Amination

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An Efficient and General Synthesis of Primary Amines by Ruthenium-Catalyzed Amination of Secondary Alcohols with Ammonia**

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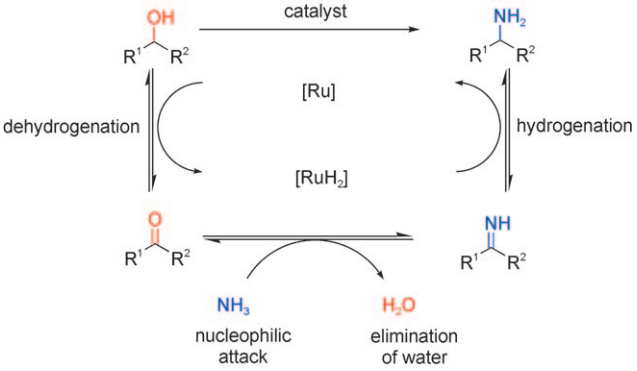
Amines are of significant importance for the bulk- and fine-chemical industry as building blocks for polymers and dyes, but also for the synthesis of new pharmaceuticals and agrochemicals.[1] In addition, a plethora of naturally bioactive compounds such as alkaloids, amino acids, and nucleotides contain amino groups. Primary amines, in particular, are useful intermediates for further derivatization reactions. Despite numerous established procedures such as the reduction of nitro compounds and nitriles, the development of novel methods for the synthesis of primary amines continues to be an active area of research.[2]

For the preparation of aliphatic primary amines probably the most important method, both in industry and in academic laboratories, is the reductive amination of the corresponding carbonyl compounds. In addition, amination of alcohols using ammonia is performed in industry with heterogeneous catalysts on a multithousand-ton scale. The overall transformation is highly atom-efficient, and water is the only side product formed.[3] Unfortunately, because of the limited activity of most heterogeneous catalysts, relatively harsh conditions (> 200 °C) are required, and the chemoselectivity is difficult to control. Owing to these problems, the substrate scope has been limited so far.

The first homogeneously catalyzed aminations of alcohols using primary and secondary amines in the presence of ruthenium complexes were reported by Grigg[4] and Watanabe[5] already in 1981. Since then, a number of applications catalyzed by mainly ruthenium- or iridium-based complexes have been described.[6] Recent elegant examples came from the groups of Williams,[7] Fujita,[8] and Kempe,[9] and from our group.[10] The overall transformation is based on the so-called "borrowing-hydrogen" methodology,[11] also known as "hydrogen autotransfer".[12] In this transformation the alcohol is dehydrogenated in situ to give the corresponding aldehyde or ketone. Subsequent condensation with the amine and final rehydrogenation leads to the desired amines (Scheme 1). Clearly, the hydrogen required for the final hydrogenation step is generated completely by dehydrogenation of the alcohol in the first reaction step. Hence, there is no need for additional hydrogen.

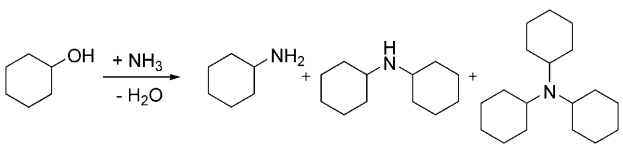


Scheme 1. Proposed mechanism for the ruthenium-catalyzed amination of secondary alcohols using ammonia.

Despite the importance of primary amines, to date the selective amination of alcohols to give primary amines has been described only by Milstein and co-workers.[13] In the presence of a defined ruthenium PNP pincer complex different primary alcohols were converted to primary amines in good to excellent yields. However, no successful aminations of secondary alcohols were described.

Based on our continuing interest in the application of the "borrowing-hydrogen" methodology for alkylation reactions using alcohols[14] and amines[15] as alkylation reagents, we started a program to develop a method for the amination of secondary alcohols using ammonia directly. To our knowledge no such reaction has been described until to date.[16] As the starting point of our investigations we examined the amination of cyclohexanol with ammonia. Obviously, this reaction can result in the formation of the primary, secondary, and tertiary amines (Scheme 2), and the major goal here is the chemoselective synthesis of the primary amine. Because of their higher nucleophilicity, primary amines are generally more reactive than ammonia, and further reaction resulting in the sequential formation of secondary and tertiary amines would be expected.

Previously, we have demonstrated that the combination of $[Ru_3(CO)_{12}]$ and various phosphine ligands generate active



Scheme 2. Possible products of the amination of cyclohexanol.

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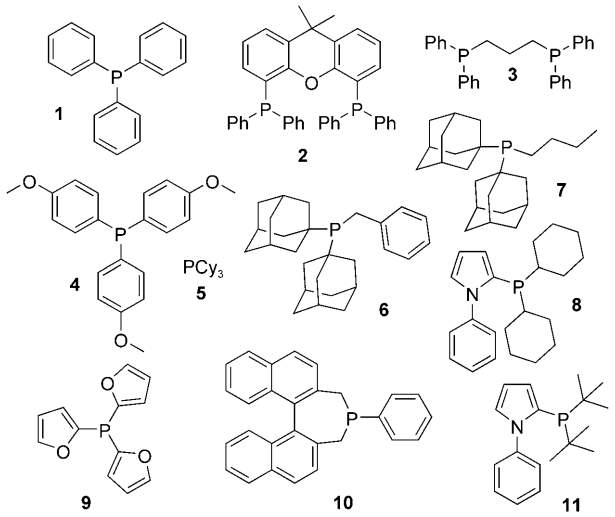
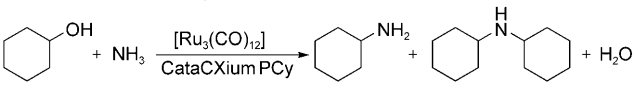
catalysts for the amination of alcohols.[17] Therefore, we tested this catalyst precursor with 23 different ligands[18] in the benchmark reaction. At 130 °C the majority of catalytic systems decomposed and gave unsatisfying results (< 5 % yield of cyclohexylamine). Standard mono- and bidentate arylphosphines such as triphenylphosphine (**1**), Xantphos[19] (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (**2**)), 1,3-bis(diphenylphosphino)propane (**3**), and tris(4-methoxyphenyl)phosphine (**4**) showed no activity (< 5 % yield of cyclohexylamine), while more electron-rich phosphines like tricyclohexylphosphine (**5**), benzyldi-1-adamantylphosphine (**6**), and *n*-butyldi-1-adamantyl-phosphine (**7**) were slightly active in this reaction (10–20 % yield of cyclohexylamine). Of all the ligands tested, CataCXium PCy (2-(dicyclohexylphosphino)-1-phenyl-1*H*-pyrrole (**8**)) showed the highest reactivity and gave cyclohexylamine in 30 % yield.



Applying $[Ru_3(CO)_{12}]$/CataCXium PCy as the most promising catalyst system, we investigated the influence of the critical reaction parameters in more detail. The concentration of ammonia should have a significant influence on the reactivity and chemoselectivity of the reaction.

Of the different solvents tested, diglyme and *tert*-amyl alcohol gave the best results (Table 1, entries 4 and 5). The differences between the yields and the conversions are caused by the formation of the ketone along with the primary and secondary imines. When the the reaction was run in heptane, toluene, and tetrahydrofuran (THF), the selectivity for the formation of the primary amine dropped (Table 1, entries 1–3). For further experiments *tert*-amyl alcohol was chosen because it can be removed easily from the products. Notably, water, which is formed during the reaction, has a negative influence on the conversion (Table 1, entries 5 and 6), which is in agreement with the proposed mechanism. Apparently, a higher concentration of water leads to increased hydrolysis of the imine to yield the ketone, which can also be hydrogenated by the catalyst. Thus, we reduced the amount of water in the reaction solution by suspending molecular sieves above the reaction mixture in a Teflon basket (Table 1, entries 5 and 7).

Table 1: Amination of cyclohexanol with ammonia in different solvents.[a]



Entry	Solvent	m_{NH_3} [g]	Conv.[b] [%]	$Y_{prim.}$[b] [%]	$Y_{sec.}$[b] [%]
1	heptane	0.2	68	36	26
2	toluene	0.2	72	36	20
3	THF	0.2	62	30	24
4	diglyme	0.2	62	49	11
5	*t*-amyl alcohol	0.2	66	46	13
6[c]	*t*-amyl alcohol	0.2	50	35	7
7[d]	*t*-amyl alcohol	0.2	79	44	25
8[e]	*t*-amyl alcohol	0.2	80	48	23
9[e]	*t*-amyl alcohol	0.3	78	52	18
10[e]	*t*-amyl alcohol	0.6	79	55	14
11[e]	*t*-amyl alcohol	1.0	80	66	4
12[d,e]	*t*-amyl alcohol	0.3	93	65	20
13[d,e]	*t*-amyl alcohol	0.6	95	87	5

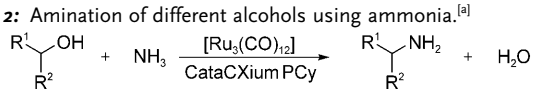
[a] Reaction conditions: 1 mmol cyclohexanol, 0.2 g (6 bar) ammonia at RT, 0.02 mmol $[Ru_3(CO)_{12}]$, 0.06 mmol CataCXium PCy, 140 °C, 20 h. [b] Conversion and yield (based on cyclohexanol) were determined by GC analysis with hexadecane as an internal standard. [c] Addition of 20 μL water. [d] Molecular sieves were suspended above the reaction mixture. [e] 150 °C.

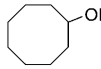
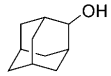
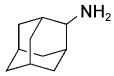
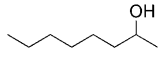
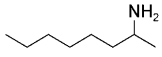
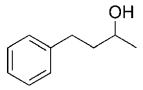
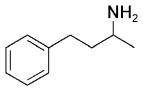
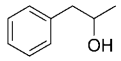
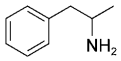
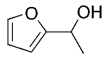
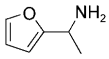
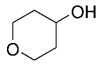
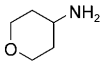
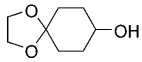
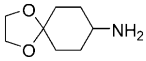
Indeed, the conversion increased to 79 %; however, a significant amount of dicyclohexylamine was still obtained. The conversion was also increased at higher temperature (150 °C), but again the amount of dicyclohexylamine increased as well (Table 1, entries 5 and 8). To reduce the formation of this secondary amine, we increased the amount of ammonia. Without molecular sieves present slightly higher yields of the primary amine were observed (Table 1, entries 8–11). However, in the presence of molecular sieves a conversion of 95 % was achieved and the yield of cyclohexylamine increased to 87 % (Table 1, entry 13)! Interestingly, the amount of ammonia does not influence the conversion of the alcohol.

To demonstrate the general applicability of the $[Ru_3(CO)_{12}]$/CataCXium PCy system for this reaction and the scope of the process, we tested various secondary alcohols. In general, catalytic experiments were conducted in the presence of 2 mol % $[Ru_3(CO)_{12}]$ and 6 mol % CataCXium PCy with 1 mmol alcohol in 1 mL *t*-amyl alcohol along with molecular sieves at 150 °C. As shown in Table 2 various secondary alcohols reacted with ammonia to give the desired products in good to excellent yields.

In most cases the use of 0.6 g ammonia resulted in the formation of significant amounts of the ketone. Hence, the amount of ammonia was increased to 1 g (Table 2, entries 3 and 6–11) to enhance the nucleophilic attack of ammonia to the ketone (Scheme 2). We assume that in those cases this is the bottleneck of the reaction. Excellent yields > 90 % were observed with 1-dimethylamino-2-propanol (Table 2, entry 11), 2-adamantanol, and 1,4-dioxaspiro[4.5]decan-8-ol (Table 2, entries 5 and 13). In the case of sterically hindered 2-adamantanol the reaction had to be conducted at higher temperature (Table 2, entries 4 and 5). It should be noted that even at high temperature the selectivity towards the formation of the primary amine was very high and the catalytic

Table 2: Amination of different alcohols using ammonia.[a]

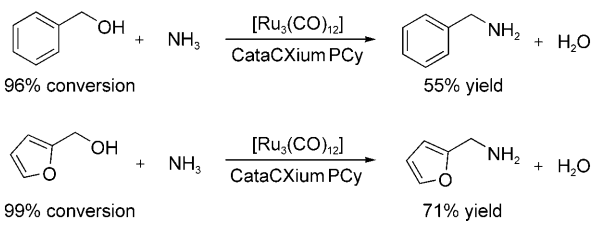


Entry	Alcohol	Product	Conv.[b] [%]	Yield[b] [%]
1[c]			100	69
2[c]			95	87
3			100	82
4[c]			46	45
5[c,e]			94	91 (86)
6			94	76
7			82	58
8			85	76
9			95	62
10			99	82
11			94	93
12[c,d]			87	77
13[c,d]			95	92

[a] Reaction conditions: 1 mmol alcohol, 1 g ammonia, 0.02 mmol $[Ru_3(CO)_{12}]$, 0.06 mmol CataCXium PCy relative to the alcohol, 150 °C, 20 h. [b] Conversion and yield (based on the alcohol) were determined by GC analysis with hexadecane as the internal standard. Yields of isolated products in brackets. [c] 0.6 g NH_3. [d] 160 °C. [e] 170 °C.

system was still active without any decomposition; this underlines the high thermal stability of the catalyst. Cyclic as well as acyclic secondary alcohols were converted into the corresponding primary amines in good to excellent yields. Notably, 1-phenyl-2-propanol gave 1-phenyl-2-propylamine, which is currently applied as a drug for treatment of attention-deficit hyperactivity disorders.[20]

Finally, some primary benzylic alcohols were also tested as substrates without further optimization. As shown in Scheme 3, both benzyl alcohol and furfuryl alcohol gave the



Scheme 3. Amination of primary alcohols using ammonia (for reaction conditions see Table 2, footnote [a]).

corresponding primary amines as the main product in moderate to good yields.

In summary, we have developed the first homogeneously catalyzed amination of secondary alcohols with ammonia to give primary amines. This novel atom-efficient and selective amination method proceeds in the presence of commercially available $[Ru_3(CO)_{12}]$/CataCXium PCy catalysts in an ammonia atmosphere without additional hydrogen sources. A variety of secondary alcohols, including also primary benzylic alcohols, were efficiently converted in good to excellent yields. We are convinced that this procedure is and will be of value for the synthesis of a variety of interesting amine building blocks.

Experimental Section

General procedure for preparation of 2-adamantylamine: In a steel pressure tube (50 mL) under an argon atmosphere $[Ru_3(CO)_{12}]$ (12.8 mg, 0.02 mmol), CataCXium PCy (20.4 mg, 0.06 mmol) and 2-adamantanol (152 mg, 1 mmol) were dissolved in *tert*-amyl alcohol (1 mL). Next, the pressure tube was closed and cooled in dry ice in order to introduce ammonia (1 g) by condensation. After the reaction mixture had been stirred at 170 °C in an oil bath under reflux conditions for 20 h, the solvent was removed under vacuum. The residue was dissolved in methanol and the solution was applied on an Isolute SCX-2 column (2 g/15 mL, Biotage). The amine was retained by the SPE column and the alcohol passed through. Afterwards the column was washed with methanol and the product was eluted stepwise with a methanolic ammonia solution (7 N). Methanol was removed under vacuum to give 2-adamantylamine as a pale yellow solid (130 mg, 86 %).

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[16] During the preparation of this manuscript we have been informed by Prof. Dr. Dieter Vogt, University of Eindhoven, that he and his co-workers have developed a similar system parallel to our investigations (D. Pingen, C. Müller, D. Vogt, *Angew. Chem.* **2010**, *122*, 8307 – 8310; *Angew. Chem. Int. Ed.* **2010**, *49*, 8130 – 8133). We thank Prof. Vogt for this information and valuable comments on this subject.

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