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sp^3 C−H Bond Activation with Ruthenium(II) Catalysts and C(3)-Alkylation of Cyclic Amines

Basker Sundararaju,[†] Mathieu Achard,[†] Gangavaram V. M. Sharma,[‡] and Christian Bruneau*[,†]

[†]UMR6226 CNRS - Université de Rennes, Sciences chimiques de Rennes, Catalyse et Organométalliques, Campus de Beaulieu, 35042 Rennes Cedex, France

[‡]Organic Chemistry Division III, D 211, Discovery Laboratory, Indian Institute of Chemical Technology (CSIR), Hyderabad 500 007, India

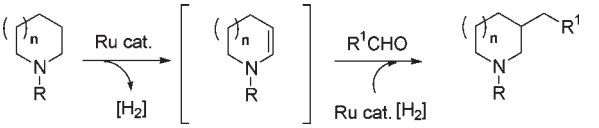
Supporting Information

ABSTRACT: A selective C(3)-alkylation via activation/functionalization of sp^3 C−H bond of saturated cyclic amines was promoted by (arene)ruthenium(II) complexes featuring a bidentate phosphino-sulfonate ligand upon reaction with aldehydes. This highly regioselective sustainable transformation takes place via initial dehydrogenation of cyclic amines and hydrogen autotransfer processes.

Considering the importance of cyclic amines and alkaloids in industry as dyes and as pharmaceutical and agrochemical drugs, straightforward and eco-friendly preparation of these compounds still represents a challenging task for chemists.[1,2] The functionalization of cyclic amines with direct formation of carbon−carbon bond requires an assisted sp^3 C−H bond activation that is still a real challenge.[3] Several functionalization at the C(2) position of cyclic aliphatic amines have been reported involving either activation of the H−C(2) bond via formal oxidative addition to a transition metal,[4] or oxidation by various types of oxidant into iminium intermediates followed by reaction with a nucleophile.[5,6] C(3)-functionalized cyclic amines represent an important class of biologically active compounds,[7] but as the H−C(3) bond of unfunctionalized cyclic amines is inert, their preparation requires multistep syntheses.[8] Indeed, functionalization of cyclic aliphatic amines at C(3) is scarce, and to the best of our knowledge only one example of C(3)-alkylation based on platinum-catalyzed oxidation of cyclic amines in the presence of oxygen followed by Michael addition and leading to C(3)-substituted enamines has been reported.[9] One approach to perform H−C(3) functionalization involves as the first step the in situ generation of reactive enamines via sp^3 C−H activation and dehydrogenation as already shown in the presence of iridium[10] and cobalt catalysts.[11] Whereas ruthenium catalysts are well-known for hydrogen transfer from alcohols,[12] they have not been used for dehydrogenation of cyclic amines except for alkylation of anilines.[13] We have thus investigated the possibility of performing a sequence of catalytic reactions from cyclic amines with ruthenium catalysts based on hydrogen transfers according to Scheme 1.

We now report that ruthenium catalysts are able to perform regioselective alkylation at the C(3) position of N-protected cyclic aliphatic amines via sequential dehydrogenation under nonoxidative conditions, C−C bond formation, and final transfer hydrogenation to produce C(3)-alkylated cyclic amines.

Scheme 1. Functionalization of Cyclic Amines Involving Hydrogen Transfer Processes



C(3)-Alkylation of *N*-benzylpyrrolidine **1a** with benzaldehyde **2a** to give the corresponding alkylated product **3a** was first attempted as a model reaction with various ruthenium precatalysts (Table 1).

Two equivalents of **1a** and one equivalent of **2a** were heated at 140 °C in the presence of 2 mol % of various ruthenium precatalysts. Ruthenium(II) and ruthenium(0) complexes such as $[RuCl_2(p\text{-cymene})]_2$, $[RuCl_2(COD)]_n$, $[Ru_3(CO)_{12}]$, were found to be rather ineffective affording low yields in **3a** (entries 1−4). However, these results showed that amine **3a** was produced as major compound along with small amount of enamine and pyrrole as side products **4a**, demonstrating that hydrogen transfer occurred.

As already observed in alkylation with alcohols involving ruthenium-catalyzed hydrogen transfer,[13,14] addition of a catalytic amount of acid (camphor sulfonic acid (CSA)) improved the conversion (entry 2). We further evaluated well-known efficient transfer hydrogenation ruthenium catalysts. Whereas Shvo catalyst[15] and $[RuCl_2(p\text{-cymene})]_2$ associated to dppf[16] revealed poor activity (entries 5, 6), neutral arene ruthenium(II) precatalysts (**A**, **B**)[14] exhibited interesting reactivities (entries 7−8). Dicationic **C**[17] afforded good results only in the presence of *tert*-butylphenylphosphinosulfonate ligand (entry 9). Especially, complexes **A** and **B** containing a phosphinesulfonate ligand (Figure 1) afforded the best conversions (entries 7, 8) with a **3a**/**4a** ratio highly in favor of the saturated amine **3a**. Comparing entries 8 and 11, the positive effect of CSA as additive was confirmed. Under the conditions of entry 11, other acids such as acetic acid and PTSA afforded lower yields of 72 and 66%, respectively. In the absence of ruthenium, CSA alone did not catalyze the transformation. Comparing entries 12 and 13 demonstrated that **1a** was also acting as hydrogen source, and the best result in terms of selectivity was obtained with 2 mol % of the ruthenium(II) complex **B** in the presence of 6 mol % of CSA

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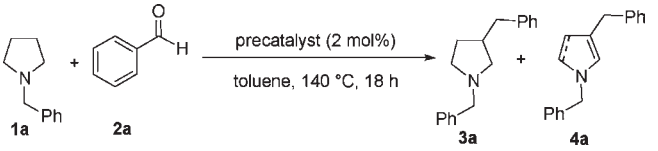
Table 1. C(3)-Functionalization of Pyrrolidine with Benzaldehyde[a]



entry	precatalyst	CSA[b]	3a/4a[c]	conv.[d]	yield[e,f]
1	$[RuCl_2(p\text{-cymene})]_2$	–	67/32	53	22
2	$[RuCl_2(p\text{-cymene})]_2$	10	71/29	86	28
3	$[RuCl_2(COD)]n$	10	70/30	81	27
4	$Ru_3(CO)_{12}$	10	94/6	53	23
5	Shvo's cat.	10	78/21	82	10
6[g]	$[Ru(p\text{-cymene})Cl_2]_2$ + dppf	10	75/25	90	39
7	**A**	–	90/10	97	69
8	**B**	–	85/15	98	62
9	**C**[h]	–	89/11	99	84(70)
10	**A**	10	89/11	99	58
11	**B**	10	88/12	99	77
12[i]	**B**	6	86/13	99	85(70)
13[j]	**B**	6	91/9	99	89(82)

[a] Reactions were carried out at 0.125 M concentration with **1a**/**2a**/precatalyst in 2.0/1/0.02 molar ratio under an inert atmosphere using a thermostatted oil bath at 140 °C. [b] Amount of acid (mol %). [c] Ratio of **3a**/**4a** determined by GC analysis. [d] Conversion based on GC analysis with respect to **2a** (tetradecane as internal standard). [e] Yield of **3a** determined by GC analysis with respect to **2a.** [f] Number in parentheses is isolated yield of **3a**. [g] Reaction performed with $[Ru(p\text{-cymene})Cl_2]_2$ and dppf in a 0.01/0.02 molar ratio. [h] **C** = $[Ru(p\text{-cymene})(CH_3CN)_2(PPh_3)][BF_4]_2$ and *tert*-butylphenylphosphino sulfonic acid in a 0.05/0.07 molar ratio at 0.5 M concentration. [i] 36 h reaction time. [j] Reaction performed with **1a**/**2a** in a 4/1 molar ratio.

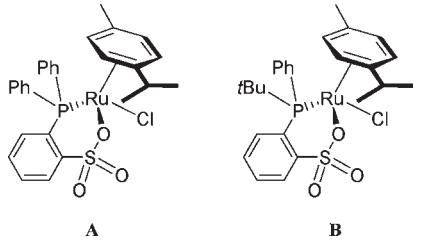
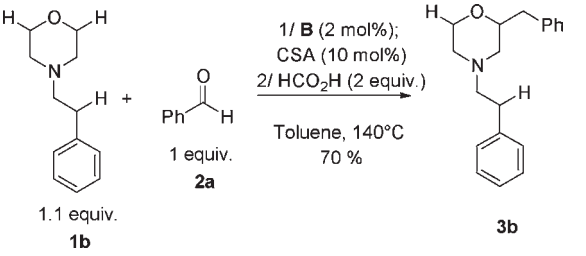


Figure 1. Arene ruthenium(II) containing phosphino sulfonate.

and a 4-fold excess of amine **1a**, which afforded 82% of **3a** after purification (entry 13). With these conditions in hands, we further evaluated the regioselectivity of this transformation. Substrate **1b** contains three competitive sites for C(3)-alkylation, two on the morpholine ring and one exocyclic site. Interestingly, during the reaction of **1b** with benzaldehyde, C(3)-alkylation only occurred at the ring position, and **3b** was formed in 80% GC yield. However, during the reaction, a substantial amount of unsaturated intermediates (about 15%) was detected. To completely eliminate the presence of these intermediates without using a large excess of amine, additional stirring in the presence of formic acid as hydrogen donor allowed complete reduction of enamine via a concomitant hydrogen autotransfer/transfer[18] and led to the formation of **3b** in 70% isolated yield (Scheme 2). This

Scheme 2. Regioselective Alkylation of N-Substituted Morpholine



result also demonstrated that the presence of the N-protecting benzyl group is not essential to achieve this process. On the other hand, no alkylation product was formed when *N*-phenylmorpholine was reacted with benzaldehyde **2a**. This observed reactivity is in favor of a mechanism involving initial formation of an exocyclic iminium ion.[19]

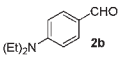
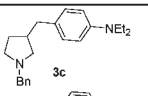
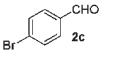
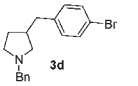
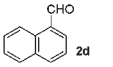
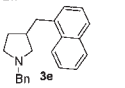
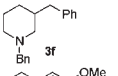
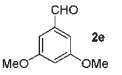
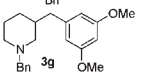
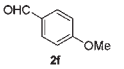
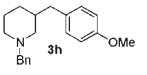
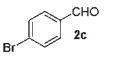
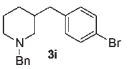
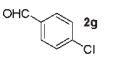
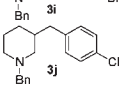
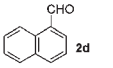
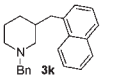
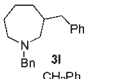
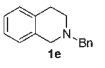
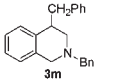
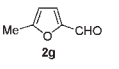
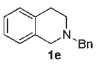
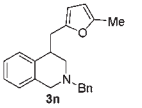
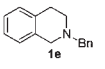
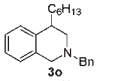
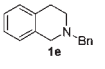
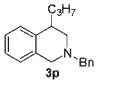
The scope of the C(3)-alkylation reaction, starting from various aldehydes and tertiary cyclic amines has been examined (Table 2). *N*-Benzylpyrrolidine **1a** was smoothly converted to the desired products with various aromatic aldehydes with up to 81% isolated yield (entries 1−3). No direct electronic effects of the substituents on the aromatic aldehydes were observed, as indifferently aldehydes bearing electron-withdrawing or electron-releasing groups were successfully engaged in this reaction. Similar results were obtained with *N*-benzylpiperidine **1c**, affording alkylated products in 72−82% yield (entries 4−9). Interestingly, a large azacycle such as azepane **1d** was found to be suitable for this methodology, and amine **3l** was obtained in 70% yield (entry 10). Then, the reaction was performed with N-alkylated tetrahydroisoquinoline (THIQ) derivatives **1e** and **1f**. In both cases, aromatic aldehydes reacted smoothly in favor of the C(3)-alkylated product (entry 11).

The structure of **3m** was unequivocally elucidated by single-crystal X-ray diffraction study (Figure 2). More importantly, the reaction was not limited to aromatic aldehydes, and aliphatic aldehydes such as hexanal and butanal provided good yields (entries 13, 14, and 16). Noteworthy, the heterocyclic aldehyde **2g** containing a furan moiety was compatible with the catalytic system affording amine **3n** and **3q** in 78 and 88% yield, respectively (entries 12 and 15). It is notable that under these alkylation conditions, halogen functionalities remained intact, thus offering opportunities for further valuable functionalization (entries 2, 7, 8).

Since cyclic amines contain two possible sites for C(3)-alkylation, we undertook the challenging dialkylation starting from *N*-methylpiperidine **1g**. Notably, in the presence of 2.5 equiv of benzaldehyde **2a**, the N,C,C-trialkylated amine **3s** was isolated in 55% yield after purification (Scheme 3). It should be noted that employing aliphatic aldehydes with N-substituted piperidine led to the competitive formation of mono- and dialkylated products even starting from an equimolar amine/aldehyde ratio.

The formation of compounds **3** can be rationalized according to Figure 3. In the presence of ruthenium catalyst amine can be converted to the corresponding iminium **I** via hydrogen transfer that affords, after hydrogen abstraction, ruthenium hydride species along with azomethine ylides **II**.[19] The geminal dehydrogenation of amine by ruthenium(II) species leading to a cyclic carbene,[20] potential precursor of enamine, cannot be excluded. The presence of acid might then facilitate the isomerization of this intermediate to enamine **III**.[19] Further condensation of the

Table 2. C(3)-Alkylation of Tertiary Amines with Aldehydes[a]

entries	aldehyde	amine	Product	Yield[b]
1	 2b	 1a	 3c	80[c]
2	 2c	 1a	 3d	76
3	 2d	 1a	 3e	81
4	 2a	 1c	 3f	72
5	 2e	 1c	 3g	81[c]
6	 2f	 1c	 3h	80
7	 2c	 1c	 3i	75[c]
8	 2g	 1c	 3j	77
9	 2d	 1c	 3k	82
10	 2a	 1d	 3l	70[c]
11	 2a	 1e	 3m	82
12	 2g	 1e	 3n	78
13	hexanal	 1e	 3o	86
14	butanal	 1e	 3p	75
15	2g	1f	3q	88
16	hexanal	1f	3r	67[c]

[a] Reactions were carried out at 0.125 M concentration with **1**/**2**/**B**/CSA in 1.2/1.0/0.02/0.1 molar ratio under an inert atmosphere using a thermostatted oil bath at 140 °C; after 16 h, 1.5 molar ratio of formic acid was added and stirred for an additional hour. [b] Isolated yield. [c] Average isolated yield based on two runs.

aldehyde **2** and acid-promoted dehydration would afford the unsaturated iminium **V**, which could be readily reduced by ruthenium hydride species arising from amine or formic acid as hydrogen donor.[21]

In conclusion, selective C(3)-alkylation of tertiary cyclic amines involving activation of sp^3 C−H bond via hydrogen transfer was efficiently catalyzed by ruthenium complex **B**. The reaction described here appears general and efficient. From a synthetic point of view, it complements the other catalytic methods used for C(2)-functionalization of cyclic amines. This new catalytic reaction makes possible the selective introduction of a variety of substituents arising from aldehydes at the C(3) position. Further studies to extend this methodology and effort to establish the detailed mechanism are in progress.

Figure 2. Structure of compound **3m**.

Scheme 3. C(3)-Dialkylation of *N*-Methylpiperidine

Figure 3. Proposed mechanism.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and data for all new compounds **3**; complete ref 2c. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
christian.bruneau@univ-rennes1.fr

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