Amination

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Direct Amination of Secondary Alcohols Using Ammonia**

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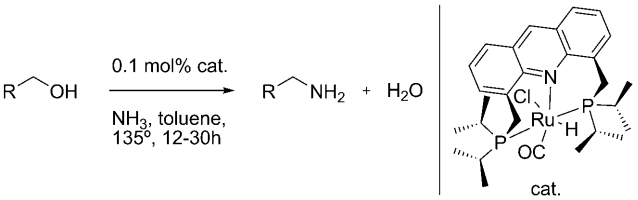
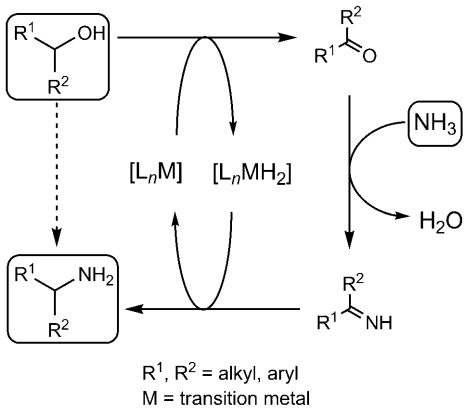
The use of bio-based feedstocks as renewable resources allows for "greener" and more (atom)efficient processes. However, these bio-based feedstocks are typically highly functionalized compounds bearing hydroxy groups, and for many applications amine functional groups are required. Current procedures for the conversion of alcohols into amines produce much waste because of the protection and deprotection steps.[1–3] To make the conversion of alcohols into amines industrially viable, the (atom)efficiency of the transformation needs to be improved, such that there is less waste, it is cheap, and readily available amine sources like ammonia can be used. The direct catalytic amination of alcohols by ammonia (Scheme 1) fulfils these requirements. In this reaction the amine is produced with water as the only by-product. We refer to this process as "hydrogen shuttling", because of the net transfer of hydrogen from the alcohol to the amine.

To date, only one example of a homogeneous catalyst is known to catalyze the direct amination of primary alcohols, and this was reported by Gunanathan and Milstein.[4] Several primary alcohols were aminated using a Ru/PNP pincer complex to give conversions of up to 100% and selectivity of up to 87% for benzylalcohol (Scheme 2). The main by-product is the secondary imine. However, it is important to note that only primary alcohols and water-insoluble alcohols were efficiently aminated with this catalytic system.



Scheme 2. Ru/PNP pincer complex for primary alcohol amination reported by Gunanathan and Milstein.[4]



Scheme 1. Direct amination of secondary alcohols with ammonia.

Using the Ru/PNP complex for secondary alcohols under identical reaction conditions yielded neither the amine nor the corresponding ketone. Furthermore, for primary alcohols considerable amounts of by-products such as secondary amines and imines were formed at higher conversions.

Closely related to the direct amination of alcohols with NH_3 is the alkylation of amines with alcohols. Examples from the early 80's are known in which amines were alkylated using alcohols under relatively harsh conditions.[5] Recently, Beller and co-workers reported that $[Ru_3(CO)_{12}]$ in combination with bulky phosphorus-based σ-donor ligands give high conversions and selectivity for secondary or tertiary amines; they reported up to 100% conversion and 99% selectivity under mild conditions.[6] With these systems, amines could be alkylated by primary alcohols, even if the alcohol bears a second, secondary alcohol.[7]

Another elegant method was published by Williams and co-workers for the alkylation of amines with alcohols in the presence of ruthenium arene complexes.[8] Amines were alkylated with various alcohols to give secondary and tertiary amines with high conversions and yields. Also examples using iridium-based catalysts in the presence of a base have been reported by the groups of Williams,[9] Kempe,[10] Fujita,[11] and Yamaguchi.[12] One example of an iridium-catalyzed amine alkylation has been reported wherein no additives are required, and it proceeds in water.[13] Williams and co-workers refer to this process as the "borrowing hydrogen methodology".[14] So far, no catalytic systems that are able to aminate secondary alcohols with NH_3 to solely form primary amines have been described.[15]

Herein we report the first examples of a homogeneous ruthenium-catalyzed direct amination of secondary alcohols

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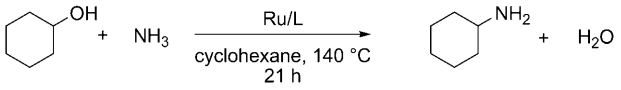
with NH_3 to obtain primary amines with high selectivity, and forming water as the only by-product (Scheme 3).



Scheme 3. Ruthenium-catalyzed direct amination of cyclohexanol with ammonia.

In searching for an efficient catalyst for the conversion of secondary alcohols using NH_3 we chose cyclohexanol as a model substrate. Starting from the systems reported by Milstein[4] and Beller,[6] a number of ruthenium complexes were tested as catalyst precursors in combination with phosphorus ligands. The best results were obtained with the combination of $[Ru_3(CO)_{12}]$ and simple phosphine ligands (Figure 1 and Table 1); cyclohexylamine was delivered with high selectivity (over 75%), even at high conversion (up to 90%). The best results were obtained when using cyclohexane as the solvent at a reaction temperature of 140°C in a stainless-steel autoclave. The ligands were systematically varied to study and optimize the reaction. The catalysts derived from bulky triarylphosphines **1** and **2** showed very poor activities, although promising selectivities towards cyclohexylamine were already observed for Ru/**1**. Notably, **1** gave good results in the ruthenium-catalyzed amine alkylation with primary alcohols as reported by Beller.[6] Next, the bulky σ-donating PCy_3 (**3**) was used, and showed complete selectivity in combination with Ru towards the primary amine, although with low activity. Consequently, one of the cyclohexyl groups in **3** was replaced by a phenyl group, giving rise to ligand **4** and the Buchwald ligand **5**, and the corresponding catalysts showed increased activity and good selectivity towards the primary amine. The catalyst derived from the pyrrole phosphine **6**, successfully used by Beller for the alkylation of amines with primary alcohols,[6] gave the best results in terms of activity and selectivity. The results obtained with catalysts derived from the N-alkyl derivative **8** and the pyridine phosphine **9** demonstrated some activity, but good selectivity.

Table 1: Conversions and selectivity in the direct amination of cyclohexanol using different ligands.

Ligand	Conv. [%][a]	Total amine selectivity [%][b]	Primary amine selectivity [%][c]
1	8.4	32.1	51.9
2	1.9	0	0
3	10.6	43.9	100
4	39.1	96.7	52.4
5	36.2	95.6	77.5
6	90.3	97.9	74.0
7	75.6	98.6	84.3
8	45.6	92.2	73.3
9	29.1	87.5	68.2

Reaction conditions: cyclohexanol (10 mmol), $[Ru_3(CO)_{12}]$ (0.1 mmol), ligand (0.6 mmol), cyclohexane (6 mL), NH_3 (l) (6 mL), 140°C, 21 h ($[Ru_3(CO)_{12}]$/L/substrate = 1:6:100). [a] Conversions were determined by GC analysis and based on the alcohol consumption and amine production [b] Σ(primary + secondary amine + secondary imine), the remainder is the intermediate ketone. [c] Percentage of the primary amine present within the total amount of amine products.

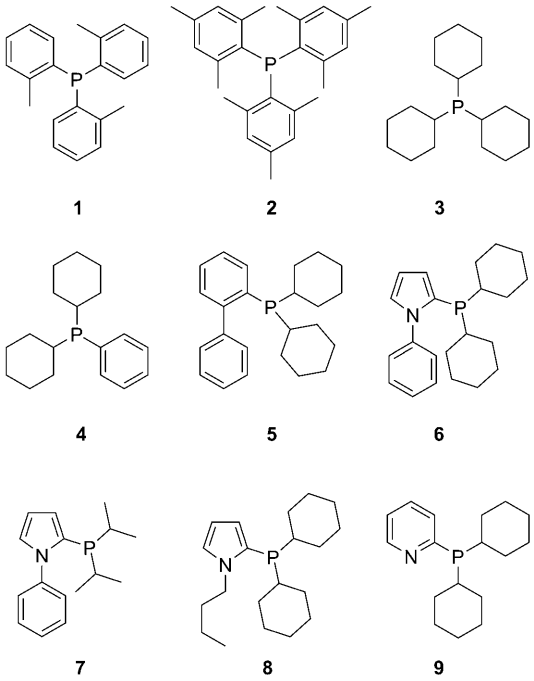


Figure 1. Ligands used in the direct amination of secondary alcohols with ammonia.

On the basis of the results achieved with the catalyst system Ru/**6**, the scope of the reaction was investigated by subjecting a range of secondary alcohols to amination reactions with ammonia. Table 2 shows that the conversions are satisfying for all substrates. Conversions are slightly lower for acyclic substrates (Table 2, entries 4–8). Aryl-substituted and also unsaturated alcohols are converted equally well (Table 2, entries 10–11). The primary amine selectivity is good to excellent for all substrates and for menthol complete selectivity is observed (Table 2, entry 12). These examples demonstrate the potential of this new transformation.

In all cases, the corresponding secondary imine was formed as the major by-product. For acyclic alcohols, more intermediate ketone was observed. In general, as a result of the higher nucleophilicity of the primary amine product, compared to that of NH_3, the secondary imine is formed. Only very little of the secondary amine (typically below 2%) was observed.

Remarkably, upon using longer reaction times the amount of secondary imines decreased in favor of the primary amine selectivity. Apparently, under the given reaction conditions, the formation of the secondary imine seems to be reversible. This effect was investigated by analyzing the reaction mixture during the course of the catalytic reaction (Figure 2). It was found that the selectivity towards the primary amines increases over time for all secondary alcohol substrates tested (Figure 3). In this process, the secondary imine can

Table 2: Different substrates used in the direct amination of secondary alcohols.

Entry	Substrate	Conv. [%][a]	Total amine selectivity [%][b]	Primary amine selectivity [%][c]
1	cyclohexanol	90.3	97.9	74.0
2	cyclopentanol	94.0	100	63.9
3	cyclooctanol	81.2	94.6	73.2
4	2-hexanol	83.7	56.2	54.5
5	2-heptanol	68.7	85.6	54.1
6	2-octanol	61.8	77.7	67.1
7	2-nonanol	94.9	53.2	51.2
8	3-hexanol	78.3	100	83.8
9	1-phenyl-ethanol	53.3	67.5	80.0
10	2-cyclohexen-1-ol	83.2	100	64.5
11	*trans*-3-penten-2-ol	60.4	95.6	77.5
12	*rac*-menthol	32.0	34.8	100

Reaction conditions: substrate (10 mmol), $[Ru_3(CO)_{12}]$ (0.1 mmol), ligand **6** (0.6 mmol), cyclohexane (6 mL), NH_3 (l) (6 mL), 140 °C, 21 h, ($[Ru_3(CO)_{12}]$/**6**/substrate = 1:6:100). [a] Conversions were determined by GC analysis, and based on the alcohol consumption and amine production [b] Σ(primary + secondary amine + secondary imine), the remainder is the intermediate ketone. [c] Percentage of the primary amine present within the total amount of the amine products.

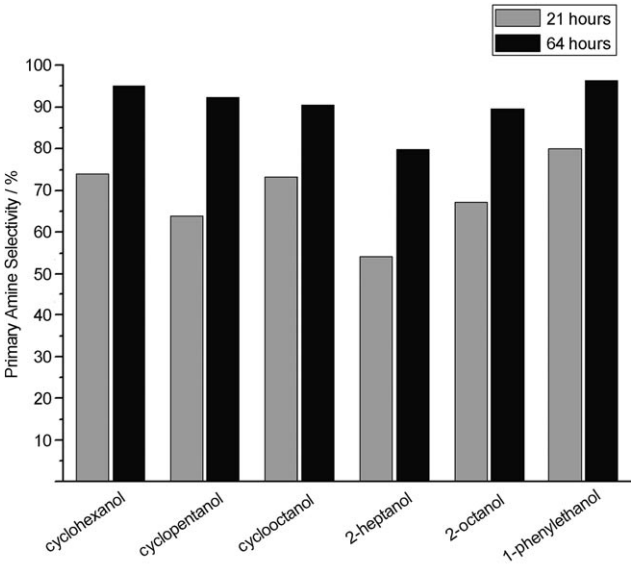


Figure 3. Primary amine selectivity for different substrates after 21 and 64 h. For cyclohexanol the selectivities are given after 21 and 92 h. Reaction conditions: substrate (10 mmol), $[Ru_3(CO)_{12}]$ (0.1 mmol), ligand **6** (0.6 mmol), cyclohexane (6 mL), NH_3(l) (6 mL), 140 °C, ($[Ru_3(CO)_{12}]$/**6**/substrate 1:6:100).

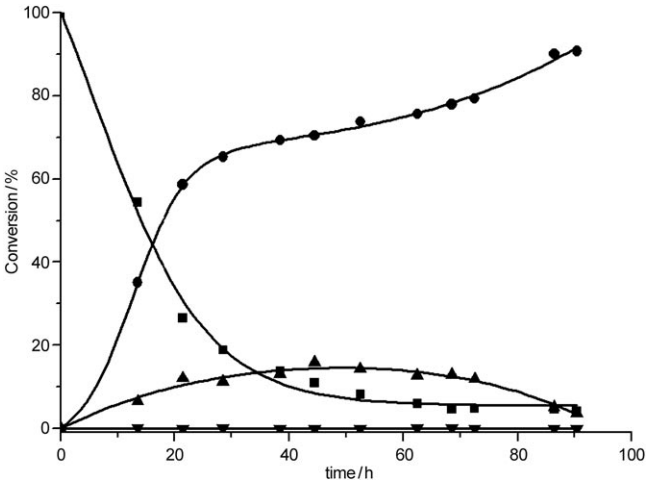
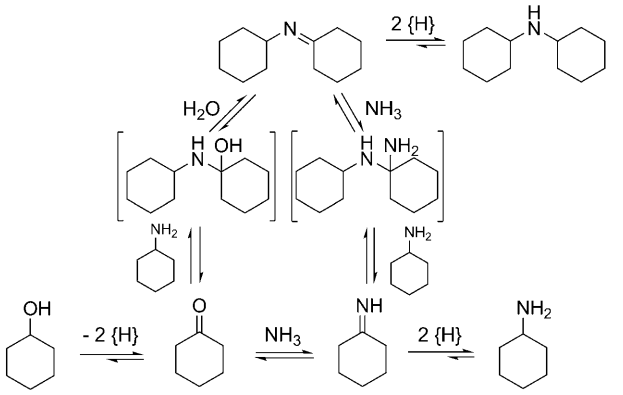


Figure 2. Production distribution over time (for reaction conditions see Table 2). ■: cyclohexanol, ●: cyclohexylamine, ▲: dicyclohexylimine, ▼: cyclohexanone.



Scheme 4. Most important equilibria for the reversibility in the direct amination of secondary alcohols. The structures within the brackets are non-observable intermediates.

be considered a reaction intermediate from which the primary amine can be formed.

To gain a better understanding of this phenomenon, a closer look was taken on the reaction intermediates and products. A number of equilibria will be involved in the total reaction scheme, thus involving the alcohol, the corresponding ketone, ammonia, the primary amine product, corresponding imines, hemiaminals, and aminals, as well as water. Only a few of those compounds were observed in the reaction mixture as determined by GC analysis. More compounds were probably not observed because of the limited stability of some of the intermediates. The most important equilibria for cyclohexanol are shown in Scheme 4.

The secondary imine can be reconverted into the ketone or the imine by reaction with either water or ammonia, respectively. Furthermore, the rates of dehydrogenation and hydrogenation directly influence these equilibria, as cyclohexanone and cyclohexylamine both participate in the equilibria leading to the secondary imine, for which the hydrogenation is apparently very slow. As Figure 3 suggests, other substrates are likely to undergo these equilibria since they exhibit similar selectivity patterns. Additional investigations are required for a complete understanding of the reaction, as well as studies on the mechanism of the ruthenium-catalyzed reaction.

In conclusion, we show for the first time an atom-efficient and very selective catalytic route for the direct synthesis of primary amines from secondary alcohols and ammonia

without the need for protecting groups. The scope of the reaction includes cyclic and acyclic aliphatic substrates, as well as unsaturated and aryl-substituted alcohols. This reaction may open up new pathways to the conversion of bio-based feedstocks into intermediates and fine chemicals. Mechanistic studies concerning the structure and properties of the catalyst are underway. Furthermore, detailed investigations into the equilibria involved in this reaction are in progress.

Experimental Section

General procedure for the direct amination of secondary alcohols: $[Ru_3(CO)_{12}]$ (0.1 mmol), ligand (0.6 mmol), cyclohexane (6 mL), and secondary alcohol (10 mmol) were consecutively added to an Ar-purged Schlenk tube. The reaction mixture was then transferred to an Ar-purged 75 mL stainless-steel autoclave. The autoclave was charged with liquid ammonia (6 mL) by means of a mass flow controller (MFC) for liquid NH_3 (Liquiflow) and heated to 140 °C for the appropriate time.

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[15] During the preparation of this manuscript we were informed by Prof. Dr. Matthias Beller, Leibniz-Institut für Katalyse an der Universität Rostock, that he and his co-workers developed a similar procedure parallel to our research (S. Imm, S. Bähn, L. Neubert, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 8303 – 8306; *Angew. Chem. Int. Ed.* **2010**, *49*, 8126 – 8129). We gratefully thank Prof. Beller for this information and the valuable comments on this subject.

