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Ruthenium Catalyzed β-C(sp^3)–H Functionalization on the 'Privileged' Piperazine Nucleus

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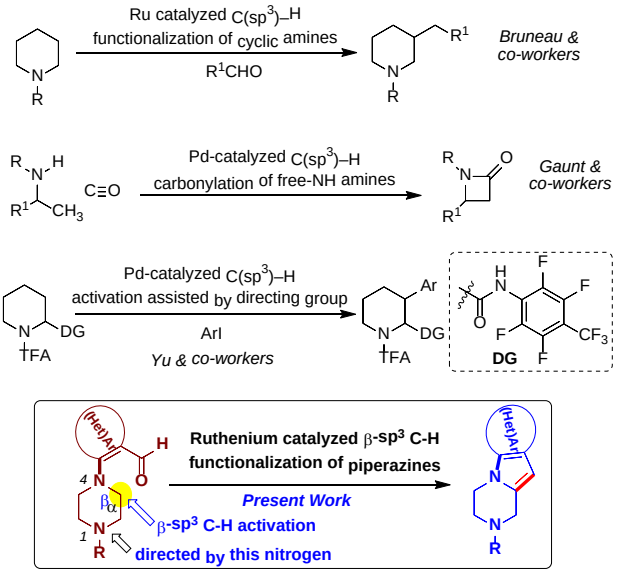
β-C(sp^3)–H functionalization on the 'privileged' piperazine nucleus has been disclosed using ruthenium catalysis. The ruthenium catalyzed synthesis of a variety of piperazine fused indoles from *ortho*-piperazinyl (hetero)aryl aldehydes is presented. This transformation takes place *via* dehydrogenation of piperazine followed by intramolecular nucleophilic addition of the transient enamine moiety onto the carbonyl group then aromatization cascade.

C(sp^3)–H activation-functionalization has emerged as an important area of research in modern organic synthesis.[1] C(sp^3)–H activation-functionalization of aliphatic (cyclic) amines provides a tool for the synthesis of various nitrogen containing derivatives including *N*-heterocycles. Generally, C(sp^3)–H functionalization on the α-carbon to nitrogen atom are well reported[1,2] while that on the β-carbon to nitrogen has received considerably less attention.[3] Bruneau group has reported ruthenium catalyzed β-C(sp^3)–H functionalization of saturated cyclic amines.[4] Gaunt and co-workers have reported the transformation of aliphatic amines to β-lactams enabled by palladium catalyzed β-C–H carbonylation.[5] Yu and co-workers have described directing group assisted, Pd/NHC catalyzed β-C(sp^3)–H arylation of saturated cyclic amines (Scheme 1).[6] However, C–H functionalization of piperazines has received significantly less attention despite the prominence of this 'privileged' moiety in several life-saving marketed drugs and continuing to be important in drug discovery programs.[7] This is probably due to the presence of two 1,4-nitrogen atoms in the ring system, interfering in selectivity and reactivity issues, making them challenging substrates for investigations in the area of C–H functionalization. In spite of these reasons there have been few reports on the α-C(sp^3)–H functionalization of piperazines—facilitated by strong bases,[8] transition metal-[9] and photoredox-catalysis.[10] However, β-C(sp^3)–H functionalization of piperazine remains a challenging problem.



Scheme 1 Recent selected examples on β-C(sp^3)–H functionalization of (cyclic) amines and present work.

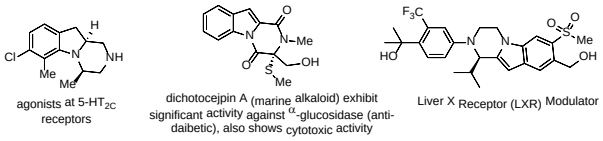


Fig 1 Biologically active *N*-fused piperazine-indole derivatives.

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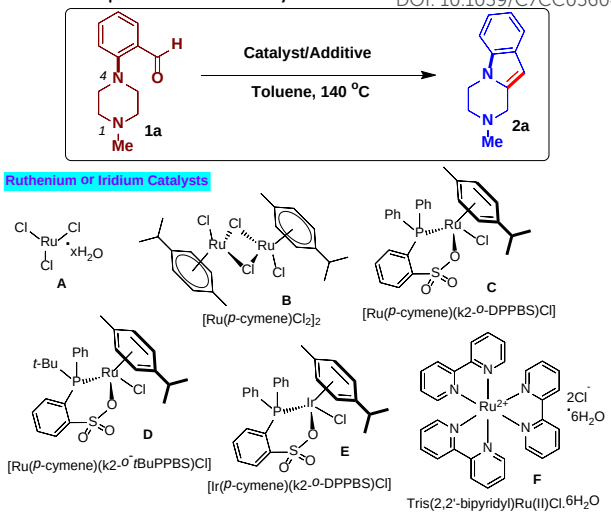
Herein we report β-C(sp^3)–H functionalization on the 'privileged' piperazine nucleus using ruthenium catalysis (Scheme 1). We envisaged that ruthenium-catalyzed dehydrogenation on *N*-alkyl piperazine would furnish iminium intermediates *en route* to enamine formation, which would add onto an electrophile to accomplish net β-C(sp^3)–H functionalization. Accordingly, we chose 2-(4-methylpiperazin-1-yl)benzaldehyde **1a** containing *N*-methyl group that assist in the enamine formation and an internal carbonyl group tethered to the N(4) of the piperazine to serve as an electrophile. This transformation would eventually furnish piperazine fused indole systems, which represent potential compounds in the area of medicinal chemistry due to their wide range of biological activities including 5-HT$_{2C}$ receptor agonists,[11] anti-diabetic, cytotoxic[12] and LXR modulator activity[13] (Figure 1).

The initial reaction of compound **1a** in the presence of $RuCl_3.xH_2O$ and camphorsulfonic acid (CSA) as an additive did not give any β-C(sp^3)–H functionalization product (Table 1, entry 1). Much to our delight, using [Ru(*p*-cymene)Cl$_2$]$_2$ **B** as a catalyst in the presence of CSA additive resulted in the corresponding piperazine fused indole **2a** in 38% yield (Table 1, entry 2). Encouraged by this result, we have screened different ruthenium/iridium catalysts and additives in this reaction (for a detailed optimization study, see supporting information). The well-defined ruthenium and iridium catalysts (**C**, **D** and **E**)[14] bearing a phosphine-benzenesulfonate ligand in the presence of CSA resulted in lower yields of the desired product (Table 1, entries 4-6). The ruthenium catalyst tris(2,2'-bipyridyl)Ru(II)Cl.6H$_2$O **F** also gave a low yield of **2a** (Table 1, entry 7). Increasing the loading of **B** to 5 mol% proved to give better results (Table 1, entry 8). Use of other acidic additives such as *p*-TSA and 3,5-DNB did not give better results (Table 1, entries 9 and 10). When molecular sieves 4 Å (0.5 g) were added to the reaction along with the additive CSA in the presence of **B**, the corresponding product was isolated in 66% yield (Table 1, entry 11). The absence of CSA as additive resulted in lower yield of **2a** (Table 1, entry 12), which confirms the presence of acid benefits the reaction. This transformation was not successful in the absence of ruthenium catalyst (Table 1, entry 13).

We selected the optimized conditions reported in entry 11 to study the scope of this transformation (Scheme 2). Initially, the nature of the substituents on the N(1) of piperazine has been checked and it was found that ethyl and *n*-propyl substituents resulted in moderate yields of the corresponding piperazine fused indoles **2b-c**. It is interesting to note that when *ortho*-piperazinylbenzaldehyde bearing a benzyl group at the N(1) position of the piperazine ring was subjected to the optimized conditions, most of the starting material remained unreacted and *N*-benzyl,*N*'-phenylpiperazine resulting from decarbonylation of the aldehyde was formed in low amount (see supporting information). This result reveals that the present catalytic system exhibits a different tolerance to the protecting group of the directing nitrogen atom since catalysts **C** and **D** were efficient for the intermolecular β-C(sp^3)-H alkylation by aldehydes starting from cyclic *N*-benzyl amines.[4a]

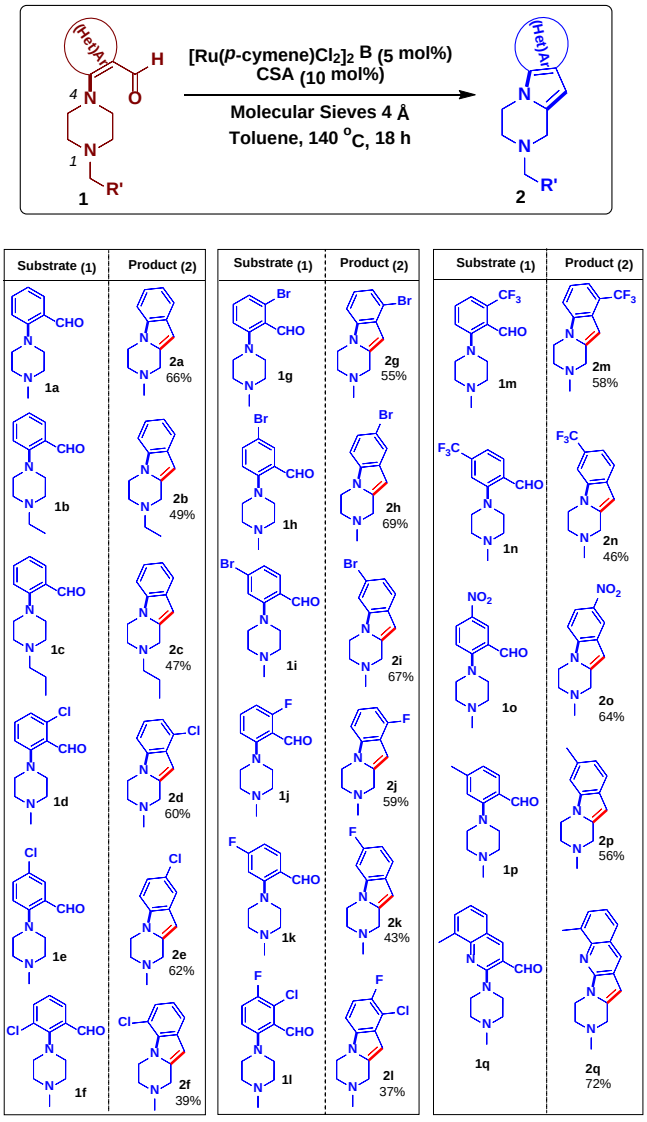
Table 1 Optimization study[a]



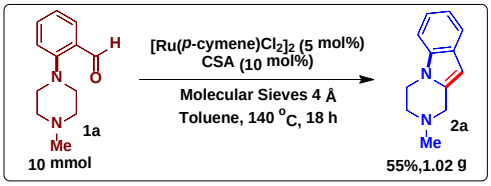
Entry	Catalyst (x mol%)	Additive (y mol%)	yield% of 2a[b]
1	**A** (2)	CSA (5)	—
2	**B** (2)	CSA (5)	38
3	**B** (2)	CSA (10)	38
4	**C** (2)	CSA (5)	19
5	**D** (2)	CSA (5)	17
6	**E** (2)	CSA (5)	21
7	**F** (2)	CSA (5)	10
8	**B** (5)	CSA (10)	56
9	**B** (5)	*p*-TSA (10)	13
10	**B** (5)	3,5-DNB (10)	–
11	***B (5)***	***CSA (10) + MS 4 Å***	***66***
12	**B** (5)	—	32
13	—	CSA (10)	–

[a]Reaction conditions: **1a** (0.6 mmol), catalyst (x mol%), additive (y mol%), toluene (2 mL); [b]Yields are for isolated products; Reactions were performed at 140 °C for 18 h; CSA = camphorsulfonic acid; *p*-TSA = *para*-toluenesulfonic acid; 3,5-DNB = 3,5-dinitrobenzoic acid; MS = molecular sieves.

Different *N*-methyl-*N'*-aryl-piperazine compounds **1d-q** have been prepared and subjected to the ruthenium catalyzed β-C–H functionalization reaction. *ortho*-Piperazinyl benzaldehydes **1d-l** bearing halogen substituents like chloro, bromo or fluoro groups at different positions have undergone the β-C(sp^3)–H functionalization to afford moderate yields of the corresponding piperazine fused indoles **2d-l** under the ruthenium catalysis conditions. Piperazine fused indoles **2m-o** bearing electron-withdrawing groups like trifluoromethyl or

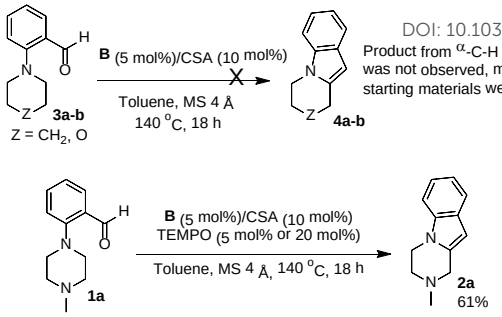


Scheme 2 Synthesis of piperazine fused indole derivatives.

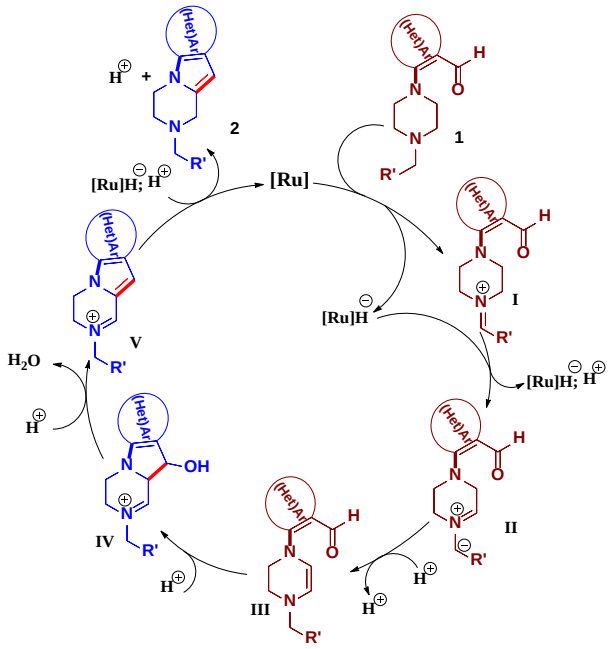


Scheme 3 Gram scale synthesis of 2-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole **2a**.

nitro groups on the benzene ring were obtained in moderate yields. *ortho*-Piperazinyl benzaldehyde **1p** bearing the electron-donating methyl group is a good substrate for this transformation, comparable to **1a**. Further, this transformation is not limited to only *ortho*-piperazinyl aromatic aldehydes as *N*-heteroaryl piperazine like 8-methyl-2-(4-methylpiperazin-1-yl)quinoline-3-carbaldehyde **1q** also served as a good substrate in this transformation to afford the corresponding piperazine fused aza-indole system **2q** in good yield. On the other hand, an acyl group in place of the carbaldehyde led to an inactive substrate.



Scheme 4 Control experiments.



Scheme 5 Plausible mechanism.

Note that the present transformation has enabled us to scale up the reaction to a gram scale for the synthesis 2-methyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole **2a** in good yield (Scheme 3).

We have performed control experiments to know whether the reaction goes through α- or β-C(sp^3)–H activation and to get insights of the mechanism. The reactions of *ortho*-*N*-piperidinyl or *ortho*-*N*-morpholinyl benzaldehyde derivatives **3a-b** under the present ruthenium catalysis conditions did not give the products **4a-b** arising from α-C(sp^3)–H functionalization while most of the substrates remained unreacted (Scheme 4, top). These experiments suggest that in the presence of ruthenium catalyst β-C(sp^3)–H activation-functionalization taking place on the piperazine nucleus where *N*-alkyl part of the piperazine is playing an essential role. The radical pathway *en route* to piperazine fused indoles may be ruled out since addition of TEMPO did not affect the reaction of the ruthenium catalyzed of *ortho*-*N*-piperazinyl benzaldehyde **1a** (Scheme 4, bottom).

Based on the control experiments and literature reports,[4] a plausible mechanism for the present ruthenium catalyzed β-C–H functionalization is depicted in the Scheme 5. Piperazine **1**

may be converted to the corresponding iminium intermediate **I** in the presence of ruthenium catalyst *via* hydrogen transfer. The intermediate **I** would then give azomethine ylide **II** along with ruthenium hydride species, after hydrogen abstraction. The presence of acid might promote the formation of enamine intermediate **III**, which would attack the carbonyl group to give intermediate **IV**. This would then undergo aromatization *via* dehydration to afford intermediate **V**, and the iminium part of it could be reduced by the ruthenium hydride species to furnish the piperazine fused indole **2**.

In conclusion, we have developed an unprecedented ruthenium catalyzed β-C(sp^3)−H functionalization on the 'privileged' piperazine nucleus. Ruthenium-catalyzed dehydrogenation and hydrogen auto-transfer process appears to be the key for this successful transformation. This protocol complements the few available catalytic methods for α-C(sp^3)−H functionalization of piperazines. Various piperazine fused indole derivatives have been synthesized using the presented method. The optimized method enabled the gram scale synthesis of a representative piperazine fused indole derivative. Explorations are underway on the intermolecular β-C(sp^3)−H functionalization using different coupling partners on piperazine and related systems using well-defined ruthenium catalysts.

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Graphical Abstract

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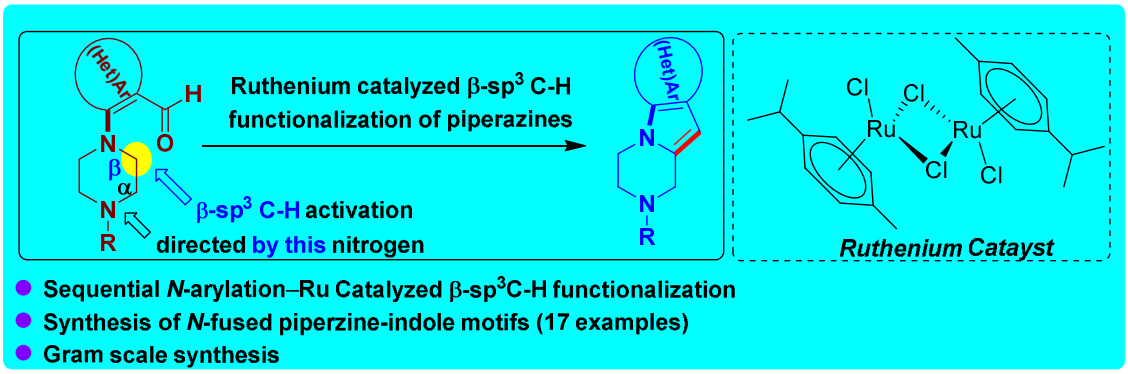
Abstract:

β-C(sp^3)–H functionalization on the 'privileged' piperazine nucleus has been disclosed using ruthenium catalysis. The ruthenium catalyzed synthesis of a variety of piperazine fused indoles from *ortho*-piperazinyl (hetero)aryl aldehydes is presented. This transformation takes place *via* dehydrogenation of piperazine followed by intramolecular nucleophilic addition of the transient enamine moiety onto the carbonyl group then aromatization cascade.



Ruthenium catalysed β-C(sp^3)–H Functionalization of piperazines has been revealed.