Simple Selective Synthesis of 2,4- and 2,6-Diarylpyridines through Metal-Free Cyclocondensation of Aromatic Ketones with Ammonium Acetate

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Abstract: A simple and selective one-pot synthesis of 2,4- and 2,6-diarylpyridines through the cyclocondensation reaction of aromatic ketones with ammonium acetate has been developed. The procedure is metal-free, convenient, and efficient, and the substrates are readily available.

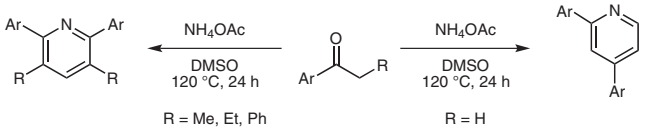
Key words: diarylpyridines, selective, cyclocondensation, aromatic ketones, ammonium acetate

Pyridine derivatives have attracted a great deal of interest, not only for their abundance in natural products and synthetic pharmaceuticals,[1] but also because they have many applications including agrochemicals,[2] ligands for metals,[3] homogeneous catalysis,[4] aromatase inhibitors,[5] anti-HIV agents,[6] and anti-cancer drugs.[7] Furthermore, they have played an increasingly important part in research fields such as coordination chemistry,[8] supramolecular chemistry,[9] materials science,[10] as well as for asymmetric synthesis.[11]

Not surprisingly, pyridine synthesis, to which a great deal of work has been devoted by chemists until recently, has long occupied a significant place in organic synthesis, resulting in the development of a wide range of synthetic methods.[12–15] Among the various reported approaches to pyridines, vapor-phase cyclization of acetophenone, formaldehyde, and ammonia,[16] arylation of the pyridine nucleus with organometallic reagents,[17] and palladium-catalyzed direct arylation of pyridine *N*-oxides[18] are considered to be the three available routes to diarylpyridines. Nevertheless, they suffer from many limitations such as complicated procedures, harsh reaction conditions, the requirement for a metal, and substrates that are not readily available. Consequently, it is desirable to find new, efficient methods for the construction of diarylpyridines.

In 1953, Ernest L. Eliel et al. reported a condensation reaction of phenylacetaldehyde with ammonia,[19] which was considered to be an abnormal Chichibabin reaction because of its unexpected 3,5-diphenylpyridine product. Perhaps because of its inefficiency, to the best of our knowledge, there have been few investigations on the utility of this reaction for the synthesis of diarylpyridines.

Enlightened by this abnormal Chichibabin reaction, it was assumed that a similar condensation reaction would happen between aromatic ketones and ammonia. In this paper, we present a simple, convenient and efficient synthesis of 2,4- and 2,6-diarylpyridines through a cyclocondensation reaction of acetophenones with ammonium acetate (Scheme 1), which appears to be a promising strategy for the direct, metal-free, and selective synthesis of 2,4- and 2,6-diarylpyridines from readily available substrates.



Scheme 1 Simple selective synthesis of 2,4- and 2,6-diarylpyridines

An initial study was performed to optimize the reaction conditions. The impact of the source of ammonia, solvent, and temperature was investigated in detail for the reaction (Table 1). In these experiments, we used 4-methoxyacetophenone (**1a**) as a model reactant. The results indicated that the solvent had a profound effect on the formation of **2a**, with dimethyl sulfoxide proving to be the solvent of choice (entries 1–10). The source of ammonia was also examined (entries 11–15) and it was shown that the reaction can also take place in the presence of several ammonium salts [NH_4OAc, NH_4HCO_3, HCO_2NH_4, $(NH_4)_2CO_3$] or an organic ammonia source, such as urea; ammonium acetate gave the best result. In addition, to optimize further the reaction conditions, the same reaction was carried out in dimethyl sulfoxide at temperatures ranging from 80 to 140 °C (Table 1, entries 16–18), with 120 °C chosen to be the reaction temperature.

For the optimal reaction conditions, **1** was reacted with ammonium acetate (3 equiv) in dimethyl sulfoxide (1 mL) at 120 °C for 24 hours and these conditions were subsequently employed when examining the substrate scope of the reaction (Table 2). Gratifyingly, a variety of acetophenones **1a–q** successfully reacted under the aforesaid conditions to afford the desired 2,4-diarylpyridines **2a–q** in good yields.

Notably, various electron-rich acetophenones (Table 2, entries 1, 3, 4, 10, 11, 16, 17) and some electron-deficient acetophenones (entries 6, 7, 13) as well as others that have well-conjugated structures (entries 14, 15) are suitable substrates for the reaction. Conversely, other electron-

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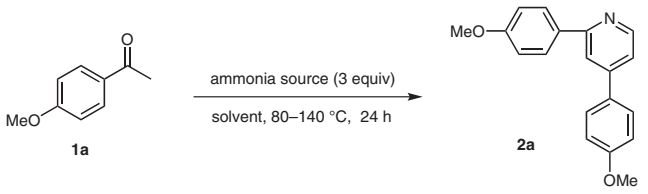
Table 1 Screening the Impact of Solvent, Ammonia Source, and Temperature[a]



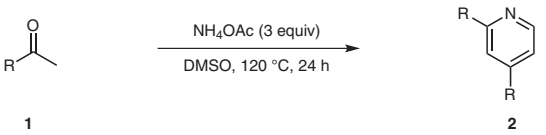
Entry	Ammonia source[b]	Solvent	Temp (°C)	Yield[c] (%)
1	NH_4OAc	DMF	120	45
2	NH_4OAc	AcOH	120	38
3	NH_4OAc	toluene	120	trace
4	NH_4OAc	$MeNO_2$	120	trace
5	NH_4OAc	MeCN	120	20
6	NH_4OAc	dioxane	120	15
7	NH_4OAc	NMP	120	42
8	NH_4OAc	AcOH–glycol (1:2)	120	53
9	NH_4OAc	glycol	120	70
10	NH_4OAc	DMSO	120	86
11	NH_4HCO_3	DMSO	120	25
12	NH_4Cl	DMSO	120	0
13	HCO_2NH_4	DMSO	120	45
14	$(NH_4)_2CO_3$	DMSO	120	60
15	$CO(NH_2)_2$	DMSO	120	53
16	NH_4OAc	DMSO	80	62
17	NH_4OAc	DMSO	100	73
18	NH_4OAc	DMSO	140	86

[a] Reaction conditions: **1a** (0.45 mmol), ammonia source (3 equiv), solvent (1 mL), 80–140 °C, 24 h.
[b] Excess ammonia was required to achieve satisfactory isolated yields and 3 equiv was a reasonable amount of the ammonia source; the optimization details are not presented in this table.
[c] Isolated yield after column chromatography.

deficient acetophenones (entries 5, 8, 9, 12) generated their cyclocondensation products in moderate yields only. In addition, 2′-substituted acetophenones, possibly because of steric hindrance, gave only traces of products (entries 18, 19), moreover, other heterocyclic ketones such as methyl 2-pyridyl ketone (**1t**) also gave only a trace of product (entry 20). Unfortunately, when butan-2-one (**1u**) and ferrocenyl methyl ketone (**1v**) were employed, the desired product was completely absent (entries 21, 22).

Encouraged by the results obtained, a subsequent study was carried out to evaluate further the substrate scope of this reaction. It was consistent with our conjecture that

Table 2 Synthesis of 2,4-Diarylpyridines **2** from 1-Substituted Ethanones **1**[a]

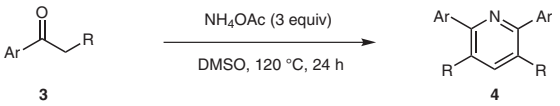


Entry	R	Product	Yield[b] (%)
1	4-$MeOC_6H_4$	**2a**	86
2	Ph	**2b**	74
3	4-MeC_6H_4	**2c**	76
4	4-$PhOC_6H_4$	**2d**	83
5[c]	4-HOC_6H_4	**2e**	53
6	4-ClC_6H_4	**2f**	72
7	4-BrC_6H_4	**2g**	71
8[c]	4-IC_6H_4	**2h**	55
9[c]	4-$HC{\equiv}CC_6H_4$	**2i**	50
10	3-MeC_6H_4	**2j**	72
11	3-$MeOC_6H_4$	**2k**	73
12[c]	3-$O_2NC_6H_4$	**2l**	53
13	3-BrC_6H_4	**2m**	70
14	4-$PhC{\equiv}CC_6H_4$	**2n**	90
15	4-PhC_6H_4	**2o**	88
16	3,4-$Me_2C_6H_3$	**2p**	82
17	3,5-$Me_2C_6H_3$	**2q**	70
18[c]	2-MeC_6H_4	**2r**	trace
19[c]	2-HOC_6H_4	**2s**	trace
20[c]	2-pyridyl	**2t**	trace
21	Et	**2u**	0
22	Fc[d]	**2v**	0

[a] Reaction conditions: **1** (0.45 mmol), NH_4OAc (3 equiv), DMSO (1 mL), 120 °C, 24 h.
[b] Isolated yield after column chromatography.
[c] The reaction time was increased to 36 h.
[d] Ferrocenyl.

3,5-disubstituted 2,6-diarylpyridines could be prepared when 2-substituted acetophenones were employed in this reaction (Table 3). In particular, electron-rich 2-substituted acetophenones were superior to electron-deficient 2-substituted acetophenones. Reaction with electron-rich 2-substituted acetophenones afforded the corresponding cyclocondensation products in good yields (70–75%, entries 2, 3), while relatively electron-deficient 2-substituted acetophenones gave the corresponding products in moderate yields (56–60%, entries 4, 5). The structure of compound **4g** (Figure 1) was confirmed by single-crystal X-ray anal-

Table 3 Synthesis of 3,5-Disubstituted 2,6-Diarylpyridines **4** from 2-Substituted Acetophenones **3**[a]



Entry	Ar	R	Product	Yield[b] (%)
1	Ph	Me	**4a**	62
2	4-MeC_6H_4	Me	**4b**	70
3	4-MeOC_6H_4	Me	**4c**	75
4	4-ClC_6H_4	Me	**4d**	60
5	3-ClC_6H_4	Me	**4e**	56
6	Ph	Et	**4f**	50
7	Ph	Ph	**4g**	55

[a] Reaction conditions: **3** (0.45 mmol), NH_4OAc (3 equiv), DMSO (1 mL), 120 °C, 24 h.
[b] Isolated yield after column chromatography.

ysis. In addition, steric hindrance by the 2-substituent in the acetophenones makes the corresponding substrates not well suited to the reaction (entries 6, 7). It is likely that the effects of steric hindrance within these substrates in the reaction make their cyclocondensation products differ from those above (Table 2) and may be a interpretation of why they provide the 3,5-disubstituted 2,6-diarylpyridines products in moderate yields only.

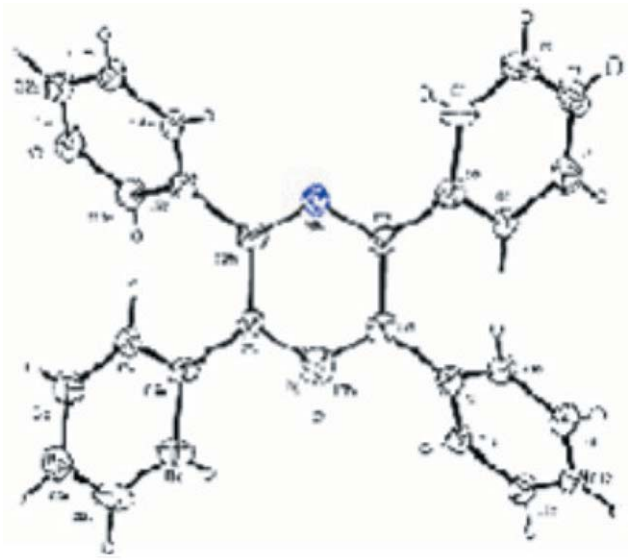
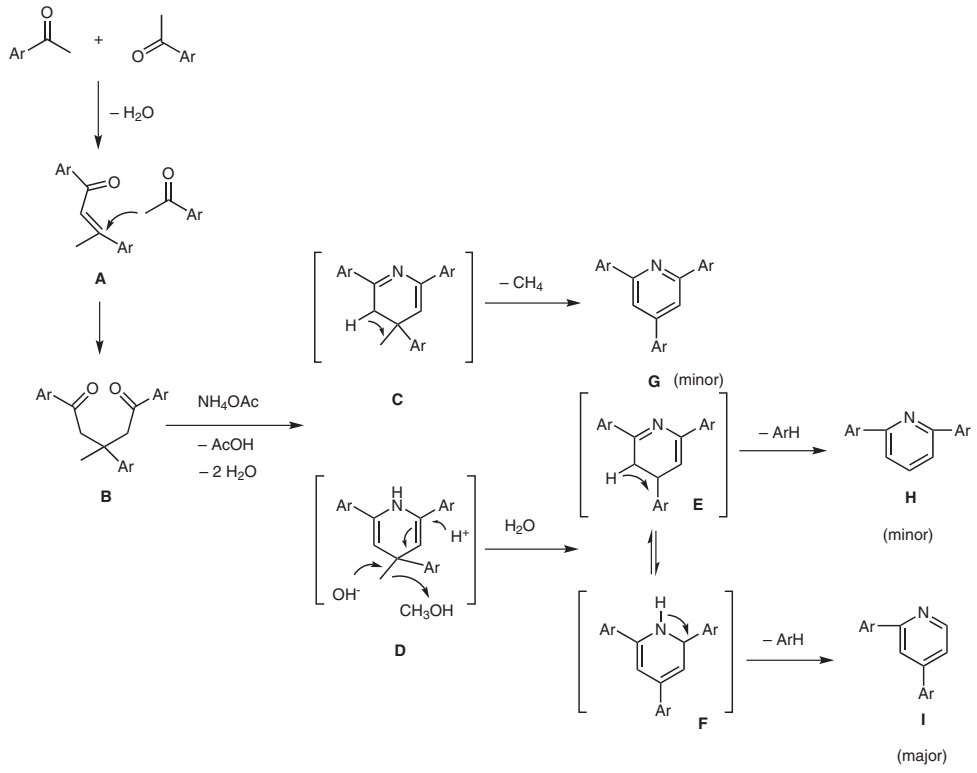


Figure 1 X-ray crystal structure of **4g**

A plausible mechanism is proposed in Scheme 2 that is based on previous reports[19,20] combined with our experiments results. Initially, the condensation of the acetophenone with itself gives **A**, which then undergoes a Michael Addition with another molecule of acetophenone leading to 1,5-dicarbonyl compound **B**. Condensation reaction of **B** in the presence of ammonium acetate affords dihydropyridine intermediates **C** and **D**. Oxidative aromatization with removal of methane from **C** would yield 2,4,6-triarylpyridine **G**, and **D** forms another two dihydropyridine intermediates **E** and **F** by removal of the methyl group.



Scheme 2 Proposed mechanism for the cyclocondensation reaction

Then, oxidative aromatization with removal one of the three aryl groups on the 2,4,6-triaryldihydropyridines **E** and **F** would provide the two diarylpyridine isomers **H** and **I**, respectively. In fact, minor 2,4,6-tris(4-methoxyphenyl)pyridine (**G**) and 2,6-bis(4-methoxyphenyl)pyridine (**H**) were detected by GC-MS in the reaction mixture of 4-methoxyacetophenone (**1a**) and ammonium acetate. In this reaction, it can be seen that ammonium acetate serves not only as a reactant but also as a catalyst.[20c] The reaction pathway of 2-substituted acetophenones **3** in this reaction yielding 3,5-disubstituted 2,6-diarylpyridines **4** is similar to this proposed mechanism.

In summary, a simple, convenient, and efficient method for the one-pot synthesis of 2,4- and 2,6-diarylpyridines from readily available aromatic ketones and ammonium acetate has been developed in our laboratory. The reaction is selective, no metal catalysts are required, and it allows the construction of aryl-substituted pyridines of both biological and synthetic interest. Many substrates are suitable for this procedure, affording various 2,4- and 2,6-diarylpyridines in moderate to good yields. This strategy may be very useful for the synthesis of 2,4- and 2,6-diarylpyridines and the corresponding natural products. A more detailed investigation on the mechanism and scope of this reaction, as well as the utilization of this reaction in the synthesis of complex molecules is ongoing in our laboratory and will be reported in due course.

NMR spectra were recorded on 400 MHz in $CDCl_3$ or acetone-d_6 and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$ or DMSO-d_6 using TMS as internal standard. IR spectra were recorded on a FT-IR spectrophotometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. All products were further characterized by ESI HRMS; copies of their ^1H NMR and ^{13}C NMR spectra are provided. All materials were purchased from common commercial sources and used without additional purification. Petroleum ether = PE.

2,4-Bis(4-methoxyphenyl)pyridine (2a) and 3,5-Dimethyl-2,6-diphenylpyridine (4a); Typical Procedures

All reactions were performed on a 0.45-mmol scale relative to **1a** and **3a**. To a soln of NH_4OAc (3 equiv) in DMSO (1 mL) in a 10-mL general monomodal reaction vial was added 4-methoxyacetophenone (0.45 mmol) or propiophenone (0.45 mmol). The reaction vial was sealed and heated in an oil bath at 120 °C for 24 h with stirring (TLC monitoring). To the mixture was added H_2O (2 mL) and it was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (2 × 5 mL), dried (anhyd $MgSO_4$), and concentrated in vacuo. The residue was subjected to flash column chromatography (silica gel, PE–EtOAc, 12:1) to gave **2a** (37.6 mg, 86%) and **4a** (23.5 mg, 62%), respectively.

2,4-Bis(4-methoxyphenyl)pyridine (2a)

Purified by flash chromatography (PE–EtOAc, 12:1) to give **2a** (86% yield) as an off-white solid; mp 147–149 °C.

IR (KBr): 3400.98, 2959.05, 1606.13, 1515.86, 1249.42, 1020.12, 813.92 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.644 (d, *J* = 5.2 Hz, 1 H), 7.995 (d, *J* = 8.4 Hz, 2 H), 7.821 (s, 1 H), 7.630 (d, *J* = 8.8 Hz, 2 H), 7.338 (d, *J* = 5.2 Hz, 1 H), 7.009 (d, *J* = 4.2 Hz, 4 H), 3.857 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.44, 157.60, 149.84, 148.60, 132.19, 130.86, 128.23, 128.16, 119.04, 117.36, 114.48, 114.08, 55.34, 55.30.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1335.

2,4-Diphenylpyridine (2b)

Purified by flash chromatography (PE–EtOAc, 12:1) to give **2b** (74% yield) as a yellow oil.

IR (neat): 3384.40, 2925.59, 1597.09, 694.46 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.732 (d, *J* = 5.2 Hz, 1 H), 8.036–8.059 (dd, *J* = 8.2 Hz, 1 Hz, 2 H), 7.922 (s, 1 H), 7.672–7.696 (m, 2 H), 7.427–7.521 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.08, 150.07, 149.26, 139.49, 138.53, 129.09, 129.00, 128.74, 127.05, 127.01, 120.22, 118.72.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}N$: 232.1121; found: 232.1117.

2,4-Di-4-tolylpyridine (2c)

Purified by flash chromatography (PE–EtOAc, 12:1) to give **2c** (76% yield) as an off-white solid; mp 91–93 °C.

IR (KBr): 3026.16, 1597.30, 809.10 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.686 (d, *J* = 5.2 Hz, 1 H), 7.941 (d, *J* = 8.0 Hz, 2 H), 7.881 (s, 1 H), 7.580 (d, *J* = 8.0 Hz, 2 H), 7.382–7.398 (dd, *J* = 4.8 Hz, 1.6 Hz, 1 H), 7.293 (d, *J* = 6.8 Hz, 4 H), 2.412 (s, 3 H), 2.409 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.96, 149.87, 149.12, 139.09, 138.96, 136.69, 135.63, 129.79, 129.46, 126.87, 119.73, 118.18, 21.25, 21.20.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}N$: 260.1434; found: 260.1435.

2,4-Bis(4-phenoxyphenyl)pyridine (2d)

Purified by flash chromatography (PE–EtOAc, 12:1) to give **2d** (83% yield) as a light-yellow solid; mp 186–188 °C.

IR (KBr): 3381.75, 3061.18, 1591.69, 1488.27, 1238.26, 827.13 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.682 (d, *J* = 5.2 Hz, 1 H), 8.017 (d, *J* = 8.8 Hz, 2 H), 7.850 (s, 1 H), 7.648 (d, *J* = 8.4 Hz, 2 H), 7.333–7.393 (m, 5 H), 7.054–7.171 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.52, 158.31, 157.47, 156.87, 156.54, 150.03, 148.53, 134.50, 133.15, 129.89, 129.79, 128.53, 128.46, 123.86, 123.53, 119.58, 119.39, 119.16, 118.95, 118.83, 117.90.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{22}NO_2$: 416.1645; found: 416.1647.

2,4-Bis(4-hydroxyphenyl)pyridine (2e)

Purified by flash chromatography (PE–EtOAc, 4:1) to give **2e** (53% yield) as a yellow solid; mp 206–208 °C.

IR (KBr): 3421.04, 1652.00, 1026.78, 628.39 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 9.796 (s, 1 H), 9.693 (s, 1 H), 8.553 (d, *J* = 5.2 Hz, 1 H), 8.034 (s, 1 H), 8.004 (d, *J* = 7.6 Hz, 2 H), 7.750 (d, *J* = 8.4 Hz, 2 H), 7.454–7.471 (dd, *J* = 5.2 Hz, 1.6 Hz, 1 H), 6.858–6.917 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.60, 158.43, 156.76, 149.66, 147.77, 129.85, 128.19, 128.09, 128.01, 118.08, 115.84, 115.53, 115.34.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{14}NO_2$: 264.1019; found: 264.1013.

2,4-Bis(4-chlorophenyl)pyridine (2f)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2f** (72% yield) as a red-brown solid; mp 102–104 °C.

IR (KBr): 2923.04, 1595.72, 1091.31, 814.73 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.715 (d, *J* = 4.8 Hz, 1 H), 7.982 (d, *J* = 8.4 Hz, 2 H), 7.830 (s, 1 H), 7.601 (d, *J* = 8.4 Hz, 2 H), 7.442–7.483 (m, 4 H), 7.389–7.405 (dd, *J* = 5 Hz, 1.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.98, 150.28, 148.18, 137.68, 136.77, 135.41, 135.31, 129.36, 128.95, 128.31, 128.26, 120.20, 118.17.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{12}Cl_2N$: 300.0341; found: 300.0345.

2,4-Bis(4-bromophenyl)pyridine (2g)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2g** (71% yield) as an orange solid; mp 137–139 °C.

IR (KBr): 3391.09, 3147.95, 1593.16, 1374.53, 1070.73, 1006.06, 811.68 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.720 (d, *J* = 5.2 Hz, 1 H), 7.919 (d, *J* = 8.8 Hz, 2 H), 7.836 (s, 1 H), 7.605–7.648 (m, 4 H), 7.527–7.554 (m, 2 H), 7.401–7.418 (dd, *J* = 5.2 Hz, 1.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.05, 150.33, 148.26, 138.12, 137.23, 132.34, 131.93, 128.61, 128.55, 123.67, 123.64, 120.22, 118.11.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{12}Br_2N$: 387.9331; found: 387.9338.

2,4-Bis(4-iodophenyl)pyridine (2h)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2h** (55% yield) as an off-white solid; mp 171–173 °C.

IR (KBr): 3384.64, 2922.09, 11596.48, 1372.21, 1001.52, 808.94 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.717 (d, *J* = 4.8 Hz, 1 H), 7.815–7.851 (m, 5 H), 7.778 (d, *J* = 8.4 Hz, 2 H), 7.391–7.412 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.16, 150.35, 148.36, 138.72, 138.32, 137.92, 137.83, 128.76, 128.72, 120.23, 118.00, 95.55, 95.34.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{12}I_2N$: 483.9054; found: 483.9052.

2,4-Bis(4-ethynylphenyl)pyridine (2i)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2i** (50% yield) as an orange oil.

IR (neat): 3290.05, 1598.16, 1468.05, 824.22 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.746 (d, *J* = 5.2 Hz, 1 H), 8.027 (d, *J* = 8.4 Hz, 2 H), 7.899 (s, 1 H), 7.609–7.664 (m, 6 H), 7.430–7.446 (dd, *J* = 4.8 Hz, 1.6 Hz, 1 H), 3.189 (s, 1 H), 3.173 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.21, 150.33, 148.44, 139.52, 138.63, 132.87, 132.57, 126.99, 126.87, 123.07, 122.86, 120.37, 118.54, 83.46, 83.02, 78.80, 78.45.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{14}N$: 280.1121; found: 280.1124.

2,4-Di-3-tolylpyridine (2j)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2j** (72% yield) as an orange oil.

IR (neat): 2920.39, 1593.85, 784.40 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.713 (d, *J* = 5.2 Hz, 1 H), 7.894 (d, *J* = 6.8 Hz, 2 H), 7.816 (d, *J* = 8 Hz, 1 H), 7.486 (d, *J* = 6.8 Hz, 2 H), 7.359–7.428 (m, 3 H), 7.236–7.274 (m, 2 H), 2.452 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.20, 149.95, 149.39, 139.52, 138.79, 138.58, 138.41, 129.74, 128.99, 128.63, 127.78, 127.75, 124.19, 124.12, 120.19, 118.82, 21.51, 21.49.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{18}N$: 260.1434; found: 260.1436.

2,4-Bis(3-methoxyphenyl)pyridine (2k)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2k** (73% yield) as an orange oil.

IR (neat): 2931.95, 1590.78, 1464.30, 1280.08, 1042.08, 782.77 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.723 (d, *J* = 4.8 Hz, 1 H), 7.901 (s, 1 H), 7.632 (d, *J* = 2 Hz, 1 H), 7.600 (d, *J* = 8 Hz, 1 H); 7.378–7.436 (m, 3 H), 7.275 (s, 1 H), 7.204 (d, *J* = 1.6 Hz, 1 H), 6.974–7.007 (m, 2 H), 3.904 (s, 3 H), 3.883 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.15, 160.07, 157.82, 149.95, 149.16, 140.92, 139.97, 130.15, 129.71, 120.41, 119.47, 119.39, 118.90, 115.12, 114.27, 112.88, 112.16, 55.37.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1334.

2,4-Bis(3-nitrophenyl)pyridine (2l)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2l** (53% yield) as a red-brown solid; mp 197–199 °C.

IR (KBr): 3371.68, 3085.71, 1525.90, 1351.61, 731.06 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.946 (s, 1 H), 8.868 (d, *J* = 5.2 Hz, 1 H), 8.572 (s, 1 H), 8.461 (d, *J* = 8 Hz, 1 H), 8.311–8.370 (m, 2 H), 8.025–8.059 (m, 2 H), 7.688–7.770 (m, 2 H), 7.582 (d, *J* = 4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.92, 150.89, 148.95, 148.87, 147.39, 140.59, 139.82, 133.01, 132.86, 130.39, 129.88, 124.01, 123.98, 122.11, 121.95, 121.25, 118.61.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{12}N_3O_4$: 322.0822; found: 322.0827.

2,4-Bis(3-bromophenyl)pyridine (2m)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2m** (70% yield) as an orange solid; mp 94–96 °C.

IR (KBr): 3061.94, 2924.29, 1591.38, 1542.39, 1461.63, 783.31 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.735 (d, *J* = 5.2 Hz, 1 H), 8.210 (s, 1 H), 7.961 (d, *J* = 8 Hz, 1 H), 7.803–7.826 (m, 2 H), 7.545–7.599 (m, 3 H), 7.333–7.421 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.64, 150.33, 147.99, 141.20, 140.38, 132.08, 130.65, 130.27, 130.12, 130.10, 125.71, 125.53, 123.29, 123.09, 120.63, 118.57.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{12}Br_2N$: 387.9331; found: 387.9336.

2,4-Bis[4-(phenylethynyl)phenyl]pyridine (2n)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2n** (90% yield) as a yellow solid; mp 183–185 °C.

IR (KBr): 3371.31, 2921.87, 1591.95, 1413.08, 821.24, 750.65, 687.56 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.744 (d, *J* = 4.8 Hz, 1 H), 8.065 (d, *J* = 8.4 Hz, 2 H), 7.933 (s, 1 H), 7.652–7.673 (m, 6 H), 7.553–7.572 (m, 4 H), 7.436–7.452 (dd, *J* = 5 Hz, 1.4 Hz, 1 H), 7.343–7.369 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.27, 150.27, 148.46, 138.95, 137.95, 132.31, 132.03, 131.66, 131.64, 128.52, 128.40, 128.36,

126.99, 126.90, 124.27, 124.05, 123.17, 122.98, 120.21, 118.41, 91.10, 90.80, 89.28, 88.82.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{22}N$: 432.1747; found: 432.1744.

2,4-Bis(biphenyl-4-yl)pyridine (2o)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2o** (88% yield) as a light-yellow solid; mp 208–210 °C.

IR (KBr): 3404.79, 1590.58, 1443.90, 1378.92, 759.88, 689.95 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.762 (d, *J* = 4.8 Hz, 1 H), 8.150 (d, *J* = 8.4 Hz, 2 H), 8.012 (s, 1 H), 7.728–7.794 (m, 6 H), 7.644–7.679 (m, 4 H), 7.444–7.493 (m, 5 H), 7.348–7.403 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.70, 150.18, 148.79, 141.99, 141.82, 140.57, 140.25, 138.35, 137.30, 128.91, 128.82, 127.82, 127.74, 127.53, 127.47, 127.43, 127.10, 120.07, 118.41.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{22}N$: 384.1747; found: 384.1742.

2,4-Bis(3,4-dimethylphenyl)pyridine (2p)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2p** (82% yield) as an off-white solid; mp 75–77 °C.

IR (KBr): 2919.88, 1597.81, 1469.45, 814.76 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.673 (d, *J* = 4.8 Hz, 1 H), 7.861 (d, *J* = 10.4 Hz, 2 H), 7.751 (d, *J* = 7.6 Hz, 1 H), 7.453 (s, 1 H), 7.422 (d, *J* = 7.6 Hz, 1 H), 7.369–7.385 (dd, *J* = 5 Hz, 1.4 Hz, 1 H), 7.241 (d, *J* = 7.6 Hz, 2 H), 2.353 (d, *J* = 2.8 Hz, 6 H), 2.317 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.09, 149.83, 149.15, 137.68, 137.56, 137.30, 137.21, 136.92, 136.14, 130.32, 129.99, 128.17, 124.38, 124.33, 119.68, 118.21, 19.87, 19.85, 19.56, 19.52.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}N$: 288.1747; found: 288.1742.

2,4-Bis(3,5-dimethylphenyl)pyridine (2q)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **2q** (70% yield) as an orange oil.

IR (neat): 2917.35, 1592.73, 1447.13, 833.72 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.687 (d, *J* = 5.2 Hz, 1 H), 7.869 (s, 1 H), 7.652 (s, 2 H), 7.382–7.398 (dd, *J* = 5 Hz, 1.4 Hz, 1 H), 7.288 (s, 2 H), 7.074 (d, *J* = 6.4 Hz, 2 H), 2.407 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.27, 149.82, 149.47, 139.54, 138.65, 138.63, 138.24, 130.61, 130.58, 124.93, 124.88, 120.15, 118.84, 21.38, 21.35.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}N$: 288.1747; found: 288.1743.

3,5-Dimethyl-2,6-diphenylpyridine (4a)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **4a** (62%) as a purple-red solid; mp 88–90 °C.

IR (KBr): 3389.56, 2955.11, 1441.07, 700.95 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.568–7.589 (m, 4 H), 7.465 (s, 1 H), 7.398–7.434 (m, 4 H), 7.326–7.362 (m, 2 H), 2.369 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.79, 141.08, 140.73, 129.21, 129.07, 128.02, 127.62, 19.59.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}N$: 260.1434; found: 260.1430.

3,5-Dimethyl-2,6-di-4-tolylpyridine (4b)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **4b** (70% yield) as an off-white solid; mp 79–81 °C.

IR (KBr): 3381.74, 2922.33, 1426.51, 908.12, 825.74, 731.89 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.480 (d, *J* = 8 Hz, 4 H), 7.429 (s, 1 H), 7.219 (d, *J* = 8 Hz, 4 H), 2.380 (s, 6 H), 2.363 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.67, 141.04, 137.90, 137.25, 129.12, 128.71, 128.66, 21.23, 19.66.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}N$: 288.1747; found: 288.1739.

2,6-Bis(4-methoxyphenyl)-3,5-dimethylpyridine (4c)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **4c** (75% yield) as an off-white solid; mp 108–110 °C.

IR (KBr): 2954.70, 1609.09, 1511.77, 1461.20, 1426.64, 1247.75, 1176.39, 1028.78, 837.19 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.558 (d, *J* = 8.8 Hz, 4 H), 7.432 (s, 1 H), 6.970 (d, *J* = 8.8 Hz, 4 H), 3.849 (s, 6 H), 2.383 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.18, 155.25, 141.13, 133.38, 130.44, 128.43, 113.41, 55.26, 19.69.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}NO_2$: 320.1645; found: 320.1639.

2,6-Bis(4-chlorophenyl)-3,5-dimethylpyridine (4d)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **4d** (60% yield) as an off-white solid; mp 140–142 °C.

IR (KBr): 3392.09, 2953.38, 1453.95, 1093.12, 830.76, 766.94 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.510 (d, *J* = 8.4 Hz, 4 H), 7.468 (s, 1 H), 7.400 (d, *J* = 8.4 Hz, 4 H), 2.356 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.69, 141.41, 138.92, 133.84, 130.55, 129.40, 128.29, 19.54.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}Cl_2N$: 328.0654; found: 328.0646.

2,6-Bis(3-chlorophenyl)-3,5-dimethylpyridine (4e)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **4e** (56% yield) as an off-white solid; mp 97–99 °C.

IR (KBr): 3398.77, 2924.00, 1565.20, 1454.17, 1424.41, 1257.73, 1079.38, 887.55, 766.51, 704.65 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.554 (s, 2 H), 7.484 (s, 1 H), 7.423–7.448 (m, 2 H), 7.342–7.358 (m, 4 H), 2.361 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.53, 142.20, 141.38, 134.11, 129.73, 129.35, 129.32, 127.92, 127.33, 19.48.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}Cl_2N$: 328.0654; found: 328.0648.

3,5-Diethyl-2,6-diphenylpyridine (4f)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **4f** (50% yield) as a yellow solid; mp 136–138 °C.

IR (KBr): 3389.84, 2967.97, 1436.79, 776.50, 698.76 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.512–7.543 (m, 5 H), 7.385–7.422 (m, 4 H), 7.323–7.359 (m, 2 H), 2.675–2.732 (q, *J* = 7.6 Hz, 4 H), 1.175–1.213 (t, *J* = 7.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.61, 140.82, 137.41, 135.43, 129.12, 128.03, 127.54, 25.30, 15.24.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}N$: 288.1747; found: 288.1740.

2,3,5,6-Tetraphenylpyridine (4g)
Purified by flash chromatography (PE–EtOAc, 12:1) to give **4g** (55% yield) as a purple-red solid; mp 202–204 °C.

IR (KBr): 3392.47, 3059.22, 2924.63, 1419.99, 757.70, 699.56 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.763 (s, 1 H), 7.487–7.511 (m, 4 H), 7.246–7.279 (m, 16 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.31, 141.15, 139.96, 139.71, 134.29, 130.18, 129.56, 128.35, 127.80, 127.21.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{22}N$: 384.1747; found: 384.1749.

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References

(1) (a) Roth, H. J.; Kleemann, A. *Drug Synthesis in Pharmaceutical Chemistry*, Vol. 1; John Wiley and Sons: New York, **1988**. (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.

(2) (a) Kawamura, S.; Hamada, T.; Sato, R. *J. Agric. Food Chem.* **1991**, *39*, 2279. (b) Matolcsy, G. *Pesticide Chemistry*; Elsevier Scientific: Amsterdam, **1998**, 427–430.

(3) (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (b) Cabeza, J. A.; del Río, I.; Pérez-Carreño, E.; Sánchez-Vega, G. M.; Vázquez-García, D. *Angew. Chem. Int. Ed.* **2009**, *48*, 555.

(4) (a) Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed.* **1994**, *33*, 497. (b) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.

(5) (a) Vaz, A. D.; Coon, M. J.; Peegel, H.; Meenon, K. M. *Drug Metab. Dispos.* **1992**, *20*, 108. (b) Selvaraj, M.; Lee, T. G. *Microporous Mesoporous Mater.* **2005**, *85*, 52.

(6) (a) Bouras, A.; Boggetto, N.; Benatalah, Z.; de Rosny, E.; Sicsic, S.; Rebound-Ravaux, M. *J. Med. Chem.* **1999**, *42*, 957. (b) Matrunola, C. A.; Moody, C. J.; Robertson, A. A. B.; Warne, M. R. *Tetrahedron Lett.* **2003**, *44*, 1627.

(7) (a) Zhao, L. X.; Sherchan, J.; Park, J. K.; Jahng, Y.; Jeong, B. S.; Jeong, T. C.; Lee, C. S.; Lee, E. S. *Arch. Pharmacal. Res.* **2006**, *29*, 1091. (b) Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Jeong, B. S.; Jeong, T. C.; Lee, C. S.; Lee, E. S. *Bioorg. Med. Chem.* **2007**, *15*, 4351.

(8) (a) Yamada, S. *Coord. Chem. Rev.* **1999**, *190*, 537. (b) Kozhevnikov, V. N.; Kozhevnikov, D. N.; Nikitina, T. V.; Rusinov, V. L.; Chupakhin, O. L.; Zabel, M.; Konig, B. *J. Org. Chem.* **2003**, *68*, 2882.

(9) Lin, C.; Kagan, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 336.

(10) Soto, E.; MacDonald, J. C.; Cooper, C. G. F.; McGimpsey, W. G. *J. Am. Chem. Soc.* **2003**, *125*, 2838.

(11) (a) Sweetman, B. A.; Müller-Bunz, H.; Guiry, P. J. *Tetrahedron Lett.* **2005**, *46*, 4643. (b) Durola, F.; Sauvage, J. P.; Wenger, O. S. *Chem. Commun.* **2006**, 171.

(12) Recent review of de novo methods for pyridine synthesis: Henry, G. D. *Tetrahedron* **2004**, *60*, 6043.

(13) For selected recent examples on the transition-metal-catalyzed synthesis of substituted pyridines: (a) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030. (b) Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2007**, *9*, 505. (c) Kase, K.; Goswami, A.; Ohtaki, K.; Tanabe, E.; Saino, N.; Okamoto, S. *Org. Lett.* **2007**, *9*, 931. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645. (e) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325.

(14) For selected recent examples on the synthesis of substituted pyridines via multicomponent reactions: (a) Senaiar, R. S.; Young, D. D.; Deiter, A. *Chem. Commun.* **2006**, 1313. (b) Evdokimov, N.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006**, *8*, 899. (c) Dash, J.; Lechel, T.; Reissig, H.-U. *Org. Lett.* **2007**, *9*, 5541. (d) Ranu, B. C.; Jana, R.; Sowmiah, S. *J. Org. Chem.* **2007**, *72*, 3152. (e) Zhu, S.-L.; Ji, S.-J.; Su, X.-M.; Sun, C.; Liu, Y. *Tetrahedron Lett.* **2008**, *49*, 1777. (f) Sasada, T.; Sakai, N.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 6905.

(15) For selected recent examples on the synthesis of substituted pyridines via using ammonium acetate as the nitrogen source: (a) Ladouceur, G. H.; Cook, J. H.; Doherty, E. M.; Schoen, W. R.; MacDougall, M. L.; Livingston, J. N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 461. (b) Rodriguez, H.; Suarez, M.; Perez, R.; Petit, A.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 3709. (c) Bowman, M. D.; Jacobson, M. M.; Pujanauski, B. G.; Blackwell, H. E. *Tetrahedron* **2006**, *62*, 4715. (d) Liéby-Muller, F.; Allais, C.; Constantieux, T.; Rodriguez, J. *Chem. Commun.* **2008**, 4207.

(16) For selected recent examples on the synthesis of diarylpyridines via vapor-phase cyclization of acetophenone, formaldehyde and ammonia: (a) Ratnamala, A.; Subrahmanyam, M.; Kumari, V. D. *Appl. Catal., A* **2004**, *264*, 219. (b) Selvaraj, M.; Lee, T. G. *Microporous Mesoporous Mater.* **2005**, *85*, 52.

(17) For selected recent examples on the synthesis of diarylpyridines via arylation of the pyridine nucleus with organometallic reagents: (a) Munoz, B.; Chixu, C.; McDonald, I. A. *Biotechnol. Bioeng.* **2000**, *71*, 78. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (c) Handy, S. T.; Wilson, T.; Muth, A. *J. Org. Chem.* **2007**, *72*, 8496.

(18) For selected recent examples on the synthesis of diarylpyridines via palladium-catalyzed direct arylation of pyridine *N*-oxides: (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Andersson, H.; Almqvist, F.; Olsson, R. *Org. Lett.* **2007**, *9*, 1335. (c) Schipper, D. J.; El-Salfiti, M.; Whipp, C. J.; Fagnou, K. *Tetrahedron* **2009**, *65*, 4977.

(19) Eliel, E. L.; McBride, R. T.; Kaufmann, S. t. *J. Am. Chem. Soc.* **1953**, *75*, 4291.

(20) (a) Engler, C.; Heine, H. *Ber. Dtsch. Chem. Ges.* **1873**, *6*, 638. (b) Reihm, P. *Justus Liebigs Ann. Chem.* **1887**, *238*, 1. (c) Elderfield, R. C.; King, T. P. *J. Am. Chem. Soc.* **1954**, *76*, 5437. (d) Sargent, L. J. *J. Org. Chem.* **1956**, *21*, 1286. (e) Adib, M.; Tahermansouri, H.; Koloogani, S. A.; Mohammadi, B.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 5957. (f) Wang, L. F.; Zhang, H. Y.; Kong, L.; Chen, Z. W.; Shi, J. G. *Helv. Chim. Acta* **2004**, *87*, 1515.