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

Raoufmoghaddam, S.

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PhD Thesis

Development of Homogeneous Catalysts for the Selective Conversion of Levulinic Acid to Caprolactam

Saeed Raoufmoghaddam

Leiden University, The Netherlands

December 2013

Development of Homogeneous Catalysts for the Selective Conversion of Levulinic Acid to Caprolactam

PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus Prof. mr. C. J. J. M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 17 december 2013
klokke 10.00 uur

door

Saeed Raoufmoghaddam
geboren te Lahijan, Iran
in 1980

Samenstelling Promotiecommissie

Promotors	Prof. Dr. E. Bouwman
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"Anyone who has never made a mistake has never tried anything new."
Albert Einstein

"The more comfortable we become with being stupid, the deeper we will wade into the unknown and the more likely we are to make big discoveries."
The importance of stupidity in scientific research, Martin A. Schwartz

To my parents
and Azadeh

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List of abbreviations

AC	autoclave
Hacac	acetylacetone
Ad	adamantyl
bcope	1,2-bis(cyclooctylphosphanyl)ethane
bisbi	2,2’-bis(diphenylphosphanylmethyl)biphenyl
bp	boiling point
nBu	n-butyl
tBu	tert-butyl
cod	1,5-cyclo-octadiene
Cy	cyclohexyl
d	doublet (in NMR)
DBFphos	1,1'-(4,6-dibenzofurandiyl)bis(1,1-diphenylphosphane)
DCM	dichloromethane
dd	doublet of doublet (in NMR)
diglyme	bis(2-methoxyethyl)ether
dirc-2	1,2-bis(cyclooctylphosphanyl)ethane
DMA	dimethyl acetamide
DPEphos	Bis(2-diphenylphosphanylphenyl)ether
dppb	1,4-bis(diphenylphosphanyl)butane
dppbz	1,2-bis(diphenylphosphanyl)benzene
dppe	1,2-bis(diphenylphosphanyl)ethane
dppf	1,1’-bis(diphenylphosphanyl)ferrocene
dppm	1,1-bis(diphenylphosphanyl)methane
1,2-dppmb	1,2-bis(diphenylphosphanylmethyl)benzene
1,3-dppmb	1,3-bis(diphenylphosphanylmethyl)benzene
dppp	1,3-bis(diphenylphosphanyl)propane
eq	equivalent
Eq	equation
Et	ethyl
Exp.	experiment
FID	flame ionization detector (GC)
FT	fourier transform (NMR)
GC (GLC)	gas chromatography (gas liquid chromatography)

GC-MS	Gas chromatography-Mass spectrometry
GVL	*gamma*-valerolactone
h	hour(s)
4-HMP	Methyl 4-hydroxypentanoate
HOAc	acetic acid
HOTf	trifluoromethanesulfonic acid
HOTs	p-toluenesulfonic acid
HPLC	high pressure liquid chromatography
i	iso
IR	infra red
J	coupling constant
M	metal
m	multiplet
m	*meta*
Me	methyl
MS	mass spectrometry
4-MMP	Methyl 4-methoxypentanoate
2-MP	Methyl 2-pentenoate (mixture of cis and trans)
3-MP	Methyl 2-pentenoate (mixture of cis and trans)
c-3-MP	methyl cis 3-pentenoate
t-3-MP	methyl trans 3-pentenoate
4-MP	Methyl 4-pentenoate
MP	methylpentenoates (mixture of 2-, 3- and 4-MP)
NMP	N-methyl 2-pyrrolidone
NMR	nuclear magnetic resonance
o	*ortho*
oMeO-dppb	1,4-bis(di(ortho-methoxyphenyl)phosphanyl)butane
oMeO-dppe	1,2-bis(di(ortho-methoxyphenyl)phosphanyl)ethane
oMeO-dppp	1,3-bis(di(ortho-methoxyphenyl)phosphanyl)propane
P	pressue (in bar)
p	*para*
2-PA	2-pentenamide (mixture of cis and trans)
3-PA	3-pentenamide (mixture of cis and trans)
4-PA	4-pentenamide
PA	pentenamides (mixture of 2-, 3- and 4-PA)
Ph	phenyl

Phen	1,10-phenanthroline
pK_a	-log (ionization constant (K_a)); acidity
PPA	phenylphosphoric acid
$P(2,4diMeOPh)_3$	tris-(2,4-dimethoxyphenyl)phosphane
$P(2,6diMeOPh)_3$	tris-(2,6-dimethoxyphenyl)phosphane
$P(O\text{-}di\text{-}tBuPh)_3$	tris(2,4-ditert-butylphenyl)phosphite
ppm	part per million
Pr	propyl
rpm	revolutions per minute
RT	room temperature
s	singlet (in NMR)
T	temperature
t	time
t	triplet (in NMR)
tert	tertiary
Htfa	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
Htmba	2,4,6-trimethylbezoic acid
TMEDA	tetramethylethylenediamine
TMS	tetramethylsilane
TOF	turnover frequency (moles converted substrate/moles catalyst*unit of time)
Tol	toluene
TON	turnover number (moles converted substrate/moles catalyst)
UV	ultra violet
xantphos	9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene
Si-xantphos	4,6-bis(diphenylphosphanyl)-10,10-dimethyl-10H-dibenzo [b,e][1,4]oxasilane
tBu-xantphos	2,7-ditert-butyl-9,9-dimethyl-4,5-bis(diphenylphosphanyl) xanthene
$xantphos(tBu)_2$	4,5-bis[di(tert-butyl)phosphanyl]-9,9-dimethylxanthene
POP-xantphos	4,5-bis(diphenylphosphanyl)-10-phenylphenoxaphosphane

oMeO-xantphos	9,9-dimethyl-4,5-bis(di(ortho-methoxyphenyl)phosphanyl) xanthene
pMeO-xantphos	9,9-dimethyl-4,5-bis(di(para-methoxyphenylphosphanyl) xanthene
homoxantphos	10,11-dihydro-4,5-bis(diphenylphosphanyl)dibenzo[b,f] oxepine
benzoxantphos	6,7-bis(diphenylphosphanyl)benzo[k,l]xanthene

1

General Introduction

Abstract

The aim of this chapter is to introduce the readers to the importance of bio-based products and their potential applications in chemical industries. Alternative routes to the widely used nylon precursor caprolactam are discussed and compared with the current fossil-based synthesis. Furthermore, an overview is given of catalytic C-N bond forming reactions such as reductive amination of aldehydes and hydroaminomethylation of alkenes. Finally, the aim of the research - the development of a novel synthesis route to caprolactam based on biomass - is revealed; the envisaged reaction sequence includes the development of new catalytic chemistry, namely reductive amidation and hydroamidomethylation.

The introduction chapter partially will be submitted as a review paper;
Raoufmoghaddam S.; Drent E.; Bouwman E.; manuscript in preparation

1.1. Biomass

Prior to the discovery of the fossil reserves, society was contingent upon biomass to supply energy demands. The discovery of crude oil, in the nineteenth century, provided a convenient and low-priced liquid fuel resource that promoted industrialization of the world. In recent years, diminishing petroleum reserves combined with an increased demand for energy and rising crude oil price have drawn attention to develop economical and energy-efficient processes for the sustainable production of fuels and chemicals. The global energy demand is predicted to grow up to 50% by 2030, which will have an additional impact on the climate as well as our planet. The recent United Nations Framework Convention on Climate Change has ratified the Kyoto Protocol that is intended to reduce global emissions by at least 20% by 2020 and by 50% - 60% by 2050 relative to the emission level in 2006.[1] Plant biomass is the only current sustainable source of chemicals and bio-fuels.[2-5] A significant advantage of bio-based products is the differences in the green-house gas emissions. The bio-fuels are generally considered to emit less green-house gas than the fossil fuels.[6-9] Nevertheless, there are also growing concerns about the overall sustainability regarding the change in land usage, intensified use of agricultural inputs and limitation on food security.

A number of materials potentially useful as bio-based feedstock such as lignocellulose, proteins, oils, lignin, hemicellulose, cellulose, or starch have been identified.[10] Lignocellulosic biomass is one of the most abundant and attractive sources of biomass for the production of bio-based chemicals.[11-14] One of the drawbacks of lignocellulosic biomass is that it typically contains 40-45 wt% oxygen which decreases the heating value. Lignocellulosic biomass can be converted into liquid fuels by three primary routes, including syngas production by gasification, bio-oil production by pyrolysis or liquefaction, or hydrolysis to produce sugar monomer units. Synthesis gas can be used to produce hydrocarbons (diesel or gasoline), methanol, and other fuels via the classical Fischer-Tropsch process.[15-18]

Cellulose (a crystalline glucose polymer) and hemicellulose (a complex amorphous polymer; the major component is a xylose monomer unit) form 60-90 wt% of terrestrial biomass. Cellulose consists of a linear polysaccharide and the top and bottom of the cellulose chains are essentially hydrophobic.[4] Upon partial acid hydrolysis, cellulose is broken into cellobiose (glucose dimer), cellotriose (glucose trimer), and cellotetrose

(glucose tetramer), whereas upon complete acid hydrolysis it forms glucose.[19] Hemicellulose is a sugar polymer that typically constitutes 20-40 wt% of biomass which is a polymer of five different sugars comprising five-carbon sugars (mostly xylose and arabinose) and six-carbon sugars (galactose, glucose, and mannose). The most abundant building block of hemicellulose is xylan (a xylose polymer linked at the 1 and 4 positions).

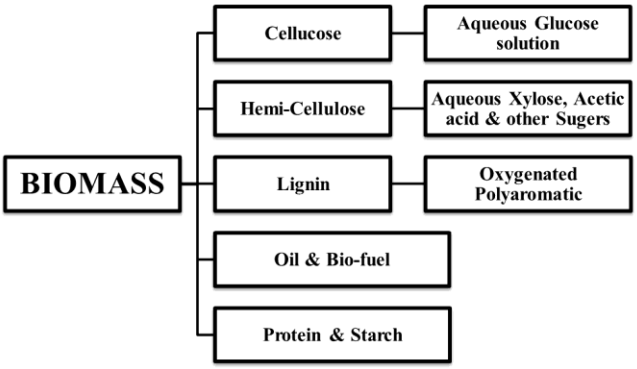


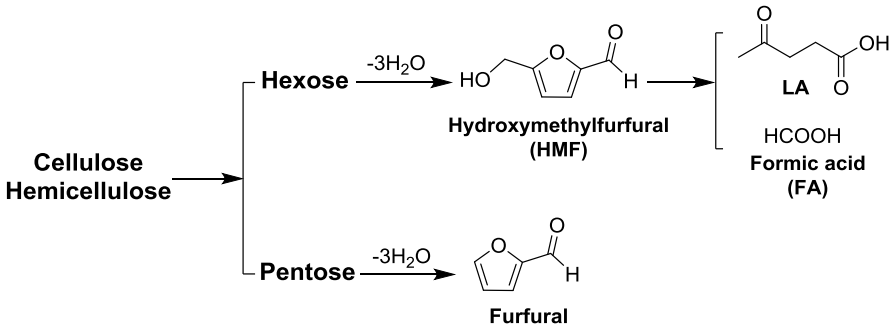
Figure 1.1. Classification of different biomass-derived feedstock

Lignin, a large polyaromatic compound, is the other major component of biomass (10-25 wt%) which is a highly branched, substituted, aromatic polymer. Lignin is often associated with cellulose and hemicellulose forming lignocellulose. Other components called extractives are defined as those compounds that are soluble in solvents such as water, ethers or methanol which involve different types of carbohydrates such as sucrose from sugarcane and amylose from corn grains.[1, 2, 18]

In the biomass conversion process cellulose and hemicellulose can be converted into xylose and glucose. Then, furfural and hydoxymethylfurfural (HMF) can be produced from the remaining sugar stream by acid-catalyzed dehydration (Scheme 1.1).[20]

HMF is one of the top building-block chemicals obtained from biomass which can be used to synthesize a broad range of chemicals currently derived from petroleum.[12, 20-23] However, obtaining a highly selective process to produce HMF is still crucial as the current procedure leads to a relatively high manufacturing cost of HMF due to the formation of by-products, thus limiting its potential as a key platform chemical.[24, 25] A number of important compounds can be formed from HMF such as

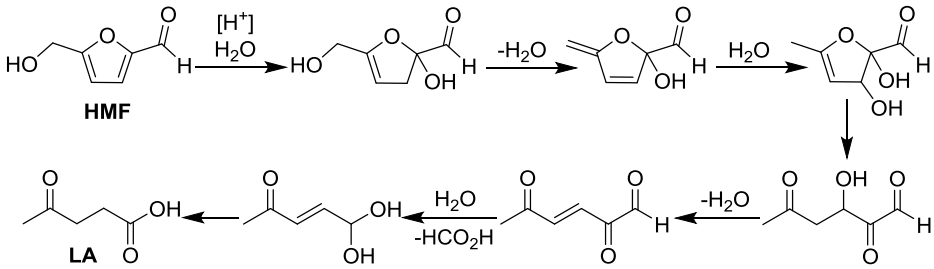
alkoxymethylfurfurals, 2,5-furandicarboxylic acid, 5-(hydroxymethyl)furoic acid, bis(hydroxymethyl)furan, 2,5-dimethylfuran and levulinic acid (LA).[26]



Scheme 1.1. Hydrolysis and degradation of cellulose and hemicellulose to furfural, HMF and levulinic acid (LA)

1.2. Bio-based levulinic acid (LA)

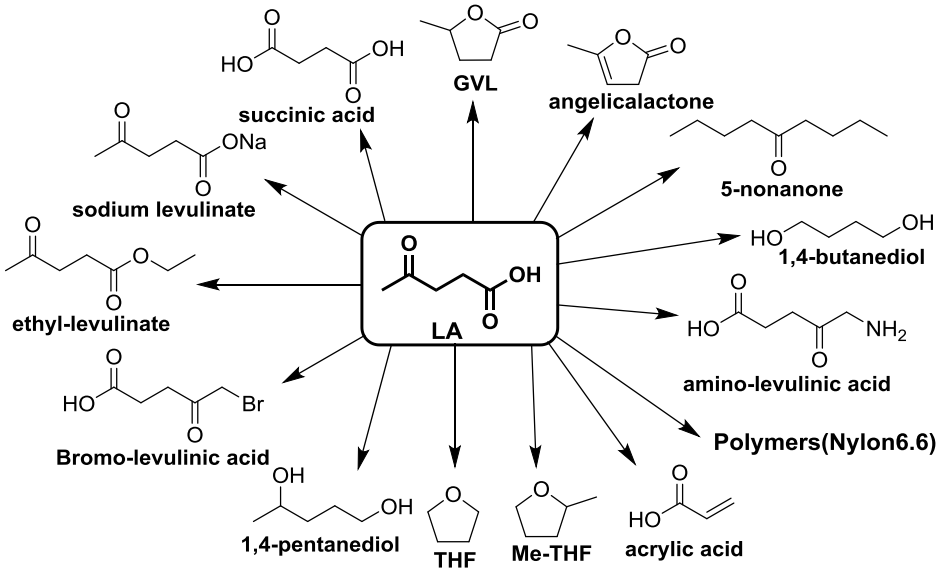
One of the key substances produced from HMF is levulinic acid (LA) which potentially is an important platform molecule for versatile industrial applications such as production of fine chemicals, pharmaceuticals, polymers, solvents and fuels.[27-31] As shown in Scheme 1.2, levulinic acid is the final acid-catalyzed dehydration product formed from cellulose together with formic acid (in a 1:1 molar ratio) and water as co-products.[32-34] The theoretical yield of LA from C6-sugars is 100 mol% or 64.5 wt% due to the coproduction of formic acid.[28, 35] Commonly, LA yields up to two-thirds of the theoretical value are attained, due to side reactions that form undesired black insoluble-materials called humins.[36]



Scheme 1.2. Proposed mechanism for formation of levulinic acid from HMF

The reactivity of the carbonyl functionalities in LA makes it an ideal intermediate for the production of useful chemicals including succinic acid, resins, polymers (nylon precursor, caprolactam), herbicides, pharmaceuticals, flavoring agents, solvents, plasticizers, antifreeze agents and biofuels/oxygenated fuel additives (Scheme 1.3).[37-41]

The current synthetic method for the production of high purity levulinic acid is based upon the conversion of maleic anhydride[42] or hydrolysis of furfuryl alcohol[43, 44] which reactions are more complicated than the acid hydrolysis of biomass. The reasons for restricted manufacturing of levulinic acid production are the cost of raw material used in the synthesis, low yield (due to the formation of undesired side reactions and polymerization of products), equipment costs, high energy input and waste disposal issues.[45]

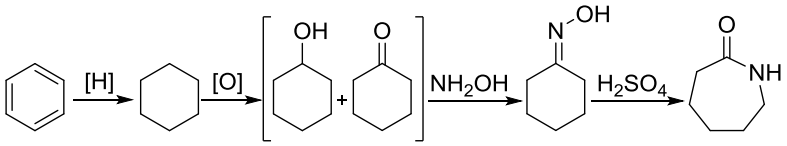


Scheme 1.3. Levulinic acid as an important platform for the production of other chemicals and fuel components

1.3. Synthesis of caprolactam

1.3.1. Industrial production

ε-Caprolactam is the polymer precursor for nylon-6, an extensively used synthetic polymer with an annual production of about four million tons.[46] Caprolactam was first introduced in the late nineteenth century by the cyclization of 1-aminocaproic acid, and then became an important chemical with commercial interest in 1938 by the poly-condensation of caprolactam producing nylon-6.[47] Caprolactam is a monomer for the nylon-6 polyamide which shows excellent properties including high strength-to-weight ratio and good chemical and thermal stability. Nylon-6 is widely used in the manufacture of fishing nets, tires, strings, industrial drive belts, fibers and plastics.[48]



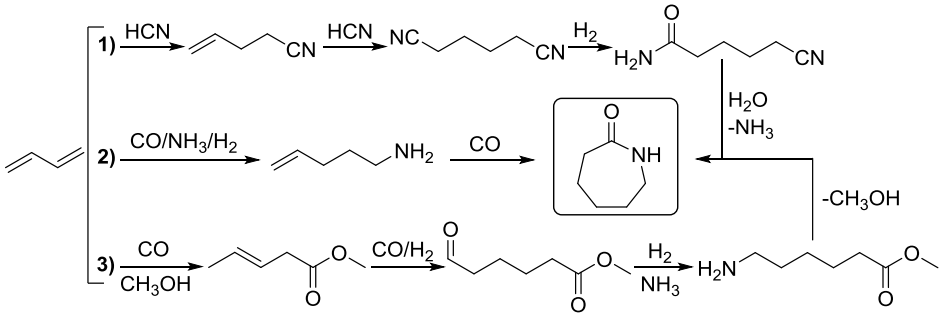
Scheme 1.4. Industrial synthetic route for the production of caprolactam

Several synthetic routes have been reported for the synthesis of caprolactam, which produce relatively large amounts of by-products, mainly ammonium sulfate. This ammonium sulfate can be used as a fertilizer, but in recent years it is being replaced by nitrate or urea fertilizers because of their higher nitrogen content. However, ammonium sulfate is still used as a fertilizer in some countries and on sulfur-poor soils.[48] The synthesis of ε-caprolactam is typically carried out in a four-step procedure[49] including synthesis of cyclohexanone either by oxidation of cyclohexane,[50, 51] or by hydrogenation of phenol,[52, 53] followed by the formation of cyclohexanone oxime.[54, 55] Through a Beckmann rearrangement of this oxime in sulfuric acid ε-caprolactam is obtained.[56-59] In the process water is added for dilution of the acid and purification process which ultimately needs to be evaporated.[60] The increasing demand for ε-caprolactam has provoked the chemical companies to extend their efforts to explore more efficient synthetic routes[61-63] as well as alternative production pathways[64] for this bulk chemical.

1.3.2. Alternative routes

1.3.2.1. Butadiene-based routes

One alternative route for the production of caprolactam comprises the hydrocyanation of butadiene to 1,6-hexanedinitrile which is a process based on homogeneous nickel phosphite catalysts. In the second step the 1,6-hexanedinitrile is hydrogenated with molecular hydrogen in presence of a Raney nickel catalyst with a good yield (conversion: 70-85% and selectivity to 6-aminohexanenitrile: 85-100%).[65, 66] The last step is the hydrolytic cyclization of 6-aminohexanenitrile, either in the gas phase or in the liquid phase with good results (90-99%) using SiO_2 or manganese zirconium oxide phosphate catalysts (Scheme 1.5).[67-71] One major disadvantage of the hydrocyanation route is the high cost of HCN as N source while one mole of N/mole of caprolactam is down-graded to an ammonium salt co-product.



Scheme 1.5. Alternative synthetic routes starting from 1,4-butadiene for the production of caprolactam; 1) via multi-step reaction consisting hydrocyanation, selective hydrogenation and cyclization; 2) via two-step reaction including hydroaminomethylation of butadiene with ammonia and intramolecular aminocarbonylation of aminopentene; 3) via multi-step reaction including methoxycarbonylation, hydroformylation, reductive amination and cyclization

Another route involves hydroaminomethylation of butadiene with ammonia[72] and a subsequent cobalt-catalyzed intramolecular aminocarbonylation to form caprolactam.[73] However, obtaining a very selective hydroaminomethylation with large excess amount of ammonia and high temperature in the first step is challenging (see also Section 1.4). Furthermore, the low selectivity for caprolactam (~40% in the best case) with the formation of different products including nylon-6 oligomers in the second step are still problematic.[73]

The third alternative route producing caprolactam from butadiene is called the hydroesterification route,[74-77] which is based on an initial methoxycarbonylation[78-81] of butadiene to form methyl 3-pentenoate (3-MP).[82, 83] The hydroesterification of butadiene with carbon monoxide and methanol in the presence of a cobalt or palladium catalyst results in high yield with only negligible amounts of by-products like methyl valerate and 4-vinylcyclohexene.[74, 84, 85] For the next step, an isomerization-hydroformylation reaction must be carried out, which results in 30-90% conversion with 65-75% selectivity to methyl 5-formylvalerate.[86] In the third step the methyl 5-formylvalerate can be either reductively aminated to 6-aminohexanoate and then cyclized, or acid hydrolyzed to 5-formylvaleric acid and then reductively aminated and subsequently cyclized (scheme 1.5).[84, 86-93] The first route (reductive amination and cyclization) can be performed in the liquid[75, 94] or the gas phase,[95] both over hydrogenation catalysts in the presence of NH_3, H_2 and NiO–MgO–SiO_2 or ruthenium on Al_2O_3 carrier with 80-95% yield.[75, 93, 95] In the second route, 5-formylvaleric acid is obtained with 74% yield[96] over cation-exchanged resin catalyst; reductive amination to 6-aminohexanoic acid in presence of a Raney Ni catalyst yields 57% of 6-aminohexanoic acid. Finally, this product is cyclized to caprolactam (95-99%) with or without a catalyst at high temperature.[48]

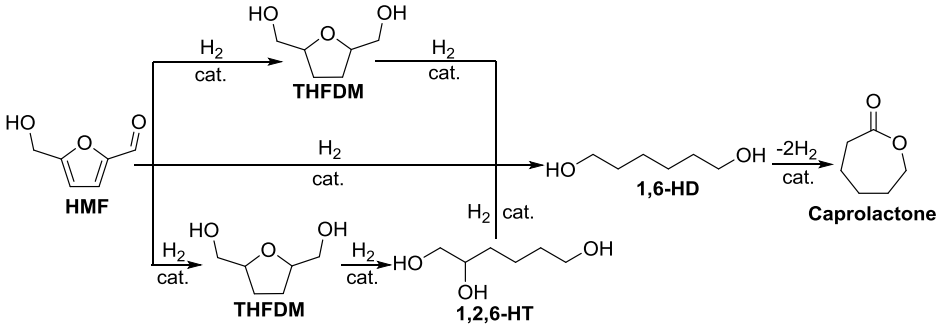
Apart from being fossil-based, the major drawbacks of the butadiene-based caprolactam routes are the necessity of several separations and recycling steps of the products and by-products as well as employing severe conditions with relatively low efficiency.[48]

1.3.2.2. Biomass-based route

Recently, an alternative route to caprolactam has been proposed based upon a multi-step catalytic conversion of hydroxymethylfurfural (HMF) to caprolactone.[64] The demonstrated reaction sequence contains several steps including hydrogenation of HMF to 1,6-hexanediol (1,6-HD) and catalytic conversion of 1,6-HD into caprolactone (Scheme 1.6).[64]

The one-step hydrogenation HMF to 1,6-HD was performed under severe conditions (270 °C, 150 bar H_2) with a mixture of copper chromite and Pd/C (1:0.6). After 16 hours, 100% conversion of HMF to a mixture of products, mainly 2,5-tetrahydrofuran-dimethanol (THFDM) was obtained (less than 4% of desired 1,6-HD). The hydrogenolytic ring opening of THFDM to 1,6-HD using CuCr (consisting of 75%

$Cu_2Cr_2O_5$ and 25% CuO) gave a maximum selectivity of 41% to 1,6-HD with 41% conversion of THFDM. On the other hand, the similar reaction using THFDM as the substrate to form 1,2,6-HT was also investigated using Rh-Re/SiO_2 catalyst. A 97% selectivity to 1,2,6-HT was obtained with only 21% THFDM conversion after 20 hours at 80 °C and 80 bar H_2. The use of higher temperatures and longer reaction time led to a drop in selectivity to 1,2,6-HT. Subsequently, in a two-step reaction, further reduction with the same catalyst in the presence of triflic acid (HOTf) at 125-180 °C and 80 bar H_2 was carried out and 99% selectivity to 1,6-HD at 17% 1,2,6-HT conversion was obtained. The direct formation 1,6-HD from THFDM under optimized condition (Rh-Re/SiO_2, 80 bar H_2, 120 °C, acid catalyst and 20 h) revealed full conversion with 86% selectivity to 1,6-HD. The final step was carried out to form caprolactone from 1, 6-HD using Ru catalyst which turned out to give 99% selectivity to the desired caprolactone.[64]



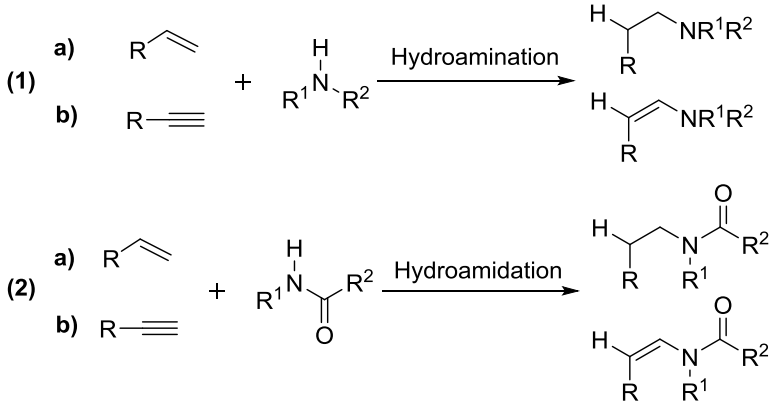
Scheme 1.6. Alternative synthetic routes reported for the conversion of bio-based HMF into caprolactone as a precursor of caprolactam

1.4. Homogeneously-catalyzed C-N bond forming reactions

1.4.1. Hydroamination and hydroamidation of alkenes and alkynes

The catalytic formation of carbon–nitrogen bonds and more importantly amide bonds offer potential advantages over conventional methods of C-N coupling reactions, where large quantities of salts are produced stoichiometrically as by-products. Among the different catalytic methods of carbon-nitrogen bond formation, the most studied and challenging methods are hydroamination and hydroamidation of alkenes and alkynes with amines and amides (Scheme 1.7).[97-106] The hydroamination of alkenes or alkynes

is defined as the addition of an H-NR^{1}R^2 bond across an alkene or alkyne providing a next higher substituted alkyl- or alkenylamine, respectively (Scheme 1.7, reaction 1a-b).

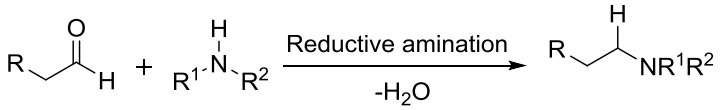


Scheme 1.7. Hydroamination; hydroamidation reactions

This reaction, which can be catalyzed both by transition metal complexes or by strong base, has been mostly studied with secondary and primary amines rather than ammonia; due to the need of high ratio of ammonia/alkene as well as the subsequent reactivity of the primary reaction product.[104, 107] The catalytic hydroamination reaction of olefins is further characterized by low rates and low catalyst turnover numbers, as the thermodynamic driving force for the intermolecular version of hydroamination is close to zero or even negative at the elevated temperatures generally required for the reaction to proceed. The related hydroamidation reaction, involving the addition of an amide's N-H bond to an alkene (Scheme 1.7, reaction 2a-b) has also been studied; application of this reaction in an intermolecular fashion suffers from similar problems as mentioned for intermolecular hydroamination, in particular with alkenes as substrate.

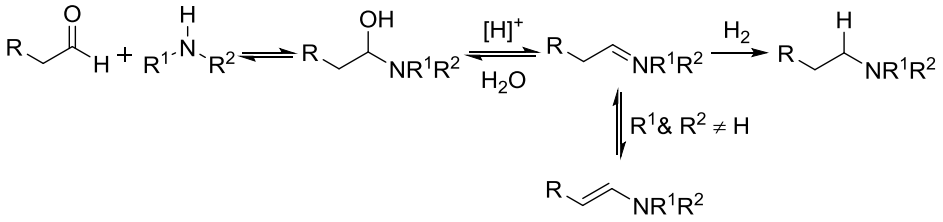
1.4.2. Reductive amination of aldehydes

The reductive amination of carbonyl compounds is of great importance in synthetic organic chemistry (Scheme 1.8).[108-111] In principle, this reaction can be performed with high atom efficiency, with very limited waste formation, fulfilling one of the requirements of green chemistry.



Scheme 1.8. Reductive amination of aldehydes

The reductive amination of aldehydes typically proceeds in several consecutive steps. Generally, the reaction progresses via the initial formation of an intermediate carbinolamine by nucleophilic addition of an amine to an aldehyde; this carbinolamine is dehydrated to form an imine, which is then reduced to form the amine product (Scheme 1.9).[108, 112-114] Some reports provided evidence suggesting a direct reduction of the carbinolamine.[108, 115] The main side reaction in the reductive amination concerns the formation of an alcohol from the competing hydrogenation of the unreacted aldehyde. Another side reaction comprises the aldol condensation of aldehyde which can be suppressed by optimizing the process.[108]



Scheme 1.9. Separate steps of the catalytic reductive amination of aldehydes

In the reductive amination the choice of reducing agent play an important role to the success of the reaction in which the imine intermediates need to be reduced selectively over the aldehydes. Traditionally, the reductive amination of aldehydes is carried out using stoichiometric amounts of reducing agents such as borohydrides,[116-119] formates,[120-123] silanes[124, 125] and many other different reagents.[126, 127] However, all of these methods are not atom efficient.

The use of heterogeneous catalysts in the reductive amination such as Raney-nickel, Pt/C, Pd/C, Pd/Al_2O_3, $Pd/CaCO_3$, $Pd(OH)_2$ and metal nanoparticles in presence of dihydrogen gas as reducing agent have also been reported.[112, 128-131]

A few homogeneously-catalyzed reductive amination reactions have been reported using transition metals (Pd, Pt, Ir, Ru and Rh) in combination with different ligands,[111, 113, 126, 132-136] as well as iron complexes[137-139] and cobalt complexes in presence of an alcoholic solvent as a source of hydrogen.[140, 141]

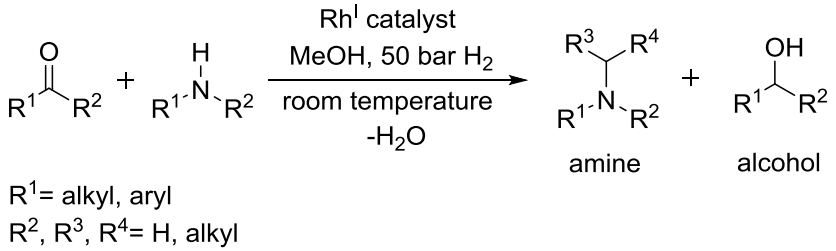
A more practical method is to employ molecular hydrogen as a reducing agent in the reaction in the presence of a catalyst. Clearly, the use of molecular hydrogen in the catalytic reductive amination is the most atom-economic and environmentally friendly, particularly in large-scale reactions.[111, 131, 142-145]

Some examples concerning the catalytic reductive amination of aldehydes using molecular hydrogen are collected in Table 1.1. The success of this procedure requires the reduction of the carbonyl compound to be relatively slower than the reduction of imine intermediate.

Table 1.1. Overview of different reaction conditions used in the catalytic reductive amination of aldehydes in presence of molecular hydrogen

aldehyde	amine	reagent	conditions	amine selectivity	research group
bezaldehyde derivatives	aniline derivatives	5 mol% $Cu(OAc)_2$, molecular Sieves	Toluene, 50 bar H_2, 120°C, 24h	75-85%	Beller (Green Chem., **2012**, 14, 2371
bezaldehyde derivatives	aniline derivatives	4 mol% $Fe_3(CO)_{12}$	Toluene, 50 bar H_2, 65°C, 24h	65-95%	Beller (Chem. Asian J. **2011**, 6, 2240)
bezaldehyde	ammonia	1 mol% Pd/C,	MeOH, 40 bar H_2, 90°C, 10h	sec. >80%	Gu (Chem.Commun. **2012**, 48, 9631)
alkyl aldehydes	Secondary amines	5 mol% [Fe^{II}], Me_3NO (5 mol%)	EtOH, 5 bar H_2, 85°C, 12h	35-90%	Renaud (Angew. Chem. Int. Ed. **2012**, 51, 4976)
aliphatic aldehydes	Secondary amines	0.2 mol% [Rh(dppb)(cod)]BF_4	MeOH, 50 bar H_2, 25°C, 20h	40-90%	Börner (Chem. Commun. **2000**, 1867; Adv. Synth. Catal. **2002**, 344, 200)
benzaldehyde derivatives	ammonia	0.5 mol% [Rh], 1.3 mol% TPPTS	H_2O/THF, 65 bar H_2, 135°C, 2h	33-86%	Beller (Org. Lett. **2002**, 4, 2055)

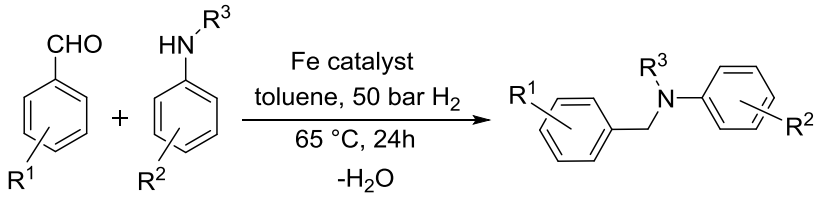
The reductive amination of aldehydes with secondary amines (like piperidine) has been reported employing a rhodium precursor in combination with bidentate phosphane ligands (Scheme 1.10).[111] The best results revealed nearly full conversions with the relatively high amine/alcohol ratios (3-12); however, the amine/alcohol ratios for the benzaldehyde derivatives were rather low (< 2).



Scheme 1.10. Reductive amination of aldehydes with secondary amines using rhodium (I) catalyst

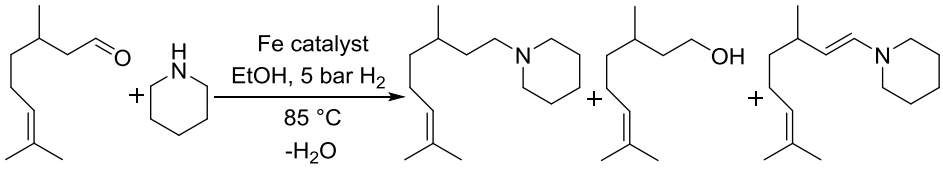
The use of chelating phosphane ligands (like dppb) for the reaction appeared to be necessary for high selectivity to the amine. Furthermore, a good correlation between the selectivity of the reaction and the basicity and steric hindrance of the amine substrate was shown. Use of more basic amines as a substrate resulted in higher selectivity and higher amine/alcohol ratios.

Beller and co-workers recently reported the use of iron carbonyl complexes in the reductive amination of carbonyl compounds with aromatic amines (Scheme 1.11).[137] The inexpensive iron catalyst gave good to excellent yields of 68–97% of alkylated amines for a range of aryl, alkyl, and heterocyclic ketones as well as aldehydes with primary and secondary anilines.



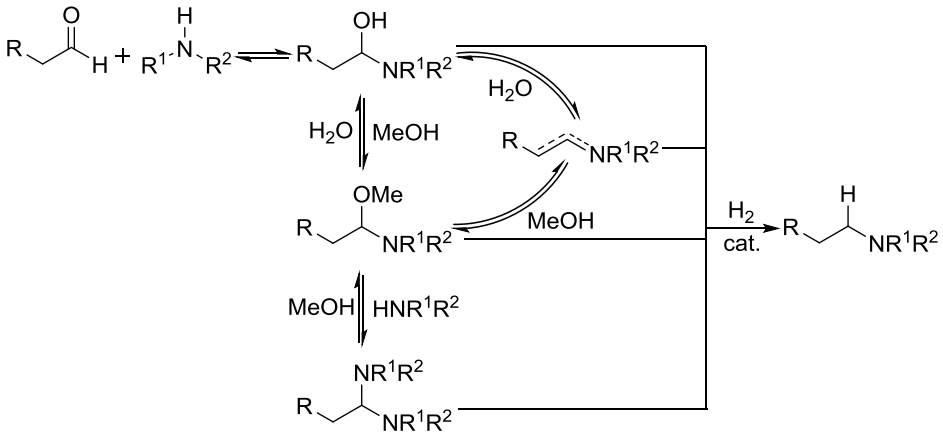
Scheme 1.11. Reductive amination of aldehydes with various aniline derivatives using Fe catalyst

More recently, the reductive amination of 3,7-dimethyl-6-octenal (citronellal) with piperidine catalyzed by iron complexes under low hydrogen pressure (5 bar H_2) and in mild reaction conditions (85 °C) in ethanol was reported (Scheme 1.12).[138] The scope of the reaction using citronellal with different amines revealed moderate to good yields (38-94%) under optimized conditions.



Scheme 1.12. Reductive amination of citronellal with piperidine using Fe catalyst

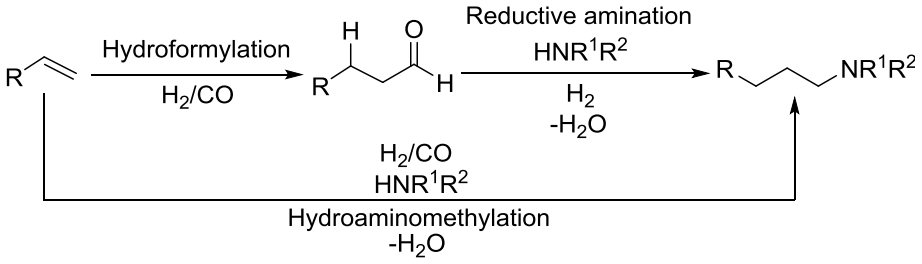
It is imperative to note that alcohol as a solvent typically has a positive role in the hydrogenolysis step and promotes the hydrogenation activity. It has been postulated that the mechanism contains several equilibrium reactions in which the intermediates ultimately undergo hydrogenation to form amine products (Scheme 1.13).[145]



Scheme 1.13. Proposed mechanism for the reductive amination of aldehydes using molecular hydrogen

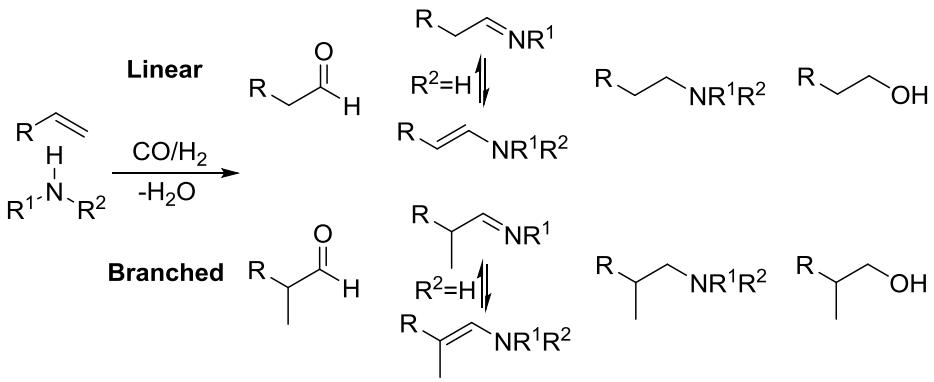
1.4.3. Hydroaminomethylation of Alkenes

The hydroaminomethylation of alkenes is a cascade reaction of two consecutive reactions. The alkene substrate first undergoes a hydroformylation reaction[146] to form an aldehyde; and then the reductive amination of the resulting aldehyde with an amine produces an N-alkylated amine (Scheme 1.14).[108-111]



Scheme 1.14. Hydroaminomethylation reaction

Despite the fact that the hydroaminomethylation reaction was originally discovered by Reppe in the early 1950s at BASF using $Fe(CO)_5$ in nearly stoichiometric amounts,[147, 148] intensive research on this topic only started in the past fifteen years. Research on this reaction until the mid-1990s revealed that relatively harsh conditions (> 150 °C) were required to give the desired amines in good yield.[149-157] Generally, the cascade hydroaminomethylation results in the formation of various intermediates and products depending on the reaction conditions and the type of catalyst used in the reaction (Scheme 1.15).



Scheme 1.15. Overview of hydroaminomethylation of alkenes; formation of various products

In the following years, most of the reports described the hydroaminomethylation as a versatile, selective and atom-efficient tool for the synthesis of a range of organic compounds, including fatty amines from unsaturated fatty acid esters,[158-161] pharmaceuticals compounds[162, 163] and heterocyclic rings *via* ring-closing intramolecular hydroaminomethylation reaction.[164-169]

The critical step in this reaction sequence is the hydrogenation of the intermediate imino compounds, which is generally hampered by the presence of carbon monoxide; however, over the last decade significant progress has been made and the problem was reduced by using alcoholic and polar solvents.[162, 170-175] In recent years, the focus has been on catalyst development to obtain the desired chemo- and regioselectivity for the reaction.

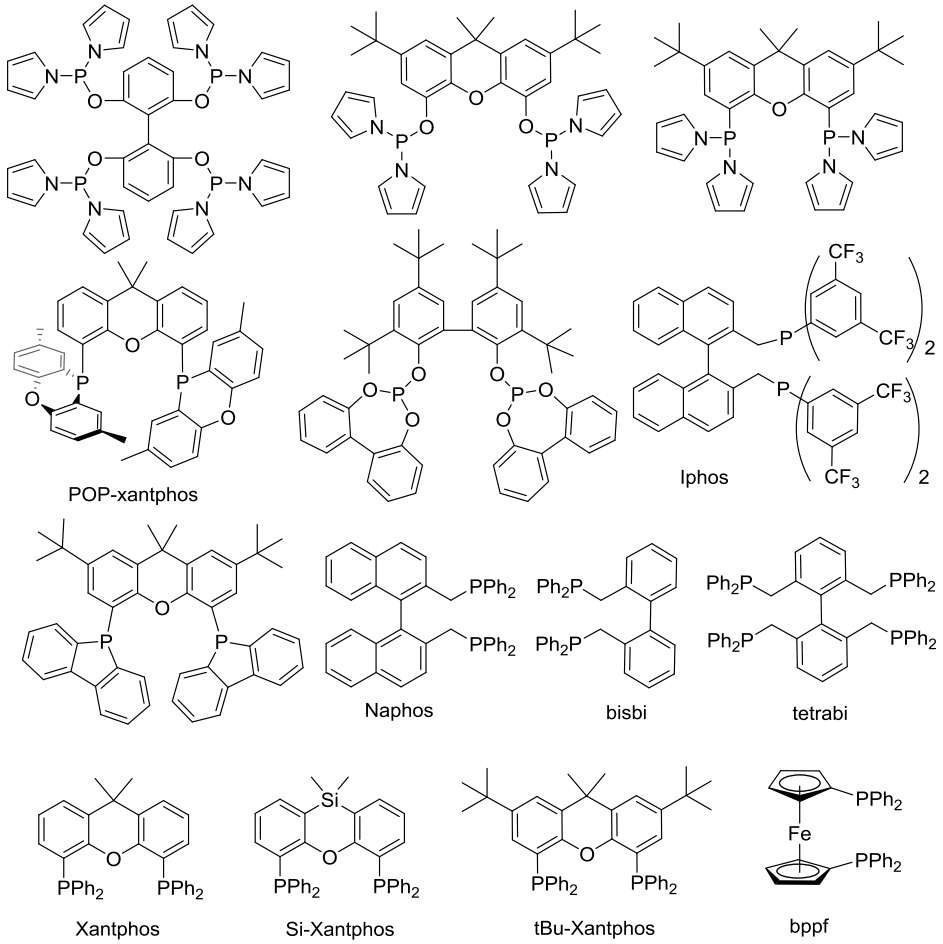
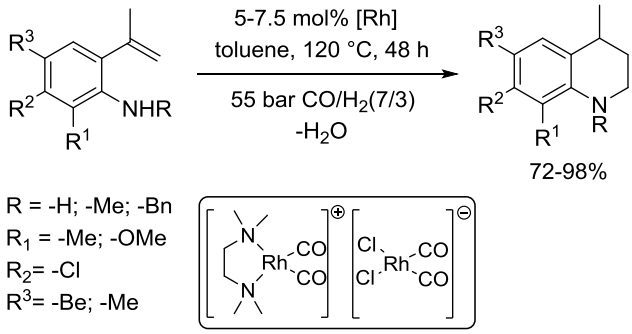


Figure 1.2. Selected ligands used in hydroaminomethylation of alkenes

To achieve good regioselectivity for the hydroformylation step the use of ligands with large bite angle (β_n) is important for obtaining good regioselectivity, promoting the formation of linear aldehydes.[146, 176, 177] The electronic properties of a ligand influences on the activity and regioselectivity of the catalytic system.[178, 179] The π-acidic ligands are known to afford high activities in rhodium-catalyzed hydroformylation.[146]

The ligands shown in Figure 1.2 are particularly adapted to produce the linear aldehyde in the hydroformylation step, even when starting from an internal alkene.[146, 176, 180-183] It has also been reported that the use of these bidentate phosphite ligands give good results in the hydrogenation step.[184, 185] Although the phosphite ligands are seemingly attractive for the hydroaminomethylation reaction, they have often been considered as unsuitable due to their sensitivity to hydrolysis.[175]

The use of bidentate phosphane ligands, such as xantphos, Naphos, Iphos, POP-xantphos bisbi and tetrabi has been reported mainly for hydroaminomethylation of aliphatic alkenes (Figure 1.2).[170, 171, 173, 186] Di-pyrrolylphosphane ligands in combination with Rh have also been introduced for the hydroaminomethylation reaction and resulted in satisfactory selectivity of amine.[172] Furthermore, the use of nitrogen-containing ligands in combination with a rhodium precursor has recently been reported showing a good selectivity, but with large catalyst loading (Scheme1.16).[168, 169, 187]



Scheme 1.16. Rhodium catalyzed intramolecular hydroaminomthylation of 2-isopropylanilines

The use of other ligands in the catalytic systems, such as bis-pyrazolylmethane (bpm),[188] mixed phosphane-amine[189, 190] and N-heterocyclic carbene (NHC) ligands [162, 167, 191] have been reported to give satisfactory selectivities (Table 1.2).The group of Beller was the first to report rhodium based catalytic systems to transform both terminal and internal alkenes into linear amines with very high regioselectivities (Table 1.2).[170, 171, 175, 192]

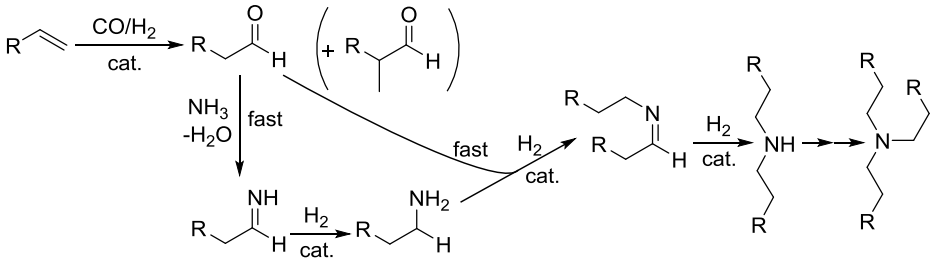
Table 1.2. Overview of different reaction conditions used in the hydroaminomethylation of alkenes

alkene	amine	reagent	condition	amine selectivity	group
1-dodecene	morpholine	1 mol% Rh, BISBIS	[Bmim][p-$CH_3C_6H_4SO_3$],CO /H_2, 130°C, 5h	45-75%	Luo (Green Chem., **2006**, 8, 545)
Intramolecular (alkene and secondary amine)		2.5-7.5 mol% Rh	toluene,CO/H_2, 120°C, 48h	60-90%	Alper (Org. Lett., **2008**,10, 485; Chem. Commun., **2007**, 2710)
1-alkenes	piperidine	0.02-0.09 mol% Rh, sulfoxantphos	[PMIM][BF_4], CO/H_2,125°C,17h	>90%	Vogt (Adv. Synth. Catal. **2008**, 350, 332)
1,1-diphenyl-ethene	piperidine	0.2 mol% Rh, carbene ligand (NHC)	toluene, CO/H_2, 125°C, 24h	11-99%	Beller (Chem. Eur. J. **2007**, 13, 1594; Tet.Lett.44, **2003**,1679)
alkenes	amine derivatives	0.4 mol% Rh, POP-xantphos or Iphos or Naphos	tol/MeOH(1/1), CO/H_2, 125°C, 16-24h	50-90%	Beller(Chem.Eur.J.**2006**,12,79; J.Am.Chem.Soc.**2003**,125,103 11;Science**2002**,297,1676)
limonene	amine derivatives	1.25 mol% Rh, PPh_3	THF, CO/H_2, 100°C, 10-19h	0-90%	Rosa (Catal. Commun. 9, **2008**,1066)
1-alkenes	amine derivatives	1 mol% Rh, biphephos	[bmim][BF_4], CO/H_2, 110°C, <1h, MW	55-90%	Taddei (Tet. Lett. 48, **2007**, 8501)
N-methylallyl-phthalimide	amine derivatives	1 mol% Rh	toluene or dioxane, CO/H_2, 100-140°C, 72h	44-96%	Elibracht (Org. Biomol. Chem., **2006**, 4, 826)
allyl alcohols	secondary amines	0.5 mol% Rh, biphephos	toluene or dioxane, CO/H_2, 120°C, 45-65h	>95%	Eilbracht (Tetrahedron 60, **2004**,11487; Tetrahedron 59, **2003**, 8265)
allyl alcohols	secondary amines	0.2 mol% Rh, biphosphite	THF, CO/H_2, 75°C, 18h	>65%	Whiteker (Org. Lett., 7, **2005**, 4795)
alkenes	secondary amines	0.1 mol% Rh, tetrabi	iPrOH/EtOH(2/1) or iPrOH, CO/H_2, 125-135°C, 12-36h	80-99%	Zhang(Chem.Eur.J.**2011**,17,14 559;Org.Lett.,14,**2012**,102; Adv.Synth.Catal.**2011**,2665; Chem.Eur.J. **2010**, 16, 4938; Org. Lett., 15, **2013**, 1036)
Styrene derivatives	aryl hydrazine	0.5 mol% Rh	toluene, CO/H_2, 100°C, 48-72h	23-57%	Eilbracht (Org. Lett., 5, **2003**, 3213)
1-octene	piperidine	0.1 mol% Rh, Xanthene-pyrrolo Ligand	tol/MeOH(1/1), CO/H_2,110°C,17h	>85%	Vogt (ChemCatChem **2009**, 1, 103)
1-alkenes	secondary amines	5-10 mol% In or Ti	toluene, CO/H_2, 80-160°C, 24-96h	5-95%	Doye (Angew. Chem. Int. Ed. **2010**, 49, 2626)

As shown in Table 1.2, the hydroaminomethylation of various alkenes (mostly terminal) with different (mostly secondary) amines has been studied using rhodium precursor in combination with phosphane ligands (or NHC ligand). The use of other metal precursors such as indium or titanium has been rarely studied and very high temperature (160 °C) must be employed in the reaction to obtain to a high conversion (Table 1.2).

The impact of solvents in the hydroaminomethylation reaction is quite considerable specifically on the hydrogenation activity. The acidity of the alcohol (for instance in a toluene/alcohol (1/1) solvent mixture) influences the catalytic performances in the hydrogenation reaction. The highest combined activity, regio- and chemoselectivity values were achieved for the reactions performed in toluene/EtOH using rhodium/bidentate phosphane catalyst (95% conversion, n/iso>200, >90% selectivity) or toluene/n-BuOH (88% conversion, n/iso=160, >98% selectivity) mixtures. The use of more acidic alcohols led to higher activities, but side-reactions like aldol condensation also occurred.[172]

The main drawback of the hydroaminomethylation reaction is that it is mostly limited to the use of secondary amines; for primary amines and more specifically ammonia the selectivity generally is particularly low because of over-alkylation.[72, 193, 194]



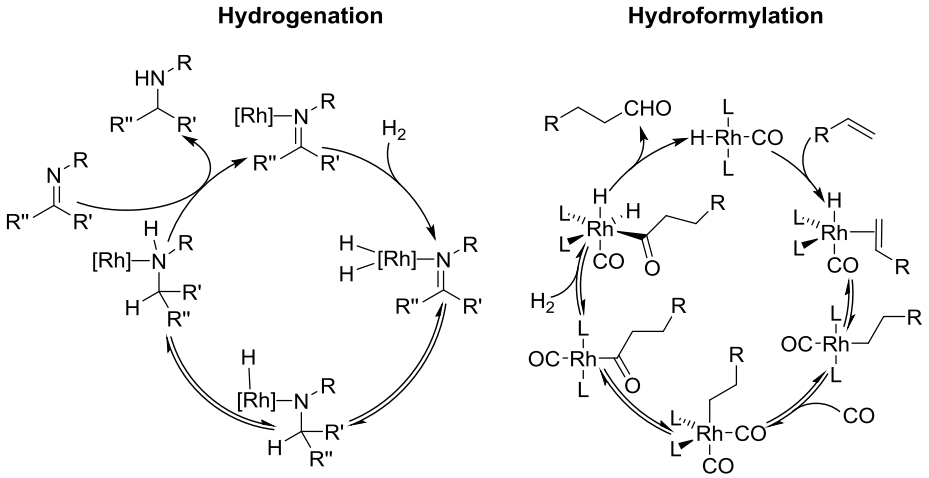
Scheme 1.17. Hydroaminomthylation of alkenes with ammonia; formation of primary, secondary and tertiary amines

The study on hydroaminomethylation with ammonia is still rarely undertaken. One of the difficulties is that the initially produced primary amine is more reactive than ammonia, and reacts preferentially to form secondary and tertiary amines. Moreover, the large excess of ammonia, which is necessary for the reductive amination step, blocks the catalytic species and as a consequent lowers the catalytic activity,

specifically for the hydrogenation step, yielding large amounts of unwanted by-products (Scheme1.17).

The mechanistic aspects of the first step of the hydroaminomethylation reaction, the hydroformylation of the alkene, is already well-established.[146] It generally involves the substitution of a CO by the alkene, hydride transfer and coordination of CO followed by migratory CO insertion in the alkyl moiety, leading to the acyl-rhodium species. Oxidative addition of dihydrogen and reductive elimination provides the aldehyde in either the linear or branched isomeric form and recovers the catalyst species.

The resulting aldehydes then react with the primary or secondary amines to generate the corresponding imines or enamines, respectively. No particular studies have been presented to understand if the rhodium complex plays a unique role in the condensation reaction. It has been observed that the linear aldehyde reacts faster with the amine than the branched aldehyde. A general proposal has been presented suggesting that the hydrogenation of the enamine or the imine takes place on the rhodium metal center, and involves coordination, oxidative addition of dihydrogen, hydride transfer providing an alkyl or an amido moiety and reductive elimination eventually leading to the product amine (Scheme 1.18).[174, 195, 196]



Scheme 1.18. General schematic catalytic cycle for hydroformylation and imine hydrogenation

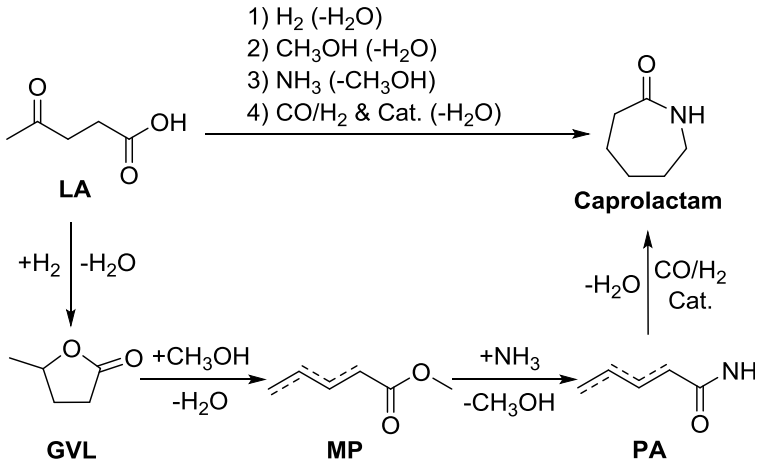
The hydrogenation step is indeed challenging and requires higher temperatures and higher partial dihydrogen pressures. The presence of large quantities of amine in the reaction supposedly modifies significantly the coordination sphere of the metal center.

1.5. Aim and outline of this thesis

1.5.1. Levulinic acid to caprolactam

As discussed in section 1.3, the current industrially applied route to produce caprolactam is based on fossil feedstock. Finding an alternative route to produce caprolactam from renewable resources like levulinic acid is highly desirable as it may reduce the environmental footprint of nylon. So far, the only report on the development of a synthetic route to bio-based caprolactam is based upon the use of hydroxymethylfurfural (HMF) as feedstock via a multi-step reaction technology.[64] Apart from the disadvantage of a multistep process, which will involve several product separation steps, this process is also energy demanding due to the requirement of significant amounts of (expensive) high pressure hydrogen.

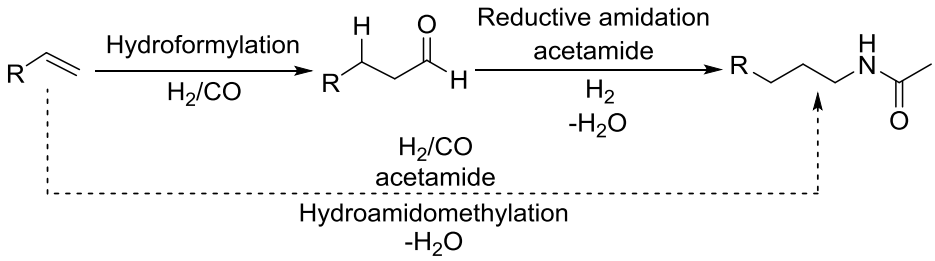
The aim of the research described in this thesis is to investigate an alternative bio-based pathway to synthesize caprolactam.



Scheme 1.19. Proposed synthetic route for the conversion of levulinic acid to caprolactam

Our proposed pathway is to obtain caprolactam from biomass-based levulinic acid starting from γ-valerolactone (GVL, derived from levulinic acid). The conversion of levulinic acid into GVL by a hydrogenation reaction, using mostly ruthenium catalysts, is reported to occur in high efficiency (>95%).[197-199] The proposed route proceeds via the acid-catalyzed reactive distillation of GVL with methanol to a mixture of isomeric methyl pentenoates (MPs), reaction of MPs with ammonia to the corresponding pentenamides (PAs), which then eventually are converted to caprolactam through a rhodium-catalyzed intramolecular hydroamidomethylation reaction (Scheme 1.19).

To reach this goal we need to study new catalytic reactions such as reductive amidation and hydroamidomethylation using transition metal catalysts. The reductive amidation is a reaction of aldehydes with amides affording alkylated amides. The envisaged hydroamidomethylation reaction comprises a cascade reaction of hydroformylation and reductive amidation (Scheme 1.20). Whereas reductive amidation and hydroamidomethylation with amides are related to the above mentioned reductive amination and hydroaminomethylation amines discussed in section 1.4.3, they do appear to display profoundly different reaction characteristics.



Scheme 1.20. Hydroamidomethylation and reductive amidation reactions

1.5.2. Contents of this thesis

In **Chapter 2**, our investigation of the homogeneously catalyzed reductive amidation of aldehydes with amides is described. The study of this novel reaction has been carried out making use of the model substrates hexanal and acetamide.

In **Chapter 3**, the direct chemo- and regioselective homogeneous rhodium-catalyzed hydroamidiomethylation of alkenes with amides is reported. The hitherto unknown hydroamidomethylation reaction comprises a cascade reaction of hydroformylation and

catalytic reductive amidation. Finding an active and selective alkene hydroamidomethylation catalyst involves the development of a catalytic system that is not only active for hydroformylation of alkenes, but under the prevailing syngas conditions also possesses the ability for a selective hydrogenation.

In **Chapter 4**, the reductive amidation of aldehydes with formamide as well as hydoamidomethylation of alkenes with formamide is described, aiming for the formation of primary amines via the subsequent decarbonylation of the resulting alkylated formamides. The investigations focus on efficiency and selectivity of the reactions to the desired alkylated formamide over alcohol as well as the decarbonylation of N-alkylformamide to form the primary amine.

In **Chapter 5**, our study of the possible conversion of γ-valerolactone (GVL) in three atom-efficient steps into the important polymer precursor ε-caprolactam is reported. GVL can be converted to a mixture of isomeric methyl pentenoates (MP) via trans-esterification with methanol. In the second step, subsequent aminolysis with ammonia leads to a mixture of pentenamides (PA). The resulting pentenamides are ultimately converted into ε-caprolactam via the rhodium-catalyzed intramolecular hydroamidomethylation reaction.

Finally, in **Chapter 6**, a detailed summary of the most significant findings of this research, followed by a general conclusion and an outlook on future perspectives is presented.

Parts of this thesis have been published;[200, 201] have been submitted for publication[202, 203] and/or are soon to be submitted.

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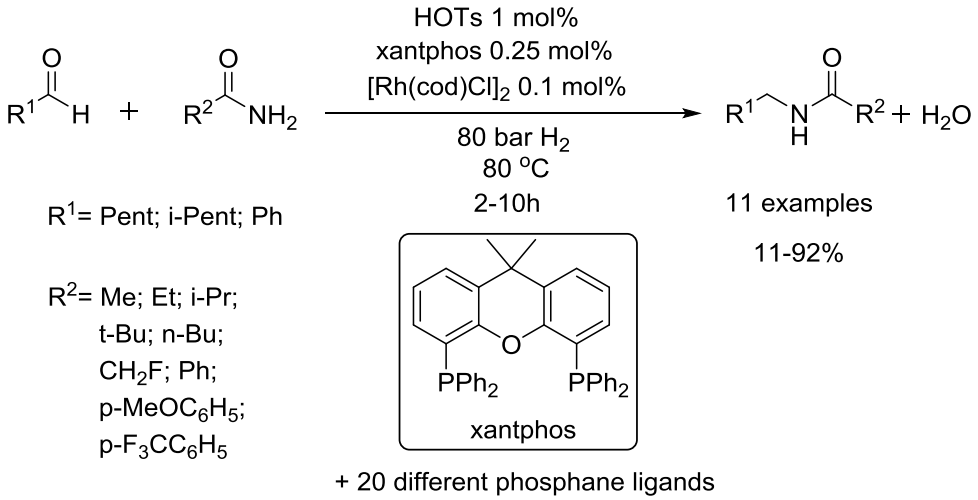
2

Rhodium-Catalyzed Homogeneous Reductive Amidation of Aldehydes



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Abstract

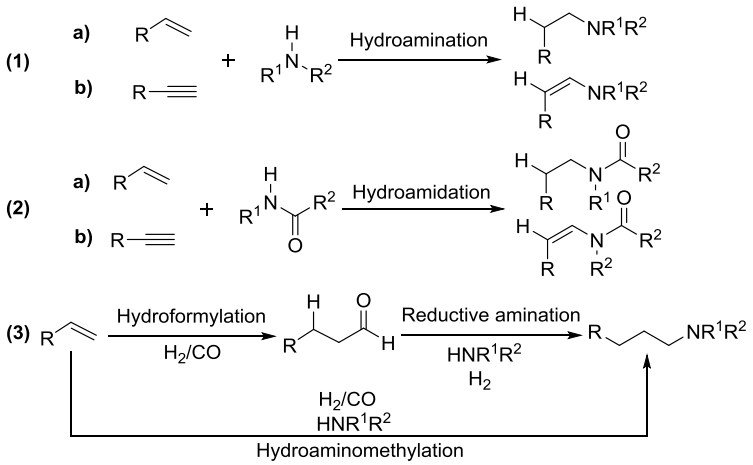
The catalytic reductive amidation of an aldehyde (hexanal) with an amide (acetamide) is reported. Apart from the desired N-hexylacetamide, the two isomeric unsaturated intermediates as well as hexanol are produced together with higher mass products that arise from aldol condensation and di-amide coupling of the aldehyde. 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 an acid co-catalyst results in high selectivity for the desired product. Under optimized conditions nearly full conversion is reached with high selectivity to the desired N-alkylamide and with a very high N-alkylamide/alcohol ratio, while producing only small amounts of by-products. The scope of the reaction has been investigated using different amides as well as aldehydes; the results show the general applicability of this novel reaction, but with electron-withdrawing amides the selectivity to N-alkylamide is lower. NMR studies showed that the nucleophilic addition of acetamide to hexanal is acid catalysed, forming N-(1-hydroxyhexyl)-acetamide in equilibrium with both hexanal and the dehydrated unsaturated imide/enamide**.** 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. Furthermore, it is proposed that the presence of acid causes a change in catalytic species, enabling a cationic Rh/xantphos hydrogenation catalyst to selectively hydrogenate the intermediates to N-hexylacetamide in the presence of hexanal.

2.1. Introduction

The reductive amidation of aldehydes with amides affording alkylated amides is a reaction with tremendous synthetic potential for application in academia as well as industry. The amide bond is one of the most significant functionalities found in many natural products. The catalytic formation of carbon–nitrogen bonds is highly attractive in organic chemistry, as well as in the bulk and fine chemical industries for the production of solvents, pharmaceutical intermediates and also in the synthesis of bioactive compounds such as amino acids.[1, 2] In this respect, catalytic conversions to N-alkylamides definitely offer potential advantages over conventional methods of C-N coupling reactions, where large quantities of salts are produced stoichiometrically as by-products.

Among the different methods of carbon-nitrogen bond formation reactions (Scheme 2.1), the most studied and challenging methods are hydroamination of alkenes and alkynes with amines,[3-8] hydroamidation of alkenes and alkynes[8-13] and the reductive amination of carbonyl compounds.[14, 15] In principle, these reactions can be performed with 100% atom efficiency, without or with very limited waste formation, fulfilling the requirement of green chemistry.

The intermolecular hydroamination of alkenes or alkynes is defined as the addition of an H-NH_2, H-NHR^1 or H-NR^1R^2 bond across an alkene or alkyne providing a next higher substituted alkyl- or alkenylamine, respectively (Scheme 2.1, reaction 1a-b).



Scheme 2.1. Hydroamination; hydroamidation; hydroaminomethylation and reductive amination reactions

This reaction, which can be catalyzed both by transition metal complexes or by strong base, has been mostly studied with secondary amines rather than ammonia or primary amines; due to the subsequent reactivity of the primary reaction product, doubly and triply alk(en)ylated products are also formed when the latter substrates are being used.[8, 16, 17] The catalytic hydroamination reaction of olefins is hampered by low rates and low catalyst turnover numbers, while the thermodynamic driving force for the intermolecular version of hydroamination is close to zero or even negative at the elevated temperatures generally required for the reaction to proceed.[17]

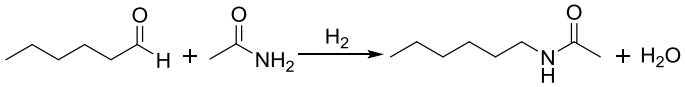
The related hydroamidation reaction, involving the addition of an amide's N-H bond to an alkene[8] or alkyne[9-13] (Scheme 2.1, reaction 2a-b) has also been studied; application of this reaction in an intermolecular fashion suffers from very similar problems as mentioned for intermolecular hydroamination, in particular with alkenes as substrate.[8]

As a possible atom-economical efficient synthesis of amines the hydroaminomethylation of alkenes has also attracted considerable attention (Scheme 2.1, reaction 3). The (exothermic) hydroaminomethylation of alkenes is a tandem reaction consisting of three steps: initial hydroformylation of alkene, followed by the condensation of the aldehyde with a primary or secondary amine to form an enamine or imine, and a final hydrogenation to give the saturated secondary or tertiary amine.[1, 2, 18-33]

The most challenging step of hydroaminomethylation, i.e. the metal-catalyzed reductive amination of aldehydes with ammonia, primary amines or secondary amines, has been extensively studied.[14, 15, 34-39] Because of the high reactivity of the imine intermediates, reductive amination of aldehydes generally is accompanied by significant build-up of heavy, oligomeric by-products, in particular with catalysts and under conditions such that hydrogenation of the imine intermediates is too slow. For ammonia and primary amines as substrates, over-alkylation of the desired primary- or secondary amines is a general issue of concern. This is a consequence of the high reactivity of the primary or secondary amines, which will act as competing substrates in the course of the reductive amination process. Separation of the reaction products is usually difficult due to small differences in the boiling points of the products. In attempts to reach higher selectivity toward the desired product, the reductive amination reaction is often carried out using a large excess of the amine substrate; however, in a

commercial application this would require costly (energy intensive) amine recycle processes.

The development of a new method for the synthesis of N-alkylamides using an amide as the substrate instead of an amine could be attractive as we reasoned that such a reductive amidation most likely would avoid the formation of over-alkylated amide side-products, due to a combination of relatively low nucleophilicity of the amide and increased steric encumbrance in the N-alkylated amide. This lower reactivity would allow application of an aldehyde/amide substrate ratio close to unity. Moreover, subsequent hydrolysis of the resulting N-alkylamide may yield a primary amine; the recovered carboxylic acid can be recycled to the corresponding amide with ammonia. Thus, the catalytic reductive amidation reaction would be a means to make primary amines, avoiding the difficulties of reductive amination with ammonia.



Scheme 2.2. Reductive amidation of hexanal with acetamide to form N-hexylacetamide

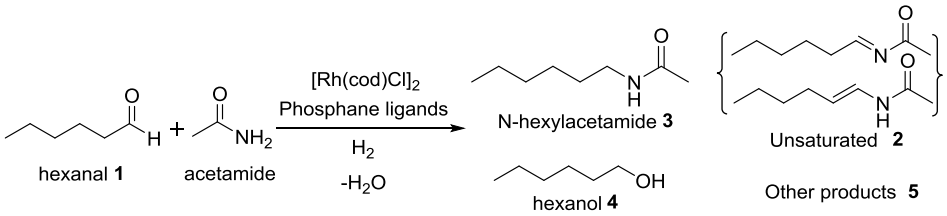
Herein, we report our studies towards the catalytic reductive amidation reaction of hexanal with acetamide (Scheme 2.2). The ultimate goal of our research is to combine the reductive amidation reaction with in situ formation of the aldehyde by hydroformylation of alkenes (hydroamidomethylation) as reported in Chapter 3.

2.2. Results

2.2.1. General considerations

The products found in a typical reductive amidation experiment with hexanal **1** and acetamide as the substrates, are shown in Scheme 2.3. Apart from the desired N-hexylacetamide **3**, the two isomeric unsaturated compounds N-(1-hexylidene)acetamide or N-1-hexenylacetamide **2** as well as hexanol **4** were observed with GC analysis. Additionally, formation of various products with higher mass (Figure 2.1), comprising aldol condensation products **5a** and the condensation product of hexanal with two molecules of acetamide **5b** was confirmed by both ^{1}H and ^{13}C NMR and mass spectroscopic analysis.The reductive amidation experiments were performed starting with 5 mmol of hexanal **1** and a small excess of acetamide (6

mmol); a quantitative product distribution was determined from GC analysis. The hexanal conversions shown in the Tables were calculated from the amount of hexanal found in the reaction mixtures after the reaction.



Scheme 2.3. Reductive amidation of hexanal with acetamide: observed products

Amounts of desired product **3**, unsaturated products N-(1-hexylidene)acetamide or N-1-hexenylacetamide **2**, and hexanol **4** were determined using calibration lines.The remainder consisted of the higher mass products **5**, which were not generally individually quantified from GC, but rather calculated as a lumped-together-number from the uneven mass-balance of hexanal-derived GLC-measurable products. In the Tables the selectivity for **2** as well as for the sum of **3**+**4** are reported. The specificity of the catalysts for reductive amidation versus hydrogenation of hexanal **1** is given as the ratio **3**/**4**.

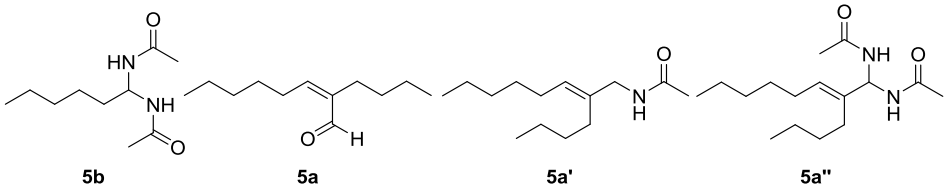


Figure 2.1. Products of higher molecular mass (**5**) observed in the reductive amidation reaction

2.2.2. Catalytic reductive amidation: initial screening studies

To investigate reductive amidation of aldehydes, we started our exploratory studies testing various rhodium precursors. As shown in Table 2.1, the precursors $[Rh(cod)Cl]_2$, $[Rh(cod)_2]BF_4$ and $[Rh(cod)_2]OTf$ turned out to yield the highest hexanal **1** conversion with only moderate differences in the **3**/**4** ratio and **3**+**4** selectivity. It appeared, however, that neither of the tested rhodium complexes showed a high hydrogenation activity nor good selectivity to the desired N-hexylacetamide **3**.

Table 2.1. Reductive amidation of hexanal with acetamide.[a]

	Rhodium precursor	Conversion %	**2** Selectivity%	**3**/**4** ratio	**3**+**4** Selectivity%
1	$[Rh(cod)Cl]_2$	56	35	14.7	30
2	$Rh(acac)(CO)_2$	25	42	3.1	12
3	$[Rh(cod)_2]BF_4$	47	29	1.9	46
4	$RhCl_3.xH_2O$	53	29	8.7	20
5	$Rh(CO)(H)(PPh_3)_3$	27	6	0.0	57
6	$[Rh(cod)_2]OTf$	58	16	2.7	54

[a] Reaction conditions: 0.01 mmol Rh precursor, 5 mmol hexanal, 6 mmol acetamide (Rh:hexanal:acetamide= 1:500:600); P_{H2} = 80 bar; T = 100 °C; t = 4h; Solvent: 25 ml diglyme; decane as internal standard

High specificity for reductive amidation versus hydrogenation of hexanal **1** is lacking, as is apparent from the relatively low **3**/**4** ratio. In addition, a significant conversion of hexanal to heavier products **5** (~35% selectivity) is apparent from the uneven hexanal-derived product balance as derived from GLC analysis. Because of its low sensitivity to air and moisture and because this precursor showed the highest product specificity **3** versus **4**, $[Rh(cod)Cl]_2$ was selected as the catalyst precursor for further studies.

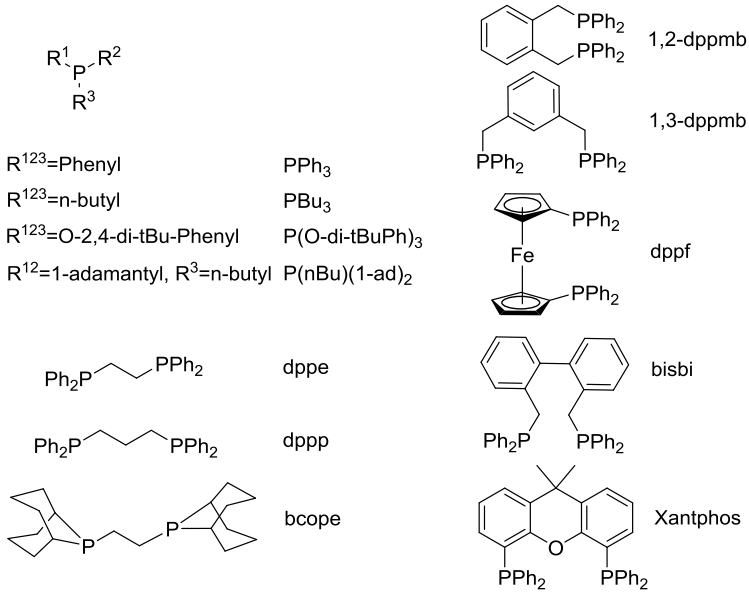
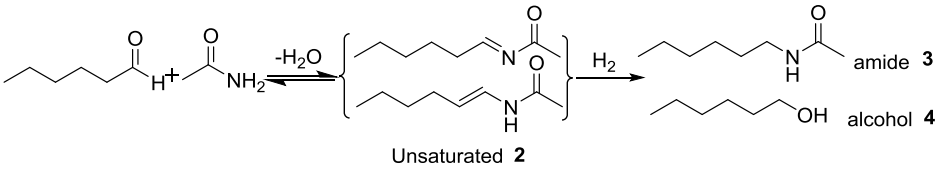


Figure 2.2. Ligands used in reductive amidation of hexanal

Table 2.2. Reductive amidation of hexanal with acetamide catalyzed by $[Rh(cod)Cl]_2$ in combination with different ligands.[a]



	Ligand	HOTs mmol	Conversion %	**2** selectivity%	**3**/**4** ratio	**3**+**4** selectivity%
1	-	-	56	35	14.7	30
2	-	0.05	80	15	4.3	30
3	PPh_3	-	14	57	0.0	6
4	PPh_3	0.05	79	16	1.0	16
5	$P(nBu)_3$	-	36	0	0.0	78
6	$P(nBu)_3$	0.05	52	0	0.3	73
7	$P(O\text{-di-tBu-Ph})_3$	-	24	8	2.5	58
8	$P(O\text{-di-tBu-Ph})_3$	0.05	78	3	20.0	43
9	$P(nBu)(1\text{-ad})_2$	-	28	7	2.3	71
10	$P(nBu)(1\text{-ad})_2$	0.05	82	2	6.5	37
11	dppe	-	21	21	0.4	49
12	dppe	0.05	73	7	10.7	22
13	dppp	-	55	42	0.6	47
14	dppp	0.05	80	5	1.9	37
15	bcope	-	100	0	0.0	92
16	bcope	0.05	100	0	0.0	78
17	1,2-dppmb	-	47	34	7.6	35
18	1,2-dppmb	0.05	75	13	5.3	36
19	1,3-dppmb	-	48	37	14.4	33
20	1,3-dppmb	0.05	78	18	18.1	22
21	dppf	-	53	14	1.5	74
22	dppf	0.05	89	5	3.0	60
23	bisbi	-	64	35	0.4	40
24	bisbi	0.05	81	12	1.1	43
25	xantphos	-	82	2	0.3	85
26	xantphos	0.05	90	0	17.5	82
27	xantphos[b]	0.05	84	1	20.6	93

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol acetamide (Rh:L:hexanal:acetamide=1:1.25(bidentate) or 2.5(monodentate):500:600); P_{H2} = 80 bar; T = 100 °C; t = 4h; Solvent: 25 ml diglyme; decane as internal standard. [b] T = 80 °C

In the following screening studies $[Rh(cod)Cl]_2$ was combined *in situ* with a large number of monodentate or bidentate phosphane ligands.

Variation in the stereo-electronic properties of the ligands was achieved by changing the P-substituent for mono-dentate ligands (Aryl, Alkyl, -OAryl or –OAlkyl), while for bi-dentate ligands also the length and structure of the backbone spacer between the P donor atoms was varied. A selection of the ligands that were tested is shown in Figure 2.2.

The catalytic results of the screening studies using the different ligands are summarized in Table 2.2. The addition of various monodentate ligands to $[Rh(cod)Cl]_2$ resulted in lower conversion of the substrate relative to that obtained with the metal complex precursor alone (*cf.* entries 1,3,5,7,9). More importantly, these catalytic systems are quite active in hexanal **1** hydrogenation as shown by the low **3/4** ratio. Introducing (a 5-fold molar excess on Rh of) p-toluenesulfonic acid (HOTs) as additive appeared to have a pronounced impact on conversion and selectivity; however, in most cases the selectivity to the desired product remained low, as for example for the ligand PPh_3 (entries 3, 4). The use of the more basic ligand $P(n\text{-}Bu)_3$ resulted in a catalytic system with high selectivity for hexanol **4** formation (80%) while here addition of acid did not have a significant effect on the **3/4** ratio (*cf.* entries 5,6). A higher product ratio **3/4** was observed with the catalytic systems containing the acid additive and the monodentate ligands $P(ad)_2(nBu)$ or $P(O\text{-}ditBuPh)_3$ (entries 7-10), but the selectivity for the total amount of hydrogenated products **3+4** is still modest. The use of catalytic systems based on the bidentate ligands generally gave higher hexanal **1** conversion.The use of the bidentate phosphane ligands dppe and dppp, however, gave only moderate overall results with a low selectivity to **3** (entries 11-14), while the addition of acid gave again rise to higher conversion, but with only a slightly higher **3/4** product ratio and formation of larger amounts of **5**.

Use of the strongly electron-donating bidentate ligand bcope resulted in full conversion of hexanal **1** yielding exclusively hexanol **4** as the hydrogenation product together with small amounts of **5**; the addition of acid merely resulted in formation of more **5**. Better results were obtained when ligands with larger bite angle are used (entries 17-26). With the ligands 1,2-dppmb and 1,3-dppmb fairly high **3/4** product ratios were achieved, but with poor total hydrogenation selectivity to **3+4**. On the other hand, use of dppf or bisbi resulted in catalytic systems with higher selectivity to **3+4**, but with only moderate **3/4**

product ratios. Much better yields of **3** were achieved with the xantphos ligand in combination with an added catalytic quantity of the acid HOTs (cf. entries 25, 26). The addition of the acid dramatically improved the **3/4** product ratio from 0.3 to 17.5 with 80% combined hydrogenation selectivity to **3+4** at a high conversion of hexanal **1** (90%). At a lower reaction temperature (80 °C), the **3/4** product ratio and **3+4** selectivity increased to, respectively ~21 and ~95% with only a slightly lower hexanal **1** conversion (entry 27).

In a next set of catalytic experiments in the presence of HOTs, the rhodium/xantphos ratio was varied (Table 2.3); the results show that increasing the rhodium/xantphos ratio from 1:1 to 1:3 ratio leads to lower conversions but only slightly lower selectivity for hydrogenated products. The use of 1.25 equivalents of xantphos on rhodium appears to give the best overall yield of N-hexylacetamide **3** (entry 2)

For the Rh/xantphos/HOTs catalytic system the use of different ratios of acetamide/hexanal ratios (1/1 up to 2/1) did not result in large changes in hexanal conversion; it appeared that a small excess of acetamide (ratio of 1.2) gave the highest conversion of hexanal and selectivity to **3** and no over-alkylation was observed (see appendix Table AI.4).

Table 2.3. The effect of Rh/xantphos ratio on the reductive amidation of hexanal with acetamide.[a]

	Rh/L ratio	Conversion %	**3/4** ratio	**3+4** Selectivity %	**3** Selectivity %
1	1/1	82	17.5	90	85
2	1/1.25	84	20.6	93	88
3	1/1.5	76	21.4	82	78
4	1/2	74	22.3	81	78
5	1/3	70	22.5	80	77

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol acetamide (Rh:hexanal:acetamide= 1:500:600); HOTs (0.05 mmol); P_{H2}=80 bar; T = 80 °C; t = 4h; Solvent: 25 ml diglyme; decane as internal standard

Screening of various reaction solvents revealed that for the Rh/xantphos/HOTs catalytic system diglyme is the most suitable solvent; the use of tetrahydrofuran (THF) gave comparable results with slightly lower selectivity to **3** (Table 2.4). Use of other solvents like toluene, mesitylene, dichloromethane and N-methylpyrrolidone resulted

in significantly lower specificity to **3** as well as lower combined hydrogenation selectivity **3**+**4**, thus leading to rather mediocre overall selectivity to **3**. When methanol was used as solvent, full conversion of hexanal **1** was obtained, however hexanal **1** was mainly (~90%) converted to the dimethyl acetal and **3** was not obtained (see appendix Table AI.5).

Table 2.4. Reductive amidation reaction of hexanal with acetamide catalyzed by $[Rh(cod)Cl]_2$ in combination with xantphos ligands in different solvents[a]

	Solvent	Conversion %	**3** selectivity %	**3**/**4** ratio	**3**+**4** selectivity %
1	Diglyme	84	88	20.6	93
2	THF	80	80	10.7	88
3	MeOH	100	0	0.0	4
4	Toluene	86	61	4.0	76
5	Mesitylene	84	59	5.6	69
6	DCM	70	57	6.7	66
7	NMP	64	48	3.8	61

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide =1:1.25:5:500:600); P_{H2}=80 bar; T=80 °C; t=4h; Solvent: 25 ml. [b] 4.8 mmol other products: acetal (4.4 mmol), hemiacetal (0.1 mmol). [c] ~0.6 mmol unsaturated intermediates 2 imide (45%), enamide (55%).

The effect of the reaction temperature on the hexanal conversion and product distribution is shown in Figure 2.3. Lowering of the reaction temperature from 120 °C to 80 °C leads to a pronounced increase in selectivity for **3**, from 70% up to 90%. At 80 °C, the formation of the heavy aldol condensation and di-amide coupled products is suppressed. Upon further lowering of the reaction temperature, however, the conversion of hexanal **1** becomes lower, while the relative amount of unsaturated intermediates **2** and other heavier products **5** increases, thus indicating that hydrogenation activity to **3**+**4** decreases with temperature below 80 °C. It thus appears that a reaction temperature of 80 °C is the optimal temperature for this catalytic system.

The effect of the hydrogen pressure on the reductive amidation was also determined (Figure 2.3). When lowering the hydrogen gas pressure from 100 to 20 bar the overall hydrogenation activity of the catalytic system significantly decreases, thus resulting in increased formation of **5**. For the remaining studies a pressure of 80 bar was applied, as

this resulted in relatively high hexanal **1** conversion combined with good selectivity to **3** (see appendix Table AI.7).

As it seemed that the xantphos ligand could play a unique role in the reductive amidation of an aldehyde to produce N-alkylamides in good selectivity, a variety of other xantphos-type ligands shown in Figure 2.4 were applied under the same acidic conditions as applied with xantphos. Catalytic results are collected in Table 2.5.

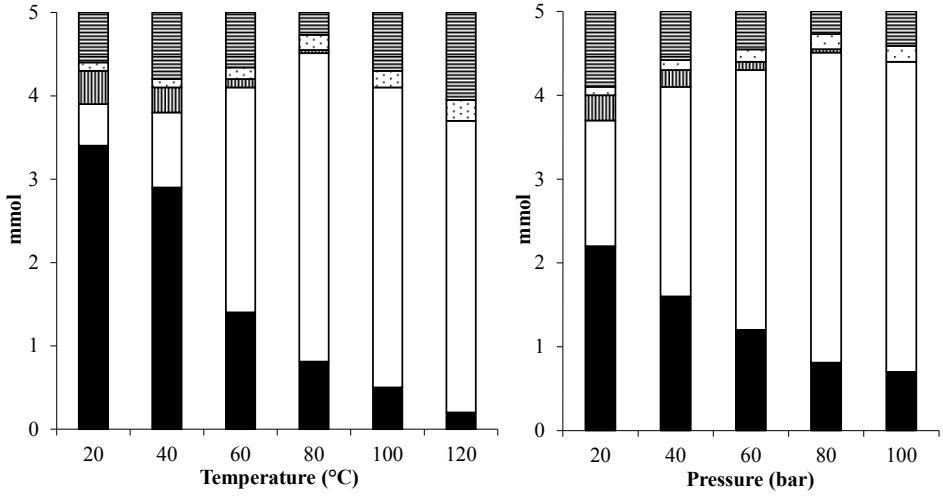


Figure 2.3. The effect of reaction temperature and pressure on product distribution in the reductive amidation reaction using the Rh/xantphos/HOTs catalytic system; Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide=1:1.25:5:500:600); P_{H2} = 80 bar; T = 80 °C; t = 4 h; Solvent: 25 ml diglyme; decane as internal standard. ■= hexanal (**1**), □= N-hexylacetamide (**3**), ▥= unsaturated N-(1-hexylidene)acetamide or N-1-hexenyl acetamide (**2**), ⁘= hexanol (**4**), ▤= other products (**5**)

The best results were obtained with xantphos and tBu-xantphos (Table 2.5, entries 1, 2). Remarkably, even relatively small modifications, such as the use of Si-xantphos or Benzo-xantphos instead of xantphos, in the catalytic system already resulted in a very significantly lower **3**/**4** ratio and lower selectivity to **3** (entry 3). Using the other xantphos-type ligands also resulted in significant suppression of the **3**/**4** ratio and selectivity to **3**+**4**.

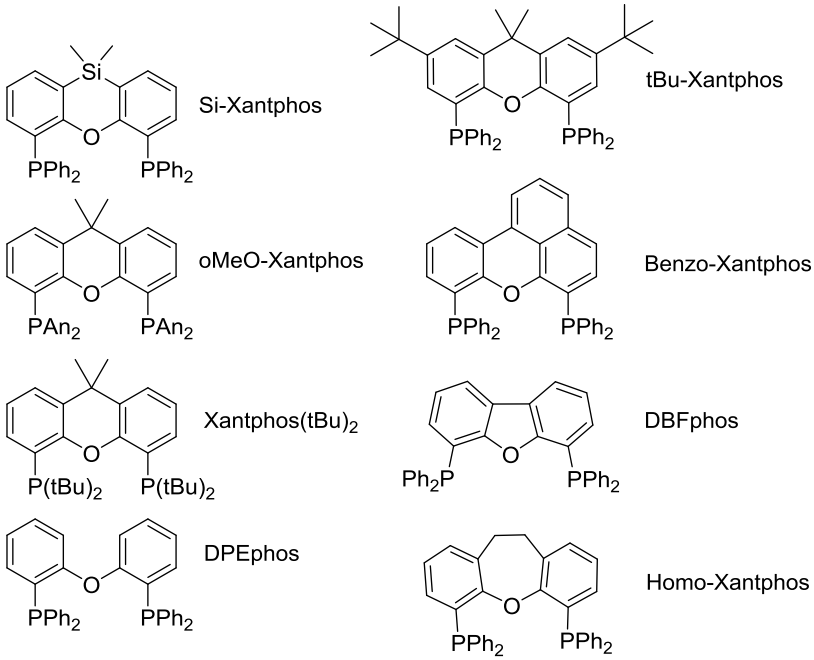


Figure 2.4. Selected xantphos-type ligands used in the reductive amidation of hexanal (An = o-anisole)

Table 2.5. Reductive amidation of hexanal with acetamide catalyzed by $[Rh(cod)Cl]_2$ in combination with different xantphos-type ligands.[a]

	Ligand	Conversion %	**2** Selectivity %	**3**/**4** ratio	**3**+**4** Selectivity %
1	xantphos	84	1	20.6	93
2	tBu-xantphos	80	4	16.9	88
3	Si-xantphos	78	11	4.1	74
4	oMeO-xantphos	60	31	6.2	12
5	xantphos$(tBu)_2$	59	28	10.2	19
6	DPEphos	64	28	6.3	34
7	DBFphos	50	29	8.8	27
8	homoxantphos	60	24	1.1	39
9	benzoxantphos	47	28	5.9	26

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol ligand, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:L:hexanal:acetamide= 1:1.25:500:600); P_{H2} = 80 bar; T = 80 °C; t = 4 h; Solvent: 25 ml diglyme; decane as internal standard

Apparently this is mainly due to a lower hydrogenation activity of these catalytic systems as also reflected by a significant increase in formation of unsaturated intermediates **2**; accumulation of these intermediates also results in increased amounts of **5** (entries 4-9).

2.2.3. Effect of acid and base additives

As shown above the addition of HOTs to the reductive amidation reaction mixture has a significant effect on the selectivity of the catalytic system based on rhodium/xantphos. This prompted us to investigate the effect of acids or bases as additives in the reaction in more detail (the pK_a values are determined in water as solvent[40]) (Table 2.6).

Table 2.6. Effect of the addition of various acids or bases on the reductive amidation of hexanal with acetamide using Rh/xantphos catalytic system.[a]

	Additive 0.05mmol	pK_a	Conversion %	**3**/**4** ratio	**3**+**4** Selectivity %	**3** Selectivity %
1	no acid		76	0.3	84	21
2	HOTs[b]	-2.7	78	2.4	84	60
3	HOTs	-2.7	84	20.6	93	88
4	HOTs[c]	-2.7	92	24.5	87	83
5	HOTs[d]	-2.7	98	30.8	84	81
6	HOTs[e]	-2.7	86	4.4	88	72
7	AcOH	4.8	70	0.1	86	9
8	H_3PO_4	2	68	0.4	76	21
9	PhH_2PO_3	1.8	68	0.7	76	32
10	TFA	-0.3	74	1.6	78	49
11	HBF_4	-4	66	12.5	82	76
12	HCl	-7	70	20.8	80	76
13	HOTf	-5.1	90	26.0	87	84
14	NMP		72	0.0	86	3
15	NEt_3		90	0.0	91	0

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 5 mmol hexanal, 6 mmol acetamide Rh:xantphos:hexanal:acetamide=1:1.25:500:600); P_{H2}= 80 bar; T = 80 °C; t = 4 h; Solvent: 25 ml diglyme; decane as internal standard. [b] 0.025 mmol HOTs. [c] 0.1 mmol HOTs. [d] 0.2 mmol HOTs [e] HOTs 12% in acetic acid.

Increasing the amount of HOTs from 0.025 to 0.05 mmol positively affects the **3**/**4** product ratio and the selectivity in favor of **3** (entries 2, 3). Addition of a larger amount

of HOTs (e.g. 8 mM; HOTs/Rh~20) leads only to a slight decrease in selectivity predominantly due to the formation of more aldol condensation products **5** (entries 4, 5). With the addition of the same amounts of significantly weaker acids such as acetic acid, phosphoric acid and phenyl phosphonic acid, hexanol **4** becomes the dominant hydrogenation product (entries 7-9), quite similar to the experiment in which no acid is added. The use of stronger acids leads to progressively higher selectivity to **3** (entries 10-13); with triflic acid (HOTf) excellent conversion with high **3**/**4** ratio and high selectivity is obtained (entry 13). Conversely, the use of the weak base N-methyl pyrrolidone (NMP) or stronger base triethylamine (NEt_3) both result in the formation of hexanol **4** as the exclusive hydrogenation product, remarkably with a similar hexanal **1** conversion rate as obtained under acidic conditions (entries 14-15).

2.2.4. Effect of acid on hydrogenation of aldehyde

To elucidate the selectivity-improving role of acid addition in reductive amidation as apparent from the spectacular increase of the **3**/**4** product ratio with the rhodium/xantphos catalytic system, the influence of acid addition on the hydrogenation of hexanal **1** to hexanol **4** was separately investigated, both in the absence and presence of an inert amide model compound, N,N'-dimethylacetamide (Table 2.7).

Table 2.7. Hydrogenation and reductive amidation of hexanal with and without acetamide.[a]

	Amide 6 mmol	HOTs mmol	Conversion %	**3**/**4** ratio	**3**+**4** Selectivity %	**4** Selectivity %
1	-		52	-	-	85
2	-	0.05	14	-	-	9
3	DMA[b]		54	-	-	81
4	DMA[b]	0.05	26	-	-	62
5	acetamide		76	0.3	84	63
6	acetamide	0.05	84	20.6	93	4

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 5 mmol hexanal, in some cases 6 mmol amide (Rh:xantphos:hexanal=1:1.25:500); p_{H2} = 80 bar; T = 80 °C; t = 4 h; Solvent: 25 ml diglyme; decane as internal standard. [b] N,N'-dimethylacetamide

In the absence of HOTs and acetamide, the rhodium/xantphos catalytic system hydrogenates hexanal **1** to hexanol **4** with about 50% conversion after 4 h at 80 °C (entry 1). Addition of a catalytic amount of HOTs causes a significant drop in

conversion; assuming first order reaction kinetics one can calculate a decrease in hydrogenation rate constant of about a factor 5 by the presence of acid.[41] The effect on the selectivity of hydrogenation is even more dramatic, due to a competing acid-catalysed aldol condensation of hexanal **1** giving **5** (Entry 2).

The use of N,N'-dimethylacetamide, added to the reaction mixture to simulate a similar reaction medium as applied in actual reductive amidation, gives a qualitatively similar result (*cf.* entries 3,4). However, likely due to the weak basicity of N,N'-dimethylacetamide the addition of HOTs now leads to a decrease in hydrogenation rate constant only by a factor of about 2.5, while maintaining a reasonably good selectivity for hydrogenation to **4**. For comparison, the data for the hexanal reduction in the presence of acetamide are summarized (entries 5, 6): without acid almost exclusively **4** is formed as the reduction product, while in presence of a catalytic quantity of HOTs, **3** is the almost exclusive reduction product.

2.2.5. Influence of added water

As in the reductive amidation of an aldehyde one equivalent of water is formed, the effect of added water in the reaction media was also investigated. Addition of 2.5 mmol of water, theoretically corresponding to about 50% conversion of hexanal **1**, already has a significant impact on the reaction; still ~75% conversion is reached, but the selectivity to **3** drops to about 70%. Increasing the amount of water to 5 mmol water has a more dramatic effect, in particular on selectivity to **3**.

Table 2.8. The influence of adding H_2O on the reductive amidation reaction of hexanal with acetamide [a]

	H_2O mmol	Conversion %	**3** selectivity %	**3**/**4** ratio	**3**+**4** selectivity %
1	-	84	88	20.6	93
2	2.5	74	70	13.0	76
3	5	58	48	7.0	55
4[b]	-	88	88	21.5	93

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:hexanal:acetamide=1:1.25:500:600); HOTs(0.05mmol); P_{H2}=80 bar; T=80 °C; t=4h; Solvent: 25 ml diglyme; decane as internal standard.[b] Molecular sieve 3Å used in the reaction

The addition of molecular sieves (3 Å) to the reaction does not have a significant effect on the conversion, but seems to have a slightly positive effect on the **3**/**4** ratio (Table 2.8).

2.2.6. Catalyst systems other than those based on Rh

Under the optimized reaction conditions shown above, we tested various other transition metal precursors (based on Ru, Pd, Pt, Ir and Co) in combination with xantphos – with or without HOTs – in the reductive amidation reaction (Table 2.9). None of the used complexes showed a performance comparable with the Rh catalysts. The catalytic system containing Rh/xantphos/HOTs turned out to be by far the most active and selective catalytic system for reductive amidation.

Table 2.9. Reductive amidation reaction of hexanal with acetamide applying different metals [a]

	Metal	HOTs mmol	Conversion %	**3** selectivity %	**3**/**4** ratio	**3**+**4** selectivity %
1	$[Rh(cod)Cl]_2$		76	21	0.3	84
2	$[Rh(cod)Cl]_2$	0.05	84	88	20.6	93
3	$Ru(acac)_3$		14	0	0.0	40
4	$Ru(acac)_3$	0.05	72	6	0.2	31
5	$Pd(OAc)_2$		12	0	0.0	0
6	$Pd(OAc)_2$	0.05	42	14	0.0	14
7	$[Ir(cod)Cl]_2$		16	0	0.0	25
8	$[Ir(cod)Cl]_2$	0.05	46	17	1.3	30
9	$Co_2(CO)_8$		14	0	0.0	0
10	$Co_2(CO)_8$	0.05	40	0	0.0	0
11	$Pt(cod)Cl_2$		48	21	2.5	29
12	$Pt(cod)Cl_2$	0.05	72	17	3.0	22

[a] Reaction conditions: 0.005 mmol metal salt, 5 mmol hexanal, 6 mmol acetamide (M:xantphos:hexanal:acetamide=1:1.25:500:600); P_{H2}=80 bar; T=80 °C; t=4h; Solvent: 25 ml diglyme; decane as internal standard

2.2.7. Product evolution in time

The product development over the time for the Rh/xantphos/HOTs catalytic system is depicted in Figure 2.5. After ten hours at 80 °C nearly full conversion (98%) (TON~500) is reached with about 88% selectivity to **3**. It is shown that the unsaturated intermediates **2** do not build up to any significant extent in this experiment, while the aldehyde concentration monotonously decreases according to an approximate first-

order reaction. This could indicate that formation of the unsaturated amide adducts is rate determining under the prevailing conditions, and that hydrogenation of these intermediates is a relatively fast reaction.

The robustness of the catalytic system in the optimized reaction conditions was investigated using 10 mmol of substrate with 0.0025 mmol of rhodium precursor in combination with xantphos and HOTs at 80 °C. After 10 hours 75% conversion of hexanal **1** was reached with 60% overall selectivity to **3**.

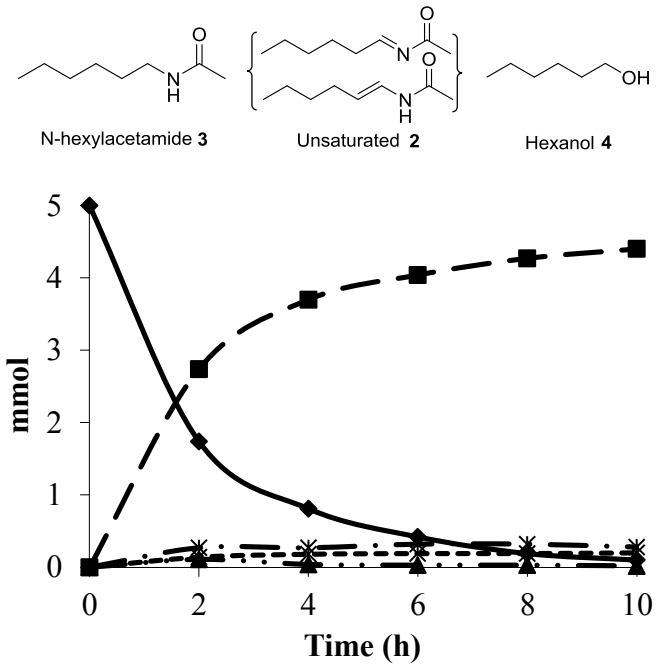


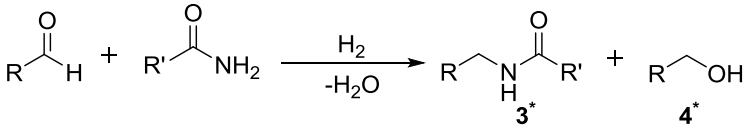
Figure 2.5. Product development in time in the reductive amidation of hexanal with acetamide; Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide=1:1.25:5:500:600); p_{H2} = 80 bar; T = 80 °C; Solvent: 25 ml diglyme; decane as internal standard. ♦=hexanal (**1**), ■= N-hexylacetamide (**3**), ▲=unsaturated N-(1-hexylidene) acetamide or N-1-hexenyl acetamide (**2**), ×= hexanol (**4**), ∗= other products (**5**) (the exact data are given in appendix Table AI.14)

The cumulative turnover number thus obtained was about 1800, i.e. quite an acceptable number considering the scale, water build-up and low catalyst concentration applied in this experiment.

2.2.8. Scope of reductive amidation; applying different amide and aldehyde substrates

A number of different N-nucleophiles were applied in the reductive amidation of hexanal **1** (Table 2.10). The use of amides with one electron-donating alkyl group at the alpha C of the amide such as propanamide and pentanamide, results in higher conversion and selectivity (entries 1, 2, 5).

Table 2.10. Scope of reductive amidation using various amides and aldehydes.[a]



	Aldehyde	Amide	Conversion[b] %	**3***/**4*** ratio	**3***+**4*** Sel.%	**3*** Sel.%[c]
1	Hexanal	Acetamide	84	21	92	88
2	Hexanal	Propanamide	90	24	93	90
3	Hexanal	Isopropylamide	77	13	85	79
4	Hexanal	tert-Butylamide	75	12	87	81
5	Hexanal	Pentanamide	92	31	95	92
6	Hexanal	Fluoroacetamide	32	2	51	35
7	Hexanal	Benzamide	58	8	81	72
8	Hexanal	p-MeO-benzamide	72	14	85	80
9	Hexanal	p-CF_3-benzamide	38	4	73	58
10	2-Me-pentanal	Acetamide	57	3	41	31
11	Benzaldehyde	Acetamide	42	0.1	63	9

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol aldehyde, 6 mmol amide (Rh:xantphos:HOTs:hexanal:amide =1:1.25:5:500:600); P_{H2} = 80 bar; T = 80 °C; t = 4 h; Solvent: 25 ml diglyme; [b] The conversion was determined by GC analysis based on the amount of aldehyde found in the reaction mixtures after the reaction; [c] The selectivity was determined by GC analysis using decane as an internal standard

The use of amides with two or three alpha-C alkyl substituents leading to bulkier alkyl amides, such as isopropylamide and tert-butylamide, results in a somewhat lower efficiency of the reaction (entries 3, 4). For comparison, application of the electron-

withdrawing fluoroacetamide results in a very significant drop in the selectivity to **3*** (entry 6). The use of benzamide also results in lower conversion and selectivity compared to acetamide. Applying p-methoxybenzamide with an electron-donating group gives higher selectivity and conversion, whereas p-trifluoromethylbenzamide with an electron-withdrawing group again results in considerably lower selectivity and conversion. Clearly, the nucleophilicity of the N atom in the amide plays a decisive role in a successful reductive amidation of aldehyde.

The branched aldehyde 2-methylpentanal and the electronically-different benzaldehyde, (entries 10, 11) are considerably less reactive in reductive amidation with acetamide; not only the conversion is lower, but also the hydrogenation activity and substrate specificity (ratio **3***/**4***) quite drastically decreases.

2.2.9. NMR study of the hexanal/acetamide mixture in the absence of Rh catalyst

The adduct formation of hexanal **1** with acetamide was studied by following the time evolution of ^{1}H NMR spectra of a 1:1 mixture hexanal/acetamide in THF-d_8 at 60 °C in the absence of the rhodium/ligand catalytic system. It appears that condensation of hexanal **1** with acetamide in THF-d_8 does not proceed in the absence of HOTs (see supporting information). However, as shown in Figure 2.6, in the presence of only 1 mol% of HOTs already after 10 minutes adduct formation between hexanal **1** and acetamide is observed, as indicated by the simultaneous formation of proton resonances at 5.25 ppm attributed to –C**H**(OH)– (**2a***) and at 7.65 ppm attributed to -N**H** of **2a** (Figure 2.6).

The intensity of these resonances keeps growing up to about 150 min; after this time resonances attributed to the dehydrated product **2** appear (the peak at 6.95 ppm can be assigned to the imide functionality–C**H**=N–(**2****)).[42] The evolution of the proton resonances is thus consistent with a two-stage addition process of the acetamide's N-H bond to hexanal **1**, initially forming the nucleophilic addition product **2a** followed by dehydration to give **2**. Small proton resonances at 5.10 and 6.70 ppm can be assigned to the other isomeric dehydration product, N-1-hexenylacetamide **2**;[42] however, the integrals of these resonances remain relatively small under our conditions.[43]

From the time evolution of the proton resonances representative for hexanal, acetamide, **2a** and **2** the time-dependent concentration of these compounds has been constructed and graphically depicted in Figure 2.7. From this Figure it is immediately

clear that the two stages in the acetamide–aldehyde addition process both involve equilibrium processes. Two separate equilibrium constants can be calculated from these data. The first equilibrium constant (K_1=2.701 M^{-1}) shows that in the presence of a catalytic amount of HOTs, addition of acetamide to hexanal forming **2a** is an equilibrium reaction that proceeds under the prevailing conditions (hexanal:acetamide=1:1; THF solvent; 60 °C) to slightly less than 50% hexanal conversion.

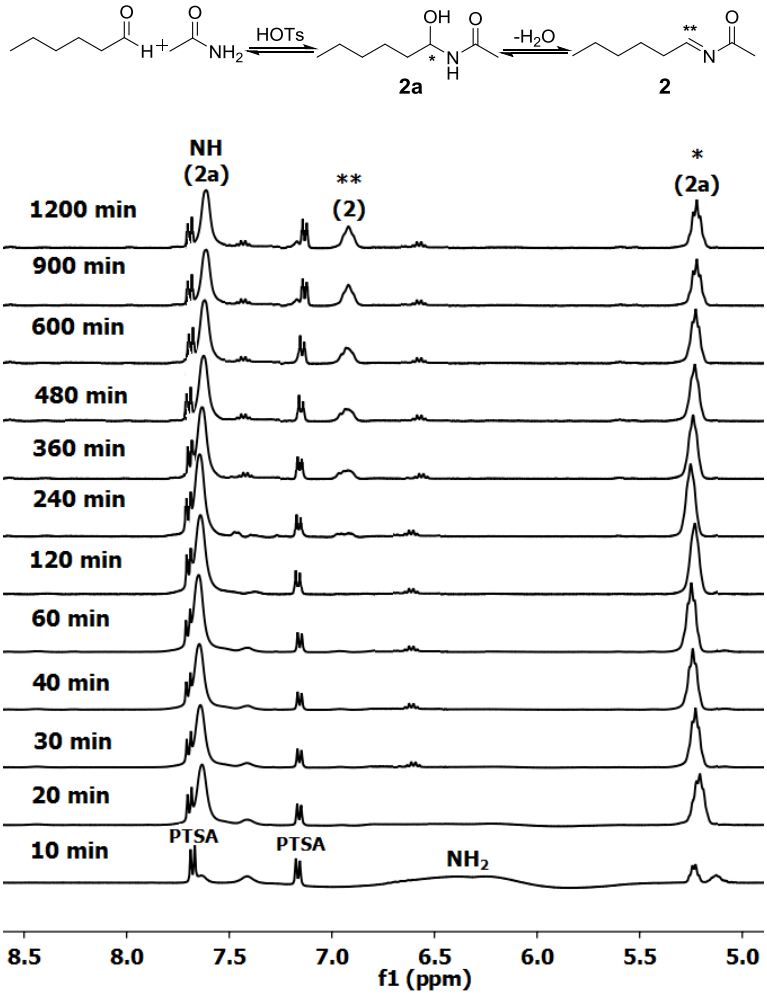


Figure 2.6. ^{1}H NMR time evolution of part of the ^{1}H NMR spectra relevant for the condensation reaction of hexanal with acetamide; hexanal:acetamide:PTSA(or HOTs)=1:1:0.01 ratio in THF-d_8; T = 60 °C)

The subsequent dehydration reaction forming **2** proceeds only to a limited extent, as shown by the apparent low value of the second equilibrium constant (K_2=0.042 M), which implies that only relatively low concentrations of **2** can be present in the reaction mixture at equilibrium. However, it must be noted that for this model study, a low reaction temperature of 60 °C was applied for practical reasons. One may expect the dehydration equilibrium (K_2) to shift to higher conversion at the higher temperatures used in the catalytic experiments (80-100 °C).

We conclude from this model study that the addition of an acetamide's N-H to the aldehyde proceeds in two consecutive stages catalyzed by (strong) acid. In this respect the addition of acetamide strongly deviates from addition of a more nucleophilic amine to aldehyde which generally involves a thermally spontaneous addition of the amine to aldehyde, forming imines (or carbinolamines) under very mild conditions. Clearly, a reduced nucleophilicity of the N atom of amides relative to amines must be responsible for this difference.

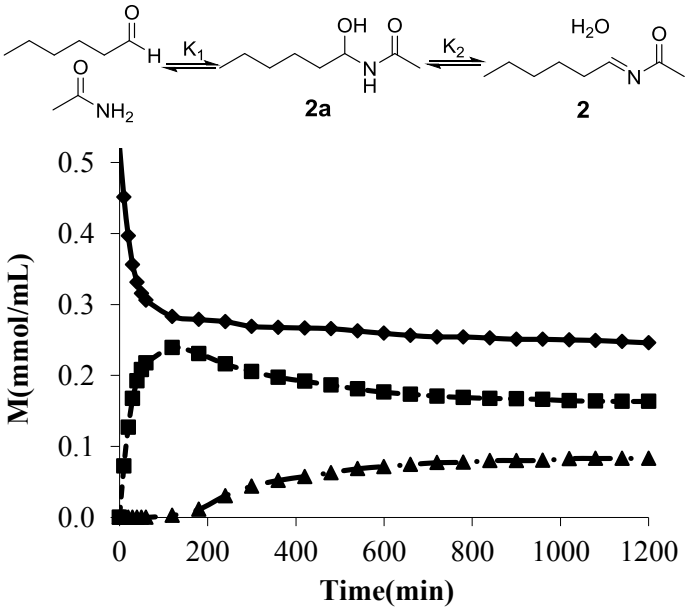
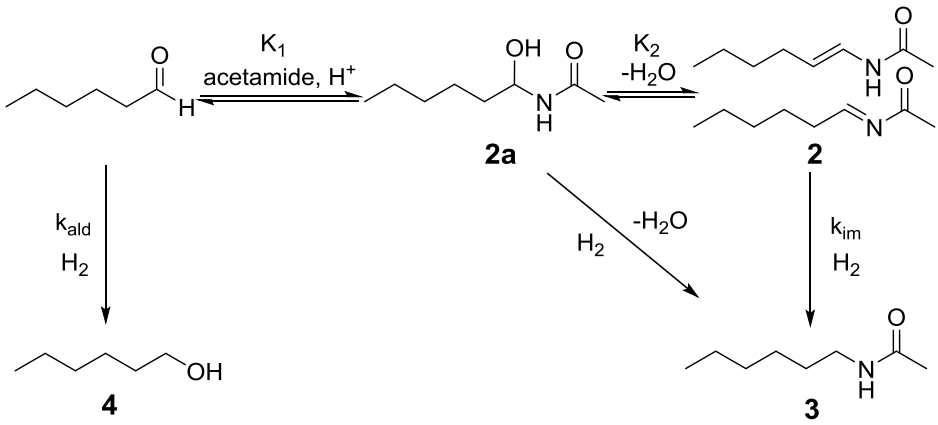


Figure 2.7. Development of the relative intensities of resonances assigned to hexanal (9.72 ppm), N-(1-hydroxyhexyl)acetamide (5.25 ppm and 7.65 ppm) and N-1-hexenylidene acetamide (6.95 ppm) in time. Hexanal:acetamide:HOTs =1:1:0.01 ratio in THF-d_8; T = 60 °C; Measuring in the first hour every 10 min and then every 60 min until 20 hours. ♦=hexanal (1), ■=2a, ▲=2

2.3. Discussion

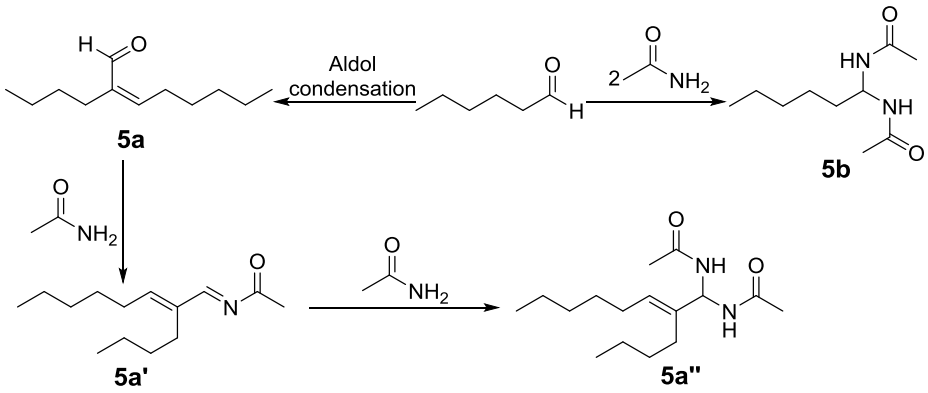
2.3.1. General considerations

The reductive amidation of hexanal **1** with acetamide comprises two sequential steps as shown in Scheme 2.4. The first step consists of two consecutive equilibrium reactions: the nucleophilic addition of acetamide to hexanal **1** yielding the intermediate **2a** which may undergo dehydration to form the two isomeric unsaturated intermediates **2** i.e N-(1-hexylidene)acetamide and to a lesser extent N-1-hexenylacetamide. Irreversible hydrogenation of these unsaturated intermediates will subsequently result in formation of desired product **3**. Direct hydrogenolysis of **2a** to give **3** may also occur, as has also been suggested for intermediate N-carbinolamines in the reductive amination of aldehyde with secondary amines.[14, 44, 45] Formation of **4** by the hydrogenation of hexanal **1** constitutes a loss of starting material, thus resulting in lower selectivity for reductive amidation.



Scheme 2.4. Catalytic reductive amidation of hexanal; formation of N-hexylacetamide **3** via N-(1-hydroxyhexyl) acetamide **2a** and imide or enamide intermediates **2**. Hexanol **4** is a by-product of the reaction

An efficient catalytic system for the reductive amidation reaction thus comprises a catalyst that has a significantly higher rate of hydrogenation of the unsaturated intermediates **2** (k_{im}) (and/or hydrogenolysis of **2a**) relative to hydrogenation of the aldehyde (k_{ald}) in combination with rapid establishment of the equilibrium addition reaction of the aldehyde with the amide. The water formed in the dehydration step in the second equilibrium eventually will have an adverse effect on this equilibrium.



Scheme 2.5. Catalytic reductive amidation; formation of other products characterized by NMR, GC and GC-MS

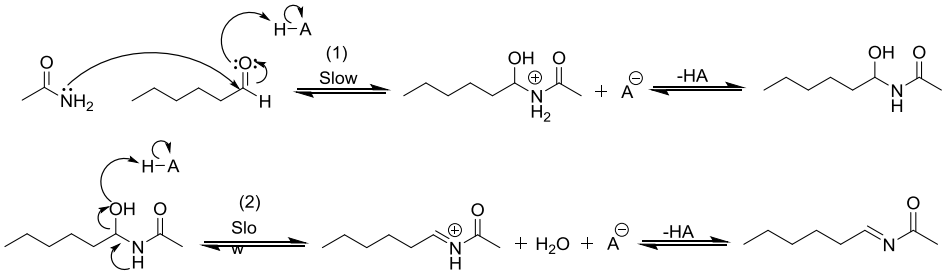
Applying an active and selective catalytic system for the hydrogenation of the unsaturated intermediates **2** (or hydrogenolysis of **2a**) not only advances the reductive amidation reaction by irreversibly removing these intermediates from the equilibria, but also avoids accumulation of the unsaturated intermediates that eventually may form heavier by-products. Possible routes to the higher-mass coupling products are shown in Scheme 2.5. In the absence of an active hydrogenation catalyst the intermediates **2** may react with a second molecule of acetamide to form the di-coupled product **5b**. The other competing side-reactions proceed via the aldol condensation of hexanal **1** yielding product **5a**; this aldol product can also undergo nucleophilic attack of acetamide to form **5a'** and the di-coupling reaction with acetamide giving **5a"**.

2.3.2. Influence of acid

For nearly all catalytic systems that have been screened in our study, the addition of a catalytic amount of acid results in higher conversion of hexanal **1** and improved selectivity to **3**. The formation of aldol condensation and di-coupling products is also promoted by the introduction of acid, as is clearly observed for those catalytic systems that have low hydrogenation activity.

The results of the NMR study show that the nucleophilic addition of acetamide's -N-H to hexanal clearly is promoted by acid (Scheme 2.6); in absence of acid (and hydrogenation catalyst) the addition reaction does not proceed at all, whereas in the

presence of acid the reaction to **2a** and the dehydrated products **2** reaches equilibrium at 60 °C in 10 h.



Scheme 2.6. Proposed mechanism of the acid-catalyzed condensation reaction of hexanal with acetamide

At a practical temperature of 80–100 °C of the catalytic reductive amidation reaction, this process will be faster. The proposed mechanism is consistent with the acid-catalyzed nucleophilic addition of inactivated amines to a carbonyl functionality as described in the literature.[46, 47] The dehydration of the intermediate N-1-carbinol-amide **2a** to form the unsaturated acetamides **2** should also be acid catalyzed, but only occurs to a relatively small extent (K_2 = 0.042 M) at 60 °C.

2.3.3. Influence of ligands, reagents and reaction conditions

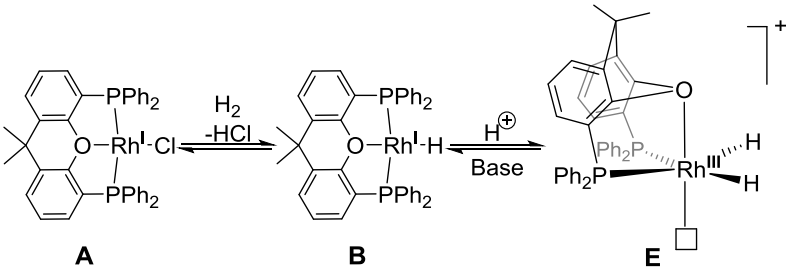
The use of different rhodium precursor complexes in the absence of ligand results in catalytic systems with reasonable conversion of hexanal **1**, but low selectivity. Notably, the use of rhodium precursors with carbonyl ligands results in lower conversions. The addition of various monodentate or bidentate phosphorous ligands to $[Rh(cod)Cl]_2$ generally leads to higher conversion of hexanal. The use of electron-donating alkylphosphane ligands results in catalytic systems that are highly selective for hydrogenation of hexanal to **3**. The use of xantphos results in a catalytic system that shows high conversion to **4** and only a very small amount of **3**, while the intermediates **2** are observed only in trace amounts. Remarkably, upon the addition of a catalytic amount of HOTs the desired reductive amidation product **3** is obtained with high selectivity of about 90% and a **3**/**4** product ratio > 20. This shows that the addition of HOTs not only leads to a more rapid establishment of the equilibrium between aldehyde and enamide/imide as shown by our NMR study, but apparently also leads to

significant changes of the relative rates of hydrogenation of the unsaturated amides **2** (giving **3**) and aldehyde (giving **4**, Scheme 2.4).

Generally, the conversion is strongly affected by the choice of the N-substrates, which supports the idea that the coupling reaction is dependent on the nucleophilicity and bulkiness around nitrogen of the substrates. Lowering of the reaction temperature from 120 °C to 80 °C results in formation of less aldol condensation products, and thus in higher overall (**3**+**4**) hydrogenation selectivity. However, at temperatures lower than 80 °C the hydrogenation activity of the catalysts is also drastically decreased, which lowers the overall hexanal **1** conversion as well as the hydrogenation selectivity; a higher aldehyde concentration profile during the reaction period will generally lead to higher amounts of heavy aldol products. Also, lower hydrogen gas pressures in the reaction lead to lower hydrogenation activity, consequently resulting in the accumulation of intermediates that eventually yields higher amounts other products **5**.

2.3.4. Mechanistic considerations

The catalytic system based on rhodium/xantphos in the absence of added acid, but in the presence of the amide, predominantly hydrogenates hexanal **1** to **4**; intermediates **2** are observed only in trace amounts. However, upon the addition of a catalytic amount of HOTs the desired product **3** is obtained with high selectivity.

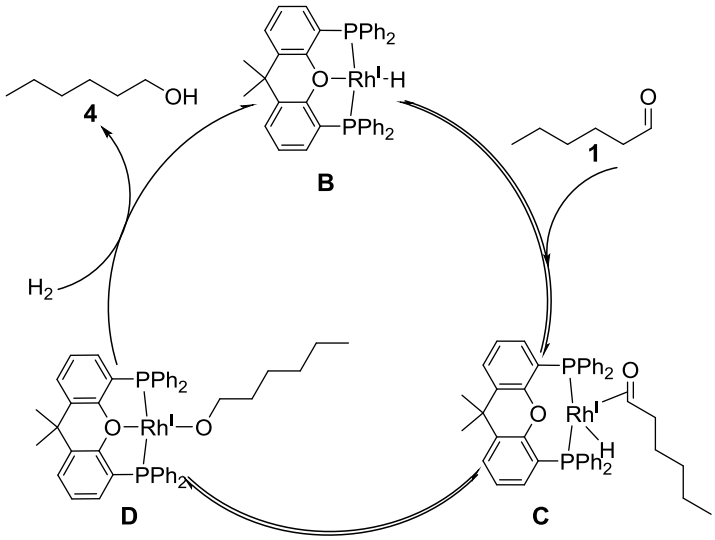


Scheme 2.7. Proposed pathways for the formation of the different catalyst precursors for the reductive amidation reaction in presence or absence of acid; □ = open site or solvent molecule

One reason for the high specificity in the hydrogenation of unsaturated amides (or hydrogenolysis of **2a**) lies in the intrinsically lower activity for aldehyde hydrogenation of the Rh/xantphos species generated in the presence of acid as shown in Table 2.6 (*cf.* entries 1 vs. 2 and 3 vs. 4).

In Scheme 2.7 a proposed pathway is given for the formation of the different catalytic species in the presence or absence of acid. Starting from $[Rh^{I}(cod)Cl]_2$ and xantphos, the complex $[Rh^{I}(xantphos)Cl]$ **A** is initially formed. In absence of acid, heterolytic splitting of dihydrogen may result in the formation of the neutral mono-hydride species $[Rh^{I}(xantphos)H]$, **B**. In the presence of acid the cationic dihydride species $[Rh^{III}(xantphos)(H)_2]^{+}$ **E** may be formed by protonation of the monohydride Rh^{I} compound.[48]

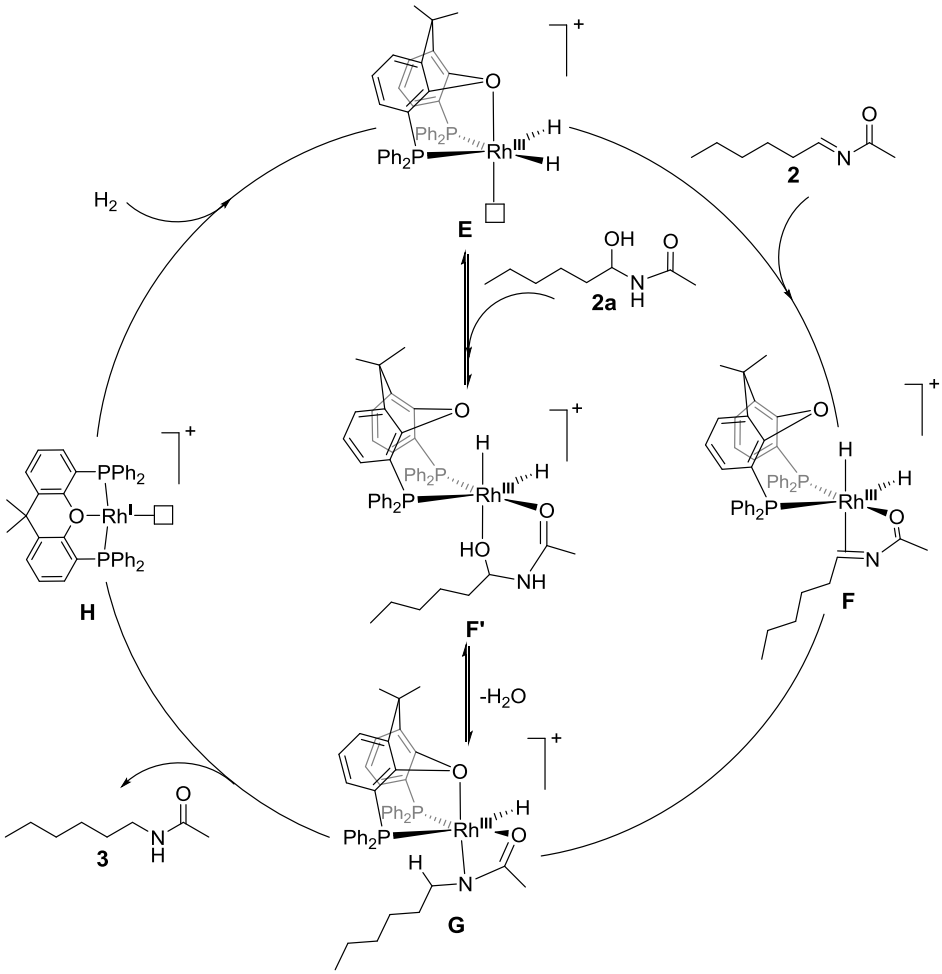
It is our hypothesis that species **B** is a selective catalyst for the hydrogenation of hexanal (Scheme 2.8). The neutral, low-valent Rh^{I} compound would favor the binding of the aldehyde via its π electrons, with subsequent migration of the hydride resulting in the formation of the Rh^{I} alkoxide species **D.** In the final step, heterolytic activation of dihydrogen yields **3** with the regeneration of mono-hydride species **B**. In this mechanism, the xantphos ligand may bind in a meridional fashion, stabilizing the catalytic species in its Rh^{I} state throughout the catalytic cycle.



Scheme 2.8. Proposed catalytic cycle for hydrogenation of hexanal

On the other hand, the cationic, high-valent species **E**, $[Rh^{III}(xantphos)(H)_2]^{+}$ 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, forming species

$[Rh(xantphos)(H)_2(imide)]^+$ **F**. A similar reasoning could hold for possible N-1-hexylideneacetamide. Then, hydride migration to the imide carbon atom results in the formation the N-hexylacetamido species **G**. Finally, N-hexylacetamide **3** is released via reductive elimination to form the Rh^I species **H**; subsequent oxidative addition of dihydrogen recovers species **E**. In this mechanism, the rhodium center is cationic and shuttling between the Rh^I and Rh^{III} oxidation state.



Scheme 2.9. Proposed catalytic cycle for the hydrogenation of intermediate N-(hexenylidene)acetamide **2** or N-(1-hydroxyhexyl)acetamide **2a**; □ = open site or solvent molecule

The selective binding and subsequent H-migration involving the N-(1-hexylidene) acetamide and N-1-hexenylacetamide intermediates **2** is thought to contribute to the unusually high substrate specificity for hydrogenation of **2** that at all times during the reaction is present in only relatively low concentrations in equilibrium with the aldehyde.

An additional factor disfavoring the hydrogenation of aldehyde could be that, in contrast with the Rh^{I} center in the absence of acid as proposed in Scheme 2.8, the now strongly electrophilic cationic dihydride Rh^{III} center would favor coordination of the hard carbonyl oxygen over π-coordination of the carbonyl bond. This carbonyl oxygen binding mode is not a suitable configuration for hexanal **1** hydrogenation, as in this case hydride migration to the carbonyl carbon is not easily possible.

From the NMR studies it is clear that in the presence of an acid (and at relatively low temperatures), instead of one of the unsaturated intermediates **2** the addition product, carbinol-amide **2a,** is predominantly present in solution. Thus, alternatively, this bi-functional carbinol-amide may also bind selectively to species **E** in the presence of aldehyde, effectively giving selective direct dehydrative hydrogenolysis of the alcohol group via a species **F'**.

The POP-pincer structure in xantphos-type ligands has been shown to be important for the stabilization of catalytic intermediates in different reactions such as intramolecular hydroamination,[49] methanol carbonylation,[50] and intermolecular hydroacylation of alkenes and alkynes.[51] Structural studies have also shown the importance of the flexibility of this ligand, with the possible *trans* bidentate and *fac* or *mer* tridentate coordination modes.[51-53] Moreover, the crystal structure of a Rh^{III} compound containing a 4-membered imido-carbonyl chelate similar to our proposal for species **G** has recently been reported.[54]

2.4. Conclusion

We have successfully developed a highly selective catalytic system comprising rhodium/xantphos/HOTs for the reductive amidation of an aldehyde with an amide to form N-alkylamides in high yield and under mild conditions. We have achieved a promising TON of 1800 with using only a small excess of amide substrate. The use of an acid co-catalyst appears to be important for both the nucleophilic addition of the amide to the aldehyde as well as the substrate specificity in the hydrogenation step. The

selective reductive amidation of aldehydes bears resemblance with the well-known transition metal catalyzed reductive amination of aldehydes, but which often suffers from the formation of substantial amounts of side-products originating from (base-catalyzed) aldol condensation and overalkylation.

We are currently seeking to utilize our reductive amidation catalytic system for a 'hydroamidomethylation' reaction, comprising a tandem hydroformylation-reductive amidation process of an alkene with syngas and an amide. For this purpose the reductive amidation catalyst must of course be able to tolerate the presence of carbon monoxide necessary for the hydroformylation step. Preliminary investigations have shown that the presence of traces CO in the reductive amidation reaction results in quenching of the hydrogenation activity and selectivity of the catalyst. Further studies are directed at ways to reduce or eliminate the CO sensitivity of the catalytic system.

2.5. Experimental Section

2.5.1. Chemicals

The solvent bis(2-methoxyethyl)ether (diglyme) was distilled from CaH_2, deoxygenated and used immediately after the purification process. All other solvents were purged with argon and purified under pressure of dry argon using an Innovative Technologies purification system. The solvents passed through activated columns under low pressure to remove trace impurities. Stainless Steel Schlenk Vacuum line and Sigma Aldrich Air-free flasks allow them to be safely transferred.

Hexanal, acetamide, propionamide, iso-propylamide, tert-butylamide, fluoroacetamide, valeramide, benzamide, p-methoxybenzamide, p-trifluoromethylbenzamide, 2-methylpentanal, benzaldehyde, decane (internal standard), hexanol, para-toluenesulfonic acid, chlorido(1,5-cyclooctadiene)rhodium(I) dimer, bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate, (acetylacetonato) dicarbonylrhodium(I), carbonylhydridotris(triphenylphosphane) rhodium(I), bis(cycloocta-1,5-diene)rhodium(I) tetrafluoridoborate, acids and bases were purchased from Acros Organics and Sigma Aldrich, the Netherlands. The monodentate ligands triphenylphosphane (PPh_3), tri-n-butylphosphane ($P(nBu)_3$), n-butyldi-1-adamantylphosphane ($P(nBu)(1\text{-}ad)_2$), tris(2,4-di-t-butylphenyl)phosphite ($P(O\text{-}di\text{-}tBuPh)_3$), the bidentate ligands 1,2-bis(diphenylphosphanyl)ethane (dppe), 1,3-bis(diphenylphosphanyl)propane (dppp), 1,1'-Bis(diphenylphosphanyl)ferrocene (dppf), 1,2-bis(diphenylphosphanylmethyl)benzene (1,2-dppmb), 1,3-bis(diphenylphosphanylmethyl)benzene (1,3-dppmb), 9,9-dimethyl-4,5-

bis(diphenyl-phosphanyl)xanthene (xantphos) and 2,2'-bis(diphenylphosphanylmethyl)biphenyl (bisbi) were purchased from Strem Chemicals, Germany. The other phosphorous ligands such as 1,2-bis(cyclooctylphosphanyl)ethane (bcope) and 2,7-di-tert-butyl-9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene (tBu-xantphos), 4,6-bis(diphenylphosphanyl)-10,10-dimethyl-10H-dibenzo[b,e][1,4]oxasilane (Si-xantphos), 9,9-dimethyl-4,5-bis(di-orthomethoxyphenyl-phosphanyl)xanthene (oMeO-xantphos) and 4,5-bis(di(tert-butyl)phosphanyl)-9,9-dimethylxanthene (di-tBu-xantphos) were generously provided by Shell Global Solutions Amsterdam b.v., where they were synthesized according to literature procedures.[55-57]

2.5.2. Apparatus

The stainless steel autoclave reactors (100 ml) were of HEL Limited, UK, equipped with magnetic stirrer, pressure transducer and temperature controlling thermocouple. A Hewlett Packard HP6890 Series auto-sampler GC system was used for regular GC analysis. GC-MS analysis were carried out on an Agilent technologies 7820A GC system series coupled with an Agilent technologies 5975 series GC-MSD system. A glovebox of M. Braun Inert gas-System GmbH, Germany, was used for storing and handling of air-sensitive phosphane ligands. Nuclear magnetic resonance spectra were recorded on a Bruker DPX300 (300MHz) or a Bruker DMX400 (400MHz) spectrometer. Innovative Technologies PureSolv MD 5 Solvent Purification System was used for drying solvents.

All reaction preparations and manipulations were performed using standard Schlenk techniques under an argon atmosphere. The catalytic reactions were carried out under varying syngas pressures and reaction temperatures.

2.5.3. Procedures

All preparations and manipulations were performed using standard Schlenk techniques under an argon atmosphere. The solvent bis(2-methoxyethyl)ether (diglyme) was distilled from CaH_2, deoxygenated and then saturated with argon and used immediately after the purification process. The catalytic reactions were carried out under varying hydrogen pressures and reaction temperatures. For all the catalytic experiments the catalyst precursor was formed *in-situ* in the autoclave by transferring the metal precursor and the selected phosphane ligands into the reactor. In the preparation of a typical catalytic reaction mixture containing solid ingredients that are not air sensitive, 0.005 mmol of $[Rh(cod)Cl]_2$ (2.46 mg, 0.01 mmol of Rh) and 0.0125 mmol of bidentate phosphane ligand or 0.025 mmol of monodentate phosphane ligand were weighed in air and transferred into an autoclave. The autoclave was closed and subsequently filled with argon using a Schlenk line connected to

one of the valves of the autoclave. Through another valve under a continuous flow of argon subsequently were added: 25 ml of dried and degassed diglyme as solvent, 3.125 mmol (0.605 ml) decane as an internal standard, 5 mmol (0.615 ml) hexanal and 6 mmol (0.354 g) acetamide (for selected experiments acid or another additive was added, dissolved in the diglyme). Then the reactor was inserted into the heating block and connected to the gas line of the reactor block with a continuous flow of N_2 gas through the gas line of autoclave to remove the air inside the gas line. The autoclave reactor was flushed three times with N_2 and one time with H_2 and finally pressurized with hydrogen gas. The reaction mixture was stirred at 500 rpm for 20-30 min to ensure complex formation.

In the set of experiments using air-sensitive ligands such as $P(nBu)_3$, $P(nBu)(1\text{-ad})_2$, bcope and di-tBu-xantphos, in a glovebox the metal precursor complex and ligand (for some experiments with other additives like acid), were weighed into a Schlenk flask and dissolved in 10 ml of dried and degassed diglyme; dissolution generally was complete in about 2-3 minutes as was visible by the formation of a transparent yellowish solution. The flask was then connected to a Schlenk line and the solution was transferred through the valve of a reactor under a continuous flow of argon into the 100 ml stainless steel autoclave reactor. The procedure for gas intake in the autoclave was carried out as described above.

The reaction mixtures were heated up to 80 °C, 100 °C or 120 °C (within 30 min) under stirring at 500 rpm. All reaction conditions of the catalytic process were controlled by computerized software panels. After standing for two, four or ten hours at this temperature, the autoclave was cooled down to room temperature over about one hour. The autoclave was then slowly vented to atmospheric pressure.

After each catalytic run the reaction mixture was taken from the reactor and immediately analyzed with gas chromatography. Calibration lines for each analyte were used to determine the conversion of the substrates and yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples. The products in Table 7 comprising N-hexylacetamide,[58-61] N-hexylpropanamide,[59, 62, 63] N-hexylisopropylamide,[59, 64] N-hexyltertbutylamide,[60, 64, 65] N-hexylpentanamide,[66] N-hexylbenzamide,[59, 67] N-hexyl-4-methoxybenzamide,[59] N-hexyl-4-trifluoromethylbenzamide,[59] N-hexyl-2-fluoroacetamide,[68] N-(2-methylpentyl)acetamide and N-benzylacetamide[58, 60] are known compounds and were identified by ^{1}H and ^{13}C NMR and GC-MS.[60]

2.5.4. GC analysis

A GC spectrum of typical reductive amidation of aldehyde is shown in the appendix I with the assignment of products. 1 µL Crude reaction mixture containing internal standard was injected into a Hewlett Packard HP6890 Series auto-sampler GC system with column HP-1MS UI (30m*0.250mm*1.00µm). All the solvents have been assigned by comparing to their standard GC spectra. All the retention values of substrate and product to undecane have been determined using commercially available or isolated standard chemicals.

Analysis conditions: 130 ºC (5 min), ramp 50ºC/min to 300 ºC, 300 ºC (3.6 min) (12 min in total).

2.5.5. Characterization data

N-hexylacetamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.88 (t, 3H, CH_3), 1.28 (m, 6H, 3*CH_2), 1.49 (m, 2H, CH_2), 1.96 (s, 3H, CH_3), 3.21 (m, 2H, CH_2), 5.73 (b, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 14.2, 23.1, 23.8, 24.2, 24.9, 32.8, 38.1, 169.2.

N-hexylpropanamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.74 (t, 3H, CH_3), 1.39 (t, 3H, CH_3), 1.48 (m, 6H, 3*CH_2), 1.65 (t, 2H, CH_2), 2.25 (m, 2H, CH_2), 3.22 (m, 2H, CH_2), 5.74 (b, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 9.2, 14.1, 22.4, 28.1, 29.3, 33.2, 33.6, 40.4, 167.6.

N-hexylisopropylamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.71 (t, 3H, CH_3), 1.21 (d, 6H, 2*CH_3), 1.31 (m, 6H, 3*CH_2), 1.68 (m, 2H, CH_2), 2.21 (m, 1H, CH), 5.46 (b, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 14.1, 19.3, 20.7, 26.7, 27.5, 29.2, 29.9, 36.7, 38.2, 168.2.

N-hexyltertbutylamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.98 (t, 3H, CH_3), 1.27 (s, 9H, 3*CH_3), 1.51 (m, 6H, 3*CH_2), 1.76 (m, 2H, CH_2), 3.15 (m, 2H, CH_2), 5.73 (b, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 12.1, 21.9, 27.6, 28.4, 30.1, 32.3, 38.6, 39.7, 173.2.

N-hexylpentanamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.72 (t, 6H, 2*CH_3), 1.43 (m, 8H, 4*CH_2), 1.59 (m, 4H, 2*CH_2), 2.21 (m, 2H, CH_2), 3.28 (m, 2H, CH_2), 5.43 (b, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 12.2, 13.8, 19.8, 20.4, 26.4, 27.6, 29.1, 29.9, 36.8, 39.7, 42.1, 169.2.

N-hexylbenzamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.89 (t, 3H, CH_3), 1.35 (m, 6H, 3*CH_2), 1.65 (m, 2H, CH_2), 3.26 (m, 2H, CH_2), 6.49 (b, 1H, NH), 7.46-7.53 (m, 3H,

3*CH), 7.68 (m, 2H, 2*CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 14.1, 21.8, 27.9, 29.1, 31.2, 32.1, 42.4, 127.2, 128.5, 132.6, 134.7, 167.7.

N-hexyl-4-methoxybenzamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.79 (t, 3H, CH_3), 1.38 (m, 6H, 3*CH_2), 1.49 (m, 2H, CH_2), 3.51 (m, 2H, CH_2), 3.71 (s, 3H, CH_3), 6.11 (b, 1H, NH), 7.69 (d, 2H, 2*CH), 7.98 (d, 2H, 2*CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 14.8, 20.3, 26.1, 29.4, 31.5, 39.1, 112.4, 126.2, 127.5, 162.9, 169.3.

N-hexyl-4-trifluoromethylbenzamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.99 (t, 3H, CH_3), 1.48 (m, 6H, 3*CH_2), 1.53 (m, 2H, CH_2), 3.38 (m, 2H, CH_2), 6.26 (b, 1H, NH), 6.95 (d, 2H, 2*CH), 7.79 (d, 2H, 2*CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 14.2, 21.3, 26.9, 28.4, 31.2, 41.1, 53.6, 124.4, 125.5, 127.8, 133.9, 136.2, 167.3.

N-hexyl-2-fluoroacetamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.91 (t, 3H, CH_3), 1.31 (m, 6H, 3*CH_2), 1.72 (m, 2H, CH_2), 3.13 (m, 2H, CH_2), 4.71-4.92 (d, 2H, FCH_2), 6.48 (b, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 13.0, 20.3, 27.4, 28.8, 32.2, 40.1, 83.6, 124.4, 125.5, 127.8, 133.9, 136.2, 172.3.

N-(2-methylpentyl)acetamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.62 (t, 3H, CH_3),0.94 (d, 3H, CH_3), 1.32 (m, 4H, 2*CH_2), 1.98 (s, 3H, CH_3), 2.29 (m, 2H, CH_2), 3.11-3.54 (m, 2H, CH_2), 6.13 (b, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 13.4, 14.4, 20.1, 24.8, 32.2, 37.9, 45.8, 169.5.

N-benzylacetamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 2.09 (s, 3H, CH_3), 4.45 (d, 2H, CH_2), 5.96 (b, 1H, NH), 6.66-7.13 (m, 5H, 5*CH). ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 20.8, 39.7, 124.2, 125.1, 130.2, 131.7, 168.7.

2.6. References

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[41] (ln(1-conv/100)=-kt => k (without acid)=0.18, while k (with acid)=0.038, assuming first-order kinetics in hexanal. In the presence of N,N'-di-Me-acetamide (entries 3 and 4 these numbers are respectively, 0.19 and 0.075
[42] The NMR assignment and chemical shift were determined by compering with NMR perdictor of ChemOffice and NMRDB simulator.
[43] Unlike NMR analysis of equilibrium hexanal/acetamide mixtures at low temperatures, the intermediate **2a** was never observed in GLC analysis. It is expected that any amount present in the reaction medium would be detected in the GLC diagram as unsaturated intermediates **2**, as dehydration is likely a rapid thermal process at 250 °C applied in the injection port of the GLC
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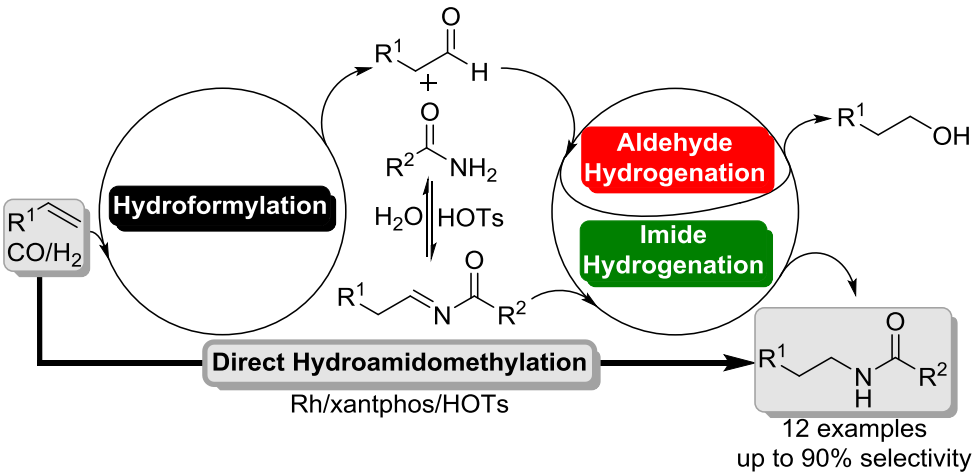
3

Chemo- and Regio-selective Homogeneous Rhodium-Catalyzed Hydroamidomethylation of Terminal Alkenes to N-Alkylamides



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Abstract

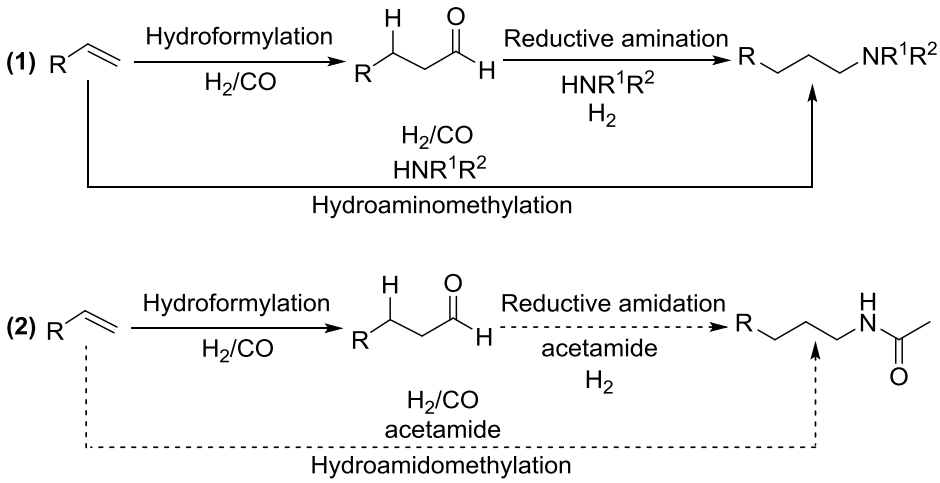
The direct mono-N-alkylation of primary amides with 1-alkenes and syngas through catalytic 'hydroamidomethylation' is reported. A selective rhodium/xantphos catalyst system has been developed for this reaction, taking 1-pentene and acetamide as model substrates. It appeared essential for proper catalyst performance that catalytic amounts of a strong acid promoter, such as p-toluenesulfonic acid (HOTs), as well as larger amounts of a weakly acidic protic promoter, particularly hexafluoroisopropyl alcohol (HOR^F) are applied. Apart from the product N-1-hexylacetamide, the isomeric unsaturated N-1-hexenylacetamide and N-(1-hexylidene)acetamide intermediates, hexanol and higher mass by-products as well as the corresponding isomeric branched products can be formed. Under optimized conditions nearly full alkene conversion can be achieved with more than 80% selectivity to the product N-1-hexylamide. Interestingly, in the presence of a relatively high concentration of HOR^F (HOR^F/diglyme ~5/1) the same catalyst system shows a remarkably high selectivity (~90%) for the formation of alcohol (hexanol) from 1-pentene with syngas, thus presenting a unique example of a selective Rh-catalyzed hydroformylation-hydrogenation tandem reaction under mild conditions.

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

One likely role of HOR^F in combination with the strong acid HOTs is to establish a dual-function catalyst system comprising a neutral [(xantphos)(CO)Rh^I-hydride] hydroformylation catalyst and a cationic [(xantphos)(CO)Rh^{III}-hydride]$^{n+}$ complex capable of selectively reducing the imide and/or eneamide intermediates, that are in a dynamic, acid-catalyzed condensation equilibrium with the aldehyde and amide.

3.1. Introduction

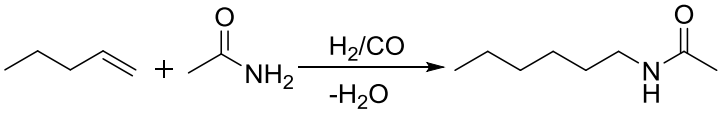
The formation of carbon-nitrogen bonds is of great interest to synthetic chemists as nitrogen-containing molecules are important in bulk and fine-chemical building blocks, solvents, surfactants, dyes, pharmaceuticals, agrochemicals and biologically-active compounds.[1-4] Among the various catalytic methods known for the synthesis of amines the hydroaminomethylation of alkenes is highly atom-economic and efficient. This cascade reaction consists of an initial hydroformylation followed by a reductive amination (Scheme 3.1),[5-12] and was originally discovered by Reppe in the early 1950s at BASF using $Fe(CO)_5$ in nearly stoichiometric amounts.[13, 14] Research on this reaction until the mid-1990s revealed that relatively harsh conditions (> 150 °C) are required to give the desired amines in good yield.[15-24] The critical step in this sequence is the hydrogenation of intermediate imino compounds, which generally is hampered by the presence of carbon monoxide; however, this problem can be reduced by using alcoholic and polar solvents.[25-29] Hydroaminomethylation of alkenes is mostly limited to the use of secondary amines; for primary amines and ammonia the selectivity generally is low because of over-alkylation.



Scheme 3.1. Hydroaminomethylation vs. hydroamidomethylation reaction

In analogy with hydroaminomethylation, the thus far unknown hydroamidomethylation reaction would comprise a cascade reaction of hydroformylation and catalytic reductive amidation (Scheme 3.1). The development of this new method for the synthesis of N-

alkylamides using an amide as the substrate instead of an amine will avoid the formation of over-alkylated side products, due to the low nucleophilicity and steric encumbrance at the amide N of the initially formed mono-N-alkyl amide. Likewise however, the low nucleophilicity of the primary amide substrate makes development of active and selective catalysts for alkylation of a (primary) amide through hydroamidomethylation a generally even more challenging enterprise than alkylation of (secondary) amines via hydroaminomethylation.



Scheme 3.2. Hydroamidomethylation of 1-pentene with acetamide to form N-hexylacetamide

Inspired by our recent achievements concerning the catalytic reductive amidation of aldehydes as described in Chapter 2,[30] we have thus undertaken an investigation into the catalytic synthesis of N-alkylamides, using primarily acetamide and 1-pentene as example substrates, through a rhodium-catalyzed hydroamidomethylation of 1-alkenes (Scheme 3.2)

Whereas in Chapter 2 we reported an efficient three-component *in situ* formed homogeneous catalyst system consisting of Rh/xantphos/HOTs acid for selective reductive amidation of aldehydes under a pure H_2 pressure,[30] in this Chapter we aim to develop hydroamidomethylation catalyst systems not only effective in hydroformylation of the alkenes, but also simultaneously efficient in reductive amidation of the *in situ* formed aldehydes under a CO-containing syngas atmosphere.

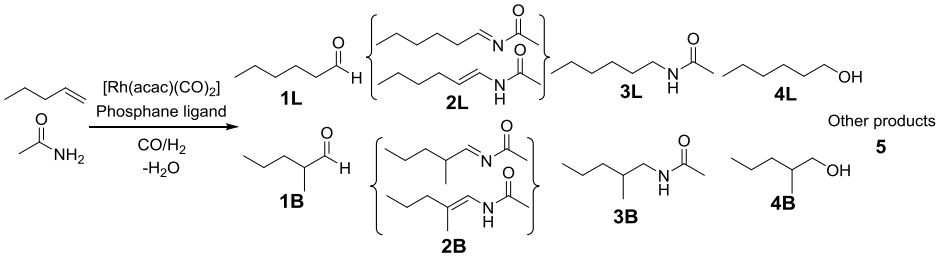
3.2. Results

3.2.1. General considerations

The products found after a typical hydroamidomethylation reaction of 1-pentene with acetamide are shown in Scheme 3.3 (Full experimental details are described in Appendix II).

Apart from the desired product N-1-hexylacetamide **3L**, depending on the efficiency and selectivity of the catalytic system the reaction mixture may comprise the isomeric

unsaturated intermediate compounds N-(1-hexylidene)acetamide and/or N-1-hexenylacetamide **2L**, hexanal **1L** and hexanol **4L** as well as all corresponding branched products (**1B**, **2B**, **3B** and **4B**).



Scheme 3.3. Hydroamidomethylation of 1-pentene with acetamide: observed intermediates, products and undesired by-products

Additionally, various products with higher mass **5** (Figure 3.1), comprising self- or cross-aldol condensation products and the di-substituted product with two molecules of acetamide, may be formed.

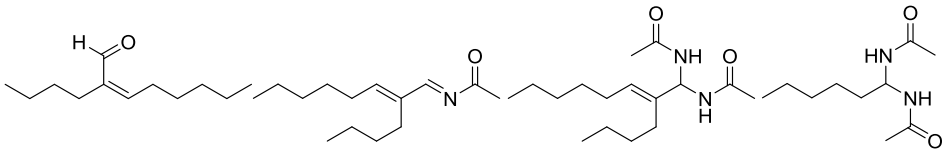


Figure 3.1. Products of higher molecular mass (**5**) observed in the hydroamidomethylation of 1-pentene with acetamide. Corresponding branched products are not shown

The reactions were performed starting with 5 mmol of 1-pentene and an equivalent amount of acetamide; the product distribution was determined by GC analysis. The conversion calculated for the reactions is based on the amount of 1-pentene found after the reaction. The amounts of linear and branched products **3L** and **3B**, unsaturated products **2L** and **2B**, hydroformylation products **1L** and **1B**, and alcohols **4L**, **4B** were determined using calibration lines. In the tables the selectivity for all products and intermediates is reported, as well as the linearity (%) of the aldehyde and N-hexylacetamide. It is worth noting that the individual amounts of both types of unsaturated compounds **2**, 1-N-hexylideneacetamide and 1-N-hexenylacetamide are generally small and present in an approximate 1:1 ratio; for clarity reasons, we have only indicated the total amount of compounds **2** in the product composition Tables.

The remainder consists of the higher mass products **5**, which were not individually quantified by GC, but rather lumped together and calculated from the mass-balance of 1-pentene. Analytical product composition data of all experiments are given in the appendix II.

3.2.2. Catalytic hydroamidomethylation of 1-pentene with acetamide: initial screening studies

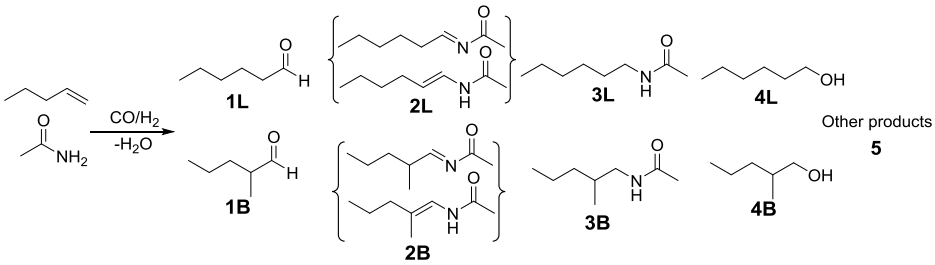
Of the various rhodium precursors $[Rh(cod)Cl]_2$, $[Rh(CO)_2(acac)]$, $[Rh(cod)_2]BF_4$, $[Rh(CO)(H)(PPh_3)_3]$ and $[Rh(cod)_2]OTf$ in combination with the xantphos ligand, $[Rh(CO)_2(acac)]$ turned out to give the highest selectivity for hexanal, with only low amounts of condensation products **5** (Table AII.1). p-Toluenesulfonic acid (HOTs) was introduced as a co-catalyst to promote the coupling reaction of hexanal with acetamide (Chapter 2);[30] however, next to a higher yield of N-1-hexylacetamide **3L** this resulted in strongly increased formation of products **5** (Table 3.1, Entries 1, 2). Although the use of trifluoromethanesulfonic acid (HOTf) resulted in higher selectivity for **3L**, still large amounts of higher molecular weight products **5** were produced (Entry 3).

Increasing the amount of HOTs also led to some increased selectivity in favor of **3L,** but also resulted in high amounts of aldol condensation and di-coupled products (Entry 4). Finally, carrying out the hydroamidomethylation reaction sequentially by first applying a syngas pressure followed by exposure to pure H_2 pressure did not improve the yield of **3L** (Entry 6); this reaction sequence also resulted in formation of large amounts of **5**.

A screening of various reaction solvents demonstrated that the product selectivity is highly dependent on solvent (Entries 7-15). The use of alcoholic solvents like methanol, ethanol, iso-propanol, n-butanol, iso-butanol and trifluoroethanol (TFE) as well as their combination with diglyme or toluene and with an acid co-catalyst resulted mainly in acid-catalyzed acetal formation of hexanal with very low selectivity toward the desired product **3** (Entries 7-13; see also Table AII.2). Use of the more acidic solvent 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HOR^F, pK_a= 9.3) in combination with diglyme (1/1) (even in the presence of HOTs) resulted in low acetal formation, but still only about 15% selectivity for the desired product **3** (Entry 15). Remarkably, a similar selectivity to hexanols (~15%) was observed with the latter solvent combination, both in absence and presence of HOTs (Entries 14, 15).

It is worth noting that the overall regio-selectivity for linear products derived from 1-pentene (hexanal, N-hexylacetamide, and hexanol) in nearly all cases is above 90%, in agreement with the intrinsically high linearity for hydroformylation of terminal alkenes with Rh/xantphos catalysts reported in literature and one of the attractive feats of the xantphos-type ligands.[31-33]

Table 3.1. Effect of solvent system on the hydroamidomethylation of 1-pentene with acetamide[a]



	Solvent	t	additive	conv.	selectivity%[c]						1	3
	10 mL	h	0.05 mmol	%	**1**	**2**	**3**	**4**	acetal	**5**	L%	L%
1	diglyme	4	-	79	89	6	0	0	-	5	97	-
2	diglyme	4	HOTs	84	36	12	13	1	-	38	97	>99
3	diglyme	4	HOTf	89	26	11	19	3	-	41	92	>99
4	diglyme	4	HOTs(0.1)	89	24	12	23	1	-	40	94	>99
5	diglyme	8	HOTs	88	31	9	19	1	-	40	96	>99
6	diglyme[b]	8+4	HOTs	88	25	8	15	3	-	49	86	>99
7	MeOH	8	-	89	81	3	0	0	0	16	96	-
8	MeOH	8	HOTs	91	26	9	1	1	56	7	96	>99
9	MeOH/tol(1/1)	8	HOTs	89	35	19	2	0	34	9	92	>99
10	MeOH/dig(1/1)	8	HOTs	90	31	17	1	0	40	11	93	>99
11	EtOH/dig(1/1)	8	HOTs	82	45	22	0	0	20	13	93	-
12	iPrOH/dig(1/1)	8	HOTs	85	43	20	7	2	16	12	92	>99
13	TFE/dig(1/1)	8	HOTs	90	47	12	1	8	12	21	93	>99
14	HOR^F/dig(1/1)	8	-	88	71	3	1	17	0	8	96	>99
15	HOR^F/dig(1/1)	8	HOTs	85	52	6	14	16	6	6	96	99

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:1-pentene:acetamide=1:2:500:500); $P(CO/H_2)$=50(1/2) bar; T=100 °C; *t* = 4-12h; Solvent: 10 ml diglyme or solvent/diglyme (v/v). [b] one-pot sequential reaction conditions; the reactor was charged with substrates in a similar fashion from the beginning of the reaction and then: 8h at 100 °C hydroformylation under syngas $P(CO/H_2)$ = 50(1/2) followed by depressurizing syngas- 3 pressurizing-depressurizing cycles with H_2-pressurizing with H_2-4h, $P(H_2)$ = 80 bar at 80 °C reductive amidation. [c] The selectivity was determined by GC analysis using decane as an internal standard

3.2.3. HOR^F as a co-solvent

Intrigued by the significantly deviating selectivity to alcohols in the experiment in a diglyme-HOR^F solvent mixture, we set forth to further examine the effects of HOR^F on the reaction characteristics more closely. Thus, we investigated the effects of an increasing HOR^F/diglyme (v/v) ratio (at constant total reaction volume) on the hydroamidomethylation reaction product composition. The results are depicted in Figure 3.2 (see also Tables AII.3 & AII.4).

Moving to a HOR^F-richer solvent mixture by gradually increasing the ratio of HOR^F/diglyme from 0/1 (pure diglyme) to 1/4 (v/v), did not considerably change the conversion of 1-pentene; the selectivity for the desired product **3,** however, increased spectacularly by almost a factor of 5 over this range of HOR^F concentration. Increasing the HOR^F concentration further to about 50% (HOR^F/diglyme = 1/1 v/v) surprisingly resulted in a drop of the selectivity to **3** with an increase in selectivity to the aldehyde **1**. Moving to a HOR^F-richer regime from the ratio of 1/1 to 5/1 resulted in a high selectivity (> 80%) to alcohol **4**, clearly at the cost of the aldehydes.

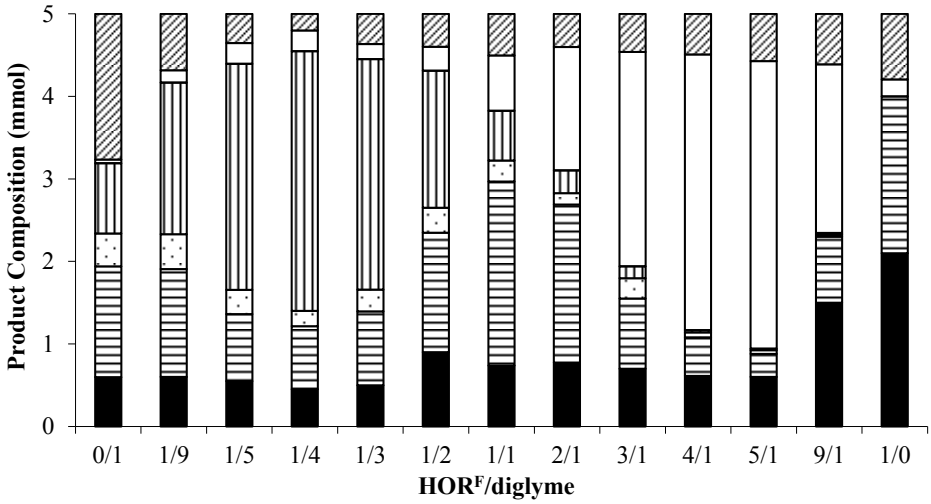


Figure 3.2. The effect of the ratio of HOR^F/diglyme on the product composition in the hydroamidomethylation of 1-pentene with acetamide catalyzed by the Rh/xantphos/HOTs system; Reaction conditions: 0.01 mmol [$Rh(CO)_2(acac)$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); T=100 °C; t=8 h; Constant volume reaction solvent: 10 mL; decane used as internal standard. ■ =1-pentene, ▤= aldehyde (**1**), ⊡= unsaturated intermediate (**2**), ▥= desired product (**3**), □= alcohol (**4**), ▨= other products (**5**); (For more detailed information see supporting information Table AII.3).

Changing the ratio from 5/1 to 1/0 (pure HOR^F) resulted in a decrease in conversion of 1-pentene with a steep decrease in selectivity to alcohol **4**, the main products being aldehyde **1** and condensation products **5.** Thus, it appears that the 1/4 ratio of HOR^F/diglyme (~20 mmol of HOR^F) gives the highest selectivity to the desired product **3**. As shown in Table AII.3 acetal formation of hexanal with HOR^F appeared undetectable, when the applied HOR^F/diglyme ratio was smaller than 1/2.

3.2.4. Optimization and scope of the hydroamidomethylation reaction in HOR^F/diglyme (1/4 v/v)

3.2.4.1. Effect of temperature and ligands

The effects of reaction temperature on the product composition are shown in Figure 3.3 and Table AII.7. It appears that the highest selectivity (~70%) for product **3** is obtained at a reaction temperature of 100 °C.

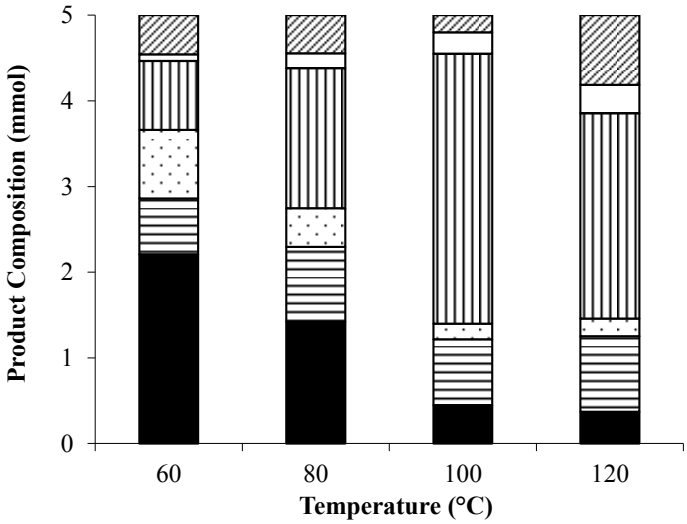


Figure 3.3. The effect of different reaction temperatures on product distribution in the hydroamidomethylation of 1-pentene with acetamide catalyzed by the Rh/xantphos/HOTs system; Reaction conditions: 0.01 mmol [$Rh(CO)_2(acac)$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); $P(CO/H_2)$=50 bar(1/2); t=8 h; Solvent: 10 mL (v/v) HOR^F/diglyme (1/4); decane as internal standard. ■=1-pentene, ▤= aldehyde (**1**), ⊡= unsaturated intermediate (**2**), ▥= desired product (**3**), □= alcohol (**4**), ▩= other products (**5**)

At the higher temperature of 120 °C the selectivity for hydroamidomethylation decreased, in particular due to formation of higher amounts of higher-mass products **5** (Table AII.7). Upon lowering the reaction temperature to 60 - 80 °C the conversion of 1-pentene dropped with a significant concentration build-up of unsaturated intermediates **2**, indicating a progressively lower rate of reduction of intermediates **2** relative to their rate of formation.

A selection of ligands with different stereo-electronic properties as potential substitutes for xantphos were also tested under the same optimal reaction conditions. An overview of the ligands is shown in Figure 3.4. The catalytic results obtained with *in situ* generated Rh/ligand/HOTs catalysts are summarized in Table 3.2.

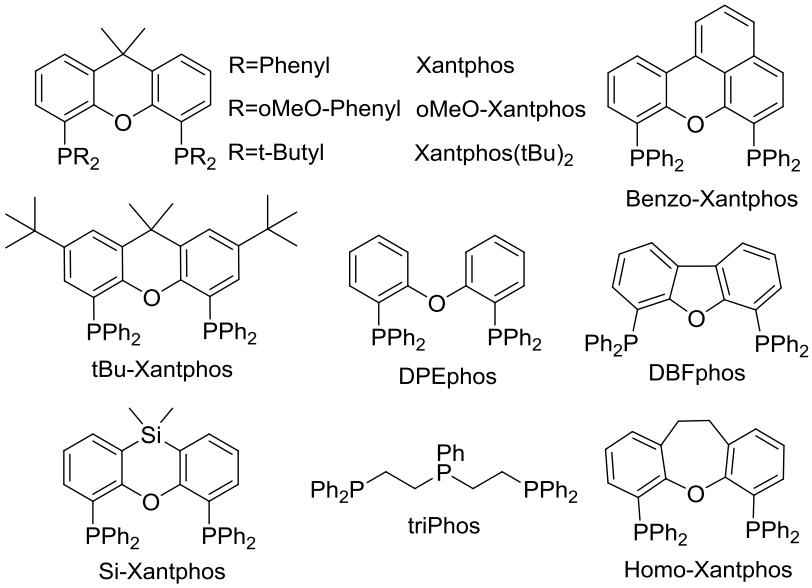


Figure 3.4. Selected ligands used in the hydroamidomethylation of 1-pentene with acetamide

In the absence of any phosphane ligand (entry 1) full conversion of 1-pentene was observed, but with a low chemoselectivity (~10%) to N-hexylacetamide. Most striking is the low regioselectivity (~70%) for **3L**, and only 30% for aldehyde product **1L**. The use of monodentate ligands like PPh_3 resulted in nearly full conversion of 1-pentene after 4 hours; however, again the linearity of the aldehyde (~50%) and the selectivity to the desired product was very low (~3%). Quite remarkably, the use of DPEphos,

considered as a more flexible analogue of xantphos, gave a low-performance catalyst with low chemoselectivity to **3** (~35%). The high regioselectivity for linear product **3L** (97%) combined with a low regioselectivity of aldehyde clearly indicates that the subsequent reductive amidation of the linear aldehyde occurs preferentially over its branched isomer.

Among the variety of different xantphos-type ligands, the best results were obtained with xantphos, Si-xantphos and tBu-substituted xantphos with selectivity to **3** of 50-60% (at 4 h reaction time) and a combined selectivity including potential precursors **1** and **2** up to 90-95%. In particular, the catalytic systems with these ligands show a relatively low accumulation of unsaturated intermediates **2**, thus showing the importance of the rigid P-O-P backbone for the selective hydrogenation.[30] The use of oMeO-xantphos gave a low-activity catalyst with low chemoselectivity to **3** and surprisingly low regioselectivity (~60%) in the aldehyde. Apparently, the bulky oMeO-phenyl substituents not only prevent binding of the aldehydes and intermediates **2,** but also of 1-pentene.

Table 3.2. Effect of various ligands on hydroamidomethylation of 1-pentene with acetamide[a]

	ligand	conversion	selectivity %[b]					**1**	**3**
		%	**1**	**2**	**3**	**4**	**5**	L%	L%
1	no	99	46	23	10	1	21	30	71
2	PPh_3	96	42	20	3	0	36	51	>99
3	DPEphos	70	37	13	34	3	14	67	97
4	triPhos	10	67	0	0	0	33	70	-
5	xantphos	83	27	9	57	4	4	95	>99
6	tBu-xantphos	80	26	8	59	3	4	96	>99
7	Si-xantphos	77	31	7	53	5	4	72	99
8	oMeO-xantphos	11	71	8	3	0	17	58	>99
9	benzoxantphos	82	52	13	16	0	19	53	>99
10	DBFphos	46	44	25	23	3	5	97	98
11	Homoxantphos	28	17	12	61	4	6	70	95
12	xantphos$(tBu)_2$	97	50	24	9	1	16	28	82

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol (bidentate) or 0.04 mmol (monodentate) ligand, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:L:HOTs:1-pentene:acetamide=1:2 (bidentate) or 4 (monodentate) :5:500:500); T=100 °C; t=4 h; $P(CO/H_2)$=50 bar(1/2); Solvent: 10 mL HOR^F/diglyme (1/4); [b] The selectivity was determined by GC analysis using decane as an internal standard

Remarkably, also low selectivity (~15%) for **3** is obtained with another xantphos-look-alike ligand, benzoxantphos. This ligand gave high alkene conversion, but low regio-selectivity (50%) for linear aldehyde **1L**, and thus exemplifies that a low regio-selectivity for hydroformylation can be accompanied by a low selectivity for reductive amidation of the aldehydes. This is also reflected by a significant accumulation (~15%) of unsaturated intermediates **2**, which eventually may result in increased amounts of **5** (Table AII.11). It is surprising that the presence of a naphthyl fragment in this ligand can have such a decisive stereo-electronic influence at the Rh center, which translates to its mediocre performance in the present hydroamidomethylation catalysis. A similar observation was made with DBFphos as ligand with a build-up of intermediate **2** up to 25%, indicative of a low hydrogenation activity for these intermediates, even though heavy-ends formation remained low with this catalyst. This latter observation suggests that not only the 'free' acid component (HOTs/Rh=5) of the catalyst system is responsible for formation of aldol-type higher mass products, but that the metal catalyst complex can also play an activating role for forming these products.

It is interesting to note that the highest selectivity for N-hexylacetamide formation (>60%) was obtained with Homo-xantphos as ligand, be it at relatively low overall activity. This catalyst combines moderate hydrogenation activity of the intermediates **2** with low heavy-ends formation.

Finally, the results with xantphos$(tBu)_2$ are remarkable in the sense that high activity for hydroformylation was observed, with almost full 1-pentene conversion, but at the same time this ligand afforded a catalyst with the almost worst performance for hydroamidomethylation with a selectivity for **3** of less than 10% and highest accumulation (~25%) of the intermediates **2**, indicating a very low activity for hydrogenation of these intermediates. The very similar product distribution as obtained when no ligand is applied (entry 1) suggests that this ligand fails to form stable complexes with rhodium.

3.2.4.2. Effect of H_2/CO ratio on hydroamidomethylation of 1-pentene

In a next set of experiments, the effect of the H_2/CO ratio on the hydroamidomethylation reaction was investigated (Figure 3.5; Table AII.5). Increasing the pressure of H_2 gas (with constant pressure of 20 bar CO) from 10 to 40 bar (Figure 3.5A) resulted in an increased conversion of 1-pentene as well as a steep increase in selectivity to **3**, with only a slight increase in yield of **1** and **4**. The use of pressures

higher than 40 bar of H_2 did not further improve the reaction efficiency to **3**. The use of CO pressures in excess of a hydrogen pressure of 20 bar resulted in a significant drop in the conversion of 1-pentene and yields of both **3** and **1**(Figure 3.5B).

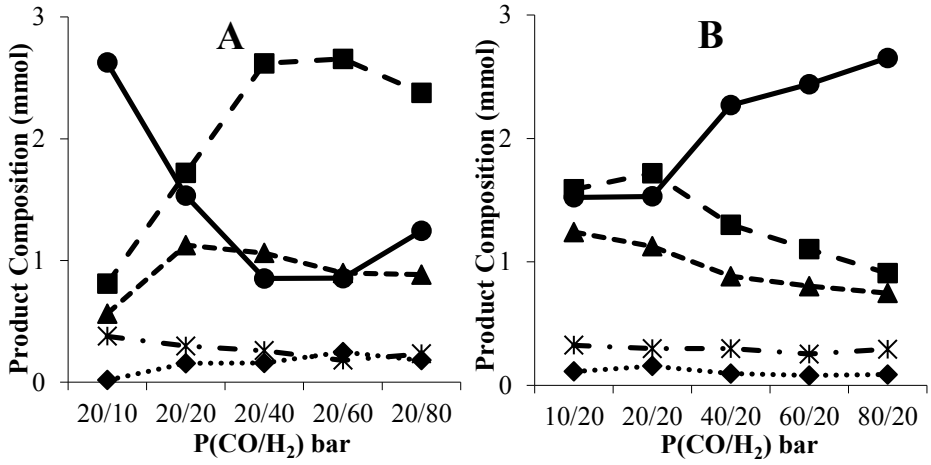


Figure 3.5. The effect of syngas ratio on the hydroamidomethylation of 1-pentene with acetamide catalyzed by the Rh/xantphos/HOTs system; (A) Effect of H_2; (B) Effect of CO; Reaction conditions: 0.01 mmol [$Rh(CO)_2$(acac)], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); T=100 °C; t=4 h; Solvent: 10 mL HOR^F/diglyme (1/4 v/v); decane as internal standard. ●=1-pentene, ▲= aldehyde (**1**), ∗= unsaturated intermediates (**2**), ■= desired product (**3**), ♦= alcohol (**4**).

3.2.4.3. Effect of water

As investigated in the reductive amidation of an aldehyde (Chapter 2, Table 2.8), water has a pronounced influence on the reaction. In the presence of water, the formation of the desired product **3** is suppressed as a consequence of the equilibrium reactions being pushed backward to the substrates in reductive amidation step. The dramatic effect on the **3**/**4** ratio can be seen in the Figure 3.6.

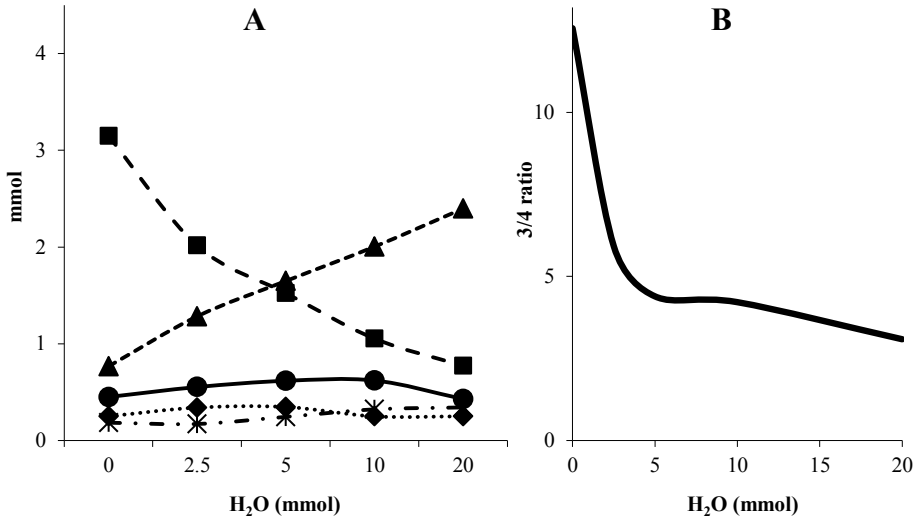


Figure 3.6. The effect of water on the hydroamidomethylation of 1-pentene with acetamide catalyzed by the Rh/xantphos/HOTs system; A) overall; B) the desired product **3**/alcohol **4** ratio; Reaction conditions: 0.01 mmol [$Rh(CO)_2(acac)$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); *T*=100 °C; *t*=8 h; Solvent: 10 mL HOR^F/diglyme (1/4 v/v); decane as internal standard. ●=1-pentene, ▲= aldehyde (**1**), ∗= unsaturated intermediates (**2**), ■= desired product (**3**), ♦= alcohol (**4**).

3.2.4.4. Alternative promoter compounds as substitute for HOR^F

The finding of HOR^F as a promoter for hydroamidomethylation catalysis prompted us to search for other compounds with similar or better performance. We hypothesized that the acidity properties of HOR^F - perhaps in addition to polarity - is a decisive parameter for its effect on catalysis. Thus, a selected number of compounds, characterized by acid strength, were screened in diglyme in the molar quantity that proved optimally effective with HOR^F. The results of this screening study are summarized in Table 3.3 (see also Table AII.13). It appears that some phenol-type compounds like phenol, 2-fluorophenol, 3-fluorophenol, 4-fluorophenol, 2-chlorophenol and 4-chlorophenol show catalyst promoter performance somewhat similar to HOR^F (*cf.* entries 2, 4, 6, 7, 8, 9, 11). In particular with 3-fluorophenol, 4-fluorophenol and 4-chlorophenol the reactions seem to show comparable product compositions as observed with HOR^F, with low accumulation of **2** and low heavy-ends **5**.

All compounds that induce selectivity for **3** above 50% have a pK_a between ~8.5 and 10, whereas the probed compounds with pK_a>10 generally have poor promoter performance. It is however clear from the general features displayed in Table 3.3 that acid strength as a sole criterion for promoter performance seems not well validated. Unfortunately, insufficient data on polarity/dielectric constant/dipole moment are available to identify a correlation with promoter performance and a more complete survey needs to be accomplished to shed more light on this matter. This, and possible further optimization studies on some promising compounds, are subject of further study.

Table 3.3. Effect of various additives in combination with diglyme on hydroamidomethylation of 1-pentene with acetamide[a]

	co-solvent 20 mmol	dielectric constant	pK_a	Conv. %	selectivity %[b] **1**	**2**	**3**	**4**	**5**	**1** L%	**3** L%
1	-	-	-	88	31	9	19	1	40	96	>99
2	HOR^F	16.8	9.2	90	19	2	68	5	5	93	>99
3	TFE	27.7	12.37	89	16	6	34	2	42	98	>99
4	PhOH	2.95-3.1	9.99	82	23	8	46	4	19	88	>99
5	triF-4-cresol	-	8.68	95	34	15	22	4	25	59	91
6	4-F-PhOH	-	9.89	86	25	3	59	4	9	92	>99
7	3-F-PhOH	-	9.29	90	22	3	66	5	4	91	>99
8	2-F-PhOH	-	8.73	88	19	4	42	2	32	93	>99
9	4-Cl-PhOH	11.2	-	91	21	3	67	6	4	90	>99
10	3-Cl-PhOH	6.26	9.12	90	61	15	8	0	16	56	>99
11	2-Cl-PhOH	7.4	8.56	88	20	3	52	3	21	92	>99
12	4-Br-PhOH	-	9.37	84	23	11	9	2	55	>99	>99
13	2,6-di-Me-PhOH	-	10.36	88	17	4	30	2	46	90	>99
14	2,6-di-iPr-PhOH	-	11.1	89	22	7	9	2	60	94	>99
15	2,6-di-tBu-PhOH	-	13.6	86	23	9	14	0	54	98	>99
16	2,6-di-Me-PhCOOH	-	3.25	88	34	5	7	2	52	96	>99
17	AcOH	6.2-6.5	4.76	89	10	9	25	1	56	98	>99
18	di-Ph-CHOH	-	13.4	87	41	14	22	2	21	95	>99
19	di-iPr-CHOH	-	~14.5	89	32	10	15	1	42	95	>99
20	H_2O	80	15.7	89	88	3	0	1	7	97	-
21	2-naphthol	4.95	9.63	85	16	8	12	1	62	99	>99

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide= 1:2:5:500:500); T=100 °C; t=8 h; $P(CO/H_2)$=50 bar(1/2); Solvent: 10 mL diglyme ; 20 mmol of co-solvent; [b] The selectivity was determined by GC analysis using decane as an internal standard

3.2.4.5. Hydroamidomethylation product development in time

Figure 3.7 shows the product-development curves in time for the Rh/xantphos/HOTs catalytic system in HOR^F/diglyme (1/4). These curves were constructed from reaction product compositions of separate identical experiments carried out during the respective residence times. The product composition development clearly shows the aldehydes and unsaturated compounds **2** to exist as reaction intermediates to ultimately form N-hexylacetamide as well as the other final products, hexanol and heavy-ends. Clearly, it can be deduced from this figure that the rate- and selectivity-determining step in the overall hydroamidomethylation reaction with the present catalytic system involves the reductive amidation of aldehydes.

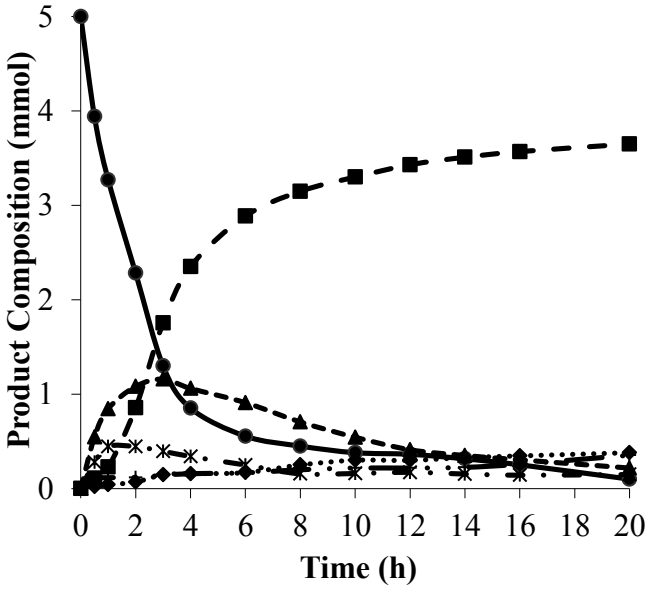


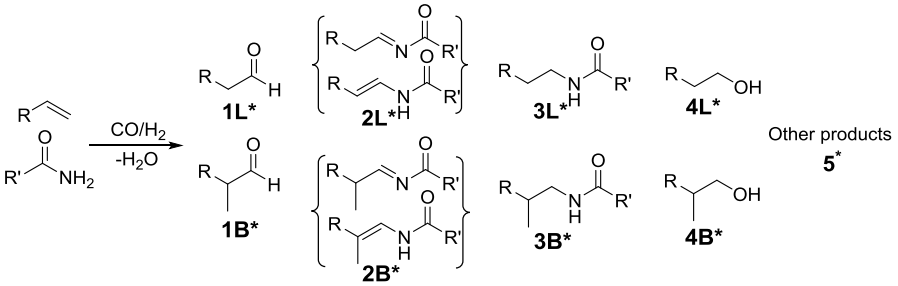
Figure 3.7. Product development in time in the hydroamidomethylation of 1-pentene with acetamide; Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); *T*=100 °C; $P(CO/H_2)$=50 bar(1/2); Solvent: 10 mL (v/v) HOR^F/diglyme (1/4); decane as internal standard. ●=1-pentene, ▲=hexanal (**1L**), ∗= unsaturated intermediates (**2L**), ■= N-1-hexylacetamide (**3L**), ♦= hexanol (**4L**), += other products (**5**). For clarity only the linear products are depicted (details are given in appendix II, Table AII.10)

3.2.4.6. Scope of the hydroamidomethylation reaction

Various higher olefins and a number of different amides were used as substrates in the hydroamidomethylation reaction using the optimized reaction conditions (Table 3.4; Table AII.12).

The use of 1-hexene or 1-octene in the reaction with acetamide gave the desired N-alkylamide with similar conversion, selectivity and linearity as for 1-pentene (entries 1-3). The use of styrene resulted in high conversion, however with decreased selectivity to the desired product **3*** (entry 4) due to the accumulation of more stable unsaturated linear intermediate **2***. Whereas the hydroformylation produces significant quantities of the branched aldehyde, this aldehyde is more reluctant to undergo reductive amidation.

Table 3.4. Hydroamidomethylation reaction using different amides and alkenes[a]



	alkene	amide	Conv.	selectivity %[b]					1*	3*
	5 mmol	5 mmol	%	**1***	**2***	**3***	**4***	**5***	L%	L%
1	1-pentene	acetamide	91	17	4	69	6	4	92	>99
2	1-hexene	acetamide	89	20	3	67	6	4	90	>99
3	1-octene	acetamide	88	24	2	62	6	7	93	>99
4	styrene	acetamide	86	20	36	33	4	8	51	>99
5	1-pentene	propanamide	90	14	5	74	3	4	96	>99
6	1-pentene	2-Me-propanamide	89	18	4	71	3	4	88	>99
7	1-pentene	pivalamide	87	25	6	61	3	5	91	>99
8	1-pentene	valeramide	93	10	2	83	4	1	90	>99
9	1-pentene	mono-F-acetamide	90	77	12	4	4	3	96	>99
10	1-pentene	benzamide	69	38	8	24	0	30	99	>99
11	1-pentene	p-MeO-benzamide	90	38	3	48	1	10	99	>99
12	1-pentene	p-CF_3-benzamide	57	29	31	21	0	18	90	>99

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol alkene, 5 mmol amide (Rh:xantphos:HOTs:alkene:amide=1:2:5:500:500); T=100 °C; t=8 h; $P(CO/H_2)$=50 bar(1/2); Solvent: 10 mL (v/v) HOR^F/diglyme (1/4); [b] The selectivity was determined by GC analysis using decane as an internal standard

The use of amides with more electron-donating carbonyl groups, such as propanamide, 2-methylpropanamide and pentanamide resulted in higher selectivity to the N-hexylamides (entries 1, 5, 6, 8). Applying an amide with bulkier carbonyl group, such as 2,2-dimethylpropanamide (pivalamide) resulted in only slightly lower selectivity to the desired product (entry 7). Application of an amide with the electron-withdrawing mono-fluoromethyl group caused a drastic drop in the selectivity to N-hexyl-fluoroacetamide (entry 9); the main product of this reaction was hexanal. The use of benzamides resulted in lower selectivity to **3*** compared to acetamide. Applying a benzamide with an electron-donating p-methoxy substituent gave again significantly higher selectivity to **3***, whereas p-trifluoromethylbenzamide with an electron-withdrawing group again resulted in lower selectivity. These results show a correlation between the efficiency of hydroamidomethylation and the nucleophilic character of the amide's N-atom; the same correlation was earlier observed with the reductive amidation of aldehydes with pure H_2, and is a clear indication of the tandem character of hydroformylation-reductive amidation in the hydroamidomethylation reaction Chapter 2).[30]

3.2.5. Influence of HOR^F in the separate steps: hydroformylation and reductive amidation

3.2.5.1. General comments

The use of a HOR^F/diglyme solvent mixture has a profound effect on the catalytic performance of the Rh/xantphos system in the hydroamidomethylation of alkenes with amides; the selectivity of the catalytic system changes significantly with the composition of the solvent mixture. As we have observed that the reductive amidation of hexanal in pure diglyme as solvent is severely inhibited by the presence of CO,[30] the separate reaction steps, hydroformylation and reductive amidation with the Rh/xantphos catalyst system, were studied in more detail.

3.2.5.2. Hydroformylation of 1-pentene

The hydroformylation of 1-pentene with the Rh/xantphos catalytic system in pure diglyme as well as in a mixture of HOR^F/diglyme (1/4 v/v) was studied. The results given in Figures 3.8A and 3.8B show that the conversion of 1-pentene in the HOR^F/diglyme mixture was generally lower than in pure diglyme. The lower conversion was particularly distinct when HOTs was present as a catalyst component (HOTs/Rh=5 (mol/mol)), giving ~90% conversion in pure diglyme but only 30% in the

HOR^F/diglyme 1/4 (v/v) mixture. Remarkably, hydroformylation with HOTs as catalyst component resulted in both solvent systems in detectably higher amounts of hexanol as well as heavy-end by-products. To simulate the presence of the weakly basic amide under actual hydroamidomethylation conditions, hydroformylation was also carried out in presence of N,N-dimethylacetamide (DMA, in equimolar amount to 1-pentene). For the pure diglyme solvent system this resulted in lower conversion (from 70% to 55%), whereas hardly any effect of DMA was discernible for the HOR^F/diglyme solvent system; the weak basicity of DMA seems to be neutralized by the excess (by about factor 4) of HOR^F. When both DMA and HOTs (DMA/HOTs=100 (mol/mol)) were applied in the catalytic reaction mixture, the catalyst *activation* effect of HOTs in pure diglyme appeared virtually unaffected, be it with reduced alcohol formation. In contrast, its activity-*reducing* effect in the HOR^F/diglyme mixture was virtually absent, suggesting a neutralizing effect between DMA and HOTs in HOR^F. Small amounts of hexanol due to the presence of HOTs were still formed in both cases (selectivity ~3 and ~7% for respectively, pure diglyme and HOR^F/diglyme mixture solvent systems (Table AII.8-1)

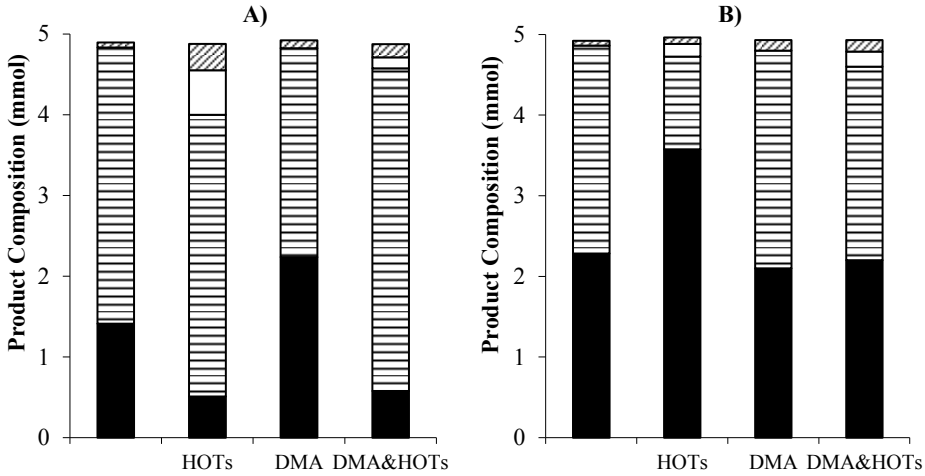


Figure 3.8. The effect of acid and base on the hydroformylation of 1-pentene catalyzed by the Rh/xantphos catalytic system; (**A**) in diglyme, (**B**) in HOR^F/diglyme 1/4 (v/v). Reaction conditions: 0.01 mmol $Rh(CO)_2(acac)$, 0.02 mmol xantphos, 0.05 mmol HOTs (in the case that acid was used), 5 mmol 1-pentene, 5 mmol N,N-dimethylacetamide (DMA: in the case that DMA was used); (Rh:xantphos:1-pentene=1:2:500); $P(CO/H_2)$=50 bar (1/2); t=2 h; Solvent: 10 ml diglyme or 10 ml HOR^F/diglyme=1/4 (v/v); decane as internal standard. ■=1-pentene, ▤= aldehyde (**1**), □= alcohol (**4**), ▩= other products (**5**)

The effect of different amounts of HOR^F on the hydroformylation reaction in the presence of HOTs catalyst component was also investigated. Both the amounts of DMA and HOTs were kept constant in the series of experiments depicted in Figure 3.9A, to simulate the presence of amide under hydroamidomethylation conditions. Using increasing ratios of HOR^F/diglyme (v/v) in this series of experiments, while keeping the total reaction volume constant, revealed that the higher the HOR^F/diglyme ratio, the higher selectivity to hexanol is observed (Figure 3.9A). However, the catalytic activity dropped gradually, as apparent from the 1-pentene conversion falling from >95% in pure diglyme to about 50% in pure HOR^F. Remarkably, when applying pure HOR^F as solvent the selectivity to hexanol dropped again to about 10% from 55% at 80 vol% of HOR^F. This observation is consistent with observations under real hydroamidomethylation conditions depicted in Figure 3.2, which show a quantitatively very similar effect at high HOR^F/diglyme ratios.

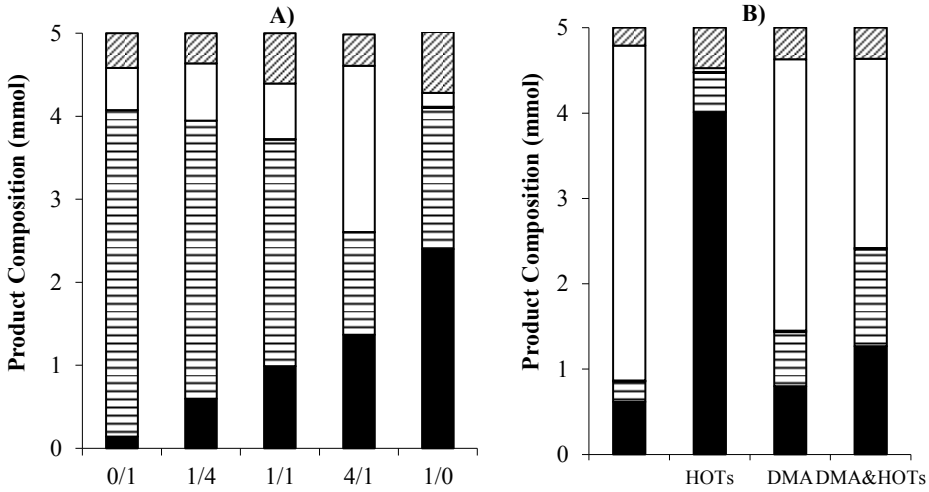


Figure 3.9. The effect of HOR^F in the absence and in the presence of acid on hydroformylation of 1-pentene catalyzed by the Rh/xantphos system; (**A**) different ratio (v/v) of HOR^F/diglyme in the presence of HOTs and DMA; (**B**) in HOR^F/diglyme 5/1 (v/v).; Reaction conditions: 0.01 mmol [$Rh(CO)_2(acac)$], 0.02 mmol xantphos, 5 mmol 1-pentene; (Rh:xantphos:1-pentene=1:2:500); 0.05 mmol HOTs (in the case that acid was used), 5 mmol N,N-dimethylacetamide (DMA: in the case that DMA was used); $P(CO/H_2)$=50 bar(1/2); t=8 h; Solvent: 10 mL HOR^F/diglyme(v/v); decane as internal standard. ■=1-pentene, ▤= aldehyde (**1**), □= alcohol (**4**), ▨= other products (**5**)

In the experiments shown in Figure 3.9B, a constant HOR^F/diglyme ratio of 5/1 (v/v) was applied, both in absence and presence of HOTs (HOTs/Rh = 5 (mol/mol) and DMA (HOR^F/DMA ~ 17 (mol/mol)). In this HOR^F-rich reaction medium in the absence of HOTs the selectivity to hexanol was boosted dramatically to 90%, while reaching a high alkene conversion of ~90%. When HOTs was present, both the alkene conversion and the selectivity to hexanol dropped dramatically. However, in the presence of DMA (DMA/HOTs=100 (mol/mol)) HOTs seems at least partly neutralized and a strong restoration of hydroformylation activity as well as regain of selectivity to hexanol became apparent (Figure 3.9B, Table AII.8-2). Again, this observation is consistent with the observations depicted in Figure 3.2 at the same HOR^F/diglyme ratio under real hydroamidomethylation conditions, thus giving confidence that addition of DMA (at amounts equimolar to 1-pentene) in the individual reaction steps truly approaches hydroformylation conditions prevailing in hydroamidomethylation reactions.

3.2.5.3. Reductive amidation of hexanal

The effects of the presence of HOR^F as a co-solvent, in particular its effect on the consequences of the application of syngas in Rh/xantphos/HOTs catalyzed reductive amidation of hexanal with acetamide is shown in Figure 3.10. When the reductive amidation of hexanal with acetamide is carried out in diglyme, the selectivity to N-hexylacetamide dropped from about 40% in pure H_2 at 50 bar to only about 10% with the addition of only 5 bar of CO (45 bar H_2). At higher CO pressure this selectivity further dropped to below 10%, while an increased amount (>15%) of unsaturated **2** became visible (Figure 3.10A).

Amazingly, a strongly *positive* effect of CO was revealed on the selectivity for reductive amidation of hexanal, when a HOR^F/diglyme (1/4(v/v)) solvent mixture was applied (Figure 3.10B).[34] Application of syngas (CO/H_2=1) even led to an *increase* in the selectivity to **3** by an order of magnitude from less than 5% at 50 bar of pure H_2 to 50% at 50 bar of syngas. It is shown that the yield of **3** (and to a lesser extent also of hexanol **4L**) increased *gradually* with increasing CO pressure, while the amount of intermediate product **2** and heavy-end products **5** simultaneously decrease, thus indicating not only an increase in the catalyst's general hydrogenation activity, but also indicating an increase in substrate specificity for hydrogenation of intermediates **2** over hexanal.

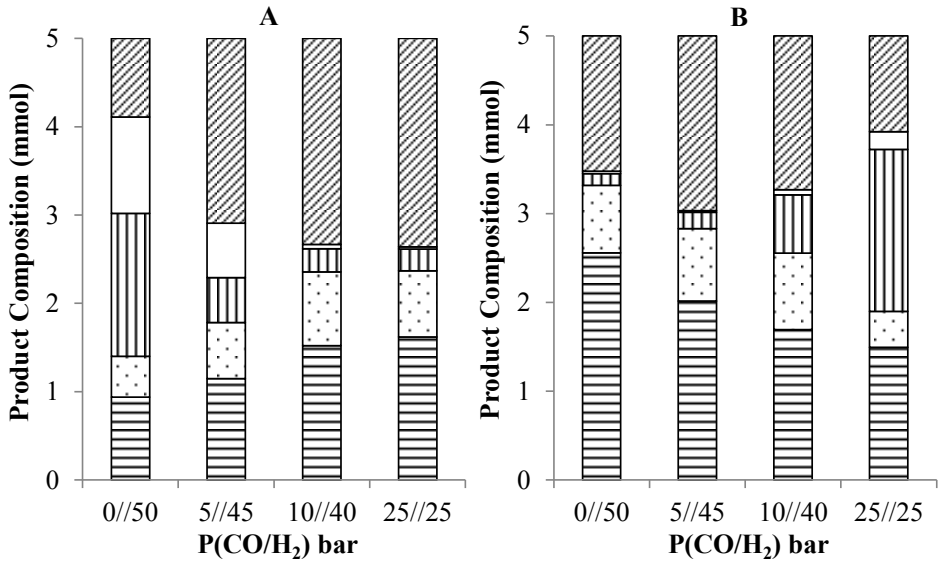


Figure 3.10. The effect of CO/H_2 partial pressures on reductive amidation of hexanal with acetamide catalyzed by the catalytic system Rh/xantphos/HOTs; (**A**) in pure diglyme, (**B**) in HOR^F/diglyme 1/4 (v/v). Reaction conditions: 0.01 mmol [$Rh(CO)_2$(acac)], 0.02 mmol xantphos, 5 mmol hexanal, 5 mmol acetamide; (Rh:xantphos:HOTs:hexanal:acetamide=1:2:5:500:500); *P*=50 bar; *t*=2 h; Solvent: 10 mL diglyme or 10 mL (v/v) HOR^F/diglyme=1/4; decane as internal standard. ▤= aldehyde (**1**), ⊡= unsaturated intermediate (**2**), ▥= desired product (**3**), □= alcohol (**4**), ▨= other products (**5**)

It is worth noting that the use of different amounts of HOR^F for the Rh/xantphos/HOTs catalyzed reductive amidation of hexanal with acetamide in a *pure* dihydrogen atmosphere showed that HOR^F strongly *retarded* reductive amidation by inhibiting the hydrogenation of the intermediate unsaturated **2**, shown to accumulate in the reaction mixture (Figure 3.11B). The presence of progressively more HOR^F resulted in gradually lower hexanal conversion (Figure 3.11B and Table AII.9). In the absence of HOTs as catalyst component however, the Rh/xantphos catalyst system in pure HOR^F as solvent led to almost exclusive hydrogenation of hexanal (Figure 3.11A), a result similar to that in diglyme as solvent.[30] However, when HOTs was applied (HOTs/Rh = 5 (mol/mol)) in the Rh/xantphos catalytic system, a significant difference between the role of the solvents diglyme and HOR^F became again apparent. Whereas in diglyme both the reductive amidation product **3** and hexanol are coproduced, in HOR^F hardly any hexanol or product **3** was formed, thus revealing that the catalytic system in HOR^F under a pure H_2 atmosphere has very poor hydrogenation activity. Under these

conditions almost exclusively unsaturated **2** and heavy-ends formation takes place (Figure 3.11A and Table AII.9**).**

All the observations reported in this section thus suggest that different Rh/xantphos complexes are operative as reductive amidation catalysts and/or aldehyde hydrogenation catalysts under different circumstances, e.g. in different solvent systems, with different reducing gas environments and with or without the presence of potential catalyst promoter compounds, such as HOTs and HOR^F.

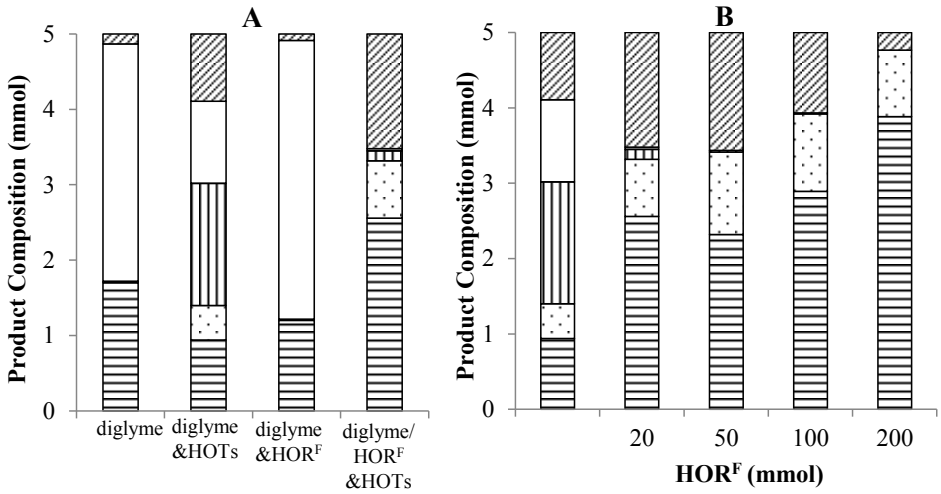


Figure 3.11. The effect of different conditions on reductive amidation of hexanal with acetamide under pure H_2 presssure catalyzed by the catalytic system Rh/xantphos/HOTs; (**A**) effect of acid in pure diglyme and in HOR^F/diglyme(1/4=v/v), (**B**) different amount of HOR^F(0-200 mmol). Reaction conditions: 0.01 mmol [$Rh(CO)_2(acac)$], 0.02 mmol xantphos, 5 mmol hexanal, 5 mmol acetamide; (Rh:xantphos:HOTs:hexanal:acetamide=1:2:5:500:500); P_{H2}=50 bar; t=2 h; Solvent: 10 mL diglyme or 10 mL (v/v) HOR^F/diglyme=1/4; decane as internal standard. ▤= aldehyde (**1**), ⊡= unsaturated intermediate (**2**), ▥= desired product (**3**), □= alcohol (**4**), ▨= other products (**5**)

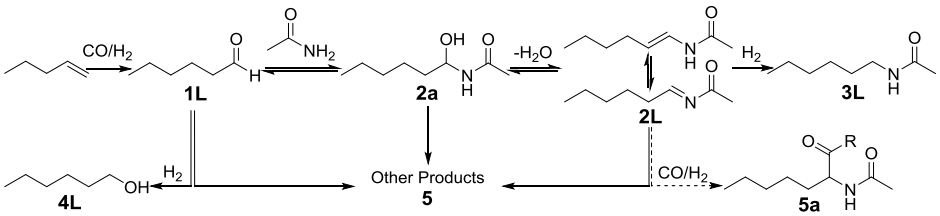
3.3. Discussion

3.3.1. General considerations

All experimental results concerning the hydroamidomethylation reaction, but in particular the development of the reaction products in time (Figure 3.7) prominently point to the fact that hydroamidomethylation of 1-pentene with acetamide comprises three sequential steps, shown schematically in Scheme 3.4. The first step is

hydroformylation of 1-pentene to aldehyde **1**. The second step consists of two equilibrium reactions: the nucleophilic addition of acetamide to hexanal followed by dehydration to form the two isomeric unsaturated intermediates N-(1-hexylidene)acetamide and N-1-hexenylacetamide **2** (Chapter 2).[30] Hydrogenation of these unsaturated intermediates would then result in formation of the desired product N-hexylacetamide **3** in the third step. The formation of hexanol **4** by the direct hydrogenation of hexanal constitutes a competing reaction of hexanal, resulting in lower selectivity for **3**.

The unsaturated intermediates (hexanal as well as **2**) may undergo various side reactions, most pronounced aldol condensation and double addition reactions, resulting in the higher mass products **5**, that are indeed observed in varying amounts depending on the reaction conditions and catalyst composition. Other reported reactions of intermediates **2** are the hydroformylation and hydrocarbonylation reactions also shown in Scheme 3.4;[35] however, the products **5a** (aldehyde nor carboxylic acid) were not observed in our reactions.



Scheme 3.4. Catalytic hydroamidomethylation of 1-pentene, a one pot synthesis of N-hexylacetamide **3L** via the formation of hexanal **1L** and intermediates **2L**; hexanol **4L** and heavy-ends **5** are undesired byproducts (For clarity only the linear products are depicted). R in **5a** can be H (CHO) or OH (COOH)

Finding active and selective alkene hydroamidomethylation catalysts thus will involve developing catalyst systems that are not only active for hydroformylation of alkenes, but under the prevailing syngas conditions also possess the ability for a selective hydrogenation of the unsaturated intermediates **2** in the presence of aldehyde **1**, compounds that are mutually involved in the condensation equilibrium shown in Scheme 3.4. In this way, the intermediates **2** will be removed selectively from the condensation equilibrium and the reaction is drawn to completion by catalytically forming the N-alkylamide product. If, on the other hand, the catalyst system has

preference for hydrogenation of the aldehyde substrate **1** over **2** the condensation equilibrium can likewise be selectively drawn to completion to alcohol **4**.

3.3.2. Considerations on the roles of catalyst promoters HOTs and HOR^F in Rh/xantphos catalyzed hydroamidomethylation of alkenes

3.3.2.1. General comments

Our studies on the catalytic reductive amidation of hexanal with acetamide using pure H_2 revealed that the optimal catalytic system comprises a rhodium precursor with a xantphos-type ligand and a catalytic amount of strong acid promoter, such as HOTs, in diglyme as reaction solvent. The addition of a catalytic amount of strong acid (HOTs/Rh ~ 5 (mol/mol)) is necessary to catalyze the addition equilibrium reaction of the amide with the aldehyde (Chapter 2).[30] In this respect, the mechanism is different from that of reductive amination of an aldehyde, in which case the addition of an amine N-H bond to the aldehyde occurs spontaneously, without involvement of any acid.[25-28] However, the added strong acid like HOTs modifies the catalytic system.

The first acid-base reaction that would take place is protonation of $[Rh(acac)(CO)_2]$ to form the $[Rh^I(xantphos)(CO)_2]OTs$ species with the release of Hacac; this Rh/xantphos species then can be feasibly converted into the well-known alkene hydroformylation catalyst $[Rh^I(xantphos)(H)(CO)]$. Additionally, the presence of HOTs may induce certain equilibrium between neutral Rh^I hydroformylation and cationic Rh^{III} hydrogenation species. One of our most prominent observations, however, is that the additional presence of a weakly acidic promoter compound such as HOR^F (in solvent-like quantities such as typically HOR^F/Rh ~ 2000 (mol/mol) at HOR^F/diglyme = 1/4 (v/v)) also has a strong impact on the course of the catalytic hydroamidomethylation reaction, as shown in Figure 3.2, creating an active hydrogenation catalyst in the CO-containing atmosphere. Similar effects are observed in the separate hydroformylation and reductive amidation reactions (Figures 3.8-3.11).

3.3.2.2. Hydroformylation

Clearly, the addition of HOR^F leads to a lower hydroformylation rate of 1-pentene (Figure 3.9). Interestingly, the rate of hydroformylation even further decreases when HOTs (HOTs/Rh~5) is added in this system; then the formation of hexanol becomes visible. A remarkable observation is the recovery of catalyst performance to a level before HOTs addition upon the addition of dimethylacetamide (DMA) in a

stoichiometric quantity relative to 1-pentene. However, a decrease in hydroformylation activity due to the presence of HOR^F remains, even if DMA is added. This is likely due to the large (4-fold mole ratio) excess of HOR^F over DMA under the given conditions.

The high acidity of HOTs ($pK_a \sim -2.7$) combined with a large excess of weakly basic DMA (DMA/HOTs ~ 100) accounts for a likely complete deprotonation of HOTs and formation of the salt. The resulting protonated $HDMA^+$ cation of course still behaves as a quite strong acid, responsible for formation of cationic Rh^{III} species as is suggested from hexanol formation (Figure 3.9B), lowering the concentration of the neutral Rh^I hydroformylation catalyst. It is thought that the distinct decrease in hydroformylation activity due to the addition of the weakly acidic HOR^F (pK_a in water ~ 9), is due to its very large excess over Rh, which thus may contribute to generation and stabilization of Rh^{III} species, similar to HOTs. Again a neutralization effect is observed when DMA (HORF/DMA ~ 4-20 (mol/mol)) is added into the reaction ($DMA + HOR^F \leftrightarrows HDMA^+ + OR^{F-}$; for which of course the equilibrium constant would be much lower than for the strong acid HOTs). The decreasing rate of hydroformylation with increasing concentration of HOR^F, while the product composition changes from hexanal to hexanol (Figure 3.9A) is fully consistent with a dual-catalyst species model, in which cationic Rh^{III} hydrogenation species are gradually replacing neutral Rh^I hydroformylation species.

Remarkably, the hydroformylation in *pure* HOR^F as solvent not only results in a low hydroformylation rate, but also in a low selectivity for alcohol formation (Figure 3.9A). Similarly, addition of HOTs at high HOR^F concentration leads to a severe drop in hydroformylation and hydrogenation activity (Figure 3.9B). This could be a consequence of the stronger electrophilic nature of the Rh^{III} center in pure HOR^F, due to easy dissociation of the associated OTs^- anions -and unavailability of more coordinating OR^{F-} anions due to protonation by much stronger acid HOTs-, from the rhodium center into the strongly polar HOR^F medium, rather causing O-coordination of the aldehyde to the Rh^{III} center instead of π-carbonyl coordination required for hydrogenation. When DMA is added, some OR^{F-} anions (DMA/Rh = 500), stronger coordinating to the Rh^{III} center, are generated by the deprotonation equilibrium with HOR^F and the orginal situation is substantially restored, again reducing the Rh^{III} metal center's electrophilicity, as diagnosed by the restoration of improved alcohol formation.

3.3.2.3. Reductive amidation

The reductive amidation of hexanal with acetamide in the presence of HOTs and using pure H_2 as the reductant is strongly inhibited by the addition of HOR^F (Figure 3.10B). Not only the hydrogenation of intermediates **2**, but also hydrogenation of aldehydes is severely suppressed by the presence of HOR^F. This could suggest that the $[Rh^{III}(xantphos)(H)_2]^+(OTs)$ species proposed to be the active Rh hydrogenation species in reductive amidation under pure H_2 pressure (Chapter 2),[30] is converted by protonation at the hydride with HOR^F to the species $[Rh^{III}(xantphos)(OTs/OR^F)_3]$ with no intrinsic activity for hydrogenation under pure H_2 pressure.

The effects of HOR^F and HOTs on reductive amidation with Rh/xantphos catalyst system under pure H_2 pressure are further illustrated in Figure 3.10A; both in diglyme and diglyme/HOR^F (~1/4 v/v) introduction of HOTs is required for the establishment of the aldehyde-amide addition equilibrium.[30] The acidity of HOR^F is not sufficiently strong to catalyze this equilibrium under the applied reaction conditions. It also appears that in the absence of HOTs but in the presence of HOR^F the Rh/xantphos catalyst is highly active for the hydrogenation of hexanal to hexanol (Figure 3.10A). This could be a consequence of the fact that aldehyde coordination to a metal center only requires one free coordination site, whereas a good catalyst for hydrogenation of compounds **2** should likely have two adjacent positions to allow for selective bidentate binding of **2** in the presence of aldehyde.

The effect of CO on reductive amidation in diglyme is as expected; with increasing CO pressure a strongly negative effect is observed on the yield of N-hexylacetamide as well as hexanol (Figure 3.11A) and consequently, the yields of unsaturated compounds **2** as well as higher condensation products significantly increase. In contrast, when the same experiments are carried out in diglyme/HOR^F the yield of N-hexylacetamide as well as hexanol strongly *increases* with CO pressure; thus a strongly *increased* general hydrogenation activity is manifested by the presence of CO. This implies that under hydroamidomethylation conditions and in the presence of HOR^F, a catalytic hydrogenation system other than the one present under pure H_2 pressure must be operative. We thus arrive at the conclusion that the cationic $[Rh^{III}(xantphos)(H)_2]^+$ species likely operative as hydrogenation catalyst under pure H_2 in an aprotic solvent like diglyme,[30] does not exist in presence of HOR^F under syngas conditions. Instead, a cationic $[Rh^{III}(xantphos)(H)(CO)_x(OTs/OR^F)]^+$ catalyst species with a mixture of OR^{F-}

and OTs^- anions associated with Rh^{III} will arise, next to neutral Rh^I hydroformylation species. The observed *increase* in reductive amidation product with associated decrease of intermediates **2** being approximately first-order in CO pressure (Figure 3.10B), is consistent with a necessary binding of CO to a cationic Rh^{III} center as catalyst in the overall rate-determining step of hydroamidomethylation, i.e. hydrogenation of the unsaturated intermediates **2**. The relative occupation of coordination sites at this Rh^{III} species by CO and the OR^{F-} / OTs^- anions will depend on the relative quantities of HOR^F, HOTs and base (amide and N-alkylamide) as well as CO/H_2 pressure, as was suggested by the separate results on hydroformylation and reductive amidation.

As implied by the effects of added amide (such as DMA) on hydroformylation with a Rh/xantphos/HOTs catalyst system we may conclude that under hydroamidomethylation conditions the amide reactant (and N-alkylamide product) also may play an important controlling role in the observed catalytic performance. It is likely that partial de-protonation of HOTs and HOR^F occurs, thus providing anions of which the reaction-medium dependent coordinating properties to Rh^{III} may control some of the catalyst's attributes, such as specificity of hydrogenation of unsaturated substrates.

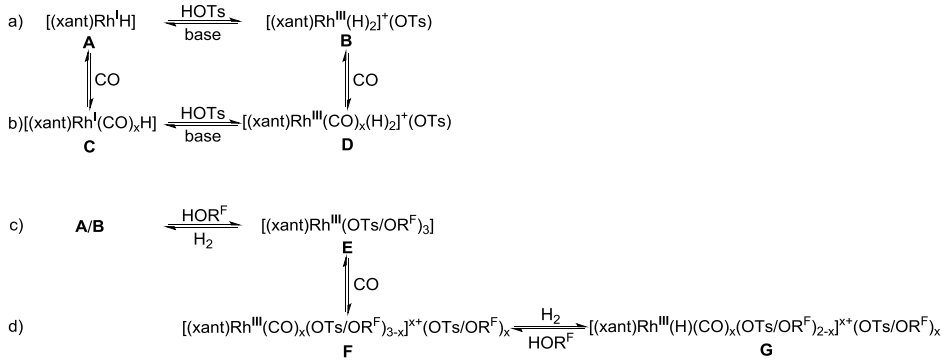
3.3.2.4. Hydroaminomethylation vs. hydroamidomethylation

The reaction conditions for hydroamidomethylation can be compared to those for the well-known hydroaminomethylation of alkenes with amines. Under the strongly basic conditions with amines as substrates, acetal formation cannot occur. Several studies of hydroaminomethylation apply simple alcohols (such as methanol) in this reaction.[25-28] In general, higher hydroaminomethylation reaction rates are observed in the presence of alkanols, thus also indicating a promoting effect of protic co-solvents in hydroaminomethylation. Although no mechanistic study into the nature of this promoting effect was published, it has been postulated that the protic solvent could somehow serve to stabilize cationic Rh hydrogenation species.[36] We want to suggest that the simple alcohols in hydroaminomethylation serve a similar purpose as HOR^F in hydroamidomethylation. The difference is that associated alkoxide anions are formed due to deprotonation of the alcohol by the strongly basic amine substrate and product. As hydroamidomethylation involves much weaker basic amide substrates and products, a stronger acidic alcohol needs to be applied in order to successfully generate alkoxide anionic species stabilizing the cationic Rh^{III} center.[37]

3.3.3. Synthesis of the overall mechanistic proposal

In our study concerning the reductive amidation of hexanal with acetamide in a pure dihydrogen atmosphere we postulated the formation of a neutral Rh^{I}-hydride species **A** to be responsible for the hydrogenation of aldehyde to alcohol, whereas a cationic Rh^{III}-dihydride species **B** would be active in the hydrogenation of the unsaturated intermediates **2** (Scheme 3.5a).[30] These two species are related via an acid/base equilibrium; it was shown that the addition of acid resulted in higher selectivity for N-hexylacetamide, whereas the addition of base resulted in the formation of hexanol.

When the reductive amidation is carried out in diglyme with a partial pressure of CO, both the hydrogenation of aldehyde and of intermediate **2** is poisoned (Figure 3.10A); remarkably the hydrogenation of hexanal seems to be the most sensitive to the presence of CO. This observation can be rationalized by the coordination of CO to both species **A** and **B**, forming **C** and **D**, respectively (Scheme 3.5b). Species **C** is a hydroformylation catalyst, known to have low hydrogenation activity. Carbon monoxide binds more strongly to Rh^{I} than to Rh^{III}, making it plausible that the hydrogenation activity of species **B** is partially retained.



Scheme 3.5. Generation of various hydrogenation catalysts in reductive amidation conditions (xant = xanthphos): a) In pure diglyme with H_2 atmosphere; b) in diglyme with H_2/CO atmosphere; c) in HOR^F/diglyme with H_2 atmosphere; d) in HOR^F/diglyme with H_2/CO atmosphere

The effect of the addition of HOR^F on the hydrogenation activity of the catalytic system in reductive amidation in a *pure* dihydrogen atmosphere is even more detrimental (Figure 3.10B); in HOR^F/diglyme (1/4) only a small amount of N-

hexylacetamide is formed. This may be rationalized by protonation of both species **A** and **B**, forming the inactive species [(xantphos)Rh^{III}(OTs/OR^F)$_3$] **E** (Scheme 3.5c).

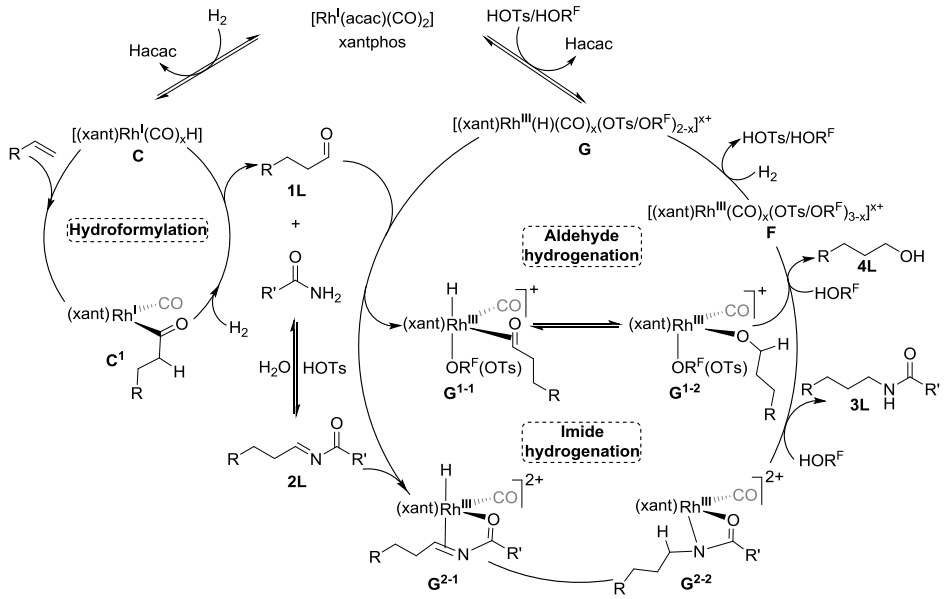
Remarkably, the hydrogenation activity of the system is restored with the addition of a partial pressure of CO; apparently carbon monoxide is able to compete with OR^{F-} anions for coordination sites at the Rh^{III} center in 'neutral' species **E**, resulting in formation of cationic species **F**. This allows for the activation of dihydrogen via heterolytic splitting, resulting in the formation of HOR^F and the cationic Rh^{III}-hydride species **G** (scheme 3.5d), that again may be an active hydrogenation catalyst.

In the hydroformylation of 1-pentene in diglyme the equilibrium shown in Scheme 3.5b is also operative; by the addition of HOTs the hydroformylation catalyst **C** is partially converted into the Rh^{III}-hydride species **D**, as apparent from the formation of some hexanol (Figure 3.8A). This conversion is reversed by the addition of the base DMA, resulting in the formation of species **C,** with hexanal as the major product. The catalytic hydroformylation system in an HOR^F/diglyme (1/4) mixture behaves almost the same, indicating that similar catalytic species are operative, albeit with lower overall activity (Figure 3.8B). The activity of the hydroformylation catalyst is inversely related to the amount of HOR^F added (Figure 3.9A); with increasing amounts of HOR^F the hydroformylation activity decreases, whereas the hydrogenation activity increases up to a HOR^F/diglyme ratio of 5/1 (Figure 3.9B). This phenomenon again may be attributed to the formation of species **D** by the weakly acidic HOR^F, lowering the concentration of hydroformylation catalyst **C**. In the presence of HOTs, but in the absence of base (DMA) the hydroformylation catalyst **C** is virtually non-existent (Figure 3.9B), and most likely species **E** and/or **F** are prevalent.

Now we are ready to consider the overall picture of the hydroamidomethylation reaction, considering the results most prominently illustrated in Figure 3.2. From these results five different regimes seem to be present when changing from a pure diglyme to a pure HOR^F solvent system. The overall picture is complicated by the different acid/base equilibria induced by the presence of base (acetamide and N-hexylacetamide, constant concentration), strong acid (HOTs, only in relatively small amounts) and weak acid (HOR^F, in increasing amounts).

Our view of the general mechanism of hydroamidomethylation is shown in Scheme 3.6. Hydroformylation of alkenes catalyzed by a neutral Rh^I species is followed by an acid-catalyzed aldehyde-amide condensation *equilibrium* involving both aldehyde and

imide substrate. This equilibrium is coupled via two hydrogenation cycles involving either the imide or the aldehyde as substrate, both catalyzed by a cationic Rh^{III} species. The competition between the latter two substrates involved in the respective catalytic cycles, thought to be governed by anion coordination to the cationic Rh^{III} center, is the basis for the chemo-selectivity of the overall hydroamidomethylation process.[38]



Scheme 3.6. Proposed overall mechanism for hydroamidomethylation of 1-alkenes

In pure diglyme an active hydroformylation catalyst is formed, but the catalytic system in the presence of CO lacks hydrogenation activity; the most prominent catalytic compound present in solution most likely is species **C**. Any Rh^{III}-hydride species present in solution is possibly blocked by coordination of CO, forming species **D** (Scheme 3.5). Addition of more of the strong acid HOTs does not present an option in the generation of a more active hydrogenation catalyst, as it results in the formation of more aldol condensation products. However, the addition of the weakly acidic and polar HOR^F as a co-solvent results in the formation of an active hydrogenation catalyst (such as species **G**) that is capable of hydrogenating the intermediate products **2** or the aldehyde **1** depending on the relative amount of HOR^F. A HOR^F/diglyme ratio of 1/4 (v/v) generates a more polar environment in which the OTs^- anions become less

coordinating thus likely providing two binding sites for imide intermediate **2** (species $\mathbf{G^{2-1}}$), resulting in an active catalytic system for hydroamidomethylation with the highest selectivity for N-alkylamides. Upon increasing the amount of HOR^F/diglyme ratio to 1/1 the hydroformylation activity is retained, but the hydrogenation activity of the catalytic system is severely inhibited; this may be due to the formation of a higher concentration (relative to [Rh]) of relatively strongly coordinating OR^{F-} anions. Upon increasing the HOR^F/diglyme ratio to 5/1 the hydroformylation activity is retained, but now hexanol is the major hydrogenation product. In this HOR^F-rich medium the OR^{F-} anions become more readily solvated allowing the binding of the monodentate substrate aldehyde, via the species $\mathbf{G^{1-1}}$. Finally, it is important to note that we believe that the hydroformylation reaction concerns a neutral catalytic species that activates H_2 by oxidative addition, shuttling between Rh^I and Rh^{III}. The hydrogenation cycles proceed via cationic Rh^{III} species; the intermediate products are protonated in the acidic medium forming species **F**. Through CO-assisted heterolytic splitting of dihydrogen - as proposed above - species **G** is then restored.

Both HOR^F and HOTs can provide anions to the cationic Rh^{III}-hydride species, by protonation of the weakly basic amide reactant. Depending on their relative amounts, relative acidic strength and coordinative properties to the Rh center, it can thus be rationalized that the immediate anionic environment around a cationic $[(xantphos)Rh^{III}H]^{2+}$ species plays an important role in the hydrogenation substrate specificity of the intermediate **2** relative to the aldehyde, both being involved in a dynamic condensation equilibrium. Such a model can rationalize the dramatic change in selectivity from N-hexylacetmide as product (>80%) at relatively low HOR^F concentration, to hexanol as the product (>90%) at a high concentration of HOR^F: At low HOR^F concentrations the weakly coordinating OTs^- anions render the Rh^{III} species receptive for binding of the bidentate substrate **2**, even in the presence of the mono-functionalized aldehyde. The aldehyde substrate, likely because of its monodentate binding, is less hindered by the anions around the Rh center: even with the intrinsically more strongly coordinating OR^{F-} anions the aldehyde's carbonyl functionality succeeds to approach the Rh^{III} center, in particular when immersed in a high concentration of polar HOR^F molecules and then can easily become hydrogenated. The relatively sharp decline in hydrogenation activity, now accompanied with a significant *decrease* in hydroformylation activity at very high $[HOR^F]$ (> 90%) may be attributed to an increased presence of a species **E**, but now associated almost exclusively with the

relatively strongly coordinating OR^{F-} anions, thus behaving more as a neutral Rh^{III} species. It is thought that this process may proceed to the extent that heterolytic activation of H_2 (producing active cationic species **F** and **G**) becomes rate-determining and relatively slow.

In this chapter we have proposed plausible catalytic events occurring in the hydroamidomethylation (hydroformylation-reductive amidation) reaction which can rationalize most of our observations. To the best of our knowledge, in reported studies concerning the related hydroaminomethylation (hydroformylation-reductive amination) reaction, no clear mechanistic proposals have been provided specifically for the second step (reductive amination) of the reaction. However, it has been proposed that the hydrogenation step benefits from the presence of protic solvents, because of the formation of cationic rhodium species.[17, 27, 28] The role of alcohol as a protic co-solvent in the tandem hydroformylation-hydrogenation reaction, in which alcohols are formed directly from alkenes, has also been explained by a mechanism based on the formation of a rhodium-carbenoid species.[39-41] In this proposed mechanism the intermediate Rh-acyl species formed in hydroformylation is directly hydrogenated (via a proton-assisted isomerization to Rh-hydroxy-carbenoid) without intermediate formation of aldehyde. However, we have shown that with the Rh/xantphos/HOTs catalytic system, the hydroamidomethylation and the related alcohol formation reactions occur via sequential steps, respectively involving aldehyde-amide adducts and free aldehyde, as indicated by the build-up of intermediates **2** and aldehydes depending on the reaction conditions. A high selectivity for one over the other can be obtained by adjusting the competitive hydrogenation of the respective molecules. We believe that one interesting aspect of the present work is the revelation of a selectivity-controlling ability of the amide substrate, presumably by acting as a weak base, the amount and type of anions, associated with the cationic Rh species as part of the overall catalyst system.

3.4. Conclusion

We have successfully developed a novel catalytic system comprising rhodium/xantphos/HOTs in presence of HOR^F as a co-solvent for the atom-economic hydroamidomethylation of terminal alkenes to form N-alkylamides. It appeared that the presence of both strong acid (HOTs) and a polar acidic solvent (HOR^F) is crucial in determining the reaction selectivity and efficiency. The strong acid is necessary for

establishing the equilibrium addition/condensation reaction between the in situ formed aldehyde and the amide. The presence of the polar, weakly acidic co-solvent is necessary for the generation and solvatation of cationic Rh^{III} hydride species that are active as hydrogenation catalysts in the presence of carbon monoxide. By choosing the right circumstances this catalytic system can be fine-tuned to make either an alcohol or an N-alkylamide from terminal alkenes. The novel hydroamidomethylation reaction has potential in the synthesis of a wide range of secondary amides, as was shown by its applicability using different olefins and different aliphatic and aromatic amides. We are currently seeking to utilize this catalytic system for the hydroamidomethylation reaction of internal alkenes with an amide to form linear N-alkylamides, for which the isomerization step of course is highly challenging.

3.5. Experimental

3.5.1. Chemical

The solvent bis(2-methoxyethyl)ether (diglyme) was distilled from CaH_2, deoxygenated and used immediately after the purification process. All other solvents were purged with argon and purified under pressure of dry argon using an Innovative Technologies purification system. The solvents passed through activated columns under low pressure to remove trace impurities. Stainless Steel Schlenk Vacuum line and Sigma Aldrich Air-free flasks allow them to be safely transferred.

1-pentene, 2-pentene, pentane, 1-hexene, 1-octene, hexanal, acetamide, propanamide, 2-methylpropanamide, 2,2-dimethylpropanamide, fluoroacetamide, valeramide, benzamide, p-methoxybenzamide, p-trifluoromethylbenzamide, decane (internal standard), hexanol, para-toluenesulfonic acid(HOTs), trifluoromethanesulfonic acid (HOTf), N,N-dimethylacetamide (DMA), bis(2-methoxyethyl) ether (diglyme), 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HOR^F), methanol, ethanol, iso-propanol, n-butanol, iso-butanol, tert-butanol, 2,2,2-trifluoroethanol (TFE) and other solvents, acids and bases were purchased from Acros Organics and Sigma Aldrich, the Netherlands and used as received.

The rhodium precursors (acetylacetonato)dicarbonylrhodium(I), chlorido(1,5-cyclooctadiene)rhodium(I) dimer, bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate, bis(cycloocta-1,5-diene)rhodium(I) tetrafluoridoborate, carbonylhydridotris(triphenylphosphane)rhodium(I) were purchased from Acros Organics and Sigma Aldrich, the Netherlands and used as received.

The phosphane ligands triphenylphosphane (PPh_3), bis(2-diphenylphosphinophenyl)ether (DPEphos), Bis(diphenylphosphinoethyl)phenylphosphane, 9,9-dimethyl-4,5-bis(diphenyl-phosphanyl)xanthene (xantphos) were purchased from Strem Chemicals, Germany and used as received.

The bi-dentate phsphane ligands bezoxantphos, homoxantphos and 1,1'-(4,6-dibenzofurandiyl)bis[1,1-diphenylphosphane (DBFphos) were purchased from Innovative Catalyst Technologies (InCatT B.V.), The Netherlands and used as received. The other phosphorous ligands such as 2,7-di-tert-butyl-9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene (tBu-xantphos), 4,6-bis(diphenylphosphanyl)-10,10-dimethyl-10H-dibenzo[b,e][1,4]oxasilane (Si-xantphos), 9,9-dimethyl-4,5-bis(di-orthomethoxyphenyl-phosphanyl)xanthene (oMeO-xantphos) and 4,5-bis(di(tert-butyl)phosphanyl)-9,9-dimethylxanthene (di-tBu-xantphos) were generously provided by Shell Global Solutions Amsterdam b.v., The Netherlands and used as received.

The other phosphorous ligands such as 2,7-di-tert-butyl-9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene (tBu-xantphos), 4,6-bis(diphenylphosphanyl)-10,10-dimethyl-10H-dibenzo[b,e][1,4]oxasilane (Si-xantphos), 9,9-dimethyl-4,5-bis(di-orthomethoxyphenyl-phosphanyl)xanthene (oMeO-xantphos) and 4,5-bis(di(tert-butyl)phosphanyl)-9,9-dimethylxanthene (di-tBu-xantphos) were generously provided by Shell Global Solutions Amsterdam b.v., where they were synthesized according to literature procedures.[31, 42, 43] All other chemicals, solvents, acids and bases were purchased from Acros Organics or Sigma Aldrich, the Netherlands.

3.5.2. Instruments

The stainless steel autoclave reactors (100 ml) were of HEL Limited, UK, equipped with magnetic stirrer, pressure transducer and temperature controlling thermocouple. A Hewlett Packard HP6890 Series auto-sampler GC system was used for regular GC analysis. GC-MS analysis were carried out on an Agilent technologies 7820A GC system series coupled with an Agilent technologies 5975 series GC-MSD system. A glovebox of M. Braun Inert gas-System GmbH, Germany, was used for storing and handling of air-sensitive phosphane ligands. Nuclear magnetic resonance spectra were recorded on a Bruker DPX300 (300MHz) or a Bruker DMX400 (400MHz) spectrometer. Innovative Technologies PureSolv MD 5 Solvent Purification System was used for drying solvents.

All reaction preparations and manipulations were performed using standard Schlenk techniques under an argon atmosphere. The catalytic reactions were carried out under varying syngas pressures and reaction temperatures.

3.5.3. Catalytic high pressure reaction

All preparations and manipulations were performed using standard Schlenk techniques under an argon atmosphere. The solvent bis(2-methoxyethyl)ether (diglyme) was distilled from CaH_2, deoxygenated and used immediately after the purification process. The catalytic reactions were carried out under varying syngas pressures and reaction temperatures. For all the catalytic experiments the active catalyst precursor was formed by *in-situ* in the autoclave by transferring the metal precursor and the selected phosphane ligands. In the preparation of a typical catalytic reaction mixture 0.01 mmol of $[Rh(acac)(CO)_2]$ (2.58 mg) and 0.02 mmol of bidentate phosphane ligand or 0.04 mmol of monodentate phosphane ligand were weighed and transferred into an autoclave. The autoclave was tightly closed and subsequently filled with argon with use of a Schlenk line that was connected to one of the valves of the autoclave. Through another valve under a continuous flow of argon subsequently was added 8 ml of dried and degassed diglyme, 2 ml of HOR^F, 3.125 mmol (0.605 ml) decane as an internal standard, 5 mmol (0.548 ml) 1-pentene and 5 mmol (0.295 g) acetamide followed by 0.05 mmol (9.51 mg) HOTs. Then the reactor was inserted into the heating block and pressurized with 50 bar (CO/H_2=1/2) syngas. This reaction mixture was stirred at 500 rpm for 30 min to ensure that complex formation was complete. The reaction mixture was heated up to 100 °C (within 30 min) under stirring at 500 rpm. All reaction conditions of the catalytic process were controlled by computerized software panels. After standing for two, four or eight hours at this temperature, the autoclave was cooled down to room temperature over about one hour. The autoclave was then carefully vented to atmospheric pressure.

After each catalytic run the reaction mixture was taken from the reactor and at once analyzed by gas chromatography. Calibration lines for each analyte were used in determining the conversion of the substrates and yields of the various products. The two isomeric unsaturated intermediates N-(1-hexylidene)acetamide and N-1-hexenylacetamide are lumped together as **2L**; generally these two isomeric compounds are present in only low amounts. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

The products in Table 3.4 comprising N-hexylacetamide,[44-47] N-heptylacetamide,[48, 49] N-nonylacetamide,[50, 51] N-(3-phenylpropyl)acetamide,[52-54] N-hexylpropanamide,[45, 55] N-hexylisopropylamide,[45, 56] N-hexyl-2,2-dimethylpropionamide (N-hexylpivalamide),[46, 56, 57] N-hexylpentanamide,[58] N-hexylbenzamide,[45, 59] N-hexyl-4-methoxybenzamide,[45] N-hexyl-4-trifluoromethylbenzamide,[45] N-hexyl-2-fluoroacetamide,[60] N-(2-

methylpentyl)acetamide and N-benzylacetamide[44, 46] are known compounds and were identified by ^{1}H and ^{13}C NMR and GC-MS.[30]

3.5.4. GC analysis

A GC spectrum of typical hydroamidomethylation of 1-pentene is shown in appendix III with the assignment of products. 1 µL Crude reaction mixture containing internal standard was injected into a Hewlett Packard HP6890 Series auto-sampler GC system with column HP-1MS UI (30m*0.250mm*1.00µm). All the solvents have been assigned by comparing to their standard GC spectra. All the retention values of substrate and product to undecane have been determined using commercially available or isolated standard chemicals.

Analysis conditions: 130 ºC (5 min), ramp 50ºC/min to 300 ºC, 300 ºC (3.6 min) (12 min in total).

3.5.5. Characterization data

For the charachterization of N-hexylacetamide; N-hexylpropanamide; N-hexylisopropylamide; N-hexyltertbutylamide; N-hexylpentanamide; N-hexylbenzamide; N-hexyl-4-methoxybenzamide; N-hexyl-4-trifluoromethylbenzamide; N-hexyl-2-fluoroacetamide; N-(2-methylpentyl)acetamide; and N-benzylacetamide: See Chapter 2, section 2.5.5.

N-heptylacetamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.62 (t, 3H, CH_3), 1.28 (m, 2H, 2*CH_2), 1.89 (s, 3H, CH_3), 2.76 (m, 2H, CH_2), 6.63 (b, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 14.1, 22.4, 23.1, 24.2, 25.2, 29.9, 33.2, 43.8, 172.2.

N-nonylacetamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 0.65 (t, 3H, CH_3), 1.25 (m, 12H, 6*CH_2), 1.69 (m, 2H, CH_2), 2.12 (s, 3H, CH_3), 3.21 (m, 2H, CH_2), 6.93 (b, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 13.1, 21.4, 22.1, 22.8, 26.1, 27.2, 28.2, 31.4, 44.2, 173.9.

N-(3-phenylpropyl)acetamide: ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 1.68 (m, 2H, CH_2), 1.98 (s, 3H, CH_3), 2.76 (m, 2H, CH_2), 2.98 (m, 2H, CH_2), 6.48 (b, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 25.2, 27.3, 30.3, 43.6, 126.1, 128.2, 141.6, 172.8.

3.6. References

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[37] It is worthwhile to briefly comment on the results of our search for alternative catalyst promoter compounds to HOR^F for hydroamidomethylation (Table 3.3). The fact that some phenolic compounds with pK_a around 9-10 show performance similar to HOR^F; suggests that the promoting effect depends upon the acidity of the promoter compounds. Only a rather narrow pK_a range of potential promoters can be applied; too strong acids cannot be used as this will lead to high rates of aldol condensation, while weaker acids such as simple alkanols cannot be used, because of aldehyde acetal formation.
[38] To explain that carbonylation or hydroformylation of the intermediates **2** does not occur in our reaction, it is thought that hydrogenation may proceed via insertion of one

of the compounds **2**, i.e. (via N-hexylideneacetamide). The C=N insertion into a cationic Rh^{III}-H species can selectively give the intermediate Rh^{III}-imido species (Rh-N-CHR), which immediately is converted to the Rh^{III} species and N-hexylacetamide through protonation in the acidic medium. If hydride migration would result in a Rh-C-NHR intermediate, it seems quite likely that CO insertion into Rh-C might occur to give Rh-C(O)-C-NHR, which may then be terminated by hydrogenolysis to the alpha-amido-aldehyde.

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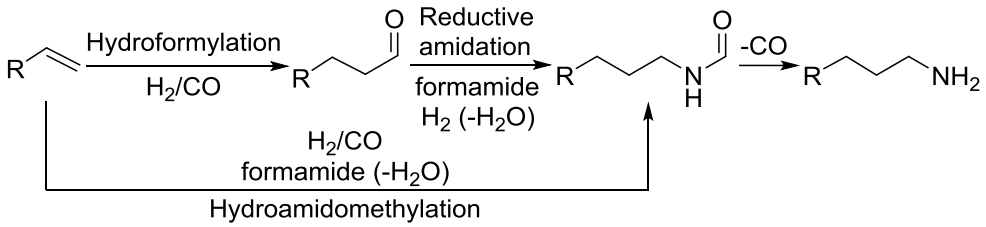
4

Towards Synthesis of Primary Amines: Investigating Rhodium-Catalyzed Homogeneous Reductive Amidation and Hydroamidomethylation with Formamide



This Chapter will be submitted as a paper;
Raoufmoghaddam S.; Kortlever R.; Drent E.; Bouwman E.; manuscript in preparation

Abstract

The catalytic reductive amidation of an aldehyde with formamide using Rh/xantphos/HOTs catalyst systems is reported, as part of an atom-efficient synthesis of primary amines from alkenes. Our studies on the reductive amidation of hexanal with formamide revealed a catalytic performance characteristically different from the reductive amidation of hexanal carried out with higher alkylamides. To achieve similar catalytic performance of the Rh/xantphos catalyst system with formamide, the strong acid HOTs component needed to be significantly increased. Under these modified conditions, a good overall selectivity to the desired N-hexylformamide (~80%) was observed while the catalytic reduction *specificity* for production of N-hexylformamide over hexanol was spectacularly increased with the higher HOTs concentrations up to a ratio N-hexylformamide/hexanol of ~60-80. More importantly, the reductive amidation reaction of aldehydes with formamide as the substrate can be applied to a wide range of aldehydes.

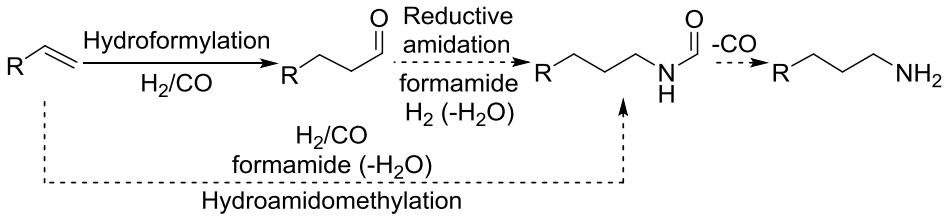
Hydroamidomethylation of an alkene (1-pentene) with formamide, involving both hydroformylation and reductive amidation of the produced aldehydes, has also been investigated. Experiments with a Rh/xantphos/HOTs catalyst system promoted by 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HOR^F), however, thus far revealed much poorer yields (~20%) to N-hexylformamide relative to those of N-hexylamides obtainable with higher alkylamides (up to 80%) under the same reaction conditions. Clearly, HOR^F is a less efficient hydrogenation promoter in hydroamidomethylation with formamide relative to acetamide as the amide substrate. It is suggested that the cause for the poorer performance in hydroamidomethylation lies in the lower nucleophilicity at N of formamide relative to higher alkyl amides. The higher acidity required for efficient reductive amidation with formamide of the intermediate aldehydes now causes HOR^F to less efficiently promote hydroamidomethylation, most likely due to its excessive (acid-catalysed) acetalisation with the aldehydes. Using N-hexylformamide as a source of n-hexylamine by decarbonylation was demonstrated by using some transition metal complexes or strong base. However, until now only stoichiometric conversions with either transition metal complexes or strong base could be obtained under the conditions applied.

4.1. Introduction

The formation of carbon-nitrogen bonds is of particular academic and industrial interest because it offers synthetic potential to a wide range of useful products in synthetic chemistry, biology, pharmaceuticals and material science.[1] Nitrogen-containing compounds, such as amines and more specifically primary amines are applied for the production of valuable bulk chemicals, dyes, pharmaceuticals and biologically active compounds.[2] Among the different catalytic methods of carbon-nitrogen bond formation, the most studied methods are hydroamination of alkenes and alkynes with amines,[2-5] hydroaminomethylation of alkenes[6-10] and the reductive amination of carbonyl compounds.[11-17] In principle, these reactions can be performed without or with very limited waste formation, fulfilling one of the requirements of 'green' chemistry. Despite recent developments in the synthesis of substituted amines,[2, 18, 19] the catalytic synthesis of primary amines is still a challenge in terms of energy usage as well as atom-efficiency.[20, 21] The currently used industrial process of making primary amines is based upon the catalytic amination of an alcohol or aldehyde with ammonia. This process holds some serious drawbacks such as employing high ammonia pressure and high temperature, thus leading to low efficiency.[22] Reductive amination of aldehydes and hydroaminomethylation of alkenes with ammonia generally suffers from over-alkylation.[14, 21] The initially produced primary amine is generally more nucleophilic and reactive than ammonia, thus resulting in the formation of substantial amounts of the secondary and tertiary amines. One approach to avoid over-alkylation has been to apply a large excess of ammonia. This method thus necessitates the application of high pressures at the required elevated reaction temperatures; excessive heavy-ends formation due to base-catalyzed aldol condensation reactions as well as energy-demanding product separations will thus generally be a consequence leading to high manufacturing costs.[14, 20, 21] The development of a new synthesis method for primary amines, avoiding over-alkylation, would be highly desirable.

Led by our recent discoveries of the catalytic reductive amidation of an aldehyde with acetamide (Chapter 2) and hydroamidomethylation of an alkene with acetamide (Chapter 3), we now propose a new synthesis route to obtain a primary amine from an alkene (Scheme 4.1). Aldehydes as intermediate products (after initial hydroformylation of alkene in the hydroamidomethylation reaction) can undergo a catalytic reductive amidation reaction with formamide to give N-alkylformamide,

which can be subsequently converted into the corresponding primary amines via a decarbonylation process. Reductive amidation (in contrast with reductive amination) of an aldehyde generally avoids over-alkylation due to the low nucleophilicity and steric encumbrance at the amide N of the initially formed mono-alkylated product (Chapter 2 and 3).[23, 24]



Scheme 4.1. Proposed catalytic formation of N-alkylformamide and subsequent decarbonylation to primary amine

In this Chapter, we report our studies towards the catalytic reductive amidation reaction of hexanal with formamide and the hydroamidomethylation of pentene with formamide to form N-hexylformamide as well as the subsequent decarbonylation of N-hexylformamide leading to the formation of n-hexylamine.

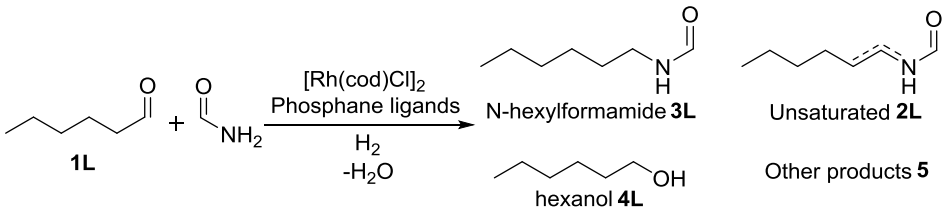
4.2. Results and Discussion

4.2.1. Reductive amidation of hexanal with formamide

The products found in a typical reductive amidation experiment with hexanal and formamide are shown in Scheme 4.2. Apart from the desired N-hexylformamide **3L**, the two isomeric unsaturated compounds N-(1-hexylidene)formamide or N-1-hexenylformamide **2L** as well as hexanol **4L** were observed.[25] Furthermore, formation of various products with higher mass, comprising condensation products **5** were also observed (Figure 4.1).

The reductive amidation experiments were performed starting with 5 mmol of hexanal and a small excess of formamide (6 mmol); a quantitative product distribution was determined from GC analysis. The hexanal conversions shown in the Tables were calculated from the amount of hexanal found in the reaction mixtures after the reaction.

Amounts of N-hexylformamide **3L**, unsaturated intermediates **2L**, and hexanol **3L** were determined using calibration lines.



Scheme 4.2. An overview of the reductive amidation of hexanal with formamide; formation of intermediates and products

The remainder consists of the higher mass products **5**, which were not individually quantified from GC, but rather calculated as a lumped-together number from the uneven mass-balance of hexanal-derived GLC-measurable products. The specificity of the catalysts for reductive amidation versus hydrogenation of hexanal is given as the ratio **3L**/**4L**. Full analytical data of all reaction mixtures are given in Appendix III.

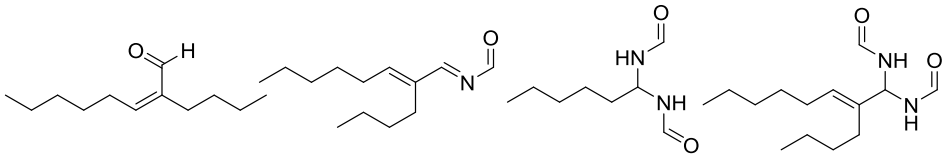


Figure 4.1. Products of higher molecular mass (**5**) observed in the reductive amidation reaction

Led by our recent work on the reductive amidation of hexanal with acetamide and higher alkylamides (Chapter 2),[23] we started our exploratory batch test studies using similar conditions (Table 4.1, Entry 1). Under this condition (80 °C, 80 bar H_2, 0.05 mmol, HOTs/Rh~5), the reaction turned out to yield 66% selectivity to the desired **3L**, but with only ~35% conversion of hexanal **1L** and a relatively low **3L**/**4L** ratio (10). The relatively low yield of **3L** of only ~20% observed in reductive amidation with formamide can be seen as a negative extrapolation of the general trend described in Chapter 2 that *increased* yields of the N-alkylamide **3** are obtained with the *more* electron-donating alkyl groups at the amide (up to 90% with higher alkyl amides).[23]

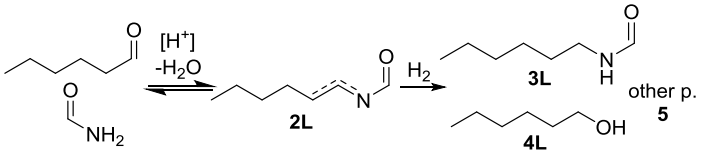
In attempts to remedy the relatively low efficiency of the reductive amidation with formamide, we found that increasing the amount of HOTs co-catalyst to 0.8 mmol (thus increasing the HOTs/Rh ratio from 5 to 80) positively affects both the **3L**/**4L** product ratio (from 10 to 75) as well as the conversion of hexanal **1L** (from 33% to 85%); the overall yield for the desired **3L** was thus significantly increased from a modest 20% up to ~65% (Entries 1-6). Whereas the catalyst's reduction *specificity* for producing **3L** over **4L** gradually increased with acid concentration, the overall *yield* of **3L** leveled off at the higher acid concentration range, predominantly due to increased formation of condensation products **5**, in particular the product hexyl-di-amide. The necessity of using a higher acid co-catalyst concentration for obtaining an acceptable conversion to **3L** when formamide is used as the substrate, can likely be interpreted as being linked to the reduced nucleophilicity at N of formamide vs. a higher alkylamide. Nucleophilicity of the amide N in $HCONH_2$ vs $RCONH_2$ likely plays a role at two levels in the mechanism of reductive amidation of aldehydes.[23] First, a reduced nucleophilicity makes addition of the amide's N-H to the aldehyde carbonyl to form the intermediate unsaturated products **2L,** a higher barrier process. Secondly, the nucleophilicity may play a role in the fate of the -C=N-(CO-) imido-moiety at the Rh/xantphos hydrogenation catalyst. This leads to an intrinsically reduced rate of hydrogenation of the functionality, due to both a reduced binding strength to the cationic Rh/xantphos center and an increased barrier for migratory insertion of the -C=N-(CO)- moiety into the Rh-H bond.

As reported in Chapter 2,[23] we identified a dual functional role of the co-catalyst HOTs: First of all, the acid HOTs co-catalyst was shown to catalyze the amide-aldehyde addition reaction to produce intermediates **2.** The supposedly higher barrier for this process with formamide must be compensated by a higher concentration of the acid co-catalyst. Furthermore, the addition of excess of acid HOTs (up to ~80 fold) to the Rh/xantphos catalyst system will also generate a more cationic $[Rh^{III}(OTs)_n/xantphos]^+$ species in a more polar acidic environment, which together are held responsible for the efficient and selective hydrogenation of the imido intermediates **2** in the presence of aldehyde, thus being responsible for the high reduction specificity as indicated by the high **3L**/**4L** product ratio.

Application of different reaction temperatures revealed that lowering of the reaction temperature from 100 °C to 60 °C led to a further increase in selectivity for **3L**, from ~70% up to 85% (Entries 3, 9, 10). Upon further lowering of the reaction temperature

to 40 °C the relative amount of unsaturated intermediates **2L** increased, thus indicating that the hydrogenation rate from **2L** to **3L** decreased (Entry 8). A temperature of 60 °C apparently is the optimal reaction temperature to obtain a high selectivity to **3** (85%) with a very high **3L**/**4L** product ratio (~60) at only slightly lower conversion of hexanal (66%). In fact, these optimized results are comparable with those obtained in the reductive amidation of hexanal with acetamide, applying the same conditions.

Table 4.1. Reductive amidation of hexanal with formamide catalyzed by $[Rh(cod)Cl]_2$ in combination with xantphos ligand [a]



	T	P (H_2)	HOTs	conversion	selectivity %[b]				**3L**/**4L**
	°C	bar	mmol	%	**2L**	**3L**	**4L**	**5**	ratio
1	80	80	0.05	33	15	66	7	12	10
2	80	80	0.1	57	9	76	4	11	19
3	80	80	0.2	70	5	81	2	12	41
4	80	80	0.4	79	8	76	1	14	60
5	80	80	0.6	81	8	76	1	14	78
6	80	80	0.8	85	7	74	1	18	75
7[c]	80	80	0.2	76	5	73	2	21	45
8	40	80	0.2	38	55	40	1	4	41
9	60	80	0.2	66	8	85	1	5	59
10	100	80	0.2	79	6	72	5	17	15
11	60	60	0.2	62	18	70	1	11	61
12	60	40	0.2	58	27	62	1	10	56
13	60	20	0.2	53	48	36	1	16	53
14[d]	60	80	0.2	72	25	61	1	13	47
15[e]	60	80	0.2	86	5	87	1	6	60

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol formamide (Rh:xantphos:hexanal: formamide=1:1.25:500:600); HOTs: 0.05-0.8 mmol;P_{H2}= 20-80 bar; T= 40-100 °C; t = 4 h; Solvent: 25 mL diglyme; [b] the selectivity was determined using decane as internal standard; [c] 7.5 mmol formamide; [d] 15 mLdiglyme; [e] 8 h; for more information see Appendix III, Table AIII.1

Applying a same low reaction temperature of 60 °C and a relatively high concentration of the co-catalyst HOTs (HOTs/Rh=20) led to a similarly high N-hexylacetamide/hexanol ratio and a selectivity to N-hexylacetamide of 90% at 83% conversion.

Lowering of the hydrogen gas pressure from 80 to 20 bar resulted in a significantly reduced overall hydrogenation activity of the catalytic system, thus resulting in a pronounced decrease in the selectivity to **3L** (from 85% to 36%) and increase in the formation of intermediates **2L** as well as other products **5** (Entries 3, 11, 12, 13). The use of more concentrated reaction media resulted in slightly higher conversion, but with the formation of higher amount of other products (entry 14). After 8 hours under optimized conditions (60 °C, 80 bar H_2) 86% conversion of hexanal with 87% selectivity to **3L** was achieved (Entry 15).

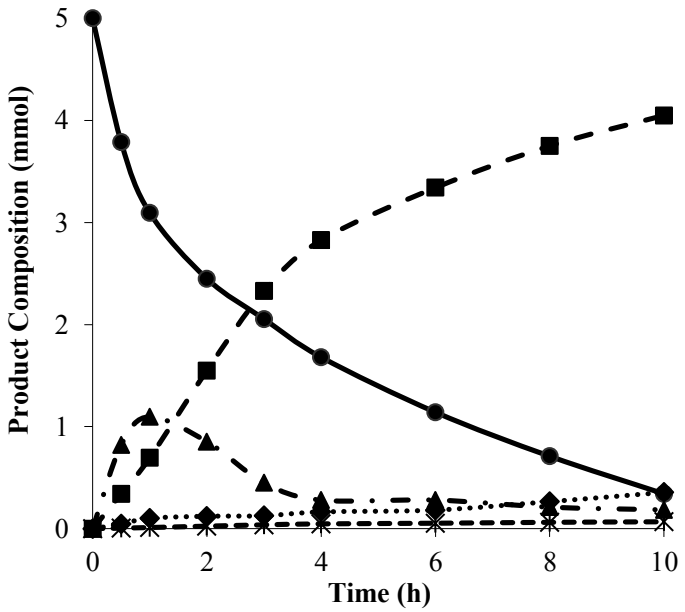
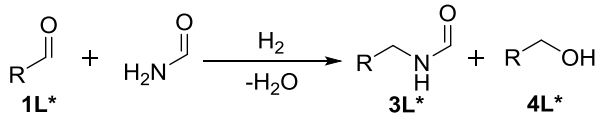


Figure 4.2. Product development in time in the reductive amidation of hexanal with formamide; Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.2 mmol HOTs, 5 mmol hexanal, 6 mmol formamide (Rh:xantphos:HOTs:hexanal:formamide=1:1.25:20:500:600); P_{H2}= 80 bar; T= 60 °C; Solvent: 25 mL diglyme; decane as internal standard. ●=hexanal (**1**), ■= N-hexylformamide (**3**), ▲=unsaturated intermediates (**2**), ♦= hexanol (**4**), ∗= other products (**5**)

The use of various other ligands in the catalytic system has been briefly explored (See Tables AIII2.1 and AIII2.2). As also established in Chapter 2 and 3,[23] the xantphos-type ligands appear to play a unique role in the Rh catalysed reductive amidation reaction.

The product development in time for the Rh/xantphos/HOTs catalytic system is depicted in Figure 4.2. After ten hours at 60 °C and a HOTs/Rh ratio of 20 nearly full conversion (~95%) is reached with 87% selectivity to **3L** and a product ratio of 60 for **3L**/**4L** (See Table AIII.3). It is shown that under the acidic conditions applied the amount of unsaturated intermediates **2L** builds up significantly in the first hour of the reaction (to about 20% of the initial hexanal intake). The build-up of **2L s**uggests that under the strongly acidic, low temperature conditions applied with formamide, the reduction of the imido intermediate **2L** to give **3L** becomes overall rate determining.

Table 4.2. Scope of reductive amidation with formamide using various aldehydes[a]



	aldehyde 5 mmol	conversion %	selectivity % 2L*	3L*	4L*	5*	3L*/4L* ratio
1	butanal	86	8	82	1	9	61
2	hexanal	86	5	87	1	6	60
3	heptanal	85	6	81	1	11	58
4	octanal	83	6	81	2	12	54
5	nonanal	82	5	84	1	9	57
6	2-Me-pentanal	35	29	44	11	16	4
7	PhCHO	25	25	27	9	40	3
8	3-Ph-propanal	85	8	79	2	11	37

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.2 mmol HOTs, 5 mmol aldehyde, 6 mmol formamide (Rh:xantphos:HOTs:aldehyde:formamide= 1:1.25:20:500:600); P_{H2}= 80 bar; T= 60 °C; t= 8 h; Solvent: 25 mL diglyme; decane as internal standard

A number of different aldehyde substrates were applied in the reductive amidation reaction with formamide (Table 4.2). The use of aldehydes with a linear electron-donating alkyl group (butanal - nonanal) resulted in high selectivity (>80%) and conversion (>80%) with excellent ratios of **3L***/**4L*** (Entries 1-5). The use of bulkier

aldehydes, such as branched 2-methylpentanal and benzaldehyde with an electronically different carbonyl moiety, were considerably less reactive in reductive amidation with formamide; not only the conversion of aldehyde was lower, but also the hydrogenation activity and substrate specificity (ratio **3L***/**4L***) drastically decreased (Entries 6, 7). Furthermore, the use of 3-phenylpropanal with similar steric hindrance and electronics of the carbonyl group in linear paraffinic aldehydes, resulted again in high conversion (85%) accompanied by high selectivity to **3L*** (~80%) with only slightly lower **3L***/**4L*** product ratio (Entry 8). Clearly, both the steric hindrance at the carbonyl and the electronic of the carbonyl group of the aldehyde substrates play an important role in the success of the reductive amidation of aldehydes with formamide (for detailed information see Table AIII.4), in fact similar to that with higher alkylamides under lower acidic conditions as shown in Chapter 2.[23]

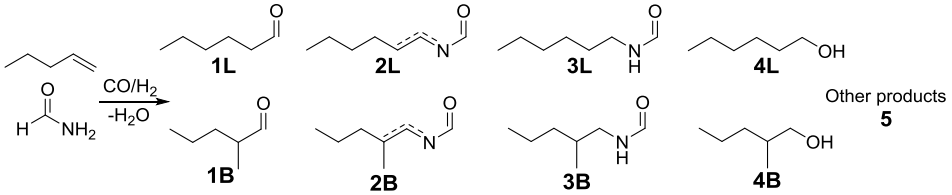
4.2.2. Hydroamidomethylation of 1-pentene with formamide

As reported in Chapter 3 Rh/xantphos complexes catalyze the direct tandem hydroformylation-reductive amidation reaction (hydroamidomethylation) of alkenes, if acidic promoters, such as 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HOR^F) are applied in combination with diglyme and HOTs as a co-catalyst. Under these conditions, reductive amidation of the *in-situ* formed aldehydes could efficiently take place in the presence of syngas. In the reactions with 1-pentene and formamide as substrates (Table 4.3), however, this turned out to give much poorer selectivities to the desired **3L** (less than 20%) than obtainable with acetamide and higher alkylamides (>80%). Increasing the amount of HOR^F promoter did indeed show a promoting effect on the hydroamidomethylation reaction with formamide, but highest yields of **3L** were still slightly less than 20% based on 1-pentene. It was noted that significant formation of acetal (produced from the reaction of the in situ formed aldehyde with HOR^F) took place (up to ~25% yield). Clearly, the relatively high concentration of strong acid HOTs, necessary with formamide as substrate for more efficient reductive amidation, now also catalyzes extensive acetal formation of hexanal with HOR^F with the associated production of water ($RCOH + 2\ HOR^F \leftrightarrows RC(OR^F)_2 + H_2O$). As acetal formation is an equilibrium reaction, the very existence of the acetal itself is not considered a likely reason for limiting the yield of **3L**. It is however more likely that the associated H_2O production must be seen as the origin of low yield of **3L** as it opposes the in-situ formation of imido intermediates **2L**. It was shown in Chapter 3 that addition of even small amounts of water already has a significantly negative effect

on the yield of hydroamidomethylation product **3L**, even with acetamide as a more nucleophilic amide substrate.[24]

Therefore, in order to suppress acetal formation, and more importantly H_2O formation, we decreased the amount of HOTs co-catalyst again from 0.2 mmol to 0.05 mmol in attempted hydroamidomethylation of 1-pentene with formamide. However, this resulted in even lower yields of the desired hydroamidomethylation product **3L** (cf. entries 6-8), thus re-confirming the need for a relatively high HOTs concentration with formamide in reductive amidation, also in tandem hydroformylation-reductive amidation under syngas conditions. It is clear that alternative hydroamidomethylation catalyst promoters should be examined to overcome the above sketched catalytic dilemma.

Table 4.3. Hydroamidomethylation of 1-pentene with formamide catalyzed by $[Rh(cod)Cl]_2$ in combination with xantphos ligand [a]



	diglyme/HOR^F	T	P (CO/H_2)	HOTs	conv.	selectivity %^{b}						1	3
	10 mL (v/v)	°C	bar	mmol	%	**1**	**2**	**3**	**4**	**acetal**	**5**	L%	L%
1	8/2	60	50(1/2)	0.2	58	72	9	5	0	5	9	98	>99
2	8/2	80	50(1/2)	0.2	73	68	8	6	0	10	8	98	>99
3	10/0	100	50(1/2)	0.2	83	44	14	4	1	0	37	97	>99
4	9/1	100	50(1/2)	0.2	84	43	10	7	1	13	27	97	>99
5	7/3	100	50(1/2)	0.2	84	41	6	11	1	26	14	97	>99
6	8/2	100	50(1/2)	0.2	87	40	8	20	0	20	12	95	>99
7	8/2	100	50(1/2)	0.1	87	54	8	15	0	13	10	95	>99
8	8/2	100	50(1/2)	0.05	86	64	7	12	0	8	9	96	>99

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol 1-pentene, 5 mmol formamide (Rh:xantphos:1-pentene: formamide=1:2:500:500); HOTs: 0.05-0.2 mmol;P(CO/H_2)= 50 (1/2) bar; T= 60-100 °C; t = 8 h; Solvent: 10 mL diglyme or diglyme/HOR^F; [b] the selectivity was determined using decane as internal standard; for more information see appendix III, Table AIII.5

4.2.3. N-alkylformamides to primary amines

We considered that the mono-N-alkylated formamide products, shown to be accessible by the reductive amidation of aldehydes and in a lesser extend by hydroamidomethylation of alkenes with formamide, in principle could serve as a convenient source of primary amines through a decarbonylation process. Decarbonylation is well-known for aldehydes,[26-29] methyl formate[30-32] and dimethylformamide (DMF).[33-36] Aldehyde decarbonylation was first discovered as a stoichiometric organometallic reaction[37-41] and was then developed into a catalytic process[27, 28] with the help of transition metal complexes, mainly of rhodium, iridium, ruthenium and palladium.[26-28, 42] DMF is well-known as a carbonylating agent in the synthesis of certain organometallic carbonyl compounds, but it is generally used in a large excess (solvent) as a source of CO in carbonylation reactions.[43, 44]

With the aim to *catalytically* produce primary amines from N-alkylformamides, its potential decarbonylation using transition metal catalysts, based on rhodium, iridium, palladium or ruthenium was briefly investigated (Table 4.4). The results obtained with N-hexylformamide as substrate under mild conditions (eg. at room temperature) show that indeed decarbonylation rapidly proceeds until conversions corresponding to the stoichiometric amount of several transition metal complexes used in the experiments (Entries 1-3,8). With a stoichiometric amount of an Rh/dppp complex decarbonylation proceeded quantitatively (>98% conversion and >90% yield to n-hexylamine) (Table 4.4, Entry 8). Increasing the reaction time (up to 24 hours) and temperature (up to 200 °C), did not improve the decarbonylation conversion or n-hexylamine yield beyond the stoichiometric amount on transition metal complex (see appendix III).

Apparently, for *catalytic* decarbonylation to occur of N-hexylformamide using transition metal catalysts, the removal of CO from the metal center after a decarbonylation event to regenerate the starting complex poses a serious problem. The transition metal complex apparently does not act as a catalyst anymore *after* coordination of a molecule of CO to the metal center. Thus, a catalytic decarbonylation cycle (eqs. i-iv) is effectively frustrated:

$$C_6H_{13}NHCHO + [L_nM^{I}Cl] \rightarrow [L_nM^{III}Cl(H)(C_6H_{13}NHCO)]^+ \qquad \text{(i)}$$

$$[L_nM^{III}Cl(H)(C_6H_{13}NHCO)]^+ \rightarrow [L_nM^{III}Cl(H)(CO)(C_6H_{13}NH)]^+ \qquad \text{(ii)}$$

$$[L_nM^{III}Cl(H)(CO)(C_6H_{13}NH)]^+ \rightarrow C_6H_{13}NH_2 + [L_nM^{I}Cl(CO)] \qquad \text{(iii)}$$

$$[L_nM^ICl(CO)] \not\rightarrow [L_nM^ICl] + CO \qquad \text{(iv)}$$

The same phenomenon has been reported[37] with the Wilkinson's complex, $[RhCl(PPh_3)_3]$, in aldehyde decarbonylation ($RhCl(PPh_3)_3$ + RCHO → $RhCl(CO)(PPh_3)_2$ + RH + PPh_3). The intermediate Rh-CO species generated in the reaction, are sometimes stable up to 200 °C, and thus are incapable of catalytic decarbonylation below this temperature. Application of a higher reaction temperature is however not a generally feasible option as it often leads to complex degradation and the formation of side-products.[38] Due to the mild reaction conditions and high yield, stoichiometric amounts of Wilkinson's catalyst are still being applied in the synthesis of a variety of target molecules in organic synthesis.[39-41]

Table 4.4. The decarbonylation of N-hexylformamide catalyzed by various catalysts in different conditions[a]

	Metal (Base) 10 mol%	Ligand 20 mol%	conversion % N-hexylformamide	Yield %[b] n-hexylamine
1	$[Rh(cod)Cl]_2$	dppp	10	10
2	$[Ir(cod)Cl]_2$	PPh_3	10	10
3	$RuCl_3.H_2O$	PPh_3	10	10
4	NaOMe		10	10
5	NaOtBu		10	10
6	Na_2CO_3		<1	-
7	$NaOR^F$		<1	-
8[c]	$[Rh(cod)Cl]_2$	dppp	99	92
9[c]	NaOMe		97	89

[a] Reaction conditions: 10 mol% metal (M) or base (B), 20 mol% ligands (L)(M(B):L:formamide=0.5:1:5) T= room temperature; t = 30 min; Solvent: 5 mL diglyme; [b] the yield was determined using decane as external standard; [c] one equivalent catalyst used in the reaction; for more information see appendix III

Decarbonylation of formamide derivatives such as N-formylsaccharin has also been reported using stoichiometric amounts of base.[45] We have briefly explored the possibility of a catalytic decarbonylation of N-hexylformamide catalyzed by strong base (Table 4.4, entries 4-7, 9). It is shown that a rapid decarbonylation indeed did occur under mild conditions with addition of strong base (such as NaOMe). However,

the maximal conversion attainable appeared again limited by the stoichiometric amount of strong base present (entries 4, 5).

With the very strong base NaOMe or NaOt-Bu applied in stoichiometric amounts relative to the formamide, n-hexylamine could be produced in higher than 90% yield after only 30 minutes at room temperature (Table 4.4, entry 9). Even at elevated temperatures, we were not able to demonstrate a decarbonylation conversion beyond stoichiometric amounts on base (see appendix III).

Decarbonylation of N-hexylformamide by the strong base NaOMe likely proceeds via initial deprotonation of the formyl H, thus stoichiometrically producing MeOH, CO and the sodium salt of N-hexylamine ($NaNHC_6H_{13}$):

$$C_6H_{13}NHCHO + NaOMe \rightarrow C_6H_{13}NHNa + MeOH + CO \qquad (v)$$

In order to make the process catalytic in NaOMe, its regeneration should take place via:

$$C_6H_{13}NHNa + MeOH \not\rightarrow C_6H_{13}NH_2 + NaOMe \qquad (vi)$$

However, although the formation of n-hexylamine is observed, seemingly the reaction step (vi) does not proceed as shown, as apparently no catalytic decarbonylation cycle in NaOMe can be sustained. It is shown that the use of weaker bases, such as Na_2CO_3 and $NaOR^F$, does not even result in stoichiometric decarbonylation (Table 4.4, entries 6, 7); these bases apparently are too weak to deprotonate N-hexylformamide.

We can thus conclude that both the development of a *catalytic* transition metal complex as well as a strong-base catalyzed decarbonylation process of N-alkylformamides to generate primary amines remains a challenging goal. Stoichiometric decarbonylation on the other hand is possible, both with several transition metal complexes as well as with strong-base. A possible way out of this catalytic problem could involve a two-step protocol consisting of a base-catalyzed reactive transesterification of N-hexylformamide with methanol continuously removing the produce methylformate, thus producing the desired primary amine (Eq vii), followed by amidation of methylformate with NH_3 to regenerate formamide (Eq. viii) as the substrate for reductive amidation.

$$C_6H_{13}NHCOH + MeOH \leftrightarrows C_6H_{13}NH_2 + HCOOMe \qquad (vii)$$

$$HCOOMe + NH_3 \leftrightarrows HCONH_2 + MeOH \qquad (viii)$$

4.3. Conclusions

We have attempted to develop a novel synthetic route for the synthesis of primary amines from alkenes employing hydroformylation, reductive amidation and decarbonylation reactions. In order to obtain N-alkylformamide, the reductive amidation was successfully developed using a highly selective catalytic system comprising rhodium/xantphos/HOTs giving a high N-alkylformamide yield under mild conditions. The use of a larger amount of acid co-catalyst appears to be important for both the nucleophilic addition of the formamide to the aldehyde as well as the substrate specificity in the hydrogenation step. Subsequently, brief investigations of the hydroamidomethylation of alkene with formamide have revealed poor conversion to N-alkylformamide. Previously discovered acidic alcoholic promoters, such as 1,1,1,3,3,3-hexafluoroisopropyl alcohol, for hydroamidomethylation catalysts with higher-alkyl amides, are significantly less effective with formamide as the substrate. This is attributed to excessive formation of acetal by-product from the intermediate aldehyde and alcohol promoter and more in particular to the associated water production under the required more acidic conditions. The produced N-alkylformamides can serve as a source of primary amines by a stoichiometric decarbonylation process with several transition metal complexes as well as strong base. The *catalytic* decarbonylation of N-alkylformamides thus far remains elusive.

4.4. Experimental

4.4.1. Chemicals

The solvent bis(2-methoxyethyl)ether (diglyme) was distilled from CaH_2, deoxygenated and used immediately after the purification process. All other solvents were purged with argon and purified under pressure of dry argon using an Innovative Technologies purification system. The solvents passed through activated columns under low pressure to remove trace impurities. Stainless Steel Schlenk Vacuum line and Sigma Aldrich Air-free flasks allow them to be safely transferred.

1-pentene, butanal, hexanal, heptanal, octanal, nonanal, 2-methylpentanal, benzaldehyde, 3-phenylpropanal, decane (internal standard), para-toluenesulfonic acid (HOTs), bis(2-methoxyethyl) ether (diglyme), 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HOR^F) methanol, ethanol and other solvents, acids and bases were purchased from Acros Organics and Sigma Aldrich, the Netherlands and used as received. The transition metal precursors

(acetylacetonato)dicarbonylrhodium(I), chlorido(1,5-cyclooctadiene)rhodium(I) dimer, rhodium(III)chloride, ruthenium(III)chloride, chlorido(1,5-cyclooctadiene)irridium(I) dimer, palladium(II)acetate, bis(dibenzylideneacetone)palladium(0), rhodium on carbon, palladium on carbon and triruthenium dodecacarbonyl were purchased from Acros Organics and Sigma Aldrich, the Netherlands and used as received. The phosphane ligands triphenylphosphane (PPh_3), tri-n-butylphosphane ($P(nBu)_3$), $P(tBu)_3$, PCy_3, $P(nOct)_3$, n-butyldi-1-adamantylphosphane ($P(nBu)(1\text{-}ad)_2$), tris(2,4-di-t-butylphenyl)phosphite ($P(O\text{-}di\text{-}tBuPh)_3$), $P(oMeO\text{-}Ph)_3$, $P(pMeO\text{-}Ph)_3$, $P(2,4\text{-}diMeO\text{-}Ph)_3$, $P(2,6\text{-}diMeO\text{-}Ph)_3$, $P(oEtO\text{-}Ph)_3$, $P(mCl\text{-}Ph)_3$, $P(pCl\text{-}Ph)_3$, $P(m\text{-}Tolyl)_3$, $P(o\text{-}Tolyl)_3$ $P(p\text{-}Tolyl)_3$, 1,3-bis(diphenylphosphanyl)propane (dppp), 1,4-bis(diphenylphosphanyl)propane (dppb), 1,2-bis(diphenylphosphanyl)propane (dppe), oMeO-dppp, pMeO-dppp, oMeO-dppb, pMeO-dppb, oMeO-dppe, tris(2,4-ditert-butylphenyl)phosphite ($P(O\text{-}di\text{-}tBu\text{-}Ph)_3$), 9,9-dimethyl-4,5-bis(diphenyl-phosphanyl)xanthene (xantphos), xantamidite and xantphite were purchased from Strem Chemicals, Germany and Sigma Aldrich, the Netherlands and used as received. The bidentate phsphane ligands bezoxantphos, homoxantphos, DBFphos and POP-xantphos were purchased from Innovative Catalyst Technologies (InCatT B.V.), The Netherlands and used as received. The other phosphane ligands such as 2,7-di-tert-butyl-9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene (tBu-xantphos), 4,6-bis(diphenylphosphanyl)-10,10-dimethyl-10H-dibenzo[b,e][1,4]oxasilane (Si-xantphos), 9,9-dimethyl-4,5-bis(di-orthomethoxyphenyl-phosphanyl)xanthene (oMeO-xantphos), 9,9-dimethyl-4,5-bis(di-paramethoxyphenyl-phosphanyl)xanthene (pMeO-xantphos) and 4,5-bis(di(tert-butyl)phosphanyl)-9,9-dimethylxanthene ($xantphos(tBu)_2$) were generously provided by Shell Global Solutions Amsterdam b.v., The Netherlands and used as received.

4.4.2. Instruments

The stainless steel autoclave reactors (100 ml) were of HEL Limited, UK, equipped with magnetic stirrer, pressure transducer and temperature controlling thermocouple. A Hewlett Packard HP6890 Series auto-sampler GC system was used for regular GC analysis. GC-MS analysis were carried out on an Agilent technologies 7820A GC system series coupled with an Agilent technologies 5975 series GC-MSD system. A glovebox of M. Braun Inert gas-System GmbH, Germany, was used for storing and handling of air-sensitive phosphane ligands. Nuclear magnetic resonance spectra were recorded on a Bruker DPX300 (300MHz) or a Bruker DMX400 (400MHz) spectrometer. A Syringe Pump NE1000 series auto-injector from ProSense B. V. (laboratory and process Equipment Company) was used for the reactive distillation pumping methanol continuously into the reaction mixture. Innovative Technologies PureSolv MD 5 Solvent Purification System was used for drying

solvents. All reaction preparations and manipulations were performed using standard Schlenk techniques under an argon atmosphere. The catalytic reactions were carried out under varying syngas pressures and reaction temperatures.

4.4.3. Catalytic high pressure reaction

4.4.3.1. Catalytic reductive amidation of aldehyde with formamide

For all the catalytic experiments the catalyst precursor was formed in-situ in the autoclave by transferring the metal precursor and the selected phosphane ligands into the reactor. In the preparation of a typical catalytic reaction mixture containing solid ingredients that are not air sensitive, 0.005 mmol of $[Rh(cod)Cl]_2$ (2.46 mg, 0.01 mmol of Rh) and 0.0125 mmol of bidentate phosphane ligand or 0.025 mmol or monodentate phosphane ligand were weighed in air and transferred into an autoclave. The autoclave was closed and subsequently filled with argon using a Schlenk line connected to one of the valves of the autoclave. Through another valve under a continuous flow of argon subsequently were added: 25 ml of dried and degassed diglyme as solvent, 3.125 mmol (0.605 ml) decane as an internal standard, 5 mmol (0.615 ml) hexanal and 6 mmol (0.199 mL) formamide followed by 0.05-0.2 mmol HOTs. Then the reactor was inserted into the heating block and connected to the gas line of the reactor block with a continuous flow of N_2 gas through the gas line of autoclave to remove the air inside the gas line. The autoclave reactor was flushed three times with N_2 and one time with H_2 and finally pressurized with hydrogen gas. The reaction mixture was stirred at 500 rpm for 30 min to ensure complex formation.

In the set of experiments using air-sensitive ligands such as $P(nBu)_3$, $P(nBu)(1\text{-}ad)_2$, bcope and di-tBu-xantphos, in a glovebox the metal precursor complex and ligand (for some experiments with other additives like acid), were weighed into a Schlenk flask and dissolved in 10 ml of dried and degassed diglyme; dissolution generally was complete in about 2-3 minutes as was visible by the formation of a transparent yellowish solution. The flask was then connected to a Schlenk line and the solution was transferred through the valve of a reactor under a continuous flow of argon into the 100 ml stainless steel autoclave reactor. The procedure for gas intake in the autoclave was carried out as described above.

The reaction mixtures were heated up to 40 °C, 60 °C, 80 °C or 100 °C (within 30 min) under stirring at 500 rpm. All reaction conditions of the catalytic process were controlled by computerized software panels. After standing for four or eight hours at this temperature, the autoclave was cooled down to room temperature over about one hour. The autoclave was then slowly vented to atmospheric pressure.

After each catalytic run the reaction mixture was taken from the reactor and immediately analyzed with gas chromatography. Calibration lines for each analyte were used to determine the conversion of the substrates and yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

4.4.3.2. Catalytic hydroamidomethylation of 1-pentene with formamide

For all the catalytic experiments the active catalyst precursor was formed by *in-situ* in the autoclave by transferring the metal precursor and the selected phosphane ligands. In the preparation of a typical catalytic reaction mixture 0.01 mmol of $[Rh(acac)(CO)_2]$ (2.58 mg) and 0.02 mmol of bidentate phosphane ligand or 0.04 mmol of monodentate phosphane ligand were weighed and transferred into an autoclave. The autoclave was tightly closed and subsequently filled with argon with use of a Schlenk line that was connected to one of the valves of the autoclave. Through another valve under a continuous flow of argon subsequently was added 10 mL of dried and degassed diglyme or 8 ml of dried and degassed diglyme, 2 ml of HOR^F, 3.125 mmol (0.605 ml) decane as an internal standard, 5 mmol (0.548 ml) 1-pentene and 5 mmol (0.166 ml) formamide followed by 0.05-0.2 mmol HOTs. Then the reactor was inserted into the heating block and pressurized with 50 bar (CO/H_2=1/2) syngas. This reaction mixture was stirred at 500 rpm for 30 min to ensure that complex formation was complete. The reaction mixture was heated up to 60-100 °C (within 30 min) under stirring at 500 rpm. All reaction conditions of the catalytic process were controlled by computerized software panels. After standing for eight hours at this temperature, the autoclave was cooled down to room temperature over about one hour. The autoclave was then carefully vented to atmospheric pressure.

After each catalytic run the reaction mixture was taken from the reactor and at once analyzed by gas chromatography. Calibration lines for each analyte were used in determining the conversion of the substrates and yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

4.4.4. Decarbonylation of N-hexylformamide

A 50 ml two neck round-bottom flask, fitted with a condenser and connected to the schlenck line, (or 100 ml autoclave) was charged with 0.72 ml N-hexylformamide (5-10 mmol) and 0.5-1 mmol of a catalyst under argon. Then 5 ml of dried and degassed solvent (diglyme or other solvents) was injected into the flask under a continuous flow of argon. The flask was fitted with a reflux condenser. The mixture was stirred or stirred and heated

to the desired temperature for 30 minutes or longer. After each catalytic run the reaction, the external standard decane was added and then the mixture was taken from the flask and at once analyzed by gas chromatography. Calibration lines for each analyte were used in determining the conversion of the substrates and yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

4.4.5. Synthetic procedures

4.4.5.1. Synthesis of N-hexylformamide

Following the reported procedure, A 500 ml round-bottom flask was charged with 33 ml hexylamine (0.25 mol), 11.5 ml formic acid (0.30 mol, 1.2 eq.) and 250 ml toluene. The flask was then attached to a Dean-Stark apparatus and heated up to reflux under stirring. The flask was insulated with aluminium foil. After 18-24 h the reaction was stopped and the flask was cooled down to room temperature. Then volatiles and solvent were removed by evaporation under reduced pressure. The product was isolated as a transparent viscous liquid with a near to quantitative yield.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K); δ_H = 8.15 (s, 1H, CHO), 6.29 (s, 1H, NH), 3.27 (q, 2H, CH_2), 1.52 (m, 2H, CH_2), 1.31 (s, 6H, 3* CH_2), 0.90 (m, 3H, CH_3).

4.4.6. GC and GC-MS analysis

GC spectra of typical **reductive amidation and hydroamidomethylation with formamide** are shown in the appendix IV with the assignment of products. 1 µL Crude reaction mixture containing internal standard was injected into a Hewlett Packard HP6890 Series auto-sampler GC system with column HP-1MS UI (30m*0.250mm*1.00µm). All the solvents have been assigned by comparing to their standard GC spectra. All the retention values of substrate and product to decane have been determined using commercially available or isolated standard chemicals.

Analysis conditions: 130 ºC (5 min), ramp 50ºC/min to 300 ºC, 300 ºC (3.6 min) (12 min in total).

GC-MS Method: 1 µL Crude reaction mixture containing internal standard was injected into a GC HP7820 Series auto-sampler GC system with column DB-5MS UI (30m*0.250mm*1.00µm) equipped with MSD 5975 Agilent series. All the solvents have been ignored by comparing to their standard GC spectra. All the retention values of substrate and product to decane have been determined using commercially available or isolated standard chemicals.

Analysis conditions: 100 °C (2.5 min), 20 °C / min to 250 °C, 250 °C (5 min) (15 min in total).

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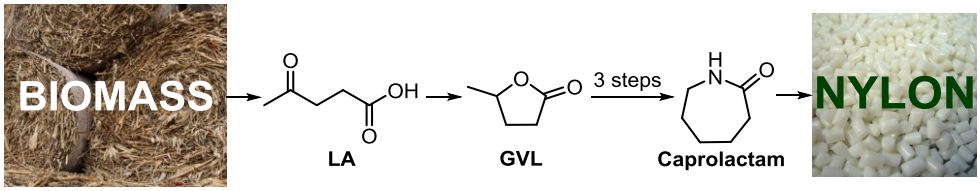
5

From Renewable Feedstock to "Green" Nylon: Catalytic Conversion of γ-Valerolactone to ε-Caprolactam



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S. Raoufmoghaddam, M. T.M. Rood, F. K.W. Buijze, E. Drent, E. Bouwman, *Chem. Eur. J.* **2013** *submitted*.

Abstract

The conversion of γ-valerolactone (GVL) in three atom-efficient steps into the important polymer precursor ε-caprolactam is reported. GVL can be obtained from the renewable resource cellulose. The bio-based GVL can be converted to a mixture of isomeric methyl pentenoates (MP) via trans-esterification with methanol; subsequent aminolysis with ammonia leads to a mixture of pentenamides (PA). The resulting pentenamides are ultimately converted into ε-caprolactam via the rhodium-catalyzed intramolecular hydroamidomethylation reaction. The hydroamidomethylation reaction consists of an initial hydroformylation of the alkene moiety of PA and subsequent ring-closing reductive amidation of the resulting aldehyde with the amide functionality.

5.1. Introduction

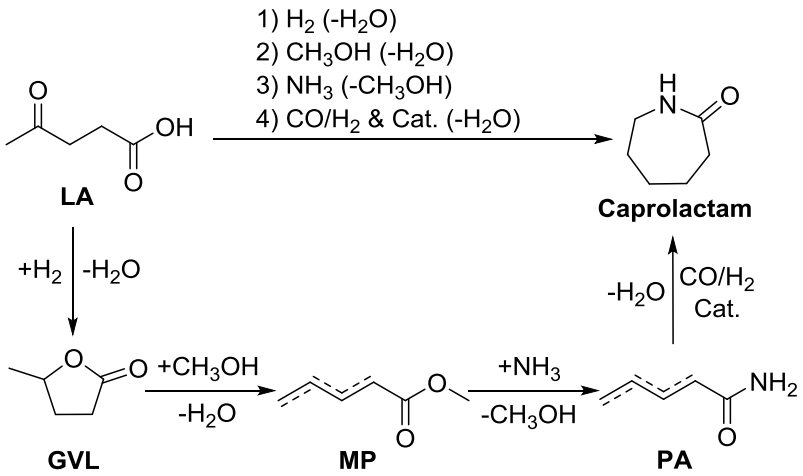
Societal concerns about climate change and long-term globally decreasing availability of fossil feedstock has stimulated chemical manufacturing industries to search for more sustainable routes to existing and new chemical products. In this respect developing alternative routes to large scale chemical products based on renewable biomass feedstock is a highly desirable goal of the chemical industry. Lignocellulosic biomass is one of the most attractive renewable feedstocks for production of bulk and fine chemicals, even more so when the novel synthesis routes from this feedstock allow for more atom and energy efficient production processes, producing less waste relative to the conventional routes.[1-3]

ε-Caprolactam is the polymer precursor for nylon-6, an extensively used synthetic polymer with an annual production of about four million tons.[4] It is traditionally synthesized from oil-based feedstock (benzene). The production of ε-caprolactam is typically carried out in a four step procedure[5] using benzene as the feedstock that is first hydrogenated to cyclohexane, which is subsequently converted to cyclohexanone by oxidation.[6, 7] The resulting cyclohexanone is then reacted with hydroxylamine to form cyclohexanone oxime,[8, 9] which is ultimately converted through a Beckmann rearrangement to ε-caprolactam.[10-12] The production of caprolactam by the traditional route suffers from a high energy demand, as well as co-production of large amounts of ammonium sulfate. The increasing demand for ε-caprolactam has provoked chemical companies to explore improvements in this classical synthesis route (e.g. Sumitomo process) as well as alternative production pathways, although most of these still rely on the use of fossil feedstock.[13-16]

An alternative route to produce caprolactam from renewable resources could be based on the use of levulinic acid, as this compound is foreseen to be readily available from cellulosic waste.[17, 18] Levulinic acid (LA) can be considered as a typical "functional platform chemical"[19] that can be converted into a range of derivatives widely usable in industrial applications,[20-22] e.g. to produce γ-valerolactone (GVL).[23-27] The conversion of LA into GVL by hydrogenation to 4-hydroxypentanoic acid using ruthenium catalysts, followed by (spontaneous) cyclization forming the lactone has been reported to occur in high efficiency (>95%).[28-30]

Herein, we report a novel synthesis route to caprolactam as depicted in Scheme 5.1, based on GVL as starting material; only water is generated as by-product of the

reactions. The first step of the proposed route proceeds via the acid-catalyzed reactive distillation of a mixture of isomeric methyl 2-, 3- and 4-pentenoates (MPs) from an acidic GVL/methanol mixture. In a subsequent reaction with ammonia this isomeric mixture of MPs is converted into the corresponding mixture of pentenamides (PAs). The selective conversion of the mixture of PAs to caprolactam is then carried out through a rhodium-catalyzed alkene isomerization- intramolecular hydroamidomethylation tandem reaction. An intermolecular version of the hydroamidomethylation reaction involving an alkene and amide as separate reactants is described in Chapter 3.



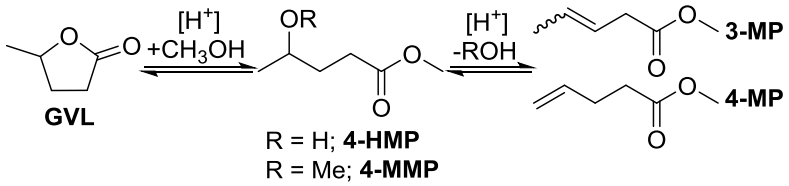
Scheme 5.1. Synthesis route for the conversion of levulinic acid to caprolactam

5.2. Result and discussion

5.2.1. Catalytic distillation of methyl pentenoates

Several patents describe the gas-phase synthesis of methyl pentenoates from GVL and methanol using solid acids as catalysts.[31, 32] Compared to the gas-phase reaction the catalytic distillation allows for relatively lower capital and energy costs as reaction and separation are combined in a single processing step with higher yield of the desired products because of the continuous removal of the methyl pentenoates formed in the reaction.[33, 34]

Trans-esterification of GVL with methanol was carried out via a reactive distillation using a strong Brønsted acid as the catalyst in the reaction mixture, following the procedure reported by Lange et al. (Scheme 5.2).[33, 34] Catalytic distillation takes the advantage of the large difference in boiling point between GVL and MPs (50 - 80 °C)[35] and drives the reaction to completion by continuously distilling the products from the equilibrium. In our study, the reported catalytic distillation was further optimized to lower reaction temperatures. During the reactive distillation process methanol must be continuously fed into the flask charged with GVL and the acid catalyst *p*-toluenesulfonic acid (HOTs). The distillate comprises a mixture of methanol, water, (cis & trans) methyl 3-pentenoates (3-MP) and methyl 4-pentenoate (4-MP) as well as small amounts of GVL, methyl 2-pentenoate (2-MP), methyl 4-methoxypentanoate (4-MMP) and methyl 4-hydroxypentanoate (4-HMP). After the reaction the residue in the bottom flask mainly consists of GVL, water and methanol, but also contains 4-MMP and 4-HMP as well as some heavy ends (see Appendix IV, Figure AIV.1 and AIV.2). Both the residual reaction mixture and the contents of the receiver flask were analyzed by GC and quantified by summation of the amounts in the distillate and bottom flask.[36]



Scheme 5.2. Reactive distillation of GVL in a stream of methanol results in a mixture of isomeric methyl pentenoates

A reaction temperature of 190 or 200 °C turned out to be the most beneficial for the conversion of GVL as well as the selectivity to MPs (Table 5.1). At these temperatures the selectivity to MPs is generally high, varying between 90-95%. Besides 3-MP and 4-MP, traces of 2-MP, 4-HMP and 4-MMP were also observed in the reaction mixture (see Appendix IV, Table IV.1). Neither dimethyl ether nor other by-products were detected, even upon placing the receiver in a liquid nitrogen trap, as similarly reported by Lange et al.[33, 34] At 190 °C the amount of intermediates was lower and a high conversion of GVL (>90%) was reached with good selectivity to MPs (95%). In the range of 150-200 °C, the reaction temperature does not have a considerable effect on

the 3-MP/4-MP ratio, which remains about 3. At temperatures higher than 200 °C the amount of GVL in the distillate increased and at temperatures lower than 150 °C the selectivity to MPs decreased. As reported, the use of higher alcohols like ethanol or butanol does not result in better selectivity to alkyl pentenoate esters compared to the results obtained with methanol.[33, 34, 37] The use of variable methanol feed rates revealed that 10 mL h^{-1} is an optimal rate; higher rates caused accumulation of GVL in the distillate and lower rates generally resulted in formation of more heavy ends.

Variation in the amount of HOTs from 1% to 10% showed that increasing the amount of HOTs increases the reaction rate and consequently decreases the reaction time (Entries 5, 7, 8). Furthermore, the use of a catalytic amount of H_2SO_4 as an alternative acid catalyst resulted in a slightly higher reaction rate (Entry 9).

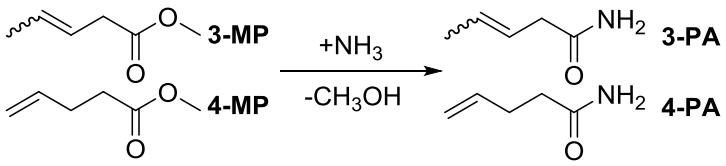
Table 5.1. Conversion of γ-valerolactone to methyl pentenoates via reactive distillation[a]

	T	conv. %	selectivity % [b]					
	°C	**GVL**	**2-MP**	**3-MP**	**4-MP**	**4-MMP**	**4-HMP**	**Other P**
1	150	40	0.2	61	24	9	1	5
2	160	54	0.2	61	26	7	0.7	4
3	170	62	0.2	66	25	5	0.5	4
4	180	63	0.2	66	23	6	0.5	4
5	190	90	0.1	73	23	2	0.2	2
6	200	91	0.2	70	22	3	0.2	5
7[c]	190	31	0.0	67	25	7	1	2
8[d]	190	56	0.2	67	23	4	1	4
9[e]	190	93	0.1	71	24	2	0	3

[a] Reaction conditions: 100 mmol (9.5 mL) GVL, 10 mmol (1.9 g) HOTs, 10 mL MeOH, T = 150 ºC – 200 ºC, t = 8 h, MeOH feed rate: 10 mL h^{-1}. The receiver flask was cooled with liquid N_2. [b] The selectivity was determined based on the amount of products in distillate and the bottom flask by GC analysis using decane as an external standard (for detailed information about the separate amounts in the distillate and the bottom flask, see Appendix IV); [c] 1 mmol HOTs; [d] 5 mmol HOTs; [e] 10 mmol (532 µL) H_2SO_4 as acid catalyst.

5.2.2. Conversion of methyl pentenoates to pentenamides

We have next investigated how the methanol solution of methyl pentenoates produced in the reactive distillation subsequently can be converted to the corresponding pentenamides (PA) (as depicted in Scheme 5.3) using various sources of ammonia, including ammonia gas, aqueous ammonia (35%) and methanolic ammonia (7 N).[38]



Scheme 5.3. Conversion of methyl pentenoates (MP) to pentenamides (PA)

Direct reaction of the methanolic distillate containing the methyl pentenoate mixture with (methanolic or aqueous) ammonia gave only low conversion to pentenamides, as expected. The reaction of the methyl esters with ammonia is an equilibrium reaction and the presence of excess of methanol pushes the equilibrium to the esters. Therefore methanol was distilled from the mixture prior to the addition of different sources of ammonia (Table 5.2). The application of 8 bar ammonia gas resulted in nearly full conversion, but the reaction was slow and needed more than 20 h residence time (Entry 1). It appeared that the use of aqueous ammonia (35%) gave the best results: a reaction at 80 °C after only 6 h resulted in >98% yield of combined PAs (Table 5.2, entry 4). Generally, 4-MP was converted more slowly than 3-MP which can be rationalized by the different inductive electron-withdrawing effect of the alkene double bond in the respective isomers. Surprisingly, pentenoic acids or ammonium pentenoates were not formed under these conditions.

Table 5.2. Results of the aminolysis of a mixture of methyl pentenoates to pentenamides (PA) using different sources of ammonia[a]

	NH_3 source	NH_3 amount	t h	conversion %	yield %[b] **3-PA**	**4-PA**
1	7N NH_3 in MeOH	50 mmol	5	13		
2	NH_3 (g)	8 bar	20	96	99	80
3	NH_4OH (35%)	50 mmol	5	93	96	80
4	NH_4OH (35%)	50 mmol	6	99	99	96

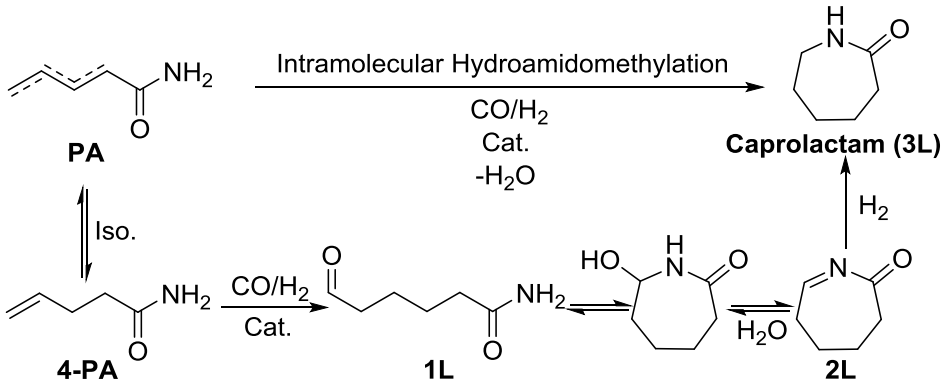
[a] Reaction conditions: 10 mmol (1.14 g) of methyl pentenoates (3-MP (7.5mmol)/4-MP (2.5mmol)); T= 80 °C; t= 5-20 h; [b] The yield was determined by GC analysis using decane as an internal standard; The amounts of the mixture of methyl pentenoates determined by injecting the mixture into GC before starting the reaction (for detailed information see Appendix IV, Table AIV.2)

Alkene double bond isomerization was also not observed, as the ratio of produced 3-PA and 4-PA was equal to the starting 3-MP/4-MP ratio at 99% overall MP conversion (Entry 4). To further study any possible occurrence of base-catalyzed isomerization, pure 4-MP was separately reacted under the same conditions; only 4-PA was formed and no other isomers were observed (see Appendix IV, Table AIV.2).

5.2.3. Intramolecular hydroamidomethylation of pentenamides to caprolactam

The regioselective intramolecular hydroamidomethylation of the resulting mixture of pentenamides (PA) is a novel and the most challenging step of the newly designed route to obtain caprolactam from levulinic acid. Inspired by our recent achievements concerning the catalytic hydroamidomethylation of alkenes (Chapter 3) and reductive amidation of aldehydes (Chapter 2) we have thus investigated the rhodium-catalyzed intramolecular hydroamidomethylation of pentenamides, a reaction that consists of an initial isomerization step (for internal pentenamides), followed by hydroformylation and a subsequent intramolecular reductive amidation reaction (Scheme 5.4).

We started our investigations of this intramolecular hydroamidomethylation reaction using pure 4-PA as the substrate under catalytic conditions as developed for the reductive amidation of an aldehyde. The use of an Rh/xanthphos catalyst system in the presence of an acid co-catalyst in a syngas atmosphere resulted in only very low yields of caprolactam (~4%; Table 5.3, entry 1).



Scheme 5.4. Intramolecular hydroamidomethylation of pentenamide to caprolactam (For clarity only the linear products are depicted)

The main product appeared to be (unsaturated) polymeric material as deduced from the insoluble white product that was formed. Soluble by-products observed in GC-MS appeared to be unsaturated dimer (m/z=240) and its hydrated derivative (m/z=258) as well as some other unidentified compounds; the higher molecular mass products could not be identified using GC-MS. It appeared that the unsaturated caprolactam (**2L**) was the major other reaction product with a total selectivity of about 40%. Only a very low amount of branched 6-ring unsaturated lactam **2B** was formed. Additionally, some 15% of hydrogenated substrate, pentanamide (valeramide, VA) was obtained. Surprisingly, this catalytic system is unable to hydrogenate the unsaturated caprolactam product, but prone to hydrogenate the unsaturated pentenamide. As we have found that the hydrogenation activity of the rhodium catalyst in the catalytic hydroamidomethylation of alkenes with acetamide is strongly promoted by the presence of 1,1,1,3,3,3-hexafluoro-isopropyl alcohol (HOR^F), we applied HOR^F as a co-additive in the reaction of 4-PA. As shown in entry 2, selective intramolecular hydroamidomethylation of 4-PA could still not be accomplished; the unsaturated lactam **2L** was the major product. Surprisingly, when the strong acid HOTs was omitted from the catalyst system, a high yield of **2L** was obtained (entry 3), and even 10% of caprolactam was formed. A very significant decrease in oligomeric material was observed, indicating that the presence of acid merely leads to (cationic) polymerization of the unsaturated lactam **2L**. A further increase of the amount of HOR^F to solvent-like quantities in the absence of HOTs resulted in a significant increase in the selectivity to caprolactam **3L** up to about 25% (Entry 4). This increase is associated with a decrease in unsaturated lactams, thus showing the promoting effect of HOR^F on the hydrogenation activity of this catalytic system in a syngas environment. Unfortunately, a significant amount of valeramide (VA) was still co-produced, which is increasing with HOR^F and HOTs concentration (Entry 5).

In our next attempts we aimed at the formation of 6-oxohexanamide **1L** by hydroformylation of 4-PA, with the intention to carry out the ring-closing reductive amidation in a separate subsequent step. Attempted hydroformylation of 4-PA with an Rh system in the absence of any phosphane ligand or in the presence of monodentate phosphane ligands in the absence of both HOR^F and HOTs gave high conversions and surprisingly showed the formation of both unsaturated cyclic products **2** with combined chemoselectivities up to about 90%. However, a modest ratio of 7- over 6-membered cyclic unsaturated products (**2L**/**2B**) was obtained, indicating a relatively low

regioselectivity for linear aldehyde formation in the hydroformylation of 4-PA (See Appendix IV, Table AIV.3).

The performance of *in situ* formed Rh catalysts in the 'hydroformylation' of 4-PA with a number of xantphos-type ligands (Figure 5.1) is shown in entries 6-9. Remarkably, good conversions (60-98%) and chemoselectivities up to 90% for the unsaturated intermediates **2** were generally obtained at 100 ºC. A very high preference (~up to 99%) for 7-membered cyclic unsaturated product **2L** versus 6-membered **2B** was observed. Additionally, small amounts of caprolactam **3L** as well as even smaller amounts of oligomer/polymer and VA were formed under these conditions (see Appendix IV, Table AIV.3).

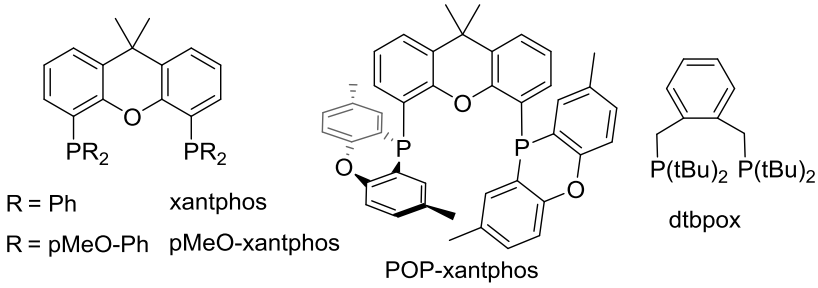
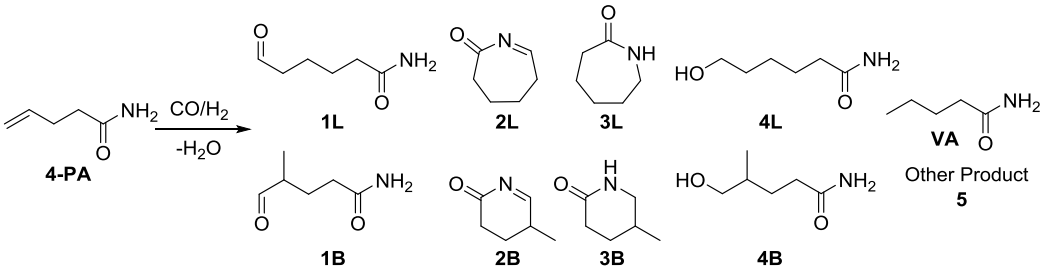


Figure 5.1. Selected ligands used in the intramolecular hydroamidomethylation of pentenamides (PA)

Apparently, the aldehyde functionality formed in the hydroformylation reaction immediately cyclizes with the amide functionality while extruding H_2O to form the unsaturated lactam **2L**. It is imperative to note that the 7-membered cyclic product is by far dominant over the 6-membered cyclic product in all experiments with xantphos-type ligands (~98%). The use of another bidentate phosphane ligand, such as dtbpox, -well-known for inducing a similarly high linear regiochemistry in palladium-catalyzed carbonylation[39] -gave not only lower catalytic activity, but also a low ratio of **2L**/**2B** indicating low regioselectivity for the linear aldehyde in hydroformylation (Entry 9). This clearly is a consequence of the ability of Rh/xantphos hydroformylation catalyst systems to impose a very high regioselectivity for the formation of the linear aldehydes from higher paraffinic alkenes.[40] Of the ligands tested the POP-xantphos ligand is the most interesting, as significant alkene bond isomerization (6% from 4-PA mainly to 3-

PA) took place under the applied reaction conditions (Entry 8). In all instants the selectivity to caprolactam was only about 10% (Entry 10).

Table 5.3. Influence of various conditions on intramolecular hydroamidomethylation of 4-PA[a]



	Ligand	t	T	P (CO/H_2)	HOTs	HOR^F	conv.	selectivity % [b]						L[c]
		h	°C	bar	mmol	mmol	%	**VA**	**1**	**2**	**3**	**4**	**5**	%
1	xantphos	8	100	50(1/2)	0.025		80	14	1	38	4	0	43	97
2	xantphos	8	100	50(1/2)	0.025	5	90	18	1	46	5	0	31	98
3	xantphos	8	100	50(1/2)		5	84	10	2	77	10	0	2	99
4	xantphos	8	100	50(1/2)		20	95	15	5	53	24	0	3	99
5	xantphos	8	100	50(1/2)	0.025	20	95	22	1	28	24	0	26	98
6	xantphos	8	100	50(1/2)			81	1	1	88	7	0	3	99
7	pMeO-xantphos	8	100	50(1/2)			62	0	2	90	2	0	6	98
8	POP-xantphos	8	100	50(1/2)			85	2	1	82	3	0	12[e]	94
9	dtbpox	8	100	50(1/2)			100	1	0	92	0	0	7	61
10	xantphos	10	100	50(1/2)			98	1	1	84	10	0	4	99
11[d]	xantphos	8+4	100-80	50(1/2)-80 H_2			100	15	1	5	68	0	12	99
12[d]	pMeO-xantphos	8+4	100-80	50(1/2)-80 H_2			91	23	1	24	46	0	7	98
13[d]	POP-xantphos	8+4	100-80	50(1/2)-80 H_2			100	20	0	11	57	0	13	96
14[d]	xantphos	10+4	100-80	50(1/2)-80 H_2			100	3	1	12	78	0	6	99
15[d]	xantphos	10+6	100-80	50(1/2)-80 H_2			100	3	1	2	88	0	6	99

[a] Reaction conditions: 2 mmol (19.8 mg) of 4-PA; 0.0025 mmol (1.24 mg) $[Rh(cod)Cl]_2$; 0.02 monodentate or 0.01 mmol bidentate ligand; $P(CO/H_2)$ = 50(1/2) bar; T = 100 °C; t = 8-10 h; 0-0.025 mmol HOTs; 0-20 mmol HOR^F; Solvent: 10 mL diglyme. [b] The amounts of products were determined by GC analysis using undecane as an internal standard; [c] overall linearity of the reaction mixture determined by GC; [d] In a one-pot two stage operation; reaction conditions: 8-10 h at 100 °C hydroformylation-depressurizing syngas-flushing with H_2- pressurizing with 80 bar H_2- 4-6 h at 80 °C hydrogenation

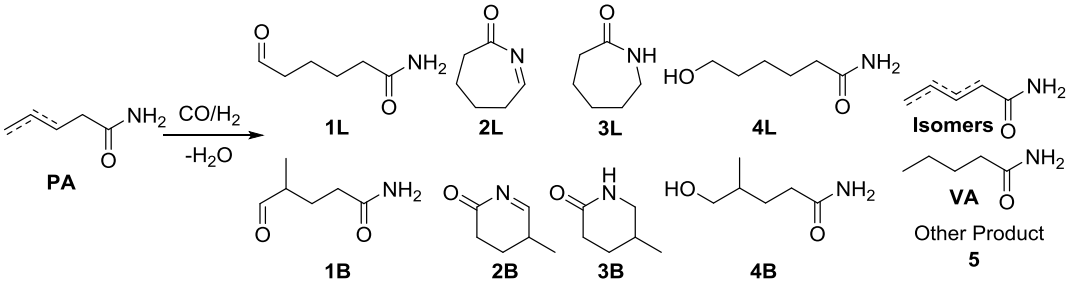
Hydroformylation of 4-PA by Rh/PPh_3 catalytic systems in THF has been reported before.[41, 42] Remarkably, it has been reported that the use of several rhodium precursors in the presence of PPh_3 resulted in >80% yield of the branched 6-membered cyclic unsaturated lactam, which was explained by the regioselectivity being driven by amide-directed "chelation control".[41] We have repeated the experiment in THF using [$RhHCO(PPh_3)_3$] as described by Ojima et al;[42] in our hands this indeed resulted in the formation of mainly product **2**, however, with a **2L**/**2B** ratio of ~0.8, similar to our reactions in diglyme (see Appendix IV, Table AIV.4).

To overcome the sluggishly proceeding hydrogenation of the unsaturated cyclic hydroformylation products under syngas conditions we attempted a two-step protocol in which Rh/xantphos was used as the single catalyst system. After the hydroformylation and subsequent cyclization stage syngas was replaced with pure dihydrogen gas and the mixture was further reacted at 80 ºC in a second stage of the reaction (Table 5.3, Entries 11-15). It was gratifying to observe in our best experiments an overall ~90% yield for caprolactam **3L** based on 4-PA as the feed, while only relatively small amounts of by-products were formed (Table 5.3, Entry 15).

Finally, as the ultimate challenge we studied the hydroamidomethylation reaction starting with an internal alkene, at first employing pure 3-pentenamide (Table 5.4, entries 1-7). Hydroformylation of 3-PA with the Rh/xantphos system under a pressure of 50 bar syngas gave only low conversion after 8 h; the main products observed were VA and **2** in addition to other products **5**, with a low **2L**/**2B** ratio (Entry 1). Using a lower pressure of 10 bar syngas resulted in a slightly higher conversion and higher selectivity for lactam **2** with a **2L**/**2B** ratio of 1. POP-xantphos is known to be a relatively good ligand for catalyzing the isomerization-hydroformylation tandem reaction of simple paraffinic alkenes yielding linear aldehydes when using lower syngas pressure (10 bar) and higher temperature (120 °C).[43-46] Application of this ligand at 100 or 120 °C in the hydroformylation of 3-PA resulted in ~50% selectivity to the unsaturated lactams **2** of which about 60-65% is the unsaturated 7-membered ring **2L** (Entries 3, 4). At 120 ºC good conversion is reached, however, a larger amount of valeramide (VA) is formed which can be explained by chelate formation of the Rh-sec-alkylamide (see below). Application of an even lower pressure of 5 bar syngas does not further improve these results (Entry 9), whereas at a higher reaction temperature of 130 °C the selectivity for **2** goes down in favor of the production of VA (Entry 6).

The use of a 1:1 mixture of 3-PA and 4-PA using the standard Rh/xantphos system resulted in approximately 50% conversion with ~70% selectivity to **2L**; however, it is clear that mainly reaction of 4-PA occurs (Entry 8). Application of the POP-xantphos system at lower pressure and higher temperature resulted in 80% conversion, the main product being **2** with 77% **2L** (Entry 9). Finally, using a mixture of pentenamides produced from GVL as the substrate gave ~80% conversion and revealed approximately 60% selectivity to **2** with ~75% overall selectivity for linear products (Entry 10, for more information Appendix IV, Table AIV.7).[47]

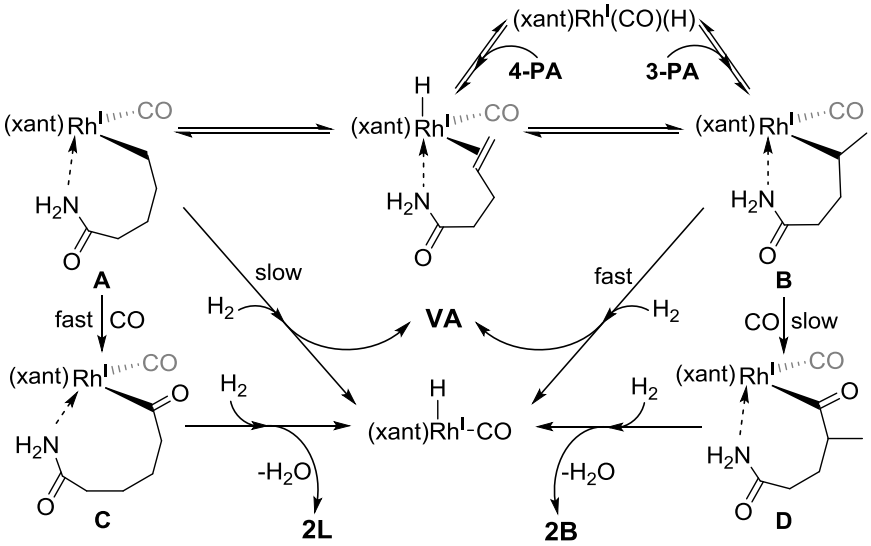
Table 5.4. Influence of various conditions on intramolecular hydroamidomethylation of pentenamides (PA)[a]



	substrate	Ligand	t	T	P(CO/H_2)	conv.	selectivity % [b]							L[d]
			h	°C	bar	%	**VA**	**Iso**[c]	**1**	**2**	**3**	**4**	**5**	%
1	3-PA	xantphos	8	100	50(1/2)	16	39	3	3	35	0	0	19	42
2	3-PA	xantphos	8	100	10(1/1)	19	18	3	0	53	0	0	26	48
3	3-PA	POP-xantphos	8	100	10(1/1)	20	20	17	0	47	1	0	15	59
4	3-PA	POP-xantphos	8	120	10(1/1)	86	32	2	2	53	2	0	9	66
5	3-PA	POP-xantphos	16	120	10(1/1)	100	34	2	2	51	1	0	11	65
6	3-PA	POP-xantphos	8	120	5(1/1)	82	29	6	2	54	0	0	9	63
7	3-PA	POP-xantphos	8	130	10(1/1)	92	42	2	2	42	0	0	12	68
8[e]	3-PA&4-PA	xantphos	8	100	50(1/2)	52	15	0	5	72	4	0	4	95
9[e]	3-PA&4-PA	POP-xantphos	8	120	10(1/1)	81	29	1	2	60	1	0	8	77
10[f	3-PA&4-PA	POP-xantphos	8	120	10(1/1)	83	31	0	2	58	2	0	8	73

[a] Reaction conditions: 2 mmol (19.8 mg) of 3-PA or 4-PA; 0.0025 mmol (1.24 mg) $[Rh(cod)Cl]_2$; 0.01 mmol ligand; P(CO/H_2)= 5-50(1/1-1/2) bar; T=100-130 °C; t=8-16 h; Solvent: 10 mL diglyme; [b] The amount of products was determined by GC analysis using undecane as an internal standard; [c] mixture of pentenamide isomers (containing minor amounts of 2-PA, 4-PA); [d] overall linearity of **1**, **2**, **3** & **4** determined by GC; [e] 3-PA and 4-PA (1 mmol each). [f] The mixture of 3-PA (1.5 mmol) and 4-PA (0.5 mmol) produced from GVL; the amounts of pentenamides was determined by injecting the mixture into GC before starting the reaction

It thus appears that the most challenging step in our synthetic route is the intramolecular hydroamidomethylation reaction starting from the mixture of pentenamides. Starting from 4-PA and using the xantphos/Rh catalytic system under 'hydroformylation' conditions results in the formation of the 7-membered unsaturated lactam **2L** in high yields. The use of rhodium systems without ligands or with ligands that do not induce high regioselectivity in hydroformylation of alkenes resulted in the formation of the 6-membered product **2B** as reported earlier,[41, 42] as well as **2L**, but also resulted in the hydrogenation of the substrate to valeramide (VA). Similarly, the use of 3-PA as a substrate resulted in a mixture of **2L** and **2B**, but with the formation of even larger amounts of VA. The formation of VA in the hydroamidomethylation reaction of pentenamides may be explained by the chelating nature of the pentenamide substrate.

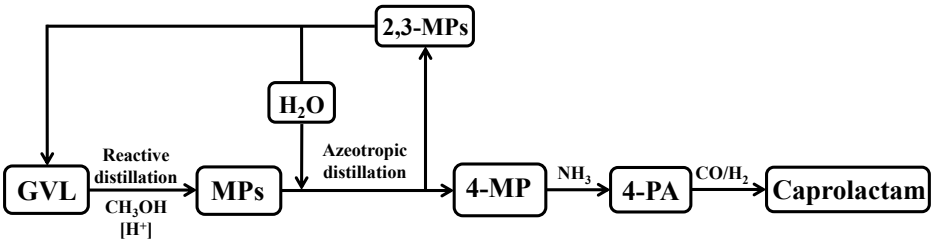


Scheme 5.5. Proposed mechanistic pathways toward the formation of various products

As depicted in scheme 5.5, coordination of 4-PA to a rhodium-hydride catalyst followed by hydride migration may either give the primary Rh-alkyl species **A** or the secondary Rh-alkyl species **B**. Both species may be further stabilized by the coordination of the amide group thus forming a 7-membered or 6-membered chelate ring, respectively.

Reaction of 3-PA with the Rh-hydride will also result in species **B** but possibly also the other isomeric secondary Rh-alkyl species; the latter may be less likely due to the more strained 5-membered chelate ring, which is in agreement with the fact that the 5-membered lactam product was not observed in our reactions. Migratory insertion of the primary Rh-alkylamide structure **A** to CO will give Rh-acyl species **C**, subsequent hydrogenolysis results in the formation of the linear aldehyde, which cyclizes to **2L**. 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, the hydrogenolysis rate of the Rh-alkyl species **B** may be promoted due to the relatively strong chelation of the amide functionality, resulting in the formation of VA.

Hence, the limiting factor that needs further research is the development of a catalyst that is able to isomerize rapidly the internal alkenes 2-PA and 3-PA to the terminal alkene 4-PA prior to hydroformylation, before hydrogenolysis of the secondary Rh-alkyl species occurs, which leads to the formation of VA.



Scheme 5.6. A Schematic outlook for the formation of caprolactam

It has been reported that GVL can be converted into 4-MP with higher selectivity (60%) using basic heterogeneous catalysts ($CsOAc/SiO_2$) at a very high temperature (350 °C),[48] but even if an efficient tandem hydroformylation-reductive amidation catalytic system with the desired additional attributes of i) high alkene isomerization-hydroformylation activity and ii) at the same time inhibiting hydrogenation of in particular the 2- and 3-PA isomers cannot be achieved, it may still be attractive to use the present Rh/xantphos catalyst system allowing close to 90% selective conversion of 4-PA only to caprolactam. In such instance isomerization/separation techniques to separate 4-MP from the mixture of 2-, 3- and 4-MPs generated via reactive distillation

by selective azeotropic distillation of 4-MP[49] with continuous recycle of the other isomers to the reactive distillation section can be advantageously undertaken (Scheme 5.6).

In conclusion, we have proposed and developed a novel reaction scheme for the atom-economic conversion of γ-valerolactone into the important polymer precursor ε-caprolactam. GVL, which may be prepared from bio-based levulinic acid, can be converted in two steps with high yields into a mixture of pentenamides via reactive distillation of GVL to methyl pentenoates and subsequent aminolysis using aqueous ammonia.

5.3. Experimental

5.3.1. General

The stainless steel autoclave reactors (100 ml) were of HEL Limited, UK, equipped with magnetic stirrer, pressure transducer and temperature controlling thermocouple. A Hewlett Packard HP6890 Series auto-sampler GC system was used for regular GC analysis. GC-MS analysis were carried out on an Agilent technologies 7820A GC system series coupled with an Agilent technologies 5975 series GC-MSD system. A glovebox of M. Braun Inert gas-System GmbH, Germany, was used for storing and handling of air-sensitive phosphane ligands. Nuclear magnetic resonance spectra were recorded on a Bruker DPX300 (300MHz) or a Bruker DMX400 (400MHz) spectrometer. A Syringe Pump NE1000 series auto-injector from ProSense B. V. (laboratory and process Equipment Company) was used for the reactive distillation pumping methanol continuously into the reaction mixture. Innovative Technologies PureSolv MD 5 Solvent Purification System was used for drying solvents. All reaction preparations and manipulations were performed using standard Schlenk techniques under an argon atmosphere. The catalytic reactions were carried out under varying syngas pressures and reaction temperatures.

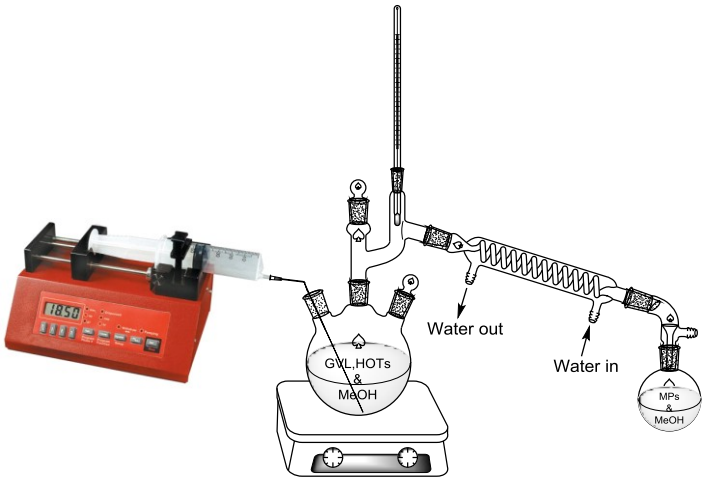
5.3.2. Chemicals

The solvent bis(2-methoxyethyl)ether (diglyme) was distilled from CaH_2, deoxygenated and used immediately after the purification process. All other solvents were purged with argon and purified under pressure of dry argon using an Innovative Technologies purification system. The solvents passed through activated columns under low pressure to remove trace impurities. Stainless Steel Schlenk Vacuum line and Sigma Aldrich Air-free flasks allow them to be safely transferred.

3-Pentenoic acid, 4-pentenoic acid, methy-3-pentenoate, gamma valerolactone, valeramide, caprolactam, methanolic ammonia (7N), ammonia gas cylinder, aqueous ammonia (35%), decane (internal standard), undecane (internal standard), para-toluenesulfonic acid (HOTs), trifluoromethanesulfonic acid (HOTf), sulfuric acid, bis(2-methoxyethyl) ether (diglyme), 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HOR^F) methanol, ethanol and other solvents, acids and bases were purchased from Acros Organics and Sigma Aldrich, the Netherlands and used as received. The rhodium precursors (acetylacetonato)dicarbonylrhodium(I), chlorido(1,5-cyclooctadiene)rhodium(I) dimer, bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate, were purchased from Acros Organics and Sigma Aldrich, the Netherlands and used as received. The phosphane ligands triphenylphosphane (PPh_3), Tris(2,4-ditert-butylphenyl)phosphite ($P(O\text{-di-tBu-Ph})_3$), 9,9-dimethyl-4,5-bis(diphenyl-phosphanyl)xanthene (xantphos), xantamidite and xantphite were purchased from Strem Chemicals, Germany and Sigma Aldrich, the Netherlands and used as received. The bidentate phosphane ligands benzoxantphos, and POP-xantphos were purchased from Innovative Catalyst Technologies (InCatT B.V.), The Netherlands and used as received. The phosphane ligands tetraphos, Bryant-5 and naphthol-3 were generously provided by DSM, The Netherlands and used as received. The other phosphane ligands such as diphenyl(2-pyridyl)phosphane (PPh_2Py), bis(di-tert-butylphosphino)-o-xylene (dtbpox), 2,7-di-tert-butyl-9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene (tBu-xantphos), 4,6-bis(diphenylphosphanyl)-10,10-dimethyl-10H-dibenzo[b,e][1,4]oxasilane (Si-xantphos), 9,9-dimethyl-4,5-bis(di-orthomethoxyphenyl-phosphanyl)xanthene (oMeO-xantphos), 9,9-dimethyl-4,5-bis(di-paramethoxyphenyl-phosphanyl)xanthene (pMeO-xantphos) and 4,5-bis(di(tert-butyl)phosphanyl)-9,9-dimethylxanthene ($xantphos(tBu)_2$) were generously provided by Shell Global Solutions Amsterdam b.v., The Netherlands and used as received.

5.3.3. Catalytic Reactive Distillation of methyl pentenoates

The reaction was performed in a 100 mL three-necked round bottom flask loaded with GVL (9.5 mL, 100 mmol) and acid catalyst (1 – 10 mmol) were dissolved in 10 mL of MeOH. The flask was connected to a micro distillation device which was connected to a 100 mL round bottom flask used as a receiver. The receiver flask was cooled down with liquid N_2. The solution was heated to a set temperature, 150 °C- 200 °C for 4-8 h. During this time MeOH was added to the bottom of the reactor flask at a rate of 10 mL/h. After a specified time, the contents of both the reactor flask and the receiver were analyzed by GC adding decane (2.5 mmol, 0.487 mL; 250 mM in 10 mL volumetric flask) as an external standard.



The reactor flask generally yielded a yellowish clear solution that contained a mixture of unreacted gamma valerolactone (GVL), methyl 4-hydroxypentenoate (4-HMP) and methyl 4-methoxypentenoate (4-MMP) intermediates, methyl 2-pentenoate (2-MP), methyl 3-pentenoate (3-MP), methyl 4-pentenoate (4-MP), and methyl para-toluenesulfonate. The receiver flask contained a clear colorless solution that was found to be a mixture of MeOH, water, 4-MP, 3-MP followed by traces of 2-MP and GVL.

5.3.4. Aminolysis of methyl pentenoates to pentenamides

5.3.4.1. In methanolic ammonia

The reaction was carried out in a 50 mL round bottom flask loaded with 5 mL of a methyl pentenoates solution in MeOH (0.9 M, a distillate from a reactive distillation experiment, concentration determined through GC calibration lines, 4.5 mmol total MP, (in approximate 3:1 ratio of 3-MP:4-MP, with traces of GVL; thus containing ~3.4 mmol 3-MP and ~1.1 mmol 4-MP) or methyl pentenoates (10 mmol, 1.14 g, ~3:1 ratio of 3-MP:4-MP, after evaporation of MeOH), NH_3 (7N) in MeOH (5 or 10 equivalent) and (1.2 mmol, 0.254 mL) undecane as an internal standard were mixed and stirred for different times at various temperatures between RT to 100 °C. After the experiment, the reaction mixture was taken and at once analyzed by gas chromatography. Calibration lines for each analyte were used in determining the yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

5.3.4.2. With ammonia gas

The reaction was carried out in a 300 mL autoclave reactor loaded with methyl pentenoates (MP) (10 mmol, 1.14 g) (after evaporation of MeOH) and (1.2 mmol, 0.254 mL) undecane as an internal standard. The autoclave was then tightly closed and subsequently filled with 6 bar of NH_3 (g) (~75 mmol) and stirred for different time and various temperatures between RT to 80 °C. After the experiment, 5 ml of dried and degassed solvent (diglyme or methanol) was added to the reaction mixture and this was then analyzed by gas chromatography. Calibration lines for each analyte were used in determining the yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

5.3.4.3. In aqueous ammonia (35%)

The reaction was carried out in a 50 mL round bottom flask loaded with methyl pentenoates (10 mmol, 1.14 g) (after evaporation of MeOH), aqueous ammonia 35% (50 mmol, 2.42 mL) and (1.2 mmol, 0.254 mL) undecane as an internal standard were mixed and stirred for 5-6 hours at various temperature between RT to 100 °C. After experiment, the reaction mixture was taken and at once analyzed by gas chromatography. Calibration lines for each analyte were used in determining the yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

5.3.5. Catalytic high pressure reaction

5.3.5.1. Catalytic intramolecualr hydroamidomethylation of pentenamides

For all the catalytic experiments the active catalyst precursor was formed by in-situ in the autoclave by transferring the 0.005 mmol of rhodium precursor as a metal and the 0.01 mmol of selected bidentate phosphane ligand or 0.02 mmol of selected mono-dentate phosphane ligand. In the preparation of the catalytic reaction mixture a rhodium precursors $[Rh(cod)Cl]_2$ (0.0025 mmol, 1.24 mg) and phosphane ligand for instance xantphos (0.01 mmol, 5.79 mg) were weighed and transferred into an autoclave. Next, the substrates 3-pentenamide or 4-pentenamide or mixture of pentenamides (2 mmol, 198 mg) were weighed and transferred into an autoclave. The autoclave was tightly closed and subsequently filled with argon with use of a Schlenk line that was connected to one of the valves of the autoclave. Through another valve under a continuous flow of argon subsequently was added 10 mL of dried and degassed solvent diglyme (or in some cases 8 mL of dried and degassed diglyme, 2 mL of HOR^F) and (1.2 mmol, 0.254 mL) undecane as an internal standard (and in some cases followed by 0.05 mmol (9.51 mg) or 0.025 mmol

(4.76 mg) HOTs). Then the reactor was inserted into the heating block and pressurized with 50 bar (CO/H_2=1/2) syngas. This reaction mixture was stirred at 500 rpm for 30 min to ensure that complex formation was complete. The reaction mixture was heated up to 100 °C (within 30 min) under stirring at 500 rpm. All reaction conditions of the catalytic process were controlled by computerized software panels. After standing for eight hours at this temperature, the autoclave was cooled down to room temperature over about one hour. The autoclave was then slowly vented to atmospheric pressure.

In a semi-one-pot reaction after depressurizing syngas and flushing with di-hydrogen gas, the reactor was pressurized with 50 - 100 bar di-hydrogen gas and then the reaction mixture heated up to 50 - 100 °C under stirring at 500 rpm for hydrogenation step. After standing for four - six hours at this temperature, the autoclave was cooled down to room temperature and then slowly vented to atmospheric pressure. After each catalytic run the reaction mixture was taken from the reactor and at once analyzed by gas chromatography. Calibration lines for each analyte were used in determining the conversion of the substrates and yields of the various products. The assignments of the products were confirmed with GC-MS and comparison with authentic and pure commercial samples.

5.3.6. Synthesis of Intermediates

5.3.6.1. Synthesis of 3-pentenamide[50-54]

Following the reported procedure, thionyl chloride (8.7 ml, 120 mmol) was added drop wise to *trans*-3-pentenoic acid (10 ml, 100 mmol) at 0 °C and the mixture was stirred at RT for 10 min and at 60 °C for 30 min. The excess thionyl chloride was evaporated and the oil was dissolved in 20 ml CH_2Cl_2. This solution was added drop wise to a solution of 7 N NH_3 in MeOH (150 ml, 1.0 mol) at 0 °C and stirred for 10 minutes at room temperature. The solvents were evaporated. Water (50 ml) was added and was extracted 2 times with 50 ml CH_2Cl_2. The combined organic layers were washed with 50 ml brine, dried over $MgSO_4$ and the solvents were removed *in vacuo* to give a white powder. Yield 7.93 g, 80%. ^{1}H-NMR ($CDCl_3$): δ = 6.65 and 5.99 (br s, 2x 1H, NH_2), 5.70-5.49 (m, 2H, 2 x CH), 2.96 (d, 2H, CH_2), 1.70 (m, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ = 175.2 ($CONH_2$), 130.8 and 123.5 (2 x CH), 39.8 (CH_2), 17.9 (CH_3).

5.3.6.2. Synthesis of 4-pentenamide

The synthesis of 4-pentenamide was performed in a similar fashion as in 3-pentenamide starting from 4-pentenoic acid (15 ml, 150 mmol), thionyl chloride (13 ml, 180 mmol) and 200 ml 7 N NH_3 solution in MeOH. The yield was 13.6 g of a white powder (92%). ^{1}H-NMR ($CDCl_3$): δ = 5.91-5.78 (m, 1H, CH), 6.0 and 5.7 (br s, 2 x 1H, NH_2), 5.13-5.02 (m,

2H, CH_2=CH), 2.44-2.30 (m, 4H, 2 x CH_2). ^{13}C-NMR ($CDCl_3$): δ = 175.6 ($CONH_2$), 136.9 (CH), 115.7 (CH_2=CH), 35.1 and 29.4 (2 x CH_2).

5.3.6.3. Synthesis of methyl 4-methoxypentenoate

According to a literature procedure,[55] GVL (4.8 mL, 50 mmol) and trimethyl orthoformate (8.2 mL, 75 mmol) were dissolved in 50 ml of MeOH. 0.1 mL of sulfuric acid was added and the mixture was stirred at 50 °C for 3 h and stirred overnight at room temperature. Trimethyl orthoformate (1 mL, 10 mmol) was added and the solution heated to 50 °C for 6.5 h. The solvents were removed in vacuo and a saturated $NaHCO_3$ solution was added. The solution was extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$, then filtered and the solvents were removed. ^{1}H NMR (300 MHz $CDCl_3$, 25 °C, TMS): δ 3.7 ppm (s, 3H; $OCOCH_3$), 3.4 ppm (q, 1H; CH), 3.3 ppm (s, 3H; $CHOCH_3$), 2.4 ppm (t, 2H; CH_2CO), 1.8 ppm (q, 2H; $CHCH_2$), 1.2 ppm (d, 3H; CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ 76.0 ppm(CH), 56.1 ppm (CH_3OCO), 51.6 ppm (CH_3OCH), 31.3 ppm (CH_2CH), 30.0 (CH_2CO), 18.9 ppm (CH_3).

5.3.7. GC and GC-MS analysis

A GC trace of typical **reactive distillation of methyl pentenoates** (MP) is shown in the Appendix IV, Figure AIV.1 and AIV.2 with the assignment of products. 1 µL Crude reaction mixture containing external standard (decane; 2.5 mmol, 0.487 mL; 250 mM in 10 mL volumetric flask) was injected into a Hewlett Packard HP6890 Series auto-sampler GC system with column HP-1MS UI (30m*0.250mm*1.00µm). All the solvents have been assigned by comparing to their standard GC spectra. All the retention values of substrate and product to decane have been determined using commercially available or isolated standard chemicals. More detailed information about heavy-ends is shown in Appendix IV.

Analysis conditions: 130 ºC (5 min), ramp 50 ºC / min to 300 ºC, 300 ºC (3.6 min) (12 min in total).

A GC trace of typical **aminolysis of methyl pentenoates** (MP) to pentenamides (PA) is shown in Appendix IV Figure AIV.3 and AIV.4 with the assignment of products. 1 µL Crude reaction mixture containing internal standard (undecane; 1.2 mmol, 0.254 mL) was injected into a Hewlett Packard HP6890 Series auto-sampler GC system with column HP-1MS UI (30m*0.250mm*1.00µm). All the solvents have been assigned by comparing to their standard GC spectra. All the retention values of substrate and product to undecane have been determined using commercially available or isolated standard chemicals. More detailed information about heavy-ends is shown in Appendix IV.

Analysis conditions: 130 ºC (5 min), ramp 50 ºC / min to 300 ºC, 300 ºC (3.6 min) (12 min in total).

A GC trace of typical **hydroamidomethylation of pentenamides** is shown in Appendix IV Figure AIV.5, AIV.6, AIV.7, AIV.9 and AIV.10 with the assignment of products. 1 µL Crude reaction mixture containing internal standard (undecane; 1.2 mmol, 0.254 mL) was injected into a Hewlett Packard HP6890 Series auto-sampler GC system with column HP-1MS UI (30m*0.250mm*1.00µm). All the solvents have been assigned by comparing to their standard GC spectra. All the retention values of substrate and product to undecane have been determined using commercially available or isolated standard chemicals. More detailed information about heavy-ends is shown in Appendix IV.

Analysis conditions: 160 °C (3.3 min), ramp 30 °C / min to 300 °C, 300 °C (4 min) (12 min in total).

GC-MS Method: 1 µL Crude reaction mixture containing internal standard was injected into a GC HP7820 Series auto-sampler GC system with column DB-5MS UI (30m*0.250mm*1.00µm) equipped with MSD 5975 Agilent series. All the solvents have been ignored by comparing to their standard GC spectra. All the retention values of substrate and product to decane or undecane have been determined using commercially available or isolated standard chemicals.

Analysis conditions: 100 °C (2.5 min), 20 °C / min to 250 °C, 250 °C (5 min) (15 min in total).

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6

Summary, Conclusions and Outlook

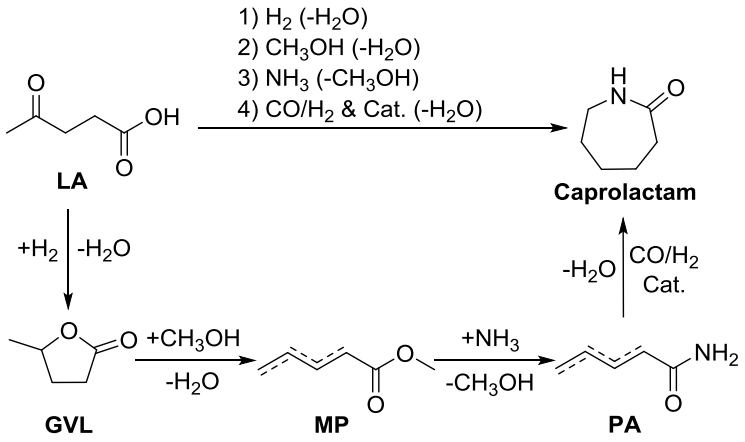
6.1. Summary

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.

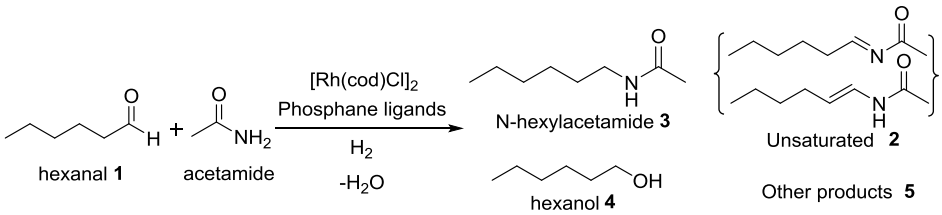
The aim of the research described in this thesis is to introduce a new synthetic route to obtain caprolactam starting from γ-valerolactone (GVL), a compound that can be produced from bio-based levulinic acid. The proposed route proceeds via the acid-catalyzed reactive distillation of GVL with methanol 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**.

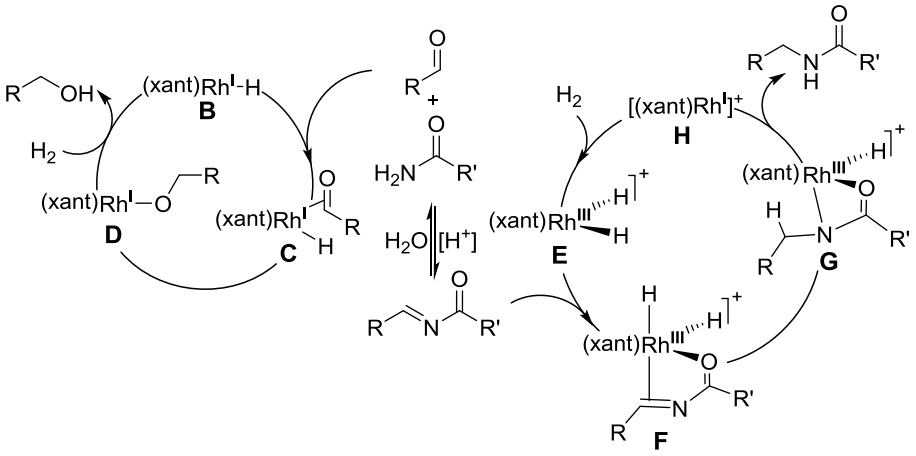


Scheme 6.2. Reductive amidation of hexanal with acetamide: observed products

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.



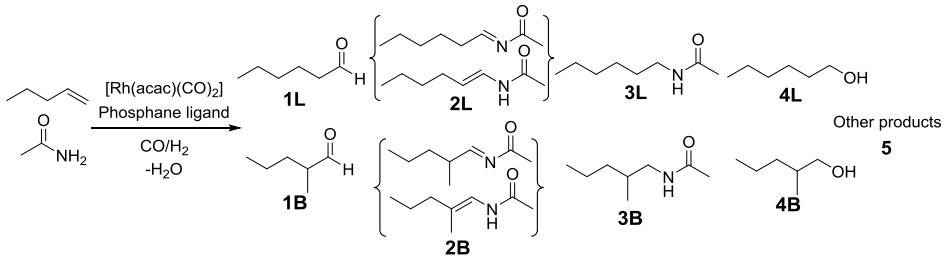
Scheme 6.3. Proposed catalytic cycle for the hydrogenation of aldehyde versus unsaturated imido intermediates

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

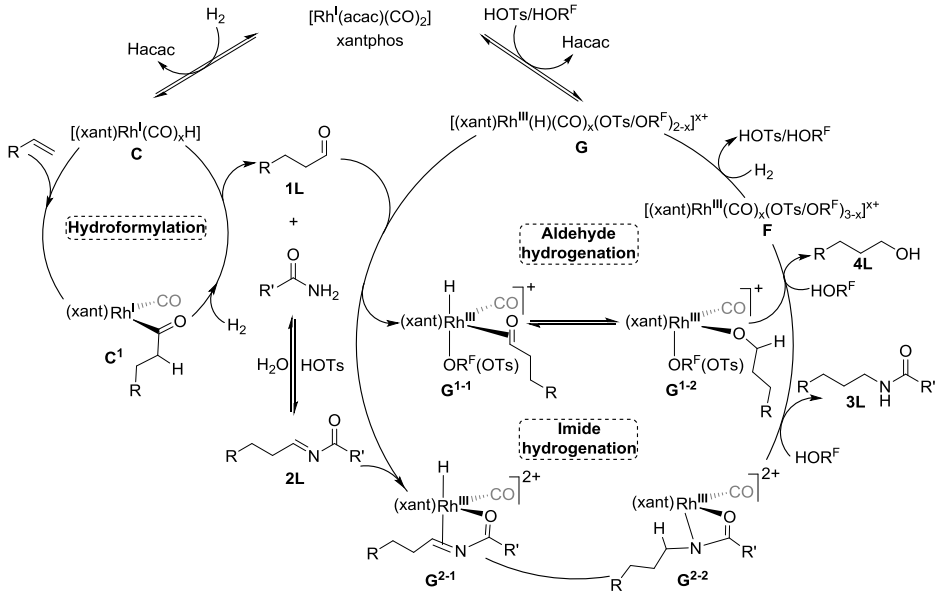
conditions nearly full alkene conversion can be achieved with more than 80% selectivity to the product N-hexylacetamide. Interestingly, in the presence of a high concentration of HOR^F (HOR^F/diglyme ~5/1 (v/v)) the same catalyst system shows a remarkably high selectivity (~90%) for the formation of 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.



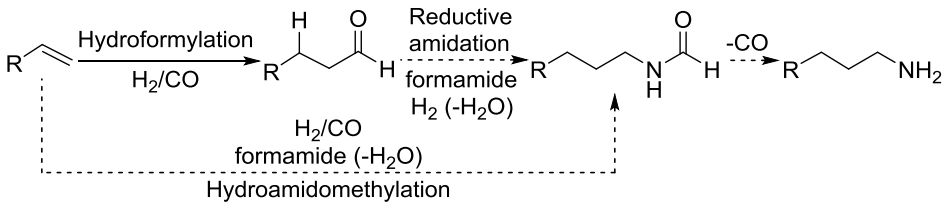
Scheme 6.5. Proposed overall mechanism for hydroamidomethylation of 1-alkenes

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

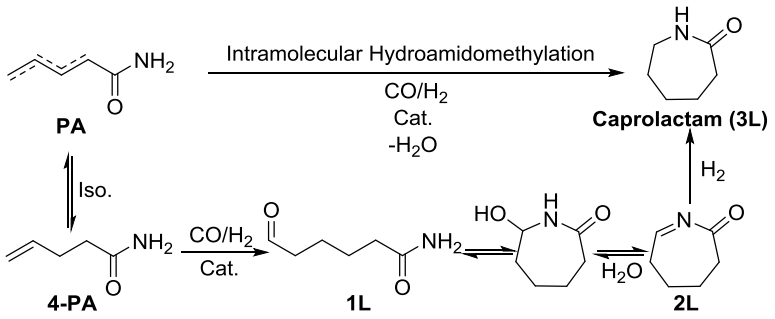
In comparison with the reductive amidation with acetamide, to achieve similar catalytic performance of the Rh/xantphos catalyst system with formamide, the amount of HOTs needed to be increased. Under these conditions, the selectivity for N-hexylformamide **3** over hexanol **4** was spectacularly increased (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.

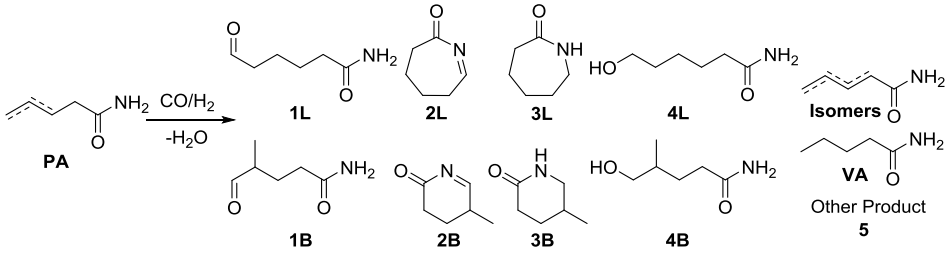
The mixture of methylpentenoates was subsequently converted into a mixture of the corresponding pentenamides (PA). It appeared that the use of ammonium hydroxide

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).

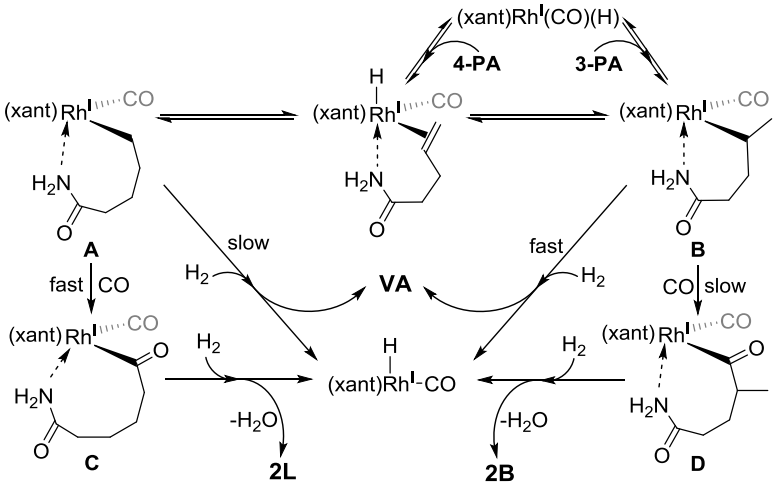


Scheme 6.8. Intramolecular hydroamidomethylation of the mixture of 3-PA and 4-PA to caprolactam: observed intermediates, products and undesired by-products

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.

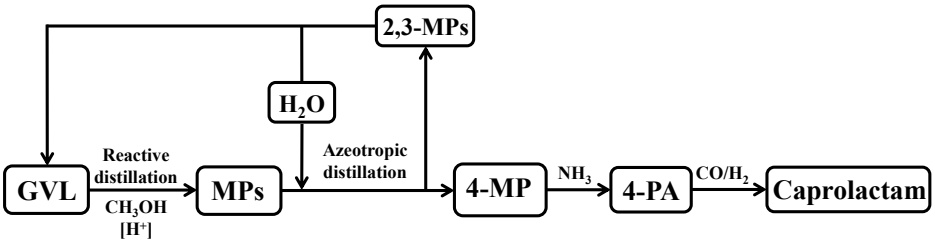
6.2.2.2. Bio-based caprolactam

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**.

Appendix I

Supporting Information of Chapter 2:

Rhodium-Catalyzed Homogeneous Reductive Amidation of Aldehydes

Full analytical data of catalytic experiments

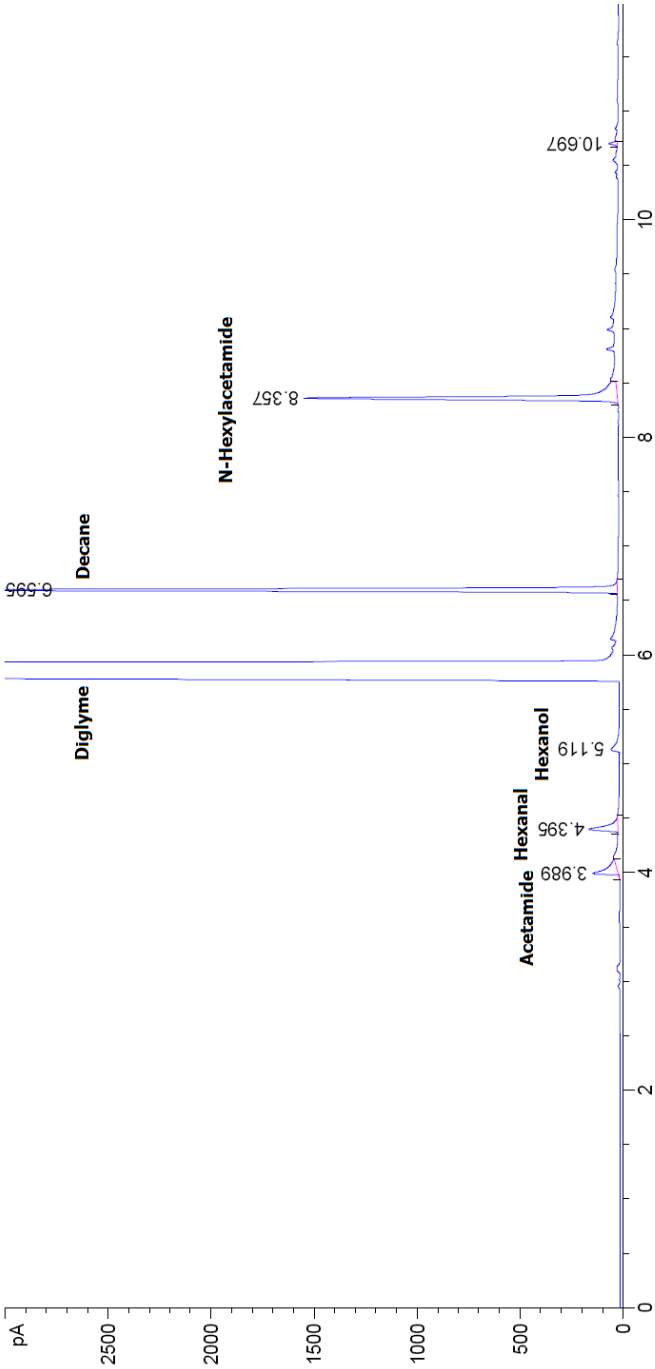
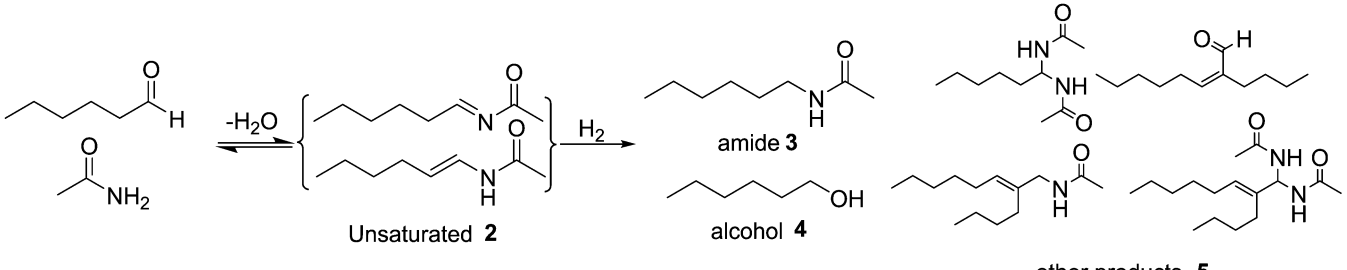


Figure AI.1. GC spectrum of reductive amidation reaction of hexanal with acetamide in the presence of HOTs: (Rh:xantphos:HOTs:hexanal:acetmide =1:1.25:5:500:600); P_{H2}=80 bar; T=80 °C; t=4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.1. Reductive amidation of hexanal with acetamide using different rhodium precursors[a]



	Metal	Hexanal **1** mmol		**3** mmol		**2** mmol		**4** mmol		**5** mmol		Conversion %		**2** selectivity %		**3/4** ratio		**3+4** selectivity %		**3** selectivity %	
		2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h
1	$[Rh(cod)Cl]_2$	3.0	2.2	0.4	0.8	1.0	1.0	0.0	0.1	0.5	1.0	22	28	40	56	12.9	14.7	23	30	52	35
2	$[Rh(CO)_2(acac)]$	4.0	3.7	0.0	0.1	0.5	0.5	0.0	0.0	0.5	0.6	19	25	48	42	0.0	3.1	2	12	0	9
3	$[Rh(cod)_2]BF_4$	3.4	2.7	0.3	0.7	0.8	0.7	0.2	0.4	0.4	0.6	33	47	46	29	1.3	1.9	29	46	16	30
4	$RhCl_3.xH_2O$	2.7	2.3	0.3	0.5	0.8	0.8	0.0	0.1	1.1	1.4	46	53	36	29	12.3	8.7	15	20	14	18
5	$Rh(CO)(H)(PPh_3)_2$	4.0	3.7	0.0	0.0	0.1	0.1	0.6	0.8	0.4	0.5	21	27	8	6	0.0	0.0	56	57	0	0
6	$[Rh(cod)_2]OTf$	3.0	2.1	0.6	1.2	0.6	0.5	0.2	0.4	0.6	0.8	41	58	29	16	2.5	2.7	42	54	30	40

[a] Reaction conditions: 0.01 mmol Rh precursor, 5 mmol hexanal, 6 mmol acetamide (Rh:L:hexanal:acetamide=1:1.25:500:600); P_{H2}=80 bar; T=100 °C; t= 2-4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.2. Reductive amidation of hexanal with acetamide catalyzed by $[Rh(cod)Cl]_2$ in combination with different ligands[a]

	Ligand	Temp. °C	HOTs mmol	Hexanal mmol		**3** mmol		**2** mmol		**4** mmol		**5** mmol		**3** selectivity %		Conversion %		**3/4** ratio		**3+4** selectivity %		**2** selectivity %	
				2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h
1	no	100		3.0	2.2	0.4	0.8	1.0	1.0	0.0	0.1	0.5	1.0	22	28	40	56	12.9	14.7	23	30	52	35
2	no	100	0.05	1.7	1.0	0.8	1.0	0.7	0.6	0.2	0.2	1.6	2.2	24	24	66	80	4.9	4.3	29	30	21	15
3	PPh_3	100		4.6	4.3	0.0	0.0	0.2	0.4	0.0	0.0	0.2	0.3	0	0	9	14	0.0	0.0	9	6	52	57
4	PPh_3	100	0.05	1.6	1.0	0.3	0.3	0.8	0.6	0.2	0.3	2.0	2.7	9	8	67	79	1.3	1.0	16	16	24	16
5	$P(nBu)_3$	100		4.2	3.2	0.0	0.0	0.0	0.0	0.6	1.4	0.2	0.4	0	0	17	36	0.0	0.0	71	78	0	0
6	$P(nBu)_3$	100	0.05	3.6	2.4	0.2	0.4	0.0	0.0	0.8	1.5	0.4	0.7	14	15	28	52	0.3	0.3	71	73	0	0
7	$P(O\text{-di-tBu-Ph})_3$	100		4.4	3.8	0.2	0.5	0.1	0.1	0.1	0.2	0.2	0.4	33	42	12	24	2.0	2.5	50	58	17	8
8	$P(O\text{-di-tBu-Ph})_3$	100	0.05	1.9	1.1	1.1	1.6	0.1	0.1	0.0	0.1	1.9	2.1	34	41	62	78	21.2	20.0	36	43	2	3
9	$P(nBu)(1\text{-ad})_2$	100		4.2	3.6	0.3	0.7	0.1	0.1	0.2	0.3	0.2	0.3	38	50	15	28	1.5	2.3	64	71	7	7
10	$P(nBu)(1\text{-ad})_2$	100	0.05	1.8	0.9	0.9	1.3	0.3	0.1	0.3	0.2	1.8	2.5	28	32	65	82	3.5	6.5	36	37	9	2
11	dppe	100		4.3	4.0	0.1	0.1	0.1	0.2	0.3	0.4	0.3	0.3	8	13	15	21	0.2	0.4	43	49	18	21
12	dppe	100	0.05	2.1	1.3	0.5	0.8	0.3	0.2	0.0	0.1	2.1	2.6	18	20	58	73	11.4	10.7	19	22	9	7
13	dppp	100		2.8	2.3	0.4	0.5	0.9	1.1	0.7	0.8	0.3	0.3	17	18	44	55	0.6	0.6	48	47	40	42
14	dppp	100	0.05	1.8	1.0	0.6	1.0	0.3	0.2	0.3	0.5	2.0	2.3	20	24	65	80	2.0	1.9	30	37	9	5
15	dirc-2	100		0.7	0.0	0.0	0.0	0.0	0.0	4.2	4.6	0.1	0.4	0	0	87	100	0.0	0.0	97	92	0	0
16	dirc-2	100	0.05	0.4	0.0	0.0	0.0	0.0	0.0	3.8	3.9	0.9	1.1	0	0	93	100	0.0	0.0	81	78	0	0
17	1,2-dppmb	100		3.1	2.7	0.4	0.7	1.1	0.8	0.1	0.1	0.4	0.7	21	31	38	47	5.5	7.6	25	35	55	34
18	1,2-dppmb	100	0.05	1.9	1.2	0.8	1.2	0.7	0.5	0.2	0.2	1.5	1.9	25	31	63	75	4.5	5.3	31	36	21	13
19	1,3dppmb	100		3.3	2.6	0.5	0.7	0.7	0.9	0.0	0.1	0.5	0.7	29	31	35	48	15.0	14.4	31	33	39	37
20	1,3dppmb	100	0.05	1.9	1.1	0.6	0.8	0.8	0.7	0.0	0.0	1.6	2.3	21	21	61	78	18.8	18.1	22	22	25	18
21	dppf	100		3.2	2.3	0.4	1.2	0.5	0.4	0.7	0.8	0.2	0.3	22	45	37	53	0.6	1.5	58	74	29	14
22	dppf	100	0.05	1.4	0.6	1.4	2.0	0.3	0.2	0.6	0.7	1.2	1.6	40	45	72	89	2.3	3.0	58	60	10	5
23	bisbi	100		2.5	1.8	0.2	0.4	0.9	1.1	0.8	0.9	0.4	0.8	10	11	49	64	0.3	0.4	44	40	38	35
24	bisbi	100	0.05	1.7	0.9	0.6	0.9	0.7	0.5	0.7	0.8	1.3	1.8	19	23	67	81	0.9	1.1	41	43	20	12
25	xantphos	100		1.7	0.9	0.7	0.9	0.0	0.1	2.2	2.6	0.4	0.5	22	22	66	82	0.3	0.3	88	85	0	2
26	xantphos	100	0.05	1.6	0.5	2.6	3.5	0.0	0.0	0.2	0.2	0.6	0.8	77	78	69	90	16.5	17.5	82	82	0	0
27	xantphos	80	0.05	1.7	0.8	2.7	3.7	0.1	0.0	0.1	0.2	0.3	0.3	84	88	65	84	19.6	20.6	88	93	3	1

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol acetamide (Rh:L:hexanal:acetamide=1:1.25(bi-dentate) or 2.5(mono-dentate):500:600); P_{H2}=80 bar; T=80-100 °C; *t*=2-4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.3. The effect of Rh/xantphos ratio on the reductive amidation of hexanal with acetamide [a]

	Rh/L ratio	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5**(mmol) **5a**	**5b**	**3** selectivity%	Conversion %	**3/4** ratio	**3+4** selectivity %
1	1/1	0.9	3.5	0.0	0.2	0.2	0.2	85	82	17.5	90
2	1/1.25	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93
3	1/1.5	1.2	3.0	0.0	0.1	0.4	0.3	78	76	21.4	82
4	1/2	1.3	2.9	0.0	0.1	0.4	0.3	78	74	22.3	81
5	1/3	1.5	2.7	0.0	0.1	0.4	0.3	77	70	22.5	80

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol acetamide (Rh:hexanal:acetamide=1:500:600);HOTs (0.05mmol); P_{H2}=80 bar; T=80 °C; t=4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.4. The effect of different acetamide/hexanal ratios on the results of reductive amidation reaction using the Rh/xantphos/H^+ catalytic system [a]

	acetamide/hexanal Molar ratio	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5** (mmol) **5a**	**5b**	**3** selectivity %	Conversion %	**3/4** ratio	**3+4** selectivity %
1	1	1.4	2.9	0.0	0.3	0.3	0.1	81	72	9.7	89
2	1.2	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93
3	1.5	0.8	3.5	0.2	0.2	0.2	0.1	83	84	17.5	88
5	2	0.7	3.0	0.4	0.2	0.2	0.5	70	86	15.0	74

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 5-10 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide=1:1.25:5:500:500-1000); P_{H2}=80 bar; T=80 °C; t=4 h; Solvent: 25 ml diglyme.

Table AI.5. Reductive amidation reaction of hexanal with acetamide catalyzed by $[Rh(cod)Cl]_2$ in combination with xantphos ligands in different solvents[a]

	Solvent	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5**(mmol) **5a**	**5b**	**3** selectivity %	Conversion %	**3/4** ratio	**3+4** selectivity %
1	Diglyme	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93
2	THF	1.0	3.2	0.0	0.3	0.3	0.2	80	80	10.7	88
3	MeOH	0.0	0.0	0.0	0.2	4.8[b]		0	100	0.0	4
4	Toluene	0.7	2.6	0.1	0.7	0.6	0.3	61	86	4.0	76
5	Mesitylene	0.8	2.5	0.1	0.4	0.8	0.4	59	84	5.6	69
6	DCM	1.5	2.0	0.1	0.3	0.7	0.4	57	70	6.7	66
7	NMP	1.8	1.5	0.6[c]	0.4	0.4	0.2	48	64	3.8	61

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide =1:1.25:5:500:600); P_{H2}=80 bar; T=80 °C; t=4h; Solvent: 25 ml. [b] 4.8 mmol other products: acetal (4.4 mmol), hemiacetal (0.1 mmol). [c] ~0.6 mmol unsaturated intermediates **2** imide (45%), enamide (55%).

Table AI.6. The effect of different reaction temperatures on product distribution in the reductive amidation reaction using the Rh/xantphos/HOTs catalytic system[a]

	Temperature °C	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5** (mmol) **5a**	**5b**	**3** selectivity %	Conversion %	**3/4**	**3+4** selectivity %
1	20	3.4	0.5	0.4	0.1	0.4	0.2	31	32	5.0	38
2	40	2.9	0.9	0.3	0.1	0.5	0.3	43	42	9.0	48
3	60	1.4	2.7	0.1	0.1	0.4	0.3	74	72	19.3	78
4	80	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93
5	100	0.5	3.6	0.0	0.2	0.4	0.3	80	90	18.0	84
6	120	0.2	3.5	0.0	0.3	0.7	0.4	72	96	14.0	77

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide= 1:1.25:5:500:600); P_{H2}=80 bar; t=4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.7. The effect of dihydrogen pressure on the reductive amidation catalyzed by the Rh/xantphos/HOTs system[a]

	Pressure bar	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5** (mmol) **5a**	**5b**	**3** selectivity %	Conversion %	**3**//**4**	**3**+**4** selectivity %
1	20	2.2	1.5	0.3	0.1	0.5	0.4	54	56	15.0	57
2	40	1.6	2.5	0.2	0.1	0.4	0.2	73	68	20.8	77
3	60	1.2	3.1	0.1	0.1	0.3	0.2	81	76	21.1	84
4	80	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93
5	100	0.7	3.7	0.0	0.2	0.3	0.1	86	86	19.5	91

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide=1:1.25:5:500:600); T=80 °C; t=4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.8. Reductive amidation of hexanal with acetamide catalyzed by $[Rh(cod)Cl]_2$ in combination with different xantphos-type ligands[a]

	Ligand	Temp. °C	Additive 0.05 mmol	Hexanal mmol		**3** mmol		**2** mmol		**4** mmol		**5** mmol		**3** selectivity %		Conversion %		**3/4**		**3+4** selectivity %		**2** selectivity %	
				2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h	2h	4h
1	xantphos	100		1.7	0.9	0.7	0.9	0.0	0.1	2.2	2.6	0.4	0.5	22	22	66	82	0.3	0.3	88	85	0	2
2	xantphos	100	HOTs	1.6	0.5	2.6	3.5	0.0	0.0	0.2	0.2	0.6	0.8	77	78	69	90	16.5	17.5	82	82	0	0
3	xantphos	80	HOTs	1.7	0.8	2.7	3.7	0.1	0.0	0.1	0.2	0.3	0.3	84	88	65	84	19.6	20.6	88	93	3	1
4	tBu-xantphos	100		2.1	1.0	0.6	0.8	0.4	0.2	1.7	2.8	0.3	0.3	20	20	58	81	0.3	0.3	78	89	14	4
5	tBu-xantphos	100	HOTs	1.7	0.7	2.5	3.3	0.1	0.1	0.2	0.2	0.5	0.8	76	75	67	87	14.3	15.5	81	80	3	2
6	tBu-xantphos	80	HOTs		1.0		3.3		0.2		0.2		0.3		83		80		16.9		88		4
7	Si-xantphos	100		2.3	1.2	0.4	0.8	0.4	0.3	1.6	2.3	0.2	0.4	16	21	54	76	0.3	0.3	75	82	16	7
8	Si-xantphos	100	HOTs	1.5	0.7	2.1	2.7	0.3	0.2	0.5	0.7	0.6	0.7	59	62	71	87	4.0	3.6	74	80	8	4
9	Si-xantphos	80	HOTs		1.1		2.3		0.4		0.6		0.6		60		78		4.1		74		11
10	oMeO-xantphos	100		3.7	3.2	0.1	0.2	0.8	1.1	0.2	0.3	0.2	0.2	10	9	25	35	0.6	0.5	25	26	60	62
11	oMeO-xantphos	100	HOTs	2.2	1.4	0.2	0.4	0.7	0.6	0.1	0.2	1.8	2.4	8	10	56	72	1.7	1.5	12	16	24	15
12	oMeO-xantphos	80	HOTs		2.0		0.3		0.9		0.0		1.7		10		60		6.2		12		31
13	xantphos(tBu)	100		3.4	3.0	0.1	0.2	1.2	1.4	0.0	0.0	0.3	0.4	5	8	31	41	2.7	4.0	7	10	75	70
14	xantphos(tBu)	100	HOTs	2.4	1.6	0.3	0.4	0.6	0.4	0.0	0.1	1.7	2.5	12	12	52	67	9.1	7.4	13	13	22	13
15	xantphos(tBu)	80	HOTs		2.1		0.5		0.8		0.0		1.6		17		59		10.2		19		28
16	DPEphos	100		2.7	1.8	0.8	1.4	0.7	0.7	0.2	0.3	0.6	0.8	32	44	46	64	3.1	4.3	43	54	32	22
17	DPEphos	100	HOTs	1.9	1.1	1.0	1.4	0.5	0.3	0.2	0.3	1.4	1.8	31	37	61	78	4.5	4.9	38	45	18	8
18	DPEphos	80	HOTs		1.8		0.9		0.9		0.1		1.2		30		64		6.3		34		28
19	DBFphos	100		3.5	2.9	0.0	0.0	0.1	0.3	0.6	0.9	0.7	0.9	1	1	29	42	0.0	0.0	41	44	9	13
20	DBFphos	100	HOTs	2.8	2.1	0.7	0.8	0.5	0.4	0.1	0.1	0.9	1.6	33	28	44	58	7.6	7.4	38	32	22	15
21	DBFphos	80	HOTs		2.5		0.6		0.7		0.1		1.1		24		50		8.8		27		29
22	homoxantphos	100		3.8	3.5	0.0	0.0	0.3	0.4	0.4	0.5	0.4	0.6	0	1	24	31	0.0	0.0	36	33	28	29
23	homoxantphos	100	HOTs	2.2	1.6	0.4	0.7	0.6	0.6	0.5	0.6	1.3	1.5	13	20	55	68	0.7	1.1	33	39	21	18
24	homoxantphos	80	HOTs		2.0		0.6		0.7		0.6		1.1		20		60		1.1		39		24
25	benzoxantphos	100		4.1	3.6	0.0	0.0	0.2	0.3	0.3	0.3	0.5	0.7	2	2	19	28	0.1	0.1	33	26	17	22
26	benzoxantphos	100	HOTs	2.7	2.1	0.5	0.8	0.6	0.5	0.1	0.2	1.1	1.5	24	27	46	59	5.1	4.8	28	32	26	16
27	benzoxantphos	80	HOTs		2.7		0.5		0.7		0.1		1.1		23		47		5.9		26		28

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol ligand, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:L:hexanal:acetamide= 1:1.25:500:600); P_{H2}= 80 bar; T= 80-100°C; t= 4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.9. Effect of the addition of various acids or bases on the reductive amidation of hexanal with acetamide using Rh/xantphos catalytic system[a]

	Additive (mmol)	pK_a	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5**(mmol) **5a**	**5b**	**3** selectivity %	Conversion %	**3/4** ratio	**3+4** selectivity %
1	-	-	1.2	0.8	0.1	2.4	0.2	0.3	21	76	0.3	84
2	HOTs(0.025)	-2.8	1.1	2.3	0.1	1.0	0.3	0.2	60	78	2.4	84
3	HOTs(0.05)	-2.8	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93
4	HOTs(0.1)	-2.8	0.4	3.8	0.0	0.2	0.4	0.2	83	92	24.5	87
5	HOTs(0.2)	-2.8	0.1	4.0	0.0	0.1	0.5	0.3	81	98	30.8	84
6	HOTs(0.05)[b]	-2.8	0.7	3.1	0.1	0.7	0.2	0.2	72	86	4.4	88
7	AcOH(0.05)	4.76	1.5	0.3	0.0	2.7	0.2	0.3	9	70	0.1	86
8	H_3PO4(0.05)	2.12	1.6	0.7	0.1	1.9	0.4	0.3	21	68	0.4	76
9	PhH_2PO_3(0.05)	1.86	1.6	1.1	0.1	1.5	0.4	0.3	32	68	0.7	76
10	TFA(0.05)	-0.25	1.3	1.8	0.2	1.1	0.4	0.2	49	74	1.6	78
11	HBF_4(0.05)	-0.4	1.7	2.5	0.1	0.2	0.3	0.2	76	66	12.5	82
12	HCl(0.05)	-8	1.5	2.7	0.1	0.1	0.4	0.2	76	70	20.8	80
13	HOTf(0.05)	-14	0.5	3.8	0.0	0.1	0.4	0.2	84	90	26.0	87
14	NMP(0.05)	-	1.4	0.1	0.0	3.0	0.2	0.3	3	72	0.0	86
15	NEt_3(0.05)	-	0.5	0.0	0.0	4.1	0.2	0.2	0	90	0.0	91

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 5 mmol hexanal, 6 mmol acetamide Rh:xantphos:hexanal:acetamide=1:1.25:500:600); P_{H2}=80 bar; T=80 °C; t= 4 h; Solvent: 25 ml diglyme; decane as internal standard. [b] HOTs 12% in acetic acid.

Table AI.10. Reductive amidation reaction of hexanal investigating acid and base effect [a]

	Additive mmol	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5**(mmol) **5a**	**5b**	**3** selectivity %	Conversion %	**3/4** ratio	**3+4** selectivity %
1	-	1.2	0.8	0.1	2.4	0.2	0.3	21	76	0.3	84
2	HOTs(0.05)	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93
3	AgOTS(0.0125)	1.9	2.0	0.1	0.4	0.3	0.3	65	62	5.0	77
4	AgOTf(0.0125)	1.8	2.2	0.1	0.3	0.3	0.3	69	64	7.3	78
5	HOTs(0.05),AgTs(0.0125)	0.5	3.8	0.0	0.1	0.4	0.2	84	90	25.5	87
6	HOTs(0.05),NaCl(0.0125)	1.2	3.0	0.0	0.2	0.4	0.2	79	76	15.0	84
7	HOTs(0.05),NaBr(0.0125)	0.6	3.5	0.0	0.1	0.4	0.3	80	88	23.2	84
8	HOTs(0.05),NaI(0.0125)	0.4	3.9	0.0	0.1	0.4	0.2	84	92	26.2	87

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:hexanal:acetamide=1:1.25:500:600); P_{H2}=80 bar; T=80 °C; t=4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.11. Reductive amidation reaction of hexanal with and without acetamide [a]

	Amide 6 mmol	HOTs mmol	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5** (mmol) **5a**	**5b**	**3** selectivity %	Conversion %	**3/4** ratio	**3+4** selectivity %	alcohol **4** selectivity %
1	-	-	2.4	-	-	2.2	0.4	-	0	52	0.0	85	85
2	-	0.05	4.3	-	-	0.1	0.6	-	0	14	0.0	9	9
3	di-Me-acetamide	-	2.3	-	-	2.2	0.5	-	0	54	0.0	81	81
4	di-Me-acetamide	0.05	3.7	-	-	0.8	0.5	-	0	26	0.0	62	62
5	acetamide	-	1.2	0.8	0.1	2.4	0.2	0.3	21	76	0.3	84	63
6	acetamide	0.05	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93	4

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 5 mmol hexanal, in some cases 6 mmol amide (Rh:xantphos:hexanal=1:1.25:500); P_{H2}=80 bar; *T*=80 °C; t=4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.12. The influence of adding H_2O on the reductive amidation reaction of hexanal with acetamide[a]

	H_2O mmol	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5**(mmol) **5a**	**5b**	**3** selectivity %	Conversion %	**3/4** ratio	**3+4** selectivity %
1	-	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93
2	2.5	1.3	2.6	0.1	0.2	0.4	0.4	70	74	13.0	76
3	5	2.1	1.4	0.2	0.2	0.6	0.5	48	58	7.0	55
4[b]	-	0.6	3.9	0.0	0.2	0.2	0.1	88	88	21.5	93

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:hexanal:acetamide=1:1.25:500:600);HOTs(0.05mmol); P_{H2}=80 bar; T=80 °C; t=4 h; Solvent: 25 ml diglyme; decane as internal standard. [b] Molecular sieve 3Å used in the reaction.

Table AI.13. Reductive amidation reaction of hexanal with acetamide applying different metals[a]

	Metal	HOTs mmol	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5** (mmol) **5a**	**5b**	**3** selectivity %	Conversion %	**3/4** ratio	**3+4** selectivity %
1	$[Rh(cod)Cl]_2$		1.2	0.8	0.1	2.4	0.2	0.3	21	76	0.3	84
2	$[Rh(cod)Cl]_2$	0.05	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93
3	$Ru(acac)_3$		4.3	0.0	0.0	0.2	0.3		0	14	0.0	40
4	$Ru(acac)_3$	0.05	1.4	0.2	0.3	0.9	1.5	0.7	6	72	0.2	31
5	$Pd(OAc)_2$		4.4	0.0	0.0	0.0	0.6		0	12	0.0	0
6	$Pd(OAc)_2$	0.05	2.9	0.3	0.4	0.0	0.9	0.5	14	42	0.0	14
7	$[Ir(cod)Cl]_2$		4.2	0.0	0.1	0.2	0.5		0	16	0.0	25
8	$[Ir(cod)Cl]_2$	0.05	2.7	0.4	0.4	0.3	0.7	0.5	17	46	1.3	30
9	$Co_2(CO)_8$		4.3	0.0	0.0	0.0	0.7		0	14	0.0	0
10	$Co_2(CO)_8$	0.05	3.0	0.0	0.0	0.0	1.3	0.7	0	40	0.0	0
11	$Pt(cod)Cl_2$		2.6	0.5	1.0	0.2	0.7		21	48	2.5	29
12	$Pt(cod)Cl_2$	0.05	1.4	0.6	1.3	0.2	1.0	0.5	17	72	3.0	22

[a] Reaction conditions: 0.005 mmol metal salt, 5 mmol hexanal, 6 mmol acetamide (M:xantphos:hexanal:acetamide=1:1.25:500:600); P_{H2}=80 bar; *T*=80 °C; t=4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.14. Product development in time in the reductive amidation of hexanal with acetamide[a]

	Time h	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5** (mmol) **5a**	**5b**	**3** selectivity %	Conversion %	**3/4** ratio	**3+4** selectivity %
1	2	1.7	2.7	0.1	0.1	0.2	0.1	84	65	19.6	89
2	4	0.8	3.7	0.0	0.2	0.2	0.1	88	84	20.6	93
3	6	0.4	4.0	0.0	0.2	0.2	0.1	88	92	21.3	92
4	8	0.2	4.3	0.0	0.2	0.2	0.1	89	96	22.5	93
5	10	0.1	4.4	0.0	0.2	0.2	0.1	89	98	22.0	93

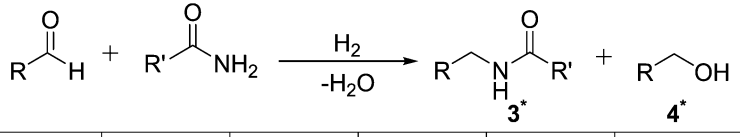
[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide=1:1.25:5:500:600); P_{H2}=80 bar; *T*=80 °C; Solvent: 25 ml diglyme; decane as internal standard.

Table AI.15. Reproducibility of the reductive amidation of hexanal with acetamide[a]

	Hexanal mmol	**3** mmol	**2** mmol	**4** mmol	**5** mmol	**3** sel%	Conversion %	**3/4**	**3+4** selectivity %
1	0.8	3.7	0.0	0.2	0.3	88	84	20.6	93
2	1.0	3.4	0.1	0.2	0.3	84	80	17.7	89
3	0.8	3.7	0.1	0.2	0.3	86	85	20.2	90
4	1.0	3.4	0.2	0.2	0.2	87	79	17.5	92
5	0.7	3.8	0.1	0.2	0.2	89	85	22.0	93
6	1.1	3.3	0.2	0.2	0.2	85	78	16.1	91
7	0.7	3.7	0.0	0.2	0.4	86	86	19.3	91
8	0.8	3.8	0.0	0.2	0.2	89	84	21.9	93
9	0.8	3.5	0.1	0.2	0.3	84	83	15.6	90
10	0.8	3.8	0.1	0.2	0.2	90	85	22.9	94
11	0.8	3.7	0.1	0.2	0.2	89	84	19.7	94
12	0.8	3.5	0.3	0.2	0.3	83	84	17.9	87
13	0.8	3.7	0.2	0.2	0.2	88	85	19.5	93
14	0.9	3.4	0.2	0.3	0.3	82	83	13.5	88
15[b]	1.5	2.3	0.4	0.3	0.6	66	71	9.0	73

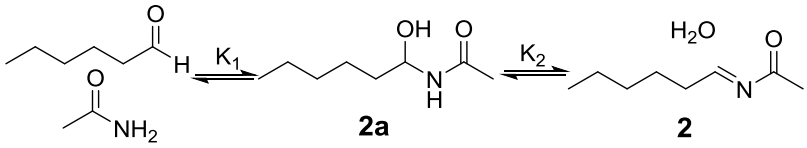
[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol hexanal, 6 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide=1:1.25:5:500:600); P_{H2}=80 bar; t=4 h; *T*=80 °C; Solvent: 25 ml diglyme; decane as internal standard. [b] Neither dried nor deoxygenated solvent from its bottle.

Table AI.16. Reductive amidation reaction using different nucleophiles/aldehydes [a]



	Aldehyde 5 mmol	Amide 6mmol	Aldehyde mmol			3* mmol			2* mmol			4* mmol			5* mmol			3* selectivity %[c]			Conversion[b] %			3*/4* ratio			3*+4* Selectivity %		
			2h	4h	10h	2h	4h	10h	2h	4h	10h	2h	4h	10h	2h	4h	10h	2h	4h	10h	2h	4h	10h	2h	4h	10h	2h	4h	10h
1	Hexanal	Acetamide	1.7	0.8	0.1	2.7	3.7	4.3	0.1	0.0	0.0	0.1	0.2	0.2	0.3	0.3	0.3	84	88	89	65	84	98	20	21	22	88	92	93
2	Hexanal	Me-acetamide	1.3	0.5	0.0	3.2	4.0	4.4	0.1	0.0	0.0	0.1	0.2	0.2	0.2	0.3	0.4	87	90	89	74	90	99	23	24	24	90	93	93
3	Hexanal	diMe-acetamide	1.8	1.1	0.4	2.2	3.1	3.6	0.4	0.3	0.2	0.2	0.2	0.3	0.3	0.3	0.5	70	79	78	63	77	92	13	13	12	75	85	85
4	Hexanal	triMe-acetamide	2.1	1.3	0.5	1.9	3.0	3.5	0.5	0.2	0.1	0.2	0.2	0.3	0.3	0.3	0.6	66	81	78	57	75	90	11	12	10	72	87	85
5	Hexanal	Valeramide	0.9	0.4	0.0	3.5	4.2	4.5	0.3	0.0	0.0	0.1	0.1	0.2	0.2	0.2	0.3	85	92	90	82	92	99	30	31	28	88	95	93
6	Hexanal	Fluoroacetamide	3.7	3.4	2.6	0.3	0.6	1.0	0.3	0.3	0.3	0.2	0.3	0.5	0.5	0.5	0.6	25	35	43	25	32	48	2	2	2	41	51	62
7	Hexanal	Benzamide	3.1	2.1	1.4	1.1	2.1	2.8	0.2	0.3	0.1	0.2	0.3	0.3	0.4	0.3	0.5	58	72	77	38	58	72	7	8	11	66	81	84
8	Hexanal	p-MeO-benzamide	2.0	1.4	0.4	2.3	2.9	3.8	0.2	0.2	0.0	0.2	0.2	0.3	0.3	0.3	0.4	77	80	83	60	72	91	12	14	11	83	85	90
9	Hexanal	p-CF_3-benzamide	3.5	3.1	2.1	0.7	1.1	2.0	0.3	0.2	0.1	0.2	0.3	0.4	0.3	0.3	0.4	47	58	69	30	38	58	3	4	5	62	73	84
12	2-Me-pentanal	Acetamide	3.1	2.2	1.1	0.5	0.9	1.4	0.9	1.2	1.5	0.2	0.3	0.4	0.3	0.4	0.6	28	31	36	39	57	78	2	3	4	39	41	46
13	benzaldehyde	Acetamide	3.2	2.9	2.1	0.1	0.2	0.3	0.4	0.4	0.6	1.0	1.1	1.4	0.3	0.4	0.5	8	9	11	35	42	57	0	0	0	65	63	59

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 0.0125 mmol xantphos, 0.05 mmol HOTs, 5 mmol aldehyde, 6 mmol amide/amine (Rh:L:HOTs:hexanal:amide=1:1.25:5:500:600); P_{H2}=80 bar; T=80 °C; t=2-10 h; Solvent: 25 ml diglyme. [b] The conversion was determined by GC analysis based on the amount of aldehyde found in the reaction mixtures after the reaction; [c] The selectivity was determined by GC analysis using decane as an internal standard.



(eq. 1)

$$K_1 = \frac{[2a]_{eq}}{[hexanal]_{eq} * [acetamide]_{eq}} = \frac{[2a]_{eq}}{[hexanal]_{eq}^{2}} = \frac{0.163}{(0.246)^2} = 2.701 \ M^{-1}$$

(eq. 2)

$$K_2 = \frac{[2]_{eq} * [H_2O]_{eq}}{[2a]_{eq}} = \frac{[2]_{eq}^{2}}{[2a]_{eq}} = \frac{(0.083)^2}{0.163} = 0.042 \, M$$

Figure AI.2. The first (K_1) and second (K_2) equilibrium constants derived from ^1H NMR.

Appendix II

Supporting Information of Chapter 3:

Chemo- and Regio-selective Homogeneous Rhodium-Catalyzed Hydroamidomethylation of Terminal Alkenes to N-Alkylamides

Full analytical data of catalytic experiments

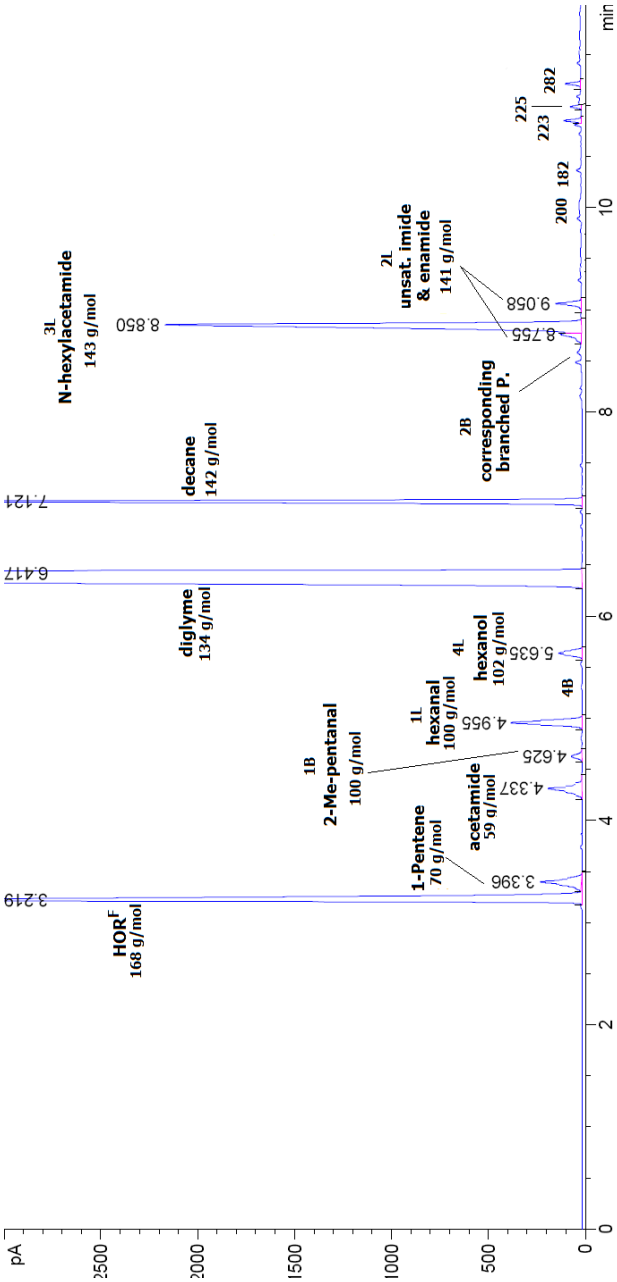
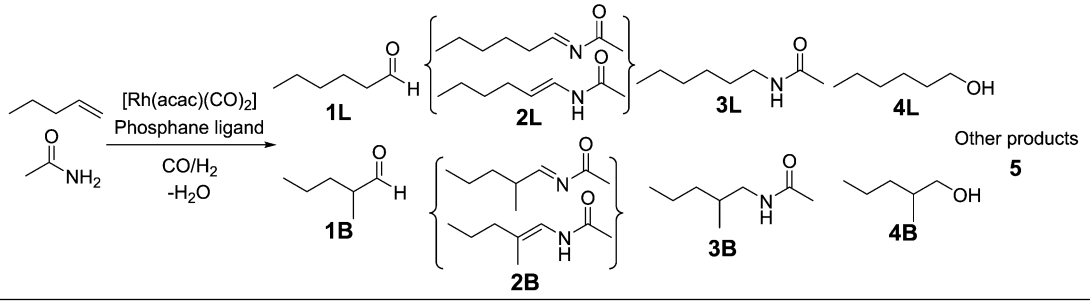


Figure AII.1. GC spectrum of hydroamidomethylation of 1-pentene with acetamide in the presence of HOTs: (Rh:xantphos:HOTs:hexanal:acetmide =1:1.25:5:500:600); P_{H2}=80 bar; T=80 °C; t=4 h; Solvent: 25 ml diglyme; decane as internal standard.

Table AII.1. Hydroamidomethylation of 1-pentene with acetamide: Initial screening results[a]



	Rh precursor	T °C	P(CO/H_2) bar	t h	additive 0.05mmol	1-pent mmol	**1L** mmol	**1B** mmol	**2L** mmol	**2B** mmol	**3L** mmol	**3B** mmol	**4L** mmol	**4B** mmol	**5** mmol	conversion %	**1** L%	**3** L%
1	$[Rh(cod)Cl]_2$	100	50(1/2)	4		0.9	2.2	0.1	0.5	0.0	0.0	0.0	0.0	0.0	1.3	83	97	-
2	$Rh(CO)_2(acac)$	100	50(1/2)	4		1.1	3.4	0.1	0.2	0.0	0.0	0.0	0.0	0.0	0.2	79	97	-
3	$Rh(cod)_2BF_4$	100	50(1/2)	4		0.9	1.7	0.1	0.6	0.0	0.0	0.0	0.0	0.0	1.6	81	97	-
4	$Rh(CO)(H)(PPh_3)_3$	100	50(1/2)	4		0.9	3.5	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.5	82	96	-
5	$Rh(cod)_2OTf$	100	50(1/2)	4		1.1	1.7	0.1	0.6	0.0	0.0	0.0	0.0	0.0	1.5	78	97	-
6	$Rh(CO)_2(acac)$	80	50(1/2)	4		2.4	1.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6	53	98	-
7	$Rh(CO)_2(acac)$	120	50(1/2)	4		0.8	3.4	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.5	85	97	-
8	$Rh(CO)_2(acac)$	100	50(1/1)	4		1.4	3.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.4	72	97	-
9	$Rh(CO)_2(acac)$	100	50(1/4)	4		1.3	3.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.4	74	97	-
10	$Rh(CO)_2(acac)$	100	50(1/5)	4		1.3	3.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.3	73	97	>99
11	$Rh(CO)_2(acac)$	100	50(1/2)	4	HOTs	0.8	1.4	0.1	0.4	0.1	0.5	0.0	0.0	0.0	1.6	84	97	>99
12	$Rh(CO)_2(acac)$	100	50(1/2)	8		0.7	3.6	0.1	0.2	0.0	0.0	0.0	0.0	0.0	0.2	85	97	>99
13	$Rh(CO)_2(acac)$	100	50(1/2)	8	HOTs	0.6	1.3	0.1	0.3	0.1	0.8	0.0	0.0	0.0	1.8	88	96	>99
14	$Rh(CO)_2(acac)$	100	50(1/2)	4	HOTs(0.1)	0.5	1.0	0.1	0.5	0.1	1.0	0.0	0.0	0.0	1.8	89	94	>99
15	$Rh(CO)_2(acac)$	100	50(1/2)	4	HOTf(0.025)	0.6	2.1	0.1	0.5	0.0	0.6	0.0	0.0	0.0	1.1	88	96	>99
16	Rh(CO) (acac)	100	50(1/2)	4	HOTf	0.6	1.1	0.1	0.5	0.0	0.9	0.0	0.1	0.0	1.8	89	92	>99
17	$Rh(CO)_2(acac)$	100	50(1/2)	4	HOTf(0.1)	0.5	0.9	0.1	0.3	0.0	1.4	0.0	0.1	0.0	1.6	90	90	>99
18	$Rh(CO)_2(acac)$	100	50(1/2)	4	HOTf(0.15)	0.5	0.5	0.1	0.4	0.0	1.6	0.0	0.1	0.0	1.7	90	82	>99
19	$Rh(CO)_2(acac)$	100	50(1/2)	4	HOTf(0.2)	0.6	0.4	0.1	0.2	0.0	1.7	0.0	0.1	0.0	1.9	88	79	>99
20	$Rh(CO)_2(acac)$	80	50(1/2)	4	HOTf(0.2)	1.7	0.8	0.0	0.6	0.0	1.0	0.0	0.0	0.0	0.9	66	96	>99
21	$Rh(CO)_2(acac)$[b]	100-80	50(1/2)-80	8+4	HOTs	0.6	0.9	0.2	0.3	0.0	0.6	0.0	0.1	0.0	2.2	88	86	>99

[a] Reaction conditions: 0.01 mmol Rh precursor, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:1-pentene:acetamide=1:2:500:500); P(CO/H_2)=50(1/2) bar; T=80-120 °C; *t*=4-12 h; Solvent: 10 ml diglyme; decane as internal standard. [b] In a semi-one-pot reaction condition: 8h at 100 °C hydroformylation- depressurzing syngas- flushing 3times with H_2- pressurizing with H_2-4h (80 bar) at 80 °C reductive amidation.

Table AII.2. Influence of various solvents on hydroamidomethylation of 1-pentene with acetamide[a]

	Solvent 10 mL	t h	HOTs mmol	1-pent mmol	**1L** mmol	**1B** mmol	**2L** mmol	**2B** mmol	**3L** mmol	**3B** mmol	**4L** mmol	**4B** mmol	**5** mmol	acetal mmol	conversion %	**1** L%	**3** L%
1	diglyme	8		0.7	3.6	0.1	0.2	0.0	0.0	0.0	0.0	0.0	0.2		85	97	>99
2	diglyme	4	0.05	0.8	1.4	0.1	0.4	0.1	0.5	0.0	0.0	0.0	1.6		84	97	>99
3	diglyme	8	0.05	0.6	1.3	0.1	0.3	0.1	0.8	0.0	0.0	0.0	1.8		88	96	>99
4	MeOH	8		0.6	3.4	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.7		89	96	-
5	MeOH	8	0.05	0.5	1.2	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.3	2.6	91	96	-
6	MeOH/toluene=1/1	8	0.05	0.6	1.5	0.1	0.8	0.0	0.1	0.0	0.0	0.0	0.4	1.5	89	92	>99
7	MeOH/diglyme=1/1	8	0.05	0.5	1.3	0.1	0.7	0.1	0.0	0.0	0.0	0.0	0.5	1.8	90	93	>99
8	MeOH/diglyme=1/4	8	0.05	0.8	1.5	0.1	0.8	0.1	0.0	0.0	0.0	0.0	0.5	1.0	85	92	>99
9	EtOH	8	0.05	0.9	1.5	0.1	0.8	0.0	0.0	0.0	0.1	0.0	0.3	1.1	83	93	>99
10	EtOH/diglyme=1/1	8	0.05	0.9	1.7	0.1	0.9	0.0	0.0	0.0	0.0	0.0	0.5	0.8	82	93	-
11	iPrOH/diglyme=1/1	8		0.9	3.3	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.7		82	97	-
12	iPrOH/diglyme=1/1	8	0.05	0.7	1.7	0.1	0.9	0.0	0.3	0.0	0.1	0.0	0.5	0.7	85	92	>99
13	nBuOH	8	0.05	0.9	0.4	0.1	1.0	0.2	0.0	0.0	0.0	0.0	0.8	1.5	82	88	>99
14	iBuOH	8	0.05	1.0	0.7	0.1	1.0	0.1	0.0	0.0	0.0	0.0	0.9	1.1	80	89	>99
15	TFE	8		0.5	2.1	0.2	0.0	0.0	0.0	0.0	1.6	0.0	0.4		89	93	>99
16	TFE	8	0.05	0.8	1.3	0.2	0.4	0.0	0.0	0.0	0.4	0.0	0.9	0.8	84	90	>99
17	TFE/diglyme=1/1	8	0.05	0.5	1.9	0.2	0.5	0.0	0.0	0.0	0.3	0.0	0.9	0.5	90	93	>99
18	HOR^F/diglyme=1/1	8		0.6	3.0	0.1	0.1	0.0	0.0	0.0	0.8	0.0	0.4		88	96	>99
19	HOR^F /diglyme=1/1	8	0.05	0.7	2.1	0.1	0.2	0.0	0.6	0.0	0.7	0.0	0.3	0.2	85	96	99

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:1-pentene:acetamide=1:2:500:500); $P(CO/H_2)$=50(1/2) bar; T=100 °C; *t*= 4-8 h; Solvent: 10 mL; decane as internal standard.

Table AII.3. Influence of various ratio of HOR^F /diglyme on hydroamidomethylation of 1-pentene with acetamide[a]

	Solvent 10 mL	t h	HOTs mmol	1-pent mmol	**1L** mmol	**1B** mmol	**2L** mmol	**2B** mmol	**3L** mmol	**3B** mmol	**4L** mmol	**4B** mmol	**5** mmol	acetal mmol	conversion %	**1** L%	**3** L%
1	HOR^F	8	-	0.9	2.1	0.1	0.1	0.0	0.0	0.0	1.2	0.0	0.6		82	95	-
2	HOR^F	4	0.05	3.6	0.5	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.3	28	76	-
3	HOR^F	8	0.05	2.1	1.4	0.5	0.0	0.0	0.0	0.0	0.2	0.0	0.4	0.4	58	74	-
4	HOR^F /diglyme=1/1	8	-	0.6	3.0	0.1	0.1	0.0	0.0	0.0	0.8	0.0	0.4		88	96	>99
5	HOR^F /diglyme=1/1	8	0.05	0.7	2.1	0.1	0.2	0.0	0.6	0.0	0.7	0.0	0.3	0.2	85	96	99
6	HOR^F /diglyme=9/1	4	0.05	3.1	1.0	0.0	0.0	0.0	0.0	0.0	0.6	0.0	0.1	0.2	38	>99	-
7	HOR^F /diglyme=9/1	8	0.05	1.5	0.8	0.0	0.0	0.0	0.0	0.0	2.0	0.0	0.3	0.3	70	>99	>99
8	HOR^F /diglyme=5/1	4	0.05	1.0	0.4	0.1	0.0	0.0	0.0	0.0	3.0	0.1	0.2	0.2	80	87	>99
9	HOR^F /diglyme=5/1	8	0.05	0.6	0.3	0.0	0.0	0.0	0.0	0.0	3.4	0.1	0.3	0.3	88	90	>99
10	HOR^F /diglyme=4/1	8	0.05	0.6	0.5	0.0	0.1	0.0	0.0	0.0	3.3	0.0	0.3	0.2	88	98	>99
11	HOR^F /diglyme=3/1	8	0.05	0.7	0.8	0.0	0.2	0.0	0.1	0.0	2.4	0.2	0.2	0.2	86	99	>99
12	HOR^F /diglyme=2/1	8	0.05	0.8	1.8	0.1	0.1	0.0	0.3	0.0	1.5	0.0	0.2	0.2	85	94	>99
13	HOR^F /diglyme=1/2	8	0.05	0.9	1.4	0.1	0.3	0.0	1.6	0.0	0.3	0.0	0.3	0.1	82	96	99
14	HOR^F /diglyme=1/3	8	0.05	0.5	0.8	0.1	0.3	0.0	2.8	0.0	0.2	0.0	0.4		90	94	99
15	HOR^F /diglyme=1/4	8	0.05	0.5	0.7	0.1	0.2	0.0	3.1	0.0	0.3	0.0	0.2		91	92	>99
16	HOR^F /diglyme=1/5	8	0.05	0.6	0.8	0.1	0.3	0.0	2.7	0.0	0.3	0.0	0.4		89	93	>99
17	HOR^F /diglyme=1/9	8	0.05	0.6	1.3	0.1	0.4	0.0	1.8	0.0	0.1	0.0	0.7		88	96	98
18	HOR^F /diglyme=1/4	4	0.05	0.9	1.1	0.1	0.3	0.0	2.4	0.0	0.2	0.0	0.2		83	95	>99
19	HOR^F /diglyme=1/4	12	0.05	0.4	0.4	0.1	0.2	0.0	3.4	0.0	0.3	0.0	0.2		93	84	>99
20	HOR^F /diglyme=1/4	8	0.025	0.5	1.6	0.1	0.3	0.0	1.8	0.0	0.2	0.0	0.5		91	96	>99
21	HOR^F /diglyme=1/4	4	0.1	0.8	0.7	0.0	0.3	0.0	2.5	0.0	0.2	0.0	0.4		83	94	>99
22	HOR^F /diglyme=1/4	8	0.1	0.4	0.4	0.0	0.1	0.0	3.1	0.0	0.3	0.0	0.6		93	89	>99
23	HOR^F /diglyme=1/4	4	-	1.3	3.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1		74	99	-
24	HOR^F /diglyme=1/4	8	-	0.7	3.9	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.2		86	98	-
25	HOR^F /diglyme=1/4	8	HOTf[b]	0.4	0.7	0.0	0.1	0.0	3.2	0.0	0.2	0.0	0.3		92	95	>99

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:1-pentene:acetamide=1:2:500:500); $P(CO/H_2)$=50(1/2) bar; T=100 °C; *t*=4-8 h; Solvent: 10 mL (v/v); decane as internal standard. [b] 0.05 mmol HOTf as an acid.

Table AII.4. Influence of different amount of HOR^F (in mmol) on hydroamidomethylation of 1-pentene with acetamide[a]

	HOR^F mmol	t h	1-pent mmol	**1L** mmol	**1B** mmol	**2L** mmol	**2B** mmol	**3L** mmol	**3B** mmol	**4L** mmol	**4B** mmol	**5** mmol	conversion %	**1** L%	**3** L%
1	1	4	0.5	1.4	0.1	0.3	0.0	1.1	0.0	0.1	0.0	1.6	89	96	>99
2	1	8	0.3	1.2	0.1	0.2	0.1	1.1	0.0	0.1	0.0	2.0	94	95	>99
3	5	4	0.6	1.3	0.1	0.3	0.0	1.6	0.0	0.1	0.0	1.1	89	95	>99
4	5	8	0.2	1.1	0.1	0.2	0.0	1.6	0.0	0.1	0.0	1.6	95	95	>99
5	10	4	0.8	1.1	0.1	0.2	0.0	2.2	0.0	0.2	0.0	0.4	84	95	>99
6	10	8	0.5	0.9	0.1	0.1	0.0	2.4	0.0	0.2	0.0	0.8	90	93	>99
7	20	4	0.9	1.0	0.1	0.2	0.0	2.5	0.0	0.2	0.0	0.1	82	95	>99
8	20	8	0.5	0.8	0.1	0.1	0.0	3.1	0.0	0.2	0.0	0.2	90	93	>99
9	40	4	1.5	1.1	0.4	0.3	0.0	1.6	0.0	0.1	0.0	0.1	69	75	>99
10	40	8	1.2	0.7	0.3	0.1	0.0	2.2	0.0	0.2	0.0	0.3	77	70	>99
11	80	4	4.0	0.6	0.0	0.1	0.0	0.1	0.0	0.1	0.0	0.1	20	>99	>99
12	80	8	2.1	1.7	0.0	0.2	0.0	0.4	0.0	0.1	0.0	0.4	58	98	>99
13	100	4	4.1	0.5	0.0	0.1	0.0	0.1	0.0	0.1	0.0	0.1	17	>99	>99
14	100	8	2.1	2.2	0.0	0.1	0.0	0.2	0.0	0.2	0.0	0.2	57	>99	>99
15	200	4	4.4	0.3	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.1	13	>99	>99
16	200	8	2.3	1.5	0.0	0.1	0.0	0.1	0.0	0.7	0.0	0.3	54	97	>99

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); $P(CO/H_2)$=50(1/2) bar; T=100 °C; *t*=4-8h; Solvent: 10 mL diglyme; decane as internal standard.

Table AII.5. Influence of different syngas ratio on hydroamidomethylation of 1-pentene with acetamide[a]

	P(CO/H_2) bar	t h	1-pent mmol	**1L** mmol	**1B** mmol	**2L** mmol	**2B** mmol	**3L** mmol	**3B** mmol	**4L** mmol	**4B** mmol	**5** mmol	conversion %	**1** L%	**3** L%
1	50(5/1)	8	2.6	0.5	0.0	0.4	0.0	0.5	0.0	0.0	0.0	0.9	48	91	>99
2	50(2/1)	8	0.6	1.3	0.1	0.3	0.0	1.7	0.0	0.2	0.0	0.8	88	93	>99
3	50(1/1)	8	0.4	0.9	0.1	0.3	0.0	2.5	0.0	0.2	0.0	0.5	91	93	>99
4	50(1/2)	8	0.5	0.7	0.1	0.2	0.0	3.1	0.0	0.3	0.0	0.2	91	92	>99
5	30(1/2)	8	0.9	1.0	0.1	0.1	0.0	2.3	0.0	0.2	0.0	0.4	81	93	>99
6	70(1/2)	8	0.5	0.9	0.2	0.2	0.0	2.8	0.0	0.3	0.0	0.2	91	85	>99
7	50(1/3)	8	0.5	0.7	0.1	0.2	0.0	2.8	0.0	0.3	0.0	0.4	90	92	>99
8	50(1/4)	8	0.5	0.7	0.1	0.2	0.0	2.8	0.0	0.3	0.0	0.3	90	91	>99
9	50(1/5)	8	0.5	0.8	0.1	0.2	0.0	2.7	0.0	0.3	0.0	0.3	90	92	>99
10	30(2/1)	4	2.6	0.6	0.0	0.4	0.0	0.8	0.0	0.0	0.0	0.6	48	99	>99
11	30(2/1)	8	1.5	0.7	0.0	0.2	0.0	1.6	0.0	0.1	0.0	0.8	70	99	>99
12	40(1/1)	4	1.5	1.1	0.0	0.3	0.0	1.7	0.0	0.2	0.0	0.2	69	99	>99
13	40(1/1)	8	0.9	0.8	0.1	0.1	0.0	2.3	0.0	0.3	0.0	0.5	82	93	>99
14	60(1/2)	4	0.9	1.0	0.1	0.2	0.0	2.6	0.0	0.2	0.0	0.1	83	94	>99
15	60(1/2)	8	0.5	0.7	0.1	0.2	0.0	3.2	0.0	0.3	0.0	0.1	91	92	>99
16	80(1/3)	4	0.9	0.8	0.1	0.2	0.0	2.7	0.0	0.2	0.0	0.2	83	93	>99
17	80(1/3)	8	0.3	0.7	0.1	0.1	0.0	3.3	0.0	0.3	0.0	0.2	95	90	>99
18	100(1/4)	4	1.2	0.8	0.1	0.2	0.0	2.4	0.0	0.2	0.0	0.1	75	92	>99
19	100(1/4)	8	0.6	0.7	0.1	0.2	0.0	3.0	0.0	0.3	0.0	0.2	88	81	>99
20	30(1/2)	4	1.5	1.2	0.0	0.3	0.0	1.6	0.0	0.1	0.0	0.2	70	99	>99
21	30(1/2)	8	0.9	1.0	0.1	0.1	0.0	2.3	0.0	0.2	0.0	0.4	81	93	>99
22	60(2/1)	4	2.3	0.8	0.1	0.3	0.0	1.3	0.0	0.1	0.0	0.2	55	94	>99
23	60(2/1)	8	1.2	0.9	0.2	0.3	0.0	1.8	0.0	0.1	0.0	0.5	77	85	>99
24	80(3/1)	4	2.4	0.8	0.0	0.2	0.0	1.1	0.0	0.1	0.0	0.3	51	95	>99
25	80(3/1)	8	1.5	0.8	0.1	0.3	0.0	1.6	0.0	0.1	0.0	0.5	69	87	>99
26	100(4/1)	4	2.7	0.7	0.0	0.2	0.0	0.9	0.0	0.1	0.0	0.3	47	93	>99
27	100(4/1)	8	1.8	0.6	0.1	0.2	0.0	1.5	0.0	0.1	0.0	0.7	63	85	>99

[a] Reaction conditions: 0.01 mmol [$Rh(CO)_2(acac)$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); *T*=100 °C; *t*=4-8 h; Solvent: 10 mL (v/v) of HOR^F/diglyme (1/4); decane as internal standard.

Table AII.6. The effect of Rh/xantphos ratio on the hydroamidomethylation of 1-penten with acetamide[a]

	Rh	t	L/Rh	1-pent	**1L**	**1B**	**2L**	**2B**	**3L**	**3B**	**4L**	**4B**	**5**	conversion	**1**	**3**
	mmol	h	ratio	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	L%	L%
1	0.001	1	2	4.5	0.2	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.1	10	>99	>99
2	0.001	2	2	3.5	0.6	0.0	0.2	0.0	0.2	0.0	0.0	0.0	0.5	30	>99	>99
3	0.001	4	2	2.4	0.7	0.2	0.2	0.1	0.4	0.0	0.0	0.0	0.9	51	82	>99
3	0.001	8	2	1.3	0.8	0.2	0.3	0.1	0.8	0.0	0.0	0.0	1.4	74	84	>99
4	0.002	1	2	4.3	0.3	0.0	0.1	0.0	0.2	0.0	0.0	0.0	0.1	14	>99	>99
5	0.002	2	2	3.2	0.7	0.0	0.4	0.0	0.4	0.0	0.0	0.0	0.3	36	>99	>99
6	0.002	4	2	2.2	0.9	0.1	0.4	0.0	0.6	0.0	0.0	0.0	0.7	55	94	>99
6	0.002	8	2	1.1	0.9	0.2	0.2	0.0	1.1	0.0	0.0	0.0	1.3	79	82	>99
7	0.0025	1	2	4.1	0.4	0.0	0.3	0.0	0.2	0.0	0.0	0.0	0.1	19	99	>99
8	0.0025	2	2	3.0	0.7	0.0	0.4	0.0	0.6	0.0	0.0	0.0	0.3	41	99	>99
9	0.0025	4	2	2.0	0.9	0.0	0.4	0.0	1.0	0.0	0.0	0.1	0.6	61	99	>99
10	0.005	1	2	3.8	0.5	0.0	0.3	0.0	0.3	0.0	0.0	0.0	0.1	24	99	>99
11	0.005	2	2	2.7	0.8	0.0	0.4	0.0	0.8	0.0	0.0	0.0	0.2	46	99	>99
12	0.005	4	2	1.3	1.1	0.2	0.3	0.0	1.8	0.0	0.1	0.0	0.3	75	87	>99
12	0.005	8	2	0.8	0.8	0.2	0.3	0.0	2.2	0.0	0.1	0.0	0.6	84	85	>99
13	0.01	1	2	3.3	0.8	0.0	0.4	0.0	0.2	0.0	0.0	0.0	0.1	35	99	>99
14	0.01	2	2	2.3	1.1	0.0	0.4	0.0	0.9	0.0	0.1	0.0	0.1	54	96	98
15	0.01	4	2	0.9	1.1	0.1	0.3	0.0	2.4	0.0	0.2	0.0	0.2	83	95	>99
15	0.01	8	2	0.5	0.7	0.1	0.2	0.0	3.1	0.0	0.3	0.0	0.2	91	92	>99
16	0.02	1	2	2.5	0.9	0.0	0.5	0.0	0.9	0.0	0.1	0.0	0.0	49	99	>99
17	0.02	2	2	1.5	0.8	0.0	0.2	0.0	2.1	0.0	0.2	0.0	0.1	69	99	>99
18	0.02	4	2	0.5	0.6	0.1	0.1	0.0	3.2	0.0	0.4	0.0	0.1	90	91	>99
18	0.02	8	2	0.3	0.4	0.1	0.1	0.0	3.5	0.0	0.4	0.0	0.1	95	87	>99
16	0.01	8	3	0.5	1.1	0.1	0.3	0.0	2.4	0.0	0.2	0.0	0.4	90	94	>99
17	0.01	8	4	0.7	1.0	0.1	0.2	0.0	2.2	0.0	0.1	0.0	0.7	86	95	>99
18	0.01	8	8	1.0	0.9	0.0	0.3	0.0	1.8	0.0	0.1	0.0	0.1	81	95	>99

[a] Reaction conditions: 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (HOTs:1-pentene:acetamide=5:500:500); *T*=100 °C; *t*=4-8h; Solvent: 10 mL (v/v) of diglyme/ HOR^F =4/1; decane as internal standard.

Table AII.7. The effect of temperature on the hydroamidomethylation of 1-penten with acetamide[a]

	T °C	1-pent mmol	**1L** mmol	**1B** mmol	**2L** mmol	**2B** mmol	**3L** mmol	**3B** mmol	**4L** mmol	**4B** mmol	**5** mmol	conversion %	**1** L%	**3** L%
1	60	2.2	0.6	0.0	0.8	0.0	0.8	0.0	0.1	0.0	0.5	56	92	>99
2	80	1.4	0.8	0.0	0.4	0.0	1.6	0.0	0.2	0.0	0.4	72	94	>99
3	100	0.5	0.7	0.1	0.2	0.0	3.1	0.0	0.3	0.0	0.2	91	92	>99
4	120	0.4	0.8	0.1	0.2	0.0	2.4	0.0	0.3	0.0	0.8	93	91	>99

[a] Reaction conditions: 0.01 mmol [$Rh(CO)_2(acac)$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); $P(CO/H_2)$=50(1/2) bar; t=8 h; Solvent: 10 mL (v/v) of diglyme/HOR^F =4/1; decane as internal standard.

Table AII.8-1. The effect of different conditions on hydroformylation of 1-pentene [a]

	additive (5 mmol)	HOR[F] mmol	t h	acid 0.05mmol	1-pent mmol	**1L** mmol	**1B** mmol	**4L** mmol	**4B** mmol	**5** mmol	conversion %	selectivity % **1**	**4**	**5**	**1** L%
1			2		1.4	3.4	0.1	0.0	0.0	0.1	72	98	0	2	97
2			4		0.6	4.1	0.1	0.0	0.0	0.2	89	95	0	5	97
3			2	HOTs	0.5	3.5	0.1	0.6	0.0	0.3	90	80	12	7	97
4			4	HOTs	0.3	2.9	0.1	1.2	0.0	0.5	94	64	26	10	96
5	N,N-diMe-acetamide		2		2.2	2.6	0.1	0.0	0.0	0.1	55	96	0	4	97
6	N,N-diMe-acetamide		4		1.4	3.3	0.1	0.0	0.0	0.2	71	94	0	6	97
7	N,N-diMe-acetamide		2	HOTs	0.6	4.0	0.1	0.1	0.0	0.2	88	93	3	4	97
8	N,N-diMe-acetamide		4	HOTs	0.3	3.8	0.1	0.4	0.0	0.3	93	85	9	6	97
9		20	2		2.3	2.6	0.1	0.0	0.0	0.1	54	98	0	2	97
10		20	4		1.3	3.3	0.1	0.0	0.0	0.3	74	93	0	7	96
11		50	2		2.2	2.6	0.1	0.0	0.0	0.1	55	97	0	3	97
12		50	2		0.9	3.4	0.1	0.1	0.0	0.4	82	87	2	11	96
13		100	4		2.1	2.6	0.1	0.2	0.0	0.1	58	92	6	2	97
14		100	2		0.8	3.5	0.1	0.4	0.0	0.2	85	86	9	5	96
15		200	2		3.5	1.1	0.0	0.3	0.0	0.1	30	78	17	5	96
16		200	4		2.3	1.5	0.1	0.9	0.0	0.3	54	58	32	10	94
17		20	2	HOTs	3.6	1.1	0.0	0.2	0.0	0.1	28	83	11	6	97
18		20	4	HOTs	2.4	1.7	0.1	0.5	0.0	0.3	52	70	20	10	96
19		50	2	HOTs	4.5	0.3	0.0	0.0	0.0	0.1	10	75	5	20	97
20		50	4	HOTs	4.1	0.6	0.0	0.0	0.0	0.3	18	64	4	32	95
21		100	2	HOTs	4.8	0.1	0.0	0.0	0.0	0.1	4	71	0	29	>99
22		100	4	HOTs	4.6	0.3	0.0	0.0	0.0	0.1	9	63	6	31	>99
23		200	2	HOTs	4.9	0.1	0.0	0.0	0.0	0.0	3	87	0	13	>99
24		200	4	HOTs	4.7	0.2	0.0	0.0	0.0	0.1	5	71	0	29	>99
25	N,N-diMe-acetamide	20	2		2.1	2.7	0.1	0.0	0.0	0.1	58	96	0	4	97
26	N,N-diMe-acetamide	20	4		1.2	3.6	0.1	0.0	0.0	0.1	76	97	0	3	97
27	N,N-diMe-acetamide(10)	20	2		1.9	2.9	0.1	0.0	0.0	0.1	62	97	0	3	97
28	N,N-diMe-acetamide(10)	20	4		0.9	3.9	0.1	0.0	0.0	0.1	82	97	0	3	97
29	N,N-diMe-acetamide	20	2	HOTs	2.2	2.4	0.1	0.2	0.0	0.1	56	88	7	5	97
30	N,N-diMe-acetamide	20	4	HOTs	1.1	3.1	0.1	0.6	0.0	0.2	78	81	15	4	97

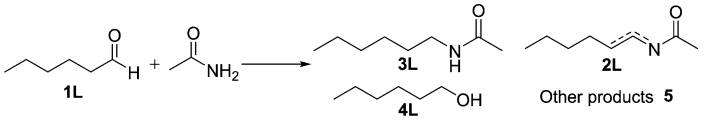
[a] Reaction conditions: 0.01 mmol [$Rh(CO)_2(acac)$], 0.02 mmol xantphos, 0.05 mmol HOTs (in the case that acid used), 5 mmol 1-pentene, 5 mmol N,N-dimethylacetamide (DMA: in the case that DMA used); (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); $P(CO/H_2)$=50 bar(1/2); t=2-4h; Solvent: 10mL diglyme; decane as internal standard.

Table AII.8-2. The effect of different conditions on hydroformylation of 1-pentene [a]

	additive (5 mmol)	HFIPA/dig 10 mL	t h	acid 0.05mmol	1-pent mmol	**1L** mmol	**1B** mmol	**4L** mmol	**4B** mmol	**5** mmol	conversion %	selectivity % **1**	**4**	**5**	**1** L%
1		5/1	2		3.7	0.7	0.0	0.4	0.0	0.1	25	59	35	6	>99
2		5/1	4		2.4	0.8	0.0	1.5	0.0	0.2	51	31	61	8	99
3		5/1	8		0.6	0.2	0.0	3.8	0.1	0.2	88	5	90	5	>99
4		5/1	2	HOTs	4.7	0.0	0.0	0.0	0.0	0.2	5	19	0	81	>99
5		5/1	4	HOTs	4.3	0.2	0.0	0.0	0.0	0.5	15	34	0	66	>99
6		5/1	8	HOTs	4.0	0.4	0.0	0.0	0.0	0.5	20	46	5	48	96
7	N,N-diMe-acetamide	5/1	2		3.8	0.7	0.0	0.3	0.0	0.2	24	58	29	13	>99
8	N,N-diMe-acetamide	5/1	4		2.9	0.8	0.0	0.9	0.0	0.4	42	36	45	18	99
9	N,N-diMe-acetamide	5/1	8		0.8	0.6	0.0	3.1	0.1	0.4	84	15	76	9	98
10	N,N-diMe-acetamide	5/1	2	HOTs	4.3	0.4	0.0	0.2	0.0	0.1	14	56	35	9	>99
11	N,N-diMe-acetamide	5/1	4	HOTs	3.1	0.8	0.0	0.8	0.0	0.3	38	44	42	14	>99
12	N,N-diMe-acetamide	5/1	8	HOTs	1.3	1	0.1	2.2	0.0	0.4	75	30	59	10	91
13	N,N-diMe-acetamide	4/1	8	HOTs	1.4	1.1	0.1	2.0	0.0	0.4	73	34	55	10	92
14	N,N-diMe-acetamide	dig	2	HOTs	0.6	4.0	0.1	0.1	0.0	0.2	88	93	3	4	97
15	N,N-diMe-acetamide	dig	4	HOTs	0.3	3.8	0.1	0.4	0.0	0.3	93	85	9	6	97
16	N,N-diMe-acetamide	dig	8	HOTs	0.1	3.8	0.1	0.5	0.0	0.4	97	81	10	9	97
17	N,N-diMe-acetamide	1/1	2	HOTs	3.0	1.3	0.0	0.2	0.0	0.5	40	67	10	23	97
18	N,N-diMe-acetamide	1/1	4	HOTs	1.9	2.0	0.1	0.4	0.0	0.6	62	67	13	20	95
19	N,N-diMe-acetamide	1/1	8	HOTs	1.0	2.5	0.2	0.7	0.0	0.6	80	68	17	15	93
20	N,N-diMe-acetamide	1/4	2	HOTs	2.2	2.4	0.1	0.2	0.0	0.1	56	88	7	5	97
21	N,N-diMe-acetamide	1/4	4	HOTs	1.1	3.1	0.1	0.5	0.0	0.3	78	81	13	7	97
22	N,N-diMe-acetamide	1/4	8	HOTs	0.6	3.3	0.1	0.7	0.0	0.4	88	76	16	8	97
23	N,N-diMe-acetamide	HOR^F	2	HOTs	4.4	0.3	0.1	0.0	0.0	0.2	12	65	0	35	87
24	N,N-diMe-acetamide	HOR^F	4	HOTs	3.8	0.6	0.2	0.0	0.0	0.4	24	69	0	31	79
25	N,N-diMe-acetamide	HOR^F	8	HOTs	2.4	1.3	0.4	0.2	0.0	0.7	52	65	6	28	76

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 0.05 mmol HOTs (in the case that acid used), 5 mmol 1-pentene, 5 mmol N,N-dimethylacetamide (DMA: in the case that DMA used); (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); $P(CO/H_2)$=50 bar(1/2); t=2-8 h; Solvent: 10mL (v/v) HOR^F/diglyme; decane as internal standard.

Table AII.9. The effect of different conditions on reductive amidation of hexanal [a]



	solvent (mL)	HOTs mmol	Time h	P(CO/H$_2$) bar	Hexanal mmol	**2L** mmol	**3L** mmol	**4L** mmol	**5** mmol	**3L** sel%	Conversion %	**3L/4L** ratio	**3L+4L** sel%
1	diglyme (10)	0.050	2	0//50	0.9	0.5	1.6	1.1	0.9	40	81	1.5	67
2	diglyme (10)	0.050	4	0//50	0.1	0.2	2.0	1.7	1.1	40	99	1.2	74
3	diglyme (10)	0.050	2	5//45	1.1	0.6	0.5	0.6	2.1	13.3	77	0.8	29
4	diglyme (10)	0.050	4	5//45	0.2	0.4	0.8	1.0	2.6	16.2	96	0.8	37
5	diglyme (10)	0.050	2	10//40	1.5	0.8	0.3	0.0	2.3	7.5	70	5.3	9
6	diglyme (10)	0.050	4	10//40	1.1	0.7	0.4	0.1	2.7	11.1	79	3.6	14
7	diglyme (10)	0.050	2	25//25	1.6	0.7	0.2	0.0	2.4	7.3	68	9.9	8
8	diglyme (10)	0.050	4	25//25	1.2	0.7	0.3	0.0	2.7	9.1	75	9.6	10
9	HOR^F /diglyme=1/4 (10)	0.050	2	0//50	2.6	0.8	0.1	0.0	1.5	5	49	4.5	7
10	HOR^F /diglyme=1/4 (10)	0.050	4	0//50	2.1	0.5	0.4	0.1	1.9	15	59	4.2	18
11	HOR^F /diglyme=1/4 (10)	0.050	2	5//45	2.0	0.8	0.2	0.0	2.0	6	60	10.4	7
12	HOR^F /diglyme=1/4 (10)	0.050	4	5//45	1.6	0.6	0.5	0.0	2.2	14	67	10.4	16
13	HOR^F /diglyme=1/4 (10)	0.050	2	10//40	1.7	0.9	0.7	0.1	1.7	20	66	11.0	22
14	HOR^F /diglyme=1/4 (10)	0.050	4	10//40	1.3	0.5	1.2	0.1	1.8	33	73	10.5	36
15	HOR^F /diglyme=1/4 (10)	0.050	2	25//25	1.5	0.4	1.8	0.2	1.1	52	70	9.1	58
16	HOR^F /diglyme=1/4 (10)	0.050	4	25//25	1.0	0.3	2.2	0.3	1.2	56	80	8.9	62
17	HOR^F /diglyme=1/2 (15)	0.050	2	0//50	2.3	1.1	0.0	0.0	1.6	1	54	-	1
18	HOR^F /diglyme=1/2 (15)	0.050	4	0//50	1.6	0.8	0.2	0.0	2.4	5	67	10.2	6
19	HOR^F /diglyme=1/1 (20)	0.050	2	0//50	2.9	1.0	0.0	0.0	1.1	1	42	-	1
20	HOR^F /diglyme=1/1 (20)	0.050	4	0//50	2.2	0.8	0.1	0.0	1.8	3	55	4.6	4
21	HOR^F /diglyme=2/1 (30)	0.050	2	0//50	3.9	0.9	0.0	0.0	0.2	0	22	-	0
22	HOR^F /diglyme=2/1 (30)	0.050	4	0//50	3.4	0.8	0.0	0.0	0.7	0	31	-	0
23c	HOR^F /diglyme=1/4 (10)	0.050	2	25//25	1.5	0.5	1.7	0.2	1.2	49	71	9.3	55
24c	HOR^F /diglyme=1/4 (10)	0.050	4	25//25	1.0	0.3	2.1	0.2	1.4	52	80	8.4	59
25	HOR^F /diglyme=1/4 (10)	0.025	2	25//25	2.5	0.7	1.2	0.1	0.6	46	51	8.9	51
26	HOR^F /diglyme=1/4 (10)	0.025	4	25//25	1.7	0.7	1.5	0.2	0.9	46	65	8.2	52
27	HOR^F /diglyme=1/4 (10)	0.010	2	25//25	3.5	0.7	0.3	0.0	0.5	18	29	8.5	20
28	HOR^F /diglyme=1/4 (10)	0.010	4	25//25	3.0	0.9	0.4	0.0	0.6	21	39	8.2	23
29	HOR^F /diglyme=1/4 (10)		2	25//25	4.9	0.0	0.0	0.0	0.1	7	3	1.8	11
30	HOR^F /diglyme=1/4 (10)		4	25//25	4.7	0.0	0.0	0.0	0.2	6	6	1.4	10
31	HOR^F /diglyme=1/4 (10)		2	0//50	1.2	0.0	0.0	3.7	0.1	0	76	0.0	97
32	HOR^F /diglyme=1/4 (10)		4	0//50	0.3	0.0	0.0	4.7	0.1	0	95	0.0	99
33	diglyme (10)		2	0//50	1.7	0.0	0.0	3.2	0.1	0	66	0.0	95
34	diglyme (10)		4	0//50	0.9	0.0	0.0	3.9	0.2	0	82	0.0	96

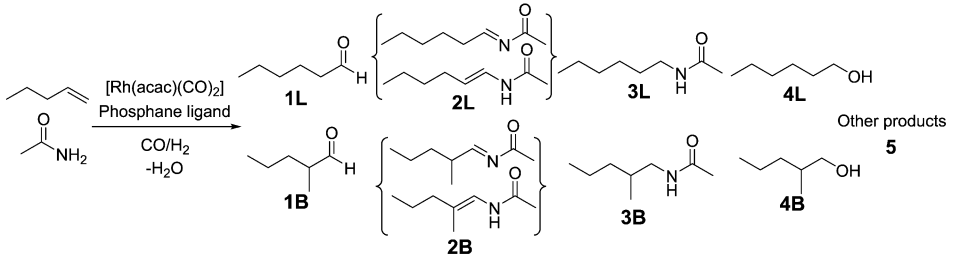
[a] Reaction conditions: 0.01 mmol [Rh(CO)$_2$(acac)], 0.02 mmol xantphos, 0.05 mmol HOTs , 5 mmol hexanal, 5 mmol acetamide (Rh:xantphos:HOTs:hexanal:acetamide=1:2:5:500:500); *P(H$_2$)*=50 bar; *t*=2-4 h; solvent: 10 mL diglyme; decane as internal standard.

Table AII.10. Product development in time in the hydroamidomethylation of 1-pentene with acetamide[a]

	Time	1-pent	**1L**	**1B**	**2L**	**2B**	**3L**	**3B**	**4L**	**4B**	**5**	conversion		Selectivity %				**1**	**3**
	h	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	**1**	**2**	**3**	**4**	**5**	L%	L%
1	0.5	3.9	0.5	0.0	0.3	0.0	0.1	0.0	0.0	0.0	0.1	21	52	26	10	2	10	>99	>99
2	1	3.3	0.8	0.0	0.4	0.0	0.2	0.0	0.0	0.0	0.1	35	49	28	13	3	7	99	>99
3	2	2.3	1.1	0.0	0.4	0.0	0.9	0.0	0.1	0.0	0.1	54	41	18	32	4	4	96	98
4	3	1.3	1.2	0.0	0.4	0.0	1.8	0.0	0.1	0.0	0.1	74	33	12	47	4	4	96	>99
5	4	0.9	1.1	0.1	0.3	0.0	2.4	0.0	0.2	0.0	0.2	83	27	9	57	4	4	95	>99
6	6	0.6	0.9	0.1	0.3	0.0	2.9	0.0	0.2	0.0	0.2	89	22	6	65	4	4	95	>99
7	8	0.5	0.7	0.1	0.2	0.0	3.1	0.0	0.3	0.0	0.2	91	17	4	69	6	4	92	>99
8	10	0.4	0.5	0.1	0.2	0.0	3.3	0.0	0.3	0.0	0.2	92	13	4	71	6	5	89	>99
9	12	0.4	0.4	0.1	0.2	0.0	3.4	0.0	0.3	0.0	0.2	93	11	4	74	6	5	84	>99
10	14	0.3	0.4	0.1	0.2	0.0	3.5	0.0	0.3	0.0	0.2	94	9	4	75	7	5	80	>99
11	16	0.3	0.3	0.1	0.1	0.0	3.6	0.0	0.3	0.0	0.3	95	8	4	75	7	5	75	>99
12	20	0.1	0.2	0.1	0.1	0.0	3.7	0.0	0.4	0.0	0.4	98	7	4	74	8	7	64	>99

[a] Reaction conditions: 0.01 mmol [$Rh(CO)_2(acac)$], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); T=100 °C; $P(CO/H_2)$=50 bar(1/2); Solvent: 10 mL (v/v) HOR^F/diglyme (1/4); decane as internal standard.

Table AII.11. Effect of various ligands on intermolecular hydroamidomethylation of 1-pentene with acetamide[a]



	ligand	t	1-pent	1L	1B	2L	2B	3L	3B	4L	4B	5	conversion	1	3
		h	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	L%	L%
1	no	4	0.0	0.7	1.6	0.3	0.8	0.3	0.1	0.0	0.0	1.1	99	30	71
2	no	8	0.0	0.3	1.4	0.2	0.7	0.6	0.3	0.1	0.1	1.3	100	19	72
3	PPh_3	4	0.2	1.0	1.0	0.4	0.6	0.1	0.0	0.0	0.0	1.7	96	51	>99
4	PPh_3	8	0.0	0.8	0.9	0.4	0.6	0.2	0.0	0.0	0.0	2.1	99	45	>99
5	DPEphos	4	1.5	0.9	0.4	0.3	0.1	1.1	0.0	0.1	0.0	0.5	70	67	97
6	DPEphos	8	0.1	1.2	1.1	0.3	0.1	1.2	0.0	0.1	0.0	0.8	97	53	99
7	triPhos	4	4.5	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	10	70	-
8	triPhos	8	4.1	0.4	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.3	19	70	-
9	xantphos	4	0.9	1.1	0.1	0.3	0.0	2.4	0.0	0.2	0.0	0.2	83	95	>99
10	xantphos	8	0.5	0.7	0.1	0.2	0.0	3.1	0.0	0.3	0.0	0.2	91	92	>99
11	tBu-xantphos	4	1.0	1.0	0.0	0.3	0.0	2.3	0.0	0.1	0.0	0.2	80	96	>99
12	tBu-xantphos	8	0.4	0.8	0.0	0.2	0.0	3.0	0.0	0.2	0.0	0.3	93	94	>99
13	Si-xantphos	4	1.2	0.9	0.3	0.3	0.0	2.0	0.0	0.2	0.0	0.2	77	72	99
14	Si-xantphos	8	0.3	0.6	0.4	0.1	0.0	2.9	0.1	0.2	0.0	0.3	93	62	98
15	oMeO-xantphos	4	4.4	0.2	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.1	11	58	>99
16	oMeO-xantphos	8	3.4	0.4	0.4	0.2	0.0	0.0	0.0	0.0	0.0	0.4	32	47	>99
17	benzoxantphos	4	0.9	1.1	1.0	0.5	0.0	0.7	0.0	0.0	0.0	0.8	82	53	>99
18	benzoxantphos	8	0.4	0.8	1.0	0.3	0.4	0.8	0.0	0.0	0.0	1.2	92	44	>99
19	DBFphos	4	2.7	1.0	0.0	0.5	0.0	0.5	0.0	0.0	0.0	0.1	46	97	98
20	DBFphos	8	0.9	1.2	0.2	0.4	0.0	1.3	0.0	0.1	0.0	0.9	82	88	>99
21	Homoxantphos	4	3.6	0.2	0.1	0.1	0.0	0.8	0.0	0.0	0.0	0.1	28	70	95
22	Homoxantphos	8	1.7	0.4	0.3	0.1	0.0	1.7	0.1	0.1	0.0	0.5	66	57	96
21	xantphos$(tBu)_2$	4	0.2	0.7	1.7	0.4	0.8	0.3	0.1	0.0	0.0	0.8	97	28	82
22	xantphos$(tBu)_2$	8	0.0	0.5	1.6	0.3	0.8	0.4	0.1	0.0	0.0	1.3	100	26	71

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol L, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:L:HOTs:1-pentene:acetamide=1:2(bidentate) or 4(monodentate):5:500:500); T=100 °C; t=4-8h; $P(CO/H_2)$=50 bar(1/2); Solvent: 10 ml HOR^F/diglyme (1/4); decane as an internal standard.

Table AII.12. Hydroamidomethylation reaction using different amides and alkenes [a]

	alkene 5mmol	amide 6mmol	Time h	alkene mmol	**1L*** mmol	**1B*** mmol	**2L*** mmol	**2B*** mmol	**3L*** mmol	**3B*** mmol	**4L*** mmol	**4B*** mmol	**5*** mmol	conversion %	**1*** L%	**3*** L%
1	1-pentene	acetamide	4	0.9	1.1	0.1	0.3	0.0	2.4	0.0	0.2	0.0	0.2	83	95	>99
2	1-pentene	acetamide	8	0.5	0.7	0.1	0.2	0.0	3.1	0.0	0.3	0.0	0.2	91	92	>99
3	1-pentene	acetamide	12	0.4	0.4	0.1	0.2	0.0	3.4	0.0	0.3	0.0	0.2	93	84	>99
4	1-hexene	acetamide	4	1.0	1.1	0.1	0.2	0.0	2.2	0.0	0.2	0.0	0.2	79	94	>99
5	1-hexene	acetamide	8	0.6	0.8	0.1	0.1	0.0	3.0	0.0	0.3	0.0	0.2	89	90	>99
6	1-hexene	acetamide	12	0.3	0.7	0.1	0.1	0.0	3.2	0.0	0.3	0.0	0.3	95	88	>99
7	1-octene	acetamide	4	0.9	1.2	0.1	0.1	0.0	2.3	0.0	0.2	0.0	0.2	81	94	>99
8	1-octene	acetamide	8	0.6	1.0	0.1	0.1	0.0	2.7	0.0	0.2	0.0	0.3	88	93	>99
9	1-octene	acetamide	12	0.3	0.9	0.1	0.0	0.0	2.9	0.0	0.3	0.0	0.4	93	92	>99
10	styrene	acetamide	4	1.3	0.5	0.9	1.0	0.3	0.9	0.0	0.0	0.0	0.0	73	34	>99
11	styrene	acetamide	8	0.7	0.4	0.4	1.2	0.3	1.4	0.0	0.1	0.1	0.3	86	51	>99
12	styrene	acetamide	12	0.4	0.4	0.5	1.2	0.4	1.6	0.0	0.1	0.1	0.3	93	43	>99
13	1-pentene	Me-acetamide	4	1.1	0.9	0.0	0.2	0.0	2.5	0.0	0.1	0.0	0.1	78	98	>99
14	1-pentene	Me-acetamide	8	0.5	0.6	0.0	0.2	0.0	3.3	0.0	0.1	0.0	0.2	90	96	>99
15	1-pentene	Me-acetamide	12	0.3	0.3	0.0	0.2	0.0	3.7	0.0	0.1	0.0	0.2	94	93	>99
16	1-pentene	diMe-acetamide	4	1.2	1.0	0.1	0.1	0.0	2.3	0.0	0.1	0.0	0.2	75	94	>99
17	1-pentene	diMe-acetamide	8	0.6	0.7	0.1	0.1	0.0	3.2	0.0	0.1	0.0	0.2	89	88	>99
18	1-pentene	diMe-acetamide	12	0.4	0.6	0.1	0.1	0.0	3.3	0.0	0.1	0.0	0.3	92	86	>99
19	1-pentene	triMe-acetamide	4	1.2	1.3	0.0	0.4	0.0	1.8	0.0	0.0	0.0	0.2	76	99	>99
20	1-pentene	triMe-acetamide	8	0.7	1.0	0.1	0.2	0.0	2.6	0.0	0.1	0.0	0.2	87	91	>99
21	1-pentene	triMe-acetamide	12	0.5	0.8	0.1	0.2	0.0	2.8	0.0	0.1	0.0	0.4	89	90	>99
22	1-pentene	Valeramide	4	1.0	0.7	0.0	0.1	0.0	2.9	0.0	0.1	0.0	0.1	80	96	>99
23	1-pentene	Valeramide	8	0.4	0.4	0.0	0.1	0.0	3.8	0.0	0.2	0.0	0.1	93	90	99
24	1-pentene	Valeramide	12	0.2	0.3	0.0	0.1	0.0	4.1	0.0	0.2	0.0	0.1	97	84	99
25	1-pentene	Fluoroacetamide	4	1.1	2.8	0.1	0.5	0.0	0.1	0.0	0.1	0.0	0.1	77	96	>99
26	1-pentene	Fluoroacetamide	8	0.5	3.3	0.1	0.5	0.0	0.2	0.0	0.2	0.0	0.1	90	96	>99
27	1-pentene	Fluoroacetamide	12	0.4	3.4	0.1	0.6	0.0	0.2	0.0	0.2	0.0	0.1	92	96	>99
28	1-pentene	Benzamide	4	3.0	1.0	0.0	0.2	0.0	0.3	0.0	0.0	0.0	0.5	39	99	>99
29	1-pentene	Benzamide	8	1.5	1.3	0.0	0.2	0.0	0.8	0.0	0.0	0.0	1.0	69	99	>99
30	1-pentene	Benzamide	12	0.9	1.4	0.0	0.3	0.0	1.2	0.0	0.0	0.0	1.1	82	97	>99
31	1-pentene	p-MeO-benzamide	4	1.2	2.1	0.0	0.1	0.0	1.4	0.0	0.0	0.0	0.1	76	99	>99
32	1-pentene	p-MeO-benzamide	8	0.5	1.7	0.0	0.1	0.0	2.2	0.0	0.0	0.0	0.5	90	99	>99
33	1-pentene	p-MeO-benzamide	12	0.3	1.6	0.0	0.1	0.0	2.3	0.0	0.0	0.0	0.7	95	98	>99
34	1-pentene	p-CF_3-benzamide	4	3.1	0.5	0.0	0.8	0.0	0.3	0.0	0.0	0.0	0.2	37	92	>99
35	1-pentene	p-CF_3-benzamide	8	2.1	0.8	0.1	0.9	0.0	0.6	0.0	0.0	0.0	0.5	57	90	>99
36	1-pentene	p-CF_3-benzamide	12	1.5	0.8	0.1	1.0	0.0	1.0	0.0	0.0	0.0	0.6	71	84	>99

[a] Reaction conditions: 0.01 mmol [$Rh(CO)_2$(acac)], 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol alkene, 5 mmol amide (Rh:xantphos:HOTs:alkene:amide= 1:2:5:500:500); T=100 °C; t=4-12h; $P(CO/H_2)$=50 bar(1/2); Solvent: 10 mL (v/v) HOR^F/diglyme (1/4); decane as internal standard.

Table AII.13-1. Influence of various co-solvents as an alternative for HOR^F on hydroamidomethylation of 1-pentene with acetamide[a]

	co-solvent	t	pK_a	1-pent	**1L**	**1B**	**2L**	**2B**	**3L**	**3B**	**4L**	**4B**	**5**	conversion	**1**	**3**
	20 mmol	h	co-solvent	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	L%	L%
1	HOR^F	4	9.2	0.9	1.0	0.1	0.2	0.0	2.5	0.0	0.2	0.0	0.1	82	95	>99
2	HOR^F	8	9.2	0.5	0.8	0.1	0.1	0.0	3.1	0.0	0.2	0.0	0.2	90	93	>99
3	TFE	4	12.37	0.9	0.8	0.0	0.5	0.0	1.2	0.0	0.0	0.0	1.5	82	99	>99
4	TFE	8	12.37	0.6	0.7	0.0	0.3	0.0	1.5	0.0	0.1	0.0	1.9	89	98	>99
5	PhOH	4	9.99	1.2	1.2	0.1	0.2	0.0	1.6	0.0	0.1	0.0	0.5	76	93	>99
6	PhOH	8	9.99	0.9	0.8	0.1	0.3	0.0	1.9	0.0	0.2	0.0	0.8	82	88	>99
7	triF-4-cresol	4	8.68	0.6	1.2	0.7	0.3	0.4	0.7	0.0	0.1	0.0	0.8	87	62	94
8	triF-4-cresol	8	8.68	0.2	1.0	0.7	0.3	0.4	1.0	0.1	0.1	0.0	1.2	95	59	91
9	4-F-PhOH	4	9.89	1.1	1.2	0.1	0.1	0.0	2.0	0.0	0.1	0.0	0.3	78	94	>99
10	4-F-PhOH	8	9.89	0.7	1.0	0.1	0.1	0.0	2.5	0.0	0.2	0.0	0.4	86	92	>99
11	3-F-PhOH	4	9.29	0.9	1.2	0.1	0.2	0.0	2.4	0.0	0.1	0.0	0.1	82	92	>99
12	3-F-PhOH	8	9.29	0.5	0.9	0.1	0.1	0.0	2.9	0.0	0.2	0.0	0.2	90	91	>99
13	2-F-PhOH	4	8.73	1.0	1.1	0.1	0.2	0.0	1.5	0.0	0.1	0.0	1.1	81	95	>99
14	2-F-PhOH	8	8.73	0.6	0.8	0.1	0.2	0.0	1.9	0.0	0.1	0.0	1.4	88	93	>99
15	4-Cl-PhOH	4	9.41	0.9	1.1	0.1	0.2	0.0	2.4	0.0	0.2	0.0	0.1	82	92	>99
16	4-Cl-PhOH	8	9.41	0.5	0.9	0.1	0.1	0.0	3.0	0.0	0.3	0.0	0.2	91	90	>99
17	3-Cl-PhOH	4	9.12	1.0	1.8	1.1	0.3	0.3	0.2	0.0	0.0	0.0	0.3	80	62	>99
18	3-Cl-PhOH	8	9.12	0.5	1.5	1.2	0.3	0.4	0.4	0.0	0.0	0.0	0.7	90	56	>99
19	2-Cl-PhOH	4	8.56	1.0	1.1	0.1	0.2	0.0	1.9	0.0	0.1	0.0	0.6	79	94	>99
20	2-Cl-PhOH	8	8.56	0.6	0.8	0.1	0.1	0.0	2.3	0.0	0.1	0.0	0.9	88	92	>99

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); $P(CO/H_2)$=50(1/2) bar; T=100 °C; *t*=4-8 h; Solvent: 10 mL diglyme; co-solvent= 20 mmol; decane as internal standard.

Table AII.13-2. Influence of various co-solvents as an alternative for HOR[F] on hydroamidomethylation of 1-pentene with acetamide[a]

	co-solvent	t	pK_a	1-pent[b]	**1L**	**1B**	**2L**	**2B**	**3L**	**3B**	**4L**	**4B**	**5**	conversion	**1**	**3**
	20 mmol	h	co-solvent	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	L%	L%
21	4-Br-PhOH	4	9.37	1.3	1.3	0.0	0.4	0.0	0.2	0.0	0.0	0.0	1.7	73	>99	>99
22	4-Br-PhOH	8	9.37	0.8	1.0	0.0	0.4	0.0	0.4	0.0	0.1	0.0	2.3	84	>99	>99
23	2,6-diMe-PhOH	4	10.36	0.9	1.0	0.1	0.3	0.0	1.0	0.0	0.1	0.0	1.6	82	93	>99
24	2,6-diMe-PhOH	8	10.36	0.6	0.7	0.1	0.2	0.0	1.3	0.0	0.1	0.0	2.0	88	90	>99
25	2,6-diiPr-PhOH	4	11.1	1.0	1.2	0.1	0.3	0.0	0.2	0.0	0.0	0.0	2.2	81	95	>99
26	2,6-diiPr-PhOH	8	11.1	0.6	0.9	0.1	0.3	0.0	0.4	0.0	0.1	0.0	2.6	89	94	>99
27	2,6-ditBu-PhOH	4	13.6	1.0	1.3	0.0	0.6	0.0	0.4	0.0	0.0	0.0	1.7	80	99	>99
28	2,6-ditBu-PhOH	8	13.6	0.7	1.0	0.0	0.4	0.0	0.6	0.0	0.0	0.0	2.3	86	98	>99
29	2,6-diMe-PhCOOH	4	3.25	1.1	1.5	0.1	0.2	0.0	0.2	0.0	0.0	0.0	1.9	78	96	>99
30	2,6-diMe-PhCOOH	8	3.25	0.6	1.4	0.1	0.2	0.0	0.3	0.0	0.1	0.0	2.3	88	96	>99
31	AcOH	4	4.76	1.1	0.5	0.0	0.5	0.0	0.9	0.0	0.0	0.0	2.0	78	>99	>99
32	AcOH	8	4.76	0.5	0.4	0.0	0.4	0.0	1.1	0.0	0.0	0.0	2.5	89	98	>99
33	diPhMeOH	4	13.4	1.0	2.1	0.1	0.6	0.0	0.7	0.0	0.1	0.0	0.5	80	96	>99
34	diPhMeOH	8	13.4	0.7	1.7	0.1	0.6	0.0	1.0	0.0	0.1	0.0	0.9	87	95	>99
35	diiPrMeOH	4	~14.5	1.0	1.6	0.1	0.7	0.0	0.4	0.0	0.0	0.0	1.2	81	96	>99
36	diiPrMeOH	8	~14.5	0.6	1.3	0.1	0.4	0.0	0.7	0.0	0.0	0.0	1.9	89	95	>99
37	H_2O	4	15.7	1.0	3.5	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.3	80	97	>99
38	H_2O	8	15.7	0.6	3.8	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.3	89	97	>99
39	2-naphthol	4	9.63	1.1	0.9	0.0	0.3	0.0	0.3	0.0	0.0	0.0	2.3	78	99	>99
40	2-naphthol	8	9.63	0.7	0.7	0.0	0.3	0.0	0.5	0.0	0.0	0.0	2.7	85	99	>99

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); $P(CO/H_2)$=50(1/2) bar; T=100 °C; *t*=8h; Solvent: 10 mL diglyme; co-solvent= 20 mmol; decane as internal standard.

Table AII.14. Influence of added water on hydroamidomethylation of 1-pentene with acetamide[a]

	t	H_2O	1-pent	**1L**	**1B**	**2L**	**2B**	**3L**	**3B**	**4L**	**4B**	**5**	conversion	**1**	**3**	**3/4**
	h	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	L%	L%	ratio
1	4	0	0.9	1.1	0.1	0.3	0.0	2.4	0.0	0.2	0.0	0.2	83	95	>99	15
2	8	0	0.5	0.7	0.1	0.2	0.0	3.1	0.0	0.3	0.0	0.2	91	92	>99	13
3	4	2.5	0.9	1.5	0.1	0.2	0.0	1.7	0.0	0.2	0.0	0.4	82	96	>99	7
4	8	2.5	0.6	1.2	0.1	0.2	0.0	2.0	0.0	0.3	0.0	0.6	89	95	>99	6
5	4	5	0.8	1.9	0.1	0.2	0.0	1.3	0.0	0.2	0.0	0.4	83	96	>99	5
6	8	5	0.6	1.6	0.1	0.2	0.0	1.5	0.0	0.3	0.0	0.6	88	95	>99	4
7	4	10	0.9	2.1	0.1	0.3	0.0	0.9	0.0	0.2	0.0	0.4	81	96	>99	4
8	8	10	0.6	1.9	0.1	0.3	0.0	1.1	0.0	0.2	0.0	0.7	88	96	>99	4
9	4	20	0.8	2.6	0.1	0.4	0.0	0.6	0.0	0.2	0.0	0.4	84	97	>99	3
10	8	20	0.4	2.3	0.1	0.3	0.0	0.8	0.0	0.2	0.0	0.8	91	97	>99	3

[a] Reaction conditions: 0.01 mmol $[Rh(CO)_2(acac)]$, 0.02 mmol xantphos, 0.05 mmol HOTs, 5 mmol 1-pentene, 5 mmol acetamide (Rh:xantphos:HOTs:1-pentene:acetamide=1:2:5:500:500); $P(CO/H_2)$=50(1/2) bar; T=100 °C; *t*=4-8 h; Solvent: 10 mL (v/v) of HOR^F/diglyme (1/4); decane as internal standard.

Appendix III

Supporting Information of Chapter 4:

Towards Synthesis of Primary Amines: Investigating Rhodium-Catalyzed Homogeneous Reductive Amidation and Hydroamidomethylation with Formamide

Full analytical data of catalytic experiments

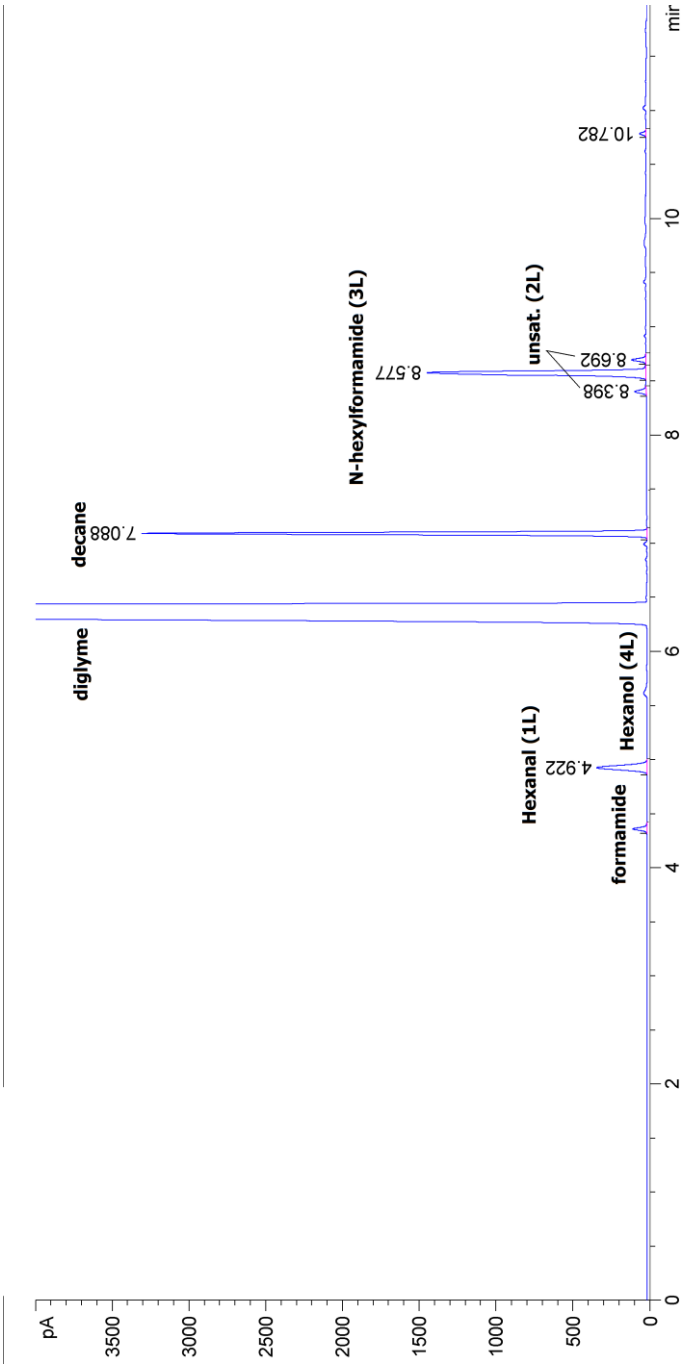
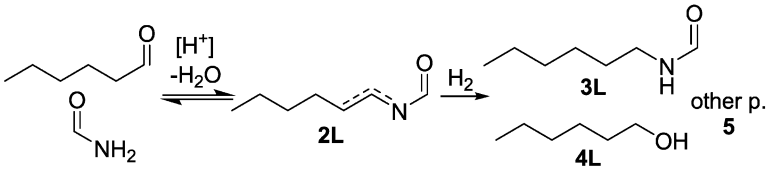


Figure AIII.1. GC spectrum of typical reductive amidation of hexanal with formamide; (Rh:xantphos:HOTs:hexanal:formamide =1:1.25:5:500:600); P_{H2}=80 bar; *T*=60 °C; *t*=4-8 h; Solvent: 25 ml diglyme; decane as internal standard

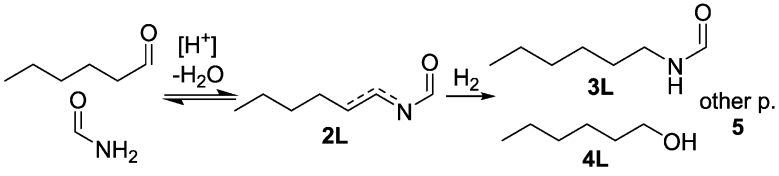
Table AIII.1. Reductive amidation of hexanal with formamide catalyzed by $[Rh(cod)Cl]_2$ in combination with xantphos ligand [a]



	formamide	t	T	P (H_2)	HOTs	diglyme	1L	2L	3L	4L	5	conv.	selectivity %[b]				3L/4L	3L+4L
	mmol	h	°C	bar	mmol	mL	mmol	mmol	mmol	mmol	mmol	%	2L	3L	4L	5	ratio	sel.%
1	6	4	80	80	0.05	25	3.4	0.3	1.1	0.1	0.2	33	15	66	7	12	10	73
2	6	8	80	80	0.05	25	2.5	0.2	1.8	0.1	0.4	50	8	72	6	14	12	78
3	6	4	80	80	0.1	25	2.1	0.3	2.2	0.1	0.3	57	9	76	4	11	19	80
4	6	8	80	80	0.1	25	1.2	0.2	2.9	0.1	0.5	76	6	76	4	14	20	80
5	6	4	80	80	0.2	25	1.5	0.2	2.8	0.1	0.4	70	5	81	2	12	41	83
6	6	8	80	80	0.2	25	0.3	0.1	3.8	0.1	0.7	94	2	82	2	14	44	83
7	6	4	80	80	0.4	25	1.0	0.3	3.0	0.1	0.6	79	8	76	1	14	60	78
8	6	8	80	80	0.4	25	0.2	0.2	3.8	0.1	0.8	95	3	79	1	16	62	80
9	6	4	80	80	0.6	25	0.9	0.3	3.1	0.0	0.6	81	8	76	1	14	78	77
10	6	8	80	80	0.6	25	0.2	0.3	3.8	0.0	0.8	97	5	78	1	16	77	79
11	6	4	80	80	0.8	25	0.7	0.3	3.1	0.0	0.8	85	7	74	1	18	75	75
12	6	8	80	80	0.8	25	0.1	0.4	3.6	0.0	1.0	99	7	72	1	20	72	73
13	7.5	4	80	80	0.2	25	1.2	0.2	2.8	0.1	0.8	76	5	73	2	21	45	74
14	7.5	8	80	80	0.2	25	0.2	0.2	3.7	0.1	0.9	97	4	76	2	18	46	77
15	6	4	40	80	0.2	25	3.1	1.0	0.8	0.0	0.1	38	55	40	1	4	41	41
16	6	8	40	80	0.2	25	2.2	1.4	1.2	0.0	0.2	56	51	42	1	6	42	43
17	6	4	60	80	0.2	25	1.7	0.3	2.8	0.0	0.2	66	8	85	1	5	59	87
18	6	8	60	80	0.2	25	0.7	0.2	3.7	0.1	0.3	86	5	87	1	6	60	89
19	6	4	100	80	0.2	25	1.1	0.2	2.8	0.2	0.7	79	6	72	5	17	15	77
20	6	8	100	80	0.2	25	0.0	0.1	3.2	0.3	1.4	100	3	64	5	28	12	69
21	6	4	60	60	0.2	25	1.9	0.5	2.2	0.0	0.3	62	18	70	1	11	61	72
22	6	8	60	60	0.2	25	0.9	0.4	3.1	0.0	0.5	81	11	77	1	12	62	78
23	6	4	60	40	0.2	25	2.1	0.8	1.8	0.0	0.3	58	27	62	1	10	56	63
24	6	8	60	40	0.2	25	1.3	0.6	2.7	0.0	0.4	74	15	72	1	12	58	73
25	6	4	60	20	0.2	25	2.4	1.3	1.0	0.0	0.4	53	48	36	1	16	53	37
26	6	8	60	20	0.2	25	1.6	1.2	1.6	0.0	0.6	67	34	48	1	16	53	49
27[c]	6	4	60	80	0.2	15	1.4	0.9	2.2	0.0	0.5	72	25	61	1	13	47	62
28[c]	6	8	60	80	0.2	15	0.3	0.6	3.2	0.1	0.8	94	13	69	1	17	52	70

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol formamide (Rh:xantphos:hexanal:formamide=1:1.25:500:600); HOTs: 0.05-0.8 mmol; P_{H2}= 20-80 bar; T = 40-100 °C; t = 4-8 h; Solvent: 25 mL diglyme; [b] the selectivity was determined using decane as internal standard.[c] 15 mLdiglyme

Table AIII.2-1. Reductive amidation of hexanal with formamide catalyzed by $[Rh(cod)Cl]_2$ in combination with different ligands [a]



	Ligand	t	1L	2L	3L	4L	5	conv.	selectivity %[b]				3L/4L	3L+4L
		h	mmol	mmol	mmol	mmol	mmol	%	2L	3L	4L	5	ratio	sel.%
1	-	4	2.8	1.2	0.5	0.0	0.5	44	53	25	1	21	33	26
2	-	8	2.0	1.3	0.8	0.0	0.8	60	44	27	1	28	30	28
3	PPh_3	4	2.7	1.0	0.9	0.0	0.4	47	43	38	2	17	21	39
4	PPh_3	8	1.7	1.2	1.3	0.1	0.8	66	35	39	2	24	19	41
5	$P(o\text{-}MeO\text{-}Ph)_3$	8	1.8	1.1	1.3	0.1	0.6	63	35	43	2	20	22	45
6	$P(p\text{-}MeO\text{-}Ph)_3$	8	1.6	1.0	1.4	0.2	0.8	67	30	41	5	24	8	46
7	$P(2,4diMeO\text{-}Ph)_3$	8	2.2	0.9	1.1	0.1	0.7	56	31	39	4	26	9	43
8	$P(2,6diMeO\text{-}Ph)_3$	8	2.5	1.0	0.7	0.0	0.8	50	41	27	2	31	17	29
9	$P(o\text{-}EtO\text{-}Ph)_3$	8	1.8	1.4	1.0	0.1	0.8	64	43	30	3	24	10	33
10	$P(o\text{-}Tolyl)_3$	8	1.7	1.3	1.0	0.1	0.9	66	39	32	3	27	11	35
11	$P(m\text{-}Tolyl)_3$	8	1.7	1.2	1.0	0.2	0.9	65	37	31	5	28	7	35
12	$P(p\text{-}Tolyl)_3$	8	1.7	1.0	1.2	0.2	0.9	66	31	36	6	26	6	42
13	$P(m\text{-}ClPh)_3$	8	1.8	1.3	0.9	0.1	1.0	64	40	27	3	30	9	30
14	$P(p\text{-}ClPh)_3$	8	1.6	1.0	1.5	0.1	0.7	67	30	46	3	21	13	49
15	$P(n\text{-}Bu)_3$	8	0.8	0.6	1.2	2.0	0.5	84	14	28	47	11	1	75
16	$P(t\text{-}Bu)_3$	8	1.3	0.8	1.8	0.4	0.7	74	22	48	12	18	4	60
17	PCy_3	8	1.1	0.7	1.7	0.6	1.0	78	17	43	15	26	3	57
18	$P(n\text{-}Oct)_3$	8	0.7	0.6	1.0	2.1	0.6	86	14	23	48	15	0	71
19	$P(Bu)(Ad)_2$	8	1.0	0.7	0.8	1.8	0.7	80	16	21	45	18	0	65
20	$P(O\text{-}di\text{-}tBuPh)_3$	8	1.8	1.0	1.2	0.1	0.8	64	31	39	4	26	9	43

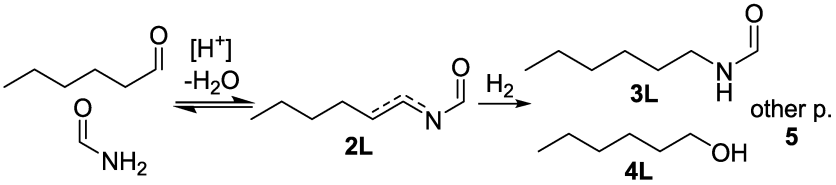
[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol formamide (Rh:ligand:hexanal:HOTs:formamide=1:(bi-dentate=1.25) or (mono-dentate=2.5):20:500:600); P_{H2}= 80 bar; T = 60 °C; t = 4-8 h; Solvent: 25 mL diglyme; [b] the selectivity determined using decane as internal standard

Table AIII.2-2. Reductive amidation of hexanal with formamide catalyzed by $[Rh(cod)Cl]_2$ in combination with different ligands [a]

	Ligand	t	**1L**	**2L**	**3L**	**4L**	**5**	conv.	selectivity %[b]				**3L/4L**	**3L+4L**
		h	mmol	mmol	mmol	mmol	mmol	%	**2L**	**3L**	**4L**	**5**	ratio	sel.%
21	dppm	8	2.0	1.7	0.3	0.0	0.9	60	58	11	0	31		11
22	dppp	8	1.9	1.3	0.5	0.0	1.2	62	42	18	1	39	18	19
23	dppb	8	2.6	0.9	0.6	0.2	0.7	48	36	26	8	30	3	34
24	o-MeOdppe	8	1.9	1.1	1.0	0.2	0.8	61	35	32	6	27	5	39
25	o-MeOdppp	8	1.8	1.8	0.2	0.0	1.1	63	56	7	0	36		7
26	p-MeOdppp	8	2.0	1.7	0.3	0.0	1.0	60	56	10	0	34		10
27	o-MeOdppb	8	2.9	0.6	0.5	0.2	0.7	41	28	26	10	36	3	36
28	p-MeOdppb	8	2.8	0.5	0.6	0.3	0.7	44	25	27	15	33	2	42
29	bcope	8	0.8	0.5	0.2	2.6	0.9	84	12	5	62	21	0	67
30	DPEphos	8	1.6	1.2	0.9	0.1	1.2	68	35	28	2	35	15	30
31	DBFphos	8	2.3	1.1	0.6	0.0	0.9	54	41	23	2	34	13	24
32	xantphos	4	1.7	0.3	2.8	0.0	0.2	66	8	85	1	5	59	87
33	xantphos	8	0.7	0.2	3.7	0.1	0.3	86	5	87	1	6	60	89
34	Si-xantphos	4	2.0	0.9	1.6	0.1	0.4	60	30	53	3	13	16	57
35	Si-xantphos	8	0.9	0.6	2.7	0.2	0.6	82	16	67	4	14	16	71
36	tBu-xantphos	4	1.7	0.3	2.9	0.0	0.1	66	9	88	1	2	64	89
37	tBu-xantphos	8	0.8	0.2	3.7	0.1	0.3	85	4	88	1	7	63	89
38	xantphos$(tBu)_2$	8	1.9	1.2	0.4	0.0	1.5	63	38	13	2	48	8	14
39	oMeO-xantphos	8	1.8	0.7	0.4	0.0	2.1	64	21	13	2	65	8	14
40	homoxantphos	8	1.9	1.2	0.6	0.1	1.2	62	39	19	2	40	11	21
41	benzoxantphos	8	2.3	1.3	0.6	0.1	0.8	55	46	23	3	28	7	26

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol formamide (Rh:ligand:HOTs:hexanal:formamide=1:(bi-dentate=1.25) or (mono-dentate=2.5):20:500:600); P_{H2}= 80 bar; T = 60 °C; t = 4-8 h; Solvent: 25 mL diglyme; [b] the selectivity determined using decane as internal standard

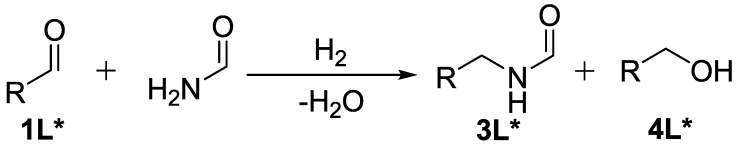
Table AIII.3. Reductive amidation of hexanal with formamide catalyzed by $[Rh(cod)Cl]_2$ in combination with xantphos ligand; time screening [a]



	t	1L	2L	3L	4L	5	conv.	selectivity %[b]				3L/4L	3L+4L
	h	mmol	mmol	mmol	mmol	mmol	%	2L	3L	4L	5	ratio	sel.%
1	0.5	3.8	0.8	0.3	0.0	0.0	24	68	28	0	4	60	29
2	1	3.1	1.1	0.7	0.0	0.1	38	58	36	1	5	58	37
3	2	2.4	0.9	1.5	0.0	0.1	51	33	61	1	5	62	62
4	3	2.1	0.5	2.3	0.0	0.1	59	15	79	1	4	61	80
5	4	1.7	0.3	2.8	0.0	0.2	66	8	85	1	5	59	87
6	6	1.1	0.3	3.3	0.1	0.2	77	7	87	1	5	62	88
7	8	0.7	0.2	3.7	0.1	0.3	86	5	87	1	6	60	89
8	10	0.3	0.2	4.0	0.1	0.4	93	4	87	1	8	60	88

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol hexanal, 6 mmol formamide (Rh:xantphos:HOTs:hexanal:formamide=1:1.25:20:500:600); P_{H2}= 80 bar; T = 60 °C; Solvent: 25 mL diglyme; [b] the selectivity was determined using decane as internal standard.

Table AIII.4. Reductive amidation of hexanal with formamide catalyzed by $[Rh(cod)Cl]_2$ in combination with xantphos ligand; scope of the reaction [a]



	aldehyde	t	1L*	2L*	3L*	4L*	5*	conv.	selectivity %[b]				3L*/L4*	3L*+4L*
	5 mmol	h	mmol	mmol	mmol	mmol	mmol	%	2L*	3L*	4L*	5*	ratio	sel.%
1	butanal	4	1.8	0.3	2.7	0.0	0.3	65	8	82	1	8	62	83
2	butanal	8	0.7	0.3	3.5	0.1	0.4	86	8	82	1	9	61	83
3	hexanal	4	1.7	0.3	2.8	0.0	0.2	66	8	85	1	5	59	87
4	hexanal	8	0.7	0.2	3.7	0.1	0.3	86	5	87	1	6	60	89
5	heptanal	4	1.7	0.3	2.8	0.0	0.2	66	8	85	1	5	57	87
6	heptanal	8	0.8	0.2	3.4	0.1	0.5	85	6	81	1	11	58	83
7	octanal	4	1.7	0.3	2.8	0.0	0.2	65	8	84	2	6	56	86
8	octanal	8	0.9	0.2	3.3	0.1	0.5	83	6	81	2	12	54	83
9	nonanal	4	1.6	0.3	2.7	0.0	0.3	67	9	81	1	8	56	83
10	nonanal	8	0.9	0.2	3.4	0.1	0.4	82	5	84	1	9	57	85
11	2-Me-pentanal	4	3.6	0.6	0.5	0.1	0.2	28	40	35	10	15	4	45
12	2-Me-pentanal	8	3.2	0.5	0.8	0.2	0.3	35	29	44	11	16	4	55
13	PhCHO	4	4.2	0.3	0.2	0.1	0.2	15	39	27	14	20	2	40
14	PhCHO	8	3.7	0.3	0.3	0.1	0.5	25	25	27	9	40	3	36
15	3-Ph-propanal	4	1.9	0.4	2.5	0.1	0.2	63	13	79	2	6	36	81
16	3-Ph-propanal	8	0.7	0.4	3.4	0.1	0.5	85	8	79	2	11	37	81

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol aldehyde, 6 mmol formamide (Rh:xantphos:HOTs:aldehyde:formamide=1:1.25:20:500:600); P_{H2}= 80 bar; T = 60 °C; t = 4-8 h; Solvent: 25 mL diglyme; [b] the selectivity was determined using decane as internal standard.

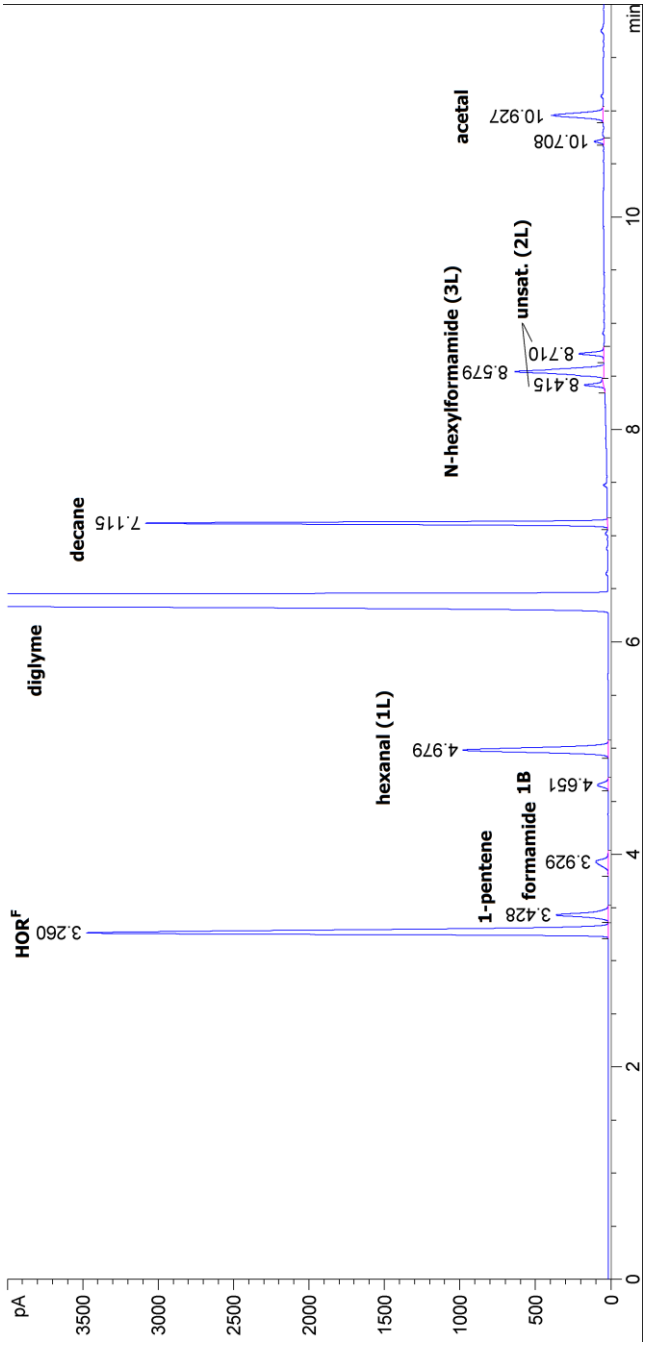
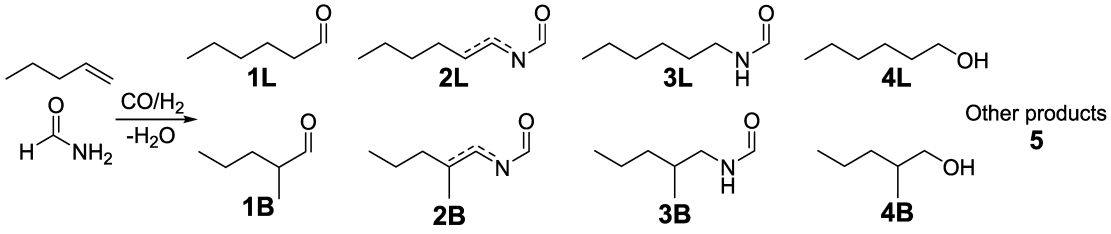


Figure AIII.2. GC spectrum of typical hydroamidomethylation of 1-pentene with formamide; (Rh:xantphos:HOTs:1-pentene:formamide =1:1.25:5:500:500); P=50 bar (CO/H_2=1/2) ; T=100 °C; t=4-8 h; Solvent: 10 ml diglyme or diglyme/HOR^F; decane as internal standard

Table AIII.5. Hydroamidomethylation of 1-pentene with formamide catalyzed by $[Rh(cod)Cl]_2$ in combination with xantphos ligand [a]



	diglyme/HOR^F	t	T	P (CO/H_2)	HOTs	1-pent	**1L**	**1B**	**2L**	**2B**	**3L**	**3B**	**4L**	**4B**	**acetal**	**5**	conv.	selectivity %[b]						**1**	**3**
	10 mL (v/v)	h	°C	bar	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	**1**	**2**	**3**	**4**	**acetal**	**5**	L%	L%
1	8/2	8	60	50(1/2)	0.2	2.1	2.1	0.1	0.3	0.0	0.1	0.0	0.0	0.0	0.2	0.3	58	72	9	5	0	5	9	98	>99
2	8/2	8	80	50(1/2)	0.2	1.4	2.4	0.1	0.3	0.0	0.2	0.0	0.0	0.0	0.4	0.3	73	68	8	6	0	10	8	98	>99
3	10/0	8	100	50(1/2)	0.2	0.8	1.8	0.1	0.5	0.1	0.1	0.0	0.0	0.0		1.5	83	44	14	4	1	0	37	97	>99
4	9/1	8	100	50(1/2)	0.2	0.8	1.7	0.1	0.4	0.0	0.2	0.0	0.0	0.0	0.5	1.1	84	43	10	7	1	13	27	97	>99
5	7/3	8	100	50(1/2)	0.2	0.8	1.6	0.1	0.3	0.0	0.4	0.0	0.0	0.0	1.1	0.6	84	41	6	11	1	26	14	97	>99
6	8/2	8	100	50(1/2)	0.2	0.6	1.7	0.1	0.3	0.0	0.8	0.0	0.0	0.0	0.9	0.5	87	40	8	20	0	20	12	95	>99
7	8/2	8	100	50(1/2)	0.1	0.7	2.2	0.1	0.3	0.0	0.6	0.0	0.0	0.0	0.5	0.4	87	54	8	15	0	13	10	95	>99
8	8/2	8	100	50(1/2)	0.05	0.7	2.7	0.1	0.3	0.0	0.5	0.0	0.0	0.0	0.3	0.4	86	64	7	12	0	8	9	96	>99

[a] Reaction conditions: 0.005 mmol $[Rh(cod)Cl]_2$, 5 mmol 1-pentene, 5 mmol formamide (Rh:xantphos:1-pentene: formamide=1:2:500:500); HOTs: 0.05-0.2 mmol; P(CO/H_2)= 50 (1/2) bar; T= 60-100 °C; t = 8 h; Solvent: 10 mL diglyme or diglyme/HOR^F; [b] the selectivity was determined using decane as internal standard

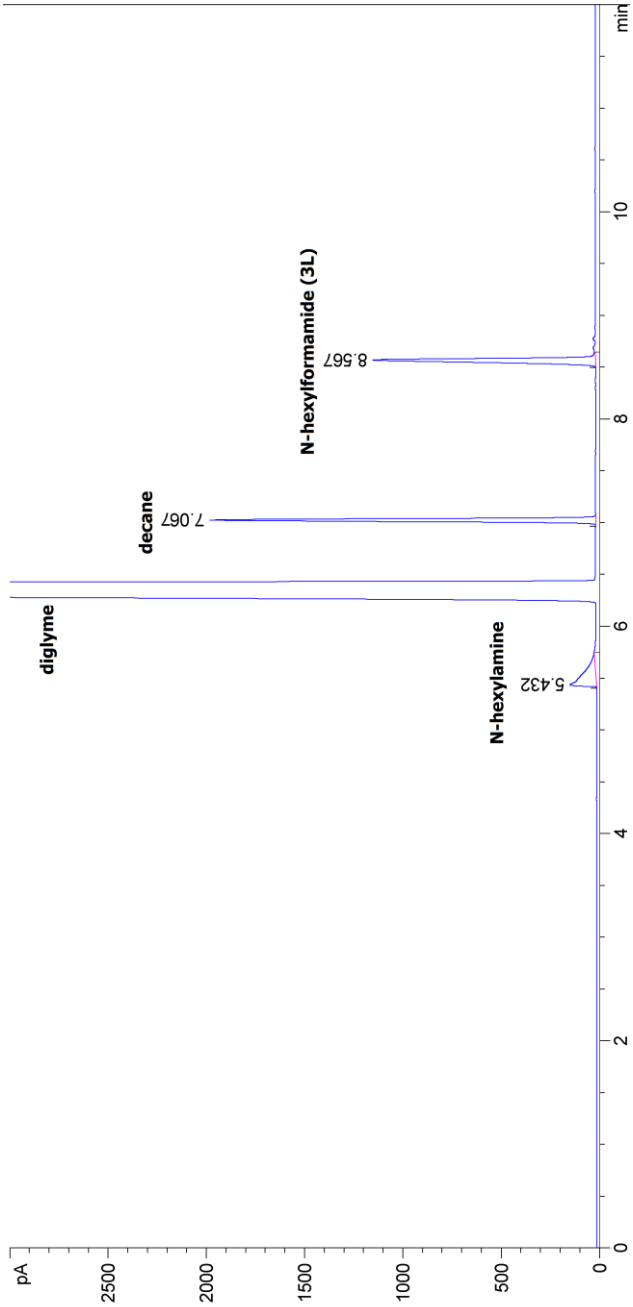


Figure AIII.3. GC spectrum of typical decarbonylation of N-hexylformamide; 10 mol% metal (M) or base (B), 20 mol% ligands (L)(M(B):L:formamide=0.5:1:5) T= room temperature; t = 30 min; Solvent: 5 mL diglyme; decane as an external standard

Appendix IV

Supporting Information of Chapter 5:

From Renewable Feedstock to "Green" Nylon: Catalytic Conversion of γ-Valerolactone to ε-Caprolactam

Full analytical data of catalytic experiments

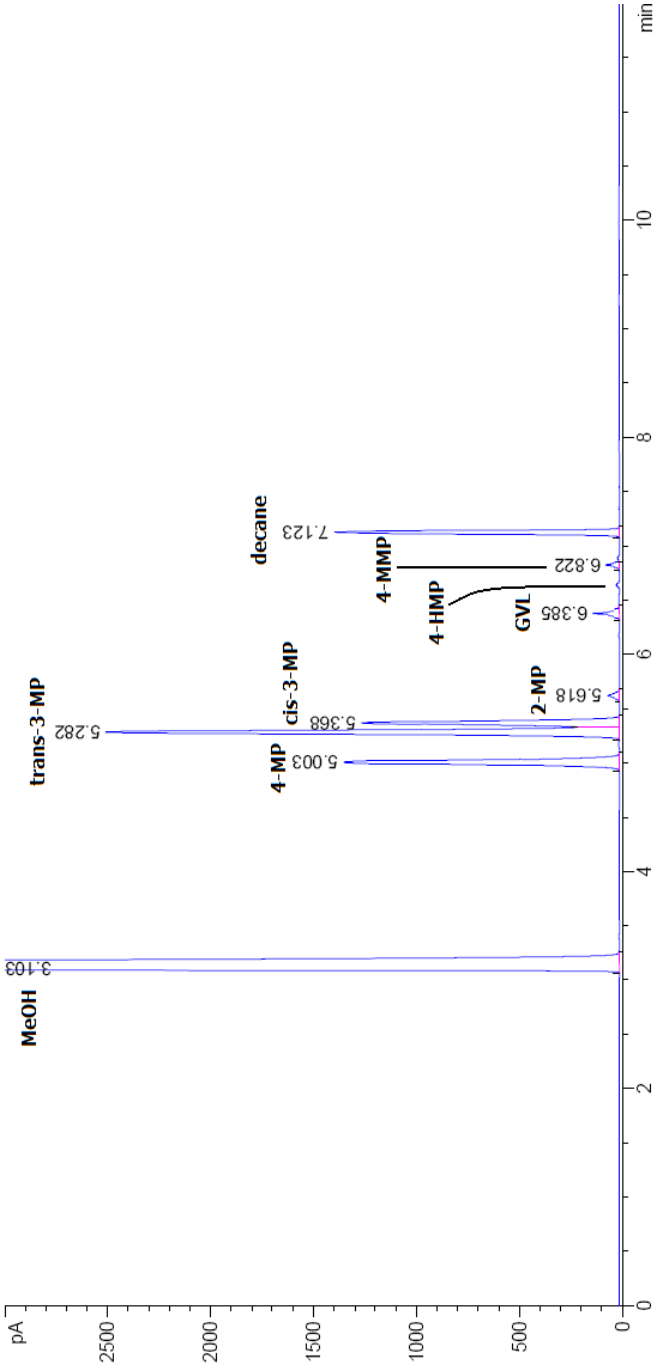


Figure AIV.1. GC spectrum of typical reactive distillation of methyl pentenoates (MP); distillate; methyl-4-pentenoate (4-MP), methyl-3-pentenoate (3-MP), methyl-2-pentenoate (2-MP), methyl-4-methoxy pentanoate (4-MMP), methyl-4-hydroxy pentanoate (4-HMP) and heavy ends

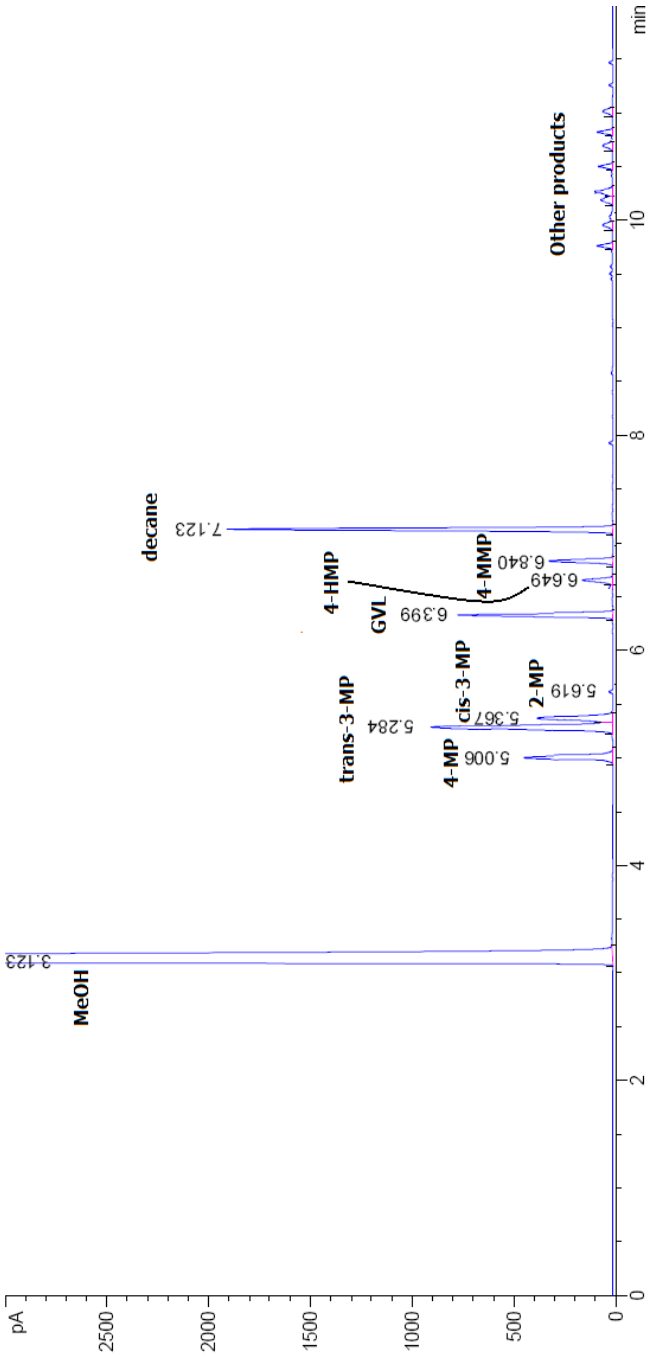
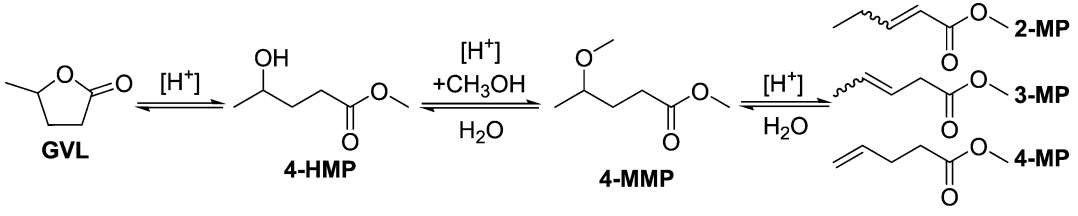


Figure AIV.2. GC spectrum of typical reactive distillation of methyl pentenoates (MP); reaction residue; methyl-4-pentenoate (4-MP), methyl-3-pentenoate (3-MP), methyl-2-pentenoate (2-MP), methyl-4-methoxy pentanoate (4-MMP), methyl-4-hydroxy pentanoate (4-HMP) and heavy ends

Table AIV.1. Conversion of GVL to MP via reactive distillation of MP [a]



				residues in the flask							contents in the distillate								
	T	t	acid	**GVL**	**c-3-MP**	**t-3-MP**	**4-MP**	**4-MMP**	**4-HMP**	**2-MP**	**GVL**	**c-3-MP**	**t-3-MP**	**4-MP**	**4-MMP**	**4-HMP**	**2-MP**	**Heavy P**	conversion %
	°C	h	mmol%	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	**GVL**
1	150	4	10	69.9	1.1	2.9	1.3	3.0	0.2	0.0	2.0	4.6	9.3	4.8	0.5	0.1	0.0	0.3	28
2	150	8	10	57.5	2.1	5.7	2.5	3.2	0.2	0.0	2.1	6.1	10.6	7.1	0.6	0.2	0.1	2.0	40
3	160	4	10	62.4	1.2	3.1	1.2	2.9	0.2	0.0	2.0	5.9	12.0	7.9	0.5	0.1	0.0	0.6	36
4	160	8	10	43.6	2.2	5.3	2.4	3.2	0.2	0.0	2.1	9.4	16.3	11.9	0.7	0.2	0.1	2.4	54
5	170	4	10	51.6	1.4	3.0	1.3	1.7	0.2	0.0	2.1	9.6	16.8	11.3	0.5	0.1	0.0	0.4	46
6	170	8	10	36.2	2.5	5.4	2.3	2.4	0.2	0.0	2.3	12.0	20.6	13.0	0.7	0.1	0.1	2.2	62
7	180	4	10	47.1	1.1	2.6	1.0	2.5	0.1	0.0	2.1	10.4	20.3	10.4	0.6	0.1	0.1	1.6	51
8	180	8	10	34.5	2.0	4.9	1.9	2.9	0.2	0.0	2.4	11.9	23.0	12.6	0.7	0.1	0.1	2.8	63
9	190	4	10	35.8	1.0	1.8	0.9	1.2	0.1	0.0	2.3	13.7	28.0	14.0	0.5	0.1	0.1	0.5	62
10	190	8	10	7.5	1.8	2.6	1.6	1.3	0.1	0.0	2.5	20.5	40.7	19.1	0.6	0.1	0.1	1.5	90
11	200	4	10	24.4	0.8	1.4	0.7	1.4	0.1	0.0	3.9	12.6	34.6	17.7	0.9	0.1	0.1	1.3	72
12	200	8	10	4.6	1.4	2.3	1.2	1.3	0.1	0.0	4.2	19.7	40.1	19.0	1.1	0.1	0.2	4.7	91
13	190	8	1	61.0	0.6	0.9	0.7	1.7	0.1	0.0	7.6	6.7	12.3	7.2	0.5	0.1	0.0	0.6	31
14	190	8	5	37.8	1.3	2.5	1.4	1.8	0.2	0.0	5.9	11.1	22.8	11.8	0.7	0.1	0.1	2.5	56
15[c]	190	8	10	5.3	1.6	2.7	1.5	1.1	0.1	0.0	2.1	19.6	42.1	20.4	0.4	0.1	0.1	2.9	93

[a] Reaction conditions: 100 mmol (9.5 mL) GVL, 1-10 mmol (0.19 g – 1.9 g) HOTs as acid catalyst, 10 mL MeOH, T = 150 ºC – 200 ºC, t = 4-8 h, MeOH feed rate: 10 mL h^{-1}. The receiver was cooled with liquid N_2. The amount of products from distillate and residue were added up together. The amount of products was determined by GC analysis using decane as an external standard. [c] 10 mmol (532 µL) H_2SO_4 as acid catalyst.

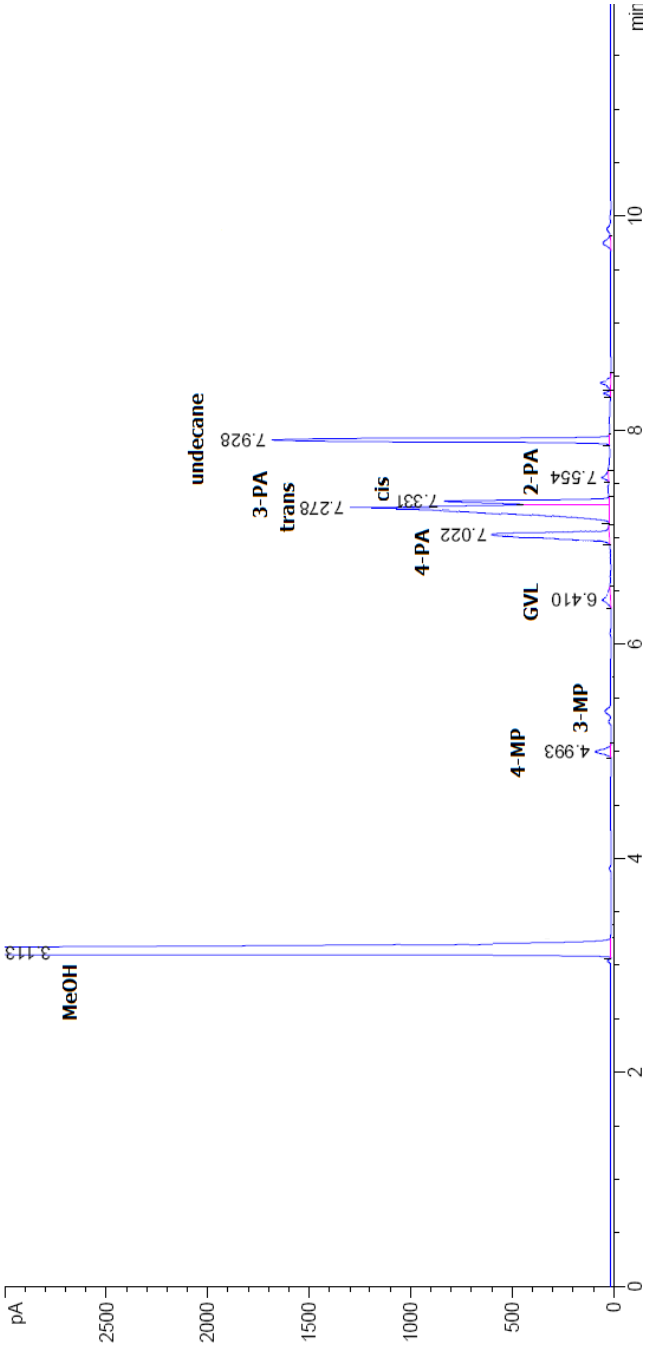


Figure AIV.3. GC spectrum of typical aminolysis of methyl pentenoates (MP) to pentenamides (PA); reaction residue; methyl-4-pentenoate (4-MP), methyl-3-pentenoate (3-MP), methyl-2-pentenoate (2-MP), 2-pentenamide (2-PA), 3-pentenamide (3-PA), 4-pentenamide (4-PA)

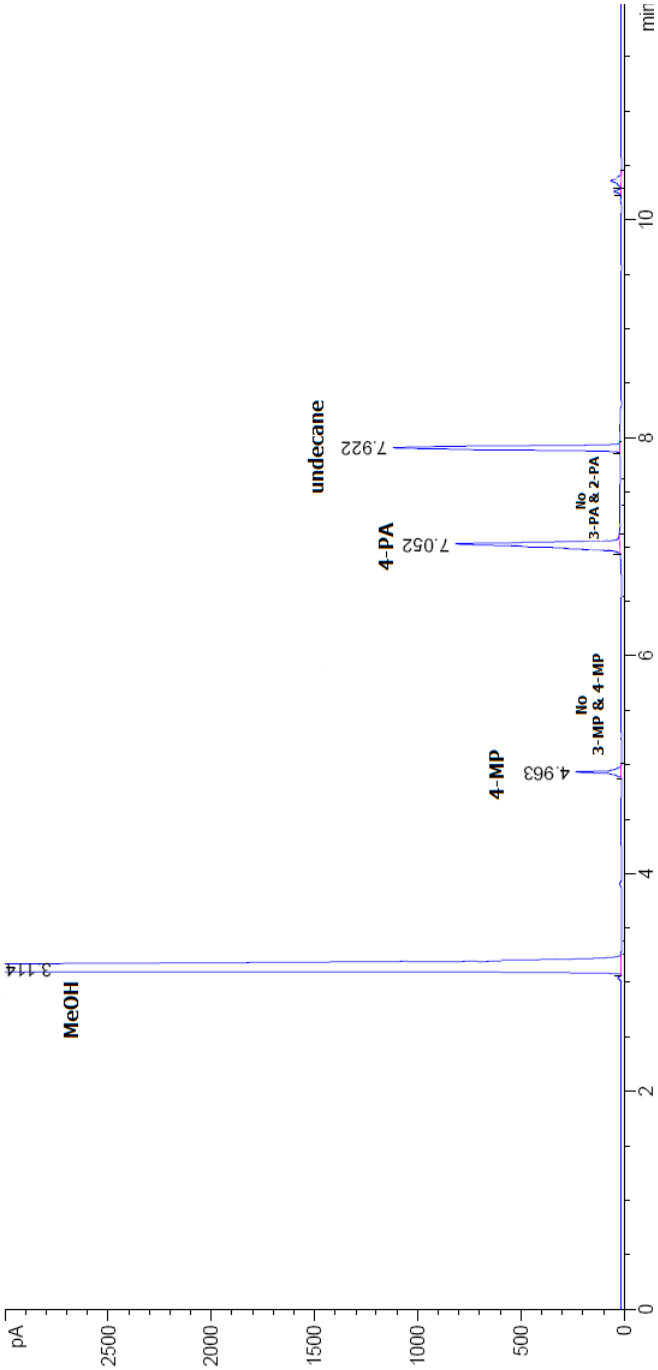
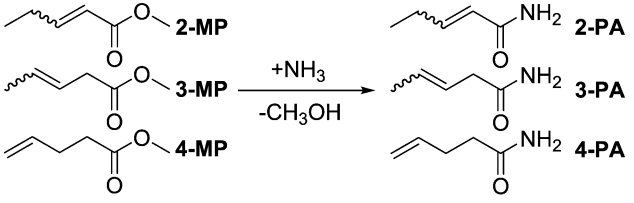


Figure AIV.4. GC spectrum of typical aminolysis of methyl 4-pentenoate (4-MP) to 4-pentenamide (4-PA)

Table AIV.2. Influence of various conditions on aminolysis of 3-MP ans 4-MP mixtures [a]



	NH_3 source	NH_3 amount	T °C	t h	**3-MP** mmol	**4-MP** mmol	**3-PA** mmol	**4-PA** mmol	**other P** mmol	conversion % **3-MP**	conversion % **4-MP**	conversion % **3-MP & 4-MP**	selectivity %[b] **3-PA**	selectivity %[b] **4-PA**	yield %
1[c]	7N NH_3 in MeOH	50 mmol	rt	5	3.2	1.2	0.1	0.0	0.1	5	4	4	50	0	2
2[c]	7N NH_3 in MeOH	50 mmol	rt	24	3.1	1.1	0.2	0.0	0.1	5	9	6	74	0	4
3[c]	7N NH_3 in MeOH	50 mmol	50	5	2.7	1.1	0.4	0.1	0.1	17	5	14	65	16	11
4[c]	7N NH_3 in MeOH	50 mmol	80	5	2.8	0.9	0.5	0.1	0.1	14	22	16	69	14	13
5	7N NH_3 in MeOH	50 mmol	80	5	6.5	2.2	0.9	0.2	0.2	13	12	13	71	16	11
6[c]	7N NH_3 in MeOH	50 mmol	100	5	2.7	1.0	0.5	0.1	0.2	18	17	18	63	13	13
7	NH_3 (g)	8 bar	rt	20	3.8	1.9	3.5	0.5	0.2	49	22	42	83	12	40
8	NH_3 (g)	8 bar	rt	72	0.2	0.6	7.2	1.8	0.2	97	76	92	78	20	90
9	NH_3 (g)	8 bar	80	20	0.0	0.4	7.5	2.0	0.1	100	84	96	78	21	95
10[c]	NH_3 (g)	8 bar	80	20	2.6	1.0	0.6	0.1	0.1	20	13	18	73	12	16
11[d]	NH_3 (g)	8 bar	80	20	6.4	2.2	0.9	0.2	0.2	14	10	13	68	15	11
12	NH_4OH (35%)	50 mmol	rt	5	5.3	2.2	2.1	0.2	0.1	29	10	24	87	8	23
13	NH_4OH (35%)	50 mmol	50	5	2.6	1.6	4.8	0.8	0.1	65	34	57	84	14	56
14	NH_4OH (35%)	50 mmol	80	5	0.2	0.4	7.2	2.0	0.1	97	82	93	77	21	92
15	NH_4OH (35%)	50 mmol	100	5	0.1	0.3	7.3	2.1	0.2	99	88	96	76	22	94
16[c]	NH_4OH (35%)	50 mmol	80	5	0.8	0.5	2.4	0.7	0.1	75	63	71	75	22	69
17	NH_4OH (35%)	25 mmol	80	5	3.2	2.2	4.1	0.3	0.1	57	10	45	91	7	44
18	NH_4OH (35%)	100 mmol	80	5	0.1	0.4	7.3	2.0	0.1	98	82	94	77	21	93
19	NH_4OH (35%)	50 mmol	80	6	0.0	0.1	7.4	2.4	0.1	100	96	99	75	24	98
20[e]	NH_4OH (35%)	50 mmol	80	5	-	0.9	-	8.9	0.2	-	91	-	-	98	89

[a] Reaction conditions: 10 mmol (1.14 g) of methyl pentenoates (3-MP(7.52mmol)/4-MP(2.48mmol)~3); T= rt-100 °C; t= 5-72 h. [b] The selectivity was determined by GC analysis using decane as an internal standard. [c] no evaporation of MeOH (4.5 mmol of methyl pentenoates; 5 mL of a methyl pentenoates solution in MeOH, 0.9 M, a typical distillate from a reactive distillation experiment, concentration determined through GC calibration lines); [d] in 5 mL diglyme.[e] 10 mmol 4-MP; The amounts of the mixture of methyl pentenoates determined by injecting the mixture into GC before starting the reaction

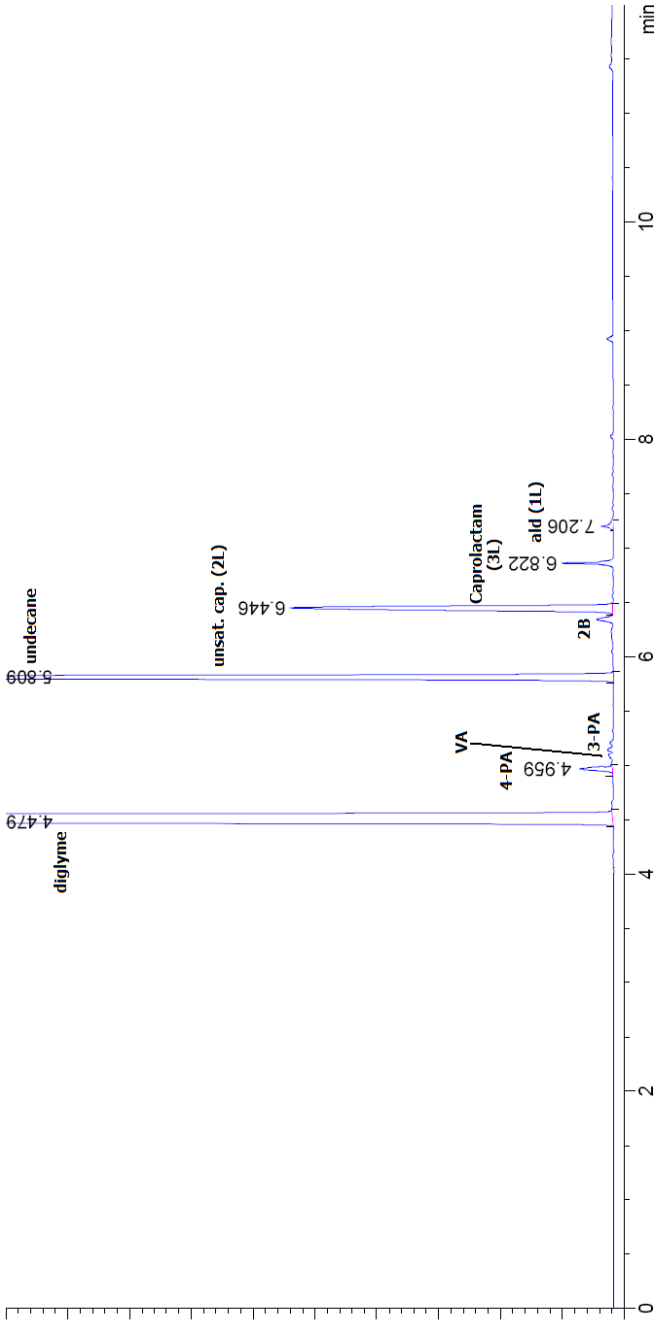


Figure AIV.5. GC spectrum of typical intramolecular hydroamidomethylation of 4-pentenamide (4-PA); before hydrogenation; valeramide (VA), 3-pentenamide (3-PA), 4-pentenamide (4-PA)

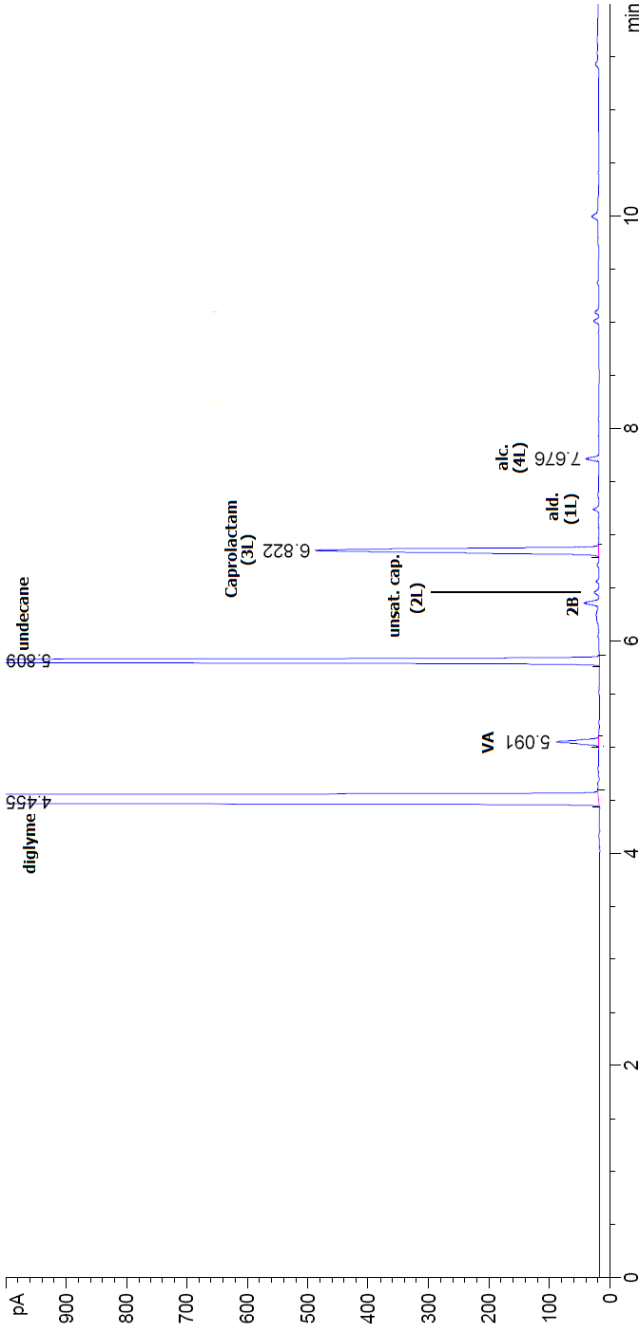


Figure AIV.6. GC spectrum of typical intramolecular hydroamidomethylation of 4-pentenamide (4-PA); after hydrogenation; valeramide (VA), 3-pentenamide (3-PA), 4-pentenamide (4-PA)

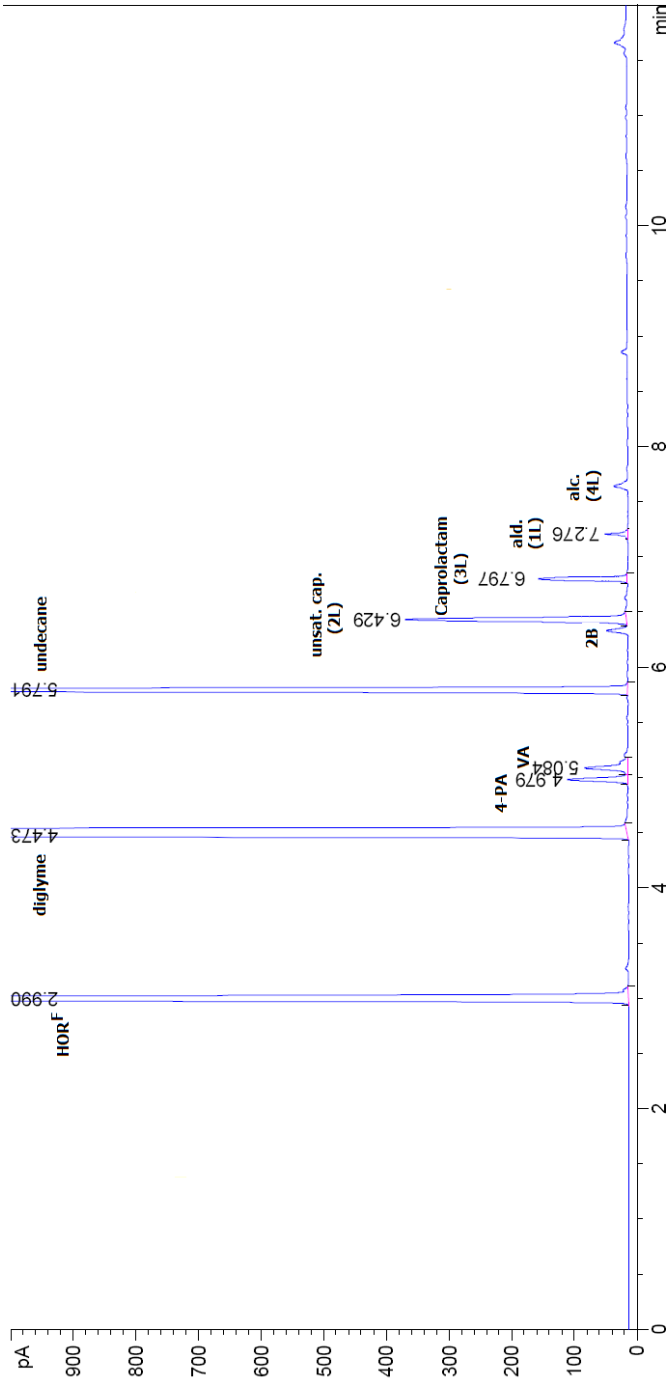
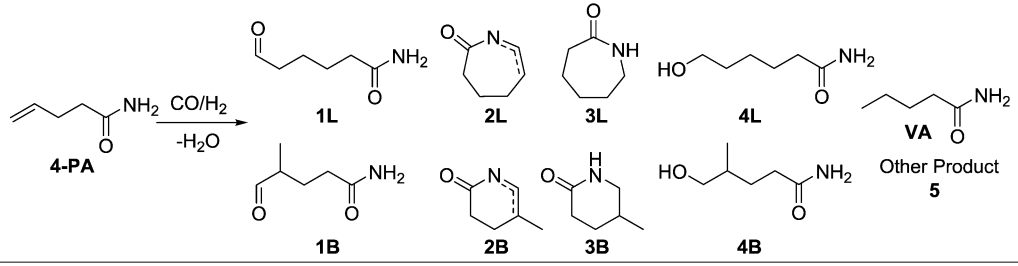


Figure AIV.7. GC spectrum of typical intramolecular hydroamidomethylation of 4-pentenamide (4-PA); in the presence of 2 mL of HOR^F; valeramide (VA), 3-pentenamide (3-PA), 4-pentenamide (4-PA)

Table AIV.3-1. Influence of various conditions on the intramolecular hydroamidomethylation of 4-PA [a]



	t	T	P (CO/H_2)	HOTs	HFIPA	**4-PA**	**VA**	**1L**	**2L**	**3L**	**4L**	**1B**	**2B**	**3B**	**4B**	**5**	conversion	**1**	**2**	**3**
	h	°C	bar	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	L%	L%	L%
1	4	100	50(1/2)	0.010		0.89	0.11	0.01	0.72	0.03	0.00	0.00	0.01	0.00	0.00	0.23	56	100	98	100
2	8	100	50(1/2)	0.010		0.46	0.18	0.01	0.89	0.06	0.00	0.00	0.02	0.00	0.00	0.38	77	100	98	100
3	4	100	50(1/2)	0.025		0.93	0.21	0.01	0.61	0.02	0.00	0.00	0.01	0.00	0.00	0.21	54	100	98	100
4	8	100	50(1/2)	0.025		0.41	0.23	0.01	0.59	0.06	0.00	0.00	0.02	0.00	0.00	0.68	80	100	97	100
5	4	100	50(1/2)	0.050		0.90	0.26	0.01	0.37	0.01	0.00	0.00	0.01	0.00	0.00	0.44	55	100	97	100
6	8	100	50(1/2)	0.050		0.35	0.29	0.01	0.46	0.04	0.00	0.00	0.02	0.00	0.00	0.83	83	100	96	100
7	4	100	50(1/2)	0.025	5	0.69	0.26	0.01	0.63	0.05	0.00	0.00	0.01	0.00	0.00	0.35	66	100	98	100
8	8	100	50(1/2)	0.025	5	0.20	0.32	0.01	0.81	0.09	0.00	0.00	0.02	0.00	0.00	0.55	90	100	98	100
9	4	100	50(1/2)		5	0.80	0.11	0.02	0.97	0.07	0.00	0.00	0.01	0.00	0.00	0.02	60	100	99	100
10	8	100	50(1/2)		5	0.33	0.16	0.03	1.27	0.16	0.00	0.00	0.02	0.00	0.00	0.03	84	100	99	100
11	4	100	50(1/2)		10	0.65	0.22	0.04	0.89	0.15	0.00	0.00	0.01	0.00	0.00	0.04	68	100	99	100
12	8	100	50(1/2)		10	0.14	0.24	0.08	1.14	0.33	0.00	0.00	0.02	0.00	0.00	0.05	93	100	98	100
13	4	100	50(1/2)		20	0.63	0.23	0.05	0.83	0.19	0.00	0.00	0.01	0.00	0.00	0.05	69	100	98	100
14	8	100	50(1/2)		20	0.11	0.28	0.10	0.98	0.44	0.00	0.00	0.02	0.00	0.00	0.06	95	100	98	100
15	8	100	50(1/2)	0.025	20	0.10	0.41	0.01	0.51	0.45	0.00	0.00	0.02	0.00	0.00	0.50	95	100	96	100
16	8	100	50(1/1)		20	0.24	0.16	0.07	1.29	0.20	0.00	0.00	0.02	0.00	0.00	0.02	88	100	98	100
17	8	100	50(1/4)		20	0.28	0.51	0.05	0.81	0.29	0.00	0.00	0.01	0.00	0.00	0.05	86	100	99	100
18	8	100	50(1/9)		20	0.31	0.74	0.03	0.62	0.21	0.00	0.00	0.02	0.00	0.00	0.07	85	100	97	100
19	8	60	50(1/2)		20	0.56	0.11	0.06	1.01	0.19	0.00	0.00	0.02	0.00	0.00	0.05	72	100	98	100
20	8	80	50(1/2)		20	0.41	0.27	0.05	0.91	0.28	0.00	0.00	0.02	0.00	0.00	0.06	80	100	98	100
21	8	120	50(1/2)		20	0.03	0.54	0.08	0.63	0.56	0.00	0.00	0.02	0.00	0.00	0.13	99	100	97	100

[a] Reaction conditions: 2 mmol (19.8 mg) of 4-PA; 0.0025 mmol (1.24 mg) $[Rh(cod)Cl]_2$ precursor, 0.01 mmol (5.79 mg) xantphos, P (CO/H_2) = 50 (1/1-1/9) bar; T = 60 °C-120 °C; *t* = 4-8 h; 0–0.05 mmol HOTs; 0-20 mmol HFIPA; Solvent: 10 mL diglyme. The amount of products was determined by GC analysis using undecane as an internal standard.

Table AIV.3-2. Influence of various conditions on the intramolecular hydroamidomethylation of 4-PA [a]

	t	T	P (CO/H_2)	HOTs	HFIPA	**4-PA**	**VA**	**1L**	**2L**	**3L**	**4L**	**1B**	**2B**	**3B**	**4B**	**5**	conversion	**1**	**2**	**3**
	h	°C	bar	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	L%	L%	L%
22	4	80	50(1/2)			1.31	0.00	0.02	0.63	0.00	0.00	0.00	0.01	0.00	0.00	0.03	35	100	99	100
23	8	80	50(1/2)			0.89	0.00	0.02	1.02	0.01	0.00	0.00	0.01	0.00	0.00	0.05	56	100	99	100
24	4	100	50(1/2)			0.87	0.01	0.01	1.04	0.04	0.00	0.00	0.01	0.00	0.00	0.02	57	100	99	100
25	8	100	50(1/2)			0.38	0.02	0.02	1.41	0.11	0.00	0.00	0.01	0.00	0.00	0.05	81	100	99	100
26	4	110	50(1/2)			0.59	0.01	0.01	1.23	0.06	0.00	0.00	0.02	0.00	0.00	0.08	71	100	98	100
27	8	110	50(1/2)			0.21	0.02	0.02	1.38	0.22	0.00	0.00	0.02	0.00	0.00	0.12	90	100	98	100
28	4	120	50(1/2)			0.41	0.02	0.01	1.32	0.08	0.00	0.00	0.02	0.00	0.00	0.14	80	100	99	100
29	8	120	50(1/2)			0.03	0.03	0.02	1.32	0.25	0.00	0.00	0.03	0.00	0.00	0.31	99	100	97	100
30	4	100	50(1/1)			0.91	0.00	0.01	1.02	0.00	0.00	0.00	0.01	0.00	0.00	0.05	55	100	99	
31	8	100	50(1/1)			0.40	0.00	0.02	1.43	0.01	0.00	0.00	0.02	0.00	0.00	0.12	80	100	99	100
32	4	100	50(1/4)			0.98	0.03	0.01	0.93	0.02	0.00	0.00	0.01	0.00	0.00	0.02	51	100	99	100
33	8	100	50(1/4)			0.52	0.04	0.01	1.24	0.12	0.00	0.00	0.02	0.00	0.00	0.05	74	100	98	100
34	4	100	50(1/9)			1.09	0.09	0.01	0.73	0.01	0.00	0.00	0.01	0.00	0.00	0.06	45	100	99	100
35	8	100	50(1/9)			0.71	0.13	0.01	0.97	0.08	0.00	0.00	0.02	0.00	0.00	0.08	65	100	98	100
36	10	100	50(1/2)			0.05	0.02	0.02	1.63	0.19	0.00	0.00	0.02	0.00	0.00	0.08	98	100	99	100
37[b]	8+4	100-100	50(1/2)-80 H_2			0.00	0.29	0.01	0.09	1.35	0.00	0.00	0.02	0.00	0.00	0.24	100	100	83	100
38[b]	8+4	100-80	50(1/2)-80 H_2			0.01	0.28	0.01	0.19	1.34	0.00	0.00	0.02	0.00	0.00	0.14	100	100	91	100
39[b]	8+4	100-60	50(1/2)-80 H_2			0.07	0.21	0.01	0.68	0.88	0.00	0.00	0.02	0.00	0.00	0.12	97	100	97	100
40[b]	8+4	100-80	50(1/2)-50 H_2			0.09	0.20	0.01	0.49	1.02	0.00	0.00	0.02	0.00	0.00	0.16	96	100	96	100
41[b]	8+4	100-80	50(1/2)-100 H_2			0.00	0.29	0.01	0.15	1.39	0.00	0.00	0.02	0.00	0.00	0.14	100	100	88	100
42[b]	10+4	100-80	50(1/2)-80 H_2			0.00	0.06	0.01	0.22	1.56	0.00	0.00	0.02	0.00	0.00	0.12	100	100	92	100
43[b]	10+6	100-80	50(1/2)-80 H_2			0.00	0.06	0.01	0.02	1.75	0.00	0.00	0.02	0.00	0.00	0.14	100	100	51	100

[a] Reaction conditions: 2 mmol (19.8 mg) of 4-PA; 0.0025 mmol (1.24 mg) $[Rh(cod)Cl]_2$ precursor, 0.01 mmol (5.79 mg) xantphos, P (CO/H_2) = 50 (1/1-1/9) bar; T = 80 °C-120 °C; *t* = 4-16 h; 0–0.05 mmol HOTs; 0-20 mmol HFIPA; Solvent: 10 mL diglyme. The amount of products was determined by GC analysis using undecane as an internal standard. [b] In a one pot two stage operation; reaction conditions: 8-10 h at 100 °C hydroformylation- depressurizing syngas- flushing with H_2- pressurizing with 50-100 bar H_2- 4-6 h at 60 °C-100 °C hydrogenation.

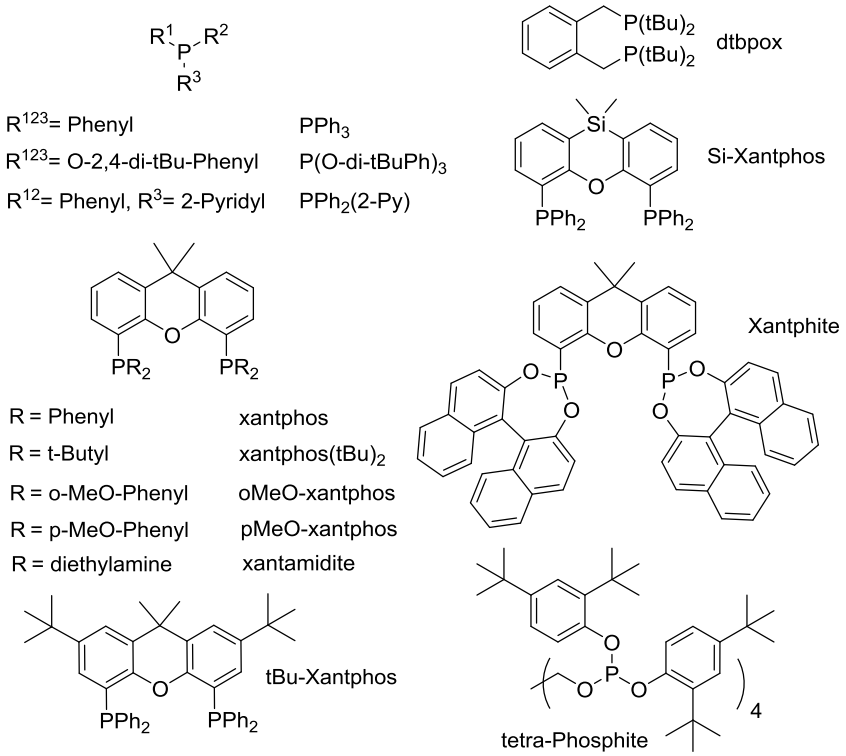


Figure AIV.8. Selected ligands used in the intramolecular hydroamidomethylation of Pentenamides (PA)

Table AIV.4-1. Product distribution in the intramolecular hydroamidomethylation of 4-PA; Influence of various ligands [a]

	Ligand	t	T	P (CO/H_2)	**4-PA**	**VA**	**1L**	**2L**	**3L**	**4L**	**1B**	**2B**	**3B**	**4B**	**5**	conversion	**1**	**2**	**3**
		h	°C	bar	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	L%	L%	L%
1	no L	8	100	50(1/2)	0.04	0.26	0.01	0.39	0.23	0.00	0.00	0.70	0.11	0.00	0.26	98	100	36	67
2	PPh_3	2	100	50(1/2)	0.29	0.01	0.01	0.97	0.00	0.00	0.00	0.51	0.00	0.00	0.21	86	100	66	
3	PPh_3	4	100	50(1/2)	0.11	0.02	0.02	1.03	0.00	0.00	0.00	0.61	0.00	0.00	0.21	95	100	63	
4	PPh_3	8	100	50(1/2)	0.00	0.02	0.02	1.08	0.00	0.00	0.00	0.65	0.00	0.00	0.23	100	100	62	
5	PPh_2Py	8	100	50(1/2)	0.06	0.00	0.08	1.05	0.01	0.00	0.00	0.55	0.00	0.00	0.25	97	100	66	100
6	$P(O\text{-di-tBuPh})_3$	2	100	50(1/2)	0.39	0.01	0.01	0.61	0.00	0.00	0.00	0.88	0.00	0.00	0.10	81	100	41	
7	$P(O\text{-di-tBuPh})_3$	4	100	50(1/2)	0.17	0.03	0.01	0.71	0.00	0.00	0.00	0.99	0.00	0.00	0.09	92	100	42	
8	$P(O\text{-di-tBuPh})_3$	8	100	50(1/2)	0.00	0.04	0.01	0.76	0.00	0.00	0.00	1.07	0.00	0.00	0.12	100	100	42	
9	dtbpox	2	100	50(1/2)	0.79	0.00	0.02	0.69	0.00	0.00	0.00	0.43	0.00	0.00	0.07	61	100	62	
10	dtbpox	4	100	50(1/2)	0.46	0.02	0.02	0.90	0.00	0.00	0.00	0.52	0.00	0.00	0.09	77	100	63	
11	dtbpox	8	100	50(1/2)	0.00	0.02	0.03	1.12	0.00	0.00	0.00	0.72	0.00	0.00	0.11	100	100	61	
12	xantphos	2	100	50(1/2)	1.36	0.00	0.01	0.62	0.00	0.00	0.00	0.00	0.00	0.00	0.01	32	100	99	
13	xantphos	4	100	50(1/2)	0.87	0.01	0.01	1.04	0.04	0.00	0.00	0.01	0.00	0.00	0.02	57	100	99	100
14	xantphos	8	100	50(1/2)	0.38	0.02	0.02	1.41	0.11	0.00	0.00	0.01	0.00	0.00	0.05	81	100	99	100
15	Si-xantphos	2	100	50(1/2)	1.52	0.00	0.01	0.42	0.00	0.00	0.00	0.01	0.00	0.00	0.03	24	100	98	100
16	Si-xantphos	4	100	50(1/2)	0.99	0.01	0.01	0.87	0.01	0.00	0.00	0.02	0.00	0.00	0.09	51	100	98	100
17	Si-xantphos	8	100	50(1/2)	0.60	0.01	0.02	1.16	0.04	0.00	0.00	0.02	0.00	0.00	0.14	70	100	98	100
18	tBu-xantphos	2	100	50(1/2)	1.28	0.00	0.01	0.68	0.01	0.00	0.00	0.00	0.00	0.00	0.01	36	100	99	100
19	tBu-xantphos	4	100	50(1/2)	0.84	0.01	0.01	1.03	0.07	0.00	0.00	0.01	0.00	0.00	0.03	58	100	99	100
20	tBu-xantphos	8	100	50(1/2)	0.38	0.02	0.02	1.40	0.12	0.00	0.00	0.01	0.00	0.00	0.05	81	100	99	100

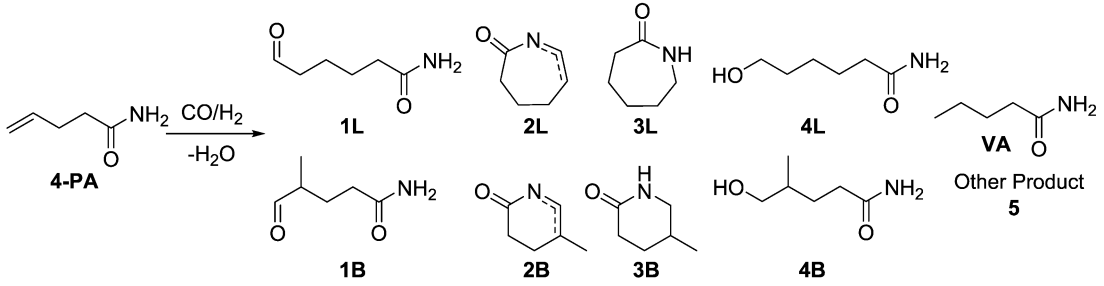
[a] Reaction conditions: 2 mmol (19.8 mg) of 4-PA; 0.0025 mmol (1.24 mg) $[Rh(cod)Cl]_2$ precursor; 0.01 mmol bidentate ligand or 0.02 mmol monodentate ligand; P (CO/H_2) = 50 (1/2) bar; T = 100 °C; *t* = 2-8 h; Solvent: 10 mL diglyme. The amount of products was determined by GC analysis using undecane as an internal standard.

Table AIV.4-2. Product distribution in the intramolecular hydroamidomethylation of 4-PA; Influence of various ligands [a]

	Ligand	t	T	P (CO/H_2)	**4-PA**	**VA**	**1L**	**2L**	**3L**	**4L**	**1B**	**2B**	**3B**	**4B**	**5**	conversion	**1**	**2**	**3**
		h	°C	bar	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	L%	L%	L%
21	xantphos(tBu)$_2$	2	100	50(1/2)	1.95	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.04	3		83	
22	xantphos(tBu)$_2$	4	100	50(1/2)	1.88	0.00	0.00	0.03	0.00	0.00	0.00	0.01	0.00	0.00	0.08	6		81	
23	xantphos(tBu)$_2$	8	100	50(1/2)	1.80	0.00	0.00	0.05	0.00	0.00	0.00	0.01	0.00	0.00	0.14	10		83	
24	oMeO-xantphos	2	100	50(1/2)	0.91	0.00	0.01	0.62	0.00	0.00	0.00	0.41	0.00	0.00	0.05	55	100	60	
25	oMeO-xantphos	4	100	50(1/2)	0.53	0.00	0.02	0.83	0.00	0.00	0.00	0.56	0.00	0.00	0.06	74	100	60	
26	oMeO-xantphos	8	100	50(1/2)	0.10	0.01	0.02	1.04	0.00	0.00	0.00	0.69	0.00	0.00	0.14	95	100	60	
27	pMeO-xantphos	2	100	50(1/2)	1.67	0.00	0.01	0.29	0.00	0.00	0.00	0.01	0.00	0.00	0.02	17	100	97	
28	pMeO-xantphos	4	100	50(1/2)	1.21	0.00	0.02	0.71	0.01	0.00	0.00	0.01	0.00	0.00	0.04	40	100	98	100
29	pMeO-xantphos	8	100	50(1/2)	0.76	0.00	0.02	1.09	0.02	0.00	0.00	0.02	0.00	0.00	0.08	62	100	98	100
30	xantphite	8	100	50(1/2)	0.36	0.07	0.03	0.77	0.02	0.00	0.00	0.39	0.00	0.00	0.36	82	100	67	100
31	xantamidite	8	100	50(1/2)	0.10	0.10	0.68	0.40	0.01	0.00	0.02	0.42	0.00	0.00	0.28	95	97	49	100
32	POP-xantphos	8	100	50(1/2)	0.29	0.03	0.02	1.32	0.04	0.00	0.00	0.09	0.00	0.00	0.21[c]	85	100	94	100
33	tetraphosphite	8	100	50(1/2)	0.38	0.26	0.02	1.02	0.04	0.00	0.00	0.04	0.00	0.00	0.25	81	100	96	100
34[b]	xantphos	8+4	100-80	50(1/2)-80 H_2	0.01	0.28	0.01	0.19	1.34	0.00	0.00	0.02	0.00	0.00	0.14	100	100	91	100
35[b]	Si-xantphos	8+4	100-80	50(1/2)-80 H_2	0.13	0.44	0.02	0.31	0.93	0.00	0.00	0.02	0.00	0.00	0.15	94	100	94	100
36[b]	tBu-xantphos	8+4	100-80	50(1/2)-80 H_2	0.01	0.27	0.01	0.17	1.38	0.00	0.00	0.02	0.00	0.00	0.14	100	100	91	100
37[b]	pMeO-xantphos	8+4	100-80	50(1/2)-80 H_2	0.19	0.41	0.02	0.41	0.83	0.00	0.00	0.02	0.00	0.00	0.12	91	100	95	100
38[b]	xantphite	8+4	100-80	50(1/2)-80 H_2	0.02	0.39	0.01	0.66	0.14	0.01	0.00	0.38	0.00	0.00	0.40	99	100	64	100
39[b]	POP-xantphos	8+4	100-80	50(1/2)-80 H_2	0.00	0.40	0.00	0.17	1.12	0.00	0.00	0.04	0.01	0.00	0.26	100		81	99
40[b]	tetraphosphite	8+4	100-80	50(1/2)-80 H_2	0.14	0.44	0.00	0.76	0.31	0.00	0.00	0.03	0.00	0.00	0.32	93		96	100

[a] Reaction conditions: 2 mmol (19.8 mg) of 4-PA; 0.0025 mmol (1.24 mg) $[Rh(cod)Cl]_2$ precursor; 0.01 mmol bidentate ligand or 0.02 mmol monodentate ligand; P (CO/H_2) = 50 (1/2) bar; T = 100 °C; t = 2-12 h; Solvent: 10 mL diglyme. The amount of products was determined by GC analysis using undecane as an internal standard. [b] In a one pot two stage operation; reaction conditions: 8 h at 100 °C hydroformylation- depressurizing syngas- flushing with H_2- pressurizing with 80 bar H_2- 4 h at 80 °C hydrogenation; [c] 0.1 mmol of other product is 3-PA.

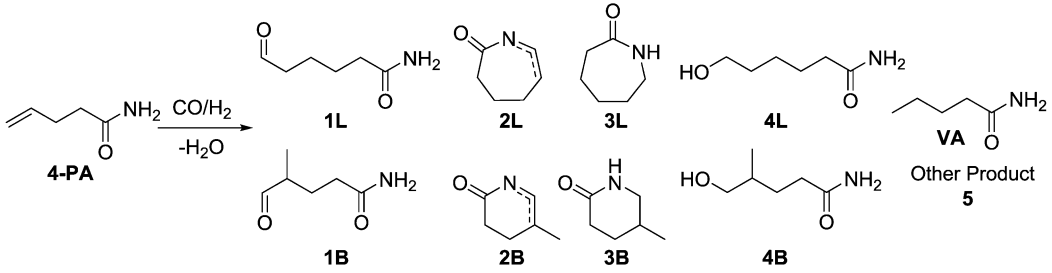
Table AIV.5. Influence of water added on the intramolecular hydroamidomethylation of 4-PA [a]



	t	T	P (CO/H_2)	HOTs	H_2O	**4-PA**	**VA**	**1L**	**2L**	**3L**	**4L**	**1B**	**2B**	**3B**	**4B**	**5**	conversion	**1**	**2**	**3**
	h	°C	bar	mmol	mL	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	L%	L%	L%
1	8	100	50(1/2)			0.38	0.02	0.00	1.41	0.11	0.00	0.00	0.01	0.00	0.00	0.08	81		99	100
2[b]	8+4	100-80	50(1/2)-80 H_2			0.01	0.28	0.00	0.19	1.34	0.00	0.00	0.02	0.00	0.00	0.15	100		91	100
3	8	100	50(1/2)		0.1	0.25	0.11	0.39	1.04	0.04	0.00	0.00	0.01	0.00	0.00	0.15	88	100	99	100
4[b]	8+4	100-80	50(1/2)-80 H_2		0.1	0.03	0.25	0.20	0.42	0.65	0.18	0.00	0.02	0.00	0.00	0.26	99	100	96	100
5	8	100	50(1/2)		0.5	0.26	0.13	0.44	0.95	0.03	0.00	0.00	0.01	0.00	0.00	0.18	87	100	99	100
6[b]	8+4	100-80	50(1/2)-80 H_2		0.5	0.03	0.28	0.15	0.31	0.56	0.27	0.00	0.02	0.00	0.00	0.37	99	100	94	100
7	8	100	50(1/2)		1	0.24	0.16	0.46	0.91	0.03	0.00	0.00	0.01	0.00	0.00	0.19	88	100	99	100
8[b]	8+4	100-80	50(1/2)-80 H_2		1	0.00	0.29	0.15	0.47	0.42	0.30	0.00	0.01	0.00	0.00	0.36	100	100	97	100
9	8	100	50(1/2)	0.025	0.5	0.19	0.25	0.12	0.61	0.01	0.00	0.00	0.02	0.00	0.00	0.80	91	100	97	100

[a] Reaction conditions: 2 mmol (19.8 mg) of 4-PA; 0.0025 mmol (1.24 mg) $[Rh(cod)Cl]_2$ precursor; 0.01 mmol (5.79 mg) xantphos; P (CO/H_2) = 50 (1/2) bar; T = 100 °C; t = 2-12 h; Solvent: 10 mL diglyme. The amount of products was determined by GC analysis using undecane as an internal standard. [b] In a one-pot two stage operation; reaction conditions: 8 h at 100 °C hydroformylation- depressurizing syngas- flushing with H_2- pressurizing with 80 bar H_2- 4 h at 80 °C hydrogenation.

Table AIV.6. Influence of various rhodium precursors on intramolecular hydroamidomethylation of 4-PA [a]



	Rh	HOTs	HOR[F]	**4-PA**	**VA**	**1L**	**2L**	**3L**	**4L**	**1B**	**2B**	**3B**	**4B**	**5**	conversion	selectivity %						L
	0.005 mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%	**PA**	**1**	**2**	**3**	**4**	**5**	%
1	$[Rh(cod)Cl]_2$			0.38	0.02	0.02	1.41	0.11	0.00	0.00	0.01	0.00	0.00	0.05	81	1	1	88	7	0	3	99
2	$[Rh(acac)(CO)_2]$			0.39	0.02	0.03	1.39	0.10	0.00	0.00	0.01	0.00	0.00	0.06	81	1	2	87	6	0	4	99
3	$[Rh(cod)_2]BF_4$			0.36	0.02	0.02	1.40	0.12	0.00	0.00	0.01	0.00	0.00	0.07	82	1	1	86	7	0	4	99
4	$[Rh(cod)_2]OTf$			0.37	0.02	0.02	1.41	0.11	0.00	0.00	0.01	0.00	0.00	0.06	82	1	1	87	7	0	4	99
5	$[Rh(cod)Cl]_2$		20	0.11	0.28	0.10	0.98	0.44	0.00	0.00	0.02	0.00	0.00	0.06	95	15	5	53	24	0	3	99
6	$[Rh(acac)(CO)_2]$		20	0.12	0.31	0.18	0.93	0.35	0.00	0.00	0.02	0.00	0.00	0.09	94	16	10	51	19	0	5	99
7	$[Rh(cod)Cl]_2$	0.025	20	0.10	0.41	0.01	0.51	0.45	0.00	0.00	0.02	0.00	0.00	0.50	95	22	1	28	24	0	26	98
8	$[Rh(acac)(CO)_2]$	0.025	20	0.09	0.39	0.02	0.55	0.37	0.00	0.00	0.02	0.00	0.00	0.56	96	20	1	30	19	0	29	98

[a] Reaction conditions: 2 mmol (19.8 mg) of 4-PA; 0.0025 mmol (1.24 mg) $[Rh(cod)Cl]_2$ precursor or 0.005 mmol other Rh precursors; 0.01 mmol xantphos ligand; P (CO/H_2) = 50 (1/2) bar; T = 100 °C; t = 8 h; Solvent: 10 mL diglyme. The amount of products was determined by GC analysis using undecane as an internal standard.

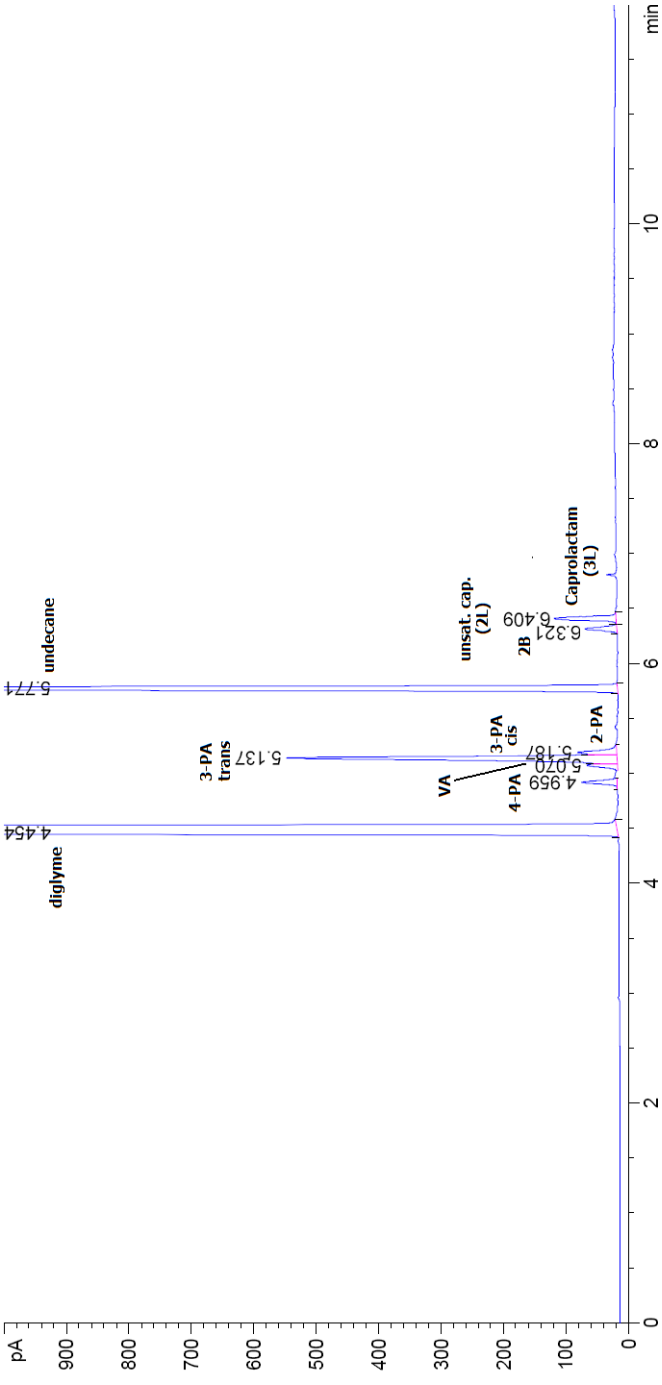


Figure AIV.9. GC spectrum of typical intramolecular hydroamidomethylation of 3-pentenamide (3-PA); at 100°C; valeramide (VA), 2-pentenamide (2-PA)3-pentenamide (3-PA), 4-pentenamide (4-PA)

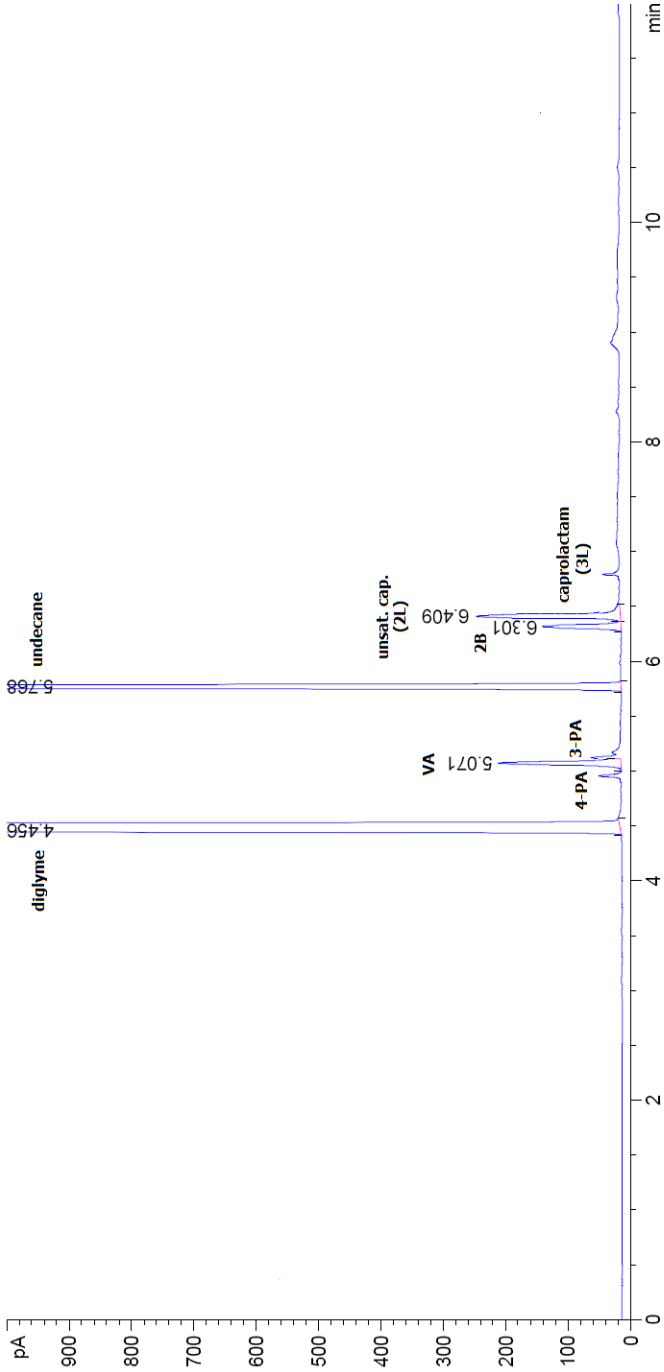


Figure AIV.10. GC spectrum of typical intramolecular hydroamidomethylation of mixture of 3-penteneamide (3-PA) and 4-pentenamide (4-PA); at 120°C; valeramide (VA), 2-pentenamide (2-PA)3-pentenamide (3-PA), 4-pentenamide (4-PA)

Table AIV.7. Influence of various conditions on intramolecular hydroamidomethylation of 4-PA [a]

	substrate	Ligand	t	T	P(CO/H_2)	**Iso**	**4-PA**	**2-PA**	**VA**	**1L**	**2L**	**3L**	**4L**	**1B**	**2-1B**	**2-2B**	**3B**	**4B**	**5**	Conv.
			h	°C	bar	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	mmol	%
1	3-PA	dtbopx	16	100	50(1/2)	0.00				0.01	0.01	0.00	0.00	0.00	0.00		0.00	0.00	0.09	6
2	4-PA	xantphos	8	100	50(1/2)	0.00	0.38		0.02	0.02	1.41	0.11	0.00	0.00	0.01		0.00	0.00	0.05	81
3	4-PA	POP-xantphos	8	100	50(1/2)	0.10	0.29		0.03	0.02	1.32	0.04	0.00	0.00	0.09		0.00	0.00	0.11	85
4	3-PA	xantphos	8	100	50(1/2)	0.01	0.01		0.12	0.01	0.04	0.00	0.00	0.00	0.07	0.00	0.00	0.00	0.06	16
5	4-PA	xantphos	8	120	50(1/2)	0.00	0.03		0.03	0.02	1.32	0.25	0.00	0.00	0.03		0.00	0.00	0.31	99
6	3-PA	xantphos	8	100	10(1/1)	0.01	0.01		0.07	0.00	0.10	0.00	0.00	0.00	0.11	0.00	0.00	0.00	0.10	19
7	3-PA&4-PA	xantphos	8	100	50(1/2)	0.00	0.02		0.16	0.02	0.74	0.05	0.00	0.03	0.01		0.00	0.00	0.04	52
8	3-PA	POP-xantphos	8	120	10(1/1)	0.03	0.03		0.56	0.02	0.60	0.03	0.00	0.01	0.28	0.05	0.00	0.00	0.16	86
9	3-PA	POP-xantphos	8	120	15(1/2)	0.02	0.02		0.65	0.02	0.49	0.03	0.00	0.01	0.28	0.08	0.00	0.00	0.17	87
10	3-PA	POP-xantphos	8	120	20(1/3)	0.01	0.01		0.69	0.02	0.40	0.02	0.00	0.01	0.26	0.07	0.00	0.00	0.24	87
11	3-PA	POP-xantphos	8	120	30(1/2)	0.02	0.02		0.72	0.02	0.38	0.01	0.00	0.01	0.31	0.11	0.00	0.00	0.17	87
12	3-PA	POP-xantphos	8	100	10(1/1)	0.07	0.06	0.01	0.08	0.00	0.11	0.01	0.00	0.00	0.08		0.00	0.00	0.06	20
13	3-PA	POP-xantphos	8	120	10(1/1)	0.06	0.05	0.01	0.54	0.02	0.64	0.01	0.00	0.01	0.30		0.00	0.00	0.13	86
14	3-PA	POP-xantphos	8	120	5(1/1)	0.09	0.08	0.01	0.48	0.02	0.55	0.01	0.00	0.01	0.29	0.03	0.00	0.00	0.15	82
15	3-PA	benz-xantphos	8	120	10(1/1)	0.10	0.08	0.02	0.18	0.02	0.26	0.01	0.00	0.01	0.23		0.00	0.00	0.16	48
16	3-PA&4-PA	POP-xantphos	8	120	10(1/1)	0.01	0.08	0.01	0.48	0.02	0.75	0.01	0.00	0.01	0.22		0.00	0.00	0.13	81
17	3-PA&4-PA	POP-xantphos	16	120	10(1/1)	0.00	0.02	0.00	0.71	0.02	0.80	0.02	0.00	0.01	0.23		0.01	0.00	0.17	98
18	3-PA	POP-xantphos	8	120	10(1/1)	0.03	0.03		0.56	0.02	0.60	0.03	0.00	0.01	0.28	0.05	0.00	0.00	0.16	86
19	3-PA	POP-xantphos	16	120	10(1/1)	0.03	0.03	0.00	0.68	0.02	0.65	0.01	0.00	0.01	0.29	0.06	0.00	0.00	0.22	100
20	3-PA	POP-xantphos	8	130	10(1/1)	0.04	0.03	0.01	0.77	0.02	0.52	0.01	0.00	0.01	0.25		0.00	0.00	0.21	92
21	3-PA	POP-xantphos	16	130	10(1/1)	0.02	0.02	0.00	0.82	0.02	0.50	0.01	0.00	0.01	0.23		0.00	0.00	0.39	100
22	3-PA	POP-xantphos	8	130	5(1/1)	0.05	0.04	0.01	0.74	0.02	0.50	0.01	0.00	0.01	0.22		0.00	0.00	0.26	91
23	3-PA	POP-xantphos	16	130	5(1/1)	0.02	0.02	0.00	0.76	0.02	0.51	0.02	0.00	0.01	0.24		0.00	0.00	0.41	99
24	3-PA	POP-xantphos	8	100	50(1/2)	0.05	0.04	0.01	0.10	0.02	0.14	0.01	0.00	0.01	0.11		0.00	0.00	0.04	24
25	3-PA	POP-xantphos	16	100	50(1/2)	0.07	0.05	0.02	0.18	0.02	0.18	0.00	0.00	0.01	0.13		0.00	0.00	0.12	36
26	3-PA	POP-xantphos	8	120	10(1/1)	0.01	0.01		0.66	0.02	0.54	0.02	0.00	0.01	0.30	0.03	0.00	0.00	0.16	88
27	3-PA	POP-xantphos	8	120	10(1/1)	0.03	0.03		0.56	0.02	0.60	0.03	0.00	0.01	0.28	0.05	0.00	0.00	0.16	86
28	3-PA	POP-xantphos	8	120	10(1/1)	0.06	0.05	0.01	0.54	0.02	0.64	0.01	0.00	0.01	0.30		0.00	0.00	0.13	86
29	3-PA	POP-xantphos	8	120	10(1/1)	0.07	0.06	0.01	0.50	0.02	0.66	0.01	0.00	0.01	0.29		0.00	0.00	0.11	84
30[b]	3-PA&4-PA	POP-xantphos	8	120	10(1/1)	0.00	0.02		0.51	0.02	0.69	0.03	0.00	0.01	0.24	0.02	0.00	0.00	0.13	83

[a] Reaction conditions: 2 mmol (19.8 mg) of 3-PA or 4-PA or mixture of pentenamides; 0.0025 mmol (1.24 mg) $[Rh(cod)Cl]_2$ precursor, 0.01 mmol (5.79 mg) xantphos, P (CO/H_2) = 50 (1/1-1/9) bar; T = 60 °C-120 °C; *t* = 4-8 h; 0–0.05 mmol HOTs; 0-20 mmol HFIPA; Solvent: 10 mL diglyme. [b] The mixture of 3-PA (1.5 mmol) and 4-PA (0.5 mmol) directly produced from GVL. The amount of products was determined by GC analysis using undecane as an internal standard; The amounts of the mixture of pentenamides determined by injecting the mixture into GC before starting the reaction

Samenvatting (Summary in Dutch)

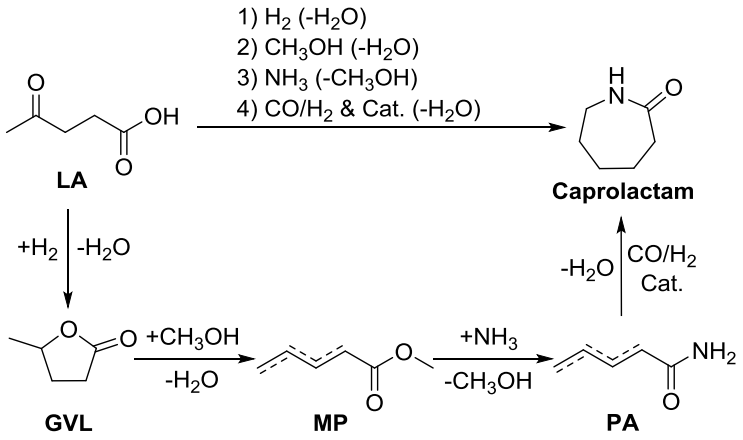
Algemene Inleiding; alternatieve routes naar caprolactam (Hfdst. 1)

Zoals beschreven in Hoofdstuk 1, is het vinden van alternatieve, duurzame grondstoffen voor de chemische industrie in de laatste jaren steeds belangrijker geworden vanwege de hoge prijs van fossiele grondstoffen en de toenemende vraag naar energie. Daarnaast is de atoomefficiënte en energie-efficiënte productie van brandstoffen en chemicaliën een onderwerp dat steeds belangrijker wordt voor de chemische industrie, voor een duurzame wereld met een verminderde uitstoot van broeikasgassen.

Lignocellulose uit biomassa is een van de meest aantrekkelijke duurzame grondstoffen voor chemicaliën. Hydroxymethylfurfural (HMF), verkregen uit lignocellulose, kan gebruikt worden om een grote verscheidenheid aan chemicaliën te maken, die op dit moment nog gemaakt worden uit aardolie. Een van de stoffen die gemaakt kan worden uit HMF is levulinezuur (LA); dit kan gebruikt worden voor de productie van chemicaliën zoals caprolactam.

ε-Caprolactam is een monomeer voor de productie van nylon-6, een veel gebruikt synthetisch polymeer met een jaarlijkse productie van ongeveer vier miljoen ton. In Hoofdstuk 1 wordt het huidige industriële proces naar caprolactam beschreven, en een overzicht gegeven van alternatieve syntheseroutes gebaseerd op butadiëen. In Hoofdstuk 1 wordt ook een gerapporteerde alternatieve synthese gebaseerd op biomassa beschreven, te weten een multi-stap katalytische omzetting van hydroxymethylfurfural (HMF) naar caprolacton.

Het uiteindelijke doel van het onderzoek beschreven in dit proefschrift is de ontwikkeling van een nieuwe syntheseroute naar caprolactam uit γ-valerolacton (GVL), een verbinding die gemaakt kan worden uit, vanuit biomassa gewonnen levulinezuur. De voorgestelde route verloopt via de zuur-gekatalyseerde reactieve destillatie van GVL met methanol tot een mengsel van isomere methyl pentenoaten (MPs). De pentenamides (PAs) die gemaakt worden door aminolyse van de MPs met ammonia, zullen uiteindelijk moeten worden omgezet naar caprolactam via een intramoleculaire hydroamidomethyleringsreactie (Schema S.1).



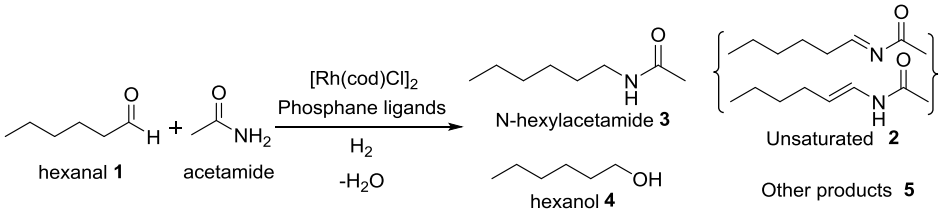
Schema S.1. Voorgestelde synthetische route voor de omzetting van levulinezuur (LA) naar caprolactam

Hydroamidomethylering is een chemische transformatie van een alkeen met een amide die tot dusver nog niet bekend was; daarom was een groot deel van het onderzoek dat beschreven is in dit proefschrift erop gericht om een effectief katalysatorsysteem te ontwikkelen voor deze nieuwe reactie. Hydroamidomethylering van een alkeen omvat een cascadereactie bestaande uit een hydroformylering van een alkeen met synthesegas naar aldehyde, gevolgd door een reductieve amidering van het aldehyde met een primaire amide. Om de hydroamidomethyleringsreactie systematisch te onderzoeken, zijn de deelstappen apart bestudeerd. Allereerst is een katalysatorsysteem ontwikkeld dat efficiënte reductieve amidering van een aldehyde met het primaire amide in puur waterstofgas katalyseert, zoals is beschreven in Hoofdstuk 2. De aanwezigheid van CO in synthesegas tijdens de beoogde hydroamidomethylering cascadereactie onderdrukt echter de hydrogeneringsreactie in de reductieve amideringsstap. Om het katalysator-vergiftigende effect van CO te overwinnen, is er gezocht naar promoters voor de hydrogeneringsreactie in de aanwezigheid van synthesegas (Hoofdstuk 3); uiteindelijk is het gelukt om de cascade hydroamidomethyleringsreactie van alkenen met amides succesvol uit te voeren. Overigens kunnen de reductieve amidering en hydromidomethyleringsreactie potentieel ook ingezet worden voor een nieuwe selectieve syntheseroute naar primaire amines uit aldehydes of alkenen; dit is beschreven in Hoofdstuk 4. Tenslotte is met de opgedane kennis getracht om de intra-moleculaire versie van hydroamidomethylering toe te passen op de ultieme substraten

4-penteenamide en 3-penteenamide voor de synthese van caprolactam, hetgeen beschreven is in Hoofdstuk 5.

Rhodium-gekatalyseerde reductieve amidering van aldehydes (Hfdst. 2)

De nieuw-ontwikkelde katalytische reductieve amidering van een aldehyde (hexanal) met een primaire amide (acetamide) onder een zuivere waterstofatmosfeer wordt gerapporteerd in Hoofdstuk 2. Zorgvuldige analyse van de reactiemengsels liet zien dat naast het gewenste N-hexylacetamide **3**, de twee isomere onverzadigde tussenproducten **2**, als ook hexanol **4** werden geproduceerd, samen met producten met hogere massa **5** die ontstaan uit aldolcondensatie en di-amide-koppeling van hexanal (Schema S.2).



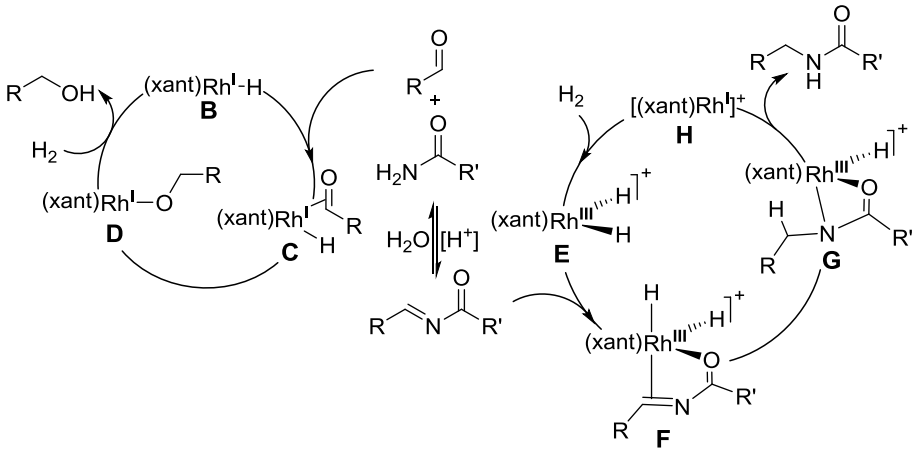
Schema S.2. Reductieve amidering van hexanal met acetamide; waargenomen producten

Toepassing van verschillende metaalverbindingen, liganden en reactiecondities toonde dat het katalytische systeem gebaseerd op $[Rh(cod)Cl]_2$ in combinatie met het ligand xantphos en een sterk zuur als co-katalysator een hoge selectiviteit voor het gewenste N-hexylacetamide **3** opleverde. Bij geoptimaliseerde condities werd een hexanal conversie van 98% behaald met meer dan 90% selectiviteit voor N-hexylacetamide **3**, met een **3**/**4** ratio van >20, en een lage hoeveelheid van bijproducten **5**.

Het gebruik van verschillende aldehydes en amides in de reactie toonde aan dat de omzetting sterk afhankelijk is van de keuze van N-substraten, wat aangeeft dat de koppelingsreactie afhankelijk is van de nucleofiliciteit van de N en de sterische hindering van de substraten bij het stikstofatoom.

NMR studies toonden aan dat de nucleofiele additie van acetamide aan hexanal door zuur word gekatalyseerd, waarbij N-(1-hydroxylhexyl)acetamide **2a** word gevormd in een evenwicht met zowel hexanal als **2** (Figuur 2.6). Een katalytisch mechanisme wordt voorgesteld waarin een sterk zuur zoals HOTs (para-tolueensulfonzuur) als co-

katalysator werkt door een snel chemisch evenwicht tussen de aldehyde, acetamide en de intermediairen **2** in te stellen, alsmede door de vorming van een kationische Rh^{III}/xantphos verbinding. Er wordt voorgesteld dat de hoge substraatspecificiteit in de hydrogenering wordt veroorzaakt door de intrinsiek lagere aldehyde-hydrogeneringsactiviteit van de kationische Rh^{III}-verbinding. De neutrale, laagvalente hydrido-Rh^{I} verbinding zou de binding van de aldehyde via de π-elektronen prefereren, waardoor alcohol **4** wordt gevormd. De kationische, hoogvalente dihydrido-Rh^{III} verbinding die aanwezig is in een zuur milieu prefereert de binding het imido-intermediair **2**, die met zowel de carbonylzuurstof als de imide onverzadigde binding coordineert, waardoor het gewenste product wordt gevormd (Schema S.3).



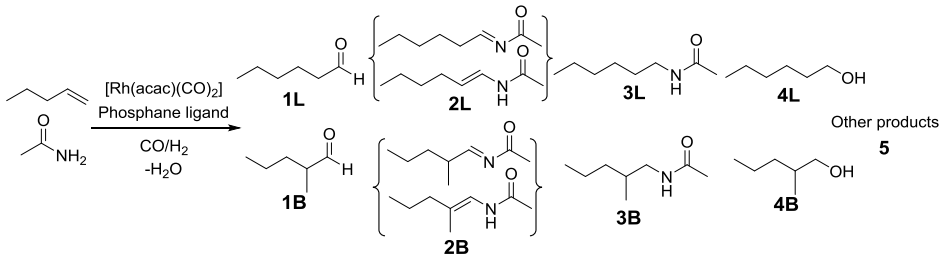
Schema S.3. Voorgestelde katalytische cycli voor de hydrogenering van een aldehyde versus onverzadigde imido-intermediairen

Het katalytische systeem met rhodium/xantphos/HOTs voor de reductieve amidering van een aldehyde met een amide geeft veelbelovende omzettingsgetallen (TON=1800) en goede opbrengsten van het gewenste product (~90%) bij relatief milde reactieomstandigheden.

Chemo- en regioselectieve homogene rhodium-gekatalyseerde hydroamidomethylering van 1-alkenen naarN-alkylamides (Hfdst. 3)

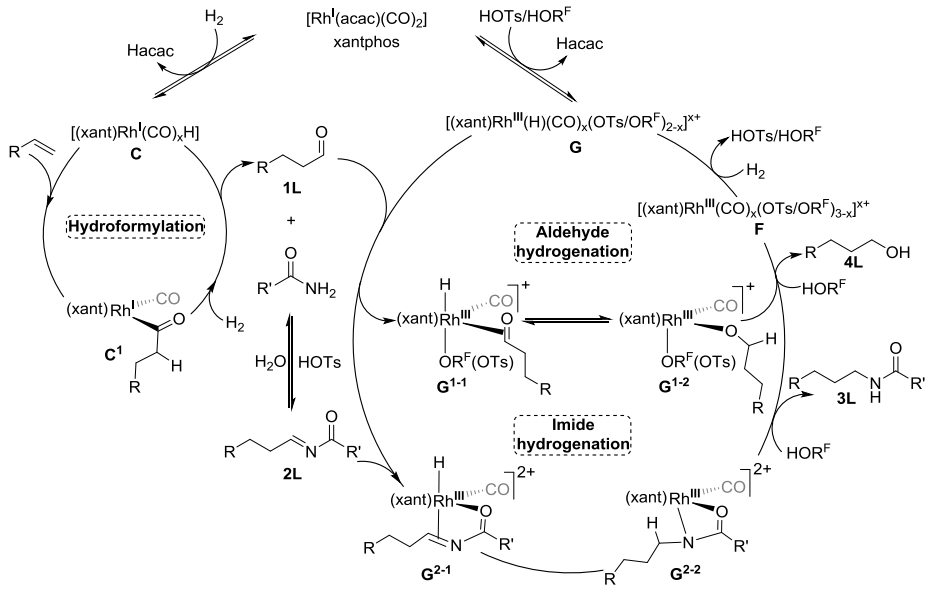
In Hoofdstuk 3 wordt beschreven hoe een katalysatorsysteem is ontwikkeld dat in staat is de vorming van aldehyde uit een alkeen met behulp van synthesegas (CO/H_2) te

combineren met reductieve amidering van deze aldehyde onder dezelfde synthesegas condities. Deze ontwikkeling maakt directe mono-N-alkylering van primaire amides met 1-alkenen en synthesegas door middel van een katalytische 'hydroamidomethyleringsreactie' – voor de eerste keer – mogelijk. Een selectief rhodium/xantphos katalysatorsysteem is zo ontwikkeld voor deze reactie, waarbij 1-penteen en acetamide als modelsubstraten zijn gebruikt. Naast het product N-hexylacetamide **3** kunnen aldehyde **1**, de isomere onverzadigde intermediairen **2**, hexanol **4** en bijproducten **5** met een hogere massa als ook de overeenkomstige isomere vertakte producten gevormd worden (Schema S.4).



Schema S.4. Hydroamidomethylering van 1-penteen met acetamide: waargenomen producten, intermediairen en bijproducten

Zoals aangetoond in het onderzoek naar de katalytische reductieve amideringsreactie (Hoofdstuk 2), is een katalytische hoeveelheid van een sterk zuur zoals HOTs nodig als katalysator voor de evenwichts-condensatiereactie van de amide met de aldehyde. Gevonden werd dat de toevoeging van een zwak zuur als promotor, zoals HOR^F (1,1,1,3,3,3-hexafluoroisopropylalcohol) in hoeveelheden als oplosmiddel, ook een sterke impact op het verloop van de katalytische hydroamidomethyleringsreactie heeft, waardoor een actieve hydrogeneringskatalysator gevormd kan worden in de aanwezigheid van CO. Bij geoptimaliseerde condities werd een bijna volledige omzetting van het alkeen waargenomen met meer dan 80% selectiviteit voor het product N-hexylacetamide. Wanneer een hoge concentratie HOR^F (HOR^F/diglyme ~5/1 (v/v)) aanwezig is, wordt met hetzelfde katalysatorsysteem een buitengewoon hoge selectiviteit (~90%) voor de vorming van hexanol uit 1-penteen en synthesegas waargenomen; hiermee wordt een uniek voorbeeld van een selectieve Rh-gekatalyseerde hydroformylering-hydrogenering tandemreactie bij milde condities gepresenteerd.



Schema S.5. Voorgesteld mechanisme voor de hydroamidomethylering van1-alkeen

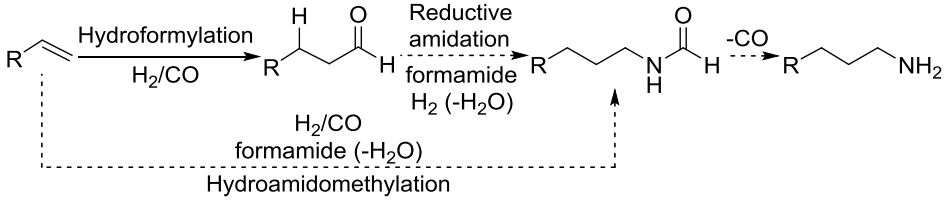
De tijdsafhankelijke productvorming tijdens hydroamidomethylerings batchexperimenten gaf bewijs voor de vorming van zowel de aldehyde als ook de onverzadigde enamido/imido verbindingen **2** als intermediaren in de reactie. Dit is een duidelijke indicatie dat de hydroamidomethylering via een drie-stap hydroformylerings-/condensatie-/hydrogeneringsreactie verloopt. Om de rol van HOTs en HOR^F te onderzoeken is het effect bestudeerd van beide stoffen op de individuele stappen van de hydroamidomethylering-cascadereactie. De conclusie is dat HOR^F in combinatie met het sterke zuur HOTs waarschijnlijk een katalysatorsysteem met twee functies maakt, dat bestaat uit een neutrale [(xantphos)(CO)Rh^I-hydride] hydroformyleringskatalysator en een kationische [(xantphos)(CO)Rh^{III}-hydride]$^{n+}$ verbinding die in staat is om de imide en/of de eenamide intermediairen (die in een dynamisch, zuur-gekatalyseerde condensatie-evenwicht zijn met de aldehyde en de amide) selectief te reduceren (Schema S.5). De competitie tussen de twee substraten die betrokken zijn in de afzonderlijke katalytische cycli, die gecontroleerd wordt door anion-coördinatie met het kationische Rh^{III}-deeltje, is de basis voor de chemoselectiviteit van de hydroamidomethyleringsreactie. Een interessante notie uit dit

werk is, dat de aanwezigheid van een amidereactant, als een zwakke base, ook een belangrijke rol speelt in de bepaling van de concentratie van anionen.

Zowel HOR^F als HOTs kan anionen leveren aan het kationische Rh^{III}-hydride-complex, via protonering van de zwak-basische amide en het product, afhankelijk van hun relatieve concentraties, relatieve zuurtegraad en coördinatie-eigenschappen met het Rh deeltje. Dit rationaliseert de drastische verandering in selectiviteit naar N-hexylacetamide als hoofdproduct (>80%) bij relatief lage HOR^F concentraties, naar hexanol als voornaamste product (>90%) bij hoge concentraties HOR^F.

Naar de synthese van primaire amines: de bestudering van rhodium-gekatalyseerde homogene reductieve amidering en hydroamidomethylering met formamide (Hfdst. 4)

De katalytische reductieve amidering van een aldehyde met formamide als ook de directe hydroamidomethylering van een alkeen met formamide als het amide substraat is beschreven in Hoofdstuk 4. De katalytische synthese van N-alkylformamides kan leiden naar een nieuwe route om primaire amines te maken uit alkenen via decarbonylering van N-alkylformamide (Schema S.6).



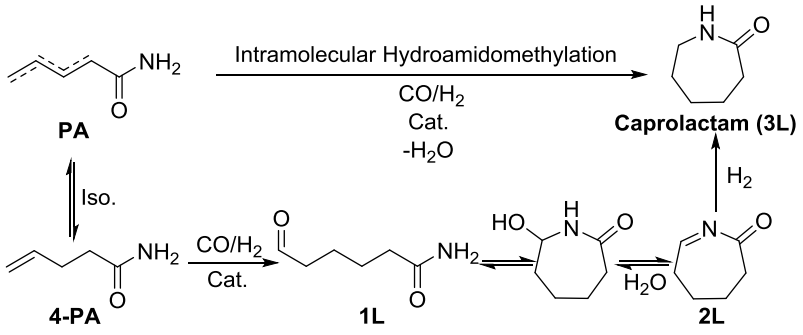
Schema S.6. De voorgestelde katalytische route naar primaire amines uit alkenen

Gebruik van het katalysatorsysteem gebaseerd op rhodium/xantphos met HOTs als co-katalysator in de reductieve amidering van hexanal met formamide resulteerde in een hoge selectiviteit voor de vorming van N-hexylformamide (tot 90%). In vergelijking met de reductieve amidering met acetamide moet de hoeveelheid van de sterk-zure co-katalysator (HOTs) verhoogd worden om een zelfde selectiviteit te bereiken voor de reactie met formamide. Onder deze condities wordt de selectiviteit voor N-hexylformamide **3** ten opzichte van hexanol **4** spectaculair verhoogd (ratio **3L**/**4L** ~60). De reductieve amideringsreactie werd verder onderzocht met verschillende aldehydes, waarmee werd aangetoond dat verschillende N-alkylformamides efficiënt gemaakt

kunnen worden. De katalytische hydroamidomethylering van penteen met formamide vertoont een relatief slechte selectiviteit voor N-hexylformamide. De hogere zuurconcentratie die nodig is voor een efficiente reductieve amidering, veroorzaakt overmatige (zuur-gekatalyseerde) acetaalvorming van HOR^F met de aldehyde. De met acetalisering gepaard gaande waterproductie wordt verantwoordelijk gehouden voor de middelmatige prestaties van de hydroamidomethyleringskatalysatoren wegens obstructie van de intermediaire aldehyde-amide adductvorming. De decarbonylering van N-hexylformamide naar N-hexylamine werd gedemonstreerd met een aantal overgangsmetaalcomplexen of een sterke base. Echter, tot dusver is alleen een stoichiometrische omzetting behaald onder de gebruikte condities.

Van duurzame grondstof naar "groene" nylon: katalytische omzetting van γ-valerolactone naar ε-caprolactam (Hfdst. 5)

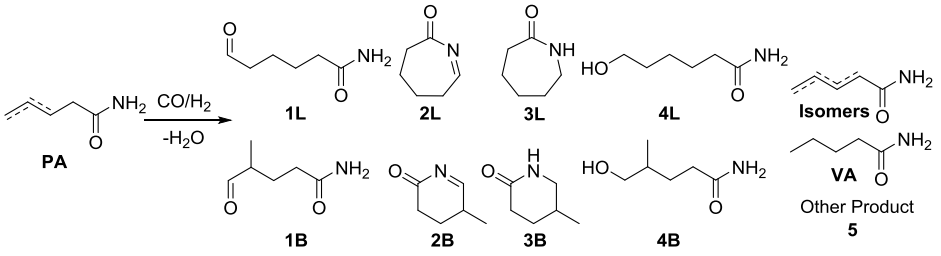
In Hoofdstuk 5 worden onze studies aangaande de conversie van GVL naar caprolactam gerapporteerd. Trans-esterificatie van GVL met methanol werd uitgevoerd volgens een gerapporteerde procedure, als een reactieve destillatie met een sterk Brønstedzuur als katalysator. Het destillatieproduct bestaat uit een mengsel van methanol, water, cis- en trans- methyl-3-pentenoaten (3-MP) en methyl-4-pentenoaat (4-MP), als ook kleine hoeveelheden GVL, methyl-2-pentenoaat (2-MP), methyl-4-methoxypentanoaat (4-MMP) en methyl-4-hydroxypentanoaat (4-HMP). Onder geoptimaliseerde omstandigheden werd bij een GVL-conversie van >90% een MPs selectiviteit van 95% behaald .



Schema S.7. Intramoleculaire hydroamidomethylering van penteenamide naar caprolactam (Voor de duidelijkheid zijn alleen de lineaire producten afgebeeld).

Het mengsel van methylpentenoaten werd vervolgens omgezet naar een mengsel van de corresponderende pentenamides (PA). Het bleek dat het gebruik van ammonium hydroxide de beste resultaten gaf: bij geoptimaliseerde condities werd een omzetting naar >98% aan PAs gehaald. In het algemeen gaat de omzetting van 4-MP langzamer dan van 3-MP, wat verklaard kan worden door het inductieve elektronenzuigende effect van de dubbele band, die sterker is bij 3-MP dan bij 4-MP. Een atoom-efficiënte en regioselectieve intramoleculaire hydroamidomethylering van de resulterende penteenamides is de belangrijkste, nieuwe stap in het maken van caprolactam (Schema S.7).

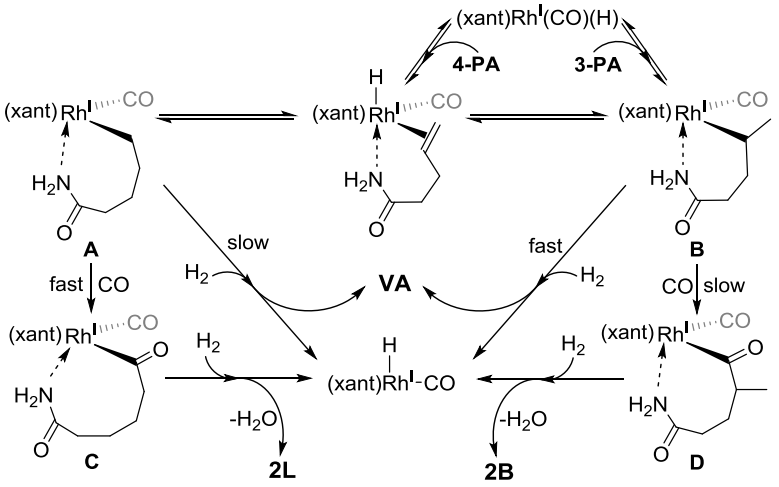
Het onderzoek naar de cascadereactie hydroformylering-reductieve amidering werd gestart met zuivere 4-penteenamide (4-PA) als substraat, onder de katalytische condities die ontwikkeld zijn voor de intermoleulaire reductieve amidering van een aldehyde met acetamide (Hoofdstuk 2, Schema S.8). Echter, zeer kleine hoeveelheden caprolactam werden verkregen. De toevoeging van HOR^F aan het reactiemengsel bevorderde de hydrogeneringsactiviteit van de katalysator in de aanwezigheid van synthesegas. Hoewel de selectiviteit naar caprolactam significant verhoogd werd, werd een aanzienlijke hoeveelheid pentaanamide (valeramide, VA) gevormd. De hoeveelheid VA en de hoeveelheid oligomeren and polymeren bleek nog veel hoger te worden wanneer een katalytische hoeveelheid HOTs aan het reactiemengsel werd toegevoegd.



Scheme S.8. Intramoleculaire hydroamidomethylering van het mengsel van 3-PA en 4-PA naar caprolactam: waargenomen producten, intermediairen en bijproducten.

Verrassend genoeg werd na een hydroformyleringsreactie van 4-PA met het Rh/xantphos systeem zonder HOTs **2L** als het voornaamste product waargenomen. Klaarblijkelijk wordt de aldehyde die gevormd wordt in de hydroformylering van 4-PA direct omgezet in onverzadigd caprolactam. Een uitstekende conversie (98%) en

selectiviteit voor het onverzadigde caprolactam **2L** (~85%) werd behaald onder geoptimaliseerde condities. Het product **2L** kon daarna bijna kwantitatief worden gehydrogeneerd naar caprolactam met hetzelfde katalysatorsysteem, door het synthesegas te vervangen door zuiver waterstofgas. Het beste resultaat toonde een algehele ~90% selectiviteit naar caprolactam **3L** met 4-PA als beginstof.



Schema S.9. Voorgestelde mechanistische wegen naar de vorming van verschillende producten bij de hydroamidomethylering van penteenamides

Uiteindelijk werd de hydroamidomethyleringsreactie bestudeerd met het mengsel van 3- en 4- penteenamides direct afkomstig uit GVL. Het gebruik van POP-xantphos als ligand in het katalysatorsysteem, een fosforligand dat in combinatie met rhodium volgens gerapporteerde onderzoeken lineaire producten geeft in de hydroformylering van interne, lineaire alkenen, resulteerde in ~80% conversie met een algehele selectiviteit van ~75% voor het cyclische lactam. Hydroamidomethylering van 3-PA resulteerde in VA als hoofdproduct, wat verklaard kan worden door het chelerende effect van het penteenamide op het actieve Rh(I)-centrum. Waarschijnlijk is de migratie-insertie van de Rh-sec-alkylamide structuur **B** met CO om de Rh-acylverbinding **D** te vormen door sterische redenen en het relatief sterke chelerende effect van de amidefunctionaliteit niet gunstig, terwijl de hydrogenolysesnelheid door hetzelfde chelerende effect in de Rh-alkylverbinding **B** verhoogd wordt (Scheme S.9). Hoewel nog verbetering behoevend kon toch nu al een veelbelovende algehele

caprolactam opbrengst van ongeveer 50-60% op basis van GVL worden gedemonstreerd. Mogelijke verbetering van de opbrengst moet vooral worden gezocht in een betere sterische en electronische afstemming van het ligand op het Rh centrum, zodat hydrogenering, van vooral de intermediaire 2- en 3-PA isomeren, wordt voorkomen.

List of Publications

PATENT

Process to Prepare Bio-based ε-Caprolactam
Raoufmoghaddam, S.; Drent, E.; Bouwman, E.; Application Number: **EP13162426**; Application filing date: April **2013**

PUBLICATIONS

Towards Synthesis of Primary Amines: Investigating Rhodium-Catalyzed Homogeneous Reductive Amidation and Hydroamidomethylation with Formamide
Raoufmoghaddam, S.; Kortlever, R.; Drent, E.; Bouwman, E.; **2013**, *to be submitted*

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Raoufmoghaddam S.; Drent E.; Bouwman E.; **2013**, *to be submitted*

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Curriculum Vitae

The author of this thesis, Saeed Raoufmoghaddam, was born in Lahijan, Iran and raised in Tehran, Iran. After receiving his highschool diploma in 1999, he was admitted (in the Iranian nation-wide entrance exam called Konkour) to commence his bachelor studies in applied chemistry at Guilan University, Rasht, Iran. In 2003-2004, he continued his education at Guilan water treatment company, Rasht, where he was a lab assisstant in the water quality control section of the laboratory. In 2004-2005, he moved to the Iranian Petrochemical Commercial Company (IPCC), Tehran, where he had an internship as a vendor for selling chemical compounds to spin-off companies. After achieving 36th rank in chemistry nation-wide graduate entrance exam among ~10000 chemistry candidates in 2006, he was admitted to continue his education at the University of Tehran. He performed his MSc thesis research in the group of Prof. Dr. M. Ghandi where he worked on the investigation and synthesis of new aminonaphthol and 1, 4-Oxazepine derivatives. In 2008, he graduated *cum laude* for his master degree in organic chemistry. Then, he was temporarily appointed as a research expert in the oil research laboratory at Behran oil company, Tehran.

In September 2009, the author moved to Leiden University, Leiden, The Netherlands, to pursue his PhD in homogeneous catalysis under supervision of Prof. Dr. E. Bouwman and Prof. Dr. E. Drent. As part of his PhD training, he was involved in assisting several organic and inorganic practical courses and the supervision of MSc students Mark Rood, Ruud Kortlever and Florine Buijze. He attended postgraduate courses including Advanced Metal-Organic Chemistry (2010), Catalysis for sustainability (2010), Catalysis, an integrated approach (2010), Innovative uses of glycerol from the biodiesel process (2011) and Physical methods in inorganic chemistry (2011).

The author also contributed at several national and international conferences, symposia and meetings in order to share his findings to peers with posters (15 times) and lectures (11 times), as listed below.

Saeed was recently admitted to commence his post-doctoral research in the group of Prof. Dr. J. N. H. Reek (HomKat) at University of Amsterdam.

2013 CatchBio progress meeting, Nunspeet, NL (Lecture & Poster); Netherlands' Catalysis and Chemistry Conference (NCCC) XIII (Poster); CatchBio user committee meeting, Lunteren, NL (2 Lectures)

2012 Netherlands' Catalysis and Chemistry Conference (NCCC) XII (Lecture); ICCOS-2012 International Conference on Catalysis in organic synthesis, Moscow, Russia (Poster); CatchBio progress meeting, Nunspeet, NL (Lecture & Poster); HRSMC symposium, Amsterdam University, Amsterdam, NL (Poster); CatchBio user committee meeting, Lunteren, NL (2 Lectures); LIC symposium, Leiden University, Leiden, NL (Poster)

2011 XIX EuCheMS-2011 International Conference on Organometallic Chemistry, Toulouse, France (Poster); CatchBio progress meeting, Nunspeet, NL (Lecture & Poster); Netherlands' Catalysis and Chemistry Conference (NCCC) XI (Poster); HRSMC symposium, Amsterdam University, Amsterdam, NL (Poster); LIC symposium, Leiden University, Leiden, NL (Poster); CatchBio user committee meeting, Lunteren, NL (2 Lectures); CatchBio symposium, Stein-Urmond, NL (Poster)

2010 CatchBio progress meeting, Nunspeet, NL (Lecture & Poster); Netherlands' Catalysis and Chemistry Conference (NCCC) X (Poster); CatchBio user committee meeting, Lunteren, NL (Lecture)

2009 CatchBio progress meeting, Nunspeet, NL (Lecture & Poster)

Nawoord
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Saeed Roufmoghaddam
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