

# Selective Synthesis of Primary Amines Directly from Alcohols and Ammonia\*\*

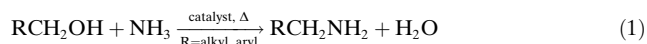
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Amines are a very important family of compounds in chemistry and biology. They are widely used in the production of pharmaceuticals, fine chemicals, agrochemicals, polymers, dyestuffs, pigments, emulsifiers, and plasticizing agents.<sup>[1]</sup> Among the amines, the terminal primary amines are the most useful, but their selective synthesis is challenging, due to their high reactivity.

Existing methods for the preparation of primary amines generally utilize stoichiometric amounts of toxic reagents and lead to poor selectivity and low atom-economy.<sup>[2–4]</sup> The conversion of alcohols to amines by conventional methods typically involves two or three steps, each step generally requiring isolation and purification, making it cumbersome for even small-scale syntheses.<sup>[5]</sup> Few classical methods are known for the stepwise, one-pot conversion of alcohols into primary amines.<sup>[6–9]</sup> An attractive method for the preparation of secondary and tertiary linear amines by hydroaminomethylation of internal olefins was reported.<sup>[10]</sup> Amines are also prepared by the reduction of amides, generally under harsh conditions to result in a mixture of products.<sup>[11]</sup> Iridium- and rhodium-catalyzed preparation of amines from the corresponding aldehydes under hydrogen pressure was also reported,<sup>[12]</sup> demonstrating homogeneous catalytic reductive amination with ammonia. Lewis acid catalyzed reductive amination methods for the synthesis of amines are also known.<sup>[13,14]</sup> Recently, synthesis of arylamines was achieved by palladium-catalyzed arylation of ammonia in dioxane.<sup>[15]</sup> Primary amines can be alkylated by alcohols to obtain secondary amines.<sup>[16]</sup> Iridium-catalyzed multialkylation of ammonium salts with alcohols was reported for the synthesis of secondary and tertiary amines, but selective synthesis of primary amines remains as a tantalizing task.<sup>[17]</sup>

Among the methods for commercial production of amines,<sup>[1,18]</sup> by far the largest and most utilized are based on the reaction of alcohols with ammonia. However, the heterogeneous processes suffer from the requirement of very high temperatures and pressures and lead to mixtures of

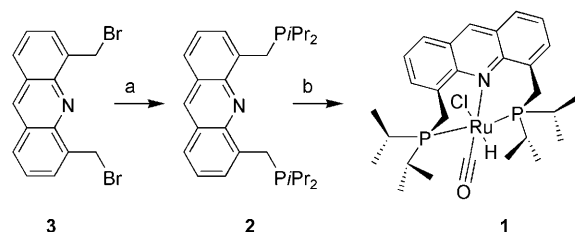
amines, as well as alkene and alkane side products.<sup>[18]</sup> Thus, selective, catalytic synthesis of primary amines directly from alcohols and ammonia with elimination of water [Eq. (1)], under relatively mild conditions, without producing waste is highly desirable economically and environmentally.



Atom-economical methods to activate alcohols (replacing the Mitsunobu protocol) for the direct nucleophilic substitution and “N centered” chemistry that precludes azides and hydrazine are among the most required processes in pharmaceutical industries.<sup>[19]</sup> Selective catalytic synthesis of primary amines is a challenge, as the primary amines are more nucleophilic than ammonia and compete with it in reaction with electrophiles such as alkyl halides or aldehydes, producing secondary amines, which can also react, leading to the formation of mixtures of products.

We have recently reported the catalytic alcohol dehydrogenative coupling to form esters,<sup>[20]</sup> hydrogenation of esters to alcohols,<sup>[21]</sup> and the unprecedented reaction of alcohols with amines to form amides with liberation of H<sub>2</sub>.<sup>[22]</sup> These reactions are catalyzed by dearomatized PNP [2,6-bis(di-*tert*-butylphosphinomethyl)pyridine] and PNN [2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine] pincer-type Ru<sup>II</sup> complexes, and involve reversible deprotonation of a pyridinyl methylene group as a key catalytic step. We have now discovered that a novel pincer complex, which lacks this pyridinyl group, is capable of efficiently catalyzing the very desirable reaction of ammonia with alcohols to selectively form primary amines and water. The reaction can proceed under mild pressure and temperature, and can be carried out under solventless conditions and on/in water.

The novel, acridine-based pincer complex [RuHCl(A-*i*Pr-PNP)(CO)] (**1**) was quantitatively prepared by reaction of the new electron-rich tridentate PNP ligand **2**<sup>[23]</sup> with [RuHCl(PPh<sub>3</sub>)<sub>3</sub>(CO)] in toluene at 65 °C for 2 h (Scheme 1). Con-



**Scheme 1.** Synthesis of ligand **2** and complex **1**: a) 1. diisopropylphosphine/MeOH, 50 °C, 48 h; 2. triethylamine, RT, 1 h, 83 %. b) [RuHCl-(PPh<sub>3</sub>)<sub>3</sub>(CO)]/toluene, 65 °C, 2 h, quantitative or [RuHCl(PPh<sub>3</sub>)<sub>3</sub>(CO)]/THF, RT, 9 h, 82 %.

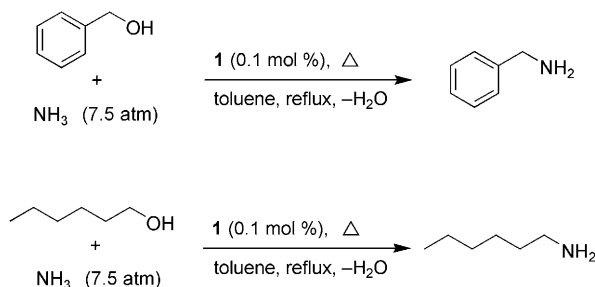
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venient to practical applications, complex **1** is stable in air for several months.

To explore the catalytic activity of complex **1**, primary alcohols were treated with ammonia in the presence of **1** (0.1 mol %). After extensive investigations (see Tables S1 and S2 in the Supporting Information), it was found that reaction in toluene heated at reflux resulted in selective synthesis of primary amines directly from primary alcohols (Scheme 2). In



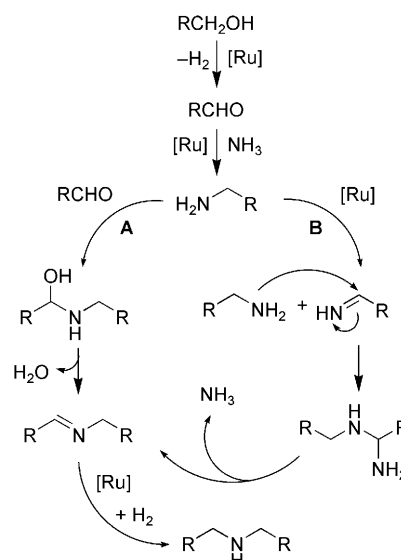
**Scheme 2.** Direct synthesis of primary amines from primary alcohols and ammonia catalyzed by the ruthenium complex **1**.

a reaction between benzyl alcohol and ammonia (7.5 atm), upon 13 h reflux, 99% conversion of benzyl alcohol occurred to provide benzylamine in 87% yield (75% yield of isolated product) and *N*-benzylidenebenzylamine (12%). Similar reaction of 1-hexanol for 15 h (87.5% conversion) provided 1-hexylamine in 63% yield and dihexylamine (3%).

When the reaction of 1-hexanol was prolonged to 24 h (see Table S2) the yield of dihexylamine increased to 18% while the 1-hexylamine yield decreased to 58% (Table S2, entry 4), raising the possibility that complex **1** catalyzes the self-coupling of primary amines to secondary amines. Exploring this possibility, an independent experiment with no ammonia and water was carried out. Indeed, heating a neat solution of complex **1** (0.1 mol %) in 1-hexylamine (b.p. 131.5 °C) at reflux in a closed system for 18 h resulted in self-coupling to give dihexylamine in 86.5% yield.<sup>[24]</sup>

Thus, in the presence of ammonia, formation of secondary amines could occur in two pathways (Scheme 3): A) reaction of the product primary amine (in competition with ammonia) with the in situ generated aldehyde to form a hemiaminal and subsequent water elimination to give the imine, which undergoes hydrogenation (Scheme 3, route A), or B) dehydrogenation of the initially formed primary amine and subsequent nucleophilic attack of another molecule of the primary amine on the formed imine and elimination of ammonia (Scheme 3, route B).

The scope of the direct amination of alcohols with ammonia catalyzed by complex **1** (0.1 mol %) in refluxing toluene was studied with respect to the alcohol (Table 1). Aryl methanols underwent facile reaction to provide benzylamines in good yields. Benzyl alcohols with electron donating groups on the benzene ring reacted faster (Table 1, entries 1, 2) than benzyl alcohols with an electron withdrawing group (Table 1, entry 3). The heteroaryl methanols exhibited excellent selectivity for primary amines. Pyridine-2-yl-methanol and 2-furylmethanol were converted to the corresponding primary



**Scheme 3.** Two possible pathways for the formation of secondary amines.

**Table 1:** Direct synthesis of amines from alcohols and ammonia catalyzed by the ruthenium complex **1**.<sup>[a]</sup>

| $\text{RCH}_2\text{OH} + \text{NH}_3 \xrightarrow[\text{Toluene, Reflux, } -\text{H}_2\text{O}]{\text{1 (0.1 mol \%), } \Delta} \text{RCH}_2\text{NH}_2 + \text{RCH}=\text{NCH}_2\text{R}$ |                     |       |       |                                  |                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-------|-------|----------------------------------|--------------------------|
| Entry                                                                                                                                                                                      | RCH <sub>2</sub> OH | t [h] | Conv. | RCH <sub>2</sub> NH <sub>2</sub> | Yield [%] <sup>[c]</sup> |
| 1                                                                                                                                                                                          |                     | 12    | 100   |                                  | 83 (70)                  |
| 2                                                                                                                                                                                          |                     | 14    | 100   |                                  | 78                       |
| 3                                                                                                                                                                                          |                     | 24    | 100   |                                  | 91                       |
| 4                                                                                                                                                                                          |                     | 30    | 100   |                                  | 96                       |
| 5                                                                                                                                                                                          |                     | 12    | 100   |                                  | 94.8                     |
| 6 <sup>[b]</sup>                                                                                                                                                                           |                     | 20    | 97    |                                  | 61 [34.6] <sup>[d]</sup> |
| 7                                                                                                                                                                                          |                     | 32    | 100   |                                  | 68.8                     |
| 8                                                                                                                                                                                          |                     | 12    | 100   |                                  | 94.5                     |
| 9 <sup>[b]</sup>                                                                                                                                                                           |                     | 18    | 93    |                                  | 67.7 (61)                |
| 10                                                                                                                                                                                         |                     | 25    | 95.5  |                                  | 82 (73)                  |
| 11                                                                                                                                                                                         |                     | 25    | 96.4  |                                  | 90 (84)                  |

[a] Complex **1** (0.01 mmol), alcohol (10 mmol), ammonia (7.5 atm), and toluene (3 mL) were heated in a Fischer–Porter reactor.<sup>[23]</sup> Conversion of alcohols and yield of products were analyzed by GC. Yield in parenthesis represents the yield of isolated product. [b] Neat reaction. Yield of isolated product is an average of two experiments. [c] The corresponding imine is the major byproduct in all reactions (analyzed by GC-MS and MS(ESI)); its yield was not determined. [d] Yield of dipentylamine.

amines in 96 and 94.8% yields, respectively (Table 1, entries 4, 5). As with 1-hexanol, 1-pentanol also reacted to result in the formation of 1-pentylamine (61%) and dipentyl-

amine (34.6%; Table 1, entry 6). 2-Phenylethanol reacted similarly but the formation of secondary amines was less favored (Table 1, entry 7). 2-methoxyethanol exhibited very good selectivity for the primary amine, providing 2-methoxyethylamine in 94.5% yield (Table 1, entry 8). Although the selectivity for linear aliphatic primary amines is still to be improved, excellent selectivity was attained for the synthesis of aryl and heteroaryl methylamines. Increasing the steric hindrance at the  $\beta$ -position of alkyl alcohols diminished the formation of imines and the corresponding secondary amines and hence increased the selectivity and yields of primary amines (Table 1, entries 9–11). It is noteworthy that the strained four-membered ring in the oxetane alcohol (Table 1, entry 11) remained intact, resulting in high yield of the primary amine. The reaction took place effectively also in neat alcohols, requiring no added solvent (Table 1, entries 6, 9).

Since the generation of a stoichiometric amount of water in the reaction did not adversely affect the catalysis by complex **1**, we explored the possibility of using water as a reaction medium. Interestingly, the direct amination of alcohols with ammonia by complex **1** proceeded “on water” very well with excellent selectivity for primary amines. While water is the natural, “greenest” possible solvent, its current applications in catalysis are limited.<sup>[25]</sup> The presence of water in large excess was advantageous since it may have led to the hydrolysis of imines formed from further reactions of the primary amines, and thus enhanced the selectivity towards primary amines (Table 2, entries 1–3). The benzyl alcohols and phenethyl alcohol, which are insoluble in water at room temperature, formed a homogeneous solution on heating and thus the reaction might be considered “in water”. Aliphatic

alcohols such as 1-hexanol were not miscible with water even on heating and the reaction took place “on water” (Table 2, entry 4).<sup>[26]</sup> Surprisingly, when water-soluble alcohols (pyridin-2-yl-methanol and 2-methoxyethanol) were subjected to direct amination reaction “in water”, the reaction became very sluggish even after prolonged heating (30 h) and the conversions were minimal,<sup>[27]</sup> in sharp contrast to excellent reactions in toluene (Table 2, entries 4 and 8).

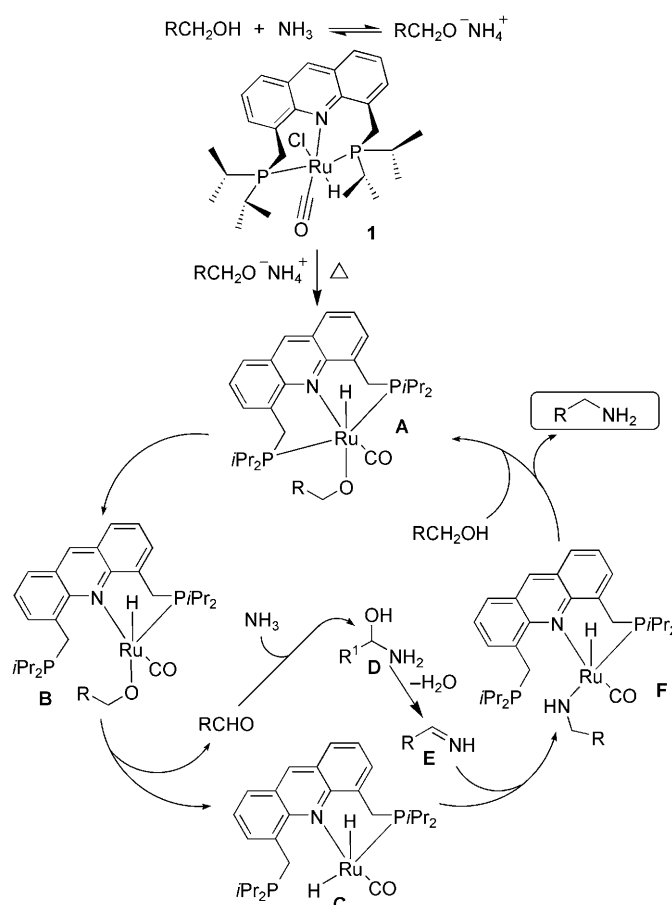
Although reactions in water alone do not improve the selectivity to the linear aliphatic primary amines, they have several practical advantages as the aqueous and organic layers separate at the end of the reaction upon cooling, and further purification of products could be carried out by vacuum distillation. The selectivity for the linear primary amines is improved by the use of co-solvents such as toluene or dioxane in water (Table 2, entries 5–7).

Although insufficient data exist at present to describe a detailed mechanism, a possible mechanism for the direct amination of alcohols with ammonia by complex **1** could involve intermediate aldehydes as delineated in Scheme 4. The aldehyde can react with ammonia to generate a hemiaminal intermediate **D**. Upon water elimination, the hemiaminal forms a terminal imine **E** which is reduced to a primary amine by the ruthenium dihydride intermediate **C** (transfer hydrogenations or “borrowing hydrogen”).<sup>[28]</sup>

**Table 2:** Direct synthesis of amines from alcohols and ammonia catalyzed by the ruthenium complex **1** in and on water.<sup>[a]</sup>

| $\text{RCH}_2\text{OH} + \text{NH}_3 \xrightarrow[\text{Water, 135 } ^\circ\text{C}]{\text{1 (0.1 mol \%), } \Delta} \text{RCH}_2\text{NH}_2 + \text{RCH=NCH}_2\text{R}$ |                                                                                     |       |       |                                                                                     |                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------|-------|-------------------------------------------------------------------------------------|--------------------------|
| Entry                                                                                                                                                                    | RCH <sub>2</sub> OH                                                                 | t [h] | Conv. | RCH <sub>2</sub> NH <sub>2</sub>                                                    | Yield [%] <sup>[b]</sup> |
| 1                                                                                                                                                                        |  | 18    | 100   |  | 95.4 (86)                |
| 2                                                                                                                                                                        |  | 18    | 100   |  | 91.7                     |
| 3                                                                                                                                                                        |  | 36    | 100   |  | 80.4 <sup>[c]</sup>      |
| 4                                                                                                                                                                        |  | 24    | 92.4  |  | 54.8 <sup>[d]</sup>      |
| 5 <sup>[e]</sup>                                                                                                                                                         |  | 28    | 89.4  |  | 74.3                     |
| 6 <sup>[f]</sup>                                                                                                                                                         |  | 30    | 99    |  | 79.7                     |
| 7 <sup>[f]</sup>                                                                                                                                                         |  | 30    | 98.7  |  | 70.0                     |

[a] Complex **1** (0.01 mmol), alcohol (10 mmol), ammonia (7.5 atm), and water (3 mL) were heated at reflux in a Fischer–Porter reactor.<sup>[23]</sup> Conversion of alcohols and yield of products were analyzed by GC; yield of isolated product in parenthesis. [b] Corresponding imine was the major byproduct in entries 1–3; corresponding acid was the byproduct in entries 5–7. [c] Corresponding acids were found in aqueous layer. [d] Hexamide was found in aqueous layer. [e] Mixture of 2 mL water and 2 mL toluene was used as solvent. [f] Mixture of 1 mL water and 2 mL dioxane was used as solvent.



**Scheme 4.** Proposed mechanism for the direct amination of alcohols with ammonia catalyzed by complex **1**.

In conclusion, we demonstrated the selective synthesis of primary amines directly from alcohols and ammonia under mild conditions, precluding the need for stoichiometric amounts of toxic reagents, high pressure, and harsh experimental conditions. The reaction is homogeneously catalyzed by a novel, air stable ruthenium pincer complex **1**, and can proceed in toluene or even in the absence of solvent or “on water”. The simplicity, generality, and excellent atom-economy of this process make it attractive for the transformations of alcohols to amines both in small and large scale applications. In addition to the selective synthesis of commercially important primary amines, this development also paves the way to install the amine function directly from alcohols in the synthesis of complex natural products and drugs without generating waste. Detailed synthetic and mechanistic studies exploring the catalytic potential of complex **1** and related complexes are underway.

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