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Graphical abstract

Synthesis of *α*, *β* and *γ*-Carbolines *via* Pd-mediated C_{sp}^2-H/N-H activation

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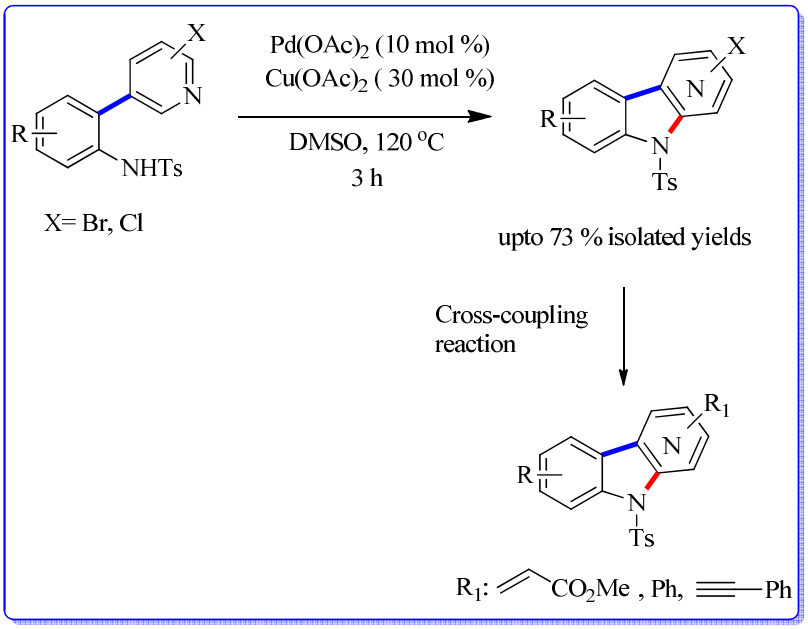

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ARTICLE TYPE

Synthesis of α, β and γ-Carbolines *via* Pd-mediated C_{sp}^2-H/N-H activation

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An efficient method for the synthesis of halo-carbolines has been developed *via* Pd-catalysed formation of C-N bond through C_{sp2}-H/N-H activation of 4-methyl-N-[2-(pyridine-3-yl)phenyl] benzenesulfonamide derivatives. $Pd(OAc)_2$ in presence of $Cu(OAc)_2$ as oxidant afforded halo-carbolines in good to excellent yields with tolerance to a variety of substituents.

The formation of carbon-nitrogen bonds *via* the coupling of inactive C-H/N-H bonds is of great challenge in organic synthesis while constructing nitrogen heterocycles and, in amination reactions as it needs no functionalisation and, moreover, this process become very attractive as the only byproduct is the hydrogen molecule.[1]

The carbolines are the key pharmacophore present in many drugs and bioactive natural products.[2] Intense interest has been directed to α-carboline (pyrido[2,3-*b*]indole) and γ-carboline (pyrido[4,3-*b*]indole) derivatives owing to their potent antiplasmodial (1), antiviral, antitumor and anticancer activity (Fig. 1).[3,4] Some of the γ-isomers of carboline identified as potent small molecule antagonists (2) of histamine H_1 (IC_{50} = 0.1 μM) and serotonin 5-HT_6(IC_{50} = 0.37 μM) receptors, anticancer agents, analogous to ellipticine/olivacine. Promising pharmacological and biological activity of these indole alkaloids urges divergent method of synthesis. A number of methods are available in literature for the synthesis of carbolines mostly involved metal catalysed annulation of alkyne,[5] Pictet-Spengler annulation[6] and related reactions.[7] Driver *et al.* has reported a synthesis *via* Ru-catalysed C-H amination of suitable azides.[8] Kundu *et al.* synthesised *α*-carboline derivatives *via* a three-component tandem reaction using acid chlorides, terminal alkynes, and 2-aminoindole hydrochlorides.[9] U. W. Maes *et al.* has reported a Pd-catalysed auto tandem process of an intramolecular direct arylation and an intermolecular Buchwald-Hartwig reaction towards the synthesis of α-carbolines.[10] An intramolecular Heck reaction of iodoindoles has been adopted by Beccalli group for the synthesis of *β*- and *γ*-carbolines.[11] Still efficient method of preparation of carbolines is needed due to their synthetic challenge and structural diversity exemplified by their potent drug activity to combat the life threatening disease.

The preparation of halogenated compound and, incorporation of halogen atom in a molecule is very difficult. From the synthetic point of view, the presence of a halogen in a molecule endow upon a widespread applications in organic synthesis. It can serve as an essential substrate in many cross-coupling reactions, different functionalization reactions and, intermediates in complex synthesis of bioactive compounds of important medicinal values. Therefore, we have devised a strategy to synthesise halogenated carbolines under ambient reaction conditions with goods yields.

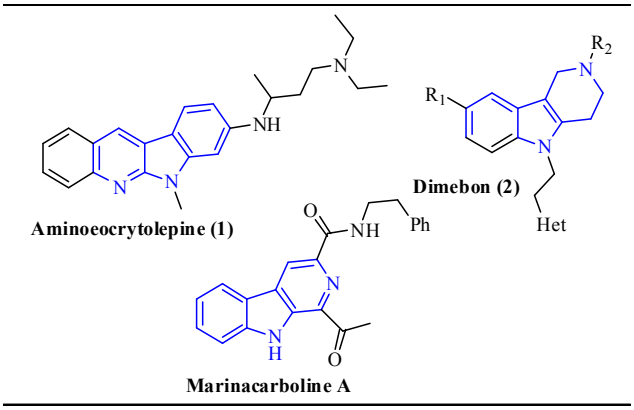
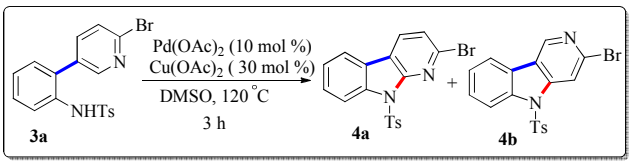


Fig 1: Some bioactive natural products

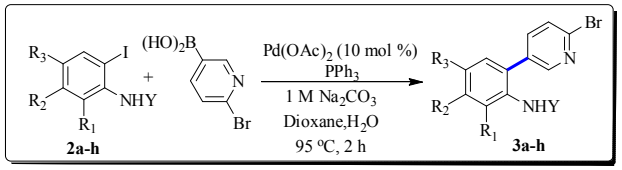
Development of alternative synthetic methods is of great importance to ensure diversified synthesis. Herein, we reported a convergent synthesis of both α- and γ-carboline in one step in moderate to good yields (Scheme 1).The cyclization precursor 4-methyl-N-[2-(pyridin-3-yl)phenyl]benzenesulfonamide (**3a**) upon action of $Pd(OAc)_2$ and anhydrous $Cu(OAc)_2$ afforded **4a** and **4b** (Scheme 1).

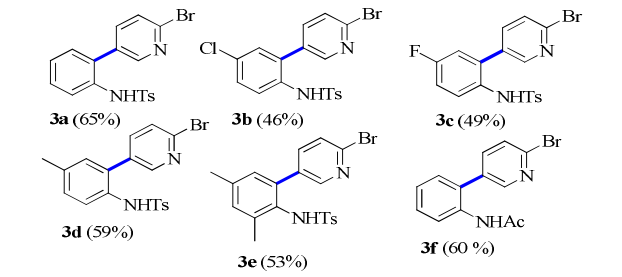


Scheme 1: Synthesis of α-and γ-carbolines

Cyclization precursors **3a-h** were prepared *via* Suzuki coupling upon N-tosylated 2-iodoanilines (**2a-h**) with (6-bromopyridin-3-yl)boronic acid in the presence of $Pd(OAc)_2$, 1M Na_2CO_3 and in dioxane: water (1:1) solvent at 95 °C temperature using the reported Suzuki coupling procedure described in Table 1.

Table 1: Synthesis of the cyclization precursor **3a-h**[a,b]

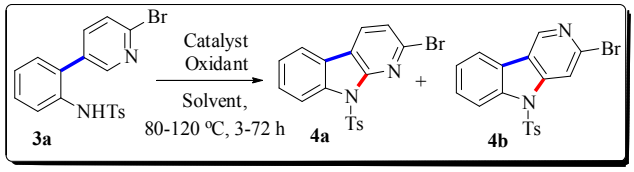




a) **Reaction conditions:** 1 mmol of the substrate **2a**, (6-bromopyridin-3-yl)boronic acid (1.2 mmol), PPh_3 (0.25 mmol), $Pd(OAc)_2$ (10 mol %), 1M Na_2CO_3 in 1:1 mixture of dioxane and H_2O, 95 °C, 2-3 h. b) Isolated yields.

Initially we started the investigation of cyclization process with **3a** (1 mmol) in the presence of Pd catalyst and an oxidant. $PdCl_2$ and $Pd(CH_3CN)_2Cl_2$ gave the product **4a** and **4b** in low yields (Table 2, entry 9,10). $Pd(OAc)_2$ worked better compared to the other Pd(II) catalyst and gave both α- and γ- carboline in good yields. Pd(0) catalyst in absence of any oxidant did not result the formation of the products. During the screening process different types of oxidants in combination with the Pd catalyst were used. Copper halides, such as CuI, CuBr gave poor yields of the products.[12] Even the $Cu(OAc)_2.H_2O$ did not afford final products even after leaving the reaction for 72 h. Among the the other oxidants, $PhI(OAc)_2$ left with the decomposed product. It was found that anhydrous $Cu(OAc)_2$ in combination with $Pd(OAc)_2$ was the best catalytic system for the cyclization reaction. Solvent DMSO gave the best results leaving behind the other analogous polar solvents. Firstly, we started the cyclisation reaction with **3a** (1 mmol) at temperature of 80 °C with 10 mol % of catalyst and 10 mol % of oxidant which afforded lower product yields. While using 10 mol% of $Cu(OAc)_2$ at the elevated temperature of 120 °C reaction gave lower yields of the products (Table 2, entry 4) even after 24 h. Increasing the oxidants loading to 20 mol % took longer time (72 h) for completion of the reaction (Table 2, entry 5) at 120 °C. Reaction gave most promising yields of products at 120 °C with catalyst and oxidant loading to 10 mol %, 30 mol % respectively in 3 h (Table 2, entry 6).[13]

Table 2: Screening of reaction conditions for the synthesis of α- and γ-carboline[a]



Entry	Catalyst	Oxidant	Solvent	Yields[b]	
				4a	**4b**
1	$Pd(OAc)_2$	CuI	DMSO	26	36
2	$Pd(OAc)_2$	CuBr	DMSO	32	46
3	$Pd(OAc)_2$	Oxone	DMSO	30	42
4[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	10	45
5[d]	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	25	70
6[e]	**$Pd(OAc)_2$**	**$Cu(OAc)_2$**	**DMSO**	**26**	**73**
7	$Pd(OAc)_2$	$PhI(OAc)_2$	DMSO	-	-
8	$Pd(OAc)_2$	$Cu(OTf)_2$	DMSO	24	36
9	$PdCl_2$	$Cu(OAc)_2$	DMSO	35	30
10	$Pd(CH_3CN)_2Cl_2$	$Cu(OAc)_2$	DMSO	20	33
11	$Pd_2(dba)_3$	-	DMSO	-	-
12	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	23	34
13	$Pd(OAc)_2$	$Cu(OAc)_2$	DMA	20	40

[a] Reaction conditions: 1 mmol of **3a**, $Pd(OAc)_2$ (10 mol %), oxidants (30 mol %), dry DMSO (3 mL), 80-120 °C, 3-72 h. [b] Isolated yields. [c] $Cu(OAc)_2$ (10 mol%), 120 °C, 24 h. [d] $Cu(OAc)_2$ (20 mol%), 120 °C, 72 h. [e] $Cu(OAc)_2$ (30 mol%), 120 °C, 3 h.

Finally, optimal reaction conditions were set to be the $Pd(OAc)_2$ (10 mol %), anhydrous $Cu(OAc)_2$ (30 mol %) at 120 °C in 3mL of DSMO solvent for 3 h (Table 2, entry 6).

Structure of the α- and γ-carboline were unnimously determined by single crystal X-ray analysis. The CCDC of the compounds **4a** (α-carboline) and **4b** (γ-carboline) are 953972 and 953973 respectively.‡ The structures were drwan using POV-Ray as shown in the Fig 2.

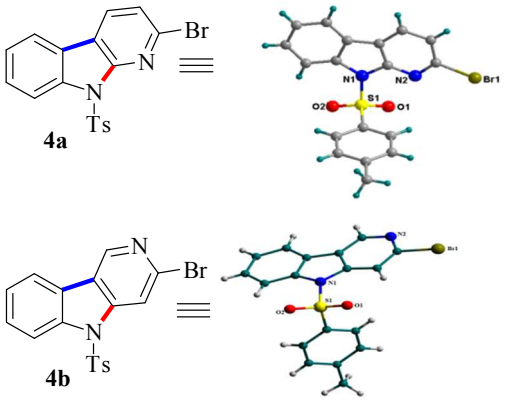
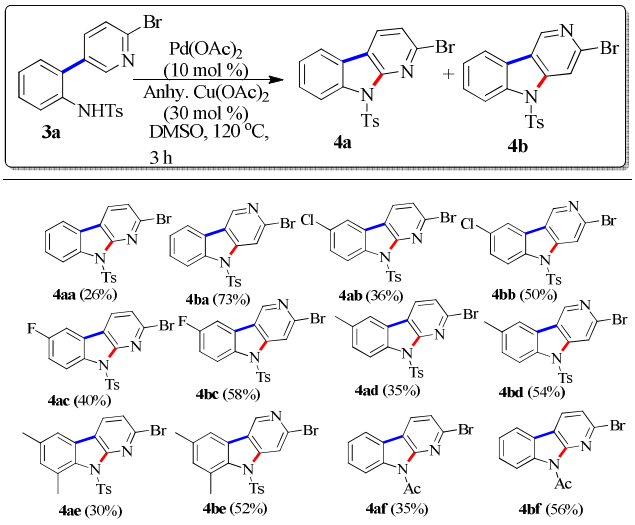


Fig 2: Single crystal structure of α- and γ- Carboline

Once we got the standard cyclization reaction conditions, investigation of general applicability of the reaction were performed. Scope of the coupling strategy was demonstrated by varying functionality of electron donating and electron

withdrawing goups in the cyclization precursors which are shown in Table 3.

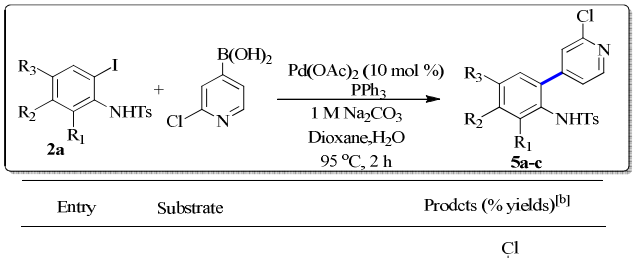
Table 3: Synthesis of α- and γ- carboline[a],[b]

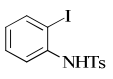
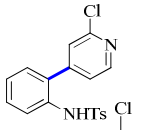
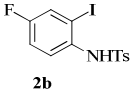
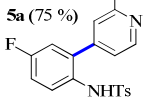
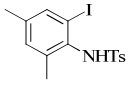
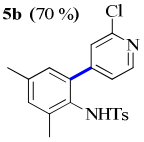


[a] Reaction conditions: 1 mmol of **3a**, $Pd(OAc)_2$ (10 mol %), anhydrous $Cu(OAc)_2$ (30 mol %), dry DMSO (3 mL), 120 °C, 3 h [b] Isolated yields.

Subsequently we have also synthesised β-carboline and few of their derivatives shown in Table 5. Precursors for the synthesis of β-carboline were obtained by using the same procedure as in the case of α,γ- carboline (Table 4).

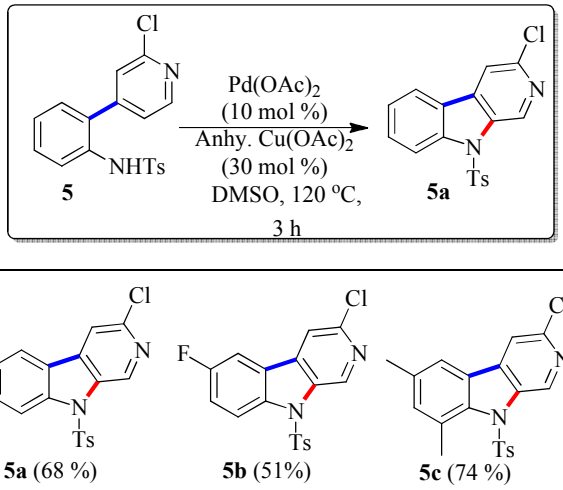
Table 4: Preparation of the precursors for synthesis of β-carboline[a]



Entry	Substrate	Prodcts (% yields)[b]
1	 **2a**	 **5a** (75 %)
2	 **2b**	 **5b** (70 %)
3	 **2e**	 **5c** (80 %)

a) **Reaction conditions:** 1 mmol of the substrate **2a**, (2-chloropyridin-4-yl)boronic acid (1.2 mmol), PPh_3 (0.25 mmol), $Pd(OAc)_2$ (10 mol %), 1M Na_2CO_3 in 1:1 mixture of dioxane and H_2O, 95 °C, 2-3 h. b) Isolated yields.

Table 5: Synthesis of β-carbolines[a],[b]



[a] **Reaction conditions:** 1 mmol of **5**, $Pd(OAc)_2$ (10 mol %), anhydrous $Cu(OAc)_2$ (30 mol %), dry DMSO (3 mL), 120 °C, 3 h. [b] Isolated yields.

The cyclization was believed to be proceed *via* association of $Pd(OAc)_2$ to N of sulphonamide to afford **I**. This pre-association of Pd facilitates the *ortho*-C-H activation of the pyridine moiety *via* acetate assisted cross metalation deprotonation (CMD) leading to formation of intermediate **II** which finally gave our desired carboline **III**. Pd(0) reoxidised to Pd (II) by $Cu(OAc)_2$ and enters into catalytic cycle (Fig 3).[14]

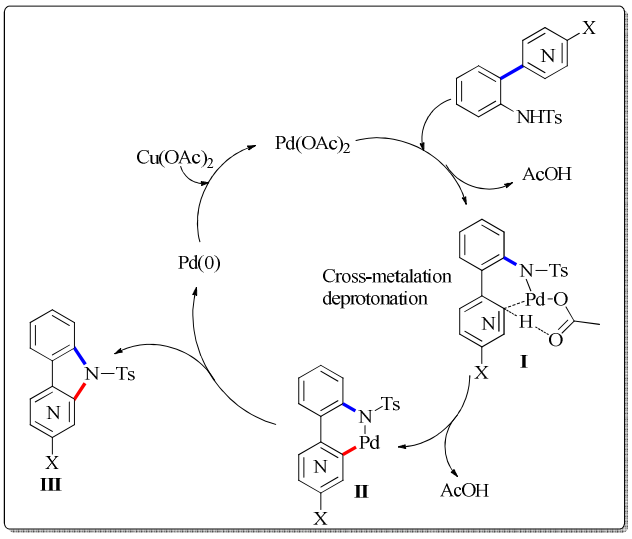
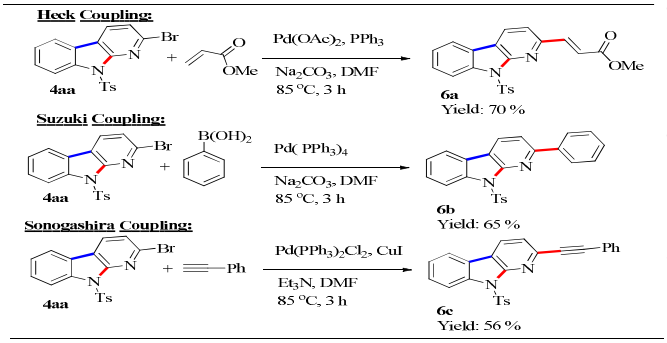


Fig 3: Plausable reaction pathway

One of the most important facts of this method is the presence of the C-halogen bond in the final carboline moiety. In the course of the reaction, interestingly it was found that the C-X bond in the cyclization precursors remained untouched even in the presence of Pd-catalysts. Pd-catalysed cyclisation afforded the different substituted halo-carbolines in good yields. Subsequently, we have functionalised this C-X bond through different cross-coupling reactions shown in Scheme 2. We anticipate that this pre-occurring C-X would be very advantageous in the course of formal total synthesis of complex molecular architectures.

Scheme 2: Different cross-coupling reactions of halo-carbolines[a]



a) Isolated yields.

Conclusions

In conclusion, we have developed an easy access to the halo-carbolines under milder reaction condition using $Pd(OAc)_2$ /$Cu(OAc)_2$ as catalytic system *via* C-H activation and subsequent functionalisation of C-X bond through different cross coupling reaction. This may find extensive application material and pharmaceutical industry and research.

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Notes and references

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‡Electronic Supplementary Information (ESI) available. CCDC for α and γ carbolines are 953972 & 953973 respectively. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x/

Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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