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Iron-Mediated One-Pot Synthesis of 3,5-Diarylpyridines from β-Nitrostyrenes

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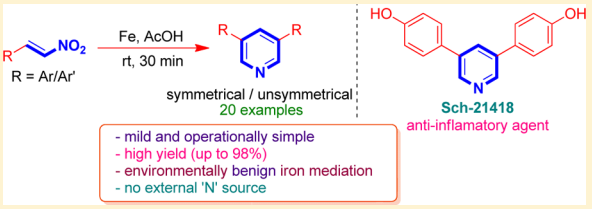
Supporting Information

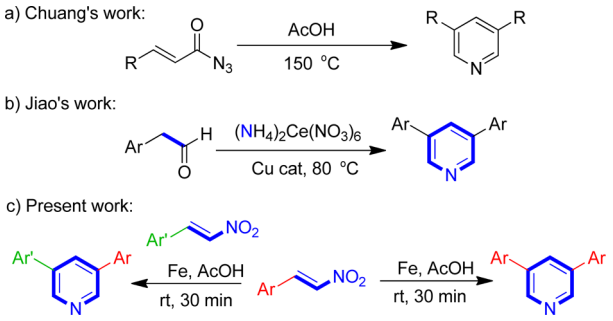
ABSTRACT: An operationally simple and mild one-pot protocol for the synthesis of a variety of 3,5-diarylpyridines from β-nitrostyrenes was achieved by using elemental iron. This reaction proceeds via reduction of the nitro group, resulting in in situ imine formation followed by trimolecular condensation with concomitant debenzylative aromatization. By employing this method, a series of symmetrical and unsymmetrical 3,5-diarylpyridines were synthesized with good to excellent yields. In addition, this method was also utilized for the synthesis of Sch-21418, an anti-inflammatory agent on gram scale.



Pyridines are one of the most widely studied class of heterocyclics to date, and their derivatives are found in several natural products which are of great importance in pharmaceutical and agrochemical research.[1,2] Some of the 3,5-disubstituted pyridines also show significant antimicrobial activity.[3] Among the substituted pyridines, Sch-21418, a 3,5-bis(4-hydroxyphenyl)pyridine, shows better inhibitory activity against inflammatory factors (e.g., interleukin-6).[4] Moreover bis-imidiazolylpyridine was shown to inhibit DNA topoisomerase II and cause cytotoxicity to *Pneumonocystis carinii* in an immunosuppressed rat model along with moderate anti-HIV-1 activity.[5] The widespread pharmacological properties of substituted pyridines have drawn considerable attention of synthetic organic chemists.[6] The synthesis of 3,5-diarylpyridine, however, still greatly depends on the transition-metal-catalyzed cross-coupling reactions at higher temperatures and prolonged reaction times.[7]

However, 3,5-disubstituted pyridines have also been constructed through the multicomponent cyclization of small molecules.[8−17] In 1953, Eliel and co-workers,[18] while studying the synthesis of the alkaloid papaverine, were able to condense homoveratric aldehyde with ammonia. Instead of papaverine, they isolated a new compound characterized as 3,5-bis(3,4-dimethoxyphenyl)pyridine. Subsequently, Chuang and co-workers[19] synthesized 3,5-disubstituted pyridines from acryloyl azides by acetic acid promoted cycloaddition (Scheme 1a). Recently, Jiao and co-workers[20] have synthesized 3,5-diarylpyridines through copper-catalyzed Chichibabin type cyclization of phenyl acetaldehyde (Scheme 1b). Moreover, cycloaddition of azadienes with enamines[21] and cross-Mannich[9a] reactions also gave 3,5-disubstituted pyridines. Most of these methods, however, suffer from low yields as well as multi-product formation. Therefore, mild and concise approaches to synthesize 3,5-diarylpyridines from inexpensive and readily available substrates are highly desirable.

Scheme 1. Synthesis of 3,5-Disubstituted Pyridines



At the onset, we attempted a reaction of 3,4,5-trimethoxy-β-nitrostyrene (**2e**) with iron (1 equiv) in acetic acid at 80 °C for 5 h to produce 2-(3,4,5-trimethoxyphenyl)acetaldehyde (**5**). Interestingly, the isolated product was identified as 3,5-bis(3,4,5-trimethoxyphenyl)pyridine[22] (**3e**) (20% yield with some of the starting material intact). Comparison of the spectroscopic data (^{1}H and ^{13}C) of the product with the reported[23] data led to the conclusion that 2-(3,4,5-trimethoxyphenyl)acetaldehyde (**5**) was not formed (Scheme 2). The ^{1}H NMR spectrum showed two mutually coupled aromatic signals (8.77 doublet with J = 1.2 Hz 2-H and 7.94 triplet with J = 1.9 Hz 1-H) which were assigned to the two

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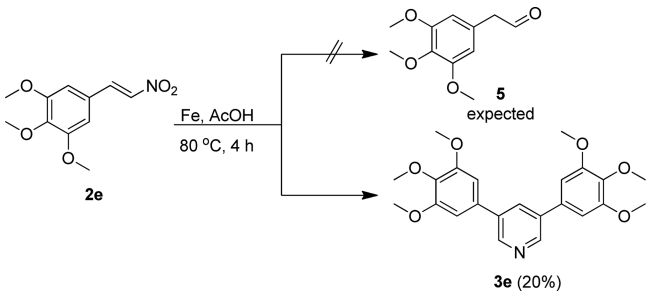
Scheme 2. Reaction of 2e with Iron in AcOH

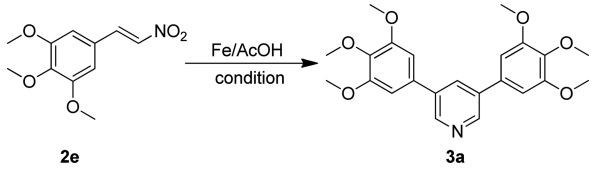


protons of C-2 and C-6 and one proton of C-4, respectively, which indicated a symmetrical molecule with a 3- and 5-substituted pyridine ring. The structure of **3e** was further confirmed by 2D NMR studies (see the Supporting Information). To develop new synthetic protocols for the pharmocologically useful molecules like 3,5-disubstituted pyridines, we further explored the possibility of a concise, one-pot synthesis of 3,5-diarylpyridines from *β*-nitrostyrenes under mild conditions.

In this paper, we report a mild and inexpensive Fe-mediated synthesis of 3,5-diarylpyridines through nitro reduction followed by condensation of the resultant enamine/imine in acetic acid at room temperature.

In view of these inspiring results, we further studied the possibility of improving the yield of **3a**. Under similar conditions, increasing the stoichiometry of iron (from 1 equiv to 2 and 3 equiv) improved the yield to 50% and 85%, respectively, (entries 2 and 3, Table 1). However, increasing the

Table 1. Optimization of Reaction Conditions



entry	reagent	equiv	solvent	temp (°C)	time (h)	yield[a] (%)
1	Fe	1	AcOH	80	5	20[b]
2	Fe	2	AcOH	80	5	50[b]
3	Fe	3	AcOH	80	5	85
4	Fe	4	AcOH	80	5	85
5	Fe	3	MeOH	70	5	
6	Fe	3	MeOH/water (1:1)	80	5	
7	Fe	3	AcOH/water (1:1)	80	5	
8	$SnCl_2·2H_2O$	1.5	MeOH	70	3	
9	Zn	3	AcOH	rt	5	
10	Zn	3	AcOH	80	5	trace
11	**Fe**	**3**	**AcOH**	**rt**	**0.5**	**92**

[a]Isolated yields. [b]Starting material recovered.

stoichiometry of iron (4 equiv) did not improve the yield further (entry 4, Table 1), and these studies revealed that 3 equiv of iron are optimal for such a reaction. We also studied the effects of various solvent systems (methanol, methanol/water (1/1), acetic acid, acetic acid/water (1/1)) and found that acetic acid was the only suitable solvent for this transformation (Table 1). Additionally, attempts to affect similar reactivity with other reducing reagents, such as $SnCl_2·2H_2O$ in methanol or Zn dust in acetic acid, were met with limited success (entries 8−10, Table 1). When the reaction was performed at room temperature using iron (3 equiv), complete consumption of nitrostyrene **2e** was observed in just 30 min, and **3e** was formed in 92% yield (entry 11, Table 1). Based on these observations, we conclude that iron (3 equiv) in acetic acid at room temperature was the optimal condition for the synthesis of 3,5-diarylpyridines from *β*-nitrostyrenes.

With these optimized reaction conditions established, several *β*-nitrostyrenes were employed for the synthesis of 3,5-diarylpyridine (Scheme 3). Electron-deficient *β*-nitrostyrenes gave the corresponding 3,5-diarylpyridines in slightly lower yields (**3j** and **3o**) when compared to other *β*-nitrostyrenes. *β*-Nitrostyrenes with halogen substituents (Cl, Br, and F) provided the corresponding 3,5-diarylpyridines with moderate yields (**3f−i,k,l**), whereas electron-rich *β*-nitrostyrenes yielded the corresponding 3,5-arylpyridines with high yields (**3b−e**), and **3m** (Sch-21418) was obtained in very high yields (98%, Scheme 3).

To investigate the synthesis of unsymmetrical 3,5-diarylpyridines using optimal conditions, a mixture of two different *β*-nitrostyrenes was reacted with iron (6 equiv or 3 equiv for each *β*-nitrostyrene) in acetic acid, and the results are summarized in Scheme 4. Although a mixture of products was formed in this reaction, the unsymmetrical products (**4a−e**, Scheme 4) were isolated (separated by column chromatography) with good yields compared to the symmetrical products (**3**, Scheme 4).

The reactivity of *β*-nitrostyrene (**2m**, 2 equiv) with phenyl acetaldehyde (**5**, 1 equiv) was also studied under the optimized conditions. The product **4b** was obtained in good yield (65%, Scheme 5a); however, some amount of **3m** was found (29%), whereas formation of **3a** was not observed. Furthermore, we carried out a reaction with **2o** under optimal conditions and expected to produce **6** via in situ nitro reduction and trimolecular condensation. It was observed that **6** was not formed; however, 1-(3,4,5-trimethoxyphenyl)propan-2-one[22] (**7**, Scheme 5b) was obtained with 93% yields. The substitution on *α*-carbon in nitrostyrene perhaps interferes with the cyclization step leading to reduction and subsequent hydrolysis.

On the basis of the bioactivity of Sch-21418 (**3m**), a gram-scale reaction was performed on **2m** (3g) which resulted in higher yields (1.5 g, 98%, Scheme 5c) of 4,4′-(pyridine-3,5-diyl)diphenol (**3m**, Sch-21418). The gram scale reaction is highly desirable from a commercial viewpoint.

■ CONCLUSION

In conclusion, an operationally simple and mild protocol for the synthesis of 3,5-diarylpyridines from the corresponding *β*-nitrostyrenes in a one-pot protocol using elemental iron was developed. This method demonstrates a convenient approach to construct both symmetrical and unsymmetrical 3,5-diarylpyridines. The reaction proceeds via an in situ reduction of nitro to imine functionality followed by trimolecular condensation and tandem debenzylative aromatization. An array of both symmetrical and unsymmetrical 3,5-diarylpyridines was synthesized with good to excellent yields. Thus, we report for the first time a spontaneous room-temperature synthesis of 3.5-diarylpyridines that is applicable to gram-scale preparation.

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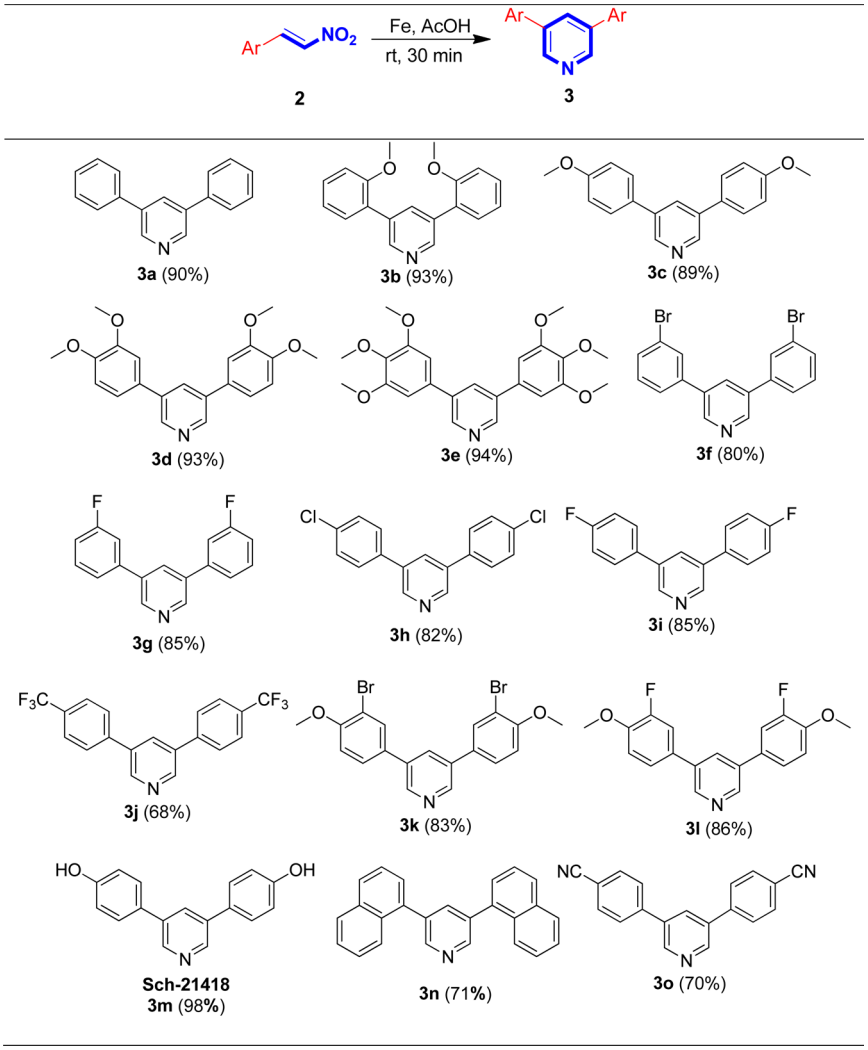
Scheme 3. Substrate Scope for the Construction of Symmetric 3,5-Diarylpyridines[a]



[a]Reaction conditions: **2** (1 equiv), Fe (3 equiv) in AcOH (5 mL), 30 min at room temperature.

EXPERIMENTAL SECTION

General Information. The reagents, chemicals, and solvents were either purchased from commercial suppliers or prepared and purified by standard techniques. The thin-layer chromatography (TLC) was performed using precoated silica gel 60 F254 Merck and TLC plates were visualized by exposure to UV light or iodine vapors. Column chromatography was performed using silica gel (60−120 mesh). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with 300, 400, and 500 MHz NMR instruments with tertramethylsilane (TMS) as an internal standard. Mass spectra were recorded by 45 electrospray ionization mass spectrometry (ESI-MS). High-resolution mass spectra (ESI-HRMS) were recorded on an ESI-QTOF mass spectrometer. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected.

General Experimental Procedure for the Synthesis of β-Nitrostyrenes 2b−p. *Method A.* To a solution of aldehyde (1 equiv) in acetic acid (30 mL) were added ammonium acetate (1.1 equiv) and nitromethane (3 equiv), and the reaction mixture was irradiated under ultrasonic frequencies (>20 kHz) at ambient temperature for 3 h. After complete consumption of starting material (monitored by TLC), the solvent was evaporated in vacuo, water was added, and the solution was extracted with ethyl acetate. The organic phase was washed with water and brine. The combined organic phases were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude products were purified by column chromatography using ethyl acetate and *n*-hexane as eluant.

Method B. To a stirred solution of aldehyde (1 equiv) and nitromethane (2.4 equiv) in methanol (25 mL) was added 1 M NaOH (10 mL) dropwise at 0 °C. The reaction mixture was stirred at 0−10 °C for 1 h. The mixture was slowly added to a solution of 8 N HCl (6 mL) to maintain the temperature between 0 and 10 °C. The reaction mixture was stirred at room temperature for 30 min. The resulting solid product was collected by filtration and washed with water. The crude product was dissolved in ethyl acetate (50 mL) and washed with water (50 mL), and the organic layer was dried over $MgSO_4$. The solvent was removed, and the residue was recrystallized with hexane/ethyl acetate to obtain the corresponding pure product.

*(E)-1-Methoxy-2-(2-nitrovinyl)benzene (**2b**).*[24] Compound **2b** was synthesized by method A: yellow solid; 197 mg (1.10 mmol), 75% yield; mp 44−46 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, J = 13.5 Hz, 1H), 7.87 (d, J = 13.5 Hz, 1H), 7.48−7.42 (m, 2H), 7.04−6.96 (m, 2H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 138.0, 135.3, 133.3, 132.2, 120.9, 118.9, 111.2, 55.5; MS (ESI) m/z 180 $[M + H]^+$.

*(E)-1-Methoxy-4-(2-nitrovinyl)benzene (**2c**).*[25] Compound **2c** was synthesized by method A: yellow crystalline solid; 205 mg (1.14 mmol), 78% yield; mp 83−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 13.6 Hz, 1H), 7.52 (d, J = 13.6 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz,

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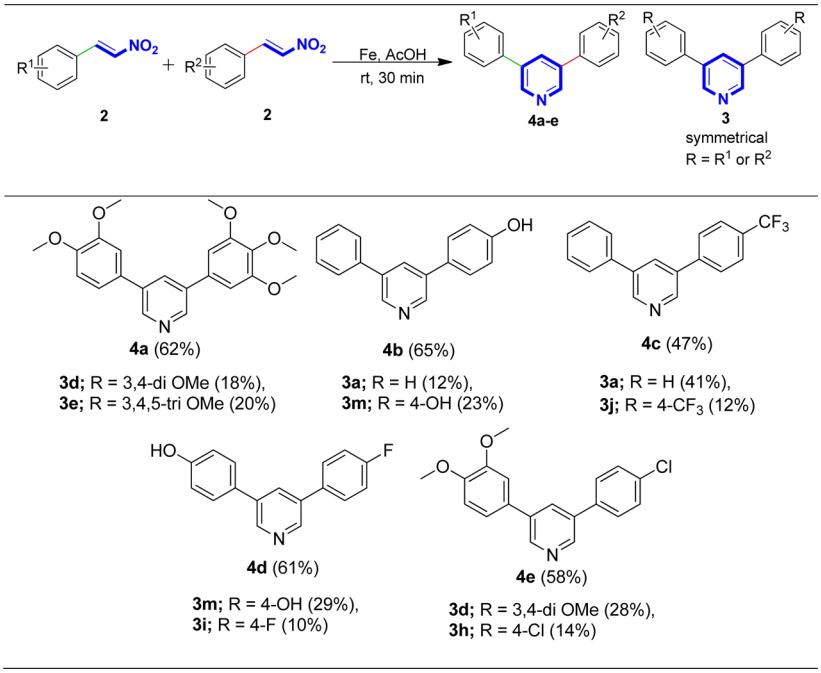
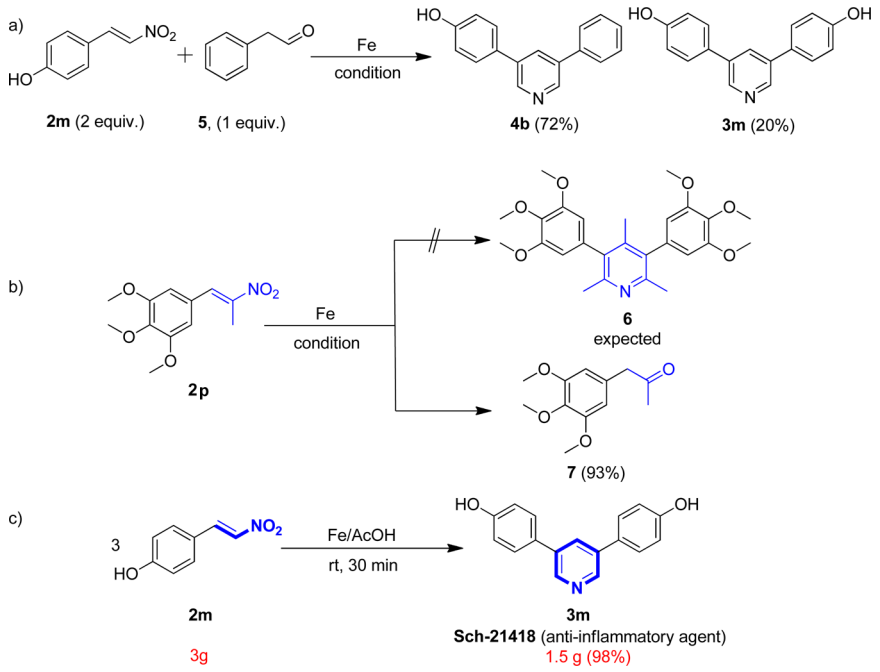
Scheme 4. Substrate Scope for the Construction of Unsymmetrical 3,5-Diarylpyridines[a]



[a]Reaction conditions: Mixture of two different β-nitrostyrenes **2** (each 1 equiv), Fe (6 equiv) in AcOH (5 mL), 30 min.

Scheme 5. (a) Reaction of 2m and Phenyl Acetaldehyde (5) Using Optimal Reaction Conditions; (b) Reaction of 2p with Iron; (c) Gram-Scale Reaction of 2m Using Optimal Conditions



$CDCl_3$) δ 162.9, 138.9, 135.0, 131.1, 122.5, 114.8, 55.5; MS (ESI) m/z 180 $[M + H]^+$.

*(E)-1,2-Dimethoxy-4-(2-nitrovinyl)benzene (**2d**).*[26] Compound **2d** was synthesized by method A: yellow solid; 203 mg (0.97 mmol), 81% yield; mp 135−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 13.6 Hz, 1H), 7.53 (d, J = 13.6 Hz, 1H), 7.18 (dd, J = 1.9, 8.2 Hz, 1H), 7.01 (d, J = 1.9 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 149.2, 139.3, 135.1, 124.6, 122.7, 111.3, 110.2, 56.0, 55.9; MS (ESI) m/z 210 $[M + H]^+$.

*(E)-1,2,3-Trimethoxy-5-(2-nitrovinyl)benzene (**2e**).*[27] Compound **2e** was synthesized by method A: yellow crystalline solid; 224 mg (0.93 mmol), 92% yield; mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 13.6 Hz, 1H), 7.54 (d, J = 13.6 Hz, 1H), 6.76 (s, 2H), 3.92 (s, 3H), 3.91 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 141.7, 139.2, 136.3, 125.2, 106.4, 61.0, 56.2; MS (ESI) m/z 240 $[M + H]^+$.

*(E)-1-Bromo-3-(2-nitrovinyl)benzene (**2f**).*[28] Compound **2f** was synthesized by method A: light green solid; 155 mg (0.68 mmol), 63% yield; mp 60−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 13.7 Hz, 1H), 7.70 (t, J = 1.7 Hz, 1H), 7.64−7.61 (m, 1H), 7.56 (d, J = 13.8 Hz, 1H), 7.50−7.46 (m, 1H), 7.34 (t, J = 7.9 Hz, 1H); ^{13}C NMR (100

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MHz, $CDCl_3$) δ 138.0, 137.3, 134.8, 132.0, 131.6, 130.8, 127.6, 123.4; MS (ESI) m/z 228 $[M + H]^+$.

*(E)-1-Fluoro-3-(2-nitrovinyl)benzene (**2g**).*[29] Compound **2g** was synthesized by method A: yellow solid; 175 mg (1.04 mmol), 65% yield; mp 42−44 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 13.6 Hz, 1H), 7.56 (d, J = 13.6 Hz, 1H), 7.47−7.42 (m, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.26−7.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, J = 248.7 Hz), 138.0, 137.6, 132.1 (d, J = 8.1 Hz), 131.0 (d, J = 8.1 Hz), 125.1 (d, J = 2.2 Hz), 119.0 (d, J = 21.3 Hz), 115.3 (d, J = 22.0 Hz); MS (ESI) m/z 168 $[M + H]^+$.

*(E)-1-Chloro-4-(2-nitrovinyl)benzene (**2h**).*[30] Compound **2h** was synthesized by method A: yellow solid; 209 mg (1.14 mmol), 80% yield; mp 112−114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 13.7 Hz, 1H), 7.56 (d, J = 13.7 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.6, 137.4, 130.2, 129.7, 128.5; MS (ESI) m/z 184 $[M + H]^+$.

*(E)-1-Fluoro-4-(2-nitrovinyl)benzene (**2i**).*[25] Compound **2i** was synthesized by method A: yellow solid; 220 mg (1.32 mmol), 82% yield; mp 98−100 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 13.7 Hz, 1H), 7.59−7.51 (m, 3H), 7.16 (t, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8 (d, J = 255.3 Hz), 137.8, 136.8, 131.2 (d, J = 8.8 Hz), 126.3 (d, J = 2.9 Hz), 116.6 (d, J = 22.0 Hz); MS (ESI) m/z 168 $[M + H]^+$.

*(E)-1-(2-Nitrovinyl)-4-(trifluoromethyl)benzene (**2j**).*[25] Compound **2j** was synthesized by method B. Light yellow solid; 139 mg (0.64 mmol), 56% yield; mp 93−95 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 13.7 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 13.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 137.0, 133.5 (q, J = 32.7 Hz), 133.4, 129.2, 126.3 (q, J = 3.6 Hz), 124.5 (q, J = 272.5 Hz); MS (ESI) m/z 218 $[M + H]^+$.

*(E)-2-Bromo-1-methoxy-4-(2-nitrovinyl)benzene (**2k**).* Compound **2k** was synthesized by method B: yellow solid; 196 mg (0.76 mmol), 82% yield; mp 132−134 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 13.7 Hz, 1H), 7.77 (d, J = 2.1 Hz, 1H), 7.51 (d, J = 13.6 Hz, 1H), 7.49 (dd, J = 2.1, 8.5 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 137.4, 135.9, 133.6, 130.4, 123.7, 112.8, 112.1, 56.5; MS (ESI) m/z 258 $[M + H]^+$.

*(E)-1-Fluoro-2-methoxy-4-(2-nitrovinyl)benzene (**2l**).*[31] Compound **2l** was synthesized by method B: light yellow solid; 194 mg (0.98 mmol), 76% yield; mp 143−145 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 13.7 Hz, 1H), 7.54 (d, J = 13.7 Hz, 1H), 7.16−7.15 (m, 1H), 7.14 (d, J = 1.1 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO−d_6) δ 154.0 (d, J = 254.7 Hz), 147.7 (d, J = 11.5 Hz), 137.8, 136.6, 126.2 (d, J = 3.8 Hz), 122.7 (d, J = 7.1 Hz), 116.2 (d, J = 19.2 Hz), 112.8, 55.8; MS (ESI) m/z 198 $[M + H]^+$.

*(E)-4-(2-Nitrovinyl)phenol (**2m**).*[32] Compound **2m** was synthesized by method A: yellow solid; 3.98 g (24.18 mmol), 59% yield; mp 163−165 °C; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 9.81 (s, 1H), 7.97 (d, J = 13.3 Hz, 1H), 7.53 (d, J = 13.3 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.4, 139.8, 134.7, 132.2, 121.0, 116.1; MS (ESI) m/z 166 $[M + H]^+$.

*(E)-1-(2-Nitrovinyl)naphthalene (**2n**).*[26] Compound **2n** was synthesized by method A: light brown solid; 160 mg (0.80 mmol), 63% yield; mp 81−83 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 13.4 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 13.4 Hz, 1H), 7.64−7.62 (m, 1H), 7.59 (t, J = 6.9 Hz, 1H), 7.51 (t, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 136.1, 133.7, 132.5, 131.5, 129.0, 127.7, 126.9, 126.7, 126.3, 125.3, 122.9; MS (ESI) m/z 200 $[M + H]^+$.

*(E)-4-(2-Nitrovinyl)benzonitrile (**2o**).*[26] Compound **2o** was synthesized by method B: light yellow solid; 138 mg (0.79 mmol), 52% yield; mp 182−184 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 13.8 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 13.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 136.5, 134.3, 132.9, 129.3, 117.7, 115.2; MS (ESI) m/z 175 $[M + H]^+$.

*(E)-1,2,3-Trimethoxy-5-(2-nitroprop-1-enyl)benzene (**2p**).*[33] Compound **2p** was synthesized by method A (nitroethane was used instead of nitromethane): light yellow solid; 165 mg (0.65 mmol), 64% yield; mp 82−84 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.65 (s, 2H), 3.91 (s, 3H), 3.89 (s, 6H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 146.9, 139.4, 133.7, 127.6, 107.4, 60.9, 56.2, 14.1; MS (ESI) m/z 254 $[M + H]^+$.

General Experimental Procedure for the Synthesis of Symmetrical 3,5-Diarylpyridines 3a−o. To a stirred solution of β-nitrostyrene (**2**, 1 equiv) in glacial acetic acid (5 mL) was added iron (3 equiv), and the reaction mixture was stirred for 30 min at room temperature. After the complete consumption of starting material (monitored by TLC), the solvent was removed in vacuo. The residue was neutralized with 10% NaOH solution, and the aqueous phase was extracted with ethyl acetate and washed with water and brine. The combined organic phases were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resultant crude product was purified by silica gel column chromatography using ethyl acetate and *n*-hexane as eluents, and the appropriate fractions were collected to yield pure products (**3a−o**).

*3,5-Diphenylpyridine (**3a**):*[34] light brown solid; 139 mg (0.60 mmol), 90% yield; mp 132−134 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, J = 2.1 Hz, 2H), 8.05 (t, J = 2.1 Hz, 1H), 7.65 (d, J = 7.2 Hz, 4H), 7.51 (t, J = 7.2 Hz, 4H), 7.43 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 137.7, 136.6, 132.8, 129.1, 128.2, 127.2; HRMS (ESI) calcd for $C_{17}H_{14}N$ m/z 232.1121 $[M + H]^+$, found 232.1124.

*3,5-Bis(2-methoxyphenyl)pyridine (**3b**):*[19] yellow solid; 151 mg (0.51 mmol), 93% yield; mp 123−125 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 1.8 Hz, 2H), 8.02 (t, J = 1.9 Hz, 1H), 7.41−7.34 (m, 4H), 7.10−7.00 (m, 4H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 148.3, 137.6, 133.3, 130.7, 129.4, 127.1, 120.9, 111.2, 55.5; HRMS (ESI) calcd for $C_{19}H_{18}NO_2$ m/z 292.1332 $[M + H]^+$, found 292.1337.

*3,5-Bis(4-methoxyphenyl)pyridine (**3c**):*[19] yellow crystalline solid; 144 mg (0.49 mmol), 89% yield; mp 234−236 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 1.8 Hz, 2H), 7.96 (t, J = 2.2 Hz, 1H), 7.58 (d, J = 8.9 Hz, 4H), 7.03 (d, J = 8.8 Hz, 4H), 3.87 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 145.9, 136.2, 131.9, 130.2, 128.3, 114.6, 55.4; HRMS (ESI) calcd for $C_{19}H_{18}NO_2$ m/z 292.1332 $[M + H]^+$, found 292.1345.

*3,5-Bis(3,4-dimethoxyphenyl)pyridine (**3d**):*[18] yellow solid; 156 mg (0.44 mmol), 93% yield; 173−175 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 1.9 Hz, 2H), 7.96 (t, J = 2.2 Hz, 1H), 7.20 (dd, J = 2.1, 8.2 Hz, 2H), 7.13 (d, J = 2.1 Hz, 2H), 7.01 (d, J = 8.3 Hz, 2H), 3.98 (s, 6H), 3.95 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 149.3, 146.2, 136.4, 132.2, 130.5, 119.7, 111.6, 110.3, 56.0, 55.9; HRMS (ESI) calcd for $C_{21}H_{22}NO_4$ m/z 352.1543 $[M + H]^+$, found 352.1545.

*3,5-Bis(3,4,5-trimethoxyphenyl)pyridine (**3e**):*[22] yellow solid; 161 mg (0.39 mmol), 94% yield; mp 227−229 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 1.2 Hz, 2H), 7.94 (t, J = 1.9 Hz, 1H), 6.81 (s, 4H), 3.95 (s, 12H), 3.92 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 146.9, 138.4, 136.8, 133.5, 132.7, 104.6, 60.9, 56.3; HRMS (ESI) calcd for $C_{23}H_{26}NO_6$ m/z 412.1755 $[M + H]^+$, found 412.1762.

*3,5-Bis(3-bromophenyl)pyridine (**3f**):* cream solid; 136 mg (0.35 mmol), 80% yield; mp 160−165 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 2H), 7.98 (t, J = 2.1 Hz, 1H), 7.78 (t, J = 1.6 Hz, 2H), 7.59−7.55 (m, 4H), 7.38 (t, J = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 139.5, 135.3, 132.8, 131.3, 130.6, 130.2, 125.8, 123.2; HRMS (ESI) calcd for $C_{17}H_{12}Br_2N$ m/z 387.9336 $[M\ (^{79}Br, ^{79}Br) + H]^+$, 389.9316 $[M\ (^{79}Br, ^{81}Br) + H]^+$, 391.9296 $[M\ (^{81}Br, ^{81}Br) + H]^+$, found 387.9332, 389.9315, 391.9295 respectively.

*3,5-Bis(3-fluorophenyl)pyridine (**3g**):*[20] cream solid; 135 mg (0.50 mmol), 85% yield; mp 137−140 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, J = 1.5 Hz, 2H), 8.01 (t, J = 2.1 Hz, 1H), 7.51−7.45 (m, 2H), 7.44−7.40 (m, 2H), 7.34 (td, J = 1.8, 9.7, 11.5 Hz, 2H), 7.14 (dt, J = 1.5, 8.4, 9.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J = 247.2 Hz), 147.4, 139.7 (d, J = 7.3 Hz), 135.5, 132.8, 130.7 (d, J = 8.0 Hz), 122.9 (d, J = 2.9 Hz), 115.2 (d, J = 21.2 Hz), 114.2 (d, J = 22.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.09; HRMS (ESI) calcd for $C_{17}H_{12}F_2N$ m/z 268.0932 $[M + H]^+$, found 268.0936.

*3,5-Bis(4-chlorophenyl)pyridine (**3h**):*[35] cream solid; 134 mg (0.44 mmol), 82% yield; mp 172−1744 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 2.1 Hz, 2H), 7.97 (t, J = 2.1 Hz, 1H), 7.57 (d, J = 8.7 Hz,

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4H), 7.48 (d, J = 8.7 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 135.9, 135.6, 134.6, 132.5, 129.3, 128.5; HRMS (ESI) calcd for $C_{17}H_{12}Cl_2N$ m/z 300.0341 $[M + H]^+$, found 300.0346.

*3,5-Bis(4-fluorophenyl)pyridine (**3i**):*[35] cream solid; 135 mg (0.50 mmol), 85% yield; mp 171−172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 1.9 Hz, 2H), 7.95 (t, J = 2.1 Hz, 1H), 7.60 (q, J = 5.2, 8.7 Hz, 4H), 7.20 (t, J = 8.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0 (d, J = 247.9 Hz), 146.8, 135.7, 133.7, 132.6, 128.9 (d, J = 8.2 Hz), 116.1 (d, J = 21.8); ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.81; HRMS (ESI) calcd for $C_{17}H_{12}F_2N$ m/z 268.0932 $[M + H]^+$, found 268.0943.

*3,5-Bis(4-(trifluoromethyl)phenyl)pyridine (**3j**):* yellow solid; 115 mg (0.31 mmol), 68% yield; mp 160−163 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (d, J = 2.1 Hz, 2H), 8.07 (t, J = 2.1 Hz, 1H), 7.77 (q, J = 8.5, 13.4 Hz, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 140.9, 135.5, 133.1, 130.7 (q, J = 33.0 Hz), 127.6, 126.1 (q, J = 2.9, 6.6 Hz), 125.3 (q, J = 272.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.77; HRMS (ESI) calcd for $C_{19}H_{12}F_6N$ m/z 368.0868 $[M + H]^+$, found 368.0875.

*3,5-Bis(3-bromo-4-methoxyphenyl)pyridine (**3k**):* yellow solid; 144 mg (0.32 mmol), 83% yield; mp 179−183 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, J = 1.6 Hz, 2H), 7.91 (t, J = 2.1 Hz, 1H), 7.83 (d, J = 2.3 Hz, 2H), 7.56 (dd, J = 2.3, 8.5 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 3.97 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 146.3, 132.0, 131.9, 131.3, 127.2, 112.5, 112.3, 56.4; HRMS (ESI) calcd for $C_{19}H_{16}Br_2NO_2$ m/z 447.9548 [M (^{79}Br, ^{79}Br) + H]$^+$, 449.9527 [M (^{79}Br, ^{81}Br) + H]$^+$, 451.9507 [M (^{81}Br, ^{81}Br) + H]$^+$, found 447.9588, 449.9567, 451.9551, respectively.

*3,5-Bis(4-fluoro-3-methoxyphenyl)pyridine (**3l**):* yellow solid; 142 mg (0.43 mmol), 86% yield; mp 187−189 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 1.9 Hz, 2H), 7.93 (t, J = 2.1 Hz, 1H), 7.23−7.17 (m, 4H), 7.16−7.13 (m, 2H), 3.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7 (d, J = 247.9 Hz), 148.1 (d, J = 11.0 Hz), 146.9, 136.0, 134.2 (d, J = 3.6 Hz), 132.7, 119.8 (d, J = 7.3 Hz), 116.6 (d, J = 18.3 Hz), 112.6 (d, J = 2.2 Hz), 56.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −135.53; HRMS (ESI) calcd for $C_{19}H_{16}F_2NO_2$ m/z 328.1144 $[M + H]^+$, found 328.1148.

*4,4′-(Pyridine-3,5-diyl)diphenol (**3m**):*[7d,36] light brown solid; 1.56 g (5.9 mmol), 98% yield; mp 256−258 °C; ^{1}H NMR (500 MHz, DMSO−d_6) δ 9.68 (s, 2H), 8.71 (d, J = 1.5 Hz, 2H), 8.09 (t, J = 2.1 Hz, 1H), 7.65 (d, J = 8.5 Hz, 4H), 6.90 (d, J = 8.5 Hz, 4H); ^{13}C NMR (125 MHz, DMSO−d_6) δ 157.6, 144.8, 135.4, 130.3, 128.1, 127.6, 115.8; HRMS (ESI) calcd for $C_{17}H_{14}NO_2$ m/z 264.1019 $[M + H]^+$, found 264.1020.

*3,5-Di(naphthalen-1-yl)pyridine (**3n**):*[20,22] yellow solid; 118 mg (0.35 mmol), 71% yield; mp 173−175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (d, J = 1.8 Hz, 2H), 8.01 (t, J = 1.8 Hz, 1H), 7.98−7.92 (m, 6H), 7.58 (d, J = 7.2 Hz, 2H), 7.56−7.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 138.8, 136.0, 135.9, 133.8, 131.4, 128.7, 128.5, 127.6, 126.6, 126.1, 125.4, 125.2; HRMS (ESI) calcd for $C_{25}H_{18}N$ m/z 332.1434 $[M + H]^+$, found 332.1442.

*4,4′-(Pyridine-3,5-diyl)dibenzonitrile (**3o**):*[5] yellow solid; 113 mg (0.40 mmol), 70% yield; mp 291−293 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 2H), 8.05 (s, 1H), 7.82 (d, J = 8.1 Hz, 4H), 7.76 (d, J = 8.2 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 141.6, 135.1, 132.9, 127.9, 118.3, 112.4; HRMS (ESI) calcd for $C_{19}H_{12}N_3$ m/z 282.1026 $[M + H]^+$, found 282.1032.

General Experimental Procedure for the Synthesis of Unsymmetrical 3,5-Diarylpyridines 4a−e. To a stirred solution of two different β-nitrostyrenes **2** (1:1, 1 mmol) in glacial acetic acid (5 mL) was added iron (6 or 3 mmol each β-nitrostyrenes), and the reaction mixture was stirred for 30 min at room temperature. After complete consumption of starting material (monitored by TLC), the solvent was removed in vacuo. The residue was neutralized with 10% NaOH solution, and the aqueous phase was extracted with ethyl acetate and washed with water and brine. The combined organic phases were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resultant crude product was purified by silica gel column chromatography using ethyl acetate and n-hexane as eluents, and the appropriate fractions were collected to yield pure products **4a−e**.

*3-(3,4-Dimethoxyphenyl)-5-(3,4,5-trimethoxyphenyl)pyridine (**4a**):* yellow solid; 98.8 mg (0.25 mmol), 62% yield; mp 186−189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80−8.73 (m, 2H), 7.98−7.93 (m, 1H), 7.20 (dd, J = 2.1, 8.3 Hz, 1H), 7.13 (s, 1H), 7.01 (dd, J = 1.9, 8.3 Hz, 1H), 6.80 (s, 2H), 3.97 (s, 3H), 3.95 (s, 9H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 149.5, 146.8, 146.6, 143.3, 138.4, 136.9, 133.5, 132.8, 132.6, 130.4, 119.7, 111.7, 110.4, 104.7, 60.9, 56.3, 56.1, 56.0; HRMS (ESI) calcd for $C_{22}H_{24}NO_5$ m/z 382.1649 $[M + H]^+$, found 382.1654.

*4-(5-Phenylpyridin-3-yl)phenol (**4b**):* yellow solid; 97.3 mg (0.39 mmol), 65% yield; mp 230−233 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.71 (s, 1H), 8.80 (dd, J = 1.7, 5.1 Hz, 2H), 8.20 (t, J = 2.1 Hz, 1H), 7.83 (d, J = 7.2 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.53 (t, J = 7.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7, 145.9, 145.4, 137.0, 135.7, 135.5, 131.1, 129.0, 128.2, 128.1, 127.4, 127.0, 115.8; HRMS (ESI) calcd for $C_{17}H_{14}NO$ m/z 248.1070 $[M + H]^+$, found 248.1072.

*3-Phenyl-5-(4-(trifluoromethyl)phenyl)pyridine (**4c**):* white solid; 64.7 mg (0.21 mmol), 47% yield; mp 160−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92−8.81 (m, 2H), 8.01−8.04 (m, 1H), 7.80−7.74 (m, 4H), 7.67−7.63 (m, 2H), 7.55−7.49 (m, 2H), 7.48−7.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 146.9, 141.1 (q, J = 47.2 Hz), 137.6 (q, J = 42.6 Hz), 136.7 (q, J = 26.3 Hz), 135.4 (q, J = 28.1 Hz), 133.1, 133.0, 132.9, 129.1 (q, J = 9.9 Hz), 128.3 (q, J = 25.4 Hz), 127.6, (q, J = 3.6 Hz), 127.2, 126.1 (q, J = 8.1 Hz); HRMS (ESI) calcd for $C_{18}H_{13}F_3N$ m/z 300.0995 $[M + H]^+$, found 300.1004.

*4-(5-(4-Fluorophenyl)pyridin-3-yl)phenol (**4d**):* light yellow solid; 97.9 mg (0.36 mmol), 61% yield; mp 226−229 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.79 (dd, J = 1.9, 11.3 Hz, 2H), 8.20 (t, J = 2.2 Hz, 1H), 7.89 (q, J = 5.4, 8.8 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.35 (t, J = 8.9 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.2 (d, J = 245.0 Hz), 157.8, 145.8 (d, J = 8.0 Hz), 145.3 (d, J = 8.8 Hz), 135.5, 134.5, 133.5, 131.2 (d, J = 9.5 Hz), 129.2 (d, J = 8.0 Hz), 128.2, 127.3, 115.8 (t, J = 8.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.62; HRMS (ESI) calcd for $C_{17}H_{13}FNO$ m/z 266.0976 $[M + H]^+$, found 266.0981.

*3-(4-Chlorophenyl)-5-(3,4-dimethoxyphenyl)pyridine (**4e**):* yellow solid; 90.1 mg (0.27 mmol), 58% yield; mp 180−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87−8.70 (m, 2H), 7.96 (s, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1, 2H), 7.19 (d, J = 7.3 Hz, 1H), 7.13 (s, 1H), 7.00 (d, J = 8.1 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 149.4, 147.0, 146.2, 136.6, 136.2, 135.5, 134.5, 132.3, 130.3, 129.3, 128.5, 119.7, 111.7, 110.3, 56.1, 56.0; HRMS (ESI) calcd for $C_{19}H_{17}ClNO_2$ m/z 326.0942 $[M + H]^+$, found 326.0945.

*1-(3,4,5-Trimethoxyphenyl)propan-2-one (**7**):*[37] light brown solid; 83.2 mg (0.37 mmol), 94% yield; mp 62−64 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (s, 2H), 3.85 (s, 6H), 3.84 (s, 3H), 3.63 (s, 2H), 2.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 153.4, 137.0, 129.7, 106.3, 60.8, 56.1, 51.2, 29.2; MS (ESI) m/z 225 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02712.

2D NMR (COSY and NOESY of **3e**), ^{1}H, and ^{13}NMR spectra for the products (PDF)

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Notes

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