Diversification of 6-bromo-2-substituted Pyridine Derivatives *via* Suzuki-Miyaura Cross-Coupling

Abigail E. Lambert and Jesse D. Carrick*

Department of Chemistry, Tennessee Technological University, 55 University Drive, Cookeville, TN 38505-0001, USA
*E-mail: jcarrick@tntech.edu

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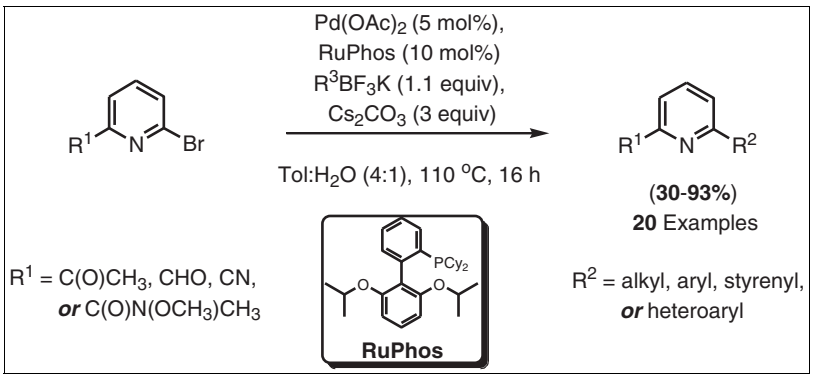
The authors dedicate this work in memory of TTU Professor Emeritus Scott H. Northrup (1951-2018)



The functionalized pyridine ring is a ubiquitous moiety in numerous research areas including materials, natural products, as well as agrochemicals and is a strategic synthon for heteroaromatic synthetic method development. Pyridinyl ligand scaffolds are also frequently incorporated into the study of metal complexes for pharmaceutical applications or separation science. Convergent access to advanced synthons is critical to experimentally defining structure activity relationships and improvement of molecular performance in the aforementioned areas. The current work describes an efficient catalyst/ligand combination for accessing 2-acetyl- and 2-procarbonyl substituted pyridines *via* Suzuki-Miyaura cross-coupling with various organotrifluoroborates. Twenty examples are described with carbonyl and procarbonyl functional groups which afford subsequent access to diversified unsymmetric ketones. Substrate scope and limitation in addition to a scale up experiment are reported.

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INTRODUCTION

Functionalized pyridines are an important class of synthons for the development of active pharmaceutical ingredients [1], natural products [2], complexant scaffolds for separations [3], as well as pyridinyl thiosemicarbazones (PTSCs) and related metal complexes. PTSCs have demonstrated efficacy against several areas of unmet clinical need including potential antibacterial and anticancer chemotherapeutics [4] *via* suspected generation of redox-active Fe complexes *in vivo* [5]. Selective, convergent methods for the reliable construction of advanced ligand scaffolds and metal–ligand candidates for structure–activity relationships and subsequent lead optimization is predicated on rapid access to diversified structures. Metal-mediated coupling of halo pyridines, especially with the oxidative addition site adjacent to the heteroatom, is a traditionally challenging synthetic transformation. Contemporary approaches by Burke [6], Yamamoto [7], and others [8] have advanced this important area of research by incorporating the use of functionalized pyridinyl reagents as nucleophiles for coupling with various aryl and heteroaryl halide electrophiles. In the current work, the polarities of the participating reagents are orthogonal to the aforementioned as organotrifluoroborates [9] were used as the transmetallating reagent with the substrate 2-acetyl-6-bromopyridine and other procarbonyl derivatives towards future construction of PTSCs. Recently we described an efficient approach to the synthesis of soft-Lewis basic heteroaromatic complexant scaffolds with potential applications in separation science by employing a Suzuki-Miyaura cross-coupling [10] strategy with $Pd(OAc)_2$, the dialkylbiaryl phosphine ligand RuPhos, [11] and various sp^2 and sp^3 hybridized potassium organotrifluoroborates [12] with numerous functionalized 6-bromo-2-pyridinyl-[1,2,4]-triazinyl substrates. We were interested in validating the scope of the described method for the current substrates amenable to forming various PTSCs and related metal complexes. PTSC-metal complexes can be accessed in a straightforward manner *via* condensation with an appropriate thiosemicarbazide followed by complexation with an appropriate metal. With the aforementioned goals in mind, we set out to assess the efficacy of this

transformation for the production of 2-carbonyl derivatives of 6-bromopyridine. Method validation, initial and expanded substrate scope with respect to functional groups amenable to carbonyl formation with various organotrifluoroborates, current substrate structural limitations, and a scale-up experiment are described herein.

RESULTS AND DISCUSSION

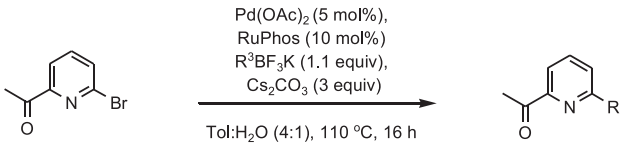
The Suzuki-Miyaura cross-coupling reaction presents strategic advantages for diversification of carbonyl substituted heteroaromatic scaffolds without the inherent risk for simple addition to the carbonyl moiety as an unwanted side reaction during the transformation. Diverse options for catalyst/ligand combinations, transmetallating reagents, mild reaction conditions, in addition to numerous commercially available materials render this transformation significant for substrate functionalization. Conversely, the use of organomagnesium reagents in the context of the Kumada coupling with pyridinyl ketones can present potential difficulties including unwanted addition to the pyridine ring or resident carbonyl functionality [13]. The preliminary substrate scope definition with organotrifluoroborates in the context of the initial substrate 6-bromo-2-acetylpyridine is delineated below in Table 1. A variety of alkyl, aryl, and heteroaryl organotrifluoroborates were attempted. Simple alkyl coupling reagents such as potassium butyl (entry 1) and potassium 3,3-dimethylbutyltrifluoroborate (entry 2) proved competent for the described transformation affording the desired products **1** and **2** in 81 and 77% isolated, purified yield, respectively. Derivatization using the phenethyl reagent was also successful (entry 3) [14]. Exploration of phenyl (entry 4) [15] and substituted aryl coupling reagents (entries 5–7) were also possible with inductive (entry 5) [16] and resonance donating effects (entries 6–7) [17] of substituents providing little difference in observed yields. Potassium vinyl trifluoroborates with a phenyl (entry 8) and saturated cyclohexyl (entry 9) ring were possible, although obtained in a lower overall yield for products **8** and **9** [18] relative to the direct aryl coupling examples described previously. The pseudo sp^2 hybridization of the cyclopropyl coupling reagent frequently presents challenges [19] for Suzuki-Miyaura cross-coupling and entry 10 was no exception [20]. Heteroaryl coupling reagents leading to the production of **11** and **12** afforded the desired products. Entry 11 presents a challenging metal-mediated coupling with the requisite oxidative addition taking place at the 2-position relative to the heteroatom on the pyridinyl scaffold in addition to the transmetallating coupling partner also residing at the 2-position of the thiophene. Entry 13 with potassium catechol trifluoroborate rounded out the successful examples executed with product **13** afforded in a similar yield (77%) to the other aromatic examples (entries 4–7). With a thorough preliminary nucleophile screening for the desired scaffold completed we set out to investigate the feasibility of functional group interconversion with other carbonyl derivative substrates and various potassium organotrifluoroborates.

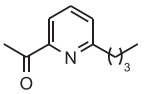
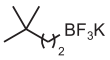
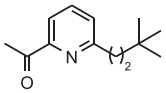
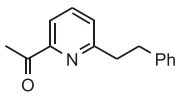
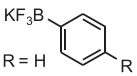
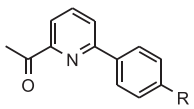
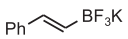
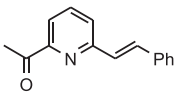
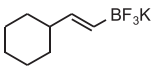
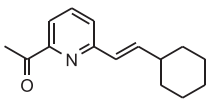
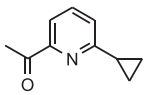
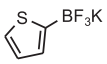
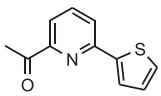
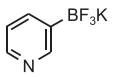
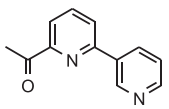
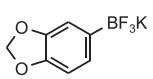
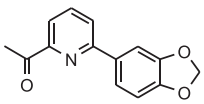
Table 2 highlights coupling examples involving 2-cyano, 2-formyl, and 2-carboxylic acid methoxy-methyl-amide-6-bromopyridine. Entries (1 and 7) employing 6-bromopyridine-2-carbonitrile afforded the desired coupling products with heteroaromatic and homologous aromatic transmetallating reagents thereby demonstrating aptitude for the reaction conditions utilized. Entry 2 with the 2-formyl substituent describes a difficult substrate with potential for oxidative degradation and/or dative bidentate chelation to the putative catalyst/ligand system leading to deleterious reaction outcomes. The aforementioned were not observed in the case of product **15** which was afforded in 93% yield. The Weinreb [21] (entries 3 and 6) and related morpholine amides present numerous opportunities for diversification through the simple addition of hard nucleophiles post Suzuki-Miyaura cross-coupling and were defined in the context of the present work. In order to facilitate acquisition of the desired pyridinyl Weinreb amide coupling products synthesis of the starting material was required. Thus, treatment of 6-bromo-pyridine-2-carboxylic acid with the requisite Weinreb imidazole carbamate (WImC) *via* a one pot process by the Heller-Sarpong procedures [22] afforded the desired amidation product in 67% average yield over two steps. Treatment of 2-carboxylic acid methoxy-methyl-amide-6-bromo pyridine with an electron-rich direct connect aryl coupling reagent (entry 3) or a styrenyl derivative (entry 6) afforded the desired coupling products **16** and **19** in 30% in the case of the former and 70% in the case of the latter [23]. The procarbonyl cyano group also proved to be a competent substrate for the investigated conditions leading to the production of the phenyl (entry 4) [24] and 4-*tert*-butylphenyl derivative (entry 5). Three additional substrates including: 6-bromo-pyridine-2-carboxylic acid, 6-bromo-pyridine-2-carbaldehyde oxime [25], and 1-(6-bromo-pyridin-2-yl)-ethanone oxime proved obstinate with the current conditions resulting in incomplete conversion of starting material and/or the provision of complex product mixtures. To validate the applicability of the described transformation for processes which supersede development scale, a scale-up reaction was performed using a previously successful experiment (Table 1) as an initial guide (Scheme 1).

Treatment of 6-bromo-2-acetylpyridine with potassium phenyltrifluoroborate on 2.5 mmol scale, which

Table 1

Suzuki-Miyaura cross-coupling of 6-bromo-2-acetylpyridine with various organ otrifluoroborates.

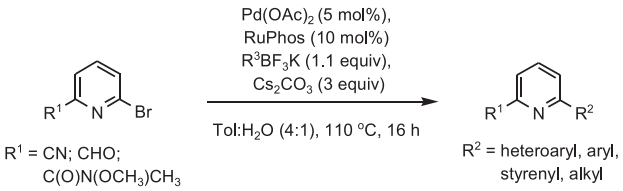


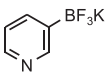
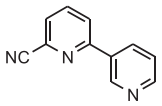
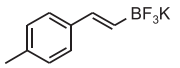
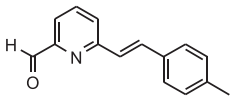
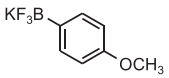
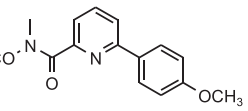
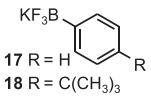
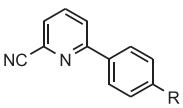
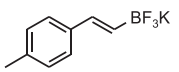
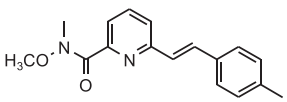
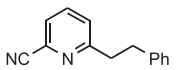
Entry	RBF_3K	Product	Yield[a]
1	$CH_3(CH_2)_3BF_3K$		**1** (81)
2			**2** (77)
3	$PhCH_2CH_2BF_3K$		**3** (72)
4 5 6 7	 **4** R = H **5** R = $C(CH_3)_3$ **6** R = OCH_3 **7** R = $N(CH_3)_2$		**4** (76) **5** (70) **6** (72) **7** (63)
8			**8** (61)
9			**9** (59)
10			**10** (50)
11			**11** (30)
12			**12** (93)
13			**13** (77)

[a] Isolated, purified yield over one synthetic step.

Table 2

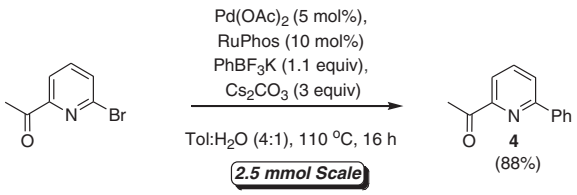
Suzuki-Miyaura cross-coupling of 6-bromo-pyridinyl procarbonyl synthons with varous organotriflu oroborates.



Entry	RBF_3K	Product	Yield[a]
1			**14** (41)
2			**15** (93)
3			**16** (30)[d]
4 5			**17** (74) **18** (68)
6			**19** (70)[c]
7	$PhCH_2CH_2BF_3K$		**20** (67)[b]

[a] Isolated, purified yield over one synthetic step, [b] Average yield from 2 experiments
[c] Product purified on neutral alumina. Purification of a previous discrete reaction on normal phase silica gel afforded the product in 22% isolated yield. [d] 30% yield afforded with normal phase silica gel purification.

Scheme 1. Suzuki-Miyaura coupling of 6-bromo-2-acetylpyridine scale-up experiment.



represented a five-fold increase in substrate concentration, afforded the desired product in increased yield to the development-scale transformation.

CONCLUSIONS

In summary, we have demonstrated a practical transformation for the acquisition of various functionalized 2-acetyl- and 2-procarbonylpyridinyl derivatives through Suzuki-Miyaura cross-coupling utilizing $Pd(OAc)_2$ and RuPhos as an efficient catalyst/ligand combination highlighted by 15 examples (9 novel) not previously disseminated in the primary literature in (30–93%) isolated yield. The transformation provides a coherent strategy for rapid diversification of electrophilic scaffolds with alkyl, aryl, and heteroaromatic coupling reagents towards synthon or library development. Compounds **14**; **16**–**20** afford

opportunities to potentially access any unsymmetric ketone derivative through use of an appropriate alkyl lithium or Grignard reagent and provide further guidance on dative Lewis basic functionality tolerance in metal-mediated coupling experiments.

EXPERIMENTAL

General. All reagents were purchased from U.S. chemical suppliers, stored according to published protocols, and used as received unless indicated otherwise. All experiments were performed in oven- or flame-dried glassware under an inert atmosphere of Ar except where indicated. Reaction progress was monitored using thin-layer chromatography on glass-backed silica gel plates and/or ^{1}H NMR analysis of crude reaction mixtures. R_F values for compounds that resulted in a concentrically observed spot on normal phase silica gel are reported using the conditions listed. All reported yields listed are for pure compounds and corrected for residual solvent, if applicable, from ^{1}H NMR spectroscopy unless otherwise indicated. Infrared spectral data was acquired from the (form) listed. All ^{1}H and ^{13}C NMR chemical shifts are reported using the δ scale and are referenced to the residual solvent signal: $CDCl_3$ (δ 7.26) for ^{1}H–NMR and chloroform (δ 77.16) for ^{13}C–NMR. Splittings are reported as follows: (s) = singlet, (d) = doublet, (t) = triplet, (dd) = doublet of doublets, (dt) = doublet of triplets, (br) = broad, and (m) = multiplet. High resolution mass spectrometry (HRMS) data was obtained utilizing electron impact ionization (EI) with a magnetic sector (EBE trisector), double focusing-geometry mass analyzer unless indicated otherwise.

1-(6-Butyl-pyridin-2-yl)-ethanone (1). R_F = 0.69, 10% MTBE:hexanes; MTBE/hexanes (gradient); yellow oil; isolated yield 0.075 g, 81%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (dd, J = 7.8, 1.0 Hz, 1H, Ar-H), 7.70 (t, J = 7.8 Hz, 1H, Ar-H), 7.29 (dd, J = 7.8, 1.0 Hz, 1H, Ar-H), 2.86–2.83 (m, 2H, CH_2), 2.71 (s, 3H, CH_3), 1.79–1.72 (m, 2H, CH_2), 1.40 (sextet, J = 7.5 Hz, 2H, CH_2), 0.97 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.1 (C=O), 162.2 (Ar-C), 153.3 (Ar-C), 136.9 (Ar-CH), 126.3 (Ar-CH), 118.9 (Ar-CH), 37.9 (CH_2), 31.8 (CH_2), 25.9 (CH_3), 22.5 (CH_2), 14.1 (CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3064, 2861, 2958, 2931, 1698, 1588, 1455, 1357, 907, 732 cm^{-1}; HRMS (EI): m/z calculated for $C_{11}H_{15}NO$: 177.1154; found: 177.1152.

1-[6-(3,3-Dimethyl-butyl)-pyridin-2-yl]-ethanone (2). R_F = 0.73, 10% MTBE:hexanes; MTBE/hexanes (gradient); yellow oil; isolated yield 0.089 g, 77%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, J = 7.8 Hz, 1H, Ar-H), 7.70 (t, J = 7.8 Hz, 1H, Ar-H), 7.31 (br-d, J = 7.8 Hz, 1H, Ar-H), 2.85–2.79 (m, 2H, CH_2), 2.75 (s, 3H, CH_3), 1.68–1.62 (m, 2H, CH_2), 0.99 (s, 9H, CH_3 × 3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.1 (C=O), 162.9 (Ar-C), 153.3 (Ar-C), 137.0 (Ar-CH), 126.1 (Ar-CH), 118.8 (Ar-CH), 44.0 (CH_2), 33.8 (CH_2), 30.7 (C), 29.5 (CH_3 × 3), 25.9 (CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3065, 2955, 2867, 1700, 1587, 1454, 1356, 812, 602, 587 cm^{-1}; HRMS (EI): m/z calculated for $C_{13}H_{19}NO$: 205.1469; found: 205.1463.

1-[6-(4-Dimethylamino-phenyl)-pyridin-2-yl]-ethanone (7). R_F = 0.53, 10% EtOAc:hexanes; EtOAc/hexanes (gradient); pale-yellow solid; mp = 147.9–150.0°C; isolated yield 0.079 g, 63%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03–7.99 (m, 2H, Ph-H), 7.84–7.74 (m, 3H, Ar-H), 6.84–6.78 (br-m, 2H, Ph-H), 3.06 (s, 6H, CH_3 × 2), 2.83 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.2 (C=O), 156.8 (Ar-C), 153.3 (Ar-C), 151.5 (Ph-C), 137.4 (Ar-CH), 127.9 (Ph-CH), 126.3 (Ph-C), 122.2 (Ar-CH), 118.4 (Ar-CH), 112.4 (Ph-CH), 40.6 (CH_3 × 2), 26.0 (CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 2924, 1695, 1609, 1582, 1529, 1442, 1367, 1313, 1203, 806 cm^{-1}; HRMS (EI): m/z calculated for $C_{15}H_{16}N_2O$: 240.1263; found: 240.1260.

1-(6-Styryl-pyridin-2-yl)-ethanone (8). R_F = 0.61, 10% EtOAc:hexanes; EtOAc/hexanes (gradient), yellow solid; mp = 54.7–56.8°C; isolated yield 0.085 g, 61%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, J = 7.8, 1.0 Hz, 1H, Ar-H), 7.79 (t, J = 7.8 Hz, 1H, Ar-H), 7.74 (d, J = 16.0 Hz, 1H, vinyl H). 7.63–7.60 (m, 2H, Ph-H), 7.54 (dd, J = 7.8, 1.0 Hz, 1H, Ar-H), 7.45–7.38 (m, 2H, Ph-H), 7.35–7.31 (m, 1H, Ph-H), 7.22 (d, J = 16.0 Hz, 1H, vinyl H), 2.82 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.8 (C=O), 155.2 (Ar-C), 153.6 (Ar-C), 137.5 (Ar-CH), 136.6 (Ar-C), 133.9 (vinyl CH), 128.9 (Ph-CH), 128.8 (vinyl CH), 127.5 (Ar-C), 127.4 (Ph-CH), 125.3 (Ph-CH), 119.9 (Ar-CH), 25.9 (CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3032, 3058, 2933, 1697, 1637, 1582, 1562, 1451, 1356, 968, 804, 734, 692, 597 cm^{-1}; HRMS (EI): m/z calculated for $C_{15}H_{13}NO$: 223.0997; found: 223.0990.

1-[6-(2-Cyclohexyl-vinyl)-pyridin-2-yl]-ethanone (9). R_F = 0.71, 10% EtOAc:hexanes; EtOAc/hexanes (gradient), brown oil; isolated yield 0.077 g, 59%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (dd, J = 7.8, 1.0 Hz, 1H, Ar-H), 7.71 (t, J = 7.8 Hz, 1H, Ar-H), 7.39 (dd, J = 7.8, 1.0 Hz, 1H, Ar-H), 6.82 (dd, J = 15.9, 7.0 Hz, 1H, vinyl H), 6.49 (dd, J = 15.9, 1.2 Hz, 1H, vinyl H), 2.75 (s, 3H, CH_3), 2.26–2.17 (m, 1H, CH), 1.89–1.83 (m, 2H, CH_2), 1.81–1.67 (m, 2H, CH_2), 1.39–1.17 (m, 6H, CH_2 × 2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.9 (C=O), 155.9 (Ar-C), 153.32 (Ar-C), 142.6 (vinyl CH), 137.2 (vinyl CH), 127.0 (Ar-CH), 124.3 (Ar-CH), 119.4 (Ar-CH), 41.1 (CH), 32.7 (CH_2), 26.3 (CH_2), 26.1 (CH_3), 25.8 (CH_2); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3003, 2924, 2851, 1698, 1651, 1583, 1449, 1356, 970, 800 cm^{-1}; HRMS (EI): m/z calculated for $C_{15}H_{19}NO$: 229.1467; found: 229.1468.

1-(6-Cyclopropyl-pyridin-2-yl)-ethanone (10). R_F = 0.81, 10% EtOAc:hexanes; EtOAc/hexanes (gradient); yellow oil; isolated yield 0.041 g, 50%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 7.7, 1.1 Hz, 1H, Ar-H), 7.65 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.32 (dd, *J* = 7.7, 1.1 Hz, 1H, Ar-H), 2.65 (s, 3H, CH_3), 2.11–2.04 (m, 1H, CH), 1.13–1.08 (m, 2H, CH_2), 1.04–0.99 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.0 (C=O), 162.5 (Ar-C), 153.2 (Ar-C), 136.6 (Ar-CH), 125.1 (Ar-CH), 118.2 (Ar-CH), 25.8 (CH_3), 17.0 (CH), 10.41 (CH_2), 10.4X (CH_2) overlaps with 10.40; IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3007, 2928, 1698, 1589, 1457, 1356, 805, 602 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{10}H_{11}NO$: 161.0841; found: 161.0840.

1-(6-Thiophen-2-yl-pyridin-2-yl)-ethanone (11). R_F = 0.66, 10% EtOAc:hexanes; MTBE/hexanes (gradient), yellow amorphous; isolated yield 0.031 g, 30%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 7.0, 1.8 Hz, 1H, Ar-CH), 7.82 (t, *J* = 7.8 Hz, 1H, Ar C-H), 7.80 (dd, *J* = 7.8, 1.8 Hz, 1H, Ar-CH), 7.65 (dd, *J* = 3.7, 1.0 Hz, 1H, Ar_t-CH), 7.43 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar_t-CH), 7.14 (dd, *J* = 5.0, 3.7 Hz, 1H, Ar_t-CH), 2.79 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.4 (C=O), 153.3 (Ar-C), 152.1 (Ar-C), 144.4 (Ar_t-C), 137.7 (Ar-CH), 128.4 (Ar-CH), 128.3 (Ar_t-CH), 125.3 (Ar_t-CH), 122.0 (Ar_t-CH), 119.7 (Ar-CH), 25.8 (CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3073, 2928, 1698, 1582, 1455, 1359, 1298, 1243, 806, 707, 593 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{11}H_9NOS$: 203.0405; found: 203.0410.

1-[2,3']Bipyridinyl-6-yl-ethanone (12). R_F = 0.16, 50% EtOAc:hexanes; EtOAc/hexanes (gradient), brown oil; isolated yield 0.094 g, 93%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.31 (br-s, 1H, Ar-H), 8.69 (br-d, *J* = 4.8 Hz, 1H, Ar-H), 8.40 (ddd, *J* = 7.8, 2.4, 1.7 Hz, 1H, Ar-H), 8.03 (dd, *J* = 5.9, 3.1 Hz, 1H, Ar-H), 7.95–7.93 (m, 2H, Ar-H × 2), 7.44 (ddd, *J* = 7.8, 4.8, 0.8 Hz, 1H, Ar-H), 2.81 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.3 (C=O), 154.1 (Ar-C), 153.8 (Ar-C), 150.5 (Ar-CH), 148.5 (Ar-CH), 138.1 (Ar-CH), 134.4 (Ar-C), 134.0 (Ar-C), 123.8 (Ar-CH), 123.6 (Ar-CH), 120.7 (Ar-CH), 25.9 (CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3011, 2927, 1698, 1586, 1453, 1438, 1357, 1311, 798, 707, 595 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{12}H_{10}N_2O$: 198.0793; found: 198.0797.

1-(6-Benzo[1,3]dioxol-5-yl-pyridin-2-yl)-ethanone (13). R_F = 0.49, 10% EtOAc:hexanes; EtOAc/hexanes (gradient), white solid; mp = 145.3–147.8°C; isolated yield 0.098 g, 77%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (dd, *J* = 7.1, 1.6 Hz, 1H, Ar-H), 7.84 (t, *J* = 7.1 Hz, 1H, Ar-H), 7.80 (dd, *J* = 7.8, 1.6 Hz, 1H, Ar-H), 7.65 (d, *J* = 1.6 Hz, 1H, Ph-H), 7.58 (dd, *J* = 8.2, 1.6 Hz, 1H, Ph-H), 6.92 (d, *J* = 8.2 Hz, 1H, Ph-H), 6.03 (s, 2H, CH_2), 2.78 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.8 (C=O), 156.1 (Ar-C), 153.4 (Ar-C), 149.0 (Ph-C), 148.6 (Ph-C), 137.8 (Ar-CH), 133.0 (Ph-C), 121.1 (Ar-CH), 119.5 (Ar-CH), 108.7 (Ph-CH), 107.5 (Ph-CH), 101.6 (CH_2), 26.0 (CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3077, 2908, 1697, 1582, 1566, 1505, 1458, 1359, 1266, 1250, 802 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{14}H_{11}NO_3$: 241.0739; found: 241.0744.

6-Bromo-pyridine-2-carboxylic acid methoxy-methyl-amide. To a 25 mL round bottom flask equipped with a magnetic stir bar at ambient temperature was charged 6-bromo-pyridine-2-carboxylic acid (0.326 g, 1.61 mmol, 1.00 equiv) in anhydrous acetonitrile (3.2 mL, 0.5 M). The resulting clear solution was treated with *N*-methoxy-*N*-methyl-1*H*-imidazole-1-carboxamide (0.500 g, 3.22 mmol, 2.00 equiv) and allowed to stand at ambient temperature for fifteen minutes before heating at 80°C for twenty-four hours. The next day the crude mixture was concentrated under reduced pressure at ambient temperature to afford a viscous slurry that was dissolved in MTBE (10 mL) and treated with an aqueous 1 M solution of HCl (5 mL). The organic layer was separated and the aqueous layer was back-extracted with (3 × 10 mL) portions of MTBE. The combined organics were dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure at ambient temperature to afford a crude semisolid which was absorbed on neutral alumina and purified using automated flash-column chromatography with an EtOAc/hexanes gradient, including a 20% isocratic hold, to afford the title compound as a clear liquid (0.194 g, 53%) [26]; R_F = 0.24, 30% EtOAc:hexanes; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (t, *J* = 7.3 Hz, 1H, Ar-H), 7.62–7.57 (m, 1H, Ar-H), 7.55 (d, *J* = 8.7 Hz, 1H, Ar-H), 3.80 (br-s, 3H, OCH_3), 3.36 (br-s, 3H, CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3080, 2977, 2935, 1658, 1578, 1408, 1381, 1123, 988, 811, 753 cm^{-1}; HRMS (EI): *m/z* calculated for $C_8H_9BrN_2O_2$ $[m - OCH_3]^+$: 212.9663; found: 212.9654.

[2,3']Bipyridinyl-6-carbonitrile (14). R_F = 0.20, 70% EtOAc:hexanes; EtOAc/hexanes (gradient), yellow solid; mp = 70.9–72.8°C; isolated yield 0.088 g, 41%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.23 (d, *J* = 2.3 Hz, 1H, Ar-H), 8.73 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar-H); 8.47–8.44 (m, 1H, Ar-H); 8.00 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar-H), 7.97 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.71 (dd, *J* = 7.4, 1.0 Hz, 1H, Ar-H), 7.50 (dd, *J* = 8.0, 5.0 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2 (Ar-C), 150.5 (Ar-CH), 147.7 (Ar-CH), 138.4 (Ar-CH), 135.4 (Ar-CH), 134.5 (Ar-C), 133.3 (Ar-C), 127.6 (Ar-CH), 124.2 (Ar-CH), 123.6 (Ar-CH), 117.7 (RCN); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3068, 2977, 2932, 2239, 1696, 1586, 1519, 1450, 1437, 1394, 1023, 798, 707, 736 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{11}H_7N_3$: 181.0640; found: 181.0647.

6-(2-p-Tolyl-vinyl)-pyridine-2-carbaldehyde (15). R_F = 0.72, 30% EtOAc:hexanes; EtOAc/hexanes (gradient); pale-yellow solid; mp = 100.1–101.2°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.13 (s, 1H, RCHO), 7.83 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.81 (dt, *J* = 7.8, 1.2 Hz, 1H, Ar-H), 7.74 (d, *J* = 16.2 Hz, 1H, vinyl H), 7.60 (dd, *J* = 7.5, 1.2 Hz, 1H, Ar-H), 7.52 (d, *J* = 8.1 Hz, 2H, Ph-H), 7.21 (d, *J* = 8.1 Hz, 2H, Ph-H), 7.20 (d, *J* = 16.2 Hz, 1H, vinyl H), 2.39 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.0 (RCHO), 156.7 (Ar-C), 152.7 (Ar-C), 139.1 (Ph-C), 137.7 (vinyl CH), 134.6 (vinyl CH), 133.6 (Ph-C), 129.7 (Ph-CH), 127.4 (Ph-CH), 125.9 (Ar-CH), 125.8 (Ar-CH), 119.8 (Ar-CH), 21.5 (CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3031, 2824, 1708, 1638, 1582, 1453, 1512, 971, 909, 815, 732 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{15}H_{13}NO$: 223.0997; found: 223.0988.

6-(4-Methoxy-phenyl)-pyridine-2-carboxylic acid methoxy-methyl-amide (16). R_F = 0.46, 70%; EtOAc: hexanes; EtOAc/hexanes (gradient); amorphous; isolated yield 0.044 g, 22%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01–7.97 (m, 2H, Ph-H), 7.81 (t, *J* = 7.4 Hz, 1H, Ar-H), 7.75 (br-d, *J* = 8.5 Hz, 1H, Ar-H), 7.52 (br-s, 1H, Ar-H), 7.04–6.97 (m, 2H, Ph-H), 3.87 (s, 3H, OCH_3), 3.81 (br-s, 3H, OCH_3), 3.49 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3 (C=O), 160.8 (Ph-C), 155.9 (Ar-C), 153.3 (Ar-C), 137.5 (Ar-CH), 131.4 (Ph-C), 128.4 (Ph-CH), 120.8 (Ar-CH), 114.27 (Ph-CH), 114.2X (Ar-CH) (overlaps with 114.27), 60.5 (OCH_3), 55.5 (OCH_3), 38.8 (CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3007, 2977, 2936, 2903, 2841, 1652, 1609, 1566, 1516, 1384, 1310, 1296, 1179, 1030, 821, 732, 583 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{15}H_{16}N_2O_3$: 272.1161; found: 272.1166.

6-(4-tert-Butyl-phenyl)-pyridine-2-carbonitrile (18). R_F = 0.62, 30% EtOAc:hexanes; EtOAc/hexanes (gradient), yellow amorphous; isolated yield 0.077 g, 68%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99–7.95 (m, 2H, Ph-H), 7.96 (br-dd, *J* = 8.1, 1.0 Hz, 1H, Ar-H), 7.86 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.60 (br-d, *J* = 7.8 Hz, 1H, Ar-H), 7.54–7.51 (m, 2H, Ph-H), 1.39 (s, 9H, CH_3 × 3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1 (Ar-C), 153.7 (Ar-C), 137.7 (Ar-CH), 134.6 (Ph-C), 133.9 (Ph-C), 126.9 (Ph-CH), 126.4 (Ar-CH), 126.1 (Ar-CH), 123.4 (Ar-CH), 117.2 (CN), 35.0 (C), 31.4 (CH_3 × 3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3073, 2908, 2871, 2235, 1609, 1586, 1558, 1446, 908, 807, 732 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{16}H_{16}N_2$ [M − CH_3]: 221.1079; found: 221.1084.

6-(2-p-Tolyl-vinyl)-pyridine-2-carboxylic acid methoxy-methyl-amide (19). R_F = 0.58, 70% EtOAc:hexanes; EtOAc/hexanes (gradient), yellow solid; mp = 101.3–103.8°C; isolated yield 0.047 g, 30%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (t, *J* = 7.9 Hz, 1H, Ar-H), 7.62 (d, *J* = 16.5 Hz, 1H, vinyl H), 7.50–7.43 (m, 4H, Ar-H × 2, Ph-H); 7.19 (d, *J* = 8.1 Hz, 2H, Ph-H), 7.15 (d, *J* = 16.5 Hz, 1H, vinyl H), 3.81 (br-s, 3H, OCH_3); 3.46 (br-s, 3H, OCH_3); 2.37 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.6 (C=O), 155.0 (Ar-C), 139.0 (Ar-CH), 138.8 (Ar-C), 137.3 (Ar-CH), 133.81 (vinyl CH), 133.78 (vinyl CH), 129.7 (Ph-C), 129.7 (Ph-CH), 127.3 (Ph-CH), 126.6 (Ar-CH), 122.8 (Ph-C), 61.7 (OCH_3), 26.3 (CH_3), 21.5 (CH_3); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3031, 2973, 2934, 1652, 1583. 1564, 1513, 1451, 1382, 990, 821, 751 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{17}H_{18}N_2O_2$: 282.1368; found: 282.1359.

6-Phenethyl-pyridine-2-carbonitrile (20). R_F = 0.45, 10% EtOAc:hexanes; EtOAc/hexanes (gradient), amorphous; isolated yield 0.082 g, 63%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.53 (dd, *J* = 7.8, 0.9 Hz, 1H, Ar-H), 7.29–7.22 (m, 3H, Ar-H, Ph-H); 7.21–7.15 (m, 3H, Ph-H, Ph-H); 3.17–3.13 (m, 2H, CH_2); 3.09–3.04 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5 (Ar-C), 140.9 (Ar-C), 137.1 (Ar-CH), 133.6 (Ph-C), 128.59 (Ph-CH), 128.5X (Ph-CH) overlaps with 128.59, 126.7 (Ar-CH), 126.3 (Ph-H), 126.2 (Ar-CH), 117.6 (CN), 39.9 (CH_2), 35.5 (CH_2); IR (ATR-$CDCl_3$): $\bar{\upsilon}_{max}$ = 3063, 3027, 2928, 2862, 2236, 1587, 1568, 1497, 1451, 802, 751, 699 cm^{-1}; HRMS (EI): *m/z* calculated for $C_{14}H_{12}N_2$ [*m* − H]$^+$: 207.0917; found: 207.0918.

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