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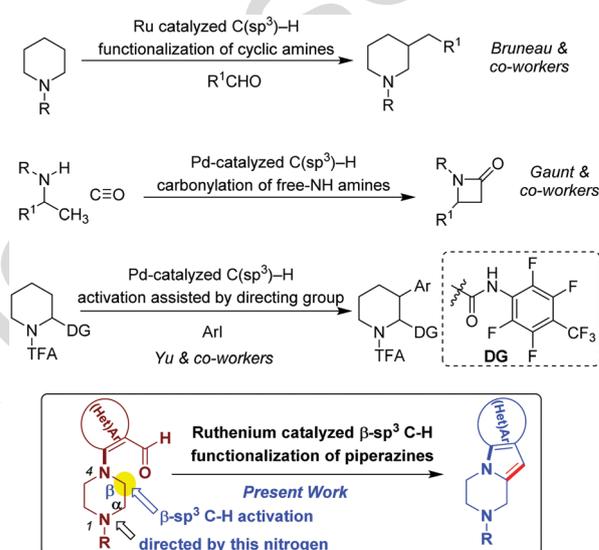
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Ruthenium catalyzed β -C(sp³)-H functionalization on the 'privileged' piperazine nucleus†

V. Muruges, ^{ab} Christian Bruneau, ^c Mathieu Achard, ^c Apurba Ranjan Sahoo, ^c Gangavaram V. M. Sharma ^a and Suriseti Suresh ^{*ab}

β -C(sp³)-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 the dehydrogenation of piperazine followed by an intramolecular nucleophilic addition of the transient enamine moiety onto the carbonyl group and aromatization cascade.

C(sp³)-H activation-functionalization has emerged as an important area of research in modern organic synthesis.¹ C(sp³)-H activation-functionalization of aliphatic (cyclic) amines provides a tool for the synthesis of various nitrogen containing derivatives including N-heterocycles. Generally, C(sp³)-H functionalization on the α -carbon to the nitrogen atom is well reported^{1,2} while that on the β -carbon to nitrogen has received considerably less attention.³ The group of Bruneau has reported ruthenium catalyzed β -C(sp³)-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 a directing group assisted Pd/NHC catalyzed β -C(sp³)-H arylation of saturated cyclic amines (Scheme 1).⁶ However, the C-H functionalization of piperazines has received significantly less attention despite the prominence of this 'privileged' moiety in several life-saving marketed drugs and continues to be important in drug discovery programs.⁷ This is probably due to the presence of two 1,4-nitrogen atoms



Scheme 1 Recent selected examples on β -C(sp³)-H functionalization of (cyclic) amines and present work.

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(sp³)-H functionalization of piperazines—facilitated by strong bases,⁸ and transition metal⁹ and photoredox-catalysis.¹⁰ However, the β -C(sp³)-H functionalization of piperazine remains a challenging problem.

Herein we report β -C(sp³)-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 an electrophile to accomplish the net β -C(sp³)-H functionalization. Accordingly, we chose 2-(4-methylpiperazin-1-yl)benzaldehyde **1a** containing an *N*-methyl group that assists 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

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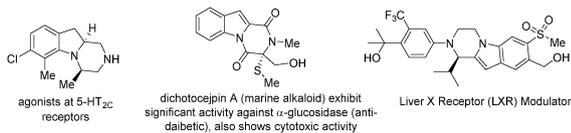


Fig. 1 Biologically active *N*-fused piperazine-indole derivatives.

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, cytotoxic¹² and LXR modulator activity¹³ (Fig. 1).

The initial reaction of compound **1a** in the presence of RuCl₃·xH₂O and camphorsulfonic acid (CSA) as an additive did not give any β-C(sp³)-H functionalization product (Table 1, entry 1). Much to our delight, using [Ru(*p*-cymene)Cl₂]₂ **B** as a catalyst in the presence of the 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 the ESI[†]). The well-defined

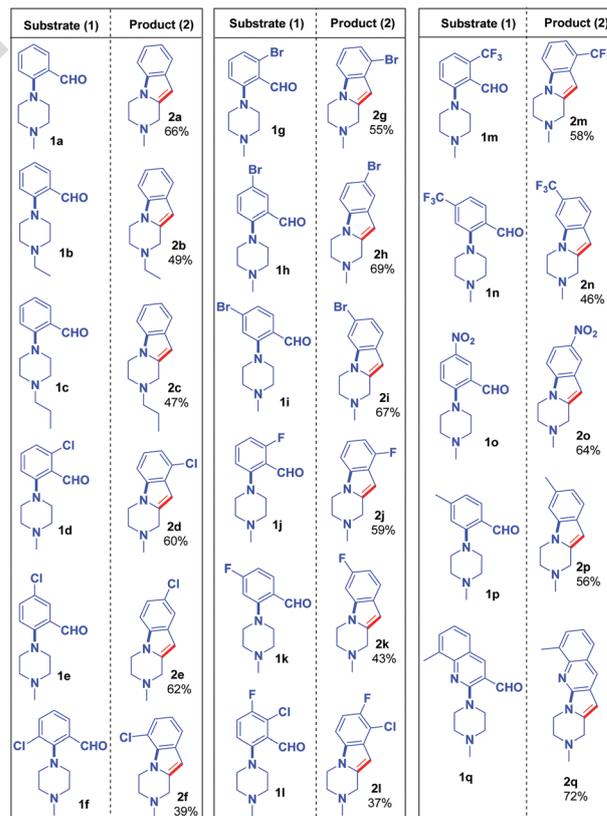
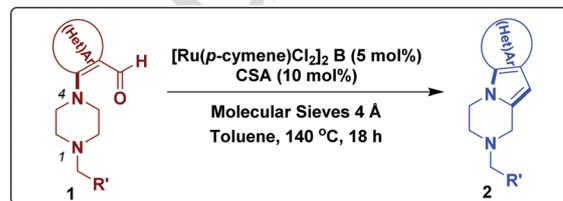
ruthenium and iridium catalysts (**C**, **D** and **E**)¹⁴ bearing a phosphine-benzenesulfonate ligand in the presence of CSA resulted in lower yields of the desired product (Table 1, entries 4–6). The ruthenium catalyst tris(2,2'-bipyridyl)Ru(II)Cl·6H₂O **F** also gave a low yield of **2a** (Table 1, entry 7). Increasing the loading of **B** to 5 mol% proved to give better results (Table 1, entry 8). The 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 an additive resulted in a lower yield of **2a** (Table 1, entry 12), which confirms that the presence of an acid benefits the reaction. This transformation was not successful in the absence of the 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) position of piperazine was checked and it was found that ethyl and *n*-propyl

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)	<i>p</i> -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.



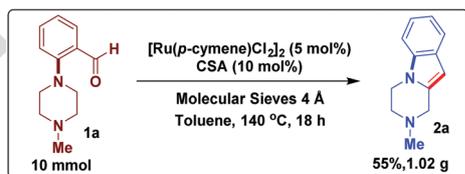
Scheme 2 Synthesis of piperazine fused indole derivatives.

1 substituents resulted in moderate yields of the corresponding
 2 piperazine fused indoles **2b–c**. It is interesting to note that
 3 when *ortho*-piperazinylbenzaldehyde bearing a benzyl group at
 4 the N(1) position of the piperazine ring was subjected to the
 5 optimized conditions, most of the starting material remained
 6 unreacted and *N*-benzyl,*N'*-phenylpiperazine resulting from the
 7 decarbonylation of the aldehyde was formed in a low amount
 8 (see ESI†). This result reveals that the present catalytic system
 9 exhibits a different tolerance to the protecting group of the
 10 directing nitrogen atom since catalysts **C** and **D** were efficient
 11 for the intermolecular β -C(sp³)-H alkylation by aldehydes start-
 12 ing from cyclic *N*-benzyl amines.^{4a}

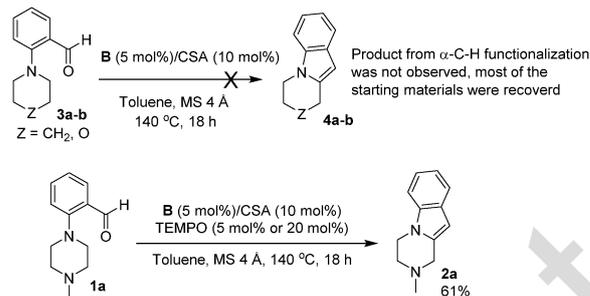
13 Different *N*-methyl-*N'*-aryl-piperazine compounds **1d–q** have
 14 been prepared and subjected to the ruthenium catalyzed β -C-H
 15 functionalization reaction. *ortho*-Piperazinyl benzaldehydes
 16 **1d–l** bearing halogen substituents like chloro, bromo or fluoro
 17 groups at different positions have undergone the β -C(sp³)-H
 18 functionalization to afford moderate yields of the corres-
 19 ponding piperazine fused indoles **2d–l** under the ruthenium
 20 catalysis conditions. Piperazine fused indoles **2m–o** bearing
 21 electron-withdrawing groups like trifluoromethyl or nitro
 22 groups on the benzene ring were obtained in moderate yields.
 23 *ortho*-Piperazinyl benzaldehyde **1p** bearing the electron-
 24 donating methyl group is a good substrate for this transfor-
 25 mation, comparable to **1a**. Furthermore, this transformation is not
 26 limited to only *ortho*-piperazinyl aromatic aldehydes as
 27 *N*-heteroaryl piperazine like 8-methyl-2-(4-methylpiperazin-1-
 28 yl)quinoline-3-carbaldehyde **1q** also served as a good substrate
 29 in this transformation to afford the corresponding piperazine
 30 fused aza-indole system **2q** in good yield. On the other hand, an
 31 acyl group in place of the carbaldehyde led to an inactive
 32 substrate.

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

36 We have performed control experiments to know whether
 37 the reaction proceeds through α - or β -C(sp³)-H activation and
 38 to get insights into the mechanism. The reactions of *ortho*-*N*-
 39 piperidinyl or *ortho*-*N*-morpholinyl benzaldehyde derivatives
 40 **3a–b** under the present ruthenium catalysis conditions did
 41 not give the products **4a–b** arising from α -C(sp³)-H func-
 42 tionalization, while most of the substrates remained unreacted
 43 (Scheme 4, top). These experiments suggest that in the
 44 presence of the ruthenium catalyst, the β -C(sp³)-H activa-
 45 tion-functionalization takes place on the piperazine nucleus where
 46 the *N*-alkyl part of the piperazine plays an essential role.



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

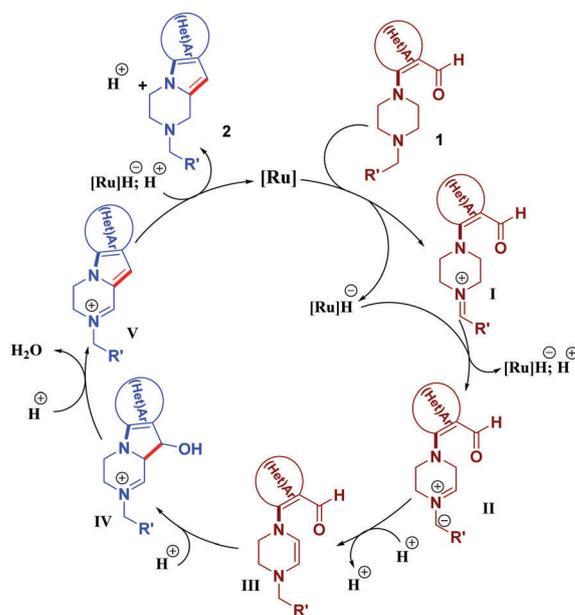


Scheme 4 Control experiments.

47 The radical pathway *en route* to piperazine fused indoles may
 48 be ruled out since the addition of TEMPO did not affect the
 49 ruthenium catalyzed reaction of *ortho*-*N*-piperazinyl benzal-
 50 dehyde **1a** (Scheme 4, bottom).

51 Based on the control experiments and literature reports,⁴ a
 52 plausible mechanism for the present ruthenium catalyzed β -C-
 53 H functionalization is depicted in Scheme 5. Piperazine **1** may
 54 be converted to the corresponding iminium intermediate **I** in
 55 the presence of a ruthenium catalyst *via* hydrogen transfer. The
 56 intermediate **I** would then give azomethine ylide **II** along with
 57 ruthenium hydride species, after hydrogen abstraction. The
 58 presence of an acid might promote the formation of enamine
 59 intermediate **III**, which would attack the carbonyl group to give
 60 intermediate **IV**. This would then undergo aromatization *via*
 61 dehydration to afford intermediate **V**, and the iminium part of
 62 it could be reduced by the ruthenium hydride species to furnish
 63 the piperazine fused indole **2**.

64 In conclusion, we have developed an unprecedented ruthe-
 65 nium catalyzed β -C(sp³)-H functionalization on the 'privileged'
 66 piperazine nucleus. The ruthenium-catalyzed dehydrogenation
 67 and hydrogen auto-transfer process appears to be the key for



Scheme 5 Plausible mechanism.

1 this successful transformation. This protocol complements the
few available catalytic methods for α -C(sp³)-H functionaliza-
tion of piperazines. Various piperazine fused indole derivatives
have been synthesized using the presented method. The opti-
5 mized method enabled the gram scale synthesis of a represen-
tative piperazine fused indole derivative. Explorations are
underway on the intermolecular β -C(sp³)-H functionalization
using different coupling partners on piperazine and related
systems using well-defined ruthenium catalysts.

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15 Conflicts of interest

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