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Copper-Catalyzed Synthesis of β- and δ-Carbolines by Double N-Arylation of Primary Amines

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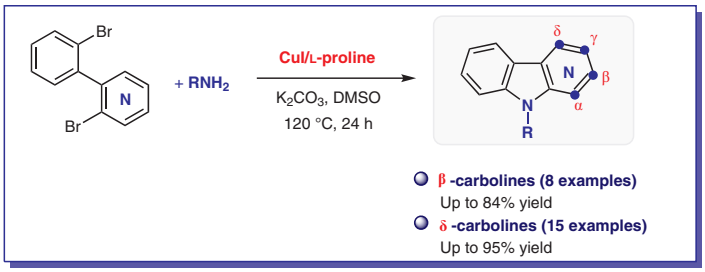

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Abstract Two efficient and practical approaches are reported for the synthesis of β- and δ-carbolines from 3,4-dibromopyridine. The synthesis is based on site-selective Cu-catalyzed double C–N coupling reactions and subsequent annulations by twofold Pd-catalyzed C–N coupling with amines.

Key words catalysis, heterocycles, cross-coupling, cyclizations, copper

Carbolines (pyridoindoles) are important compounds, due to their presence in many alkaloids and pharmaceuticals.[1] There are four different carboline regioisomers and especially β-carbolines appear frequently in natural products.[2] In 1984, eudistomin A was isolated from *Eudistoma olivaceum*. Later, a big family of eudistomin derivatives (B–W) was isolated from nature (Figure 1).[3] In 1986, manzamine A was isolated from the Okinawa sponge genus *Haliclona*.[4] Up to now, there are more than 80 manzamine alkaloids which were isolated from several marine sponge species.[2] Canthine alkaloids, containing the core of β-carbolines, were isolated from several plant families (*Rutaceae*, *Simaroubaceae*, *Amaranthaceae*, *Caryophyllaceae*) and from marine organisms.[2] Natural β-carbolines exhibit a wide range of important medicinal activities, for example, anti-Alzheimer, anti-cancer, anti-inflammatory, anti-HIV, and antimalarial activities.[1,2] In addition, the β-carboline structure is present in many synthetic drugs, such as in ZK91296, ZK93426 (anxiogenic agents) or Abecamil (an anxiolytic drug) (Figure 1).[5] In comparison to β-carbolines, only a few δ-carbolines were isolated as natural products. Examples include cryptolepine, cryptoquindoline, cryptomisrine, jusbetonin, and quindoline.[6] These natural alkaloids were isolated from *Cryptolepis sanguinolenta* and *Justicia bentonica*, which have been known as traditional medicines for the treatment of malaria and of other infectious diseases in Central and West Africa.[6] In recent studies it has been shown that δ-carboline derivatives exhibit important bioactivities, such as anti-inflammatory,[7] antitumor,[8] antimalarial,[9] antimicrobial,[10] and antiviral[11] activities.

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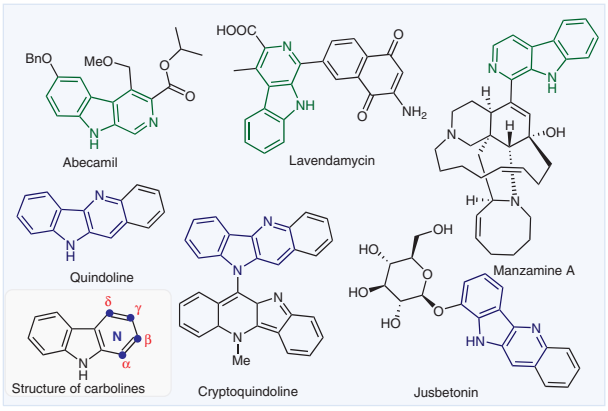


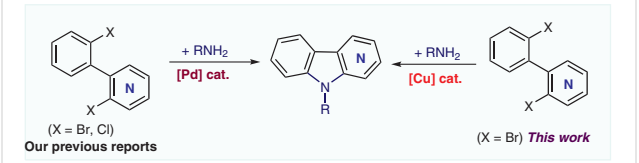
Figure 1 Several natural alkaloids containing the carbazole core

Carboline derivatives also play a role in the development of novel light-emitting devices (hole-transporting, luminescent, and host materials).[12] In order to improve electron-carrier mobility, quantum yield efficiency, and stability of organic materials, the carbazole moiety of such materials was successfully replaced by β- and δ-carboline structures.[12]

Due to their importance, a variety of classical and modern methods have been developed for the synthesis of carboline derivatives. Classical methods for the synthesis of β-carbolines rely on the Cadogan,[13] Bischler–Napieralski,[14] and Pictet–Spengler[15] reactions. In 2011, Cuny *et al.* developed a metal-free synthesis of four types of carbolines based on photostimulated cyclization of anilinohalopyridines *via* the $S_{RN}1$ mechanism.[16] Efficient catalytic approaches to β-carbolines have also been reported.[17] For example, Shu *et al.* demonstrated an Au-catalyzed synthesis of 3-amino-β-carbolines *via* [4+2] cycloaddition of azides and ynamides.[17a] In addition, β- and γ-carbolines were prepared by Ru- and Rh-catalyzed [2+2+2] cycloadditions.[17b] Recently, a Cu-catalyzed arene–ynamide cyclization has been described.[17c] Several syntheses of β-carbolines by using palladium catalysts have been reported. The first study on the synthesis of four types of carbolines *via* a tandem process of Pd-catalyzed amination and intramolecular arylation reactions has been reported in 1999.[17d] Typical reports on the Pd-catalyzed synthesis of β-carbolines involve iminoannulation reactions of alkynes,[17e,f,h] tandem C–N coupling/C–H activation reactions of anilines with halopyridines,[17i] cyclizations of tryptophan-derived isocyanides and aryl iodides,[17j] α-arylations of ketones with 3-bromoindoles,[17k] and cyclizations of vinylindoles.[17l] Recently, we described an efficient synthesis of β-carboline derivatives from 3,4-dibromopyridine *via* site-selective Pd-catalyzed C–C coupling reactions with *o*-bromophenyl boronic acid, followed by twofold cyclizations with amines.[17m]

In contrast to α-, β-, and γ-carbolines, several synthetic methods using Pd catalysis have been also reported for the synthesis of δ-carbolines.[17n–s] In 1997, Yang et al. developed the synthesis of δ-carboline derivatives by application of domino Pd-catalyzed cyclizations of α-(*o*-bromoanilino)-alkenenitriles.[17n] In order to prepare 3,4-disubstituted δ-carbolines, the Dupas group developed cyclization reactions of indole amines with 1,3-dicarbonyl compounds.[17o] In 2011, Ablordeppey *et al.* reported a practical method for the preparation of δ-carboline derivatives in moderate yields by intramolecular Pd-catalyzed arylation of *N*-aryl-3-aminopyridine.[17p] In 2012, Detert *et al.* reported a six-step synthesis of δ-carbolines starting from 2-chloro-3-nitropyridine.[17q] In the same year, the Cao group developed a method for the preparation of δ-carbolines using a Pd-catalyzed cyclization of 2-iodoanilines with *N*-tosylenynamines.[17r] In 2015, we reported a convenient synthesis of δ-carboline derivatives from 1,2-dibromopyridine via sequential site-selective Pd-catalyzed C–C/C–N coupling reactions.[17s]

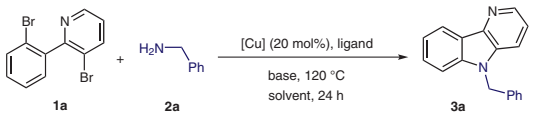
Known methods often result in the formation of regioisomeric products or require the use of expensive transition-metal catalysts (Au, Rh, Ru, Pd). In our previous work related to the chemoselective synthesis of carbolines,[17m,s] we studied twofold Pd-catalyzed C–N coupling reactions as the key steps for the formation of the carboline rings. The application of inexpensive, stable, and readily available copper salts instead of expensive transition-metal catalysts in combination with often expensive ligands is of considerable current interest in the field of organic synthesis. Recently, we have reported a practical method using Cu catalyst for the synthesis of carbazole derivatives.[18] In exploration of further applications in Cu-catalyzed double C–N coupling reactions, herein, we wish to report a convenient, inexpensive, and practical method for the Cu-catalyzed synthesis of β- and δ-carboline derivatives from readily available starting materials (Scheme 1). Our methodology shows tolerance of many functional groups and proceeds in good yields and with high selectivity.



Scheme 1 Synthesis of carbolines by double N-arylation reactions

The starting material 3-bromo-2-(2-bromophenyl)pyridine (**1a**) was prepared following our previously reported procedure.[17s] The twofold C–N coupling reaction of **1a** with benzyl amine (**2a**, 1.5 equiv), using 20 mol% of Cu catalyst in combination with 24 mol% of ligand at 120 °C resulted in the formation of the desired carboline **3a** (Table 1). Several key reaction factors which may influence this transformation, including copper source, ligand, and solvent, were screened to optimize the yield. In order to find a suitable li-

Table 1 Optimization of the Synthesis of δ-Carboline[a]

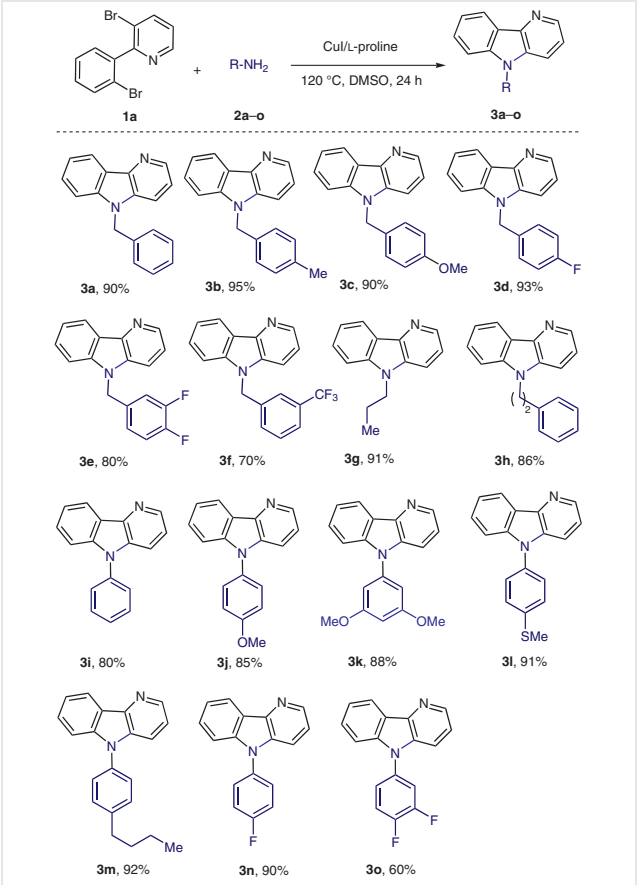


Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	BINAP	K_2CO_3	DMSO	45
2	CuI	dppe	K_2CO_3	DMSO	36
3	CuI	IPr·HCl	K_2CO_3	DMSO	52
4	CuI	1,10-phenanthroline	K_2CO_3	DMSO	42
5	CuI	bipyridine	K_2CO_3	DMSO	40
6	CuI	L-proline	K_2CO_3	DMSO	90
7	CuI	L-proline	K_3PO_4	DMSO	79
8	CuI	L-proline	Cs_2CO_3	DMSO	82
9	CuI	L-proline	KO*t*Bu	DMSO	47
10	CuI	L-proline	KOH	DMSO	72
11	CuBr	L-proline	K_2CO_3	DMSO	85
12	CuCl	L-proline	K_2CO_3	DMSO	83
13	CuI	L-proline	K_2CO_3	DMF	82
14	CuI	L-proline	K_2CO_3	NMP	85
15	CuI	L-proline	K_2CO_3	dioxane	–
16	–	L-proline	K_2CO_3	DMSO	–

[a] Reaction conditions: **1a** (1.3 mmol), **2a** (2.0 equiv), base (3 equiv), [Cu] catalyst (20 mol%), ligand (20 mol%), 120 °C, 24 h.
[b] Yields of isolated products.

gand, we initially chose K_2CO_3 as the base and DMSO as the solvent. Our initial optimizations started with employment of phosphine and carbene ligands, for example, BINAP, dppe, IPr which, however, gave carboline **3a** in only low yields (entries 1–3). Then, bipyridine ligands were examined which also did not result in satisfactory results (entries 4, 5). Recently, amino acids and their derivatives were shown to be efficient bidentate ligands in combination with copper sources for C–N coupling reactions.[19] We employed simple L-proline as the ligand which gave the desired product in 90% yield (entry 6). Then, a quick examination using different bases was carried out. However, other bases did not give better yields of the carboline product (entries 7–10). In order to understand the influence of the copper sources in this reaction, we carried out some further optimizations using other common copper salts, such as CuBr and CuCl (entries 11, 12). Indeed, an 85% yield of carboline product was observed using CuBr as the catalyst. Subsequently, we tried to evaluate the role of the solvent and used, for example, NMP, DMF, and dioxane under the standard conditions described above (entries 13–15). Still, an 85% yield of δ-carboline product was obtained when the reaction was carried out in NMP. However, only trace amounts of product were observed when dioxane was employed. Finally, a control experiment without using CuI catalyst was performed which did not give even trace amounts of δ-carboline product (entry 16). In contrast, employment of $PdCl_2$ instead of CuI provided the product, albeit in only 15% yield. It seems unlikely to us that the reaction might be catalyzed by Pd impurities present in the copper iodide as the purity of CuI was relatively high (Aldrich, 99%). In addition, phosphane ligands as typical for Pd(0)-catalyzed Buchwald–Hartwig reactions were not present in the reaction mixture.

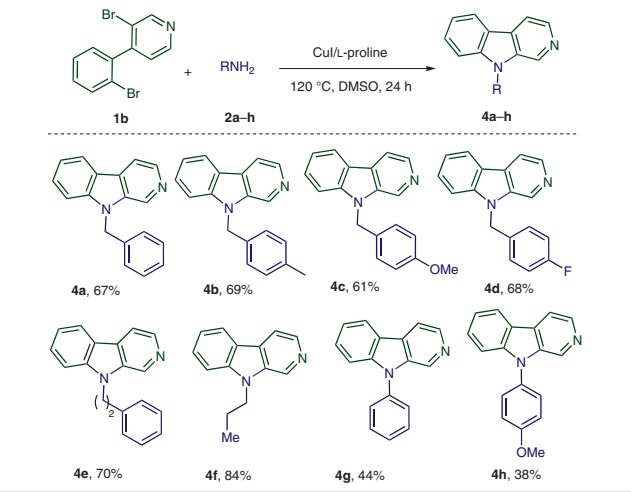
With our optimized conditions in hand,[20,21] we studied the substrate scope of this transformation using several different amines, and indeed, a series of products could be successfully prepared (Scheme 2). δ-Carboline derivatives bearing with a variety of functional groups were obtained in 60–95% yields (**3a–o**). The use of both benzylic and aliphatic amines resulted in high yields. In fact, with benzyl amine derivatives containing electron-donating groups (methyl and methoxy), up to 95% yield of the desired carboline was isolated (**3b**). In contrast, lower yields were obtained in the presence of electron-withdrawing groups, due to the weaker nucleophilic properties of these amines (**3d–**



Scheme 2 Synthesis of δ-carboline derivatives **3a–o**. *Reagents and conditions*: **2a–o** (2.0 equiv), K_2CO_3 (3 equiv), [Cu] catalyst (20 mol%), ligand (20 mol%), 120 °C, 24 h; yields of isolated products are given.

f). Subsequently, anilines were employed, and the desired carboline products could again be isolated in good yields (**3i–o**).

Finally, we applied our procedure to the synthesis of β-carboline derivatives (**4a–h**) by double Cu-catalyzed cyclization of intermediate **1b** with amines **2a–h**. The desired β-carbolines **4a–h** could be prepared in 38–84% yields.[22,23] While the reactions of benzylic and aliphatic amines with **1b** proceeded in good yields (**4a–f**, Scheme 3), employment of anilines resulted only in moderate yields.



Scheme 3 Synthesis of β-carboline derivatives **4a–h**. *Reagents and conditions*: **2a–h** (2.0 equiv), K_2CO_3 (3 equiv), [Cu] catalyst (20 mol%), ligand (20 mol%), 120 °C, 24 h; yields of isolated products are given.

In conclusion, we have reported a practical, inexpensive, and efficient one-pot synthesis of β- and δ-carboline derivatives. The reactions rely on twofold Cu-catalyzed C–N coupling reactions of 2,2′-dibromobiaryl compounds with amines with tolerance of many functional groups. Our procedure could be advantageous for applications in both medicinal chemistry and materials science.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1720461.

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(20) **Preparation of 3-Bromo-2-(2-bromophenyl)pyridine (1a)**
2,3-Dibromopyridine (2.00 g, 8.44 mmol), 2-bromophenyl boronic acid (1.70 g, 8.44 mmol), and $Pd(PPh_3)_4$ (488 mg, 0.422 mmol) were added to a 250 mL Schlenk flask. The mixture was backfilled several times with argon. To the mixture were added K_2CO_3 (1 M, 25 mL), 5 drops of aqueous KOH (10%) and 35 mL of THF, then backfilled several times with argon. The reaction was heated at 70 °C for 18 h. The solvent was evaporated in vacuo. The residue was extracted with ethyl acetate and water. The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated *in vacuo*. The yellow residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 20:1) to yield 3-bromo-2-(2-bromophenyl)pyridine (**1a**)[17s] (2.20 g, 85%) as a colorless oil.

(21) **General Procedure for the Synthesis of 5*H*-Pyrido[3,2-*b*]indoles 3a–o**
3-Bromo-2-(2-bromophenyl)pyridine (**1a**, 100 mg, 0.32 mmol), 4-fluoroaniline (116 mg, 0.958 mmol), copper(I) iodide (12 mg, 0.064 mmol, Aldrich, 99%), L-proline (11 mg, 0.096 mmol), and K_2CO_3 (132 mg, 0.958 mmol) were dissolved in DMSO (1.5 mL) and heated at 120 °C for 24 h. After cooling, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 5:1) to yield 5-(4-methylbenzyl)-5*H*-pyrido[3,2-*b*]indole (**3b**, 85 mg, 95%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.57 (s, 1 H), 8.46 (s, 1 H), 7.65 (s, 1 H), 7.56–7.50 (m, 1 H), 7.42 (d, *J* = 8.2 Hz, 1 H), 7.35 (d, *J* = 6.8 Hz, 2 H), 7.07 (d, *J* = 7.9 Hz, 2 H), 7.01 (d, *J* = 7.9 Hz, 2 H), 5.47 (s, 2 H), 2.29 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 141.4, 137.5, 133.5, 129.6, 127.9, 126.4, 120.2, 109.3, 21.1. HRMS (ESI): *m/z* calcd for $C_{19}H_{16}N_2$ $[M + 1]^+$: 273.1386; found: 273.1401.

(22) **Preparation of 3-Bromo-4-(2-bromophenyl)pyridine (1b)**
3,4-Dibromopyridine (2.00 g, 8.44 mmol), 2-bromophenylboronic acid (1.70 g, 8.44 mmol), and $Pd(PPh_3)_4$ (488 mg, 0.422 mmol) were added to a 250 mL Schlenk flask. The mixture was backfilled several times with argon. To the mixture were added K_2CO_3 (1 M, 25 mL), 5 drops of aqueous KOH (10%), and 35 mL of THF, then backfilled several times with argon. The reaction was heated at 70 °C for 18 h. The solvent was evaporated *in vacuo*. The residue was extracted with ethyl acetate and water. The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 20:1) to yield 3-bromo-4-(2-bromophenyl)pyridine (**1b**)[17m] (2.30 g, 80%) as a colorless syrup.

(23) **General Procedure for the Synthesis of 9*H*-pyrido[3,4-*b*]indoles 4a–h**
3-Bromo-2-(2-bromophenyl)pyridine (**1a**, 100 mg, 0.32 mmol), 4-fluoroaniline (116 mg, 0.958 mmol), copper(I) iodide (15.4 mg, 0.08 mmol), L-proline (11 mg, 0.096 mmol), and K_2CO_3 (132 mg, 0.958 mmol) were dissolved in DMSO (1.5 mL) and heated at 160 °C for 24 h. After cooling, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 5:1) to yield 9-phenethyl-9*H*-pyrido[3,4-*b*]indole (**4e**, 61 mg, 70%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.72 (s, 1 H), 8.43 (d, *J* = 4.9 Hz, 1 H), 8.14 (dt, *J* = 7.9, 1.0 Hz, 1 H), 7.95 (d, *J* = 5.2 Hz, 1 H), 7.56 (ddd, *J* = 8.4, 7.1, 1.2 Hz, 1 H), 7.39–7.33 (m, 1 H), 7.32–7.23 (m, 2 H), 7.25–7.20 (m, 1 H), 7.23–7.17 (m, 2 H), 7.17 (ddt, *J* = 7.7, 5.7, 1.6 Hz, 1 H), 7.11–7.05 (m, 2 H), 4.59 (t, *J* = 7.4 Hz, 2 H), 3.15 (t, *J* = 7.4 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 141.1, 138.5, 138.2, 131.7, 128.8, 128.7, 128.7, 128.6, 128.5, 126.9, 126.4, 122.0, 121.1, 119.8, 109.4, 45.3, 35.5. HRMS (ESI): *m/z* calcd for $C_{19}H_{16}N_2$ $[M + 1]^+$: 273.1386; found: 273.1400.