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Synthesis of Polyfunctional Pyridines *via* Copper-Catalyzed Oxidative Coupling Reactions

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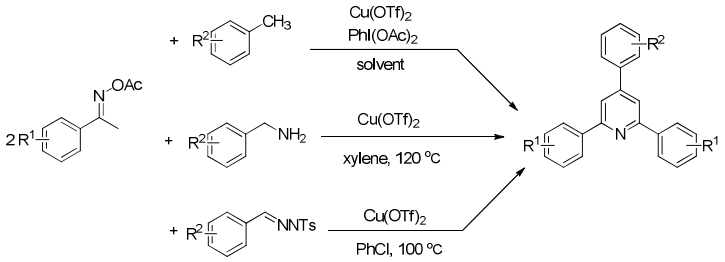


Abstract: An efficient and concise approach for the synthesis of polysubstituted pyridines has been achieved through copper-catalyzed oxidative sp^3 C−H coupling of oxime acetates with toluene derivatives. Besides, benzylamine and *p*-toluenesulfonylhydrazone were also introduced to react with oxime acetates to enrich the diversity of this synthetic method. These transformations provide highly flexible and facile preparation of substituded pyridines and thus are useful in practical synthesis.

Introduction

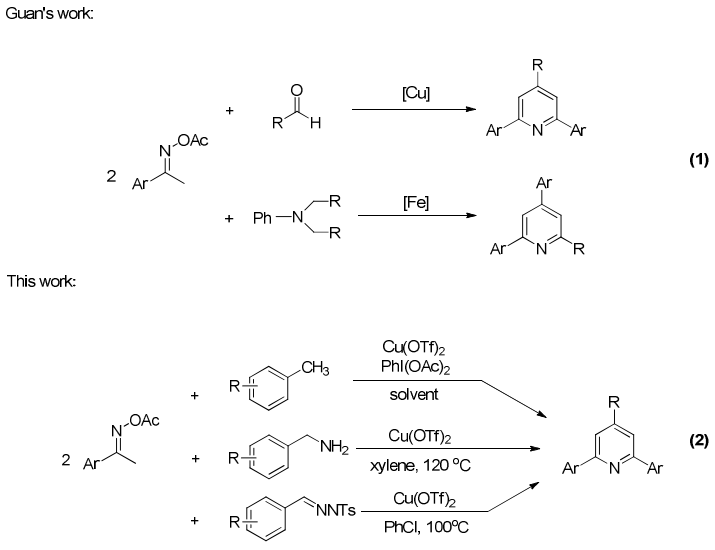
Functionalized pyridines have been well recognized as privileged *N*-heterocycles, which are found in a broad array of natural products, medicines, and functional materials.[1] In particular, they play an important role in organic synthesis as building blocks and find use in catalysis and

coordination chemistry.[2] Thus, much effort has been devoted to efficient syntheses of pyridine derivatives using a variety of protocols.[3] Despite efficiency and importance in chemical synthesis, many existing transformations can sometimes face the limitation of relatively harsh reaction conditions or the utilization of the costly starting materials. Therefore, the development of a more concise and straightforward procedure for acquisition of pyridine derivatives from easily available starting materials is still highly desirable.

Ketoximes and derivatives are meritorious synthetic building blocks[4] as highly effective candidates for the Beckmann rearrangement and Semmler−Wolff reaction.[5] Oxime derivatives have emmerged as versatile building blocks, especially for the synthesis of pyridines, thus, transition metal-catalyzed coupling reactions using oximes and their derivatives as substrates in pyridine synthesis have gained increased attention.[6] Synthetic transformations of oximes via metal-mediated N−O bond cleavage have been pioneered by Narasaka.[7] Later, the group of Zhu[8] and Hartwig[9] have reported Pd-catalyzed cyclization of ketoxime carboxylates. Besides, Guan's group achieved the Cu-catalyzed condensation of ketoxime acetates and aldehydes for the synthesis of pyridines in 2011. Very recently, Fe-catalyzed cyclization of ketoxime carboxylates and *N,N*-dialkylanilines for the synthesis of polysubstituted pyridines has also been developed by Guan's group (scheme 1, eq 1).[10]

Here we present a useful synthetic method for preparation of polysubstituted pyridines through copper-catalyzed oxidative sp^3 C−H coupling of oxime acetates with toluene derivatives. Moreover, benzylamine and *p*-toluenesulfonylhydrazone were also employed to react with oxime acetates to enrich the diversity of synthetic methods for the synthesis of substituted pyridines (scheme 1, eq 2).

Scheme 1. Synthetic approaches to pyridines from oximes

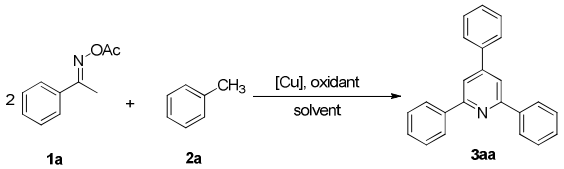


Results and Discussion Sections

We initially investigated our reaction by employing acetophenone oxime acetate **1a** and toluene **2a** as model substrates in the presence of $Cu(OTf)_2$ catalyst in toluene (2.0 mL) at 100 °C for 8 h under air atmosphere. Encouragingly, the reaction provided the product 2,4,6-triphenylpyridine **3aa** in 23% yield (Table 1, entry 1). Subsequently, various oxidants were tested to optimize the reation conditions. Compared with O_2, TBHP, MnO_2, and DTBP, $PhI(OAc)_2$ proved to be

the optimal oxidants, affording the desired product **3aa** in 76% yield (Table 1, entries 2-6). Screening of other common metal catalysts, such as CuBr, $Cu(OAc)_2$, CuI, and $FeCl_3$ showed that $Cu(OTf)_2$ was the best choice (Table1, entries 8-11). Further investigation of reaction solvents revealed that toluene gave the best yield, while other solvents including Dioxane, DMSO and PhCl offered lower results (Table 1, entries 12-14). It is worth mentioning that the yield of **3aa** was increased to 72% when temperature raised to 120 ^{o}C under the condition of PhCl as solvent (Table 1, entry 15). Besides, lower yields of desired product were observed when the temperature was changed (Table 1, entries 16-17). When trying to vary the amount of $PhI(OAc)_2$, we discovered that the reaction with two equivalents of $PhI(OAc)_2$ afford the optimal result (Table 1, compared with entries 6 and 18).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

Entry	Catalyst	Oxidant	Solvent	Yield[b] (%)
1	$Cu(OTf)_2$	Air	Toluene	23
2	$Cu(OTf)_2$	O_2	Toluene	31
3	$Cu(OTf)_2$	TBHP	Toluene	55
4	$Cu(OTf)_2$	MnO_2	Toluene	44
5	$Cu(OTf)_2$	DTBP	Toluene	63
6	**$Cu(OTf)_2$**	**$PhI(OAc)_2$**	**Toluene**	**76**
7	-	$PhI(OAc)_2$	Toluene	Nd
8	CuBr	$PhI(OAc)_2$	Toluene	21
9	$Cu(OAc)_2$	$PhI(OAc)_2$	Toluene	14
10	CuI	$PhI(OAc)_2$	Toluene	12

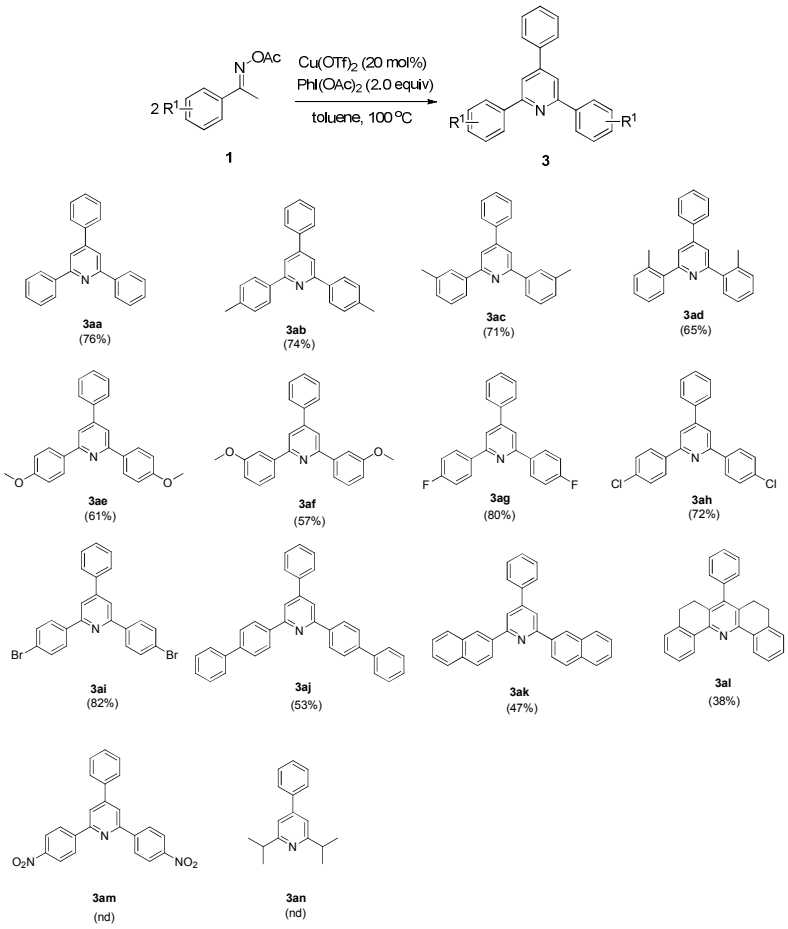
11	$FeCl_3$	$PhI(OAc)_2$	Toluene	61
12	$Cu(OTf)_2$	$PhI(OAc)_2$	Dioxane	27
13	$Cu(OTf)_2$	$PhI(OAc)_2$	DMSO	Trace
14	$Cu(OTf)_2$	$PhI(OAc)_2$	PhCl	59
15[c]	$Cu(OTf)_2$	$PhI(OAc)_2$	PhCl	72
16[d]	$Cu(OTf)_2$	$PhI(OAc)_2$	Toluene	58
17[e]	$Cu(OTf)_2$	$PhI(OAc)_2$	Toluene	70
18[e]	$Cu(OTf)_2$	$PhI(OAc)_2$	Toluene	67

[a]Reaction conditions: **1a** (0.2 mmol), catalyst (20 mol%), oxidant (2.0 equiv), solvent (2.0 mL), 100 °C, 8 h. [b]Yields of isolated products. [c]120 °C. [d]80 °C. [e]$PhI(OAc)_2$ (3.0 equiv). BHP = tert-butylhydroperoxide (5.0-6.0 M in decane), DTBP = di-t-butyl peroxide, DMSO = dimethyl sulfoxide.

With the optimized conditions in hand, the generality of oxime acetates was first explored, and the results were summarized in Table 2. This coupling reaction tolerated a wide range of substituents on the aromatic ring of oxime acetates. We found that substrates with electron-donating groups on the aromatic ring produced the corresponding pyridines in good yields (**3ab-3af**), including *ortho*- methyl, *meta*- methyl, *para*-methyl, and methoxy at the *para*-, *meta*-position. In addition, electron-withdrawing groups such as para- F, Cl, Br on the aromatic ring seemed to be compatible well under the optimal reaction conditions with excellent yields (**3ag-3ai**). Disappointingly, *p*-nitro-substituted oxime acetate was not tolerated in this transformation and did not give the desired product **3am**, which indicated that strong electronic effect hindered this transformation. In addition, the *p*-phenyl-substituted oxime acetate, α-tetralone oxime acetate, benzylideneacetone oxime acetate and 2-acetylnaphthalene oxime acetate also afforded the corresponding

pyridines (**3aj-3al**) in moderate yields respectively. Besides, the isobutyraldehyde oxime acetate was also investigated, but the expected product **3an** was not observed under the standard conditions.

Table 2. Synthesis of pyridines from different oxime acetates[a,b]



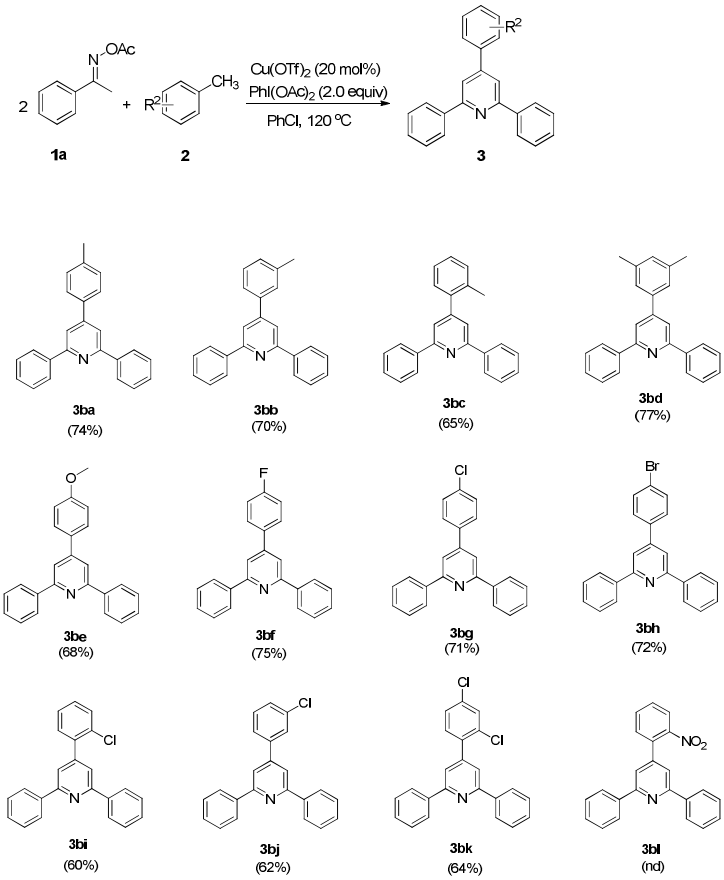
[a]Reaction conditions: **1** (0.2 mmol), catalyst $Cu(OTf)_2$(20 mol%), $PhI(OAc)_2$ (0.4 mmol) in toluene (2.0 mL) at 100 °C for 8 h.

[b]Isolated yields.

In order to acquire a variety of polyfunctional pyridines, the compatibility of the present method was further expanded by the utilization of a wide range of substituted toluenes (Table 3). However, it should be noted that reaction conditions were slightly changed: PhCl was

considered as the best reaction solvent and the optimal temperature for the reaction was determined to be 120 °C (Table 1, entry 15). Initially, both electron-rich and electron-deficient benzenes proceeded successfully to obtain the desired products in good yields (**3ba-3bk**). Disappointingly, strong electron-deficient group (2-NO_2) was found to be incompatible and the desired product could not be produced under the certain reaction conditions, perhaps due to the strong electronic effect (**3bl**).

Table 3. Synthesis of pyridines from diverse arylmethane[a,b]

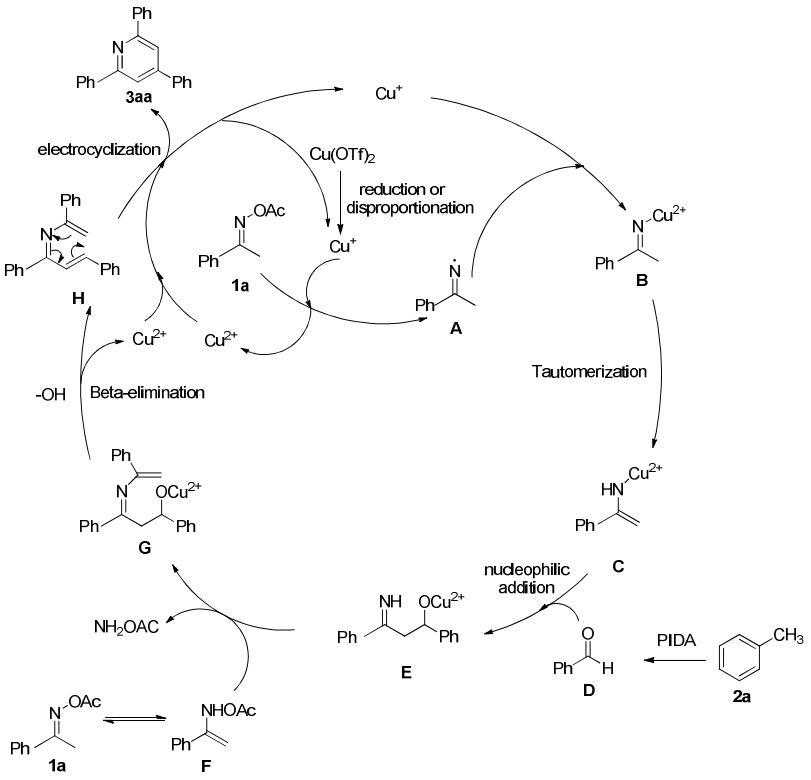


[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), catalyst $Cu(OTf)_2$(20 mol%), $PhI(OAc)_2$ (0.4 mmol) in PhCl (2.0 mL) at 120 °C for 8 h.

[b]Isolated yields.

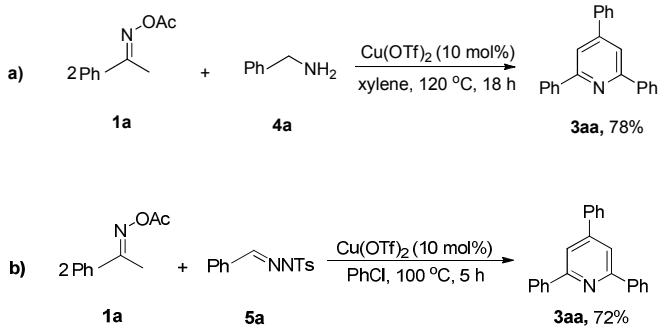
Based on previous studies and literature reports,[10a,11,12,13,14] a plausible reaction mechanism is proposed as shown in Scheme 2 to explain the formation of product **3aa**. Firstly, $Cu(OTf)_2$ would be converted into Cu^+ by either a reduction or disproportionation.[11] Under the action of Cu^+, the N-O bond of the oxime acetate **1a** cleavages and would afford the imine radical **A** which reacts promptly with another Cu^+ to give N-Cu^{2+} intermediate **B**.[12,13] Tautomerization of **B** would offer the intermediate **C**, while toluene **2a** would be easily converted to benzaldehyde **D** by the oxidation with the presence of $PhI(OAc)_2$. Next, nucleophilic addition of **C** to **D** would afford imine intermediate **E**.[13] In the meantime, another oxime acetate **1a** could tautomerize to the intermediate **F**. Subsequently, the intermediate **G** would be formed by condensation reaction of **E** with **F**.[10a] Then intermediate **G** through beta-elimination would afford an aza-hexa-1,3,5-triene intermediate **H**. Finally, the intermediate **H** generated underwent electrocyclization to furnish the desired product **3aa**.[14] Meanwhile, the Cu^{2+} would be reduced to active Cu^+, which completed the catalytic cycle.

Scheme 2. Possible mechanism



To widen the diversity of synthetic strategies to produce polysubstituted pyridines, the building blocks including benzylamine (**4a**), *p*-toluenesulfonylhydrazone (**5a**) were introduced into this class of reactions. The reaction of benzylamine (**4a**) and **1a** was carried out in the presence of $Cu(OTf)_2$ (10 mol%) and xylene (2.0 mL) at 120 °C, and the desired product **3aa** was isolated in 78% yield (Scheme 3a). Besides, *p*-toluenesulfonylhydrazone (**5a**) was also compatible in the reaction to form the desired product **3aa** in 72% yield (Scheme 3b). These reactions are fascinating, obtaining a range of polysubstituted pyridines through a useful, efficient and simple method by using easily available starting materials.

Scheme 3. Alternative transformations to construct polysubstituted pyridines



Conclusion

In summary, we have developed a practical Cu-catalyzed oxidative coupling reaction to construct polysubstituted pyridines via oxidative cleavage of C(sp^3)-H. Besides, two other alternative transformations were also presented to enrich the diversity of synthetic methods for the preparation of substituted pyridines. These processes afforded some new approaches to polysubstituted pyridines with advantages including ready availability of the starting materials, operational simplicity, cheap catalysts and mild conditions. Further studies on reaction mechanism details and the synthetic applications of this transformation are now under investigation in our group.

Experimental Section

General remarks. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300MHz and 100MHz in $CDCl_3$. All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard.

The high-resolution mass spectra (HRMS) were recorded on an FT-ICR mass spectrometer using electrospray ionization (ESI). Products were purified by flash chromatogrgraphy on 200-300 mesh silica gel. All melting points were determined without correction. Unless otherwise noted, commercially reagents were used without further purification.

General procedure for the synthesis of 3 (3aa/3ba as an example)

Synthesis of 3aa: A test tube was charged with oxime acetates (0.2 mmol), $Cu(OTf)_2$(20mol%), $PhI(OAc)_2$(0.4 mmol) in toluene (2.0 mL). The mixture was stirred at 100 ^oC for 8 h under air atmosphere. When the reaction was completed (monitored by TLC), the mixture was cooled to room temperature. The mixture was diluted with water and extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 40:1) to yield the isolated product **3aa**.

Synthesis of 3ba: A test tube was charged with oxime acetate (0.2 mmol), toluene (0.4 mmol), $Cu(OTf)_2$ (20 mol%), $PhI(OAc)_2$ (0.4 mmol) in PhCl (2.0 mL). The mixture was stirred at 120 ^oC for 8 h under air. When the reaction was completed (detected by TLC), the mixture was cooled to room temperature. The mixture was diluted with water and extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporation. The residue was purified by column

chromatography on silica gel (petroleum ether/EtOAc = 40:1) to yield the isolated product **3ba**.

2,4,6-triphenyl-pyridine (3aa). White solid (23.3 mg, 76%); m. p. 102-104 °C (lit.[15] m. p. 133-134 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 – 8.15 (m, 4H), 7.88 (d, *J* = 1.0 Hz, 2H), 7.77 – 7.71 (m, 2H), 7.56 – 7.42 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 150.2, 139.6, 139.0, 129.1, 129.0, 128.9, 128.7, 127.2, 127.1, 117.1; HRMS (ESI) calcd for $C_{23}H_{18}N$ $[M+H]^+$ 308.1434; found: 308.1437.

2,6-bis(4-methylphenyl)-4-phenylpyridine (3ab). White solid (24.8 mg, 74%); m. p. 126-128 °C (lit.[16] m. p. 157.4-157.9 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 4H), 7.83 (s, 2H), 7.73 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.56 – 7.41 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 4H), 2.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 150.0, 139.3, 138.9, 136.9, 129.4, 129.0,128.9, 127.1, 127.0, 116.5, 21.3; HRMS (ESI) calcd for $C_{25}H_{22}N$ $[M+H]^+$ 336.1747; found: 336.1749.

2,6-bis(3-methylphenyl)-4-phenylpyridine (3ac). White solid (23.8 mg, 71%); m. p . 127-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2 Hz, 4H), 7.85 – 7.81 (m, 2H), 7.73 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.56 – 7.42 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 4H), 2.43 (s, 6H); ^{13}C NMR (75 MHz,

CDCl3) δ 157.6, 150.1, 139.5, 138.3, 129.8, 129.1, 128.6, 127.9, 127.2, 124.3, 117.2, 21.6; HRMS (ESI) calcd for $C_{25}H_{22}N$ $[M+H]^+$ 336.1747; found: 336.1748.

2,6-bis(2-methylphenyl)-4-phenylpyridine (3ad). White solid (21.7 mg, 65%); m. p. 129-131 °C(lit.[21] m. p. 129-130 °C); ^{1}H NMR (300 MHz, CDCl3) δ 7.72 (dd, *J* = 7.4, 0.9 Hz, 2H), 7.59 (d, *J* = 0.7 Hz, 2H), 7.50 (ddd, *J* = 7.8, 5.6, 2.9 Hz, 4H), 7.37 – 7.23 (m, 7H), 2.48 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 148.8, 140.7, 138.5, 135.9, 130.7, 129.8, 129.1, 129.0, 128.2, 127.1, 125.8, 120.1, 20.6; HRMS (ESI) calcd for $C_{25}H_{22}N$ $[M+H]^+$ 336.1747; found: 336.1749.

2,6-bis(4-methoxylphenyl)-4-phenylpyridine (3ae). White solid (22.4 mg, 61%); m. p. 98-100 °C (lit.[19] m. p. 98-99 °C) ; ^{1}H NMR (300 MHz, CDCl3) δ 8.16 (d, *J* = 8.9 Hz, 4H), 7.80 – 7.69 (m, 4H), 7.49 (dt, *J* = 8.5, 6.9 Hz, 3H), 7.03 (d, *J* = 8.9 Hz, 4H), 3.87 (s, 6H); ^{13}C NMR (75 MHz, CDCl3) δ 160.4, 156.9, 149.9, 139.3, 132.3, 129.0, 128.8, 128.3, 127.1, 115.7, 114.0, 55.4; HRMS (ESI) calcd for $C_{25}H_{22}NO_2$ $[M+H]^+$ 368.1645; found: 368.1648.

2,6-bis(3-methoxylphenyl)-4-phenylpyridine (3af). Colorless liquid (20.9 mg, 57%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 2H), 7.82 – 7.78 (m, 2H), 7.77 – 7.71 (m, 4H), 7.55 – 7.50 (m, 2H), 7.48 – 7.38 (m, 3H),

7.00 (dd, J = 7.9, 2.3 Hz, 2H), 3.92 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 157.2, 150.2, 141.1, 139.0, 129.7, 129.2, 129.1, 127.2, 119.6, 117.5, 114.8, 112.7, 55.4; HRMS (ESI) calcd for $C_{25}H_{22}NO_2$ $[M+H]^+$ 368.1645; found: 368.1648.

2,6-bis(4-fluorophenyl)-4-phenylpyridine (3ag). White solid (27.2 mg, 80%); m. p. 150-152 °C; ^{1}H NMR (300 MHz, CDCl3) δ 8.21 – 8.11 (m, 4H), 7.80 (d, J = 1.1 Hz, 2H), 7.75 – 7.67 (m, 2H), 7.58 – 7.41 (m, 3H), 7.25 – 7.11 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (d, J_{CF} = 247.5 Hz), 156.4, 150.4, 138.8, 135.5 (d, J_{CF} =3.0 Hz), 129.1, 129.1, 128.9 (d, J_{CF} = 8.3 Hz), 127.1, 116.7, 115.6 (d, J_{CF} = 21.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.68; HRMS (ESI) calcd for $C_{23}H_{16}F_2N$ $[M+H]^+$ 344.1246; found: 344.1249.

2,6-bis(4-chlorophenyl)-4-phenylpyridine (3ah). White solid (27.1 mg, 72%); m. p. 162-164 °C (lit.[19] m. p. 126-127 °C); ^{1}H NMR (300 MHz, CDCl3) δ 8.15 – 8.09 (m, 4H), 7.83 (s, 2H), 7.71 (dd, J = 7.7, 1.5 Hz, 2H), 7.54 – 7.44 (m, 7H); ^{13}C NMR (75 MHz, CDCl3) δ 156.3, 150.5, 138.6, 137.7, 135.3, 129.2, 128.9, 128.7, 128.3, 127.1, 117.1; HRMS (ESI) calcd for $C_{23}H_{16}Cl_2N$ $[M+H]^+$ 376.0655; found: 376.0658.

2,6-bis(4-bromophenyl)-4-phenylpyridine (3ai). White solid (38.1 mg, 82%); m. p. 164-166 °C (lit.[19] m. p. 101-102 °C); ^{1}H NMR (300 MHz,

CDCl3) δ 8.05 (dd, *J* = 8.6, 2.1 Hz, 4H), 7.84 (s, 2H), 7.70 (d, *J* = 1.1 Hz, 2H), 7.62 (dd, *J* = 8.6, 2.1 Hz, 3H), 7.51 (dd, *J* = 8.4, 6.6 Hz, 4H); ^{13}C NMR (75 MHz, CDCl3) δ 156.2, 150.4, 138.5, 138.0, 131.7, 129.1, 128.5, 127.0, 123.5, 117.0; HRMS (ESI) calcd for $C_{23}H_{16}Br_2N$ $[M+H]^+$ 463.9644; found: 463.9646.

2,6-di-4-biphenylyl-4-phenylpyridine (3aj). White solid (24.3 mg, 53%); m. p. 191-193 °C (lit.[22] m. p. 192-193 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 – 8.27 (m, 4H), 7.98 – 7.93 (m, 2H), 7.83 – 7.74 (m, 6H), 7.71 (d, *J* = 7.7 Hz, 5H), 7.54 – 7.45 (m, 6H), 7.40 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 141.8, 140.6, 138.4, 129.7, 129.1, 129.0, 128.8, 127.5, 127.4, 127.2, 127.1, 117.0; HRMS (ESI) calcd for $C_{35}H_{26}N$ $[M+H]^+$ 460.2060; found: 460.2063.

2,6-di-2-naphthalenyl-4-phenylpyridine (3ak). White solid (19.2 mg, 72%); m. p. 156-157 °C; ^{1}H NMR (300 MHz, CDCl3) δ 8.69 (s, 2H), 8.42 (dd, *J* = 8.6, 1.7 Hz, 2H), 8.08 – 7.98 (m, 6H), 7.92 – 7.88 (m, 2H), 7.83 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.54 (dq, *J* = 6.8, 4.3 Hz, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 150.2, 138.9, 136.8, 133.7, 133.5, 129.1, 129.0, 128.7, 128.3, 127.7, 127.2, 126.4, 126.2, 124.9, 117.4; HRMS (ESI) calcd for $C_{31}H_{22}N$ $[M+H]^+$408.1747; found: 408.1749.

5,6,8,9-Tetrahydro-7-phenyldibenz[c,h]acridine (3al). White solid

(13.8 mg, 38%); m. p. 169-171 °C (lit.[20] m. p. 164-165°C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 2H), 7.45 – 7.36 (m, 3H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 8.8 Hz, 4H), 2.90 – 2.74 (m, 4H), 2.64 (dd, *J* = 8.7, 5.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 147.6, 138.1, 138.0, 135.5, 131.1, 128.8, 128.8, 128.8, 127.8, 127.6, 127.2, 125.5, 28.3, 26.0; HRMS (ESI) calcd for $C_{27}H_{22}N$ $[M+H]^+$ 360.1747; found: 360.1749.

4-(4-methylphenyl)-2,6-diphenylpyridine (3ba): White solid (23.7 mg, 74%); m. p. 117-119 °C (lit.[18] m. p. 123-124 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.0 Hz, 4H), 7.87 (s, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.43 (m, 6H), 7.33 (d, *J* = 7.8 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 150.0, 139.6, 139.1, 136.1, 129.8, 129.0, 128.7, 127.1, 127.0, 116.9, 21.3; HRMS (ESI) calcd for $C_{24}H_{20}N$ $[M+H]^+$ 322.1590; found: 322.1593.

4-(3-methylphenyl)-2,6-diphenylpyridine (3bb). White solid (22.4 mg, 70%); m. p.112-114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.18 (m, 4H), 7.88 (d, *J* = 0.9 Hz, 2H), 7.52 (dd, *J* = 12.8, 6.5 Hz, 6H), 7.44 (dd, *J* = 10.9, 4.2 Hz, 3H), 7.28 (d, *J* = 7.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 150.3, 139.6, 139.0, 138.8, 129.7, 129.0, 128.7, 127.9, 127.1, 124.3, 117.1, 21.5; HRMS (ESI) calcd for $C_{24}H_{20}N$ $[M+H]^+$ 322.1590; found: 322.1592.

4-(2-methylphenyl)-2,6-diphenylpyridine (3bc). White solid (20.8 mg, 65%); m. p. 108-110 °C (lit.[18] m. p. 120-122 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 – 8.14 (m, 4H), 7.67 (s, 2H), 7.54 – 7.41 (m, 6H), 7.33 (q, J = 3.4 Hz, 4H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156. 8, 151.3, 139.8, 139.5, 135.1, 130.7, 129.2, 129.0, 128.7, 128.5, 128.3, 127.1, 126.1, 119.3, 20.4; HRMS (ESI) calcd for $C_{24}H_{20}N$ $[M+H]^+$ 322.1590; found: 322.1594.

4-(3,5-dimethylphenyl)-2,6-phenylpyridine (3bd). White solid (24.7 mg, 77%); m. p. 119-121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 – 8.18 (m, 5H), 7.87 (s, 2H), 7.50 (d, J = 7.8 Hz, 6H), 7.35 (s, 2H), 2.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 150.4, 139.6, 139.0, 138.7, 130.6, 128.9, 128.6, 127.1, 125.0, 117.1, 21.4; HRMS (ESI) calcd for $C_{25}H_{22}N$ $[M+H]^+$ 336.1747; found: 336.1749.

4-(4-methoxyphenyl)-2,6-diphenylpyridine (3be). White solid (22.8 mg, 68%); m. p. 100-102 °C (lit.[15] m. p. 99-100 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 – 7.97 (m, 4H), 7.87 (d, J = 9.6 Hz, 2H), 7.80 – 7.68 (m, 2H), 7.57 – 7.21 (m, 8H), 2.42 (d, J = 14.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 157.5, 149.7, 139.8, 131.4, 129.0, 128.7, 128.4, 127.2, 116.7, 114.6, 55.5; HRMS (ESI) calcd for $C_{24}H_{20}NO$ $[M+H]^+$ 338.1540; found: 338.1543.

4-(4-fluorophenyl)-2,6-diphenylpyridine (3bf). White solid (25.3 mg, 78%); m. p. 138-140 °C (lit.[16] m. p. 203.4-204.6 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 – 8.14 (m, 4H), 7.86 (d, J = 17.2 Hz, 2H), 7.78 – 7.68 (m, 2H), 7.48 (dd, J = 14.6, 7.5 Hz, 6H), 7.34 – 7.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (d, J_{CF} = 246.0 Hz), 157.6, 149.1, 139.4, 135.1 (d, J_{CF} = 3.0 Hz), 129.1, 129.0 (d, J_{CF} = 5.3 Hz), 128.7, 127.1, 116.9, 116.1 (d, J_{CF} = 21.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.52; HRMS (ESI) calcd for $C_{23}H_{17}FN$ $[M+H]^+$ 326.1340; found: 326.1342.

4-(4-chlorophenyl)-2,6-diphenylpyridine (3bg). White solid (24.2 mg, 71%); m. p. 130-132 °C (lit.[16] m. p. 125.9-127.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.13 (m, 4H), 7.83 (s, 2H), 7.67 (d, J = 8.5 Hz, 2H), 7.55 – 7.39 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 148.9, 139.4, 137.5, 135.2, 129.3, 129.1, 128.7, 128.4, 127.1, 116.8; HRMS (ESI) calcd for $C_{23}H_{17}ClN$ $[M+H]^+$ 342.1044; found: 342.1047.

4-(4-bromophenyl)-2,6-diphenylpyridine (3bh). White solid (27.8 mg, 72%); m. p. 132-134 °C (lit.[19] m. p. 166-167 °C); ^{1}H NMR (300 MHz, CDCl3) δ 8.22 – 8.16 (m, 4H), 7.83 (s, 2H), 7.66 – 7.60 (m, 3H), 7.55 – 7.44 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 149.2, 139.6, 138.2, 132.5, 129.4, 129.0, 127.4, 123.6, 117.0; HRMS (ESI) calcd for $C_{23}H_{17}BrN$ $[M+H]^+$ 386.0539; found: 386.0542.

4-(2-chlorophenyl)-2,6-diphenylpyridine (3bi). White solid (20.5 mg, 60%); m. p. 108-110 °C (lit.[18] m. p. 113-114 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 – 8.15 (m, 4H), 7.77 (d, *J* = 2.1 Hz, 2H), 7.55 – 7.36 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 148.5, 139.4, 138.5, 132.3, 131.0, 130.4, 129.8, 129.1, 128.8, 128.7, 127.5, 127.2, 127.1, 119.4; HRMS (ESI) calcd for $C_{23}H_{17}ClN$ $[M+H]^+$ 342.1044; found: 342.1046.

4-(3-chlorophenyl)-2,6-diphenylpyridine (3bj). White solid (21.2 mg, 62%); m. p. 117-119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 – 8.12 (m, 4H), 7.86 (d, *J* = 14.8 Hz, 2H), 7.63 – 7.42 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 148.8, 140.9, 139.3, 135.1, 130.4, 129.2, 129.0, 129.0, 128.7, 127.3, 127.1, 125.4, 116.9; HRMS (ESI) calcd for $C_{23}H_{17}ClN$ $[M+H]^+$ 342.1044; found: 342.1048.

4-(2,4-dichlorophenyl)-2,6-diphenylpyridine (3bk). Colorless liquid (24.1 mg, 64%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 – 8.08 (m, 4H), 7.80 – 7.67 (m, 2H), 7.57 – 7.35 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 147.5, 139.2, 137.0, 135.0, 133.1, 131.6, 130.1, 129.2, 128.7, 127.5, 127.2, 127.1, 119.2; HRMS (ESI) calcd for $C_{23}H_{16}Cl_2N$ $[M+H]^+$ 376.0655; found: 376.0658.

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all reaction products. The

materials are available free of charge on the ACS Publications website.

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