Published in final edited form as:
J Org Chem. 2011 June 3; 76(11): 4721–4727. doi:10.1021/jo200425m.

Development of a Two-step Route to 3-PBC and βCCt, Two Agents Active Against Alcohol Self-Administration in Rodent and Primate Models

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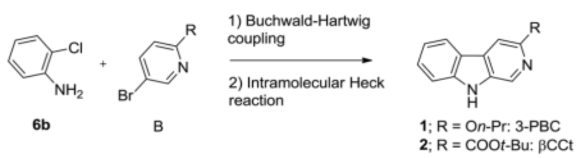
Abstract



In order to gain access to 3-propoxy-β-carboline hydrochloride (3-PBC·HCl) (**1·HCl**), and β-carboline-3-carboxylate-t-butyl ester (βCCt) (**2**), potential clinical agents active against alcohol self-administration, a two-step route was developed. This process involves a palladium catalyzed Buchwald-Hartwig coupling and an intramolecular Heck reaction. This two-step route provides rapid access to multigram quantities of 3-PBC (**1**) and βCCt (**2**), as well as analogs for studies of alcohol self-administration. The overall yield of 3-PBC (**1**) was improved from 8 % to 50 % in this route.

The $GABA_A$ receptor is the major inhibitory neurotransmitter receptor of the central nervous system (CNS) and the site of action of a variety of pharmacologically and clinically important drugs, such as benzodiazepines, barbiturates, neuroactive steroids, anesthetics and convulsants.[1] There are several disease states thought to be associated with the improper functioning of this system, including anxiety, epilepsy, insomnia, depression, bipolar disorder, and schizophrenia, as well as mild cognitive impairment and Alzheimer's disease.[2]

Alcohol addiction and dependence remain significant public health concerns, impacting physical and mental well-being, family structure and occupational stability. The design of clinically safe and effective drugs that reduce alcohol addiction and dependence remains a high priority.[3,4] While the precise neuromechanisms regulating alcohol-seeking behaviors remain unknown, there is now compelling evidence that the $GABA_A$ receptors within the striatopallidal and extended amygdala system are involved in the "acute" reinforcing actions of alcohol.[5–9]

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Supporting Information Available: Copies of spectra and crystallographic information files (CIFs). This material is available free of charge via the Internet at http://pubs.acs.org

The beta-carbolines 3-propoxy-β-carboline hydrochloride **1 · HCl** (3-PBC) · HCl and β-carboline-3-carboxylate-t-butyl ester **2** (βCCt) are mixed benzodiazepine agonist-antagonist ligands with binding selectivity at α1 receptors (see Figure 1).[10–12] In studies which involve the α1 subtype, the orally active **1·HCl** and **2** were observed to selectively reduce alcohol-motivated behaviors in a variety of experiments.[10,13] Moreover, both **1·HCl** and **2** displayed mixed weak agonist-antagonist profiles *in vivo* in alcohol P and HAD rats, and may be capable of reducing alcohol intake while eliminating or greatly reducing the anxiety associated with habitual alcohol, abstinence or detoxification.[10,13] These types of ligands, subsequently, may be ideal clinical agents for the treatment of alcohol dependent individuals.

The synthesis of both **1** and **2** have been accomplished previously.[14–17] The overall yield of **1** (via 6 steps) as reported previously was 8 %; while that of **2** (5 steps) was 35% from DL-tryptophan. The syntheses involved a number of steps, some of which occurred in low yields.

In 2005 Weerts et al. reported that 3-PBC·HCl significantly reduced alcohol self-administration in baboons.[18] More importantly, it reduced craving in the subjects as well.[18] This important result led to the interest in a short and concise synthesis of 3-PBC (**1**), capable of scale up to multigram levels, as well as a similar route to βCCt (**2**). Retrosynthetically, both of these compounds can be envisioned to arise from a substituted aniline **A** and a substituted pyridine derivative **B** (Scheme 1).

As shown in Scheme 2, bromopyridine **3**[19] was reacted with aniline **4a** in toluene at 100°C in the presence of 5 mol % $Pd(OAc)_2$ and 7.5 mol% X-Phos to obtain diarylamine **5a** in 93 % yield. Various conditions were screened to effect a coupling reaction between **3** and aniline **4a** in high yield.[20–23] Other combinations of conditions (lower temperature, different ligands, different bases, copper-based methods) resulted either in inferior yields and/or debromination of **3**. In similar fashion, **5b** was obtained from **3** and 2′-chloroaniline **4b** in 91 % yield.

Once diarylamines **5a** and **5b** were in hand as potential precursors to **1**, various methods to carry out the required intramolecular cyclization were attempted. A Heck-type coupling reaction and CH activation/oxidative coupling-cyclization reaction were more appealing because of atom economy.[23, 24] In recent years, such direct arylation reactions have been developed extensively.[25–30] One advantage is the preactivated, functionalized arenes can be replaced with a simple arene, consequently reducing the number of steps and overall cost of the process.[25]

Various approaches for the construction of substituted carbazoles via coupling processes have been described in the literature.[29–33] Bedford et al. have carried out a microwave-mediated one-pot synthesis of carbazoles from 2-chloroanilines via consecutive amination and CH activation.[30] Budén et al. have used photostimulated reactions of chloro diarylamines for the synthesis of substituted carbazoles.[31] However, the issue of regioselectivity was not addressed in those reports since the authors dealt with reactions leading to a symmetrical product or one of the possible positions for cyclization was blocked. Hostyn and co-workers have described palladium catalyzed regioselective synthesis of α-carbolines by using 2,3-dichloropyridines and substituted anilines.[32] Recently Sridharan et al. have reported a $Pd(OAc)_2$ promoted cyclodehydrogenation of diphenylamines to carbazole using $Cu(OAc)_2$ as an oxidant.[33] In addition Ohno et al. have carried out the synthesis of substituted carbazoles by intramolecular oxidative direct arylation in an aerobic atmosphere.[29] Interestingly the extension of these methods for the synthesis of β-carbolines had not been demonstrated to these authors knowledge.

With this history in mind, initial attempts were made to cyclize **5a** using catalytic Pd (II)-mediated oxidative coupling. Diarylamine **5a** failed to cyclize using $Pd(OAc)_2$ as a Pd (II) source and $Cu(OAc)_2$ as the co-oxidant for palladium even after heating in refluxing toluene or in acetic acid.[29] Interestingly, when the reaction was carried out at 120°C in acetic acid as a solvent with an oxygen atmosphere, **5a** appeared to react, and the β-carboline **1** was obtained as an equimolar mixture with its regiosiomer, a δ-carboline, **6.** However, the reaction did not go completion in 15 hours and only 30 % combined yield was obtained. Further modifications of these conditions with **5a** (longer duration, increased catalytic loading) did not result in any improvement in the yield, nor ratio of **1** to **6**.

At this point it was decided to explore a Heck-type cyclization of model compound **5b** utilizing Pd(0) as a catalyst. Initial attempts, which included previously reported Buchwald-Hartwig amination conditions [$Pd(OAc)_2$, X-Phos, Cs_2CO_3 or NaO*t*-Bu, toluene, 100°C] did not provide β-carboline **1** even after heating for 24 hours (Table 1, entries 1 and 2). Use of polar solvents such as DMF or DMA led to dechlorination of the starting material (entries 3 and 4). Air-stable mono-dentate ligand $(t\text{-Bu})_3P{\cdot}HBF_4$ had been used previously for similar types of transformations in a different system.[30] Interestingly, $Pd(OAc)_2$ with $(t\text{-Bu})_3P{\cdot}HBF_4$ as a catalyst in the presence of NaO*t*-Bu in DMA gave 32 % yield of the mixture of regioisomers **1** and **6**. A large amount of decomposition products were observed on TLC (entry 5). When K_2CO_3 was employed as the base, the reaction went smoothly within 16 hours at 120°C and afforded a readily separable mixture of regioisomers **1** and **6** in a ratio of 1.75:1 (entries 6 and 7). Substitution of $(t\text{-Bu})_3P{\cdot}HBF_4$ with ligand $Cy_3P{\cdot}HBF_4$ afforded comparable results (entry 8). The desired β-carboline **1** and its regioisomer **6** (δ-carboline) can be differentiated from each other by examination of their corresponding ^{1}H NMR spectra. In addition, X-ray crystal structures (Supporting Information) of both regioisomers **1** and **6** were obtained to further confirm the structures.

Since many 3-substituted β-carbolines exhibit subtype selectivity at $\alpha1\beta_{2/3}\gamma2$ BZR/GABAergic receptors it was decided to apply these conditions for the synthesis of various substituted β-carbolines previously reported.[14,15,17, 34–36] In addition, it was important to evaluate the effect of different substitutions located *ortho* to the pyridyl nitrogen atom on the regioselectivity of the process (Scheme 3). The required bromopyridine ether derivatives **7a-g** are commercially available and can be synthesized via known literature procedures.[19] Buchwald-Hartwig aminations of **7a**–**g** with 2-chloroaniline led to the chloro diarylamines **8a**–**g** smoothly in 81–92 % yields. Heck-type cyclization of **8a**–**g** afforded the regioisomers: β-carbolines **9a**–**g** and δ-carbolines **10a**–**g** in good yields (Table 2). The substituents *ortho* to the pyridyl nitrogen atom appeared to have some effect on the regioselectivity. The smaller substituents (Me, Et) tended to provide equimolar amounts of the regioisomers **9** and **10** (Table 2, entries 1 and 2); while the bulkier substituents (*i*-Pr, *t*-Bu) afforded the β-carbolines as the major product (entries 3 and 6). The best ratio of **9** to **10** for a β-carboline was obtained for the 5-bromo-2-*t*-butoxypyridine (1.9 : 1; entry 6).

Large scale synthesis of 3-PBC (1) and βCCT (2)

Because 3-PBC·HCl (**1**·**HCl**) reduced alcohol self-administration in primates[18] while both 3-PBC·HCl (**1**·**HCl**) and βCCt (**2**) had been shown to reduce a`lcohol self-administration in both alcohol preferring (P) and high alcohol drinking (HAD) rats when given orally and systemically, a large scale synthesis of 3-PBC (**1**) and βCCt (**2**) via this short route was required. This synthesis of 3-PBC (**1**) and βCCt (**2**) is illustrated in Scheme 4. In regard to the synthesis of 3-PBC (**1**), the Buchwald-Hartwig amination step was scaled up to the 50 gram level (87 % yield); while the Heck-type cyclization reaction was performed on a 20 gram scale. The overall conversion of *N*-(2-chlorophenyl)-6-propoxypyridin-3-amine (**5b**) into 3-PBC (**1**) via this two-step route was 50 %, as compared to 8 % previously obtained.[14, 15] The large scale synthesis of βCCt (**2**) via this process is shown in Scheme 4. The Buchwald-Hartwig amination of *tert*-butyl 5-bromopicolinate **11**[37] with 2-chloroaniline afforded the coupled diarylamine **12** in 94 % yield on 50 gram scale. Heck-type cyclization of **12** was carried out on 10 gram scale and afforded a mixture of βCCT (**2**) and its regioisomer **13** in 83 % yield. (Ratio of **2:13** = 2:1). The overall yield of βCCT (**2**) from **11** on 10 gram scale was 52 %, as compared to the previous yield of 35 %.[16]

In summary, a two-step route to the two anti-alcohol agents of biological interest, 3-PBC (**1**) and βCCT (**2**), has been developed in much improved yields as compared to their earlier reported syntheses. This two step synthesis of 3-PBC (**1**) and βCCT (**2**) is capable of scale-up which cuts down the number of steps in the reported routes from 6 and 5, respectively, to 2. The yield of 3-PBC (**1**) via this two-step route was 50 %, as compared to the previously reported 8 %; while that for βCCT (**2**) was 52 %, as compared to the previous yield of 35 %. In addition, to extend the SAR in vivo, different β-carboline analogs **9a–g** were synthesized in superior yields. It is easy to separate the β-carboline and δ-carboline regioisomers from each other by flash chromatography. Further studies are underway to render this transformation regiospecific.

Experimental Section

General Methods

All reactions were performed in oven-dried round bottomed flasks or in resealable screw-cap test tubes or heavy-wall pressure vessels. Stainless steel syringes or cannulae were used to transfer air-sensitive liquids. Chemical shifts are reported in δ (ppm) relative to TMS in $CDCl_3$ as internal standard (^{1}H NMR) or the residual $CHCl_3$ signal (^{13}C NMR).

General procedure for the synthesis of diarylamines: Representative procedure for the synthesis of *N*-(2-chlorophenyl)-6-propoxypyridin-3-amine (5b)—5-Bromo-2-propoxypyridine **3**[19] (0.65 g, 3 mmol), $Pd(OAc)_2$ (33.7 mg, 0.15 mmol), Cs_2CO_3 (1.17 g, 3.6 mmol) and X-Phos (107 mg, 0.225 mmol) were added to a screw-cap vial. The vial was fitted with a rubber septum; evacuated and back-filled with argon. 2-Chloroaniline **4b** (0.4 g, 3.15 mmol) was injected into the vial with a syringe under a positive pressure of argon. Toluene (10 mL) was added via a syringe. The rubber septum was replaced with a screw-cap and the sealed vial was introduced into a pre-heated oil bath at 100 °C. After 15 h the reaction mixture was filtered through a short pad of celite, washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel; 20:1; hexanes/ethyl acetate) to afford **5b** (0.73 g, 93 %) as a pale yellow oil: TLC (20% EtOAc/hexanes), *Rf*: 0.73; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 2.7 Hz, 1H), 7.49 (dd, J_1 = 8.7 Hz; J_2 = 2.7 Hz, 1H), 7.34 (dd, J_1 = 8.1 Hz; J_2 = 1.5 Hz, 1H), 7.09 (dd, J_1 = 8.4 Hz; J_2 = 1.2 Hz, 1H), 6.86 (dd, J_1 = 8.4 Hz; J_2 = 1.5 Hz, 1H), 6.76 (m, 2H), 5.90 (br, 1H), 4.27 (t, J = 6.9 Hz, 2H), 1.84 (m, 2H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2, 142.3, 142.0, 135.3, 131.0, 129.6, 127.6, 120.1, 119.5, 113.5, 111.4, 67.8, 22.4, 10.6; HRMS–ESI (*m/z*) calcd for $C_{14}H_{16}ClN_2O$ $[M+H]^+$: 263.0951, found: 263.0961.

***N*-phenyl-6-propoxypyridin-3-amine (5a)—**Following the general procedure, **3**[19] (0.43 g, 2 mmol) with aniline **4a** (0.2 g, 2.10 mmol), $Pd(OAc)_2$ (22.5 mg, 0.10 mmol), X-Phos (71.4 mg, 0.15 mmol), and Cs_2CO_3 (0.78 g, 2.4 mmol) after flash chromatography (silica gel, 20:1 hexanes/ethyl acetate) afforded **5a** (0.43 g, 93 %): off-white solid; TLC (20% EtOAc/hexanes), *Rf*: 0.33; mp: 60.6–61.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, J = 2.7 Hz, 1H), 7.47 (dd, J_1 = 8.7 Hz, J_2 = 3.0 Hz, 1H), 7.25 (m, 2H), 7.87 (m, 3H), 6.74 (d, J = 8.7 Hz, 1H), 5.46 (br, 1H), 4.25 (t, J = 6.6 Hz, 2H), 1.82 (m, 2H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 145.0, 139.9, 133.3, 132.6, 129.4, 119.9, 115.3, 111.1, 67.7, 22.4, 10.5; Anal.: calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27; found: C, 73.75; H, 7.08; N, 12.10.

***N*-(2-chlorophenyl)-6-methoxypyridin-3-amine (8a)—**Following the general procedure, 5-bromo-2-methoxypyridine **7a**[19] (0.5 g, 2.66 mmol) with **4b** (0.36, 2.8 mmol), $Pd(OAc)_2$ (29.9 mg, 0.13 mmol), X-Phos (89.1 mg, 0.20 mmol), and Cs_2CO_3 (1.04 g, 3.2 mmol) after flash chromatography (silica gel, 20:1 hexanes/ethyl acetate) afforded **8a** (0.56 g, 89 %): yellow oil; TLC (20% EtOAc/hexanes), *Rf*: 0.62; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, J = 2.7 Hz, 1H), 7.50 (dd, J_1 = 8.7 Hz; J_2 = 2.7 Hz, 1H), 7.35 (dd, J_1 = 7.9 Hz; J_2 = 1.3 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.87 (dd, J_1 = 8.2 Hz; J_2 = 1.3 Hz, 1H), 6.75 (m, 2H), 5.92 (br, 1H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 142.0, 141.8, 135.1, 131.2, 129.5, 127.5, 120.1, 119.5, 113.5, 111.2, 55.5; HRMS–ESI (*m/z*): calcd for $C_{12}H_{12}ClN_2O$ $[M+H]^+$: 235.0638, found: 235.0628.

***N*-(2-chlorophenyl)-6-ethoxypyridin-3-amine (8b)—**Following the general procedure, 5-bromo-2-ethoxypyridine **7b**[19] (0.303 g, 1.5 mmol) with **4b** (0.2 g, 1.575 mmol), $Pd(OAc)_2$ (16.8 mg, 0.075 mmol), X-Phos (26.7 mg, 0.112 mmol), and Cs_2CO_3 (0.85 g, 1.8 mmol) after flash chromatography (silica gel, 20:1 hexanes/ethyl acetate) afforded **8b** (0.35 g, 94 %): light brown solid; TLC (20% EtOAc/hexanes), *Rf*: 0.68; mp: 49.5–51.0°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 2.7 Hz, 1H), 7.49 (dd, J_1 = 8.7 Hz; J_2 = 2.8 Hz, 1H), 7.35 (dd, J_1 = 7.9 Hz; J_2 = 1.4 Hz, 1H), 7.09 (t, J = 7.9 Hz, 1H), 6.86 (dd, J_1 = 8.4 Hz; J_2 = 1.5 Hz, 1H), 6.77 (m, 2H), 5.90 (br, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9, 142.2, 141.8, 135.1, 130.9, 129.5, 127.5, 120.0, 119.4, 113.4, 111.3, 61.8, 14.6; HRMS–ESI (*m/z*): calcd for $C_{13}H_{14}ClN_2O$ $[M+H]^+$: 249.0795, found: 249.0799.

***N*-(2-chlorophenyl)-6-isopropoxypyridin-3-amine (8c)—**Following the general procedure, 5-bromo-2-isoprpoxypyridine **7c**[19] (0.22 g, 1.0 mmol) with **4b** (0.134 g, 1.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), X-Phos (35.7 mg, 0.075 mmol), and Cs_2CO_3 (0.39 g, 1.2 mmol) after flash chromatography (silica gel, 20:1 hexanes/ethyl acetate) afforded **8c** (0.247 g, 94 %): pale yellow oil; TLC (20% EtOAc/hexanes), *Rf*: 0.65; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 2.7 Hz, 1H), 7.47 (dd, J_1 = 8.7 Hz; J_2 = 2.8 Hz, 1H), 7.34 (dd, J_1 = 7.9 Hz; J_2 = 1.4 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.87 (dd, J_1 = 8.2 Hz; J_2 = 1.4 Hz, 1H), 6.61 (m, 2H), 5.89 (br, 1H), 5.20 (m, 1H), 1.38 (d, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 142.2, 141.9, 135.2, 130.6, 129.5, 127.5, 120.0, 119.3, 113.4, 111.8, 68.1, 22.0; HRMS–ESI (*m/z*): calcd for $C_{14}H_{16}ClN_2O$ $[M+H]^+$: 263.0951, found: 263.0963.

6-butoxy-*N*-(2-chlorophenyl)pyridin-3-amine (8d)—Following the general procedure, 5-bromo-2-butoxypyridine **7d**[19] (0.23 g, 1.0 mmol) with **4b** (0.134 g, 1.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), X-Phos (35.7 mg, 0.075 mmol), and Cs_2CO_3 (0.39 g, 1.2 mmol) after flash chromatography (silica gel, 20:1 hexanes/ethyl acetate) afforded **8d** (0.25 g, 91 %): colorless oil; TLC (20% EtOAc/hexanes), *Rf*: 0.71; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 2.8 Hz, 1H), 7.48 (dd, J_1 = 8.8 Hz; J_2 = 2.8 Hz, 1H), 7.34 (dd, J_1 = 7.9 Hz; J_2 = 1.4 Hz, 1H), 7.09 (t, J = 8.4 Hz, 1H), 6.86 (dd, J_1 = 8.2 Hz; J_2 = 1.4 Hz, 1H), 6.77 (m, 2H), 5.90 (br, 1H), 4.31 (t, J = 6.7 Hz, 2H), 1.79 (m, 2H), 1.52 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 142.2, 141.9, 135.2, 130.9, 129.5, 127.5, 120.0, 119.4, 113.4, 111.3, 65.9, 31.1, 19.2, 13.8; HRMS–ESI (*m/z*): calcd for $C_{15}H_{18}ClN_2O$ $[M+H]^+$: 277.1108, found: 277.1102.

***N*-(2-chlorophenyl)-6-isobutoxypyridin-3-amine (8e)—**Following the general procedure, 5-bromo-2-isoprpoxypyridine **7e**[19] (0.23 g, 1.0 mmol) with **4b** (0.134 g, 1.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), X-Phos (35.7 mg, 0.075 mmol), and Cs_2CO_3 (0.39

g, 1.2 mmol), after flash chromatography (silica gel, 20:1 hexanes/ethyl acetate) afforded **8e** (0.257 g, 93 %): light green oil; TLC (20% EtOAc/hexanes), *Rf*: 0.69; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 2.2 Hz, 1H), 7.49 (dd, J_1 = 8.7 Hz; J_2 = 2.6 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.77 (m, 2H), 5.90 (br, 1H), 4.08 (d, J = 6.7 Hz, 2H), 2.12 (m, 1H), 1.05 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2, 142.2, 141.9, 135.2, 130.9, 129.5, 127.5, 120.0, 119.4, 113.4, 111.3, 72.5, 30.7, 19.2; HRMS–ESI (*m/z*): calcd for $C_{15}H_{18}ClN_2O$ $[M+H]^+$: 277.1108, found: 277.1099.

6-(*tert*-butoxy)-*N*-(2-chlorophenyl)pyridin-3-amine (8f)—Following the general procedure, 2-(benzyloxy)-5-bromopyridine **7f**[19] (0.229 g, 1.0 mmol) with **4b** (0.134 g, 1.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), X-Phos (35.7 mg, 0.075 mmol), and Cs_2CO_3 (0.39 g, 1.2 mmol) after flash chromatography (silica gel, 20:1 hexanes/ethyl acetate) afforded **8f** (0.252 g, 91 %): colorless oil; TLC (20% EtOAc/hexanes), *Rf*: 0.81; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, J = 2.8 Hz, 1H), 7.44 (dd, J_1 = 8.7 Hz; J_2 = 2.7 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.10 (t, J = 8.7 Hz, 1H), 6.92 (d, J = 8.1 Hz, 1H), 6.77 (t, J = 7.2 Hz, 1H), 6.70 (d, J = 8.7 Hz, 1H), 5.89 (br, 1H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.6, 141.7, 141.6, 134.2, 130.9, 129.5, 127.5, 120.1, 119.4, 113.9, 113.6, 79.5, 28.6; HRMS–ESI (*m/z*): calcd for $C_{15}H_{18}ClN_2O$ $[M+H]^+$: 277.1108, found: 277.1116.

6-(benzyloxy)-*N*-(2-chlorophenyl)pyridin-3-amine (8g)—Following the general procedure, 2-(benzyloxy)-5-bromopyridine **7g**[19] (0.263 g, 1.0 mmol) with **4b** (0.134 g, 1.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), X-Phos (35.7 mg, 0.075 mmol), and Cs_2CO_3 (0.39 g, 1.2 mmol) after flash chromatography (silica gel, 20:1 hexanes/ethyl acetate) afforded **8g** (0.28 g, 90 %): off-white solid; TLC (10% EtOAc/hexanes), *Rf*: 0.63; mp: 101.2–102.3°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, J = 2.7 Hz, 1H), 7.51 (m, 3H), 7.39 (m, 4H), 7.10 (t, J = 8.4 Hz, 1H), 6.90 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.78 (m, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1H), 5.92 (br, 1H), 5.40 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 141.2, 140.3, 136.8, 135.3, 131.9, 129.6, 128.8, 128.4, 127.9, 127.6, 120.6, 120.0, 114.1, 111.8, 68.4; Anal.: calcd for $C_{18}H_{15}ClN_2O$ 0.05 $CH_3(CH_2)_4CH_3$: C, 69.76; H, 5.02; N, 8.89; found: C, 69.98; H, 4.86; N, 9.01.

***tert*-butyl 5-[(2-chlorophenyl)amino]picolinate (12)—**Following the general procedure, *tert*-butyl 5-bromopicolinate **11**[37] (50 g, 194 mmol) with **4b** (26 g, 203 mmol), $Pd(OAc)_2$ (2.18 g, 9.7 mmol), X-Phos (6.9 g, 14.55 mmol), and Cs_2CO_3 (75.9 g, 233 mmol) after flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded **12** (55.6 g, 94 %): lustrous off-white solid; TLC (50% EtOAc/hexanes), *Rf*: 0.46; mp: 147.8–149.4°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (d, J = 2.7 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.01 (t, J = 8.1 Hz, 1H), 6.34 (br, 1H), 1.63 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1, 141.8, 141.3, 139.6, 137.4, 130.3, 127.7, 125.8, 124.4, 123.5, 122.5, 118.5, 81.7, 28.2; Anal.: calcd for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62; N, 9.19; found: C, 62.67; H, 5.65; N, 8.95.

General procedure for Heck cyclization: Representative procedure for the synthesis of 3-propoxy-9*H*-pyrido[3,4-*b*]indole (3-PBC; 1) and 2-propoxy-5*H*-pyrido[3,2-*b*]indole (6)—$Pd(OAc)_2$ (22.4 mg, 0.1 mmol), $(t\text{-Bu})_3P$ HBF_4 (58 mg, 0.2 mmol), 5b (263 mg, 1.0 mmol) and K_2CO_3 (276 mg, 2.0 mmol) were added to a screw-cap vial. The vial was fitted with a rubber septum, evacuated and back-filled with argon. Degassed DMA (4.0 mL) was added via a syringe. The rubber septum was replaced with a screw cap and this sealed tube was introduced in a preheated oil bath at 120 °C. After stirring for 16 h, the reaction mixture was allowed to cool to rt. The reaction mixture was passed through a short pad of celite which was further washed with ethyl acetate until no product (TLC; silica gel) was detected in the eluent. The combined filtrates were washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel; 5:1 hexanes/ethyl acetate) to afford **3-PBC** (**1**) (127 mg): colorless crystals; mp 119.3–120.5°C.; Anal. calcd for $C_{14}H_{14}N_2O$·0.33 H_2O: C, 72.43; H, 6.36; N, 12.07; found: C, 72.48; H, 6.49; N, 11.78. A hydrochloride salt of **1** was prepared by the reported method to obtain 3-PBC·HCl (**1**·**HCl**): yellow solid; mp 194.7–195.6°C (lit.[15] mp 194.0–195.0°C). The data for this compound matched in all aspects (^{1}H NMR, mp) with that reported in the literature.[15]

And **6** (72 mg): white solid: TLC (50% EtOAc/hexanes) R_f: 0.63; mp 123.2–124.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, J = 7.8 Hz, 1H), 7.99 (br, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.46 (m, 2H), 7.27 (m, J_1 = 7.1 Hz, J_2 = 1.8 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 4.45 (t, J = 6.6 Hz, 2H), 1.91 (m, 2H), 1.11 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 140.2, 138.4, 128.3, 126.8, 122.6, 121.5, 120.6, 119.8, 111.3, 108.8, 67.8, 22.7, 10.8; Anal. calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38; found: C, 74.17; H, 6.30; N, 12.30.

[Combined yield = 199 mg, 88 %].

3-methoxy-9*H*-pyrido[3,4-*b*]indole (9a) and 2-methoxy-5*H*-pyrido[3,2-*b*]indole (10a)—Following the general procedure, **8a** (130 mg, 0.55 mmol), $Pd(OAc)_2$ (12.4 mg, 0.055 mmol), (t-Bu)$_3$P HBF_4 (31.9 mg, 0.11 mmol) and K_2CO_3 (152 mg, 1.11 mmol) after flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded **9a** (48 mg): off-white solid; HRMS–ESI (*m/z*): calcd for $C_{12}H_{11}N_2O$ $[M+H]^+$: 199.0871, found: 199.0877. Hydrochloride salt of **9a**: light brown solid; mp: 214.8–216.0°C (lit.[15] mp 215.0–217.0°C). The data for this compound matched in all aspects (^{1}HNMR, mp) with that reported in the literature.[15]

And **10a** (40 mg): light brown solid; TLC (50% EtOAc/hexanes), *Rf*: 0.72; mp: 94.5–97.0°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 7.9 Hz, 1H), 8.01 (br, 1H), 7.67 (d, J = 8.7 Hz, 1H), 7.46 (m, 2H), 7.29 (m, J_1 = 6.7 Hz, J_2 = 2.1 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 4.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 140.0, 138.1, 129.3, 128.2, 126.7, 121.3, 120.4, 119.9, 111.1, 108.5, 53.5; HRMS–ESI (*m/z*): calcd for $C_{12}H_{11}N_2O$ $[M+H]^+$: 199.0871, found: 199.0876.

[Combined yield = 88 mg, 81 %].

3-ethoxy-9*H*-pyrido[3,4-*b*]indole (9b) and 2-ethoxy-5*H*-pyrido[3,2-*b*]indole (10b)—Following the general procedure, **8b** (75 mg, 0.3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), (t-Bu)$_3$P HBF_4 (17.4 mg, 0.06 mmol) and K_2CO_3 (83 mg, 0.6 mmol) after flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded **9b** (30 mg) as yellow-brown solid; HRMS–ESI (*m/z*): calcd for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1028, found: 213.1018. Hydrochloride salt of **9b** was a yellow solid; mp: 222.0–223.3°C (lit.[15] mp 221.0–223.0°C). The data for this compound matched in all aspects (^{1}HNMR, mp) with that reported in the literature.[15]

And **10b** (24 mg) as off-white crystals; TLC (20% EtOAc/hexanes), *Rf*: 0.35; mp: 130.4–131.1°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, J = 7.8 Hz, 1H), 7.91 (br, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.45 (m, 2H), 7.27 (m, 2H), 6.83 (d, J = 8.7 Hz, 1H), 4.56 (q, J = 6.9 Hz, 2H), 1.49 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 140.2, 128.3, 126.9, 122.4, 121.6, 120.7, 119.8, 111.2, 108.6, 61.9, 14.9; HRMS–ESI (*m/z*): calcd for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1028, found: 213.1019.

[Combined yield = 54 mg, 85 %].

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3-isopropoxy-9*H*-pyrido[3,4-*b*]indole (9c) and 2-isopropoxy-5*H*-pyrido[3,2-*b*]indole (10c)—Following the general procedure, **8c** (263 mg, 1.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), (*t*-Bu)$_3$P HBF_4 (58 mg, 0.2 mmol) and K_2CO_3 (276 mg, 2.0 mmol) after flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded **9c** (131 mg) as an off-white solid; HRMS–ESI (*m/z*): calcd for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1184, found: 227.1176. Hydrochloride salt of **9c**: brown solid; mp: 169.5–171.3°C (lit.[34] mp 168.0–172.0°C). The data for this compound matched in all aspects (^{1}H NMR, mp) with that reported in the literature.[34]

And **10c** (72 mg) as an off-white solid; TLC (20% EtOAc/hexanes), *Rf*: 0.38; mp: 105.6–107.7°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 7.8 Hz, 1H), 8.04 (br, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.44 (m, 2H), 7.27 (t, J = 7.4 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 5.56 (m, J = 6.3 Hz, 1H), 1.46 (d, J = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 140.1, 138.2, 128.1, 126.6, 122.4, 121.3, 120.4, 119.6, 111.1, 109.2, 68.0, 22.1; HRMS–ESI (*m/z*): calcd for $C_{14}H_{15}N_2O$ $[M+H]^+$: 227.1184, found: 227.1173.

[Combined yield = 203 mg, 90 %].

3-butoxy-9*H*-pyrido[3,4-*b*]indole (9d) and 2-butoxy-5*H*-pyrido[3,2-*b*]indole (10d)—Following the general procedure, **8d** (125 mg, 0.45 mmol), $Pd(OAc)_2$ (10.1 mg, 0.045 mmol), (*t*-Bu)$_3$P HBF_4 (26.1 mg, 0.09 mmol) and K_2CO_3 (125 mg, 0.9 mmol) after flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded **9d** (48.2 mg) as a buff colored solid; HRMS–ESI (*m/z*): calcd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1341, found: 241.1346. Hydrochloride salt of **9d**: light yellow solid; mp: 178.0–180.0°C (lit.[34] mp 178.0–181.0°C). The data for this compound matched in all aspects (^{1}HNMR, mp) with that reported in the literature.[34]

And **10d** (35.8 mg): off-white solid; TLC (20% EtOAc/hexanes), *Rf*: 0.35; mp: 113.3–115.5°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 7.8 Hz, 1H), 7.05 (br, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.43 (m, 2H), 7.27 (m, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 4.50 (t, J = 6.6 Hz, 2H), 1.87 (m, 2H), 1.57 (m, 2H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 140.0, 138.2, 128.2, 126.6, 122.3, 121.3, 120.4, 119.6, 111.1, 108.6, 65.8, 31.3, 19.3, 13.9; HRMS–ESI (*m/z*): calcd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1341, found: 241.1347.

[Combined yield = 84 mg, 87 %].

3-Isobutoxy-9*H*-pyrido[3,4-*b*]indole (9e) and 2-isobutoxy-5*H*-pyrido[3,2-*b*]indole (10e)—Following the general procedure, **8e** (139 mg, 0.50 mmol), $Pd(OAc)_2$ (11.3 mg, 0.05 mmol), (*t*-Bu)$_3$P HBF_4 (29 mg, 0.10 mmol) and K_2CO_3 (138 mg, 1.0 mmol) after flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded **9e** (63 mg) as an off-white crystalline solid; HRMS–ESI (*m/z*): calcd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1341, found: 241.1337. Hydrochloride salt of **9e**: light yellow solid; mp: 221.5–223.0°C (lit.[35] mp 222.0–223.0°C). The data for this compound matched in all aspects (^{1}HNMR, mp) with that reported in the literature.[35]

And **10e** (45 mg): off-white solid; TLC (20% EtOAc/hexanes), *Rf*: 0.31; mp: 120.5–121.4°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 7.8 Hz, 1H), 7.04 (br, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.45 (m, 2H), 7.27 (m, J_1 = 7.9 Hz, J_2 = 1.5 Hz, 1H), 6.84 (d, J = 8.7 Hz, 1H), 4.27 (d, J = 6.7 Hz, 2H), 2.20 (m, 2H), 1.10 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 140.0, 138.1, 128.2, 126.6, 122.3, 121.3, 120.4, 119.6, 111.1, 108.6, 72.4, 28.1, 19.4; HRMS–ESI (*m/z*): calcd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1341, found: 241.1335.

[combined yield = 108 mg, 93 %].

3-(*tert*-butoxy)-9*H*-pyrido[3,4-*b*]indole (9f) and 2-(*tert*-butoxy)-5*H*-pyrido[3,2-*b*]indole (10f)—Following the general procedure, **8f** (100 mg, 0.36 mmol), $Pd(OAc)_2$ (8.0 mg, 0.036 mmol), $(t\text{-}Bu)_3P\ HBF_4$ (21 mg, 0.072 mmol) and K_2CO_3 (100 mg, 0.72 mmol) after flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded **9f** (48 mg): colorless crystals; TLC (50% EtOAc/hexanes), *Rf*: 0.30; mp: 207.9–209.8°C (lit.[36] 208.0–212.0°C); HRMS–ESI (*m/z*): calcd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1341, found: 241.1339. The data for this compound matched in all aspects (^{1}HNMR, mp) with that reported in the literature.[36]

And **10f** (25 mg): light brown solid; TLC (50% EtOAc/hexanes), *Rf*: 0.59; mp: 110.5–112.2°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, *J* = 7.8 Hz, 1H), 7.94 (br, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.45 (m, 2H), 7.27 (t, *J* = 6.3 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 1.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.7, 140.1, 138.3, 128.2, 126.6, 122.7, 120.7, 120.4, 119.6, 111.8, 111.0, 79.3, 29.8; HRMS–ESI (*m/z*): calcd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1341, found: 241.1349.

[Combined yield = 73.0 mg, 85 %].

3-(benzyloxy)-9*H*-pyrido[3,4-*b*]indole (9g) and 2-(benzyloxy)-5*H*-pyrido[3,2-*b*]indole (10g)—Following the general procedure, **8g** (65 mg, 0.21 mmol), $Pd(OAc)_2$ (4.7 mg, 0.021 mmol), $(t\text{-}Bu)_3P\ HBF_4$ (12.2 mg, 0.042 mmol) and K_2CO_3 (58 mg, 0.42 mmol) after flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded **9g** (30 mg): off-white solid; HRMS–ESI (*m/z*): calcd for $C_{18}H_{15}N_2O$ $[M+H]^+$: 275.1184, found: 275.1194. Hydrochloride salt of **9g**: yellow solid; mp: 197.8–199.2°C (lit.[35] mp 198.0–199.0°C). The data for this compound matched in all aspects (^{1}HNMR, mp) with that reported in the literature.[35]

And **10g** (20 mg): white solid; TLC (20% EtOAc/hexanes), *Rf*: 0.23; mp: 137.5–139.5°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.1 Hz, 1H), 7.96 (br, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.40 (m, 6H), 6.91 (d, *J* = 8.7 Hz, 1H), 5.60 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 140.1, 138.1, 137.9, 128.4, 128.3, 127.7, 126.8, 122.4, 121.4, 120.5, 119.8, 111.2, 108.9, 67.7; HRMS–ESI (*m/z*): calcd for $C_{18}H_{15}N_2O$ $[M+H]^+$: 275.1184, found: 275.1196.

[Combined yield = 50 mg, 87 %].

Large scale synthesis of 3-PBC (1) and βCCt (2)

Step 1: General procedure: Representative procedure for the synthesis of *N*-(2-chlorophenyl)-6-propoxypyridin-3-amine (5b)—$Pd(OAc)_2$ (2.6 g, 11.6 mmol), **3** (50 g, 231.4 mmol), Cs_2CO_3 (90.5 g, 277.7 mmol) and X-Phos (8.3 g, 17.3 mmol) were added to a three-neck flask with a reflux condenser. The flask was evacuated and back-filled with argon. **4b** (31 g, 25.6 mL, 243 mmol) was injected into the flask with a syringe. Toluene (500 mL) was added via a cannula and the flask was introduced into a pre-heated oil bath at 100°C. After 15 h at 100°C the reaction mixture was cooled down to rt, filtered through a short pad of celite, and the pad was washed with ethyl acetate. The combined organic eluents were washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (20:1; hexanes/ethyl acetate) to afford **5b** (52.9 g, 87 %).

Large scale synthesis of *tert*-butyl-5-[(2-chlorophenyl)amino]picolinate (12)—Following the general procedure, the *tert*-butyl 5-bromopicolinate **11**[37] (50 g, 194 mmol) was reacted with **4b** (26 g, 25.6 mL, 203 mmol), $Pd(OAc)_2$ (2.18 g, 9.7 mmol), Cs_2CO_3 (75.9 g, 233 mmol) and X-Phos (6.9 g, 14.55 mmol). Purification by flash chromatography (silica gel, 5:1 hexanes/ethyl acetate) afforded **12** (55.6 g, 94 %).

Step 2 general procedure: Representative procedure for large scale synthesis of 3-propoxy-9*H*-pyrido[3,4-*b*]indole (3-PBC; 1)—5b (20 g, 76.1 mmol), $Pd(OAc)_2$ (1.71 g, 7.61 mmol), $(t\text{-Bu})_3P\ HBF_4$ (4.41 g, 15.22 mmol) and K_2CO_3 (21 g, 152.2 mmol) were added to a heavy-wall pressure vessel (350 mL). The vessel was fitted with a rubber septum, evacuated and back-filled with argon. Degassed DMA (250 mL) was added to this vial via a cannula. The rubber septum was replaced with a Teflon screw cap and this sealed vessel was introduced in a pre-heated oil bath at 120°C. After stirring at this temperature for 16 h, the reaction mixture was allowed to cool to rt and was passed through a short pad of celite, which was further washed with ethyl acetate until no product (TLC; silica gel) was detected in the eluent. The combined filtrate was washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude solid was purified by flash chromatography (5:1; hexanes/ethyl acetate) to afford **3-PBC** (**1**) (10 g, 58 %).

Large scale synthesis of *tert*-butyl 9*H*-pyrido[3,4-*b*]indole-3-carboxylate (βCCt; 2)—Following the general procedure, **12** (10 g, 32.8 mmol), $Pd(OAc)_2$ (735 mg, 3.28 mmol), $(t\text{-Bu})_3P\ HBF_4$ (1.9 g, 6.56 mmol) and K_2CO_3 (9.06 g, 65.6 mmol) after flash chromatography (silica gel, 1:1 hexanes/ethyl acetate) afforded βCCt (**2**) (4.87 g, 55.6 %): white solid; mp 302.5–303.4°C (lit.[17] mp 301–303°C). The spectral data for this compound matched in all aspects (^{1}H NMR) with that reported in the literature.[17]

The regioisomer *tert*-butyl 5*H*-pyrido[3,2-*b*]indole-2-carboxylate (**13**): fluffy white solid (2.43 g, 27.4%); TLC (2:1 EtOAc/hexanes), *Rf*: 0.53; mp: 218–219.2°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (br, 1H), 8.45 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.52 (m, 2H), 7.31 (t, J = 7.2 Hz, 1H), 1.69 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 142.8, 141.6, 141.2, 134.6, 128.6, 122.5, 122.4, 122.0, 120.9, 117.1, 111.3, 81.8, 28.3; Anal.: $C_{16}H_{16}ClN_2O_2{\cdot}0.1\ CH_2Cl_2$: C, 69.89; H, 5.90; N, 10.13; found: C, 69.93; H, 6.07; N, 9.89.

Supplementary Material

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Acknowledgments

We thank the NIMH (MH 046851) (JMC), and NIAAA (AA016179) as well as the Lynde and Harry Bradley Foundation for generous financial support. The crystallographic analysis was carried out at the Naval Research Laboratory.

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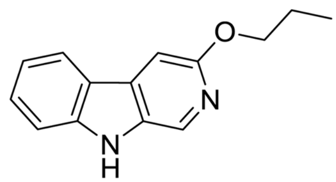
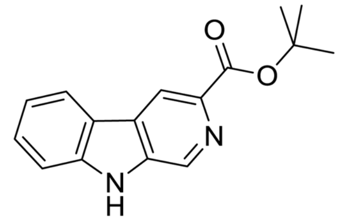


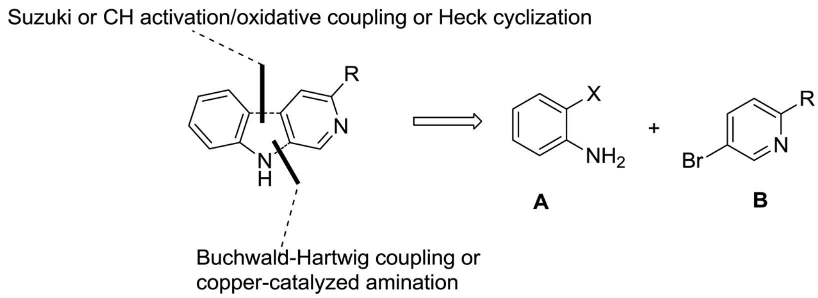
3-PBC (1)



βCCt (2)

Figure 1.

Structures of 3-PBC (**1**) and βCCt (**2**)



Scheme 1.
Retrosynthetic analysis of **1** and **2**

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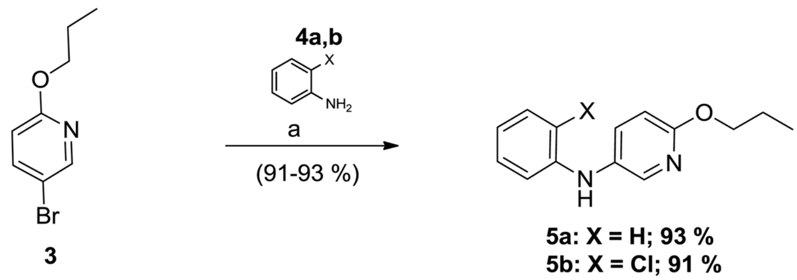
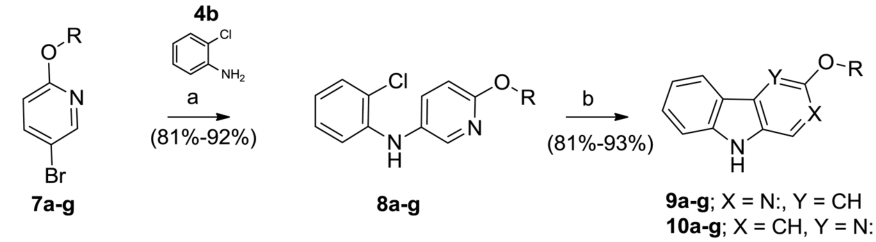


Scheme 2.

Synthesis of intermediates **5a** and **5b**

Reagents and conditions: (a) 5 mol% $Pd(OAc)_2$, 7.5 mol% X-Phos, 1.5 eq. Cs_2CO_3, toluene, 100°C, 15 h



7a, R = Me
7b, R = Et
7c, R = *i*-Pr
7d, R = *n*-Bu
7e, R = *i*-Bu
7f, R = *t*-Bu
7g, R = Bn

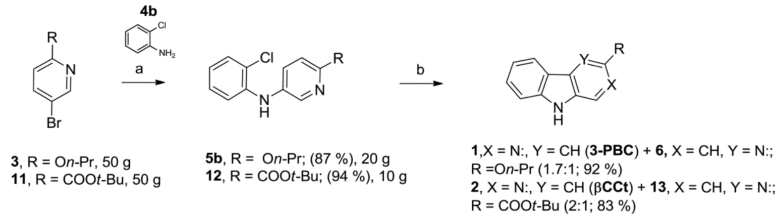
8a, R = Me
8b, R = Et
8c, R = *i*-Pr
8d, R = *n*-Bu
8e, R = *i*-Bu
8f, R = *t*-Bu
8g, R = Bn

9a & **10a**, R = Me
9b & **10b**, R = Et
9c & **10c**, R = *i*-Pr
9d & **10d**, R = *n*-Bu
9e & **10e**, R = *i*-Bu
9f & **10f**, R = *t*-Bu
9g & **10g**, R = Bn

Scheme 3.

Synthesis of substituted carboline analogs

Reagents and conditions: (a) 5 mol% $Pd(OAc)_2$, 7.5 mol% X-Phos, 1.5 eq. Cs_2CO_3, toluene, 100°C, 15 h; (b) $Pd(OAc)_2$, $(t\text{-}Bu)_3P.HBF_4$, K_2CO_3, DMA, 120°C, 16 h



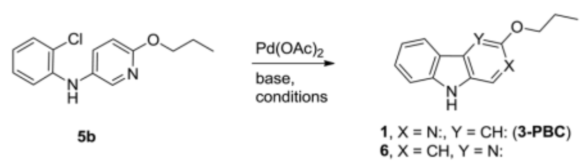
Scheme 4.

Large-scale synthesis of 3-PBC (**1**) and βCCt (**2**) using the new route

Reagents and conditions: (a) 5 mol% $Pd(OAc)_2$, 7.5 mol% X-Phos, 1.5 eq. Cs_2CO_3, toluene, 100°C, 15 h; (b) $Pd(OAc)_2$, (*t*-Bu)$_3$P.HBF_4, K_2CO_3, DMA, 120°C, 16 h

Table 1

Optimization of conditions for the cyclization of **5b** to **1**[a]



entry	ligand	base	solvent	temp (time)	results (yield)[b]
1	X-Phos	Cs_2CO_3	toluene	100°C (24 h)	no reaction
2	X-Phos	NaO*t*-Bu	toluene	100°C (24 h)	no reaction
3	X-Phos	NaO*t*-Bu	DMF	120°C (24 h)	dechlorination
4	X-Phos	NaO*t*-Bu	DMA	120°C (24 h)	dechlorination
5	$(t\text{-Bu})_3P \cdot HBF_4$	NaO*t*-Bu	DMA	120°C (24 h)	32 % yield (mixture of **1** and **6**) + decomposed material
6	$(t\text{-Bu})_3P \cdot HBF_4$	K_2CO_3	DMA	120°C (24 h)	52 % **1** + 30 % **6**
7	(*t*-Bu)3P $\cdot HBF_4$	K_2CO_3	DMA	120°C (16 h)	56 % **1** + 32 % **6**
8	$Cy_3P \cdot HBF_4$	K_2CO_3	DMA	120°C (16 h)	55 % **1** + 30 % **6**

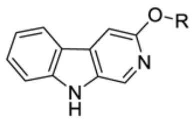
[a]The reactions were carried out using **5b** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.02 mmol), and base (0.2 mmol) in solvent (1.0 mL) under argon.

[b]Isolated yield.

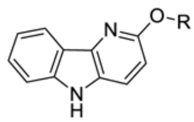
Table 2

Ratios of β (**9**) and δ (**10**) carbolines

entry	R	Yield[a] (9 : 10)
1	Me	81 % (1.2 : 1)
2	Et	85 % (1.25 : 1)
3	*i*-Pr	90 % (1.8 : 1)
4	*n*-Bu	87 % (1.35 : 1)
5	*i*-Bu	93 % (1.4 : 1)
6	*t*-Bu	85 % (1.9 : 1)
7	Bn	87 % (1.5 : 1)



9a-g



10a-g

[a]Combined isolated yield