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Disubstituted Pyridines: The Double-Coupling Approach

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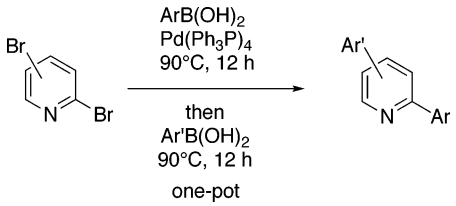


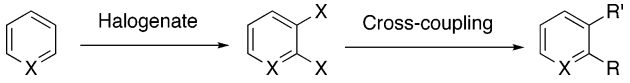
A one-pot procedure leading to disubstituted pyridines from the starting dibromopyridines is described. Key features include the ability to couple a range of aryl and even alkenylboronic acids at the 2,3 and/or 2,5 positions with excellent regiocontrol under a standard set of conditions. Further, isolated yields are greatly improved by the use of neutral alumina in place of silica for product purification. Finally, the intrinsic electronic bias of the pyridine ring can be overcome by using a bromoiodopyridine.

Introduction

Heteroaromatics are found at the core of a wide variety of interesting organic molecules, ranging from pharmaceutical agents (such as Lipitor and Celebrex) to OLED materials.[1] In many cases, these compounds are prepared via a range of classic condensation reactions (such as the Paal−Knorr synthesis of pyrroles).[2] Although clearly effective, such approaches are not always well suited for the preparation of numerous derivatives, particularly if unusual substitution patterns or functional groups are required. In this respect, cross-coupling reactions can be much more efficient, since the haloheteroaromatic is frequently a known compound and then, from this simple starting material, an increasingly wide range of alkyl, alkenyl, alkynyl, aryl, and even heteroatom substituents can be installed.[3]

Despite this apparent advantage, the cross-coupling approach can prove to be rather lengthy if multiple substituents are to be installed as it requires both a halogenation and a coupling step for each substituent. If one wishes to create a shorter, more convergent, yet highly flexible cross-coupling approach, then the obvious solution is to employ polycouplings of polyhaloheteroaromatics (Scheme 1). Such an approach does require three questions to be addressed: (1) can all of the halogens can be installed in one step, (2) can each halogen be regioselectively coupled, and (3) can multiple couplings be performed in the same reaction flask?

SCHEME 1. General Polycoupling Approach



In examining these three requirements, it is clear that multiple halogens can be installed in a single reaction as many polyhaloheteroaromatics have been reported in the literature and many others are commercially available. For the second requirement, recent reports have noted that regioselective couplings are generally achievable for a wide range of polyhaloheteroaromatics and that such regioselectivity is predictable.[4,5] Where the evidence is less clear is in the area of performing multiple cross-couplings in the same reaction flask. Indeed, there are only a handful of reports of such reactions on polyhaloheteroaromatics,[6−8] the most recent being our report of regioselective double-couplings of dibromopyrrole aldehydes.[9]

As a result of our success with dibromopyrrole aldehydes, we were interested in examining the application of similar

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conditions to other dibromoheteroaromatics. In this paper, we report our results on the double-coupling of dibromopyridines.

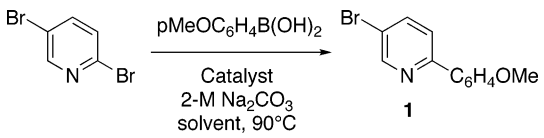
Results and /Discussion

Since 2,5-dibromopyridine is a readily available material, there have been a number of reports of regioselective cross-couplings of this compound. Thus, regioselective aminations,[10] Stille couplings,[11] Suzuki couplings,[12] Negishi couplings,[13] Sonogashira couplings,[14] and even Kumada-type couplings have appeared in the literature.[15] In every case, coupling was determined to occur first at the more electron-deficient C2 position. In most cases, only this first coupling was performed, although in a few cases, a second coupling was then carried out at the C5 position after isolation and purification of the C2-coupled product.[14]

Although the regioselectivity of the coupling of this compound is clearly established, the ability to perform a second coupling, particularly in a one-pot fashion, remained to be demonstrated. To that end, 2,5-dibromopyridine was subjected to a Suzuki coupling with p-methoxyphenylboronic acid using aqueous sodium carbonate as the base. Several different palladium catalysts were examined, as were two variations in solvent (Table 1). This modest screening identified tetrakis-(triphenylphosphine)palladium(0) in a 3:1 mixture of toluene and ethanol as the most promising reaction conditions, affording monocoupled product **1** in a modest 46% yield.

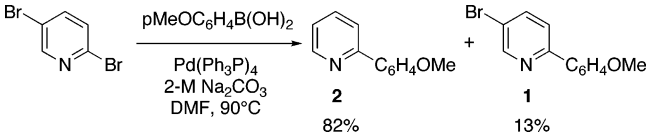
Interestingly, in the case of reactions using DMF as the solvent, the major product with phosphine-ligated palladium catalysts was not coupling product **1**, but rather the dehalogenated coupling product **2** (Scheme 2). Conveniently, this byproduct enabled us to confirm the expected regiochemistry of these couplings, since a comparison of the ^{1}H NMR spectrum of **2** with that reported in the literature showed that the two were identical.[16] The mechanism of this dehalogenation remains unclear. Initially it was felt that the DMF might be serving as a source of sodium formate via hydrolysis under the basic conditions. This formate could then serve as a hydrogen source for transfer hydrogenation of the second bromide. However, studies with DMF-d_7 revealed no deuterium incorporation and still resulted in product **2**, rendering this mechanistic pathway unlikely.[17]

TABLE 1. Coupling Conditions Studies

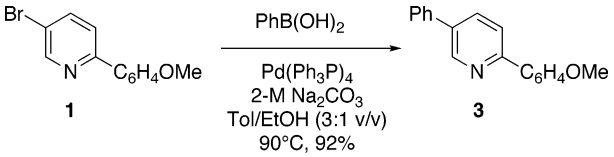


entry	catalyst	solvent	% yield
1	$Pd(Ph_3P)_4$	toluene/EtOH (3:1 v/v)	46
2	$Pd(OAc)_2$	toluene/EtOH (3:1 v/v)	17
3	$Pd(OAc)_2/tBu_3P$	toluene/EtOH (3:1 v/v)	13
4	$Pd(Ph_3P)_4$	DMF	13
5	$Pd(OAc)_2$	DMF	5
6	$Pd(OAc)_2/tBu_3P$	DMF	12

SCHEME 2. Dehalogenation in the Coupling of 2,5-Dibromopyridine



SCHEME 3. Coupling of 2-Aryl-5-bromopyridine



With the first coupling in hand, the next question was what conditions would be required for the second coupling. It was expected that somewhat more forcing conditions would be required due to the fact that the C5 position significantly less electron deficient than the C2 position. Fortunately, a second brief survey of reaction conditions noted that the same solvent and catalyst system were effective for this second coupling, affording product **3** in 92% yield, although using DMF as the solvent was almost equally effective (89% isolated yield of **3**) and interestingly did not result in any detectible dehalogenation (Scheme 3).

With coupling conditions in hand, the stage was set for the one-pot double-coupling reaction of 2,5-dibromopyridine (Table 2). Much to our delight, this reaction did afford product **3** in 70% yield (compared to a 41% yield over the two couplings if the intermediate monocoupled product was isolated prior to the second coupling). Of equal importance was the observation that these same reaction conditions proved effective for electron-

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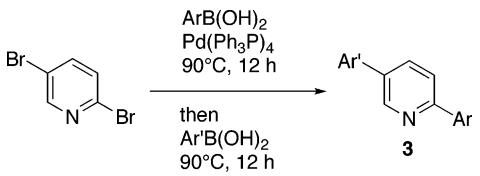
(17) More recent work on the regioselective Suzuki coupling of 4,5-dibromothiophene-2-carboxaldehyde also exhibits this same dehalogenation after initial coupling at C5 when DMF is employed as the solvent. It should also be noted that no dehalogenation is observed in either the thiophene or pyridine series in DMF in the absence of a boronic acid.

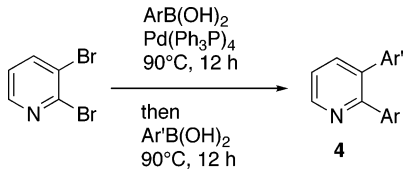
TABLE 2. Double-Couplings of 2,5-Dibromopyridine



entry[a]	Ar	Ar′	yield[b] (%)
1	$pMeOC_6H_4$	Ph	70 (87)
2	Ph	$pMeOC_6H_4$	45 (68)
3	pFC_6H_4	Ph	34
4	$pMeOC_6H_4$	heptenyl	42 (61)
5	heptenyl	$pAcC_6H_4$	46
6	$pMeOC_6H_4$	$pAcOC_6H_4$	33 (54)
7	Ph	heptenyl	44
8	Ph	$pAcOC_6H_4$	40

[a] Base = 2-M Na_2CO_3, solvent =toluene/EtOH (3:1 v/v). [b] Isolated yield. Value in parentheses is for isolation using neutral alumina.

TABLE 3. Double-Couplings of 2,3-Dibromopyridine



entry[a]	Ar	Ar′	yield[b] (%)
1	$pMeOC_6H_4$	Ph	(86)
2	Ph	$pMeOC_6H_4$	(72)
3	Ph	Heptenyl	58
4	$pMeOC_6H_4$	$pAcC_6H_4$	43 (78)
5	$3,4,5\text{-}TriMeOC_6H_4$	$3\text{-}MeO\text{-}4\text{-}iPrOC_6H_4$	28

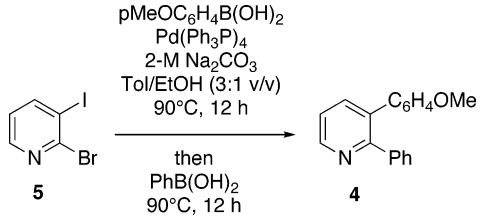
[a] Base = 2-M Na_2CO_3, solvent =toluene/EtOH (3:1 v/v). [b] Isolated yield. Value in parentheses is for isolation using neutral alumina.

rich and electron-deficient aryl rings and even for an alkenyl boronic acid (Table 2, entries 4 and 5).

One troubling aspect was the fairly modest isolated yields of these reactions. By TLC, these double couplings were relatively clean, so it was expected that the yield of the desired product should be much higher. Assuming that to be true, then the isolation of the products must be the problem. After some consideration, it was felt that much of the product might be being lost on the silica used for the column chromatography. To test this hypothesis, representative reactions were purified using neutral alumina for the column chromatography. Much to our delight, the isolated yields did increase dramatically (typically around 20%).

Given the general electronic similarities of the 3 and 5 positions of pyridine, it was hoped that the same set of reaction conditions could be directly translated to the double coupling of 2,3-dibromopyridine. Gratifyingly, they did, with the double coupling with *p*-methoxyphenylboronic acid and then phenylboronic acid affording the desired product **4** in an excellent 86% yield. Other boronic acid pairs worked as well and, again, switching to neutral alumina for purification significantly improved the isolated yields (Table 3, entry 4). The regiochemistry of the first coupling was proven by stopping the reaction after the first coupling and then removing the second bromine using catalytic hydrogenation. The resulting product exhibited spectral properties identical to that reported for 2-(4′-methoxyphenyl)pyridine.[16]

SCHEME 4. Double-Coupling of 2-Bromo-3-iodopyridine



Although the intrinsic regioselectivity of the pyridine ring system is well established, we were intrigued by the potential to reverse this bias. In particular, a report by Deng that the Kumada-type coupling of 2-bromo-4-iodopyridine affords the product of initial coupling at C4 raised the possibility that such a method might be general.[6] To this end, 2-bromo-3-iodopyridine **5** was prepared according to the literature method.[6] Suzuki coupling of pyridine **5** with *p*-methoxyphenylboronic acid and then phenylboronic acid under our standard conditions afforded a material **4** that was identical with that synthesized from the same two boronic acids (in reverse order) and 2,3-dibromopyridine (Table 3, entry 2 and Scheme 4). Clearly, this supports the idea that the greater reactivity of the iodo group is capable of overcoming the intrinsic electronic bias of a heteroaromatic ring system. This feature is expected to be of general potential use in these dihalocoupling reactions.

In conclusion, we have developed conditions for the regioselective, one-pot, double-coupling of dibromopyridines. These reactions proceed with a high degree of regioselectivity and reasonable-to-good overall yield. The use of an iodo group enables the intrinsic regioselectivity of the dibromo systems to be overcome, as evidenced by the coupling of compound **5**. The double-coupling conditions should prove to be of considerable use in the synthesis of a wide range of substituted pyridines and may be applicable to the triple-coupling of tribromopyridines. This extension is currently under investigation and its results will be reported in due course.

Experimental Section

General Procedure for the Coupling Reactions. To a solution of 0.100 g (0.422 mmol) of 2,5-dibromopyridine in 9 mL of toluene and 3 mL of EtOH was added 0.076 g (0.506 mmol) of 4-methoxyphenylboronic acid, followed by 2 mL of 2 M Na_2CO_3 and 0.0243 g (0.021 mmol) of tetrakis(triphenylphosphine)palladium(0). The reaction was stirred for 12 h at 90 °C under argon. After 12 h, 0.0830 g (0.50619 mmol) of 4-acetylphenylboronic acid and 2 mL of 2 M Na_2CO_3 was added, and the reaction was left to stir for another 12 h at 90 °C under argon. After completion, the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The resulting organic layer was dried with $MgSO_4$, filtered, and concentrated in vacuo to afford a solid. The solid was purified via flash chromatography using either silica (Natlund International, 230−400 mesh) or activated neutral alumina (Aldrich, Brockmann 1, 150 mesh) and the solvent systems indicated for each compound.

2-(4′-Methoxyphenyl)-5-phenylpyridine (Table 2, Entry 1). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0771 g (70%) of the product as a white solid: mp = 210−211 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (d, J = 2.3 Hz, 1H), 8.00 (d, J = 6.8 Hz, 2H), 7.92 (dd, J = 2.3, 8.6 Hz, 1H), 7.74 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 7.4 (Hz, 2H), 7.49 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 6.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 148.0, 137.8, 135.1, 131.7, 129.8, 128.2, 128.0, 127.8, 127.0, 123.4, 119.7, 114.3, 55.5; IR (neat) 3009, 2931, 2856, 1604, 1502, 1469, 1439, 1371, 1229,

834, 777, 700 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{15}NO$ 261.1154, found 261.1153.

5-(4′-Methoxyphenyl)-2-phenylpyridine (Table 2, Entry 2). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0496 g (45%) of the product as white crystals: mp = 205−207 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.90 (d, J = 2.2 Hz, 1H), 8.41 (d, J = 6.9 Hz, 2H), 7.91 (dd, J = 2.2, 8.6 Hz, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 7.0 Hz, 2H), 7.49 (t, 2H), 7.43 (t, 1H), 7.03 (d, J = 6.9 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 155.7, 147.8, 139.2, 134.6, 130.1, 129.0, 128.9, 128.2, 127.3, 126.8, 120.4, 114.7, 55.4; IR (neat) 3004, 2930, 2855, 1614, 1522, 1470, 1435, 1371, 1231, 836, 777, 705 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{15}NO$ 261.1154, found 261.1153.

2-(4′-Fluorophenyl)-5-phenylpyridine (Table 2, Entry 3). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0357 g (34%) of the product as a tan solid: mp = 167−168 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.86 (d, J = 2.2 Hz, 1H), 8.03 (dd, J = 6.9, 9.0 Hz, 2H), 7.91 (dd, J = 2.2, 8.6 Hz, 1H), 7.78−7.68 (m, 2H), 7.59 (dd, J = 7.0, 9.0 Hz, 2H), 7.52−7.41 (m, 2H), 7.18 (dt, J = 6.4, 9.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 147.9, 135.0, 133.9, 133.7, 132.2 (d, J = 26 Hz), 131.5, 128.5 (d, J = 3.4 Hz), 128.6, 128.4, 120.0, 116.1 (d, J = 149 Hz), 115.7 (d, J = 63 Hz); IR (neat) 3004, 2930, 2855, 1614, 1522, 1470, 1435, 1371, 1231, 836, 777, 705 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{12}FN$ 249.0954, found 249.0955.

5-Heptenyl-2-(4′-methoxyphenyl)pyridine (Table 2, Entry 4). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0477 g (42%) of the product as a tan solid: mp = 136−138 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, J = 1.7 Hz, 1H), 7.94 (d, J = 7.2 Hz, 2H), 7.70 (dd, J = 1.7, 8.6 Hz, 1H), 7.59 (d, J = 8.6 Hz, 1H), 6.99 (d, J = 7.2 Hz, 2H), 6.40−6.29 (m, 2H), 3.85 (s, 3H), 2.23 (q, 2H), 1.49−1.46 (m, 2H), 1.35−1.32 (m, 4H), 0.91 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 155.3, 147.8, 133.1, 133.0, 132.0, 131.3, 128.0, 126.2, 119.5, 114.2, 55.4, 33.3, 31.6, 29.0, 22.7, 14.2; IR (neat) 2924, 2852, 1604, 1465, 1361, 1187, 962, 815 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{23}NO$ 281.1780, found 281.1782.

5-(4′-Acetylphenyl)-2-heptenylpyridine (Table 2, Entry 5). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0546 g (46%) of the product as a yellow solid: mp = 87−88 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, J = 2.3 Hz, 1H), 8.06 (d, J = 7.1 Hz, 2H), 7.85 (dd, J = 2.3, 8.4 Hz, 1H), 7.68 (d, J = 7.1 Hz, 2H), 7.35 (d, J = 8.4 Hz, 1H), 6.81 (dt, J = 6.9, 15.4 Hz, 1H), 6.54 (d, J = 15.4 Hz, 1H), 2.66 (s, 3H), 2.29 (q, 2H), 1.55−1.50 (m, 2H), 1.37−1.33 (m, 4H), 0.92 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 155.9, 147.9, 142.5, 137.2, 136.3, 134.9, 133.1, 129.4, 129.2, 129.1, 127.5, 127.0, 121.0, 33.0, 31.6, 28.7, 26.8, 22.6, 14.1; IR (neat) 2924, 2854, 1732, 1700, 1604, 1465, 1361, 125, 1187, 962, 818 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{23}NO$ 293.1778, found 293.1776.

5-(4′-Acetylphenyl)-2-(4′-methoxyphenyl)pyridine (Table 2, Entry 6). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0424 g (33%) of the product as a tan solid: mp = 112−114 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 6.3 Hz, 2H), 7.96 (d, J = 6.3 Hz, 2H), 7.72 (d, J = 6.8 Hz, 2H), 7.69 (d, J = 8.6 Hz, 1H), 7.18 (dd, J = 2.0, 8.6 Hz, 1H), 7.01 (d, J = 6.8 Hz, 2H), 3.86 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 149.6, 136.8, 136.6, 129.1, 129.0, 129.0, 128.2, 127.5, 127.4, 127.3, 121.5, 119.9, 114.2, 55.4, 29.8; IR (neat) 2924, 2853, 1732, 1681, 1466, 1435, 1270, 1240, 1177, 828, 781, 734 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{17}NO_2$ 303.1260, found 303.1259.

5-Heptenyl-2-phenylpyridine (Table 2, Entry 7). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0490 g (44%) of the product as a yellow solid: mp = 116−117 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J = 2.1 Hz, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.70 (dd, J = 2.1, 7.1 Hz, 1H), 7.65 (d, J = 7.1 Hz, 1H), 7.50−7.38 (m, 3H), 6.41−6.33 (m, 2H), 2.25 (q, 2H), 1.55−1.50 (m, 2H), 1.37−1.33 (m, 4H), 0.92 (t, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.6, 150.0, 139.3, 133.6, 133.2, 132.0, 128.8, 128.7, 126.8, 126.1, 120.2, 33.3, 31.6, 29.0, 22.6, 14.2; IR (neat) 2924, 1604, 1465, 1361, 1250, 1187, 962, 805 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{21}N$ 251.1674, found 251.1673.

2-Phenyl-5-(4′-acetyl)pyridine (Table 2, Entry 8). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0461 g (40%) of the product as a tan solid: mp = 110−112 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, J = 2.3 Hz, 1H), 8.05 (d, J = 6.3 Hz, 2H), 7.96 (dd, J = 2.3, 6.7 Hz, 1H), 7.81 (d, J = 6.7 Hz, 1H), 7.65 (d, J = 6.3 Hz, 2H), 7.50−7.40 (m, 5H), 2.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 156.3, 148. 2, 139.1, 137.7, 135.2, 129.2, 129.1, 128.9, 128.1, 127.1, 126.9, 120.5, 29.8; IR (neat) 2924, 2853, 1732, 1681, 1466, 1435, 1173, 828, 779, 720 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{15}NO$ 273.1154, found 273.1157.

2-(4′-Methoxyphenyl)-3-phenylpyridine (Table 3, Entry 1). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0943 g (86%) of the product as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 4.5 Hz, 1H), 7.69 (d, J = 6.2 Hz, 1H), 7.35−7.15 (m, 8H), 6.77 (d, J = 6.8 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 156.6, 148.0, 140.4, 139.6, 135.8, 132.9, 131.7, 129.8, 128.1, 127.7, 121.9, 113.3, 55.4; IR (neat) 2835, 1607, 1513, 1418, 1246, 1175, 1024, 835, 781, 758, 699 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{15}NO$ 261.1154, found 261.1152.

3-(4′-Methoxyphenyl)-2-phenylpyridine (Table 3, Entry 2). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0793 g (72%) of the product as a red oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, J = 4.5 Hz, 1H), 7.69 (d, J = 6.2 Hz, 1H), 7.32−7.15 (m, 8H), 6.76 (d, J = 6.8 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 156.3, 148.4, 140.3, 138.6, 135.8, 132.7, 131.3, 129.6, 128.5, 127.2, 121.7, 113.4, 55.3; IR (neat) 2970, 1539, 1456, 1365, 1225, 799, 679 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{15}NO$ 261.1154, found 261.1155.

3-Heptenyl-2-phenylpyridine (Table 3, Entry 3). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0614 g (58%) of the product as a brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 4.5 Hz, 1H), 7.74 (d, J = 6.2 Hz, 1H), 7.47 (d, J = 6.8 Hz, 2H), 7.12 (dd, J = 4.5, 6.2 Hz, 1H), 6.90 (d, J = 6.8 Hz, 2H), 6.35 (d, J = 15.4 Hz, 1H), 6.10 (dt, J = 7.0, 15.4 Hz, 1H), 3.70 (s, 3H), 2.18−2.12 (m, 2H), 1.44−1.36 (m, 4H), 0.82 (t, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 136.7, 134.2, 131.8, 131.1, 130.8, 121.8, 121.4, 116.1, 114.6, 113.8, 55.3, 33.0, 31.1, 29.7, 27.9, 14.1; IR (neat) 2930, 2871, 1683, 1607, 1433, 1176, 1277, 1110, 832, 783 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{21}N$ 251.1674, found 251.1671.

3-(4′-Acetylphenyl)-2-(4′-methoxyphenyl)pyridine (Table 3, Entry 4). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0997 g (78%) of the product as a tan solid: mp = 162−164 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.69 (dd, J = 2.8, 4.5 Hz, 1H), 7.88 (d, J = 6.5 Hz, 2H), 7.69 (dd, J = 2.8, 6.2 Hz, 1H), 7.34−7.25 (m, 5H), 6.76 (d, J = 6.8 Hz, 2H), 3.78 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 159.9, 156.5, 149.0, 145.4, 138.4, 135.8, 134.8, 132.2, 131.3, 129.8, 128.5, 121.8, 113.6, 55.3, 26.7; IR (neat) 2930, 2871, 1724, 1683, 1433, 1176, 1277, 1111, 837, 783, 713 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{17}NO_2$ 303.1260, found 303.1259.

3-(3′-Isopropoxy-4′-methoxyphenyl)-2-(3′,4′,5′-trimethoxyphenyl)pyridine (Table 3, Entry 5). EtOAc (10%) in hexanes was used as the chromatography solvent to afford 0.0483 g (28%) of the product as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (dd, J = 2.8, 4.5 Hz, 1H), 7.77 (dd, J = 2.8, 6.2 Hz, 1H), 7.32 (dd, J = 4.5, 6.2 Hz, 1H), 7.23 (s, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.62 (s, 2H), 4.50 (heptet, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.69 (s, 6H), 1.35 (d, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 153.3, 152.8, 148.4, 138.3, 136.0, 135.6, 135.3, 122.2, 121.7, 115.8, 113.8, 107.3, 106.9, 104.2, 61.1, 61.0, 56.3, 56.0, 22.1; IR (neat) 2928, 1585, 1507, 1462, 1406, 1342, 1238, 1123,

1004, 784, 681 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{27}NO_5$ 409.1889, found 409.1892.

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Supporting Information Available: Spectra (^1H and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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