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Practical Synthesis of α-Trifluoromethylated Pyridines Based on Regioselective Cobalt-Catalyzed [2+2+2] Cycloaddition using Trifluoromethylated Diynes with Nitriles

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Abstract: Regioselective cobalt-catalyzed [2+2+2] cycloaddition using fluorine-containing diynes with nitriles was described. Cycloaddition of fluorinated diynes with nitriles under the influence of $CoCl_2$(phen), zinc bromide, and zinc dust in dichloroethane at 80 °C for 3 h took place smoothly, exclusively affording the corresponding α-fluoroalkylated pyridines in excellent yields. In addition, dinitriles as substrate were also found to be suitable for this reaction, giving the corresponding fluoroalkylated bipyridine derivatives in excellent yields.

Keywords: α-Fluoroalkylated pyridines; Cobalt catalyst; [2+2+2] Cycloadditions; Nitriles; Regioselective

Introduction

Since the introduction of a trifluoromethyl (CF_3) group into heterocycles often causes various unique biological properties arising from modified electron density, acidity, hydrogen-bonding patterns, and so on, α-CF_3-pyridine derivatives have been widely recognized as vital organic substances in pharmaceutical and agrochemical industries.[1] For example, a fungicide, picoxystrobin (Figure 1, **I**), which is classified under the strobilurin family and commercialized by Dupont, works as a mitochondrial cytochrome-bc1 complex inhibitor.[2] Bicyclopyrone (**II**) is a herbicide which acts by inhibiting 4-hydroxyphenylpyruvate dioxygenase (HPPD), leading to the destruction of chlorophyll in plants.[3] Sulfoxaflor (**III**) is a systemic insecticide which acts as an insect neurotoxin.[4] On the other hand, enasidenib with two α-CF_3 pyridinyl cores (**IV**), is a medication for the treatment of refractory acute myeloid leukemia.[5] In this way, the α-CF_3 pyridinyl core is one of the most important fragments in the design of bioactive substances, and therefore the establishment of a practical and efficient synthetic protocol for such a unit is highly desirable.

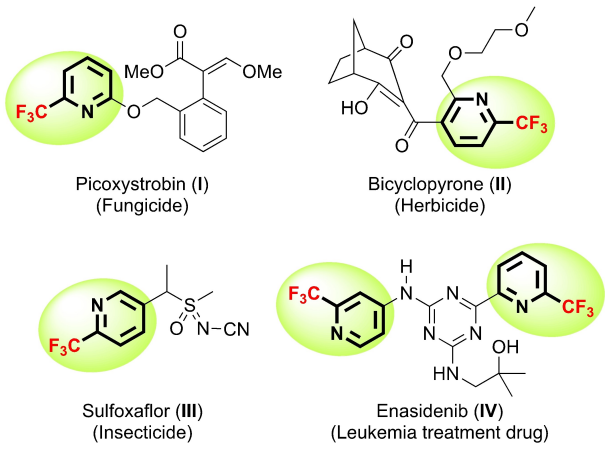


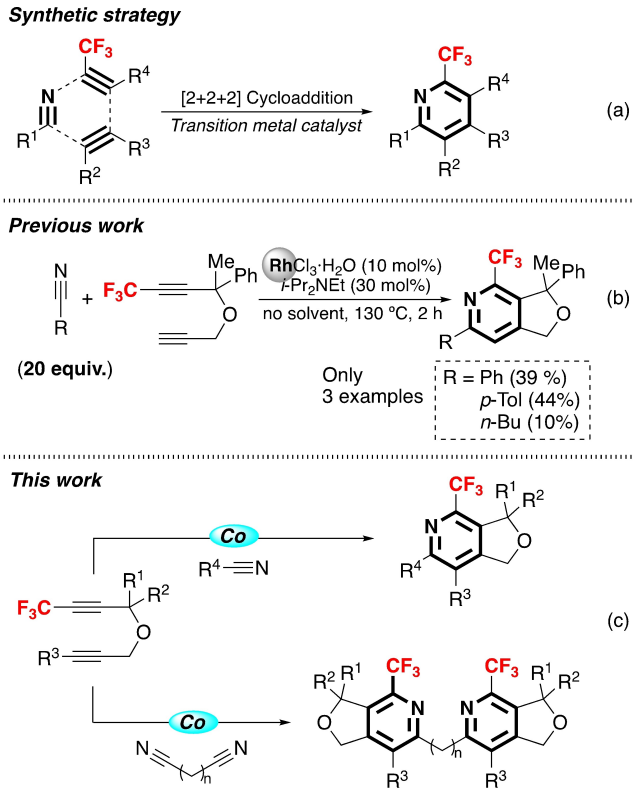
Figure 1. Bioactive compounds with α-CF_3-pyridine framework (s).

Various types of α-CF_3 pyridine derivatives have been synthesized so far by direct method using various trifluoromethylating reagents as well as building-block approach *via* chemical transformations starting from CF_3-containing synthetic units.[6] However, there have been still only a handful of synthetic methods that can be employed on an industrial scale due to the high cost of trifluoromethylating reagents and the risk of their explosion in the former method and the multi-step reaction process in the latter method. On the other hand, the synthesis of multi-substituted pyridines *via* [2+2+2] cycloaddition using trifluoromethylated alkynes, non-fluorinated alkynes, and nitriles in the presence of transition metal catalysts is very promising because it allows us to construct the complicated pyridine skeletons from readily available and structurally simple substrates in a single step (Scheme 1, (a)).[7,8]

Our research group has reported that the [2+2+2] cycloaddition of the trifluoromethylated diyne with some nitriles in the presence of rhodium chloride and diisopropylethylamine leads to the construction of the corresponding multi-substituted pyridine derivatives (Scheme 1, (b)).[9b] However, a rare metal, rhodium, is extremely expensive, and this reaction requires the use of 10 mol% of the transition metal as well. Moreover, employing 20 equivalents of nitrile brings about the desired products in only 44% yield at most, and in particular, the cycloaddition with aliphatic nitrile provides only 10% of the corresponding pyridine derivative. Due to these drawbacks, further investigation of this cycloaddition is strongly desirable.

Cobalt-catalyzed [2+2+2] cycloaddition is a very practical synthetic protocol for the construction of aromatics, especially pyridines, due to the unique reactivity of cobalt metal belonging to the first-transition metal, which is different from other homologous transition metals, and low cost and low toxicity.[10]

Herein was investigated in detail the synthesis of multi-substituted pyridine derivatives *via* [2+2+2] cycloaddition of CF_3-diynes with various nitriles or dinitriles using cobalt catalyst (Scheme 1(c)).



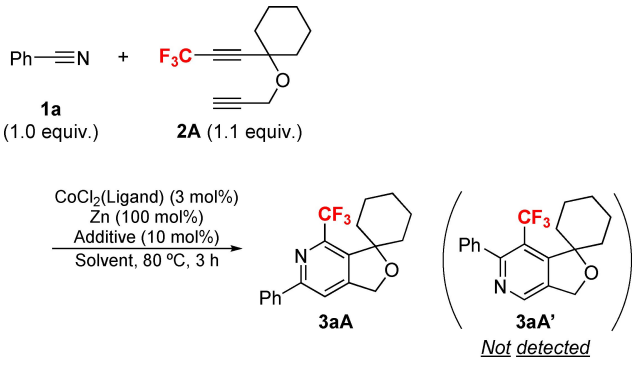
Scheme 1. Synthesis of α-trifluoromethylated pyridine derivatives *via* transition metal-catalyzed cycloaddition.

Results and Discussion

We initiated cobalt-catalyzed [2+2+2] cycloaddition using benzonitrile **1a** and trifluoromethylated diyne **2A** to optimize the reaction conditions, as shown in Table 1.[10d,11a]

To a solution of 3 mol% of $CoCl_2$((*S*)-BINAP), 100 mol% of Zn, and 10 mol% of ZnI_2 in CH_3CN was added 1.0 equiv. of benzonitrile **1a** and 1.1 equiv. of trifluoromethylated diyne **2A**, and the mixture was heated at 80 °C for 3 h, however, a trace amount of the pyridine **3aA** was obtained. As shown in Entries 2–5, we screened the various solvents. In the case of DMF and 1,4-dioxane, the result was not improved (Entries 2 and 3), whereas the reaction using toluene as solvent gave the trifluoromethylated pyridine derivative in 11% yield (Entry 4). Additionally, the yield was greatly improved to 41% in DCE as solvent (Entry 5). As shown in Entries 6–9, we carried out the reaction in the presence of cobalt catalysts having various phosphine ligands. Cycloaddition reaction with the cobalt catalysts coordinated by 1,2-bis (diphenylphosphino)ethane (dppe), 1,4-bis (diphenylphosphino)butane (dppb), or 1,1'-bis (diphenylphosphino)ferrocene (dppf) were used as a bidentate ligand, however, the yield of desired cycloadducts **3aA** were not improved. Even when the ligand was switched from a bidentate to a monodentate ligand, PPh_3, the trifluoromethylated pyridine **3aA** were not obtained at all (Entry 9). It should be noted that the use of nitrogen ligand, like *N,N,N',N'*-tetramethylethylenediamine (TMEDA), 2,2'-bipyridyl (bpy), 1,10-phenanthroline (phen), pyridine, is very efficient for the construction of trifluoromethylated pyridine (Entries 10–13), in particular, the cycloaddition reaction using phen gave the pyridine **3aA** in 56% yield (Entry 12). Even when a phosphine or nitrogen ligand-free catalyst, $CoCl_2$ was used, the pyridine **3aA** was obtained in 43% yield (Entry 14). Changing the additive from ZnI_2 to $ZnBr_2$ and $ZnCl_2$

Table 1. Table 1. Screening for the reaction conditions of cobalt-catalyzed [2+2+2] cycloaddition.[a]



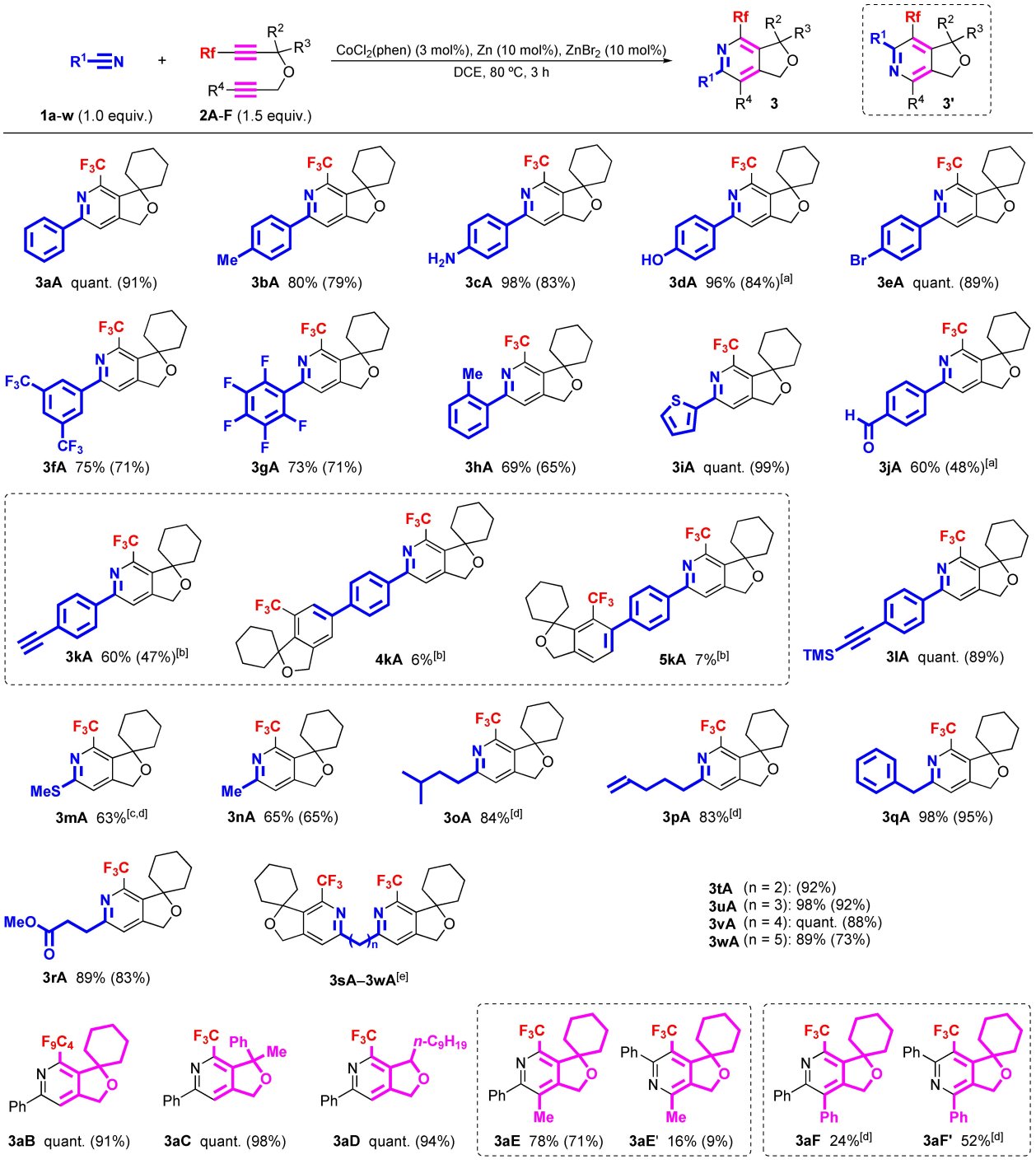
Entry	Solvent	Ligand	Additive	Yield[b]/% of **3aA**
1	CH_3CN	(*S*)-BINAP	ZnI_2	trace
2	DMF	(*S*)-BINAP	ZnI_2	0
3	1,4-Dioxane	(*S*)-BINAP	ZnI_2	trace
4	Toluene	(*S*)-BINAP	ZnI_2	11
5	DCE	(*S*)-BINAP	ZnI_2	41
6	DCE	dppe	ZnI_2	trace
7	DCE	dppb	ZnI_2	22
8	DCE	dppf	ZnI_2	27
9[c]	DCE	PPh_3	ZnI_2	0
10	DCE	TMEDA	ZnI_2	47
11	DCE	bpy	ZnI_2	45
12	DCE	phen	ZnI_2	56
13[c]	DCE	Pyridine	ZnI_2	34
14	DCE	None	ZnI_2	43
15	DCE	phen	$ZnBr_2$	79
16	DCE	phen	$ZnCl_2$	75
17	DCE	phen	–	trace
18[d]	DCE	phen	$ZnBr_2$	quant.
19[d,e]	DCE	phen	$ZnBr_2$	0
20[d,f]	DCE	phen	$ZnBr_2$	trace
21[d,g]	DCE	phen	$ZnBr_2$	quant.

[a] Reaction conditions: **1a** (0.5 mmol), **2A** (1.1 mmol), Zn (100 mol%), additive (10 mol%), cobalt catalyst (3 mol%), Solvent (1.5 mL), 80 °C, 3 h.
[b] Determined by ^{19}F NMR.
[c] $CoCl_2(Ligand)_2$ was used.
[d] 1.5 equiv. of **2A** was used.
[e] Without catalyst.
[f] Without Zn.
[g] 10 mol% of Zn was used.

improved the yield considerably, leading to the product in 79% yield (Entry 15) and 75% yield (Entry 16), respectively. As shown in entry 17, the reaction without zinc halide produced a trace amount of pyridine **3aA**, indicating that an additive is crucial for the present [2+2+2] cycloaddition. When the amount of trifluoromethylated diyne **2A** was increased from 1.1 to 1.5 equivalents, the desired pyridine **3aA** was obtained quantitatively (Entry 18). The reaction without cobalt catalyst or Zn did not lead to the desired product **3aA** at all (Entries 19 and 20). As shown in Entry 21, it was revealed that the reaction was sufficiently complete even when the amount of Zn was reduced from 100 mol% to 10 mol%. In all cases, the regioisomer **3aA'** was not detected at all.

With the optimal reaction conditions (Table 1, Entry 21), we carried out [2+2+2] cycloaddition reaction using various nitriles **1** and fluoroalkylated diynes **2A**, as shown in Scheme 2. To our satisfaction, our protocol was suitable for a variety of substrates. Furthermore, it should be noted that all reactions proceeded very smoothly, giving α-fluoroalkylated pyridines **3** exclusively, except for the reaction of internal diynes **2E** and **2F**.

Substrates **1** having an electron-donating substituent on the benzene ring of the nitrile, such as Me (**1b**), NH_2 (**1c**), OH (**1d**), reacted very efficiently, leading to the desired α-trifluorometylated pyridines **3bA**, **3cA**, and **3dA** in excellent yields (80–98%). Nitriles **1** having various electron-withdrawing groups, such as Br (**1e**), and 3,5-$(CF_3)_2$ (**1f**), were also found to be applicable in the cobalt-catalyzed cycloaddition to afford the corresponding pyridines **3eA** and **3fA** in high yields. The reaction using bulky substrates **1**, like pentafluorobenzonitrile (**1g**) and *o*-methylbenzonitrile (**1h**), gave the corresponding cyclic products in good yields (73%, 69%). When 2-cyanothiophene (**1i**) was used as a substrate, the trifluoromethylated pyridine **3iA** was obtained quantitatively, whereas the benzonitrile with a formyl group (**1j**) showed less reactivity, giving the desired pyridine **3jA** in 60% yield. When 4-ethynylbenzonitrile (**1k**) was used, the corresponding pyridine **3kA** was obtained in 60% yield, together with a small amount of **4kA** (6%) and **5kA** (7%) derived from the [2+2+2] cycloaddition which proceeded at both an ethynyl and a cyano moieties. In the case of the substrate (**1l**) having a TMS-protected ethynyl group, on the other hand, the **3lA** was exclusively produced. Methyl thiocyanate (**1m**) could also be applied successfully for this reaction (63%) under the modified reaction conditions using 100 mol% of Zn and 10 mol% of $CoCl_2$(phen). It should be noted that various aliphatic nitriles which were not applicable in rhodium-catalyzed system (Scheme 1, (b)), could also participate in the [2+2+2] cycloaddition well.[9b] When acetonitrile (**1n**) and isocapronitrile (**1o**) were used as a substrate, the corresponding trifluoromethylated pyridines **3nA** and **3oA** were obtained in 65% and 84% yield, respectively. Even the aliphatic nitrile with an unsaturated bond (**1p**) reacted well. Phenylacetonitrile (**1q**) and aliphatic nitrile having an ethoxycarbonyl group (**1r**) were also applicable, giving the corresponding pyridines **3qA** (98%) and **3rA** (89%). We also evaluated the reaction using dinitriles (**3sA–3wA**) because the synthesis of molecules with two fluoroalkylated pyridinyl cores is quite rare. Cobalt-catalyzed [2+2+2] cycloaddition of malono-

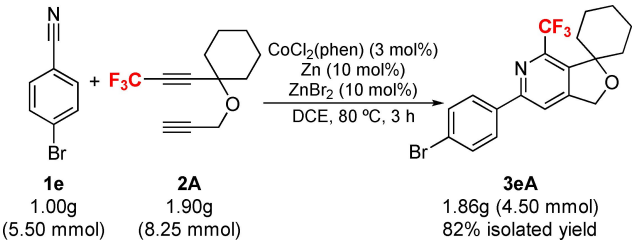


Scheme 2. Cobalt-catalyzed [2+2+2] cycloaddition of various nitriles **1** with fluoroalkylated diynes **2**. Yields are determined by ^{19}F NMR. The values in parentheses show isolated yield of **3**. [a]With 100 mol% of Zn. [b]1.0 equiv. of **2A** was used. [c]Carried out for 24 h using 100 mol% of Zn, 10 mol% of $CoCl_2$(phen). [d]Hard to be purified, [e]Carried out for 24 h using 3.0 equiv. of **2A**, 100 mol% of Zn, 10 mol% of $ZnBr_2$, and 5 mol% of $CoCl_2$(phen).

nitrile (**1s**) with 3.0 equiv. of trifluoromethylated diyne **2A** in the presence of 100 mol% of Zn, 10 mol% of $ZnBr_2$, and 5 mol% of $CoCl_2$(phen) in DCE at 80 °C for 24 h proceeded very smoothly to afford the corresponding dipyridine derivative **3sA** quantitatively. The **3sA** formed a single crystal suitable for X-ray crystallographic analysis by recrystallization from hexane. Then, the results confirmed the expected dipyridine structure of **3sA**. Changing the number of the alkylene carbon from 1 to 2–5, on the other hand,

did not affect the results, leading to the desired fluoroalkylated dipyridine **3 tA–3 wA** in excellent yields.

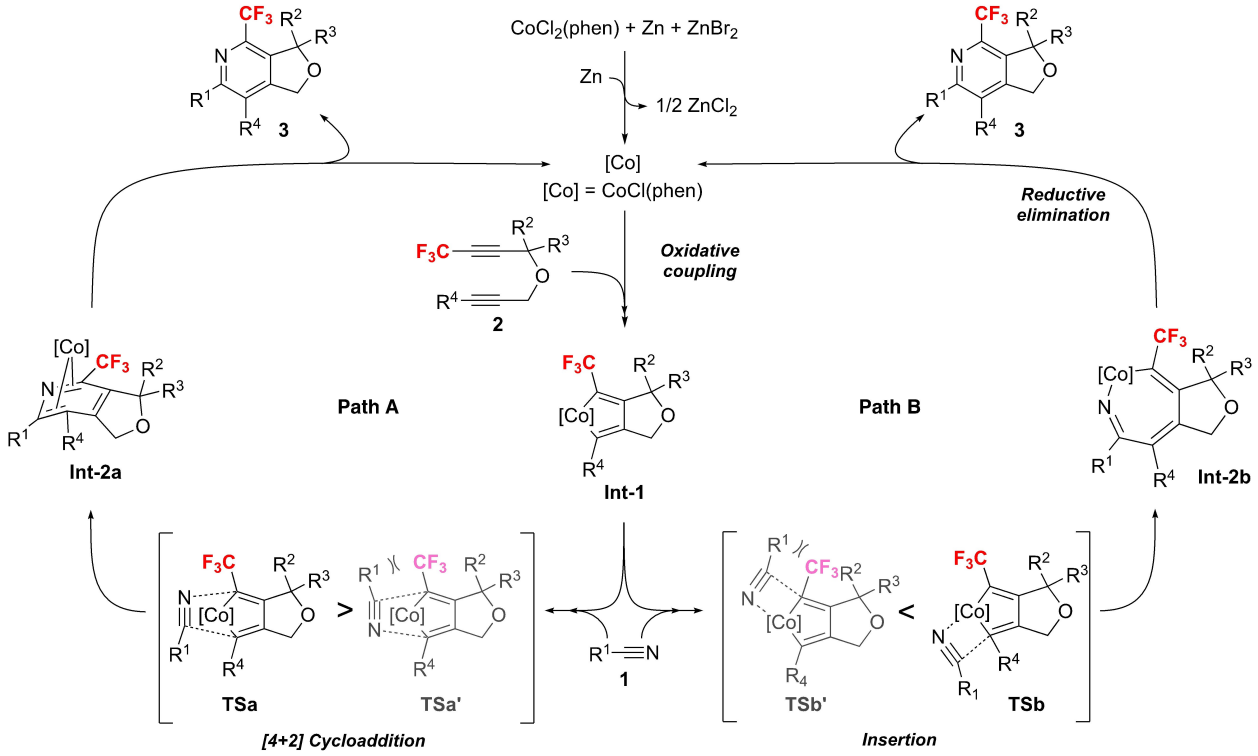
The scope of structurally various types of fluoroalkylated diynes **2** was then investigated. The cyclization reaction with nonafluoroalkylated diyne (**2B**), instead of trifluoromethylated one, took place smoothly, leading to the corresponding cyclic product **3 aB** quantitatively. We found that changing the substituent of the diyne from the spiro-cyclohexyl group to phenyl/methyl groups (**2C**) and nonyl group/H (**2D**) did not affect the reactivity. In the case of the internal diyne with a methyl group as R^4 (**2E**), the reaction produced the desired fluoroalkylated pyridine **3 aE** in 78% yield, together with the regioisomer **3 aE'** in 16% yield, whereas the diyne having a phenyl group as R^4 showed reverse selectivity, leading to **3 aF** and **3 aF'** in 24% and 52% yield, respectively.



Scheme 3. Gram-scale preparation of trifluoromethylated pyridine *via* cobalt-catalyzed [2+2+2] cycloaddition.

We also demonstrated the gram-scale preparation of trifluoromethylated pyridine through the present cobalt-catalyzed [2+2+2] cycloaddition reaction, as shown in Scheme 3. Thus, treatment of 1.00 g (5.50 mmol) of *p*-bromobenzonitrile (**1 e**) with 1.90 g (8.25 mmol) of trifluoromethylated diyne **2A** in the presence of 3 mol% of $CoCl_2$(phen) and 10 mol% each of $Zn/ZnBr_2$ in DCE at 80 °C for 3 h gave 1.86 g (4.50 mmol) of the corresponding pyridine **3 eA** in 82% isolated yield.

On the basis of the above results and previous reports,[8d,11a,12] two types of proposed mechanisms for the cobalt-catalyzed [2+2+2] cycloaddition of the fluoroalkylated diynes **2** with nitriles **1** are depicted in Scheme 4.[13] Thus, the cobalt(II) catalyst is reduced by $Zn/ZnBr_2$ system to generate the cobalt(I) active species.[14] Then, the oxidative coupling of the cobalt(I) with the diyne **2** furnishes the cobaltacyclopentadiene complex intermediate **Int-1**. One of the proposed reaction mechanisms includes [4+2] step of **Int-1** with nitrile **1** (**Path A**). In the case of R^4=H, the cobalt complex **Int-2 a** is regioselectively formed *via* transition state **TSa**, not **TSa'**, while avoiding a large steric repulsion between a substituent R^1 and a CF_3 group in the transition state. Then, reductive elimination of the cobalt(I) complex gives rise to the desired fluoroalkylated pyridine derivative **3**. Another reaction mecha-



Scheme 4. Proposed reaction mechanism.

nism (**Path B**), on the other hand, includes an insertion step instead of the [4+2] cycloaddition step. Thus, the nitrile **1** inserts regioselectively into the bond between Co and the carbon with R^4 *via* transition state **TSb**, not **TSb'**, while avoiding a large steric repulsion between a CF_3 group and R^1. Then, the formation of the 7-membered ring intermediate **Int-2b**, followed by reductive elimination, gives rise to the desired fluoroalkylated pyridine **3**, together with regeneration of the Co(I) species.

When internal diynes **2E** (R^4=Me) and **2F** (R^4=Ph) were used, on the other hand, the reaction *via* **TSa'** or **TSb'** partially proceeds to provide the regioisomer **3aE'** or **3aF'** in addition to **3aE** or **3aF** since a large steric repulsion occurs not only between R^1 (=Ph) and a CF_3 group, but also R^1 (=Ph) and R^4 (=Me or Ph).

Conclusion

In summary, we accomplished the novel synthesis of *α*-fluoroalkylated pyridines *via* cobalt-catalyzed [2+2+2] cycloaddition of fluorine-containing diynes with nitriles. This strategy is superior to precedented methods because of its advantageous features such as (i) inexpensive and abundant catalyst, (ii) wide range of the substrate scope with excellent yields and regioselectivities, and (iii) scalable up to gram level.[15] Furthermore, we have succeeded in the reaction using dinitrile, forming the dipyridyl structures at one step. We believe that this process using cobalt catalysts would become an efficient and useful protocol for fluorine-containing pyridines of biological interest.

Experimental Section

General Information

^{1}H and ^{13}C NMR spectra were obtained using an AVANCE III 400 NMR spectrometer (^{1}H: 400 MHz and ^{13}C: 100 MHz) in chloroform-*d* ($CDCl_3$) (Bruker, Germany), and the chemical shifts are reported in parts per million (ppm) based on the residual proton signal of the NMR solvent. ^{19}F NMR (376 MHz) spectra were obtained using AVANCE III 400 NMR spectrometer in $CDCl_3$ with $CFCl_3$ (δ_F=0 ppm) as an internal standard (Bruker, Germany). The Bruker AVANCE III 400 NMR spectrometer was used for determining the yield of the products with trifluoromethylbenzene ($CF_3C_6H_5$) or hexafluorobenzene (C_6F_6) as internal references. Infrared spectra (IR) were taken on a JASCO FT/IR 4100 type A spectrometer as a film on a NaCl film or KBr plate; all spectra are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were recorded on a JMS-700MS spectrometer (JEOL, Japan) using the fast-atom bombardment (FAB) method.

All reactions were carried out using dried glassware with a magnetic stirring bar and routinely monitored by ^{19}F NMR spectroscopy or thin-layer chromatography (TLC). All chemicals were of reagent grade and, if necessary, purified in the usual manner before use. Fluoroalkylated diynes **2** used in this research were prepared according to the literature.[9b] Column chromatography was carried out on silica gel (Wako gel® 60 N, 38–100 μm) and TLC analysis was performed on silica gel TLC plates (Merck, Silica gel $60F_{254}$).

X-ray Crystallography: A colorless prismic crystal of **3sA** having approximate dimensions of 0.15×0.12×0.10 mm was mounted on a glass fiber. All measurements for **3sA** were made on a diffractometer with filtered Mo*Kα* radiation (λ=0.71073 Å) and a rotating anode generator using a VariMax with PILATUS/DW (Rigaku); Compound **3sA** triclinic, a=29.095(3) Å, b=11.4067(15) Å, c=8.3862(9) Å, α=90, β=90, γ=90, V=2783.2(6) Å^3, T=173(2) K, space group *Pbcn*, Z=4 reflection measured. The final R_1 and wR_2 were 0.0571 and 0.1854 ($I>2\sigma(I)$). All calculations were performed using the CrystalStructure crystallographic software package. The structure was solved by direct methods and expanded using Fourier techniques. The structural model was refined by a full-matrix least-squares method using SHELXL-2014/6.[16] All calculations were performed using the SHELXL program. Crystallographic data for this compound has been deposited with the Cambridge Crystallographic Data Centre as supplementary data no. CCDC 2027273 (**3sA**). Copy of the data can be obtained free of charge by applying to The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (https://summary.ccdc.cam.ac.uk/structure-summary-form).

Typical Procedure for [2+2+2] Cycloaddition

In a 30 mL two-necked round bottomed-flask, equipped with a magnetic stirring bar, were placed benzonitrile **1a** (0.050 g, 0.482 mmol), trifluoromethylated alkyne **1A** (0.172 g, 0.747 mmol), Zn (3.3 mg, 0.050 mmol), ZnBr (0.011 g, 0.049 mmol), $CoCl_2$(phen) (4.6 mg, 0.015 mmol) in DCE (1.5 mL) in glove box, and the resulting mixture was stirred at 80 °C. After 3 h, the reaction mixture was cooled to room temperature and subjected to flash column chromatography using silica gel as stationary phase and EtOAc as mobile phase. After removal of solvent from the eluent under reduced pressure, the residue was purified by silica gel column chromatography (Hexane/AcOEt=20/1) to give the corresponding Spiro[cyclohexane-1,3'-6'-phenyl-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (**3aA**) (0.147 g, 0.441 mmol).

Spiro[cyclohexane-1,3'-6'-phenyl-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3aA)

Yield: 91% (147 mg); White oil, Eluent of the column chromatography: Hexane/EtOAc=20/1; ^{1}H NMR ($CDCl_3$): δ 1.25–1.45 (m, 1H, Cy*H*), 1.55–1.78 (m, 7H, Cy*H*), 2.05 (td, J=13.0, 5.0 Hz, 2H, Cy*H*), 5.08 (s, 2H, CH_2), 7.41–7.52 (m, 3H, Ar*H*), 7.76 (s, 1H, Ar*H*) 8.02–8.10 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.6 (Cy), 25.0 (Cy), 34.0–34.4 (m, Cy), 69.2 (O–CH_2), 88.4 (O–*C*), 115.8 (Ar), 122.0 (q, J=274.7 Hz, CF_3), 127.1 (Ar), 129.0 (Ar), 129.8 (Ar), 137.7 (Ar), 139 1 (Ar), 141.4 (q, J=35.1 Hz, CF_3–*C*), 154.3 (Ar), 155.8 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.19 (s, 3F); IR (neat) 2933, 2857, 1775, 1609, 1448, 1374, 1222, 1186, 1056, 906 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{19}H_{19}F_3NO$: 334.1417, Found: 334.1419.

Spiro[cyclohexane-1,3'-6'-(4-methylphenyl)-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 bA)

Yield: 80% (134 mg); White solid, M.p. 138.2-138.6 °C, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^{1}H NMR ($CDCl_3$): δ 1.25–1.44 (m, 1H, Cy*H*), 1.53–1.84 (m, 7H, Cy*H*), 2.04 (td, J = 13.0, 5.1 Hz, 2H, Cy*H*), 2.41 (s, 3H, CH_3), 5.06 (s, 2H, CH_2), 7.29 (d, J = 8.1 Hz, 2H, Ar*H*), 7.73 (s, 1H, Ar*H*), 7.94 (d, J = 8.1 Hz, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 21.3 (*C*H_3), 22.5 (Cy), 25.0 (Cy), 34.0–34.2 (m, Cy), 34.0–35.0 (m, Cy), 69.1 (O–*C*H_2), 88.3 (O–*C*), 115.4 (Ar), 122.0 (q, J = 274.6 Hz, *C*F_3), 126.9 (Ar), 129.6 (Ar), 134.8 (Ar), 138.7 (Ar), 139 9 (Ar), 141.2 (q, J = 35.1 Hz, CF_3–*C*), 154.1 (Ar), 155.8 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.20 (s, 3F); IR (KBr) 2943, 2655, 1605, 1448, 1373, 1126, 1046, 906 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{20}H_{21}F_3NO$: 348.1575, Found: 348.1585.

Spiro[cyclohexane-1,3'-6'-(4-aminophenyl)-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 cA)

Yield: 83% (143 mg); Yellow solid, M.p. 158.2–159.2 °C, Eluent of the column chromatography: Hexane/EtOAc = 3/2; ^{1}H NMR ($CDCl_3$): δ 1.25–1.39 (m, 1H, Cy*H*), 1.55–1.81 (m, 7H, Cy*H*), 2.02 (td, J = 13.0, 5.1 Hz, 2H, Cy*H*), 3.87 (bs, 2H, NH_2), 5.02 (d, J = 0.68 Hz, 2H, CH_2), 6.74 (d, J = 8.6 Hz, 2H, Ar*H*), 7.62 (s, 1H, Ar*H*), 7.88 (d, J = 8.6 Hz, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.6 (Cy), 25.0 (Cy), 34.0–34.5 (m, Cy), 69.1 (O–*C*H_2), 88.3 (O–*C*), 114.3 (Ar), 115.1 (Ar), 121.1 (q, J = 274.5 Hz, *C*F_3), 127.8 (Ar), 128.4 (Ar), 137.7 (Ar), 141.0 (q, J = 34.9 Hz, CF_3–*C*), 148.2 (Ar), 153.9 (Ar), 155.8 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.22 (s, 3F); IR (KBr) 3478, 3384, 2926, 2361, 1636, 1370, 1186, 1116 cm^{-1}; HRMS (FAB): calcd for $[M^+]$ $C_{19}H_{19}F_3N_2O$: 348.1449, Found: 348.1454.

Spiro[cyclohexane-1,3'-6'-(4-hydroxyphenyl)-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 dA)

Yield: 84% (147 mg); White solid, M.p. 151.0–152.0 °C, Eluent of the column chromatography: Hexane/EtOAc = 2/1; ^{1}H NMR ($CDCl_3$): δ 1.24–1.41 (m, 1H, Cy*H*), 1.62–1.84 (m, 7H, Cy*H*), 2.04 (td, J = 13.0, 4.9 Hz, 2H, Cy*H*), 5.06 (s, 2H, CH_2), 5.11 (s, 1H, O*H*), 6.93 (d, J = 8.6 Hz, 2H, Ar*H*), 7.68 (s, 1H, Ar*H*), 7.97 (d, J = 8.6 Hz, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.6 (Cy), 25.1 (Cy), 34.0–34.4 (m, Cy), 69.2 (O–*C*H_2), 88.5 (O–*C*), 115.0 (Ar), 115.9 (Cy), 122.0 (q, J = 274.6 Hz, *C*F_3), 128.8 (Ar), 130.5 (Ar), 138.3 (Ar), 141.3 (q, J = 35.1 Hz, CF_3–*C*), 154.1 (Ar), 155.5 (Ar), 157.4 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.24 (s, 3F); IR (KBr) 3338, 2934, 2858, 1608, 1445, 1376, 1223, 1142 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{19}H_{19}F_3NO_2$: 350.1368, Found: 350.1377.

Spiro[cyclohexane-1,3'-6'-(4-bromophenyl)-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 eA)

Yield: 89% (183 mg); White solid, M.p. 132.8–133.5 °C, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^{1}H NMR ($CDCl_3$): δ 1.25–1.43 (m, 1H, Cy*H*), 1.62–1.78 (m, 7H, Cy*H*), 2.04 (td, J = 13.0, 5.0 Hz, 2H, Cy*H*), 5.07 (s, 2H, CH_2), 7.60 (d, J = 8.6 Hz, 2H, Ar*H*), 7.73 (s, 1H, Ar*H*), 7.92 (d, J = 8.6 Hz, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.5 (Cy), 25.0 (Cy), 34.0–34.5 (m, Cy), 69.1 (*C*H_2), 88.4 (O–*C*), 115.5 (Ar), 121.8 (q, J = 274.7 Hz, *C*F_3), 128.6 (Ar), 132.1 (Ar), 136.4 (Ar), 139.5 (Ar), 141.4 (q, J = 35.1 Hz, CF_3–*C*), 154.49 (Ar), 154.54 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.24 (s, 3F); IR (KBr) 2973, 2931, 2846, 1607, 1190, 1374, 1146, 832 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{20}H_{18}BrF_3NO$: 312.0524, Found: 312.0535.

Spiro[cyclohexane-1,3'-4'-trifluoromethyl-6'-(3,5-bistrifluoromethylphenyl)-[1*H*]-furo[3,4-c] pyridine] (3 fA)

Yield: 71% (178 mg); White solid, M.p. 123.3–124.0 °C, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^{1}H NMR ($CDCl_3$): δ 1.21–1.44 (m, 1H, Cy*H*), 1.65–1.90 (m, 7H, Cy*H*), 2.05 (td, J = 12.9, 4.9 Hz, 2H, Cy*H*), 5.12 (s, 2H, CH_2), 7.86 (s, 1H, Ar*H*), 7.95 (s, 1H, Ar*H*), 8.50 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.5 (Cy), 25.0 (Cy), 34.1–34.3 (m, Cy), 69.1 (O–*C*H_2), 88.6 (O–*C*), 116.3 (Ar), 121.8 (q, J = 274.6 Hz, *C*F_3), 123.39 (q, J = 272.7 Hz, *C*F_3), 123.0–123.5 (m, Ar), 127.2–127.3 (m, Ar), 132.5 (q, J = 33.5 Hz, CF_3–*C*), 139.7 (Ar), 141.0 (Ar), 142.1 (q, J = 35.8 Hz, CF_3–*C*), 152.6 (Ar), 155.4 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −63.37 (s, 6F), −62.27 (s, 3F); IR (KBr) 2936, 2852, 1606, 1447, 1344, 1273, 1108, cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{21}H_{17}F_9NO$: 470.1166, Found: 470.1172.

Spiro[cyclohexane-1,3'-6'-(2,3,4,5,6-pentafluorophenyl)-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 gA)

Yield: 71% (149 mg); Colorless oil, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^{1}H NMR ($CDCl_3$): δ 1.25–1.45 (m, 1H, Cy*H*), 1.69–1.90 (m, 7H, Cy*H*), 2.05 (td, J = 12.7, 5.2 Hz, 2H, Cy*H*), 5.10 (s, 2H, CH_2), 7.52 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.5 (Cy), 25.0 (Cy), 34.0 (q, J = 2.6 Hz, Cy), 69.1 (O–*C*H_2), 88.8 (O–*C*), 114.2 (td, J = 15.9, 3.4 Hz, *C*–F), 121.6 (q, J = 274.8 Hz, *C*F_3), 121.9 (Ar), 138.0 (dm, J = 253.5 Hz, F–*C*), 141.8 (dm, J = 256.3 Hz, F–*C*), 142.3 (q, J = 36.0 Hz, CF_3–*C*), 145.0 (dm, J = 251.6 Hz, F–*C*), 145.3 (Ar), 154.7 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −161.68 (td, J = 21.5, 7.6 Hz, 2F), −152.94 (t, J = 21.5 Hz, 1F), −143.21 (dd, J = 21.5, 7.6 Hz, 2F); IR (neat) 2935, 2857, 1655, 1606, 1524, 1499, 1373, 1292, 1200, 1138, 993 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{19}H_{14}F_8NO$: 424.0948, Found: 424.0956.

Spiro[cyclohexane-1,3'-6'-(2-methylphenyl)-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 hA)

Yield: 65% (110 mg); White solid, M.p. 80.5–81.0 °C, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^{1}H NMR ($CDCl_3$): δ 1.23–1.43 (m, 1H, Cy*H*), 1.62–1.90 (m, 7H, Cy*H*), 2.07 (td, J = 12.8, 5.1 Hz, 2H, Cy*H*), 5.08 (s, 2H, CH_2), 7.24–7.48 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 20.6 (Me), 22.6 (Cy), 25.0 (Cy), 34.0–34.5 (m, Cy), 69.1 (O–*C*H_2), 88.5 (O–*C*), 119.7 (Ar), 122.0 (q, J = 274.6 Hz, *C*F_3), 126.2 (Ar), 129.0 (Ar), 129.8 (Ar), 131.3 (Ar), 136.6 (Ar), 138.6–138.7 (m, Ar), 140.8 (q, J = 35.2 Hz, CF_3–*C*), 153.7 (Ar), 158.5 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −61.99 (s, 3F); IR (KBr) 2972, 2939, 2852,

2360, 1608, 1451, 1377, 1227, 1110 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{20}H_{21}F_3NO$: 348.1575, Found: 348.1581.

Spiro[cyclohexane-1,3'-6'-(2-thienyl)-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 iA)

Yield: 99% (170 mg); Colorless oil, Eluent of the column chromatography: Hexane/EtOAc = 10/1; ^1H NMR ($CDCl_3$): δ 1.20–1.41 (m, 1H, Cy*H*), 1.65–1.85 (m, 7H, Cy*H*), 2.02 (td, J = 12.9, 5.0 Hz, 2H, Cy*H*), 5.04 (s, 2H, CH_2), 7.12 (t, J = 4.4 Hz, 1H, Ar*H*), 7.43 (d, J = 4.4 Hz, 1H, Ar*H*), 7.63 (s, *1*H, Ar*H*), 7.64 (d, J = 4.4 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.5 (Cy), 25.0 (Cy), 34.1–34.5 (m, Cy), 68.9 (O–CH_2), 88.3 (O–*C*), 114.2 (Ar), 121.7 (q, J = 274.7 Hz, CF_3), 125.6 (Ar), 128.1 (Ar), 128.5 (Ar), 138.7 (Ar), 141.1 (q, J = 35.4 Hz, CF_3–*C*), 151.0 (Ar), 154.2 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.33 (s, 3F); IR (neat) 2932, 2855, 1608, 1452, 1179, 1139, 903 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{17}H_{17}F_3NOS$: 340.0983, Found: 340.0984.

Spiro[cyclohexane-1,3'-6'-(4-formylphenyl)-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 jA)

Yield: 48% (86 mg); Yellow solid, M.p. 36.0–37.0 °C, Eluent of the column chromatography: Hexane/EtOAc = 5/1; ^1H NMR ($CDCl_3$): δ 1.22–1.42 (m, 1H, Cy*H*), 1.60–1.90 (m, 7H, Cy*H*), 2.05 (td, J = 13.0, 5.2 Hz, 2H, Cy*H*), 5.10 (s, 2H, CH_2), 7.85 (s, 1H, Ar*H*), 8.00 (d, J = 8.3 Hz, 2H, Ar*H*), 8.23 (d, J = 8.3 Hz, 1H, Ar*H*), 10.09 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.5 (Cy), 25.0 (Cy), 34.0–34.3 (m, Cy), 69.1 (O–CH_2), 88.5 (O–*C*), 116.59 (Ar), 121.8 (q, J = 274.6 Hz, CF_3), 127.7 (Ar), 130.3 (Ar), 137.0 (Ar), 140.3 (Ar), 141.8 (q, J = 35.1 Hz, CF_3–*C*), 143.0 (Ar), 154.2 (Ar), 154.8 (Ar), 191.9 (*C*=O); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.27 (s, 3F); IR (KBr) 2932, 2857, 2362, 1708, 1605, 1444, 1374, 1179, 1126, 1050 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{20}H_{19}F_3NO_2$: 362.1368, Found: 362.1370.

Spiro[cyclohexane-1,3'-6'-(4-ethynylphenyl)-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 kA)

Yield: 47% (86 mg); Colorless viscous liquid, Eluent of the column chromatography: Hexane/EtOAc = 10/1; ^1H NMR ($CDCl_3$): δ 1.25–1.45 (m, 1H, Cy*H*), 1.65–1.85 (m, 7H, Cy*H*), 2.04 (td, J = 13.0, 4.8 Hz, 2H, Cy*H*), 3.19 (s, 1H, C≡C–*H*), 5.06–5.08 (m, 2H, CH_2), 7.60 (d, J = 8.5 Hz, 2H, Ar*H*), 7.75 (s, 1H, Ar*H*), 8.02 (d, J = 8.5 Hz, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.6 (Cy), 25.0 (Cy), 34.0–34.2 (m, Cy), 69.2 (O–CH_2), 78.9 (C≡*C*), 83.4 (C≡*C*), 88.5 (O–*C*), 115.9 (Ar), 121.9 (q, J = 274.6 Hz, CF_3), 127.0 (Ar), 132.8 (Ar), 137.8 (Ar), 139.5 (Ar), 141.6 (q, J = 34.8 Hz, CF_3–*C*), 154.5 (Ar), 154.8 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.24 (s, 3F); IR (neat) 3300, 2933, 2856, 1775, 1607, 1447, 1374, 1220, 1187, 845 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{21}H_{19}F_3NO$: 358.1419, Found: 358.1416.

Spiro[cyclohexane-1,3'-4'-trifluoromethyl-6'-[4-(2-trimethysilylethynyl)phenyl]-[1*H*]-furo[3,4-c]pyridine] (3 lA)

Yield: 89% (190 mg); White solid, M.p. 152.5-153.5 °C, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^1H NMR ($CDCl_3$): δ 0.27 (s, 9H, CH_3), 1.20–1.42 (m, 1H, Cy*H*), 1.60–1.90 (m, 7H, Cy*H*), 2.04 (td, J = 12.8, 4.9 Hz, 2H, Cy*H*), 5.07 (s, 2H, CH_2), 7.57 (d, J = 8.5 Hz, 2H, Ar*H*), 7.76 (s, 1H, Ar*H*), 8.01 (d, J = 8.5 Hz, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 0.01 (CH_3), 22.5 (Cy), 25.0 (Cy), 34.1 (d, J = 2.2 Hz, Cy), 69.1 (O–CH_2), 88.4 (O–*C*), 96.3 (C≡C), 104.8 (C≡C), 115.8 (Ar), 121.9 (q, J = 274.8 Hz, CF_3), 124.6 (Ar), 126.8 (Ar), 132.5 (Ar), 137.3 (Ar), 139.4 (Ar), 141.4 (q, J = 35.2 Hz, CF_3–*C*), 154.4 (Ar), 154.7 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.27 (s, 3F); IR (KBr) 2902, 2855, 2340, 2160, 1606, 1450, 1374, 1140, 1011 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{24}H_{27}F_3NOSi$: 430.1814, Found: 430.1817.

Spiro[cyclohexane-1,3'-6'-methyl-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 nA)

Yield: 65% (87 mg); White solid, M.p. 73.7–73.9 °C, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^1H NMR ($CDCl_3$): δ 1.24–1.40 (m, 1H, Cy*H*), 1.60–1.80 (m, 7H, Cy*H*), 1.99 (td, J = 13.1, 5.0 Hz, 2H, Cy*H*), 2.60 (s, 3H, CH_3), 4.97 (s, 2H, CH_2), 7.19 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.6 (Cy), 24.1 (CH_3), 25.0 (Cy), 34.1–34.2 (m, Cy), 68.9 (O–CH_2), 88.4 (O–*C*), 119.4 (Ar), 122.0 (q, J = 274.3 Hz, CF_3), 138.0 (Ar), 140.9 (q, J = 34.8 Hz, CF_3–*C*), 153.7 (Ar), 157.2 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.56 (s, 3F); IR (KBr) 2958, 2853, 2358, 1612, 1449, 1489, 1127, 1061, 889 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{14}H_{17}F_3NO$: 272.1262, Found: 272.1255.

Spiro[cyclohexane-1,3'-6'-benzyl-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 qA)

Yield: 95% (151 mg); Colorless oil, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^1H NMR ($CDCl_3$): δ 1.40–1.60 (m, 1H, Cy*H*), 1.75–2.00 (m, 7H, Cy*H*), 2.19 (td, J = 12.7, 5.0 Hz, 2H, Cy*H*), 4.41 (s, 2H, PhCH_2), 5.11 (s, 2H, OCH_2), 7.40–7.60 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.5 (Cy), 25.0 (Cy), 34.0–34.2 (m, Cy), 44.1 (Ph–CH_2), 68.9 (O–CH_2), 88.2 (O–*C*), 118.8 (Ar), 122.0 (q, J = 274.5 Hz, CF_3), 126.8 (Ar), 128.8 (Ar), 129.3 (Ar), 138.4 (Ar), 138.5 (Ar), 140.8 (q, J = 34.9 Hz, CF_3–*C*), 153.9 (Ar), 159.9 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −61.94 (s, 3F); IR (neat) 2932, 2856, 1777, 1603, 1449, 1373, 1173, 1132 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{20}H_{21}F_3NO$: 348.1575, Found: 348.1581.

Methyl 3-(spiro[cyclohexane-1,3'-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridin]-6'-yl)propanoate (3 rA)

Yield: 83% (139 mg); White solid, M.p. 79.0–80.2 °C, Eluent of the column chromatography: Hexane/EtOAc = 5/1; ^1H NMR ($CDCl_3$): δ 1.20–1.40 (m, 1H, Cy*H*), 1.60–1.80 (m, 7H, Cy*H*), 1.98 (td, J = 13.1, 4.9 Hz, 2H, Cy*H*), 2.83 (t, J = 7.2 Hz, 2H, CH_2), 3.16 (s, J = 7.2 Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 4.97 (s, 2H, OCH_2), 7.23 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.5 (Cy), 24.9 (Cy), 32.3 (CH_2), 32.4 (CH_2), 34.0–34.1 (m, Cy), 51.6 (Me), 68.9 (O–CH_2), 88.2 (O–*C*), 119.0 (Ar), 121.9 (q, J = 274.4 Hz, CF_3), 138.5 (Ar), 140.9 (q, J = 35.0 Hz, CF_3–*C*), 153.6 (Ar), 158.6 (Ar), 173.5 (*C*=O); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.11 (s, 3F); IR (KBr) 2942, 2854, 2365, 1738, 1612, 1380, 1171, 1050 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{12}H_{21}F_3NO_3$: 344.1474, Found: 344.1468.

Bis(spiro[cyclohexane-1,3'-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridin]-6'-yl)methane (3 sA)

Yield: 92% (974 mg); White solid, M.p. 82.0–82.4 °C, Eluent of the column chromatography: Hexane/EtOAc = 5/1; ^{1}H NMR ($CDCl_3$): δ 1.20–1.40 (m, 1H, Cy*H*), 1.60–1.80 (m, 7H, Cy*H*), 1.98 (td, J = 13.0, 4.8 Hz, 2H, Cy*H*), 4.42 (s, 2H, CH_2), 4.97 (s, 4H, CH_2), 7.40 (s, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.5 (Cy), 25.0 (Cy), 34.0–34.2 (m, Cy), 45.9 (*C*H_2), 69.0 (O–*C*H_2), 88.3 (O–*C*), 119.8 (Ar), 121.9 (q, J = 274.5 Hz, *C*F_3), 139.1 (Ar), 141.1 (q, J = 35.1 Hz, CF_3–*C*), 154.2 (Ar), 157.1 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −61.96 (s, 3F); IR (KBr) 2928, 2856, 2360, 1610, 1449, 1375, 1291, 1193, 1172, 1066 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{27}H_{29}F_6O_2N_2$: 527.2133, Found: 527.2125.

Bis(spiro[cyclohexane-1,3'-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridin]-6'-yl)ethane (3 tA)

Yield: 92% (253 mg); White solid, M.p. 95.0–97.0 °C, Eluent of the column chromatography: Hexane/EtOAc = 5/1; ^{1}H NMR ($CDCl_3$): δ 1.20–1.40 (m, 2H, Cy*H*), 1.60–1.72 (m, 14H, Cy*H*), 1.98 (td, J = 13.1, 4.7 Hz, 4H, Cy*H*), 3.33 (s, 4H, Cy*H*), 4.96 (s, 2H, CH_2), 7.20–7.30 (s, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.5 (Cy), 25.0 (Cy), 34.0–34.2 (m, Cy), 36.4 (*C*H_2), 68.9 (O–*C*H_2), 88.3 (O–*C*), 119.4 (Ar), 122.0 (q, J = 274.5 Hz, *C*F_3), 138.4 (Ar), 140.8 (q, J = 34.8 Hz, CF_3–*C*), 153.5 (Ar), 159.5 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.02 (s, 3F); IR (KBr) 2936, 2850, 2361, 1609, 1449, 1373, 1062 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{28}H_{31}F_6N_2O_2$: 541.2290, Found: 541.2279.

Bis(spiro[cyclohexane-1,3'-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridin]-6'-yl)propane (3 uA)

Yield: 92% (259 mg); White solid, M.p. 114.0–114.8 °C, Eluent of the column chromatography: Hexane/EtOAc = 5/1; ^{1}H NMR ($CDCl_3$): δ 1.20–1.40 (m, 2H, Cy*H*), 1.60–1.85 (m, 14H, Cy*H*), 1.98 (td, J = 13.0, 4.9 Hz, 4H, Cy*H*), 2.22 (quin, J = 7.5 Hz, 2H, CH_2), 2.92 (t, J = 7.5 Hz, 4H, CH_2), 4.97 (s, 4H, OCH_2), 7.21 (s, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.5 (Cy), 25.0 (Cy), 28.8 (*C*H_2), 34.0–34.2 (m, Cy), 36.8 (*C*H_2), 68.8 (O–*C*H_2), 88.2 (O–*C*), 118.9 (Ar), 122.0 (q, J = 274.7 Hz, *C*F_3), 138.2 (Ar), 140.8 (q, J = 34.8 Hz, CF_3–*C*), 153.6 (Ar), 160.3 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.98 (s, 3F); IR (KBr) 2934, 2856, 2362, 1615, 1448, 1380, 1170, 1112, 1066 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{29}H_{33}F_6N_2O_2$: 555.2446, Found: 555.2447.

Bis(spiro[cyclohexane-1,3'-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridin]-6'-yl)butane (3 vA)

Yield: 88% (247 mg); White solid, M.p. 139.0–139.6 °C, Eluent of the column chromatography: Hexane/EtOAc = 5/1; ^{1}H NMR ($CDCl_3$): δ 1.25–1.90 (m, 20H, Cy*H*, CH_2), 2.00 (td, J = 13.0, 5.0 Hz, 4H, Cy*H*), 2.89 (t, J = 6.6 Hz, 4H, CH_2), 4.98 (s, 4H, OCH_2), 7.19 (s, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.65 (Cy), 25.0 (Cy), 29.0 (*C*H_2), 34.0–34.2 (m, Cy), 37.4 (*C*H_2), 68.9 (O–*C*H_2), 88.3 (O–*C*), 118.7 (Ar), 122.0 (q, J = 274.4 Hz, *C*F_3), 138.2 (Ar), 140.9 (q, J = 34.7 Hz, CF_3–*C*), 153.6 (Ar), 160.8 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −61.98 (s, 3F); IR (KBr) 2931, 2854, 2362, 1612, 1450, 1381, 1319, 1120, 1054 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{30}H_{35}F_6N_2O_2$: 569.2603, Found: 569.2605.

Bis(spiro[cyclohexane-1,3'-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridin]-6'-yl)pentane (3 wA)

Yield: 73% (217 mg); Colorless oil, Eluent of the column chromatography: Hexane/EtOAc = 5/1; ^{1}H NMR ($CDCl_3$): δ 1.22–1.39 (m, 2H, Cy*H*), 1.45 (quin, J = 7.7 Hz, 2H, CH_2), 1.60–1.85 (m, 18H, Cy*H*, CH_2), 2.00 (td, J = 13.1, 5.0 Hz, 2H, Cy*H*), 2.84 (t, J = 7.7 Hz, 4H, CH_2), 4.98 (s, 4H, OCH_2), 7.17 (s, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.4 (Cy), 24.9 (Cy), 28.9 (*C*H_2), 29.3 (*C*H_2), 33.9–34.1 (m, Cy), 37.5 (*C*H_2), 68.8 (O–*C*H_2), 88.2 (O–*C*), 118.5 (Ar), 121.9 (q, J = 274.5 Hz, *C*F_3), 138.0 (Ar), 140.8 (q, J = 34.8 Hz, CF_3–*C*), 153.4 (Ar), 160.9 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −62.01 (s, 3F); IR (neat) 2932, 2858, 1777, 1612, 1449, 1378, 1173, 1132, 1065 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{31}H_{37}F_6N_2O_2$: 583.2759, Found: 583.2755.

Spiro[cyclohexane-1,3'-4'-nonafluorobutyl-6'-phenyl-[1*H*]-furo[3,4-c]pyridine] (3 aB)

Yield: 91% (222 g); Yellow oil, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^{1}H NMR ($CDCl_3$): δ 1.25–1.45 (m, 1H, Cy*H*), 1.65–1.90 (m, 7H, Cy*H*), 2.06 (td, J = 13.0, 4.7 Hz, 2H, Cy*H*), 5.09 (s, 2H, CH_2), 7.42–7.52 (m, 3H, Ar*H*), 7.76 (s, 1H, Ar*H*), 8.04 (dm, J = 8.2 Hz, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.7 (Cy), 25.1 (Cy), 34.6 (t, J = 4.5 Hz, Cy), 69.3 (O–*C*H_2), 89.1 (O–*C*), 106.0–123.0 (m, 4 C, *C*$_4F_9$), 127.1 (Ar), 129.0 (Ar), 129.9 (Ar), 137.4 (Ar), 140.9 (Ar), 142.1 (t, J = 28.0 Hz, CF_2–*C*), 154.5 (Ar), 155.6 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −125.40 to −125.30 (m, 2F), −120.10 to −119.90 (m, 2F), −105.28 (t, J = 12.9 Hz, 3F), −81.38 (t, J = 10.0 Hz, 3F); IR (neat) 2934, 2859, 1610, 1448, 1235, 1212, 1135 cm^{-1}; HRMS (FAB): calcd for $[M^+]$ $C_{22}H_{18}F_9NO$: 483.1245, Found: 483.1233.

3-Methyl-3,6-diphenyl-4-trifluoromethyl-1,3-dihydrofuro[3,4-c]pyridine (3 aC)

Yield: 98% (177 mg); Colorless oil, Eluent of the column chromatography: Hexane/EtOAc = 10/1; ^{1}H NMR ($CDCl_3$): δ 1.25–1.45 (m, 1H, Cy*H*), 1.55–1.78 (m, 7H, Cy*H*), 2.05 (td, J = 13.0, 5.0 Hz, 2H, Cy*H*), 5.08 (s, 2H, CH_2), 7.41–7.52 (m, 3H, Ar*H*), 7.76 (s, 1H, Ar*H*) 8.02–8.10 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 24.7–24.8 (m, *C*H_3), 70.0 (O–*C*H_2), 89.3 (O–*C*), 115.7 (Ar), 121.4 (q, J = 275.1 Hz, *C*F_3), 126.4 (Ar), 127.2 (Ar), 128.2 (Ar), 129.0 (Ar), 137.4 (Ar), 138.2 (Ar), 142.1 (q, J = 35.7 Hz, CF_3–*C*), 154.2 (Ar), 156.6 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −63.66 (s, 3F); IR (neat) 3062, 3033, 2942, 2851, 1610, 1446, 1375, 1191, 1136, 1048 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{21}H_{17}F_3NO$: 356.1262, Found: 356.1260.

3-Nonyl-6-phenyl-4-Trifluoromethyl-1,3-dihydrofuro[3,4-c]pyridine (3 aD)

Yield: 94% (182 mg); White solid, M.p. 40.8–41.0 °C Eluent of the column chromatography: Hexane/EtOAc = 10/1; ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 6.8 Hz, 3H, C_8H_{16}–*C*H_3) 1.16–1.54 (m,

14H, C_7H_{14}–CH_3), 1.66–1.78 (m, 1H, CH_2–C_8H_{17}), 1.82–1.93 (m, 1H, CH_2–C_8H_{17}), 5.12 (d, J = 14.1 Hz, 1H, CH_2–O), 5.19 (d, J = 14.1 Hz, 1H, CH_2–O), 5.52–5.61 (m, 1H, CH–C_9H_{19}), 7.42–7.54 (m, 3H, Ar*H*), 7.77 (s, 1H, Ar*H*) 8.02–8.08 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 14.2 (C_9H_{19}), 22.8 (C_9H_{19}), 25.7 (C_9H_{19}), 29.42 (C_9H_{19}), 29.46 (C_9H_{19}), 29.61 (C_9H_{19}), 29.64 (C_9H_{19}), 32.0 (C_9H_{19}), 35.4 (C_9H_{19}), 71.2 (CH_2), 83.1 (O–*C*), 115.6 (Ar), 121.8 (q, J = 274.6 Hz, CF_3), 127.2 (Ar), 129.0 (Ar), 135.1 (Ar), 137.7 (Ar), 141.5 (q, J = 35.7 Hz, CF_3–*C*), 153.4 (Ar), 156.7 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −65.72 (s, 3F); IR (KBr) 2917, 2848, 1617, 1459, 1375, 1220, 1124 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{23}H_{29}F_3NO$: 392.2201, Found: 392.2195.

Spiro[cyclohexane-1,3'-7'-methyl-6'-phenyl-4'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 aE)

Yield: 71% (123 mg); White solid, M.p. 126.0–128.0 °C, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^{1}H NMR ($CDCl_3$): δ 1.25–1.42 (m, 1H, Cy*H*), 1.68–1.90 (m, 7H, Cy*H*), 2.06 (td, J = 13.2, 4.8 Hz, 2H, Cy*H*), 2.29 (s, 3H, CH_3), 5.03 (s, 2H, CH_2), 7.38–7.50 (m, 3H, Ar*H*), 7.52–7.58 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 16.4 (CH_3), 22.6 (Cy), 25.0 (Cy), 34.3–34.4 (m, Cy), 69.2 (O–CH_2), 89.4 (O–*C*), 122.1 (q, J = 273.7 Hz, CF_3), 128.2 (Ar), 128.4 (Ar), 128.6 (Ar), 129.4 (Ar), 138.66 (q, J = 35.2 Hz, CF_3–*C*), 138.70 (Ar), 138.74 (Ar), 153.0 (Ar), 157.0 (Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −61.66 (s, 3F); IR (KBr) 2936, 2858, 2364, 1598, 1448, 1375, 1224, 1131, 1048 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{20}H_{21}F_3NO$: 348.1575, Found: 348.1583.

Spiro[cyclohexane-1,1'-4'-methyl-6'-phenyl-7'-trifluoromethyl-[1*H*]-furo[3,4-c]pyridine] (3 aE')

Yield: 9% (16 mg); Colorless oil, Eluent of the column chromatography: Hexane/EtOAc = 20/1; ^{1}H NMR ($CDCl_3$): δ 1.22–1.40 (m, 1H, Cy*H*), 1.67–1.90 (m, 7H, Cy*H*), 2.07 (td, J = 13.1, 4.6 Hz, 2H, Cy*H*), 2.51 (s, 3H, CH_3), 5.01 (s, 2H, CH_2), 7.35–7.45 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$): δ 22.3 (CH_3), 22.6 (Cy), 25.0 (Cy), 33.1 (d, J = 3.5 Hz, Cy), 67.7 (O–CH_2), 90.7 (O–*C*), 117.6 (q, J = 32.1 Hz, CF_3–*C*), 124.4 (q, J = 274.5 Hz, CF_3), 128.1 (Ar), 128.3 (Ar), 128.5 (Ar), 134.2 (Ar), 141.1 (Ar), 154.2 (Ar), 154.9–155.0 (m, Ar), 158.2–158.3 (m, Ar); ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ −48.76 (s, 3F); IR (neat) 2936, 2858, 2364, 1598, 1448, 1375, 1225, 1175, 1131, 1048 cm^{-1}; HRMS (FAB): calcd for $[M+H]^+$ $C_{20}H_{21}F_3NO$: 348.1575, Found: 348.1583.

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[13] According to the previous reports about the reaction mechanism based on the computational study,[12a,12c] the reaction pathway depends on the used substrate. Furthermore, most computational studies[12] have been done using the CpCo complex, but not the XCo one (X = Cl, Br, or I). Therefore, at this stage, it is difficult to decide whether the reaction proceeds *via* [4 + 2] cycloaddition step or insertion step.

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[15] Even when the present reaction was carried out for the same reaction time as rhodium catalytic system shown in Scheme 1 (b), the desired pyridine **3 aA** was obtained in excellent yield (97% NMR yield). [Reaction conditions: **1 a** (0.5 mmol), **2A** (1.5 mmol), Zn (10 mol%), $ZnBr_2$ (10 mol%), $CoCl_2$(phen) (3 mol%), DCE (1.5 mL), 80 °C, *2 h.*] This result indicates that cobalt-catalyzed [2 + 2 + 2] cycloaddition reaction proceeds more efficiently than the corresponding rhodium-catalyzed one. This is possibly because cobalt is a relatively hard acid than rhodium, whereas nitrogen is a hard base based on the HSAB theory. Thus, cobalt is able to coordinate with a nitrile smoothly, which could accelerate the insertion reaction or [4 + 2] cycloaddition reaction.

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