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Three-Component Synthesis of Perfluoroalkyl- or Perfluoroaryl-Substituted 4-Hydroxypyridine Derivatives and Their Palladium-Catalyzed Coupling Reactions

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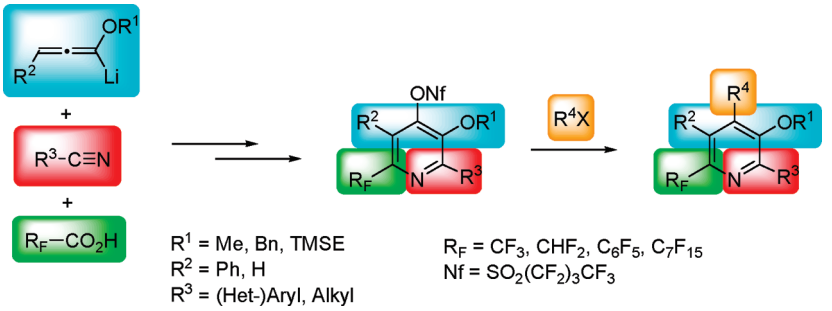

A three-component reaction with lithiated alkoxyallenes, nitriles, and perfluorinated carboxylic acids as precursors led to a series of perfluoroalkyl- or perfluoroaryl-substituted 4-hydroxypyridine derivatives. These compounds were converted into 4-pyridyl nonaflates which can be employed as versatile building blocks for the synthesis of π-conjugated compounds with use of palladium-catalyzed couplings. Suzuki reactions at C-4 and C-3 of the pyridine ring proceeded with moderate to high yields. In addition, Suzuki−Miyaura, Stille, or Buchwald−Hartwig coupling reactions have also been studied and afforded the corresponding highly substituted pyridine derivatives. Starting from an arylated propargylic ether the three-component reaction led to a pentasubstituted 4-hydroxypyridine derivative that could also be employed in palladium-catalyzed processes at C-4 and at C-3 of the pyridine core. With this simple approach the sterically highly crowded 3,4,5-triphenyl-substituted pyridine derivative **37a** could be prepared and studied by an X-ray analysis. With acetonitrile as precursor a different reaction pathway was found when this component was used in excess resulting in a pyridine derivative with a new substitution pattern. In summary, the methods described here allow a flexible and fairly efficient entry to a variety of highly substituted pyridine derivatives bearing perfluorinated alkyl or aryl groups.

Introduction

The development of efficient methods for the synthesis of fluorinated compounds is an area of strong interest because of the great importance of these products in bioorganic, medicinal, and synthetic chemistry.[1,2] The incorporation of perfluoroalkyl groups into organic molecules often induces a dramatic influence on the physical, chemical, and biological properties. For this reason an increasing number of organofluorine compounds find diverse applications in material science, agrochemicals, and pharmaceuticals.[1,2] We have recently discovered a novel and efficient three-component reaction for the preparation of highly substituted 4-hydroxy-6-(trifluoromethyl)pyridines **3** (Scheme 1).[3] The addition of an excess of lithiated alkoxyallenes **1** to nitriles, followed by quenching with an excess of trifluoroacetic acid (TFA) furnished enamides **2** together with 4-hydroxypyridines **3**. Full conversion to the desired pyridine derivatives **3** can be accomplished by subjecting the enamide intermediates **2** to an intramolecular aldol-type condensation with

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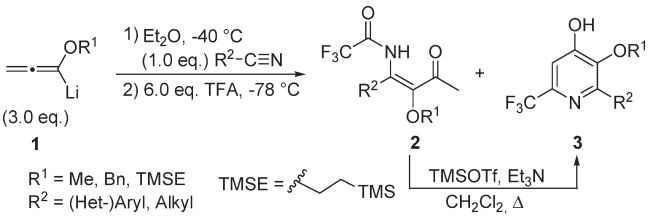
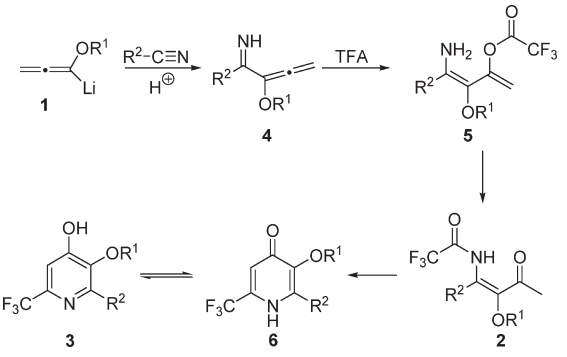
SCHEME 1. General Route to 4-Hydroxy-6-(trifluoromethyl)-pyridine Derivatives 3



trimethylsilyl triflate and triethylamine as reagents. Although they constitute an important class of ring systems found in numerous drugs and pharmaceuticals there are only a restricted number of reports concerning the synthesis of trifluoromethylated heteroaromatic compounds.[4,5] Significantly, synthetic methods efficiently leading to trifluoromethyl-substituted pyridines[2,4] commence from pyridyl precursors and approaches from nonpyridine precursors are inherently limited. In this regard, our method offers a new and significant application wherein TFA is used as the reagent to incorporate the CF_3 group and lithiated alkoxyallenes are employed as crucial C-3 building blocks.[6,7]

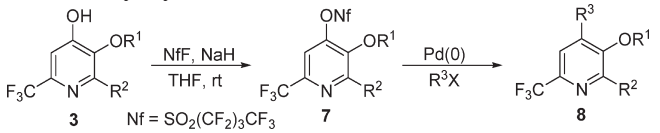
The unique mechanism of this three-component reaction is depicted in an abbreviated version in Scheme 2; it has already been described in earlier publications in more detail.[3,7a] The first step is the formation of an allenyl imine **4** resulting from the addition of lithiated alkoxyallene **1** to the nitrile carbon. Upon treatment with an excess of trifluoroacetic acid the protonated species of **4** is attacked by the carboxylate at the central allene carbon to form intermediate **5**. A subsequent acyl transfer gives the enamide **2**. A partial acid-catalyzed aldol-type condensation of enamide **2** affords pyridin-4-one **6**, which is in equilibrium with its tautomeric 4-hydroxypyridine **3**. In most cases of this report the 4-hydroxypyridine tautomer is the predominant form (in $CDCl_3$ at room temperature).

SCHEME 2. Proposed Mechanism for the Formation of Enamide 2 and 4-Hydroxypyridine 3



The 4-hydroxy and the 3-alkoxy group of pyridine derivatives **3** offer a range of opportunities for subsequent synthetic manipulation and diverse functionalizations. Pyridine derivatives such as **8** should be accessible by palladium-catalyzed coupling reactions of the corresponding nonaflates **7** (Scheme 3).

SCHEME 3. Subsequent Palladium-Catalyzed Coupling Reactions of 4-Pyridyl Nonaflates 7



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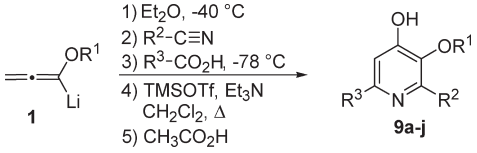
The generality of heteroaryl nonaflates[8,9] as halide or triflate equivalents in cross coupling reactions has been scarcely studied compared to alkenyl or aryl fluoroalkylsulfonates.[10,11] As a first demonstration of this option we have recently reported that the 4-pyridyl nonaflates **19a**−**c** could efficiently be employed in palladium-catalyzed Sonogashira reactions with alkynes and Suzuki couplings with arylboronic acids.[3] In continuation of our interest in nonaflate chemistry,[11] we now describe our results with substituted 4-pyridyl nonaflate derivatives[9] and the reactivity of these pseudohalide electrophiles in Suzuki reactions[12] and related processes. Moreover, recent advances in polymer and organic-based electrooptic devices, such as light-emitting diodes[13] and field-effect transistors,[14] encouraged us to exploit these derivatives as possible precursors in the synthesis of novel π-conjugated heteroaromatic compounds. There are reports on electronic systems based on heterocycles with a (trifluoromethyl)aryl group.[15] It is also known that an enhancement of photophysical properties[16] of compounds may occur upon introduction of fluorine. Therefore, we envisioned that extended π-systems equipped with trifluoromethylated pyridine groups would also be interesting building blocks for the synthesis of functional materials. In this report we describe for the first time the scope and limitations of the three-component synthesis of 6-perfluoroalkyl- or 6-perfluoroaryl-substituted 4-hydroxypyridines and 4-pyridyl nonaflates in full detail. We also demonstrate that our approach allows the preparation of pentasubstituted pyridine derivatives. Representative palladium-catalyzed couplings either at 4- or 3-position, including examples under formation of C−S or C−N bonds, lead to a variety of new fluorinated heterocycles.

Results and Discussion

Following the reaction conditions briefly described in the Introduction a variety of 4-hydroxypyridine derivatives could be prepared. Table 1 demonstrates that different alkoxyallenes such as benzyloxyallene, methoxyallene, or even the acid labile (2-trimethylsilyl)ethoxyallene are suitable precursors for the synthesis of highly substituted 4-hydroxypyridines **9a**−**j**. A broad range of nitriles (aliphatic, functionalized aliphatic, aromatic, or heteroaromatic) can successfully be used in this reaction introducing different substituents R^2. With respect to carboxylic acids, trifluoroacetic acid, perfluorooctanoic acid, and perfluorobenzoic acid were employed to provide perfluorinated substituents R^3. With this standard procedure the yields of the corresponding 4-hydroxypyridines are often only moderate after two steps, but the simplicity of the procedure compensates for the moderate efficacy in many examples.

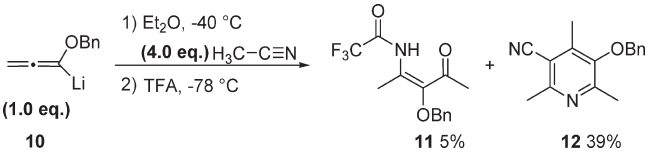
TABLE 1. Synthesis of 6-Perfluoroalkyl- and 6-Perfluorophenyl-Substituted 4-Hydroxypyridines 9



entry	R^1	R^2	R^3	**9**, yield [%]
1	Bn	*t*Bu	CF_3	**9a**, 50
2	TMSE	*t*Bu	CF_3	**9b**, 42
3	3-$MeOC_6H_4CH_2$	*t*Bu	CF_3	**9c**, 37
4	Bn	Me	CF_3	**9d**, 43
5	Me	Me	CF_3	**9e**, 37
6	Me	$(CH_2)_3CH{=}CH_2$	CF_3	**9f**, 32
7	Me	2-Thienyl	CF_3	**9g**, 67
8	Me	CMe_2OH	CF_3	**9h**, 23
9	Me	*t*Bu	C_6F_5	**9i**, 43
10	Me	*t*Bu	C_7F_{15}	**9j**, 27

In general, this method can also be performed with only 1 equiv of lithiated alkoxyallene and an excess of nitrile. In most cases the yields do not dramatically differ between these two protocols. However, for α-acidic nitriles such as acetonitrile a surprising outcome was observed as illustrated in Scheme 4 (for the "normal" conditions see Table 1, entries 4 and 5). Here the modified reaction conditions did not lead to the desired mixture of enamide **11** and 4-hydroxypyridine **9d** but to a completely different pyridine

SCHEME 4. Formation of Pyridine Derivative 12 with an Excess of Acetonitrile



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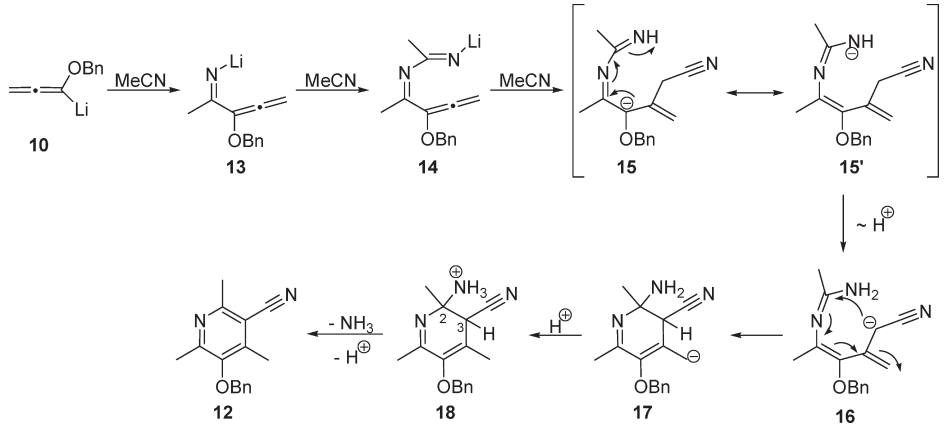
SCHEME 5. Proposed Mechanism of the Formation of Pyridine Derivative 12

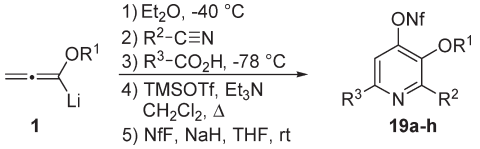


derivative **12** and only 5% of **11**. The X-ray analysis of pyridine derivative **12** proves its constitution (see the Supporting Information).[17] Regarding the substitution pattern it is obvious that **12** consists of one alkoxyallene unit and three acetonitrile moieties without incorporation of the carboxylic acid (Scheme 4).[18]

A plausible mechanism of this newly detected transformation is depicted in Scheme 5. As for the standard pathway, acetonitrile acts as an electrophile and adds to the lithiated alkoxyallene to furnish lithiated allenyl imine **13** (Scheme 5). Due to the present excess of acetonitrile this species then attacks again an acetonitrile molecule to give intermediate **14**, which may subsequently deprotonate a third acetonitrile molecule. Alternatively, lithiated alkoxyallene may also directly deprotonate acetonitrile. The generated acetonitrile anion then adds to the central carbon of the allenyl system to give anion **15**, which can also be represented by its mesomeric formula **15′**. After proton migration to intermediate **16** and cyclization to **17** a protonation by TFA occurs under the release of ammonia leading to the aromatic heterocycle **12**. The moderate yields for 4-hydroxypyridines **9**, in particular for nitriles with small and/or α-acidic substituents (Table 1), may be due to similar side reactions as involved in the multistep mechanism leading to compound **12**.

For the planned palladium-catalyzed reactions the required 4-pyridyl nonaflates were prepared in high yields by subjecting the 4-hydroxypyridine derivatives **9** to sodium hydride in the presence of commercially available nonafluorobutanesulfonyl fluoride (NfF).[11] Owing to their numerous potential applications we tried to simplify the preparation of the fairly stable 4-pyridyl nonaflates (Table 2). The crude reaction mixture at the 4-hydroxypyridine stage was directly used for the next step and gratifyingly nonaflates **19a**−**h** were isolated after column chromatography on silica gel in gram scale with moderate to good overall yields (26−62%, based on the corresponding alkoxyallenes **1** or nitriles).

TABLE 2. Direct Synthesis of Perfluoroalkyl- and Perfluorophenyl-Substituted 4-Pyridyl Nonaflates 19

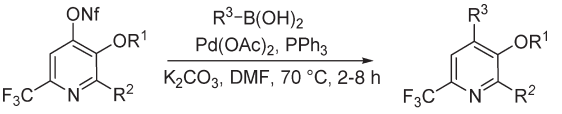


1 **19a-h**

entry	R^1	R^2	R^3	**19**, yield [%][a]
1	Bn	*t*Bu	CF_3	**19a**, 37
2	TMSE	*t*Bu	CF_3	**19b**, 30
3	Me	*t*Bu	CF_3	**19c**, 62[3a]
4	Me	*c*Pr	CF_3	**19d**, 38
5	Me	Ph	CF_3	**19e**, 48
6	Me	*n*Oct	CF_3	**19f**, 51
7	Me	*t*Bu	CHF_2	**19g**, 26
8	Me	*t*Bu	C_6F_5	**19h**, 41

[a]Overall yields for three steps.

TABLE 3. Suzuki Couplings of 4-Pyridyl Nonaflates 19 with Different Arylboronic Acids Leading to 4-Arylpyridine Derivatives 20



19a-c **20a-f**

entry	R^1	R^2	R^3	*t* [h]	**20**, yield [%]
1	Me	*t*Bu	4-NC-C_6H_4	8	**20a**, 81
2	Me	Ph	4-MeO-C_6H_4	4	**20b**, 74
3	TMSE	*t*Bu	Ph	4	**20c**, 69
4	Bn	*t*Bu	Ph	2	**20d**, 99
5	Bn	*t*Bu	4-MeO-C_6H_4	2	**20e**, 60
6	Me	*t*Bu	*trans*-2-styryl	8	**20f**, 88

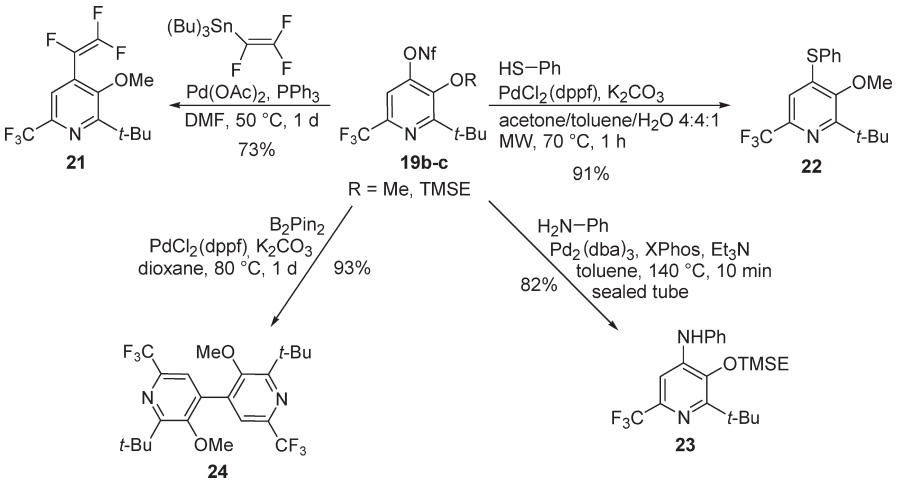
The Suzuki couplings[12] of nonaflates **19a**−**c** with aryl boronic acids were carried out with use of a catalytic system consisting of $Pd(OAc)_2/PPh_3$ and K_2CO_3 in DMF at 70 °C to provide heterobiaryl scaffolds. The corresponding 4-aryl-substituted pyridine derivatives **20a**−**f** were obtained in good to excellent yields (60−99%, Table 3).

We also examined the applicability of the 4-pyridyl nonaflates as coupling partners in other palladium-catalyzed processes such as Stille,[19] Buchwald−Hartwig,[20] and

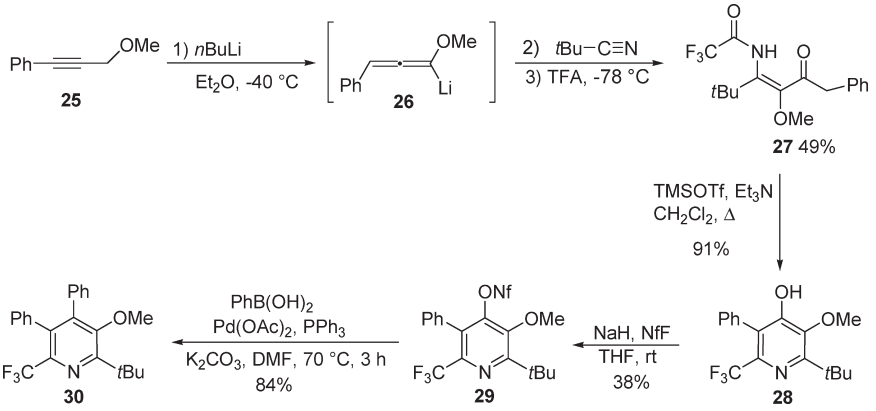
(17) CCDC-750423 (for **12**) and CCDC-750424 (for **37a**) contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(18) For a related process with incorporation of two arylnitrile units leading to pyrimidines, see: Blangetti, M.; Deagostino, A.; Prandi, C.; Zavattaro, C.; Venturello, P. *Chem. Commun.* **2008**, 1689–1691.

SCHEME 6. Palladium-Catalyzed C−C, C−S, and C−N Couplings of 4-Pyridyl Nonaflates 19b,c



SCHEME 7. Three-Component Synthesis of 5-Substituted Pyridine Derivatives 28, 29, and 30 Starting from γ-Substituted Propargylic Ether 25



Miyaura[21] reactions (Scheme 6). The Stille coupling was performed by treating nonaflate **19c** and tributyl(trifluorovinyl)stannane[22] with $Pd(OAc)_2$, PPh_3 in DMF at 50 °C for 1 day to furnish compound **21** bearing two perfluorinated substituents. A C−S cross coupling with nonaflate **19c** and thiophenol was achieved to give compound **22** with microwave conditions developed by Zhang.[23] The C−N cross coupling with aniline to **23** was performed under slightly modified conditions as reported by Buchwald.[9c] In this case a weaker base such as triethylamine has been used instead of DBU. The homocoupling of **19c** with bis(pinacolato)diborane[21] gave the desired highly substituted symmetric 4,4′-bipyridine derivative **24**. All products **21**−**24** could be obtained in good to high yields (73−93%). The examples of Table 3 and Scheme 6 demonstrate that the 4-pyridyl nonaflates introduced in this study are very suitable coupling partners and that a variety of interestingly substituted heterocyclic compounds should be available with these methods.

To extend the aromatic π-system at C-5 of the resulting pyridine core we developed a simple route starting from a terminally substituted propargylic ether such as **25** (Scheme 7). The corresponding enamide **27** was obtained under standard conditions via base induced isomerization of alkyne **25** to lithiated allene **26**. Enamide **27** was then subjected to the general cyclization-nonaflation conditions to give 4-pyridyl nonaflate **29**. Finally, the Suzuki coupling reaction with phenylboronic acid afforded the pentasubstituted pyridine derivative **30**.

The alkoxy group at C-3 of 4-hydroxypyridine derivatives or their subsequent products constitutes an ideal tool for additional modifications at the pyridine ring. A third extension of the π-system could be easily achieved by deprotection of the 3-alkoxy group followed by nonaflation of the free hydroxy group and subsequent palladium-catalyzed couplings (Scheme 8). The benzyl group of **20d** could be cleaved by using a mixture of TFA and 1,2-dichloroethane at 80 °C. The deprotection of methoxy-substituted pyridine **30** was carried out by treatment with trimethylsilyl iodide in 1,2-dichloroethane at 80 °C. The corresponding 3-hydroxypyridines **31** and **32** were subsequently converted into nonaflates **33** and **34**

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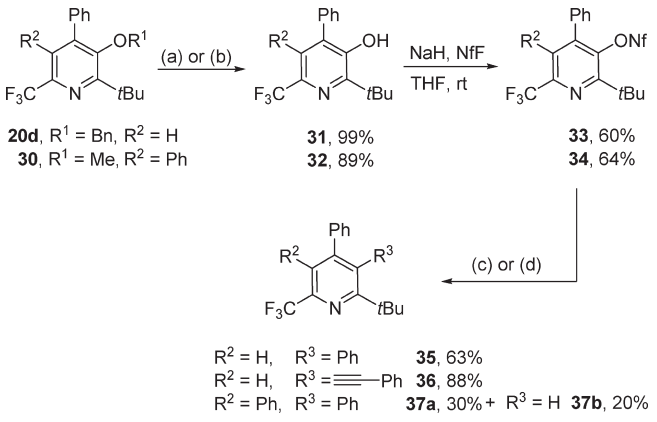
SCHEME 8. Modifications at C-3 of Pyridines: Synthesis of Di- and Triphenyl-Substituted Pyridine Derivatives 35, 36, and 37a[a]



[a]Reagents and conditinos: (a) TFA, 1,2-$C_2H_4Cl_2$, 80 °C, sealed tube; (b) TMSI, 1,2-$C_2H_4Cl_2$, 80 °C, sealed tube; (c) Suzuki reaction: $PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, iPr_2NH, DMF, 70 °C; (d) Sonogashira reaction: phenylacetylene, $Pd(OAc)_2$, PPh_3, CuI, DMF, 70 °C.

under standard conditions, which were then subjected to the final palladium-catalyzed couplings. Suzuki and Sonogashira reactions of nonaflate **33** gave the expected products **35** and **36** in moderate to good yields. Applying Suzuki cross coupling to **34** with phenyl boronic acid gave the desired 3,4,5-triphenyl-substituted pyridine **37a** together with reduction product **37b**. The X-ray analysis of pyridine derivative **37a** proves the constitution and shows interesting structural features (see the Supporting Information).[17] Quite remarkably, the C-4 phenyl group is arranged almost perpendicular to the pyridine core, while in a compound like hexaphenylbenzene (HPB)[24a] interplanar angles between 62° and 71° only are observed. Furthermore, the ^{1}H NMR spectra of **37a** show a high field shift of two phenyl protons to 6.62 ppm, which is slightly stronger than in HPB[24b] that only shows a signal at 6.84 ppm. This observation might be directly traced back to a higher shielding effect of the perpendicularly arranged C-4 phenyl group to its neighbor phenyl groups.

Conclusions

In summary, highly flexible synthetic routes leading to various tetra- or penta-substituted 6-perfluoroalkyl- or 6-perfluorophenyl-substituted 4-hydroxypyridine derivatives have been developed. The three-component synthesis employing fluorinated carboxylic acids as one key component combined with palladium-catalyzed processes allows the introduction of a broad range of substituents at the pyridine ring. If acetonitrile is used as electrophile an excess of this component leads to a different mechanism and the predominating formation of a 3-cyanopyridine derivative was observed. Trifluoromethyl-substituted 4-pyridyl nonafluorobutanesulfonates were found to be excellent substrates for diverse palladium-catalyzed coupling reactions. We have hence established a rapid, flexible, and efficient access to 3,4-di- and 3,4,5-triaryl-substituted pyridines bearing perfluoroalkyl or perfluoraryl groups at C-6.

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Experimental Section

Typical Procedure for Preparation of 4-Hydroxypyridines: 3-Methoxy-2-(thiophen-2-yl)-6-(trifluoromethyl)pyridin-4-ol (9g). Methoxyallene (0.69 mL, 8.30 mmol) was dissolved in diethyl ether (17 mL) and *n*-butyllithium (2.76 mL, 6.90 mmol, 2.5 M in hexanes) was added at −40 °C. After 25 min at −50 to −40 °C the solution was cooled to −78 °C and thiophene-2-carbonitrile (0.235 mL, 2.50 mmol) was added. After the solution was stirred for 4 h at this temperature trifluoroacetic acid (1.21 mL, 16.4 mmol) was added and the mixture was warmed overnight to room temperature. Then the reaction mixture was quenched with satd aq $NaHCO_3$ solution (15 mL) and extracted with dichloromethane (3 × 15 mL). The combined organic phases were dried with Na_2SO_4 and then evaporated. The residue was dissolved in dichloromethane (25 mL) and treated at 0 °C with triethylamine (1.05 mL, 7.50 mmol) and trimethylsilyl triflate (1.45 mL, 7.50 mmol). The mixture was heated under reflux for 3 d and then quenched at room temperature with satd aq NH_4Cl solution (15 mL) and extracted with dichloromethane (3 × 10 mL), then the combined organic phases were evaporated to provide the crude product. The resulting crude product was dissolved again in dichloromethane (20 mL) and treated first with TFA (0.08 mL, 1 mmol) and then with water (20 mL). Next it was extracted with dichloromethane (3 × 5 mL) and the combined organic extracts were dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 1:1) to afford 460 mg (67%) of **9g** as a brownish viscous liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.83 (s, 3 H, OMe), 7.13 (s, 1 H, 5-H), 7.14 (dd, J = 5.1, 3.7 Hz, 1 H, 4′-H), 7.46 (dd, J = 5.0, 1.1 Hz, 1 H, 3′-H), 7.93 (dd, J = 3.7, 1.1 Hz, 1 H, 5′-H) ppm. OH could not be detected. ^{13}C NMR ($CDCl_3$, 126 MHz): δ 60.6, 107.7 (q, $^3J_{CF}$ = 2.7 Hz), 122.2 (q, $^1J_{CF}$ = 274 Hz), 127.9, 128.9, 129.2, 139.0, 142.1, 144.1 (q, $^2J_{CF}$ = 34.1 Hz), 146.8, 157.4 ppm. IR (film): ν 3440−3400 (O—H), 3100 (=C—H), 2940, 2840 (C−H), 1600−1580 (C=C) cm^{-1}. MS (EI): m/z (%) 275 (1) $[M]^+$, 232 (100), 77 (52), 43 (13). HRMS (EI): calcd for $C_{11}H_8F_3NO_2S$ 275.02280, found 275.02355.

Typical Procedure for One-Pot Preparation of 4-Pyridinyl Nonaflates: 2-Cyclopropyl-3-methoxy-6-(trifluoromethyl)pyridin-4-yl nonaflate (19d). Methoxyallene (900 mg, 12.9 mmol) was dissolved in diethyl ether (25 mL) and *n*-butyllithium (4.63 mL, 11.6 mmol, 2.5 M in hexanes) was added at −40 °C. After 25 min at −50 to −40 °C the solution was cooled to −78 °C and cyclopropylnitrile (0.32 mL, 4.29 mmol) was added. After the solution was stirred for 4 h at this temperature trifluoroacetic acid (1.98 mL, 25.7 mmol) was added and the mixture was warmed overnight to room temperature. The reaction mixture was then quenched with satd aq $NaHCO_3$ solution (20 mL) and extracted with dichloromethane (3 × 25 mL). The combined organic phases were dried with Na_2SO_4 and then evaporated. The residue was dissolved in dichloromethane (25 mL) and treated at 0 °C with triethylamine (1.80 mL, 12.9 mmol) and trimethylsilyl triflate (2.48 mL, 12.9 mmol). The mixture was heated under reflux for 3 d and then quenched at room temperature with satd aq NH_4Cl solution (20 mL), extracted with dichloromethane (3 × 25 mL), dried with Na_2SO_4, and evaporated to provide the crude product. The resulting crude product was dissolved in THF (25 mL) and NaH (514 mg, 60% in mineral oil, 12.9 mmol) was added under an argon atmosphere. Nonafluorobutanesulfonyl fluoride (2.31 mL, 12.9 mmol) was added dropwise at room temperature. The mixture was stirred at room temperature overnight and quenched by slow addition of methanol and water. It was then extracted with ethyl acetate (3 × 25 mL), dried with Na_2SO_4, and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10:1) to afford 832 mg (38%) of **19d** as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.11−1.14,

1.19−1.23 (2 m, 2 H each, 2′-H, 3′-H), 2.45 (m_c, 1 H, 1′-H), 4.01 (s, 3 H, OMe), 7.28 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ 11.4, 11.8, 62.2, 111.2 (q, $^3J_{CF}$ = 2.8 Hz), 120.6 (q, $^1J_{CF}$ = 274 Hz), 144.1 (q, $^2J_{CF}$ = 36.2 Hz), 148.1, 148.5, 162.1 ppm. ^{19}F NMR ($CDCl_3$, 470 MHz): δ −68.0 (s, CF_3), −80.6, −109.0, −120.6, −125.6 (4 m, ONf) ppm. IR (film): ν 3095−3005 (=C—H), 2950−2840 (C−H), 1745−1595 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd for $C_{14}H_{10}F_{12}NO_4S$ $[MH]^+$ 516.0134, found 516.0135.

Typical Procedure for Suzuki Coupling Reaction: 2-*tert*-Butyl-3-(benzyloxy)-4-phenyl-6-(trifluoromethyl)pyridine (20d). A mixture of 4-pyridyl nonaflate **19a** (120 mg, 0.198 mmol), phenyl boronic acid (35 mg, 0.287 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol), PPh_3 (10 mg, 0.039 mmol), and K_2CO_3 (27 mg, 0.195 mmol) in DMF (2 mL) was heated to 70 °C for 2 h under an argon atmosphere. The mixture was allowed to cool to room temperature and diluted with water (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phase was dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 40:1) to give 76 mg (99%) of **20d** as a colorless solid. Mp 57 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.48 (s, 9 H, *t*-Bu), 4.48 (s, 2 H, 1′-H), 7.08−7.62 (m, 10 H, Ph), 7.52 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ 29.4, 38.6, 74.5, 121.0 (q, $^3J_{CF}$ = 2.9 Hz), 121.8 (q, $^1J_{CF}$ = 274 Hz), 127.7, 128.0, 128.3, 128.5, 128.9, 129.0, 136.2, 136.4, 141.0 (q, $^2J_{CF}$ = 34.4 Hz), 143.2, 153.6, 163.2 ppm. IR (KBr): ν 3090−3040 (=C—H), 3000−2875 (C—H), 1600−1550 (C=C) cm^{-1}. MS (EI): *m*/*z* (%) 385 (11) $[M]^+$, 91 (100). $C_{23}H_{22}F_3NO$ (385.4) calcd for C 71.67, H 5.75, N 3.63, found C 71.73, H 5.59, N 3.68.

Preparation of 2-*tert*-Butyl-3-methoxy-6-(trifluoromethyl)-4-(trifluorovinyl)pyridine (21). A mixture of 4-pyridyl nonaflate **19c** (261 mg, 0.491 mmol), $Pd(OAc)_2$ (5.5 mg, 0.025 mmol), PPh_3 (26 mg, 0.098 mmol), and tributyl(1,2,2-trifluorovinyl)stannane (292 mg, 0.786 mmol) in DMF (2.3 mL) was heated to 50 °C for 1 d under an argon atmosphere. The mixture was allowed to cool to room temperature, diluted with brine (3 mL), and extracted with diethyl ether (3 × 3 mL). The combined organic phase was dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 40:1) to give 112 mg (73%) of **21** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.42 (s, 9 H, *t*-Bu), 3.89 (s, 3 H, OMe), 7.49 (s, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ 29.0, 38.7, 60.6 (qd, $^5J_{CF}$ = 3.1 Hz), 119.1, 121.6 (q, $^1J_{CF}$ = 273 Hz), 124.4 (ddd, J_{CF} = 233, 51.1, 21.9 Hz), 126.6 (ddd, J_{CF} = 21.9, 5.7, 0.9 Hz), 140.4 (q, $^2J_{CF}$ = 35.3 Hz), 153.2 (ddd, J_{CF} = 294, 283, 51.1 Hz), 155.1, 164.0 ppm. ^{19}F NMR ($CDCl_3$, 470 MHz): δ −67.6 (s, CF_3), −96.9 (dd, J = 59.7, 32.2 Hz, 1′-F), −111.0 (dd, J = 115.0, 59.7 Hz, 2′-F^b), −170.1 (dd, J = 115.0, 32.2 Hz, 2′-F^a) ppm. IR (film): ν 2965−2870 (=C—H, C—H), 1770 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd for $C_{13}H_{13}F_6NO$ $[MH]^+$ 314.0974, found 314.0966.

Preparation of 2-*tert*-Butyl-3-methoxy-4-(phenylthio)-6-(trifluoromethyl)pyridine (22). 4-Pyridyl nonaflate **19c** (267 mg, 0.503 mmol), $PdCl_2$(dppf) (41 mg, 0.050 mmol), thiophenol (62 μL, 0.60 mmol), and K_2CO_3 (139 mg, 1.01 mmol) were dissolved in a 4:4:1 mixture of acetone, toluene, and H_2O (4.5 mL) and heated to 70 °C for 1 h under an argon atmosphere in a microwave reactor. The mixture was allowed to cool to room temperature, diluted with brine (5 mL), and extracted with ethyl acetate (3 × 5 mL). The combined organic phase was dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 40:1) to give 156 mg (91%) of **22** as a colorless solid. Mp 52 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.45 (s, 9 H, *t*-Bu), 4.00 (s, 3 H, OMe), 7.47 (s, 1 H, 5-H), 7.23−7.30, 7.48−7.52 (2 m, 3 H, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 126 MHz): δ 28.9, 39.1, 62.0, 113.1 (q, $^3J_{CF}$ = 2.8 Hz), 120.7 (q, $^1J_{CF}$ = 274 Hz), 127.1, 127.5, 129.1, 130.2, 137.0, 142.1 (q, $^2J_{CF}$ = 35.9 Hz), 149.5, 166.3 ppm. IR (KBr): ν 3070−3050 (=C—H), 2960−2870 (C—H), 1590−1570 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd for $C_{17}H_{18}F_3NOS$ $[MH]^+$ 342.1134, found 342.1147.

Preparation of 2-*tert*-Butyl-*N*-phenyl-6-(trifluoromethyl)-3-[2-(trimethylsilyl)ethoxy]pyridin-4-amine (23). A mixture of 4-pyridyl nonaflate **19b** (227 mg, 0.368 mmol), $Pd_2(dba)_3$ (6.7 mg, 0.007 mmol), XPhos (14 mg, 0.029 mmol), aniline (0.47 mL, 0.478 mmol), and Et_3N (0.13 mL, 1.01 mmol) in toluene (1.4 mL) was heated in an ACE-sealed tube to 140 °C for 10 min under an argon atmosphere. The mixture was allowed to cool to room temperature, diluted with brine (3 mL), and extracted with diethyl ether (3 × 5 mL). The combined organic phase was dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 10:1) to give 124 mg (82%) of **23** as a colorless oil. ^{1}H NMR ($CDCl_3$, 700 MHz): δ 0.05 (s, 9 H, TMS), 1.26 (m_c, 2 H, 2′-H), 1.45 (s, 9 H, *t*-Bu), 4.00 (m_c, 2 H, 1′-H), 6.34 (s_{br}, 1 H, NH), 7.28 (s, 1 H, 5-H), 7.15−7.19, 7.39−7.42 (2 m, 3 H, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 176 MHz): δ −1.4, 19.1, 29.8, 38.2, 70.5, 103.6 (q, $^3J_{CF}$ = 2.5 Hz), 121.7 (q, $^1J_{CF}$ = 274 Hz), 121.7, 124.4, 129.8, 143.4, 139.5, 142.1 (q, $^2J_{CF}$ = 33.9 Hz), 145.6, 161.0 ppm. IR (film): ν 3410 (N—H), 3060−2870 (=C—H, C—H), 1590−1580 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd for $C_{21}H_{29}F_3N_2OSi$ $[MH]^+$ 411.2074, found 411.2092.

Preparation of 2,2′-Di-*tert*-butyl-3,3′-dimethoxy-6,6′-bis-(trifluoromethyl)-4,4′-bipyridine (24). A mixture of 4-pyridyl nonaflate **19c** (245 mg, 0.461 mmol), $PdCl_2$(dppf) (30 mg, 0.026 mmol), B_2Pin_2 (59 mg, 0.232 mmol), and K_2CO_3 (191 mg, 1.38 mmol) in dioxane (3 mL) was heated to 80 °C for 1 d under an argon atmosphere. The mixture was allowed to cool to room temperature, diluted with brine (4 mL), and extracted with dichloromethane (3 × 5 mL). The combined organic phase was dried with Na_2SO_4 and concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/ethyl acetate = 40:1) to give 100 mg (93%) of **24** as a colorless solid. Mp 118−120 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.46 (s, 18 H, *t*-Bu), 3.41 (s, 6 H, OMe), 7.59 (s, 2 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$, 176 MHz): δ 29.1, 38.8, 60.6, 120.6 (q, $^3J_{CF}$ = 2.9 Hz), 122.6 (q, $^1J_{CF}$ = 274 Hz), 136.7, 140.9 (q, $^2J_{CF}$ = 35.1 Hz), 154.8, 163.7 ppm. IR (KBr): ν 3005−2850 (=C—H, C—H), 1595−1540 (C=C) cm^{-1}. MS (EI): *m*/*z* (%) 464 (14) $[M]^+$, 449 (60), 433 (100), 403 (20), 69 (10), 57 (92). HRMS (EI): calcd for $C_{22}H_{26}F_6N_2O_2$ $[M]^+$ 464.18985, found 464.18876. $C_{22}H_{26}F_6N_2O_2$ (464.4) calcd for C 56.89, H 5.64, N 6.03, found C 56.45, H 5.14, N 5.89.

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Supporting Information Available: Characterization data for all compounds, including copies of ^{1}H and ^{13}C NMR spectra for all compounds and X-ray crystallographic data for **12** and **37a** in CIF format.[25,26] This material is available free of charge via the Internet at http://pubs.acs.org.

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