Development of homogeneous catalysts for the selective conversion of levulinic acid to caprolactam

Raoufmoghaddam, S.

Citation

Raoufmoghaddam, S. (2013, December 17). *Development of homogeneous catalysts for the selective conversion of levulinic acid to caprolactam*. Retrieved from https://hdl.handle.net/1887/22931

Author: Raoufmoghaddam, Saeed
Title: Development of homogeneous catalysts for the selective conversion of levulinic acid to caprolactam
Issue Date: 2013-12-17

6

Summary, Conclusions and Outlook

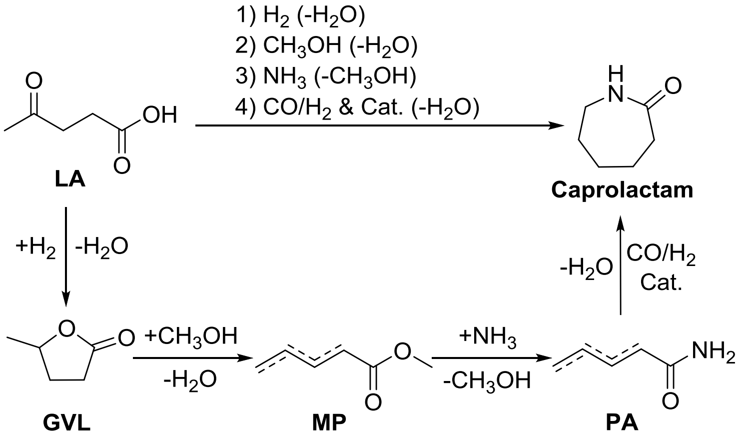
6.1. Summary

6.1.1. General Introduction; Alternative routes to caprolactam (Ch 1)

As described in chapter 1, finding an alternative feedstock form renewable resources has become increasingly important in the recent years due to the high price of fossil feedstock and increasing energy demands. Furthermore, the atom-economical and energy-efficient production of fuels and chemicals is an issue of concern in chemical industries for a more sustainable environment with lower green-house gas emissions.

Lignocellulosic biomass is one of the most attractive renewable feedstock, which has drawn increasing attention for the production of a number of building block chemicals. Hydroxylmethylfurfural (HMF) obtained from biomass can be used to synthesize a broad range of chemicals currently derived from petroleum. One of the substances produced from HMF is levulinic acid (LA) which can be used for the production of performance chemicals such as caprolactam.

ε-Caprolactam is the polymer precursor for nylon-6, an extensively used synthetic polymer with an annual production of about four million tons. In chapter 1 an overview is given of the current industrial process for the production of caprolactam, as well as alternative routes that have been developed based on butadiene. Finally, one alternative bio-based caprolactam synthesis is described, that is based upon a multi-step catalytic conversion of hydroxymethylfurfural (HMF) to caprolactone.



Scheme 6.1. Synthetic route for the conversion of levulinic acid to caprolactam.

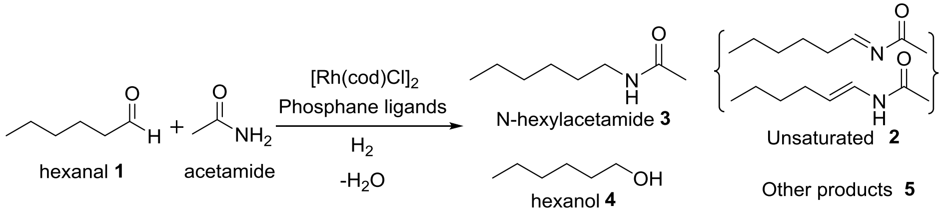
The aim of the research described in this thesis is to introduce a new synthetic route to obtain caprolactam starting from γ-valerolactone (GVL), a compound that can be produced from bio-based levulinic acid. The proposed route proceeds via the acid-catalyzed reactive distillation of GVL with methanol to a mixture of isomeric methyl pentenoates (MPs). Ultimately, the corresponding pentenamides (PAs), produced from aminolysis of the MPs with ammonia, will have to be converted via an intramolecular hydroamidomethylation reaction to form caprolactam (Scheme 6.1).

Hydroamidomethylation was a hitherto unknown transformation and therefore much effort described in this thesis was devoted to the development of effective catalysts for this synthetically interesting reaction involving N-alkylation of primary amides with syngas. Hydroamidomethylation of an alkene constitutes a cascade reaction an initial hydroformylation of alkene to aldehyde followed by reductive amidation of the resulting aldehyde with amide. In order to systematically investigate the hydroamidomethylation reaction, we have first developed a catalyst system for the reductive amidation reaction which can be efficiently carried out in the presence of H_2. However, the presence of CO would suppress the hydrogenation step in the reductive amidation reaction. In order to prevent the CO poisoning effect, we had to find promoters for the hydrogenation in the presence of syngas; thus successfully able to perform a cascade hydroamidomethylation reaction of alkenes. Therefore, prior to focus on the conversion of LA to caprolactam, and in order to fully understand the mechanistic insights, we investigated both the new model reactions (reductive amidation of aldehydes as well as the cascade hydroaminomethylation of alkenes). Furthermore, reductive amidation and hydromidomethylation can be further potentially utilized for the selective synthesis of primary amines from aldehydes or alkenes.

6.1.2. Rhodium-catalyzed homogeneous reductive amidation of aldehydes (Ch 2)

The newly developed catalytic reductive amidation of an aldehyde (hexanal) with an amide (acetamide) is reported in Chapter 2. Careful analysis of the reaction mixture revealed that apart from the desired N-hexylacetamide **3**, the two isomeric unsaturated intermediates **2** as well as hexanol **4** are produced together with higher mass products **5** that arise from aldol condensation and di-amide coupling of hexanal (Scheme 6.2).

Screening of different catalyst precursor salts, ligands and reaction conditions led to the finding that the catalytic system based on $[Rh(cod)Cl]_2$ in combination with the ligand xantphos and a strong acid co-catalyst yields high selectivity for desired N-hexylacetamide **3**. Under optimized conditions a hexanal conversion of 98% is reached with more than 90% selectivity to the desired N-hexylacetamide **3** and with a **3**/**4** ratio of >20, while producing only small amounts of by-products **5**.

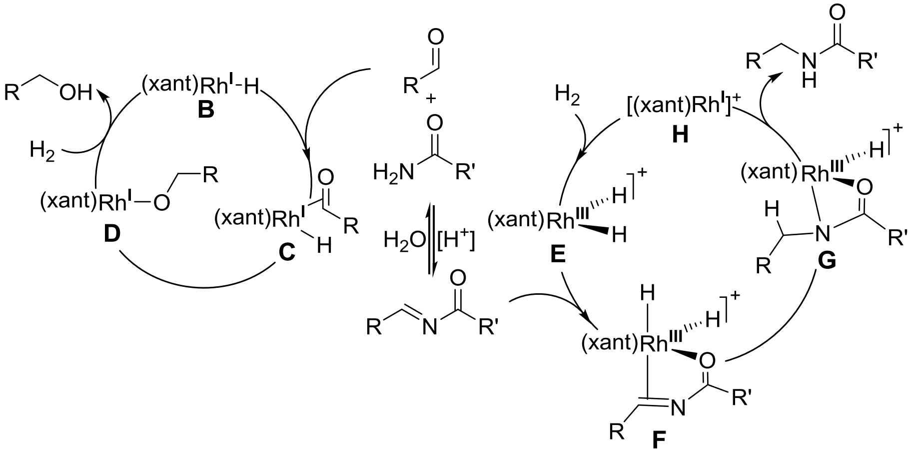


Scheme 6.2. Reductive amidation of hexanal with acetamide: observed products

Employing of various aldehydes and amides in the reaction revealed that the conversion is strongly affected by the choice of the N-substrates, which indicates that the coupling reaction is dependent on the nucleophilicity at N and bulkiness around nitrogen of the substrates.

NMR studies revealed that the nucleophilic addition of acetamide to hexanal is acid catalyzed forming N-(1-hydroxyhexyl)acetamide **2a** in an equilibrium with both hexanal and **2** (Figure 2.6). A catalytic mechanism is proposed in which a strong acid such as HOTs acts as a co-catalyst by establishing a rapid chemical equilibrium between the aldehyde, acetamide and the intermediates **2**, and enabling a cationic Rh/xantphos hydrogenation catalyst to selectively hydrogenate the intermediates **2** to **3** in the presence of the aldehyde. It is proposed that one possible reason for the high substrate specificity in hydrogenation is the observed intrinsically lower aldehyde hydrogenation activity of the cationic Rh^{III} species proposed to be present as the main hydrogenation catalyst in the acidic medium. The neutral, low-valent hydrido-Rh^{I} species would favor the binding of the aldehyde via its π electrons, yielding alcohol **4**. The cationic, high-valent dihydrido-Rh^{III} species present in the acidic medium would favor binding of the imido intermediate **2** through both the carbonyl oxygen and the imide double bond over the π-bond of the aldehyde's carbonyl, yielding the desired product (Scheme 6.3).

The catalytic system comprising rhodium/xantphos/HOTs for the reductive *amidation* of an aldehyde with an amide has been shown to give promising turnover numbers (TON=1800) and good yields of the desired product (~90%) under relatively mild conditions.

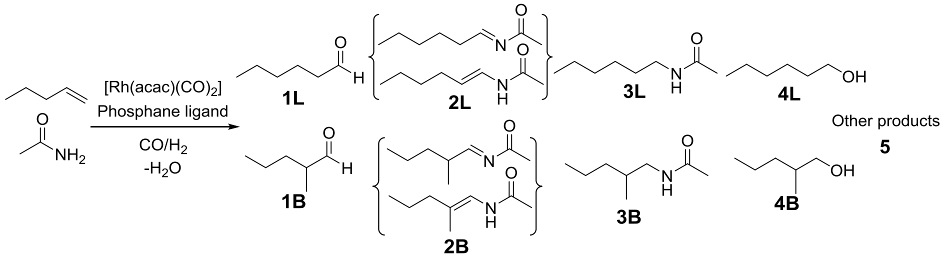


Scheme 6.3. Proposed catalytic cycle for the hydrogenation of aldehyde versus unsaturated imido intermediates

6.1.3. Chemo- and regio-selective homogeneous rhodium-catalyzed hydroamidomethylation of 1-alkenes to N-alkylamides (Ch 3)

The direct mono-N-alkylation of primary amides with 1-alkenes and syngas through a catalytic hydroamidomethylation reaction is described in Chapter 3. A selective rhodium/xantphos catalyst system has been developed for this reaction, taking 1-pentene and acetamide as model substrates. Apart from the product N-hexylacetamide, the isomeric unsaturated intermediates, hexanol and higher mass by-products as well as the corresponding isomeric branched products can be formed (Scheme 6.4).

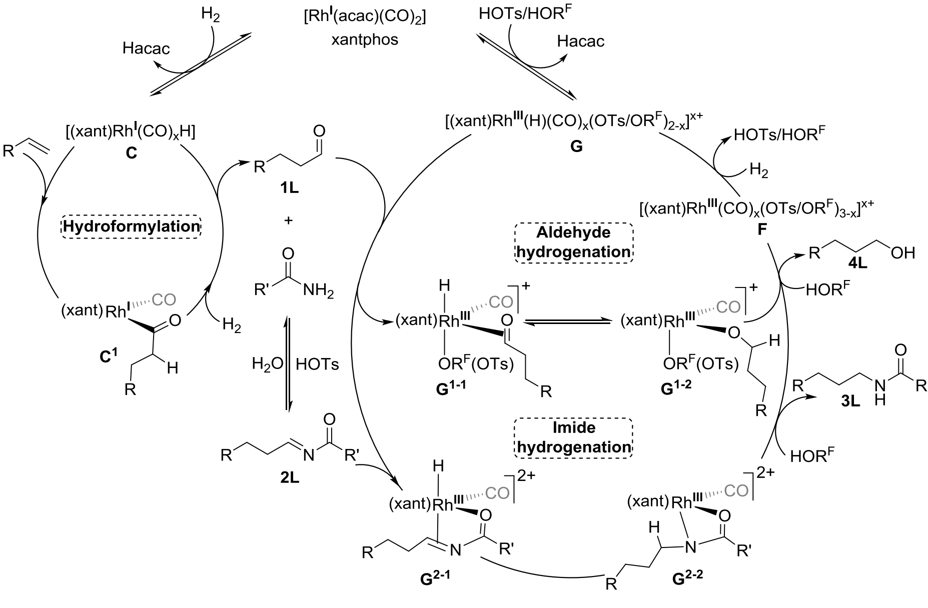
As shown in our studies on the catalytic reductive amidation reaction (Chapter 2), a catalytic amount of a strong acid promoter such as p-toluenesulfonic acid (HOTs), is necessary to catalyze the equilibrium reaction of the amide with the aldehyde. It was found that the additional presence of a weakly acidic promoter compound such as HOR^F (1,1,1,3,3,3-hexafluoroisopropylalcohol) in solvent-like quantities also has a strong impact on the course of the catalytic hydroamidomethylation reaction, creating an active hydrogenation catalyst in the CO-containing atmosphere. Under optimized conditions nearly full alkene conversion can be achieved with more than 80% selectivity to the product N-hexylacetamide. Interestingly, in the presence of a high concentration of HOR^F (HOR^F/diglyme ~5/1 (v/v)) the same catalyst system shows a remarkably high selectivity (~90%) for the formation of hexanol from 1-pentene with syngas, thus presenting a unique example of a selective Rh-catalyzed hydroformylation-hydrogenation tandem reaction under mild conditions.



Scheme 6.4. Hydroamidomethylation of 1-pentene with acetamide: observed products, intermediates and by-products

The time-dependent product formation during hydroamidomethylation batch experiments showed evidence for intermediacy of both aldehyde and unsaturated enamido/imido compounds **2**, clearly indicating that a three-step hydroformylation/condensation/hydrogenation reaction sequence takes place in hydroamidomethylation.

To elucidate the role of HOTs and HOR^F we studied their respective effects on the individual reactions constituting the overall cascade hydroamidomethylation reaction. We conclude that one likely role of HOR^F in combination with the strong acid HOTs is to establish a dual-function catalyst system comprising of a neutral [(xantphos)(CO)Rh^I-hydride] hydroformylation catalyst and a cationic [(xantphos)(CO)Rh^{III}-hydride]$^{n+}$ species capable of selectively reducing the imide and/or eneamide intermediates that are in a dynamic, acid-catalyzed condensation equilibrium with the aldehyde and amide (Scheme 6.5). The competition between the two substrates involved in the respective catalytic cycles, postulated to be governed by anion coordination to the cationic Rh^{III} center, is the basis for the chemo-selectivity of the overall hydroamidomethylation process. One interesting notion gained from this work is that the presence of the amide reactant, as a weak base, also plays a significant role in controlling the anion supply.



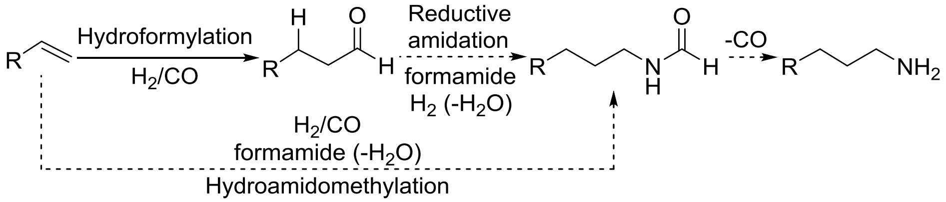
Scheme 6.5. Proposed overall mechanism for hydroamidomethylation of 1-alkenes

Both HOR^F and HOTs can provide anions to the cationic Rh^{III}-hydride species, by protonation of the weakly basic amide reactant and product, depending on their relative concentrations, relative acidic strength and coordination properties to the Rh center. Such a notion rationalizes the dramatic change in selectivity from N-hexylacetamide as major product (>80%) at relatively low HOR^F concentration, to hexanol as the major product (>90%) at a high concentration of HOR^F.

6.1.4. Towards Synthesis of Primary Amines: Investigating Rhodium-Catalyzed Homogeneous Reductive Amidation and Hydroamidomethylation with Formamide (Ch 4)

The catalytic reductive amidation of an aldehyde with formamide as well as the direct hydroamidomethylation of an alkene with formamide is described in Chapter 4. The catalytic synthesis of N-alkylformamides may lead to a new route to primary amines from alkenes via subsequent decarbonylation of the N-alkylformamide (Scheme 6.6).

Use of the catalytic system based on a rhodium precursor in combination with xantphos ligand and the acid co-catalyst HOTs in the reductive amidation of hexanal with formamide gave a high selectivity for the formation of N-hexylformamide (up to 90%).



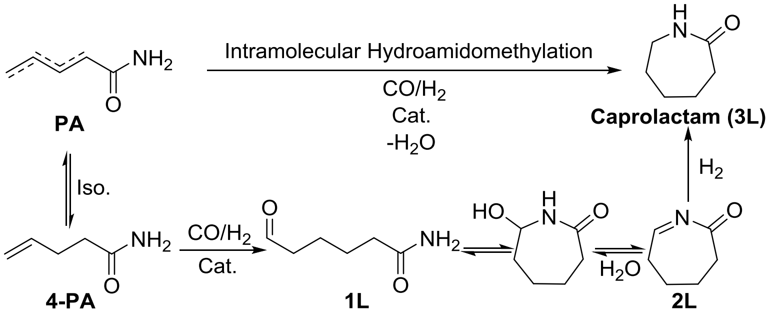
Scheme 6.6. An overview of catalytic formation of primary amine

In comparison with the reductive amidation with acetamide, to achieve similar catalytic performance of the Rh/xantphos catalyst system with formamide, the amount of HOTs needed to be increased. Under these conditions, the selectivity for N-hexylformamide **3** over hexanol **4** was spectacularly increased (ratio **3L/4L** ~60). The scope of the reductive amidation reaction was investigated using different aldehydes, showing that the formation of different N-alkylformamides can be efficiently implemented. The catalytic hydroamidomethylation of pentene with formamide so far revealed poor selectivity to N-hexylformamide. The higher acid concentration required for an efficient reductive amidation, causes excessive (acid-catalyzed) acetalisation of HOR^F with the aldehyde. The decarbonylation of N-hexylformamide to form n-hexylamine was demonstrated by using some transition metal complexes or strong base. However, until now only stoichiometric conversion could be obtained using either transition metal complexes or strong base under the conditions applied.

6.1.5. From renewable feedstock to “green” nylon: Catalytic conversion of γ-valerolactone to ε-Caprolactam (Ch 5)

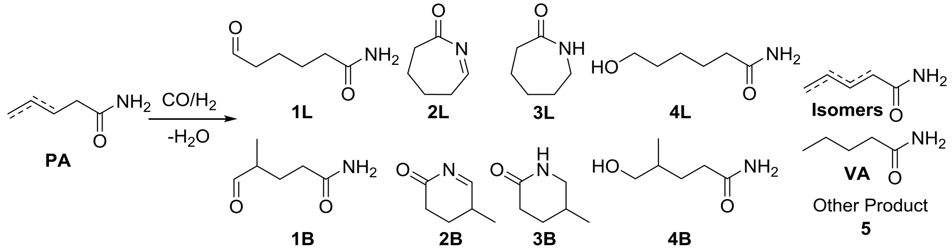
In Chapter 5 our investigations concerning the conversion of GVL to caprolactam are reported. Trans-esterification of GVL with methanol was carried out as a reactive distillation using a strong Brønsted acid as the catalyst in the reaction mixture, following a reported procedure. The distillate mixture comprises a mixture of methanol, water, cis and trans methyl 3-pentenoates (3-MP) and methyl 4-pentenoate (4-MP) as well as trace amounts of GVL, methyl 2-pentenoate (2-MP), methyl 4-methoxypentanoate (4-MMP) and methyl 4-hydroxypentanoate (4-HMP). The best result (GVL conversion >90% and MPs selectivity 95%) was achieved at 190 °C.

The mixture of methylpentenoates was subsequently converted into a mixture of the corresponding pentenamides (PA). It appeared that the use of ammonium hydroxide gave the best results: under optimized conditions >98% yield of PAs was obtained. Generally, the conversion of 4-MP proceeds more slowly than that of 3-MP, which can be explained by the inductive electron-withdrawing effect of the double bond being stronger in 3-MP than in 4-MP.



Scheme 6.7. Intramolecular hydroamidomethylation of pentenamide to caprolactam (For clarity only the linear products are depicted).

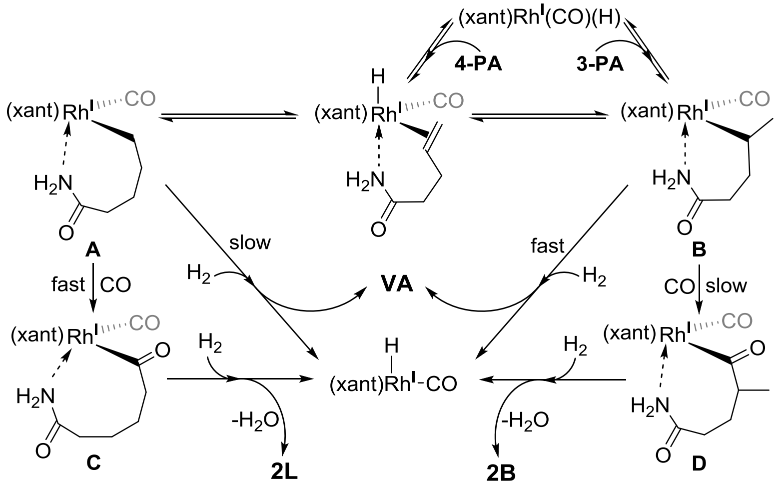
The atom-efficient and regioselective intramolecular hydroamidomethylation of the resulting pentenamides is the key step of the process to obtain caprolactam (Scheme 6.7).



Scheme 6.8. Intramolecular hydroamidomethylation of the mixture of 3-PA and 4-PA to caprolactam: observed intermediates, products and undesired by-products

We started to investigate the cascade hydroformylation-reductive amidation using pure 4-pentenamide (4-PA) as substrate under catalytic conditions developed for the reductive amidation of aldehyde (Scheme 6.8). However, only very low yields of caprolactam were obtained. The addition of HOR^F to the reaction mixture turned out to promote the hydrogenation activity of the catalyst in the presence of syngas. Although the selectivity to caprolactam significantly increased, a considerable amount of valeramide (VA) was formed. The amount of VA formed as well as the amount of oligomers and polymers appeared to be much higher when a catalytic amount of HOTs was introduced into the reaction mixture.

Surprisingly, after an attempted hydroformylation reaction of 4-PA with the Rh/xantphos system in the absence of HOTs, the main product formed in the reaction appeared to be **2L**. Apparently, the aldehyde formed in the hydroformylation of 4-PA immediately cyclizes to form the unsaturated caprolactam. An excellent conversion (98%) and selectivity for unsaturated caprolactam **2L** (~85%) was obtained under optimized conditions. The resulting **2L** then could be hydrogenated almost quantitatively to caprolactam with the same catalytic system when syngas was replaced with pure dihydrogen gas. The best result showed an overall ~90% selectivity for caprolactam **3L** based on 4-PA as the feed.



Scheme 6.9. Proposed mechanistic pathways toward the formation of various products in the hydroamidomethylation of pentenamides

Finally, the hydroamidomethylation reaction using the mixture of pentenamides produced from GVL was also studied. The use of POP-xantphos in the hydroformylation of the mixture of 3-PA and 4-PA, resulted in ~80% conversion with ~60% selectivity for the 7-membered unsaturated cyclic lactam with ~75% overall selectivity to linear products. In comparison with 4-PA, hydroamidomethylation of 3-PA results in VA as a major product, which may be explained by the chelating nature of the pentenamide. Probably, the migratory insertion of the Rh-sec-alkyl-amide structure **B** to CO to form Rh-acyl species **D** may be *disfavored* for steric reasons and relatively strong chelation of the amide functionality, whereas the hydrogenolysis rate of the Rh-alkyl species **B** may be increased due to the chelation of the amide functionality, resulting in the formation of VA (Scheme 6.9).

6.2. Conclusions and Outlook

6.2.1. General conclusions

The aim of the research described in this thesis was to investigate a new catalytic pathway toward ε-caprolactam starting from biomass-derived levulinic acid. γ-Valerolactone (GVL) can be synthesized from levulinic acid (LA), obtained from lignocellulosic biomass, via a hydrogenation reaction. The proposed route to caprolactam from the resulting bio-based GVL proceeds via trans-esterification, aminolysis and intramolecular hydroamidomethylation reactions as shown in Scheme 6.1.

The most challenging step in this reaction sequence appeared to be the intramolecular hydroamidomethylation reaction necessary to convert pentenamides to caprolactam.

The detailed studies into the separate steps led to the development of a highly selective catalyst system for the novel reductive amidation of aldehydes forming N-alkylamides in high yield and under mild conditions.

For the hydroamidomethylation of alkenes the same catalyst system in presence of syngas was shown to have insufficient hydrogenation activity. It was found that the presence of the polar, weakly acidic co-solvent appeared to be beneficial for the generation of a catalyst species that is active as a hydrogenation catalyst in the presence of carbon monoxide. By choosing the right conditions this catalytic system can be fine-tuned to make either an alcohol or an N-alkylamide from alkenes. Moreover, a mechanistic consideration not only helped in understanding the role of HOR^F in the novel hydroamidomethylation reaction, but also can be used to explain the general role of polar solvents in the hydroaminomethylation reaction.

Finally, the intramolecular hydroamidomethylation of the mixture of pentenamides was carried out, yielding caprolactam. Hydroformylation of the internal alkene 3-PA gives lower chemo- and regioselectivity (in comparison with terminal alkene 4-PA), which can be slightly improved by using of modified bidentate phosphane ligands such as POP-xantphos under lower syngas pressure and higher temperature. However, employing higher temperatures promotes hydrogenation of substrate (mostly 3-PA), thus predominantly forming VA as a by-product.

6.2.2. Outlook

6.2.2.1. The formation of primary amines

Despite recent developments in the synthesis of substituted amines, the production of primary amines is still a challenge in terms of energy demands as well as atom-efficiency (Chapter 1). Reductive amination of aldehydes and hydroaminomethylation of alkenes with ammonia is generally plagued with over-alkylation.[1, 2] The initially produced primary amine is generally more nucleophilic and reactive than ammonia, thus resulting in the formation of secondary and tertiary amines. Introducing an alternative synthesis method to catalytically form primary amines would thus be highly desirable. The hydroamidomethylation and reductive amidation reactions, as developed in our studies do not give rise to overalkylation, likely due to the lower nucleophilicity (than amine) at N of the amide functionality, as well as steric encumbrance of the formed mono-N-alkylated amide. N-alkyl amides can in principle be hydrolyzed to form the corresponding primary amine and the acid. However, this reaction is not catalytic and produces stoichiometric amounts of acid or salt. On the other hand, N-alkylformamides can in principle be decarbonylated to form the corresponding primary amine with the release of CO.

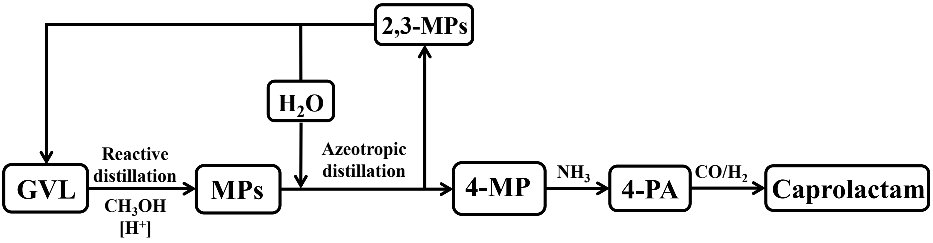
The direct hydramidomethylation of pentene with formamide so far gave only very low yields of N-hexylformamide. It appeared that HOR^F is not an effective hydrogenation promoter in the reaction with formamide due to the acetalization reaction caused by the necessary higher acid concentrations. Thus investigations to find an alternative reagent to replace HOR^F as promotor for the hydrogenation activity of the catalytic system will be required. Preferentially, a promotor should be found that does not form acetals with the intermediate aldehyde (such as sterically hindered phenols). Unfortunately, although the stoichiometric decarbonylation occurs almost quantitatively, either with several transition metal complexes or with strong-base, the *catalytic* decarbonylation of N-alkylformamide so far remains a challenge. A possible way out of this problem could involve a two-step catalytic protocol consisting of i) base-catalyzed *reactive* transesterification of the N-alkylformamide with methanol, continuously removing produced methylformate, thus producing the desired primary amine, followed by ii) amidation of methylformate with NH_3 to regenerate formamide as the substrate for the reductive amidation.

6.2.2.2. Bio-based caprolactam

The production of caprolactam from GVL, via the reactions proposed in this PhD thesis, constitutes a novel alternative and atom-efficient route starting from biomass. Despite the promising results, different strategies need to be developed in order to increase the overall efficiency to the desired caprolactam. It appeared to be challenging to control the regio- and chemoselectivity of the intramolecular hydroamidomethylation reaction of a mixture of 3- and 4-pentenamide to form caprolactam. The limiting factor is the isomerization of the internal alkenes to the terminal alkene, a reaction which must take place faster than hydroformylation or any other competing reaction, especially hydrogenation. The obvious way to achieve higher selectivity to the desired caprolactam is to further fine-tune the ligand in the catalytic system in order to give a better selectivity for the linear product in the hydroformylation step starting from internal alkenes. Modifying the ligands properties in the catalytic system, changing the electronic properties with rigid backbone spacer in xantphos or Naphos, Iphos and triphos type ligands, or using of a mixed catalyst system (such as Rh and Ni) under the optimized conditions (high temperature and low syngas pressure) could favor β-hydrogen elimination and reinsertion to give the Rh-primary alkyl species necessary for the formation of caprolactam.

Another alternative approach for achieving a higher yield of caprolactam is to utilize isomerization/separation techniques to more effectively convert levulinic acid (LA) into a pure 4-PA feed, e.g. by separating 4-MP from the mixture of MPs via azeotropic distillation with water (Scheme 6.10).[3] Furthermore, it has been reported that GVL can be converted into 4-MP with higher selectivity (60%) using a basic solid catalyst ($CsOAc/SiO_2$) at a very high temperature (350 °C), which would make a better starting point for the azeotropic distillation.[4]

The new reactions reductive amidation and hydroamidomethylation, reported in this thesis, may potentially be used for the catalytic production of important bulk chemicals. Clearly, further research is required in order to deepen knowledge on each specific area. Although we have created the fundaments for an alternative bio-based route for the synthesis of caprolactam, there are still serious challenges that need to be tackled in order to obtain a more efficient and industrially applicable process.



Scheme 6.10. A Schematic outlook for the formation of caprolactam

6.3. References

[1] T. Gross, A. M. Seayad, M. Ahmad, M. Beller, *Org. Lett.* **2002**, *4*, 2055.
[2] B. Zimmermann, J. Herwig, M. Beller, *Angew. Chem. Int. Ed.* **1999**, *38*, 2372.
[3] R. Kummer, H. W. Schneider, D. Zimmerling, *US Patent 4561942 A*, **1985**.
[4] L. E. Manzer, *WO Patent 2004/007421 A1*, **2004**.