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Volume 52 | Number 1 | 4 January 2016 | Pages 1–216

ChemComm

Chemical Communications
www.rsc.org/chemcomm

ISSN 1359-7345

COMMUNICATION
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Versatile Synthesis of Functionalized β and γ-Carbolines via Pd-Catalyzed C-H Addition to Nitriles/Cyclization Sequences

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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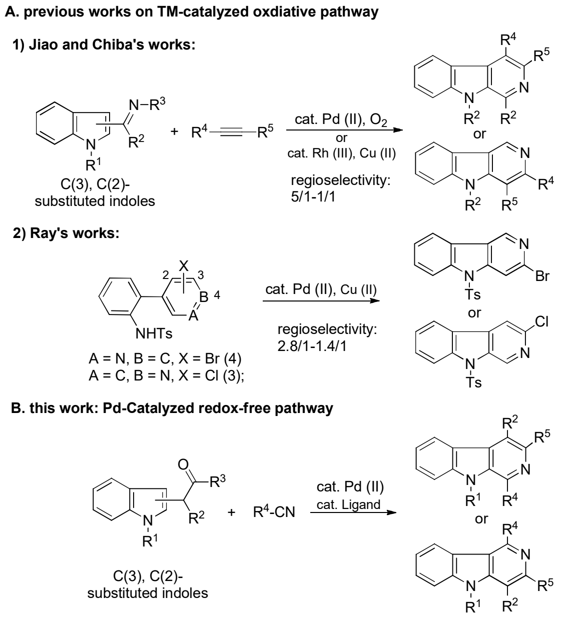
The first example of versatile synthesis of functionalized *β*-carbolines and *γ*-carbolines via a redox-free Pd-catalyzed C–H addition of indole to nitrile/cyclization sequence is reported. A wide range of functionalized *β*-carbolines and γ-carbolines can be prepared from readily accessible indoles and nitriles in good to excellent yields under the optimal conditions.

Carbolines (pyrido[*x*,*y*-*b*]indoles) constitute one of the most important and abundant nitrogen-containing heterocyclic ring systems. In particular, the privileged pyrido[3,4-b]indole (*β*-carboline) and pyrido[4,3-b]indole (*γ*-carboline) scaffolds are significant structural motifs and prevalent in a variety of bioactive natural products and medicinally relevant compounds. [1] They also have found many important applications in synthetic chemistry[1b, 2] and materials science. [3] Consequently, many protocols have been developed for the synthesis of these azaheterocyclic systems. [1b, 4] Among them, the approaches based on the Pictet–Spengler (PS) and Bischler–Napieralski (B-N) reactions for *β*-carbolines, and the Graebe–Ullman method for *γ*-carbolines are the most widely used. [1b, 5] Recently, transition-metal catalyzed cyclization has emerged as an alternative approach to access those scaffolds. [4, 6] Notably, the annulation *via* transition-metal catalyzed C–H bond functionalization has proven to be an attractive and powerful synthetic strategy to prepare heterocycles due to its efficient and sustainable features, [7] but received limited successes in the construction of both *β*-carboline and *γ*-carboline scaffolds. Jiao and co-workers reported a Pd-catalyzed direct dehydrogenative annulation reaction of internal alkynes and performed imines for the preparation of *β*-carbolines and *γ*-carbolines, and Chiba *et al* demonstrated the similar transformation to construct *β*-carbolines *via* Ru-catalysis (Scheme 1, A-1). [8a-c] Subsequently, Ray *et al.* reported a Pd-mediated oxidative annulation reaction *via* intramolecular C–H/N–H activation (Scheme 1, A-2). [8d] However, these methods need oxidants, and suffered from the low regioselectivities and the limited accessibility of a variety of substitution patterns with regard to the fused-pyridine core ring. Therefore, a general and straightforward synthesis of *β*-carbolines and *γ*-carbolines from available starting material with high efficiency is still highly desirable.



Scheme 1 Synthetic strategy

Nitriles are common platform chemicals in the commodity chemical industry, and the low cost coupled with versatile transformations of these molecules underlies their use in industrial and academic communities. Although several transition-metal catalyzed [2+2+2] cyclization reaction between diynes and nitriles have been demonstrated to prepare carbolines,[9] the construction of cyclic frameworks incorporating nitriles as key components *via* transition-metal catalyzed C–H bond functionalization is still underdeveloped, presumably due to the inherently inert nature of nitriles,

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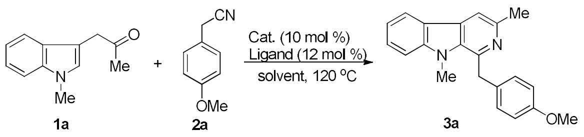
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8CC00040A

despite its holding the potential in constructing azaheterocycle compounds serving as C-N building block.

Recently, remarkable advances in transition-metal-catalyzed C-H bond additions to nitriles have been accomplished, but they normally provide acyclic aryl ketone products, in which nitriles serve as only C building block.[10] In principle, resultant ketimine intermediates of this process may be utilized in the assembling azaheterocyclic skeletons as C-N building blocks in an atom economic way upon coupling with appropriate functional groups, instead of the hydrolysis to afford ketones. We recently disclosed the Pd-catalyzed intramolecular C–H addition of indoles bearing cyanohydrin components to nitriles for the synthesis of carbazoles and tetrahydropyrido[1,2-a]indole derivatives.[11] With the goal of the development of a practical and efficient synthetic approach for the construction of various N-heterocycles from readily available starting materials *via* direct C-H bond functionalization, herein, we report a diverse synthesis of functionalized *β*-carbolines and *γ*-carbolines *via* a redox-free Pd-catalyzed C–H addition of indole to nitrile/cyclization sequence (Scheme 1, B).

Table 1 Optimization of the reaction conditions [a]



1a **2a** **3a**

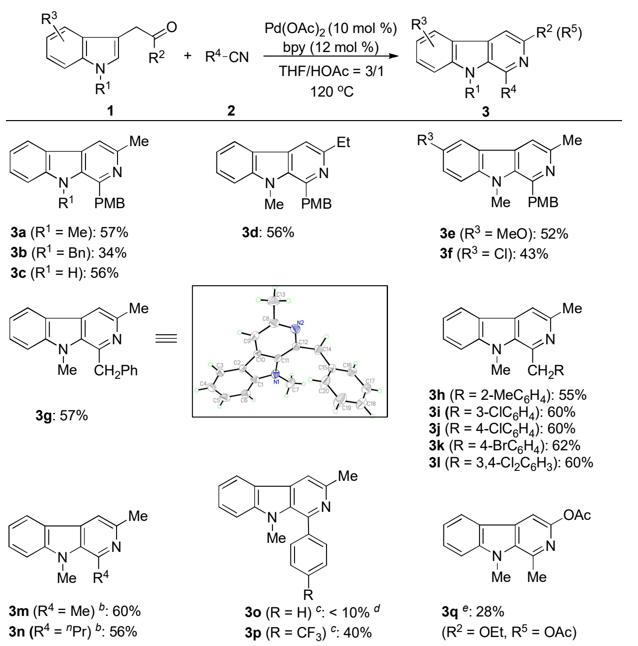
Entry	Cat.	Ligand	Solvent	*t* (h)	Yield (%)[b]	Conv. (%)[c]
1	$Pd(OAc)_2$	bpy	NMA/HOAc=3/1	28	nr	-
2	$Pd(OAc)_2$	bpy	NMA	28	nr	-
3	$Pd(OAc)_2$	bpy	HOAc	28	26	28
4	$Pd(OAc)_2$	phen	HOAc	28	28	80
5	$Pd(OAc)_2$	L-1	HOAc	28	29	40
6	$Pd(OAc)_2$	L-2	HOAc	28	24	28
7	$Pd(OAc)_2$	L-3	HOAc	28	< 1	-
8	$Pd(OAc)_2$	-	HOAc	28	< 1	90
9	$Pd(acac)_2$	bpy	HOAc	28	30	50
10	$Pd(TFA)_2$	bpy	HOAc	28	26	63
11	$Pd(OAc)_2$	bpy	THF/HOAc=3/1	28	39	42
12	$Pd(OAc)_2$	bpy	DMF/HOAc=3/1	28	12	13
13	$Pd(OAc)_2$	bpy	dioxane/HOAc=3/1	28	16	28
14	$Pd(OAc)_2$	bpy	DCE/HOAc=3/1	28	30	84
15[d]	$Pd(OAc)_2$	bpy	THF/HOAc=3/1	10	< 1	>95
16	$Pd(OAc)_2$	bpy	THF/HOAc=3/1	48	57	68

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (10 mol %) and ligand (12 mol %) in solvent (c = 0.4 *M*). [b] Isolated yields. [c] Based on recovered starting material **1a**. [d] $AgSbF_6$ (30 mol %) was added. bpy: 2,2'-bipyridine; phen: 1,10-phenanthroline; L-1: 4,4'-Dimethyl-2,2'-bipyridyl; L-2: 5,5'-Dimethyl-2,2'-bipyridyl; L-3: 6,6'-Dimethyl-2,2'-bipyridyl; NMA: N-methylacetamide

Our study began with the evaluation of Pd-catalyzed (2)C–H addition of indole to nitrile/cyclization sequence to prepare *β*-carbolines. Although Pd(II)-catalyzed intermolecular indoyl (3)C-H addition to nitrile, which furnished ketone derivatives, has been reported, [10d, e] the employment of 3-substituted indoles in such intermolecular C–H addition transformation has not been developed. The results are illustrated in Table 1. The initial investigation was examined by the reaction of 1-(1-methyl-1H-indol-3-yl)propan-2-one **1a** with 4-methoxyphenylacetonitrile **2a** in NMA/HOAc (3/1) in the presence of $Pd(OAc)_2$ (10 mol %), and 2,2'-bipyridine (bpy) (12 mol %) at 120 °C, which were previously identified as the optimal reaction conditions for the intramolecular indoyl (2)C-H addition to nitriles.[11] However, no reaction occurred, and the similar result was obtained when NMA was employed as a sole solvent (Table 1, entries 1-2). To our delight, the expected C–H addition/cyclization sequence occurred by using HOAc as a solvent, which afforded the desired *β*-carboline **3a**, but with low yield and conversion (Table 1, entry 3). The influence of ligand on the reaction outcome was subsequently probed (Table 1, entries 4-8). The similar result was obtained when 5,5'-dimethyl-2,2'-bipyridyl (L-2) was employed, while 1,10-phenanthroline (phen) and 4,4'-dimethyl-2,2'-bipyridyl (L-1) gave the marginal increasing yields of **3a**, but with the higher conversions of **1a**. No reaction happened in the presence of 6,6'-dimethyl-2,2'-bipyridyl (L-3) or the absence of ligand. The former is presumably ascribed to the steric hindrance effect of L-3. Other Pd(II) catalysts such as $Pd(TFA)_2$ and $Pd(acac)_2$ were surveyed, and both provided inferior results, with regard to the yield of **3a** and conversion of **1a** (Table 1, entries 9-10). Further investigation on solvents revealed that both THF/HOAc (3/1) and DCE/HOAc (3/1) gave improved yields of the desired product, while THF/HOAc (3/1) as a solvent system was more promising (Table 1, entries 11-14). Screening of other solvents did not improve the chemical outcome of this transformation.[12] In addition, the addition of $AgSbF_6$ (30 mol %) which may conduce to the generation of cationic Pd(II) intermediate, and thereby activate nitrile, failed to give the desired product (Table 1, entry 15). Notably, the increasing yield was obtained when the reaction was performed in 120 °C for 48 hours (Table 1, entry 16). Further survey on other reaction parameters such as additives, reaction temperature, concentration, and the ratio of **1a** and **2a** did not improve the chemical outcome of this transformation (for details see the SI).

Under the optimized reaction conditions, we next explored the generality of the Pd-catalyzed C-H addition/cyclization sequence for the preparation of *β*-carboline derivatives (Table 2). Other than N-methyl 3-substituted indole **1a**, N-benzyl substituted analogue **1b** can give the desired product **3b** in relatively low yield. Notably, free (NH) indole could also be employed in the cyclization reaction to deliver the desired product **3c** with the similar yield to that of substrate **1a**, which can easily be transformed into other *β*-carboline derivatives with different N-substituents. The reaction between indole bearing ethyl ketone unit with 4-methoxyphenylacetonitrile proceeded smoothly, and gave substituted *β*-carboline **3d** in 56% yield. In addition, both electron-donating and electron-withdrawing substituents at the benzene ring of indole core were tolerated, affording the desired products **3e** and **3f** in 52% and 43% yields respectively. Next, we investigated the reactions of N-methyl 3-substituted indole **1a** with various nitriles. Significantly, a broad range of aromatic substituents of phenylacetonitriles were tolerated, with both electron-

Table 2 Substrates scope for preparation of β-carbolines [a]

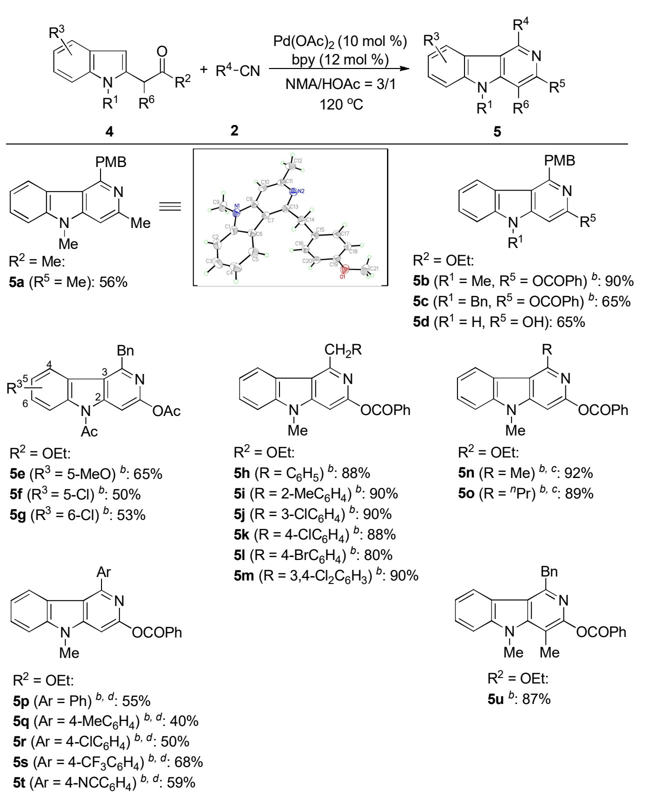


[a] Reaction conditions: **1** (0.4 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), bpy (12 mol %) and solvent (THF/HOAc = 3/1, c = 0.4 *M*) in 120 °C for 48 h. Yields shown are of isolated products. [b] **2** (1 mL). [c] **2** (3 equiv.). [d] Impure. [e] Acetylation of corresponding pyrido[3,4-b]indol-3-ol led to esterified product **3q** with good solubility. PMB = *p*-Methoxybenzyl

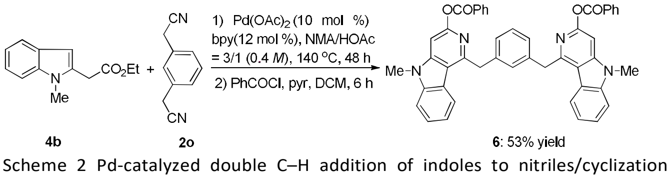
donating and electron-withdrawing substituents affording the desired products (**3g**-**3l**) in 55-62% yields, regardless of the substitution patterns. Aliphatic nitriles such as acetonitrile and butyronitrile can also serve as good reaction partners, and react with **1a** to give the corresponding alkyl substituted β-carbolines in 56-60% yields. When aryl nitriles were employed, the reactions proceeded rather sluggishly. The reaction with 4-(trifluoromethyl)benzonitrile delivered the desired product **3p** in 40% yield. Furthermore, Pd-catalyzed cyclization of N-methyl indole-3-acetic acid ethyl ester with acetonitrile was examined, and the expected cyclization sequence furnished the desired pyrido[3,4-b]indol-3-ol, which underwent further acetylation to give esterified product **3q**, [13] albeit with relatively low yield.

We next turned our attention to the synthesis of γ-carbolines by employing 2-substituted indole substrates with nitriles. Under the modified reaction conditions (NMA/HOAc (3/1) as a solvent system), 1-(1-methyl-1H-indol-2-yl)propan-2-one reacted with 4-methoxyphenylacetonitrile **2a** producing the desired product **5a** in 56% yield. Notably, unlike 3-substituted indole **1** with ester unit, the reaction between ethyl 2-(1-methyl-1H-indol-2-yl)acetate and **2a** proceeded smoothly, providing the desired hydroxy substituted γ-carboline followed by the acylation to give **5b** in high yield. [13] Both *N*-benzyl and N-unsubstituted analogues can provide the desired pyrido[4,3-b]indol-3-ol derivatives (**5c** and **5d**), but with relatively low yields. Electron-donating group (OMe) and electron-withdrawing group (Cl) at the 5-or 6-positions of the aromatic rings of N-unsubstituted indoles **4** were well tolerated, delivering the cyclization products (**5e**-**5g**) in 50-65% yields. In addition, a variety of phenylacetonitriles with different aromatic substituents and aliphatic nitriles were also evaluated, leading to the corresponding hydroxy substituted γ-carboline derivatives (**5h**-**5o**) in good to high yields. In contrast to the preparation β-carbolines from aryl nitriles, the reactions between 2-substituted indole with aryl nitriles **2** worked well, with both electron-donating and electron-withdrawing substituents affording the desired products (**5p**-**5t**) in 40-68% yields. Notably, ethyl 2-(1-methyl-1H-indol-2-yl)propanoate can also serve as a suitable substrate to provide the desired multi-substituted γ-carboline **5u** in high yield.[14] In addition, the structures of functionalized β- and γ-carbolines were unambiguously confirmed by the exemplification of X-ray crystal structural analyses of products **3g** and **5a**. [15]

Table 3 Substrates scope for preparation of γ-carbolines [a]



[a] Reaction conditions: **4** (0.4 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), bpy (12 mol %) and solvent (NMA/HOAc = 3/1, c = 0.4 *M*) in 120 °C for 9-48 h. Yields shown are of isolated products. [b] Acylation of corresponding pyrido[4,3-b]indol-3-ols (R^2 = OEt) led to esterified products **5** with good solubility. [c] **2** (1 mL). [d] **2** (3 equiv.).



Scheme 2 Pd-catalyzed double C–H addition of indoles to nitriles/cyclization sequence

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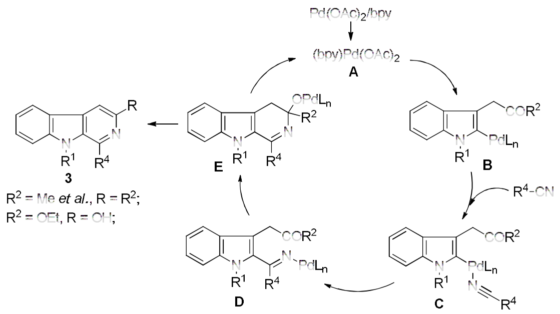
Furthermore, treatment of ethyl 2-(1-methyl-1H-indol-2-yl)acetate **4b** with 2,2'-(1,3-phenylene)diacetonitrile **2o** can afford bis-*γ*-carboline derivative **6** in good yield *via* a Pd-catalyzed double C–H addition of indole to nitrile/cyclization sequence under the modified reaction conditions.



Scheme 3 Proposed mechanism

Proposed mechanism was illustrated in Scheme 3 for the Pd-catalyzed cyclization with the exemplification of C-3 substituted indole substrate **1** with nitrile. In analogy to other processes involving Pd-catalyzed C-H bond functionalization,[10d-e, 11] this catalytic process may involve a direct palladation at the C-2 position of indole core with [(bpy)Pd(OAc)$_2$] **A**, which gives a palladium complex **B**. The coordination of the nitrile provides intermediate **C**, which undergoes an addition of the indolyl group to the nitrile to form the corresponding ketimine Pd(II) complex **D**. The reaction between intermediate **D** and neighboring carbonyl group would led to species **E**, which undergoes the protonolysis and aromatization to give product **3** and regenerates the Pd(II) species **A**.

In summary, we have developed a new protocol for the diverse synthesis of functionalized *β*-carbolines and *γ*-carbolines *via* a redox-free Pd-catalyzed C–H addition of indole to nitrile/cyclization sequence. Under the optimal conditions, a diversity of functionalized *β*-carbolines and *γ*-carbolines can be prepared from readily available starting materials in good to high yields. The catalytic system tolerates a broad substrate scope. Further studies on the synthetic application of this strategy to the catalytic construction of other azaheterocyclic frameworks is in progress in our laboratory.

We are thankful for the financial support from the National Natural Science Foundation of China (No. 21772063).

Conflicts of interest

There are no conflicts to declare.

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12 For details, see the Supporting Information.

13 Acylation of corresponding products (R^2 = OEt) is necessary to obtain derived products **3** or **5** with good solubility for the purification and NMR analysis.

14 The corresponding 2-substituted analogue **1** did not give the desired multi-substituted *β*-carboline under the optimized reaction conditions.

15 CCDC 1813722 (compound **3g**) and CCDC 1813723 (compound **5a**), see the Supporting Information for details.