J_{CF}$ = 274 Hz, CF_3), 122.9, 124.8, 128.6, 128.7, 128.9, 129.1, 130.3, 131.1 (s, 6 d, s, Ph), 141.5 (q, $^2J_{CF}$ = 35 Hz, C-6), 127.1, 159.0, 159.5, 165.2 (4s, C-2, C-3a, C-4, C-7a) ppm. IR (film): $\tilde{\nu}$ = 3085–3030 (=C–H), 2960–2850 (C–H), 2195 (C≡C), 1600–1560 (C=C) cm^{-1}. MS (EI, 80 eV, 130 °C): *m*/*z* (%) = 419 (56) $[M]^+$, 404 (7) $[M - CH_3]^+$, 342 (15) $[M - C_6H_5]^+$, 101 (7) $[C_8H_5]^+$, 77 (31) $[C_6H_5]$, 69 (32) $[CF_3]^+$, 57 (100) $[C_4H_9]^+$. HRMS calcd. for $C_{18}H_{16}F_3NO$: 419.14969; found 419.14862.

2-*tert*-Butyl-5-iodo-3-methoxy-6-(trifluoromethyl)pyridin-4-ol (25): A mixture of pyridine **24** (229 mg, 0.919 mmol), K_2CO_3 (381 mg, 2.76 mmol), I_2 (700 mg, 2.76 mmol) in MeCN (5 mL) was heated to 70 °C for 3 d in a sealed tube. The mixture was cooled to room temperature and diluted with satd. aq. $Na_2S_2O_5$ solution (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 10:1) to give 280 mg (81%) of **25** as a colourless oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.38 [s, 9 H, $C(CH_3)_3$], 3.91 (s, 3 H, OMe), 6.38 (br. s, 1 H, OH) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 29.0, 37.9 [q, s, $C(CH_3)_3$], 60.9 (q, OMe), 80.0 (s, C-5), 121.1 (q, $^1J_{CF}$ = 275 Hz, CF_3), 142.3 (q, $^2J_{CF}$ = 34 Hz, C-6), 144.0, 155.8, 160.3 (3 s, C-2, C-3, C-4) ppm. IR (film): $\tilde{\nu}$ = 3430–3420 (O–H), 2960–2860 (C–H), 1705–1690 (C=C) cm^{-1}. $C_{11}H_{13}F_3INO_2$ (375.1): calcd. C 35.22, H 3.49, N 3.73; found C 35.40, H 3.24, N 3.75.

6-*tert*-Butyl-7-methoxy-2-phenyl-4-(trifluoromethyl)furo[3,2-*c*]pyridine (26): According to method A, pyridine **25** (207 mg, 0.552 mmol), $Pd(OAc)_2$ (9 mg, 0.039 mmol), PPh_3 (29 mg, 0.110 mmol), CuI (5 mg, 0.028 mmol), phenylacetylene (66 mg, 0.662 mmol) in DMF (2.54 mL) and diisopropylamine (1.27 mL) provided the crude product. Column chromatography on silica gel (hexane/ethyl acetate, 30:1) afforded 192 mg (99%) of **26** as a colourless solid; m.p. 140 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 4.36 (s, 3 H, OMe), 7.12 (s, 1 H, 3-H), 7.42–7.88 (m, 5 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 29.1, 38.3 [q, s, $C(CH_3)_3$], 98.4 (d, C-3), 122.2 (q, $^1J_{CF}$ = 274 Hz, CF_3), 125.3, 125.4, 128.9, 129.0, 129.8 (s, 3 d, s, C-3a, Ph), 131.3 (q, $^2J_{CF}$ = 35.5 Hz, C-4), 141.8, 151.1, 153.9, 157.9 (4s, C-6, C-7, C-7a, C-2) ppm. IR (KBr): $\tilde{\nu}$ = 3000–2840 (C–H), 1620–1560 (C=C) cm^{-1}. $C_{19}H_{18}F_3NO_2$ (349.3): calcd. C 65.32, H 5.19, N 4.01; found C 65.17, H 5.00, N 4.06.

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