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Synthesis of Indolines by Copper-Mediated Intramolecular Aromatic C−H Amination

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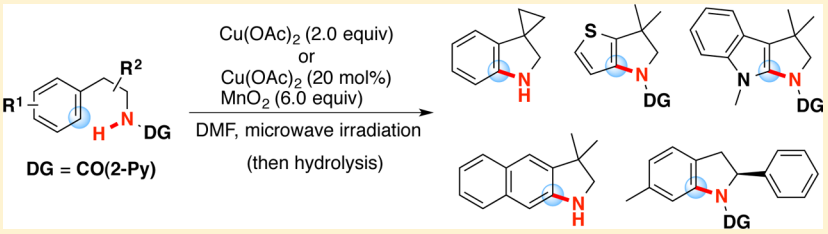
Supporting Information



ABSTRACT: A $Cu(OAc)_2$-mediated intramolecular aromatic C−H amination proceeds with the aid of a picolinamide-type bidentate coordination group to deliver the corresponding indolines in good yields. The reaction occurs smoothly even under noble-metal-free conditions, and in some cases the use of an MnO_2 terminal oxidant renders the process catalytic in Cu. The mild oxidation aptitude of $Cu(OAc)_2$ and/or MnO_2 accommodates the formation of electron-rich thiophene- and indole-fused indoline analogues. The Cu-based system can provide an effective approach to various indolines of potent interest in pharmaceutical and medicinal chemistry.

INTRODUCTION

Indolines are representative alicyclic N-heterocycles and are ubiquitous in biologically active compounds and pharmaceutical targets.[1] Many research groups thus have studied and developed versatile methodologies for the efficient synthesis of indolines. Among them, metal-catalyzed C−N cross-coupling ranks as a powerful and reliable access to the above targets. This process generally includes a two-step sequence: i.e., halogenation of an aromatic C−H bond followed by intramolecular aromatic C−N formation by Pd,[2] Cu,[3] or Ni[4] catalyst. On the other hand, recent advances in metal-mediated C−H activation[5] can skip the prefuctionalization, that is halogenation, of the starting aromatic compounds and provide a potentially more efficient and atom-economical C−H amination approach to the indoline structure.[6] However, most precedents still rely on palladium catalysts and relatively strong F^+- or I(III)-based oxidants. Moreover, the synthesis of electron-rich heteroarene-fused indoline analogues under such oxidative conditions is still challenging, probably due to the harsh conditions associated with the above strong oxidants. Therefore, there still remains a large demand for further development of the intramolecular aromatic C−H amination directed toward the indoline synthesis.

Meanwhile, our group[7] and others[8] focused on Cu salts as inexpensive, less toxic, and abundant alternatives to noble transition metals and succeeded in the development of some unique transformations via directed C−H cleavage. In the course of this study, we recently found the $Cu(OAc)_2/MnO_2$-catalyzed intramolecular C−H/N−H coupling for the synthesis of carbazoles.[7g,9] The mild reaction conditions allow relatively oxidation labile electron-rich heteroaromatic substrates to be adopted in the oxidative C−H amination. The observed unique feature of the Cu/Mn catalysis encouraged us to develop a Cu-based system for the construction of other related N-heterocycles. Herein, we report $Cu(OAc)_2$-mediated and $Cu(OAc)_2/MnO_2$-catalyzed intramolecular C−H aminations for the synthesis of indolines. Similar to the previous carbazole construction, the reaction proceeds smoothly under noble-metal-free conditions and tolerates a wide range of substrates, including electron-rich thiophene and indole (Scheme 1). To the best of our knowledge, this is the first successful synthesis of indolines by Cu-promoted intramolecular C−H amination.[10]

RESULTS AND DISCUSSION

We initially prepared some 2-methyl-2-phenylpropan-1-amines **1** and attempted the C−H amination with 2.0 equiv of $Cu(OAc)_2$ in DMF under microwave irradiation (200 °C, 40 min), which are the standard stoichiometric conditions in our previous work,[7g] to identify an appropriate substituent on the nitrogen atom (Scheme 2). To our delight, substrates bearing the picolinoyl[11] (**1a**) and quinolinoyl[12] (**1a-COQ**) groups showed promising activity, while the benzamide **1a-Bz** and parent **1a-H** did not form the indoline ring at all. The above results apparently suggest the critical effect of the N,N-bidentate coordination ability in **1a** and **1a-COQ**. In view of the more ready availability and better reactivity with the picolinamide **1a**, we began to optimize catalytic conditions (Table 1). Among the terminal oxidants we tested, only MnO_2 worked well, and the corresponding indoline **2a** was detected in

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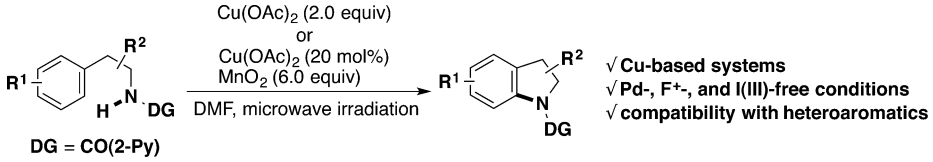
Scheme 1. Copper-Mediated and Copper-Catalyzed Intramolecular Aromatic C−H Amination for the Synthesis of Indolines



Scheme 2. Effects of Substituents on Nitrogen in Copper-Mediated C−H Amination for Synthesis of Indoline 2

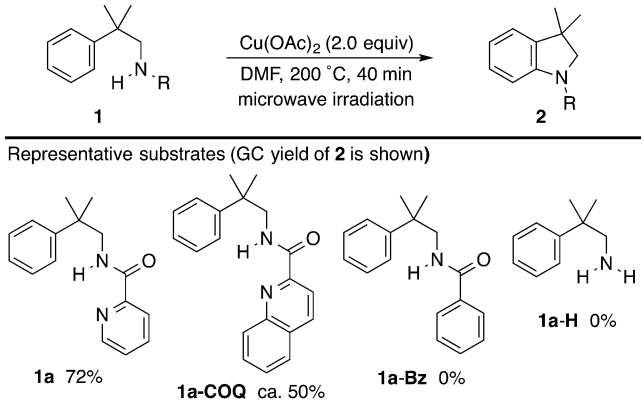
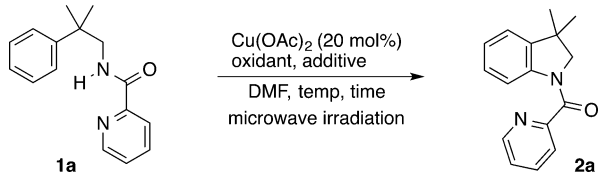


Table 1. Optimization Studies for Copper-Catalyzed Intramolecular C−H Amination of 1a[a]



entry	oxidant (amt (equiv))	additive (amt (equiv))	temp (°C)	time (min)	GC yield (%)
1	MnO_2 (2.0)	none	200	90	41
2	MnO_2 (4.0)	none	200	60	54
3	$Na_2S_2O_8$ (4.0)	none	200	60	0
4	$K_2S_2O_8$ (4.0)	none	200	60	0
5	MnO_2 (4.0)	AcOH (1.0)	200	60	32
6	MnO_2 (4.0)	none	250	60	51
7	MnO_2 (4.0)	none	180	60	40
8	MnO_2 (6.0)	none	200	90	61
9[b]	MnO_2 (6.0)	none	200	90	0

[a]Reaction conditions: **1a** (0.25 mmol), $Cu(OAc)_2$ (0.050 mmol), oxidant, additive, DMF (1.5 mL). [b]Without $Cu(OAc)_2$.

54% GC yield (entries 1−4). Inconsistent with the precedented carbazole formation,[7g] the addition of AcOH was detrimental (entry 5). Neither increasing nor decreasing the reaction temperature improved the GC yield of **2a** (entries 6 and 7). Finally, with 6.0 equiv of MnO_2 and a prolonged reaction period (90 min), we obtained **2a** in 61% GC yield (entry 8). Excess MnO_2 was essential for a satisfactory conversion, probably because of its lower solubility in DMF. The control experiment without $Cu(OAc)_2$ confirmed the Cu catalysis in this process (entry 9).

We subsequently implemented the Cu-promoted C−H amination of various phenylethylamines **1**. For all substrates, both stoichiometric (A) and catalytic (B) conditions were applied. In several cases, including the model material **1a**, an additional hydrolysis was performed for easy purification of the indoline product through simple acid/base extraction (see the Experimental Section for details). Representative products are shown in Scheme 3. In addition to **2a-H**, the reaction accommodated electronically diverse functions such as Me, Ph, MeO, CF_3, and Cl (**2b-H**, **2c-H**, **2d-H**, **2e**, and **2f-H**). The stoichiometric conditions A generally gave higher yields, but the catalytic conditions B were specifically suitable for the Cl-substituted substrate owing to the suppression of the undesired, competitive protodechlorination (**2f-H**). When the substituent was introduced at the meta position on the benzene ring, sterically more accessible C−H bonds were selectively aminated (**2g-H** and **2h-H**). In contrast, the reaction of an ortho-substituted substrate was sluggish, probably due to steric factors (**2i**).[13] It should be noted that the mild oxidation aptitude of the present $Cu(OAc)_2$ and MnO_2 enabled the formation of thiophene- and indole-fused indoline analogues **2j,k** even under oxidative conditions. The Cu-based systems could also be applicable to the vinylic C−H amination, and the dihydropyrrole **2l** was obtained, albeit in a moderate yield.

Some substitution patterns at the benzylic position were tolerated: 3-methyl-3-phenylindoline (**2m-H**) and spiroindoline **2n-H** as well as monosubstituted 3-phenylindoline (**2o-H**) and 3-methylindoline **2p** were readily available. The *gem*-dimethyl and phenyl groups α to the nitrogen were also compatible under the reaction conditions (**2q,r**). It should be noted that the C−H amination proceeded with only slight to negligible erosion of enantiomeric purities of optically active starting materials (**2p,r**), which was confirmed by chiral HPLC analysis with authentic racemic samples (see the Supporting Information for details). Such chiral indolines are especially useful and are frequently found in biologically active and natural products.[1] On the other hand, the simplest phenylethylamine was the relatively reluctant substrate (**2s**),[14] thus indicating a positive Thorpe−Ingold effect[15] in the cyclization event. Although the above substituent-dependent reactivity remains to be addressed, conformationally regulated 3,3-disubstituted indolines obtained herein are known to show biological activity higher than that of the parent unsubstituted indolines and have received some attention in the field of medicinal chemistry.[16] Additionally notable is that all experiments conducted in Scheme 3 could be set up on the benchtop and performed without any special precautions related to air and moisture.

Some deuterium-labeling studies were next performed with **1a-d_5** (Scheme 4). The following experiments were carried out under the conventional heating conditions with an oil bath (170 °C, N_2), because under microwave-assisted conditions the reaction proceeded in the course of the preheating time up to 200 °C, and the conversion at an early stage was difficult to monitor. When the reaction was stopped in 1 h and the recovered starting material was analyzed by NMR, no H/D scrambling was observed. Additionally, major kinetic isotope effect (KIE) values of 2.5 and 2.6 were obtained from the parallel and competitive reactions of **1a** and **1a-d_5** (see the Supporting Information for detailed kinetic profiles in the parallel reaction). The above results suggest the irreversible,

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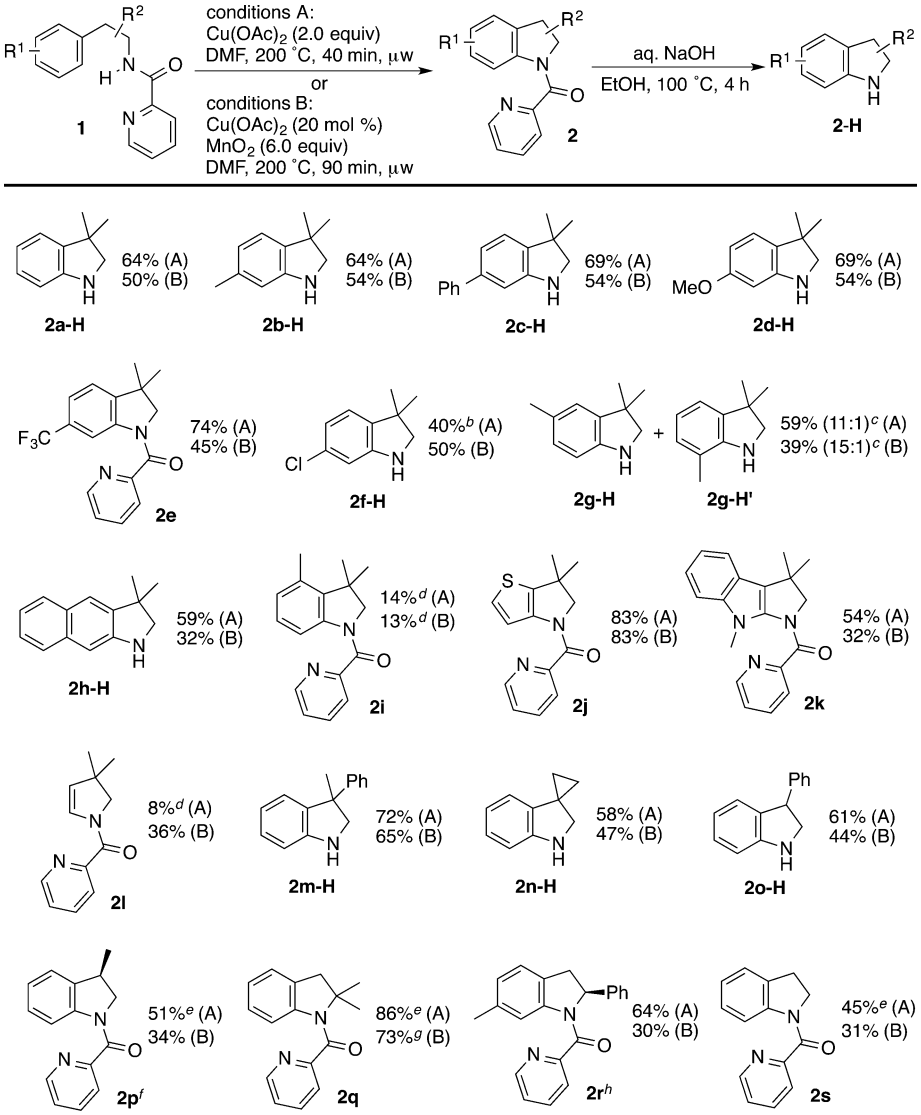
Scheme 3. Synthesis of Various Indolines 2 and 2-H by Copper-Mediated and Copper-Catalyzed Intramolecular C−H Amination of 1[a]



[a]Reaction conditions A: **1** (0.25 mmol), $Cu(OAc)_2$ (0.50 mmol), DMF (1.5 mL), 200 °C, 40 min, microwave irradiation. Reaction conditions B: **1** (0.25 mmol), $Cu(OAc)_2$ (0.050 mmol), MnO_2 (1.5 mmol), DMF (1.5 mL), 200 °C, 90 min, microwave irradiation. Hydrolysis: crude **2**, aqueous NaOH (6.0 M, 1.0 mL), EtOH (3.0 mL), 100 °C, 4 h. The yields are given. The conditions employed are given in parentheses (A or B). [b]NMR yield. The protodechlorination product, namely **2a-H**, was also formed in 13% NMR yield. [c]**2g-H**:**2g-H′** ratio. [d]GC yield. [e]20 min. [f]Starting from **1p** with 93:7 er. [g]With 0.25 mmol of AcOH. [h]Starting from **1r** with 99:1 er.

rate-limiting, and product-determining C−H cleavage of the substrate. On the other hand, addition of the radical scavengers TEMPO and galvinoxyl had a minor impact on the reaction efficiency, thus indicating that a single electron transfer (SET) pathway is less likely (Scheme 5).

On the basis of literature information and our findings, we are tempted to assume the reaction mechanism of **1a** to give **2a** is as follows (Scheme 6). Initial neutral and anionic N,N-bidentate coordination of the picolinamide moiety in **1a** to the $Cu(OAc)_2$ species **3** occurs to form the chelated cyclometalated Cu complex **4** with the liberation of AcOH. The crucial effect of the picolinamide-type directing groups in Scheme 1 is consistent with the proposed coordination mode. Subsequent irreversible, rate-limiting C−H cupration (**4** → **5**) is followed by one-electron oxidation (disproportionation) of Cu(II) into Cu(III)[17] with an additional $Cu(OAc)_2$ to generate the Cu(III) intermediate **6**. Productive reductive elimination provides the desired indoline **2a** along with the CuOAc species **7**. The catalytic cycle is completed by the MnO_2/AcOH-promoted reoxidation of **7** into the starting $Cu(OAc)_2$ species **3**.[18] Additionally, MnO_2 also reoxidizes the CuOAc species generated through the disproportionation. Although the detailed mechanism in the C−H cleavage step is still unclear, it is considered to involve an acetate-ligand-assisted concerted metalation−deprotonation pathway.[19]

■ CONCLUSION

We have developed a $Cu(OAc)_2$-mediated intramolecular aromatic C−H amination protocol for the synthesis of indolines. Moreover, the use of cheap and abundant MnO_2 renders the reaction catalytic in $Cu(OAc)_2$. The reaction proceeds smoothly even without Pd catalysts and F^+- and

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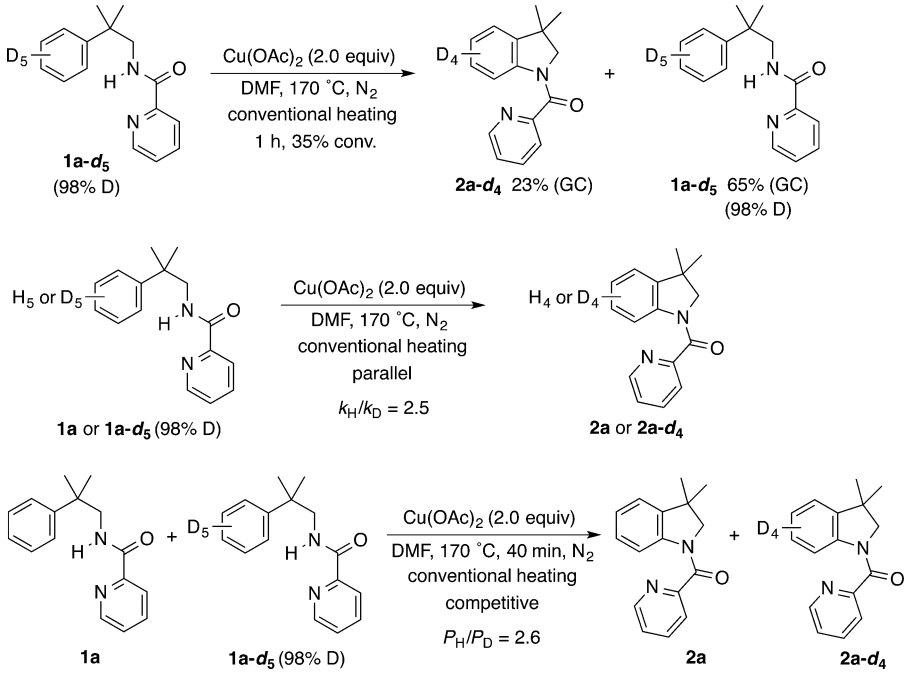
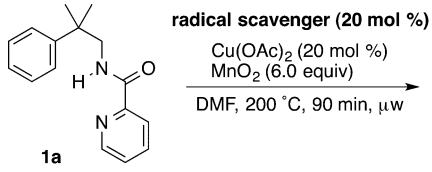
Scheme 4. Deuterium-Labeling Experiments

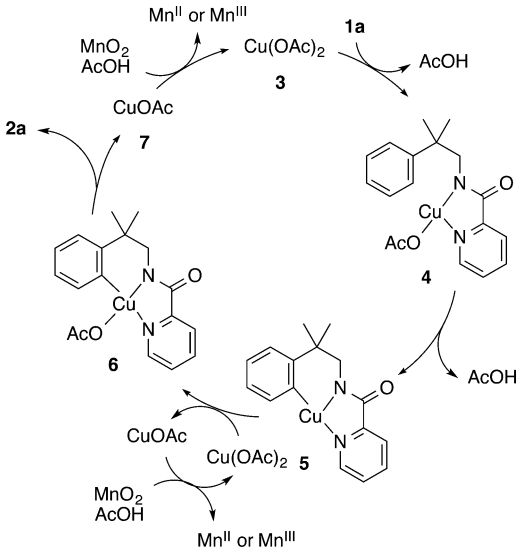


Scheme 5. Effects of Radical Scavengers



radical scavenger	GC yield of **2a**
none	61%
TEMPO	60%
galvinoxyl	53%

Scheme 6. Plausible Mechanism



I(III)-based oxidants, which are common promoters in the precedented C−H amination.[6] The mild oxidation aptitudes of both $Cu(OAc)_2$ and MnO_2 also allow the otherwise challenging formation of electron-rich thiophene- and indole-fused indoline analogues under oxidative conditions. Some deuterium-labeling experiments suggest irreversible, rate-limiting, and product-determining C−H cupration directed by the picolinamide-type bidentate coordination group. Detailed mechanistic studies and further development of related C−H activation catalysis based on Cu are ongoing in our laboratory.

EXPERIMENTAL SECTION

Instrumentation and Chemicals. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 400, 100, and 376 MHz, respectively, for $CDCl_3$ or DMSO-d_6 solutions. HRMS data were obtained by EI or APCI using a double-focusing mass spectrometer or TOF, respectively. GC analysis was carried out using a silicon OV-17 column (2.6 mm i.d. × 1.5 m) or a CBP-1 capillary column (0.5 mm i.d. × 25 m). TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck silica gel $60F_{254}$. Silica gel was used for column chromatography. Gel permeation chromatography (GPC) was performed with a $CHCl_3$ eluent (3.5 mL/min, UV detector). Microwave irradiation was conducted with Initiator$^+$ (Biotage), and the reaction temperature was measured by an internal probe. Unless otherwise noted, materials obtained from commercial suppliers were used as received. DMF was dried on a Glass Contour Solvent dispending system (Nikko Hansen & Co., Ltd.) prior to use. The starting amides **1a**−**m** were prepared from the corresponding benzyl nitriles in three steps: i.e., methylation, reduction, and condensation with picolinoyl chloride (see the following experimental procedure). Compounds **1n**−**s** were synthesized by the condensation of the commercially available parent secondary amines with picolinoyl chloride under the same conditions as in the synthesis of **1a**−**m**. The enantiomeric ratios of **1p**,**r** were 93:7 and 99:1 er, respectively, because the commercial sources, (*R*)-(+)-2-phenyl-1-propylamine (93:7 er, from TCI) and (*S*)-(+)-1-phenyl-2-(*p*-tolyl)ethylamine (99:1 er, from TCI), were employed without further optical resolution.

Preparation of Starting Materials 1. The synthesis of 2-methyl-2-phenylpropanenitrile (**1a**) is representative: sodium hydride (60 wt %, 1.5 g, 38 mmol) was placed in a 100 mL two-necked reaction flask,

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and the flask was flushed with nitrogen. Tetrahydrofuran (THF, 30 mL) and 2-phenylacetonitrile (1.8 g, 15 mmol) were then added at 0 °C, and the resulting solution was stirred at room temperature for 1 h. Iodomethane (6.4 g, 45 mmol) was then added at 0 °C, and the resulting solution was stirred at room temperature for an additional 13 h. The resulting mixture was quenched with water at 0 °C. The mixture was extracted with dichloromethane, and the combined organic layers were dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (5/1, v/v) gave 2-methyl-2-phenylpropanenitrile (2.1 g, 15 mmol) in 96% yield.

Lithium aluminum hydride (0.83 g, 22 mmol) was placed in a 100 mL two-necked reaction flask, and the flask was flushed with nitrogen. Tetrahydrofuran (THF, 30 mL) and 2-methyl-2-phenylpropanenitrile (2.1 g, 15 mmol) were added at 0 °C, and the resulting solution was stirred at room temperature for 4 h. The resulting mixture was then quenched with a minimum amount of water at 0 °C and filtered through a short pad of Celite. The filtrate was extracted with dichloromethane, and the combined organic layers were dried over sodium sulfate. Concentration in vacuo gave 2-methyl-2-phenylpropan-1-amine (2.0 g, 13 mmol) in 87% yield.

Pyridine-2-carbonyl chloride hydrochloride (2.6 g, 14 mmol) and *N*,*N*-dimethyl-4-aminopyridine (0.48 g, 3.9 mmol) were placed in a 100 mL two-necked reaction flask, and the flask was flushed with nitrogen. Dichloromethane (26 mL), triethylamine (2.9 g, 29 mmol), and the crude 2-methyl-2-phenylpropan-1-amine (1.9 g, 13 mmol) obtained above were added, and the mixture was stirred at room temperature for 24 h. The resulting mixture was then quenched with water. The mixture was extracted with dichloromethane, and the combined organic layers were dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (2/1, v/v) gave *N*-(2-methyl-2-phenylpropyl)-picolinamide (**1a**; 3.0 g, 12 mmol) in 91% yield.

Preparation of 1a-d_5. A 100 mL two-necked reaction flask was flushed with nitrogen. Tetrahydrofuran (THF, 20 mL) and 1-bromo-2,3,4,5,6-pentadeuteriobenzene (1.6 g, 10 mmol) were added. Butyllithium (1.6 M hexane solution, 6.9 mL, 11 mmol) was then added at −78 °C, and the resulting solution was stirred for 30 min at the same temperature. Trimethoxyborane (1.4 g, 13 mmol) was added, and the mixture was stirred for an additional 30 min at −78 °C. The resulting mixture was then warmed to room temperature and quenched with 1 M aqueous HCl. The mixture was extracted with dichloromethane, and the combined organic layers were dried over magnesium sulfate. Concentration in vacuo gave 2,3,4,5,6-pentadeuteriophenylboronic acid (1.3 g, 10 mmol). The crude material was used for the next step without further purification.

2,3,4,5,6-Pentadeuteriophenylboronic acid (1.3 g, 10 mmol), $Ni(acac)_2$ (64 mg, 0.25 mmol), triphenylphosphine (130 mg, 0.50 mmol), and potassium phosphate (6.4 g, 30 mmol) were placed in a 50 mL two-necked reaction flask equipped with a reflux condenser, and the flask was flushed with nitrogen. Toluene (30 mL) and bromoacetonitrile (580 mg, 5.0 mmol) were added, and the resulting solution was stirred at 80 °C for 3 h.[20] After being cooled to room temperature, the resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (5/1, v/v) gave 2-(2,3,4,5,6-pentadeuteriophenyl)acetonitrile (460 mg, 3.8 mmol) in 76% yield.

This compound was converted to **1a-d_5** by the same three-step sequence as for **1a**: i.e., methylation, reduction, and condensation. The three-step yield is 32% (98% D).

Typical Procedure for Synthesis of N−H Indolines 2-H. The synthesis of **2a-H** is representative.

Conditions A. $Cu(OAc)_2$ (91 mg, 0.50 mmol), *N*-(2-methyl-2-phenylpropyl)picolinamide (**1a**; 64 mg, 0.25 mmol), and *N*,*N*-dimethylformamide (DMF, 1.5 mL) were placed in a 2 mL microwave vessel. The vessel was sealed with a cap, and the mixture was irradiated under microwave reactor conditions at 200 °C for 40 min. The resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate. The volatile materials were evaporated under high vacuum. The residual oil, ethanol (3 mL), and 6 M aqueous NaOH (1 mL) were placed in a 100 mL recovery flask equipped with a reflux condenser, and the flask was flushed with nitrogen. The resulting solution was stirred at 100 °C for 4 h. The resulting mixture was quenched with water and extracted five times with 0.5 M aqueous HCl. The combined aqueous layer was neutralized with 6 M aqueous NaOH (4 mL) and then extracted three times with Et_2O. The combined organic layer was dried over magnesium sulfate. Concentration in vacuo gave 3,3-dimethylindoline (**2a-H**; 24 mg, 0.16 mmol) in 64% yield in an analytically pure form.

Conditions B. $Cu(OAc)_2$ (9.1 mg, 0.050 mmol), *N*-(2-methyl-2-phenylpropyl)picolinamide (**1a**; 64 mg, 0.25 mmol), manganese dioxide (130 mg, 1.5 mmol), and *N*,*N*-dimethylformamide (DMF, 1.5 mL) were placed in a 2 mL microwave vessel. The vessel was sealed with a cap, and the mixture was irradiated under microwave reactor conditions at 200 °C for 90 min. The resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate. After concentration under reduced pressure, the residual oil, ethanol (3 mL), and 6 M aqueous NaOH (1 mL) were placed in a 100 mL recovery flask equipped with a reflux condenser, and the flask was flushed with nitrogen. The resulting solution was stirred at 100 °C for 4 h. The resulting mixture was quenched with water and extracted 5 times with 0.1 M aqueous HCl. The combined aqueous layer was neutralized with 6 M aqueous NaOH (2 mL) and then extracted three times with Et_2O. The combined organic layers were dried over magnesium sulfate. Concentration in vacuo gave 3,3-dimethylindoline (**2a-H**; 19 mg, 0.13 mmol) in 50% yield in an analytically pure form.

*3,3-Dimethylindoline (**2a-H**).* Conditions A: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 24 mg (64%). Conditions B: purified by acid/base extraction with 0.1 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (2 mL); 19 mg (50%), oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 6H), 3.30 (s, 2H), 6.63 (ddd, J = 0.8, 1.2, 7.4 Hz, 1H), 6.74 (ddd, J = 0.8, 7.2, 7.6 Hz, 1H), 7.02 (ddd, J = 0.8, 1.2, 7.6 Hz, 1H), 7.04 (ddd, J = 1.2, 7.2, 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 27.7, 41.8, 61.7, 109.7, 118.9, 122.1, 127.4, 138.5, 150.4. HRMS (EI): m/z (M^+) calcd for $C_{10}H_{13}N$ 147.1048, found 147.1049.

*3,3,6-Trimethylindoline (**2b-H**).* Conditions A: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 26 mg (64%). Conditions B: purified by acid/base extraction with 0.1 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (2 mL); 21 mg (53%), oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 6H), 2.26 (s, 3H), 3.29 (s, 2H), 6.48 (t, J = 0.8 Hz, 1H), 6.56 (ddd, J = 0.8, 1.6, 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.6, 27.7, 41.5, 62.0, 110.6, 119.5, 121.8, 135.8, 137.3, 150.6. HRMS (EI): m/z (M^+) calcd for $C_{11}H_{15}N$ 161.1204, found 161.1206.

*3,3-Dimethyl-6-phenylindoline (**2c-H**).* Conditions A: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 8 times) and 6 M aqueous NaOH (6 mL); 39 mg (69%). Conditions B: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 8 times) and 6 M aqueous NaOH (6 mL); 30 mg (54%). Mp: 59.5−60.5 °C (from Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (s, 6H), 3.36 (s, 2H), 3.78 (bs, 1H), 6.85 (d, J = 1.6 Hz, 1H), 6.96 (dd, J = 1.6, 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.54 (d, J = 7.2 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 27.7, 41.7, 62.0, 108.5, 118.2, 122.3, 127.0, 127.3, 128.7, 137.8, 141.0, 142.0, 151.0. HRMS (EI): m/z (M^+) calcd for $C_{16}H_{17}N$ 223.1361, found 223.1362.

*6-Methoxy-3,3-dimethylindoline (**2d-H**).* Conditions A: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 30 mg (69%). Conditions B: purified by acid/base extraction with 0.1 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (2 mL); 24 mg (54%), oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 6H), 3.31 (s, 2H), 3.75 (s, 3H), 6.22 (d, J = 2.4 Hz, 1H), 6.28 (dd, J = 2.4, 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H). ^{13}C{^{1}H}

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NMR (100 MHz, $CDCl_3$): δ 27.9, 41.2, 55.5, 62.2, 96.4, 103.5, 122.3, 131.1, 151.7, 160.0. HRMS (EI): *m/z* (M^+) calcd for $C_{11}H_{15}NO$ 177.1154, found 177.1154.

*6-Chloro-3,3-dimethylindoline (**2f-H**).* Conditions A: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 23 mg (**2f-H** 40% + **2a-H** 13%). Conditions B: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 23 mg (50%), oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, 6H), 3.32 (s, 2H), 6.58 (d, *J* = 2.0 Hz, 1H), 6.67 (dd, *J* = 2.0, 8.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 27.7, 41.4, 61.9, 109.6, 118.4, 122.8, 132.9, 137.0, 151.6. HRMS (EI): *m/z* (M^+) calcd for $C_{10}H_{12}ClN$: 181.0658, found 181.0662.

*3,3,5-Trimethylindoline (**2g-H**).* Conditions A: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 24 mg (59%, **2g-H**:**2g-H′** 11:1). Conditions B: purified by acid/base extraction with 0.1 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (2 mL); 16 mg (39%, **2g-H**:**2g-H′** 15:1), oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 6H), 2.27 (s, 3H), 3.28 (s, 2H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.86 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.0, 27.6, 41.9, 62.0, 109.8, 122.9, 127.7, 128.3, 138.9, 148.0. HRMS (EI): *m/z* (M^+) calcd for $C_{11}H_{15}N$ 161.1204, found 161.1205.

*3,3-Dimethyl-2,3-dihydro-1H-benzo[f]indole (**2h-H**).* Conditions A: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 8 times) and 6 M aqueous NaOH (6 mL); 29 mg (59%). Conditions B: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 8 times) and 6 M aqueous NaOH (6 mL); 16 mg (32%). Mp: 71.5−73.0 °C (from Et_2O). ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 6H), 3.38 (s, 2H), 3.97 (bs, 1H), 6.85 (s, 1H), 7.18 (ddd, *J* = 0.8, 7.2, 8.0 Hz, 1H), 7.29 (ddd, *J* = 0.8, 7.2, 8.0 Hz, 1H), 7.42 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 27.9, 41.4, 61.6, 102.5, 120.6, 122.1, 125.5, 125.9, 127.8, 129.0, 134.7, 141.7, 149.3. HRMS (EI): *m/z* (M^+) calcd for $C_{14}H_{15}N$ 197.1204, found 197.1205.

*3-Methyl-3-phenylindoline (**2m-H**).* Conditions A: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 38 mg (72%). Conditions B: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 34 mg (65%), oil. ^1H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 3H), 3.57 (d, *J* = 8.8 Hz, 1H), 3.72 (d, *J* = 8.8 Hz, 1H), 3.77 (bs, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.97 (td, *J* = 1.2, 7.6 Hz, 1H), 7.09 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.19 (tt, *J* = 1.6, 6.8 Hz, 1H), 7.26−7.35 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 26.3, 49.8, 63.9, 110.1, 119.2, 124.3, 126.3, 126.7, 127.8, 128.3, 137.2, 147.8, 150.9. HRMS (EI): *m/z* (M^+) calcd for $C_{15}H_{15}N$ 209.1204, found 209.1206.

*Spiro[cyclopropane-1,3′-indoline] (**2n-H**).* Conditions A: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 21 mg (58%). Conditions B: purified by acid/base extraction with 0.1 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (2 mL); 17 mg (47%), oil. ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (dt, *J* = 1.6, 5.2 Hz, 2H), 0.99 (dt, *J* = 1.6, 5.2 Hz, 2H), 3.58 (s, 2H), 3.80 (bs, 1H), 6.60 (ddd, *J* = 0.4, 1.2, 7.6 Hz, 1H), 6.63 (td, *J* = 0.8, 7.6 Hz, 1H), 6.69 (dt, *J* = 0.8, 7.6 Hz, 1H), 6.99 (dt, *J* = 1.2, 7.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.6, 24.6, 55.6, 109.3, 118.5, 118.9, 126.8, 134.5, 151.9. HRMS (EI): *m/z* (M^+) calcd for $C_{10}H_{11}N$ 145.0891, found 145.0892.

*3-Phenylindoline (**2o-H**).* Conditions A: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 30 mg (61%). Conditions B: purified by acid/base extraction with 0.5 M aqueous HCl (5 mL × 5 times) and 6 M aqueous NaOH (4 mL); 21 mg (44%), oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.50 (t, *J* = 9.2 Hz, 1H), 3.80 (bs, 1H), 3.94 (t, *J* = 9.2 Hz, 1H), 4.49 (t, *J* = 9.2 Hz, 1H), 6.71 (dt, *J* = 0.8, 7.2 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 7.07 (tt, *J* = 0.8, 7.6 Hz, 1H), 7.21−7.34 (m, 5H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 48.8, 56.8, 109.9, 119.2, 125.2, 126.8, 127.9, 128.3, 128.7, 132.5, 143.7, 151.7. HRMS (EI): *m/z* (M^+) calcd for $C_{14}H_{13}N$ 195.1048, found 195.1049.

Typical Procedure for Synthesis of N-Picolinoyl Indolines 2. The synthesis of **2j** is representative.

Conditions A. $Cu(OAc)_2$ (91 mg, 0.50 mmol), *N*-(2-methyl-2-(thiophen-2-yl)propyl)picolinamide (**1j**, ;65 mg, 0.25 mmol), and *N*,*N*-dimethylformamide (DMF, 1.5 mL) were placed in a 2 mL microwave vessel. The vessel was sealed with a cap, and the mixture was irradiated under microwave reactor conditions at 200 °C for 40 min. The resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (2/1, v/v) gave (6,6-dimethyl-5,6-dihydro-4*H*-thieno[3,2-*b*]pyrrol-4-yl)(pyridin-2-yl)methanone (**2j**; 54 mg, 0.21 mmol) in 83% yield.

Conditions B. $Cu(OAc)_2$ (9.1 mg, 0.050 mmol), *N*-(2-methyl-2-(thiophen-2-yl)propyl)picolinamide (**1j**; 65 mg, 0.25 mmol), manganese dioxide (130 mg, 1.5 mmol), and *N*,*N*-dimethylformamide (DMF, 1.5 mL) were placed in a 2 mL microwave vessel. The vessel was sealed with a cap, and the mixture was irradiated under microwave reactor conditions at 200 °C for 90 min. The resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layers were dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (2/1, v/v) gave (6,6-dimethyl-5,6-dihydro-4*H*-thieno[3,2-*b*]pyrrol-4-yl)(pyridin-2-yl)methanone (**2j**; 53 mg, 0.21 mmol) in 83% yield.

*(3,3-Dimethyl-6-(trifluoromethyl)indolin-1-yl)(pyridin-2-yl)-methanone (**2e**).* Conditions A: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 59 mg (74%). Conditions B: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 36 mg (45%). Mp: 94.0−95.0 °C (from $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 6H), 4.21 (s, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.38−7.44 (m, 1H), 7.88 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 8.60 (s, 1H), 8.65 (dt, *J* = 1.6, 5.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 28.2, 40.8, 65.3, 115.1, 121.8, 122.3, 124.4 (q, *J* = 271.4 Hz), 124.7, 125.5, 130.2 (q, *J* = 31.9 Hz), 137.3, 142.7, 145.3, 148.1, 153.9, 166.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.00. HRMS (EI): *m/z* (M^+) calcd for $C_{17}H_{15}F_3N_2O$ 320.1136, found 320.1137.

*(6,6-Dimethyl-5,6-dihydro-4H-thieno[3,2-b]pyrrol-4-yl)(pyridin-2-yl)methanone (83:17 Mixture of Rotamers) (**2j**).* Conditions A: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 54 mg (83%). Conditions B: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 53 mg (83%). Mp: 90.0−91.0 °C (from CH_2Cl_2); ^1H NMR (400 MHz, DMSO-d_6, at 25 °C): δ 1.34 (s, 0.83 × 6H for major isomer), 1.40 (s, 0.17 × 6H for minor isomer), 4.22 (s, 0.17 × 2H for minor isomer), 4.43 (s, 0.83 × 2H for major isomer), 5.07 (d, *J* = 5.2 Hz, 0.17 × 1H for minor isomer), 7.13 (d, *J* = 5.2 Hz, 0.17 × 1H for minor isomer), 7.42 (d, *J* = 5.2 Hz, 0.83 × 1H for major isomer), 7.45 (d, *J* = 5.2 Hz, 0.83 × 1H for major isomer), 7.56 (ddd, *J* = 1.2, 4.8, 7.6 Hz, 0.83 × 1H for major isomer), 7.55−7.62 (m, 0.17 × 1H for minor isomer), 7.63 (d, *J* = 7.6 Hz, 0.17 × 1H for minor isomer), 7.89 (td, *J* = 1.2, 7.6 Hz, 0.83 × 1H for major isomer), 8.00 (dt, *J* = 1.6, 7.6 Hz, 0.83 × 1H for major isomer), 7.97−8.04 (m, 0.17 × 1H for minor isomer), 8.65 (td, *J* = 0.8, 4.8 Hz, 0.17 × 1H for minor isomer), 8.67 (qd, *J* = 0.8, 4.8 Hz, 0.83 × 1H for major isomer). ^1H NMR (400 MHz, DMSO-d_6, at 105 °C): δ 1.38 (s, 6H), 4.40 (bs, 2H), 7.34 (bs, 2H), 7.53 (dd, *J* = 5.2, 8.0 Hz, 1H), 7.83 (brs, 1H), 7.97 (dt, *J* = 2.0, 7.6 Hz, 1H), 8.65 (d, *J* = 4.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, at 25 °C) for mixture δ 28.8, 28.9, 41.1, 66.6, 69.0, 114.7, 117.4, 122.5, 12.1, 125.5, 127.6, 127.7, 137.1, 137.4, 137.5, 137.7, 143.7, 148.2, 149.0, 153.0, 162.5 (all observed signals are shown because of complication associated with rotamers.). HRMS (EI): *m/z* (M^+) calcd for $C_{14}H_{14}N_2OS$ 258.0827, found 258.0827.

*Pyridin-2-yl(3,3,8-trimethyl-3,8-dihydropyrrolo[2,3-b]indol-1(2H)-yl)methanone (**2k**).* Conditions A: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent followed by GPC; 41 mg (54%). Conditions B: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent followed by GPC; 26 mg (34%), oil. ^1H NMR (400 MHz,

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$CDCl_3$): δ 1.43 (s, 6H), 3.93 (s, 3H), 4.34 (s, 2H), 7.11 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.16 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.42−7.47 (m, 2H), 7.88 (dt, *J* = 1.6, 7.6 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 8.68 (d, *J* = 4.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 27.6, 33.2, 39.1, 73.2, 110.3, 114.3, 117.5, 120.0, 120.3, 122.2, 124.8, 125.9, 137.3, 139.8, 142.6, 148.6, 153.2, 165.9. HRMS (EI): *m*/*z* (M^+) calcd for $C_{19}H_{19}N_3O$ 305.1528, found 305.1530.

*(3,3-Dimethyl-2,3-dihydro-1H-pyrrol-1-yl)(pyridin-2-yl)-methanone (72:28 Mixture of Rotamers) (**2l**).* Conditions B: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 18 mg (36%), oil. ^1H NMR (400 MHz, DMSO-d_6, at 25 °C): δ 1.12 (s, 0.28 × 6H for minor isomer), 1.16 (s, 0.72 × 6H for major isomer), 3.66 (s, 0.72 × 2H for major isomer), 3.87 (s, 0.28 × 2H for minor isomer), 5.20 (d, *J* = 4.4 Hz, 0.72 × 1H for major isomer), 5.38 (d, *J* = 4.4 Hz, 0.28 × 1H for minor isomer), 6.95 (d, *J* = 4.4 Hz, 0.28 × 1H for minor isomer), 7.20 (d, *J* = 4.4 Hz, 0.72 × 1H for major isomer) 7.52−7.57 (m, 0.28 × 1H for minor isomer), 7.56 (ddd, *J* = 1.2, 4.8, 7.6 Hz, 0.72 × 1H for major isomer), 7.83 (td, *J* = 1.2, 7.6 Hz, 0.72 × 1H for major isomer), 7.83−7.87 (m, 0.28 × 1H for minor isomer), 7.97 (dt, *J* = 1.6, 7.6 Hz, 0.28 × 1H for minor isomer), 7.98 (dt, *J* = 1.6, 7.6 Hz, 0.72 × 1H for major isomer), 8.63 (ddd, *J* = 0.8, 1.6, 4.8 Hz, 0.72 × 1H for major isomer), 8.62−8.66 (m, 0.28 × 1H for minor isomer). ^1H NMR (400 MHz, DMSO-d_6, at 115 °C): δ 1.17 (s, 6H), 3.71 (bs, 2H), 5.20 (bs, 1H), 7.17 (bs, 1H), 7.51 (ddd, *J* = 0.8, 5.2, 7.6 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.94 (dt, *J* = 1.2, 7.6 Hz, 1H), 8.62 (d, *J* = 4.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6, at 25 °C) for mixture δ 27.9, 28.2, 40.5, 43.7, 59.6, 61.6, 122.6, 123.4, 124.1, 124.2, 125.5, 125.6, 127.2, 128.6, 137.4, 137.6, 148.1, 148.2, 152.5, 152.9, 162.5, 162.6. HRMS (APCI): *m*/*z* ($[M + H]^+$) calcd for $C_{12}H_{15}N_2O$ 203.1179, found 203.1179.

*(R)-(3-Methylindolin-1-yl)(pyridin-2-yl)methanone (**2p**).* Conditions A: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent followed by GPC; 30 mg (51%). Conditions B: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent followed by GPC; 20 mg (37%), oil. $[\alpha]_D^{20}$ = −0.18° (*c* 0.50, $CHCl_3$, 93:7 er). ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, *J* = 6.8 Hz, 3H), 3.43−3.50 (m, 1H), 3.90 (dd, *J* = 7.2, 11.2 Hz, 1H), 4.50 (dd, *J* = 9.2, 11.2 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 5.2 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.64 (d, *J* = 4.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 19.6, 35.3, 58.5, 117.9, 123.4, 124.2, 124.5, 125.0, 127.6, 137.1, 137.3, 142.8, 148.0, 154.6, 166.0. HRMS (APCI): *m*/*z* ($[M + H]^+$) calcd for $C_{15}H_{15}N_2O$ 239.1179, found 239.1178.

*(2,2-Dimethylindolin-1-yl)(pyridin-2-yl)methanone (**2q**).* Conditions A: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 54 mg (86%). Conditions B: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 46 mg (73%). Mp: 126.0−127.0 °C (from CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 1.70 (s, 6H), 3.06 (s, 2H), 5.30−6.30 (bs, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.89 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.41 (qd, *J* = 1.2, 4.8, 7.6 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.85 (dt, *J* = 1.6, 7.6 Hz, 1H), 8.61 (qd, *J* = 0.8, 4.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 26.0, 45.6, 67.7, 115.9, 123.3, 123.6, 125.37, 125.42, 126.6, 130.6, 137.4, 142.3, 149.3, 155.1, 167.3. HRMS (APCI) *m*/*z* ($[M + H]^+$) calcd for $C_{16}H_{17}N_2O$ 253.1335, found 253.1333.

*(S)-(6-methyl-2-phenylindolin-1-yl)(pyridin-2-yl)methanone (**2r**).* Conditions A: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent followed by GPC; 50 mg (64%). Conditions B: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent followed by GPC; 23 mg (30%). Mp: 132.0−133.0 °C (from $CHCl_3$). $[\alpha]_D^{20}$ = −3.14° (*c* 0.50, $CHCl_3$, 99:1 er). ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.97 (dd, *J* = 2.8, 16.0 Hz, 1H), 3.76 (dd, *J* = 10.0, 16.0 Hz, 1H), 6.20 (d, *J* = 8.8 Hz, 1H), 6.80−7.23 (m, 9H), 7.51 (t, *J* = 5.6 Hz, 1H), 8.34 (s, 1H), 8.54 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.9, 38.4, 63.7, 118.1, 124.0, 124.6, 125.3, 125.5, 127.1, 127.3, 128.6 (2C), 136.8, 137.8, 144.0, 144.3, 147.7, 154.8, 167.6. HRMS (APCI): *m*/*z* ($[M + H]^+$) calcd for $C_{21}H_{19}N_2O$: 315.1492, found 315.1494.

*Indolin-1-yl(pyridin-2-yl)methanone (**2s**).* Conditions A: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 25 mg (45%). Conditions B: purified by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v) as an eluent; 17 mg (31%). Mp: 99.5−101.0 °C (from CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 3.15 (t, *J* = 8.4 Hz, 2H), 4.35 (t, *J* = 8.4 Hz, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 5.6 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.63 (d, *J* = 4.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 28.8, 50.7, 118.1, 124.3, 124.5, 124.7, 125.1, 127.5, 132.3, 137.2, 143.4, 148.1, 154.7, 166.2. HRMS (APCI): *m*/*z* ($[M + H]^+$) calcd for $C_{14}H_{13}N_2O$: 225.1022, found 225.1028.

■ ASSOCIATED CONTENT

Supporting Information

Detailed kinetic profiles for the reaction of **1a** and **1a-d_5**, ^1H, $^{13}C\{^1H\}$, and ^{19}F NMR spectra for products, and chiral HPLC charts of **2p**,**r**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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