Direct Synthesis of Secondary Amines From Alcohols and Ammonia Catalyzed by a Ruthenium Pincer Complex

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Abstract Efficient and selective direct synthesis of secondary amines from primary alcohols and ammonia with liberation of water has been achieved, with high turnover numbers and with no generation of waste. In case of benzylic alcohols, imines rather than amines are obtained. This atom economical, environmentally benign reaction is homogeneously catalyzed by a well-defined bipyridine based Ru(II)-PNN pincer complex.

Keywords Alcohol · Secondary amine · Ammonia · Ru-pincer complex · Homogenous catalysis

1 Introduction

Amines and their derivatives are a very important class of compounds in chemistry and biology. They are highly versatile building blocks for various organic synthetic targets and are used as dyes, color pigments, electrolytes, agricultural chemicals, herbicides, polymers, and functionalized materials [1]. In addition, they are essential pharmacophores in numerous biologically active compounds, and amine groups are present in vitamins,

hormones, alkaloids, neurotransmitters, or natural toxics [2, 3]. Owing to their extensive applications, the development of versatile and efficient methods for the synthesis of secondary amines has attracted much interest in the area of catalysis. Because of the abundance and low price of ammonia, much attention has been focused on its use as a nitrogen source for organic synthesis [4, 5]. Recent reports on homogeneous catalytic systems using ammonia as the substrate include palladium-catalyzed telomerization of butadiene and ammonia giving primary alkylamines [6], Pd-catalyzed allylic amination [7], copper- and palladium-catalyzed coupling reactions of ammonia with aryl halides to form arylamines [8–10], rhodium- and iridium-catalyzed reductive aminations of carbonyl compounds with ammonium formate and ammonia to afford primary alkylamines [11–13] and palladium-catalyzed arylation of ammonia to afford di- and triarylamines [10].

In the context of “green and sustainable chemistry” (GSC), the catalytic synthesis of amines from readily available alcohols using ammonia and generating no hazardous waste is of much current interest. In 2008, we reported the first direct homogeneous catalytic selective amination of primary alcohols to primary amines using ammonia [14]. Later, the research groups of Vogt [15] and Beller [16] developed methods for the conversion of secondary alcohols to primary amines with ammonia. Catalytic methods for the synthesis of secondary amines starting from alcohols and amines were described by Williams [17, 18], Yamaguchi [19, 20], Beller [21, 22], Yus [23, 24] and Kempe [25, 26]. Multi alkylation of ammonia to get either secondary or tertiary amines was developed by Yamaguchi, Fujita and co-workers using an iridium complex as catalyst [27, 28]. Herein, we report the selective synthesis of secondary amines from alcohols and ammonia with liberation of water, with considerable

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Fig. 1 Ru(II)-pincer complexes

Fig. 2 X-ray structure of complex **3** (50 % probability level). Hydrogen atoms (except hydride) were omitted for clarity. Selected bond distances (Å): Ru1–N1 2.113(2), Ru1–N2 2.090(2), Ru1–P1 2.2403(8), Ru1–C24 1.839(4). Selected angles (deg): N2–Ru1–C24 175.39(12), N2–Ru1–H1 91.4(10), Cl1–Ru1–H1 175.1(10), N1–Ru1–P1 161.10(7)

turnover numbers (up to ~500) and with no generation of waste.

Our group has established several environmentally benign atom economical reactions, catalyzed by pincer

complexes of ruthenium based on pyridine and acridine backbones, as outlined in recent reviews [29–33]. Of late we have developed the dearomatized bipyridine-based Ru(II)-pincer complex **5** (Fig. 1) and explored its catalytic activity towards the hydrogenation of amides [34], biomass-derived cyclic diesters [35], and urea derivatives [36] as well as organic carbonates, carbamates and formates [37]. The parent hydrido chloride pincer complex **2** catalyzes in the presence of catalytic base (in situ generation of the active dearomatized complex **5**) several unique environmentally benign reactions such as conversion alcohols to carboxylic acid salts using water as the oxygen atom source [38], dehydrogenative cross-esterification reaction between primary and secondary alcohols [39], synthesis of pyrroles, pyridines and quinoline by dehydrogenative coupling of amino alcohols with secondary alcohols [40, 41] and catalytic coupling of nitriles with amines to selectively form imines under mild hydrogen pressure [42].

Recently we found that the pre-catalyst **3** analogue of **2**, efficiently catalyzes in the presence of catalytic base the dehydrogenative coupling of primary alcohols with secondary amines to form tertiary amides [43], and the direct catalytic olefination of alcohols using sulfones, with liberation of H₂ [44]. Herein we report the catalytic activity of the pre-catalyst **3** in bis-alkylation of ammonia with primary alcohols to get secondary amines, or imines (in the case of benzylic alcohols) selectively.

2 Results and Discussion

We have previously reported the preparation of the pincer complex **3**, by reaction of 6-diphenylphosphinomethyl-2,2′-bipyridine [BPy(Ph)PNN] with [RuHCl(PPh₃)₃(CO)] in THF at 65 °C [43]. The structure of **3** was confirmed in the current study by a single-crystal X-ray diffraction study, using orange crystals grown from a solution of CH₂Cl₂:THF 4:1 (Fig. 2). Complex **3** exhibits a distorted octahedral geometry around the ruthenium center, with the CO ligand coordinated *trans* to the central nitrogen atom of the pincer system, and the hydride is located *trans* to the chloride.

Exploring the catalytic amination activity of complex **3**, primary alcohols were reacted with ammonia in the

Scheme 1 Catalytic synthesis of secondary amines (or imines) from alcohols and NH₃

presence of catalytic amounts of **3** (0.2 mol%) and KO^tBu (0.2 mol%) in toluene (Scheme 1). Thus, heating a dry toluene solution of 1-butanol (10 mmol), complex **3**

(0.2 mol%) and KO^tBu (0.2 mol%) with NH₃ (7 atm) at 135 °C resulted in 48 % conversion of 1-butanol to yield dibutylamine (34 % yield by GC), and 1-butylamine

Scheme 2 Overall mechanistic scheme for the catalytic formation of secondary amines or imines from alcohols and ammonia

Table 1 Direct synthesis of secondary amines (or imines) from primary alcohols and ammonia catalyzed by the ruthenium complex **3** and base, according to Scheme 1

Entry	Alcohol	Product	Conversion	Yield ^a
1 ^b			48	34 + 14 ^c
2			96	88 (7) ^d
3			90	86 (3)
4			99	85 (13)
5			87	80 (7)
6			92	80 (9)
7			84	79 (5)
8			99	82 (15)
9			99	74 (21)

Reaction condition: Complex **3** (0.02 mmol), KO^tBu (0.02 mmol), primary alcohol (10 mmol), ammonia (7 atm), and toluene (2 mL) were heated at 135 °C in a Fischer-Porter reactor for 48 h

^a Conversion of alcohols and yield of products were analyzed by GC

^b Reaction time: 18 h

^c Yield of primary amine

^d Yield in parenthesis represents the yield of the corresponding ester

(14 %), after 18 h (Table 1, entry 1). When the reaction of 1-butanol was prolonged to 48 h the yield of dibutylamine increased to 88 % while 1-butylamine completely disappeared, and 7 % of butyl butyrate were also formed (Table 1, entry 2), indicating that complex **3** catalyzes the conversion of the initially formed primary amines to secondary amines under these conditions [14]. Exploring the scope of this reaction, various aliphatic primary alcohols were subjected to amination using 7 atm of NH_3 . Secondary amines were selectively formed, with no primary or tertiary amines being observed. Minor amounts of the corresponding esters were also formed in all cases, as a result of dehydrogenative coupling of alcohols (Table 1) [39, 45]. No amides were observed under these conditions, although complex **3** in the presence of catalytic base catalyzes the dehydrogenative coupling of primary alcohols with secondary amines to form tertiary amides [43]; however, this reaction requires efficient release of the generated H_2 , which is not possible in a reaction carried out in a sealed system under pressure. Reaction of 1-hexanol with ammonia yielded dihexylamine in 86 % yield together a small amount of hexyl hexanoate (3 % yield) and overall 90 % conversion of the alcohol after 48 h (Table 1, entry 3). The activated 2-methoxyethanol gave almost quantitative conversion to bis-2-methoxyethylamine in 85 % yield and 13 % yield of the corresponding ester, respectively (Table 1, entry 4). 3-methyl-1-butanol underwent amination and selectively yielded the corresponding secondary amine in moderate yield (79 %; Table 1, entry 7). Notably, reaction of benzylic alcohols resulted in formation of imines as the main products, with no secondary amine being formed. Thus, reaction of toluene solutions of benzyl alcohols (10 mmol) with ammonia (7 atm) and catalytic amounts of **3** and KO^tBu (0.02 mmol) at 135 °C for 48 h, resulted in complete conversion, with selective formation of the corresponding imines and H_2 (Table 1, entries 8–9). We have previously reported the dehydrogenative coupling of alcohols and amines (not ammonia) to form imines, catalyzed by a PNP-type Ru pincer complex [46].

A possible overall mechanistic scheme for the formation of secondary amines from primary alcohols and ammonia is as follows (Scheme 2): 1) formation of the primary amine via borrowing hydrogen strategy [29, 47]; an intermediate aldehyde formed by dehydrogenation of the alcohol reacts with ammonia to form an imine **a** (via water elimination from a hemiaminal intermediate), which undergoes hydrogenation. 2) a similar reaction of the primary amine, in competition with ammonia, with the intermediate aldehyde, to form an alkyl imine **b** which undergoes hydrogenation to form the secondary amine (Path **A**; in case of aliphatic systems). In the case of benzylic amines, the formed benzyl imine **b** does not undergo

hydrogenation, perhaps because of its stabilization as a result of conjugation of the double bond with the arene moiety. This imine **b** can also be formed by addition of the primary amine to the initially formed imine **a**, followed by ammonia liberation (path **B**), although this is less likely under ammonia pressure.

3 Conclusions

In summary, we have developed a new atom-economical, environmentally benign catalytic system for the direct synthesis of secondary amines from alcohols and ammonia. The reaction is homogeneously catalyzed by the bipyridine-based Ru(II)-PNN pincer complex **3** in the presence of an equimolar amount of base (relative to Ru). The reactions of ammonia with aliphatic alcohols gave secondary amines exclusively, while those of aromatic alcohols afforded imines selectively. Only 0.2 mol% catalyst is needed. The efficiency, selectivity, atom-economy and mild reaction conditions of this process make it attractive for the selective synthesis of secondary amines or imines from readily available, renewable alcohols.

4 Experimental

All experiments with metal complexes and phosphine ligands were carried out under N_2 in a Vacuum Atmospheres glovebox equipped with a MO 40-2 inert gas purifier, or using standard Schlenk techniques. All non-deuterated solvents were refluxed over sodium/benzophenoneketyl and distilled under argon atmosphere. All solvents were degassed with argon and kept in the glove box over 4 Å molecular sieves. CD_2Cl_2 was used as received. Most of the chemicals (alcohols) used in the catalytic reactions were purified according to standard procedures (vacuum distillation). GC analysis were carried out using a Carboxen 1000 column on a HP 690 series GC system or HP-5 cross linked 5 % phenylmethylsilicone column (30 m $\times$ 0.32 mm $\times$ 0.25 μm film thickness, FID) on a HP 6890 series GC system using *m*-xylene (1 mmol) as an internal standard.

4.1 Synthesis of $\text{RuHCl}(\text{CO})([\text{BPy}(\text{Ph})\text{PNN}])$ (**3**)

The hydrido-chloride pincer complex **3** was prepared by a reaction of the ligand $[\text{BPy}(\text{Ph})\text{PNN}]$ with $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ according to a previously reported procedure from our group [43]. Crystals suitable for a single-crystal X-ray diffraction study were obtained from a mixture of CD_2Cl_2 : THF (20 mg in 0.4: 0.1 mL) at -32 °C after several days (~ 10 days).

4.2 X-ray Crystal Structure Determination of **3**

A crystal was mounted in a MiTeGen loop and flash frozen in a nitrogen stream at 120 K. Data were collected on a Bruker Apex-II CCD diffractometer generator equipped with a sealed tube with MoK α radiation ($\lambda = 0.71073$ Å) and a graphite monochromator. The structure was solved using direct methods with AUTOSTRUCTURE module based on F^2 [48, 49].

Chemical Formula: $2(\text{C}_{24}\text{H}_{20}\text{ClN}_2\text{OPRu})\cdot\text{C}_4\text{H}_8\text{O}$, Orange, plate, $0.10 \times 0.10 \times 0.01$ mm³, monoclinic, $C2/c$, $a = 29.1301(11)$ Å, $b = 12.5264(4)$ Å, $c = 13.5058(5)$ Å, $\beta = 108.826(3)$ deg., $V = 4664.6(3)$ Å³, $Z = 4$, $fw = 1111.92$, $D_c = 1.583$ Mg/m³, $\mu = 0.880$ mm⁻¹. Full matrix least-squares of refinement based on F^2 gave an agreement factor $R = 0.0323$ for data with $I > 2\sigma(I)$ and $R = 0.0599$ for all data (4757 reflections) with a goodness-of-fit of 1.006. Idealized hydrogen atoms were placed and refined in the riding mode, with the exception of the hydride ligand H1-Ru, which was located in the difference map and refined independently.

4.3 General Procedure for the Catalytic Direct Amination of Alcohols to Amines

Complex **3** (0.02 mmol), KO^tBu (0.02 mmol), an alcohol (10 mmol), and toluene (2 mL) were added to a 90 mL Fischer-Porter tube under an atmosphere of purified nitrogen in a Vacuum Atmospheres glovebox. The tube was taken out of the glovebox and was purged by three successive cycles of pressurization/venting with NH₃ (20 psi), then pressurized with NH₃ (7 atm). The solution was heated at 135 °C (bath temperature) with stirring for 48 h (Table 1). After cooling to room temperature, excess NH₃ was vented off carefully and the products were analyzed by GC using *m*-xylene as an internal standard.

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