Microwave-Assisted Iridium-Catalyzed Synthesis of Nicotine and Anabasine Derivatives

Tushar Dattu Apsunde, Mark L. Trudell*

Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA
Fax +1(504)2806860; E-mail: mtrudell@uno.edu

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Abstract: Various functionalized nicotine and anabasine analogues are synthesized via a three-step sequence that exploits a microwave-assisted iridium-catalyzed N-heterocyclization of 1,4- and 1,5-diols for the construction of the pyrrolidine and piperidine ring systems. The microwave-assisted N-heterocyclization furnishes derivatives of nicotine and anabasine in good yields (50–75%) with overall yields ranging from 30–50%.

Key words: pyridine alkaloids, iridium, microwave, green chemistry, N-heterocyclization

Nicotine (**1**) and anabasine (**2**) (Figure 1) are pyridine alkaloids commonly found in species of the Solanaceae plant family (e.g. *Nicotiana tabacum* and *Nicotiana rustica*).[1] These pyridine alkaloids can modulate neuronal nicotinic acetylcholine receptors (nAChRs), which affect the central nervous system (CNS).[2] The pharmacological actions of pyridine alkaloids and related derivatives on the central nervous system has attracted considerable attention as potential therapeutic targets for a variety of disease-states and pathological conditions mediated by nicotinic acetylcholine receptors.[2–5] Nevertheless, toxicity and abuse potential has limited the use of nicotine-related drugs for central nervous system disorders.[2] Therefore, new analogues of nicotine with unique nicotinic acetylcholine receptor subtype selectivity remain important pharmacological targets for the development of novel therapeutics with improved safety profiles. To this end, considerable effort has been focused on the development of new synthetic methods for the construction nicotine derivatives.[6–8] Although a variety of methods have been reported, there is still a need for versatile and practical methods for the synthesis of nicotine-related derivatives.

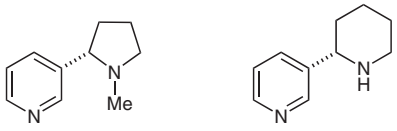
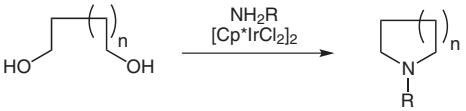


Figure 1 Pyridine alkaloids from *Nicotiana* species

Fujita and co-workers reported the use of (pentamethylcyclopentadienyl)iridium dichloride dimer ($[Cp^*IrCl_2]$)$_2$ for the preparation of cyclic amines via N-alkylation of diols by primary amines.[9] This methodology allowed for the synthesis of N-heterocyclic products without generation of harmful by-products (H_2O is the only by-product), and thus is an attractive green chemistry process. Previously, we were the first to describe the application of the iridium-catalyzed N-heterocyclization reaction for the synthesis of nicotine-related compounds, and the first total synthesis of the alkaloid, noranabasamine.[10,11] Further studies by Zhao and co-workers showed that N-heterocyclization of simple amine/alcohol systems proceeded under solvent-free, base-free microwave-assisted conditions (Scheme 1).[12]



Scheme 1 The iridium-catalyzed N-heterocyclization reaction

Based on these findings, it was of interest to explore further the application of these conditions for a green synthesis of nicotine and anabasine-related analogues. Herein, we report the efficient three-step synthesis of nicotine and anabasine analogues employing a microwave-assisted iridium-catalyzed N-heterocyclization of 1,4- and 1,5-diols.

Our approach relied upon the initial synthesis of the 1-(3-pyridinyl)diols using methodology previously developed in our laboratory.[11] As illustrated in Scheme 2, 3-bromopyridine (**3a**), or 5-bromo-2-methoxypyridine (**3b**) was treated initially with *n*-butyllithium at –78 °C in diethyl ether. γ-Butyrolactone or δ-valerolactone was then added to the resulting lithiated pyridine derivative to afford the corresponding hydroxy ketones **4** or **5**, in high yields.

Subsequent reduction with sodium borohydride in methanol afforded the required intermediate diols **6** and **7** in good overall yields. 1-(Quinolin-3-yl)butane-1,4-diol (**9**) was prepared in similar fashion from 3-bromoquinoline (**3c**) and γ-butyrolactone (Scheme 2).

Initially, we explored and optimized the reaction conditions for the synthesis of *N*-benzylnornicotine (**10a**) (Table 1). The reaction of the diol **6a** and benzylamine was performed under normal reflux and microwave-assisted conditions. When the reaction was performed in the absence of a base and solvent (Table 1, entries 1 and 2),

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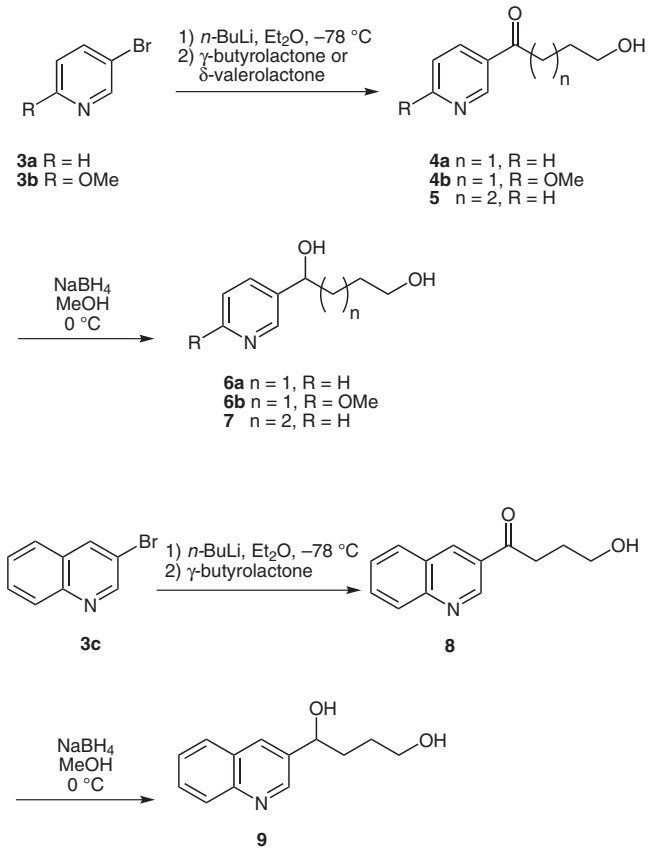
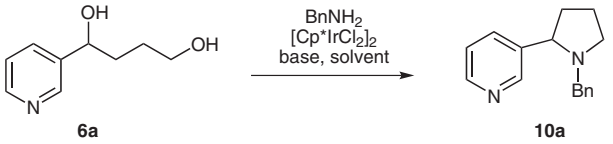


Scheme 2 Synthesis of 1,4- and 1,5-diols

compound **10a** was formed in low yields. Even using a base ($NaHCO_3$) and toluene as the solvent did not improve substantially the yields of **10a** (Table 1, entries 3 and 4). The highly polar nature and poor solubility of the diol in toluene encouraged us to explore water as a solvent for this transformation. The yield of the reaction was improved considerably (50%, Table 1, entry 5) when water was used as the solvent under reflux conditions. Moreover, the use of water as the solvent in the heterocyclization facilitated by microwave irradiation resulted in both an increased yield and a shorter reaction time (Table 1, entry 6). Further evaluation of the base determined that sodium carbonate was superior to sodium bicarbonate, sodium acetate and potassium carbonate (Table 1, entries 6–9), and led to an optimized yield of 75%.

The microwave-assisted N-heterocyclization of 1,4-butanediols and 1,5-pentanediols was performed under optimized aqueous conditions to prepare a series nicotine and anabasine derivatives. As summarized in Table 2, the reaction of 1,4-diol **6a** with methylamine gave a modest yield (50%) of nicotine. The lower than expected yield is believed to be due to the high volatility of methylamine in water at the elevated temperatures of the microwave conditions. Alternatively, the reaction of benzylamine or 4-methoxybenzylamine with the 1,4- and 1,5-diols provided good yields of the corresponding cyclization products. In addition, the N-heterocyclization of diol **9** afforded the corresponding quinoline derivative **13** in 78% yield (Figure 2).

Table 1 Optimization of the N-Heterocyclization Reaction

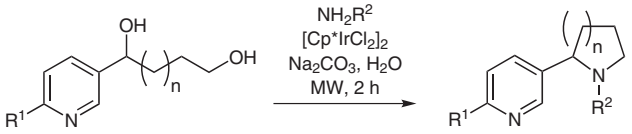


6a 10a

Entry	Solvent	Base	Conditions	Yield (%)[a]
1	–	–	reflux, 17 h	10
2	–	–	MW, 2 h	15
3	toluene	$NaHCO_3$	reflux, 17 h	<10
4	toluene	$NaHCO_3$	MW, 2 h	20
5	H_2O	$NaHCO_3$	reflux, 17 h	50
6	H_2O	$NaHCO_3$	MW, 2 h	60
7	H_2O	NaOAc	MW, 2 h	65
8	H_2O	Na_2CO_3	MW, 2 h	75
9	H_2O	K_2CO_3	MW, 2 h	35

[a] Yield of isolated product. MW = microwave.

Table 2 Synthesis of Nicotine and Anabasine Analogues



Diol	R^1	n	R^2	Product	Yield (%)[a]
6a	H	1	Me	**1**	50
6a	H	1	Bn	**10a**	75
6b	OMe	1	Bn	**10b**	78
6a	H	1	4-$MeOC_6H_4CH_2$	**11a**	73
6b	OMe	1	4-$MeOC_6H_4CH_2$	**11b**	75
7	H	2	Bn	**12a**	70
7	H	2	4-$MeOC_6H_4CH_2$	**12b**	75
9	–	–	Bn	**13**	78

[a] Yield of isolated product.

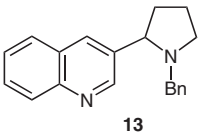


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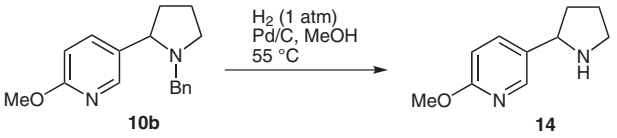
Figure 2

To further demonstrate the utility of this approach, we converted the *N*-benzylnornicotine analogue **10b** into the corresponding nornicotine derivative **14**. Hydrogenolysis (1 atm) of **10b** over palladium on carbon (Pd/C) at 55 °C afforded **14** in 75% yield (Scheme 3).



Scheme 3 Hydrogenolysis of *N*-benzylnornicotine analogue **10b**

In summary, we have developed an efficient three-step synthesis of nicotine and anabasine derivatives from readily available starting materials. The key step involves the aqueous microwave-assisted, iridium-catalyzed N-heterocyclization reaction of pyridinylbutane-1,4-diols and pyridinylpentane-1,5-diols with various amines. The application of this versatile and green chemistry process toward the synthesis of novel nicotinic acetylcholine receptor ligands is currently under investigation and will be reported elsewhere.

All chemicals were purchased from Aldrich Chemical Company and used as received unless otherwise noted. Microwave-assisted N-heterocyclization reactions were carried out using a StartSYNTH multicavity instrument with start rotor from Milestone. The maximum microwave power was 1200 W and the reaction temperature was monitored by an internal infrared sensor. All the reactions were performed in glass reactor tubes with a maximum working pressure of 15 bars and maximum temperature of 230 °C. Thin-layer chromatography (TLC) was performed on silica gel plates (250 mm) purchased from Sorbent Technologies. Compounds were made visual with UV light, iodine or phosphomolybdic acid. Chromatography was accomplished with silica gel 60 Å (230–400 mesh) purchased from Sorbent Technologies. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian 400 MHz NMR spectrometer at ambient temperature in $CDCl_3$. ^{1}H NMR chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. ^{13}C NMR chemical shifts are reported as δ values (ppm) relative to $CDCl_3$ (77.0 ppm). Atlantic Microlab, Inc., Norcross, GA performed all CHN microanalyses.

Hydroxy Ketones 4a,b and 5; General Procedure
Under an N_2 atm, bromopyridine **3** (1 equiv) was added to anhyd Et_2O (20 mL) and cooled to –78 °C. A soln of *n*-BuLi (2.5 M in hexane, 1.2 equiv) was added dropwise, and the mixture was stirred for 15 min. A soln of γ-butyrolactone or δ-valerolactone (1.1 equiv) in Et_2O (5 mL) was added and the mixture was stirred for 2 h. The mixture was allowed to warm to r.t. and brine (20 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL) and the combined organic layers dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2–MeOH, 92:8) to afford the hydroxy ketones **4a**,**b** and **5** as oils.

4-Hydroxy-1-(pyridine-3-yl)butan-1-one (4a)
The title product was prepared from 3-bromopyridine (**3a**) (2.0 g, 12.5 mmol), γ-butyrolactone (1.2 g, 13.9 mmol) and *n*-BuLi (6.0 mL, 15.0 mmol, 2.5 M in hexane) in anhyd Et_2O (30 mL). Purification by flash chromatography afforded the product as a yellow oil; yield: 1.4 g (65%). The spectroscopic data were consistent with those reported previously for this compound.[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.03 (s, 1 H), 8.61 (d, *J* = 3.6 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 7.34–7.30 (m, 1 H), 3.91 (br s, 1 H), 3.63 (t, *J* = 6.0 Hz, 2 H), 3.04 (t, *J* = 7.2 Hz, 2 H), 1.92–1.89 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3, 153.3, 149.5, 135.8, 132.4, 124.0, 61.5, 35.6, 26.8.

4-Hydroxy-1-(6-methoxypyridin-3-yl)butan-1-one (4b)
The title product was prepared from 5-bromo-2-methoxypyridine (**3b**) (2.0 g, 10.6 mmol), γ-butyrolactone (1.0 g, 11.7 mmol) and *n*-BuLi (5.1 mL, 12.7 mmol, 2.5 M in hexane) in anhyd Et_2O (30 mL). Purification by flash chromatography afforded the product as a yellow oil; yield: 1.5 g (70%). The spectroscopic data were consistent with those reported previously for this compound.[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, *J* = 2.4 Hz, 1 H), 8.13 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.77 (d, *J* = 8.8 Hz, 1 H), 3.99 (s, 3 H), 3.74–3.73 (m, 2 H), 3.07 (t, *J* = 7.2 Hz, 2 H), 2.02–1.97 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.4, 166.4, 149.1, 138.3, 126.7, 111.1, 61.7, 54.1, 35.0, 27.0.

5-Hydroxy-1-(pyridin-3-yl)pentan-1-one (5)
The title product was prepared from 3-bromopyridine (**3a**) (2.0 g, 12.5 mmol), δ-valerolactone (1.4 g, 13.9 mmol) and *n*-BuLi (6.0 mL, 15 mmol, 2.5 M in hexane) in anhyd Et_2O (30 mL). Purification by flash chromatography afforded the product as a yellow oil; yield: 1.7 g (65%). The spectroscopic data were consistent with those reported previously for this compound.[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.14 (d, *J* = 4.0 Hz, 1 H), 8.73 (dd, *J* = 8.0, 4.0 Hz, 1 H), 8.22 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.41–7.39 (m, 1 H), 3.67 (t, *J* = 4.8 Hz, 2 H), 3.05–3.01 (m, 2 H), 1.87–1.82 (m, 2 H), 1.67–1.63 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.2, 153.2, 149.4, 135.7, 132.3, 123.9, 61.9, 38.6, 32.1, 20.3.

Diols 6a,b and 7; General Procedure
Powdered $NaBH_4$ (1.5 equiv) was added to a well stirred soln of hydroxy ketone **4a**,**b** or **5** (1 equiv) in anhyd MeOH at 0 °C. After 2 h, $NaHCO_3$ was added to the reaction mixture and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to afford the diols **6a**,**b** or **7** as viscous oils.

1-(Pyridin-3-yl)butane-1,4-diol (6a)
The title product was prepared from **4a** (1.0 g, 6.0 mmol) and $NaBH_4$ (0.34 g, 9.0 mmol) in anhyd MeOH (20 mL). Purification by flash chromatography (CH_2Cl_2–MeOH, 92:8) afforded a colorless oil; yield: 0.96 g (95%). The spectroscopic data were consistent with those reported previously for this compound.[13]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 4.0 Hz, 1 H), 8.38 (dd, *J* = 8.0, 4.0 Hz, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.24 (dd, *J* = 8.0, 4.0 Hz, 1 H), 4.95 (br s, 1 H), 4.73 (t, *J* = 6.4 Hz, 1 H), 3.69 (br s, 1 H), 3.68–3.64 (m, 2 H), 1.87–1.82 (m, 2 H), 1.68–1.62 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 147.6, 140.8, 134.2, 123.8, 71.8, 62.6, 36.7, 29.1.

1-(6-Methoxypyridin-3-yl)butane-1,4-diol (6b)
The title product was prepared from **4b** (1.0 g, 5.2 mmol) and $NaBH_4$ (0.30 g, 7.77 mmol) in anhyd MeOH (20 mL). Purification by flash chromatography afforded a colorless oil; yield: 0.90 g (90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1 H), 7.46 (d, *J* = 0.8 Hz, 1 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 5.06 (br s, 1 H), 4.48 (t, *J* = 6.4 Hz, 1 H), 4.43 (br s, 1 H), 3.76 (s, 3 H), 3.47–3.43 (m, 2 H), 1.70–1.61 (m, 2 H), 1.52–1.43 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 144.5, 137.1, 133.3, 110.8, 71.4, 62.2, 53.7, 36.0, 29.0.

Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.75; H, 7.55; N, 6.99.

1-(Pyridin-3-yl)pentane-1,5-diol (7)
The title product was prepared from **5** (1.0 g, 5.2 mmol) and $NaBH_4$ (0.30 g, 7.8 mmol) in anhyd MeOH (20 mL). Purification by flash chromatography afforded a colorless oil; yield: 0.90 g (95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 1.6 Hz, 1 H), 8.38 (dd, *J* = 6.4, 1.2 Hz, 1 H), 7.70–7.69 (m, 1 H), 7.26–7.23 (m, 1 H), 4.68 (t, *J* = 5.6 Hz, 1 H), 3.58 (t, *J* = 6.4 Hz, 2 H), 1.82–1.70 (m, 2 H), 1.71–1.65 (m, 2 H), 1.45–1.36 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 147.6, 141.0, 134.27, 123.8, 71.8, 62.6, 38.8, 32.4, 22.1.

Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.22; H, 8.45; N, 7.67.

1-(Quinolin-3-yl)butane-1,4-diol (9)
Under an N_2 atm, 3-bromoquinoline (**3c**) (2.0 g, 9.6 mmol) was added to anhyd Et_2O (30 mL) and the resulting soln cooled to –78 °C. A soln of *n*-BuLi (4.6 mL, 11.4 mmol, 2.5 M in hexane) was added dropwise and the mixture stirred for 15 min. A soln of γ-butyrolactone (0.95 g, 10.5 mmol) in Et_2O (5 mL) was added and the mixture was stirred for 2 h. The mixture was allowed to warm to r.t. and brine (20 mL) was added. The mixture was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to furnish ketone **8** as a light yellow oil. The crude ketone **8** was dissolved in anhyd MeOH (20 mL) and cooled to 0 °C. Powdered $NaBH_4$ (0.52 g, 14.22 mmol) was added in one portion and the mixture was stirred for 2 h. Purification by flash chromatography (10% MeOH–CH_2Cl_2) afforded **9** as a yellow oil; overall yield over two steps: 1.1 g (50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (d, *J* = 2.0 Hz, 1 H), 8.06 (s, 1 H), 7.98 (d, *J* = 8.4 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.63–7.57 (m, 1 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 4.87 (t, *J* = 6.0 Hz, 1 H), 3.69–3.60 (m, 3 H), 1.92–1.87 (m, 2 H), 1.71–1.01 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.5, 147.2, 138.0, 133.1, 129.6, 128.7, 128.1, 127.1, 110.5, 72.0, 62.5, 36.7, 29.2.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.59; H, 7.03; N, 6.11.

Microwave-Assisted N-Heterocyclization; General Procedure
The diol (1 equiv) was added to a well stirred soln of $[Cp^*IrCl_2]_2$ (5 mol%) and Na_2CO_3 (1.1 equiv), in H_2O (5 mL), in a microwave reactor tube under an N_2 atm. The amine (1 equiv) was added to the soln and the mixture was irradiated at 110 °C for 2 h. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3% MeOH–CH_2Cl_2) to afford the cyclic amine.

(±)-Nicotine (1)
The title product was prepared from **6a** (100 mg, 0.60 mmol), $[Cp^*IrCl_2]_2$ (12 mg, 0.015 mmol), Na_2CO_3 (1.3 mg, 0.015 mmol) and 40% aq $MeNH_2$ soln (0.050 mL, 0.60 mmol). Purification by flash chromatography afforded a brown oil; yield: 48 mg (50%). The spectroscopic data were consistent with a commercial sample and those reported previously for this compound.[14]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 2.0 Hz, 1 H), 8.49 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 6.8 Hz, 1 H), 3.25 (t, *J* = 7.6 Hz, 1 H), 3.09 (t, *J* = 8.0 Hz, 1 H), 2.35–2.29 (m, 1 H), 2.24–2.16 (m, 4 H), 2.00–1.74 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 149.7, 135.8, 124.0, 75.8, 61.9, 35.7, 29.9, 26.8.

3-(1-Benzylpyrrolidin-2-yl)pyridine (10a)
The title product was prepared from **6a** (100 mg, 0.60 mmol), $[Cp^*IrCl_2]_2$ (12 mg, 0.015 mmol), Na_2CO_3 (1.3 mg, 0.015 mmol) and $BnNH_2$ (64 mg, 0.60 mmol) in H_2O (5 mL). Purification by flash chromatography afforded a colorless oil; yield: 105 mg, (75%). The spectroscopic data were consistent with those reported previously for this compound.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, 1 H), 8.48 (d, *J* = 3.6 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.33–7.18 (m, 6 H), 3.81 (d, *J* = 13.2 Hz, 1 H), 3.44–3.40 (m, 1 H), 3.13–3.09 (m, 2 H), 2.28–2.18 (m, 2 H), 1.89–1.68 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 148.8, 135.2, 128.8, 128.7, 128.4, 127.2, 123.9, 67.2, 58.3, 53.7, 35.5, 22.7.

5-(1-Benzylpyrrolidin-2-yl)-2-methoxypyridine (10b)
The title product was prepared from **6b** (100 mg, 0.50 mmol), $[Cp_2^*IrCl_2]_2$ (12 mg, 0.012 mmol), Na_2CO_3 (1.1 mg, 0.012 mmol) and $BnNH_2$ (0.053 g, 0.50 mmol). Purification by flash chromatography afforded a colorless oil; yield: 100 mg (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.14 (d, *J* = 2.4 Hz, 1 H), 7.75 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.29–7.20 (m, 5 H), 6.76 (d, *J* = 8.8 Hz, 1 H), 3.94 (s, 3 H), 3.80 (d, *J* = 12.0 Hz, 1 H), 3.33–3.31 (m, 1 H), 3.08–3.06 (m, 2 H), 2.19–2.14 (m, 2 H), 1.89–1.86 (m, 1 H), 1.80–1.69 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 146.3, 139.7, 138.2, 132.0, 128.4, 127.0, 111.3, 66.6, 58.1, 53.5, 35.1, 22.5.

Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.00; H, 7.73; N, 10.28.

3-[1-(4-Methoxybenzyl)pyrrolidin-2-yl]pyridine (11a)
The title product was prepared from **6a** (100 mg, 0.60 mmol), $[Cp_2^*IrCl_2]_2$ (12 mg, 0.015 mmol), Na_2CO_3 (1.3 mg, 0.015 mmol) and 4-methoxybenzylamine (82 mg, 0.60 mmol). Purification by flash chromatography afforded a colorless oil; yield: 110 mg (73%). The spectroscopic data were consistent with those reported previously for this compound.[15]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (d, *J* = 1.6 Hz, 1 H), 8.49 (dd, *J* = 4.4, 1.6 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H), 7.25 (dd, *J* = 8.0, 4.4 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 3.78 (s, 3 H), 3.73 (d, *J* = 12.8 Hz, 2 H), 3.38 (t, *J* = 8.0 Hz, 1 H), 3.10–3.02 (m, 2 H), 2.64–2.19 (m, 2 H), 1.77–1.67 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 149.8, 148.8, 139.7, 135.2, 129.6, 123.8, 114.0, 113.8, 67.0, 57.6, 55.4, 53.5, 35.5, 22.7.

2-Methoxy-5–[1-(4-methoxybenzyl)pyrrolidin-2-yl]pyridine (11b)
The title product was prepared from **6b** (100 mg, 0.50 mmol), $[Cp_2^*IrCl_2]_2$ (12 mg, 0.012 mmol), Na_2CO_3 (1.1 mg, 0.012 mmol) and 4-methoxybenzylamine (69 mg, 0.50 mmol). Purification by flash chromatography afforded a colorless oil; yield: 110 mg (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 1.6 Hz, 1 H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 6.82 (d, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 8.4 Hz, 1 H), 3.93 (s, 3 H), 3.77 (s, 3 H), 3.73 (d, *J* = 12.8 Hz, 1 H), 3.28 (t, *J* = 8.0 Hz, 1 H), 3.05 (t, *J* = 8.0 Hz, 1 H), 2.98 (d, *J* = 12.8 Hz, 1 H), 2.22–2.10 (m, 2 H), 1.89–1.65 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 158.7, 146.2, 138.2, 132.0, 131.7, 130.0, 113.7, 111.3, 66.4, 57.3, 55.4, 53.6, 53.4, 35.1, 22.4.

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.40; H, 7.52; N, 9.11.

3-(1-Benzylpiperidin-2-yl)pyridine (12a)[16]
The title product was prepared from **7** (100 mg, 0.55 mmol), $[Cp^*IrCl_2]_2$ (14 mg, 0.013 mmol), Na_2CO_3 (1.2 mg, 0.013 mmol) and $BnNH_2$ (55 mg, 0.55 mmol). Purification by flash chromatography afforded a colorless oil; yield: 100 mg, (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 1.6 Hz, 1 H), 8.48 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.34–7.18 (m, 6 H), 3.70 (d, *J* = 13.6 Hz, 1 H), 3.16 (dd, *J* = 11.2, 2.8 Hz, 1 H), 2.99 (d, *J* = 11.6 Hz, 1 H), 2.85 (d, *J* = 13.6 Hz, 1 H), 1.99–1.92 (m, 2 H), 1.81–1.75 (m, 2 H), 1.65–1.42 (m, 2 H), 1.42–1.37 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 148.9, 141.2, 139.5, 135.1, 128.8, 128.4, 127.1, 124.0, 66.7, 60.3, 53.5, 37.2, 26.0, 25.2.

Anal. Calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.77; H, 8.21; N, 11.00.

3-[1-(4-Methoxybenzyl)piperidin-2-yl)pyridine (12b)
The title product was prepared from **7** (100 mg, 0.55 mmol), $[Cp^*IrCl_2]_2$ (14 mg, 0.013 mmol), Na_2CO_3 (1.2 mg, 0.013 mmol) and 4-methoxybenzylamine (75 mg, 0.55 mmol). Purification by flash chromatography afforded a colorless oil; yield: 129 mg (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (s, 1 H), 8.48 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.80 (d, *J* = 7.6 Hz, 1 H), 7.26–7.24 (m, 1 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 3.78 (s, 3 H), 3.61 (d, *J* = 13.6 Hz, 1 H), 3.15 (dd, *J* = 7.2, 2.4 Hz, 1 H), 2.98 (d, *J* = 11.6 Hz, 1 H), 2.79 (d, *J* = 13.6 Hz, 1 H), 1.96–1.89 (m, 1 H), 1.80–1.72 (m, 2 H), 1.63–1.50 (m, 3 H), 1.41–1.30 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 149.7, 148.8, 141.3, 135.1, 131.3, 130.0, 123.9, 113.7, 66.6, 59.3, 55.4, 53.3, 37.3, 26.0, 25.2.

Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.50; H, 7.91; N, 9.78.

3-(1-Benzylpyrrolidin-2-yl)quinoline (13)
The title product was prepared from **9** (100 mg, 0.50 mmol), $[Cp^*IrCl_2]_2$ (12 mg, 0.012 mmol), Na_2CO_3 (1.1 mg, 0.012 mmol) and $BnNH_2$ (53 mg, 0.50 mmol). Purification by flash chromatography afforded a colorless oil; yield: 100 mg (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.05 (s, 1 H), 8.17 (s, 1 H), 8.12 (d, *J* = 8.8 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.67 (t, *J* = 7.2 Hz, 1 H), 7.56 (t, *J* = 7.2 Hz, 1 H), 7.34–7.19 (m, 5 H), 3.85 (d, *J* = 12.8 Hz, 1 H), 3.59 (t, *J* = 7.6 Hz, 1 H), 3.15 (d, *J* = 12.8 Hz, 1 H), 2.34–2.27 (m, 2 H), 2.01–1.81 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 148.1, 139.5, 137.0, 134.4, 129.5, 129.2, 129.0, 128.6, 128.4, 127.8, 127.1, 126.8, 67.5, 58.5, 53.7, 35.5, 22.9.

Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.29; H, 7.08; N, 9.53.

2-Methoxy-5-(pyrrolidin-2-yl)pyridine (14)
5-(1-Benzylpyrrolidin-2-yl)-2-methoxypyridine (**10b**) (100 mg, 0.37 mmol),) and 10% Pd/C (10 mg) were stirred in EtOH under H_2 (1 atm) for 2 h at 55 °C. After the reaction was complete (TLC), the mixture was filtered through Celite. The solvent was removed under reduced pressure to afford the nornicotine derivative as a light yellow oil; yield: 51 mg (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 4.0 Hz, 1 H), 7.79 (dd, *J* = 4.8, 2.4 Hz, 1 H), 6.72 (d, *J* = 4.8 Hz, 1 H), 5.73 (br s, 1 H, NH), 4.37 (t, *J* = 6.8 Hz, 1 H), 3.88 (s, 3 H), 3.36–3.34 (m, 1 H), 3.21–3.16 (m, 1 H), 2.16–2.14 (m, 1 H), 2.10–2.01 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 147.0, 138.4, 123.8, 111.5, 60.8, 53.8, 45.1, 31.6, 24.0.

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.12; H, 8.15; N, 15.67.

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