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Graphical Abstract

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Synthesis of Multiply Arylated Pyridines

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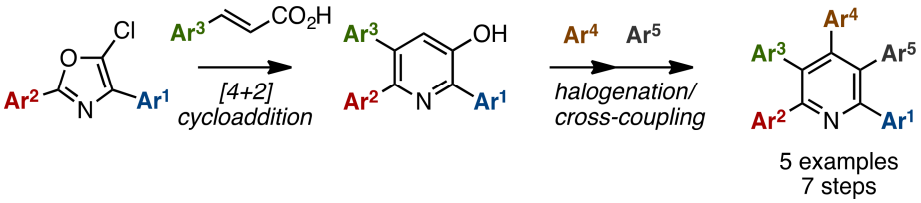

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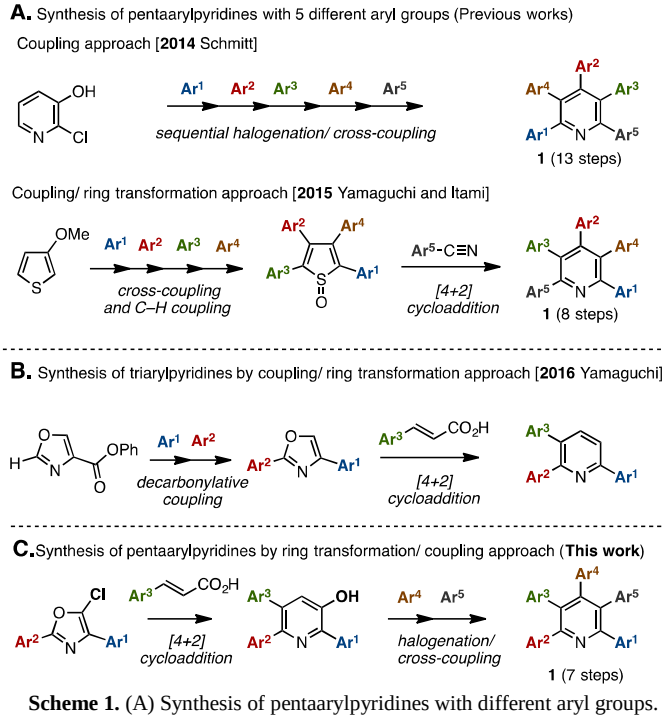
ABSTRACT

We have achieved a synthesis of multiply arylated pyridines by using a [4+2] cycloaddition of 2,4-diaryl-5-chloroxazoles and cinnamic acids as a key reaction. The resulting hydroxytriarylpyridines can be derivatized into triarylpyridines, tetraarylpyridines and pentaarylpyridines by sequential cross-couplings. This synthetic method allows for facile and rapid access to highly arylated pyridines with different aryl substituents.

1. Introduction

Multiply arylated pyridines are extremely useful as pharmaceutical cores, ligands and organic materials.[1] Therefore, the development of efficient and flexible synthetic methods toward these molecules with controlled regioselectivity would be necessary for the correlation of structures to physical properties, as well as the construction of diversified chemical libraries. A number of methods has been established for the synthesis of multiply arylated pyridines (e.g., cyclization, cycloaddition, and coupling),[2] however, the synthesis of pentaarylpyridines, which are fully aryl-substituted pyridines (especially with different aryl groups), is still rare.[3–6]

In 2014, Schmitt and co-workers accomplished the first synthesis of pentaarylpyridine (**1**) with five different aryl groups by sequential halogenations and cross-couplings starting from 2-chloro-3-hydroxypyridine (Scheme 1A).[5] Although this method can introduce aryl substituents on pyridine with complete regioselectivity, many synthetic operations (13 steps) are required. In the following year, our group successfully demonstrated the synthesis of multiply arylated arenes including **1** by a coupling/ ring transformation approach.[6] Tetraarylthiophene *S*-oxides, prepared by regioselective cross-couplings and C–H couplings followed by oxidation of the sulfur atom, underwent [4+2] cycloaddition with an arylnitrile to afford **1** as a 1:1 mixture of regioisomers (8 steps). Very recently, our group also used a similar synthetic approach to synthesize 2,3,6-triarylpyridines (Scheme 1B).[7]



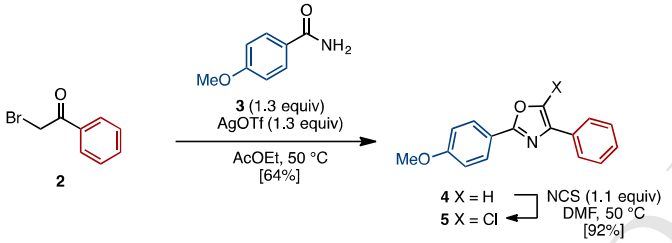
Scheme 1. (A) Synthesis of pentaarylpyridines with different aryl groups. (B) Synthesis of triarylpyridines by a coupling/ring transformation approach. (C) Synthesis of pentaarylpyridines by a ring transformation/coupling approach.

Phenyl oxazole-4-carboxylate was coupled with two arylating agents by nickel-catalyzed decarbonylative coupling to afford 2,4-diaryloxazoles,[8] and subsequently, [4+2] cycloaddition of the resulting diaryloxazoles with cinnamic acid derivatives provided 2,3,6-triarylpyridines with complete regioselectivity. Motivated by a challenge to generate a new synthesis of pentaarylpyridines (**1**) with five different aryl groups, we planned to introduce a functional group handle on 2,3,6-triarylpyridine (Scheme 1C). Thus, we selected 5-chloro-2,4-diaryloxazole as the starting material and [4+2] cycloaddition with cinnamic acids would produce hydroxylated triarylpyridines. Then, halogenation and cross-couplings would give **1** in a fewer number of steps. Herein, we report the synthesis of multiply arylated pyridines such as triarylpyridine, tetraarylpyridine, and pentaarylpyridine with different aryl substituents.

2. Results and Discussion

2.1. Synthesis of hydroxytriarylpyridines

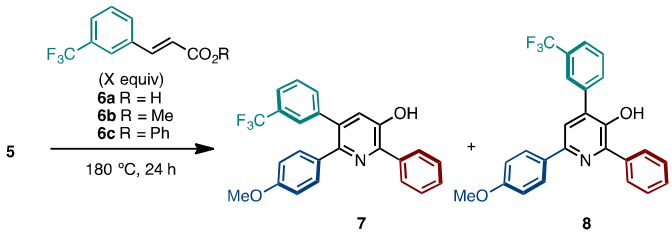
The synthesis of hydroxytriarylpyridines, which is a key intermediate in our synthetic plan, commenced with condensation of commercially available bromoacetophenone (**2**) and 4-methoxybenzamide (**3**) (Scheme 2). Treatment of a mixture of **2** and **3** with stoichiometric silver triflate in ethyl acetate gave 2,4-diaryloxazole **4** in 64% yield.[7,10] Subsequently, chlorination of **4** using *N*-chlorosuccinimide (NCS) afforded 5-chloro-2,4-diaryloxazole **5** in excellent yield.



Scheme 2. Synthesis of 5-chloro-2,4-diaryloxazole **5**.

Then, a [4+2] cycloaddition of the resulting 5-chloro-2,4-diaryloxazole **5** and cinnamic acid derivatives **6** was carried out (Table 1).[9] Compound **5** was reacted with 4.0 equivalents of (*E*)-3-(3-(trifluoromethyl)phenyl)acrylic acid (**6a**) according to our reported procedure (180 ºC in *o*-dichlorobenzene as a solvent), but this resulted in trace product (entry 1). Then, the reaction was conducted without solvent to furnish the desired 3-hydroxy-2,5,6-triarylpyridine **7** in 11% yield, along with its regioisomer, 3-hydroxy-2,4,6-triarylpyridine **8**, in 5% yield (entry 2). This reaction likely occurs by [4+2] cycloaddition of **5** and **6a** to produce a six-membered cycloadduct, followed by decarboxylation and loss of HCl. As a scavenger of HCl, addition of diisopropylethylamine was effective, as both product **7** and **8** were obtained with increased yields (43% and 18%, respectively), but the regioselectivity did not change (entry 3). Other cinnamic acid derivatives such as methyl ester **6b** and phenyl ester **6c** did not work at all (entries 4 and 5). The amount of **6a** can be decreased to 2.5 equivalents to furnish triarylpyridines **7** and **8** in 60% total yield (1.3 g scale). However, even with an extensive screening of additives and solvents, the regioselectivity did not improve. Since **7** and **8** can be easily separated by column chromatography, we moved onward to the synthesis of multiply arylated pyridines.

Table 1. [4+2] Cycloaddition of 2,4-diaryloxazole **5** and cinnamic acid derivatives **6**.

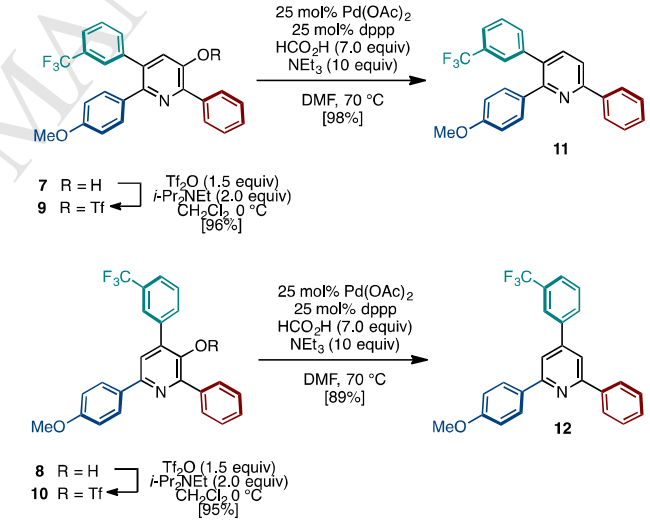


Entry	**6**/ X (equiv)	Additive	**7**/% yield	**8**/% yield
1[a]	**6a**/ 4.0	–	<5	<1
2	**6a**/ 4.0	–	11	5
3	**6a**/ 4.0	*i*-Pr_2NEt	43	18
4	**6b**/ 4.0	*i*-Pr_2NEt	0	0
5	**6c**/ 4.0	*i*-Pr_2NEt	0	0
6	**6a**/ 2.5	*i*-Pr_2NEt	43	17

[a] *o*-Dichlorobenzene was used as the solvent.

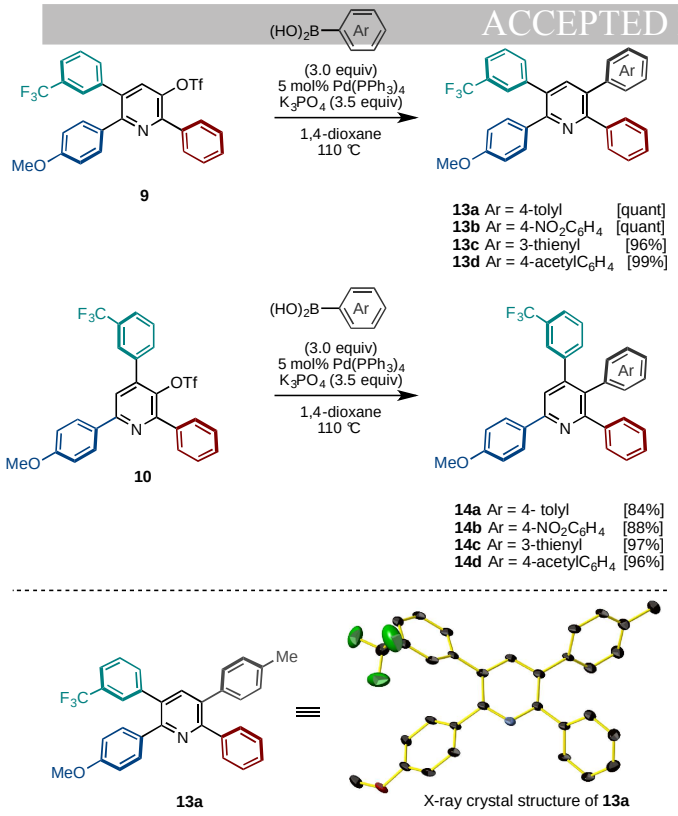
2.2. Synthesis of triarylpyridines and tetraarylpyridines

3-Hydroxy-2,5,6-triarylpyridine **7** and 3-hydroxy-2,4,6-triarylpyridine **8** can be converted to the corresponding triarylpyridines (Scheme 3). After converting **7** and **8** to triflates **9** and **10**, reduction of both triflates under palladium catalysis [$Pd(OAc)_2$/ dppp:1,3-bis(diphenylphosphino)propane] using formic acid/NEt_3 as the hydrogen source afforded the corresponding triarylpyridines **11** and **12** in 98% and 89% yield, respectively.[8]



Scheme 3. Synthesis of triarylpyridines **11** and **12**.

The intermediate triflates **9** and **10** can also be converted to tetraarylpyridines **13** and **14** with four different aryl groups by Suzuki–Miyaura cross-coupling (Scheme 4). Triflate **9** was coupled with a variety of arylboronic acids in the presence of catalytic $Pd(PPh_3)_4$ and K_3PO_4 in 1,4-dioxane at 110 ºC to afford the corresponding 2,3,5,6-tetraarylpyridines **13a–13d** in excellent yields. When subjected to the same procedure, triflate **10** was transformed to the corresponding 2,3,4,6-tetraarylpyridines **14a–14d**. The molecular structure of **13a** was determined by X-ray crystallography, thereby confirming the presence of four different aryl groups on the pyridine core.

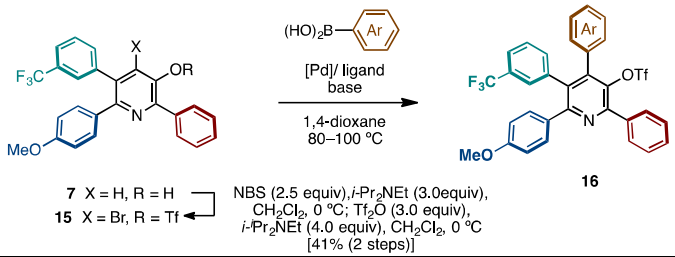


Scheme 4. Synthesis of tetraarylpyridines **13** and **14**. In the ORTEP drawing of tetraarylpyridine **13a**, hydrogen atoms are omitted for clarity and thermal ellipsoids are drawn at 50% probability.

2.3. Synthesis of pentaarylpyridines

3-Hydroxy-2,5,6-triarylpyridine **7** was then used in the synthesis of pentaarylpyridines. Treatment of **7** with *N*-bromosuccinimide (NBS) afforded a C4-brominated pyridine, then triflation led to bromopyridinetriflate **15** in 41% overall yield. Next, a bromo-selective Suzuki–Miyaura cross-coupling was performed (Table 2). When compound **15** was coupled with 3-thienylboronic acid using a standard palladium catalyst and a base [$Pd(PPh_3)_4$, K_3PO_4], the desired coupling product **16a** was obtained in very low yield (entry 1). Under these reaction conditions, no bromo-selectivity was observed, and by-products resulting from reaction with triflate, as well as dibromo-detriflated product and recovered starting material were obtained. In contrast, when the catalyst was changed to $Pd_2(dba)_3$/*Pt*-Bu_3, the reaction proceeded smoothly to produce **16a** in 69% yield with complete bromo-selectivity (entry 2). However, when the arylboronic acid was changed to 4-tolylboronic acid, the yield of coupling product **16b** decreased to 13% yield (entry 3). To overcome this problem, the ratio of Pd/ligand was critical.[12] When the ratio of Pd/ligand was 1/2, the product was produced in low yield, whereas a 1/1 ratio dramatically increased the yield of **16b** to 73% (entry 4). This protocol can be used not only for 4-tolylboronic acid, but also for 3-thienylboronic acid and for 4-(ethoxyphenyl)boronic acid: the coupling reaction of these arylboronic acids with **15** produced the corresponding coupling products **16a** and **16c** in 82% and 84% respectively, with complete bromo-selectivity (entries 5 and 6).

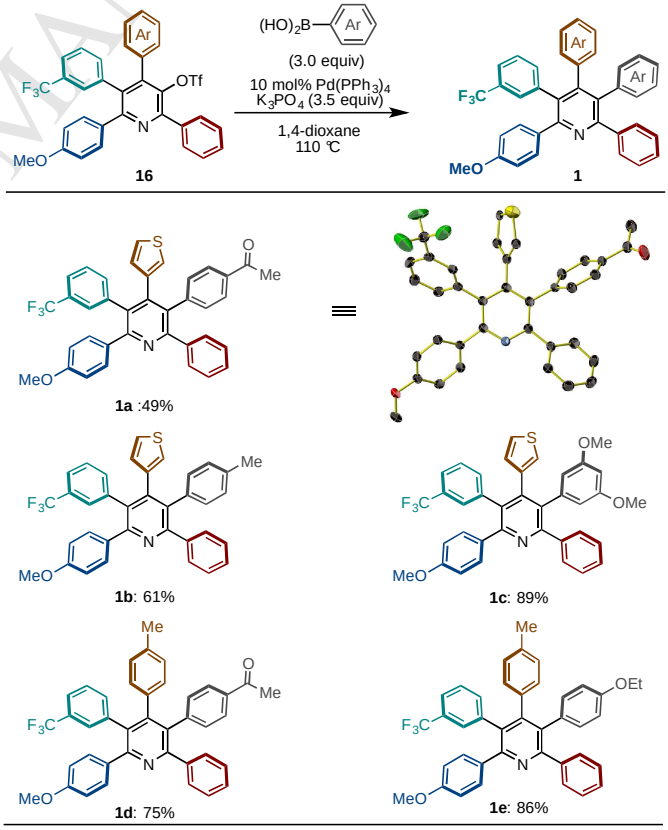
Table 2. Bromo-selective Suzuki–Miyaura coupling of aryl bromide **15** and arylboronic acids.



Entry	Ar	Pd/ mol%	Ligand/ mol%	Base	**16** /%[c]
1	3-thienyl	$Pd(PPh_3)_4$ /5	–	K_3PO_4	14 (**16a**)
2[a]	3-thienyl	$Pd_2(dba)_3$ /2.5	P*t*-Bu_3/10	NaOH	69 (**16a**)
3[a]	4-tolyl	$Pd_2(dba)_3$ /2.5	P*t*-Bu_3/10	NaOH	13 (**16b**)
4[b]	4-tolyl	$Pd_2(dba)_3$ /2.5	P*t*-Bu_3/5	K_3PO_4	73 (**16b**)
5[b]	3-thienyl	$Pd_2(dba)_3$ /2.5	P*t*-Bu_3/5	K_3PO_4	82 (**16a**)
6[b]	4-EtOC$_6$H$_4$	$Pd_2(dba)_3$ /2.5	P*t*-Bu_3/5	K_3PO_4	84 (**16c**)

[a]1,4-Dioxane/H_2O was used as the solvent. [b]Toluene/H_2O was used as the solvent.

With triflated tetraarylpyridines **16** in hand, the introduction of the final aryl group was carried out (Scheme 5). Compounds **16** were coupled with arylboronic acids in the presence of a palladium catalyst [$Pd(PPh_3)_4$] and K_3PO_4 in 1,4-dioxane at 110 ºC to give a variety of pentaarylpyridines **1a–1e** in good to moderate yields. The molecular structure of **1a** was determined by X-ray crystallography, unambiguously establishing the connection of five different aryl groups onto the central pyridine.



Scheme 5. Synthesis of pentaarylpyridines **1**. In the ORTEP drawing of pentaarylpyridine **1a**, hydrogen atoms are omitted for clarity and thermal ellipsoids are drawn at 50% probability.

3. Conclusion

In summary, we have demonstrated the synthesis of pentaarylpyridines with five different aryl groups by a ring transformation/coupling approach. 5-Chloro-2,4-diaryloxazole is

a convenient precursor to hydroxypyridines by utilizing a [4+2] cycloaddition. The introduction of all the aryl groups is flexible, as all the aryl groups are theoretically modifiable. The key hydroxytriarylpyridine intermediate can also lead to triarylpyridines and tetraarylpyridines in a two-step sequence. This combined pyridine synthesis/substitution route allows for a rapid structural diversification that bodes well for applications in organometallic, pharmaceutical and materials chemistry.

4. Experimental

Unless otherwise noted, all reactants or reagents including dry solvents were obtained from commercial suppliers and used as received. Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of argon and N_2 in dried glassware using standard vacuum-line techniques. All cross-coupling reactions were performed in 8-mL glass tubes equipped with screw cap and heated in an oil bath unless otherwise noted. All work-up and purification procedures were carried out with reagent-grade solvents in air. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm). Flash column chromatography was performed with Biotage Isolera® equipped with Biotage SNAP Cartridge KP-Sil columns and hexane/EtOAc as an eluent. Preparative thin-layer chromatography (PTLC) was performed using Wakogel B5-F silica coated plates (0.75 mm) prepared in our laboratory. Preparative gel permeation chromatography (GPC) was performed with a JAI LC-9204 instrument equipped with JAIGEL-1H/JAIGEL-2H columns using chloroform as an eluent. The high-resolution mass spectra were conducted on Thermo Fisher Scientific Exactive (ESI). Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA-400 (^{1}H 400 MHz, ^{13}C 100 MHz) and JEOL JMN-ECA-600II with Ultra COOL™ probe (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, dt = doublet of triplets, td = triplet of doublets, q = quartet, m = multiplet, br s = broad singlet), coupling constant (Hz), and integration.

*4.1. Procedure for the synthesis of 5-chloro-2-(4-methoxyphenyl) -4-phenyloxazole (**5**)*

Using a procedure in the literature[10], **4** was synthesized in 64% yield. To a round-bottom flask containing a magnetic stirring bar and **4** (2.01 g, 8.0 mmol, 1.0 equiv) was added dry DMF (26 mL). *N*-Chlorosuccinimide (NCS: 1.07 g, 8.0 mmol, 1.0 equiv) was added in one portion, and the resulting mixture was heated overnight at 50 °C in an oil bath. After cooling to room temperature, the mixture was diluted with EtOAc and then washed three times with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford **5** (2.12 g, 93% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.97 (m, 4H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 9.2 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 161.6, 159.7, 133.9, 130.0, 129.9, 128.5, 128.1, 127.9, 126.3, 119.4, 114.2, 55.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{13}ClNO_2$ $[M+H]^+$: 286.0629, found 286.0630.

*4.2. Procedure for the [4+2] cycloaddition of **5** and cinnamic acid **6a***

To a screw cap test tube containing a magnetic stirring bar were added **5** (1.29 g, 4.5 mmol, 1.0 equiv), 3-(trifluoromethyl)cinnamic acid (**6a**: 2.43 g, 11.25 mmol, 2.5 equiv), and *N*,*N*-diisopropylethylamine (582 mg, 4.5 mmol, 1.0 equiv). The tube was sealed with a screw cap and heated at 180 °C for 24 hours. After cooling, the mixture was diluted with EtOAc and treated with Na_2CO_3aq for 30 min. The water phase was extracted three times with EtOAc. The combined organic phase was washed with brine, and then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. After removing highly polar impurities by a short silica-gel pad with EtOAc as an eluent, the crude mixture was purified by Isolera® (hexane/EtOAc = 20:1 to 5:1) to afford triaryl hydroxypyridines **7** (813 mg, 43% yield) and **8** (321 mg, 17% yield).

*4.2.1. 6-(4-Methoxyphenyl)-2-phenyl-5-(3-(trifluoromethyl)phenyl)pyridin-3-ol (**7**).*

White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.49–7.44 (m, 3H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.07 (s, 1H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.37 (br s, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 149.0, 148.6, 144.9, 140.2, 136.0, 134.2, 132.9, 131.3, 131.2, 130.6 (q, *J* = 32.6 Hz), 129.0, 128.7, 128.6, 128.5, 126.1 (q, *J* = 3.8 Hz), 126.0, 123.9 (q, *J* = 273 Hz), 123.8 (q, *J* = 2.9 Hz), 113.3, 55.1; HRMS (ESI) *m/z* calcd for $C_{25}H_{19}F_3NO_2$ $[M+H]^+$: 422.1362, found 422.1358.

*4.2.2. 6-(4-Methoxyphenyl)-2-phenyl-4-(3-(trifluoromethyl)phenyl)pyridin-3-ol (**8**).*

Pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 9.2 Hz, 2H), 7.93 (s, 1H), 7.87–7.81 (m, 3H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.56 (s, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 9.2 Hz, 2H), 5.57 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 149.8, 146.1, 145.0, 136.73, 136.67, 135.4, 132.4, 131.6, 131.1 (q, *J* = 32.5 Hz), 129.14, 129.05, 128.9, 127.7, 126.0 (q, *J* = 3.8 Hz), 125.1 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 274 Hz), 120.0, 114.0, 55.3 (one peak is missing due to overlapping.); HRMS (ESI) *m/z* calcd for $C_{25}H_{19}F_3NO_2$ $[M+H]^+$: 422.1362, found 422.1356.

*4.3. Procedure for the synthesis of 6-(4-methoxyphenyl)-2-phenyl-5-(3-(trifluoromethyl)phenyl)pyridin-3-yl trifluoromethanesulfonate (**9**)*

In a round-bottom flask, 2,5,6-triaryl-3-hydroxypyridine **7** (400 mg, 0.95 mmol, 1.0 equiv) and *N*,*N*-diisopropylethylamine (245 mg, 1.9 mmol, 2.0 equiv) were dissolved in dry CH_2Cl_2 (2.0 mL) and cooled to 0 °C. To this mixture was slowly added a solution of trifluoromethanesulfonic anhydride (402 mg, 1.42 mmol, 1.5 equiv) in CH_2Cl_2 (1.0 mL). After stirring the mixture for 1 hour, $NaHCO_3$ aq. was added. The mixture was extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. This crude material was purified by Isolera® (hexane/EtOAc = 10:1 to 5:1) to afford **9** (504 mg, 96% yield) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.72 (s, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.57–7.48 (m, 4H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 156.2, 150.3, 142.8, 138.9, 135.0, 133.9, 132.8, 132.4, 131.5, 131.2 (q, *J* = 32.6 Hz), 130.4, 129.8, 129.4, 129.2, 128.5, 126.1 (q, *J* = 2.9 Hz), 123.7 (q, *J* = 273 Hz), 124.7 (q, *J* = 3.9 Hz), 118.3 (q, *J* = 322 Hz), 113.6, 55.2; HRMS (ESI) *m/z* calcd for $C_{26}H_{18}F_6NO_4S$ $[M+H]^+$: 554.0855, found 554.0855.

*4.4. Procedure for the synthesis of 6-(4-methoxyphenyl)-2-phenyl-4-(3-(trifluoromethyl)phenyl)pyridin-3-yl trifluoromethanesulfonate (**10**)*

In a round-bottom flask, 3-hydroxy-2,4,6-triarylpyridine **8** (300 mg, 0.71 mmol, 1.0 equiv) and *N*,*N*-diisopropylethylamine (184 mg, 1.4 mmol, 2.0 equiv) were dissolved in dry CH_2Cl_2 (1.5 mL) and cooled to 0 °C. To this mixture was slowly added a solution of trifluoromethanesulfonic anhydride (301 mg, 1.1 mmol, 1.5 equiv) in CH_2Cl_2 (0.75 mL). After stirring the mixture for 1 hour, the mixture was added $NaHCO_3$ aq. was added. The mixture was extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. This crude material was purified by Isolera® (hexane/EtOAc = 10:1 to 5:1) to afford **10** (374 mg, 95% yield) as a yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.2 Hz, 2H), 8.01–7.86 (m, 3H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.58–7.46 (m, 3H), 7.01 (d, *J* = 9.2 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 156.4, 153.2, 143.8, 140.1, 136.1, 135.5, 132.7, 131.4 (q, *J* = 32.6 Hz), 129.9, 129.7, 129.5, 128.7, 128.5, 126.3 (q, *J* = 3.2 Hz), 123.7 (q, *J* = 273 Hz), 119.9, 117.6 (q, *J* = 321 Hz), 114.2, 55.4 (two carbon peaks are missing due to overlapping); HRMS (ESI) *m/z* calcd for $C_{26}H_{18}F_6NO_4S$ $[M+H]^+$: 554.0855, found 554.0857.

*4.5. Procedure for the synthesis of triarylpyridine **11** and **12** by Pd-catalyzed reduction using formic acid*

To a dried screw cap test tube containing a magnetic stirring bar were added triarylpyridine triflate (**9** or **10**: 11.2 mg, 20 µmol, 1.0 equiv), $Pd(OAc)_2$ (1.14 mg, 5.1 µmol, 25 mol%), and 1,3-bis(diphenylphosphino)propane (dppp: 2.1 mg, 5.1 µmol, 25 mol%). The tube was evacuated *in vacuo* and refilled with N_2 gas three times. To this were added formic acid (6.5 mg, 0.14 mmol, 7.0 equiv), triethylamine (20.5 mg, 0.20 mmol, 10 equiv), and DMF (60 µL). The tube was sealed with a screw cap, and then heated at 110 °C in an oil bath. Reaction progress was monitored by TLC. After cooling to room temperature, the mixture was passed through a short silica-gel pad with EtOAc as an eluent and concentrated *in vacuo*. The residue was purified by PTLC to afford triarylpyridines **11** or **12**.

*4.5.1. 2-(4-Methoxyphenyl)-6-phenyl-3-(3-(trifluoromethyl)phenyl)pyridine (**11**)*

Purification by PTLC (hexane/EtOAc = 10:1) gave **11** (8.0 mg, 98% yield) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.8 Hz, 2H), 7.76 (s, 2H), 7.56 (s, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.41–7.35 (m, 4H), 6.80 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.6, 156.4, 156.2, 141.1, 139.3, 138.9, 133.0, 132.4, 132.2, 131.5, 130.9 (q, *J* = 31.7 Hz), 129.1, 128.7, 127.0, 126.1 (q, *J* = 2.9 Hz), 124.0 (q, *J* = 270 Hz), 123.8 (q, *J* = 4.2 Hz), 118.2, 113.5, 55.3 (one peak is missing due to overlapping); HRMS (ESI) *m/z* calcd for $C_{25}H_{19}F_3NO$ $[M+H]^+$: 406.1413, found 406.1410.

*4.5.2. 2-(4-Methoxyphenyl)-6-phenyl-4-(3-(trifluoromethyl)phenyl)pyridine (**12**)*

Purification by PTLC (hexane/EtOAc = 10:1) gave **12** (7.3 mg, 89% yield) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.2 Hz, 2H), 8.18 (d, *J* = 9.0 Hz, 2H), 7.97 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 1.2 Hz, 1H), 7.81 (d, *J* = 1.2 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.7, 157.7, 157.4, 148.7, 140.1, 139.4, 131.9, 131.6 (q, *J* = 33.2 Hz), 130.5, 129.6, 129.2, 128.7, 128.4, 127.1, 125.5 (q, *J* = 3.0 Hz), 124.00 (q, *J* = 4.4 Hz), 123.99 (q, *J* = 274 Hz), 116.3, 116.2, 114.1, 55.4; HRMS (ESI) *m/z* calcd for $C_{25}H_{19}F_3NO$ $[M+H]^+$: 406.1413, found 406.1413.

*4.6. Procedure for the synthesis of 2,3,5,6-tetraarylpyridine by Suzuki–Miyaura coupling (**13a–13d**)*

To a dried screw cap test tube containing a magnetic stirring bar were added **9** (1.0 equiv), arylboronic acid (3.0 equiv), K_3PO_4 (3.5 equiv), and $Pd(PPh_3)_4$ (10 mol%). The tube was evacuated *in vacuo* and refilled with N_2 gas three times. To the tube was added dry 1,4-dioxane (0.10 M) under a stream of N_2 gas. The tube was sealed with a screw cap, and then heated at 110 °C in an oil bath. Reaction progress was monitored by TLC. After cooling to room temperature, the mixture was passed through a short silica-gel pad with EtOAc as an eluent and concentrated *in vacuo*. The residue was purified by PTLC to afford 2,3,5,6-tetraarylpyridines **13**.

*4.6.1. 2-(4-Methoxyphenyl)-6-phenyl-5-(p-tolyl)-3-(3-(trifluoromethyl)phenyl)pyridine(**13a**)*

Purification by PTLC (hexane/EtOAc = 10:1) gave **13a** (27 µmol scale, 14.1 mg, quant) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.60 (s, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.53–7.49 (m, 2H), 7.45–7.36 (m, 4H), 7.32–7.24 (m, 3H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.6, 155.8, 154.8, 141.0, 140.9, 139.9, 137.1, 136.5, 134.0, 133.0, 132.3, 131.9, 131.5, 130.9 (q, *J* = 31.7 Hz), 130.1, 129.4, 129.1, 128.7, 127.84, 127.81, 126.2 (q, *J* = 2.9 Hz), 124.0 (q, *J* = 271 Hz), 123.9 (q, *J* = 2.9 Hz), 113.5, 55.3, 21.2; HRMS (ESI) *m/z* calcd for $C_{32}H_{25}F_3NO$ $[M+H]^+$: 496.1883, found 496.1880.

*4.6.2. 2-(4-Methoxyphenyl)-5-(4-nitrophenyl)-6-phenyl-3-(3-(trifluoromethyl)phenyl)pyridine (**13b**)*

Purification by PTLC (hexane/EtOAc = 4:1) and then GPC gave **13b** (36 µmol scale, 19.1 mg, quant) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.8 Hz, 2H), 7.74 (s, 1H), 7.61 (s, 1H), 7.58 (d, *J* = 6.6 Hz, 1H), 7.49–7.42 (m, 6H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.35–7.26 (m, 3H), 6.80 (d, *J* = 7.8 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.9, 156.2, 156.0, 147.0, 146.4, 140.7, 140.3, 139.0, 132.9, 132.5, 131.7, 131.5, 131.3, 131.1 (q, *J* = 33 Hz), 130.4, 130.1, 129.0, 128.5, 128.2, 126.1 (q, *J* = 2.9 Hz), 124.2 (q, *J* = 4.2 Hz), 123.9 (q, *J* = 272 Hz), 123.7, 113.6, 55.3; HRMS (ESI) *m/z* calcd for $C_{31}H_{22}F_3N_2O_3$ $[M+H]^+$: 527.1577, found 527.1579.

*4.6.3. 2-(4-Methoxyphenyl)-5-(4-nitrophenyl)-6-phenyl-3-(3-(trifluoromethyl)phenyl)pyridine (**13c**)*

Purification by Isolera® (hexane/EtOAc = 20:1 to 5:1) gave **13c** (36 µmol scale, 16.9 mg, 96% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.60 (s, 1H), 7.58–7.47 (m, 3H), 7.42–7.34 (m, 4H), 7.34–7.26 (m, 3H), 7.24–7.12 (m, 2H), 6.83 (dd, *J* = 5.2, 1.6 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 156.0, 154.9, 140.7, 140.5, 140.0, 139.7, 133.0, 132.4, 131.7, 131.4, 130.9 (q, *J* = 32.5 Hz), 129.8, 128.9, 128.8, 128.6, 128.1, 127.9, 126.1 (q, *J* = 3.8 Hz), 125.6, 123.93 (q, *J* = 3.8 Hz) 123.92 (q, *J* = 274 Hz), 123.5, 113.5, 55.2; HRMS (ESI) *m/z* calcd for $C_{29}H_{21}F_3NOS$ $[M+H]^+$:488.1290, found 488.1293.

*4.6.4. 1-(4-(6-(4-Methoxyphenyl)-2-phenyl-5-(3-(trifluoromethyl)phenyl)pyridin-3-yl)phenyl)ethan-1-one(**13d**)*

Purification by Isolera® (hexane/EtOAc = 20:1 to 2:1) gave **13d** (36 µmol scale, 18.8 mg, 99% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.74 (s, 1H), 7.61 (s, 1H), 7.59–7.53 (m, 1H), 7.47 (dd, *J* = 8.4, 2.4 Hz, 2H), 7.45–7.34 (m, 6H), 7.32–7.24 (m, 3H), 6.80 (d, *J* = 8.4 Hz, 2H),

3.80 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 159.7, 155.9, 155.6, 144.4, 140.8, 140.5, 139.3, 135.8, 132.9, 132.8, 132.4, 131.5, 131.0 (q, *J* = 32.6 Hz), 130.1, 129.7, 128.9, 128.5, 128.2, 128.0, 126.1 (q, *J* = 3.9 Hz), 124.1 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 273 Hz), 113.5, 55.2, 26.6 (one peak is missing due to overlapping); HRMS (ESI) *m/z* calcd for $C_{33}H_{25}F_3NO_2$ $[M+H]^+$: 524.1832, found 524.1832.

*4.7. Procedure for the synthesis of 2,3,4,6-tetraarylpyridine by Suzuki–Miyaura coupling (**14a–14d**)*

To a dried screw cap test tube containing a magnetic stirring bar were added **10** (1.0 equiv), arylboronic acid (3.0 equiv), K_3PO_4 (3.5 equiv), and $Pd(PPh_3)_4$ (10 mol%). The tube was evacuated *in vacuo* and refilled with N_2 gas three times. To the tube was added dry 1,4-dioxane (0.10 M) under a stream of N_2 gas. The tube was sealed with a screw cap, and then heated at 110 °C in an oil bath. Reaction progress was monitored by TLC. After cooling to room temperature, the mixture was passed through a short silica-gel pad with EtOAc as an eluent and concentrated *in vacuo*. The residue was purified by PTLC to afford 2,3,4,6-tetraarylpyridines **14**.

*4.7.1. 6-(4-Methoxyphenyl)-2-phenyl-3-(p-tolyl)-4-(3-(trifluoromethyl)phenyl)pyridine (**14a**)*

Purification by PTLC (hexane/EtOAc = 10:1) gave **14a** (27 µmol scale, 11.1 mg, 84% yield) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 9.0 Hz, 2H), 7.68 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.44–7.36 (m, 3H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.24–7.18 (m, 3H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 7.8 Hz, 2H), 6.75 (d, *J* = 7.8 Hz, 2H), 3.88 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.6, 158.0, 155.4, 149.0, 140.91, 140.87, 136.5, 134.2, 132.6, 132.1, 131.5, 131.1, 130.3 (q, *J* = 31.7 Hz), 130.2, 128.6, 128.3, 127.5, 127.4, 126.2 (q, *J* = 2.9 Hz), 123.93 (q, *J* = 4.4 Hz), 123.89 (q, *J* = 270 Hz), 119.1, 114.1, 55.4, 21.1 (one peak is missing due to overlapping); HRMS (ESI) *m/z* calcd for $C_{32}H_{25}F_3NO$ $[M+H]^+$: 496.1883, found 496.1879.

*4.7.2. 6-(4-Methoxyphenyl)-3-(4-nitrophenyl)-2-phenyl-4-(3-(trifluoromethyl)phenyl)pyridine (**14b**)*

Purification by PTLC (hexane/EtOAc = 4:1) gave **14b** (36 µmol scale, 16.7 mg, 88% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.2 Hz, 2H), 7.94 (d, *J* = 9.2 Hz, 2H), 7.73 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 7.39–7.29 (m, 3H), 7.29–7.18 (m, 4H), 7.07 (d, *J* = 9.2 Hz, 2H), 7.01 (d, *J* = 9.2 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 157.8, 156.5, 148.8, 146.4, 145.1, 139.9, 139.8, 132.4, 132.3, 130.80 (q, *J* = 33.5 Hz), 130.79, 130.0, 129.8, 128.8, 128.5, 128.0, 127.9, 126.0 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 2.9 Hz), 123.6 (q, *J* = 273 Hz), 123.1, 119.1, 114.2, 55.3; HRMS (ESI) *m/z* calcd for $C_{31}H_{22}F_3N_2O_3$ $[M+H]^+$: 527.1577, found 527.1579.

*4.7.3. 6-(4-Methoxyphenyl)-2-phenyl-3-(thiophen-3-yl)-4-(3-(trifluoromethyl)phenyl)pyridine (**14c**)*

Purification by Isolera® (hexane/EtOAc = 20:1 to 2:1) gave **14c** (36 µmol scale, 17.1 mg, 97% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 2H), 7.68 (s, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.48–7.30 (m, 5H), 7.30–7.18 (m, 3H), 7.06 (dd, *J* = 4.8, 2.4 Hz, 1H), 7.00 (dd, *J* = 8.4 Hz, 2H), 6.66 (dd, *J* = 2.4, 1.6 Hz, 1H), 6.52 (dd, *J* = 4.8, 1.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 158.3, 155.6, 149.1, 140.8, 140.7, 137.2, 132.3, 131.3, 130.4 (q, *J* = 32.5 Hz), 129.8, 129.7, 128.5, 128.3, 127.6, 127.1, 125.9 (q, *J* = 3.9 Hz), 125.4, 125.1, 124.2 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 273 Hz), 118.9, 114.1, 55.3 (one peak is missing due to overlapping); HRMS (ESI) *m/z* calcd for $C_{29}H_{21}F_3NOS$ $[M+H]^+$: 488.1290, found 488.1286.

*4.7.4. 1-(4-(6-(4-Methoxyphenyl)-2-phenyl-4-(3-(trifluoromethyl)phenyl)pyridin-3-yl)phenyl)ethan-1-one (**14d**)*

Purification by Isolera® (hexane/EtOAc = 20:1 to 2:1) gave **14d** (36 µmol scale, 18.2 mg, 96% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.2 Hz, 2H), 7.71 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.39 (s, 1H), 7.38–7.29 (m, 3H), 7.29–7.17 (m, 4H), 7.02 (d, *J* = 9.2 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 160.8, 157.8, 156.0, 148.9, 142.9, 140.3, 140.2, 135.2, 132.5, 131.6, 131.1, 130.9, 130.5 (q, *J* = 32.5 Hz), 130.1, 128.6, 128.4, 127.9, 127.8, 127.7, 126.0 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 2.8 Hz), 123.7 (q, *J* = 274 Hz), 119.0, 114.1, 55.4. 26.5; HRMS (ESI) *m/z* calcd for $C_{33}H_{25}F_3NO_2$ $[M+H]^+$: 524.1832, found 524.1834.

*4.8. Procedure for the synthesis of 4-bromo-6-(4-methoxyphenyl)-2-phenyl-5-(3-(trifluoromethyl)phenyl)pyridin-3-yl trifluoromethanesulfonate (**15**)*

To a round-bottom flask containing a magnetic stirring bar and **7** (337 mg, 0.80 mmol, 1.0 equiv) and *N*,*N*-diisopropylethylamine (310 mg, 2.4 mmol, 3.0 equiv) was added dry CH_2Cl_2 (9.4 mL). This mixture was cooled to 0 °C, and then *N*-bromosuccinimide (285 mg, 1.6 mmol, 2.0 equiv) was added in one portion. After stirring at 0 °C for 1 hour, $NaHCO_3$ aq. was added. The mixture was extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The crude material was immediately purified by Isolera® (hexane/EtOAc = 10:1 to 4:1) to afford 4-bromo-6-(4-methoxyphenyl)-2-phenyl-5-(3-(trifluoromethyl)phenyl)pyridin-3-ol (213.9 mg, 53% yield) as a white solid. Owing to the instability of this product, this was quickly used in the next triflation step. The obtained molecule (213.9 mg, 0.43 mmol, 1.0 equiv) and *N*,*N*-diisopropylethylamine (221.0 mg, 1.71 mmol, 4.0 equiv) were dissolved in dry CH_2Cl_2 (17.5 mL) and cooled to 0 °C. To this mixture was slowly added trifluoromethanesulfonic anhydride (362 mg, 1.28 mmol, 3.0 equiv). After stirring the mixture for 30 min, $NaHCO_3$ aq. was added. The mixture was extracted three times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. This crude material was purified by Isolera® (hexane/EtOAc = 10:1 to 4:1) to afford **15** (211.8 mg, 41% yield in 2 steps) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.57–7.45 (m, 5H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 157.2, 152.3, 141.1, 138.5, 135.4, 135.2, 133.9, 131.5, 131.0, 130.9 (q, *J* = 32.6 Hz), 130.5, 130.1, 129.5, 129.1, 128.5, 127.6 (q, *J* = 3.8 Hz), 125.1 (q, *J* = 4.0 Hz), 123.7 (q, *J* = 275 Hz), 118.0 (q, *J* = 323 Hz), 113.4, 55.2; HRMS (ESI) *m/z* calcd for $C_{26}H_{17}BrF_6NO_4S$ $[M+H]^+$: 631.9960, found 631.9961.

*4.9. Procedure for the bromo-selective cross-coupling of **15***

To a screw cap test tube containing a magnetic stirring bar were added **15** (1.0 equiv), arylboronic acid (3.0 equiv), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol%), and $P(t\text{-}Bu)_3 \cdot HBF_4$ (10 mol%). The tube was evacuated *in vacuo* and refilled with N_2 gas three times. To the tube were added degassed K_3PO_4 aq. (1 M, 2.0 equiv) and toluene (0.125 M) under a stream of N_2 gas. The tube was sealed with a screw cap, and then heated overnight at 80 °C in an oil bath. After cooling to room temperature, water and EtOAc were added. The mixture was extracted three times with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and then concentrated *in vacuo*. The residue was purified by PTLC to afford triflated 2,3,5,6-tetraarylpyridines **16**.

*4.9.1. 6-(4-Methoxyphenyl)-2-phenyl-4-(thiophen-3-yl)-5-(3-(trifluoromethyl)phenyl)pyridin-3-yl trifluoromethanesulfonate **(16a)***

Purification by PTLC (hexane/EtOAc = 10:1) gave **16a** (63 µmol scale, 27.2 mg, 82% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.58–7.45 (m, 3H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.23–7.16 (m, 5H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.68 (dd, *J* = 5.2, 1.2 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 156.9, 152.0, 141.5, 141.1, 137.6, 135.9, 134.1, 133.8, 131.9, 131.32, 131.26, 130.4 (q, *J* = 32.5 Hz), 129.7, 129.5, 128.8, 128.5, 127.74 (q, *J* = 3.9 Hz), 127.68, 125.8, 124.0 (q, *J* = 3.9 Hz), 123.6 (q, *J* = 274 Hz), 117.6 (q, *J* = 322 Hz), 113.4, 55.2 (one peak is missing due to overlapping); HRMS (ESI) *m/z* calcd for $C_{30}H_{20}F_6NO_4S_2$ $[M+H]^+$: 636.0732, found 636.0730.

*4.9.2. 6-(4-Methoxyphenyl)-2-phenyl-4-(p-tolyl)-5-(3-(trifluoromethyl)phenyl)pyridin-3-yl trifluoromethanesulfonate **(16b)***

Purification by PTLC (hexane/EtOAc = 10:1) gave **16b** (31.6 µmol scale, 14.9 mg, 73% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.54–7.44 (m, 3H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.23–7.15 (m, 3H), 7.12 (s, 1H), 7.11–6.89 (br s, 5H), 6.73 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 156.9, 152.0, 145.8, 141.4, 138.8, 137.6, 136.0, 134.4, 133.9, 131.4, 131.3, 130.5, 130.2 (q, *J* = 32.6 Hz), 129.64, 129.56, 129.3, 128.7, 128.5, 128.3, 128.1 (q, *J* = 3.8 Hz), 123.7 (q, *J* = 2.9 Hz), 123.6 (q, *J* = 274 Hz), 117.6 (q, *J* = 322 Hz), 113.4, 55.2, 21.2; HRMS (ESI) *m/z* calcd for $C_{33}H_{24}F_6NO_4S$ $[M+H]^+$: 644.1325, found 644.1322.

*4.9.3. 4-(4-Ethoxyphenyl)-6-(4-methoxyphenyl)-2-phenyl-5-(3-(trifluoromethyl)phenyl)pyridin-3-yl trifluoromethanesulfonate **(16c)***

Purification by PTLC (hexane/EtOAc = 5:1, and then CH_2Cl_2) gave **16c** (17.9 mg, 84% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 6.8 Hz, 2H), 7.54–7.43 (m, 3H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.24–7.16 (m, 3H), 7.14 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.04–6.91 (br s, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 3.98 (q, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 159.2, 156.9, 152.0, 145.5, 141.6, 137.6, 136.0, 134.4, 134.0, 132.0, 131.5, 131.3, 130.3 (q, *J* = 33.5 Hz), 129.63, 129.56, 128.5, 128.4, 128.2 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.2, 123.69 (q, *J* = 3.9 Hz), 123.65 (q, *J* = 273.1 Hz),117.6 (q, *J* = 321.9 Hz), 114.2, 113.4, 63.4, 55.2, 14.6; HRMS (ESI) *m/z* calcd for $C_{34}H_{26}F_6NO_5S$ $[M+H]^+$: 674.1430, found 674.1429.

*4.10. Procedure for the synthesis of pentaarylpyridines **1***

To a dried screw cap test tube containing a magnetic stirring bar were added **16** (1.0 equiv), arylboronic acid (3.0 equiv), K_3PO_4 (3.5 equiv), and $Pd(PPh_3)_4$ (10 mol%). The tube was evacuated *in vacuo* and refilled with N_2 gas three times. To the tube was added dry 1,4-dioxane (0.10 M) under a stream of N_2 gas. The tube was sealed with a screw cap, and then heated at 110 °C in an oil bath. Reaction progress was monitored by TLC. After cooling to room temperature, the mixture was passed through a short silica-gel pad with EtOAc as an eluent and concentrated *in vacuo*. The residue was purified by PTLC (hexane/EtOAc = 10:1) to afford pentaarylpyridines **1**.

*4.10.1. 1-(4-(6-(4-Methoxyphenyl)-2-phenyl-4-(thiophen-3-yl)-5-(3-(trifluoromethyl)phenyl)pyridin-3-yl)phenyl)ethan-1-one **(1a)***

Purification by PTLC (hexane/EtOAc = 2:1) gave **1a** (36.7 µmol scale, 10.8 mg, 49% yield) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 2H), 7.38–7.34 (m, 3H), 7.29 (d, *J* = 9.0 Hz, 2H), 7.24–7.16 (m, 5H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.91 (dd, *J* = 4.8, 3.0 Hz, 1H), 6.73 (d, *J* = 9.0 Hz, 2H), 6.51 (d, *J* = 3.0 Hz, 1H), 6.37 (d, *J* = 4.8 Hz, 1H), 3.76 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.8, 159.3, 156.8, 156.5, 145.7, 143.9, 140.2, 139.5, 137.1, 135.0, 134.1, 132.6, 132.5, 132.1, 131.5, 131.2, 130.11 (q, *J* = 31.7 Hz), 130.10, 129.0, 128.1, 127.9 (q, *J* = 2.9 Hz), 127.8, 127.7, 127.6, 125.2, 124.8, 123.8 (q, *J* = 272 Hz), 123.2 (q, *J* = 4.4 Hz), 113.3, 55.2, 26.5; HRMS (ESI) *m/z* calcd for $C_{37}H_{27}F_3NO_2S$ $[M+H]^+$: 606.1709, found 606.1709.

*4.10.2. 2-(4-Methoxyphenyl)-6-phenyl-4-(thiophen-3-yl)-5-(p-tolyl)-3-(3-(trifluoromethyl)phenyl)pyridine **(1b)***

Purification by PTLC (hexane/EtOAc = 2:1) gave **1b** (15.7 µmol scale, 5.5 mg, 61% yield) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.8, 2.4 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 2H), 7.22–7.15 (m, 5H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.90 (dd, *J* = 4.8, 3.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 9.0 Hz, 2H), 6.50 (d, *J* = 3.0 Hz, 1H), 6.38 (d, *J* = 4.8 Hz, 1H), 3.75 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 157.0, 155.8, 145.9, 140.8, 139.9, 137.6, 136.0, 135.2, 134.2, 133.7, 132.8, 132.1, 131.5, 130.7, 130.2, 130.0 (q, *J* = 31.5 Hz), 129.3, 128.3, 128.0, 127.5, 127.4, 125.0, 124.2, 123.9 (q, *J* = 270 Hz), 123.0 (q, *J* = 4.2 Hz), 113.2, 55.2, 21.2 (one peak is missing due to overlapping); HRMS (ESI) *m/z* calcd for $C_{36}H_{27}F_3NOS$ $[M+H]^+$: 578.1760, found 578.1757.

*4.10.3. 3-(3,5-Dimethoxyphenyl)-6-(4-methoxyphenyl)-2-phenyl-4-(thiophen-3-yl)-5-(3-(trifluoromethyl)phenyl)pyridine **(1c)***

Purification by PTLC (hexane/EtOAc = 10:1) gave **1c** (31.5 µmol scale, 17.4 mg, 89% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 6.8 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 9.2 Hz, 2H), 7.25–7.15 (m, 5H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.94 (dd, *J* = 5.6, 2.8 Hz, 1H), 6.72 (d, *J* = 9.2 Hz, 2H), 6.56 (dd, *J* = 2.8, 1.2 Hz, 1H), 6.43 (dd, *J* = 5.6, 1.2 Hz, 1H), 6.19 (t, *J* = 2.0 Hz, 1H), 6.09 (d, *J* = 2.0 Hz, 2H), 3.75 (s, 3H), 3.50 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 159.2, 156.9, 156.0, 145.6, 140.7, 140.0, 139.8, 137.5, 134.2, 133.4, 132.7, 132.0, 131.5, 130.0 (q, *J* = 32.5 Hz), 129.8, 129.2, 128.0, 127.6, 127.5, 124.9, 124.3, 123.8 (q, *J* = 274 Hz), 123.1 (q, *J* = 2.8 Hz), 113.2, 109.3, 99.6, 55.23, 55.20 (one peak is missing due to overlapping); HRMS (ESI) *m/z* calcd for $C_{37}H_{29}F_3NO_3S$ $[M+H]^+$: 624.1815, found 624.1810.

*4.10.4. 1-(4-(6-(4-Methoxyphenyl)-2-phenyl-4-(p-tolyl)-5-(3-(trifluoromethyl)phenyl)pyridin-3-yl)phenyl)ethan-1-one **(1d)***

Purification by PTLC (hexane/EtOAc = 10:1) gave **1d** (31.1 µmol scale, 14.3 mg, 75% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.37 (dd, *J* = 7.6, 2.4 Hz , 2H), 7.31–7.27 (m, 3H), 7.24–7.12 (m, 5H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.80–6.50 (br s, 6H), 3.76 (s, 3H), 2.50 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 159.2, 156.7, 156.4, 150.3, 143.9, 140.4, 139.5, 136.5, 134.8, 134.5, 134.1, 132.6, 132.4, 132.0, 131.5, 130.1, 129.8 (q, *J* = 32.6 Hz), 128.3 (q, *J* = 2.9 Hz), 128.1, 127.9, 127.7, 127.5, 123.8 (q, *J* = 274 Hz), 122.9 (q, *J* = 3.9 Hz), 113.2, 55.2, 26.5, 21.0 (three peaks are missing due to overlapping); HRMS (ESI) *m/z* calcd for $C_{40}H_{31}F_3NO_2$ $[M+H]^+$: 614.2301, found 614.2299.

*4.10.5. 3-(4-Ethoxyphenyl)-6-(4-methoxyphenyl)-2-phenyl-4-(p-tolyl)-5-(3-(trifluoromethyl)phenyl)pyridine **(1e)***

Purification by PTLC (hexane/EtOAc = 5:1) gave **1e** (31.1 µmol scale, 16.5 mg, 86% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 6.8, 2.8 Hz, 2H), 7.31–7.24 (m, 3H), 7.21–7.17 (m, 3H), 7.15–7.10 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.81–6.48 (br s, 4H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* =

9.2 Hz, 2H), 6.54 (d, *J* = 8.0 Hz, 2H), 3.89 (q, *J* = 7.2 Hz, 2H), 3.75 (s, 3H), 2.14 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 157.2, 157.1, 155.6, 150.5, 141.0, 139.9, 135.9, 134.7, 134.5, 133.1, 132.9, 132.3, 132.0, 131.5, 130.4, 130.2, 129.7 (q, *J* = 32.6 Hz), 128.4 (q, *J* = 3.8 Hz), 127.9, 127.8, 127.5, 127.2, 123.9 (q, *J* = 274 Hz), 122.7 (q, *J* = 3.8 Hz), 113.5, 113.1, 63.1, 55.2, 21.0, 14.7 (one peak is missing due to overlapping); HRMS (ESI) *m/z* calcd for $C_{40}H_{33}F_3NO_2$ $[M+H]^+$: 616.2458, found 616.2457.

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Supplementary Material

All compounds ^{1}H and ^{13}C NMR spectra and data for X-ray crystallography of **13a** and **1a** were provided as Supplementary material.

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