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Synthetic Methods

Transition-Metal-Catalyzed C–H Bond Functionalizations: Feasible Access to a Diversity-Oriented β-Carboline Library

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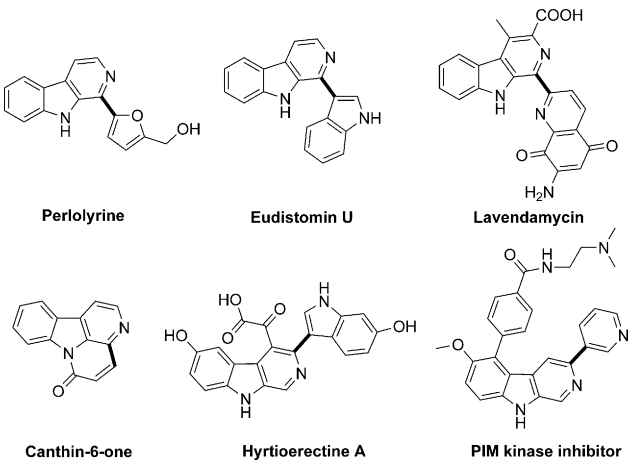
Abstract: Diversification of the β-carboline skeleton has been demonstrated to assemble a β-carboline library starting from the tetrahydro-β-carboline framework. This strategy affords feasible access to heteroaryl-, aryl-, alkenyl-, or alkynyl-substituted β-carbolines at the C1, C3, or C8 position through three categorically different types of transition-metal-catalyzed C–C bond-forming reactions, in the presence of multiple potentially reactive positions. These site-selective functionalizations include; 1) the Cu-catalyzed C1/C3-selective decarboxylative C_{sp^3}–C_{sp^2} and C_{sp^3}–C_{sp} coupling of hexahydro-β-carboline-3-carboxylic acid with a C–H bond of a heteroarene or terminal alkyne; 2) the chelation-assisted Pd-catalyzed C1/C8-selective C–H arylation of hexahydro-β-carboline with aryl boron reagents; and 3) the chelation-assisted Pd-catalyzed C1/C3-selective oxidative C–H/C–H cross-coupling of β-carboline-*N*-oxide with arenes, heteroarenes, or alkenes. The saturated structural feature of the hexahydro-β-carboline framework can increase reactivity and control site selectivity. The robustness of these approaches has been demonstrated through the synthesis of hyrtioerectine analogues and perlolyrine. We believe that these strategies could provide inspiration for late-stage diversifications of bioactive core scaffolds.

Introduction

In the field of modern drug discovery, rapidly accessing molecular diversity, in compounds that are based on an identified lead compound, can be challenging.[1] Transition-metal-catalyzed cross-coupling reactions are some of the most reliable methods for C–C bond formations. Direct site-selective functionalization of intrinsic functional groups in bioactive molecules would be an ideal strategy to rapidly assemble a diversity-oriented library of drug candidates.[2] For these reactions to occur, the compounds do not require preactivation, minimizing the number of synthetic steps and avoiding the preparation of organic halides and organometallic reagents. Nevertheless, the application of this strategy may face three major challenges, including; 1) site selectivity among multiple reactive positions; 2) divergent functionalizations at one site; and 3) nonproductive coordination of the heteroatom of heterocycles with metal centers.

The β-carboline derivatives, bearing a tricyclic pyrido[3,4-*b*]indole core, are important indole alkaloids. These compounds are widely distributed in natural products, pharmaceuticals, and bioactive molecules. Some derivatives exhibit effects on the central nervous system (CNS), for example, demonstrating an affinity for benzodiazepine receptors (BZRs), 5-HT_{2A}, and 5-HT_{2C} receptors, and displaying antimicrobial, antiviral, and antiparasitic activities, and antitumor properties (for example, IκB kinase, PIM kinase, and cyclin-dependent kinase (CDK) inhibition) (Scheme 1).[3,4] In the past decades, investigation of the structure–bioactivity relationships of functionalized β-carboline derivatives has attracted intensive interest. A large number of research reports have demonstrated that attachment of the (hetero)aryl or alkenyl functional groups to the C1 and/or C3 site of the carboline scaffold is capable of increasing



Scheme 1. Natural products and pharmaceutical drugs containing a (hetero)-aryl- or alkenyl-substituted β-carboline skeleton.

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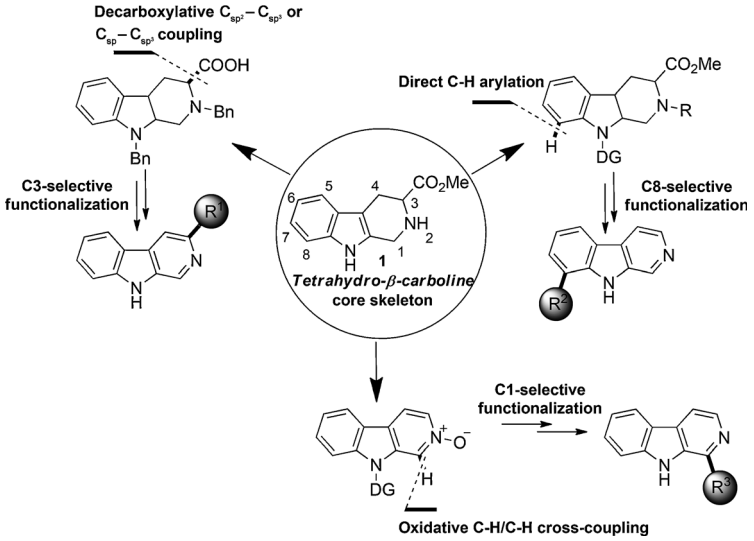
the biological activity.[5] Thus, chemists have devoted much effort towards developing new synthetic methods for the preparation of various functionalized β-carboline derivatives. A multistep synthesis, including either the Bischler–Napieralski cyclodehydration or the Pictet–Spengler cyclization followed by sequential aromatization, has proven to be an efficient route to 1-(hetero)aryl substituted β-carbolines.[6] However, these methods have turned out to be less efficient for introducing (hetero)aryl functional groups into other positions of the tricyclic β-carboline skeleton. The C1-, C3-, C4-, C5-, or C6-(hetero)aryl-substituted β-carbolines can be obtained through traditional transition-metal-catalyzed C–X/C–M cross-coupling reactions, after the selective introduction of a halogen atom into the corresponding site of the β-carboline skeleton.[7] Nevertheless, these time-consuming and tedious prefunctionalizations may limit the rapid assessment of molecular diversity. In particular, 8-(hetero)aryl-substituted β-carbolines are surprisingly underdeveloped, probably owing to the synthetic difficulty in producing these compounds. Despite significant progress in synthetic methods, the development of a robust strategy to assemble a diversity-oriented β-carboline library remains a challenge. Therefore, in line with our ongoing interest in forging (hetero)aryl–(hetero)aryl, alkenyl–(hetero)aryl, and alkynyl–(hetero)aryl structural units through direct C–H bond functionalization, we herein, highlight the viability of these approaches in the diversity-oriented synthesis (DOS) of (hetero)aryl, alkenyl, and alkynyl β-carbolines. Subsequently, these strategies are successfully applied to the synthesis of hyrtioerectine analogues and perlolyrine.



Scheme 2. Design of a diversity-oriented β-carboline library from a tetrahydro-β-carboline core.

Results and Discussion

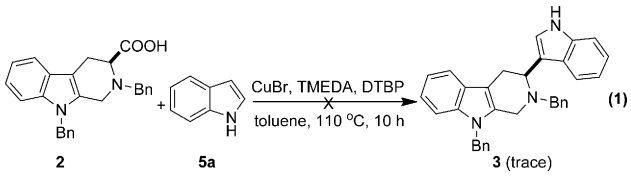
Molecular design

The β-carboline core possesses seven different reactive C–H bonds, possibly leading to low reactivity or lack of selectivity for C–H bond functionalizations. Thus, it is a substantial challenge to establish a diversity-oriented library of (hetero)aryl, alkenyl, and alkynyl β-carbolines through site-selective C–H bond cleavage of the carboline scaffold. On the other hand, the saturated analogue of β-carboline, the tetrahydro-β-carboline (THBC) core, is frequently found in many naturally occurring and synthetic indole alkaloids, exhibiting various important biological activities.[8] Herein, we disclose that this saturated structural feature can unlock reactivity and control site selectivity. Thereby, divergent functionalizations could become a feasible and concise route to the diversity-oriented synthesis of substituted β-carbolines. Our blueprint for the synthesis of a variety of β-carbolines is illustrated in Scheme 2. The current methodology involves three categorically different types of site-selective functionalizations, in the presence of multiple reactive positions; 1) Cu-catalyzed C3-selective C_{sp^3}-decarboxylative coupling of hexahydro-β-carboline-3-carboxylic acid with a C–H bond of a heteroarene or alkyne; 2) chelation-assisted Pd-catalyzed C8-selective direct C–H arylation of 9-substituted hexahydro-β-carboline with aryl boron reagents; and 3) chelation-assisted Pd-catalyzed C1-selective oxidative C–H/C–H cross-coupling of β-carboline-*N*-oxide with arenes, heteroarenes, or alkenes. All substrates involved in the above-mentioned reactions are easily accessible from methyl tetrahydro-β-carboline-3-carboxylate **1** (Scheme 2). The tetrahydro-β-carboline skeleton serves as a bridge to introduce various functional groups (for example, heteroaryl, aryl, alkynyl, and alkenyl groups) at the C1, C3, or C8 position through divergent functionalizations, rapidly assembling a diversity-oriented β-carboline library.

C3-selective C_{sp^3}-decarboxylative coupling of hexahydro-β-carboline-3-carboxylic acid for the preparation of hyrtioerectine analogues

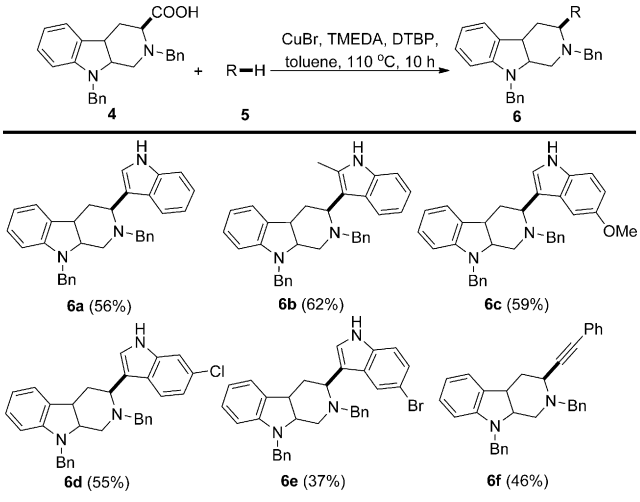
Usually, the synthesis of 3-(hetero)aryl-substituted β-carbolines relies on sequential aromatization of tetrahydro-β-carboline-3-carboxylic acid, Curtius rearrangement, diazotization, bromination, and transition-metal-catalyzed C–X/C–M cross-coupling reactions.[7a] Therefore, it is highly desirable to develop step-economical routes towards 3-substituted β-carbolines. In recent years, decarboxylative coupling reactions have emerged as an important synthetic tool for C–C bond formations because a large number of carboxylic acid substrates are readily available.[9] Li and co-workers have developed intermolecular decarboxylative C_{sp^3}–C_{sp^3}, C_{sp^3}–C_{sp^2} and C_{sp^3}–C_{sp} cross-coupling reactions of α-amino acids with various nucleophiles by using copper or iron catalysts.[9d–f] However, to date the decarboxylative coupling reactions have scarcely been applied to the synthesis of complex bioactive molecules. Tetrahydro-β-carboline-3-carboxylic acids contain a six-membered cyclic α-amino acid unit and, thus, may perform selective functionalizations at the C3 position by decarboxylative coupling reactions with nucleophiles. With this in mind, we started our investigation by treat-

ment of tetrahydro-β-carboline-3-carboxyl acid **2** with the NH-free indole **5a**, in a copper-catalyzed system. Disappointedly, only a trace amount of desired coupled product **3** was observed [Eq. (1)] (Bn = benzyl; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DTBP = di-*tert*-butyl peroxide).



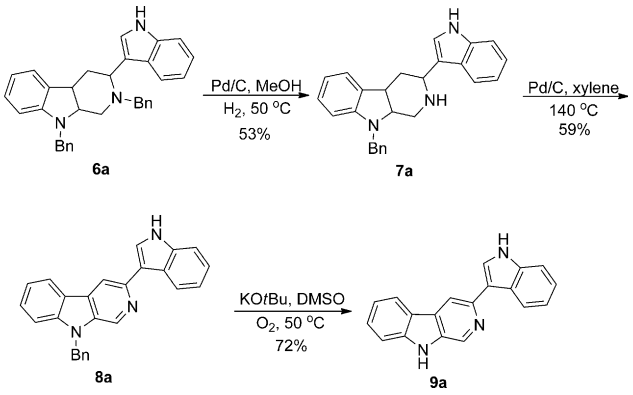
Subsequently, we were pleased to discover that hexahydro-β-carboline-3-carboxylic acid **4**, which was synthesized by means reduction of the indole double bond of **2**,[10] could smoothly undergo the C_{sp^3}–C_{sp^2} decarboxylative coupling with **5a** to afford coupled product **6a** with complete C3 selectivity. Although it is possible that the reaction might proceed via an imine-type intermediate,[9d] none of the C1-coupled product was observed, probably because of the steric hindrance caused by the benzyl groups at the N2 and N9 positions. After screening several parameters (for example copper source, ligand, oxidant, and solvent) the highest yield obtained was 56% (Table S1, see the Supporting Information). The optimized catalytic system was composed of CuBr (15 mol%), TMEDA (30 mol%), and DTBP (1.5 equivalents) in toluene, at 110 °C for 10 h.

With the optimized conditions in hand, we explored the scope of indoles. As shown in Scheme 3, a variety of indoles could be used in this coupling reaction to afford the corresponding products in acceptable yields (Scheme 3, **6a**–**e**). This process was amenable to various functional groups on the indole ring, such as methoxyl, bromo, and chloro groups, that could then be subjected to further transformations. In addition, phenyl acetylene provided the C3-alkynyl β-carboline (Scheme 3, **6f**).[11]



Scheme 3. Reactions were carried out by using **4** (0.25 mmol), **5** (1.5 equiv), CuBr (15 mol%), TMEDA (30 mol%), DTBP (1.5 equiv), and toluene (1 mL) at 110 °C for 10 h, under N_2. Yields based on **4**. The NOESY and ^{1}H NMR analysis indicated that coupled products **6a**–**e** contained two diastereoisomers with *cis*/*trans* ratios in the range of 1: 0.62–0.95. The alkynylation afforded the *trans*-diastereospecific C3-alkynyl β-carboline.

Hyrtioerectine analogues, isolated from the marine sponge *Hyrtios reticulatus*, contain a 3-heteroaryl β-carboline skeleton, which exhibits potent cytotoxic activities against human tumor cells.[3f] The synthesis of the hyrtioerectine analogue **9a** was achieved by using coupled product **6a** as the starting material (Scheme 4). Initially, compound **6a** was transformed into **7a** by debenzylation with Pd/C under a hydrogen atmosphere. Subsequently, aromatization with Pd/C in xylene[12a] gave **8a**, followed by deprotection, to afford desired product **9a**, by using KO*t*Bu in DMSO in the presence of O_2.[12b] The current strategy not only streamlined the traditional synthetic routes, based on C–X/C–M coupling, but also tolerated various functional groups.[7a,b]

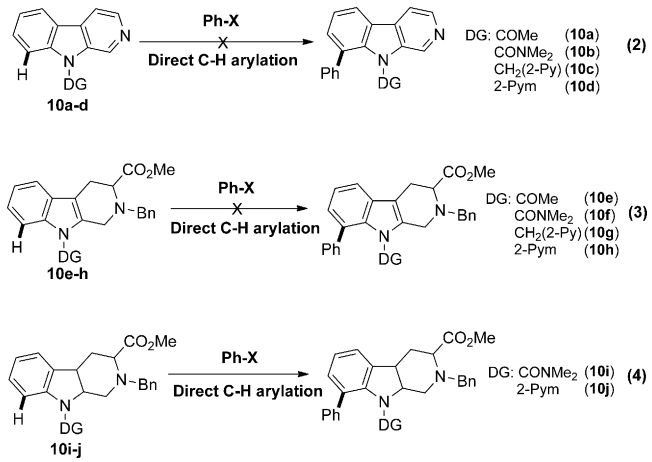


Scheme 4. Synthesis of hyrtioerectine analogue **9a**.

Selective direct C8 arylation of 9-substituted hexahydro-β-carboline

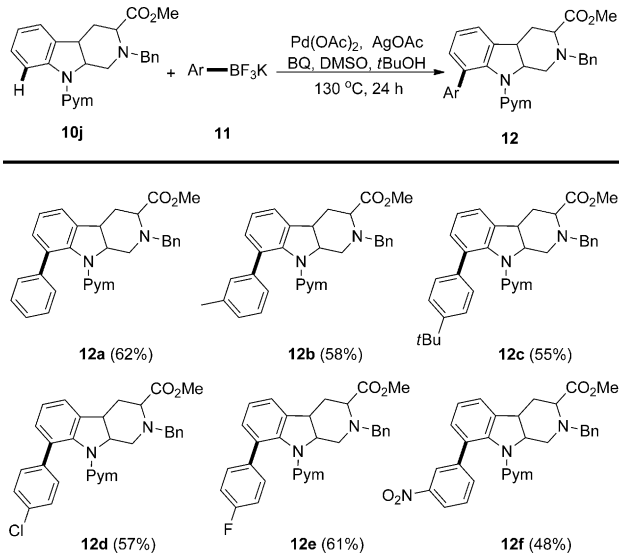
The synthesis of 8-aryl β-carbolines has, thus far, been underrepresented. As mentioned above, the introduction of a (hetero)-aryl substituent on the benzene ring of β-carbolines usually requires time-consuming and tedious prefunctionalization.[7d–g] Recently, great progress has been made in Pd-catalyzed direct C–H bond arylation, directed by functional groups, such as pyridine, amide, carboxylic acid, imine, and oxime groups.[13] Thus, we initially focused on the C8-selective arylation of β-carboline **10a**–**d** and tetrahydro-β-carboline **10e**–**h** with diaryliodonium salts, aryl halides, or borates by the introduction of various directing groups (DGs), for example, acetyl (COMe), *N*,*N*-dimethylcarbamoyl ($CONMe_2$), 2-pyridylmethyl (CH_2(2-Py)), and 2-pyrimidyl (2-Pym), at the N9 position, [Eq. (2)] and [Eq. (3)]. Despite several attempts, the above reactions did not exhibit promising results. We presumed that the rigidity of skeleton might not facilitate the formation of the six-membered cyclopalladated intermediate.

On the basis of these observations, we envisioned that more flexible 9-substituted hexahydro-β-carbolines **10i**–**j** could be



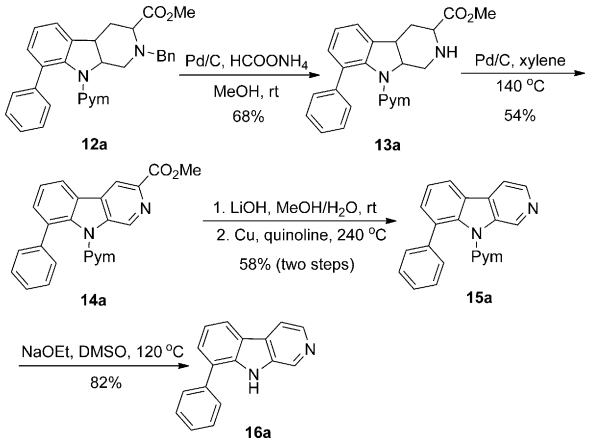
coupled with various arylating reagents by tethering a suitable and readily removable directing group at the N9 position [Eq. (4)] (Table S2, see the Supporting Information). The coupling reaction between 9-(pyrimidin-2-yl) hexahydro-β-carboline, **10j**, and potassium phenyltrifluoroborate, **11a**, gave the desired C8-aryl product, **12a**, in 28% yield by using $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2.0 equivalents), BQ (1.0 equivalent; BQ = 1,4-benzoquinone), and *t*BuOH as a solvent. After screening several parameters (ligand, oxidant, solvent, and temperature), the best result provided a 62% yield (Table S2, see the Supporting Information). Under the optimized reaction conditions, we screened the scope of potassium aryltrifluoroborate coupling partners (Scheme 5). We were pleased to find that a variety of potassium aryltrifluoroborates afforded the corresponding products, **12b–f**, in satisfactory yields.[14]

To further highlight the usefulness of our strategy, the synthesis of 8-aryl β-carboline from 8-aryl-substituted hexahydro-



Scheme 5. Reactions were carried out by using **10j** (0.15 mmol), **11** (3.0 equiv), $Pd(OAc)_2$ (10 mol%), BQ (1.0 equiv), AgOAc (2.0 equiv), DMSO (4.0 equiv), and *t*BuOH (1.2 mL) at 130 °C for 24 h, under N_2. Yields of isolated product are based on **10j**. The NOESY analysis showed that the relative configuration of **10j** remained intact for products **12a–f**.

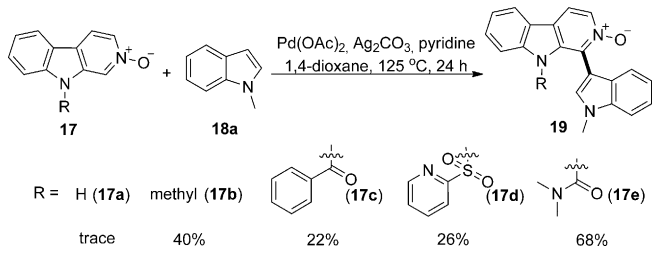
β-carboline was performed. Firstly, **12a** was subjected to debenzylation, to form **13a**, with Pd/C and ammonium formate. Next, aromatization with Pd/C in xylene gave **14a**. The hydrolysis of **14a** with LiOH in MeOH and H_2O, and the subsequent decarboxylation, produced **15a** in moderate yield.[15] Finally, the pyrimidyl group was removed by using NaOEt in DMSO at 120 °C, affording desired product **16a** (Scheme 6). We anticipate that this efficient approach to 8-aryl β-carbolines could provide a starting point for the investigation of the biological activity of these compounds.



Scheme 6. Synthesis of 8-aryl β-carboline **16a**.

C1-selective oxidative C–H/C–H cross-coupling of β-carboline-*N*-oxide

After completing the C3- and C8-selective functionalizations, we turned our attention to the C1-selective functionalization of β-carboline. Recently, transition-metal-catalyzed oxidative C–H/C–H cross-coupling between a heteroarene and an olefin, a simple arene, or a heteroarene has proven to be one of the most promising routes towards the synthesis of heteroaryl–alkenyl, heteroaryl–aryl and heteroaryl–heteroaryl structural units, effectively avoiding time-consuming prefunctionalization of both coupling partners.[16] Given that the C1–H bond is located *ortho* to the nitrogen atom of the pyridine ring,[17] the catalytic oxidative C–H/C–H cross-coupling of β-carboline-*N*-oxides with various (hetero)arenes or alkenes could be an ideal strategy to form C1-(hetero)aryl and C1-alkenyl β-carbolines. The key challenge in achieving C1 functionalization is control of the regioselectivity between the C1 and C3 positions. By using three equivalents of Ag_2CO_3 as an oxidant and one equivalent of pyridine as an additive, in the presence of $Pd(OAc)_2$ (10 mol%), in 1,4-dioxane at 125 °C, for 24 h, the oxidative C–H/C–H cross-coupling of *N*9-methyl-β-carboline-*N*-oxide, **17b**, with *N*-methylindole, **18a**, provided the C1-heteroarylated product in 40% yield. However, the homocoupled product of **18a** was also produced. Subsequently, we found that the chelation-assisted strategy could not only enhance the C1 reactivity of β-carboline-*N*-oxide, but could also prevent homocoupling. After screening different directing groups, it was found that the *N*,*N*-dimethylcarbamoyl group gave the highest yield

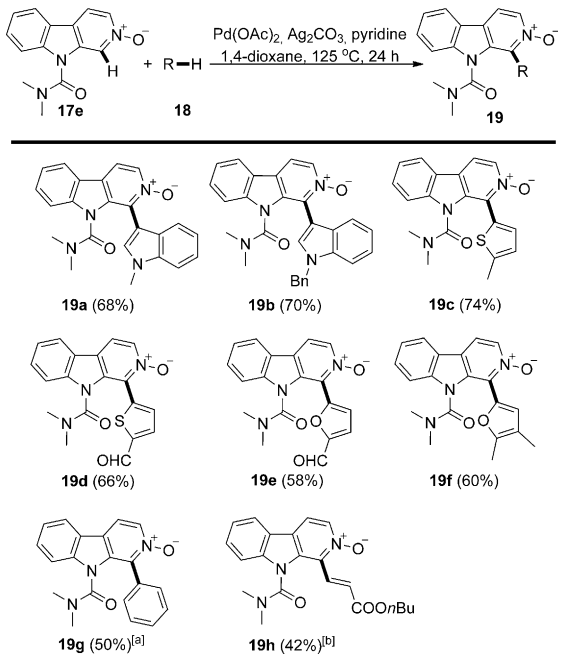


Scheme 7. Screening of the directing groups. Reactions were carried out by using *N*-substituted β-carboline-*N*-oxide **17** (0.25 mmol), *N*-methylindole **18a** (3.0 equiv), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (3.0 equiv), pyridine (1.0 equiv), and 1,4-dioxane (1 mL) at 125 °C for 24 h, under N_2. Yields of isolated product are based on **17**.

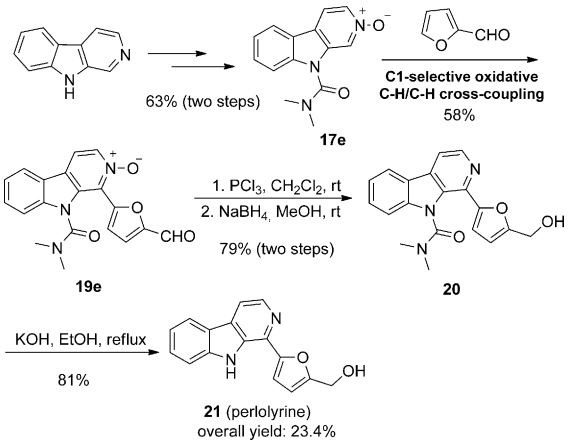
(Scheme 7). The cross-coupling of β-carboline-*N*-oxide **17e** with **18a** afforded 1-substituted β-carboline-*N*-oxide **19a** in 68% (Table S3, see the Supporting Information).

We next examined the scope of the reaction with respect to the heteroarene coupling partners. It was gratifying to find that this catalyst system could accelerate the C1–H bond functionalization of *N*,*N*-dimethylcarbamoyl-β-carboline-*N*-oxide **17e** with various electron-rich heteroarenes (for example, indoles, furans, and thiophenes; Scheme 8, **19a**–**f**). In addition, simple arenes and alkenes could also couple with **17e** to afford the C1-aryl- and C1-alkenyl-substituted β-carboline-*N*-oxides, respectively (Scheme 8, **19g** and **19h**). It is noteworthy that 3-substituted and 1,3-disubstituted β-carboline-*N*-oxides were not detected in these cross-coupling reactions.

Perlolyrine is a β-carboline alkaloid that displays strong yellow fluorescence as well as remarkable biological activities.[3d] In 2011, Detert and co-workers developed a synthetic route towards perlolyrine, starting from commercially available 2-iodoaniline, in an overall yield of 15–20% in 11 steps.[18] Herein, we demonstrate a new pathway for the synthesis of perlolyrine, involving a Pd-catalyzed oxidative C–H/C–H cross-coupling reaction (Scheme 9). Firstly, β-carboline was installed



Scheme 8. Reactions were carried out by using **17e** (0.25 mmol), **18** (3.0 equiv), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (3.0 equiv), pyridine (1.0 equiv), and 1,4-dioxane (1 mL) at 125 °C for 24 h, under N_2. Yields of isolated product are based on **17e**. [a] Benzene (1 mL) was used instead of 1,4-dioxane. [b] PivOH (3.0 equiv) was added instead of pyridine.



Scheme 9. Synthesis of perlolyrine.

with the *N*,*N*-dimethylcarbamoyl group, followed by oxidation to afford corresponding N-oxide **17e** in 63% yield over two steps. Subsequently, the C1-selective oxidative C–H/C–H cross-coupling reaction was used as the key step to furnish the furan moiety. The sequential reductions, by PCl_3 and $NaBH_4$, and the deprotection of *N*,*N*-dimethylcarbamoyl by using KOH afforded the target molecule in 23.4% overall yield in six steps.

Conclusion

In summary, we have demonstrated the diversification of the β-carboline core and the assembly of a β-carboline library. These strategies involve three categorically different types of transition metal-catalyzed C–C bond-forming reactions, in the presence of multiple reactive positions, affording an efficient route towards heteroaryl-, aryl-, alkenyl-, and alkynyl-substituted β-carbolines at the C1, C3, or C8 position. The saturated structural feature of the hexahydro-β-carboline framework can unlock reactivity and control site selectivity. The feasibility of this method has been demonstrated by the total synthesis of perlolyrine and the rapid preparation of hyrtioerectine analogues. We believe that our strategy could become a promising method for the late-stage diversifications of drug molecules.

Experimental Section

General procedure for the C_{sp^3}-decarboxylative coupling of hexahydro-β-carboline-3-carboxylic acid with heteroarenes and alkynes

A flame-dried Schlenk tube with a magnetic stirrer bar was charged with **4** (59.8 mg, 0.15 mmol), heteroarene or alkyne **5** (0.23 mmol, 1.5 equivalents), CuBr (3.3 mg, 22.5 μmol, 15 mol%),

TMEDA (6.7 μL, 45.0 μmol, 30 mol%), DTBP (42.5 μL, 0.23 mmol, 1.5 equivalents), and toluene (1.0 mL). The reaction mixture was stirred at room temperature for 10 min and then heated at 110 °C for 10 h, under a N_2 atmosphere. After being cooled to ambient temperature, the resulting solution was diluted with CH_2Cl_2 (20 mL), filtered through a Celite pad, and washed with CH_2Cl_2 (10–20 mL). The combined organic phases were concentrated and the residue was purified by column chromatography on silica gel to provide the desired product.

General procedure for the direct arylation of 9-(pyrimidin-2-yl) hexahydro-β-carboline with potassium aryltrifluoroborates

A pressure tube with a magnetic stirrer bar was charged with **10j** (60.1 mg, 0.15 mmol), potassium aryltrifluoroborate **11** (0.45 mmol, 3.0 equivalents), $Pd(OAc)_2$ (3.4 mg, 15 μmol, 10 mol%), 1,4-benzoquinone (16.2 mg, 0.15 mmol, 1.0 equivalent), AgOAc (50.1 mg, 0.30 mmol, 2.0 equivalents), DMSO (42.6 μL, 0.60 mmol, 4.0 equivalents), and *t*BuOH (1.2 mL). The reaction mixture was successively stirred at room temperature for 10 min and at 130 °C for 24 h, under a N_2 atmosphere. After being cooled to ambient temperature, the reaction was diluted with CH_2Cl_2 (20 mL), filtered through a Celite pad, and washed with CH_2Cl_2 (10 mL). The filtrate was washed with an aqueous solution of Na_2CO_3 (1 M, 5 mL) and the resulting aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were washed with water (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to provide the desired product.

General procedure for the oxidative C–H/C–H cross-coupling of β-carboline-*N*-oxide with heteroarenes, arenes, and alkenes

A flame-dried pressure tube with a magnetic stirrer bar was charged with **17e** (63.8 mg, 0.25 mmol), heteroarene, arene, or alkene **18** (0.75 mmol, 3.0 equivalents), $Pd(OAc)_2$ (5.6 mg, 25.0 μmol, 10 mol%), pyridine (20.1 μL, 0.25 mmol, 1.0 equivalent), Ag_2CO_3 (206.8 mg, 0.75 mmol, 3.0 equivalents), and 1,4-dioxane (1.0 mL) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 10 min, and then warmed to and stirred at 125 °C for 24 h. After being cooled to ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (20 mL), filtered through a Celite pad, and washed with CH_2Cl_2 (10–20 mL). The combined organic phases were concentrated and the residue was purified by column chromatography on silica gel to provide the desired product.

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Keywords: arylation · C–H bond functionalization · decarboxylative coupling · oxidative cross-coupling · β-carboline

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