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Ruthenium-Catalyzed Cascade N- and C(3)-Dialkylation of Cyclic Amines with Alcohols Involving Hydrogen Autotransfer Processes

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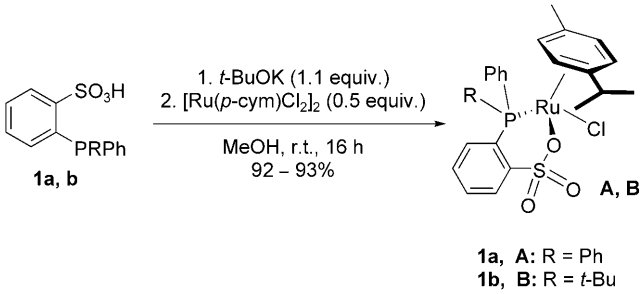
Abstract: An unprecented N- and C(3)-dialkylation of unactivated amines by a cascade reaction *via* borrowing hydrogen methodology using new (arene)ruthenium(II) complexes featuring phosphinosulfonate ligands is described. This reaction is highly regioselective and produces water as the only side product.

Keywords: borrowing hydrogen; homogeneous catalysis; hydrogen autotransfer; P,O chelates; ruthenium

The N-alkylation of amines with alcohols *via* a hydrogen autotransfer strategy using homogeneous or heterogeneous ruthenium,[1,2] iridium,[3,4] copper,[5] platinum,[6] nickel,[7] rhodium,[1b,8] or iron[9] catalysts has become a powerful tool for N–C bond formation.[10] Likewise, C–C bond formation reactions have also been investigated starting from carbonucleophiles or ylides with alcohols by a similar strategy.[11–14] This transformation involves the conversion of alcohols into aldehydes or ketones as transient intermediates *via* an oxidative hydrogen elimination. The *in situ* generated carbonyl groups are reactive towards nucleophiles such as amines and lead to the formation of iminium cationic species or imines, affording the expected N-alkylated amines after reduction, with water as sole side product. Although several examples adopting this strategy have been documented for the construction of N-alkylated amines,[1–10] and C-alkylated products arising from alcohols,[11–14] a one-step process for the simultaneous alkylation of both the N atom and the unactivated C(3) carbon of secondary amines is so far unknown and corresponds to a formal C–H activation for the later. Such modifications are of a great interest and would afford new routes to get access to functionalized amines of known biological interest[15] which usually require multistep syntheses.[16]

Herein, we report an unprecedented N- and C(3)-dialkylation of unactivated cyclic amines in the presence of new ruthenium precatalysts based on phosphinosulfonate ligands acting as P,O chelates, involving the borrowing hydrogen methodology. During the course of our studies on the applications of N,O- and P,O-chelating ligands in ruthenium-catalyzedreactions,[17] we synthesized in good yields the new (arene)ruthenium(II) complexes **A** and **B** featuring phosphinobenzenesulfonate ligands **1a** and **1b** starting from $[Ru(p\text{-cymene})Cl_2]_2$ (Scheme 1). Crystal struc-



Scheme 1. Preparation of complexes **A** and **B**.

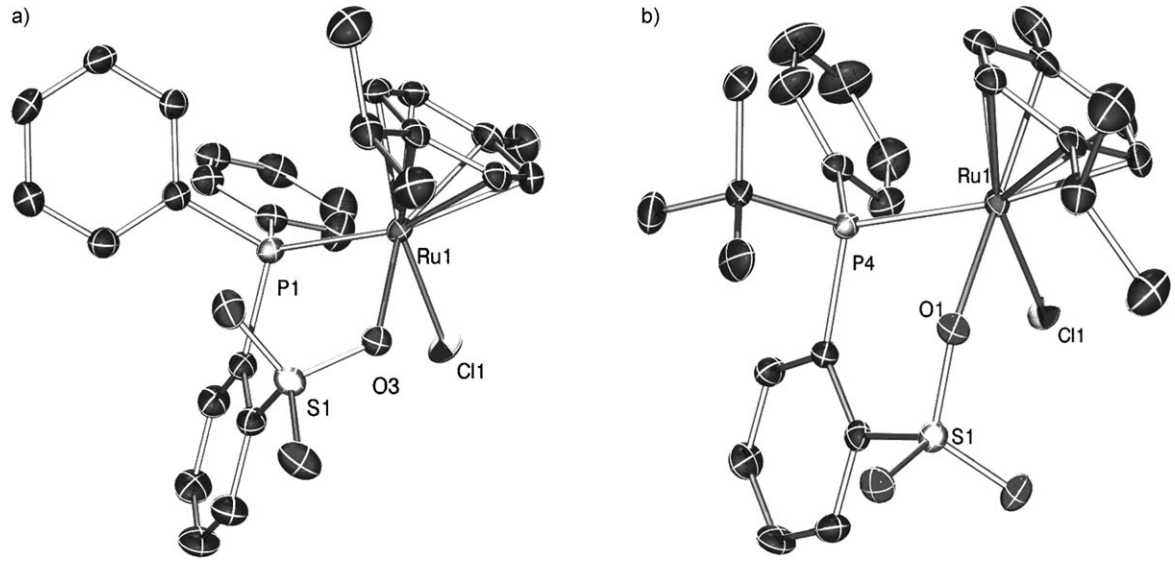
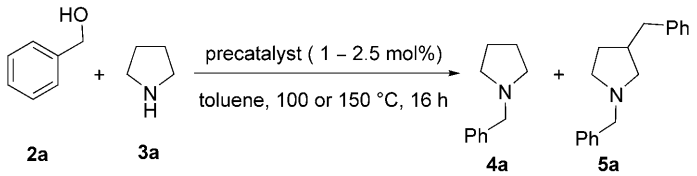


Figure 1. Structures of **A** and **B**·2 CH_2Cl_2 at 50% probability ellipsoids. All hydrogen atoms and solvent are omitted for clarity. Selected bond lengths [Å] and angles [°]. Complex **A**: Ru(1)–Cl(1) 2.399, Ru(1)–P(1) 2.357, Ru(1)–O(3) 2.118, P(1)–Ru(1)–O(3) 90.71, O(3)–Ru(1)–Cl(1) 80.85. Complex **B**: Ru(1)–Cl(1) 2.401, Ru(1)–P(4) 2.368, Ru(1)–O(1) 2.127, P(4)–Ru(1)–O(1) 79.92, O(1)–Ru(1)–Cl(1) 89.35.

tures of these complexes revealed that the phosphinosulfonate coordinates as a bidentate ligand through the phosphine and one oxygen atom (Figure 1).[18]

The results from the initial evaluation of the precatalysts **A** and **B** in the N-alkylation of amines are presented in Table 1. Reaction of 1 equivalent of benzyl alcohol **2a** with pyrrolidine **3a** in the presence of

Table 1. N-alkylation and N- and C(3)-dibenzylation of pyrrolidine **3a** with benzyl alcohol **2a**.[a]



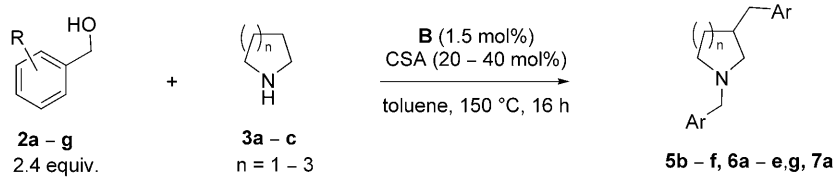
Entry	Catalyst	Additive[b]	Solvent	**4a/5a**	Conversion[c]
1	**A**	none	toluene	97/3	65%
2[d]	**A**	none	neat	100/0	95% (92)
3	**B**	none	toluene	93/7	80%
4	**B**	none	water	100/0	85%
5	**B**	none	neat	83/17	93%
6[e]	**B**	CSA (10)	toluene	40/60	99%
7[e]	**B**	CSA (15)	toluene	37/63	99%
8[e]	**B**	CSA (20)	toluene	31/69	99%
9[e]	**B**	CSA (30)	toluene	25/75	99%
10[e]	**B**	CSA (40)	toluene	12/88	99% (80)
11[e]	**B**	CSA (100)	toluene	25/32	15%

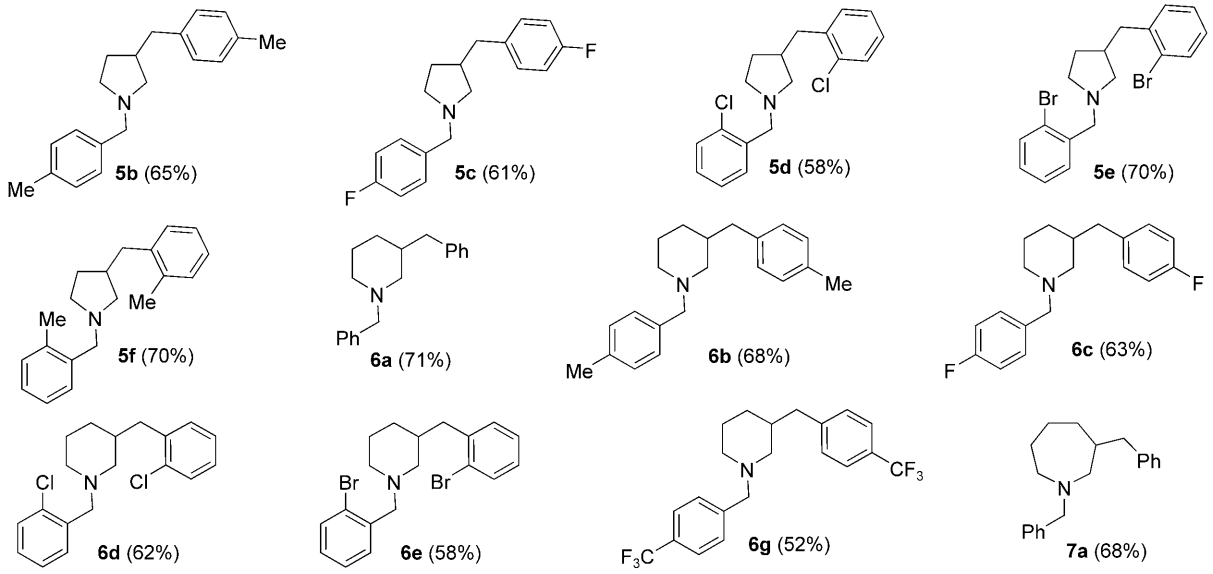
[a] Reactions were carried out at 0.9 M concentration (except entries 2 and 4) with **2a**/**3a**/precatalyst in a 1/1.1/0.025 molar ratio under an inert atmosphere using a thermostated oil bath at 150 °C (except entry 2).
[b] Amount of additive in mol%.
[c] Conversion based on GC analysis (tetradecane as internal standard), number in parentheses is isolated yield of the major compound (**4a** in entry 2 and **5a** in entry 10).
[d] Reaction performed with **2a**/**3a**/**A** in a 1.05/1.0/0.010 molar ratio at 100 °C.
[e] Reaction performed with **2a**/**3a**/**B** in a 2.5/1.0/0.015 molar ratio at 150 °C, CSA = camphorsulfonic acid (mol% with respect to **3a**).

2.5 mol% of **A** and **B** (entries 1 and 3) in toluene at 150 °C for 16 h afforded the N-alkylated amine **4a** in good conversion with complex **B**, featuring an electron-rich phosphine, while modest conversion was obtained with **A**. The side-product that was observed in both reactions was identified as the N- and C(3)-dibenzylated amine **5a**. This result presents the first example, although in very poor yield, for the N- and C-dialkylation of an unactivated amine involving ruthenium-catalyzed hydrogen autotransfer strategy. It is noteworthy that the exclusive formation of **4a**, with no traces of **5a** under neat conditions at 100 °C provided the best reaction conditions to produce **4a** in 92% isolated yield with precatalyst **A** (entry 2). The reaction in water in the presence of complex **B** also presents an interesting potential (entry 4). However, the 83/17 **4a**/**5a** ratio with 93% conversion under solvent-free conditions with **B** (entry 5), prompted us to optimize the reaction conditions to selectively form **5a** employing precatalyst **B**. Thus, reaction with 10 mol% of camphorsulfonic acid (CSA) as additive with **2a** (2.5 equiv.) and **3a** led to full conversion of **3a** and afforded the disubstituted amine **5a** together with **4a** in a 40/60 **4a**/**5a** ratio (entry 6). In addition to CSA, the order of addition of the substrates was found to be crucial. Thus, reaction of **3a** with CSA before catalyst addition was essential to ensure the formation of the ammonium sulfonate in order to achieve complete conversion, and possibly to inhibit protonation of the phosphine leading to the formation of unchelated inactive ruthenium species. Finally, 40 mol% of CSA was found to afford **5a** in 80% isolated yield after purification by silica gel chromatography (entry 10). Increased amounts of CSA did not improve the selectivity towards **5a**, while the conversion drastically dropped (entry 11). Having established the best reaction conditions for N- and C(3)-dibenzylation, the general applicability of this cascade reaction was next evaluated (Table 2).

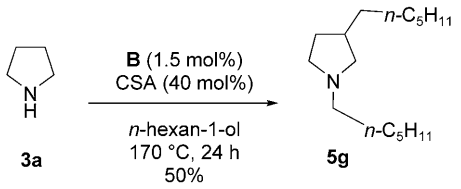
Accordingly, reaction of **3a** with *para*- and *ortho*-substituted benzylic alcohols **2b**–**2f** afforded N- and C(3)-dialkylated amines **5b**–**5f** in 58–80% isolated yield, respectively. Piperidine **3b** with diverse benzylic alcohols **2a**–**2e**, **2g** gave amines **6a**–**6e**, **6g** in 52–71% yields. Furthermore, the reaction of azepane **3c** with **2a** allowed the formation of the disubstituted azepane **7a** in 68% yield but with lower amount of CSA (20 mol%). It is important to note that attempts to react the 4-membered cyclic amine azetidine in the presence of benzyl alcohol were unsuccessful, presumably due to hydrolysis of the iminium intermediate and ring opening. Analysis of these results (Table 2) amply demonstrates that the influence of either elec-

Table 2. General applicability of the reaction.[a]





[a] Yields in parentheses are of isolated products.



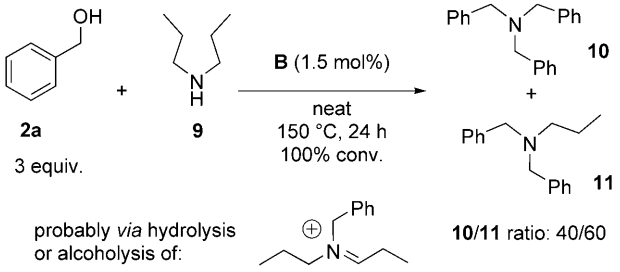
Scheme 2. Dialkylation of **3a** with hexan-1-ol.

tron-withdrawing or electron-releasing groups is minimal.

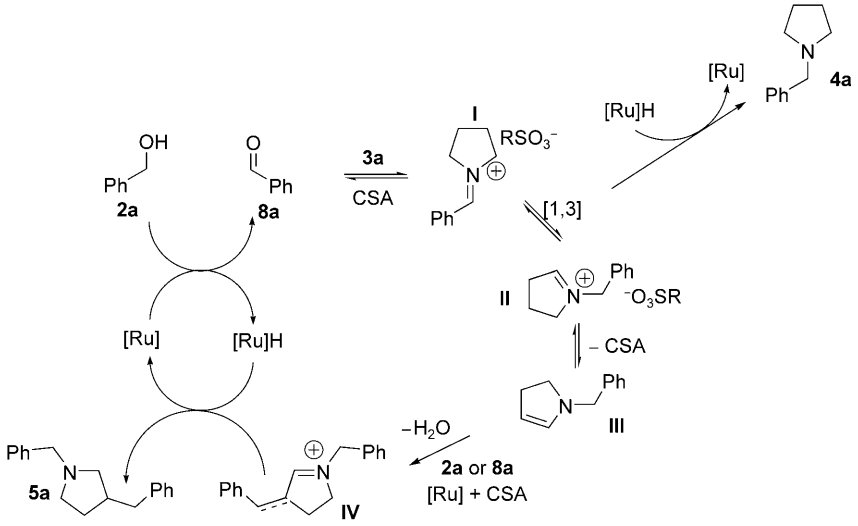
We showed that the methodology could be extended to aliphatic alcohols. Indeed, pyrrolidine reacted with *n*-hexan-1-ol at 170°C in the presence of 1.5 mol% of **B** to give the dialkylated pyrrolidine **5g** in 50% isolated yield. This reactivity reveals that C(3)-alkylation took place only at the cyclic carbon of the amine and not at the aliphatic side chain introduced during the first step as confirmed by NMR analyses (Scheme 2).[19]

A plausible mechanism based on an autotandem catalytic cycle[20] is depicted in Scheme 3. Benzyl alcohol **2a** is converted into aldehyde **8a** along with the generation of the ruthenium hydride species according to a well-accepted mechanism.[10] The *in situ* generated **8a** reacts with the amine to form the iminium ion **I** which, in the absence of acidic additive, undergoes reduction and gives **4a**. However, in the presence of sulfonic acid, as reported earlier by Williams and Beller in the case of indole derivatives,[21] **I** might rearrange into the iminium ion **II** *via* a [1,3] hydride shift. Deprotonation of **II** might lead to the formation of enamine **III** as key intermediate. Thus, we also assume that the presence of CSA facilitates the equilibration of the two iminium ions and thereby lowers the formation of **4a** resulting from the reduction of iminium ions **I** or **II**. Finally, enamine **III**, would lead *via* nucleophilic substitution of **2a** or aldol-type reaction on **8a**[3h,14] to the iminium species **IV** which, in turn, would afford the expected dialkylated amine **5a** after reduction in the presence of the ruthenium hydride species. It is noteworthy that under the present reaction conditions, in the absence of any amine, **2a** gave dibenzyl ether as the exclusive product, while in contrast, without CSA, benzyl benzoate[22] was obtained as the major product. These results suggest that the nucleophilic substitution on **2a** with **III** cannot be ruled out. The unsuccessful attempts to react N-alkylated amine **4a** to afford the amine **5a** further consolidates that **4a** is not involved in the catalytic cycle and supports the proposed mechanism. At this stage, we were unable to extend the reaction to aliphatic acyclic amines such as dipropylamine **9**. In contrast to cyclic amines, the formation of aldehyde products resulting from the hydrolysis of the iminium ion is not reversible under these conditions. Thus, during the reaction of **9** in the presence of benzyl alcohol **2a** an N-dealkylation–N-benzylation cascade occurred affording a mixture of di- and tri-benzylamines **10** and **11** with full conversion (Scheme 4).[23]

In conclusion, we have designed and prepared new (arene)Ru(II) complexes. Complex **B** is very efficient



Scheme 4. Dealkylation benzylation cascade.



Scheme 3. Proposed mechanism.

to promote the unprecedented catalytic reaction affording N- and C(3)-dialkylated cyclic amines from benzylic alcohols and unactivated secondary amines. Interestingly, this methodology would allow the access of C(3)-substituted cyclic secondary amines by a simple hydrogenolysis. This C(3)-alkylation of cyclic amines by an ecofriendly cascade reaction producing only water as side product, may open new avenues for C–C bond formation.

Experimental Section

Preparation of [Ru(*p*-cymene)(k^2-*o*-*t*-BuPPBS)Cl] Complex B

Phosphine **1b** (0.652 mmol) and *t*-BuOK (0.717 mmol) were added to a 25-mL flame-dried Schlenk tube. The sealed Schlenk tube was evacuated and filled with argon three times. Minimum amount of MeOH (degassed by nitrogen purge for 30 min) was added and the solution was stirred for 30 min. To this solution $[Ru(p\text{-cymene})Cl_2]_2$ (0.200 g, 0.326 mmol) was added. After stirring for 14 h, the solvent was evaporated, and then the crude was dissolved in 30 mL of dichloromethane. The solution was cannulated to remove the inorganic salt. The filtrate was reduced to a minimum amount, and covered with hexane leading to the formation of red crystals of complex **B**; yield: 0.360 g (93%). ^{1}H NMR (500 MHz, CD_2Cl_2): $\delta = 8.05$ (t, 2H, $J = 8.5$ Hz), 7.83 (dd, 1H, $J = 4.3$, 7.7 Hz), 7.51–7.41 (m, 4H), 7.20 (t, 1H, $J = 8.0$ Hz), 7.07 (t, 1H, $J = 8.9$ Hz), 5.97 (d, 1H, $J = 6.1$ Hz), 5.72 (d, 1H, $J = 6.1$ Hz), 5.67(m, 2H), 2.24 (sept, 1H, $J = 6.8$ Hz), 1.54 (d, 9H, $J = 14.3$ Hz), 1.22 (s, 3H), 1.14 (d, 6H, $J = 6.8$ Hz); ^{31}P (81 MHz, CD_2Cl_2): $\delta = 42.05$; ^{13}C NMR (125 MHz, CD_2Cl_2): $\delta = 151.2$, 151.1, 135.0, 133.4, 133.2, 132.9, 131.4, 130.94, 130.93, 129.1, 129.0, 128.6, 128.5, 127.9, 127.8, 126.6, 126.2, 107.9, 94.6, 90.7, 85.3,82.3, 38.4, 38.2, 30.8, 29.8, 29.7, 22.5, 21.2, 16.1; elemental analysis: calcd. for $C_{26}H_{32}ClO_3PRuS$: C 52.74, H 5.45; found: C 52.70, H 5.46.

General Procedure for Dialkylation

To a stirred solution of amine **3** (0.42 mmol) in 1 mL of toluene was added D-(+)-camphorsulfonic acid (0.17 mmol). After stirring for 1 min, alcohol **2** (1.05 mmol) and [Ru] catalyst (0.0063 mmol) were sequentially added. Then the reaction mixture was evacuated by vacuum-argon cycles 5 times and stirred at 150 °C for 16 h. After evaporation of the solvent, the residue was directly purified by column chromatography (EtOAc/PE) to afford the expected dialkylated amine.

Acknowledgements

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