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Synthesis of C-4 Substituted Amido Nicotine Derivatives via Copper(I)- and (II)-Catalyzed Cross-Coupling Reactions

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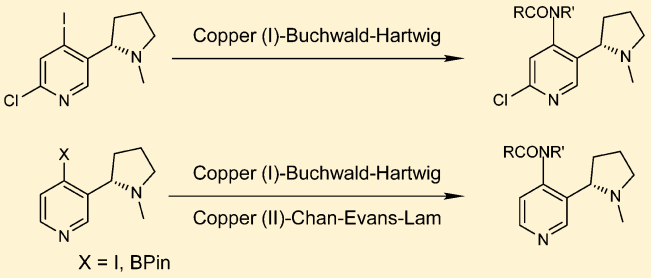
Supporting Information

ABSTRACT: The syntheses of seven novel amido nicotine derivatives **12**–**18** from (*S*)-nicotine are presented. (*S*)-Nicotine and (*S*)-6-chloronicotine derivatives were cross-coupled with the corresponding amides **6**–**10** at the C-4 position of the pyridine ring via copper(I)-mediated reactions. Derivatives **16**–**18** were also obtained via copper(II)-mediated reactions from (*S*)-nicotine containing a C-4 boronic acid pinacol ester group. The optimization of reaction conditions for both routes provided a useful method for preparing C-4 amide-containing nicotine analogs.



Since (*S*)-nicotine (**1**, Figure 1) was first isolated in 1828,[1] the alkaloid and analogs have received special interest from the scientific community because of their interaction with nicotinic acetylcholine receptors (nAChRs) of the nervous system[2] and the potential for treating central nervous system (CNS) disorders, such as Parkinson's disease (PD), Alzheimer's disease, and attention-deficit disorder.[3] Recently, its importance was further emphasized when the studies of neuronal nAChRs subtypes were fueled by several lines of research.[4]

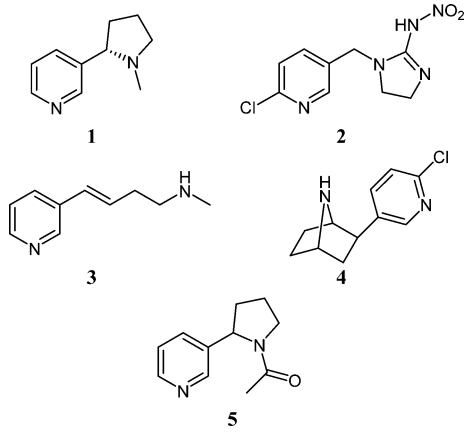


Figure 1. Chemical structure of (*S*)-nicotine (**1**) and analogs, imidacloprid (**2**), metanicotine (**3**), epibatidine (**4**), and *N*-acetylnornicotine (**5**).

Accumulating evidence has shown that the efficacy of certain CNS drugs depended on their specific interaction with different nAChRs subtypes. Quik and Wonnacott found that selective degeneration of dopaminergic neurons, which signaled PD, was regulated by ligands of $\alpha4\beta2^*$ and $\alpha6\beta2^*$ AChRs.[5] Nicotinic drugs that targeted these subunits had demonstrated antinigrostriatal damage effect. Although (*S*)-nicotine has been recognized as the prototypical agonist of nAChRs, its selectivity on subtypes of AChRs is not significant. Moreover, the toxicity on cardiovascular, neuromuscular, and gastrointestinal systems further limits its application. The need of finding a more effective nicotine-like pharmacophore is clear and the imminent goal is to synthesize selective nicotine analogs that exhibit limited side effects.[6] Many synthetic efforts in this area have focused on modifying the pyrrolidine ring of nicotine, such as pyrrolidine ring-opening[7] or adding a linker between the two heterocyclic rings.[8] The synthesis and biological activities of several analogs, e.g., imidacloprid, metanicotine, epibatidine, and acetylnornicotine (**2**, **3**, **4**, and **5**, Figure 1) have been studied in detail.[2,4e,9] In contrast, modification on the pyridine ring of nicotine was not studied in detail until recently.[4e,8,10] Our group has developed methodologies for the regioselective synthesis of nicotine derivatives. The substitutions at all positions (C-2, 4, 5, and 6) of the pyridine ring of nicotine have been accomplished by starting from commercially available (*S*)-nicotine.[11] The concise synthesis of 5-ethynylnicotine analog SIB-1508,[12] (*S*)-brevicolline,[13] and (*S*)-macrostomine[14] using (*S*)-nicotine as the starting material has also been reported.

Amidation of aromatic rings can be concisely realized by transition metal-mediated cross-coupling reactions.[15] As part of our nicotine analog program, a study was initiated to develop syntheses of C-4 amidated nicotine derivatives as potential nAChRs agonists. The synthesis of seven novel nicotine derivatives from (*S*)-nicotine via copper(I)- or (II)-mediated cross-coupling reactions are reported herein.

The amides pyrrolidinone (**6**), 2-pyridone (**7**), isoquinolinones (**8** and **9**), and formamide (**10**) were chosen as coupling

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partners for the synthesis of C-4 substituted (*S*)-nicotine derivatives due to their potential for pharmacological function and further elaboration (Figure 2). A useful C-4 substitution

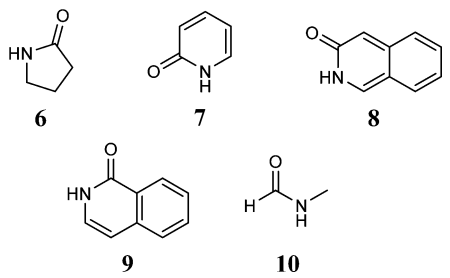


Figure 2. Amides used for the synthesis of C-4 substituted amido (*S*)-nicotine analogs.

was developed by us after finding that (*S*)-6-chloronicotine (**11**) can be lithiated at the C-4 position using *n*-BuLi.[11] A regioselective C-4 lithiation of (*S*)-nicotine using the alkyllithium, $TMSCH_2Li$, was reported by Gros and co-workers.[16] These methods paved the way to the successful synthesis of C-4 amido nicotine derivatives (**12**–**18**) via a copper(I)-mediated Buchwald-Hartwig type reaction (Figure 3). Boronic acid pinacol ester (BPin) was also successfully

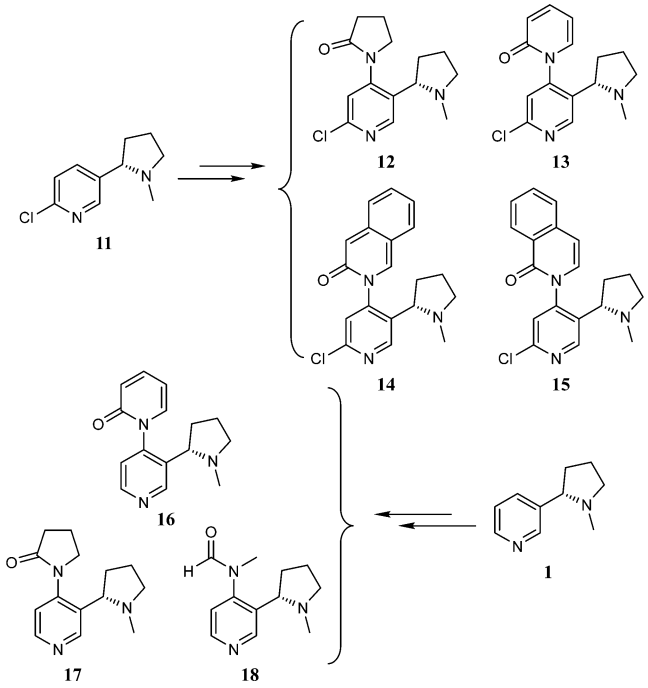
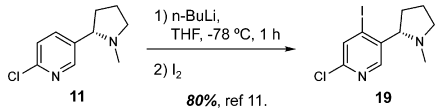


Figure 3. C-4 substituted nicotine derivatives targeted for the amidation of **11** and **1**.

introduced at the C-4 position of **1**, and the copper(II)-mediated Chan–Evans–Lam (CEL) route was utilized to prepare analogs **16**–**18**.

(*S*)-6-Chloronicotine (**11**) was iodinated at the C-4 positon to give **19** using our directed metalation reaction[11] (Scheme 1). The cross-coupling reaction between **19** and amides **6**–**9** using different reaction conditions (bases, copper(I) salts, and ancillary ligands) was studied to afford the desired C-4 substitution products. Buchwald and co-workers had compared the efficacy of different 1,2-diamine ligands for the amidation of

Scheme 1. Synthesis of (*S*)-6-Chloro-4-iodo-nicotine (19) from (*S*)-6-Chloronicotine (11)



aryl halides.[17] The bidentate *N*,*N*′-dimethylethylenediamine (DMEDA) **L1** or *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine were reported to be the most active ligands. Later, *β*-keto ester **L2** (Table 1) and 1,10-phenanthroline were also found to deliver high reactivity.[18] The choice of base was speculated to play an important role since the rate of deprotonation of the amide was suggested to match the rate of amidation. The inorganic bases that are thermodynamically strong with low solubility in organic solvents were found to be most effective.[17,19]

Based on these studies, the efficacy of the bidentate ligands was explored for the synthesis of **12**–**15**. While **13** was prepared using CuBr as catalyst and *β*-keto ester **L2** as ligand (entry 2, Table 1), the same catalytic system delivered poor yields for the other substrates. The use of CuI as catalyst and DMEDA **L1** as ligand delivered higher yields (entries 1, 3, and 4) and seemed to be more applicable for our substrates. The use of 1,4-dioxane made the solubility of the inorganic, strong base less favored and delivered the highest yield (entry 3). In general, a temperature of 90 °C and a long reaction time (>20 h) were required to obtain moderate to good yields of product.

Next, the synthesis of the C-4 amido (*S*)-nicotine derivatives **16**-**18** was investigated. Iodination at the C-4 position of **1** to afford (*S*)-4-iodonicotine (**20**, Table 2) was realized via the smooth metalation using $TMSCH_2Li$ as the base.[16] As before, a survey of solvent, temperature, and reaction time was performed to optimize the preparation of **16**–**18**. The investigation was initiated by studying temperature effects. No reaction occurred when the temperature was below 110 °C in 1,4-dioxane (entries 1, 6, and 9, Table 2). By elevating the temperature to 110 °C and using DMSO as solvent, the coupling reaction proceeded. Polar, aprotic solvents, such as DMF or DMSO, have been used to facilitate the *N*-arylation of the polar amides and carbamates.[18a,20] While DMSO worked well as a solvent for the preparation of **16** and **17** (entries 3, 4 and 7), with amide **10** it produced side products with similar polarity to the desired product **18** affecting the low yield observed (entry 8). In contrast, the reaction with optimized yield was performed when toluene was used as the solvent for preparing **18** (entry 10). The increase in yield was not significant when the reaction time was prolonged to 48 h.

The syntheses of the C-4 amido nicotine derivatives **16**–**18** were expected to proceed via the copper(II)-promoted Chan–Evans–Lam (CEL) reaction from the C-4 borate-functionalized nicotine **22** (Scheme 2) and amides **6**, **7**, and **10**. The boronic ester substituent was introduced at the C-4 position via lithiation using $TMSCH_2Li$. First, trimethyl borate was employed as electrophile and the 4-boronic acid-nicotine was readily prepared; however, all attempts on reacting the boronic acid with a diol (1,3-propanediol, ethylene glycol or pinacol) in toluene with water azeotropically removed[21] failed. Fortunately, reaction of pinacolborate **21** with the C-4 lithiated nicotine provided the desired (*S*)-4-BPin-nicotine **22**.

Typical CEL conditions were applied for preparing **16** from **22** and **7** using $Cu(OAc)_2$ as catalyst, pyridine as base, CH_2Cl_2

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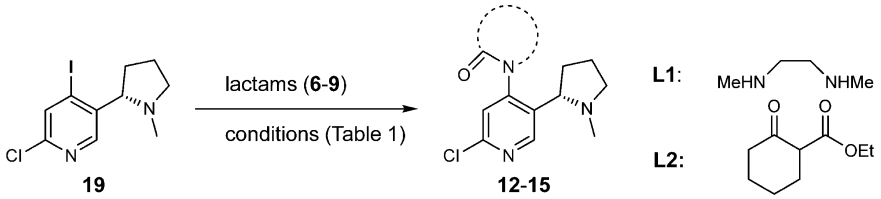
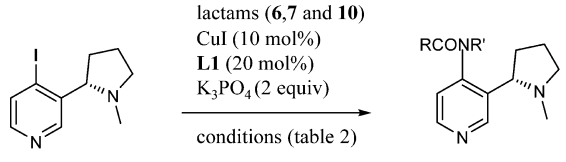
Table 1. C-4 Amidation of 19 via Copper(I)-Mediated Cross-Coupling



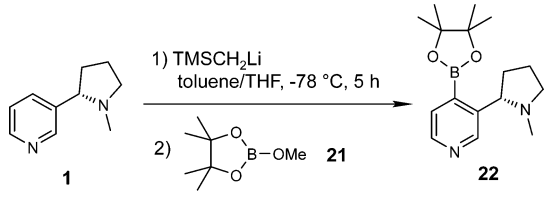
entry	lactams	conditions	product	yield
1	**6** (1.3 equiv)	CuI (20 mol%), **L1** (30 mol%), K_3PO_4 (2 equiv), 1,4-dioxane, 90 °C, 20 h	**12**	36%
2	**7** (1.2 equiv)	CuBr (10 mol%), **L2** (20 mol%), Cs_2CO_3 (2 equiv), THF/DMSO (1:1), 60 °C, 48 h	**13**	45%
3	**8** (1.2 equiv)	CuI (10 mol %), **L1** (30 mol%), K_3PO_4 (2 equiv), 1,4-dioxane, 90 °C, 48 h	**14**	67%
4	**9** (1.2 equiv)	CuI (5 mol%), **L1** (10 mol%), K_3PO_4 (2 equiv), 1,4-dioxane, 90 °C, 60 h	**15**	45%

Table 2. Reaction Optimization for the C-4 amidation of (*S*)-Nicotine Derivatives 16-18 via Copper(I) Iodide-Mediated Cross-Coupling



entry	amides	conditions	product	yield
1	**7**	1,4-dioxane, 100 °C, 48 h	NR	NA
2	**7**	DMSO, 100 °C, 48 h	**16**	39%
3	**7**	DMSO, 110 °C, 48 h	**16**	69%
4	**7**	DMSO, 110 °C, 24 h	**16**	67%
5	**6**	DMSO, 100 °C, 48 h	**17**	< 10%
6	**6**	1,4-dioxane, 110 °C, 48 h	NR	NA
7	**6**	DMSO, 110 °C, 28 h	**17**	62%
8	**10**	DMSO, 110 °C, 28 h	**18**	22%
9	**10**	1,4-dioxane, 110 °C, 28 h	NR	NA
10	**10**	toluene, 110 °C, 28 h	**18**	51%

Scheme 2. Synthesis of (*S*)-4-BPin-Nicotine (22) from (*S*)-Nicotine (1)



as solvent, and powdered 4 Å molecular sieves (MS) at room temperature in air (entry 1, Table 3). Although the conditions were quite mild and afforded the desired product **16** in moderate yield, no reaction occurred using amide **6** for the preparation of **17**. Replacement of CH_2Cl_2 with THF at 70 °C provided significant increase in the formation of both **16** and **17** (entries 2 and 5). While excess amount of **6** (3.0 equiv) was used to increase the yield at 70 °C, the use of triethylamine instead of pyridine afforded **17** in lower yield (entry 4). Similar reactions at 80 °C in MeCN were reported to be efficient for C–N bond formation for aryl BPin substrates.[22] These conditions were directly applied to the preparation of **18** but resulted in low yield (entry 6). When MeCN was replaced by propionitrile and the temperature was increased to 98 °C, the yield of **18** was increased to a moderate level (entry 7).

In summary, the synthesis of four C-4 amido (*S*)-6-chloronicotine derivatives (**12**–**15**) and the corresponding three C-4 amido (*S*)-nicotine derivatives (**16**–**18**) were accomplished in 2–3 steps with moderate to good yields from commercially available (*S*)-nicotine. Compounds **16**–**18** were prepared through both the copper(I)-mediated Buchwald–Hartwig and the copper(II)-mediated CEL-type reactions. Investigation of various synthetic methodologies and nicotinic intermediates including **11**, **20**, and **22** has resulted in methods for amidation at the C-4 position of the pyridine ring of (*S*)-nicotine. The work reported here can be used for the preparation of various nicotine analogs, which may be beneficial as potential drug candidates in the future.

EXPERIMENTAL SECTION

(*S*)-3-(1-Methylpyrrolidin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (22). The pinacolborate reagent **21** was prepared by following the procedure of Lin and co-workers.[23] $TMSCH_2Li$ (5.2 mL, 0.76 M in hexane, 4 mmol, 2 equiv) was added dropwise to a solution of (*S*)-nicotine **1** (323 mg, 2 mmol, 1 equiv) in toluene (3 mL) at 0 °C. The orange solution was warmed up to rt (20 °C) and stirred for 5 h. Pinacolborate **21** (632 mg, 4 mmol, 2 equiv) was dissolved in freshly distilled THF (4 mL) and stirred with 4 Å molecular sieves at the same time. The solution of **21** was transferred via syringe to a new flask and cooled to −78 °C. Then the slurry of **1** was added dropwise using a syringe with thick needle (16 gauge). The red mixture was stirred for 30 min at −78 °C and then 1 h at rt. The reaction was quenched at −78 °C with stoichiometric amount of pinacol (0.236 g, 2 mmol) followed by saturated $NaHCO_3$ solution (1 mL). After extraction with Et_2O, the organic layer was dried over K_2CO_3 and concentrated under reduced pressure. The yellow oil was Kugelrohr distilled at 1 mmHg. As soon as temperature reached 120 °C, most volatile side products were removed and the residue remaining in the flask was allowed to cool to rt. The product was purified by column chromatography (SiO_2, 40% isopropanol/1% TEA/EtOAc) to afford 254 mg (44%) of **22** as a pale yellow oil. $[\alpha]_D^{20}$ −95 (c 0.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1H, J = 4.8 Hz), 8.26 (s, 1H), 7.39 (d, 1H, J = 4.7 Hz), 4.18 (dd, 1H, J = 6 and 7.6 Hz), 3.71 (m, 1H), 2.65 (m, 1H), 2.61 (s, 3H), 2.39 (m, 1H), 1.96 (m, 3H); ^{13}C NMR (700 MHz, $CDCl_3$) δ 152.8, 148.5, 144.4, 140.4, 126.5, 80.9, 74.5, 56.6, 46.1, 33.2, 26.9, 26.8, 25.6; DEPT (175 MHz, $CDCl_3$) δ CH, CH_3: 148.1, 144.0, 126.1, 74.1, 45.8, 26.5, 26.4; CH_2: 56.2, 33.2, 25.6; IR (neat) 3046, 2931, 2970, 1594, 1547, 1413, 1275, 1228, 1118, 1153, 1054, 960, 877, 834, 754, 696, 626 cm^{-1}; HRMS calcd for $C_{16}H_{25}BN_2O_2$ $(M+H)^+$ 289.2082, found 289.2075.

(*S*)-1-(2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridin-4-yl)-pyrrolidin-2-one (12). A round-bottom flask was charged with **19** (95 mg, 0.29 mmol, 1 equiv), K_3PO_4 (125 mg, 0.59 mmol, 2 equiv), CuI (11 mg, 0.059 mmol, 20 mol%), 1, 4-dioxane (5 mL) and DMEDA (**L1**, 10 μL, 0.094 mmol, 30 mol%) under nitrogen. The mixture was stirred for 30 min at rt and then pyrrolidin-2-one (**6**, 33.5 mg, 0.38 mmol, 1.3 equiv) was added. The reaction was warmed up to

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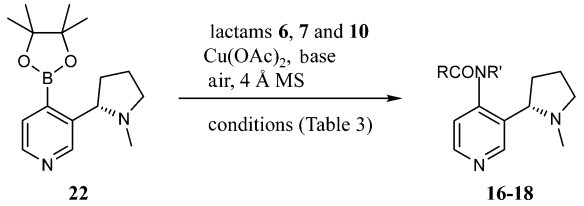
Table 3. Reaction Optimization for the C-4 Amidation of (*S*)-Nicotine Derivatives via Copper(II) Acetate-Mediated Cross-Coupling



22 **16-18**

entry	amides (equiv)	$Cu(OAc)_2$ (equiv)	base (equiv)	conditions	product	yield
1	**7** (1.2)	1.8	pyridine, 2.4	CH_2Cl_2, rt, 28 h	**16**	50%
2	**7** (1.2)	1.8	pyridine, 2.4	THF, 70 °C, 28 h	**16**	75%
3	**6** (1.5)	1.8	pyridine, 2.4	CH_2Cl_2, rt, 48 h	NR	NA
4	**6** (3.0)	1.8	triethylamine, 2.4	THF, 70 °C, 28 h	**17**	37%
5	**6** (3.0)	1.8	pyridine, 2.4	THF, 70 °C, 28 h	**17**	81%
6	**10** (1.2)	1.0	pyridine, 2.0	CH_3CN, 80 °C, 28 h	**18**	23%
7	**10** (1.2)	1.0	pyridine, 2.0	propionitile, 98 °C, 28 h	**18**	44%

90 °C and stirred for 20 h. The reaction was allowed to cool to rt and saturated aqueous $NaHCO_3$ (3 mL) was added. Extraction was performed with CH_2Cl_2. The combined organic layers were dried over K_2CO_3, filtered through a pad of Celite and concentrated *in vacuo*. The crude product was purified by radial PLC (SiO_2, 10% EtOAc/1% TEA/hexanes) to afford 30 mg (36%) of **12** as a clear oil. $[\alpha]_D^{20}$ −110 (c 1.30, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 7.06 (s, 1H), 3.65−3.79 (m, 2H), 3.11−3.21 (m, 2H), 2.55 (t, J = 8.0 Hz, 1H), 2.20−2.30 (m, 4H), 2.12 (s, 3H), 1.87−1.96 (m, 1H), 1.74−1.81 (m, 1H), 1.63−1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 151.5, 150.2, 147.7, 136.1, 121.2, 64.1, 57.0, 51.1, 40.6, 34.4, 31.2, 23.0, 19.4; IR (neat) 3469, 2850, 2924, 2786, 1700, 1577, 1556, 1464, 1402, 1289, 1119, 1080, 971 cm^{-1}; HRMS calcd for $C_{14}H_{18}ClN_3O$ $(M+H)^+$ 280.1211, found 280.1212.

(*S*)-2′-Chloro-5′-(1-methylpyrrolidin-2-yl)-2H-[1,4′-bipyridin]-2-one (13). A round-bottom flask was charged with **19** (220 mg, 0.68 mmol, 1 equiv), Cs_2CO_3 (467 mg, 1.43 mmol, 2 equiv), CuBr (10 mg, 0.07 mmol, 10 mol%), THF/DMSO (1:1, 4 mL), and ethyl 2-oxocyclohexanecarboxylate (**L2**, 22 μL, 0.14 mmol, 20 mol%) under nitrogen. The mixture was stirred for 30 min at rt and then pyridin-2(1H)-one (**7**, 78 mg, 0.82 mmol, 1.2 equiv) was added. The mixture was heated at 60 °C for 48 h. The reaction was allowed to cool to rt and EtOAc/Et_2O (1:1, 5 mL) was added. The suspension was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by radial PLC (SiO_2, 10% EtOAc/1% TEA/hexanes) to afford 186 mg (45%) of **13** as a clear oil. $[\alpha]_D^{20}$ −123 (c 0.65, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.23 (dd, J = 5.2, 2.4 Hz, 1H), 7.78 (td, J = 7.6, 2.4 Hz, 1H), 7.13 (td, J = 5.2, 1.2 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.95 (s, 1H), 3.45 (t, J = 8.4 Hz, 1H), 3.19 (td, J = 7.6, 1.6 Hz, 1H), 2.16−2.28 (m, 2H), 2.22 (s, 1H), 1.84−1.92 (m, 1H), 1.71−1.78 (m, 1H), 1.62−1.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 161.2, 150.3, 150.2, 148.1, 140.3, 130.2, 120.4, 114.9, 112.8, 62.6, 57.0, 40.9, 33.9, 22.9; IR (neat) 2942, 2779, 1678, 1586, 1562, 1457, 1428, 1235, 1079, 931, 777 cm^{-1}; HRMS calcd for $C_{15}H_{16}ClN_3O$ $(M+H)^+$ 290.1055, found 290.1051.

(*S*)-2-(2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridin-4-yl)-isoquinolin-3(2H)-one (14). To a mixture of **19** (96 mg, 0.3 mmol, 1 equiv), K_3PO_4 (126 mg, 0.59 mmol, 2 equiv), and CuI (6 mg, 0.03 mmol, 10 mol%) in freshly distilled 1, 4-dioxane (5 mL) was added **L1** (10 μL, 0.094 mmol, 30 mol%) at rt under nitrogen. After stirring for 30 min, isoquinolin-3(2H)-one (**9**, 52 mg, 0.35 mmol, 1.2 equiv) was added and the new mixture was stirred for another 30 min at rt. The mixture was then warmed to 90 °C and stirred for 48 h. The mixture was allowed to cool to rt and saturated aqueous $NaHCO_3$ solution (3 mL) was added. Extractions were performed with CH_2Cl_2 and the combined organic extracts were dried over anhydrous K_2CO_3, filtered through a pad of Celite, and concentrated *in vacuo*. Purification was carried out by radial PLC (SiO_2, 30% EtOAc/1% TEA/hexanes) to afford 68 mg (67%) of **14** as a clear oil. $[\alpha]_D^{20}$ −112 (c 1.80, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.55 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.34 (s, 1H), 6.74 (s, 1H), 3.60 (t, J = 8.4 Hz, 1H), 3.21 (td, J = 8.4, 2.0 Hz, 1H), 2.29−2.37 (m, 2H), 2.27 (s, 3H), 1.85−1.93 (m, 1H), 1.66−1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 157.4, 152.1, 150.2, 150.0, 139.1, 131.4, 129.2, 127.9, 127.2, 126.8, 126.3, 112.8, 107.5, 62.4, 57.0, 40.9, 33.8, 22.9; IR (neat) 2966, 2779, 1630, 1561, 1458, 1436, 1347, 1268, 1235, 1156, 964, 934, 752 cm^{-1}; HRMS calcd for $C_{19}H_{18}ClN_3O$ $(M+H)^+$ 340.1211, found 340.1206.

(*S*)-2-(2-Chloro-5-(1-methylpyrrolidin-2-yl)pyridin-4-yl)-isoquinolin-1(2H)-one (15). A round-bottom flask was charged with **19** (115 mg, 0.36 mmol, 1 equiv), K_3PO_4 (151 mg, 0.71 mmol, 2 equiv), CuI (3 mg, 0.018 mmol, 5 mol%), freshly distilled 1,4-dioxane (3 mL), and **L1** (10 μL, 0.036 mmol, 10 mol%) under nitrogen. The mixture was stirred for 30 min at rt and then isoquinolin-1(2H)-one (**8**, 62 mg, 0.43 mmol, 1.2 equiv) was added. The reaction was heated at 90 °C for 60 h. The reaction was allowed to cool to rt and saturated aqueous $NaHCO_3$ solution (3 mL) was added. Extraction was performed with CH_2Cl_2. The combined organic layers were dried over K_2CO_3, filtered through a pad of Celite and concentrated *in vacuo*. Purification was carried out by radial PLC (SiO_2, 30% EtOAc/1% TEA/hexanes) to afford 55 mg (45%) of **15** as a colorless oil. $[\alpha]_D^{20}$ −90 (c 1.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 6.8 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 5.6 Hz, 1H), 7.17 (s, 1H), 3.43 (t, J = 8.0 Hz, 1H), 3.15 (t, J = 8.0 Hz, 1H) 2.22 (s, 3H), 2.16−2.20 (m, 2H) 1.83−1.92 (m, 1H), 1.69−1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 158.7, 150.4, 150.2, 139.5, 138.9, 131.4, 130.9, 127.9, 126.7, 123.7, 119.6, 118.1, 116.6, 62.7, 56.9, 40.9, 34.0, 22.9; IR (neat) 3058, 2967, 2873, 2840, 2783, 1631, 1586, 1562, 1496, 1455, 1366, 1341, 1233, 1078, 1057, 923, 819 cm^{-1}; HRMS calcd for $C_{19}H_{18}ClN_3O$ $(M+H)^+$ 340.1211, found 340.1201.

(*S*)-3′-(1-Methylpyrrolidin-2-yl)-2H-[1, 4′-bipyridin]-2-one (16). *Copper(I)-Mediated Reaction.* A round-bottom flask was charged with **20** (70 mg, 0.24 mmol, 1 equiv), K_3PO_4 (103 mg, 0.49 mmol, 2 equiv), CuI (5 mg, 0.024 mmol, 10 mol%), DMSO (4.5 mL), and **L1** (5.2 μL, 0.049 mmol, 20 mol%) under nitrogen. The mixture was stirred for 30 min at rt and then pyridin-2(1H)-one (**7**, 28 mg, 0.29 mmol, 1.2 equiv) was added. The reaction was heated to 110 °C and stirred for 48 h. The mixture was allowed to cool to rt and H_2O (5 mL) was added. Extraction was performed with Et_2O. The combined organic layers were washed with brine and saturated aqueous $NaHCO_3$ solution sequentially, dried over K_2CO_3, filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 50% EtOAc/1% TEA/hexanes) to afford 41 mg (69%) of **16** as a colorless oil.

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Copper(II)-Mediated Reaction. A vial was charged with **22** (17 mg, 0.057 mmol, 1 equiv), anhydrous pyridine (0.011 mL, 0.14 mmol, 2.4 equiv), anhydrous $Cu(OAc)_2$ (19 mg, 0.11 mmol, 1.8 equiv), molecular sieves (4 Å, powder, 4 mg), THF (5 mL) and pyridin-2(1H)-one (**7**, 7 mg, 0.069 mmol, 1.2 equiv). The mixture was stirred under air at 70 °C for 28 h. The reaction was allowed to cool to rt and passed through a pad of Celite. After concentration under reduced pressure, the crude product was purified by column chromatography (SiO_2, 50% EtOAc/1% TEA/hexanes) to afford 11 mg (75%) of **16** as a colorless oil. $[\alpha]_D^{20}$ −79 (c 0.47, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.42 (d, J = 5.7 Hz, 1H), 8.20 (ddd, J = 5.1, 2.1, and 0.9 Hz, 1H), 7.74 (ddd, J = 8.1, 7.2, and 2.1 Hz, 1H), 7.07 (ddd, J = 7.2, 5.1, and 0.9 Hz, 1H), 6.97 (ddd, J = 8.1, 0.9, and 0.9 Hz, 1H), 6.90 (d, J = 5.7 Hz, 1H), 3.45−3.50 (m, 1H), 3.17−3.23 (m, 1H), 2.19−2.29 (m, 1H), 2.22 (s, 3H), 2.13−2.18 (m, 1H), 1.82−1.98 (m, 1H), 1.63−1.79 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.3, 159.6, 151.0, 149.3, 148.0, 140.0, 130.8, 119.7, 115.1, 112.4, 62.8, 57.1, 40.9, 33.8, 22.9; IR (neat) 3053, 2942, 2844, 2781, 1677, 1566, 1468, 1425, 1267, 1247, 1141, 1042, 987, 889, 830, 774, 664 cm^{-1}; HRMS calcd for $C_{15}H_{17}N_3O$ $(M+H)^+$ 256.1444, found 256.1442.

(*S*)-1-(3-(1-Methylpyrrolidin-2-yl)pyridin-4-yl)pyrrolidin-2-one (17). *Copper(I)-Mediated Reaction.* A round-bottom flask was charged with **20** (77 mg, 0.27 mmol, 1.0 equiv), K_3PO_4 (113 mg, 0.53 mmol, 2.0 equiv), CuI (5 mg, 0.027 mmol, 10 mol%), DMSO (5 mL) and **L1** (5.7 μL, 0.053 mmol, 20 mol%) under nitrogen. The mixture was stirred for 30 min at rt and then pyrrolidin-2-one (**6**, 94 mg, 1.1 mmol, 4.1 equiv) was added. The reaction was heated to 110 °C and stirred for 28 h. The mixture was allowed to cool to rt and H_2O (5 mL) was added. Extraction was performed with Et_2O. The combined organic layers were washed with brine and saturated aqueous $NaHCO_3$ solution sequentially, dried over K_2CO_3, filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 1% TEA/1% MeOH/EtOAc) to afford 40 mg (62%) of **17** as a yellow oil.

Copper(II)-Mediated Reaction. A vial was charged with **22** (31 mg, 0.11 mmol, 1 equiv), anhydrous pyridine (0.05 mL, 0.65 mmol, 2.4 equiv), anhydrous $Cu(OAc)_2$ (63 mg, 0.35 mmol, 1.8 equiv), molecular sieves (4 Å, powder, 5 mg), THF (5 mL), and pyrrolidin-2-one (**6**, 25.7 μL, 0.33 mmol, 3 equiv). The reaction was stirred under air at 70 °C for 28 h. The mixture was allowed to cool to rt and passed through a pad of Celite. After concentration under reduced pressure, the crude product was purified by column chromatography (SiO_2, 1% TEA/1% MeOH/EtOAc) to afford 21 mg (81%) of **17** as a colorless oil. $[\alpha]_D^{20}$ −98 (c 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.85 (dd, J = 5.1 and 0.6 Hz, 1H), 7.01 (d, J = 5.2 Hz, 1H), 3.78 (m, 1H), 3.68 (m, 1H), 3.19 (m, 2H), 2.57 (t, J = 8.1 Hz, 2H), 2.24 (m, 4H), 2.14 (s, 3H), 1.94 (m, 1H), 1.75 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 174.7, 151.6, 149.2, 145.3, 136.6, 120.7, 64.5, 57.0, 51.2, 40.7, 34.3, 31.2, 23.0, 19.3; IR (neat) 2934, 2848, 2781, 1704, 1587, 1488, 1457, 1414, 1308, 1245, 1167, 1112, 1042, 901, 838, 673 cm^{-1}; HRMS calcd for $C_{14}H_{19}N_3O$ $(M+H)^+$ 246.1601, found 246.1599.

(S)-*N*-Methyl-*N*-(3-(1-methylpyrrolidin-2-yl)pyridin-4-yl)-formamide (18). *Copper(I)-Mediated Reaction.* A round-bottom flask was charged with **20** (154 mg, 0.53 mmol, 1 equiv), K_3PO_4 (226 mg, 1.07 mmol, 2 equiv), CuI (10 mg, 0.053 mmol, 10 mol%), toluene (8 mL), and **L1** (11.5 μL, 0.107 mmol, 20 mol%) under nitrogen. The mixture was stirred for 30 min at rt and then *N*-methylformamide (**10**, 48 mg, 0.8 mmol, 1.5 equiv) was added. The reaction was heated to 110 °C and stirred for 28 h. The reaction was allowed to cool to rt and H_2O (10 mL) was added. Extraction was performed with Et_2O. The combined organic layers were washed with brine and saturated aqueous $NaHCO_3$ solution sequentially, dried over K_2CO_3, filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, 30% hexanes/1% TEA/EtOAc) to afford 59 mg (51%) of **18** as a colorless oil.

Copper(II)-Mediated Reaction. A vial was charged with **22** (47 mg, 0.16 mmol, 1 equiv), anhydrous pyridine (0.026 mL, 0.32 mmol, 2 equiv), anhydrous $Cu(OAc)_2$ (29 mg, 0.16 mmol, 1 equiv), molecular sieves (4 Å, powder, 5 mg), propionitrile (5 mL), and *N*-methylformamide (**10**, 12 μL, 0.2 mmol, 1.2 equiv). The reaction was stirred under air at 98 °C for 28 h. The reaction was allowed to cool to rt and passed through a pad of Celite. After concentration under reduced pressure, the crude product was purified by column chromatography (SiO_2, 30% hexanes/1% TEA/EtOAc) to afford 16 mg (44%) of **18** as a colorless oil. $[\alpha]_D^{20}$ −99 (c 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.53 (d, J = 5.1 Hz, 1H), 8.10 (s, 1H), 7.02 (d, J = 5.1 Hz, 1H), 3.27 (m, 1H), 3.21 (s, 3H), 2.24 (m, 2H), 2.16 (m, 1H), 2.11 (s, 3H), 1.97 (m, 1H), 1.78 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.4, 152.3, 149.5, 148.0, 136.1, 121.3, 63.96, 56.8, 40.5, 35.2, 33.8, 23.0; IR (neat) 2938, 2880, 2848, 2781, 1685, 1583, 1487, 1457, 1405, 1338, 1295, 1224, 1113, 1042, 983, 900, 841, 683 cm^{-1}; HRMS calcd for $C_{12}H_{17}N_3O$ $(M+H)^+$ 220.1444, found 220.1442.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02319.

Copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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