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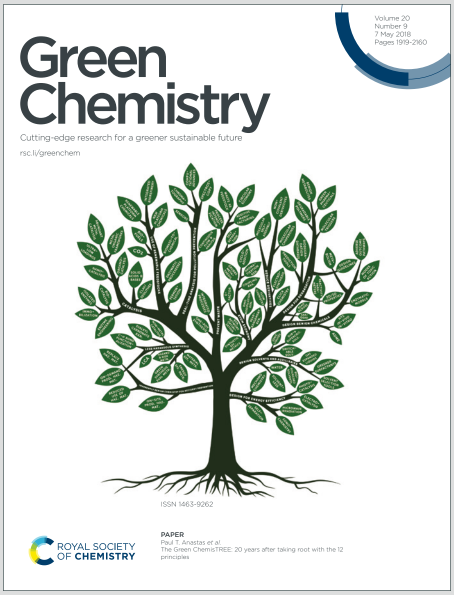

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Sustainable hydrogenation of Aliphatic Acyclic Primary Amides to Primary Amines with Recyclable Heterogeneous Ruthenium-Tungsten Catalysts

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The hydrogenation of amides is a straightforward method to produce (possibly bio-based) amines. However current amide hydrogenation catalysts have only been validated in a rather limited range of toxic solvents and the hydrogenation of aliphatic (acyclic) primary amides has been seldomly investigated. Here, we report the use of a new and relatively cheap ruthenium-tungsten bimetallic catalyst in the green and benign solvent cyclopentyl methyl ether (CPME). Besides the effect of the Lewis acid promotor, NH_3 partial pressure is identified as the key parameter leading to high primary amine yields. In our model reaction with hexanamide, yields of up to 83% hexylamine could be achieved. Beside the NH_3 partial pressure, we investigated the effect of the catalyst support, PGM-Lewis acid ratio, H_2 pressure, temperature, solvent tolerance and product stability. Finally, the catalyst was characterized and proven to be very stable and highly suitable for the hydrogenation of a broad range of amides.

Introduction

Catalytic hydrogenation of amides is a green and sustainable method for the production of valuable amines. With an annual aliphatic amine consumption of more than 2 Mton, amines are widely used for the synthesis of e.g. pharmaceuticals, agrochemicals, dyes, polymers, fabric softeners etc.[1-2] However, the hydrogenation of amides is a challenging reaction, because of their high stability.[3]

Traditionally, amide reduction is achieved with either copper chromite-based hydrogenation catalysts or by applying an excess of hydride reagents. Both methods have severe shortcomings and lack sustainability. The requirement of stoichiometric amounts of hydride reagents such as $LiAlH_4$ or $NaBH_4$ results in large quantities of inorganic chemical waste and an extensive product workup, whereas copper chromite-based catalysts require extreme reaction conditions (e.g. >200 bar H_2, 250-350°C) and high catalyst loadings, require specific disposal and generally have a low selectivity for the primary amine.[4-6]

Over the last few decades, progress has been made with the development of heterogeneous bimetallic catalysts operating under mild reaction conditions. The first such catalyst was reported in 1988 in a BP patent, which claimed a Pd/Re/high surface area graphite/zeolite 4A catalyst for the reduction of amides at 130 bar H_2 and 200°C. Currently, a variety of bimetallic catalysts have been reported, containing a platinum group metal (Pt, Pd, Rh or Ru) promoted by a group 5, 6 or 7 metal oxide (V, Mo or Re); these catalysts are active within a operational window of 70-200°C and 30-100 bar H_2.[3,7-23,43] Although several amides have successfully been hydrogenated to the corresponding amines with high yields and/or selectivity (at least 70% yield), several issues still need to be addressed. First, these catalysts have only been validated in a surprisingly narrow range of toxic solvents e.g. 1,2-dimethoxyethane (DME), hexane and 1,4-dioxane. A smart solvent choice however, can drastically reduce pollution, contribute to a better air quality and reduce the overall environmental footprint of the

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process.[24] Secondly, the hydrogenation of aliphatic, acyclic primary amides has been rarely investigated with these new bimetallic catalysts; most reports use cyclic or more activated amides as reactants, such as ε-caprolactam or *N*-acetylmorpholine. In as far as aliphatic acyclic primary amides are considered, they are usually converted to the alcohol or secondary amine, or must be hydrogenated under extreme reaction conditions (e.g. in liquid ammonia, at high temperatures etc.) to "selectively" obtain the primary amine.[6] Nevertheless, a mild catalytic system able to selectively reduce aliphatic acyclic primary amides, could be a powerful tool to produce even bio-based primary amines. As of today, several bio-based amines, e.g. 1,10-diaminodecane and fatty amines, are synthesized from the corresponding carboxylic acids in a multistep process: first, the carboxylic acid reacts with ammonia at high temperature; next, the resulting amide is dehydrated over an alumina or zinc oxide catalyst at 280-400°C, and finally, the nitrile is hydrogenated to the amine at a temperature of 80-140°C with 10-40 bar H_2, over a nickel catalyst.[2,25-29] This energy-intensive dehydration-hydrogenation process could be significantly shortened by a direct aliphatic amide reduction, requiring less energy. Additionally, we expect that in the near future this pathway will receive an increase in interest, since more and more amines may be produced from bio-based platform molecules, e.g. butyric acid, propionic acid, adipic acid etc.[30-31]

In this work, we report on $RuWO_x/MgAl_2O_4$ as a new and recyclable catalyst for the selective hydrogenation of aliphatic primary amides in cyclopentyl methyl ether (CPME) and under mild hydrogenation conditions, i.e. with limited addition of NH_3 and H_2. To our knowledge, this is the first report of an amide hydrogenation process in CPME as a benign and environmentally friendly reaction solvent.[32-33]

Experimental

Supported bimetallic M-M'O_x catalysts (where M = Ru, Rh or Pt, M' = V, Mo or W and support = SiO_2, TiO_2 or $MgAl_2O_4$ spinel) were prepared with 4 wt% M and a M-M' ratio of 1-8 by impregnation. First, in a typical synthesis of $RuWO_x/MgAl_2O_4$, $RuCl_3.xH_2O$ (0.52 mmol), $(NH_4)_{10}H_2(W_2O_7)_6$ (0.065 mmol of tungsten), $MgAl_2O_4$ (1.25 g) and water (12 mL) are mixed together and stirred at ambient temperature to evaporate water. Secondly, when all the water is removed, the pre-catalyst is dried further overnight in an oven at 60°C. Finally, the material is granulated (250-500 µm) and reduced at 450°C (4°C min^{-1}, 100 mL min^{-1} H_2, for 4 h) in a quartz U-tube. Catalysts with Rh or Pt are first oxidized at 350°C and reduced afterwards. Initially $RuWO_x/SiO_2$-Ca^{2+} catalysts were prepared by first stirring $RuWO_x/SiO_2$ (0.1 g) in a solution of $Ca(OH)_2$ in water (0.005 M, 10 mL) overnight. Next the catalyst was filtered and dried in an oven at 150°C for 4 h. However, this lowered the catalytic activity due to tungstate leaching. This method was improved by depositing 0.025 mmol of Ca^{2+} (or 0.05 mmol Na^+,

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K^+ or Cs^+) on 1 g of $RuWO_x/SiO_2$ via incipient wetness impregnation and drying the material at 150°C for 4 h. $PtVO_x$/HAP was synthesized as described by Mitsudome (2017).

With the prepared catalysts, reactions were performed in a 25 mL high pressure Parr batch reactor. In a typical reaction, the reactor is filled with an amide (e.g. hexanamide), $RuWO_x/MgAl_2O_4$ (4 wt% Ru, Ru-W = 1-8, 5 mol% Ru), undecane (internal standard, 20 µL) and cyclopentyl methyl ether (CPME, 10 mL). Then, the reactor is sealed, purged (3x N_2; 3x H_2) and successively pressurized with the desired amounts of NH_3 and H_2 (typically 6 bar NH_3 and 50 bar H_2). After an appropriate reaction time at the desired temperature (200°C, stirred at 830 rpm), the reactor is cooled down in an ice bath. The pressure is then released after which the reactor can be opened. The reaction mixture is transferred to a glass reaction vial (11mL) which is then sealed and centrifuged. The mixture is then analyzed via GC, GC-MS and NMR.

Results and discussion

At the onset of our research, several Ru-based catalysts were modified with different molar ratios of cheap group 5 to 7 metal oxides (Mo, W and V). The solids were screened in the hydrogenation of hexanamide (**1**) to hexylamine (**3**), allowing to determine the best metal combination and composition for the reduction of aliphatic acyclic primary amides. These initial experiments were performed at 180°C with 40 bar H_2, 0.5 mol% Ru in DME for 16 h (Figure 1). For all metal oxides, there appears to be a clear optimum at a Ru/Metal oxide ratio of 8. $RuWO_x/SiO_2$ (Ru/W = 8) was proven to be the best catalyst, yielding 38% hexylamine (**3**) at 69% conversion; alternative compositions are $RuMoO_x/SiO_2$ and $RuVO_x/SiO_2$ respectively, with a yield of 35% and 30% hexylamine (**3**) at 67% and 70% conversion. All these catalysts are superior when compared to simple Ru-catalysts, such as Ru/SiO_2. Beside the formation of our desired product, hexanol (**2**) and dihexylamine (**4**) were formed as well. Especially secondary amine formation is a predominant side reaction. Interestingly, unsupported Ru-Mo nanoparticles, as already described by Beamson et al., allowed to obtain 77% butylamine yield (and 22% butanol) at 160°C, with 100 bar H_2, in DME. Moreover, further addition of any metal oxide to a catalyst with the same ratio of 8-1, lowered the catalytic activity. This drop in activity is presumably caused by a coverage of the Ru particles, lowering the availability of H* species for the reduction of hexanamide. We also noticed that the Lewis acid metal oxides must be located on (or in contact with) the Ru particles, since catalysts prepared by consecutive deposition of first W, followed by Ru, did not show a superior catalytic activity. In our further experiments, we choose to work with $RuWO_x/SiO_2$, since this catalyst performed best.

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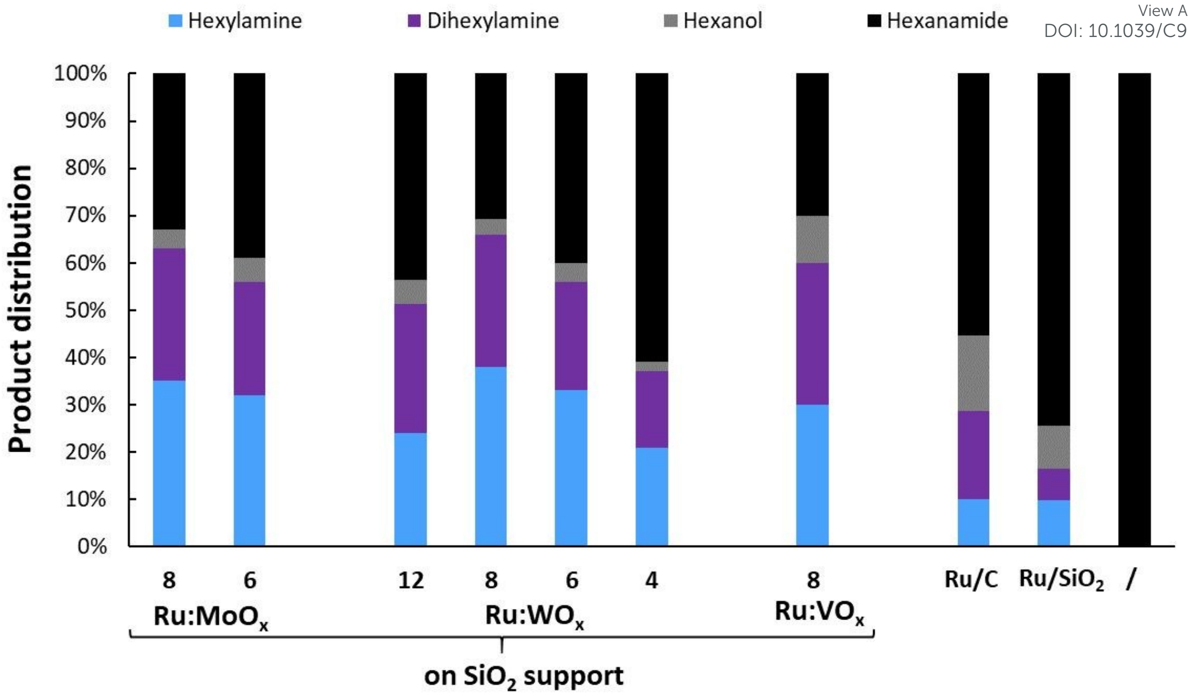

Figure 1 – Variation of the catalysts' metal combination and composition. Reaction conditions: hexanamide (1 mmol), 180°C, 40 bar H_2; 0.5 mol% Ru (4 wt% Ru on catalyst, 5 wt% Ru for Ru/C), undecane (20 µL), DME (10 mL), 16 h.

Next, the solvent tolerance of the RuWO$_x$-catalyst was investigated. As mentioned, the commonly used DME is a very toxic compound. Furthermore, it easily forms explosive peroxides which generally makes it unsafe to work with, especially in contact with H_2.[34] A benign, preferably bio-based reaction solvent would be far more desirable. Therefore, the hydrogenation activity of RuWO$_x$/SiO$_2$ was tested in several solvents, selected from green solvent guides (Figure 2).[35] The reduction of hexanamide (**1**) could be successfully achieved in any ether solvent, but not in an alcohol. We suggest that the amide-catalyst bond is too weak to sufficiently overcome the catalyst's interaction with the hydroxyl group of an alcohol solvent. Ethers interact a lot less with bimetallic catalysts and are therefore excellent solvents for amide hydrogenation. It can be noticed that the hydrogenation rate increases with decreasing solvent polarity (~dielectic constant, ε_r): DME (ε_r = 7.2) < MeTHF(ε_r = 7) < CPME (ε_r = 4.76) < TAME (ε_r = 2.6). However, the rate of secondary amine formation also increases in the same order (Supporting information, **Error! Reference source not found.**). CPME was selected as the best reaction solvent for a number of reasons; first, there appears to be a good balance between hydrogenation activity and secondary amine formation. Secondly, the low heat of vaporization (CPME: 289.5 kJ/kg vs MeTHF: 364.4 kJ/kg) and extremely low solubility of water in CPME (0.3 g water/100 g CPME) ensure an easy and energy-saving workup when applied in a real industrial process. Thirdly, CPME is very stable and resistant to peroxide formation, which makes it safe to work with.[36] After a typical reaction in CPME, a concentration of less than 0.001M cyclopentane was observed. These traces of cyclopentane do not interfere with the reaction, thus the solvent can be reused for many

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cycles. The other cleavage product, methanol, was not detected. Possibly, methanol is transformed to volatile consecutive products e.g. CH_4 or to methylamine, which migrate to the gas phase.[43]

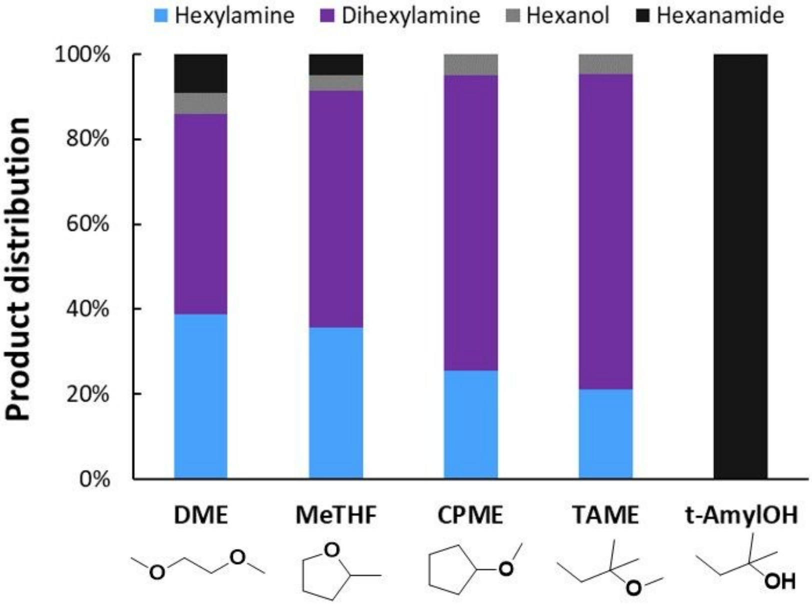

Figure 2 – Variation of the reaction solvent for the hydrogenation of hexanamide. Reaction conditions: hexanamide (1 mmol), 180°C, 40 bar H_2, 1 mol% Ru ($RuWO_x/SiO_2$), undecane (20 µL), solvent (10 mL), 16 h.

After selecting CPME as a reaction solvent, a broader catalyst screening was performed (Figure 3 & **Error! Reference source not found.**, **Error! Reference source not found.**). Commercial PGM on carbon supports performed very poorly, except for Ru/C. Such "single metal catalysts" can be further improved by depositing small amounts of tungsten on the surface; not only does this improve the catalytic activity, also the selectivity for C-O cleavage (amine formation) over C-N cleavage (alcohol formation) increases (Figure 3 & **Error! Reference source not found.**). However, the formation of secondary amines cannot be suppressed by tungsten deposition. Nonetheless, since amine condensation requires a combination of metal and acid catalysis, one may improve the selectivity for the primary amine by lowering the amount of Brønsted acid sites. This could either be achieved by wielding more basic (or at least less acidic) supports, e.g. rutile, or by stirring the slightly acidic $RuWO_x$ on fumed silica in a basic solution of e.g. $Ca(OH)_2$, followed by a drying step (**Error! Reference source not found.**).[37-38] Regarding this second option, despite the catalyst's high stability, one must be careful not to leach out any tungsten as tungstate, since this will lower the catalytic activity. In this catalyst screening, $RuWO_x/SiO_2\text{-}Ca^{2+}$ was the catalyst with the highest selectivity for the primary amine (63% selectivity, 53% conversion); the reaction proceeds without hydrolysis of hexanamide (**1**) (Figure 3 and **Error! Reference source not found.**). More remarkably, our $RuWO_x/SiO_2\text{-}Ca^{2+}$ performs better than $PtVO_x$/Hydroxyapatite (Figure 3), described by Mitsudome et al. in 2017, an extremely active

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catalyst able to reduce a variety of amides at reaction conditions as low as 70°C and 1 bar H_2.[7]

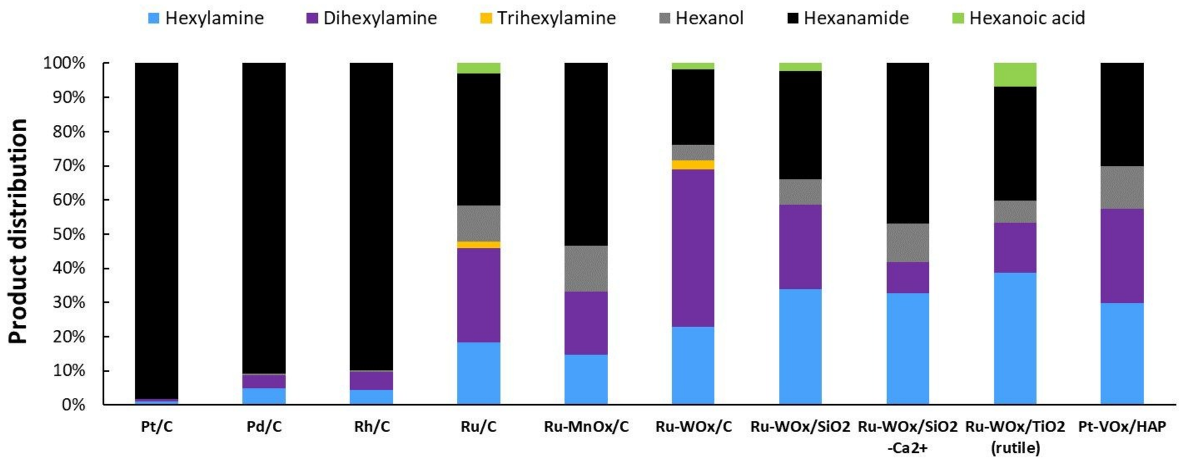

Figure 3 – Variation of the amide hydrogenation catalyst. Reaction conditions: hexanamide (1 mmol), 180°C, 50 bar H_2; 0.5 bar NH_3; 0.5 mol% Ru (or same weight other PGM), undecane (20 µL), CPME (10 mL), 16 h.

To further investigate the amide hydrogenation and unravel the mechanisms behind it, hydrogenation experiments with $RuWO_x/SiO_2$-Ca^{2+} were performed at different temperatures (160°C, 180°C and 200°C) and time profiles were recorded (Figure 4). All three time profiles have a similar shape. In two parallel pathways, hexanamide (**1**) is hydrogenated towards hexylamine (**3**) (C-O cleavage) and hexanol (**2**) (C-N cleavage). From the initial slopes, it is deduced that amine formation is promoted over alcohol formation when increasing the temperature. After this initial phase, a consecutive product is detected, viz. dihexylamine (**4**). Although it can be formed from solely the primary amine, dihexylamine (**4**) is mainly the result of a condensation reaction between hexanol (**2**) and hexylamine (**3**) since this reaction is much faster (**Error! Reference source not found.**). To be more precise, both the amine and alcohol are at constant equilibrium with trace amounts of their corresponding imine and aldehyde. These unsaturated molecules will react with amines, and after NH_3 elimination and reduction, secondary or even tertiary amines are formed (as for Ru/C). Hexanol (**2**) can be transformed into hexylamine (**3**) as well (after reaction with NH_3); at 160°C the rates of C-O and C-N cleavage are roughly the same. Nevertheless, after a reaction time of 5h, the hexanol (**2**) yield reaches a maximum while the amount of hexylamine (**3**) still increases. These observations gave rise to the reaction network depicted in Figure 5. For all the screened reaction temperatures, a maximum in hexylamine (**3**) yield was observed at 90-92% conversion, with 50 bar H_2, 0.5 bar NH_3, in CPME. The hydrogenation experiment at 200°C resulted in the highest yield of 50% hexylamine (**3**) (90% conversion). We did not perform hydrogenation experiments above 200°C, regarding the higher energy costs and increased rate of undesired side reactions, e.g. amine-imine condensation and deamination (at 200°C, <1% hexane yield at full conversion).

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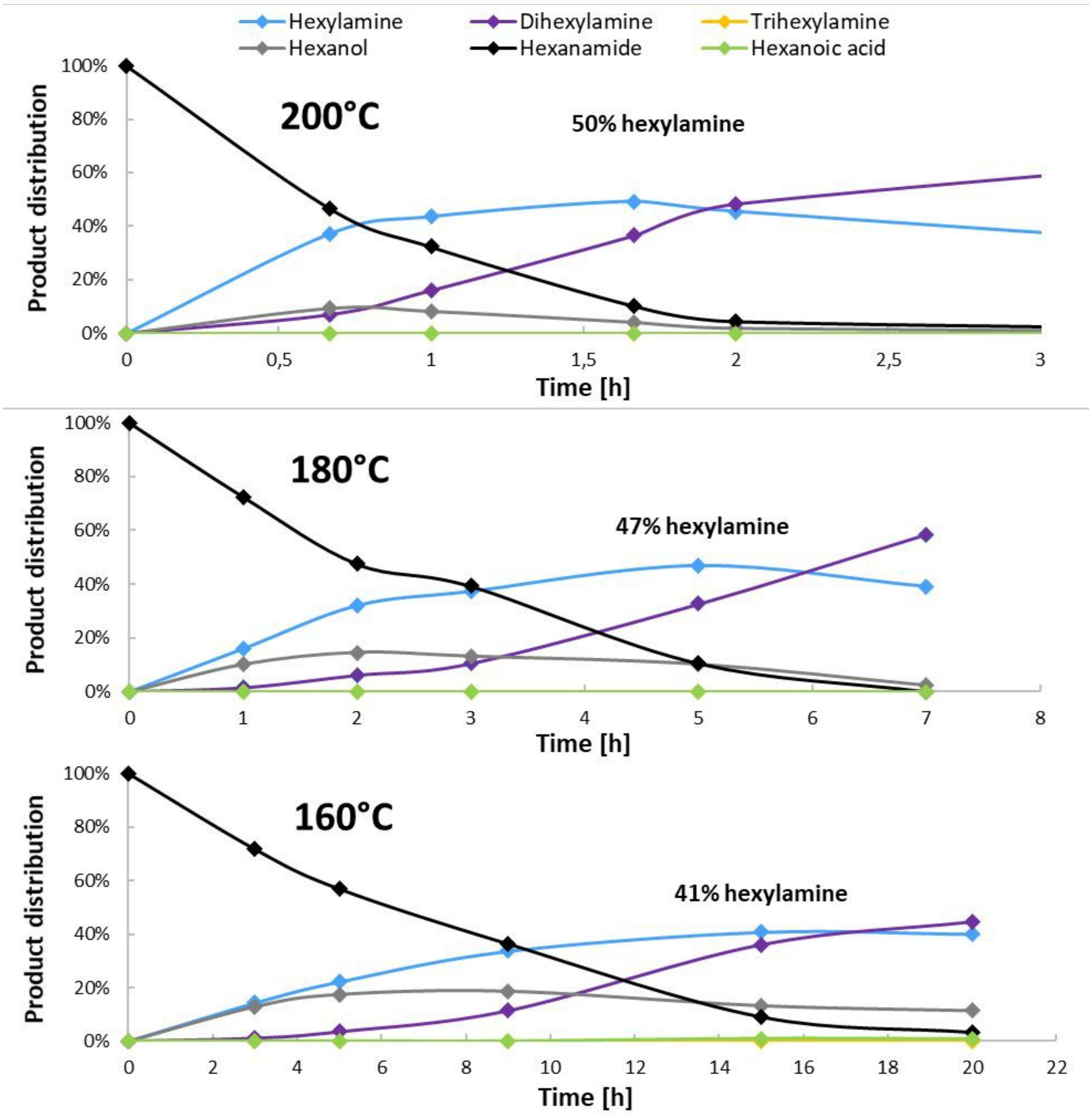

Figure 4 – Time profiles of hydrogenation of hexanamide at different temperatures: (top) 200°C, (middle) 180°C and (bottom) 160°C. Reaction conditions: hexanamide (1 mmol), 50 bar H_2; 0.5 bar NH_3, 5 mol% Ru ($RuWO_x/SiO_2$-Ca^{2+}), undecane (20 µL), CPME (10 mL).

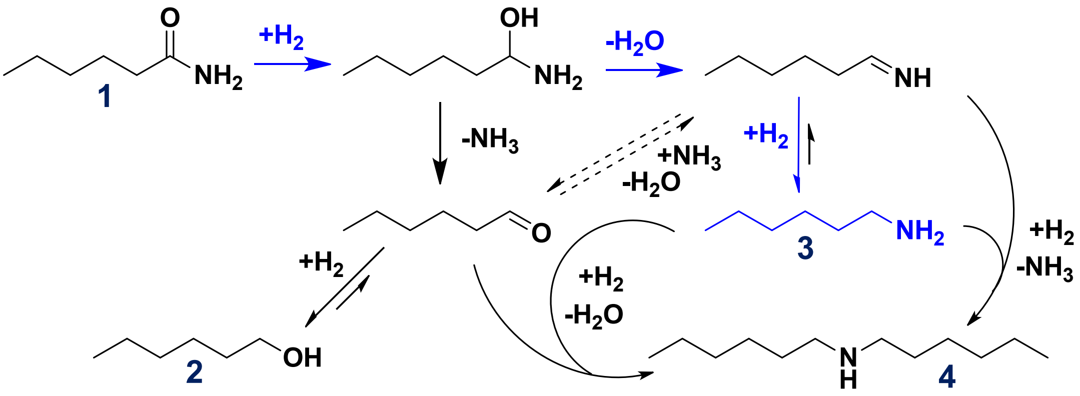

Figure 5 – Reaction network of the hydrogenation of hexanamide with $RuWO_x$-catalyst.

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In order to further increase the primary amine yield, the ammonia and hydrogen pressure were optimized. As one might expect, the addition of ammonia increases the selectivity for hexylamine (**3**), since more alcohol is converted to hexylamine (**3**) and secondary amine formation is hindered. On the other hand, compared to the amide, ammonia is preferentially adsorbed on the catalyst and therefore it lowers the catalytic activity of $RuWO_x/SiO_2$-Ca^{2+}. Thus, there is a clear trade-off between selectivity and activity (Figure 6). Assuming a first order reaction (**Error! Reference source not found.**), we attempted to determine the reaction order in $[NH_3]$ (**Error! Reference source not found.** – S 11). It appears that the relation between $\ln(v_{init})$ and $\ln([NH_3])$ is not linear. At low concentrations of ammonia (P_{NH3} between 0.5 – 1 bar) the reaction order is -0.3, whereas at higher concentrations of ammonia (P_{NH3} > 2 bar) the reaction order is approximately -0.9. We expect that the influence of amine products is similar to the influence of ammonia. However, the amine concentration is very low in comparison with the concentrations of ammonia. Therefore, the inhibiting effect of amine products is probably limited.

Since it was our goal to obtain the highest possible primary amine yield under safe and eco-friendly conditions, we selected 6 bar NH_3 (= 4.5 M of ammonia in CPME at room temperature, determined by weight) as ideal, with 77% hexylamine (**3**) yield (88% conversion, 88% selectivity). This, to our knowledge, is already better than the best available results for bimetallic catalysts described in literature, as described by Beamson et al. (2010) and Hirosawa et al. (1996).[12,20] In an industrial set-up, controlled addition of ammonia is a powerful tool to steer towards the desired ratio of primary vs secondary amines, since secondary amines are in some cases even more valuable than primary amines, e.g. dimethylamine.[39] Excess of ammonia can be easily recycled, e.g. by degassing and cooling to liquid ammonia.

Whereas ammonia is applied to steer the selectivity, hydrogen mostly has an influence on the hydrogenation rate (combined with 6 bar NH_3). **Error! Reference source not found.** in the Supporting Information shows that 25 bar H_2 suffices to obtain an acceptable hydrogenation rate.[39]

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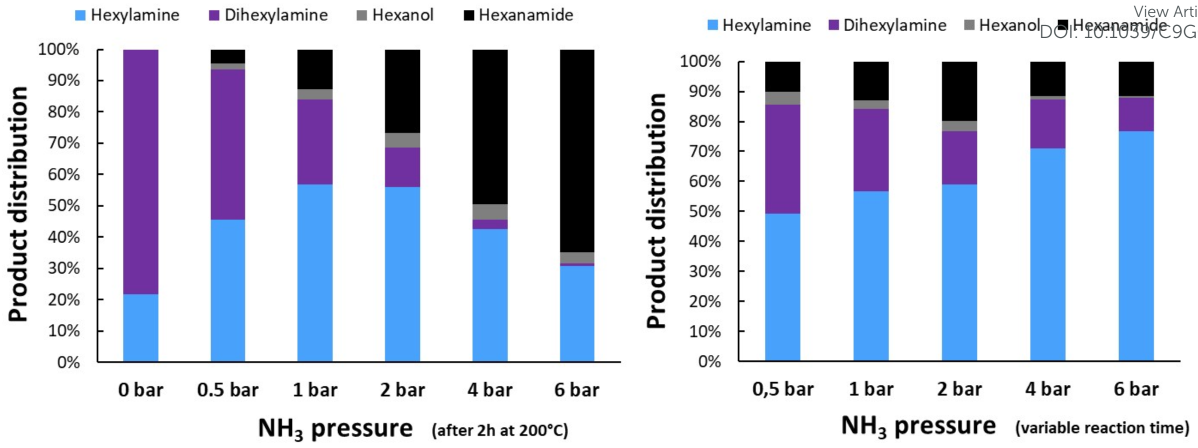

Figure 6 – Variation of the ammonia pressure in hydrogenation experiments of hexanamide: (left) fixed reaction time of 2h; (right) variable reaction time, with ~90% conversion. Reaction conditions: hexanamide (1 mmol), 200°C, 50 bar H_2, 5 mol% Ru ($RuWO_x/SiO_2$-Ca^{2+}), undecane (20 µL), CPME (10 mL).

With 6 bar of ammonia to control the primary amine selectivity, the contribution of a basic catalyst support fades away. In Figure 7, $RuWO_x$ on fumed SiO_2 is compared with basic cation loaded SiO_2 and spinel ($MgAl_2O_4$, $CaAl_2O_4$) supports. Whereas $RuWO_x/SiO_2$ has a hexylamine (**3**) selectivity of 84%, a selectivity of 85-90% is observed for $RuWO_x$ on a basified support (at ~90% conversion). Even more interesting is the behaviour of $RuWO_x$/spinel. Wielding a spinel support drastically increased the catalytic activity, with 83% hexylamine (**3**) yield at full conversion for $RuWO_x/MgAl_2O_4$ (initial TOF of $2.2*10^{-4}$ s^{-1}). To investigate this difference in reaction rate, $RuWO_x/SiO_2$ and $RuWO_x/MgAl_2O_4$ both were characterized with N_2-physisorption and TEM(-EDX) (see Supporting Information). It appeared that, while $RuWO_x/SiO_2$ has the highest BET surface area (395 m²/g, vs 159 m²/g in case of $RuWO_x/MgAl_2O_4$), $RuWO_x/MgAl_2O_4$ has the smallest Ru particle size, resulting in a higher catalytic activity due to an increased specific metal surface (Ru particle diameter of 1.5 - 2 nm vs 2 - 3 nm for $RuWO_x/SiO_2$). A similar effect was observed when comparing the performance of Ru/C with Ru/SiO_2 (Figure 1, < 2nm vs 2 - 3 nm for Ru/SiO_2). The TEM-EDX data also show that W is very evenly distributed over the entire surface, not making clusters like Ru does.

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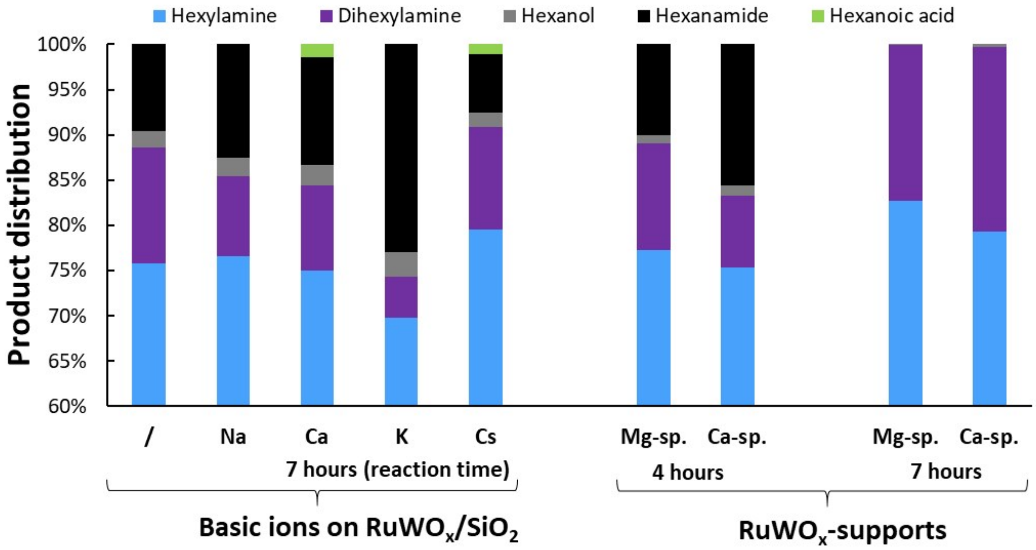

Figure 7 – Catalytic screening of RuWO$_x$ on various supports: (left) SiO$_2$ vs Na-, Ca-, K- & Cs-loaded SiO$_2$ (7 h); (right) Mg- vs Ca-spinel (4 h & 7 h). Reaction conditions: hexanamide (1 mmol), 200°C, 50 bar H$_2$, 6 bar NH$_3$, 7 mol% Ru, undecane (20 µL), CPME (10 mL).

To investigate the stability of RuWO$_x$/MgAl$_2$O$_4$, a recycling test was performed along with ICP analysis and XRD of both fresh and used catalyst. The recycling test showed that RuWO$_x$/MgAl$_2$O$_4$ can be used at least 5 times without losing any catalytic activity nor selectivity (the same goes for RuWO$_x$/SiO$_2$, **Error! Reference source not found.**); after each run, a nearly full conversion with a selectivity for the primary amine of approximately 80% was observed. This is a rather interesting observation since literature states that the selectivity of Beamson's Ru-Mo catalyst for the primary amine drops significantly after three runs.[12] The high stability of this RuWO$_x$-catalyst could be confirmed by ICP; both Ru and W content in the mixture after reaction were below the detection limits (1 ppb), which represents a leaching below 0.005% and 0.02% respectively. The recorded XRD patterns do not show any Ru peaks and essentially remain the same, once again illustrating the high stability of the catalyst (no sintering, Ru nanoparticles are too small to be detected by XRD, **Error! Reference source not found.**). Since the catalyst does not show signs of deactivation, we are unable to calculate a turnover number (TON) until catalyst deactivation. However, a complete conversion can be reached with even just 0.5 mol% of Ru, which means that at the end of a single run, the TON amounts to at least 200.

A last key factor that requires investigation, is the (Lewis) acidity of the catalyst. It has been proposed that these bimetallic compounds are excellent catalysts for the hydrogenation of amides because the metal oxide promotor presents Lewis acid sites. These Lewis acids sites help with the adsorption of amides to the surfaces. As a result, the interface PGM-metal oxide acquires a high catalytic activity. To investigate the (Lewis) acidity of the catalyst, NH$_3$-TPD was performed. The data clearly show that there are two types of (Lewis) acid sites on the catalyst's surface (Figure 8). Based on the cumulative amount of NH$_3$ adsorbed to the

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surface, we calculated that there are 0.055 mmol acid sites per g of catalyst. This is approximately the same as the amount of tungsten per g of catalyst. It is logical to assign these acid sites to the tungsten species, since the catalytic support is typically basic ($MgAl_2O_4$ spinel). The data thus suggest a very high, nearly monoatomic dispersion of tungsten. This was also suspected after analysing the TEM data. In literature, similar observations have been made for Mo, which is chemically similar to W.[44]

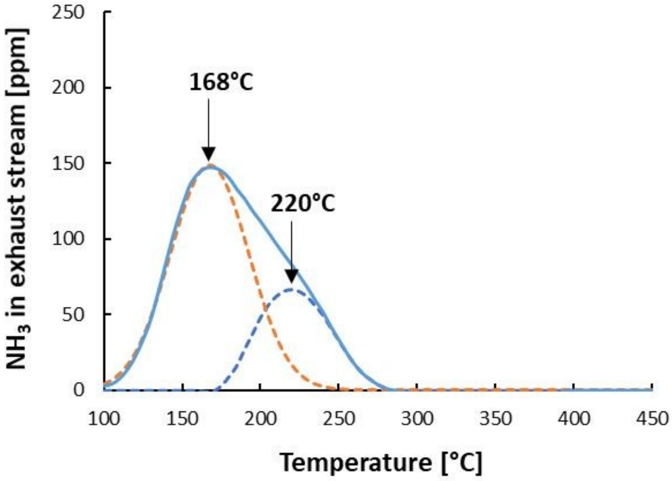

Figure 8 – NH_3-TPD with $RuWO_x/MgAl_2O_4$-catalyst. After a phase of NH_3 adsorption 100°C and flushing the catalyst with pure N_2, the catalyst bed was gradually heated (5°C/min) and the actual desorption takes place. The NH_3 exhaust was monitored.

Finally, a substrate scope investigation was performed to illustrate the range of applicability (Table 1 & supporting information). High yields of the corresponding primary amines were obtained for all aliphatic monofunctional primary amides (entries 1–5). The high yields and selectivities are consistently obtained for chain lengths between C3 and C12. Hydrogenation experiments with primary α,ω-diamides produced some interesting results; short bifunctional molecules tend to follow a deamination/decarbonylation pathway resulting in monofunctional primary amides, which react further as expected (entry 6). In case of longer α,ω-diamides, each amide group reacts more independently. However, once an ‘amino-amide’ of appropriate chain length is formed, the molecule easily performs an intramolecular transamination resulting in a cyclic secondary amide. Only small amounts of the α,ω-diamine can be detected. This explains why the results for adipamide and caprolactam are virtually the same, with a yield of 85% azepane.[40] In these two reactions, hexylamine is the main side product, presumably formed after hydrogenolysis of the azepane ring. Such a cyclization reaction was not observed for the C10 diamide, viz. decanediamide (entry 9). Acyclic secondary and tertiary amides with very short N-substituents were reduced as well, although this probably does not proceed via a direct hydrogenation of the secondary/tertiary amides themselves (entries 10 & 12); rather ammonolysis will take place first, yielding primary amides which react further to primary amines. The short amines (e.g. methyl-, dimethylamine) were not detected due to their very low boiling points (e.g. -6°C and 7°C

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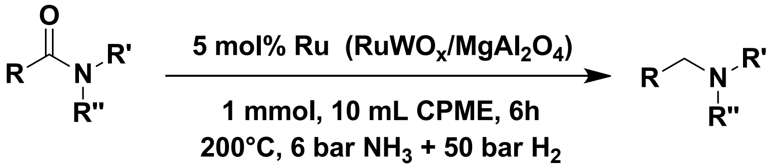
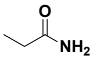
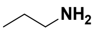
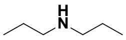
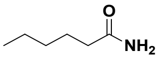
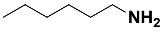
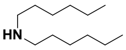
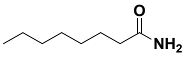
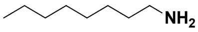
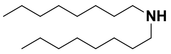
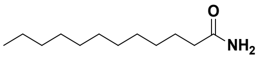
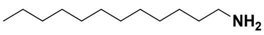
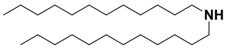
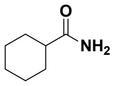
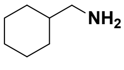
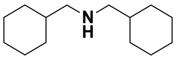
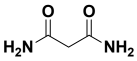
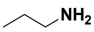
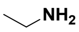
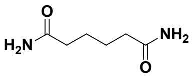
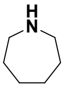
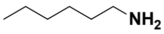
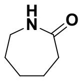
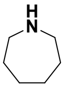
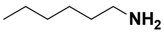
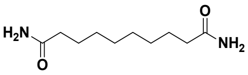
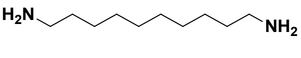
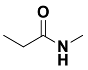
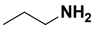
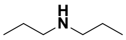
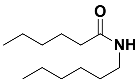
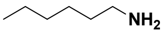
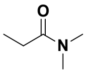
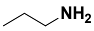
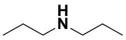
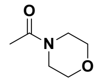
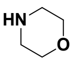
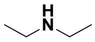
respectively). If the N-substituent is more bulky, the ammonolysis does not proceed, leading to a low hydrogenation rate (entry 11). More activated tertiary amides such as N-acetylmorpholine, can be easily hydrogenated as well (entry 13). Such molecules have an increased preference for a C-N cleavage over C-O cleavage (45% morpholine yield). At 200°C, however, the morpholine ring itself isn't stable. Besides morpholine, diethylamine and some minor side product, the hydrogenation of *N*-acetylmorpholine resulted in a large amount of ethanol and ethylamine (see supporting information).

Table 1 – Substrate scope investigation with $RuWO_x/MgAl_2O_4$.



	Substrate	X [a] [%]	Major product	S [b] [%]	Minor product	S [b] [%]
1		96		84		15
2		> 99		83		17
3		99		81		17
4		97		82		14
5		> 99		80		18
6		> 99		30		23[c]
7		> 99		85		8
8		> 99		85		6
9		> 90[d]	main product [d]:			> 50%
10		93[e]		87		13
11		6		> 99	/	/
12		57[e]		88		9
13		> 99		45		17

[a] Conversion. [b] Selectivity. [c] Very volatile compound; therefore, yields are underestimated by analysing the liquid phase. [d] 1,10-decanediamine partially precipitates out of CPME resulting in an less precise product yield calculation. [e] Mixture of original amide and propionamide.

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Additionally, we discovered that secondary amines are not necessarily dead-end products. With nearly any commercial PGM supported on carbon, we were able to cleave dihexylamine (**4**) into hexylamine (**3**) with 62% yield (Ru & Pt on carbon supports, Figure 10). The reverse reaction with hexylamine (**3**) showed that this is the equilibrium position between mono- and dihexylamine at 200°C, 10 bar H_2, 6 bar NH_3 (= 4.5 M of ammonia) in CPME (Figure 9 & **Error! Reference source not found.**). The capability to valorize secondary(/tertiary) amines opens up many possibilities. First, 100% yield of the primary amine is in theory possible. However, this would require a continuous isolation of the primary amine from the secondary amine. Secondly, one can opt to perform the difficult amide hydrogenation in the absence of ammonia to selectively obtain the secondary amine (Figure 6) and perform an ammonolysis afterwards. Although a one-step hydrogenation process provides higher yields, the two-step process would drastically increase the hydrogenation rate and replace a single hydrogenation process at elevated pressure, by a combined process operating under milder conditions. To our knowledge, the ammonolysis of secondary or tertiary amines has only been reported once, viz. by Olin et al. in 1937.[41] In their work, a yield of approximately 33% monobutylamine could be obtained from dibutylamine with a MnO_x/C catalyst, operating at 292°C starting from a molar composition of 10-1 ammonia-dihexylamine.

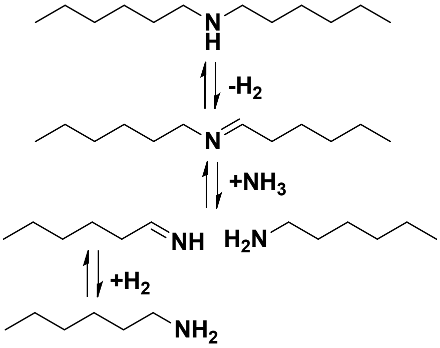

Figure 9 – Proposed reaction scheme of the ammonolysis of secondary amines.

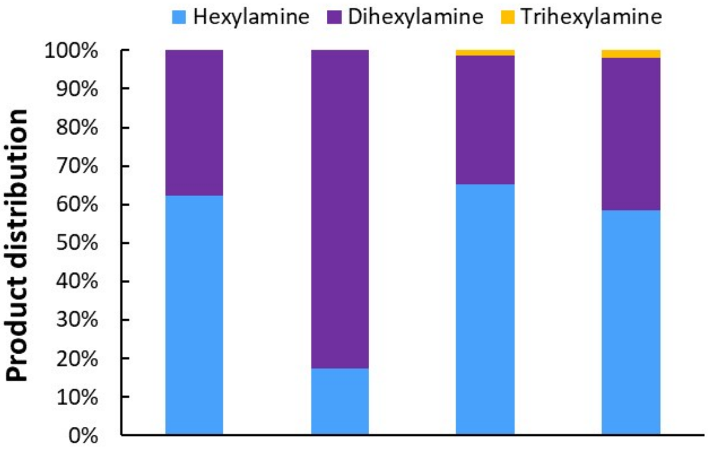

Figure 10 – Ammonolysis of dihexylamine with different commercial PGM/C. Reaction conditions: hexanamide (1 mmol), 200°C, 10 bar H_2, 6 bar NH_3, 5 mol% Ru, undecane (20 µL), CPME (10 mL), 5 h.

Conclusion

In conclusion, our new and relatively cheap ruthenium-tungsten bimetallic catalyst performed excellently for the hydrogenation of aliphatic acyclic primary amides, such as hexanamide (**1**). Reactions were conducted in CPME. Despite the fact that CPME slightly lowers the selectivity for the primary amine, this benign and green alternative is a major improvement when compared to the commonly used toxic solvents such as DME, dioxane and hexane. It is also very stable, safe to work with and ensures an efficient product workup.

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To improve the primary amine selectivity, we explored the use of a strongly basic support (e.g. a spinel), and the use of NH_3 partial pressure; the latter option is most effective. At relatively high NH_3 pressures, the additional effect of a basic support is noticeable but small. After a further optimization, a yield of up to 83% of hexylamine (**3**) could be obtained with $RuWO_x/MgAl_2O_4$ at 200°C, with 50 bar H_2 and 6 bar NH_3 (= 4.5 M of ammonia), using 5 mol% Ru after 6 h in CPME (initial TOF of $2.2*10^{-4}$ s^{-1}). This green catalytic system is thus a significant improvement in comparison with current technologies for the hydrogenation of aliphatic acyclic primary amides. Finally, $RuWO_x$-catalysts were proven to be very robust and applicable on a wide range of primary amides.

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Graphical abstract

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