ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 10745–10747

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Rhodium(III)-catalyzed allylic C–H bond amination. Synthesis of cyclic amines from ω-unsaturated *N*-sulfonylamines†

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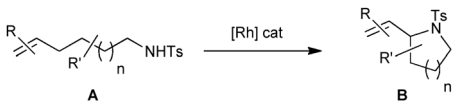
Received 21st August 2012, Accepted 10th September 2012
DOI: 10.1039/c2cc36067e

For the first time, intramolecular allylic amination was conducted using rhodium(III) according to an "inner-sphere" type mechanism with amines activated by only one electron-withdrawing group. The activation of C(sp^3)–H bonds was chemoselective and allows the access to a variety of substituted cyclic amines such as pyrrolidines and piperidines.

C–H activation and functionalization has emerged as a powerful tool in organic synthesis and is an area of intense focus.[1] Due to the prevalence of amino derivatives in biologically active molecules, the formation of carbon–nitrogen bonds by reaction of a nitrogen atom with a non-activated C–H bond is of importance.[2] Two strategies are used to realize the amination of C–H bonds. The first, and most reported one, is the use of a nitrenoid species for the insertion of a nitrogen atom into a C–H bond according to an "outer-sphere" mechanism.[3,4] The second strategy involves direct activation of a C–H bond by a metal to form a carbon–metal bond, which is then functionalized by an amine to create the C–N bond following an "inner sphere" mechanism.[5] We have to point out that in the "inner sphere" mechanism, the nucleophilic amines have to be strongly activated by two electron-withdrawing groups.

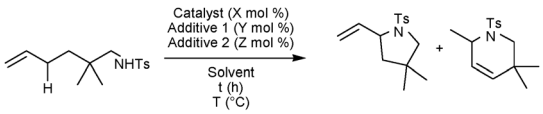
Herein, we would like to report the first rhodium(III)-catalyzed intramolecular C(sp^3)–H amination using amines only activated by one electron-withdrawing group such as *N*-tosylamines **A** which led to cyclic amines of type **B** (Scheme 1).[6]

Based on previous results, rhodium(I),[7] rhodium(II),[4] and rhodium(III),[8,9] highly reactive species in oxidative C–H bond functionalization, have been examined. Among the mono-activated ω-unsaturated amines (*N*-Boc, *N*-SO_2R, *N*-C(O)-R, *N*-S(O)-R), ω-unsaturated *N*-tosylamides revealed to be the more promising substrates. Upon extensive screening of the reaction conditions with ω-unsaturated *N*-tosylamide **1**, rhodium(I), cationic or not, and rhodium(II) were found to be ineffective in forming compounds **2** and **3**. In contrast, cationic rhodium(III) (Table 1) displayed significant catalytic activity and good selectivity for the C–H amination, as pyrrolidine **2** and tetrahydropyridine **3** were formed after 20 h at 120 °C in 55% yield in a 20/1 ratio using $[RhCp^*Cl_2]_2$/$AgSbF_6$/$Cu(OAc)_2{\cdot}H_2O$ in *t*-amyl alcohol (Table 1, entry 1). Switching from *t*-amyl alcohol to 1,4-dioxane led to better yield of **2** and **3**, as these compounds were obtained in 73% global yield in a 5.7/1 ratio after 16 h at 120 °C (Table 1, entry 2). Increasing or decreasing the catalytic amount of $[RhCp^*Cl_2]_2$ did not give satisfactory results (Table 1, entries 3 and 4). In addition, all the reactants were necessary for the reaction to take place. Indeed, by performing control experiments



Scheme 1 General scheme.

Table 1 Optimisation of reaction conditions



Entry	Solvent	Catalytic system (mol%)	*t* (h)	*T* (°C)	Yield[a] (**2**/**3**) (%)
1	*t*-AmOH	$[RhCp^*Cl_2]_2$ (5), $Cu(OAc)_2$ (210) $AgSbF_6$ (20)	20	120	55 (> 20/1)
2	Dioxane	$[RhCp^*Cl_2]_2$ (5), $Cu(OAc)_2$ (210) $AgSbF_6$ (20)	16	120	73[c] (5.7/1[b])
3	Dioxane	$[RhCp^*Cl_2]_2$ (10), $Cu(OAc)_2$ (240) $AgSbF_6$ (40)	4	120	63[d] (only **2**)
4	Dioxane	$[RhCp^*Cl_2]_2$ (2.5), $Cu(OAc)_2$ (210) $AgSbF_6$ (10)	20	120	Traces
5	Dioxane	$[(MeCN)_3RhCp^*](SbF_6)_2$ (5) $Cu(OAc)_2$ (210)	16	120	70[c] (2.5/1[b])
6	DCE	$[(MeCN)_3RhCp^*](SbF_6)_2$ (5) $Cu(OAc)_2$ (210)	16	83	77[c] (5/1[b])

[a] Isolated yield. [b] Separable products. [c] Complete conversion. [d] Incomplete conversion.

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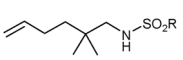
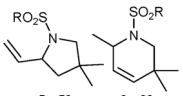
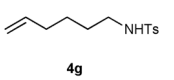
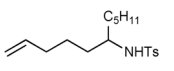
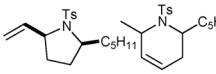
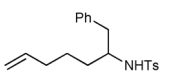
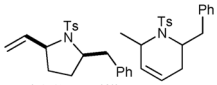
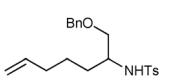
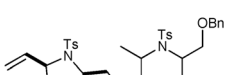
without $[RhCp^*Cl_2]_2$, $AgSbF_6$ or $Cu(OAc)_2{\cdot}H_2O$, no conversion of the starting material was observed. As $AgSbF_6$ is not easy to handle (very hygroscopic, rapid degradation), the stable cationic rhodium(III) $[(MeCN)_3RhCp^*](SbF_6)_2$ was tested.[10] The use of this catalyst (5 mol%) in the presence of $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv.) under the same conditions as previously described (1,4-dioxane, 120 °C, 16 h) gave satisfactory results, as **2** and **3** were obtained in 70% yield, however in a 2.5/1 ratio (Table 1, entry 5). Finally, using $[(MeCN)_3RhCp^*](SbF_6)_2$ (5 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv.) in 1,2-dichloroethane (DCE) revealed to be the best conditions, as the transformation of **1** proceeded smoothly at 83 °C and, after 16 h, *N*-tosylpyrrolidine **2** and *N*-tosyltetrahydropyridine **3** were isolated in 77% yield in a 5/1 ratio in favour of **2** (Table 1, entry 6).

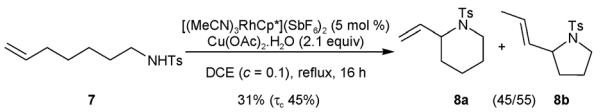
As tosylamide **1** gave satisfactory results, diversely substituted *N*-arylsulfonamides **4a–4f** were examined. Among the different electron-withdrawing protecting groups tested, the best in terms of yield and selectivity was the *p*-methoxybenzenesulfonyl group as compound **4a** was transformed into pyrrolidine **5a** and tetrahydropyridine **6a** in 61% yield in a ratio of 15/1 in favour of **5a** (Table 2, entry 1). The use of more electron-withdrawing groups, such as benzenesulfonyl (compound **4b**), *p*-bromobenzenesulfonyl (compound **4c**) and *p*-nitrobenzenesulfonyl (compound **4d**) groups, increased the acidity of the corresponding sulfonamides, but decreased their reactivity (Table 2, entries 2–4). In addition, when *o*-nitrobenzenesulfonylamide **4e**, a more acidic sulfonamide, was examined, no evolution was observed (Table 2, entry 5). In contrast, treatment of alkylsulfonamide **4f** with $[(MeCN)_3RhCp^*](SbF_6)_2$/$Cu(OAc)_2{\cdot}H_2O$ led to the desired compounds **2g** and **3g** in 42% yield in a 4/1 ratio (Table 2, entry 6).

Table 2 Scope of the reaction[a]

Entry	*N*-tosylamide	Products	Yield[b] % (τ_C)	**5**/**6**
1	 **4a-4f**	 **5a-5f** **6a-6f**	61 (100)	15/1
2			32 (40)	7/1
3			25 (28)	3/1
4			14 (30)	4/1
5			— (0)	—
6			42 (100)	4/1[c]
7	 **4g**	 **5g**	50 (60)	—
8	 **4h**	 **5h** (*cis*/*trans*: 4/1) **6h**	50	9/1[c]
9	 **4i**	 **5i** (*cis*/*trans*: 4/1) **6i**	25 (75)	15/1[c]
10	 **4j**	 **5j** (*cis*/*trans*: 4/1) **6j**	30 (83)	7/1[c]

[a] Reaction conditions: **4** (0.1 mmol), catalyst (5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv.), DCE (1 mL), 83 °C, 16 h. [b] Isolated yields. [c] Inseparable products. Ratio determined by ^1H NMR.

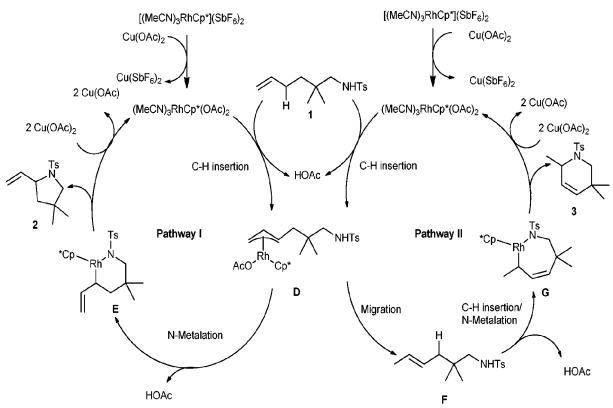
A variety of ω-unsaturated *N*-tosylamines **4g–4h** were cyclized to test the generality of the method. When *N*-hex-5-en-tosylamide **4g** was involved in the C–H amination, 2-vinylpyrrolidine **5g** was the only isolated product formed in 50% isolated yield for a conversion of 60% of **4g**, after 16 h (Table 2, entry 7). The use of α-branched *N*-tosylamides **4h–4j** led to a better conversion of the starting material producing pyrrolidines **5h–5j** and piperidines **6h–6j** in favor of the *cis*-pyrrolidines **5h–5j** (*cis*-**5**/*trans*-**5** = 4/1) (Table 2, entries 8–10). It is worth noting that only traces of the product corresponding to the C–H insertion in aromatic bonds were observed in the case of **4i** (Table 2, entry 9), and no traces of insertion in the benzylic C–H bond were detected when **4j** was involved in the C–H amination process (Table 2, entry 10). We have to point out that longer reaction times did not improve the conversions and yields, and by increasing the catalytic amount of rhodium(III) species to 10 mol%, a complete conversion of the starting material was observed without improvement in the yield of products **5** and **6**. The reaction was extended to the formation of piperidines, as *N*-hept-6-en-tosylamide **7** was cyclized into 2-vinylpiperidine **8a** and 2-crotylpyrrolidine **8b** in a ~1/1 ratio, in 31% isolated yield with a conversion of 45% of **7** (Scheme 2).



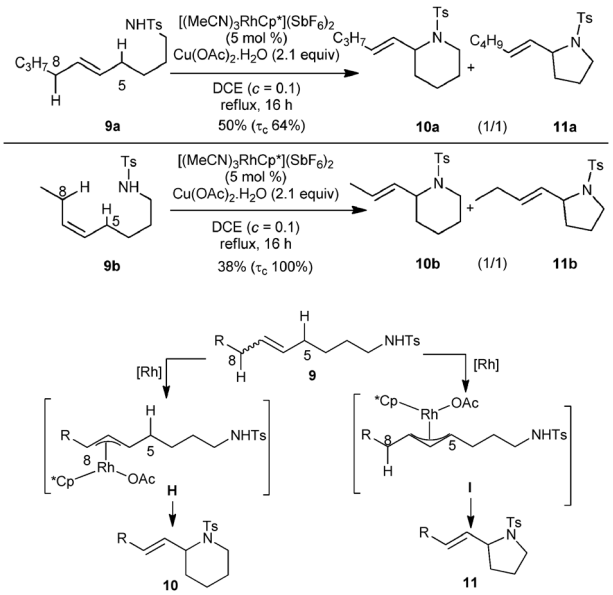
Scheme 2 Synthesis of piperidines.

Based on the observed data and on the described rhodium(III) catalytic cycles,[8,9,11] the formation of tetrahydropyridines and pyrrolidines from ω-unsaturated *N*-tosylamides can be explained by two pathways (Scheme 3). At first, a π-allylic rhodium intermediate **D** can be formed and *N*-metalation can then occur to produce intermediate **E**, which leads to pyrrolidine **2** after reductive elimination. An alternative pathway leading to tetrahydropyridine **3** can take place *via* the formation of the non-terminal olefin **F** resulting from the migration of a hydrogen. From **F**, a π-allylic rhodium complex can be formed and *N*-metalation can occur to produce **G**, which can lead to tetrahydropyridine **3a** after reductive elimination.

In order to verify our hypothesis concerning the π-allylic rhodium complex, compounds **9a** and **9b**, with respectively an

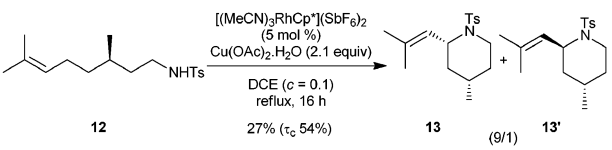


Scheme 3 Catalytic cycles.



Scheme 4 Control experiments.

E- and a *Z*-double bond, were prepared. It is worth noting that those compounds possess two different allylic C–H bonds at C5 and C8. Thus, substrates **9a** and **9b** were treated with $[(MeCN)_3RhCp^*](SbF_6)_2/Cu(OAc)_2{\cdot}H_2O$ in refluxing DCE for 16 h to give in both cases piperidines **10** and pyrrolidines **11** in a 1/1 ratio, possessing an *E*-double bond, whatever the starting material (Scheme 4). The formation of piperidines **10a** and **10b** can be explained by the insertion of the rhodium catalyst in the allylic C–H bond at C8 to form π-allylic complex **H**, which after *N*-metalation led to a 7-membered metalacycle producing piperidines **10a** and **10b**. In addition, pyrrolidine **11b** was obtained with a total isomerization of the double bond. These two observations are in accordance with the formation of the π-allylic complexes **H** and **I**. In order to avoid the formation of intermediate **H**, sterically hindered *N*-tosylamide **12** was synthesized and treated with $[(MeCN)_3RhCp^*](SbF_6)_2/Cu(OAc)_2{\cdot}H_2O$ in refluxing DCE, for 16 h (Scheme 5). Under these conditions, only piperidines **13** and **13′** were isolated in a 9/1 ratio.



Scheme 5 Synthesis of piperidines.

In summary, we have shown for the first time that a rhodium(III) catalyst is able to catalyze $C(sp^3)$–H amination, transforming ω-unsaturated *N*-sulfonylamides into pyrrolidines and piperidines in moderate to good yields *via*, probably, a π-allylic complex intermediate. In addition, this transformation is selective towards allylic C–H bonds as aromatic, benzylic and ethereal C–H bonds are not reactive under these conditions. Further studies to increase the regioselectivity and to confirm the mechanism of this reaction are under investigation.

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