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Fully Regiocontrolled Polyarylation of Pyridine

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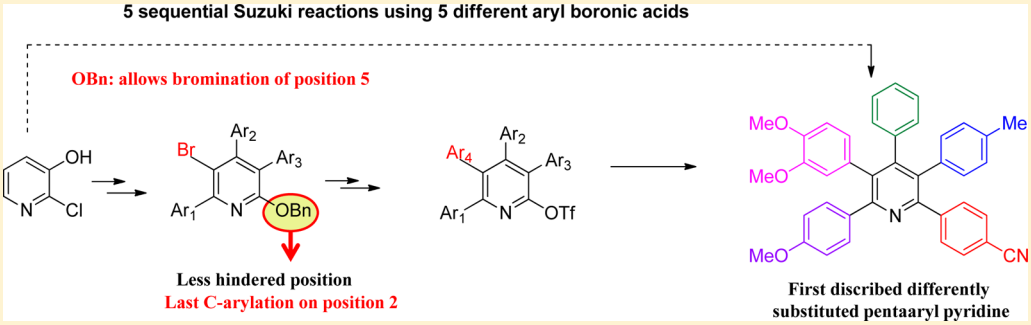
Supporting Information



ABSTRACT: Starting from commercially available 2-chloro-3-hydroxypyridine, a new route leading to the first protypical pentaarylpyridine bearing five different substituents is reported. This strategy involves a set of five sequential but fully regiocontrolled Suzuki−Miyaura reactions and highlights the 2-OBn pyridine protecting group as a key intermediate. The 2-OBn group played a double role: (i) it allowed additional bromination at position 5 and (ii) it could afford the reactive OTf species for the last C-arylation step at the less hindered 2 position of the tetraarylpyridine. The photophysical properties of the novel compounds are also described. The synthesized pentaarylpyridine derivative exhibit a large Stokes shift, strong solvatochromism, and quantum yield values up to 0.47; thus, they constitute promising building blocks for the design of environment-sensitive probes.

INTRODUCTION

Pyridine derivatives represent an important class of six-membered heterocycles prevalent in a number of biologically active natural products[1−7] and pharmaceutical drugs.[8−12] They have significant applications in many fields of chemistry.[13] In particular, they are useful building blocks for the preparation of chiral ligands[14−16] and new materials with important photo- or electrochemical properties.[17−20] Several strategies have been developed to control the polysubstitution of a pyridine ring.[21−24] However, these methods suffer from limited chemical diversity and either sometimes fail because of steric hindrance, particularly for tetra- or pentasubstituted pyridines, or afforded low yields. Herein, we describe a versatile strategy based on a set of sequential Suzuki−Miyaura Pd-catalyzed cross-coupling reactions that allow for regiocontrolled aryl substitutions at the five positions of a pyridine ring, resulting in a large amount of chemical diversity in good yields.

Among the various strategies developed to control the polysubstitution of pyridine, simple condensation reactions based on the classical Hantzsch reaction, various cycloadditions,[21,22] thermal rearrangements of triazines,[23] and multicomponent reactions[24] combining Michael acceptors with malonitrile afforded numerous polyfunctionalized pyridines. However, the products contained specific functional groups resulting from the use of specific reagents in these methodologies (i.e., CN, CO_2Et, or CF_3 residues). Pd- or Cu-catalyzed cross-coupling reactions offer novel perspectives in organic synthesis. Although initially these reactions were conducted with halobenzenes, they have now been extended to heteroaromatic halides such as halopyridines.

By combining various Pd-catalyzed reactions (such as Suzuki−Miyaura, Buchwald−Hartwig, and Sonogashira reactions), di- or trisubstituted pyridines have been prepared starting from commercially available starting materials such as 2,6-dichloro-4-iodopyridine or 3,4,5-triiodopyridine.[25−28] However, the regioselective monosubstitution of symmetrical halogens in positions 2/6 or 3/5, using Pd-catalyzed reactions generally results in complex mixtures of mono- and disubstituted aryl pyridines.[25,28,29] A better regiocontrolled

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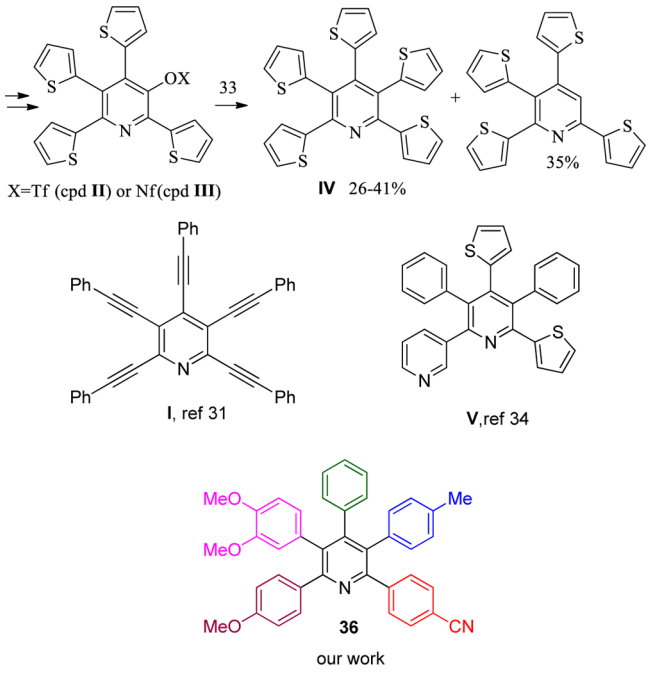
substitution was observed when 2-chloro-3,4-diiodopyridine was used, which resulted in differently substituted 2,3,4-triarylpyridine derivatives[30] owing to the different chemical reactivities of both iodine atoms.

However, it became significantly more challenging to increase the number of substitutions (more than three or four) at the pyridine nucleus, and very few studies have reported the synthesis of pentasubstituted pyridine derivatives. Recently, Langer et al. reported multiple Sonogashira reactions on pentachloropyridine to afford the corresponding pentaalkynylpyridine (compound I).[31] Reissig and co-workers attempted the synthesis of poly(2-thienyl)pyridine; their strategy was efficient for the synthesis of trisubstituted[32] (2,3,5 and 2,4,6) and tetrasubstituted (2,3,5,6 and 2,3,4,6) poly(2-thienyl)-pyridines. However, the introduction of the fifth thienyl substituent was more difficult because of the loss of reactivity resulting from the steric hindrance generated by the presence of two aromatic rings at positions 2 and 4 as the neighboring substituents of the remaining 3-OTf (compound II) or ONf (compound III). However, after efforts to improve the final step of the reaction, the authors obtained penta(2-thienyl)-pyridines (compound IV)[33] in moderate yields (26–41%, Scheme 1). Few other studies dealing with the synthesis of

Scheme 1. Known Examples for Pentasubstitution of Pyridine



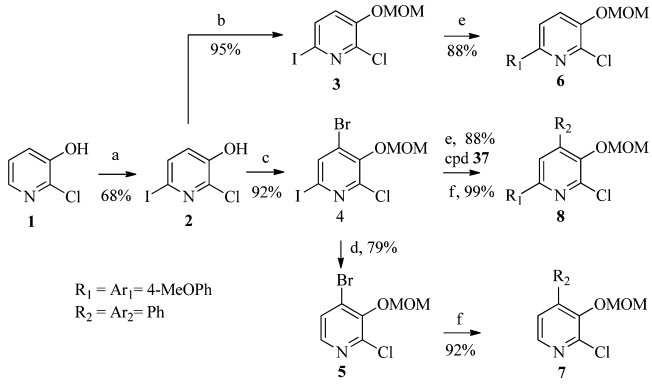
differently tetra- or pentasubstituted pyridines have been reported using specific cycloaddition reactions (e.g., involving the dimerization of neutral 2-azadienes (compound V)[34] or the subsequent Pd-catalyzed cyclization of allenyl imines)[35]. Some limitations of diversity of aryl substituents resulted from either the specific reaction mechanism[34] (Scheme 1) or the unavailability of the amino allenes.[35]

In this article, we report the synthesis of tri-, tetra-, and pentasubstituted arylpyridines using complementary methods by combining regioselective halogenations, protection/activation of phenol groups, and cross-coupling reactions.

RESULTS AND DISCUSSION

Commercially available 2-chloro-3-hydroxypyridine **1** was first treated with iodine in basic medium to afford 6-iododerivative **2** in satisfactory yield after precipitation in water at pH 6 (Scheme 2). This first step could be scaled up on a multigram

Scheme 2. Preparation of Key Intermediates 3–5 Leading to Successive Regiocontrolled C-Arylation of Tri-, Tetra-, and Pentasubstituted Pyridines[a]



[a]Reagents and conditions: (a) I_2, Na_2CO_3, H_2O, rt; (b) MOMCl, iPr_2NH, CH_2Cl_2, rt; (c) (i) NBS, iPr_2NH, CH_2Cl_2, rt; (ii) MOMCl, rt; (d) *i*PrMgCl 2 M, −78 °C, THF, MeOH; (e) $Pd(PPh_3)_4$, 4-MeOPhB$(OH)_2$, Na_2CO_3, toluene/EtOH/H_2O, 90 °C; (f) PhB$(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O, 90 °C.

scale with 68% yield.[36,37] To ensure high chemoselectivity, bromination was performed using NBS in the presence of diisopropylamine. The di- and trihalogenated hydroxypyridine intermediates were first O-protected as MOM ethers before performing the Pd-catalyzed cross-coupling reactions. O-MOM intermediates **3** and **4** were obtained in nearly quantitative yields. Moreover, trihalogenated pyridine **4** was also efficiently used as a substrate in halogen/metal-exchange reactions and underwent clean magnesiation at −78 °C in THF in the presence of *i*PrMgCl.[38] The organomagnesium intermediate was trapped with methanol to afford 2-chloro-4-bromo-OMOM-pyridine **5** in 79% yield. All three halogenated O-MOM pyridines, **3**–**5**, were then submitted to the first C-arylation reaction occurring at position 6 (compound **6**, R_1=Ar_1), position 4 (compound **7**, R_2=Ar_2), or to two sequential C-arylation reactions at positions 6 and 4 (compound **8**, R_1=Ar_1, R_2=Ar_2). All of these Suzuki–Miyaura reactions afford the expected aryl derivatives in good yields (up to 90%, see the Supporting Information for details). 3-OMOM pyridine intermediates **6**, **7**, and **8** further provided compounds **22** and **34**, **23** and **35**, and **24** and **36**, respectively, as detailed in Scheme 3.

Notably, the OH group in hydroxypyridine **2** plays a double role: (i) as an ortho-para-directing group, it favors further halogenations in positions 6 and/or 4 of the pyridine nucleus and (ii) it could be easily transformed into OTf or ONf[33] and thus could be employed for further C-arylation reactions. Finally, resulting aryl pyridines **6**–**8** seemed to be promising candidates for building highly polyarylated pyridines (Scheme 3). However, their application, particularly in the synthesis of pentaarylpyridine, is limited by some drawbacks. Reissig and co-workers already emphasized the rather disappointing reactivity of the highly hindered 3-OTf and 3-ONf derivatives of 2,4,5,6-tetra(2-thienyl)pyridine, as shown in Scheme 1, and

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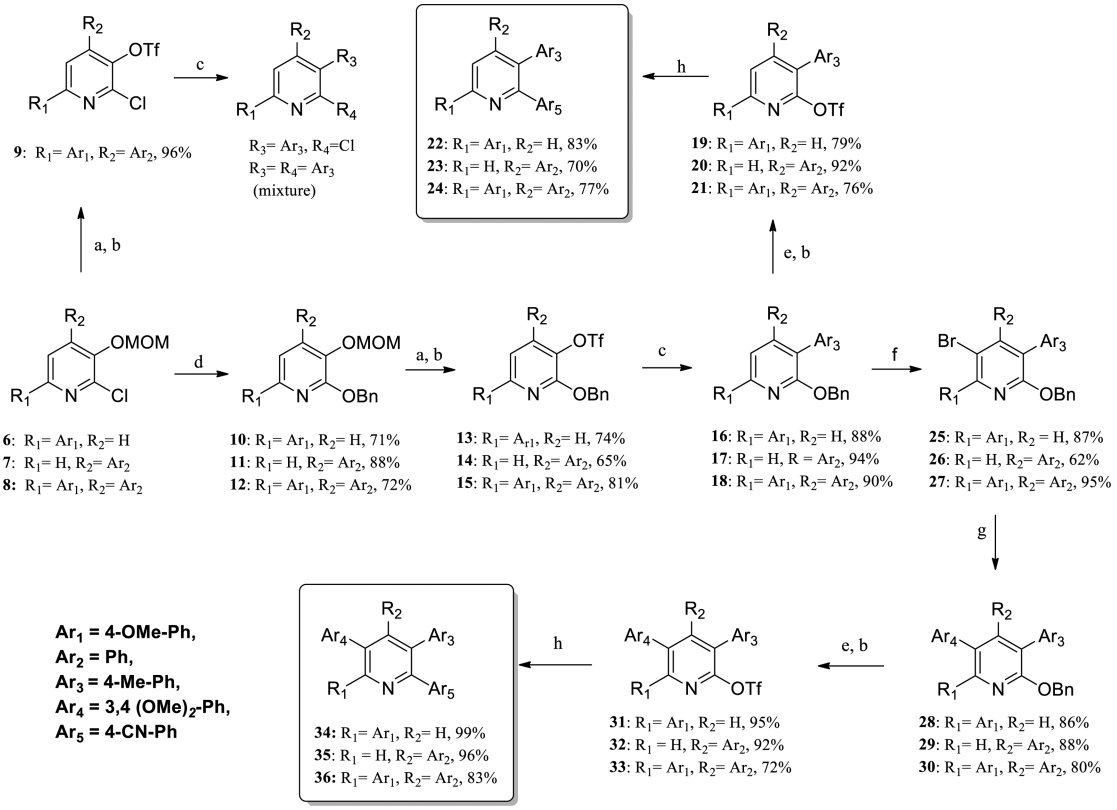
Scheme 3. Detailed Strategy Leading to Diversely Polyarylated Pyridines[a]



[a]Reagents and conditions: (a) Amberlyst, CH_2Cl_2/MeOH, rt; (b) Tf_2O, Et_3N, CH_2Cl_2, rt; (c) 4-MePhB$(OH)_2$, 5% $Pd(PPh_3)_4$, K_3PO_4, 1,4-dioxane, 110 °C; (d) BnOH, 2.5% $Pd(OAc)_2$, 5% Xantphos, Cs_2CO_3, 1,4-dioxane, 110 °C; (e) HCl 4 N/1,4-dioxane, CH_2Cl_2, 40 °C; (f) NBS, DMF, 40 °C; (g) 3,4-$(MeO)_2$PhB$(OH)_2$, 5% $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O, 110 °C; (h) 4-CNPhB$(OH)_2$, 5% $Pd(PPh_3)_4$, K_3PO_4, 1,4-dioxane, 110 °C.

the yield of 2,3,4,5,6-penta(2-thienyl)pyridine (26−41%) could not be optimized. Moreover, they recovered approximately 35% of 2,4,5,6-tetra(2-thienyl)pyridine owing to the reductive elimination of 3-OTf or 3-ONf groups at position 3 of pyridine (Scheme 1).

A poor regioselectivity was also observed for 2-Cl-3-OTf intermediate **9**, as its C-arylation using of *p*-tolylboronic acid resulted in a complex mixture of 2-*p*-tolyl and 2,3-di-*p*-tolyl pyridine (Scheme 3).

From these results, it became clear that the last C-arylation step to be performed on a highly hindered tetraarylpyridine should be carried out at the least bulky position (i.e., position 2) close to the pyridine nitrogen. An OBn group is the most suitable protecting group for 2-OH because (i) its ortho/para-directing effect would allow bromination at position 5 (pyridines **25**−**27**) and (ii) it could be deprotected and the resulting 2-OH group can be transformed to the 2-OTf group for further reaction (pyridines **19**−**21** and **31**−**33**). Different reaction conditions were explored for the preparation of the OBn-MOM ethers **10**−**12**. As previously reported,[39] in the presence of $Pd(OAc)_2$ and BINAP, the reaction proceeded very sluggishly (10% yield). When BINAP was replaced by Josiphos, MOM ether **12** was obtained in nearly quantitative yield on a small scale; however, the yields varied on larger scales. Finally, the use of Xantphos afforded the expected 2-OBn-3-OMOM derivatives **10**−**12** in 71−88% yields after purification. Starting from compound **11** (R_1 = H, R_2 = Ph), corresponding OTf **14** was recovered after the chemoselective deprotection of the O-MOM protecting group using Amberlyst (15 Wet) followed by the treatment with triflic anhydride. Surprisingly, pyridine-OTf **14** reacted smoothly with *p*-tolylboronic acid (**17**, Ar_3 = *p*-MePh, 94%) in spite of the expected neighboring effects of both the phenyl group at position 3 and the OBn group at position 2. The resulting product, 3,4-diaryl-2-OBn-pyridine **17**, was then deprotected and transformed to 2-OTf intermediate **20**, which then afforded corresponding 2,3,4-triaryl pyridine **23** after an additional Suzuki−Miyaura reaction using *p*-cyanophenylboronic acid. One of the key steps leading to pentaarylpyridines involves the additional functionalization at position 5 of 2-benzyloxypyridines **16**−**18**. The bromination of **17** was carried out using NBS in DMF to afford 5-bromoderivative **26** in 62% yield, which was reacted with 3,4-dimethoxy-phenylboronic acid to afford triaryl-2-OBn-pyridine **29** in good yield. After the deprotection of **29** and O-triflation of the corresponding 2-hydroxypyridine intermediate, the last sequential Suzuki−Miyaura reaction afforded 2,3,4,5 tetraarylpyridine **35** in 96% yield (15% yield over 11 steps, Scheme 3).

To validate our general strategy and to establish the high versatility of 2-benzyloxypyridine key intermediates **16**−**18** in particular, novel differently substituted pentaarylpyridine **36** ($Ar_1 \neq Ar_2 \neq Ar_3 \neq Ar_4 \neq Ar_5$) was prepared starting from **18**. The bromination of **18** followed by the C-arylation at position 5 (Ar_4 = 3,4-$(MeO)_2$Ph) afforded corresponding 3,4,5,6-tetraaryl-2-OBn-pyridine **30** in 80% yield. The debenzylation of **30** followed by O-triflation (72% for the two steps) afforded final OTf key intermediate **33** that reacted nearly quantitatively

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with *p*-cyanophenylboronic acid to afford pentaarylpyridine **36** (13% yield over 13 steps).

The crystal structure of the first described differently substituted pentaarylpyridine **36** has been determined (Figure 1). The five phenyl ring bonded to the pyridine core are not coplanar with the latter, with dihedral angles of 46.3, 58.8, 68.7, 61.8, and 44.9° between the phenyl ring planes in the 2, 3, 4, 5, and 6 positions of the pyridine ring, respectively. In addition, the bonds joining the aryl substituents to the pyridine ring are believed to be essentially σ bonds (1.488−1.497 Å).

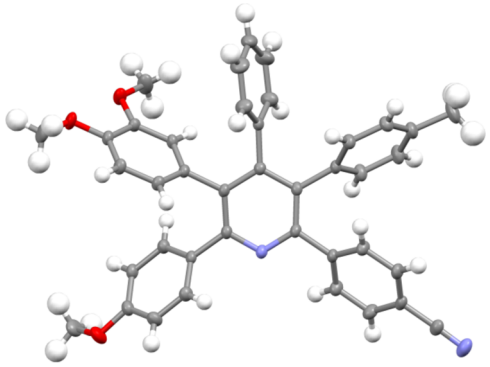


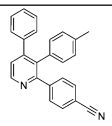
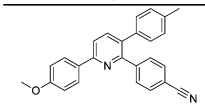
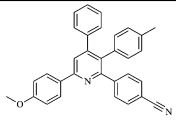
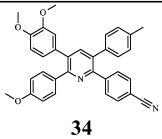
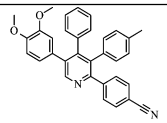
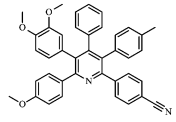
Figure 1. ORTEP drawing of **36** with 50% probability displacement ellipsoids.

The photophysical properties of the unsymmetrically substituted pyridine derivatives in various solvents are listed in Table 1. The pyridine derivatives show intense and broad absorption spectra with a maximum centered around 300 nm (Table 1).

The influence of the substituent attached to the pyridine moiety on the absorption properties appeared limited, as only slight bathochromic shifts were observed when the number of aromatic rings increased around the central pyridine ring.

Unlike the absorption spectra, the emission spectra were found to be quite sensitive to the substitution pattern. Indeed, when the central pyridine moiety is substituted by three aromatic rings, an additional substitution at position 6 with *p*-methoxyphenyl shifted the emission maximum to the red and increased the quantum yield, as shown by the comparison of compounds **22** and **23**. In contrast, these parameters were less affected when a phenyl ring was inserted at position 4, as can be seen from the comparison of compound **24** with compound **22**. Although large Stokes shifts of about 95 000 cm^{-1} were observed for all three compounds (**22**, **23**, and **24**), their maximum emission wavelengths showed only a limited

Table 1. Fluorescence Properties of Compounds 22−24 and 34−36[a]

Compounds	Solvent	Absorption		Emission		Stokes shift
		λ_{max} (nm)	ε (x 10^{-4} $M^{-1}.cm^{-1}$)	λ_{max} (nm)	Φ (%)	(cm^{-1})
	$CHCl_3$	293	1.9	400	1.9	9130
	EtOH	290	1.5	402	2.1	9610
23	DMSO	290	1.8	412	4.0	10200
	$CHCl_3$	308	5.2	439	3.5	9690
	EtOH	308	5.2	445	4.1	10000
22	DMSO	308	4.4	456	6.6	10540
	$CHCl_3$	295	4.0	415	2.9	9800
	EtOH	295	3.7	421	2.5	10140
24	DMSO	295	4.4	434	2.5	10860
	$CHCl_3$	326	3.1	459	20	8890
	EtOH	n. d.	n. d.	n. d.	n. d.	n. d.
34	DMSO	316	3.0	503	48	11760
	$CHCl_3$	315	2.3	432	39	8600
	EtOH	314	2.6	478	48	10930
35	DMSO	316	2.6	502	43	11720
	Cyclohexane	322	1.4	414	7	6900
	$CHCl_3$	316	2.2	454	31	9620
	AcOEt	319	1.5	454	31	9320
36	EtOH	316	1.7	483	47	10940
	DMSO	316	2.1	507	43	10940

[a]Errors on the ε and Φ values are estimated at 10%. n.d, not determined because **34** is very slightly soluble in EtOH.

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dependence on the solvent. Ab initio calculations on compound **24** taken as an example (Figure 2) showed that the electronic

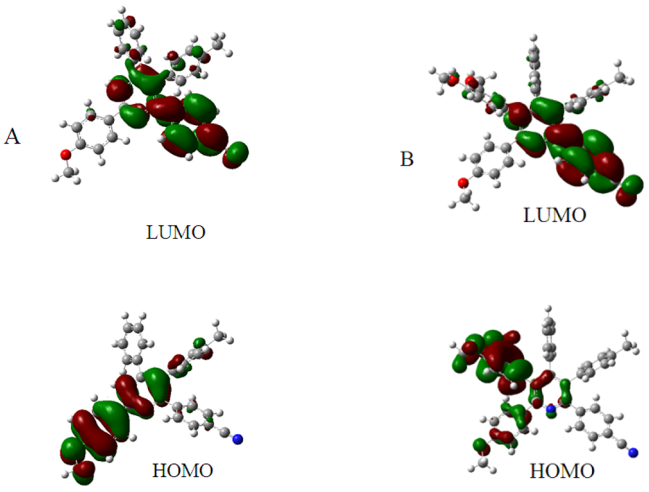

Figure 2. Frontier molecular orbitals involved in the electronic transitions of compounds **24** (A) and **36** (B).

distribution in the highest occupied molecular orbital (HOMO) is mainly located on the *p*-methoxyphenyl substituent at position 6. In contrast, this electronic distribution is shifted toward the benzonitrile substituent at position 2 in the lowest unoccupied molecular orbital (LUMO), indicating an internal charge transfer (ICT) between the ground and excited states. Accordingly, the charge density on the *p*-methoxyphenyl group increases from 0.08 to 0.31 and that of the benzonitrile substituent decreases from 0.04 to −0.29 in the S0 → S1 transition. Furthermore, TDDFT/6-31g calculations indicated substantial structural changes in the geometry of the S1 state as compared to the S0 one; the most remarkable changes being the decrease from 39 to 23° of the angle between the benzonitrile substituent and the pyridine ring on one hand and the decrease from 15 to 8° for the angle between the *p*-methoxyphenyl and pyridine rings, on the other hand. These structural changes between the S0 and S1 states are in line with a conformational relaxation in the excited state that may well explain the large Stokes shift observed for compound **24**. Moreover, the calculated magnitude of the dipole moment in chloroform was found to increase from 6.5 D in the ground-state S0 to 16 D in the excited-state S1. This limited increase in the dipole moment that accompanies the ICT in the S0 → S1 transition is consistent with the limited solvatochromism observed with this compound.

Importantly, a dramatic increase in the quantum yield as well as a strong solvatochromism was observed for compounds **34**, **35**, and **36**, where position 5 of the pyridine ring was substituted with the electron-donor 3,4-$(MeO)_2$Ph substituent. For compound **36**, the electronic distribution in HOMO (Figure 2B) is mainly located on the 3,4-$(MeO)_2$Ph substituent. Oppositely, in LUMO, this electron distribution is located on the electron-acceptor benzonitrile group at position 2 of the pyridine ring. This indicates that the S0 → S1 transition is accompanied by an ICT between the two substituents, which resulted in a strong increase (from 0.06 to 0.51) of the charge density on the 3,4-$(MeO)_2$Ph substituent together with a strong decrease (0.027 to −0.38) of the charge density on the benzonitrile group. In line with these larger changes in charge densities as compared to compound **24**, a value of 27 D was calculated for the excited-state dipole moment of compound **36** in chloroform. This large value, as compared to the 6.6 D value of the S0 dipole moment, readily explains the strong solvatochromism observed for compound **36**. This similar strong solvatochromism is typical for compounds exhibiting ICT between their donor−acceptor substituents.[40−46] Moreover, as for compound **24**, the substantial change in the geometry of the S1 state as compared to the S0 state, with a notable decrease from 36 to 6° in the angle between the benzonitrile and pyridine rings as well as a decrease from 63 to 50° in the angle between the 3,4-$(MeO)_2$Ph and pyridine rings, well explains the large Stokes shift observed with compound **36** in apolar solvents.

CONCLUSIONS

The stepwise synthesis of differently tetrasubstituted (2,3,4,5, 2,3,5,6, and 2,3,4,6) pyridines described in this article consists of a highly efficient strategy based on the regio and chemoselective control of the reactivity of differently substituted functional groups (halides and OTf) on the pyridine nucleus. This allows progressive C-arylation of the different combinations of positions on pyridine when prototypical Pd-catalyzed Suzuki−Miyaura cross-coupling reactions are used. All of the different intermediates were prepared in good yields. The selection of position 2 of pyridine as the last step of substitution in highly substituted pyridines proved to be highly efficient because the 2-OBn pyridine intermediates still allowed sufficient reactivity for additional bromination at position 5 and could finally afford a reactive 2-OTf species for the last substitution reaction. The method was applied successfully to the first synthesis of a prototypical pentaarylpyridine bearing five different substituents ($Ar_1 \neq Ar_2 \neq Ar_3 \neq Ar_4 \neq Ar_5$). The high versatility of the strategy presented here opens a large avenue to novel applications of this efficient method for building, in a combinatorial manner, pyridines bearing up to five different substituents if we consider the possible use of alkenyl or alkyl boronic acids or the introduction of various substituted alkynes using Sonogashira reaction and other types of C−C substitution reactions using Pd or Cu catalysts. This method offers an enlarged chemical diversity around the pyridine nucleus and may lead to novel pyridine compounds with new chemical or pharmacological properties. In particular, the photophysical properties of the novel compounds were investigated. Compounds **34**, **35**, and **36** may be of special interest owing to their very large Stokes shifts (up to 12 000 cm^{-1}), fluorescence quantum yields (up to 47%), and strong solvatochromic properties. Therefore, these compounds are promising building blocks for the development of environment-sensitive probes.

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under a nitrogen or argon atmosphere in flame-dried glassware as indicated. Chemicals and solvents were used without further purification. Analytical TLC was performed using silica gel plates, and plates were visualized by exposure to ultraviolet light. Compounds were purified using flash chromatography on silica gel (particle size 0.040−0.063 mm). Yields refer to isolated compounds, estimated to be >97% pure as determined by ^{1}H NMR or HPLC. ^{1}H and ^{13}C NMR spectra were recorded at 300 or 400 MHz and 100 MHz, respectively. All chemical shift values, δ, and coupling constants, J, are quoted in ppm and Hz, respectively, with the following abbreviations used for multiplicity: s, singlet; d, doublet; t, triplet; m, multiplet; and br, broad. RP-HPLC-MS was performed using a C18 column (30 mm ×1 mm;

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1.9 μm) using the following parameters: (1) solvent system: A (CH_3CN) and B (0.05% TFA in H_2O); (2) linear gradient: t = 0 min, 98% B; t = 5 min, 5% B; t = 6 min, 5% B; t = 7 min, 98% B; t = 9 min, 98% B; (3) flow rate: 0.3 mL/min; (4) column temperature: 50 °C; (5) ratio of products: determined by integration of spectra recorded at 210 or 254 nm; (6) ionization mode: MM-ES + APCI. High-resolution spectra (HRMS) were recorded on a QTOF mass analyzer with electrospray ionization (ESI). HPLC were performed using the following parameters: flow rate: 0.5 mL/min; column temperature: 30 °C; solvent system: A (MeOH) and B (0.05% TFA in H_2O); conditions: t = 0−1 min, 50−60% of B; t = 1−10 min, 60 to 100% of B; and t = 10−15 min, 100% of B. Infrared analyses were performed by FT-IR, and wavenumbers wereare expressed in cm^{-1}. Absorbance spectra were recorded with a UV−vis spectrophotometer equipped with a thermostatted multicell holder maintained at 20.0 °C. Fluorescence spectra were measured with a spectrofluorimeter equipped with a thermostatted cell compartment at 20.0 °C. Spectra were corrected for the emission of the solvent, the lamp fluctuations, and the wavelength dependence of the optics and detectors in the emission pathway. All solvents (cyclohexane, chloroform, ethyl acetate, ethanol, and dimethyl sulfoxide) were of spectroscopic grade. Fluorescence intensities were recorded in dilute solutions (ca. 1 μM), and quantum yields were calculated using quinine sulfate in 0.05 M H_2SO_4 as a reference (0.53 ± 0.02[47]) with an excitation wavelength of 316 nm. The refractive indices of the organic solvents for the compounds (1.424 for cyclohexane, 1.444 for chloroform, 1.370 for ethyl acetate, 1.359 for ethanol, and 1.476 for dimethyl sulfoxide) and the aqueous solvent for the standard (1.333) were taken into account for quantum yield calculations.[48]

Computational Method. Ab initio calculations were performed as described in Kenfack et al.[49] The equilibrium structure of compound **36** at ground-state S0 was determined using the density functional theory (DFT) in conjunction with the 6-31g basis set for all atoms, starting from the X-ray crystallographic structure of compound **36** (Figure 1). For the ground-state structure of compound **24**, we used the same protocol except that we replaced the 3,4-$(MeO)_2$Ph substituent by a hydrogen atom in the crystallographic structure of compound **36**. The most stable conformations of the first excited state for both compounds were also calculated using the time-dependent density functional theory (TDDFT) with the same basis set. The global hybrid functional PBE0 was adopted in all of our calculations.

General Procedures for Pd(0)-Catalyzed Suzuki Reaction. *Method A. General Suzuki−Miyaura procedure associate with the use of Na_2CO_3 (preparation of compounds **6**, **7**, **8**, and **37**).* A microwave vial (oven-dried and under nitrogen) containing a Teflon stirrer bar was charged with the corresponding halogeno-pyridine derivatives (1 equiv, 1 mmol, compounds **3**, **4**, **5**, and **37**), corresponding boronic acid (0.9 equiv, 0.9 mmol), and Na_2CO_3 (2 equiv, 2 mmol) followed by the addition of a mixture of toluene/EtOH/H_2O 6:1:1 (10 mL). The vessel was evacuated and backfilled with nitrogen (this process was repeated a total of three times), and $Pd(PPh_3)_4$ (0.05 equiv, 0.05 mmol) was introduced. The reaction mixture was then capped properly and placed in a preheated oil bath at 90 °C until complete conversion of the starting material was detected. The reaction mixture was monitored by HPLC analysis and was usually complete within 2 h. The reaction mixture was then concentrated under vacuum, and the crude product was purified by chromatography on silica gel using EtOAc/heptane 1:9 to afford expected products **6**, **37**, **7**, and **8**.

*Method B. General Suzuki−Miyaura procedure associate with the use of OTf-pyridine derivatives (preparation of compounds **16**, **17**, **18**, **22**, **23**, **24**, **34**, **35**, and **36**).* A microwave vial (oven-dried and under nitrogen) containing a Teflon stirrer bar was charged with the corresponding OTf-pyridine derivatives (1 equiv, 1 mmol, compounds **13**, **14**, **15**, **19**, **20**, **21**, **31**, **32**, and **33**), corresponding boronic acid (1.5 equiv, 1.5 mmol), and K_3PO_4 (3 equiv, 3 mmol) followed by the addition of anhydrous 1,4-dioxane (10 mL). The vessel was evacuated and backfilled with nitrogen (this process was repeated a total of three times), and $Pd(PPh_3)_4$ (0.05 equiv, 0.05 mmol) was introduced. The reaction mixture was then capped properly and placed in a preheated oil bath at 110 °C until complete conversion of the starting material was detected. The reaction mixture was monitored by HPLC analysis and was usually complete within 2 h. The reaction mixture was concentrated under vacuum, and the crude product was purified by chromatography on silica gel using EtOAc/heptane 1:9 to give expected products **17**, **18**, **22**, **23**, **24**, **34**, **35**, and **36**.

*Method C. General Suzuki−Miyaura procedure associate with the use of 3,4-dimethoxyphenylboronic acid (preparation of compounds **28**, **29**, and **30**).* A microwave vial (oven-dried and under nitrogen) containing a Teflon stirrer bar was charged with the corresponding 5-bromopyridine derivatives (1 equiv, 1 mmol, compounds **25**, **26**, and **27**), 3,4-dimethoxyphenylboronic acid (2 equiv, 2 mmol), and Na_2CO_3 (3 equiv, 3 mmol) followed by the addition of a mixture of toluene/EtOH/H_2O 6:1:1 (10 mL). The mixture vessel was evacuated and backfilled with nitrogen (this process was repeated a total of three times), and $Pd(PPh_3)_4$ (0.05 equiv, 0.05 mmol) was introduced. The reaction mixture was then capped properly and placed in a preheated oil bath at 110 °C until complete conversion of the starting material was detected. The reaction mixture was monitored by HPLC analysis and was usually complete within 2 h. The reaction mixture was concentrated under vacuum, and the crude product was purified by chromatography on silica gel using EtOAc/heptane 1:9 to give expected products **28**, **29**, and **30**.

General Procedure for the Buchwald−Hartwig Reaction: Preparation of 2-OBn Pyridines (Preparation of Compounds 10, 11, and 12). *Method D. General procedure for the Buchwald−Hartwig reaction using Xantphos.* A microwave vial (oven-dried and under nitrogen) containing a Teflon stirrer bar was charged with the corresponding 2-Cl-Pyridine derivatives (1 equiv, 1 mmol, compounds **6**, **7**, and **8**), benzyl alcohol (3 equiv, 3 mmol), and Cs_2CO_3 (4 equiv, 4 mmol) followed by the addition of anhydrous toluene (2.5 mL). The mixture vessel was evacuated and backfilled with nitrogen (this process was repeated a total of three times), and then $Pd(OAc)_2$ (0.025 equiv, 0.025 mmol) and Xantphos (0.05 equiv, 0.05 mmol) were added. The reaction mixture was then capped properly and placed in a preheated oil bath at 110 °C until complete conversion of the starting material was detected. The reaction mixture was monitored by HPLC analysis and was usually complete within 2 h. The reaction mixture was concentrated, and the crude product was purified by chromatography on silica gel using EtOAc/heptane 1/9 to give expected products **10**, **11**, and **12**.

Method E. General procedure for the Buchwald−Hartwig reaction using Josiphos. A microwave vial (oven-dried and under nitrogen) containing a Teflon stirrer bar was charged with the corresponding 2-Cl-Pyridine derivatives (1 equiv, 1 mmol, compound **8**), benzyl alcohol (1.5 equiv, 1.5 mmol), and Cs_2CO_3 (2 equiv, 2 mmol) followed by the addition of anhydrous toluene (6.7 mL). The mixture vessel was evacuated and backfilled with nitrogen (this process was repeated a total of three times), and then $Pd(OAc)_2$ (0.05 equiv, 0.05 mmol) and Josiphos (0.1 equiv, 0.1 mmol) were added. The reaction mixture was then capped properly and placed in a preheated oil bath at 110 °C until complete conversion of the starting material was detected. The reaction mixture was monitored by HPLC analysis and was usually complete within 2 h. The reaction mixture was concentrated, and the crude product was purified by chromatography on silica gel using EtOAc/heptane 1/9 to give expected product **12**.

General Procedure for Removal of the MOM Ether Group and Preparation of Pyridin-3-yl Trifluoromethanesulfonate Derivatives (Preparation of Compounds 9, 13, 14, and 15). *Method F. Step1: Removal of the MOM Ether Group.* A round-bottomed flask containing a stirrer bar was charged with MOM-protected pyridine derivatives (1 equiv, 1 mmol, compounds, **8**, **10**, **11**, and **12**), CH_2Cl_2/MeOH 1:9 (50 mL), and Amberlyst (15 mmol/g, 10 equiv, 10 mmol). The flask was cupped with a rubber septum and placed under a nitrogen atmosphere. The resulting mixture was stirred vigorously at rt until complete conversion of the starting material was detected. The reaction mixture was monitored by HPLC analysis and was usually complete within 2 h. After filtration through a pad of Celite, the solvent was evaporated in vacuo to afford the corresponding 3-hydroxypyridine as a yellow oil, which was

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immediately used without further purification for the preparation of the pyridine-3yl trifluoromethanesulfonate.

Step2: Preparation of Pyridine-3-yl Trifluoromethanesulfonate. The crude 3-hydroxypyridine derivative was dissolved in anhydrous CH_2Cl_2 (5 mL) and cooled to 0 °C via an ice bath. Et_3N (1.5 equiv, 1.5 mmol) was added followed by triflic anhydride (1.2 equiv, 1.2 mmol). The ice bath was removed after 5 min, and the solution was stirred at rt for an additional 2 h. The solvent was concentrated, and the crude product was purified by chromatography on silica gel using EtOAc/heptane 1/9 to give expected products **9**, **13**, **14**, and **15**.

General Procedure for Removal of Bn Ether Group and Preparation of Pyridine-2-yl Trifluoromethanesulfonate Derivatives (Preparation of Compounds 19, 20, 21, 31, 32, and 33). *Method G. Step 1: Removal of the Bn Ether Group.* A round-bottomed flask containing a stirrer bar was charged with 2-O-Benzyl protected pyridine derivatives (1 equiv, 1 mmol, compounds **16**, **17**, **18**, **28**, **29**, and **30**) in a mixture of anhydrous CH_2Cl_2 (6.7 mL) and HCl 4 N/dioxane (10 equiv, 10 mmol). The reaction mixture was stirred at 40 °C until complete conversion of the starting material was detected. The reaction mixture was monitored by HPLC analysis and was usually complete within 2 h. After evaporation of the volatiles, the residue was diluted with EtOAc and successively washed with brine and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was immediately used without further purification for the preparation of the pyridine-2yl trifluoromethanesulfonate.

Step 2: Preparation of Pyridine-2-yl Trifluoromethanesulfonate. To a solution of the crude 2-hydroxypyridine derivative in anhydrous CH_2Cl_2 (6.7 mL) was added pyridine (3 equiv, 3 mmol) followed by triflic anhydride (1.2 equiv, 1.2 mmol). The solution was stirred at rt for 2 h. The solvent was concentrated, and the crude product was purified by chromatography on silica gel using EtOAc/heptane 1:9 to give expected products **19**, **20**, **21**, **31**, **32**, and **33**.

Representative Preparation of 2-OBn-5-bromo-pyridine Derivatives (Preparation of Compounds 25, 26, and 27). *Method H.* To a solution of the corresponding 2-OBn pyridine derivatives (1 equiv, 1 mmol, compounds **16**, **17**, and **18**) in anhydrous DMF (10 mL) was added NBS (1 equiv, 1 mmol). The reaction mixture was stirred at 40 °C until complete conversion of the starting material was detected. The reaction mixture was monitored by HPLC analysis and was usually complete within 1−3 h. The solvent was concentrated, and the crude product was purified by chromatography on silica gel using EtOAc/heptane 1:9 to give expected products **25**, **26**, and **27**.

2-Chloro-6-iodopyridin-3-ol 2. 2-Chloro-3-pyridinol **1** (10 g, 77.2 mmol) and Na_2CO_3 (18 g, 169.8 mmol) were solubilized in H_2O (200 mL), and I_2 (19.6 g, 77.2 mmol) was then added. The solution was stirred at rt for 2 h. The pH of the solution was lowered with HCl 2 N until pH 6 was reached. The resulting precipitate was filtered, washed with cool water, and dried. The solid was then dissolved in a minimum of EtOAc (15 mL) and dropped into heptane (70 mL), where it precipitated. The precipitate was filtered, the filtrate was concentrated, and this precipitation process was repeated twice. All recovered solids were mixed together. 2-Chloro-6-iopyridin-3-ol **8** (13.5 g, 52.7 mmol, 68%) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.2, 137.6, 134.5, 126.5, 100.7. IR: 2961, 2824, 2746, 2662, 2697, 1552, 1452, 1392, 1286, 1222, 1085, 615. mp 141−143 °C.

2-Chloro-6-iodo-3-(methoxymethoxy)pyridine 3. A round-bottomed flask (oven-dried and under Argon) containing a stirrer bar was charged with 2-chloro-6-iopyridin-3-ol **2** (3.0 g, 11.7 mmol), iPr$_2$NH (2.67 mL, 18.8 mmol), and anhydrous CH_2Cl_2 (75 mL). Chloro(methoxy)methane (1.41 g, 17.6 mmol) was then added, and the resulting reaction mixture was stirred at rt until complete conversion of the starting material was detected. The reaction mixture was monitored by HPLC analysis and was complete within 2 h. After evaporation of the volatiles, the residue was diluted with EtOAc and successively washed with brine and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by chromatography on silica gel using EtOAc/heptane 1:9 to afford **3** (3.33 g, 11.1 mmol, 95%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 5.26 (s, 2H), 3.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 140.7, 133.8, 125.0, 103.2, 94.8, 56.3. IR: 2959, 2831, 1549, 1426, 1069, 963. mp 35−37 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_7H_7ClINO_2$, 299.9283; found, 299.9288.

4-Bromo-2-chloro-6-iodo-3-(methoxymethoxy)pyridine 4. A round-bottomed flask (oven-dried and under Argon) containing a stirrer bar was charged with 2-chloro-6-iodopyridin-3-ol **2** (5.0 g, 19.6 mmol), anhydrous CH_2Cl_2 (120 mL), iPr$_2$NH (4.43 mL, 31.3 mmol), and NBS (3.5 g, 19.6 mmol). The resulting reaction mixture was stirred at rt until complete conversion of the starting material was detected. The reaction mixture was monitored by HPLC analysis and was complete within 2 h. Chloro(methoxy)methane (2.36 g, 29.36 mmol) was then added, and the solution was stirred for an additional 1 h. After evaporation of the volatiles, the residue was diluted with EtOAc and successively washed with brine and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by chromatography on silica gel using EtOAc/heptane 1:9 to afford **4** (6.80 g, 18.0 mmol, 92%) as a light yellow solid. Chemical purity (90%), 10% of the corresponding **4**, 6-dibromo-2-chloro-3-(methoxymethoxy)pyridine, was detected by LC−MS. The product was used for the next steps without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 5.21 (s, 2H), 3.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 145.6, 137.8, 129.8, 107.2, 99.8, 58.6. IR: 3090, 2958, 2830, 1513, 1418, 1380, 1311, 1204, 1159, 1065, 1099, 908, 652. mp 91−93 °C. HRMS (ESI-TOF) m/z [M + H]$^+$-MOM calcd for $C_5H_2BrClINO$, 333.8126; found, 333.8127.

4-Bromo-2-chloro-3-(methoxymethoxy)pyridine 5. A round-bottomed flask (oven-dried and under Argon) containing a stir bar was charged with 4-bromo-2-chloro-6-iodo-3-(methoxymethoxy)pyridine **4** (2.5 g, 6.6 mmol) and anhydrous THF (12 mL). The resulting mixture was cooled at −78 °C, and a solution of iPrMgCl 2 M in THF (3.14 mL, 6.28 mmol) was added dropwise. After 45 min at −78 °C, MeOH (1.14 mL, 28.1 mmol) was added followed by NH_4Cl (4 mL). The reaction mixture was extracted with EtOAc, and the organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by chromatography on silica gel using EtOAc/heptane 5:95 to afford **5** (1.24 g, 4.93 mmol, 79%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 5.0 Hz, 1H), 7.47 (d, J = 5.0 Hz, 1H), 5.24 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 146.3, 144.3, 128.5, 127.5, 99.4, 58.2. IR: 2930, 1540, 1368, 1160, 1068, 922. mp 76−78 °C. HRMS (ESI-TOF) m/z [M + H]$^+$-MOM calcd for $C_5H_3BrClNO$, 207.9159; found, 207.9160.

2-Chloro-3-(methoxymethoxy)-6-(4-methoxyphenyl)-pyridine 6. Following general method A and starting from **3** (2.29 g, 7.63 mmol) and 4-methoxyphenylboronic acid (1.06 g, 6.96 mmol), **6** was obtained as a light yellow solid (1.71 g, 6.11 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 9.0 Hz, 2H), 7.58−7.49 (m, 2H), 6.97 (d, J = 9.0 Hz, 2H), 5.29 (s, 2H), 3.86 (s, 3H), 3.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 150.5, 147.7, 141.0, 130.3, 127.8, 124.6, 118.8, 114.1, 95.3, 56.5, 55.3. IR: 2958, 2935, 2901, 2843, 1607, 1514, 1438, 1252, 1144, 1067, 819. mp 91−93 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{14}ClNO_3$, 280.0735; found, 280.0741.

2-Chloro-3-(methoxymethoxy)-4-phenylpyridine 7. Following general method A and starting from **5** (1.38 g, 4.39 mmol) and phenylboronic acid (509 mg, 4.17 mmol), **7** was obtained as a white solid (959 mg, 3.84 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 5.0 Hz, 1H), 7.50−7.46 (m, 2H), 7.42−7.32 (m, 3H), 7.16 (d, J = 5.0 Hz, 1H), 4.75 (s, 2H), 3.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 146.5, 145.4, 144.5, 135.6, 129.0, 128.8, 128.6, 124.5, 99.2, 57.5. IR: 2958, 2829, 1579, 1370, 1158, 1061, 927. mp 66−68 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{12}ClNO_2$, 250.0629; found, 250.0636.

2-Chloro-3-(methoxymethoxy)-6-(4-methoxyphenyl)-4-phenylpyridine 8. Following general method A and starting from **37** (464 mg, 1.30 mmol) and phenylboronic acid (144 mg, 1.18 mmol), **8**

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was obtained as a white solid (414 mg, 1.17 mmol, 99%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 2H), 7.61 (d, J = 6.5 Hz, 2H), 7.58 (s, 1H), 7.54−7.41 (m, 3H), 6.98 (d, J = 9.0 Hz, 2H), 4.85 (s, 2H), 3.87 (s, 3H), 3.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 152.7, 145.9, 145.8, 145.1, 136.1, 130.1, 129.1, 128.7, 128.6, 128.2, 120.3, 114.1, 99.3, 57.5, 55.4. IR: 2950, 2910, 2826, 1606, 1592, 1416, 1247, 1148, 1030, 935. mp 114−116 °C. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{18}ClNO_3$, 356.1048; found, 356.1047.

2-Chloro-6-(4-methoxyphenyl)-4-phenylpyridin-3-yl Trifluoromethanesulfonate 9. Following general method F and starting from **8** (500 mg, 1.40 mmol), **9** was obtained as a white solid (598 mg, 1.35 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.8 Hz, 2H), 7.66 (s, 1H), 7.53 (s, 5H), 7.01 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 156.2, 146.5, 145.0, 138.3, 133.8, 129.9, 129.0, 128.9, 128.8, 128.7, 120.6, 118.0 (q, J = 317 Hz), 114.4, 55.4. IR: 2923, 2853, 1590, 1516, 1426, 1412, 1209, 1177, 1133, 874. mp 143−145 °C. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{13}ClF_3NO_4S$, 444.0279; found, 444.0289.

2-(Benzyloxy)-3-(methoxymethoxy)-6-(4-methoxyphenyl)-pyridine 10. Following general method D and starting from **6** (672 mg, 2.40 mmol) and benzyl alcohol (747 μL, 7.21 mmol), **10** was obtained as a white solid (595 mg, 1.70 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 6.8 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.40−7.35 (m, 2H), 7.33−7.28 (m, 1H), 7.22 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 9.0 Hz, 2H), 5.62 (s, 2H), 5.25 (s, 2H), 3.87 (s, 3H), 3.53 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 153.8, 147.1, 139.9, 137.9, 131.6, 128.4, 128.0, 127.7, 127.5, 124.7, 114.0, 112.4, 95.6, 67.5, 56.3, 55.3. IR: 2953, 2834, 1609, 1455, 1244, 1155, 981. mp 79−81 °C. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{21}NO_4$, 352.1543; found, 352.1552.

2-(Benzyloxy)-3-(methoxymethoxy)-4-phenylpyridine 11. Following general method D and starting from **7** (182 mg, 0.729 mmol) and benzyl alcohol (226 μL, 2.19 mmol), **11** was obtained as a white solid (206 mg, 0.641 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 5.3 Hz, 1H), 7.61−7.57 (m, 2H), 7.52−7.48 (m, 2H), 7.47−7.42 (m, 2H), 7.42−7.36 (m, 3H), 7.36−7.30 (m, 1H), 6.93 (d, J = 5.3 Hz, 1H), 5.49 (s, 2H), 4.94 (s, 2H), 2.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 143.8, 141.0, 137.6, 137.2, 136.3, 129.3, 128.4, 128.2, 128.1, 127.9, 127.8, 118.7, 98.1, 68.0, 56.9. IR: 3061, 3031, 2953, 1594, 1422, 1355, 953. mp 80−82 °C. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{19}NO_3$, 322.1438; found, 322.1445.

2-(Benzyloxy)-3-(methoxymethoxy)-6-(4-methoxyphenyl)-4-phenylpyridine 12. Following general method D and starting from **8** (1.03 g, 2.89 mmol) and benzyl alcohol (450 μL, 3.34 mmol), **12** and **41** were obtained: **12** was obtained as a colorless oil (1894 mg, 2.09 mmol, 72%) and **41** was obtained as a white solid (229 mg, 0.714 mmol, 25%). Following general method E and starting from **8** (300 mg, 0.84 mmol) and benzyl alcohol (131 μL, 1.26 mmol), **12** was obtained as a colorless oil (299 mg, 0.70 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 7.3 Hz, 2H), 7.49−7.43 (m, 2H), 7.41−7.37 (m, 3H), 7.35−7.33 (m, 2H), 6.98 (d, J = 8.8 Hz, 2H), 5.61 (s, 2H), 4.95 (s, 2H), 3.87 (s, 3H), 2.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 156.5, 148.7, 144.4, 137.6, 136.8, 136.0, 131.5, 129.3, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 114.2, 114.0, 98.2, 67.8, 56.9, 55.3. IR: 3032, 2955, 2835, 1608, 1450, 1351, 1249, 1157, 952. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{25}NO_4$, 428.1856; found, 428.1861.

2-(Benzyloxy)-6-(4-methoxyphenyl)pyridin-3-yl Trifluoromethanesulfonate 13. Following general method F and starting from **10** (579 mg, 1.65 mmol), **13** was obtained as a white solid (535 mg, 1.22 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 8.3 Hz, 1H), 7.54−7.51 (m, 2H), 7.43−7.38 (m, 2H), 7.36−7.33 (m, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.00(d, J = 9.0 Hz, 2H), 5.61 (s, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 154.6, 154.1, 136.4, 132.2, 131.5, 130.1, 128.4, 128.3, 128.0, 127.9, 114.2, 112.4, 118.7 (q, J = 316 Hz), 68.4, 55.4. IR: 2960, 1608, 1599, 1455, 1423, 1362, 1246, 870. mp 50−52 °C. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{16}F_3NO_5S$, 440.0774; found, 440.0782.

2-(Benzyloxy)-4-phenylpyridin-3-yl Trifluoromethanesulfonate 14. Following general method F and starting from **11** (400 mg, 1.12 mmol), **14** was obtained as a colorless oil (296 mg, 0.723 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 5.3 Hz, 1H), 7.58−7.52 (m, 2H), 7.49 (s, 5H), 7.44−7.38 (m, 2H), 7.38−7.33 (m, 1H), 7.00 (d, J = 5.3 Hz, 1H), 5.55 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 145.5, 144.7, 136.0, 133.5, 131.2, 129.5, 128.9, 128.8, 128.4, 128.2, 128.1, 119.0, 118.0 (q, J = 318 Hz), 69.0. IR: 3033, 2927, 1611, 1424, 1208, 1137. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{14}F_3NO_4S$, 410.0668; found, 410.0682.

2-(Benzyloxy)-6-(4-methoxyphenyl)-4-phenylpyridin-3-yl Trifluoromethanesulfonate 15. Following general method F and starting from **12** (880 mg, 2.06 mmol), **15** was obtained as a white solid (859 mg, 1.66 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 9.0 Hz, 2H), 7.51 (d, J = 7.3 Hz, 2H), 7.48−7.38 (m, 5H), 7.38−7.31 (m, 2H), 7.31−7.22 (m, 2H), 6.95 (d, J = 9.0 Hz, 2H), 5.58 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 155.5, 153.2, 145.2, 136.4, 134.1, 130.2, 129.6, 129.4, 128.9, 128.7, 128.4, 128.3, 128.2, 128.0, 118.1 (q, J = 323 Hz), 114.4, 114.1, 68.8, 55.4. IR: 3033, 2936, 2838, 1608, 1549, 1420, 1352, 1204, 1176, 1137. mp 129−130 °C. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{20}F_3NO_5S$, 516.1087; found, 516.1092.

2-(Benzyloxy)-6-(4-methoxyphenyl)-3-(*p*-tolyl)pyridine 16. Following general method B and starting from **13** (523 mg, 1.19 mmol) and 4-methylphenylboronic acid (243 mg, 1.78 mmol), **16** was obtained as a white solid (399 mg, 1.05 mmol, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 9.0 Hz, 2H), 7.70 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.49 (d, J = 6.9 Hz, 2H), 7.41−7.30 (m, 4H), 7.30−7.21 (m, 2H), 7.03 (d, J = 9.0 Hz, 2H), 5.62 (s, 2H), 3.89 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 159.5, 152.8, 139.2, 138.2, 137.0, 133.8, 131.6, 129.0, 128.9, 128.3, 127.9, 127.5, 127.3, 122.1, 114.0, 112.6, 67.3, 55.3, 21.2. IR: 3029, 2922, 1608, 1585, 1450, 1246, 811. mp 117−119 °C. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{23}NO_2$, 382.1801; found, 382.1812.

2-(Benzyloxy)-4-phenyl-3-(*p*-tolyl)pyridine 17. Following general method B and starting from **14** (326 mg, 0.796 mmol) and 4-methylphenylboronic acid (162 mg, 1.19 mmol), **17** was obtained as a white solid (263 mg, 0.748 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 5.3 Hz, 1H), 7.39−7.31 (m, 4H), 7.30−7.25 (m, 1H), 7.25−7.21 (m, 3H), 7.15−7.13 (m, 2H), 7.10−7.03 (m, 4H), 7.01 (d, J = 5.3 Hz, 1H), 5.49 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 150.8, 145.1, 139.4, 138.0, 136.4, 132.0, 131.0, 129.4, 128.4, 128.2, 128.0, 127.3, 127.2, 127.1, 123.2, 119.0, 67.5, 21.3. IR: 3029, 2922, 1584, 1548, 1409, 1352, 1320, 1001. mp 116−118 °C. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{21}NO$, 352.1696; found, 352.1709.

2-(Benzyloxy)-6-(4-methoxyphenyl)-4-phenyl-3-(*p*-tolyl)-pyridine 18. Following general method B and starting from **15** (90 mg, 0.148 mmol) and 4-methylphenylboronic acid (30 mg, 0.223 mmol), **18** was obtained as a white solid (62 mg, 0.134 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.8 Hz, 2H), 7.42−7.36 (m, 2H), 7.35 (s, 1H), 7.32 −7.28 (m, 2H), 7.25−7.18 (m, 4H), 7.15−7.12 (m, 2H), 7.05 (d, J = 7.9 Hz, 2H), 7.03−6.99 (m, J = 7.9 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 5.56 (s, 2H), 3.85 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 160.4, 152.5, 151.5, 140.0, 138.4, 136.2, 132.1, 131.7, 131.1, 129.4, 128.4, 128.2, 128.0, 128.0, 127.3, 127.2, 120.9, 114.4, 114.0, 67.4, 55.4, 21.3. IR: 3030, 2929, 2835, 1607, 1588, 1513, 1343, 1250, 1173, 1137. mp 112−114 °C. HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{32}H_{27}NO_2$, 458.2114; found, 458.2100.

6-(4-Methoxyphenyl)-3-(p-tolyl)pyridin-2-yl Trifluoromethanesulfonate 19. Following general method G and starting from **16** (270 mg, 0.708 mmol), **19** was obtained as a white solid (236 mg, 0.557 mmol, 79%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 9.0 Hz, 2H), 7.89 (d, J = 7.8 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 154.8, 152.7, 141.9, 138.7, 130.8, 129.5, 129.2, 128.8, 128.3, 125.7, 119.2, 118.6 (q, J = 312 Hz), 114.4, 55.4, 21.3. IR: 2928, 1603, 1460, 1419,

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1213, 1133, 905, 833, 815. mp 84−86 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{16}F_3NO_4S$, 424.0825; found, 424.0835.

4-Phenyl-3-(*p*-tolyl)pyridin-2-yl Trifluoromethanesulfonate 20. Following general method G and starting from **17** (164 mg, 0.467 mmol), **20** was obtained as a white solid (169 mg, 0.430 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J = 5.3 Hz, 1H), 7.43 (d, J = 5.0 Hz, 1H), 7.30−7.21 (m, 3H), 7.15−7.07 (m, 4H), 7.04−6.97 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 154.0, 146.4, 138.1, 137.4, 130.3, 129.2, 129.0, 128.9, 128.3, 128.3, 127.6, 125.5, 118.3 (q, J = 321 Hz), 21.3. IR: 2926, 1596, 1419, 1207, 910. mp 110−112 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{14}F_3NO_3S$, 394.0719; found, 394.0728.

6-(4-Methoxyphenyl)-4-phenyl-3-(*p*-tolyl)pyridin-2-yl Trifluoromethanesulfonate 21. Following general method G and starting from **18** (150 mg, 0.329 mmol), **21** was obtained as a white solid (124 mg, 0.248 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 9.0 Hz, 2H), 7.78 (s, 1H), 7.31−7.25 (m, 3H), 7.18 − 7.15 (m, 2H), 7.13−7.07 (m, 2H), 7.05−7.00 (m, 4H), 3.89 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 154.5, 154.5, 154.0, 138.1, 137.9, 130.4, 129.3, 129.2, 129.1, 128.9, 128.3, 128.3, 128.2, 124.6, 120.6, 118.5 (q, J = 323 Hz), 114.3, 55.4, 21.3. IR: 2925, 1599, 1418, 1218, 1176. mp 134−136 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{20}F_3NO_4S$, 500.1138; found, 500.1146.

4-(6-(4-Methoxyphenyl)-3-(*p*-tolyl)pyridin-2-yl)benzonitrile 22. Following general method B and starting from **19** (80 mg, 0.189 mmol) and 4-cyanophenylboronic acid (42 mg, 0.283 mmol), **22** was obtained as a white solid (59 mg, 0.157 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 9.0 Hz, 2H), 7.80−7.74 (m, 2H), 7.63−7.54 (m, 4H), 7.13 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 155.5, 154.1, 145.2, 139.5, 137.4, 136.1, 134.0, 131.5, 131.2, 130.8, 129.3, 129.3, 128.1, 119.0, 118.6, 114.1, 111.2, 55.3, 21.1. IR: 2923, 2836, 2226, 1607, 1581, 1448, 1249, 815. mp 173−174 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{20}N_2O$, 377.1648; found, 377.1657.

4-(4-Phenyl-3-(*p*-tolyl)pyridin-2-yl)benzonitrile 23. Following general method B and starting from **20** (156 mg, 0.397 mmol) and 4-cyanophenylboronic acid (87 mg, 0.595 mmol), **23** was obtained as a white solid (95 mg, 0.275 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 5.0 Hz, 1H), 7.48 (d, J = 8.5 Hz, 2H), 7.41−7.35 (m, 3H), 7.26−7.19 (m, 3H), 7.12−7.04 (m, 2H), 6.92−6.86 (d, J = 8.0 Hz, 2H), 6.76−6.67 (d, J = 8.0 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 150.3, 148.3, 145.5, 138.9, 137.0, 134.8, 133.7, 131.4, 131.0, 130.6, 129.2, 128.8, 128.0, 127.6, 124.6, 118.9, 111.0, 21.2. IR: 3052, 2922, 2226, 1607, 1576, 1391. mp 131−133 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{18}N_2$, 347.1543; found, 347.1551.

4-(6-(4-Methoxyphenyl)-4-phenyl-3-(*p*-tolyl)pyridin-2-yl)-benzonitrile 24. Following general method B and starting from **21** (110 mg, 0.220 mmol) and 4-cyanophenylboronic acid (49 mg, 0.33 mmol), **24** was obtained as a white solid (77 mg, 0.170 mmol, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13−8.06 (d, J = 8.9 Hz, 2H), 7.74 (s, 1H), 7.51−7.45 (m, 4H), 7.26−7.20 (m, 3H), 7.16−7.08 (m, 2H), 7.05−6.97 (d, J = 8.9 Hz, 2H), 6.92−6.84 (d, J = 8.1 Hz, 2H), 6.78−6.71 (d, J = 8.1 Hz, 2H), 3.87 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 155.7, 155.4, 150.9, 146.0, 139.5, 136.7, 134.0, 132.4, 131.3, 131.3, 131.1, 130.8, 129.2, 128.7, 128.2, 128.0, 127.4, 120.3, 119.0, 114.1, 110.8, 55.4, 21.1. IR: 2925, 2226, 1607, 1582, 1513, 1251. mp 170−172 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{32}H_{24}N_2O$, 453.1961; found, 453.1962.

2-(Benzyloxy)-5-bromo-6-(4-methoxyphenyl)-3-(*p*-tolyl)-pyridine 25. Following general method H and starting from **16** (300 mg, 0.708 mmol), **25** was obtained as a white solid (282 mg, 0.613 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.78 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.40−7.33 (m, 2H), 7.32−7.29 (m, 1H), 7.29−7.25 (m, 2H), 7.00 (d, J = 8.8 Hz, 2H), 5.50 (s, 2H), 3.90 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 158.3, 152.2, 143.3, 137.8, 137.6, 132.1, 131.6, 131.0, 129.0, 129.0, 128.3, 127.6, 127.5, 124.3, 113.2, 110.2, 67.8, 55.3, 21.2. IR: 3031, 2929, 2835, 1608, 1510, 1428, 1248, 1030, 820. mp 143−145 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{22}BrNO_2$, 460.0907; found, 460.0902.

2-(Benzyloxy)-5-bromo-4-phenyl-3-(*p*-tolyl)pyridine 26. Following general method H and starting from **17** (263 mg, 0.748 mmol), **26** was obtained as a white solid (200 mg, 0.465 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.33−7.30 (m, 4H), 7.29−7.26 (m, 1H), 7.26−7.20 (m, 3H), 7.05−7.01 (m, 2H), 6.99−6.91 (m, 4H), 5.43 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 151.0, 146.8, 138.0, 137.5, 136.6, 131.6, 130.4, 129.6, 128.2, 128.2, 127.7, 127.5, 127.4, 127.2, 126.0, 114.3, 67.7, 21.2. IR: 3029, 2923, 1562, 1405, 1306, 1243, 1034. mp 107−109 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{25}H_{20}BrNO$, 430.0801; found, 430.0810.

2-(Benzyloxy)-5-bromo-6-(4-methoxyphenyl)-4-phenyl-3-(*p*-tolyl)pyridine 27. Following general method H and starting from **18** (293 mg, 0.64 mmol), **27** was obtained as a white solid (327 mg, 0.61 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.8 Hz, 2H), 7.28−7.22 (m, 4H), 7.22−7.11 (m, 5H), 6.99 (m, 2H), 6.91 (d, J = 8.8 Hz, 2H), 6.89−6.87 (m, 3H), 5.36 (s, 2H), 3.80 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 159.1, 153.7, 152.9, 139.4, 137.9, 136.4, 133.0, 131.8, 131.2, 130.5, 129.7, 128.2, 128.2, 127.6, 127.4, 127.3, 127.0, 124.2, 113.1, 112.8, 67.6, 55.3, 21.2. IR: 2929, 1608, 1513, 1412, 1341, 1249, 1031. mp 61−63 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{32}H_{26}BrNO_2$, 536.1219; found, 536.1207.

2-(Benzyloxy)-5-(3,4-dimethoxyphenyl)-6-(4-methoxyphenyl)-3-(*p*-tolyl)pyridine 28. Following general method C and starting from **25** (222 mg, 0.482 mmol) and 3,4-dimethoxyphenylboronic acid (175 mg, 0.964 mmol), **28** was obtained as a light yellow solid (214 mg, 0.413 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 7.0 Hz 2H), 7.42−7.36 (m, 4H), 7.33−7.28 (m, 1H), 7.26 (d, J = 7.0 Hz, 2H), 6.86−6.83 (m, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.68 (s, 1H), 5.60 (s, 2H), 3.91 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 158.4, 151.6, 148.6, 148.0, 141.5, 138.2, 137.3, 133.5, 132.9, 132.4, 131.2, 129.1, 129.0, 128.9, 128.3, 127.6, 127.4, 122.3, 121.7, 113.3, 113.2, 111.2, 67.5, 55.9, 55.7, 55.2, 21.2. IR: 2999, 2930, 2835, 1607, 1513, 1429, 1246. mp 65−68 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{34}H_{31}NO_4$, 518.2326; found, 518.2316.

2-(Benzyloxy)-5-(3,4-dimethoxyphenyl)-4-phenyl-3-(*p*-tolyl)pyridine 29. Following general method C and starting from **26** (149 mg, 0.346 mmol) and 3,4-dimethoxyphenylboronic acid (126 mg, 0.693 mmol), **29** was obtained as a light yellow solid (149 mg, 0.306 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.38−7.30 (m, 4H), 7.29−7.25 (m, 1H), 7.06−6.97 (m, 7H), 6.86−6.81 (m, 2H), 6.79−6.76 (m, 2H), 6.35−6.31 (m, 1H), 5.51 (s, 2H), 3.85 (s, 3H), 3.47 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 149.6, 148.0, 147.7, 145.7, 138.0, 137.9, 136.1, 132.2, 131.0, 130.8, 130.7, 130.6, 128.2, 128.2, 127.5, 127.2, 127.1, 126.6, 123.8, 121.8, 113.7, 110.7, 67.4, 55.7, 55.5, 21.2. IR: 2930, 1604, 1517, 1453, 1250, 1237, 1027. mp 58−60 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{33}H_{29}NO_3$, 488.2220; found, 488.2235.

2-(Benzyloxy)-5-(3,4-dimethoxyphenyl)-6-(4-methoxyphenyl)-4-phenyl-3-(*p*-tolyl)pyridine 30. Following general method C and starting from **27** (300 mg, 0.56 mmol) and 3,4-dimethoxyphenylboronic acid (204 mg, 1.12 mmol), **30** was obtained as a white solid (265 mg, 0.446 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.36 (m, 2H), 7.35−7.23 (m, 5H), 7.03−6.94 (m, 7H), 6.82−6.72 (m, 4H), 6.53 (d, J = 8.3 Hz, 1H), 6.39 (dd, J = 2.0, 8.3 Hz, 1H), 6.31 (d, J = 2.0 Hz, 1H), 5.56 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.44 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 158.8, 152.7, 151.8, 148.0, 147.2, 138.6, 138.5, 135.9, 133.4, 132.6, 131.3, 131.2, 130.8, 130.4, 128.1, 128.1, 127.4, 127.1, 127.1, 126.1, 124.3, 122.2, 115.4, 115.4, 112.9, 110.3, 67.2, 55.6, 55.6, 55.2, 21.2. IR: 2928, 2835, 1607, 1514, 1416, 1345, 1242, 1237. mp 75−77 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{40}H_{35}NO_4$, 594.2639; found, 594.2650.

5-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-3-(*p*-tolyl)-pyridin-2-yl Trifluoromethanesulfonate 31. Following general method G and starting from **28** (199 mg, 0.38 mmol), **31** was

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obtained as a white solid (205 mg, 0.366 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.43−7.36 (d, J = 8.9 Hz, 2H), 7.35−7.29 (d, J = 8.3 Hz, 2H), 6.90−6.85 (m, 2H), 6.80 (d, J = 8.9 Hz, 2H), 6.70 (s, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.68 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 153.6, 151.1, 148.9, 148.9, 143.8, 138.9, 136.0, 131.4, 131.0, 130.5, 130.1, 129.6, 128.9, 126.1, 121.7, 118.6 (q, J = 293 Hz), 113.5, 112.8, 111.4, 55.9, 55.8, 55.3, 21.3. IR: 2935, 2838, 1607, 1513, 1420, 1251, 1220. mp 153−155 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{28}H_{24}F_3NO_6S$, 560.1349; found, 560.1362.

5-(3,4-Dimethoxyphenyl)-4-phenyl-3-(*p*-tolyl)pyridin-2-yl Trifluoromethanesulfonate 32. Following general method G and starting from **29** (122 mg, 0.25 mmol), **32** was obtained as a white solid (121 mg, 0.229 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.13−7.01 (m, 5H), 6.98−6.91 (m, 2H), 6.85−6.78 (m, 4H), 6.37 (s, 1H), 3.86 (s, 3H), 3.49 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 152.2, 148.6, 148.4, 147.2, 137.8, 137.6, 136.3, 130.2, 130.2, 129.2, 129.0, 128.7, 128.4, 127.9, 127.4, 122.1, 118.4 (q, J = 316 Hz), 113.3, 110.9, 55.8, 55.6, 21.2. IR: 2933, 1587, 1512, 1417, 1212, 1136, 922. mp 62−64 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{22}F_3NO_5S$, 530.1243; found, 530.1241.

5-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-4-phenyl-3-(*p*-tolyl)pyridin-2-yl Trifluoromethanesulfonate 33. Following general method G and starting from **30** (265 mg, 0.45 mmol), **33** was obtained as a white solid (203 mg, 0.319 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 9.0 Hz, 2H), 7.07−6.92 (m, 7H), 6.82−6.69 (m, 4H), 6.58 (d, J = 8.3 Hz, 1H), 6.43 (dd, J = 2.0, 8.0 Hz, 1H), 6.32 (d, J = 2.0 Hz, 1H), 3.79 (s, 6H), 3.46 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 154.9, 154.6, 152.4, 148.4, 147.9, 137.5, 137.0, 135.0, 131.5, 131.0, 130.3, 130.0, 129.6, 129.5, 128.6, 127.4, 126.9, 126.2, 123.8, 118.4 (q, J = 318 Hz), 114.7, 113.2, 110.6, 55.7, 55.6, 55.2, 21.2. IR: 2932, 1607, 1517, 1416, 1252, 1226, 1209, 735. mp 83−85 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{34}H_{28}F_3NO_6S$, 636.1662; found, 636.1664.

4-(5-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-3-(*p*-tolyl)pyridin-2-yl)benzonitrile 34. Following general method B and starting from **31** (190 mg, 0.30 mmol) and 4-cyanophenylboronic acid (866 mg, 0.45 mmol), **34** was obtained as a white solid (175 mg, 0.297 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.65−7.59 (d, J = 8.5 Hz, 2H), 7.58−7.52 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.18−7.09 (m, 4H), 6.93−6.84 (m, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.72 (s, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.66 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 155.2, 152.7, 148.7, 148.6, 144.8, 141.0, 137.6, 136.0, 134.7, 134.3, 132.3, 132.0, 131.6, 131.3, 130.8, 129.4, 129.3, 121.7, 119.0, 113.5, 113.0, 111.3, 111.2, 55.9, 55.8, 55.3, 21.2. IR: 2933, 2836, 2226, 1607, 1514, 1429, 1248. mp 275−277 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{34}H_{28}N_2O_3$, 513.2173; found, 513.2176.

4-(5-(3,4-Dimethoxyphenyl)-4-phenyl-3-(p-tolyl)pyridin-2-yl)benzonitrile 35. Following general method B and starting from **32** (109 mg, 0.206 mmol) and 4-cyanophenylboronic acid (45 mg, 0.309 mmol), **35** was obtained as a white solid (95 mg, 0.197 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.49 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.09−7.02 (m, 3H), 6.89−6.79 (m, 6H), 6.71 (d, J = 8.0 Hz, 2H), 6.40 (d, J = 2.0 Hz, 1H), 3.87 (s, 3H), 3.48 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 149.3, 148.4, 148.4, 148.2, 145.5, 137.3, 136.6, 135.9, 135.4, 134.1, 131.4, 131.0, 130.5, 130.4, 130.1, 128.6, 127.7, 126.8, 122.1, 118.9, 113.5, 110.9, 110.8, 55.8, 55.5, 21.1. IR: 2933, 2835, 2226, 1605, 1510, 1250. mp 217−219 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{33}H_{26}N_2O_2$, 483.2067; found, 483.2075.

4-(5-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)-4-phenyl-3-(p-tolyl)pyridin-2-yl)benzonitrile 36. Following general method B and starting from **33** (80 mg, 0.189 mmol) and 4-cyanophenylboronic acid (42 mg, 0.283 mmol), **36** was obtained as a white solid (59 mg, 0.157 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J = 8.5 Hz, 4H), 7.35 (d, J = 8.8 Hz, 2H), 7.03−6.95 (m, 3H), 6.87−6.70 (m, 8H), 6.55 (d, J = 8.5 Hz, 1H), 6.45 (dd, J = 2.0, 8.3 Hz, 1H), 6.37 (d, J = 2.0 Hz, 1H), 3.84−3.74 (m, 6H), 3.46 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 156.4, 154.1, 150.6, 148.1, 147.5, 145.7, 138.1, 136.4, 134.6, 134.1, 133.8, 133.6, 133.2, 131.3, 131.3, 131.0, 130.8, 130.6, 128.4, 126.3, 123.9, 119.0, 116.3, 115.0, 113.1, 110.7, 110.4, 55.6, 55.6, 55.2, 21.1. IR: 2927, 2226, 1607, 1513, 1246. mp 240−242 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{40}H_{32}N_2O_3$, 589.2486; found, 589.2495.

4-Bromo-2-chloro-3-(methoxymethoxy)-6-(4-methoxyphenyl)pyridine 37. Following general method A and starting from **4** (1.0 g, 2.64 mmol) and 4-methoxyphenylboronic acid (366 mg, 2.41 mmol), **37** was obtained as a white solid (763 mg, 2.13 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 9.0 Hz, 2H), 7.80 (s, 1H), 6.98 (d, J = 9.0 Hz, 2H), 5.24 (s, 2H), 3.87 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 153.2, 145.7, 145.7, 129.3, 128.8, 128.3, 123.3, 114.3, 99.7, 58.5, 55.4. IR: 3012, 2971, 2936, 2832, 1604, 1506, 1232, 1155, 1061, 1021, 921. mp 93−95 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{13}BrClNO_3$, 357.9840; found, 357.9847.

2-Chloro-3-(methoxymethoxy)-4,6-bis(4-methoxyphenyl)-pyridine 38. Following general method A and starting from **4** (1.0 g, 2.64 mmol) and 4-methoxyphenylboronic acid (366 mg, 2.41 mmol), **38** was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$ δ 7.94 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 9.0 Hz, 2H), 7.55 (s, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 4.85 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 3.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 160.0, 152.6, 145.8, 145.3, 144.9, 130.3, 130.2, 128.2, 128.1, 120.1, 114.1, 114.0, 99.1, 57.7, 55.3, 55.3. IR: 2929, 2836, 1607, 1507, 1434, 1242, 1174, 1157, 928. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{20}ClNO_4$, 386.1153; found, 386.1162.

5-(Methoxymethoxy)-2-(4-methoxyphenyl)-4-phenylpyridine 41. Following general method D and starting from **8** (1.03 g, 2.89 mmol) and benzyl alcohol (450 μL, 3.34 mmol), **41** was obtained as a white solid (229 mg, 0.714 mmol, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.91 (d, J = 8.8 Hz, 2H), 7.71 (s, 1H), 7.67−7.60 (m, 2H), 7.56−7.43 (m, 3H), 7.04 (d, J = 8.8 Hz, 1H), 5.22 (s, 2H), 3.87 (s, 3H), 3.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 150.3, 149.8, 135.6, 135.2, 129.1, 129.0, 128.5, 128.4, 122.5, 114.5, 95.9, 77.3, 76.7, 56.5, 55.4. IR: 2937, 2837, 1607, 1477, 1243, 1150, 976. mp 79−81 °C. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{19}NO_3$, 322.1438; found, 322.1440.

■ ASSOCIATED CONTENT

Supporting Information

Optimization data, NMR spectra, fluorescent spectra, atom coordinates, absolute energies, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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