The potential of hydroaminomethylation : directing the cascade

The Potential of Hydroaminomethylation

Directing the Cascade

This research has been financially supported by the NWO-ACTS Aspect program (ASPECT 053.62.009).

Coverdesign by Anique Pfennings

Printed at Wöhrmann Print Service, Zutphen

A catalogue record is available from the Eindhoven University of Technology Library

The Potential of Hydroaminomethylation – Directing the Cascade / by Bart Hamers – Eindhoven : Technische Universiteit Eindhoven, 2009.
Proefschrift. – ISBN 978-90-8570-411-9
Subject headings: rhodium-catalysed hydroaminomethylation / phosphorus ligands / coordination chemistry / solvent influences / selectivity / catalyst recycling

The Potential of Hydroaminomethylation

Directing the Cascade

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Technische Universiteit Eindhoven, op gezag van
de rector magnificus, prof.dr.ir. C.J. van Duijn,
voor een commissie aangewezen door het College
voor Promoties in het openbaar te verdedigen op
donderdag 22 oktober 2009 om 16.00 uur

door

Bart Hamers

geboren te Born

Dit proefschrift is goedgekeurd door de promotor:

prof.dr. D. Vogt

Copromotor:
dr. C. Müller

‘Don’t ask yourself if it’s a long road.
Ask yourself if it’s a good journey.’

Sidney Poitier

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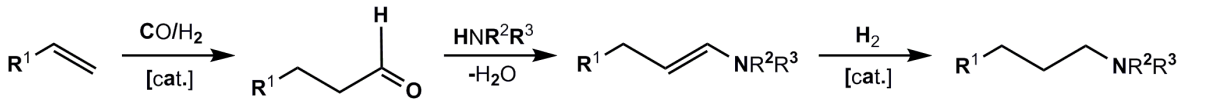
1

Hydroaminomethylation, a cascade reaction with potential

Amines are important building blocks in the bulk chemical as well as in the pharmaceutical industry. Classical syntheses of amines often lead to large amounts of waste, mainly inorganic salts. One of the most promising new reactions for the production of amines in terms of atom-efficiency, activity, selectivity, and applicability is the hydroaminomethylation of alkenes in which water is the only side product. Especially the possibility to synthesise primary amines atom-efficiently from cheap alkene feedstocks and ammonia by hydroaminomethylation makes this an interesting reaction from an industrial point of view. Although the hydroaminomethylation has been discovered already in 1949, intensive research with respect to this reaction has been performed during the last 15 years. A review of the most interesting aspects of this reaction will be presented in this chapter.



aldehyde **enamine** **desired amine product**

Part of this work will be submitted for publication:
B. Hamers, C. Müller, D. Vogt, *manuscript in preparation*

1.1 Relevance and preparation of amines

Besides the relevance of amines in the human body in the form of DNA and amino acids, amines are also important in everyday life for a broad range of building blocks and end products such as polymers, lubricating oils, waterproofing agents in textiles, detergents, dyes, pesticides, pharmaceuticals, and even stabilisers for explosives. Although the production scale of polymer and pharmaceutical products is completely different, illustrative examples showing the relevance of amines can be found for both product classes.

In the class of polymer products, 1,6-diaminohexane, 1,4-diaminobutane, ε-caprolactam, and 11-aminoundecanoic acid are examples of important amine building blocks for the synthesis of the polyamides Nylon-6,6, Nylon-4,6, Nylon-6, and Nylon-11, respectively. Most Nylon types are synthesised *via* a polycondensation reaction of the amine functionality with a carboxylic acid functional group or *via* a ring-opening polymerisation. The stiffness and high melting points of polyamides are important properties, which are mostly caused by intermolecular hydrogen bonding. Nylon finds its applications in many important products such as ballistic vests, airbags, tights and other textiles, dental floss, fishing lines, chords of musical instruments, insulating coatings of cables et cetera.

Many pharmaceutical products or active pharmaceutical ingredients contain amino groups. Methylphenidate (Fig. 1.1), for example, is derived from amphetamine and is the active ingredient in pharmaceuticals such as Ritalin and Concerta, which are the most commonly prescribed psychostimulants in the treatment of attention-deficit hyperactivity disorder (ADHD), sleeping disorders and narcolepsy.[1,2] This drug acts by increasing levels of norepinephrine, serotonin and dopamine in the brain, inducing euphoria. Another well-known pharmaceutical is Imipramine (Fig. 1.1) which is the first drug of the class of tricyclic antidepressants to be developed in the late 1950s.[3] These tricyclic antidepressants have mainly been used in the treatment of major depression and insomnia, although alternatives, also including amine functionalities, have been developed during the last decade.[4]

Consequently, the preparation of amines is an important issue in synthetic chemistry.[5,6] Many different organic reactions for the synthesis of amines such as nucleophilic substitution of haloalkanes, Buchwald-Hartwig reaction of amines and aryl halides, reduction of nitriles, amides, or nitro compounds, and Gabriel synthesis are known. The industrial process for the production of amines usually produces large amounts of waste, mainly inorganic salts, together with the desired amine product. In many cases, the amount of waste produced is even much larger than the amount of product. Since sustainability is an important issue in chemical

industry, waste reduction is one of the major objectives. Such waste reduction is possible by using atom-efficient reactions, which are often transition metal-catalysed reactions. Examples of catalytic methods to synthesise amines are reactions like palladium-catalysed amination of aryl halides,[7,8] hydroamination of alkenes,[9] hydrocyanation of alkenes[10,11] combined with a reduction to the amine, reductive amination of aldehydes and ketones,[12,13] and hydroaminomethylation.

Hydroamination and hydrocyanation reactions both have atom efficiencies of 100%. This is not completely true for hydroaminomethylation reactions, as water is liberated in the condensation step. However, hydroamination reactions show a relatively high reaction barrier, while an additional reduction step is necessary after the hydrocyanation reaction in order to produce amines. These disadvantages make them less useful for fast, efficient, and selective syntheses of amines. This chapter will mainly focus on the hydroaminomethylation reaction, which is a promising reaction to fulfil the above-mentioned requirements of waste reduction in combination with fast and selective catalysis.

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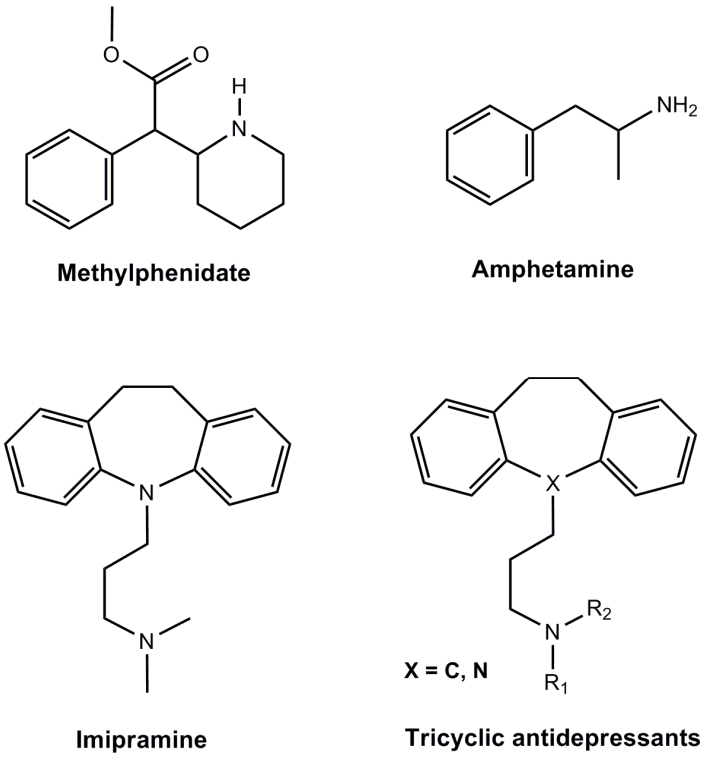
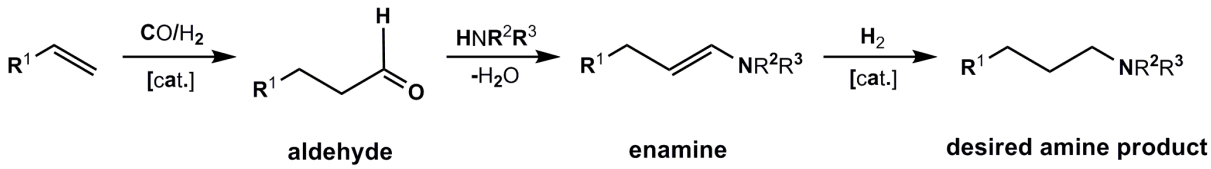


Figure 1.1: *Examples of pharmaceuticals containing amine functionalities.*

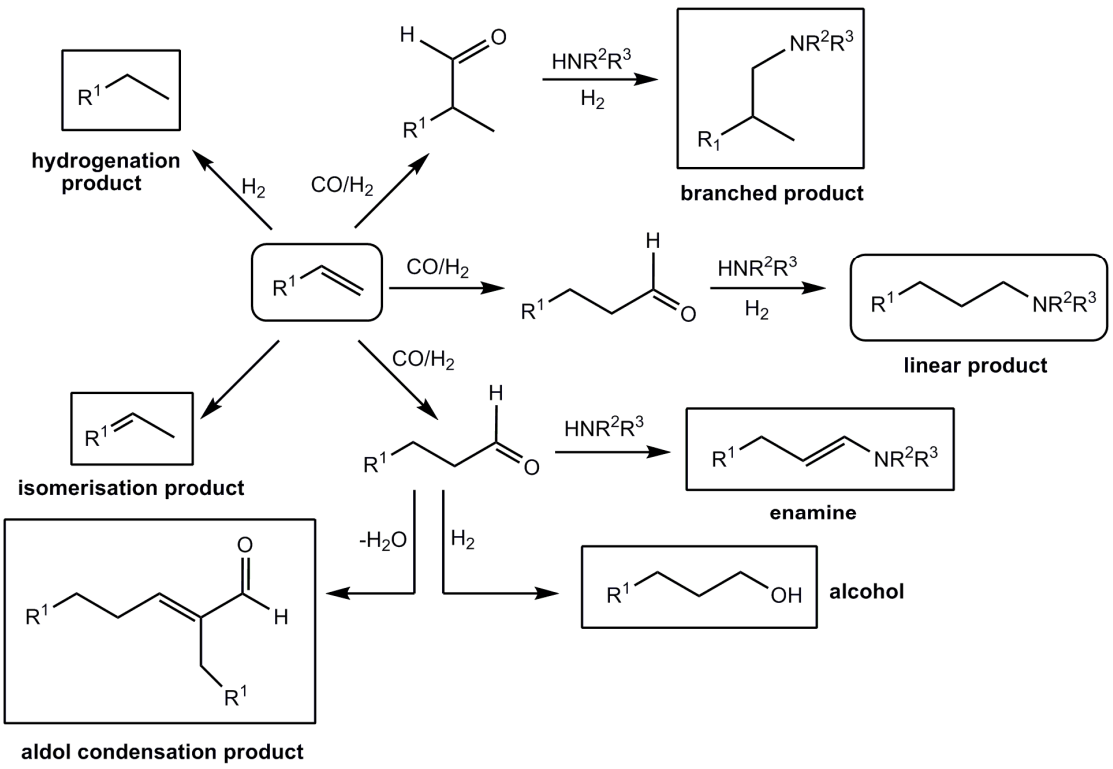
1.2 General aspects of hydroaminomethylation reactions

The hydroaminomethylation (HAM; Scheme 1.1), discovered already in 1949 in the laboratories of BASF by Walter Reppe,[14,15] is a promising reaction to fulfil the aforementioned requirement of waste reduction since water is the only side product. HAM is a one-pot cascade reaction, starting with the hydroformylation of an alkene, consecutive condensation of the intermediate aldehyde with the substrate amine, and subsequent hydrogenation of the formed enamine or imine to the desired amine product. In this reaction, primary and secondary amines, as well as ammonia can be used as the amine substrate. The HAM with ammonia is particularly challenging in terms of chemoselectivity, since the desired primary amine is more nucleophilic than ammonia, leading to a higher reactivity towards the intermediate aldehyde, which in turn results in the formation of a secondary amine.[16]



Scheme 1.1: *Illustration of the hydroaminomethylation reaction, consisting of a hydroformylation and a reductive amination*

As described above, HAM consists of a hydroformylation and a reductive amination. This also implies that side products of both reactions might be observed in the HAM reaction, as indicated in Scheme 1.2. In the HAM of alkenes, both the linear and the branched amines can be formed, although linear amines are most frequently the desired products. This regioselectivity is already determined in the first reaction step, the hydroformylation. Chemoselectivity, which comprises the selectivity to the amine product, is mainly determined in the reductive amination step. Very important in this respect is the hydrogenation of the C=N double bond of the enamine or imine.[17,18] In order to gain more insight into the HAM reaction, both reaction steps (hydroformylation and reductive amination) are discussed separately.



Scheme 1.2: *Overview of the most frequently observed side reactions together with the desired reaction to the linear amine.*

1.2.1 Hydroformylation

The hydroformylation reaction, also known as the oxo reaction in industry, has been discovered by Roelen in 1938.[19] This catalytic reaction to produce aldehydes from alkenes under synthesis gas pressure, has become one of the largest homogeneously catalysed reactions with annual production volumes exceeding 8 million tonnes.[20,21] The industrial oxo process is mostly Co- or Rh-catalysed and the aldehyde products and their hydrogenation products (alcohols) find their application in a variety of products such as detergents, surfactants or plasticisers, underlining the importance of hydroformylation in industrial chemistry.

Although the first oxo processes were Co-catalysed, the Rh-catalysed hydroformylation was introduced in the 1970s, showing considerably improved activities and selectivities. Initial Rh-catalysed hydroformylations were based on unmodified precursors. However, it was demonstrated that much lower pressures could be applied upon using triphenylphosphine-modified rhodium precursors,[22-24] which is an important issue with respect to industrial realisation. Both Co- and Rh-catalysed oxo processes are operated

nowadays in chemical industry. Catalyst recovery, especially with the expensive rhodium catalysts, selectivity and high turnover numbers in combination with "cheap" process operation are important aspects of this process.[25]

In the early 1960s, a mechanism for the cobalt-catalysed hydroformylation was proposed by Heck and Breslow, which is accepted as the general mechanism for Co- and Rh-catalysed hydroformylation at present (Fig. 1.2).[26]

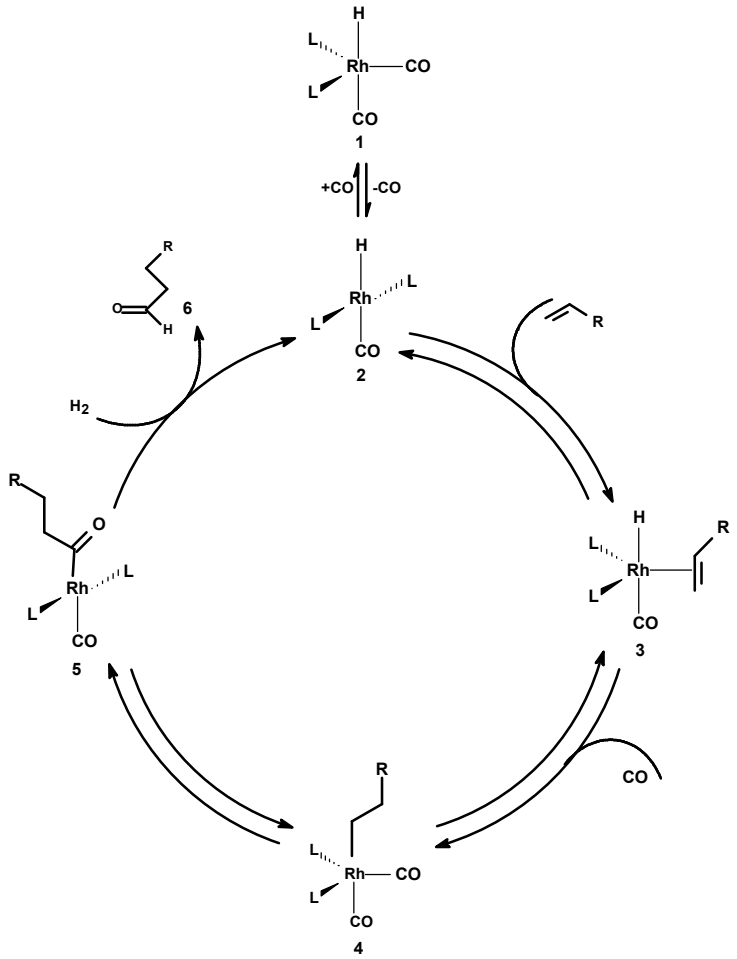


Figure 1.2: *Proposed catalytic cycle of the Rh-catalysed hydroformylation.*

The mechanism starts with the dissociation of one carbon monoxide ligand from complex **1**, which is the resting state of the catalyst, leading to the formation of the hydride species containing an empty coordination site (**2**). Coordination of an alkene to complex **2** leads to the formation of complex **3**, and a migratory insertion of the alkene into the rhodium-hydride bond results in the formation of the alkyl species **4**. Subsequently, a CO ligand inserts into the rhodium-alkyl bond resulting in the acyl species **5** and hydrogenolysis, possibly *via* an oxidative addition of hydrogen followed by a reductive elimination, gives the product aldehyde (**6**) and regenerates the unsaturated Rh-complex **2**. Furthermore,

β-hydrogen elimination of the alkyl species (**4**) may lead to isomerisation and the formation of less reactive internal alkenes. On the other hand, this isomerisation step is important in the reaction towards linear aldehydes *via* hydroformylation of internal alkenes, which have potential as alternative and cheap feedstocks in chemical industry.

Formation of the branched aldehyde is a possible side reaction in hydroformylation reactions. If the formation and/or further reaction of the linear alkyl complex instead of the branched alkyl complex is preferred, this side reaction can be limited. Ligand effects can have a large influence on activity and selectivity and in order to limit the formation of the branched aldehyde, high concentrations of bulky monodentate ligands can be applied. The increased steric crowding around the metal centre upon applying bulky ligands leads to a preference for the formation of linear alkyl complexes although reaction rates will be decreased.

For bidentate ligands, the natural bite angle (β_n) concept has been introduced by Casey and Whiteker (Fig. 1.3).[27] This bite angle is defined as the phosphorus-metal-phosphorus angle in a complex. It has been concluded that large bite angle ligands can easily coordinate in a bis-equatorial mode to a metal centre. This means that bidentate ligands with rigid and bulky backbones and large bite angles in combination with rhodium lead to a preference for the formation of linear aldehydes. In addition to BISBI,[28-30] especially the diphosphine ligand Xantphos and its derivatives (**7**; Fig. 1.3) have been studied extensively because of their tuneable bite angle and high linear-to-branched (l/b) ratios in hydroformylation reactions.[31-34] One special case of a Xantphos derivative, Xantphenoxaphos (**8**; Fig. 1.3), in combination with rhodium has been shown to give high isomerisation activity under hydroformylation conditions, which leads to the formation of the terminal aldehyde from internal alkenes in good selectivity.[35,36] Similar results were reported by Beller and co-workers, using the ligand NAPHOS (**9**; Fig. 1.3) in combination with rhodium.[37]

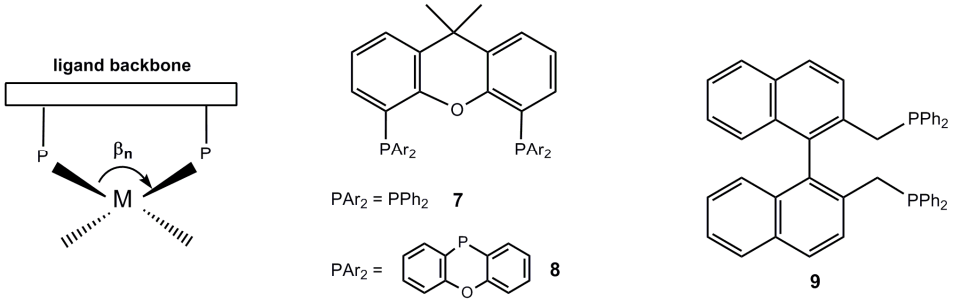


Figure 1.3: *Illustration of the bite angle in a metal complex and several diphosphine ligands used in hydroformylation: Xantphos(**7**),[38,39] Xantphenoxaphos (**8**)[40] and NAPHOS (**9**)[41 42].*

Beside the steric properties of a ligand, also the electronic properties are important with respect to activity and selectivity. In general, phosphites are better π-acceptors than phosphines, which is often indicated by the electronic parameter χ, introduced by Tolman.[25,43,44] This electronic parameter has been determined for a range of monodentate ligands by measuring the CO stretch vibration of Ni carbonyl complexes containing the particular ligand. The basic phosphine tris(*tert*-butyl)phosphine has a χ-value of zero per definition. The difference in CO stretch frequency with respect to tris(*tert*-butyl)phosphine gives the corresponding χ-value of a ligand. The better the π-acceptor properties of a ligand, the higher the χ-value will be. An overview of these χ-values and corresponding IR frequencies are given in Table 1.1 for a range of monodentate phosphorus ligands.[25]

Table 1.1: *Typical values for the electronic parameter χ, introduced by Tolman, for various monodentate phosphorus ligands.*

Ligand PR_3, R =	χ-value	IR frequency of $NiL(CO)_3$ [cm^{-1}]
*t*Bu	0	2056
*n*Bu	4	2060
4-$C_6H_4NMe_2$	5	2061
Ph	13	2069
4-C_6H_4F	16	2072
CH_3O	20	2076
PhO	29	2085
CF_3CH_2O	39	2095
Cl	41	2097
$(CF_3)_2CHO$	54	2110
F	55	2111
CF_3	59	2115

Coordinated to a metal, phosphite ligands will compete with the coordinated CO ligands for the back-donation of electron density from the metal to the ligand. This results in a weaker metal-CO bonding, which is an advantage in hydroformylation since CO has to dissociate first before an alkene can coordinate to the metal. Especially bulky diphosphite ligands, which give higher linearities than the monodentate analogues, combine high activities with good selectivities.[45-48] Examples of this class of ligands are the bulky diphosphite ligands, such as BIPHEPHOS (**10**; Fig. 1.4), developed by Bryant and co-

workers at Union Carbide.[46] An additional advantage of phosphite ligands is their (often) easy preparation and stability towards oxygen.

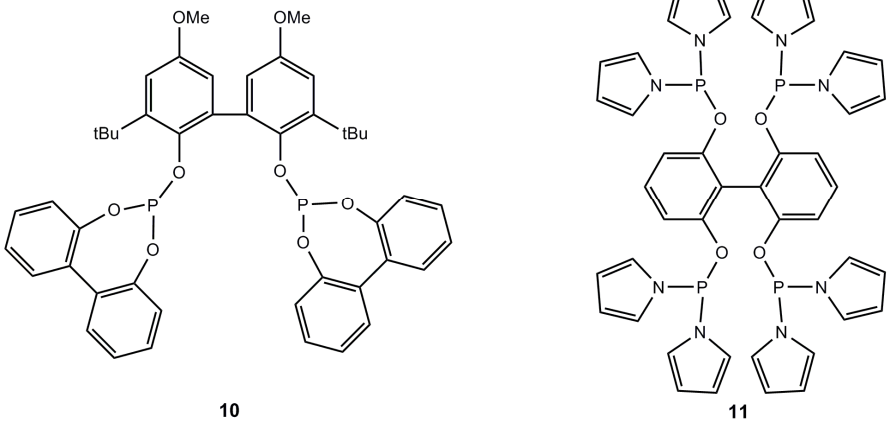


Figure 1.4: *Illustration of Union Carbide ligand BIPHEPHOS (**10**) and Tetraphos (**11**).*

Another π-acceptor ligand, which has been developed recently and which shows high activity and excellent selectivity in Rh-catalysed hydroformylation, even of internal alkenes, is the chelating tetraphosphorus ligand based on a 1,1'-biphenyl backbone (Tetraphos; **11**; Fig. 1.4).[49-51] The bulky substituents in this ligand are closer to the phosphorus atom in comparison to corresponding phosphite ligands, probably increasing the regioselectivity in this way.

From the above-mentioned aspects, it can be concluded that the steric and electronic properties of the applied ligands have a large influence on the activity and (regio)selectivity in transition metal-catalysed hydroformylation reactions. However, in order to perform a hydroaminomethylation reaction, the catalyst should not only display good performance in hydroformylation, but also in the reductive amination.

1.2.2 Reductive amination

The reductive amination of carbonyl compounds in itself is a cascade reaction consisting of a condensation of an aldehyde or ketone with an amine, followed by the hydrogenation of the enamine or imine to yield the desired amine product (reaction steps 2 and 3 in Scheme 1.1). Although also indirect reductive amination procedures are known, in which the enamine or imine is isolated before the consecutive hydrogenation reaction is performed, the direct approach is closely related to the hydroaminomethylation reaction.

Homogeneously catalysed reductive aminations were first described by Markó and Bakos in 1974 applying rhodium and cobalt carbonyl catalysts under rather harsh conditions (p = 300 bar, T = 200ºC).[52] However, no further investigations on homogeneously catalysed reductive amination were reported until the 1990s, when the reductive amination of a chiral product, the grass herbicide (S)-Metalochlor, was reported by Blaser and co-workers.[53] An iridium-based catalyst in combination with the ferrocene-based ligand Xyliphos was applied under relatively mild conditions (p = 80 bar, T = 50ºC).

In the early 2000s, a rhodium-catalysed reductive amination of aldehydes and α-keto acids was reported by Börner and co-workers.[54] The reaction was performed under 50 bar hydrogen pressure in methanol at room temperature applying [Rh(cod)(dppb)BF_4] as the catalyst. This catalyst has also been used in the hydrogenation of enamines and imines,[55,56] which probably makes it a suitable catalyst for the reductive amination as well. Several compounds, such as hemi-aminals (**14**), *N,O*-acetals (**15**), aminals (**16**), imines (**17**), and enamines (**18**) are possible intermediates in the direct reductive amination especially upon applying methanol as the solvent (Fig. 1.5). The equilibria between these intermediates were studied to a certain extent and it was found that hemi-aminals (**14**) and *N, O*-acetals (**15**) are possibly key intermediates in the reductive amination.[13] In principle, all intermediates can be successfully reduced with homogeneous rhodium catalysts,[57] which is an important requirement for direct reductive amination with these catalysts.

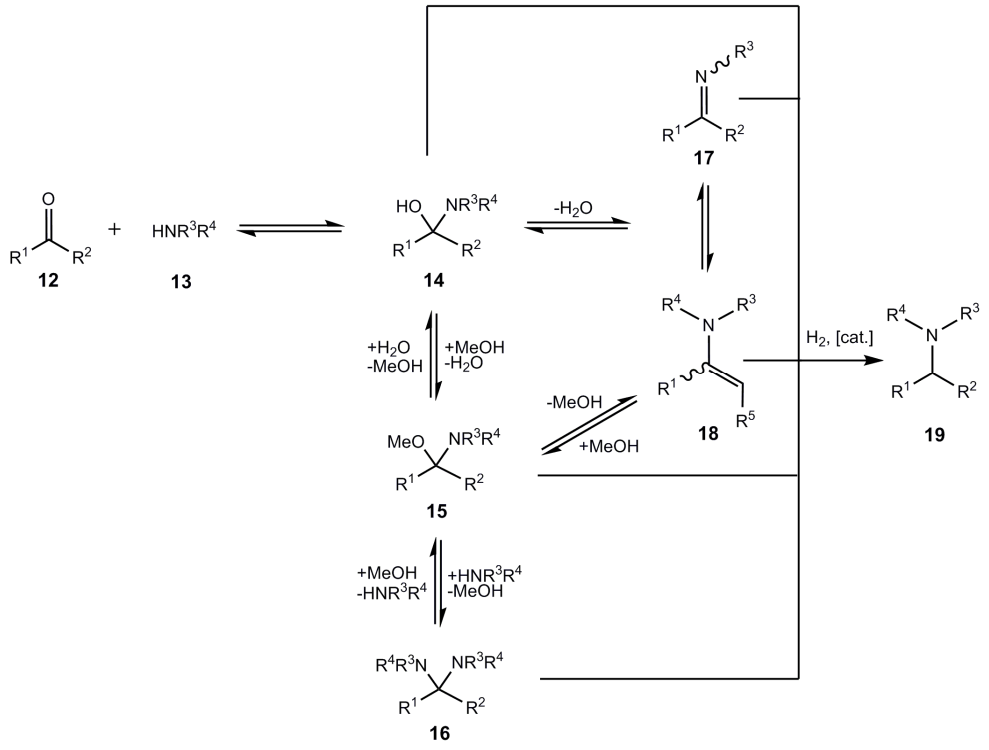


Figure 1.5: *Illustration of possible intermediates in the reductive amination reaction.*[13]

In order to synthesise primary amines *via* the direct reductive amination, ammonia or an ammonia derivative has to be used as the substrate. A first example of a reductive amination with ammonia was described by Beller and co-workers in the early 2000s.[58] Primary amines were produced in good yield (86%) and selectivity (97%) by reacting benzaldehyde with ammonia in a biphasic system. A water-soluble rhodium and iridium complex bearing the water-soluble phosphine ligand TPPTS was used as the catalyst. Certain amounts of ammonium acetate turned out to lower the amount of alcohol formed by hydrogenation of the aldehyde. A bimetallic catalyst based on Rh/Ir gave improved results in case of aliphatic aldehydes.

Kitamura and co-workers described an alternative approach towards primary amines from ketones.[59] A primary amine was produced by reaction of acetophenone and ammonium formate, the so-called Leuckart-Wallach reaction,[60,61] upon using a Cp*Rh(III) catalyst and subsequent acidic hydrolysis.

Recently, the direct reductive amination of various aldehydes and ketones with primary amines was performed using a cationic iridium catalyst, which has been proposed to be effective for reductive amination.[62,63] No ligands were applied in this system and very good conversion and yield towards the desired secondary amine were observed. The ionic liquid [BMIM][BF_4] turned out to be the best solvent for the reductive amination of acetophenone with benzylamine in combination with [$Ir(cod)_2BF_4$] giving conversions of 98% and yields of 97% of the desired secondary amine product.

In addition to these reports on reductive aminations, the stereoselective reductive amination has been described in literature using rhodium-, iridium-, and ruthenium-based catalysts bearing chiral ligands.[64-67] Interesting results with respect to transfer hydrogenation of imines and direct reductive amination of aldehydes catalysed by triazole-derived iridium(I) carbene complexes were obtained by Crabtree and co-workers. Unfortunately, the imine had to be produced prior to the addition of the catalyst. Otherwise, the aldehyde would be reduced to the alcohol preferentially.[68]

An important aspect in the direct reductive amination turns out to be the hydrogenation of the imine or the possible intermediates. Selectivity is thus an important issue since the starting compounds (*i.e.* aldehydes) should preferentially not be reduced to the corresponding alcohols. Rh/Ir-based catalysts might be useful in this respect since iridium is known to hydrogenate C=N double bonds efficiently.

1.3 A concise review on hydroaminomethylation

Although the hydroaminomethylation (HAM) has been discovered already in the late 1940s, the majority of the reports concerning this reaction stems from the last 10-12 years. An example by Kalck and Baig described the Rh-catalysed HAM reaction under mild conditions in 1992.[69] The conversions were high in this reaction, but selectivities to the amine were only moderate. Most reports from the late 1990s describe the synthesis of a variety of organic molecules, containing secondary and tertiary amines using a rhodium-catalysed HAM reaction, including an example by Breit concerning the diastereoselective HAM upon applying a substrate-bound ligand.[70-81] As an example, the synthesis of 1,4-diamines (**21**) *via* allylhalides (**20**) and a secondary amine using the HAM reaction has been described (Fig. 1.6).[76] Also intramolecular HAM reactions in order to form cyclic amines (**24**) or lactams (**25**) have been described in literature (Fig. 1.6).[82-86] In the aforementioned reports the HAM has been described as a one-pot, alternative pathway for the synthesis of a range of pharmacologically active/organic compounds. An overview of a variety of these reactions can be found in a review article by Eilbracht and co-workers.[87]

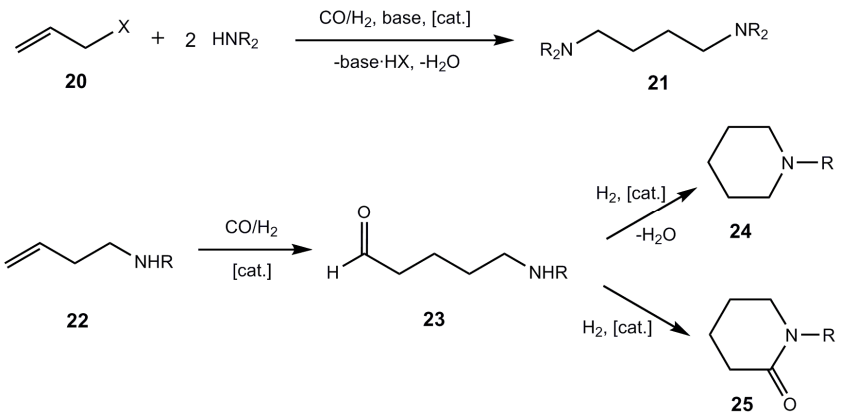


Figure 1.6: *Synthesis of a 1,4-diamine (**21**) via HAM of an allylhalide and the intramolecular HAM to a cyclic amine (**24**) or cyclic amide (**25**).*[76,87]

In the following years, several reports described the use of Rh-catalysed HAM as a versatile, selective and atom-efficient tool for the synthesis of a range of organic compounds, including the synthesis of heterocyclic rings *via* ring-closing HAM reaction.[88-100] The Rh-catalysed HAM of unsaturated fatty acid esters (**29**), and of higher olefins (**26**) towards the corresponding amino fatty acid esters and fatty amines has been described (Fig. 1.7).[101-103] Because of double bond isomerisation in these substrates, the corresponding isomers and

the hydrogenated product of the fatty acid esters can be observed as well. These compounds are important products or intermediates of products in everyday life. In general, relatively harsh reaction conditions (p > 70 bar; T > 120ºC) are necessary in order to complete the reactions in good yield.

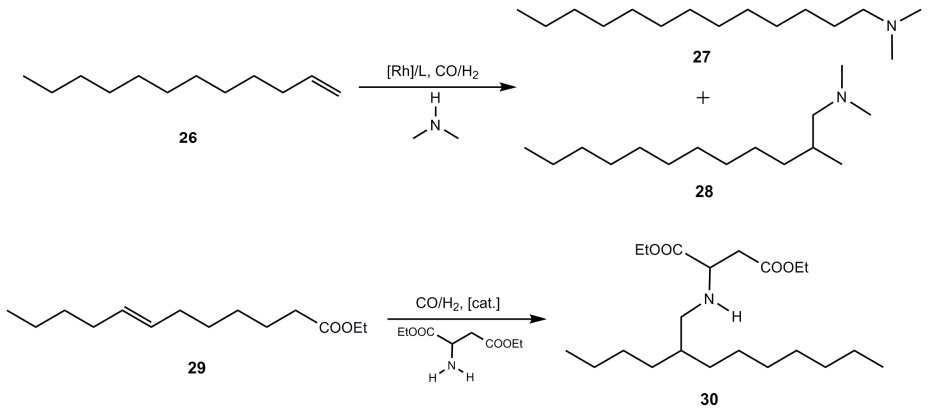


Figure 1.7: *Synthesis of fatty amines (**27**, **28**) and amino fatty acid esters (only one regioisomer shown) (**30**) via HAM.*[102,103]

Obviously, pharmaceuticals are important products containing amine functionalities. The synthesis of various pharmaceuticals using Rh-catalysed HAM reactions was described by Beller and co-workers and Whiteker and co-workers.[104-106] Whiteker describes the synthesis of the pharmaceuticals Ibutilide (**33**; an antiarrhythmic drug; Fig. 1.8) and Aripiprazole (**36**; used in the treatment of schizophrenia; Fig. 1.8) in 55%-67% yield and with high l/b ratios (up to l/b = 48). A bulky diphosphite ligand was used in combination with $[Rh(CO)_2(acac)]$. Beller described the synthesis of several pharmaceuticals with a broad range of pharmacological activities. These compounds were synthesised in high yield (75%-99%) and high linearity (l/b > 99).

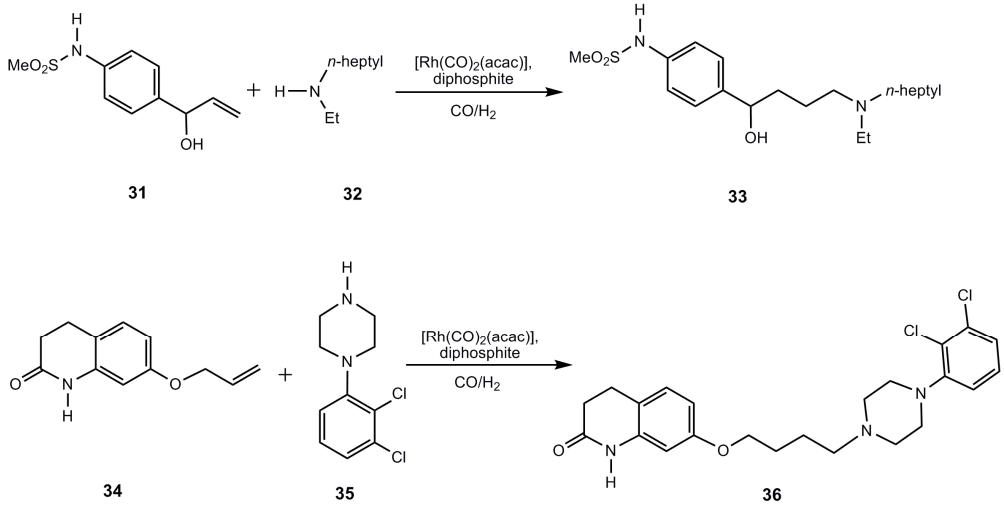


Figure 1.8: *Synthesis of Ibutilide (**33**) and Aripiprazole (**36**) via HAM.*[105]

Most literature examples make use of Rh- or Rh/Ir-catalysts in the HAM reaction. However, some literature examples mention the use of ruthenium or cobalt instead of rhodium. In an example of HAM with Ru upon using harsh reaction conditions (p = 150 bar; T = 150ºC) conversions and chemoselectivities turned out to be good.[107] The regioselectivity was improved upon lowering the temperature and decreasing the reaction pressure in this particular case, while chemoselectivity remained satisfying.[108] However, the conversion decreased considerably in this case.

Although the following example is not exactly a HAM reaction, it is very closely related. The remarkable Co-catalysed synthesis of ε-caprolactam *via* aminopentene was described by Sen and co-workers (Fig. 1.9).[109] Also in this case, rather harsh reaction conditions (p = 70 bar; T = 165ºC) were applied. Aminopentene (**37**) is a possible intermediate in the double HAM reaction of butadiene and therefore an interesting substrate. Ring-closing of the carbonylated product **39** to the desired ε-caprolactam **40** was achieved in good regioselectivity. In order to form the lactam instead of the cyclic amine, which is possible upon intramolecular condensation of the carbonylated product and the amine and consecutive hydrogenation under hydroformylation conditions, no hydrogen pressure was applied in the reaction.

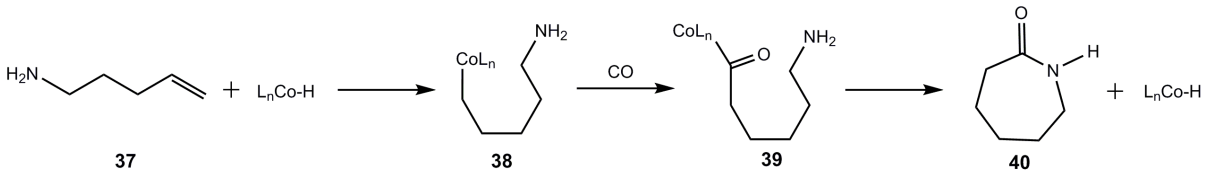


Figure 1.9: *Synthesis of ε-caprolactam from aminopentene via carbonylation/intramolecular ring-closing.*[109]

From the aforementioned, it can be concluded that ruthenium and cobalt catalysts are less reactive in comparison to rhodium catalysts. On the other hand, rhodium is a very expensive metal. For that reason, it would be advantageous to recycle the catalyst in order to reduce the costs of Rh-catalysed HAM reactions. HAM reactions in biphasic systems in order to recycle the catalyst were described by Luo and co-workers. Mild reaction conditions were used in combination with a Rh-catalyst containing a TPPTS ligand. However, amine selectivities and regioselectivities were disappointing.[110] Upon performing this reaction in a biphasic system with the bidentate ligand BISBIS, both chemo- and regioselectivity increased considerably.[111] This Rh-BISBIS system was also applied for the HAM in ionic liquids.[112]

Regio- and chemoselectivity were moderate in this case. Catalyst recycling was possible in this system, but the regioselectivity decreased considerably upon recycling.

Regioselective synthesis of amines is very important, especially if this would be possible by using internal alkenes or a mixture of alkenes. Selective synthesis of linear amines from internal alkenes was described by Beller and co-workers and Van Leeuwen/Beller and co-workers. In the report by Beller and co-workers, the HAM of internal alkenes with secondary amines and a Rh-catalyst containing different phosphine ligands (NAPHOS, IPHOS), was described.[113] Amine selectivity and regioselectivity were moderate at high conversion, whereas high regioselectivity was obtained at low conversions. However, the aforementioned binaphthol-based ligands NAPHOS and IPHOS are reported to give good regioselectivity in the HAM reaction of 1-pentene.[114] The joint publication of Van Leeuwen, Beller and co-workers showed efficient HAM of internal alkenes with a range of secondary amines leading to high amine selectivities and regioselectivities under optimal reaction conditions.[115] A Rh-Xantphenoxaphos catalyst was used and as expected when using a diphosphine ligand, the reaction rate was rather low. The examples show that ligands and reaction conditions are of great importance in the HAM with respect to the regioselectivity upon using internal alkenes.

The importance of reaction conditions is underlined by an example from Beller and co-workers in which enamines were selectively produced (Fig. 1.10).[116] A similar catalyst system to the one used in the HAM reactions described above, containing rhodium and the ligand NAPHOS, was used in this example. However, upon changing the metal precursor to $[Rh(CO)_2(acac)]$, changing to an aprotic solvent and lowering the reaction temperature to T = 65ºC, and the reaction pressure to p = 10 bar CO/H_2, enamines (**43**, **44**) were produced selectively. The regioselectivity to the linear enamine **44** was excellent. Reaction conditions and solvents turn out to have an important influence on the selectivity.

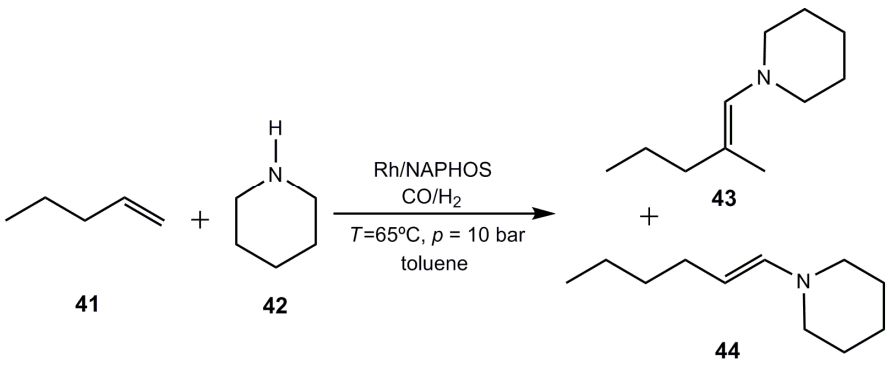


Figure 1.10: *Selective synthesis of enamines by using a Rh/NAPHOS system.*[116]

Aliphatic primary amines are important products in the chemical industry. In order to prepare primary amines *via* HAM reactions, ammonia or an ammonia derivative has to be used. The first HAM with ammonia was described by Knifton and Lin in 1993.[16] Cobalt octacarbonyl in combination with several phosphine ligands was described in the HAM of 1-hexene and ammonia. However, selectivities to the primary amine were rather poor. The first efficient HAM with ammonia was reported in 1999 by Beller and co-workers.[117] A biphasic system in combination with a water-soluble bimetallic Rh/Ir catalyst containing the monodentate ligand TPPTS or the bidentate ligand BINAS was applied. The catalysis takes place in the water phase and the products are re-extracted into the organic phase. Only short chain alkenes (propene, butene and pentene) can be used because of the low to negligible water-solubility of long chain alkenes. The yields were good with values up to 90% and the selectivity for the primary amine could be increased up to 91% under optimal reaction conditions.

An interesting and elegant approach by protecting the amines with carbon dioxide upon applying $scCO_2$ as a solvent and as a dynamic protection group has been reported by Leitner, Eilbracht and co-workers (Fig. 1.11).[118] In the intramolecular ring-closing of ethyl methallylic amine (**45**), CO_2 acts as a dynamic protection group by forming a carbamate with the amine group preventing coordination of the amine to the metal centre. In this way the side reaction to the cyclic amide (**48**), which is the prevailing product in organic solvent, was suppressed and the desired mono- and biheterocyclic products (**46**, **47**) could be synthesised in good yield *via* consecutive carbonylation/condensation/hydrogenation. This protection approach can also be used for the protection of primary amines in HAM reactions with ammonia, in this way preventing the consecutive reaction of the primary amine with the intermediate aldehyde.

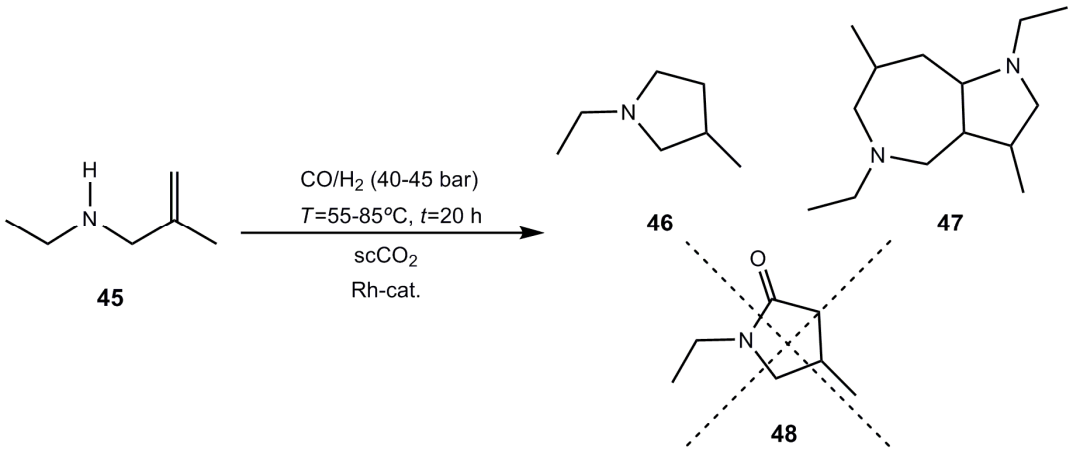


Figure 1.11: *Selective synthesis of cyclic amines in $scCO_2$.*[118]

An alternative route towards primary amines *via* HAM upon applying $scNH_3$ was described by Beller and co-workers.[119,120] Several Xantphos-based and binaphthol-based phosphine ligands in combination with Rh-, Ir-, and Rh/Ir-catalysts were applied. The reaction conditions were rather harsh (p > 180 bar; T = 140ºC) and selectivities to the primary amine up to 60% (15% secondary amine) were observed, while l/b ratios were between 1 and 1.5. Furthermore, the thermodynamic properties of HAM reaction mixtures were investigated at these high pressures.[121]

Recently, the microwave-assisted HAM of terminal alkenes has been reported.[122] The Rh/Xantphos or Rh/BIPHEPHOS systems were applied and the reactions went to completion within 30 minutes. However, only low pressure (6-7 bar synthesis gas) was applied and the HAM with primary amine resulted in the formation of enamine. No hydrogenation was observed in this particular case. Upon applying secondary amines as the substrate, this effect was not observed and the desired amine products were formed.

1.4 Aim and scope of this research

The hydroaminomethylation reaction is an atom-efficient and versatile reaction towards a broad range of amine compounds which find their application in a large number of products in chemical industry, such as pharmaceuticals, polymers and surfactants. Rhodium-based catalysts have been shown to give very active and selective systems, especially in combination with phosphine ligands. In contrast, the selective synthesis of aliphatic primary amines *via* hydroaminomethylation reactions with NH_3 turned out to be rather difficult and challenging according to literature examples. In order to develop a deeper understanding of the hydroaminomethylation reaction in combination with improvements towards the applicability of this reaction in industrial chemistry, hydroaminomethylation reactions are studied with a focus on catalyst recycling, product distributions, influence of reaction parameters, new ligands, and the application of ammonia as a substrate. Besides, the coordination chemistry of a novel ligand system will be studied in order to gain more insight on structure/performance relationships.

Chapter 2 describes the hydroaminomethylation of *n*-alkenes and piperidine in a biphasic imidazolium-based ionic liquid (IL) system. Sulfoxantphos in combination with rhodium was used as the catalyst. High turnover frequencies in combination with excellent chemo- and regioselectivities were obtained. After the reaction, catalyst recycling was enabled by phase separation of the catalyst/IL phase and the product/organic phase. Product

distributions in organic solvent and in IL were monitored in time in order to investigate the formation of products and intermediates during the course of the reaction. It was shown that the nature of the precatalyst and the organic solvent have a profound effect on the activity and selectivity in the system.

Chapter 3 deals with the synthesis of novel, π-acidic, xanthene-based amino-functionalised ligands and their application in the hydroaminomethylation of *n*-alkenes with piperidine. In combination with rhodium, the dipyrrolylphosphine-functionalised ligand leads to very high activities and excellent selectivities with l/b ratios up to 200. The pKa value of the alcohol in the solvent mixture turned out to have a profound effect on the performance of this system. Activities were enhanced by acidic media, whereas less acidic media increased regio- and chemoselectivity, as well as the degree of isomerisation.

In Chapter 4, the ligands introduced in Chapter 3 are applied in the rhodium-catalysed hydroaminomethylation of internal alkenes. The influence of catalyst preformation, reaction temperature, solvent mixture, and syngas ratio on the performance is investigated. Furthermore, the effect of adding a monodentate ligand to the catalytic system was examined. The regioselectivity could be improved by addition of triphenylphosphine to the system.

Chapter 5 is dedicated to the coordination chemistry of the novel, xanthene-based amino-functionalised ligands with rhodium and platinum in order to clarify the structure/performance relationship. The complexes were studied by (high pressure) NMR and IR spectroscopy in order to reveal the electronic and steric properties of the ligands. An X-ray crystal structure was determined for the complex *trans*-[RhCl(CO)(**Xantphos**)].

Chapter 6 gives an outlook on future perspectives of hydroaminomethylation reactions. An elegant route to primary amines *via* hydroaminomethylation with ammonia and dynamic protection of the primary amine is described. In order to avoid the side reaction of the desired primary amine with the intermediate aldehyde, carbon dioxide can form a carbamate with the amine, in this way preventing further reaction. It is shown that ammonium carbamate can be used in order to protect primary amines as the *N*-alkylammonium *N*-alkylcarbamates. One CO_2 molecule protects two amine functionalities in this case. Upon releasing the pressure and heating the salt, CO_2 is released and the primary amine will be available in its deprotected form. In this way, hydroaminomethylation with ammonia (derivatives) to synthesise primary amines selectively might be feasible in the near future.

1.5 References

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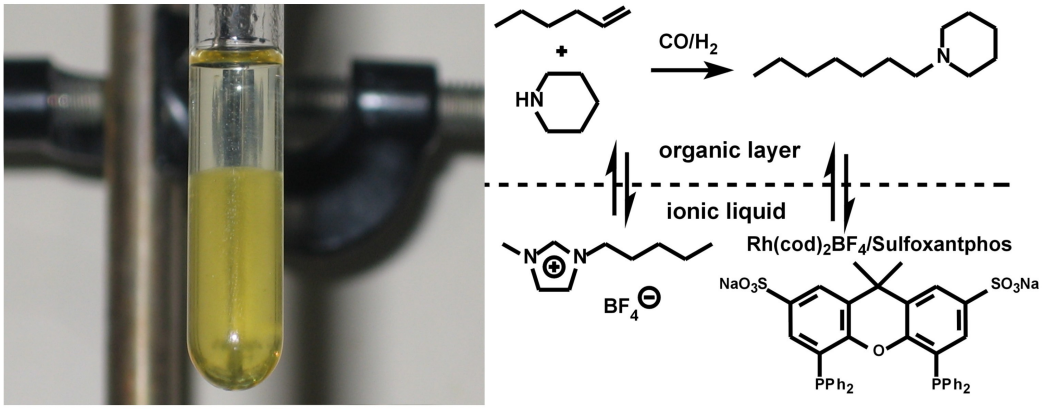
2

Hydroaminomethylation of *n*-alkenes in a biphasic ionic liquid system

Hydroaminomethylation reactions were performed successfully in an imidazolium-based ionic liquid using a rhodium/Sulfoxantphos system by reacting piperidine with different n-alkenes, affording yields higher than 95% of the resulting amine with turnover frequencies of up to 8400 h^{-1}, along with high regioselectivity for the linear amines with l/b ratios up to 78. Additionally, facile quantitative catalyst recovery was accomplished and recycling of the catalyst and product separation were achieved by a fast phase separation after the reaction. The product distribution was monitored in time at different temperatures both in an organic solvent and in the ionic liquid in order to investigate and compare the course of the formation of (side) products and intermediates in these reactions. Furthermore, it was shown that the nature of the Rh-precatalyst has a profound effect on the activity and selectivity. Protic organic solvents and ionic liquids containing a C-H acidic bond in the imidazolium part have a beneficial effect on the hydrogenation activity of the catalyst systems.



Part of this work has been published:
B. Hamers, P.S. Bäuerlein, C. Müller, D. Vogt, *Adv. Synth. Catal.* **2008**, *350(2)*, 332-342.

2.1 Introduction

2.1.1 Ionic Liquids

Although the first ionic liquid (IL) synthesised dates back to 1914,[1] the use and application of ionic liquids[2-6] has increased extensively during the last two decades in academic as well as in industrial chemistry. By definition, these salts have a melting point below 100°C and contain at least one organic ion. Their very particular characteristics like the almost negligible vapour pressure[7,8] and the ability to be a liquid at room temperature make ILs very interesting as 'green designer solvents' and explain their popularity. Moreover, ILs have the ability to form biphasic systems, which simplify product separation by means of distillation or phase separation enormously, leading to the utilisation of these solvents in a wide range of reactions. Even more important in this respect is the almost infinite number of anion-cation combinations (Fig. 2.1), offering the possibility to tailor the IL for the needs of a reaction system in a modular approach.

Additionally, it was discovered in the groups of Wasserscheid and Leitner that chiral information included in ILs could be transferred to the reactants in several reactions.[9-12] It turned out to be possible to synthesise chiral products by using a chiral IL, while the catalysts or ligands were achiral. Obviously, the chiral IL induced chiral information to the products during the catalytic cycle. This also paved the way to the utilisation of ILs as organocatalysts.

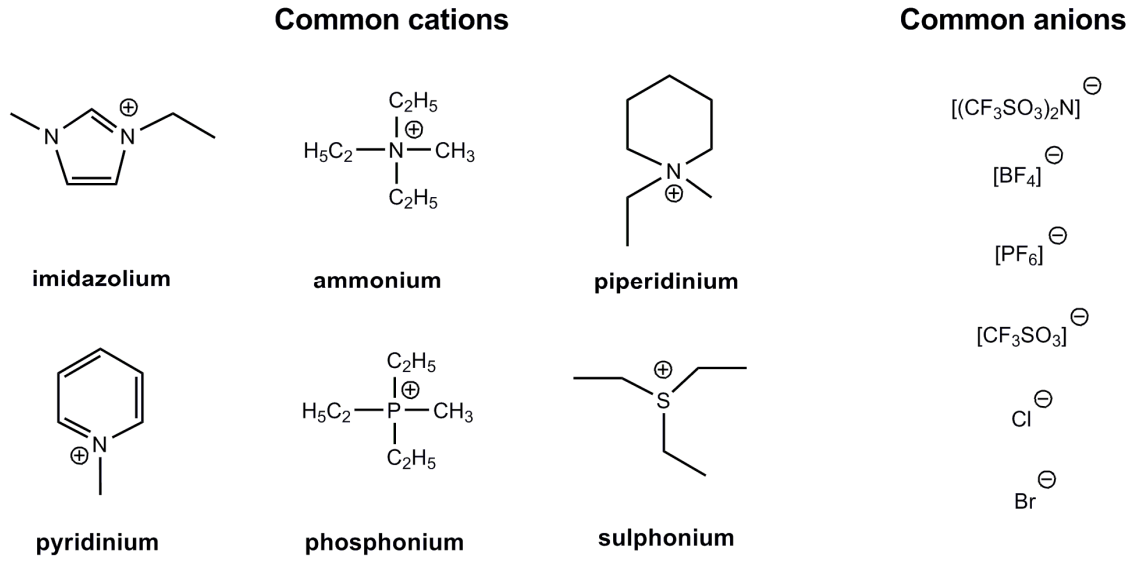


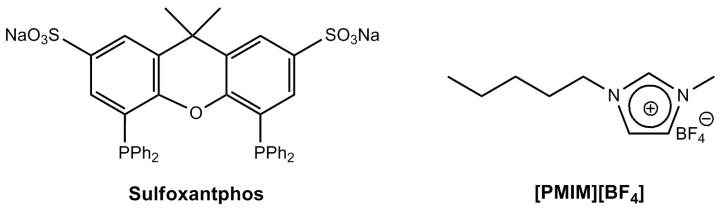
Figure 2.1: *Commonly used cations and anions for the synthesis of ionic liquids. In September 2009, an open access database on ILs will be launched containing physical properties and bio-compatibility data: www.il-eco.uft.uni-bremen.de.*

2.1.2 Catalyst recycling

Beside the improvement of activity and selectivity, one of the actual challenges in homogeneous catalysis is the recyclability of the catalyst. Especially with expensive transition metals like rhodium it is highly advantageous to reuse the catalyst. Several approaches, such as catalyst immobilisation,[13-16] homogeneous catalysis by molecular weight enlarged ligands in combination with membrane separation[17-21] and conducting the reaction in a biphasic system[22-25] have been followed in order to improve the performance, selectivity and recyclability of homogeneous catalytic systems. An example of a biphasic system applied industrially is the Ruhrchemie/Rhône-Poulenc process,[26] which is a biphasic Rh-catalysed hydroformylation using a sulphonated, water-soluble triarylphosphine ligand (TPPTS).[27-29] Since the solubility of higher alkenes in water is too low, this system is only suited for the production of butanal and pentanal from propene and 1-butene.

A possible approach to catalyst recycling using a biphasic system also includes performing reactions in ionic liquids. In 1972, Parshall described the hydroformylation of ethene in molten salts. However, the melting points of these media were above 60°C, creating some difficulties in handling these particular systems since they are solid at room temperature.[30] Further examples of hydroformylation in similar media or room temperature ionic liquids (RTILs) appeared in the following decades.[2] More recent examples by Van Leeuwen and co-workers demonstrated the application of hydroformylation in ILs,[31] and the use of Sulfoxantphos as a suitable ligand system.[32] Wang and co-workers have recently shown the successful application of hydroaminomethylation (HAM) in an ionic liquid based biphasic system.[23] However, no data concerning activity, product distribution during the reaction or the influence of different parameters have been reported up to now for the HAM in ILs. In addition, there is still room for improvement of the regio- and chemoselectivity as well as the activity of the catalysts.

The low-viscous 1-methyl-3-pentyl-imidazolium tetrafluoroborate [PMIM][BF_4], which is immiscible with the hydroaminomethylation substrates and products, was chosen as the reaction medium for the Rh/Sulfoxantphos[33,34] system (Fig. 2.2). A facile product recovery is therefore anticipated.



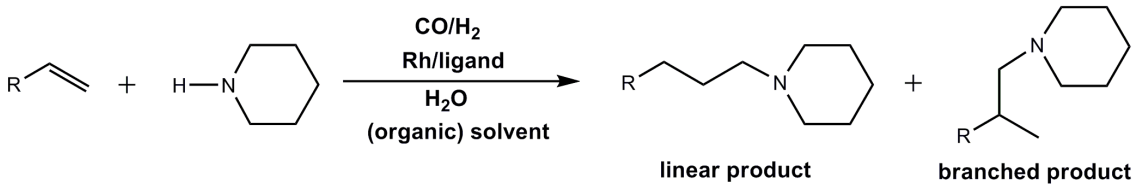
Sulfoxantphos **[PMIM][BF_4]**

Figure 2.2: *The water-soluble ligand Sulfoxantphos and the ionic liquid [PMIM][BF_4] used in recycling experiments.*

Detailed studies of the performance of this catalyst system in IL, giving high chemo- and regioselectivity to linear amines in the hydroaminomethylation reaction of *n*-alkenes with piperidine, are reported in this chapter. Effective catalyst recycling was achieved in combination with a method in which substrates are simply added to the reaction mixture. Additionally, the turnover frequencies were determined in order to get more insight into the activity of the system under different circumstances. Furthermore, the influences of the reaction time, reaction temperature and the rhodium precursor were investigated by monitoring the product distribution during the course of the hydroaminomethylation reactions.

2.2 Biphasic catalysis and catalyst recycling

The hydroaminomethylation reaction was first investigated in [PMIM][BF_4], applying the Rh/Sulfoxantphos system and 1-octene and piperidine as the substrates (Scheme 2.1). Formation of a biphasic system was observed, facilitating the product recovery exceptionally. In addition, a good activity and selectivity could be obtained (Tab. 2.1). It was confirmed in a glass autoclave that the catalytic system was not only biphasic at room temperature, but also at reaction temperature (125°C). Although the regioselectivity was slightly lower in the IL compared to the Rh/Xantphos system in toluene/MeOH (Tab. 1, entry 1 and 5), the selectivity to the amine was improved. The conversion in the IL was comparable to the one in toluene/MeOH and a higher substrate-to-rhodium (S/Rh) ratio could be used without formation of considerable amounts of aldol condensation products and *N*-formylpiperidine, which were the main side products in the reaction performed in toluene/MeOH.



Scheme 2.1: *Hydroaminomethylation of n-alkenes with piperidine.*

Using the sulphonated system in the IL, the product layer could be completely removed, new substrate was added to the IL and the reaction was performed again. The S/Rh ratio was increased in the subsequent runs and the catalyst could be reused several times keeping conversion and especially chemoselectivity at a high level, while only the regioselectivity decreased

considerably (Tab. 2.1, entries 1-4). In this case the drop in regioselectivity is attributed to partial oxidation of the ligand during phase separation, since the complete reaction mixture was removed from the autoclave for this purpose. As shown in Table 2.1, it is important to distinguish between total conversion (column 4), which is the conversion of all alkenes (1-octene and internal alkenes), and conversion of solely 1-octene (column 5). The latter is the conversion of only 1-octene present in the reaction mixture at that time. As the conversion of 1-octene reaches 99%, only the remaining internal alkenes can be converted, leading to more branched product.

Table 2.1: *Hydroaminomethylation of 1-octene in IL; recycling experiments and comparison to hydroaminomethylation in toluene/MeOH.*[a]

Entry	Cycle	S/Rh	Conv. [%]	Conv. 1-octene [%]	Isomerised octene [%]	Sel.(amine) [%]	l/b
1	1	1150	94.4	99.2	4.8	98.6	52.1
2	2	2750	96.2	99.7	3.5	99.2	27.3
3	3	8850	86.1	96.9	10.8	93.7	11.8
4[b]	4	8850	92.3	99.1	6.8	82.5	2.5
5[c]	-	1150	94.4	99.3	4.9	87.3	62.0

[a] *Conditions:* 1-octene 7-25 mmol, piperidine 8-29 mmol, [PMIM][BF_4] 8 mL, [$Rh(cod)_2$]BF_4 = 0.02–0.09 mol%, L/Rh = 3.8, T = 125°C, p(CO/H_2 (1:2)) = 36 bar (cold pressure), t = 17 h, 400 rpm. [b] t = 90 h. [c] Solvent: toluene/MeOH (1:1) 8 mL.

To overcome the problem of ligand oxidation, two possible solutions were investigated. In the first case, the product layer was removed from the autoclave by syringe under a flow of argon leaving the IL/catalyst solution in the autoclave. New degassed substrate was immediately added and the reaction was performed again. In the second approach the layer separation was avoided completely and new substrate was simply added to the reaction mixture at the end of the preceding reaction.

Both options gave very satisfying results. Table 2.2 shows the results of recycling the catalyst solution by adding new and even different substrates using the same catalyst solution. In this procedure new alkene was added without removing the product layer in between the runs (Tab. 2.2, entries 1-3). After completion of the third reaction the product layer was removed and analysed. The catalyst solution in the IL was used again and the same procedure of adding new substrate was followed (Tab. 2.2, entries 4 and 5). Conversion, chemo- and regioselectivity were in the same range for the different alkenes. However, in the case of a lower conversion of approximately 89% (Tab. 2.2, entry 5), the results suggest an increased chemoselectivity of up to 97.3% to the amine. The decrease in regioselectivity for entry 5 might be due to the fact that a small

amount of internal octenes, which were formed by isomerisation in the first run, remained in the IL leading to a lower l/b ratio in the end.

Table 2.2: *Hydroaminomethylation of n-alkenes in IL; recycling experiments by addition of different substrates without phase separation.*[a]

Entry	Cycle	S/Rh	Substrate	Conv. [%]	Conv. 1-alkene [%]	Isomerised alkene [%]	Sel. (amine) [%]	l/b
1	1	1800	1-octene	96.4	99.6	3.2	90.8	35.1
2	2	4500	1-decene	88.4	95.8	7.4	96.5	44.4
3	3	4500	1-hexene	92.7	95.9	3.2	92.4	33.5
4	4	3600	1-dodecene	87.8	96.1	8.1	96.8	20.0
5	5	3600	1-octene	89.1	99.5	11.7	97.3	18.1

[a] *Conditions:* alkene 10–22 mmol, piperidine 12–25 mmol, [PMIM][BF_4] 7 mL, [Rh(cod)$_2$]BF_4 = 0.02–0.06 mol%, L/Rh = 4.5, T = 125°C, p(CO/H_2 (1:2)) = 36 bar (cold pressure), t = 18 h, 400 rpm.

The results of the recycling experiments, in which only the product layer and not the catalyst solution was removed from the autoclave after the reaction, are summarised in Table 2.3. Again, conversion and chemo- and regioselectivity were very satisfying. The low chemoselectivity in entry 3 (Tab. 2.3) is merely due to a certain amount of incompletely hydrogenated enamine, which can be regarded as a reaction intermediate of the product. After the final run, the catalyst solution was removed from the autoclave and extracted with Et_2O. The ether solution was analysed (Tab. 2.3, entry 4) and compared to the result obtained from the product layer analysis (Tab. 2.3, entry 3). Both results are basically identical, indicating that analysis of the reaction mixture can be performed both *via* direct analysis of the product layer as well as after extraction of the IL phase.

Table 2.3: *Hydroaminomethylation of n-alkenes in IL; recycling experiments with phase separation in the autoclave.*[a]

Entry	Cycle	Substrate	Conv. [%]	Conv. 1-alkene [%]	Isomerised alkene [%]	Sel. (amine) [%]	l/b
1	1	1-octene	92.8	99.2	6.4	99.0	27.7
2	2	1-hexene	94.1	97.2	3.1	93.4	38.3
3	3	1-octene	89.8	97.9	8.1	79.8	32.7
4[b]	3	1-octene	89.7	98.2	8.5	79.9	33.1

[a] *Conditions:* alkene 19–24 mmol, piperidine 22–28 mmol, [PMIM][BF_4] 7 mL, [Rh(cod)$_2$]BF_4 = 0.03 mol%, L/Rh = 3.7, S/Rh = 4000, T = 125°C, p(CO/H_2 (1:2)) = 36 bar (cold pressure), t = 17 h, 400 rpm, analysis of product layer. [b] Analysis of extraction layer (Et_2O) after extraction of IL phase.

The product phase in these recycling experiments was analysed for rhodium and phosphorus leaching by means of ICP-OES. It turned out that the amount of Rh was close to the detection limit (< 0.09%) while the P-leaching was determined to be 0.45%. Furthermore, the solubility of a PMIM-Sulfoxantphos species in the organic layer was determined by means of NMR spectroscopy. Traces of the ionic liquid could be detected by ^{1}H NMR and ^{19}F NMR spectroscopy, suggesting IL leaching, while the ^{31}P NMR spectrum did not reveal any ligand leaching. Apparently, a very small amount of the IL was dissolved in the product phase whereas almost no Rh- and P-leaching could be detected.

The influence of parameters such as temperature, reaction time, and S/Rh ratio was investigated as presented in Table 2.4. Obviously, when applying larger S/Rh ratios, the conversion is expected to decrease to some extent at a given reaction time, corresponding to the intrinsic kinetics. However, the S/Rh ratio does not affect the conversion and selectivity to a high extent at T = 125ºC and 18 h reaction time, showing that the catalyst is fast (Tab. 2.4, entries 1-3). As expected, the reaction time has a large influence on the l/b ratio. A key point here is the fact that the rate of hydroformylation for 1-alkenes is much higher than the rate for internal alkenes, formed by slow isomerisation throughout the course of the reaction. The conversion of *n*-alkenes is always virtually complete (> 99+%) after 18 h (Tab. 2.4, entries 1-4). This effect of the reaction time on the l/b ratio is well documented for the hydroformylation of terminal alkenes where isomerisation plays a role.[35] The internal alkenes, accumulating during the reaction, are especially converted to branched aldehydes at high conversion (longer reaction time) thereby lowering the l/b ratio in time. This effect is also present in the hydroaminomethylation as depicted in Figure 2.3. Therefore, shortening the reaction time and lowering the reaction temperature will most probably lead to higher l/b ratios because of the decreased isomerisation rate under these conditions.

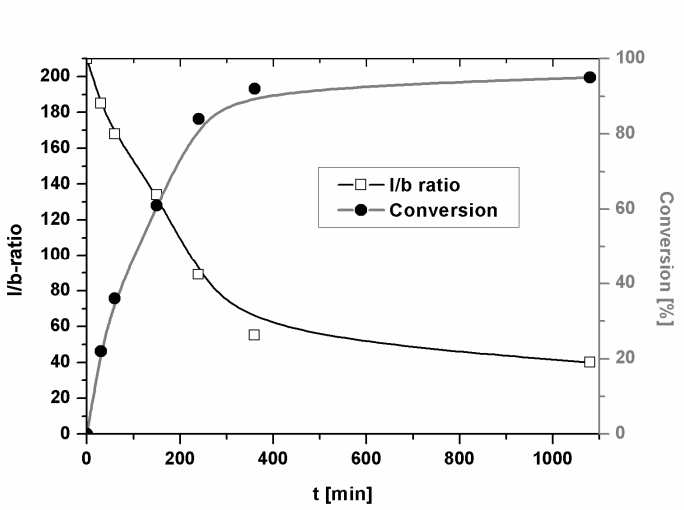


Figure 2.3: *Conversion* versus *l/b ratio of a hydroaminomethylation reaction in time.*

Accordingly, the reaction temperature mainly affects the regioselectivity. Lowering the reaction temperature from $T = 125°C$ to $T = 110°C$ leads to an increased l/b ratio (Tab. 2.4, entries 1 and 4), caused by the slower isomerisation of 1-octene at lower temperature and the higher rate of hydroformylation for 1-octene compared to the one for internal isomers. As expected, limiting the conversion by shortening the reaction time has a profound effect on the regioselectivity. A high l/b ratio of 78 after only 4 hours reaction time was observed (Tab. 2.4, entry 7), while the conversion of 1-octene is only slightly lower.

Table 2.4: *Hydroaminomethylation of 1-octene in IL; effects of different parameters on activity and selectivity.*[a]

Entry	Cycle	*T* [ºC]	S/Rh	*t* [h]	Conv. [%]	Conv. 1-octene [%]	Isomerised octene [%]	Sel.(amine) [%]	l/b
1	1	125	750	18	94.3	99.4	5.1	94.9	28.1
2	-	125	3750[b]	18	93.2	99.2	6.0	97.7	30.2
3	-	125	4700[b]	18	92.7	99.1	6.4	96.0	29.5
4	2	110	750	18	94.1	99.3	5.2	93.4	44.8
5	3	110	750	6	90.1	96.7	6.6	76.0(87.7)[c]	68.5
6	4	110	750	6	91.2	97.7	6.5	65.6(78.9)[c]	72.8
7	5	110	750	4	89.2	95.4	6.2	46.7(77.3)[c]	78.4

[a] *Conditions:* 1-octene 18 mmol, piperidine 21 mmol, ionic liquid [PMIM][BF_4] 6 mL, [Rh(cod)$_2$]BF_4 = 0.13 mol%, L/Rh = 4.0, *p*(CO/H_2 (1:2)) = 36 bar (cold pressure), 400 rpm. [b] [Rh(cod)$_2$]BF_4 = 0.025 mol%. [c] Enamine reaction intermediate included in calculation.

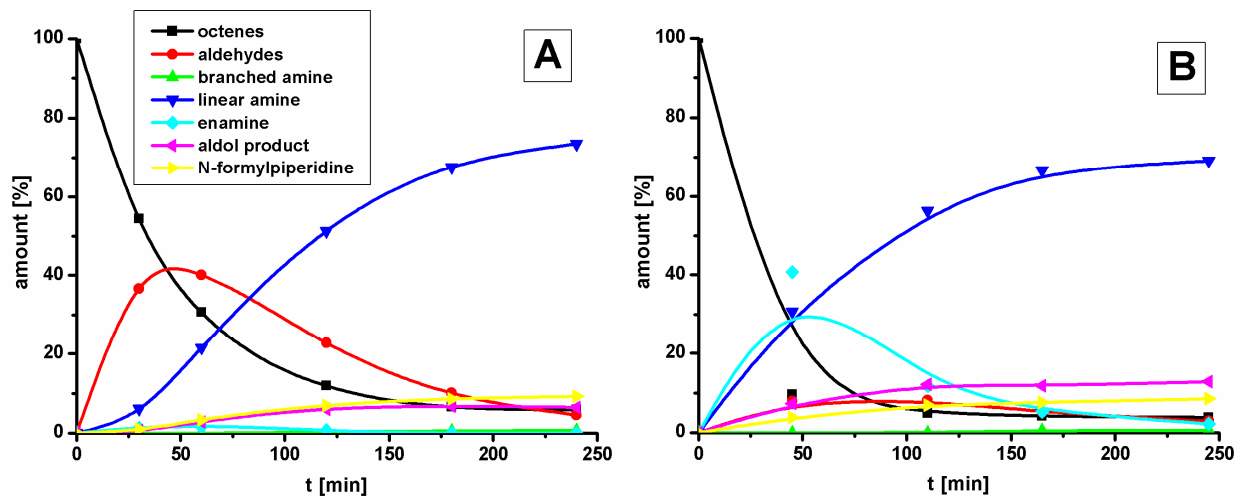
Strikingly, the amine selectivity even dropped to 47% upon recycling, as shown in entries 5-7 of Table 2.4. However, this effect is partially due to the fact that the intermediate enamine, being the only other major component in the reaction mixture besides linear amine and aldol condensation product, is not included as a product in the calculation of amine selectivity, but as a nitrogen-containing side product. Possibly, the reaction rate of the hydroformylation reaction is fast in comparison to the reaction rates of the condensation reaction and hydrogenation of the enamine, leading to an accumulation of aldehyde, which could account for the considerable amount of aldol product formed. Another possibility might be the accumulation of water in the IL formed during the reaction and leading to a higher reaction rate for the aldol condensation reaction upon recycling of the catalyst. Removing the water by evaporation under reduced pressure after several catalytic runs might solve this problem most probably.

2.3 Product distribution in time

Monitoring the product distribution in time (Fig. 2.4), the influence of the temperature and the reaction time was studied in more detail and the hydroaminomethylation reaction was performed in toluene/MeOH as well as in the IL at T = 110°C and T = 125°C. During the reaction in the organic solvent, samples were taken from the reaction mixture *via* a capillary and analysed by GC. It was found that the hydroaminomethylation reaction in organic solvents was fast at both temperatures, although the reaction was faster at T = 125°C. At this temperature a transient accumulation of enamine was observed implying that the hydrogenation of the enamine is slower than the hydroformylation and condensation reaction. For the reaction in an organic solvent at T = 110°C the rate of hydrogenation seems to be more in balance with the hydroformylation, since no accumulation of enamine was observed. However, at this temperature a transient accumulation of aldehyde was observed, which indicates that the condensation reaction is slower than the hydroformylation reaction. An advantage of performing the reaction at a lower temperature is that the amount of aldol side product is lower.

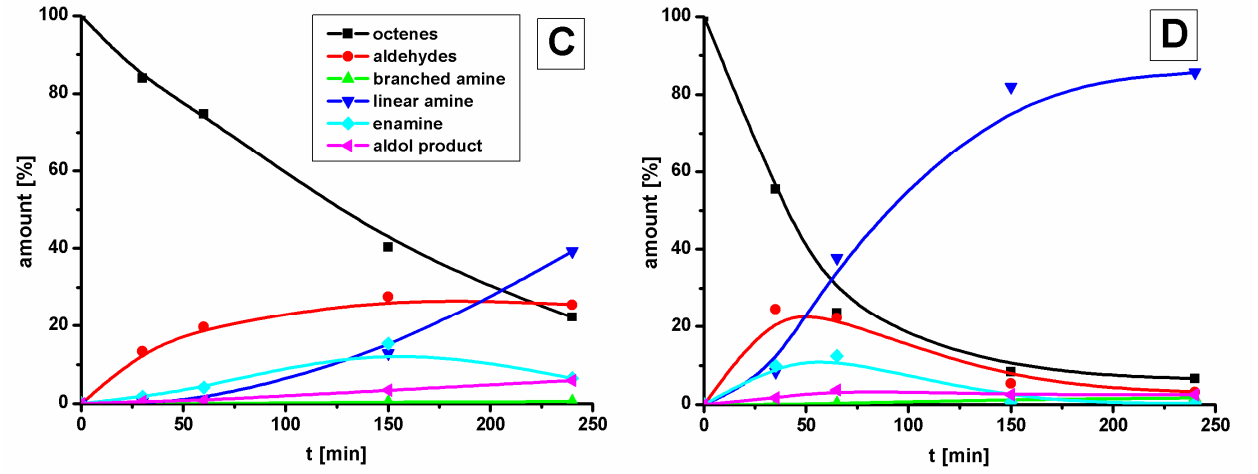
Because the reactor setup was not suitable for taking samples from an IL medium under reaction conditions, every single data point in time had to be determined by a separate run. The reaction in the IL turned out to be slower, in particular at T = 110°C. Nevertheless, the selectivities for the hydroaminomethylation in the IL were in general better than in toluene/MeOH. The chemoselectivity was higher since the formation of aldol condensation products was suppressed almost completely in the IL and the formation of *N*-formylpiperidine, which is known to be a problem for HAM in the presence of methanol,[36] could not be detected. Conversions and regioselectivities were comparable to the results obtained in toluene/MeOH. At a reaction temperature of T = 110°C, the regioselectivity could even be improved, and remained excellent in the recycle runs.

The reason for the slow reaction at T = 110°C could be mass transfer limitation due to viscosity effects and a consequently lower concentration of synthesis gas in the ionic liquid layer. However, upon increasing the stirring rate to 800 rpm and 1200 rpm, only a slight increase in conversion of octene was observed while more enamine and aldol condensation product were found at the expense of the linear amine at a stirring rate of 800 rpm (Fig. 2.5). Apparently, the reaction is not mass transfer limited, although it is difficult to draw a clear conclusion concerning the stirring rate and mass transfer limitations in this system from these results.



A. Toluene/MeOH; 110°C **B.** Toluene/MeOH; 125°C

Conditions: 1-octene 9 mmol, piperidine 11 mmol, toluene/MeOH (1:1) 4 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 400 rpm.

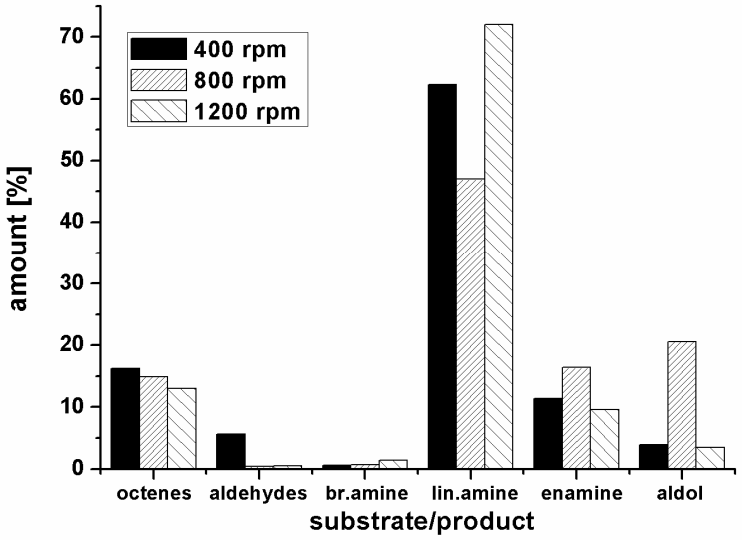


C. IL; 110°C **D.** IL; 125°C

Conditions: 1-octene 13 mmol, piperidine 15 mmol, $[PMIM][BF_4]$ 4 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, S/Rh = 1050, L/Rh = 4.0, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 400 rpm.

Figure 2.4: *Product distribution during the hydroaminomethylation reaction of 1-octene.*

As the stirring rate has little influence on the total conversion, it seems plausible that decreasing the reaction temperature by only 15°C leads to the observed decrease of the reaction rate in the IL system. For that reason several experiments with different S/Rh ratios were performed. As expected, it turned out that the effect caused by different S/Rh ratios is much more pronounced at T = 110°C than at T = 125°C. Especially at higher S/Rh ratios (> 1200), conversions were lower than 90% after 6 hours, but were reproducible in the recycle runs. In order to obtain conversions higher than 90% a reaction time of 16 hours is necessary when applying a S/Rh ratio of 2800.



Conditions: 1-octene 13 mmol, piperidine 15 mmol, ionic liquid [PMIM][BF_4] 4 mL, [Rh(cod)$_2$]BF_4 = 0.1 mol%, S/Rh = 1100, L/Rh = 4, T = 110°C, t = 6 h, p(CO/H_2 (1:2)) = 36 bar (cold pressure).

Figure 2.5: *Product distribution of the hydroaminomethylation reaction of 1-octene in IL at three different stirring rates.*

Given that higher S/Rh ratios lead to lower conversions after 6 hours at T = 110°C, it seems likely that a high l/b ratio should be observed because of the earlier mentioned conversion restriction. In fact, the l/b ratio remains almost constant in the recycle runs and drops only slightly after 5 recycles. Thus, optimal reaction condition in terms of conversion and chemo- and regioselectivity seem to be T = 110°C, 6 hours reaction time and S/Rh < 1000, leading to comparably good results in the recycle runs (Tab. 2.5).

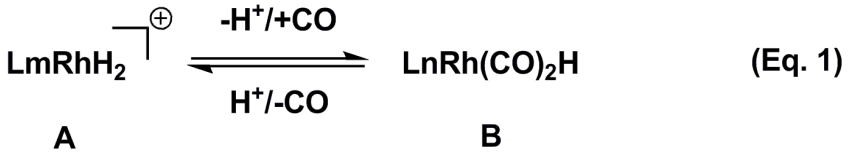
Table 2.5: *Hydroaminomethylation of 1-octene in IL; Results of recycle runs at T = 110°C, t = 6 h, S/Rh = 800.*[a]

Entry	Cycle	S/Rh	Conv. [%]	Conv. 1-octene [%]	Isomerised alkene [%]	Sel. (amine) [%]	l/b
1	1	790	92.9	98.3	5.4	96.5	54.5
2	2	800	93.0	98.2	5.2	94.3	55.5
3	3	820	93.2	98.4	5.2	92.3	54.2

[a] *Conditions:* 1-octene 11 mmol, piperidine 13 mmol, ionic liquid [PMIM][BF_4] 4 mL, L/Rh = 4.0, t = 6 h, T = 125°C, p(CO/H_2 (1:2)) = 36 bar (cold pressure), 400 rpm.

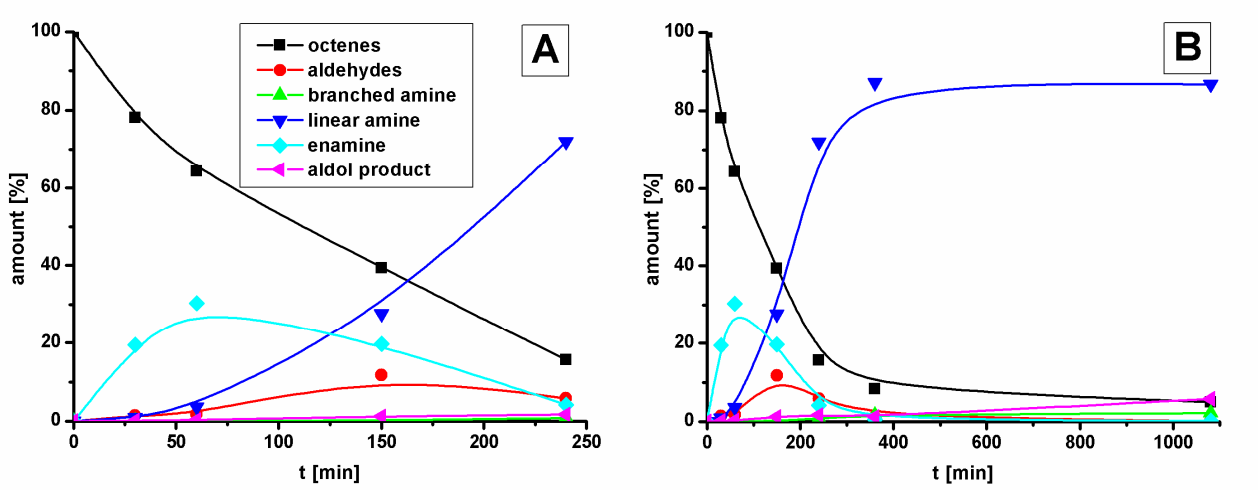
2.4 Influence of the catalyst precursor

Taking into account that the hydroaminomethylation consists of a hydroformylation and a hydrogenation step, the cationic precursor $[Rh(cod)_2]BF_4$ is most often used in hydroaminomethylation reactions as it can be converted to a cationic rhodium species, which is known to be a good hydrogenation catalyst (Eq. 1, **A**). However, the neutral Rh precursor $[Rh(CO)_2(acac)]$ is usually used in hydroformylation reactions because the trigonal bipyramidal hydrido-dicarbonyl complex **B** (Eq. 1), which is the resting state of the hydroformylation catalyst, is easily formed from this Rh(I) precursor. Consequently, complex **B** has to be generated when using $[Rh(cod)_2]BF_4$ as the catalyst precursor for the hydroformylation to take place. This equilibrium shift might be induced by a base, which could be piperidine in the here applied system. Furthermore, it might be possible that the formation of complex **B** is slower in the IL at T = 110°C in comparison to T = 125°C. Therefore, the hydroaminomethylation reaction was performed under these conditions using a binary system consisting of both metal precursors $[Rh(CO)_2(acac)]$ and $[Rh(cod)_2]BF_4$ (1:1).



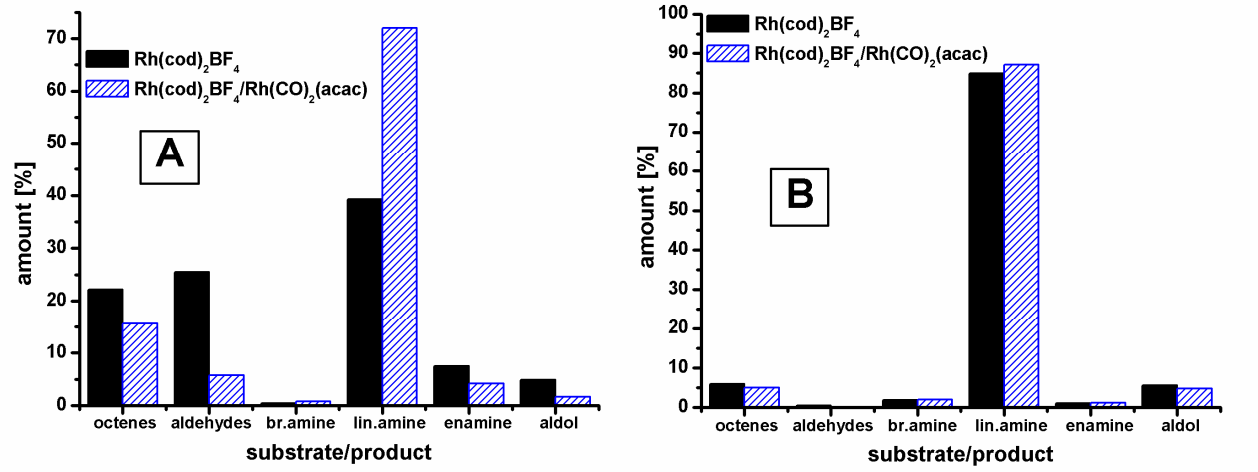
(Eq. 1)

Indeed, the use of this binary precatalyst resulted in a faster conversion of 1-octene (Fig. 2.6) in comparison to the use of solely $[Rh(cod)_2]BF_4$. Yet, the most distinct difference is the fact that mainly linear amine could be obtained after 4 hours reaction time while less linear amine and large amounts of aldehyde and enamine were obtained upon using solely $[Rh(cod)_2]BF_4$ (Fig. 2.7A). Even after 18 hours reaction time, the regio- and chemoselectivity were excellent using the binary precatalyst (Fig. 2.6A and 2.7B), although the difference between the binary precatalyst and $[Rh(cod)_2]BF_4$ was not as pronounced as for a reaction time of 4 hours. Apparently, the combination of the two rhodium precursors has an advantageous effect on the HAM and more particularly on the condensation and hydrogenation reaction, although it is expected that addition of the $[Rh(CO)_2(acac)]$ precatalyst would increase the reaction rate of the hydroformylation.



Conditions: 1-octene 13 mmol, piperidine 15 mmol, ionic liquid [PMIM][BF_4] 4 mL, S/Rh = 1000, L/Rh = 4, T = 110°C, p(CO/H_2 (1:2)) = 36 bar (cold pressure), 400 rpm.

Figure 2.6: *Product distribution of the hydroaminomethylation reaction of 1-octene in IL using a binary Rh precatalyst ([Rh(CO)$_2$(acac)] / [Rh(cod)$_2$]BF$_4$ (1:1)). The left-hand figure shows a close-up of the first 4 hours of the reaction.*



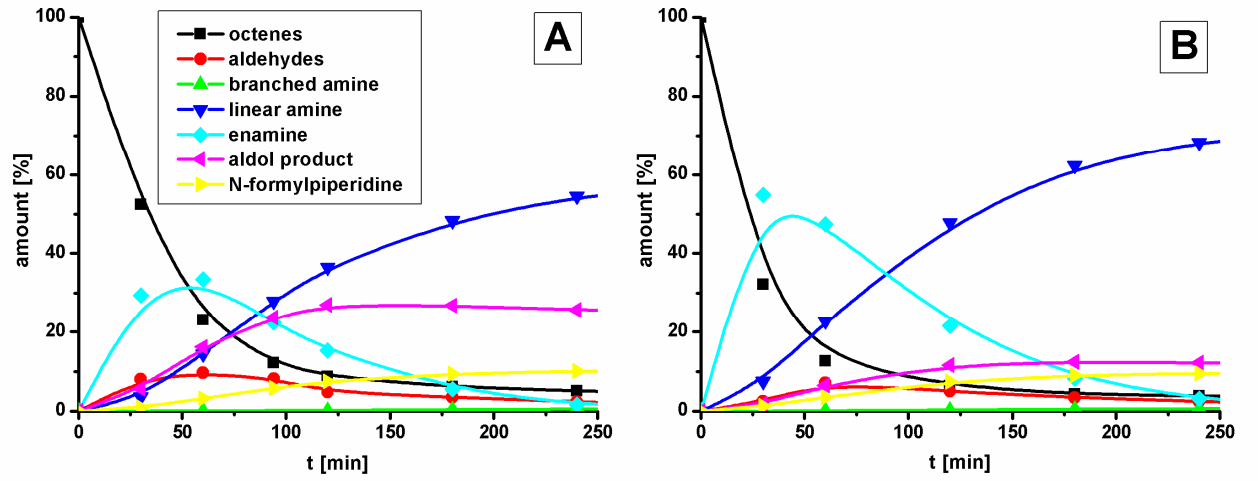
A: t = 4 h **B:** t = 18 h

Conditions: 1-octene 13 mmol, piperidine 15 mmol, ionic liquid [PMIM][BF_4] 4 mL, S/Rh = 1000, L/Rh = 4, T = 110°C, p(CO/H_2 (1:2)) = 36 bar (cold pressure), 400 rpm.

Figure 2.7: *Comparison of the product distributions of the hydroaminomethylation reaction of 1-octene in IL using different Rh precursors.*

In order to investigate the effect of the binary precatalyst in more detail, reactions with different catalyst precursor ratios (Rh^+/Rh = 1:3, 1:1 and 3:1 and solely [$Rh(CO)_2$(acac)]) were performed in toluene/MeOH while the product distribution was followed in time. Obviously, the reaction in toluene/MeOH gives much more aldol product and *N*-formylpiperidine in comparison to the reaction in the IL because of the earlier mentioned effect of MeOH in the HAM. The reaction with the binary precatalyst (1:1) turned out to give improved results with respect to the conversion

and especially selectivity compared to the reaction using only $[Rh(CO)_2(acac)]$ (Fig. 2.8). The results with this binary precatalyst even showed an optimum in terms of conversion of octenes in comparison to the results of the reactions using the binary precatalyst with the ratios Rh^+/Rh = 1:3 and Rh^+/Rh = 3:1, and solely $[Rh(cod)_2]BF_4$. However, the more $[Rh(CO)_2(acac)]$ was used as precatalyst, the more aldol condensation product and *N*-formylpiperidine were formed, which is most likely due to the higher reaction rate of the condensation reaction. Another possibility might be that the equilibrium shifted towards the hydroformylation catalyst, slowing down the hydrogenation and consequently giving rise to more side product formation, since more aldehyde and enamine were present in the reaction mixture. For the reaction performed in the IL, the condensation side reactions obviously play a less important role since they are nearly absent in the first runs. This means that the binary precatalyst mixture (1:1) might be even more beneficial.



Conditions: 1-octene 13 mmol, piperidine 14 mmol, toluene/MeOH 8 mL, S/Rh = 1000, L/Rh = 4, T = 110°C, $p(CO/H_2\ (1:2))$ = 36 bar (cold pressure).

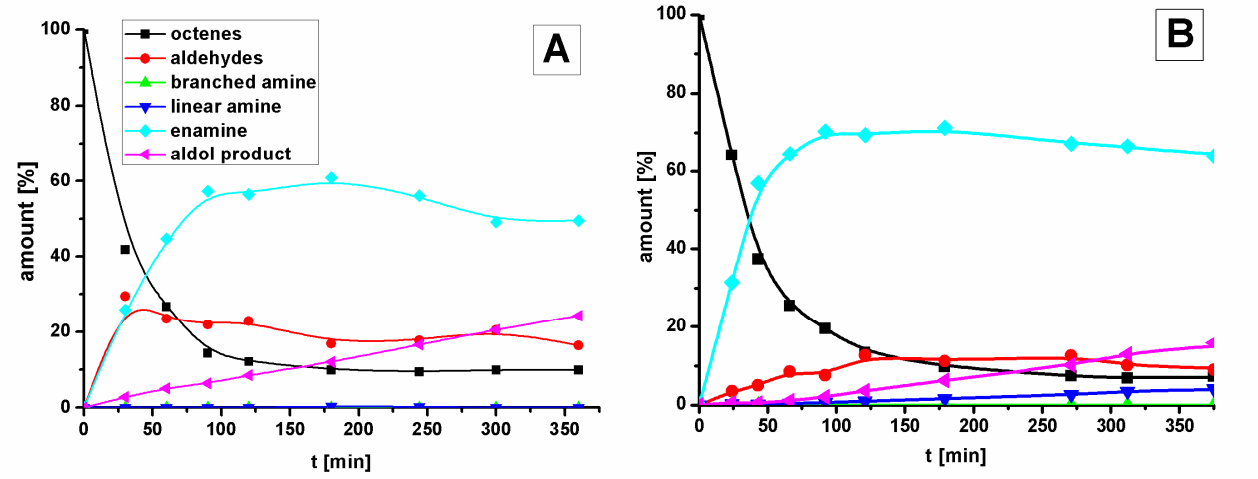
Figure 2.8: *Product distribution of the hydroaminomethylation reaction of 1-octene in toluene/MeOH using $[Rh(CO)_2(acac)]$ (**A**) and a mixed Rh precursor ($[Rh(CO)_2(acac)]$ / $[Rh(cod)_2]BF_4$ (1:1)) (**B**).*

2.5 Solvent effect in the hydroaminomethylation

Strikingly, performing the HAM with $[Rh(CO)_2(acac)]$ in toluene, in absence of MeOH, no amine product was obtained and only enamine and aldehyde could be detected. In the presence of water formed by the condensation reaction, the aldol condensation product is formed in large amounts (Fig. 2.9A). Even at T = 130°C no amine product could be obtained in the HAM in toluene. Taking into account literature examples of HAM reactions in aprotic solvents, showing less

efficient hydrogenation of the enamine[36,37], these results suggest that MeOH or another protic solvent is necessary[38] for the hydrogenation step in the hydroaminomethylation.

Nevertheless, it is known from literature that toluene might lead to the formation of Rh-arene complexes,[39] which could account for the inhibition of the hydrogenation activity during the HAM in toluene. For this reason, HAM reactions were also performed in THF with $[Rh(CO)_2(acac)]$ and $[Rh(cod)_2]BF_4$ as the catalyst precursors. Also in these reactions the hydrogenation activity was negligible. Even after a reaction time of almost 23 hours, only 0.8% amine product could be observed in the HAM with $[Rh(CO)_2(acac)]$ in THF while the conversion of octenes was 95% (Fig. 2.9B). In the HAM with $[Rh(cod)_2]BF_4$ in THF, 9% amine product was obtained along with a conversion of 93% after almost 23 hours.

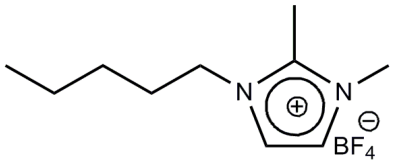


A. toluene **B.** THF

Conditions: 1-octene 13 mmol, piperidine 14 mmol, solvent 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, S/Rh = 1050, L/Rh = 4.0, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), T = 110°C, 800 rpm.

Figure 2.9: *Product distribution during the hydroaminomethylation reaction in aprotic solvents.*

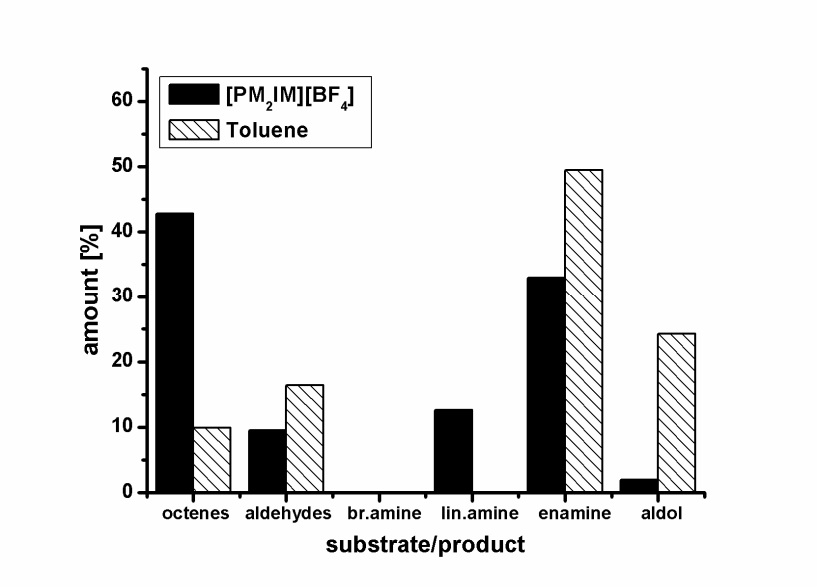
We assume that the C-H acidic imidazolium part of the ionic liquid acts as a protic species.[40] This hypothesis was verified performing the reaction in 1-pentyl-2,3-dimethyl-imidazolium tetrafluoroborate ($[PM_2IM][BF_4]$; Fig. 2.10), which does not contain an acidic H atom. It turned out that the hydrogenation of the enamine was very slow and thus rate-limiting. Comparable to the HAM in toluene, a slow reaction rate and an accumulation of intermediate products were observed for the reaction in $[PM_2IM][BF_4]$ (Fig. 2.11). On the other hand, the amount of condensation products formed was significantly lower than in the reaction in organic solvents. Apparently, also the reaction in this IL leads to an extraordinarily selective reaction because of a slower aldol condensation reaction.



[PM$_2$IM][BF$_4$]

Figure 2.10: *Ionic liquid [PM$_2$IM][BF$_4$] without an acidic C-H bond in the imidazolium part.*

In summary, a protic solvent seems to be a prerequisite in the HAM reactions in order to generate hydrogenation activity. Most probably, this proton is necessary to shift the equilibrium depicted in Equation 1 to the cationic Rh(III) species **A**, which is proposed to be the actual hydrogenation catalyst, especially since piperidine could act as a base, thus shifting the equilibrium towards the neutral Rh(I) species **B**. This might also explain the fact that a maximum amount of enamine could be observed upon using [Rh(CO)$_2$(acac)] as a precatalyst. Moreover, the amount of *N*-formylpiperidine and aldol condensation products formed in the HAM increases following the order [Rh(cod)$_2$]BF$_4$ < [Rh(CO)$_2$(acac)] / [Rh(cod)$_2$]BF$_4$ (1:3) < [Rh(CO)$_2$(acac)] / [Rh(cod)$_2$]BF$_4$ (1:1) < [Rh(CO)$_2$(acac)] / [Rh(cod)$_2$]BF$_4$ (3:1) < [Rh(CO)$_2$(acac)]. This can be explained by increasing amounts of the hydroformylation catalyst present, slowing down the hydrogenation of the enamine and thus giving rise to more condensation products.



Conditions: 1-octene 13 mmol, piperidine 15 mmol, solvent 4-8 mL, [Rh(CO)$_2$(acac)] = 0.1 mol%, S/Rh = 2000, L/Rh = 4, T = 110°C, t = 6 h, p(CO/H$_2$ (1:2)) = 36 bar (cold pressure), L = (Sulfo)xantphos, 400 rpm.

Figure 2.11: *Comparison between HAM in toluene and in PM$_2$IM: inhibition of hydrogenation.*

2.6 Turnover frequencies

For the determination of the turnover frequency (TOF), the HAM of 1-octene with piperidine in the IL was performed in autoclaves equipped with mass flow controllers. The TOF at 20% conversion was determined both for the hydroaminomethylation and the hydroformylation reactions at different temperatures and pressures (Tab. 2.6). Given that both hydroformylation and hydrogenation are catalysed by a Rh complex in the HAM, the TOF for the HAM is the sum of the TOF for hydrogenation and the TOF for hydroformylation which can be calculated applying the following definition for TOF: (mol product) · (mol catalyst)$^{-1}$ · h^{-1}.

As expected, the hydroformylation of 1-octene is faster at lower pressure, since the rate of the hydroformylation reaction has a negative order in CO pressure because of the necessary CO dissociation from the metal complex to form the active catalyst species (Tab. 2.6, entry 1 and 2). The same effect of an increased activity at a lower total pressure is also observed in the hydroaminomethylation, probably initiated by the above-mentioned effect on the reaction rate in hydroformylation (Tab. 2.6, entry 4-5 and 6-7). This effect is observed both in toluene/MeOH and in IL, with entry 5 in Table 2.6 being an extreme example of this effect. Furthermore, it can be concluded that gas solubility in the IL is of the same order of magnitude than in toluene/MeOH. In case of low gas solubilities, like in water, reaction rates are in general very low because of the limited amount of gas in solution. In this example, reaction rates would increase upon increasing the pressure up to a certain maximum. After this value, reaction rates will decrease again following the same effect as described above.[41]

The reaction rate of the hydroformylation in IL was of the same order of magnitude than the reaction rate in toluene/MeOH (Tab. 2.6, entries 2 and 3) although the use of a different Rh precursor makes it more difficult to compare the results. It was expected that by using [Rh(CO)$_2$(acac)] (Tab. 2.6, entry 2) the reaction would be faster since this neutral complex is the precursor of choice for hydroformylation reactions. However, the hydroformylation in the IL (Tab. 2.6, entry 3) is faster than the reaction in toluene/MeOH. Nevertheless, from Figure 2.4 (B and D) and Table 2.6 (entries 7 and 8) it can be concluded that this does not apply for the hydroaminomethylation. Performing the HAM at p = 30 bar leads to a higher chemoselectivity, but to a lower regioselectivity in comparison to the HAM at p = 50 bar. Since the reaction at p = 30 bar is faster, probably large amounts of internal alkenes accumulate and thus react at high conversion, leading to a lower regioselectivity. The HAM at T = 110°C and p = 50 bar (Tab. 2.6, entry 4) gives a chemoselectivity comparable to the HAM at T = 125°C and p = 30 bar (Tab. 2.6, entry 6) and a TOF slightly lower than for the HAM at T = 125°C and p = 50 bar (Tab. 2.6, entry 7) while the

regioselectivity is better compared to entries 6 and 7 (Tab. 2.6). For the hydroaminomethylation, T = 110°C and p = 50 bar seem to be the optimal reaction conditions in terms of selectivity.

Table 2.6: *Determination of the turnover frequency (TOF) for hydroaminomethylation and hydroformylation experiments.*[a]

Entry	Reaction type	T [°C]	p [bar][b] CO/H_2 (1:2)	Solvent	Rh precur-sor	l/b	Sel. product [%]	TOF [h^{-1}][c]
1[d,e]	HF	110	30	**A**	**1**	28.3	95.5	4500
2[d,e]	HF	110	50	**A**	**1**	26.0	93.7	2200
3[d]	HF	110	50	**B**	**2**	36.9	96.9	3800
4	HAM	110	50	**B**	**2**	41.4	96.1	3900
5[e,f]	HAM	110	120	**B**	**2**	31.1	84.7	700
6	HAM	125	30	**B**	**2**	15.2	97.9	8400
7	HAM	125	50	**B**	**2**	22.7	91.0	5000
8[e]	HAM	125	50	**A**	**2**	17.1	44.2[g]	11000

[a] 1-octene, piperidine (for HAM only), solvent 6 mL, L/Rh = 4, S/Rh = 2000-3000, t = 18 h, **A** = toluene/MeOH, **B** = [PMIM][BF_4], **1** = [$Rh(CO)_2$acac], **2** = [$Rh(cod)_2$]BF_4, 400 rpm. [b] Pressure at reaction temperature. [c] TOF at 20 % conversion. [d] CO/H_2 (1:1). [e] Solvent 10 mL. [f] t = 6 h, 1200 rpm. [g] Large amount of aldol product.

2.7 Conclusions

In this chapter, it has been shown that the hydroaminomethylation of *n*-alkenes with piperidine in ionic liquids, gives rise to less side product formation compared to the reaction in toluene/MeOH. Subsequent reuse of the catalyst is possible by simple phase separation without any significant leaching of rhodium or ligand into the product layer. High chemo- and regioselectivities were achieved in the recycle steps. Oxidation of the ligand was avoided by performing the phase separation in the autoclave or by simple addition of substrates after completion of the initial reaction. The influence of different reaction parameters was investigated by monitoring the product distribution in a model reaction as well as in the ionic liquid. In addition, turnover frequencies were determined. Reaction time and temperature turned out to strongly influence chemo- and regioselectivity because of conversion limitation. S/Rh ratio dependency was not observed at T = 125°C, but was much more pronounced for a reaction temperature of T = 110°C. A reaction temperature of T = 110°C, a reaction time of 4 to 6 hours and a S/Rh ratio smaller than 1000 were found to be the optimal reaction conditions in terms of conversion and regio- and chemoselectivity, also in the recycle steps. Applying a binary Rh precatalyst is advantageous in this reaction. Protic

organic solvents or ionic liquids with a C-H acidic bond in the imidazolium part of the ionic liquid turned out to be necessary for the hydrogenation of the intermediate enamine to occur. This was explained by the equilibrium between the resting state of the hydroformylation species and the expected cationic species of the hydrogenation catalyst.

2.8 Experimental section

All air or water sensitive operations were performed using standard Schlenk techniques under purified argon atmosphere. Toluene and dichloromethane were purified over custom-made alumina columns. Ethyl acetate, piperidine, methanol, and ethanol were distilled from CaH_2 and 1-hexene, 1-octene, 1-decene, 1-dodecene were purified by distillation from Na_2SO_4 and percolation over activated neutral alumina. All solvents and substrates were degassed prior to use. Chemicals were purchased from Acros Chimica, Merck KGaA, Biosolve B.V. and Aldrich Chemical Co. $[Rh(acac)(CO)_2]$ was obtained as a generous loan from OMG and $[Rh(cod)_2]BF_4$ was synthesised according to a literature procedure. 9,9-Dimethyl-2,7-bissulfonato-4,5-bis(diphenylphosphino)xanthene sodium salt was prepared according to a literature procedure.[33] Hydrogen gas (99.999%), carbon monoxide gas (99.997%) and synthesis gas (CO (99.997%)/H_2 (99.999%); 1:1) were purchased from Hoek Loos and synthesis gas (CO (99.9%)/H_2 (99.9996%); 1:2) was purchased from Praxair. Gas chromatographic analyses were run on a Shimadzu GC-17A instrument and an Ultra 2 column (25 m x 0.2 mm). GC/MS analyses were conducted on a HP6890 chromatograph with a Leco Pegasus II mass spectrometer and a DB-1MS column (10 m x 0.1 mm). NMR data were recorded on a Varian Oxford 200 MHz and a Varian Mercury Vx 400 MHz NMR spectrometer. Gas uptake was monitored by Bronkhorst EL-Flow mass flow controllers with a range from 0 to 150 mL/min.

General procedure for hydroaminomethylation experiments

Reactions were performed in 75-mL home-made stainless steel autoclaves. In a typical experiment, the autoclave was charged with a solution of $[Rh(cod)_2]BF_4$ (7.2 mg, 17.8 μmol; cod = 1,5-cyclooctadiene) or $[Rh(CO)_2(acac)]$ (4.6 mg, 17.8 μmol) (acac = acetylacetonate) or a combination of these Rh precursors and Sulfoxantphos (55.8 mg, 71.3 μmol) or Xantphos (41.3 mg, 71.3 μmol) in 4 mL of the ionic liquid or toluene/MeOH. 1-Octene (2.0 g, 18 mmol) and piperidine (1.7 g, 20 mmol) were added and the autoclave was purged three times using CO (p = 10-12 bar) to remove the remaining argon from the autoclave. Subsequently, the autoclave was pressurised with CO (p = 12 bar) and H_2 (p = 24 bar) and heated to reaction temperature. After 18 hours the autoclave was cooled to room temperature in an ice bath and the gases were vented. Phase separation was immediate and the product layer was removed from the autoclave by syringe under an argon atmosphere. The catalyst solution was ready to be used in a new catalytic run. The product layer was analysed by GC and GC/MS. In these analyses the l/b-ratio could be determined within an error range of 0.05%.

Hydroaminomethylation reactions in toluene/MeOH, from which samples were taken during the reaction, were conducted in a similar way as described above, in an autoclave equipped with a tailor-made sample system that consisted of a capillary with an inner diameter of 0.25 mm, combined with a two-way and a three-way valve.[42] The sample was taken by means of the pressure inside the autoclave. The connection between the two valves was used to collect the sample (estimated volume 50 μL). By opening the two-way valve the sample was collected in a GC vial, diluted with MeOH/Et_2O and analysed by GC. After finishing the reaction, cooling the autoclave and venting the gases, the reaction mixture was removed from the autoclave and analysed by GC and GC/MS.

General procedure for the determination of the turnover frequency (TOF)

Typical hydroaminomethylation and hydroformylation experiments were performed as described above, except for the fact that the substrates were added *via* a dropping funnel, in home-made, automated 100-mL stainless steel autoclaves. All hydroformylation experiments were performed with CO/H_2 (1:1) while all other experiments were conducted using CO/H_2 (1:2). After loading the autoclave, it was purged four times with synthesis gas (CO/H_2 1:2), pressurised to reaction pressure with synthesis gas (CO/H_2 1:2) and heated to reaction temperature. The reaction mixture was stirred for 10 to 15 minutes in order to saturate the solution with synthesis gas. Subsequently, the substrates were added via the dropping funnel, and the reaction was started. During the reaction the gas uptake was monitored by mass flow controllers (Bronkhorst; 0-150 mL/min) and the turnover frequency at 20% conversion was calculated from the originating gas uptake curves combined with the total conversion calculated from the GC chromatograms and the S/Rh ratio.

Synthesis of 1-Pentyl-3-methyl-imidazolium tetrafluoroborate (1)

1-Methylimidazole (60 mL, 0.752 mol) was mixed with 1-bromopentane (93.20 mL, 0.752 mol). The mixture was stirred at 50 °C for 24 hours. Subsequently, the liquid was diluted in acetone (100 mL) and sodium tetrafluoroborate (85 g, 0.774 mol) was added. The mixture was stirred for 48 hours at room temperature and then filtered. After evaporation of the acetone the liquid was filtered once more and washed with diethyl ether (30 mL). The remaining diethyl ether in the product was removed under vacuum to yield the product as a slightly yellow liquid (177 g, 729 mmol, 97%). ^{1}H-NMR (400 MHz, CD_3OD): δ = 8.83 (s, 1H), 7.60 (t, 1H, *J* = 1.8 Hz), 7.54 (s, 1H, *J* = 1.8 Hz), 4.20 (t, 2H, *J* = 7.4 Hz), 3.92 (s, 3H), 1.87-1.91 (m, 2H), 1.32-1.40 (m, 4H), 0.92 (t, 3H, *J* = 7.1 Hz) ppm. ^{13}C-NMR (100 MHz, CD_3OD): δ = 136.40, 123.50, 122.19, 49.38, 35.02, 29.38, 27.92, 21.68, 12.75 ppm. ^{19}F-NMR (376 MHz, CD_3OD): δ = –153.70 ppm.

Synthesis of 1-Pentyl-2,3-methyl-imidazolium tetrafluoroborate (2)

1,2-Dimethylimidazole (7.0 g, 72.8 mmol) was mixed with 1-bromopentane (7.81 mL, 72.8 mmol) and 1,1,1-trichlorethane (25 mL) as a solvent. The mixture was stirred at 50 °C for 24 hours.

1,1,1-Trichlorethane was decanted and the residue was diluted in acetone (30 mL) and sodium tetrafluoroborate (8.5 g, 77.4 mmol) was added. Further work-up was identical to work-up for compound **1** to yield the product as a slightly yellow liquid (17 g, 66.1 mmol, 91%). ^{1}H-NMR (400 MHz, CD_3OD): δ = 7.48 (d, 1H, *J* = 2.1 Hz), 7.44 (d, 1H, *J* = 2.1 Hz), 4.15 (t, 2H, *J* = 7.4 Hz), 3.81 (s, 3H), 2.61 (s, 3H), 1.84 (m, 2H), 1.37 (m, 4H), 0.93 (t, 3H, J = 7.0 Hz) ppm. ^{13}C-NMR (100 MHz, CD_3OD): δ = 145.55, 122.15, 120.74, 48.00, 33.96, 29.05, 28.00, 21.80, 12.79, 8.06 ppm. ^{19}F-NMR (376 MHz, CD_3OD): δ = −154.06 ppm.

ICP-OES (Inductively Coupled Plasma Optical Emission Spectrometry)

Rhodium and phosphorus leaching were analysed by means of ICP-OES. Samples were prepared by removal of the volatiles from the organic layer under reduced pressure and subsequent calcination of the residue at 500 ºC over 72 hours. Afterwards, the residue was dissolved in 2 mL HNO_3 (65%) and diluted with distilled water to 25 mL in a measuring flask. Before starting the measurements on the samples, a calibration curve for Rh and P was prepared. The measurements were performed with a SPECTRO CIROS^{CCD} spectrometer equipped with a free running 27.12 MHz generator at a power of 1400 W. The sample introduction was performed by a cross-flow nebuliser with a double pass Scott type spray chamber and a sample uptake rate of 2 mL/min. The outer gas flow was 12 L/min, the intermediate gas flow was 1 L/min and the nebuliser gas flow was 1.00 L/min.

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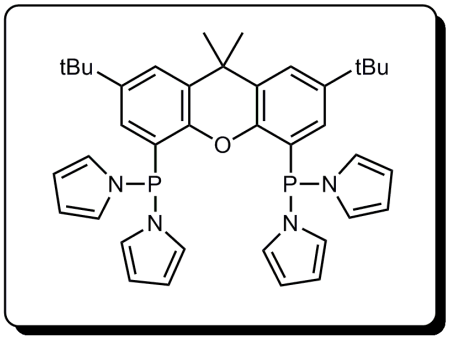
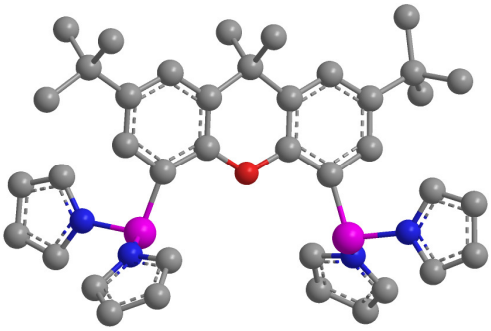
3

Fast and selective hydroaminomethylation of *n*-alkenes using xanthene-based amino-functionalised ligands

In order to increase the activity and to maintain a good selectivity in the hydroaminomethylation reaction in comparison to Rh/phosphine-catalysed systems, a new π-acidic ligand, the bis-[(dipyrrolyl)phosphino]xanthene, was synthesised. In combination with rhodium, this ligand leads to outstanding activities and selectivities with turnover frequencies of 6200 h^{-1} and very high l/b ratios exceeding 200. Furthermore, it was shown that the pKa value of the alcohol used in the solvent mixture has a profound effect on the performance of the catalytic systems. Acidic media enhance the activity, while less acidic media increase the regio- and chemoselectivity, as well as the degree of double bond isomerisation.





Part of this work has been published:
B. Hamers, E. Kosciusko-Morizet, C. Müller, D. Vogt, *ChemCatChem* **2009**, *1*, 103-106.

3.1 Introduction

As already described in Chapter 1, amines are of great importance as building blocks, intermediates, and products in industrial chemistry[1,2] and have wide-spread applications in polymers, additives, anti-foam agents, detergents, dyes, pesticides, and pharmaceuticals. The preparation of amines has received a lot of attention, which is illustrated by a Houben-Weyl volume with over 1000 pages dedicated to the synthesis of amino compounds.[3] Nowadays, a trend towards the use of atom-efficient amination reactions for the synthesis of amines, particularly reactions catalysed by homogeneous catalysts, can be observed. Easy and selective synthetic access, waste reduction, availability, and price of starting materials are important considerations in this respect. The hydroaminomethylation (HAM) is a promising reaction to fulfil the above-mentioned requirements. Other catalytic methods to synthesise amines are reactions as palladium-catalysed amination of aryl halides,[4,5] hydroamination of alkenes,[6] and reductive amination of aldehydes and ketones.[7, 8]

In order to be of interest from an industrial perspective, the reaction, or better the process, has to be fast, selective and possibly cheap. In general, this means that the catalyst has to be active, selective and reasonably inexpensive along with large turnover numbers. It is well-known that metal precursors and particularly ligands can have a large influence on these catalyst properties in homogeneous catalysis.[9] Since hydroformylation is the first step in the hydroaminomethylation cascade and the regioselectivity is determined already in this step, ligands used for hydroformylations are mostly also the ligands of choice in the HAM in order to obtain high yields and selectivities. Some examples of common phosphine and phosphite ligands, which display excellent performance in the hydroformylation and hydroaminomethylation reaction in combination with rhodium, are depicted in Figure 3.1.[10-21]

Generally speaking, the better the π-acceptor character of a ligand, the more active the catalyst will be in hydroformylation and typically also in hydroaminomethylation. However, phosphite ligands, which are good π-acceptor ligands, often show an increased activity, but a decreased regioselectivity in comparison to the σ-donating phosphine ligands. This effect is mainly caused by the enhanced hydroformylation activity for internal alkenes and the steric bulk being further away from the metal centre compared to phosphine ligands. Consequently, depending on the application, a compromise between activity and selectivity has to be found.

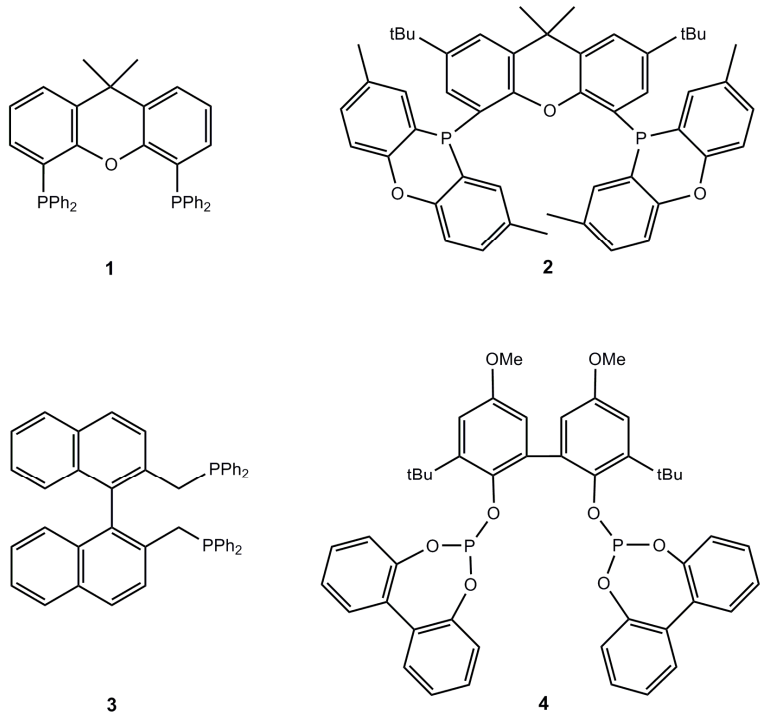


Figure 3.1: *Illustration of commonly used phosphine and phosphite ligands in Rh-catalysed hydroformylation and hydroaminomethylation reactions.* ***1****:* ***Xantphos****, Haenel,[22] Van Leeuwen[14,22]; **2**: **Xantphenoxaphos**, Van Leeuwen[23]; **3**: **NAPHOS**, Kumada,[24] Herrmann,[25] Beller[11,12]; **4**: **BIPHEPHOS**, Bryant[17,18].*

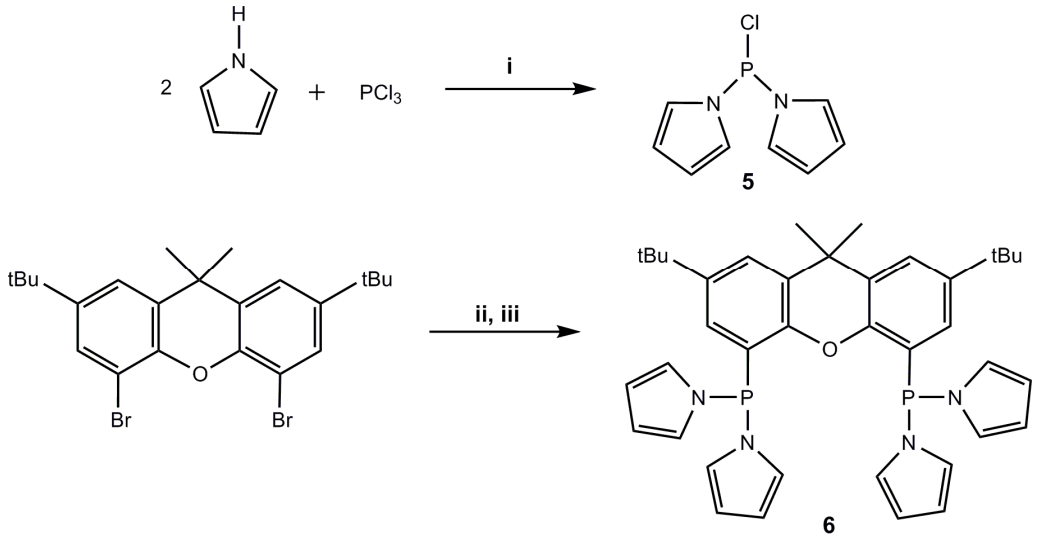
In addition to the aforementioned activity and regioselectivity, chemoselectivity is also an important issue in HAM reactions. In order to avoid all possible side reactions mentioned in Chapter 1, it is important to convert the intermediates preferably instantaneously and selectively to the desired amine product. This means that the catalyst should not only display high activity and selectivity in the hydroformylation, but also in the hydrogenation reaction. Some literature examples address the problem of hydrogenation activity. The hydrogenation activity can be increased by addition of an iridium catalyst, which is well-known for its ability to hydrogenate C=N double bonds efficiently, to the rhodium catalyst, in this way creating a so-called dual catalyst.[26-29] However, also catalyst systems starting from a single rhodium precursor have shown to be able to efficiently catalyse the complete HAM sequence. As already shown in Chapter 2, a protic solvent is necessary in that case in order to shift and maintain the equilibrium between the two active catalytic Rh species.

Pyrrole substituents on the phosphorus atom lead to π-acidic phosphorus ligands.[30,31] A few examples of the advantageous properties of this type of ligands in hydroformylation can be found in literature.[32-34] In order to improve the activity and to retain high selectivity in the HAM, ligands with a very good π-acceptor character were developed by functionalising the well-known and

frequently used xanthene [35-39] and dihydroxyxanthene backbone with dipyrrolylphosphine.[40] In this way χ-values typical for phosphonites and phosphites were approached.[41,42] Moreover, these ligands induce more steric hindrance close to the rhodium centre, because of the higher degree of substitution of nitrogen in comparison to oxygen in corresponding phosphonite and phosphite ligands. This combination of electronic and steric properties is regarded to be important in order to combine a high selectivity with a high activity. The performance of these ligands in Rh-catalysed HAM reactions of *n*-alkenes is described and the influence of the pKa value of alcohols in the reaction media is investigated in this chapter.

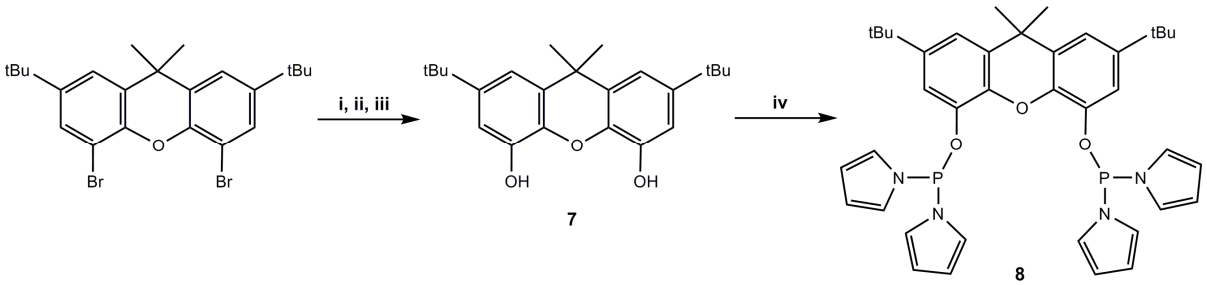
3.2 Ligand synthesis

The first step in the synthesis of bis-[(dipyrrolyl)phosphino]xanthene **6** (DPX) is the lithiation of dibromoxanthene. Subsequently, this lithiated species is reacted with chlorodipyrrolylphosphine **5**, synthesised by addition of triethylamine and two equivalents of pyrrole to a PCl_3 solution, yielding the pure ligand DPX as a white solid after a few washing steps and a crystallisation from MeOH in 22% yield. The reaction scheme for this synthesis is depicted in Scheme 3.1. The ligand was fully characterised by elemental analysis and ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and shows a resonance at $\delta = 67.6$ ppm in the ^{31}P NMR spectrum.



Scheme 3.1: *Synthetic route to bis-[(dipyrrolyl)phosphino]xanthene ligand* ***6*** *(DPX): i)* Et_3N*, THF, –40ºC/r.t., 18 h; ii) nBuLi, THF, –60ºC, 2 h; iii)* ***5****, toluene, –60ºC/r.t., 18 h.*

Additionally, starting from dihydroxyxanthene (**7**), the corresponding bis-[(dipyrrolyl)phosphino]amidate ligand **8** (DPXO) was synthesised, which is expected to have an even larger χ-value. First, dihydroxyxanthene had to be synthesised from dibromoxanthene by lithiation, subsequent reaction with BH_3, and hydrolysis to the desired compound. The resulting dihydroxyxanthene was reacted with chlorodipyrrolylphosphine to give the amidate ligand **8** as an off-white solid in 74% yield. The reaction steps for this reaction sequence are shown in Scheme 3.2. The ligand was fully characterised by elemental analysis and ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and shows a resonance at δ = 107.7 ppm in the ^{31}P NMR spectrum.



Scheme 3.2: *Synthetic route to bis-[(dipyrrolyl)phosphino]amidate ligand **8** (DPXO): i) nBuLi, THF, –60°C, 2 h; ii) BH_3, THF, –15°C/r.t., 18 h; iii) H_2O, 3M KOH, 30% H_2O_2, reflux, 2h; iv) Et_3N, **5**, THF, r.t., 18 h.*

Similar to the routes shown in Schemes 3.1 and 3.2 the corresponding ligands **9** and **10** with 3-methylindole substituents on the phosphorus atom were synthesised. A representation of these ligands is shown in Figure 3.2. It is expected that these ligands in combination with rhodium will give increased regioselectivity in the HAM reactions because of the larger bulk of the substituents in comparison to the pyrrole substituents. Especially, the synthesis of ligand **9** was less efficient than the synthesis of the pyrrole equivalent and the yield was disappointing. Ligand **9** and **10** were obtained as white solids in 14% and 38% yield, respectively. Both ligands were fully characterised by elemental analysis or MALDI-TOF-MS and ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. Ligand **9** and **10** show a resonance at δ = 64.0 ppm and at δ = 104.9 ppm, respectively in the ^{31}P NMR spectrum.

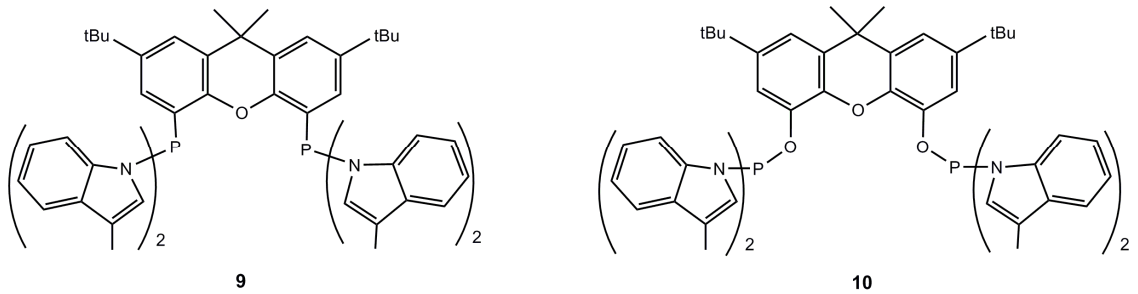
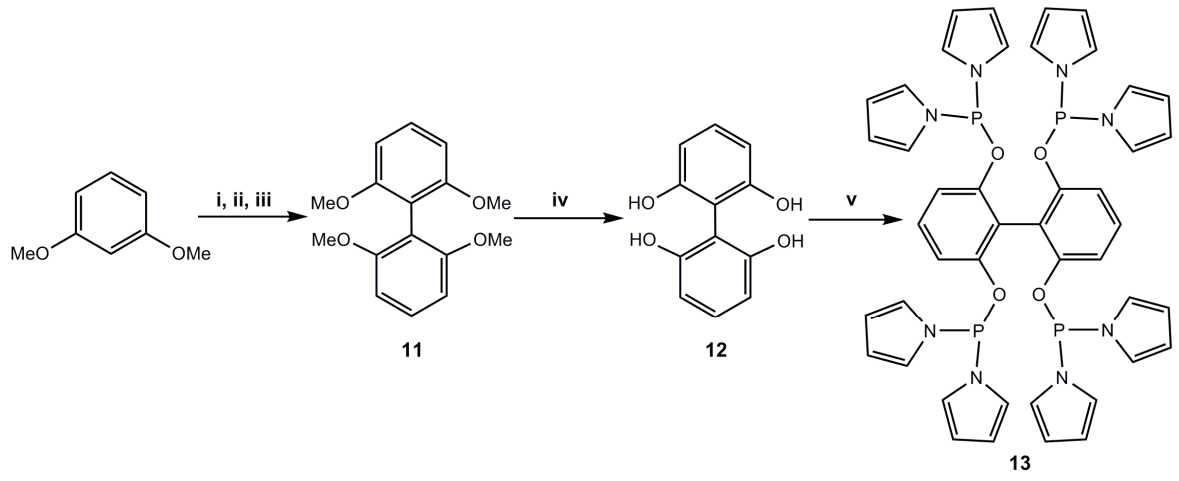


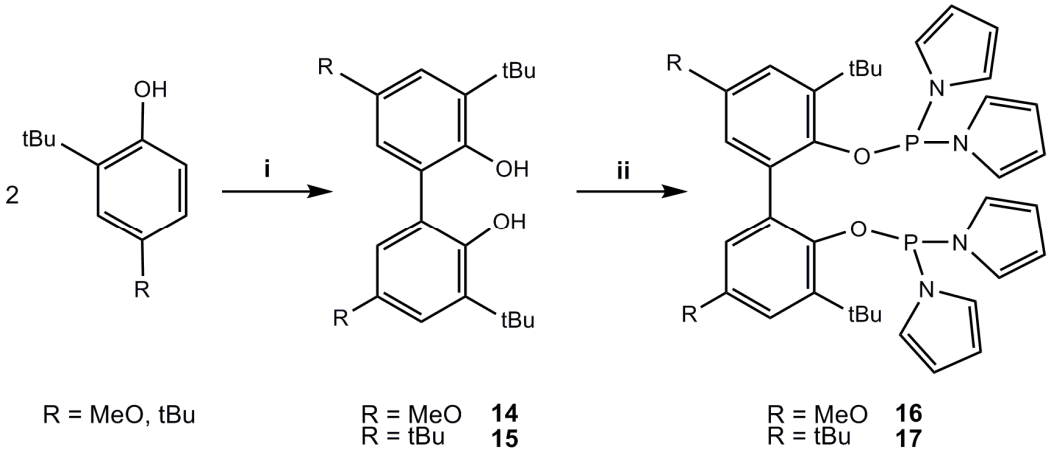
Figure 3.2: *Representation of 3-methylindole substituted ligands **9** and **10**.*

In order to compare the aforementioned ligands in HAM reactions with analogous ligands, the Tetraphos ligand **13** and comparable ligands **16** and **17** with only two phosphorus atoms attached to the biphenyl backbone were prepared following adjusted literature procedures (Schemes 3.3 and 3.4).[32,34,37,43] These ligands are reported to give very good regioselectivities in the hydroformylation of *n*-alkenes or even internal alkenes in combination with high turnover frequencies. For the synthesis of Tetraphos ligand **13**, compound **5** was added to a solution of triethylamine and tetrahydroxybiphenyl, which was prepared from 1,3-dimethoxybenzene by lithiation and subsequent Cu-catalysed coupling and deprotection with BBr_3 following a further literature procedure.[44] After a reaction time of 6 hours at room temperature, the pure ligand was obtained as a white solid after a crystallisation step in 30% yield. The ligand was fully characterised by elemental analysis and ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and shows a resonance at δ = 107.9 ppm in the ^{31}P NMR spectrum.

Ligands **16** and **17** were synthesised in a similar way, starting from the corresponding substituted dihydroxybiphenyl backbones, yielding the ligands as white solids in 68% and 76% yield, respectively. Both ligands were fully characterised by elemental analysis and ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. Ligand **16** and **17** show a resonance peak at δ = 107.1 ppm and at δ = 107.0 ppm, respectively in the ^{31}P NMR spectrum.



Scheme 3.3: *Synthetic route to Tetraphos ligand **13**: i) nBuLi, Et_2O, 0°C/r.t., 18 h; ii) CuI, r.t., 2.5 h; iii) 2-iodo-1,3-dimethoxybenzene, pyridine, 50°C, 3 days; iv) BBr_3, CH_2Cl_2, –78°C/r.t., 1 h; v) Et_3N, **5**, THF, r.t., 6 h.*



Scheme 3.4: *Synthetic route to biphenyl backbone ligands **16** and **17**: i) KOH/$K_3Fe(CN)_6$, MeOH/H_2O, r.t., 3 h; ii) Et_3N, **5**, THF, r.t., 18 h.*

3.3 Catalysis

In order to compare the performance of the Rh/ligand combinations, hydroaminomethylation reactions were performed in toluene/MeOH (1:1). $[Rh(cod)_2]BF_4$ was used as the metal precursor, the substrates used were 1-octene and piperidine and the reaction was performed at 110°C with a reaction time of 18 hours. Conversion was high for the entire selection of Rh/ligand combinations, but the regioselectivity was only moderate or even low (Tab. 3.1). Furthermore, the chemoselectivity was high in all reactions, but exceptionally high for Rh/**6**. The main side product in all HAM reactions was the aldol condensation product. The most deviant results were obtained with Rh/**16** and Rh/**17**, which give rise to a high degree of isomerisation, leading to very low l/b ratios. Apparently, not only the hydroformylation activity for terminal alkenes, but also for internal alkenes is high with these catalysts. In fact, good regioselectivities in hydroformylation were only described at rather low conversions (~20-30%).[32] These ligands are probably not bulky and rigid enough to induce high regioselectivities. From this first screening, it became clear that ligand **6** is a very promising candidate in the HAM reaction in terms of chemo- and regioselectivity.

Table 3.1 *Results of Rh-catalysed hydroaminomethylation reactions with various ligands at t = 18 h.*[a]

Entry	Ligand	S/Rh	Isomerised octene [%]	Conv. [%]	Sel.(amine) [%]	l/b
1	**6**	1050	1.1	98.8	99.5	12.3
2[b]	**8**	1140	0.2	99.8	81.2	1.7
3	**9**	1060	2.2	97.8	94.6	2.6
4[b]	**10**	1040	0.2	99.8	85.5	1.7
5[b]	**13**	1050	-	99.9	86.5	2.0
6	**16**	1050	7.0	92.8	93.7	0.5
7	**17**	1050	8.2	91.3	77.3	0.7

[a] 1-octene 10 mmol, piperidine 11 mmol, toluene/MeOH (1:1) 8 mL, L/Rh = 4–4.5, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110 °C, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm, t = 18 h. [b] t = 21 h.

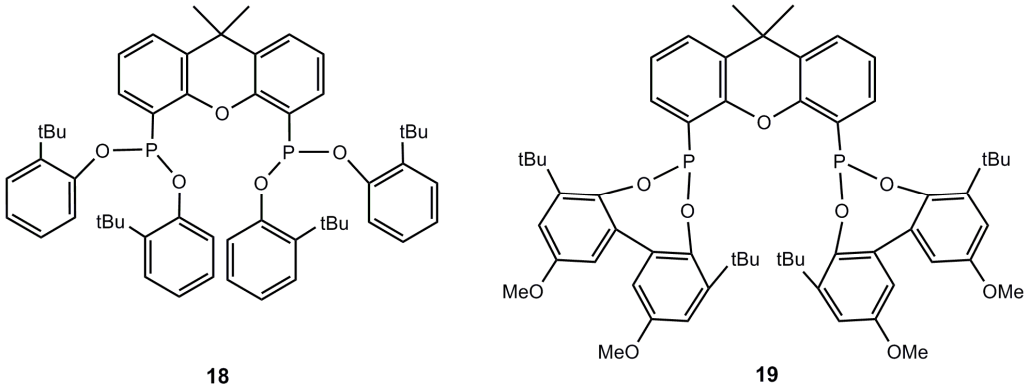
The reason for the disappointing regioselectivity (*vide supra*) may be explained by the length of the reaction time. Due to partial double bond isomerisation of the substrate, the slower reacting internal octenes accumulate in the reaction mixture. At high conversions, these will also be hydroformylated leading to a drastic decrease in regioselectivity. If the reaction is stopped at around 98-99% conversion of 1-octene, which is the conversion of all octenes added up with isomerised alkenes, the regioselectivity will improve significantly. From this point on, mainly internal alkenes will be hydroformylated. Upon decreasing the reaction time to 1 hour (94-95% conversion of all octenes), the regioselectivity in the reaction with Rh/**6** actually improved dramatically while conversion of 1-octene and chemoselectivity were almost not affected (Tab.3.2; entry 1). In the HAM with Rh/**13**, the conversion was very low and only aldehydes were observed after 1 hour reaction time (Tab. 3.2; entry 4). For the systems Rh/**8** and Rh/**10**, conversion was already high and the regioselectivity was actually improved, but the chemoselectivity was unexpectedly low. Large amounts of the intermediate enamine, but especially the aldehyde were observed. It can be concluded that the hydroformylation reaction is fast, but the activity for the subsequent reductive amination is low. Again, Rh/**6** gives the most promising results.

Table 3.2 *Results of Rh-catalysed hydroaminomethylation reactions with various ligands at t = 1 h.*[a]

Entry	Ligand	S/Rh	Isomerised octene [%]	Conv. [%]	Sel.(amine) [%]	l/b
1	**6**	1050	4.3	94.5	98.6	50.1
2	**8**	1140	1.5	82.0	10.8[b]	17.4
3	**10**	1040	2.1	95.0	29.4[b]	2.7
4	**13**	1060	2.0	24.4	- [c]	4.0[d]

[a] 1-octene 10 mmol, piperidine 11 mmol, toluene/MeOH (1:1) 8 mL, L/Rh = 4–4.5, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm, t = 1 h. [b] Large amounts of intermediates. [c] No amines observed. [d] l/b ratio of aldehydes.

In addition to this, the performance of ligand **6** in HAM was compared to the performance of bulky diphosphonite ligands **18** and **19** (Fig. 3.3), reported by the group of Vogt a few years ago. These ligands, which are expected to be π-acceptor ligands too, gave interesting results in Rh-catalysed hydroformylations, even for internal alkenes.[38,45] Obviously, these ligands perform also well in the HAM (Tab. 3.3), giving rise to high or moderate regioselectivities, even after long reaction times. However, the selectivity of Rh/**18** and Rh/**19** to the amine is surprisingly low after 1 hour reaction time in comparison to Rh/**6**. This might be explained by a lower hydrogenation activity of the diphosphonite based catalysts, leading to an accumulation of the intermediate enamine. Clearly, the dipyrrole based catalyst outperformed the bulky diphosphonites in the HAM, in this way again showing its potential as an active and selective catalyst in combination with rhodium in this reaction.



18 **19**

Figure 3.3: *Illustration of bulky diphosphonites **18** and **19** based on the xanthene backbone.*

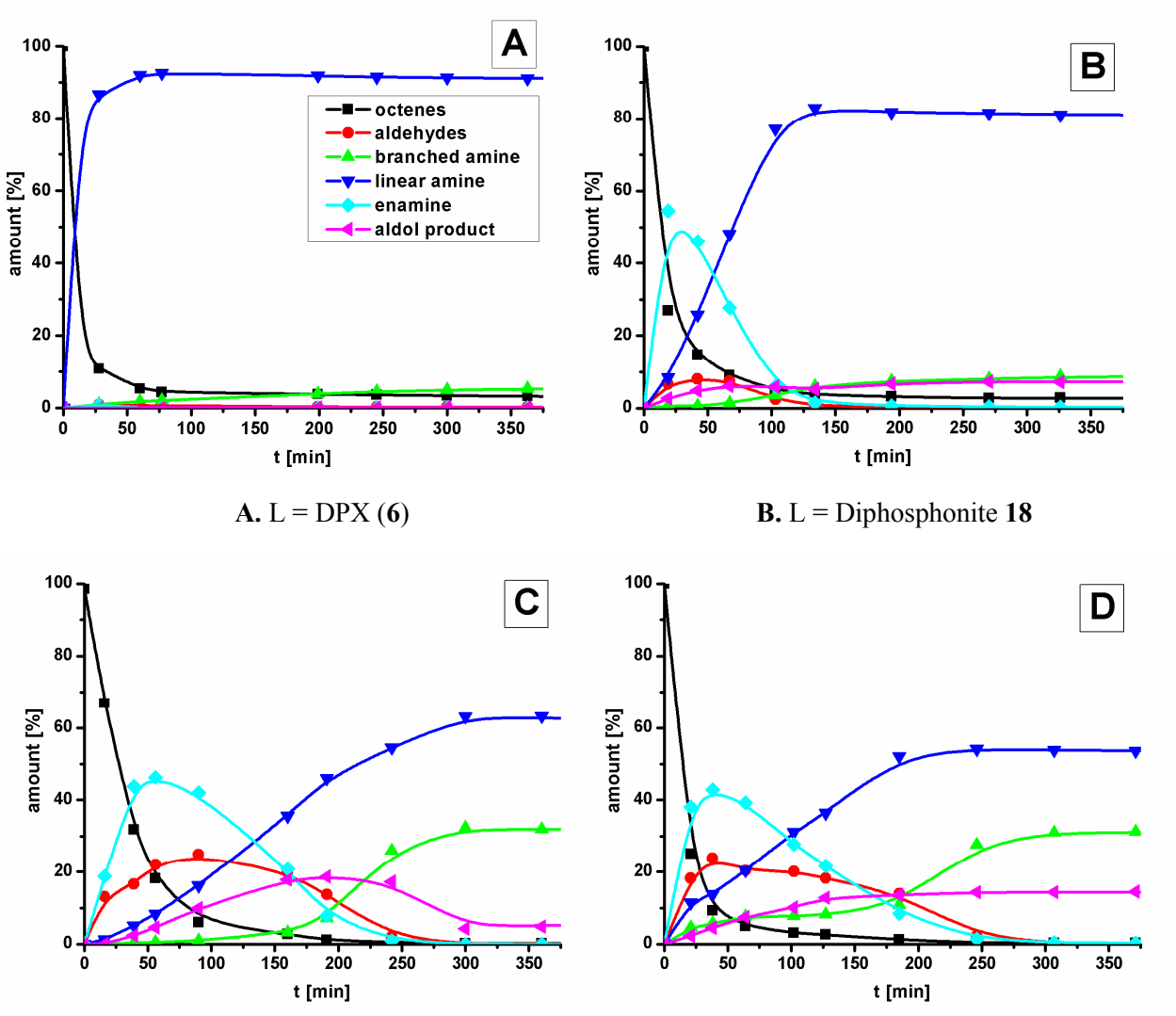
Table 3.3 *Results of Rh-catalysed hydroaminomethylation reactions with DPX and bulky diphosphonites.*[a]

Entry	Ligand	S/Rh	Isomerised octene [%]	Conv. [%]	Sel.(amine) [%]	l/b
1	**6**	1050	4.3	94.5	98.7	50.1
2	**18**	970	2.9	91.0	54.5	33.7
3	**19**	1090	2.6	95.1	81.0	49.4
4[b]	**18**	970	1.1	98.7	91.8	7.3
5[b]	**19**	1090	1.4	98.2	94.3	14.4

[a] 1-octene 10 mmol, piperidine 11 mmol, toluene/MeOH (1:1) 8 mL, L/Rh = 4–4.5, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm, t = 1 h ($X_{(1\text{-octene})}$ = 99%). [b] t = 21 h.

The HAM with Rh/**6** appeared to be very fast and selective. In order to investigate the distribution of products and intermediates in time more thoroughly and to verify the hypotheses for the lower activity or selectivity of the other catalyst systems, samples were taken during HAM reactions and analysed by means of GC. Plotting the consumption of substrate and formation of intermediates and products *versus* time (Fig. 3.4A) shows that not only the regio- and chemoselectivity, but also the activity in hydroformylation and hydrogenation were extraordinarily high for Rh/**6**. Almost no intermediate product was observed during the reaction and after 1 hour reaction time; only amine product and internal alkenes could be detected as shown already in Table 3.2. In the HAM with Rh/**18** (Fig. 3.4B), an accumulation of enamine was observed, which makes the above-mentioned explanation of decreased hydrogenation activity plausible. The product distribution of the HAM with Rh/**19** was almost identical compared to the system shown in Figure 3.4B.

Upon repeating this procedure with DPXO (**8**), the results were amazingly different (Fig. 3.4C). The consumption of octenes was comparably fast as observed for Rh/**6**, but the reductive amination of the intermediates was much slower, leading to their accumulation and consequently to the formation of large amounts of the aldol condensation product. Furthermore, the hydroformylation activity for the internal alkenes seemed to be increased, which led to the formation of the branched aldehyde/amine already at the start of the reaction. HAM reaction with Rh/**10** gave comparable results as HAM using Rh/**8** (Fig. 3.4D). Fast consumption of octenes was observed in combination with accumulation of the intermediate aldehyde and enamine and formation of aldol condensation products and branched amine. The amount of linear amine product formed in this reaction is even lower than in case of Rh/**8**.



A. L = DPX (**6**)

B. L = Diphosphonite **18**

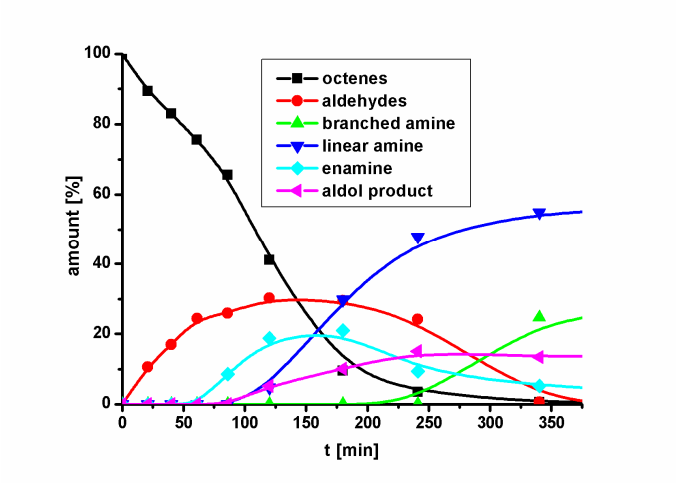
C. L = **8**

D. L = **10**

Conditions: 1-octene 10 mmol, piperidine 11 mmol, toluene/MeOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm.

Figure 3.4: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 1-octene using different ligands.*

Furthermore, the product distribution in the HAM with Rh/**13** was monitored (Fig. 3.5). The reaction is slow in comparison to the xanthene-based amino-functionalised ligands and in particular in comparison to Rh/**6**. Large amounts of intermediate aldehyde and enamine were observed and the formation of amine only starts after approximately 90 minutes leading to considerable amounts of the aldol condensation product in the reaction mixture. The conversion of 1-octene was almost complete after 4 hours, whereas still large amounts of the intermediates were present. As a consequence, also the branched amine was observed in substantial amounts upon longer reaction times. Because of the rather disappointing performance of the described catalytic systems (*vide supra*), the Rh/**6** system has been used for further investigations.



Conditions: 1-octene 10 mmol, piperidine 11 mmol, toluene/MeOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm, L = **13**.

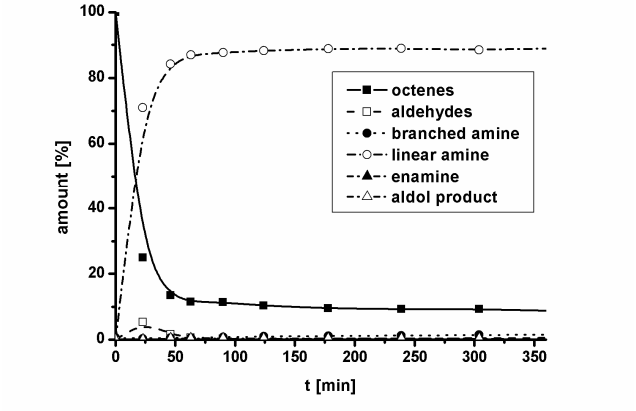
Figure 3.5: *Product distribution during the Rh-catalysed HAM reaction of 1-octene using Tetraphos (**13**).*

3.4 Solvent mixture composition

In order to investigate any effects of the solvent mixture composition on activity and selectivity, a HAM reaction was performed in toluene/*n*BuOH (Fig. 3.6). The results implied that the solvent mixture composition indeed influenced this reaction. When changing from toluene/MeOH to toluene/*n*BuOH, the reaction rate decreased slightly. More interestingly, the regioselectivity increased considerably (l/b = 160) and a higher isomerisation rate was observed. A HAM reaction in toluene/*n*BuOH was performed in the parallel automated autoclaves, AMTEC SPR16, which is equipped with a mass flow controller, to determine the turnover frequency (TOF). The TOF at 20% conversion was calculated from the originating gas uptake curve and the calculated conversion from the GC chromatogram according to the definition stated in Chapter 2. This TOF turned out to be 6200 h^{-1} in toluene/*n*BuOH, underlining the fact that this is a very active system. According to the activity derived from the product distribution graphs the TOF should be even higher in toluene/MeOH. In order to accurately determine the TOF, substrates need to be added under actual reaction conditions, after the catalyst preformation. However, in the way the substrates were added in the automated AMTEC SPR16 reactors, this was not feasible for low boiling solvents.

It has been discussed already in Chapter 2 that the protic solvent influences the equilibrium between the neutral and cationic Rh species, which are active in hydroformylation and hydrogenation, respectively. For a systematic investigation on the effect of the protic co-solvent, the HAM was performed in solvent mixtures using alcohols with different pKa values (Fig. 3.7).

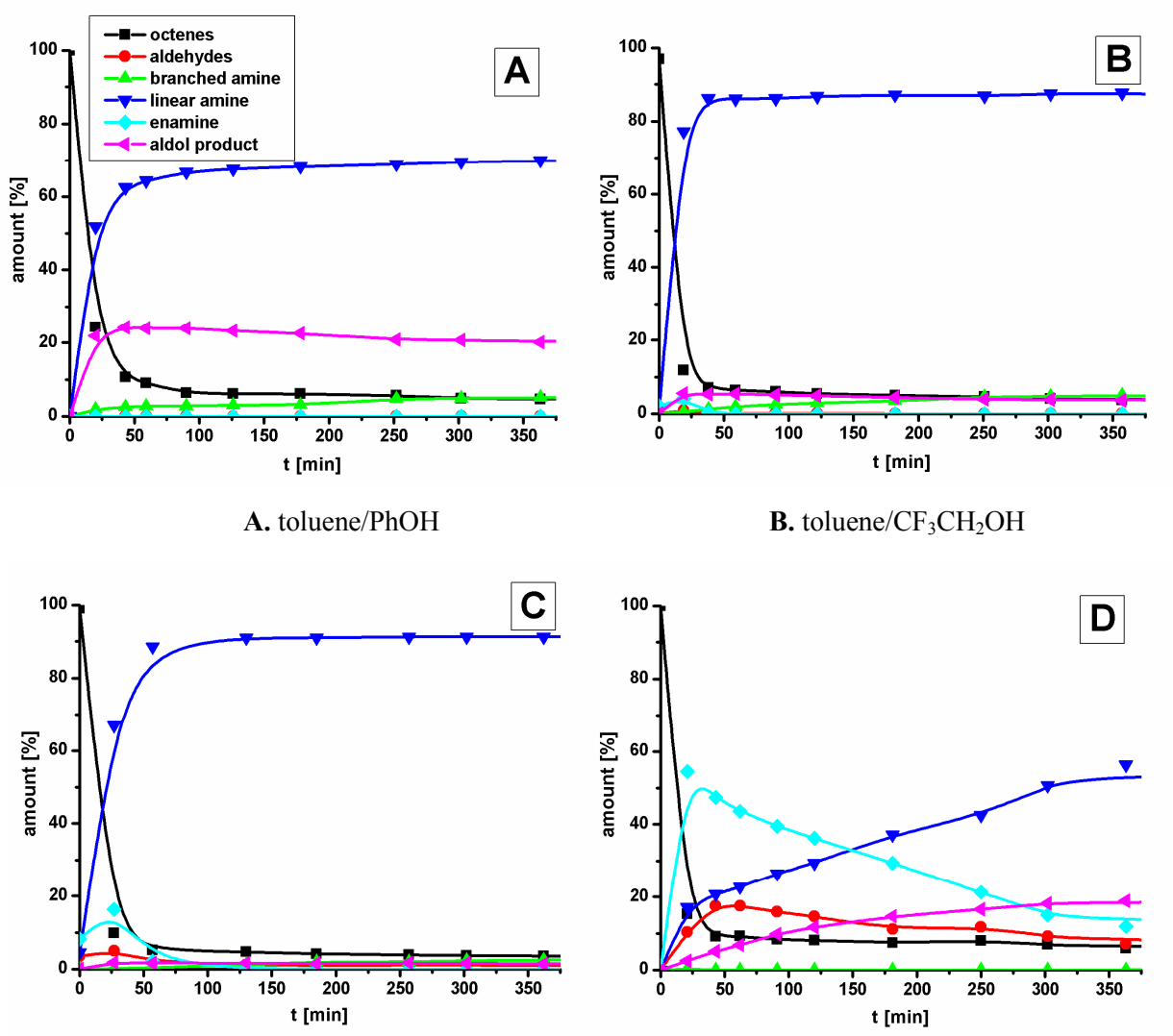
Especially the HAM in toluene/PhOH (Fig. 3.7A) and toluene/*t*BuOH (Fig. 3.7D) showed completely different behaviour. The reaction in the more acidic solvent (PhOH) showed high activity for both hydroformylation and hydrogenation, but also led to the formation of large amounts of aldol condensation products and to the branched amine. In contrast, the reaction in toluene/*t*BuOH displayed a similar activity for the hydroformylation, but a noticeably decreased hydrogenation activity, which can be derived from the accumulation of intermediates during the reaction. However, the branched amine was not detected at all in this case! The results for the HAM in toluene/trifluoroethanol (Fig. 3.7B), or toluene/EtOH (Fig. 3.7C) confirmed this trend. The reaction in toluene/CF_3CH_2OH displays the highest activity and a rough calculation of substrate consumption and linear amine formation in time from the product distribution graph showed that the TOF at 20% conversion is approximately 10000 h^{-1}.



Conditions: 1-octene 10 mmol, piperidine 11 mmol, toluene/*n*BuOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, *T* = 110°C, S/Rh = 1000, L/Rh = 4.0, *p*(CO/H_2 (1:2)) = 36 bar (cold pressure), 800 rpm, L = **6**.

Figure 3.6: *Product distribution during the Rh-catalysed HAM reaction of 1-octene with DPX (**6**) in toluene/nBuOH.*

Apparently, acidic alcohols (PhOH, trifluoroethanol) facilitate the aldol condensation reaction and give rise to high activities, also for the hydroformylation of internal alkenes, which consequently leads to decreased regio- and chemoselectivity (Tab. 3.4; entry 1 and 2). On the contrary, the less acidic alcohol (*t*BuOH) proves to give slightly lower activities, mainly in the hydrogenation reaction, resulting in an accumulation of the intermediate aldehyde and enamine, which in turn also leads to the formation of the aldol condensation products, but to a superb l/b ratio (Tab. 3.4; entry 6). The reactions in toluene/EtOH and toluene/*n*BuOH exhibit the best results, leading to excellent activities as well as regio- and chemoselectivities (Tab. 3.4; entry 4 and 5). Moreover, the HAM in toluene/*n*BuOH leads to an increased isomerisation rate, which is an important feature when carrying out regioselective HAM reactions starting from internal alkenes.



A. toluene/PhOH

B. toluene/CF_3CH_2OH

C. toluene/EtOH

D. toluene/*t*BuOH

Conditions: 1-octene 10 mmol, piperidine 11 mmol, toluene/alcohol (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm, L = DPX (**6**).

Figure 3.7: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 1-octene in different toluene/alcohol mixtures.*

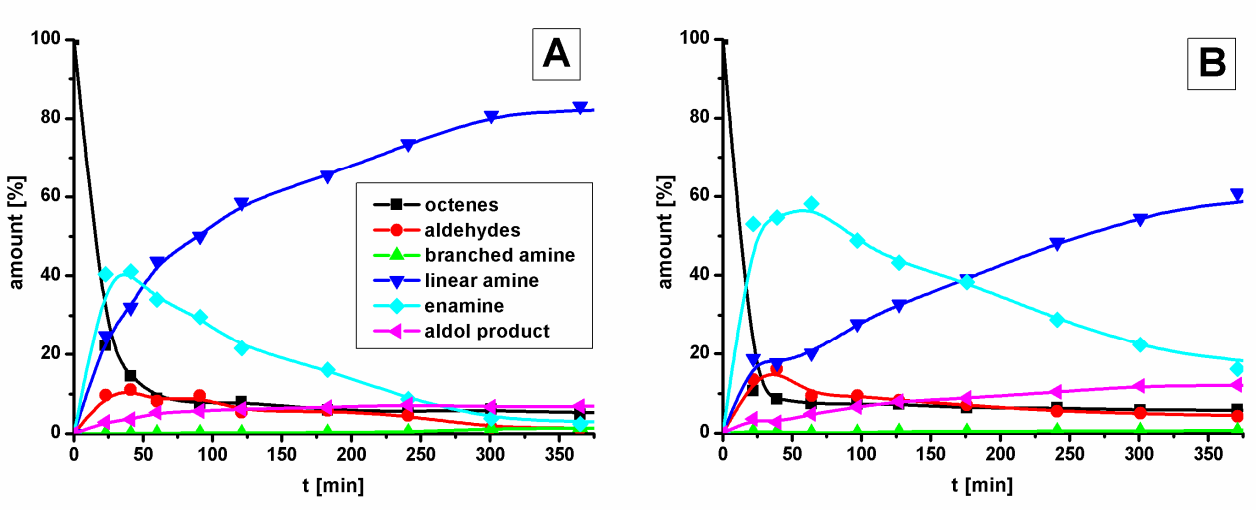
Table 3.4 *Results of Rh-catalysed hydroaminomethylation reactions in different solvent mixtures.*[a]

Entry	Alcohol	pKa	t [min]	Isomerised octene [%]	Conv. [%][b]	Sel.(amine) [%]	l/b
1	PhOH	10	60	7.6	91.1	73.5	24
2	CF_3CH_2OH	12.4	45	6.0	93.0	94.0	75
3	MeOH	15.5	60	4.2	94.7	99.0	51
4	EtOH	16.0	60	4.2	94.8	93.8	231
5	*n*BuOH	16.9	60	10.5	88.5	98.9	160
6	*t*BuOH	18.2	65	8.1	90.8	25.1	>500

[a] 1-octene 10 mmol, piperidine 11 mmol, toluene/alcohol 8 mL, S/Rh = 1100, L/Rh = 4.0, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm, L = DPX (**6**). [b] $Conv._{(1\text{-octene})}$ = ~ 99 %.

In order to investigate to which extent the ratio alcohol/toluene in the solvent mixtures influences the involved equilibria, the ratio toluene/MeOH was varied. The alcohol in the solvent mixture probably has a large influence on the equilibrium between the cationic and neutral Rh species, which might have a clear effect on the catalytic results. Figure 3.8 shows the product distributions of a HAM reaction with the Rh/**6** in toluene/MeOH (3:1) (Fig. 3.8A) and toluene/MeOH (7:1), respectively (Fig. 3.8B). There is a clear difference between these two graphs and an even larger difference can be observed in comparison to the product distribution in toluene/MeOH (1:1) (Fig. 3.4A). Obviously, the hydrogenation activity was decreased, while the condensation reaction was faster upon lowering the relative amount of alcohol present in the solvent mixture, leading to an accumulation of the intermediate enamine. Furthermore, the rate of isomerisation is increased upon lowering the quantity of alcohol in the solvent mixture, although the formation of branched amine was not increased. Evidently, the effect of the alcohol in the solvent mixture is not catalytic since the activity changes upon increasing the amount of alcohol. Probably, the change in solvent polarity upon changing the ratio toluene/MeOH has an additional influence on all equilibria involved, leading to the observed change in selectivity and activity.

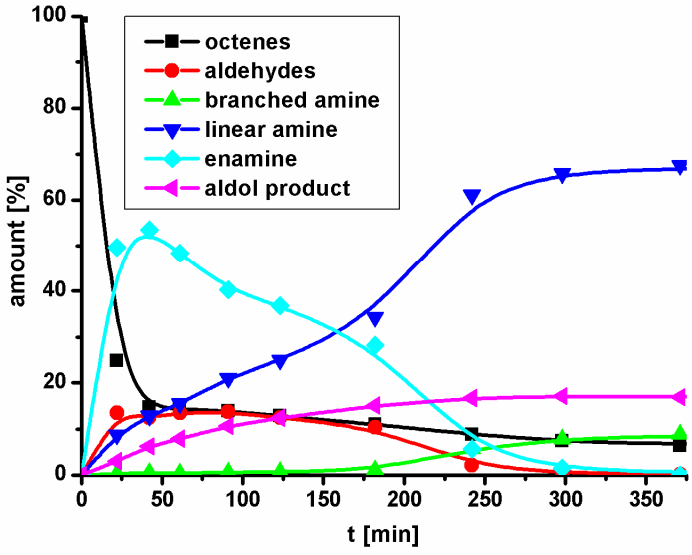
Most likely, the basic piperidine has an opposite effect on the equilibria in comparison to the more acidic alcohols, leading to increased hydroformylation rates, but decreased hydrogenation rates. This means that the effect of the piperidine will prevail when smaller amounts of alcohol are present in comparison to the piperidine. Addition of a larger excess of piperidine in the HAM will give comparable results as reactions in which smaller amounts of alcohol were present (*vide supra*). Figure 3.9 shows the product distribution in such a system. Indeed, this product distribution is very well comparable to Figure 3.8A and B, which means that the alcohol counteracts the effect that piperidine has on the equilibria. Also here, an increased isomerisation was observed, which confirms the assumption that the relative acidity of the system has an influence on hydrogenation, hydroformylation and isomerisation rates. Most probably, all equilibria involved in the HAM reaction are influenced by piperidine and the alcohol in the solvent mixture, which generates a very complicated system.



A. toluene/MeOH (3:1) **B.** toluene/MeOH (7:1)

Conditions: 1-octene 10 mmol, piperidine 11 mmol, toluene/MeOH 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm, L = DPX (**6**).

Figure 3.8: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 1-octene in different toluene/MeOH mixtures.*



Conditions: 1-octene 10 mmol, piperidine 23 mmol, toluene/MeOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm, L = DPX (**6**).

Figure 3.9: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 1-octene using a large excess of piperidine.*

3.5 Conclusions

In this chapter, it has been shown that performing Rh-catalysed hydroaminomethylation reactions with novel π-acidic ligand, Rh/**6**, leads to outstanding activities with turnover frequencies of up to 6200 h^{-1} as well as to excellent selectivities with l/b ratios exceeding 200. The corresponding catalyst Rh/**8**, which is expected to have even better π-acceptor properties shows similar activity, but a dramatic decrease in selectivity in comparison to Rh/**6**. Furthermore, it has been demonstrated that the pKa value of the alcohol used in the solvent mixture has a profound effect on the performance of the catalyst systems. By using acidic media, the activity is enhanced, while less acidic media increase the regio- and chemoselectivity, as well as the degree of double bond isomerisation. This last characteristic is an interesting feature in the hydroaminomethylation of internal alkenes. In addition, the relative amounts of piperidine and alcohol in the HAM reaction have a clear effect on the resulting product distribution, thus on the equilibria and reaction rates involved. The foregoing means that the reaction can be directed by the choice and composition of the solvent mixture.

3.6 Experimental section

All air- or water-sensitive operations were performed using standard Schlenk techniques under purified argon atmosphere. Toluene, tetrahydrofuran, *n*-hexane, and dichloromethane were purified over custom-made alumina columns. Piperidine, triethylamine, methanol, ethanol, *tert*-butanol, trifluoroethanol, phenol and *n*-butanol were distilled from CaH_2. 1-Octene was purified by distillation from Na_2SO_4 and percolation over neutral activated alumina. Solvents and substrates were degassed prior to use. Chemicals were purchased from Acros Chimica, Merck KGaA, Biosolve B.V. and Aldrich Chemical Co. $[Rh(cod)_2]BF_4$ was synthesised according to a literature procedure. Hydrogen gas (99.999%), carbon monoxide gas (99.997%) and synthesis gas (CO (99.9%)/H_2 (99.9996%); 1:2) was purchased from Praxair. Gas chromatographic analyses were run on a Shimadzu GC-17A instrument and an Ultra 2 column (25 m x 0.2 mm). GC/MS analyses were conducted on a HP6890 chromatograph with a Leco Pegasus II mass spectrometer and a DB-1MS column (10 m x 0.1 mm). NMR data were recorded on a Varian Oxford 200 MHz and a Varian Mercury Vx 400 MHz NMR spectrometer. Matrix assisted laser desorption/ionization mass – time of flight (MALDI-TOF) analyses were obtained using a PerSeptive Biosystems Voyager-DE PRO spectrometer using an α-cyanohydroxycinnamic acid matrix. Elemental analysis was performed on a Perkin Elmer 2400 series II CHNS/O Analyser.

General procedure for hydroaminomethylation experiments

Reactions were performed in 75-mL home-made stainless steel autoclaves. In a typical experiment, the autoclave was charged with a solution of $[Rh(cod)_2]BF_4$ (3.2 mg, 7.9 μmol; cod = 1,5-cyclooctadiene) and the appropriate bidentate ligand (32.4 μmol) in 8 mL of a toluene/alcohol mixture. Alkene (10 mmol) and piperidine (11 mmol) were added and the autoclave was purged three times using CO (p = 12 bar) to remove the remaining argon from the autoclave. Subsequently, the autoclave was pressurised with CO and H_2 to the desired pressure and heated to reaction temperature. After a certain reaction time, the autoclave was cooled to r.t. in an ice bath and the gases were vented. The reaction mixture was removed from the autoclave, filtered over alumina and analysed by GC and GC/MS. In these analyses the l/b-ratio could be determined within an error range of 0.05%.

In order to determine the product distribution in hydroaminomethylation, samples were taken during the reaction in toluene/alcohol mixtures in an autoclave equipped with a tailor-made sample-system that consisted of a capillary with an inner diameter of 0.25 mm, combined with a two-way and a three-way valve. The sample was taken by means of the pressure inside the autoclave. The connection between the two valves was used to collect the sample (estimated volume 50 μL). By opening the two-way valve the sample was collected in a GC vial, diluted with MeOH/Et_2O and analysed by GC(-MS).

General procedure for the determination of the turnover frequency (TOF)

Typical hydroaminomethylation experiments were performed in the AMTEC SPR16 parallel reactors as described above with 8 mL total volume and toluene/*n*BuOH as the solvent. After loading the autoclave, a preformation with synthesis gas (CO/H_2 1:2), was performed. After addition of the substrate, the reaction was started. During the reaction the gas uptake was monitored by a mass flow controller and the turnover frequency was calculated from the originating gas uptake curve at 20% conversion.

Synthesis of chlorodipyrrolylphosphine (5)[32]

A solution of triethylamine (5.1 g; 50.4 mmol) and pyrrole (2.9 g; 43.6 mmol) in THF (25 mL) was added to a cooled (–40°C) and stirred solution of PCl_3 (3.0 g; 21.8 mmol) in THF (10 mL). The reaction mixture was warmed to r.t. overnight and the triethylamine salts were filtered off using a filter cannula. The solvent was removed in vacuo and the coloured liquid residue was distilled to yield the pure product as a colourless liquid in 91% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.15 (t, 4H, *J* = 1.8 Hz), 6.46 (d, 4H, *J* = 2.0 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 103.55 ppm.

Synthesis of 4,5-bis[(dipyrrolyl)phosphino]-3,6-di-*tert*-butyl-9,9-dimethylxanthene (6)

4,5-Dibromo-3,6-di-*tert*-butyl-9,9-dimethylxanthene (3.0 g; 6.2 mmol) was dissolved in THF (100 mL) and cooled to –60°C. *n*-Butyllithium (2.5 M in hexanes; 6.3 mL; 15.8 mmol) was added dropwise to this solution

leading to a turbid reaction mixture, which was slowly warmed to r.t. and stirred for 2 hours. The reaction mixture was cooled to –60°C again and chlorodipyrrolylphosphine (**5**) (15.6 mmol) in toluene (20 mL) was added dropwise to the reaction mixture. The reaction mixture was slowly warmed to r.t., stirred overnight and filtered over neutral alumina. The solvent was evaporated in vacuo, dichloromethane (100 mL) was added and after two hours stirring, the suspension was filtered and the solvent removed in vacuo. *n*-Hexane was added (120 mL), stirred overnight, filtered and the solvent was removed in vacuo yielding a yellowish/off-white, sticky solid. The solid was dissolved in MeOH (~80 mL) at reflux and slowly cooled to r.t.. Afterwards, it was stored at 4°C overnight, yielding the pure product as white crystals in 22% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (s, 2H), 6.72 (s, 8H), 6.24 (t, 8H, *J* = 2.2 Hz), 6.14 (s, 2H), 1.56 (s, 6H), 1.08 (s, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.56, 129.13, 126.51, 125.40, 124.28, 124.13, 111.84, 110.34, 34.52, 32.26, 31.43, 29.27 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 67.59 ppm. Anal. Calc. for $C_{39}H_{44}N_4OP_2$: C, 72.43; H, 6.86; N, 8.66. Found: C, 72.34; H, 6.97; N, 4.76.

Synthesis of 4,5-dihydroxy-3,6-di-tert butyl-9,9-dimethylxanthene (7)

4,5-Dibromo-3,6-di-*tert*-butyl-9,9-dimethylxanthene (5.1 g; 10.7 mmol) was dissolved in 150 mL THF and cooled to –60°C. *n*-Butyllithium (2.5 M in hexanes; 6.3 mL; 15.8 mmol) was added dropwise to this solution and the reaction mixture was stirred for 2 hours while it was slowly warmed to r.t.. After this, the reaction mixture was cooled on an ice/salt bath and BH_3 (100 mL, 1.0 M in THF) was added dropwise to the reaction mixture. After addition, the reaction mixture was allowed to warm to r.t. under stirring overnight. The turbid reaction mixture was cooled on an ice bath and hydrolysed very carefully with 26 mL H_2O yielding a clear solution with a small amount of white precipitate. 3 M KOH (32 mL) and 30% H_2O_2 (11.0 g) were added subsequently and the reaction mixture was heated to reflux (~78°C) for 2 hours. After cooling the solution to r.t., the reaction mixture was acidified to pH 4–5 with 18% HCl. After phase separation, the organic phase was extracted twice with 75 mL brine, dried over Na_2SO_4 and the solvent was removed in vacuo. MeOH (65 mL) was added to the residue, stirred for 30 minutes and the solid was filtered off. The solvent from the filtrate was removed in vacuo yielding the product as an off-white solid in 83% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.31 (b, 2H), 7.04 (s, 2H), 6.84 (s, 2H), 1.65 (s, 6H), 1.32 (m, 18H) ppm. ^{13}C NMR (100 MHz, acetone-d_6): δ = 146.02, 144.26, 135.70, 129.78, 113.16, 111.07, 34.15, 31.99, 30.87, 28.36 ppm.

Synthesis of bis-[(dipyrrolyl)phosphamidato]-3,6-di-*tert*-butyl-9,9-dimethylxanthene (8)

4,5-Dihydroxy-3,6-di-*tert*-butyl-9,9-dimethylxanthene (**7**) (2.0 g; 5.6 mmol) and triethylamine (1.4 g; 13.8 mmol) were dissolved in THF (20 mL) and added dropwise to a stirred solution of chlorodipyrrolylphosphine (**5**) (11.9 mmol) in THF (20 mL) yielding a yellowish suspension overnight. The reaction mixture was filtered over neutral alumina and washed with THF (3 x 25 mL). The solvent was evaporated and an off-white solid was obtained. Toluene (20 mL) was added to this solid and the mixture was filtered once more over neutral alumina and washed with toluene (2 x 20 mL) to remove the remaining

salts. The product was obtained as an off-white solid after removal of the solvent in vacuo in 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (s, 2H), 7.08 (s, 8H), 6.61 (s, 2H), 6.32 (s, 8H), 1.63 (s, 6H), 1.24 (s, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.06, 139.53, 139.42, 130.89, 121.85, 121.77, 120.17, 118.15, 116.51, 116.41, 112.47, 112.45, 112.43, 34.89, 32.45, 31.65, 31.28 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 107.73 ppm. Anal. Calc. for $C_{39}H_{44}N_4O_3P_2$: C, 69.01; H, 6.53; N, 8.25. Found: C, 70.40; H, 6.74; N, 7.45.

Synthesis of 4,5-bis[di(methylindolyl)phosphino]-3,6-di-*tert*-butyl-9,9-dimethylxanthene (9)

3-Methylindole (2.9 g; 22.1 mmol) and triethylamine (3.0 g; 29.6 mmol) were dissolved in THF (20 mL) and added to a cooled (–40°C) PCl_3 (1.5g; 10.9 mmol) solution in THF (30 mL) under vigorous stirring. The reaction mixture was stirred overnight at r.t.. Salts were filtered off with a filter cannula yielding a colourless chlorodi(methylindolyl)phosphine solution.

4,5-Dibromo-3,6-di-*tert*-butyl-9,9-dimethylxanthene (1.9 g; 4.0 mmol) was dissolved in THF (70 mL) and cooled to –60°C. *n*-Butyllithium (2.5 M in hexanes; 3.8 mL; 9.5 mmol) was added dropwise to this solution, which was slowly warmed to r.t. and stirred for 2 hours.

The reaction mixture was cooled to –60°C again and the chlorodi(methylindolyl)phosphine solution was added dropwise to the reaction mixture. The reaction mixture was slowly warmed to r.t., stirred overnight and filtered over neutral alumina. The solvent was evaporated in vacuo, dichloromethane (50 mL) was added and after two hours stirring, the suspension was filtered and the solvent removed in vacuo. *n*-Hexane was added (60 mL), stirred overnight, filtered and the solvent was removed in vacuo. The residue was dissolved in MeOH (~100 mL) at reflux and slowly cooled to r.t., filtered and the procedure was repeated with the solid residue, yielding the product as a white solid in 14% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (m, 4H), 7.42 (t, 4H), 7.23 (m, 8H), 6.97 (s, 2H), 6.94 (s, 2H), 6.81 (m, 4H), 2.26 (s, 6H), 1.65 (s, 12H), 1.33 (s, 18H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 63.97 ppm. MALDI-TOF-MS: (m/z) calcd.: 902.42; observed: 903.16 ($M+H^+$).

Synthesis of bis-[di(methylindolyl)phosphamidato]-3,6-di-*tert*-butyl-9,9-dimethylxanthene (10)

3-Methylindole (0.8 g; 6.1 mmol) and triethylamine (3.2 g; 31.6 mmol) were dissolved in toluene (20 mL) and cooled to –60°C. PCl_3 (0.5 g; 3.6 mmol) was added dropwise to this solution and the reaction mixture was reacted overnight at 45°C. 4,5-Dihydroxy-3,6-di-*tert*-butyl-9,9-dimethylxanthene (**7**) (0.5 g; 1.4 mmol) was dissolved in toluene (20 mL), added dropwise to the stirred reaction mixture and heated to reflux overnight. The reaction mixture was filtered over neutral alumina and washed with toluene (3 x 20 mL). The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (20 mL), filtered once more over neutral alumina and washed with CH_2Cl_2 (3 x 20 mL). The product was obtained as a white solid after removal of the solvent in vacuo in 38% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, 4H), 7.38 (d, 4H), 7.18 (s, 4H), 7.06 (m, 10H), 6.51 (s, 2H), 2.02 (s, 6H), 1.54 (s, 12H), 1.03 (s, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.90, 139.82, 139.33, 131.72, 130.87, 123.77, 122.64, 120.86, 118.90, 117.84, 116.53, 112.09, 34.88,

34.30, 31.59, 9.54 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 104.91 ppm. Anal. Calc. for $C_{59}H_{60}N_4O_3P_2$: C, 75.78; H, 6.47; N, 5.99. Found: C, 76.27; H, 6.73; N, 5.47.

Synthesis of 2,2',6,6'-Tetramethoxybiphenyl (11)

1,3-Dimethoxybenzene (3.3 g; 23.9 mmol) was dissolved in dry Et_2O (50 mL) and the solution was cooled with an ice bath. *n*-Butyllithium (2.5 M in hexanes; 13 mL; 32.5 mmol) was added dropwise to this solution and the reaction mixture was stirred overnight while it was slowly warmed to r.t.. Cu(I)I (4.6 g; 24.2 mmol) was added in small portions to the turbid reaction mixture, which turned deep purple. The reaction mixture was stirred for 2.5 h at r.t. and 2-iodo-1,3-dimethoxybenzene (5.0 g; 18.9 mmol) was added in small portions. Directly after this, pyridine (50 mL) was added. The dark reaction mixture was stirred for 1 h and heated to 60°C while Et_2O was distilled off. The remaining reaction mixture was reacted at 50°C for 3.5 days under inert atmosphere, cooled to r.t., poured onto ice, acidified with HCl (4 M), filtered over a Büchner funnel and dried at 40°C in vacuo. The product was precipitated by addition of a concentrated CH_2Cl_2 solution to EtOH, to yield the pure product as a white solid in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, 2H, *J* = 8.3 Hz), 6.66 (d, 4H, *J* = 8.4 Hz), 3.72 (s, 12H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.42, 128.71, 112.43, 104.47, 56.16 ppm.

Synthesis of 2,2',6,6'-Tetrahydroxybiphenyl (12)

2,2',6,6'-Tetramethoxybiphenyl (**11**; 4.6 g; 16.8 mmol) was dissolved in dry CH_2Cl_2 (65 mL) and the solution was cooled to –78°C. Boron tribromide (~1.0 M in CH_2Cl_2; 68 mL; 68 mmol) was added dropwise to this solution and the reaction mixture was slowly warmed to r.t.. H_2O (75 mL) was added very carefully and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The pure product was obtained as a white solid after precipitation from warm EtOH in 71% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.52 (b, 4H), 7.02 (t, 2H, *J* = 8.0 Hz), 6.47 (d, 4H, *J* = 8.1 Hz) ppm. ^{13}C NMR (100 MHz, acetone-d_6): δ = 156.47, 129.04, 107.91, 107.00 ppm.

Synthesis of Tetraphos ligand (13)

Tetrahydroxybiphenyl (**12**; 1.5 g; 6.9 mmol) and triethylamine (4.0 g; 37.8 mmol) were dissolved in THF (100 mL) and added dropwise to a solution of chlorodipyrrolylphosphine (**5**) (6.0 g; 30.9 mmol) in THF (75 mL). The reaction mixture was stirred for 6 hours at r.t. and filtered over neutral alumina. The solvent was evaporated and the residue was dissolved in toluene, filtered and dried in vacuo. The product was obtained as a white solid in 30% yield after crystallisation from THF/acetone by slowly cooling and evaporating the solvent. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, 2H, *J* = 8.2 Hz), 6.65 (m, 16H), 6.63 (s, 4H), 6.22 (t, 16H, *J* = 2.2 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.52, 130.58, 121.13, 117.84, 115.03, 112.42 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 107.93 ppm. Anal. Calc. for $C_{44}H_{38}N_8O_4P_4$: C, 60.97; H, 4.42; N, 12.93. Found: C, 60.66; H, 4.09; N, 13.04.

Synthesis of 2,2'-Dihydroxy-3,3'-di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl (14)

2,4-Di-*tert*-butyl-phenol (11.3 g; 54.8 mmol) was dissolved in MeOH (300 mL). KOH (11.1 g; 197.8 mmol) and $K_3Fe(CN)_6$ (18.3 g; 55.6 mmol) dissolved in H_2O (350 mL) was added dropwise to this solution in 1 h. The solution was stirred for 2 h and H_2O (150 mL) was added giving a yellow suspension which was stirred for an additional hour. The suspension was extracted with EtOAc (1 x 500, 1 x 300 and 1 x 200 mL) and Et_2O (1 x 150 mL). The organic layers were washed with 200 mL brine, dried over Na_2SO_4, filtered over alumina and the solvent was evaporated, yielding a yellow solid. This solid was stirred in acetonitrile (100 mL) and filtered, yielding the pure product as a white solid in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, 2H, *J* = 2.4 Hz), 7.13 (d, 2H, *J* = 2.3 Hz), 5.22 (s, 2H), 1.46 (s, 18H), 1.32 (s, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.21, 145.88, 138.93, 123.20, 115.26, 111.76, 55.73, 35.17, 29.49 ppm. Anal. Calc. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.92; H, 8.44.

Synthesis of 2,2'-Dihydroxy-3,3',5,5'-tetra-*tert*-butyl-1,1'-biphenyl (15)

3-*Tert*-butyl-4-hydroxyanisole (21.8 g; 120.9 mmol) was dissolved in MeOH (550 mL). KOH (23.7 g; 422.4 mmol) and $K_3Fe(CN)_6$ (39.7 g; 120.6 mmol) dissolved in H_2O (550 mL) was added dropwise to this solution in 1 h. The reaction mixture was stirred overnight, H_2O (250 mL) was added, stirred for another 2 h and extracted with EtOAc (3 x 400 mL) and Et_2O (1 x 300 mL). The organic layers were washed with 400 mL brine, dried over $MgSO_4$ and the solvent was evaporated, yielding a yellow-orange solid. This solid was stirred in *n*-hexane (60 mL) and filtered, yielding the pure product as a white solid in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (d, 2H, *J* = 2.8 Hz), 6.63 (d, 2H, *J* = 3.1 Hz), 5.02 (s, 2H), 3.78 (s, 6H), 1.43 (s, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.45, 150.41, 147.08, 146.80, 141.70, 141.60, 126.44, 125.44, 124.90, 124.54, 122.87, 122.73, 121.41, 121.26, 112.02, 111.71, 35.26, 34.99, 34.73, 34.13, 31.57, 31.54, 31.41, 30.15 ppm. Anal. Calc. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.92; H, 8.44.

Synthesis of 1,1'-Biphenyl-2,2'-diyl-3,3'-di-*tert*-butyl-5,5'-dimethoxy-bis(dipyrrolylphosphoramidate) (16)

2,2'-Dihydroxy-3,3'-di-*tert*-butyl-5,5'-dimethoxy-1,1'-biphenyl (**14**; 1.7 g; 4.7 mmol) was dissolved in THF (50 mL) and added dropwise to an ice bath cooled solution of chlorodipyrrolylphosphine (**5**; 1.9 g; 9.6 mmol) and triethylamine (3.0 g; 29.6 mmol) in THF (100 mL). The reaction mixture was stirred overnight and the solvent was removed in vacuo. The residue was dissolved in toluene (75 mL), filtered over neutral alumina, washed with toluene (1 x 25 mL) and the solvent was evaporated to yield the product as a white solid in 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (s, 2H), 6.77 (m, 8H), 6.62 (s, 2H), 6.19 (m, 8H), 3.79 (s, 3H), 3.48 (s, 3H), 1.41 (s, 9H), 1.15 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.67, 155.43, 152.17, 146.69, 146.56, 129.04, 128.57, 128.49, 128.23, 121.88, 121.70, 121.20, 121.04, 115.56, 115.38, 112.21, 112.16, 55.65, 55.08, 35.16, 34.94, 29.86, 29.51 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 107.10 ppm. Anal. Calc. for $C_{38}H_{44}N_4O_4P_2$: C, 66.85; H, 6.50; N, 8.21. Found: C, 67.54; H, 6.58; N, 7.37.

Synthesis of 1,1'-Biphenyl-2,2'-diyl-3,3'5,5'-tetra-*tert*-butyl-bis(dipyrrolylphosphoramidate) (17)

2,2'-Dihydroxy-3,3',5,5'-tetra-*tert*-butyl-dimethoxy-1,1'-biphenyl (**15**; 2.0 g; 4.9 mmol) was dissolved in THF (50 mL) and added dropwise to an ice bath cooled solution of chlorodipyrrolylphosphine (**5**; 2.1 g; 10.6 mmol) and triethylamine (3.0 g; 29.6 mmol) in THF (100 mL). The reaction mixture was stirred overnight and the solvent was removed in vacuo. The residue was dissolved in toluene (75 mL), filtered over neutral alumina, washed with toluene (1 x 25 mL) and the solvent was evaporated to yield the product as a white solid in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (s, 2H), 7.14 (s, 2H), 6.64 (m, 8H), 6.19 (m, 8H), 1.38 (s, 18H), 1.17 (s, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.77, 142.99, 136.23, 125.28, 124.84, 122.31, 35.21, 34.46, 31.64, 29.67 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 107.03 ppm.

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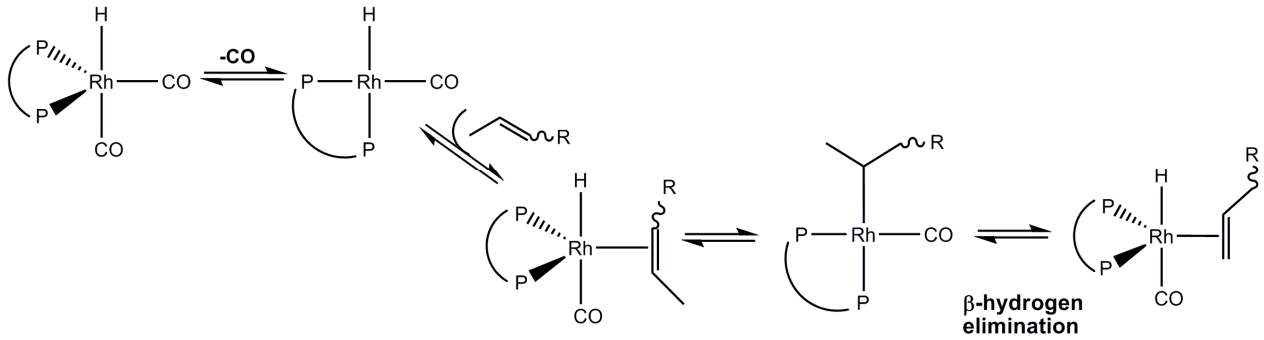
4

Hydroaminomethylation of internal alkenes using xanthene-based amino-functionalised ligands

In this chapter, the Rh-catalysed hydroaminomethylation of internal alkenes towards linear amines is described using amino-functionalised ligands. Bulky and rigid substituents were introduced and the ligand backbone was functionalised with a (bis-indolyl)phosphine moiety in order to increase the regioselectivity in this process. However, bis-[(dipyrrolyl)phosphino]xanthene, introduced in Chapter 3, again turned out to be the best performing ligand in combination with rhodium. Although the reaction is slower than in case of n-alkenes, catalyst activities are still reasonably high. The influence of catalyst preformation, reaction temperature, solvent mixture, and syngas ratio are described. Furthermore, the effect of adding a monodentate ligand (phosphines or phosphites) to the reaction mixture was investigated. Interestingly, the regioselectivity could be increased considerably by addition of triphenylphosphine to the catalyst mixture, which can be explained by changing the isomerisation rate related to β-hydrogen elimination in this particular way.



This work will be submitted for publication:
B. Hamers, E. Kosciusko-Morizet, C. Müller, D. Vogt, *manuscript in preparation.*

4.1 Introduction

Regioselective catalytic transformations of internal alkenes towards the corresponding linear products are relatively difficult, because of the necessary isomerisation step to the *n*-alkene prior to the actual catalytic reaction. In fact, this is still one of the challenges in homogeneous catalysis, which might explain why reports on regioselective hydroformylation and especially regioselective hydroaminomethylation of internal alkenes to linear aldehydes and linear amines, respectively, are rather rare in literature. In order to achieve the selective formation of linear aldehydes from internal alkenes, a high isomerisation activity to the thermodynamically less stable terminal alkene (thermodynamically equilibrium octenes: only 2% *n*-octene) is required in combination with the selective formation of the linear rhodium alkyl complex. As a consequence, β-hydrogen elimination should be preferred over the migratory insertion of CO into the rhodium alkyl bond of a branched species (Fig. 4.1). Although the terminal alkene is less stable, alkene addition is much faster than for internal alkenes. This means that the small amount of terminal alkene that is formed by isomerisation will react faster and a selective catalyst will show preferential migratory insertion of CO with the resulting linear rhodium alkyl intermediate, leading to the formation of linear aldehydes. Reaction conditions promoting the alkene isomerisation can be used in order to improve the regioselectivity. These isomerising reaction conditions are high reaction temperature and low pressure. Upon using low pressure, the CO insertion into the Rh-alkyl bond will be less favourable, leading to a higher degree of β-hydrogen elimination and consequently a higher degree of isomerisation. Upon increasing the temperature, not only the activity for isomerisation will increase, but also the activity for hydroformylation of both the internal and the terminal alkenes increases. However, upon applying higher temperatures in the hydroformylation of internal alkenes, improved l/b ratios are generally observed. This means that up to a certain temperature the increase in isomerisation rate is larger than the increase in hydroformylation rate. Nevertheless, the hydroformylation rate for internal alkenes will also increase upon raising the temperature, leading to an optimum in l/b ratio at a particular temperature.

Since the regioselectivity is determined in the hydroformylation step of the hydroaminomethylation reaction, comparable catalyst systems can be used in order to obtain regioselective formation of linear amines in the hydroaminomethylation as well. However, it should be noted that reaction conditions and composition of the reaction mixture are different for hydroaminomethylations, which has its impact on the involved equilibria and possibly leads to different catalytic outcome.

One of the earlier examples of regioselective hydroformylation of internal alkenes to linear aldehydes is described in a patent from DuPont and DSM.[1] In this example, the synthesis and application of a bulky diphosphite ligand bearing electron withdrawing substituents on the binaphthyl backbone was described. Crucial for the necessary isomerisation to take place seem to be these electron withdrawing groups on the ligand backbone. A high regioselectivity (up to 97% of the linear aldehyde) was obtained in the hydroformylation of *n*-alkenes and methyl-3-pentenoate.

Another ligand which has been used in the Rh-catalysed isomerisation/hydroformylation reactions is the so-called BIPHEPHOS (compound **4**, Chapter 3), which is a biphenol-based diphosphite ligand. This class of ligands was synthesised and patented in the 1980s by Union Carbide.[2,3] Hydroformylation of internal alkenes, even 4-octene, was performed with Rh/BIPHEPHOS in the groups of Behr and Kragl leading to selectivities of up to 90% for the linear aldehyde.[4-6]

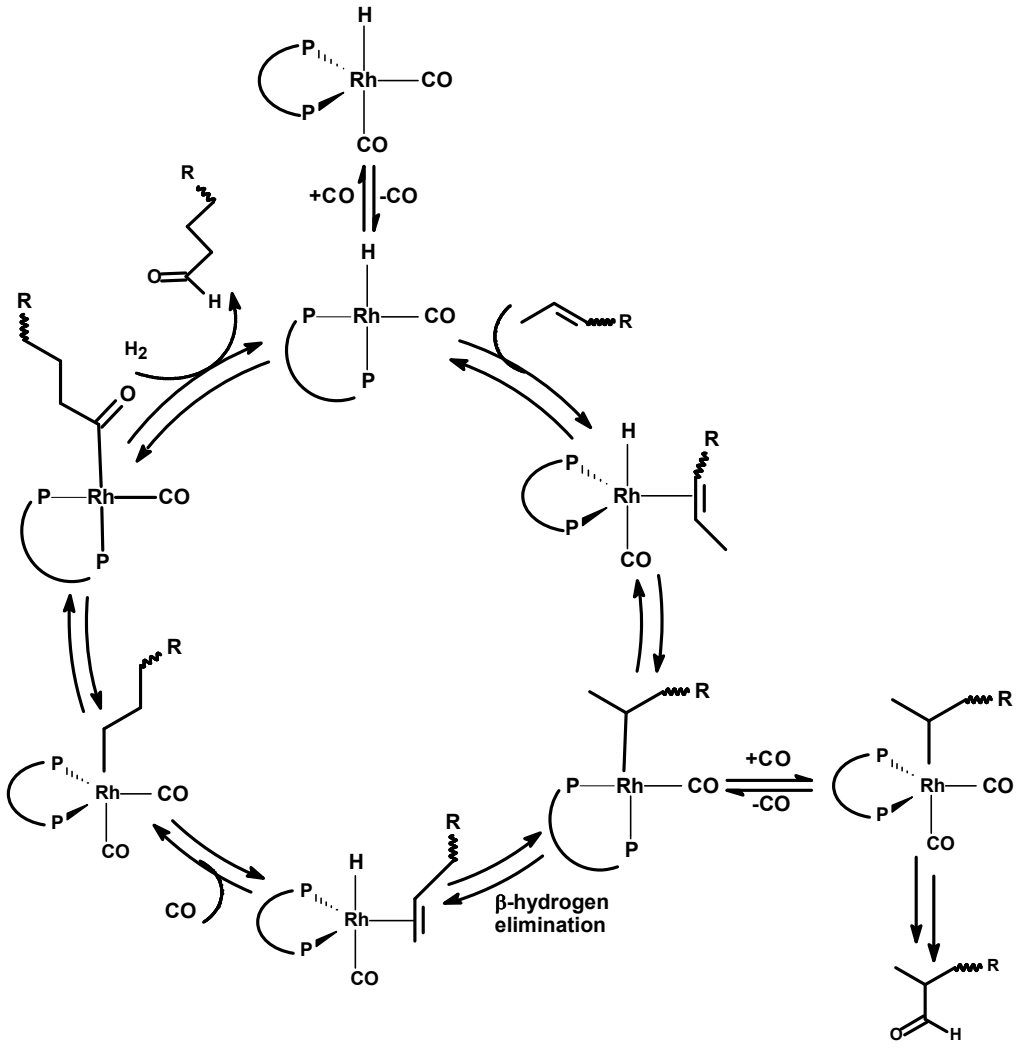


Figure 4.1: *Proposed catalytic cycle for the Rh-catalysed hydroformylation, including an isomerisation step by β-hydrogen elimination.*

Two more recent examples of regioselective hydroformylation of internal alkenes were reported by the groups of Beller and Zhang. Beller and co-workers described the Rh-catalysed hydroformylation of 2-alkenes in a biphasic water/organic solvent system using the water-soluble ligand BINAS (sulphonated NAPHOS; compound **1**; Fig. 4.2).[7-9] Selectivities to the linear aldehyde of up to 99% were reported under isomerising conditions (high temperature, low CO partial pressure). However, the reaction is relatively slow and the yield of aldehydes is only moderate. Zhang and co-workers demonstrated the regioselective Rh-catalysed hydroformylation of 2-octene with the Tetraphos ligand (compound **13**, Chapter 3) with linearities of up to 98% and fast reaction.[10]

More important are the high regioselectivities (up to 96% of linear aldehyde) in the hydroformylation of butene mixtures and Raffinate II under isomerising hydroformylation conditions, described in the patent literature by BASF.[11-13] The applied catalysts, also based on diaminoylphosphine-functionalised xanthene and biphenyl backbones and thus comparable to the ligands introduced in Chapter 3, appear to be promising in the hydroformylation of internal alkenes.

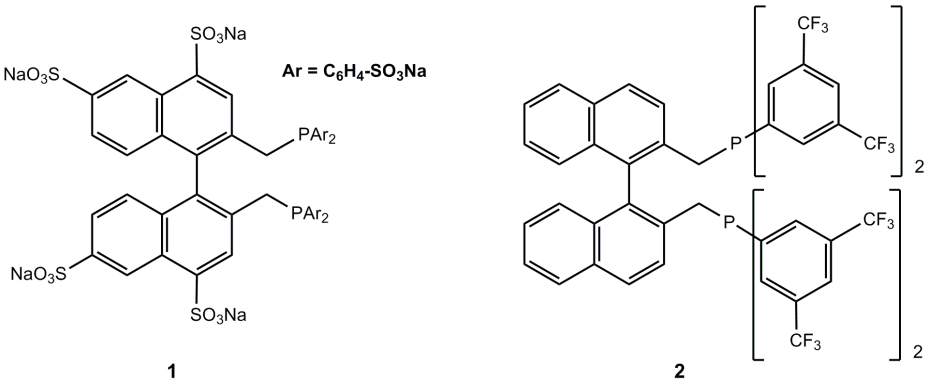


Figure 4.2: *Illustration of phosphine ligands used in the regioselective Rh-catalysed hydroformylation reactions of internal alkenes.* ***1****: BINAS, Herrmann*[9, 14]*;* ***2****: IPHOS, Beller.*[15]

Further literature examples concerning the hydroformylation of internal alkenes with a range of different ligands show varying results in terms of linearity of the resulting aldehydes (ranging from 40 to 90%).[16-19] The small number of literature examples confirms the difficulty of the regioselective hydroformylation of internal alkenes. On the other hand, the regioselective hydroformylation of internal alkenes towards a single branched aldehyde is also rather complex. Only a few literature examples can be found addressing this topic.[20,21] Especially, the phosphabarrelene-rhodium system is very promising in this respect since the hydroformylation of internal alkenes is virtually free of isomerisation upon using this ligand.[22] A similar effect was

observed in the Rh-catalysed hydroformylation of 2-butene upon using a phosphinine-based ligand leading to very high regioselectivities of the branched aldehyde.[23] In this particular reaction, 97% of the branched aldehyde 2-methylbutanal was obtained. Furthermore, a similar effect could be obtained in the HAM of 2-octene using a phosphabarrelene-based ligand.[24] After 20 hours reaction time, the reaction was complete and a 1:1 mixture of branched aldehydes and branched amines was obtained. 2-Methyl-octylpiperidine was detected as the main amine product (63% of all amines) and 2-methyloctanal and 2-ethylheptanal were observed as the main aldehyde products (88% of all aldehydes; ~1:1).

Although literature examples of regioselective hydroformylation towards linear aldehydes are already scarce, examples of regioselective hydroaminomethylations are even less common. Beller and co-workers described the hydroaminomethylation of several 2-alkenes with varying secondary amines in a Rh/IPHOS (compound **2**, Fig. 4.2) catalyst system.[25] Regioselectivities between 71% and 94% for the linear amine were obtained, but conversions were only moderate in most cases after 24 hours reaction time while the chemoselectivity to the amine was good. In a joint publication from the groups of Van Leeuwen and Beller, the regioselective hydroaminomethylation of internal alkenes with several secondary amines using a Rh/Xantphenoxaphos (compound **2**, Chapter 3) system was reported.[26] Conversions after 16 hours reaction time were in general good with linearities of up to 96%. Most interestingly, the hydroaminomethylation of an industrial mixture of octenes with piperidine gave 81% of the linear amine product. Obviously, the isomerising HAM has only been investigated with phosphine ligands. Phosphite ligands could give higher isomerisation rates, but their stability towards hydrolysis is a major problem in this reaction.

In this chapter, the hydroaminomethylation of internal alkenes will be investigated. It is expected that in combination with rhodium, the π-acceptor ligands introduced in Chapter 3 show improved isomerisation rates in comparison to the commonly used basic phosphines. The higher electrophilicity of the metal centre might lead to increased activities of the alkyl species towards β-hydrogen elimination. Ligands with more bulky and rigid substituents on the xanthene backbone in addition to the ligands that were already used in Chapter 3 will be introduced in order to improve the aspect of regioselectivity of the catalyst. Furthermore, the reaction conditions will be varied in order to study their effect on the resulting regioselectivity in these catalytic systems.

4.2 Synthesis of substituents and ligands

The synthesis of the rigid moieties depicted in Figure 4.3 was attempted in order to prepare the corresponding chloro(diaminoyl)phosphines which will be used to functionalise the xanthene backbone. Apart from compound **6**, the synthesis of these compounds was successful.

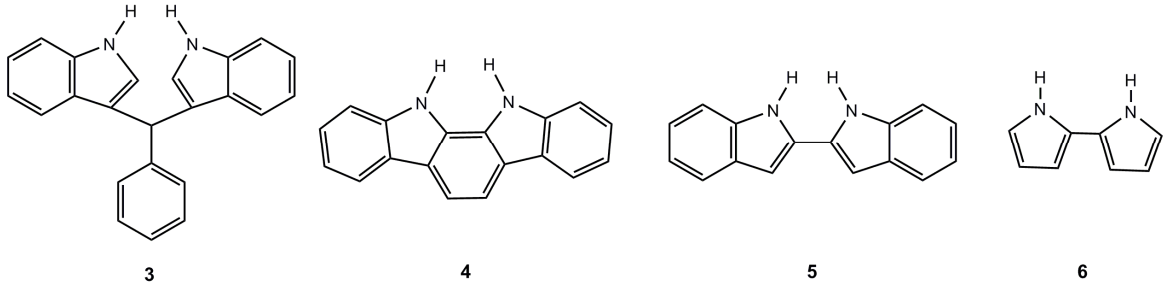
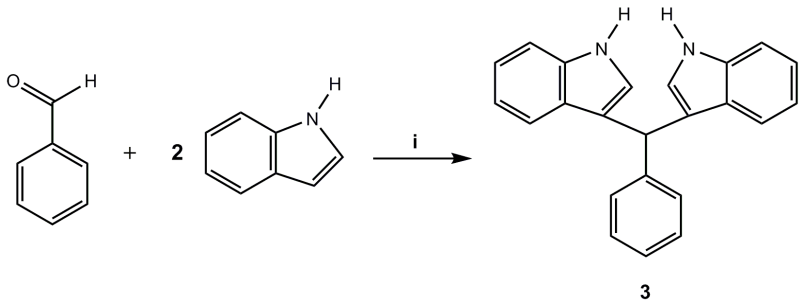


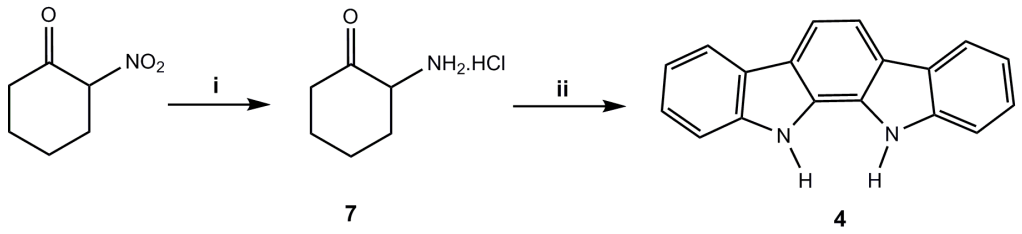
Figure 4.3: *Illustration of rigid moieties for the functionalisation of the ligand backbone.*

Various methods for the synthesis of compound **3** *via* condensation of indole with a carbonyl compound are described in literature. One possible route is a solvent-free reaction of benzaldehyde and indole at room temperature with $SiCl_4$ as the catalyst giving the product in good yield after a short work-up procedure.[27] The same reaction is also possible without a catalyst in a protic solvent (H_2O, MeOH) although reported yields were lower in this case and reaction times are relatively long.[28] An interesting and comparable route is the condensation of benzaldehyde and indole in an EtOH/H_2O mixture with picric acid as the catalyst. The yield in this reaction is high, but a yellow-coloured compound was obtained which turned out to be very difficult to purify *via* column chromatography or recrystallization. For that reason, the synthesis was carried out following a solvent-free procedure with trityl chloride (chlorotriphenylmethane) as the catalyst (Scheme 4.1).[29] This reaction was performed in a mortar at room temperature with a reaction time of 15 minutes. The reaction mixture was subsequently extracted with EtOAc, filtered over a silica column and the solvent was evaporated yielding the pure product **3** in good yield (~70%).



Scheme 4.1: *Synthetic route to bis(indolyl)methane **3**: i) $ClCPh_3$, r.t., 15 min.*

Compounds similar to **4** are very interesting because they exhibit biological activities, such as antifungal,[30] antimicrobial[31] and antitumor activity.[30,32] Consequently, many synthetic procedures for these compounds can be found in literature. The synthesis of **4** starts from 2-aminocyclohexanone hydrochloride and phenylhydrazine hydrochloride using the Fischer indole synthesis (Scheme 4.2).[33] Since 2-aminocyclohexanone is not commercially available, it had to be synthesised first. One possible route is the bromination of cyclohexanone, followed by amination. After several attempts to brominate cyclohexanone with *N*-bromosuccinimide[34-36] and *p*-toluenesulfonic acid as a catalyst,[37] the reaction was successful yielding 2-bromocyclohexanone. However, the amination turned out to be troublesome. Meanwhile, an attempt was made to reduce 2-nitrocyclohexanone to the corresponding aminocyclohexanone by using Pd/C in a formic acid/hydrochloric acid mixture.[38] Although the product was formed, the yields were disappointing. A very successful alternative turned out to be the reduction of nitrocyclohexanone by Pt-S/C in ethanol with a small amount of HCl under hydrogen atmosphere (Scheme 4.2).[39] The pure product **7** was obtained after precipitation with acetone and simple filtration. Furthermore, the formation of the amine could be followed by using the Kaiser test for amines.[40]



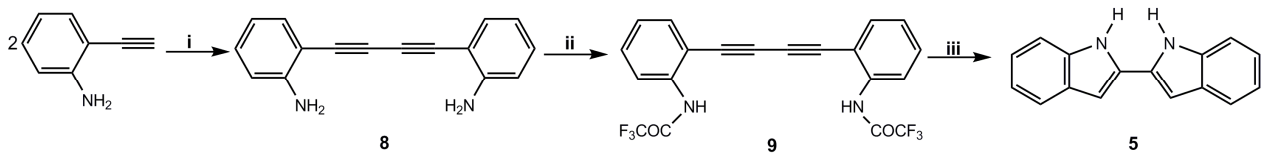
Scheme 4.2: *Synthetic route to indolocarbazole **4**: i) Pt-S/C (5 w%), EtOH/HCl, H_2, 55ºC, 16 h; ii) Phenylhydrazine·HCl, AcOH/TFA, 110ºC, 16 h.*

Compound **7** was dissolved in an acidic medium (95% HOAc/TFA) together with phenylhydrazine hydrochloride and refluxed for 16 hours (Scheme 4.2). The acidity of the solution determines the yield in many cases according to literature and the aforementioned mixture of acids was reported to give satisfactory results.[41] After cooling to room temperature, hydrolysis with water, filtration and washing with water, the pure product **4** was obtained.

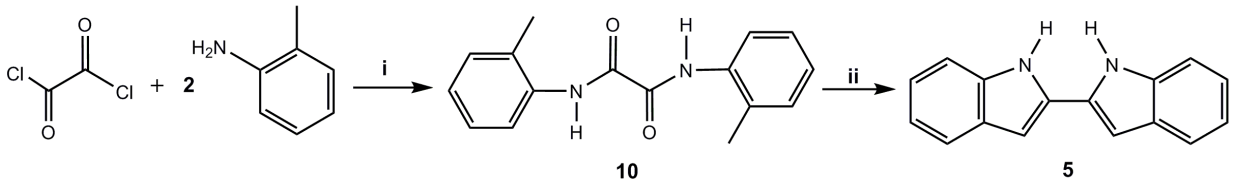
Synthesis of compounds comparable to **5** has been described in literature in various ways.[42-48] First the diacetylene **8** was synthesised by coupling 2-ethynylaniline in pyridine/MeOH with [$Cu(OAc)_2$] as the catalyst (Scheme 4.3).[47] The diacetylene product **8** was quantitatively obtained after tedious work-up. The synthesis of the intended bis-indolyl compound was attempted by

reacting the diacetylene **8** with KH in NMP. However, the bis-indolyl product was not obtained. In a new attempt, diacetylene **8** was reacted to the bis-trifluoroacetanilide **9** first, by reacting the diacetylene **8** with trifluoroacetic anhydride (TFAA).[46,49] Compound **9** was then ring-closed with $[Pd(PPh_3)_4]$ in the presence of a base to yield the crude bis-indolyl compound **5** (Scheme 4.3), which turned out to be difficult to purify by column chromatography.[48] Another possible reaction path (Scheme 4.4) *via* reaction of *o*-toluidine and oxalylchloride in THF with addition of triethylamine was attempted. This reaction yields bis-tolyloxamide **10** in moderate yield as a white crystalline powder, which can be ring-closed with K/*t*BuOH giving the bis-indolyl compound **5** at higher temperature.

Although the synthesis of **6** and analogous structures by coupling of pyrroles with phenyliodine bis(trifluoroacetate) has been described in literature[50-52] the reaction turned out to be rather troublesome and only very small amounts of the desired bipyrrole product were obtained.



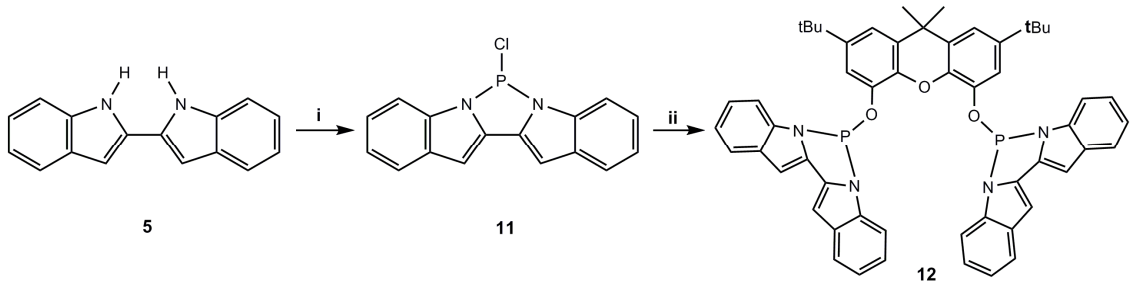
Scheme 4.3: *Synthetic route to bis-indolyl* ***5****: i) [Cu(OAc)₂·H₂O], MeOH/pyridine, r.t., 46 h; ii) TFAA, 2,6-di-tert-butyl-4-methylpyridine, CH_2Cl_2, r.t., 40 h; iii) K_2CO_3, [Pd(PPh₃)₄], acetonitrile, 85ºC, 26 h.*



Scheme 4.4: *Alternative synthetic route to bis-indolyl* ***5****: i) Et_3N, THF, 0ºC/r.t., 16 h; ii) K, tert-butanol, 50ºC/16 h, 90ºC/2 h, 190ºC/4 h, 220ºC/16 h.*

The synthesised moieties **3-5** were further reacted with PCl_3 in order to prepare the corresponding chloro(bis-aminoyl)phosphines. However, reaction of **3** and **4** with PCl_3 only gave the mono-functionalised phosphorus compounds. Apparently, the spatial arrangement in these molecules was not appropriate for the formation of the desired chloro(bis-aminoyl)phosphines. Fortunately, the chloro(bis-indolyl)phosphine **11** could be formed from **5** by reaction with PCl_3. This compound was used to functionalise the xanthene backbone following the standard procedure introduced in Chapter 3 to yield ligand **12** (Scheme 4.5). Compound **12** was obtained as an

off-white solid in 17% yield and was fully characterised by elemental analysis and ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The ligand shows a signal at $\delta = 78.9$ ppm in the ^{31}P NMR spectrum.



Scheme 4.5: *Synthetic route to ligand **12**: i) Et_3N, PCl_3, THF, –60ºC/reflux, 16 h; ii) dihydroxyxanthene, 0ºC/reflux, 16 h.*

4.3 Catalysis

4.3.1 Xanthene with rigid, bulky substituents

Ligand **12** was first investigated in a Rh-catalysed HAM reaction of 1-octene in order to make a comparison to the performance of ligand **13**, which turned out to be a very good ligand in the HAM of *n*-alkenes as shown in Chapter 3. Unfortunately, the results obtained in this reaction were not very promising (Fig. 4.5). The rate of hydroformylation was high, but large amounts of the intermediate aldehyde and enamine were obtained, which means that the hydrogenation rate was low in comparison to the hydroformylation rate. Consequently, this leads to the formation of large amounts of aldol condensation product. Apparently, catalysts based on the more bulky ligands behave very efficiently in the hydroformylation reaction, but seem to be much less efficient in the hydrogenation step of the HAM. Furthermore, large amounts of intermediate products are still present at the moment the conversion of 1-octene is almost complete (t = 100 min.). In order to convert these to the desired product, the reaction time has to be prolonged which means that from this point on, also large amounts of the branched aldehyde and thus branched amine are formed. However, relatively large amounts of the branched aldehyde and amine could be observed also before t = 100 minutes. Apparently, this catalyst is not very regioselective and because of the accumulation of intermediates also not very chemoselective. As the isomerisation rate is also very low with this catalyst system, **13** was used for all further investigations on the Rh-catalysed hydroaminomethylation of internal alkenes.

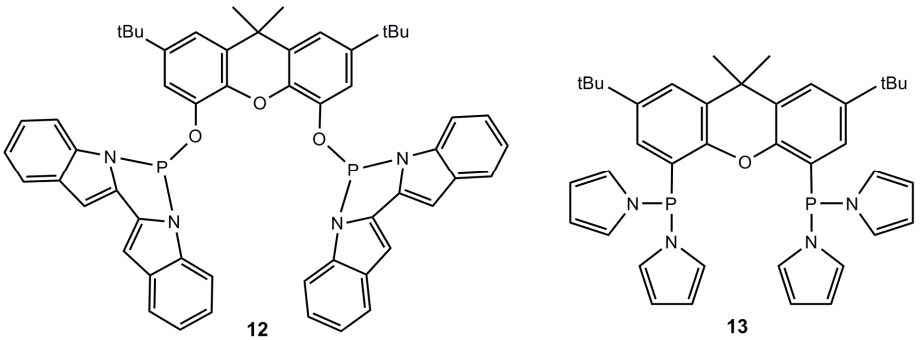
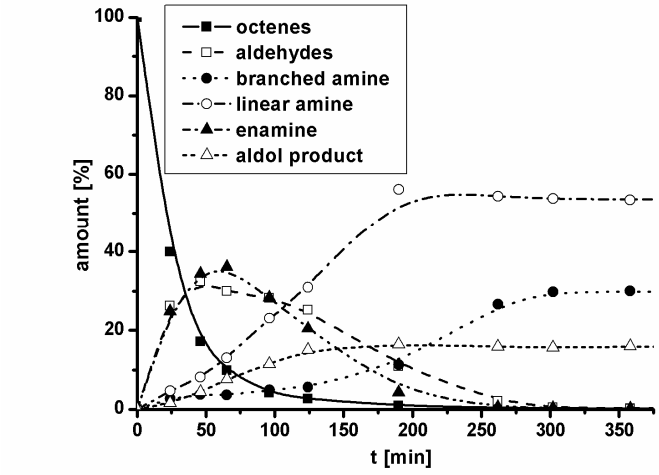


Figure 4.4: *Illustration of ligands **12** and **13**.*



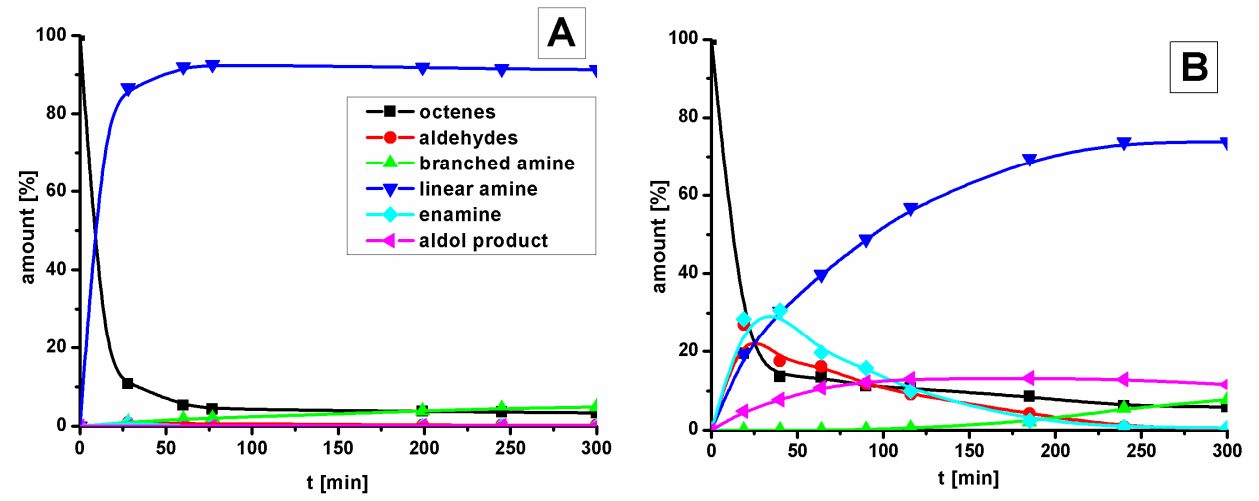
Conditions: 1-octene 9 mmol, piperidine 10 mmol, toluene/MeOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm, L = **12**.

Figure 4.5: *Product distribution during the hydroaminomethylation reaction of 1-octene using ligand **12**.*

4.3.2 Synthesis gas ratio

In the isomerisation/hydroformylation, typical isomerisation conditions are high temperatures and low syngas pressures in order to promote the β-hydrogen elimination, leading to a higher isomerisation rate. In general, there will be an optimum in the applied reaction temperature and pressure since by increasing the temperature, also the activity towards hydroformylation of internal alkenes increases. In the hydroaminomethylation reaction a comparable mechanism applies. However, in this reaction, a high H_2 partial pressure and a higher reaction temperature are desirable for the hydrogenation of the intermediate enamine. For that reason, a syngas ratio of 1:6 is applied in the isomerisation/HAM in order to increase the isomerisation rate without loss of hydrogenation activity.

The effect of the different syngas ratio was first monitored in the Rh-catalysed HAM of 1-octene with DPX (**13**) as the ligand (Fig. 4.6). The reaction using a syngas ratio of 1:6 (Fig. 4.6B) shows completely different behaviour compared to the stoichiometric syngas ratio (1:2). Apparently, the hydrogenation activity is slightly decreased, leading to a slower formation of the linear amine and formation of aldol condensation product. Most importantly, however, is the observation that the amount of isomerisation is considerably increased upon changing the syngas ratio to 1:6. This is an important requirement for the hydroaminomethylation of internal alkenes.

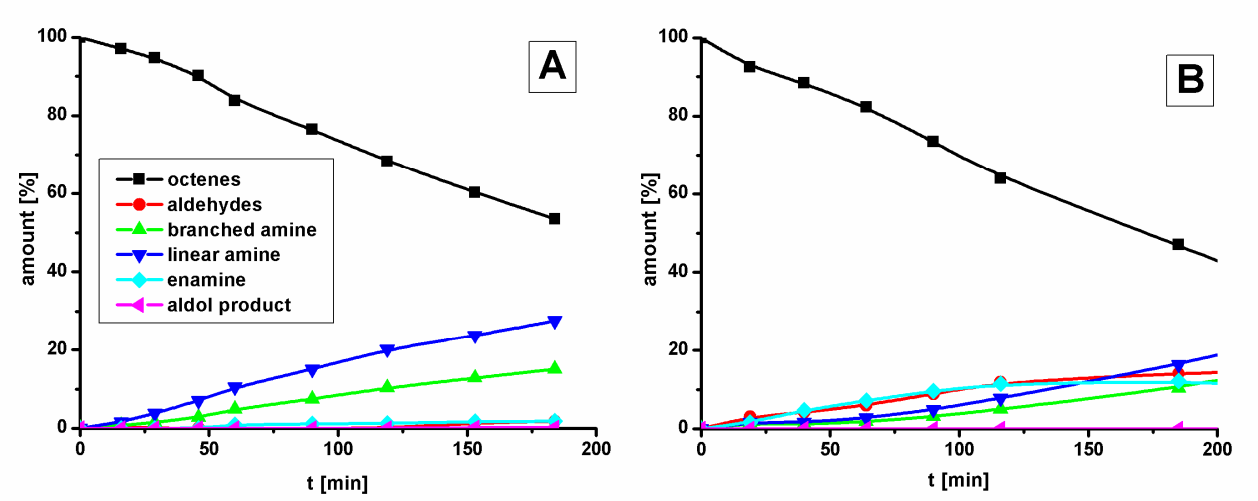


A. CO/H_2 = 1:2 **B.** CO/H_2 = 1:6

Conditions: 1-octene 9 mmol, piperidine 10 mmol, toluene/MeOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2)$ = 36 bar (cold pressure), 800 rpm, L = **13**.

Figure 4.6: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 1-octene at two different syngas ratios.*

A comparable result was obtained by changing the syngas ratio from 1:2 to 1:6 in the HAM of 2-octene (Fig. 4.7). The consumption of octenes was slower in comparison to the HAM of 1-octene, since the hydroformylation activity for internal alkenes and the isomerisation rates are much lower than in the hydroformylation of 1-alkenes. However, no significant difference in 2-octene conversion was observed upon changing the syngas ratio. Analogous to the reaction of 1-octene with a syngas ratio of 1:6, the intermediate reaction products could be detected in the HAM of 2-octene (Fig. 4.7B). Unfortunately, the regioselectivity was not increased in this reaction and the l/b ratio turned out to be 1.3, which is in the same range as in the reaction with a syngas ratio of 1:2. The effect of the syngas ratio seems to be relatively small in the HAM of 2-octene in toluene/MeOH.



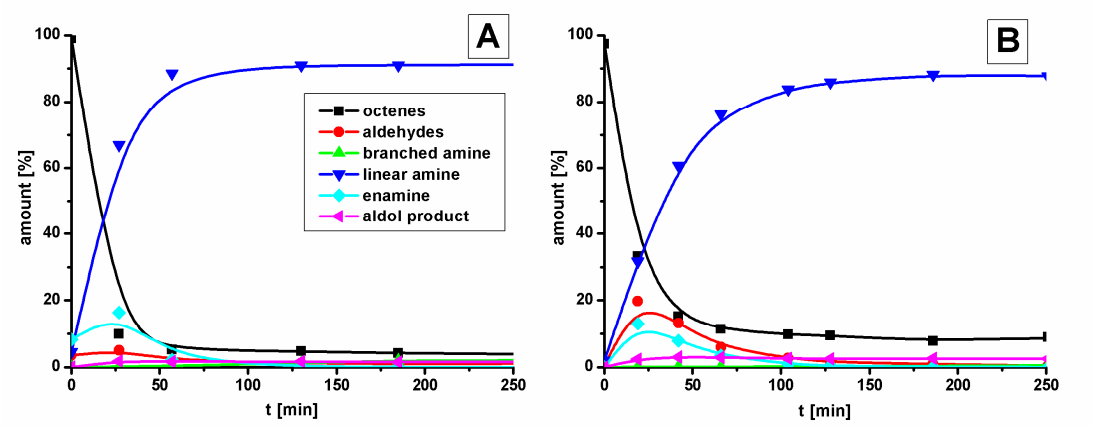
A. CO/H_2 = 1:2 **B.** CO/H_2 = 1:6

Conditions: 2-octene 9 mmol, piperidine 10 mmol, toluene/MeOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2)$ = 36 bar (cold pressure), 800 rpm, L = **13**.

Figure 4.7: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 2-octene with two different syngas ratios.*

4.3.3 Effect of catalyst preformation

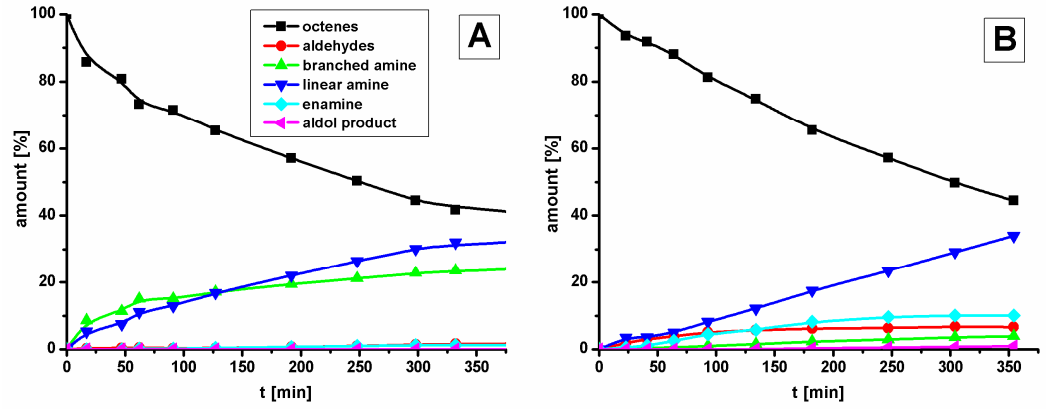
Commonly in hydroformylation reactions, the catalyst resting state is preformed from the Rh-precursor under syngas pressure, before the substrate is added. In this way, catalyst activity and selectivity are improved. For that reason, the effect of catalyst preformation was investigated in the HAM reaction. Especially since the HAM of 2-alkenes is relatively slow, this might give a different result. First, preformation was investigated in the HAM of 1-octene (Fig. 4.8B). The reactor was pressurised to 36 bar (CO/H_2; room temperature) and heated to 110°C, which are the actual reaction conditions. A preformation time of 30 minutes was applied. After the preformation, the substrates, 1-octene and piperidine, were added to the catalyst solution by opening the valve of the dropping funnel, which has an open gas connection to the actual reaction chamber. It was observed that both hydroformylation and hydrogenation activity were slightly decreased compared to the HAM without preformation. However, the chemoselectivity was not influenced by the preformation. Interestingly, the rate of isomerisation turned out to be increased in the HAM with preformation and in addition to this, the regioselectivity was increased. The l/b ratio actually increased from 40 without preformation to 85 with preformation after a reaction time of 6 hours. Upon shorter reaction times the differences were even larger and a l/b ratio larger than 500 was observed in the HAM with preformation after 1 hour reaction time (98% conversion of 1-octene). A similar effect could be observed upon using different toluene/alcohol solvent mixtures.



A. No preformation **B.** Preformation: 30 min.

Conditions: 1-octene 9 mmol, piperidine 10 mmol, toluene/EtOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:2)) = 36 bar (cold pressure), 800 rpm, L = **13**.

Figure 4.8: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 1-octene with and without catalyst preformation.*



A. No preformation **B.** Preformation: 30 min.

Conditions: 2-octene 9 mmol, piperidine 10 mmol, toluene/*n*BuOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:6)) = 36 bar (cold pressure), 800 rpm, L = **13**.

Figure 4.9: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 2-octene with and without catalyst preformation.*

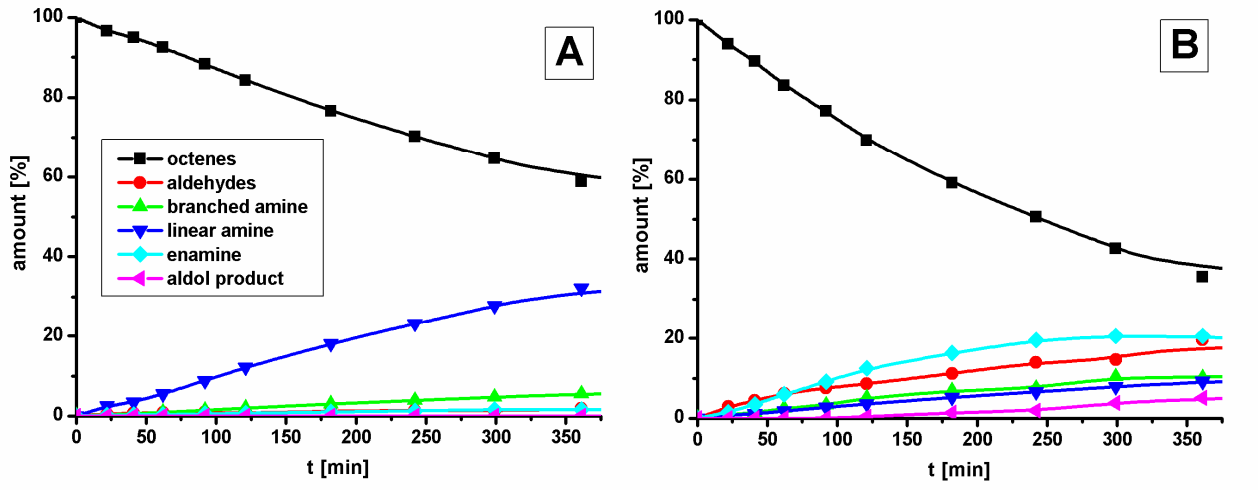
A comparable effect was observed in the HAM of 2-octene upon preformation (Fig. 4.9). The chemoselectivity in the reaction without preformation was good, but the regioselectivity was poor and a l/b ratio of only 1.4 (59% linear amine) was observed after 6 hours reaction time (Fig. 4.9A). The HAM with preformation was somewhat slower, leading to a small accumulation of intermediates, but the regioselectivity was increased to 8.8 (~90% linear amine) after 6 hours reaction (~56% conversion; Fig. 4.9B). Moreover, the regioselectivity increased slightly during the reaction. Evidently, a short preformation turns out to drastically improve the regioselectivity in the HAM of 2-octene. Thus, all further HAM reactions of 2-octene were performed with a short preformation.

4.3.4 Influence of reaction temperature

It is well-known that the reaction temperature can have a large influence, especially on activity, but also on regio- and chemoselectivity. Therefore, the influence of the reaction temperature on the activity and selectivity in the HAM reaction of 2-octene was investigated (Fig. 4.10). Reactions were performed at 100°C and 120°C and the results were compared to the HAM at 110°C (Fig. 4.9B).

As expected, the reaction rate increases upon increasing the reaction temperature. However, not only the activity is influenced, a large difference in selectivity could be observed as well for the various reaction temperatures. At T = 100°C, the chemoselectivity turned out to be excellent and no accumulation of intermediates could be observed (Fig. 4.10A). Furthermore, the regioselectivity was rather good at this temperature, although the calculated l/b ratio of 5.8 (~85% linear amine) after 6 hours reaction time was not as good as the reported regioselectivity at T = 110°C (*vide supra*). At T = 120°C, relatively large amounts of accumulated intermediates were observed, which also led to the formation of aldol condensation product, thus lowering the chemoselectivity (Fig. 4.10B). The regioselectivity at this reaction temperature was very poor and more branched than linear amine was formed.

From these results, it can be concluded that a reaction temperature of 110°C seems to be the optimum in terms of regio- and chemoselecitivity in the HAM of 2-octene.



A. T = 100°C **B.** T = 120°C

Conditions: 2-octene 9 mmol, piperidine 10 mmol, toluene/*n*BuOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:6)) = 36 bar (cold pressure), 800 rpm, preformation = 30 min., L = **13**.

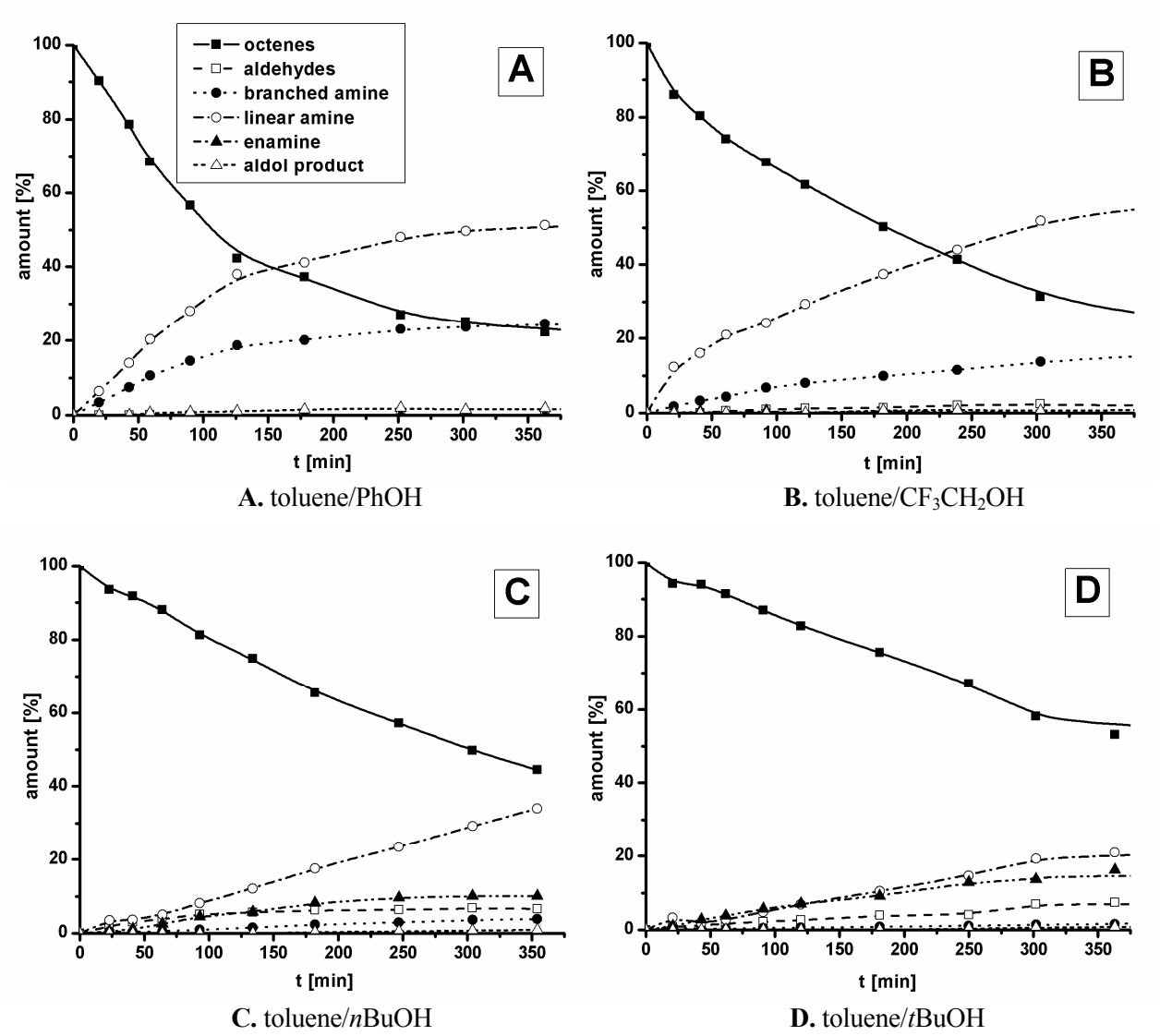
Figure 4.10: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 2-octene at two different reaction temperatures.*

4.3.5 Solvent influence

It has been shown already in Chapters 2 and 3 that the solvent mixture composition can have a large influence on the activity and selectivity in HAM reactions. Moreover, the alcohol in the solvent mixture seems to have an effect on the isomerisation rate, which is of great importance in the HAM reaction of internal alkenes. Therefore, HAM reactions of 2-octene were performed in several solvent mixtures by varying the nature of the alcohol (Fig. 4.11).

The reactions in the solvent mixtures containing the more acidic phenol (Fig. 4.11A) and trifluoroethanol (Fig. 4.11B), were comparable. Both reactions were fast in comparison to the reaction in toluene/*n*BuOH. Chemoselectivity was very high and no accumulation of intermediates could be observed. However, the hydroformylation activity for the internal alkene was also high, which led to the formation of both linear and branched amine in large amounts. The l/b ratio in the reaction in toluene/PhOH turned out to be 2.1 (~68% linear amine) after 6 hours reaction time (~78% conversion), while the l/b ratio in the reaction in toluene/CF_3CH_2OH turned out to be 3.8 (~79% linear amine) after 6 hours (~72% conversion). In both cases the conversion was almost complete (~90% conversion) after 20 hours reaction time while the l/b ratio turned out to be almost constant after 5-6 hours reaction. The reaction in toluene/*t*BuOH was slower than in toluene/*n*BuOH, which is in accordance with the earlier observed trend. An accumulation of intermediates was observed and the hydrogenation activity seemed to be decreased, leading to a slow formation of amine. Most interestingly, the regioselectivity was very high in this solvent mixture with a l/b ratio of 14.7 (~94% linear amine) after 6 hours reaction time. However, the l/b ratio decreased to 7.2 (~88% linear amine) after 20 hours reaction time, which is still an acceptable regioselectivity in the HAM of 2-octene.

A similar trend as observed in Chapter 3 could be noticed in HAM reactions of 2-octene upon changing the solvent mixture composition. The more acidic alcohols increase the activity, but lead to a low regioselectivity while the less acidic alcohols show a decreased activity, but an increased regioselectivity in HAM reactions of 2-octene. Chemoselectivity is very high for all different solvent mixtures and it turns out that the reaction in toluene/*n*BuOH is a good compromise for reaching good activities and selectivities.



A. toluene/PhOH **B.** toluene/CF_3CH_2OH

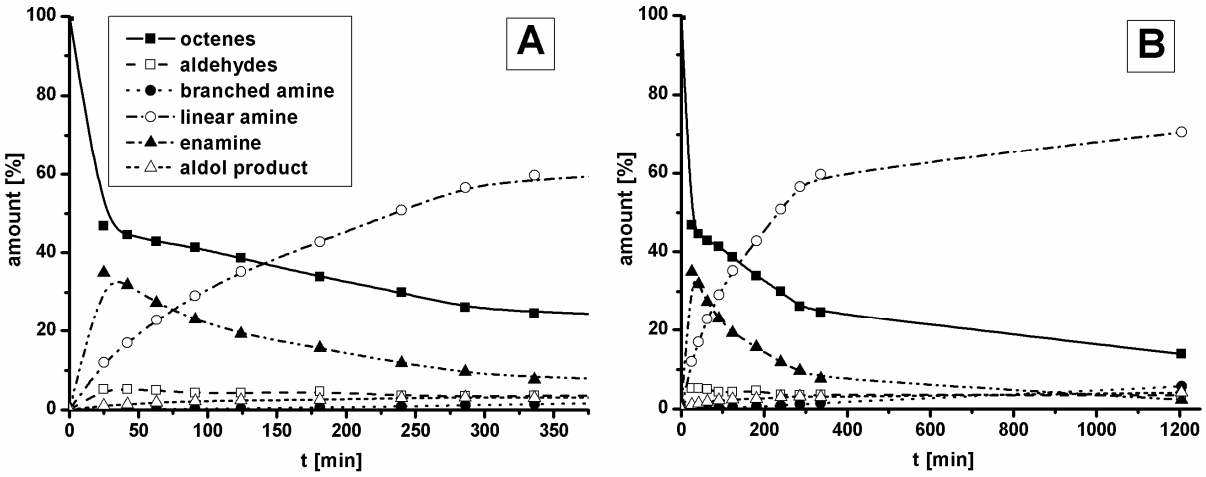
C. toluene/*n*BuOH **D.** toluene/*t*BuOH

Conditions: 2-octene 9 mmol, piperidine 10 mmol, toluene/alcohol (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2$ (1:6)) = 36 bar (cold pressure), 800 rpm, preformation = 30 min., L = **13**.

Figure 4.11: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 2-octene in different solvent mixtures.*

It is well-known that the isomerisation rate in Co-catalysed hydroformylation reactions is often higher than in Rh-catalysed reactions, although rather harsh conditions (high T and p) are usually necessary for cobalt systems. For this reason, a Rh-catalysed HAM reaction was performed under standard reaction conditions with addition of $[Co_2(CO)_8]$ in order to increase the isomerisation rate. However, the expected positive effect was not observed. Actually, a decreased activity was obtained in combination with a l/b ratio smaller than 1, which means that even more branched than linear amine was formed.

Furthermore, a HAM reaction was performed in toluene/*n*BuOH with a 1:1 mixture of 1- and 2-octene (Fig. 4.12). It is likely that a relatively high concentration of 1-octene can be maintained throughout the reaction by isomerisation in order to keep the regioselectivity high. The product distribution in Figure 4.12 shows a clear bend at 50% conversion in the consumption of octenes. This is the point at which most of the 1-octene is consumed and the isomerisation rate of 2-octene to the terminal alkene becomes important. The chemoselectivity was excellent in this reaction and only an accumulation of enamine was observed. High regioselectivity (l/b = 41) was obtained up to a reaction time of 6 hours. However, the l/b ratio after 20 hours reaction time at approximately 90% conversion turned out to be 12 (~92% linear amine), which is nearly identical to the value without 1-octene addition. No advantage could be obtained by addition of 1-octene to the substrate mixture.



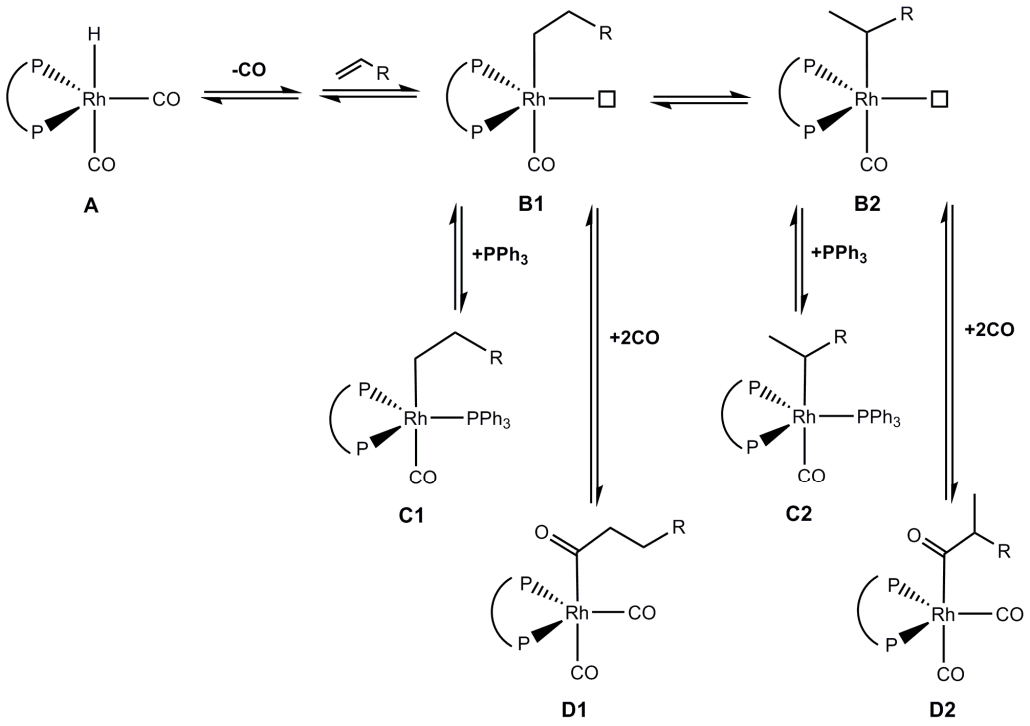
Conditions: 1-octene 4.5 mmol, 2-octene 4.5 mmol, piperidine 10 mmol, toluene/*n*BuOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, $p(CO/H_2\ (1:6))$ = 36 bar (cold pressure), 800 rpm, preformation = 30 min., L = **13**.

Figure 4.12: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of a 1:1 mixture of 1- and 2-octene. The left-hand figure shows a close-up of the first 6 hours of the reaction.*

4.3.6 Addition of a monodentate phosphorus ligand

In order to increase the isomerisation rate in the isomerising HAM of 2-octene, the effect of adding a monodentate phosphine or phosphite ligand to the reaction mixture was investigated. As mentioned before, the reaction conditions and especially the temperature and partial pressures of CO and H_2 can have a large influence on the isomerisation rate. The main reason for this is that the equilibria in the catalytic cycle of the hydroformylation are influenced, leading to either increased or decreased rates for the CO insertion and β-hydrogen elimination. Addition of a

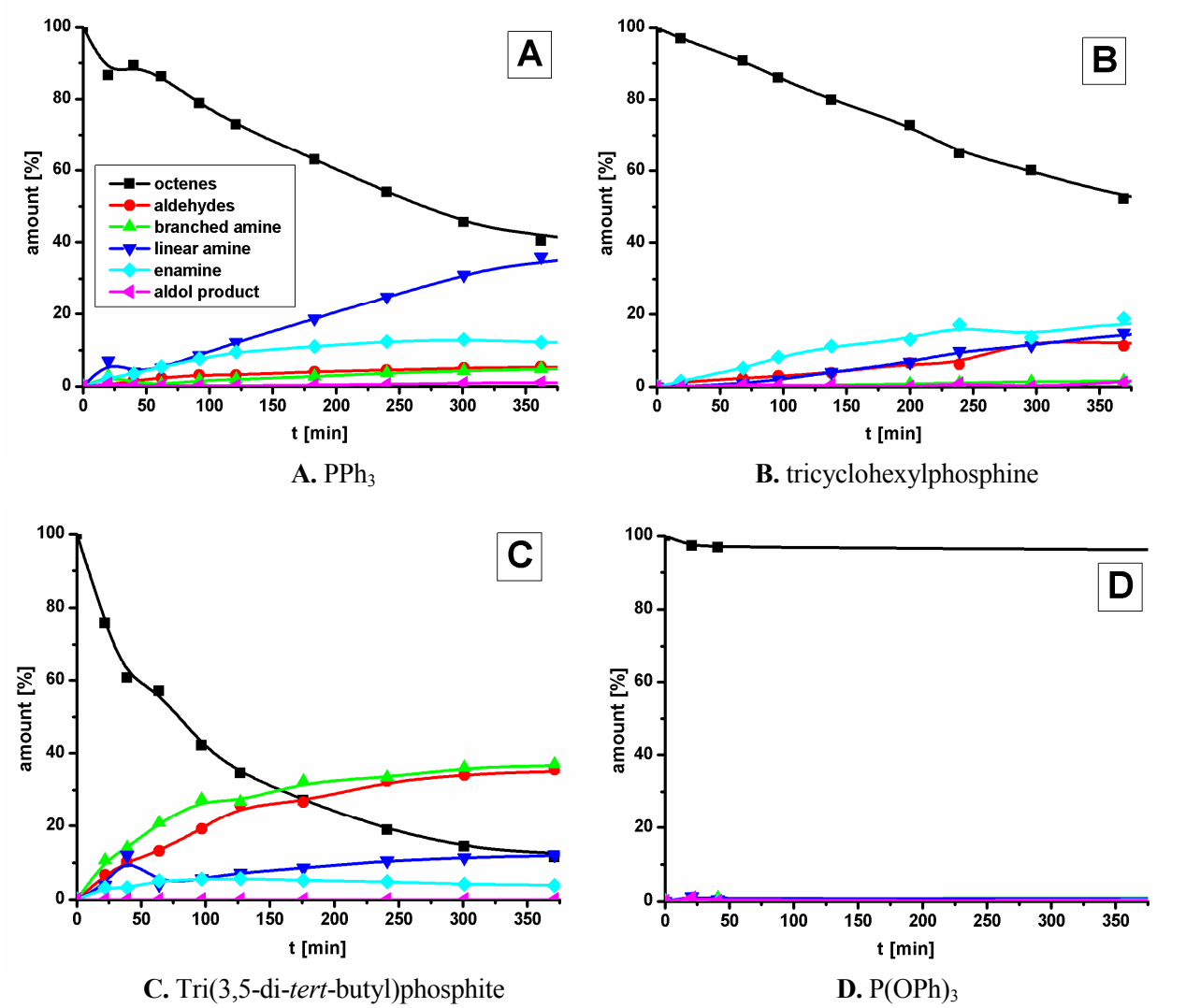
monodentate ligand might lead to a similar effect (Scheme 4.6). By addition of a monodentate ligand, an additional equilibrium is established, represented by structures **C1** and **C2** in Scheme 4.6. This additional equilibrium leads to a decreased rate of CO-insertion because of competition between the two equilibria leading to the complexes **C** and **D**. Moreover, an increased rate of β-hydrogen elimination can be observed since complex **B** will be present in a higher concentration, which is a statistical effect. Although the isomerisation rate will increase upon addition of a monodentate ligand, the total reaction rate will decrease. In case of large amounts of the monodentate ligand or upon adding strongly coordinating ligands, the reaction might even be inhibited, since the highly stable complex formed, might be catalytically inactive.



Scheme 4.6: *Equilibria of rhodium complexes important for the rate of isomerisation upon addition of triphenylphosphine.*

Two monodentate phosphine ligands (triphenylphosphine and tricyclohexylphosphine) and two monodentate phosphite ligands (tri(3,5-di-*tert*-butyl)phosphite and triphenylphosphite) were studied in the addition experiments in the HAM of 2-octene (Fig. 4.13). Four equivalents of the monodentate ligand were inserted in addition to the four equivalents of bidentate ligand which are present in common HAM reactions.

Apparently, triphenylphosphite coordinates very strongly to the rhodium complex, which leads to a complete inhibition of the reaction (Fig. 4.13D). No conversion could be obtained. Upon using tri(3,5-di-*tert*-butyl)phosphite, the reaction rate was fast, but the regioselectivity for the linear amine was very disappointing (Fig. 4.13C). Probably, this very bulky ligand replaces the chelating ligand in the rhodium complex because of a stronger coordination and the size. The resulting complex is highly active for terminal as well as for internal alkenes leading to disappointing regioselectivities. Furthermore, an accumulation of the intermediate aldehyde could be observed.



A. PPh_3 **B.** tricyclohexylphosphine

C. Tri(3,5-di-*tert*-butyl)phosphite **D.** $P(OPh)_3$

Conditions: 2-octene 9 mmol, piperidine 10 mmol, toluene/*n*BuOH (1:1) 8 mL, $[Rh(cod)_2]BF_4$ = 0.1 mol%, T = 110°C, S/Rh = 1000, L/Rh = 4.0, P/Rh = 4, $p(CO/H_2$ (1:6)) = 36 bar (cold pressure), 800 rpm, preformation = 30 min., L = **13**, P = monodentate ligand.

Figure 4.13: *Product distribution during the Rh-catalysed hydroaminomethylation reaction of 2-octene upon addition of different monodentate phosphine and phosphite ligands.*

Addition of monodentate phosphines shows completely different results. The reaction rate was slightly decreased in both cases and especially in case of addition of tricyclohexylphosphine, an accumulation of enamine was observed and hydrogenation activity appeared to be relatively low (Fig. 4.13B). However, the regioselectivity turned out to be promising and a l/b ratio of 10.1 (~91% linear amine) was obtained after 6 hours reaction time. In fact, the l/b ratio increased slightly during the reaction. The HAM with addition of triphenylphosphine turned out to be a good compromise with respect to regioselectivity and activity. The hydrogenation activity was still high, leading to the formation of the amine. A l/b ratio of 9.4 (~90% linear amine) after 6 hours reaction time was observed. Although the differences are only small, it appears that there is a favourable effect of the addition of monodentate phosphines. Upon addition of more equivalents of monodentate ligand, this effect on regioselectivity might be reinforced, although the activity might decrease considerably.

4.4 Conclusions

In this chapter, it has been shown that performing Rh-catalysed hydroaminomethylation reactions of 2-octene with the π-acidic ligand bis-[(dipyrrolyl)phosphino]xanthene **13**, leads to good activities and selectivities with l/b ratios of up to 15 (~94% linear amine). The influences of syngas ratio, preformation, reaction temperature, solvent mixture composition and the addition of a monodentate ligand were investigated. Although the influence of the syngas ratio turned out to be limited, the other variables had a large influence on both activity and selectivity in the HAM of 2-octene. Optimal reaction conditions, which means a good compromise in terms of activity and selectivity (~90% linear amine) turned out to be a preformation time of 30 minutes, a syngas ratio of 1:6, a reaction temperature of 110°C, toluene/*n*BuOH as the solvent mixture and the addition of triphenylphosphine in order to improve the isomerisation rate. Higher regioselectivities could be obtained upon using tricyclohexylphosphine as the monodentate ligand (~91% linear amine) or upon using toluene/*t*BuOH as the solvent mixture (~94% linear amine). However, the activity was slightly lower in both cases. Apparently, lower activities, such as described for phosphine ligands earlier in literature, have a positive effect on the regioselectivity and to date, no systems have been described which combine both high activity and selectivity in the HAM of internal alkenes. Overall, the investigated catalytic system gives interesting results and good regioselectivities in the HAM of 2-octene.

4.5 Experimental section

All air- or water-sensitive operations were performed using standard Schlenk techniques under purified argon atmosphere. Toluene, tetrahydrofuran, *n*-hexane, and dichloromethane were purified over custom-made alumina columns. Piperidine, triethylamine, ethyl acetate, methanol, ethanol, *tert*-butanol, trifluoroethanol, phenol and *n*-butanol were distilled from CaH_2. 1-Octene and 2-octene were purified by distillation from Na_2SO_4 and percolation over neutral activated alumina. All solvents and substrates were degassed prior to use. Chemicals were purchased from Acros Chimica, Merck KGaA, Biosolve B.V. and Aldrich Chemical Co. $[Rh(cod)_2]BF_4$ was synthesised according to a literature procedure. Hydrogen gas (99.999%), carbon monoxide gas (99.997%) and synthesis gas (CO (99.9%)/H_2 (99.9996%); 1:2) were purchased from Praxair. Gas chromatographic analyses were run on a Shimadzu GC-17A instrument and an Ultra 2 column (25 m x 0.2 mm). GC/MS analyses were conducted on a HP6890 chromatograph with a Leco Pegasus II mass spectrometer and a DB-1MS column (10 m x 0.1 mm). NMR data were recorded on a Varian Oxford 200 MHz and a Varian Mercury Vx 400 MHz NMR spectrometer. Elemental analysis was performed on a Perkin Elmer 2400 series II CHNS/O Analyser.

General procedure for hydroaminomethylation experiments

Reactions were performed in 75-mL home-made stainless steel autoclaves. In a typical experiment, the autoclave was charged with a solution of $[Rh(cod)_2]BF_4$ (3.2 mg, 7.9 μmol; cod = 1,5-cyclooctadiene) and the appropriate bidentate ligand (32.4 μmol) in 8 mL of a toluene/alcohol mixture. Alkene (9 mmol) and piperidine (10 mmol) were added and the autoclave was purged three times using CO (p = 12 bar) to remove the remaining argon from the autoclave. Subsequently, the autoclave was pressurised with CO and H_2 to the desired pressure and heated to reaction temperature. In case of a preceding preformation, the reactor was filled with the catalyst solution and the substrates were added to the dropping funnel. The reactor was pressurised to the desired reaction pressure and heated to the desired reaction temperature. After 30 minutes preformation, the substrates were added to the catalyst solution by opening the valve of the dropping funnel. After a certain reaction time, the autoclave was cooled to r.t. in an ice bath and the gases were vented. The reaction mixture was removed from the autoclave, filtered over alumina and analysed by GC and GC/MS. In these analyses the l/b-ratio could be determined within an error range of 0.05%.

In order to determine the product distribution in hydroaminomethylation, samples were taken during the reaction in toluene/alcohol mixtures from an autoclave equipped with a tailor-made sample-system that consisted of a capillary with an inner diameter of 0.25 mm, combined with a two-way and a three-way valve. The sample was taken by means of the pressure inside the autoclave. The connection between the two valves was used to collect the sample (estimated volume 50 μL). By opening the two-way valve the sample was collected in a GC vial, diluted with MeOH/Et_2O and analysed by GC(-MS).

Synthesis of phenyl(bis-indolyl)methane (3)

This compound was prepared according to a modified literature procedure.[29]

Tritylchloride (0.5 g; 1.9 mmol) was added to a well-ground mixture of indole (2.5 g; 21.3 mmol) and benzaldehyde (1.2 g; 11.3 mmol) in a mortar. The mixture was thoroughly mixed with a pestle and was left standing for 15 minutes at r.t. After this, the residue was extracted with EtOAC and filtered over a short silica column. The solvent was removed in vacuo and the pure product was obtained as a light yellow solid in 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 2H), 7.36 (m, 6H), 7.26 (t, 2H, *J* = 0.8 Hz), 7.17 (m, 3H), 7.00 (t, 2H, *J* = 7.0 Hz), 6.66 (s, 2H), 5.89 (s, 1H) ppm.

Synthesis of indolocarbazole (4)

2-Aminocyclohexanone hydrochloride **7** (0.86 g; 5.8 mmol) was dissolved in acetic acid (25 mL; 95%) and trifluoroacetic acid (9 mL). Phenylhydrazine hydrochloride was added to this solution under stirring. The reaction mixture was heated to 110ºC and stirred at reflux overnight (16 h). The resulting light brown suspension was cooled to r.t., filtered and washed with H_2O to yield the pure product as a white powder after drying in a vacuum oven (72 h; 60ºC) in 92% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ = 10.61 (b, 2H), 8.16 (d, 2H, J = 7.4 Hz), 7.95 (s, 2H), 7.60 (d, 2H, *J* = 8.1 Hz), 7.38 (t, 2H, *J* = 8.1 Hz), 7.22 (t, 2H, *J* = 8.1 Hz) ppm.

Synthesis of bis-indolyl (5); procedure I

Acetonitrile (42 mL) was added to diacetylene **9** (0.7 g; 1.7 mmol) and K_2CO_3 (1.2 g; 8.7 mmol) and $Pd(PPh)_3$ (144 mg; 0.12 mmol) were added to this stirred suspension. The yellow suspension was heated to 86ºC, stirred for 25 hours, subsequently cooled to r.t. and stirred overnight. EtOAc/H_2O (120 mL; 1:1) was added, layers were separated and the H_2O-layer was extracted with EtOAc (2 x 80 mL). The combined organic layers were washed with H_2O (1 x 40 mL), dried over Na_2SO_4, filtered and the solvent was removed in vacuo, yielding the product as a yellow solid in 77% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ = 10.74 (b, 2H), 7.56 (d, 2H, *J* = 7.7 Hz), 7.41 (d, 2H, *J* = 8.0 Hz), 7.12 (t, 2H, *J* = 8.0 Hz), 7.03 (t, 2H, *J* = 8.0 Hz), 6.94 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.34, 131.52, 129.11, 121.95, 120.16, 119.69, 110.96, 98.66 ppm.

Synthesis of bis-indolyl (5); procedure II

Potassium (13.4 g; 342.7 mmol) was added to *tert*-butanol (260 mL) at 30ºC. This mixture was stirred overnight at 50ºC. Afterwards, bis-tolyloxamide **10** was added to the reaction mixture and stirred for 2 hours. The reaction mixture was heated to 90ºC and *tert*-butanol was distilled off. Subsequently, the reaction mixture was heated to 90ºC and a white sublimate could be obtained which was removed in vacuo. After this, the reaction mixture was heated to 225ºC in a sand bath for 2 hours, cooled to r.t., H_2O (150 mL) and EtOH (100 mL) were carefully added, the suspension was filtered, washed with pentane (3 x 75 mL; 1:1), the

residual dark solid was extracted with acetone and filtered over celite. The solvent was removed in vacuo and the product was obtained as a slightly yellow solid in 43% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ = 10.74 (b, 2H), 7.56 (d, 2H, *J* = 7.7 Hz), 7.41 (d, 2H, *J* = 8.0 Hz), 7.12 (t, 2H, *J* = 8.0 Hz), 7.03 (t, 2H, *J* = 8.0 Hz), 6.94 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.34, 131.52, 129.11, 121.95, 120.16, 119.69, 110.96, 98.66 ppm.

Synthesis of 2-aminocyclohexanone hydrochloride (7)

2-Nitrocyclohexanone (2.1 g; 14.8 mmol) was weighed in a Schlenk flask and dissolved in EtOH (60 mL) and HCl (3 mL). Pt-S/C (0.27 g; 5 w%) was added to the stirred solution and H_2 was bubbled through the suspension for 5 minutes. After this, the reaction mixture was heated to 55ºC for 7 hours under hydrogen atmosphere. The reaction mixture was cooled to r.t., H_2 was again bubbled through the suspension and the reaction mixture was stirred overnight. The reaction mixture was filtered, washed with MeOH (2 x 15 mL) and the solvent was removed in vacuo yielding a yellow, viscous oil. Acetone (120 mL) was added to this oil and a white precipitate formed, which was filtered and dried in a vacuum oven overnight (40ºC), yielding the pure product as a white solid in 35% yield. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.94 (s, 2H), 4.05 (dd, 1H, *J* = 6.6, 6.2 Hz), 2.51 (m, 2H), 2.15 (m, 2H), 1.89 (m, 2H), 1.67 (m, 2H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 174.91, 60.12, 40.31, 33.34, 26.40, 22.23 ppm.

Synthesis of 2,2'-(buta-1,3-diyne-1,4-diyl)dianiline (8)

$Cu(OAc)_2 \cdot H_2O$ (6.8 g; 34.1 mmol) was dissolved in MeOH/pyridine (120 mL; 1:1), 2-ethynylaniline (2.1 g; 17.9 mmol) was added to this solution and stirred for 46 hours at r.t..Afterwards, the reaction mixture was cooled in an ice bath and H_2O was added, which coloured the solution darker blue and a precipitate was obtained. To this dark blue coloured suspension, Et_2O (150 mL) was added. After phase separation, the organic layers were washed with $CuSO_4$(aq.) solution until no colour change of the $CuSO_4$ solution could be observed anymore upon addition of the organic phase. The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo, yielding the product as a yellow solid in 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, 2H, *J* = 8.1 Hz), 7.16 (t, 2H, *J* = 8.4 Hz), 6.69 (m, 4H), 4.31 (b, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.46, 133.01, 130.61, 117.97, 114.39, 106.21, 79.68, 78.98 ppm.

Synthesis of N,N'-(2,2'-(buta-1,3-diyne-1,4-diyl)bis(2,1-phenylene))bis(2,2,2-trifluoroacetamide) (9)

Diacetylene **8** (1.0 g; 5.1 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (2.3 g; 11.2 mmol) were dissolved in CH_2Cl_2 (12 mL) and trifluoroacetic anhydride (3.9 g; 18.6 mmol) was added slowly from a pipette. A white precipitate had formed by the end of the addition and the suspension was stirred overnight at r.t.. The next morning, no precipitate could be observed anymore. Solvents and volatile reactants were removed in vacuo, CH_2Cl_2 (40mL) was added, EtOH (40 mL) was added to the vigorously stirred solution and a white precipitate was obtained. The pure product was obtained after filtration and drying in vacuo as a white solid

in 46% yield. ^{1}H NMR (400 MHz, acetone-d_6): δ = 10.03 (b, 2H), 7.83 (d, 2H, *J* = 8.1 Hz), 7.71 (d, 2H, *J* = 7.7 Hz), 7.59 (t, 2H, *J* = 8.1 Hz), 7.42 (t, 2H, *J* = 7.7 Hz) ppm. ^{19}F NMR (376 MHz, acetone-d_6): δ = –76.34 ppm.

Synthesis of bis-tolyloxamide (10)

Oxalylchloride (30.3 g; 238.7 mmol) was added dropwise to THF (70 mL), the solution was cooled to 0ºC and *o*-toluidine (50.1 g; 467.6 mmol) and triethylamine (47.3 g; 467.4 mmol) in THF (100 mL) were added in 1 hour. After addition, the reaction mixture was stirred for additional 2 hours at 0ºC. The reaction mixture was allowed to reach r.t. overnight and H_2O (300 mL) was added carefully. Afterwards, EtOAc (450 mL) was added, the reaction mixture was heated to 100ºC for two hours, the resulting solid was filtered off and washed with petroleum ether, yielding the pure product as a white solid in 54% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (b, 2H), 8.07 (d, 2H, *J* = 8.3 Hz), 7.26 (m, 4H), 7.15 (t, 2H, *J* = 8.7 Hz), 2.38 (s, 6H) ppm.

Synthesis of bis-[(bis-indolyl)phosphamidato]-3,6-di-*tert*-butyl-9,9-dimethylxanthene (12)

Bis-indolyl **5** (0.73 g; 3.1 mmol) and triethylamine (1.6 g; 15.8 mmol) were dissolved in THF (20 mL), cooled to –60ºC and PCl_3 (0.44 g; 3.2 mmol) was added dropwise. The dark reaction mixture was warmed to r.t. and reacted at reflux overnight, leading to the chloro(bis-indolyl)phosphine **11**. ^{31}P NMR (162 MHz, crude): δ = 101.8 ppm.

Dihydroxyxanthene (0.48 g; 1.4 mmol) was dissolved in THF (15 mL) and added dropwise to the reaction mixture at r.t.. Afterwards, the reaction mixture was heated to reflux overnight. After cooling to r.t., the reaction mixture was filtered over neutral alumina, washed with THF (3 x 20 mL), the solvent was removed, yielding a brown solid. CH_2Cl_2 (15 mL) was added to the residual solid, an off-white precipitate was obtained, filtered *via* a filter cannula and the product was obtained in 17% yield as an off-white solid after drying. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, 4H, *J* = 8.1 Hz), 7.40 (d, 4H, *J* = 7.7 Hz), 7.05 (t, 4H, *J* = 8.1 Hz), 6.96 (t, 4H, *J* = 7.7 Hz), 6.62 (s, 2H), 6.49 (s, 4H), 5.75 (s, 2H), 0.89 (s, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.68, 138.00, 137.00, 136.67, 135.04, 134.01, 129.05, 123.77, 121.54, 121.15, 118.44, 116.48, 112.11, 98.76, 53.83, 34.00, 32.45, 30.91 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 78.92 ppm. Anal. Calc. for $C_{55}H_{48}N_4O_3P_2$: C, 75.50; H, 5.53; N, 6.40. Found: C, 74.53; H, 5.35; N, 6.21.

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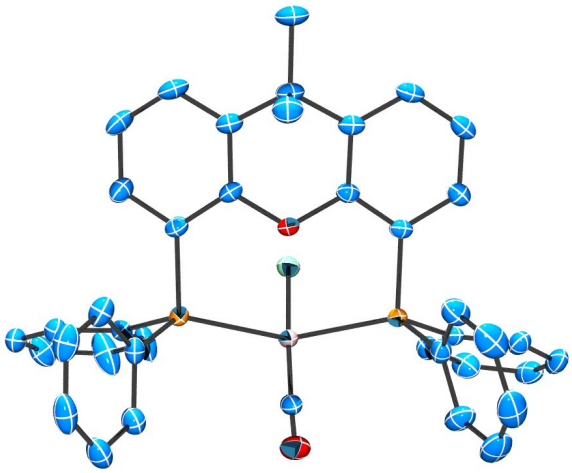
5

Coordination chemistry of xanthene-based amino-functionalised ligands

*Three recently synthesised xanthene-based amino-functionalised ligands, for which application in catalysis was discussed in Chapters 3 and 4, have been studied with respect to their coordination behaviour to rhodium and platinum. In combination with rhodium, these compounds (**1**, **2** and **3**) display interesting catalytic results in the hydroaminomethylation reaction. In order to clarify their structure/performance relationship, especially since compound **3** is a polydentate ligand, the coordination behaviour was investigated. The structural properties of the ligands were studied by NMR spectroscopy of the corresponding rhodium and platinum complexes, while the electronic properties were examined by studying the IR frequencies of the CO stretch vibrations in the particular rhodium-carbonyl complexes. For two ligands, the corresponding selenides were synthesised. The NMR coupling constant $J_{Se\text{-}P}$ can be used as a measure for the σ-donor ability of a ligand. Furthermore, the coordination behaviour of the ligands was investigated by high pressure NMR and IR spectroscopic measurements under actual hydroformylation reaction conditions. The ligands are compared to the diphosphine ligand Xantphos, which performs very well in regioselective hydroformylations.*



This work will be submitted for publication:
B. Hamers, C. Müller, M. Lutz, A. L. Spek, D. Vogt, *manuscript in preparation.*

5.1 Introduction

The performance of transition metal complexes in homogeneous catalysis largely depends on the coordination geometry around the metal centre and the electronic and steric properties of the ligands. The coordination geometry is mainly determined by the bulkiness and spatial arrangement of the applied ligands. Subtle variation of the steric bulk or the ligand backbone leads to considerable differences in coordination behaviour, which has its repercussions on the catalyst performance. In addition, the electronic properties of a ligand can have a significant influence on the activity, but also on the selectivity of a catalyst system. Especially in hydroaminomethylation reactions where the reaction rate of the intermediate aldehyde and enamine to the desired amine product determines the selectivity to a large extent, the electronic properties of a ligand can have a large influence on selectivity as well. If the intermediates in this reaction are converted slowly to the product, large amounts of side products will be formed. In contrast, the selectivity to the desired product will be high if the activity to convert the intermediates is high. In order to derive a deeper understanding of these structure/performance relationships, the coordination behaviour of ligands to a metal centre is often investigated. Several examples of investigations into the coordination behaviour of bidentate phosphorus ligands can be found in literature.[1-7]

NMR and IR spectroscopy are frequently used methods to investigate the coordination behaviour of ligands, in addition to single crystal X-ray analysis. Whereas NMR spectroscopy mainly provides information about the spatial arrangement of the ligand-to-metal coordination, IR spectroscopy provides information about the electronic properties of the catalyst complex by the value of the CO stretch frequency of complexes in which a carbonyl ligand is present.[8] A major advantage of these spectroscopic methods is the fact that the coordination behaviour of ligands can be investigated under the actual reaction conditions by applying high pressure NMR and IR spectroscopic techniques.[9-11] These high pressure spectroscopic techniques are also very well suited for mechanistic studies of catalytic reactions and in order to disclose the coordination mode of a ligand (*vide infra*).[12,13]

The resting state of the active species in the rhodium-catalysed hydroformylation is a species with trigonal bipyramidal geometry. The bidentate phosphorus ligand in this complex [$RhH(CO)_2$(**P^P**)] can either coordinate in equatorial-equatorial (ee) or in equatorial-axial (ea) fashion (Fig. 5.1). It has been suggested that decreasing basicity of the phosphorus ligand shifts the equilibrium to ee coordination which has a favourable effect on the regioselectivity in hydroformylation.[14] Beside electronic effects, also the bite angle, which induces steric effects as well, has been indicated to play an important role.[6,13-16] Obviously, the three-dimensional

arrangement is considerably different for these two possible coordination modes, which can be investigated by means of high pressure NMR and IR spectroscopy. A disadvantage of high pressure NMR spectroscopy is the necessity of relatively high rhodium concentrations, which possibly leads to the formation of the catalytically inactive dimeric species.[17]

Indicative for the coordination mode is the hydride signal in the ^{1}H NMR spectrum. In case of ee coordination, both phosphorus atoms are *cis* to the hydride and typically, a small value (< 30 Hz) is observed for the coupling constant $J_{P\text{-}H}$.[18,19] Upon ea coordination, one phosphorus atom is *cis* with respect to the hydride, while the other phosphorus atom is coordinated *trans* to the hydride. Typical values of the coupling constant $J_{P\text{-}H}$ are > 100 Hz for the phosphorus atom *trans* to the hydride. In fact, three different coupling constants are expected for ea coordinated complexes: a $J_{Rh\text{-}H}$ coupling constant, a small coupling constant $J_{P\text{-}H}$ and a larger coupling constant $J_{P\text{-}H}$ for the phosphorus atom *trans* to the hydride.[11,20] The coupling constant $J_{P\text{-}P}$ is generally only observed at low temperatures in these complexes because of the fast exchange of phosphorus atoms in the complex on the NMR time scale at room temperature. Additionally, the shifts and coupling constants in ^{31}P NMR spectra can provide important information about the corresponding complex. The coupling constant $J_{Rh\text{-}P}$ is larger in ee complexes than in ea complexes and thus also a good indicator for the coordination mode in a complex.

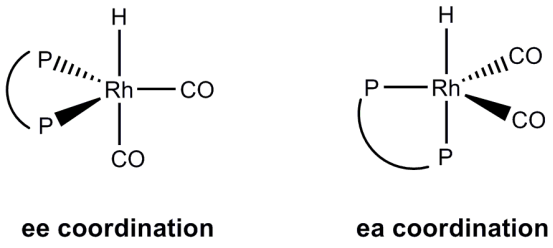


Figure 5.1: *Illustration of the two possible coordination modes in a trigonal bipyramidal rhodium complex: equatorial-equatorial (ee) and equatorial-axial (ea) coordination.*

Equatorial-axial ligand exchange, so-called fluxional behaviour, has been observed in trigonal bipyramidal and square-pyramidal complexes and can be explained by pseudo-rotational mechanisms like Berry-type and turnstile rotations.[21-23] Equatorial-axial phosphorus exchange requires two successive Berry interconversions *via* a high energy intermediate containing an equatorially coordinated hydride ligand. Consequently, these mechanisms are not likely to occur in complexes containing bidentate ligands, since large variations in bite angle are required for the diphosphine ligands.[10,19] This mechanism might only be possible with very flexible bidentate

ligands with large bite angles, displaying limited energy strain. Another rearrangement mechanism has been proposed by Meakin for square-pyramidal complexes and has also been proposed for trigonal bipyramidal structures.[10,19,23,24] In this mechanism, the hydride moves towards the equatorial plane and the simultaneous movement of the CO ligands leads to a coordinated species in which the phosphorus atoms are interconverted (Fig. 5.2). This low-energy rearrangement is much more likely, especially since no variation in the bite angle of the ligand is required, leading to much lower energy constraints.

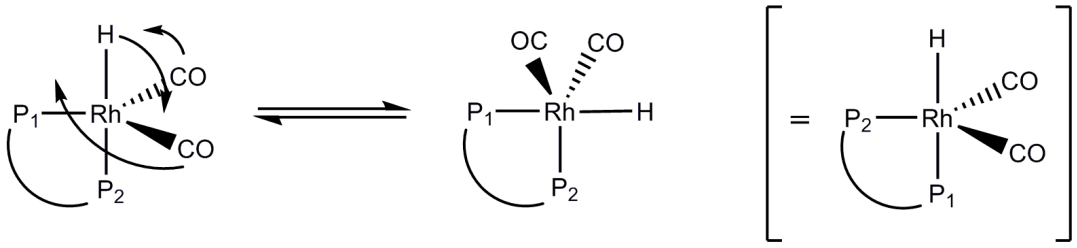


Figure 5.2: *Illustration of the interconversion mechanism for trigonal bipyramidal complexes described by Meakin.*

In addition to NMR spectroscopy, high pressure FT-IR spectroscopy can provide useful information about the coordination mode in the trigonal bipyramidal complex [RhH(CO)$_2$(**P^P**)] by investigating the corresponding CO stretch vibrations.[25] The asymmetrical as well as the symmetrical stretch vibrations can be observed in general. CO stretch vibrations of complexes containing an ee coordinating bidentate phosphorus ligand can be observed at higher wave numbers (2100-1975 cm^{-1}) than complexes with an ea coordinating phosphorus ligand (2035-1920 cm^{-1}). The vibrations of complexes containing ee coordination are in general identical in intensity, whereas the vibrations of complexes containing an ea coordination mode of the ligand show a vibration at higher wave number of lower intensity in comparison to the vibration at lower wave number.[14,26]

The most frequently reported chelating phosphorus ligands in literature, also with respect to their coordination chemistry, are diphosphines, diphosphites, diphosphonites and diphosphinites.[2,27-34] Although phosphorus amidites, phosphorus amides, and aminophosphines are less common, some examples of coordination chemistry applying these ligands can be found in literature.[7,35-37] However, the coordination chemistry of xanthene-based amino-functionalised ligands **1** and **2** and Tetraphos ligand **3** (Fig. 5.3) has not been reported to date. This chapter describes the coordination chemistry of these (dipyrrolyl)phosphine-functionalised compounds with rhodium and platinum.

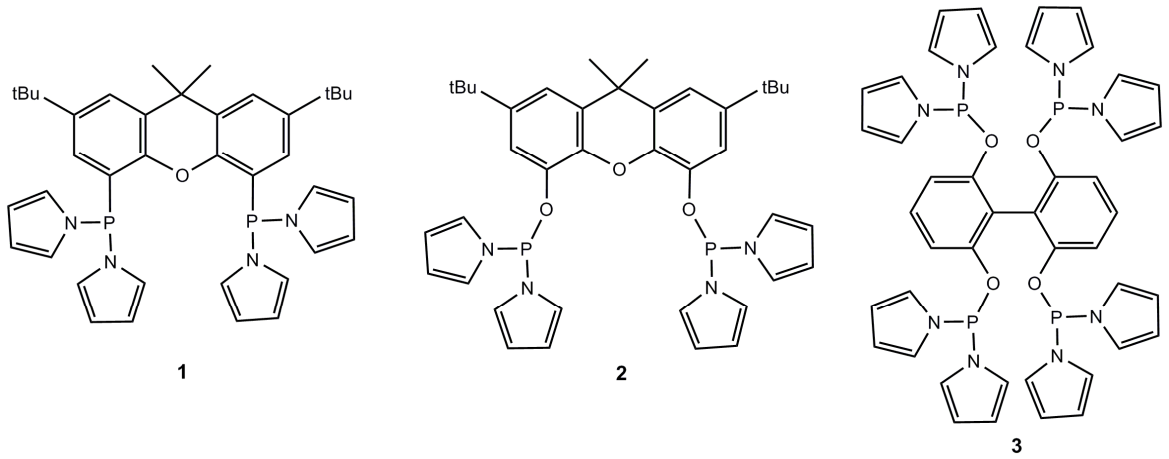


Figure 5.3: *Illustration of ligands **1–3** used in the coordination studies with transition metals described in this chapter.*

5.2 Coordination chemistry

The coordination behaviour of compounds **1–3** with rhodium and platinum was investigated. The complexes were studied using (high pressure) IR and ^{1}H and ^{31}P NMR spectroscopy and compared to the corresponding complexes containing the diphosphine ligand Xantphos. Furthermore, the molecular structure in the crystal of *trans*-[RhCl(CO)(**Xantphos**)] was determined by X-ray crystallography and is described here.

5.2.1 Rhodium

Rhodium complex **4** based on ligand **1** was prepared from the dimeric precursor $[Rh(CO)_2(\mu\text{-}Cl)]_2$ in dichloromethane at room temperature yielding a yellow/orange solid (Fig. 5.4). Using the same method, a rhodium complex was prepared from $[Rh(CO)_2(\mu\text{-}Cl)]_2$ and ligand **2** in dichloromethane at room temperature, yielding a yellow solid. One doublet at δ = 100.0 ppm with a coupling constant of $J_{Rh\text{-}P}$ = 226 Hz was observed in the ^{31}P NMR spectrum of complex **4**, showing the formation of *trans*-[RhCl(CO)(**1**)]. Although this coupling constant is rather large, this is frequently observed in rhodium complexes with ligands displaying good π-acceptor properties.[38]

On the other hand, large rhodium-phosphorus coupling constants might also indicate the formation of *cis*-complexes.[32] The ^{31}P NMR spectrum of complex **5** containing ligand **2**, shows a set of three doublets at δ = 122.5, δ = 115.7 and δ = 111.7 ppm with coupling constants $J_{Rh\text{-}P}$ of 279, 267 and 191 Hz, respectively. This indicates the formation of several different complexes for

this ligand. The intensity of these doublets was identical, but the coupling constant of the doublet at δ = 111.7 ppm was distinctly smaller. This smaller coupling constant might indicate a *cis*-complex, in contrast to the *trans*-complexes with larger coupling constants. Possibly, the face-to-face dimeric complex *cis*, *cis*-[{RhCl(CO)(μ-**2**)}$_2$] or the monomeric complex ci*s*-[RhCl(CO)(**2**)] was formed in addition to the *trans* complexes *trans*, *trans*-[{RhCl(CO)(μ-**2**)}$_2$] and *trans*-[RhCl(CO)(**2**)] containing ligand **2** (Fig.5.5).

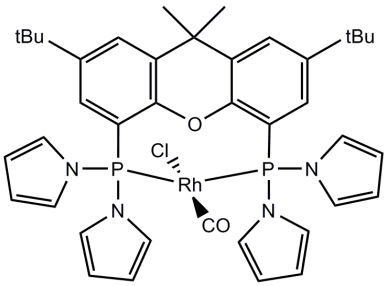


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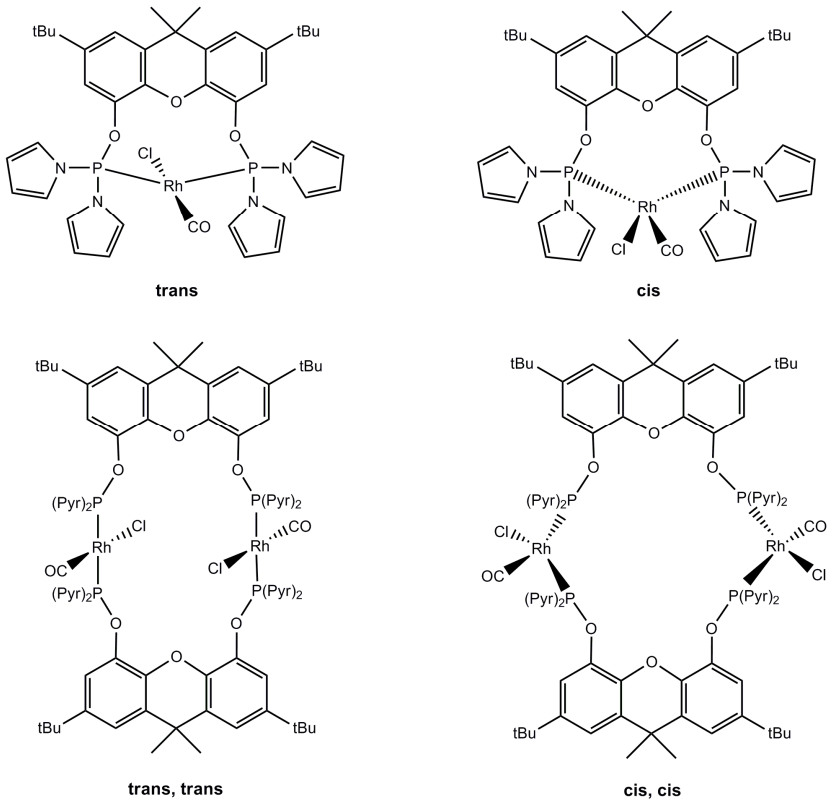
Figure 5.4: *Illustration of complex **4**, trans-[RhCl(CO)(**1**)]*.



Complex 5

Figure 5.5: *Illustration of possible coordination modes of **2** in complex **5**: monomeric trans and cis (upper drawings) and dimeric trans and cis (lower drawings) complexes.*

The IR spectrum (ATR mode) of complex **4** shows a CO stretch vibration at ν = 1999 cm^{-1}. This value is in between the typical values for the corresponding rhodium complexes containing monodentate phosphites[39] (ν ~ 2015 cm^{-1}), dipyrrolylphosphines[40] (ν ~ 2007 cm^{-1}) and phosphinites[35] (ν ~ 1990 cm^{-1}), and comparable to the value for rhodium complexes based on diphosphonites (ν ~ 1997 cm^{-1}).[33] This shows that **1** has similar π-acceptor properties compared to diphosphonite ligands. The CO stretch vibration of ν = 2021 cm^{-1} in complex **5** is comparable to the value for phosphite ligands. This implies that ligand **2** has better π-acceptor properties than ligand **1**, which is most likely due to the additional oxygen atom in the ligand backbone. Unfortunately, no crystals suitable for X-ray diffraction could be obtained in order to elucidate the molecular structure of complexes **4** and **5** in the crystal.

In order to compare the aforementioned complexes to a similar rhodium complex containing a diphosphine ligand, the complex *trans*-[RhCl(CO)(**Xantphos**)] (**6**) was prepared using the same metal precursor as described above. This complex displays one doublet in the ^{31}P NMR spectrum at δ = 21.1 ppm with a coupling constant of $J_{Rh\text{-}P}$ = 131 Hz, which is a typical value for a diphenylphosphine complex. The CO stretch vibration of ν = 1984 cm^{-1} indicates that Xantphos has mainly σ-donor properties in contrast to **1** and especially **2**, as expected. This implies that these π-acceptor ligands should lead to very active complexes in Rh-catalysed hydroformylations or hydroaminomethylations as indeed observed in Chapters 3 and 4.

Crystals suitable for X-ray diffraction were obtained for *trans*-[RhCl(CO)(**Xantphos**)] (**6**) by layering a dichloromethane solution with acetonitrile. The molecular structure of complex **6** in the crystal is shown in Figure 5.6. Data on selected bond lengths, distances, and angles are given in Table 5.1. For comparison reasons, information on complex **7** (Fig. 5.7) containing a diphosphonite ligand,[33,41] which has electronic properties comparable to ligand **1** (*vide supra*), are included. From the molecular structure in the crystal, it can be derived that both phosphorus atoms are *trans* to each other as expected from the ^{31}P NMR data, as they only show one doublet with a Rh-P coupling constant typical for *trans* coordination of a phosphine ligand to the rhodium centre.

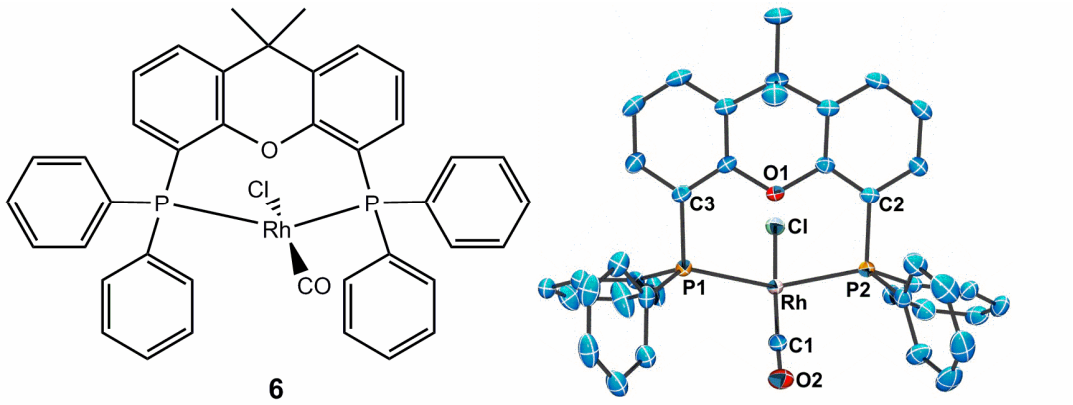


Figure 5.6: *ORTEP representation of complex* ***6****, trans-[RhCl(CO)(****Xantphos****)]. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.*

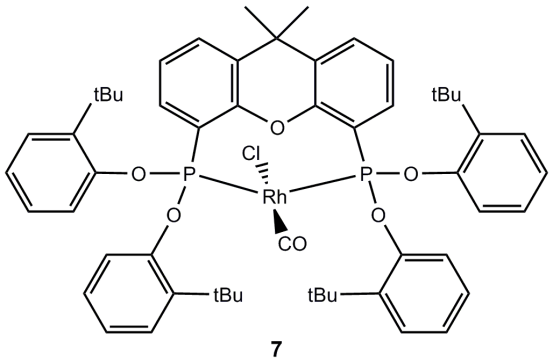


Figure 5.7: *Illustration of complex 7, trans-[RhCl(CO)(****diphosphonite****)]. The ligand has electronic properties comparable to ligand* ***1****.*[33,41]

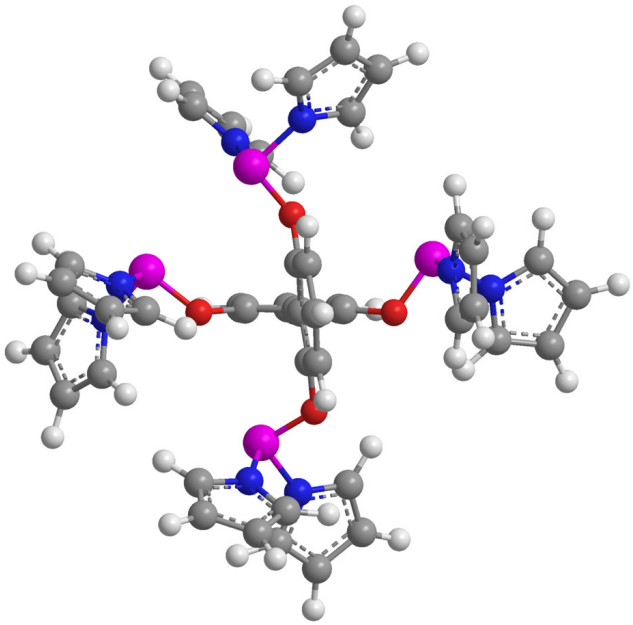


Figure 5.8: *ChemDraw 3D model of Tetraphos ligand* ***3****.*

The geometry around the rhodium atom in complex **6** is distorted square planar, which can be deduced from the P_1-Rh-P_2 bite angle of 152.78(1)º and the Cl-Rh-C_1 angle of 171.88(6)º. Many values of complexes **6** and **7** are comparable to a large extent. However, the Rh-P and Rh-Cl bond lengths are slightly larger in complex **6**. Obviously, this also affects the Rh-P_2-C_2 and Rh-P_1-C_3 angles, which are smaller in comparison to the corresponding angles in complex **7**. Most probably, this effect stems from a larger back-donation from the metal to the phosphorus atom in complex **7**, because of the better π-acceptor properties of the applied ligand. Apart from the Rh-O_1 distance, which is smaller in complex **6**, the other bond lengths and angles are comparable for both complexes.

Table 5.1 *Selected bond lengths, distances and angles for complex **6**, trans-[RhCl(CO)(**Xantphos**)] in comparison to **7** containing a diphosphonite ligand.[33,41] Standard deviations are given in parentheses.*

Bond lengths/Distances (Å)			Angles (º)		
	6	**7**		**6**	**7**
Rh-P_1	2.3035(4)	2.2583(7)	P_1-Rh-P_2	152.78(1)	147.19(3)
Rh-P_2	2.2915(4)	2.2668(7)	P_1-Rh-Cl	88.56(2)	88.49(3)
Rh-Cl	2.4055(5)	2.3504(8)	P_2-Rh-Cl	88.89(2)	-
Rh-C_1	1.8070(2)	1.818(3)	Rh-C_1-O_2	177.98(17)	174.1(2)
Rh-O_1	2.6255(16)	2.7193(16)	P_1-Rh-C_1	95.16(6)	95.52(8)
P_2-C_2	1.8281(17)	1.826(3)	P_2-Rh-C_1	91.05(6)	-
P_1-C_3	1.8378(17)	-	Cl-Rh-C_1	171.88(6)	166.11(8)
C_1-O_2	1.147(3)	1.149(3)	Rh-P_2-C_2	104.13(5)	109.74(9)
			Rh-P_1-C_3	103.82(6)	-

Ligand **3** is different in comparison to ligands **1** and **2** because of the four phosphorus atoms present in this molecule. In order to investigate the coordination chemistry of this ligand, a rhodium complex was prepared from $[Rh(CO)_2(\mu\text{-}Cl)]_2$. The expected complex **8** is a dinuclear Rh species since the ligand is able to coordinate two rhodium centres (Fig. 5.7). In order to investigate the possible spatial arrangements of this ligand upon complexation, a 3D model was generated using ChemDraw3D (Fig. 5.8). From this model and rough calculations, it could be derived that complexation as shown in Figure 5.9 is the most probable configuration. Other coordination modes are nearly impossible since the phosphorus atoms cannot approach each other close enough to chelate a metal atom.

The aforementioned preparation method with dichloromethane at room temperature was not suitable for the preparation of this complex. Therefore, this complex was prepared in toluene at 75ºC overnight after removing the solvent in vacuo, yielding a yellow solid. However, instead of a clear doublet, which would indicate Rh-P coupling, a broad signal was observed in the ^{31}P NMR spectrum, while the signal of the free ligand had completely disappeared. This broad signal might indicate fluxional behaviour or a dynamic exchange of ligands.[10] An absorption in the carbonyl region ($\nu \sim 2021$ cm^{-1}) was observed in the IR spectrum, which is identical to the value for complex **5**, implying good π-acceptor properties. The observed absorption is situated at a different position in comparison to the absorption of $[Rh(CO)_2(\mu\text{-}Cl)]_2$, indicating coordination of the phosphorus ligand. Nevertheless, no clear conclusion with respect to the coordination of ligand **3** could be drawn from the available data. Unfortunately, no crystals suitable for X-ray diffraction could be obtained in order to elucidate the molecular structure of complex **8** in the crystal. A compilation of determined chemical shifts and coupling constants for the above-mentioned rhodium complexes is given in Table 5.2.

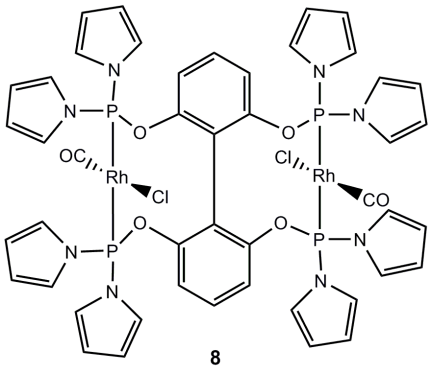


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Figure 5.9: *Illustration of the expected complex **8**, trans-[{RhCl(CO)}$_2$**(3)**], a dinuclear Rh species.*

Table 5.2 *Spectroscopic data of complexes [RhCl(CO)**(P^P)**] with ligands **1–3** and Xantphos.*

Complex	$\delta(^{31}P)$ [ppm][a]	$J_{Rh\text{-}P}$ [Hz][a]	ν_{CO} [cm^{-1}][b]
[RhCl(CO)(**1**)] (**4**)	100.02	225.9	1999
[RhCl(CO)(**2**)] (**5**)	122.46, 115.74, 111.67	266.5, 279.4, 191.2	2021
[RhCl(CO)(**3**)] (**8**)	110.63	-	2022
[RhCl(CO)(**Xantphos**)] (**6**)	21.05	130.8	1984

[a] Measured in $CDCl_3$. [b] FT-IR: ATR mode, solid.

5.2.2 Platinum

The coordination chemistry of ligands **1**–**3** with platinum was also studied. Complexation of ligand **3** with rhodium gave no satisfactory results, since only a broad signal was observed in the ^{31}P NMR spectrum. However, complexation with platinum might give a complex that can be studied with spectroscopic techniques in order to reveal the complexation behaviour. The precursor used for these experiments was [Pt(cod)Cl_2]. Upon reaction with bidentate phosphorus ligands containing a xanthene backbone or a comparable, rigid backbone, the formation of *cis*-platinum complexes (*cis*-[$PtCl_2$(**P^P**)]) is generally observed. Since no carbonyl ligand is present in this complex, the electronic properties can not be investigated *via* the CO stretch vibrations obtained from IR spectroscopy. However, the coupling constant $J_{Pt\text{-}P}$ of the phosphorus signal and the ^{195}Pt satellites in ^{31}P NMR spectra are well understood and useful parameters, and a measure for the electronic properties and the coordination behaviour (*cis* or *trans*).

A platinum complex containing ligand **1** (complex **9**) was prepared from the precursor [Pt(cod)Cl_2] in dichloromethane at reflux for 8 hours. After cooling the solution to room temperature and removing the solvent in vacuo, **9** was obtained as a white solid. Using an identical method, a platinum complex was prepared with ligand **2** (complex **10**). Upon applying this preparation method, *cis* complexes are usually obtained. The general trend observed in literature for *cis* complexes shows an increase in the value of the coupling constant $J_{Pt\text{-}P}$ going from diphosphines (J ~ 3500-3700 Hz),[42-45] diphosphinites (J ~ 4000-4300 Hz),[46,47] diphosphonites (J ~ 5000-5200 Hz)[32,33,41] to diphosphites (J ~ 5700-5800 Hz).[42,44] In contrast to this, typical values for coupling constants in *trans*-[Pt(**phosphine**)$_2Cl_2$] complexes are in the range of $J_{Pt\text{-}P}$ = 1800-2600 Hz.[48-50] Since the investigated ligands **1** and **2** have comparable electronic properties to diphosphonites or diphosphites and are expected to coordinate in *cis* fashion, a coupling constant of $J_{Pt\text{-}P}$ ~ 5000 Hz is expected for complexes **9** and **10**. This value has already been confirmed in literature for monodentate aminophosphines by the coupling constant of $J_{Pt\text{-}P}$ = 4800 Hz determined for a *cis*-[$PtCl_2${**P(pyrrolyl)$_3$**}$_2$] complex.[51]

The observed coupling constants for **9** and **10** are indeed in the expected range for *cis*-platinum complexes containing π-acceptor ligands such as **1** and **2** (Fig. 5.10). One singlet flanked by ^{195}Pt satellites was observed in each ^{31}P spectrum of complexes **9** and **10** at δ = 47.7 ppm and δ = 63.7 ppm, respectively, indicating the formation of platinum complexes with the corresponding ligands. A coupling constant of $J_{Pt\text{-}P}$ = 4500 Hz is observed in the ^{31}P spectrum of complex **9**, which is a value in between those observed for diphosphinites and diphosphonites. Complex **10** shows a coupling constant of $J_{Pt\text{-}P}$ = 5199 Hz, a value in the range of diphosphonite

ligands. Furthermore, the aforementioned trend of increased coupling constants with increased π-acceptor properties of the ligand was observed, since ligand **10** is expected to be a better π-acceptor ligand than **9**. Unfortunately, no crystals suitable for X-ray analysis could be obtained in order to confirm the assigned *cis* coordination of the ligands in these complexes.

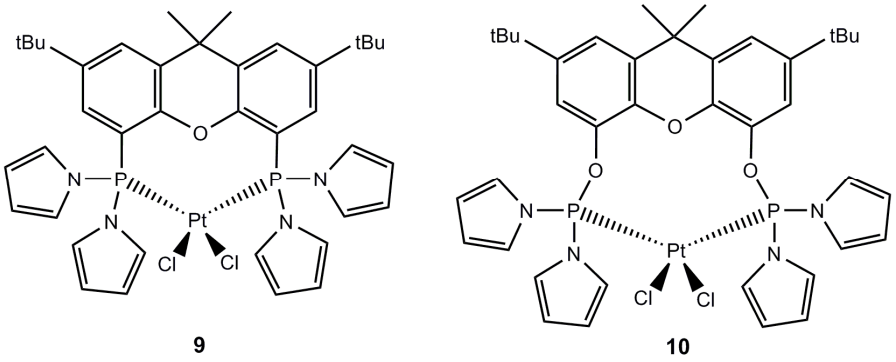

Figure 5.10: *Illustration of complex **9**, cis-[Pt(Cl)$_2$(**1**)] and complex **10**, cis-[Pt(Cl)$_2$(**2**)].*

Similar to the preparation method described for complexes **9** and **10**, complex **11** was prepared starting from [Pt(cod)Cl$_2$] and ligand **3**. The complex was obtained as a white solid and one resonance with the accompanying ^{195}Pt satellites was observed in the ^{31}P NMR spectrum at δ = 61.7 ppm with a coupling constant of $J_{Pt\text{-}P}$ = 5221 Hz. These values are almost identical to the ones of complex **10**, which is consistent with the large similarity of the substituents surrounding the phosphorus atom in both complexes. According to the value of $J_{Pt\text{-}P}$, also in this complex, *cis* coordination of the phosphorus atoms to the platinum centre is the actual coordination mode (Fig. 5.11). A compilation of determined chemical shifts and coupling constants for these platinum complexes is given in Table 5.3.

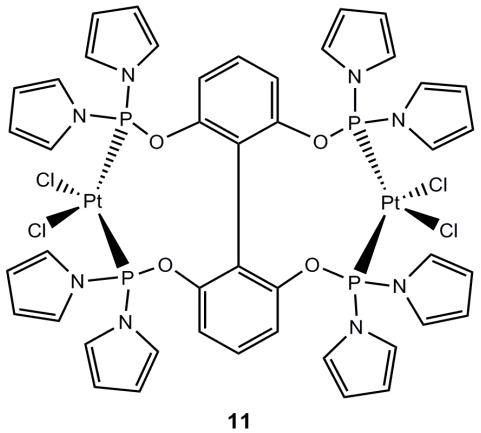

Figure 5.11: *Illustration of complex **11**, the dimeric species cis-[{Pt(Cl)$_2$ }$_2$(**3**)].*

Table 5.3 *Spectroscopic data of complexes* [Pt(Cl)$_2$(**P^P**)] *with ligands **1–3** and selenide compounds **12** and **13**.*

Complex	δ(^{31}P) [ppm][a]	J_{Rh-P} [Hz][a]	J_{Se-P} [Hz][a]
[Pt(Cl)$_2$(**1**)] (**9**)	47.67	4500	-
[Pt(Cl)$_2$(**2**)] (**10**)	63.69	5199	-
[Pt(Cl)$_2$(**3**)] (**11**)	61.73	5221	-
12	48.37	-	906
13	52.93	-	989

[a] Measured in $CDCl_3$.

5.2.3 Selenium

Apart from the coupling constant J_{Pt-P} derived from platinum complexes by ^{31}P NMR spectroscopy, also the coupling constant J_{Se-P} observed in ^{31}P NMR spectra of the corresponding phosphorus selenides is known to specifically provide information on the σ-donor ability of the phosphorus ligand.[52] In order to investigate the basicity of ligands **1** and **2**, these ligands were reacted with selenium to prepare the analogous diselenides **12** and **13**, respectively (Fig. 5.12). The reaction was performed in toluene at reflux overnight (16 hours), yielding the desired compounds as white solids.

A singlet at δ = 48.37 ppm flanked by ^{77}Se satellites with a coupling constant of J_{Se-P} = 906 Hz was observed in the ^{31}P spectrum of compound **12**. For compound **13**, a singlet was observed at δ = 52.9 ppm flanked by ^{77}Se satellites with a coupling constant of J_{Se-P} = 989 Hz. Values for coupling constants J_{Se-P} are in the range of 700-800 Hz for phosphine selenides,[52-54] in the range of 800-975 Hz for triaminophosphine selenides,[55,56] and in the range of 950-1100 Hz for selenophosphates,[52,56] which are derived from the corresponding phosphites. The values for compounds **12** and **13** nicely match with the expected range of coupling constants according to these literature values. Furthermore, the coupling constant J_{Se-P} of compound **13** is larger than the coupling constant J_{Se-P} of **12**, approaching the typical value of phosphites. Because of the expected lower σ-donor ability of compound **13**, this higher value correlates adequately with the expected trend for the coupling constant J_{Se-P}. These results confirm the assumption that ligand **2** has comparable π-acceptor properties to diphosphites, while ligand **1** can be compared to diphosphonites. The determined shifts and coupling constants are compiled in Table 5.3.

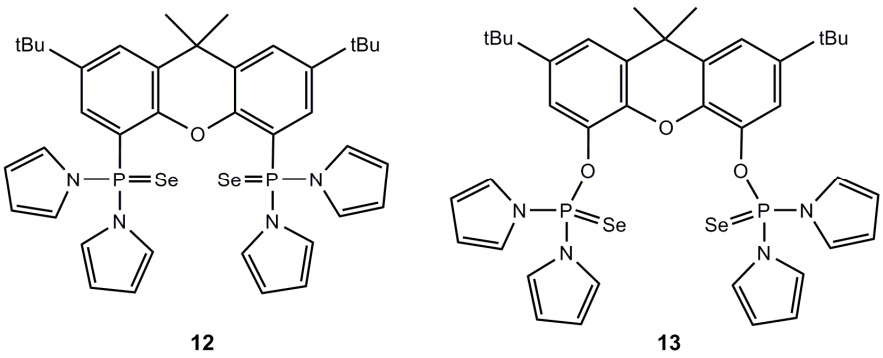

Figure 5.12: *Illustration of selenide compounds **12** and **13**.*

5.2.4 High pressure NMR and IR experiments

High pressure NMR and IR experiments were performed in order to investigate the rhodium complexes under hydroformylation/hydroaminomethylation reaction conditions. Therefore, rhodium complexes containing ligands **1**–**3** were prepared by pressurising a mixture of the corresponding ligand and [Rh(acac)(CO)$_2$] in benzene-d$_6$ in a high pressure NMR tube to p = 20 bar with synthesis gas (1:1) at 45 ºC overnight (16 hours), yielding a light yellow complex solution.

First, the complex containing ligand **1**, [RhH(**1**)(CO)$_2$], was studied by ^{1}H and ^{31}P NMR spectroscopy. A broad singlet was observed in the hydride region of the ^{1}H NMR spectrum at δ = –9.0 ppm. A doublet at δ = 91.6 ppm with a coupling constant of $J_{Rh\text{-}P}$ = 178 Hz was observed in the ^{31}P NMR spectrum. The broad singlet is an indication that the ligand coordinates in an ee fashion to the rhodium atom, usually leading to very small $J_{P\text{-}H}$. Furthermore, the coupling constant $J_{Rh\text{-}P}$ is quite large which is an indication of the good π-acceptor properties of the ligand, but is also observed for ee coordinating ligands.[35]

Additionally, complexes containing ligands **2** and **3** were investigated in a similar way. The complex [RhH(**3**)(CO)$_2$] showed identical results to complex [RhH(**1**)(CO)$_2$]. Also here a broad singlet was observed in the ^{1}H NMR spectrum at δ = –10.7 ppm. A doublet at δ = 136.6 ppm with a coupling constant of $J_{Rh\text{-}P}$ = 219 Hz was observed in the ^{31}P NMR spectrum. The results for this complex also indicate ee coordination of the ligand to the metal centre and even better π-acceptor properties.

In contrast to this, a doublet of triplets at δ = –9.6 ppm was observed in the ^{1}H NMR spectrum for the hydride signal of complex [RhH(**2**)(CO)$_2$] (Fig. 5.13) with coupling constants of $J_{Rh\text{-}H}$ = 4.5 Hz and $J_{P\text{-}H}$ = 30.6 Hz. The presence of a doublet of triplets could be an indication that

the ligand coordinates in an ea mode, in combination with fast exchange of the phosphorus atoms on the NMR time scale. However, the coupling constant J_{P-H} is smaller than the characteristic values observed for ea coordination, while this value is at the upper limit for ee coordination. A doublet at δ = 135.8 ppm with a coupling constant J_{Rh-P} of 200 Hz was observed in the ^{31}P NMR spectrum. In fact, this value was expected to be in the same range as the coupling constant of J_{Rh-P} = 219 Hz in [RhH(**3**)$(CO)_2$] and, again, indicates ee coordination and good π-acceptor properties of complexes containing this ligand. Since coupling constants of ea isomers are generally smaller than those of ee isomers,[7] the value of the coupling constant J_{Rh-P} in combination with the aforementioned data indicates that **2** coordinates in an ee fashion.

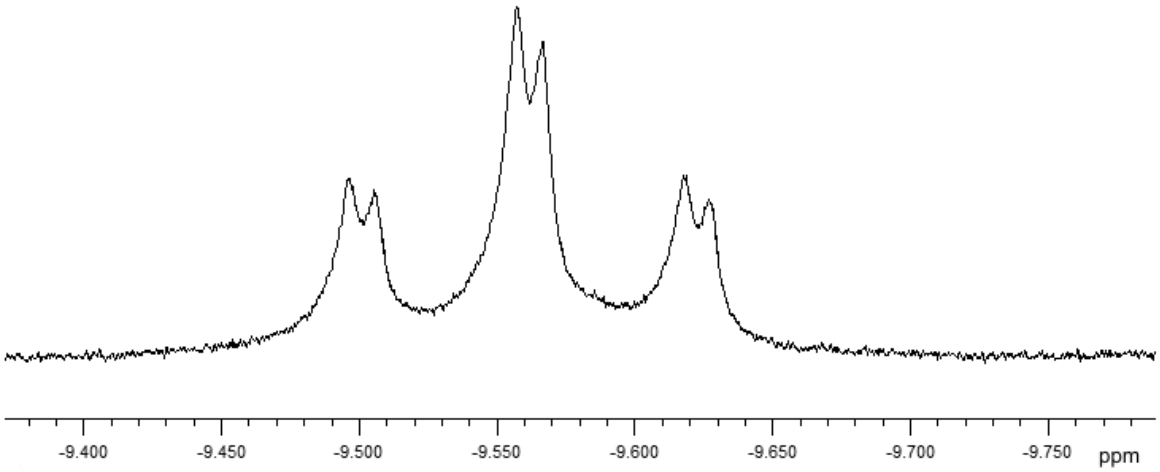

Figure 5.13: *^1H NMR spectrum of [RhH(**2**)$(CO)_2$], hydride region. Spectrum measured in benzene-d_6 at room temperature and p = 20 bar CO/H_2 (1:1).*

Complex [RhH(**1**)$(CO)_2$] was also studied by means of high pressure IR spectroscopy. For that purpose, a home-made 50 mL stainless steel autoclave with an integrated flow cell equipped with a mechanical stirrer, temperature control and an IR spectrometer was filled with the catalyst/metal precursor solution, pressurised to p = 20 bar and heated to T = 60ºC. IR spectra were recorded from the moment the desired temperature was reached and the formation of the complex was observed. After approximately 3 hours, the complex formation was complete and four carbonyl absorptions were observed at ν = 2062, 2018, 2000, and 1974 cm^{-1}. The absorptions at 2062 cm^{-1} and 2000 cm^{-1} were identical in intensity and can be ascribed to ee coordination of the ligand. In contrast, the absorption at 2018 cm^{-1} was clearly lower in intensity than the absorption at 1974 cm^{-1}, which is a clear indication of ea coordination. According to these results, both ee and ea coordination are present in the complex, although no straightforward conclusion from these data can be drawn with respect to the ratio of ee and ea coordination in the complex.

However, according to the data obtained by high pressure NMR spectroscopy, the ee coordination mode is the prevailing coordination mode. In summary, high pressure NMR spectroscopy data of rhodium complexes containing aminophosphine ligands **1**–**3** indicate ee coordination of these ligands although the presence of an ea coordination mode was confirmed by IR spectroscopy for the rhodium complex containing ligand **1**. All determined values are compiled in Table 5.4.

Table 5.4 *Spectroscopic data of trigonal bipyramidal complexes [RhH(**P^P**)(CO)$_2$] with ligands **1**–**3**.*

Complex	$\delta(^1H)$ [ppm][a]	$\delta(^{31}P)$ [ppm][a]	J_{P-H} [Hz]	J_{Rh-H} [Hz]	J_{Rh-P} [Hz]	ν_{CO} [cm^{-1}][b]
[RhH(**1**)(CO)$_2$]	–9.0 (br)	91.6	n.d.	n.d.	178	2062, 2018, 2000,1974
[RhH(**2**)(CO)$_2$]	–9.6 (dt)	135.8	30.6	4.5	200	n.d.
[RhH(**3**)(CO)$_2$]	–10.7 (br)	136.6	n.d.	n.d.	219	n.d.

[a] Measured in benzene-d$_6$. [b] Measured in 2-methyltetrahydrofuran.

5.3 Conclusions

This chapter deals with the coordination chemistry of novel aminophosphine ligands **1**–**3** with rhodium and platinum, leading to the expected *trans*-[RhCl(CO)(**P^P**)] complexes for ligand **1**, and *cis*-[Pt(**P^P**)Cl$_2$] complexes for ligands **1**–**3**. The coordination chemistry was investigated under reaction conditions by high pressure NMR and IR spectroscopy.

Ligands **2** and **3** show comparable and very good π-acceptor properties, which are in the same range of diphosphonite and diphosphite ligands. Especially the CO stretch vibrations, for *trans*-[RhCl(CO)(**P^P**)] complexes and the coupling constants J_{Rh-P} in *cis*-[Pt(**P^P**)Cl$_2$] complexes, were useful in this respect. Ligand **1** shows slightly lower π-acceptor properties, which are still in the range of diphosphonites. Corresponding selenides were prepared from ligands **1** and **2** in order to confirm the data with respect to their electronic properties. This method shows a slightly increased phosphorus basicity for ligand **1** which is in accordance with other data obtained. Still, the values for the coupling constants J_{Se-P} are in the range of diphosphonites and diphosphites.

The X-ray crystal structure was determined for the complex *trans*-[RhCl(CO)(**Xantphos**)]. Various bond lengths, distances and angles were compared to structural data of diphosphonite ligands, which have electronic properties similar to these aminophosphine ligands. The most striking difference is the Rh-P bond length, which is smaller in the Rh-diphosphonite complex, due to increased back-donation from metal to phosphorus upon complexation with this ligand.

Investigations using high pressure NMR and IR spectroscopy showed the formation of trigonal bipyramidal rhodium species under CO/H_2 reaction conditions. High pressure NMR spectroscopy data of rhodium complexes containing aminophosphine ligands **1**–**3** clearly indicated an ee coordination mode of these ligands in the complex. High pressure IR spectroscopy confirmed the presence of an ee coordination mode, although ea coordination was also observed. However, the ratio of ee:ea coordination could not be determined by the available IR data. On the basis of the NMR data, ee coordination was expected to be the prevailing coordination mode. Large π-acceptor abilities were observed in these complexes by the large coupling constants $J_{Rh\text{-}P}$, typical for diphosphites.

5.4 Experimental section

All air- or water-sensitive operations were performed using standard Schlenk techniques under purified argon atmosphere. Toluene, *n*-hexane, Et_2O, and dichloromethane were purified over custom-made alumina columns. 2-Methyltetrahydrofuran and acetonitrile were distilled from CaH_2. Solvents and benzene-d_6 were degassed prior to use. Chemicals were purchased from Acros Chimica, Merck KGaA, Biosolve B.V., and Aldrich Chemical Co. $[Rh(acac)(CO)_2]$ was obtained as a generous loan from OMG and $[Pt(cod)Cl_2]$ was synthesised according to a literature procedure.[57] Synthesis gas (CO (99.997%)/H_2 (99.999%); 1:1) was purchased from Linde Gas. NMR data were recorded on a Varian Mercury Vx 400 MHz or Varian Unity Inova 500 MHz NMR spectrometer. Elemental analysis was performed on a Perkin Elmer 2400 series II CHNS/O Analyser. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer and on a Shimadzu 8300 FT-IR spectrometer (high pressure experiment).

General procedure for high pressure NMR experiments

High pressure NMR experiments were performed on a Varian Unity Inova 500 MHz NMR spectrometer. A 10 mm (outer diameter) sapphire tube with a concentrical, self-fitting titanium valve, able to spin at 15-17 Hz,[58] was used. In a typical experiment, $[Rh(acac)(CO)_2]$ (7.0 mg; 27.1 μmol) and 1.05-1.1 equivalents of ligand were dissolved in 1.8 mL of degassed benzene-d_6 and the solution was stirred for 30 minutes. The catalyst solution was then transferred to the sapphire tube, which was oven-dried and under argon atmosphere and argon flow. The tube was flushed three times with 10 bar of synthesis gas and then pressurised to p = 20 bar with synthesis gas (1:1). Preformation was performed by heating the tube in an oil bath at T = 45ºC overnight (16 hours). After cooling the tube to r.t., the spectra were recorded.

General procedure for high pressure FT-IR experiments

High pressure FT-IR experiments were carried out using a home-made 50 mL stainless steel autoclave with an integrated flow cell equipped with ZnS windows, a mechanical stirrer, temperature control and a Shimadzu 8300 FT-IR spectrometer. The IR autoclave was flushed for 2 hours with synthesis gas before the start of the experiment. In a typical experiment, $[Rh(acac)(CO)_2]$ (4.0 mg; 15.5 μmol) and 2 equivalents of ligand were dissolved in 15 mL of degassed 2-methyltetrahydrofuran and the solution was stirred for 30 minutes. The catalyst solution was then transferred to the IR autoclave under argon flow. The autoclave was flushed three times by applying 8 bar of synthesis gas pressure and subsequent release of pressure. Then, the autoclave was pressurised to 17 bar with synthesis gas (1:1), heated to 60ºC under stirring (600 rpm) and pressurised to the desired reaction pressure of 20 bar. After this, the measurement was started and spectra were recorded at certain time intervals.

Synthesis of *trans*-[RhCl(CO)(1)] (complex 4)

Ligand **1** (65.0 mg; 100.5 μmol) in dichloromethane (3 mL) was slowly added to $[Rh(CO)_2Cl]_2$ (19.5 mg; 50.2 μmol) in dichloromethane (4 mL). The red/orange solution turned yellow upon addition of the ligand. The reaction mixture was stirred overnight at r.t. yielding an orange/yellow solution. The solvent was removed in vacuo yielding the rhodium complex as a yellow/orange solid in 76% yield. No crystals suitable for X-ray diffraction could be obtained using layering and gas diffusion techniques with CH_2Cl_2/CH_3CN and CH_2Cl_2/Et_2O. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (s, 4H), 6.85 (s, 8H), 6.15 (s, 8H), 1.91 (s, 6H), 1.09 (s, 18H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 100.02 ppm (d, J_{Rh-P} = 225.9 Hz). FTIR (ATR mode, solid, cm^{-1}): ν 1999 (Rh(CO)).

Synthesis of rhodium complex 5

Ligand **2** (209.8 mg; 309.1 μmol) in dichloromethane (7 mL) was slowly added to $[Rh(CO)_2Cl]_2$ (60.1 mg; 154.6 μmol) in dichloromethane (10 mL). The orange solution turned yellow upon addition of the ligand. The reaction mixture was stirred overnight at r.t. yielding a yellow solution. The solvent was removed in vacuo yielding the rhodium complex as a yellow solid in 97% yield. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 122.46, 115.74, 111,67 ppm (d, d, d, J_{Rh-P} = 266.5, 279.4, 191.2 Hz). FTIR (ATR mode, solid, cm^{-1}): ν 2021 (Rh(CO)).

Synthesis of *trans*-[RhCl(CO)(Xantphos)] (complex 6)

Xantphos (56.6 mg; 97.8 μmol) in dichloromethane (3 mL) was slowly added to $[Rh(CO)_2Cl]_2$ (19.0 mg; 48.9 μmol) in dichloromethane (3 mL). The red/orange solution turned yellow/orange upon addition of the ligand. The reaction mixture was stirred for 2 hours at r.t. yielding a yellow/orange solution. The solvent was removed in vacuo yielding the rhodium complex as a yellow solid in 89% yield. Crystals suitable for X-ray crystallography were obtained by layering with CH_2Cl_2/CH_3CN. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (m,

4H), 7.36 (m, 14H), 7.15 (m, 8H), 1.68 (br, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.82, 133.85, 132.83, 130.02, 128.29, 128.24, 124.03, 53.85 35.64 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 21.05 ppm (d, J_{Rh-P} = 130.8 Hz). FTIR (ATR mode, solid, cm^{-1}): ν 1984 (Rh(CO)).

Synthesis of [{RhCl(CO)}$_2$(3)] (complex 8)

Tetraphos ligand **3** (160.8 mg; 185.5 μmol) in dichloromethane (3 mL) was slowly added to $[Rh(CO)_2Cl]_2$ (72.1 mg; 185.5 μmol) in dichloromethane (4 mL). The red/orange solution turned yellow/orange upon addition of the ligand. The reaction mixture was stirred for 2 hours at r.t. yielding a yellow/orange solution. The solvent was removed in vacuo, but the desired complex was not obtained, since only the signal of the free ligand was observed in the ^{31}P NMR spectrum. Subsequently, toluene was added and the reaction mixture was stirred overnight at 75°C. Then, the reaction mixture was cooled to r.t. and the solvent was removed in vacuo yielding a yellow solid. No crystals suitable for X-ray diffraction could be obtained using layering and gas diffusion techniques with CH_2Cl_2/CH_3CN. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (m, 2H), 7.54 (m, 2H), 7.18 (m, 2H), 6.73 (br, 16H), 6.24 (br, 16H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 110.63 ppm (br). FTIR (ATR mode, solid, cm^{-1}): ν 2022 (Rh(CO)).

Synthesis of *cis*-[Pt(Cl)$_2$(1)] (complex 9)

Ligand **1** (50.8 mg; 78.5 μmol) in dichloromethane (5 mL) was slowly added to $[Pt(cod)Cl_2]$ (29.1 mg; 77.8 μmol) in dichloromethane (6 mL). The colourless solution was stirred overnight at r.t., but only a small amount of product was obtained. Then, the reaction mixture was heated to reflux for 8 hours, cooled to r.t. and the solvent was removed in vacuo yielding the platinum complex as a white solid in 87% yield. No crystals suitable for X-ray diffraction could be obtained using layering techniques with CH_2Cl_2/CH_3CN and CH_2Cl_2/Et_2O. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 2H), 7.58 (m, 2H), 6.70 (br s, 8H), 6.08 (s, 8H), 1.84 (s, 6H), 1.29 (s, 18H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 47.67 ppm (s, J_{Pt-P} = 4500 Hz).

Synthesis of *cis*-[Pt(Cl)$_2$(2)] (complex 10)

Ligand **2** (72.9 mg; 107.5 μmol) in dichloromethane (5 mL) was slowly added to $[Pt(cod)Cl_2]$ (40.3 mg; 107.7 μmol) in dichloromethane (6 mL). The colourless solution was stirred at r.t. for 4 hours and the solvent was removed in vacuo to yield the platinum complex as a white solid in 95% yield. No crystals suitable for X-ray diffraction could be obtained using layering and gas diffusion techniques with CH_2Cl_2/CH_3CN and CH_2Cl_2/Et_2O. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (s, 2H), 6.84 (m, 8H), 6.66 (s, 2H), 6.23 (m, 8H), 1.74 (s, 6H), 1.23 (s, 18H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 63.69 ppm (s, J_{Pt-P} = 5199 Hz).

Synthesis of *cis*, *cis*-[{Pt(Cl)$_2$}$_2$(3)] (complex 11)

Ligand **3** (60.3 mg; 69.6 μmol) in dichloromethane (4 mL) was slowly added to [Pt(cod)Cl$_2$] (51.5 mg; 137.6 μmol) in dichloromethane (6 mL). The colourless solution was stirred at r.t. over the weekend (62 hours). The solvent was removed in vacuo and the remaining solid was washed with *n*-hexane (2 mL) to yield the platinum complex as a white solid in 83% yield. No crystals suitable for X-ray diffraction could be obtained using layering and gas diffusion techniques with CH_2Cl_2/CH_3CN. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (t, 2H, J = 8.42 Hz), 6.91 (s, 8H), 6.78 (m, 12H), 6.44 (s, 8H), 6.21 (s, 8H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 61.73 ppm (s, $J_{Pt\text{-}P}$ = 5221 Hz).

Synthesis of 4,5-bis[(dipyrrolyl)phosphino]-3,6-di-*tert*-butyl-9,9-dimethylxanthene selenide [DPX-selenide] (12)

Ligand **1** (50.1 mg; 77.5 μmol) and an excess selenium (31.4 mg; 397.7 μmol) were weighed in a Schlenk flask and toluene (6 mL) was added. The suspension was heated at reflux overnight (16 hours), cooled to r.t. and filtered. The solvent was removed in vacuo to yield the complex as an off-white solid in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 2H), 7.46 (s, 2H), 7.03 (br s, 4H), 6.62 (s, 4H), 6.40 (s, 4H), 6.26 (s, 4H), 1.64 (s, 6H), 1.17 (s, 9H), 1.12 (s, 9H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 48.37 ppm (s, $J_{Se\text{-}P}$ = 906 Hz).

Synthesis of bis-[(dipyrrolyl)phosphamidato]-3,6-di-*tert*-butyl-9,9-dimethylxanthene selenide [DPXO-selenide] (13)

Ligand **2** (57.8 mg; 85.2 μmol) and an excess selenium (31.8 mg; 402.7 μmol) were weighed in a Schlenk flask and toluene (6 mL) was added. The suspension was heated at reflux for 4 hours, cooled to r.t. and filtered. The solvent was removed in vacuo and a white precipitate was formed upon addition of *n*-hexane (3 mL) to the remaining oil. The solid was isolated by filtration and dried in vacuo to yield the pure compound as a white solid in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (s, 2H), 7.18 (m, 8H), 6.44 (s, 2H), 6.25 (m, 8H), 1.62 (s, 6H), 1.17 (s, 18H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 52.93 ppm (s, $J_{Se\text{-}P}$ = 989 Hz).

Crystallographic data for *trans*-[RhCl(CO)(Xantphos)] (complex 6)

$C_{40}H_{32}ClO_2P_2Rh$, F_w = 744.96, 0.36 x 0.48 x 0.51 mm, monoclinic, $P2_1/c$ (no. 14), A = 11.8674(2) Å, B = 18.1780(4) Å, c = 19.4419(3) Å, α = 90º, β = 121.370(1)º, γ = 90º, V = 3581.04(12) Å^3, Z = 4, d_{calc} = 1.382 g/cm^3, μ (Mo-Kα) = 0.674 mm^{-1}, T = 150 K, total reflections: 70082, unique reflections: 8226; R_{int} = 0.021, [I>2σ(I)] = 7178, S = 1.08, wR_2 (F^2) = 0.0624, R_1 = 0.0240, F(000) = 1520.

5.5 References

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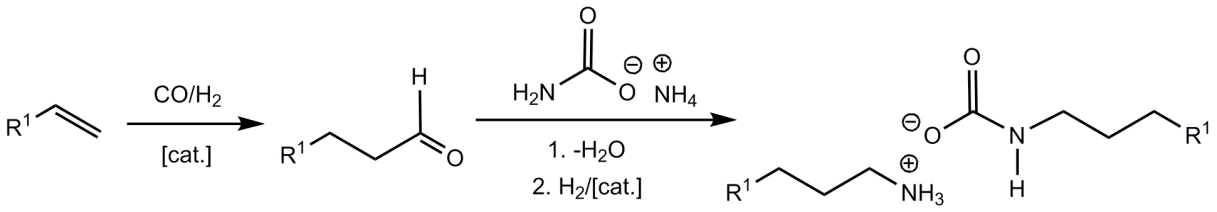
6

Future perspectives on hydroaminomethylation

Although the hydroaminomethylation reaction is a promising and atom-efficient alternative for the classical production process towards amines, this reaction has not been applied on a large scale in industry to date. On the other hand, in recent (patent) literature, more and more publications concerning this interesting reaction can be found. The main reasons for its absence in industry might be that most publications mention rhodium, which is a very expensive metal. Moreover, no chemo- and regioselective synthesis of linear primary amines via hydroaminomethylation with NH_3 has been reported up to now. Most probably, this reaction will first be applied in fine chemical or pharmaceutical industry, since smaller product volumes and higher added value are common practice in these industries. For bulk chemical application, this reaction needs further optimisation for which intensive and challenging research is necessary. This chapter deals with these possibilities and the future of hydroaminomethylation. Hydroaminomethylation with protected amines and the opportunities of primary amine protection by using ammonium carbamate as a combined substrate/dynamic protection group will be presented.



6.1 Introduction

In current industrial chemistry, waste reduction, energy efficiency, atom efficiency and the availability and price of starting materials are of very high importance. For that reason, companies continuously search for alternative production technologies in order to meet these requirements. In this respect, atom-efficient catalytic reactions are promising as they allow to reduce waste production. Especially homogeneous catalysis opens up a range of opportunities with regard to these issues, which paves the way to the use of mixtures of alkenes as substrates and highly atom economic processes.[1]

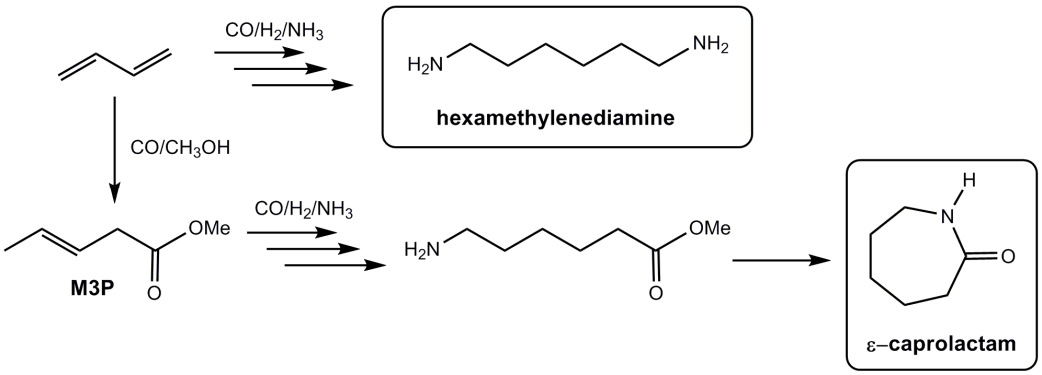
As shown already in Chapter 1, the hydroaminomethylation reaction is a very promising, atom-efficient reaction for the production of amines in which water is the only side product. As the amount of side products (mainly inorganic salts) formed per kg of product is large in pharmaceutical and fine chemical industry compared to bulk chemical industry (Tab. 6.1),[2] large improvements with respect to waste reduction can be made there. The high added value of these products makes it more likely that expensive Rh- or Rh/Ir- catalysed reactions to synthesise amines will be implemented first in pharmaceutical or fine chemical industry. Nevertheless, also in bulk chemical processes large improvements can be made upon applying the HAM in the production of amines in comparison to the classical routes. However, to make these processes profitable, very high turnover numbers, recyclable or cheap catalysts, and high selectivities towards primary amines are needed for a broad range of alkene and amine substrates including mixtures of internal and terminal alkenes.

Table 6.1: *Amount of side product formed per kg product in comparison to the annual production in the various chemical industries.*[2]

Entry	Chemical Industry	Annual production [ton]	kg side product / kg product
1	Bulk chemicals	10^4–10^6	<1 – 5
2	Fine chemicals	10^2–10^4	5 – 50
3	Pharmaceuticals	10–10^3	25 – >100

Two interesting examples of target reactions in bulk chemical industry are the double hydroaminomethylation of 1,3-butadiene with ammonia towards hexamethylenediamine and the HAM of methyl-3-pentenoate, a product synthesised *via* methoxycarbonylation of 1,3-butadiene. Reaction with ammonia towards aminohexanoate and a subsequent ring-closure would lead to a new route towards ε-caprolactam (Scheme 6.1). Both products are important bulk chemicals in the

production of Nylon, an important product for many applications such as clothing, airbags, ballistic vests and molded plastic parts. Hexamethylenediamine is a building block in the synthesis (polycondensation) of Nylon-6,6, while ε-caprolactam forms the basis for the production of Nylon-6. Hexamethylenediamine is produced commercially by catalytic hydrogenation of adiponitrile, which is produced by three different multi-step processes, often run under harsh conditions or upon using very poisonous reactants (i.e. hydrogen cyanide). ε-Caprolactam is mainly produced nowadays by the cyclohexanone process, which is also a multistep process including a low conversion step and a Beckmann rearrangement in which large amounts of ammonium sulphate are produced. If the synthesis of these compounds can be performed selectively and with high turnover numbers *via* HAM, both Nylon building blocks can be synthesised from cheap feedstocks (butadiene, CO, H_2, NH_3, MeOH) in combination with an enormous waste reduction, less reaction and purification steps and consequently a considerable cost reduction.



Scheme 6.1: *Possible synthesis of hexamethylenediamine and ε-caprolactam from cheap feedstocks by hydroaminomethylation.*

The double functionalisation of 1,3-butadiene by HAM can proceed stepwise *via* several possible intermediates like aminopentene. Selective formation of the linear primary diamine is an important issue in this reaction. Another possibility is the initial formation of 1,6-hexanedial before the functionalisation with amine by reductive amination takes place. The reaction towards the formation of 1,6-hexanedial has been studied in literature and, as expected, turned out to be rather difficult.[3,4] First, the conjugated isomerisation product 2-pentenal, which can be formed *via* isomerisation of 3-pentenal is quite stable and prone to hydrogenation. However, isomerisation activity is needed, since an isomerisation from 3-pentenal to 4-pentenal has to occur in order to produce 1,6-hexanedial. Secondly, the occurring condensation reactions with the formed aldehydes

lead to complex reaction mixtures. Only one literature example can be found in which moderate selectivities towards 1,6-hexanedial were obtained albeit both hydroformylation steps were performed separately in this example.[5] For this reason, HAM with ammonia will be investigated with simple alkenes first. Mainly, the synthesis of linear primary aliphatic amines will be discussed. Thereby, the focus will be on the use of ammonia and its derivatives. Also a protection/deprotection approach using benzylamine or phthalimide will be regarded. This chapter deals with some interesting future perspectives, possibilities and ideas with respect to the HAM reaction.

6.2 Ammonia in the hydroaminomethylation reaction

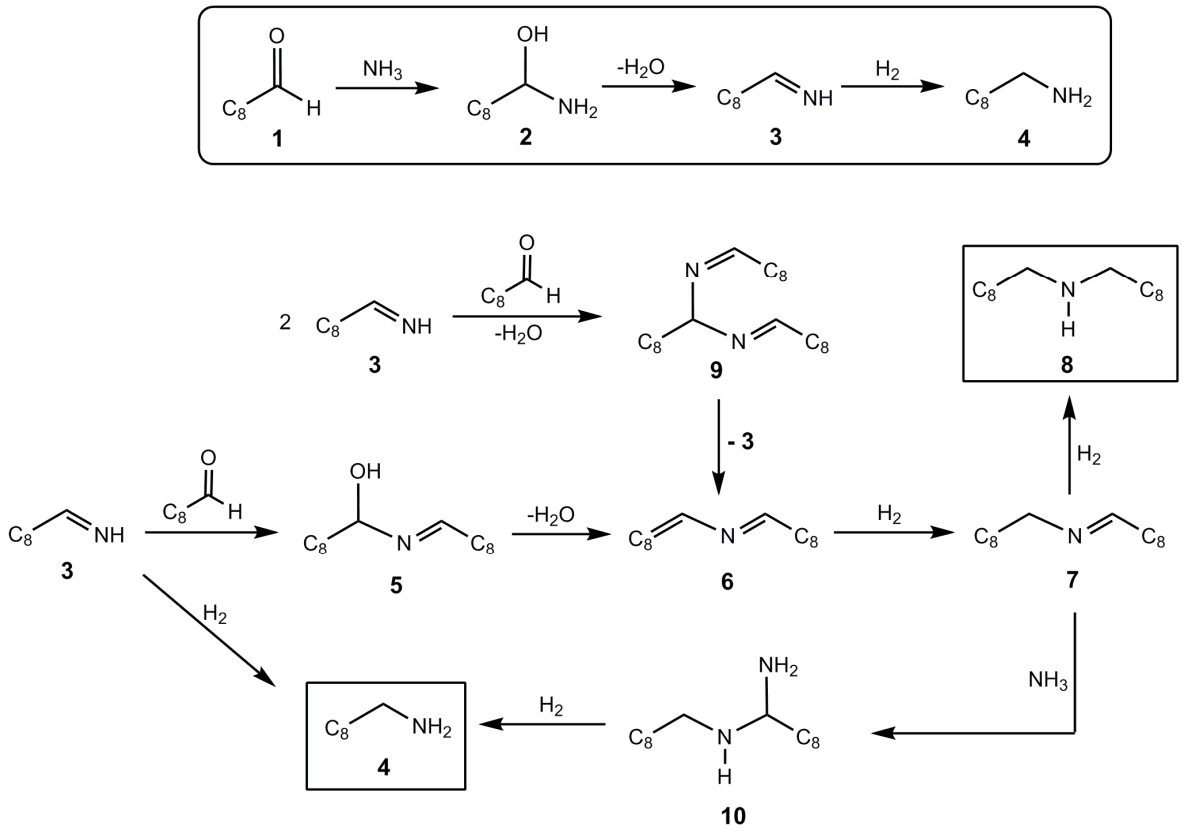
Ammonia or an ammonia derivative as an amine source is a requirement in the HAM towards primary amines, which are of high industrial relevance as mentioned in the introduction. However, one of the difficulties in this reaction is the fact that the synthesised primary amine is a better nucleophile than NH_3 and will preferentially react with the intermediate aldehyde, in this way forming a secondary amine. In turn, this secondary amine can also react with intermediate aldehyde leading to a tertiary amine.[6] One possibility to overcome this selectivity issue is to use a large excess of ammonia, using liquid or even supercritical ammonia in the most extreme case. In this way the chance that a primary amine reacts with the intermediate aldehyde is reduced. However, upon performing the reaction with large excesses of ammonia, NH_3, being a ligand itself, will compete with the ligands applied. Consequently this leads to a loss of regioselectivity in the hydroformylation step, resulting in large amounts of branched amine.

Such a catalytic reaction of an alkene with ammonia has been studied by Knifton in the late 1990s.[7] [$Co_2(CO)_8$] and phosphines were used as the catalyst under harsh reaction conditions (T = 200ºC and p = 140 bar). Reasonable selectivities were obtained at low conversion, but higher conversions led to a decrease in selectivity. Lowering the reaction temperature had a negative effect on the reactivity and a large excess of ammonia could lead to complete inhibition of the reaction (both for the hydroformylation and for the reductive amination).

Other examples stem from Beller and co-workers. One example makes use of a biphasic system and a bimetallic (Rh/Ir) catalyst in which selectivities of up to 91% for the primary amine were obtained.[8] Water soluble ligands (TPPTS[9,10], BINAS[11,12]) were used in this case in order to perform the reaction in the water phase while the organic phase contained the reactants and products. However, a consequence of this approach is that only short chain alkenes can be used because of water solubility aspects. It was suggested that the extraction of products from the catalyst phase leads to a high selectivity for the primary amine in this reaction. On the other hand, both

aldehyde and primary amine will be present in the organic phase, potentially leading to enamine formation and consecutively to amine product upon re-extraction into the water phase containing the catalyst. The bimetallic catalyst was used in order to increase the hydrogenation rate, since it is well-known that iridium is an efficient catalyst for C=N double bond hydrogenation. Also in this reaction, an excess of ammonia in comparison to alkene was used.

In the second example supercritical ammonia was used in order to selectively synthesise primary amines *via* HAM.[13-15] Also in this case, a bimetallic Rh/Ir catalyst was applied together with rather harsh reaction conditions (T = 140ºC and p = 190-240 bar). In this system, also long chain alkenes could be used and 1-octene was applied as the substrate. At optimal reaction conditions, 60% of the primary amine was obtained together with a regioselectivity of 57% towards the linear amine, in combination with 16% secondary amine and 4% alkane in pure MeOH as the solvent and a syngas ratio of 1:3. The regioselectivity decreased upon increasing the CO partial pressure. In contrast, the hydrogenation of the alkene increased upon increasing the H_2 partial pressure. This means that the CO/H_2 ratio influences both regio- and chemoselectivity. Interestingly, the best results were obtained in absence of a ligand and upon addition of acetic acid.



Scheme 6.2: *Reductive amination of nonanal with ammonia and possible intermediates.*

As shown in these examples (*vide supra*) it is difficult to synthesise primary amines with ammonia *via* HAM. Furthermore, besides the standard selectivity issues in HAM, such as regioselectivity, aldol condensation reactions, hydrogenation of starting compounds to alkanes or hydrogenation of intermediate aldehyde to alcohols, some other difficulties turn up when using ammonia as the amine source. The condensation reaction of aldehyde (**1**) and ammonia gives an imine (**3**), which can be hydrogenated to the desired primary amine (**4**), but many intermediates, like hemiaminals (**2** and **5**), diiminoaminal (**9**), enimine (**6**), diamine (**10**) and secondary imine (**7**), which can lead to the secondary amine upon hydrogenation, are possibly also formed (Scheme 6.2).[16] Furthermore, (hemi)acetals can be formed from the intermediate aldehyde upon using an alcohol in the solvent mixture or with an alcohol formed from the aldehyde in the reaction mixture (Fig. 6.1). From this (hemi-)acetal, a methyl ether can be formed although this product was only observed in slow reactions with [$Rh(CO)_2$acac] as the metal precursor. In case of the above-mentioned intermediates fast and efficient hydrogenation of the imine or its intermediates is important in order to obtain the desired amine product. In fact, it has been suggested that hydrogenation of the intermediates is faster than the hydrogenation of the primary imine.

hemiacetal **acetal**

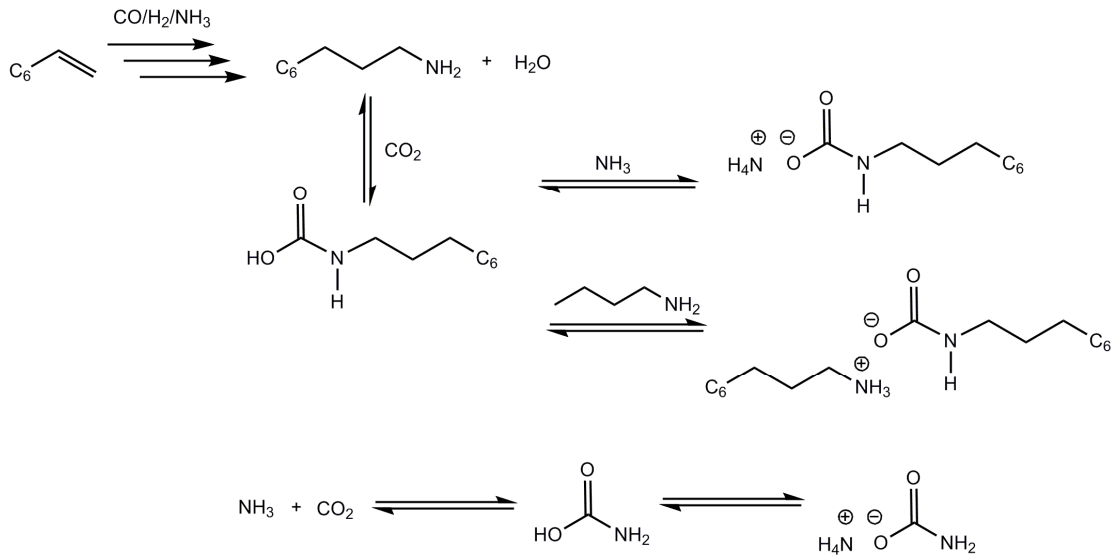
Fig. 6.1: *Possible acetal products from nonanal and MeOH.*

6.3 Protection by carbon dioxide

Since it is very difficult to prepare primary amines *via* HAM with ammonia selectively, the use of protection groups is a possible solution. On the other hand, protection groups have the large disadvantage that an additional reaction step, the deprotection, has to be included. However, a very elegant solution to this problem is the protection of the primary amine with carbon dioxide by formation of carbamic salts. Although carbon dioxide is in general a rather unreactive molecule, it has proven its potential in organic chemistry[17] and it combines rapidly with amines to form carbamates.[18, 19] This method is used industrially in so-called amine treating units and CO_2 scavengers in order to remove carbon dioxide from gas streams or to capture and store CO_2.[20-25] Recently, this reaction has been used for gas sensing,[26-28] in the reversible formation of organogels[29-31] and has even been described for CO_2 capture with ionic liquids.[32]

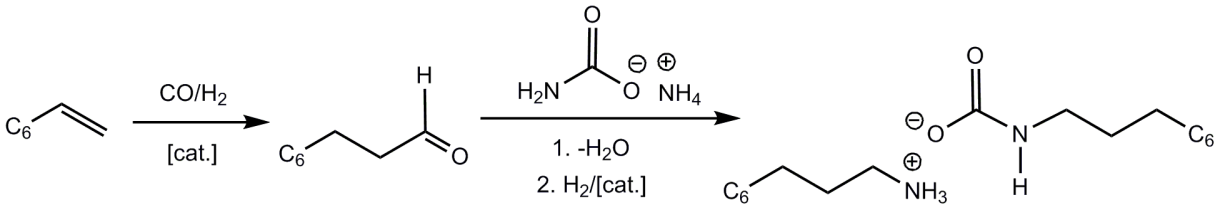
The aforementioned reaction with CO_2 has been recently investigated under hydroaminomethylation conditions in supercritical carbon dioxide. In this example a secondary amine substrate is protected in order to prevent an intramolecular cyclisation reaction before the actual hydroformylation and subsequent intermolecular condensation/hydrogenation can take place.[33] In a reaction with a primary alkylamine, one carbon dioxide molecule protects two amine molecules as an *N*-alkylammonium *N*-alkylcarbamate (Scheme 6.3). Another possibility is the formation of a carbamic salt from carbon dioxide, one primary amine molecule and one molecule of NH_3. The carbamic salt is preferably insoluble in the applied solvent system because of separation reasons. Upon releasing the pressure after reaction and upon heating if necessary, CO_2 will be released, liberating the desired primary amine. Although this is a very promising alternative for the synthesis of primary amines by hydroaminomethylation, this route is also a very challenging one.

In order to selectively protect the primary amine formed in the reaction, carbon dioxide has to be added to the autoclave at a certain rate, depending on the rate of amine formation. However, this rate is not constant during the reaction, making it rather difficult to dose CO_2 in the appropriate amount to the reaction mixture. If CO_2 is present in excess at the start of the reaction, it will form ammonium carbamate with ammonia. This could lead to a situation in which no free ammonia is present for the reaction and the reactor will just be filled with ammonium carbamate (Scheme 6.3). One possible solution to this problem could be the addition of CO_2 *via* a high-pressure ISCO syringe pump, which can be adjusted very accurately.



Scheme 6.3: *Carbon dioxide protection of a primary amine and the possible formation of ammonium carbamate.*

Although it seems that an excess of carbon dioxide in combination with ammonia will give an inactive salt, it might also be possible that this ammonium carbamate can be used as ammonia source under the right reaction conditions. Possibly, a small amount of ammonia is present in its unprotected form at reaction temperature in the hydroaminomethylation reactions. In this case, it is available for the condensation with the present aldehyde. After hydrogenation, the primary amine will be protected by the free carbon dioxide (Scheme 6.4). Since it is also possible to form the secondary amine by reaction of the imine with the intermediate aldehyde as shown in Scheme 6.2, it is important to hydrogenate the imine fast and selectively to the primary amine.



Scheme 6.4: *Hydroaminomethylation and consecutive primary amine protection by using ammonium carbamate as the ammonia source.*

Analysis of carbamic acids and *N*-alkylammonium *N*-alkylcarbamates (carbamic salts) has been described in literature and the most common analysis techniques for these compounds turned out to be ^{1}H and ^{13}C NMR spectroscopy.[18,26,29,34] However, in addition to these techniques, also differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), IR spectroscopy, elemental analysis and even X-ray diffraction have been used to analyse these compounds.[19,35] Especially DSC in combination with TGA turned out to be useful and complementary techniques, but also ^{1}H and ^{13}C NMR spectroscopy in DMSO-d_6, or alternatively, in another NMR solvent, are very useful techniques to analyse these compounds. In the analysis of octylammonium-octylcarbamate for example,[35] four endothermic transitions were observed in the DSC thermogram. In combination with the results of TGA, these could be addressed to hydrocarbon chain rearrangement (~56ºC), melting (~88ºC), degradation to amine and CO_2 (~120ºC) and boiling of the amine (~178ºC). In combination with the data from NMR analysis, which clearly show the presence of NH-, NH_3^+- and C=O-functionalities, the identity of these compounds was determined.

The possibility of performing the hydroaminomethylation reaction as described above with ammonium carbamate as the ammonia source was investigated by addition of nonylamine to ammonium carbamate in an autoclave. Ammonium carbamate was prepared by mixing NH_3 and CO_2 in an autoclave. CO_2 was added to the autoclave by means of a syringe pump while NH_3 was

added using a liquiflow meter. In this way, it is possible to add exact amounts of both reagents. After one hour, the pressure in the autoclave was released and the amount of ammonium carbamate could be analysed by weighing the autoclave, since the mass of the empty autoclave was also determined. Subsequently, the appropriate amount of nonylamine was added to the autoclave and the autoclave was heated to 75ºC overnight (16 h). A similar procedure was repeated in an autoclave at room temperature. After releasing the pressure and opening the reactor, the remaining white solid was transferred to a Schlenk flask and analysed by DSC, elemental analysis, IR spectroscopy and ^{1}H and ^{13}C NMR spectroscopy. According to the NMR spectra, nonylammonium nonylcarbamate was formed in the reaction. Especially the ^{13}C NMR spectrum shows a clear signal in the carbonyl region. Additionally, also the other analytical techniques indicated the formation of nonylammonium-nonylcarbamate according to literature data, although boiling of free nonylamine was not observed in the DSC thermogram since this amine has a boiling point above 200ºC.[35] Possibly, ammonium carbamate can be used as the ammonia source and additionally as the protection agent of the synthesised primary amine in HAM reactions.

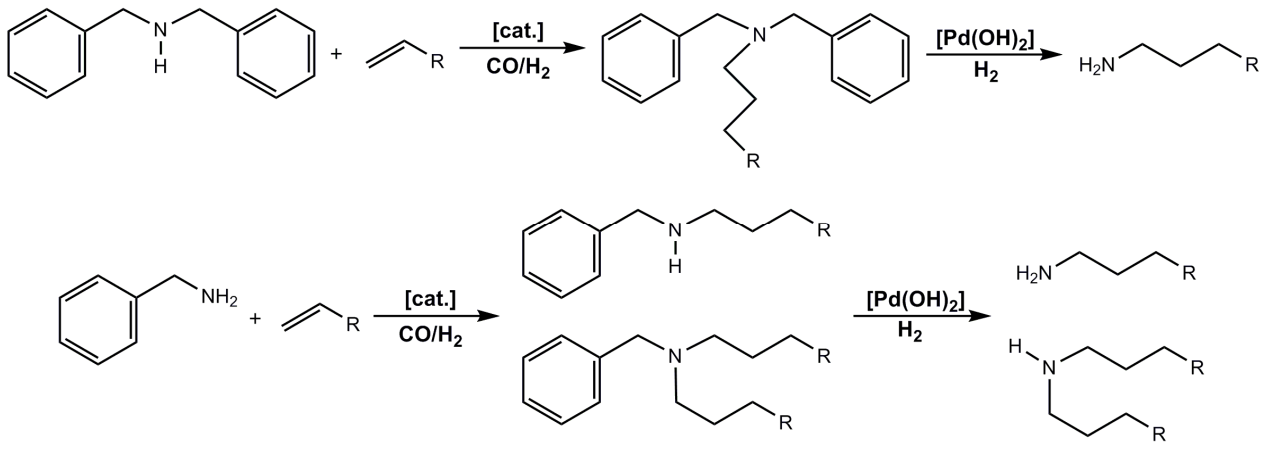
In a following experiment, the hydroaminomethylation of 1-octene with ammonium carbamate as the combined ammonia source/protection group was performed. This experiment was carried out under standard hydroaminomethylation conditions in toluene/MeOH, at a reaction temperature of 80ºC, which is lower than the generally applied 110-125ºC, and with an excess of ammonium carbamate. The experiment was repeated twice and the analysis of the reaction mixture with NMR spectroscopy turned out to be difficult. Upon analysing the reaction mixture by means of GC, secondary amine and aldehyde were detected.

The principle of applying ammonium carbamate in order to protect the primary amine as a carbamate has been shown. This principle is very promising and seems to be feasible. However, the practical realisation and implementation in the HAM reaction needs further investigation.

6.4 Primary amines by sequential HAM/deprotection

Apart from the protection of the desired amine product after its formation, it is also possible to use an amine substrate in the hydroaminomethylation which already contains the protection group and leads to a primary amine after deprotection.[16,36] Benzylamine or dibenzylamine are examples of possible substrates for the hydroaminomethylation with protected amines and can be regarded as an ammonia equivalent. After the HAM of one of these amines with an alkene, the resulting product can be debenzylated under hydrogenation conditions, leading to a primary amine product (Scheme 6.5). It has been demonstrated in the Rh-catalysed HAM

reaction of 1-octene with cyclohexylamine using the DPX ligand introduced in Chapter 3 that this reaction is fast concerning the hydroformylation and condensation steps, leading to 99% conversion of 1-octene after 40 minutes reaction time.[37] However, the hydrogenation step is slow, leading to large amounts of enamine and consequently also to the tertiary amine product. Therefore, the dibenzylamine is the preferred substrate, since this secondary amine leads specifically to the tertiary amine in the HAM, while the HAM with benzylamine certainly leads to a mixture of secondary and tertiary amines, which in turn leads to two different amine products after deprotection. This deprotection can be performed with the so-called Pearlman's catalyst, $Pd(OH)_2/C$, which is well-known for its good performance in debenzylation reactions.[38]

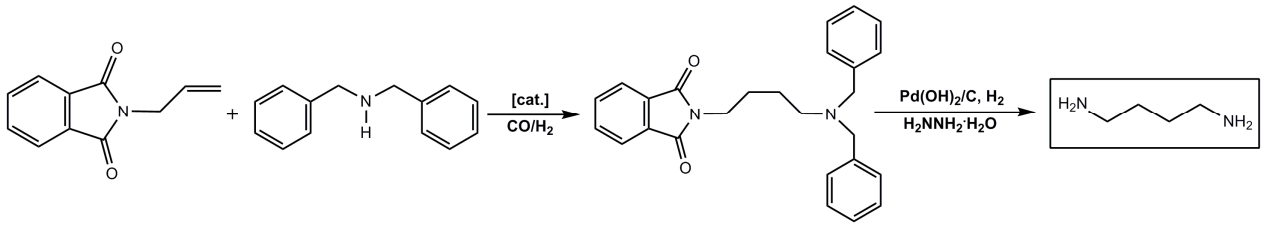


Scheme 6.5: *Representation of Rh-catalysed hydroaminomethylation of 1-alkene with benzylamine or dibenzylamine and its consecutive debenzylation to the amine products.*

Other compounds that can be used in the HAM/deprotection sequence leading to primary amines are phthalimides. Some examples of reaction sequences for the synthesis of functionalised amines and synthesis of the corresponding phthalimide derivatives can be found in literature.[39-45] These *N*-substituted phthalimides can be reacted with different kinds of reagents, leading to a broad range of possible amine products after deprotection of the amine functionality with hydrazine. An *N*-alkenylphthalimide for example can be hydroformylated to the corresponding aldehyde, which can be reacted with a range of compounds with different functionalities in order to prepare useful amine compounds after deprotection.[44] Reasonably, these *N*-alkenylphthalimides can also be hydroaminomethylated, which creates many opportunities regarding the synthesis of functionalised amino compounds.[43] In combination with the above-mentioned amine protection with benzyl groups, it might also be possible to synthesise primary

diamine compounds *via* this hydroaminomethylation/deprotection sequence. Hydroaminomethylation of *N*-allylphthalimide, which was synthesised from potassium phthalimide and allyl chloride, with dibenzylamine leads to 1,4-diaminobutane after deprotection with hydrazine and a debenzylation step (Scheme 6.6). Upon using *N*-pentenylphthalimide and dibenzylamine in the hydroaminomethylation, it should also be possible to synthesise hexamethylenediamine following this reaction sequence.

Obviously, the described reaction pathway *via* hydroaminomethylation and deprotection is not as straightforward and atom-efficient as the intended hydroaminomethylation of 1,3-butadiene with ammonia. However, the latter one is also rather troublesome because of selectivity problems as described earlier in this chapter. Therefore, the combination of hydroaminomethylation and consecutive deprotection is an alternative pathway towards primary amines or even primary diamines. The waste production in combination with the additional steps upon deprotection means that the reaction is not atom-efficient any longer, and leads to higher process costs. For that reason, this route will be more appropriate in fine chemical processes because of the higher added value of the products.



Scheme 6.6: *Representation of the hydroaminomethylation of N-allylphthalimide with dibenzylamine and its consecutive debenzylation and deprotection with hydrazine to yield 1,4-diaminobutane.*

6.5 Conclusions

In order to become more interesting from an industrial point of view, hydroaminomethylation reactions need to be highly selective, atom-efficient and should preferably start from cheap feedstocks in combination with high turnover numbers. Cheap catalysts ought to be used or at least catalyst recycling should be possible. Ammonia is the preferred amine source for the production of primary amines *via* hydroaminomethylation, but induces several difficulties. In order to avoid further reaction of the desired primary amine with the intermediate aldehyde, the reaction conditions need to be adjusted to this specific reaction environment. More promising, however, might be the use of a dynamic protection group such as carbon dioxide, which can protect the primary amine by formation of a carbamic acid and a consecutive reaction step to a carbamate with

another amine molecule. Upon venting the gases, the carbamic salts easily decompose, releasing carbon dioxide and yielding the unprotected primary amine. It has been demonstrated that CO_2 protection of a primary aliphatic amine is possible using ammonium carbamate as the amination agent. Under reaction conditions this salt provides NH_3 and CO_2 in the right stoichiometry. However, in order to apply ammonium carbamate in a HAM reaction, the reaction conditions and appropriate concentrations of the reagents have to be optimised.

Alternatively, substrates containing the protection group beforehand can be used in the hydroaminomethylation to primary amines. A HAM reaction of dibenzylamine or benzylamine with an alkene leads to a product that can subsequently be debenzylated, yielding a primary amine. Furthermore, *N*-alkenylphthalimides can be applied in hydroaminomethylation reactions, resulting in the formation of a functionalised phthalimide. This compound can be deprotected with hydrazine leading to a functionalised primary amine. Obviously, dibenzylamine and *N*-alkenylphthalimides can be combined in the hydroaminomethylation reaction in order to prepare primary diamine molecules after debenzylation and deprotection of the phthalimide functionality. However, this method is not as attractive as the direct alternative with ammonium carbamate because of the lower atom efficiency and additional deprotection reactions, which involve additional process costs.

Hydroaminomethylation with ammonia or ammonia derivatives in order to prepare primary (di)amines is a very promising reaction. The principle of primary amine protection with ammonium carbamate has been shown and further intensive research with respect to the optimisation of the various (reaction) conditions in the HAM reaction with ammonium carbamate is necessary in order to fulfil the requirements for industrial application.

6.6 Experimental section

All air- or water-sensitive operations were performed using standard Schlenk techniques under purified argon atmosphere. Toluene was purified over custom-made alumina columns. Chloroform, DMF and methanol were distilled from CaH_2. 1-Octene was purified by distillation from Na_2SO_4 and percolation over neutral activated alumina. All solvents and substrates were degassed prior to use. Chemicals were purchased from Acros Chimica, Merck KGaA, Biosolve B.V. and Aldrich Chemical Co. $[Rh(cod)_2]BF_4$ was synthesised according to a literature procedure. Hydrogen gas (99.999%), carbon monoxide gas (99.997%) and synthesis gas (CO (99.9%)/H_2 (99.9996%); 1:2) were purchased from Praxair. Ammonia (99.98%) and carbon dioxide were purchased from Scott Specialty Gases. Gas chromatographic analyses were run on a Shimadzu GC-17A instrument and an Ultra 2 column (25 m x 0.2 mm). GC/MS analyses were conducted on a HP6890 chromatograph with a Leco Pegasus II mass spectrometer and a DB-1MS column (10 m x 0.1 mm). NMR data were recorded on a Varian Oxford 200 MHz and a Varian Mercury Vx 400 MHz NMR

spectrometer. Elemental analysis was performed on a Perkin Elmer 2400 series II CHNS/O Analyser. Melting points were determined on a Büchi Melting Point B-540 Apparatus. IR spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer.

Procedure for hydroaminomethylation with ammonium carbamate

Reactions were performed in 75-mL home-made stainless steel autoclaves. In a typical experiment, the autoclave was charged with NH_3 (2.4 mL) and CO_2 (7.5 mL). After an hour the gases were vented and the autoclave was weighed in order to determine the amount of ammonium carbamate (2.9 g, 45 mmol) in the autoclave. A solution of $[Rh(cod)_2]BF_4$ (1.8 mg, 4.4 μmol; cod = 1,5-cyclooctadiene) and Xantphos (18.1 μmol) in 4 mL toluene/MeOH was added. Afterwards, 1-octene (17 mmol) in 4 mL toluene/MeOH was added and the autoclave was purged two times using CO (p = 12 bar) to remove the remaining argon from the autoclave. Subsequently, the autoclave was pressurised with CO and H_2 to the desired pressure in a ratio of 1:2 and heated to T = 80°C. The stirring rate in these reactions was 800 rpm. After a certain reaction time, the autoclave was cooled to r.t. in an ice bath and the gases were vented. The reaction mixture was removed from the autoclave and analysed by GC and NMR spectroscopy.

Procedure for protection of nonylamine with ammonium carbamate

Reactions were performed in 75-mL home-made stainless steel autoclaves. In a typical experiment, the autoclave was charged with NH_3 (1.2 mL) and CO_2 (2.5 mL). After an hour the gases were vented and the autoclave was weighed in order to determine the amount of ammonium carbamate (1.5 g, 23 mmol) in the autoclave. One equivalent of nonylamine (3.1 g, 22 mmol) in relation to the ammonium carbamate was added and the reactor was heated to or kept at the appropriate temperature (T = 80°C or r.t.) overnight. Then, the autoclave was cooled in an ice bath and the gases were vented. The white solid was transferred from the autoclave to a Schlenk flask and analysed by ^{1}H and ^{13}C NMR spectroscopy, DSC, IR spectroscopy and elemental analysis. It turned out that nonylammonium-nonylcarbamate had been formed. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.54 (br, 3H), 4.27 (br, 1H), 2.99 (t, 2H, J = 7.0 Hz), 2.69 (t, 2H, J = 7.7 Hz), 1.51 (m, 2H), 1.38 (m, 2H), 1.23 (m, 24H), 0.85 (t, 6H, J = 6.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.45, 41.85, 40.51, 31.86, 30.70, 30.50, 29.63, 29.35, 29.26, 26.84, 22.64, 14.04 ppm. Anal. Calc. for $C_{19}H_{42}N_2O_2$: C, 69.04; H, 12.81; N, 8.47. Found: C, 69.79; H, 13.10; N, 8.44. FTIR (ATR mode, solid, cm^{-1}): ν 3330, 2919, 2851, 1649, 1570, 1486, 1466, 1432, 1390, 1314, 1150. DSC (phase transition, [ºC]): 57.4, 91.6, 138.4(broad). M.p.: 82-87 ºC.

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The Potential of Hydroaminomethylation

Directing the Cascade

Amino compounds are important building blocks or end products in a broad range of durable and consumer goods in everyday life such as polymers, airbags, textiles, insecticides, and pharmaceuticals. Classical syntheses of amines often lead to large amounts of waste, mainly inorganic salts. One of the most promising new reactions for the production of amines in terms of atom-efficiency, activity, selectivity, and applicability is the hydroaminomethylation of alkenes in which water is the only side product. Especially the possibility to synthesise primary amines atom-efficiently from cheap alkene feedstocks and ammonia by hydroaminomethylation makes this an interesting reaction from an industrial point of view. Although the hydroaminomethylation has been discovered already in 1949 by Reppe at BASF, most research with respect to this reaction has been performed during the last 15 years. In **Chapter 1**, the most relevant and interesting literature with respect to the hydroaminomethylation reaction, is reviewed.

Chapter 2 deals with catalyst recycling in a biphasic ionic liquid system. Hydroaminomethylation reactions were performed successfully in an imidazolium-based ionic liquid using a rhodium/Sulfoxantphos system by reacting piperidine with different *n*-alkenes, affording yields higher than 95% of the resulting amine with turnover frequencies of up to 8400 h^{-1}, along with high regioselectivity for the linear amines with l/b ratios up to 78. Additionally, facile quantitative catalyst recovery was accomplished and recycling of the catalyst and product separation were achieved by a fast phase separation after the reaction. The product distribution was monitored in time at different temperatures both in an organic solvent and in the ionic liquid in order to investigate and compare the course of the formation of (side) products and intermediates in these reactions. Furthermore, it was shown that the nature of the Rh-precatalyst has a profound effect on the activity and selectivity. Protic organic solvents and ionic liquids containing a C-H acidic bond in the imidazolium part have a beneficial effect on the hydrogenation activity of the catalyst systems.

Chapter 3 is dedicated to the very fast and selective hydroaminomethylation with a novel class of ligands. In order to increase the activity and to maintain a good selectivity in the hydroaminomethylation reaction in comparison to Rh/phosphine-catalysed systems, a

new π-acidic ligand, the bis-[(dipyrrolyl)phosphino]xanthene, was synthesised. In combination with rhodium, this ligand leads to outstanding activities and selectivities with turnover frequencies of 6200 h^{-1} and very high l/b ratios exceeding 200. Furthermore, it was shown that the pKa value of the alcohol used in the solvent mixture has a profound effect on the performance of the catalytic systems. Acidic media enhance the activity, while less acidic media increase the regio- and chemoselectivity, as well as the degree of double bond isomerisation.

Chapter 4 describes the Rh-catalysed hydroaminomethylation of internal alkenes towards linear amines is described using amino-functionalised ligands. Bulky and rigid substituents were introduced and the ligand backbone was functionalised with a (bis-indolyl)phosphine moiety in order to increase the regioselectivity in this process. However, bis-[(dipyrrolyl)phosphino]xanthene, introduced in Chapter 3, again turned out to be the best performing ligand in combination with rhodium. Although the reaction is slower than in case of *n*-alkenes, catalyst activities are still reasonably high. The influence of catalyst preformation, reaction temperature, solvent mixture, and syngas ratio are described. Furthermore, the effect of adding a monodentate phosphorus ligand (phosphines or phosphites) to the reaction mixture was investigated. Interestingly, the regioselectivity could be increased considerably by addition of triphenylphosphine to the catalyst mixture, which can be explained by changing the isomerisation rate related to β-hydrogen elimination in this particular way.

Chapter 5 involves the coordination chemistry of the novel xanthene-based amino-functionalised ligands, which were discussed in Chapters 3 and 4, to rhodium and platinum. In combination with rhodium, these compounds display interesting catalytic results in the hydroaminomethylation reaction. In order to clarify their structure/performance relationship, the coordination behaviour was investigated. The structural properties of the ligands were studied by NMR spectroscopy of the corresponding rhodium and platinum complexes, while the electronic properties were examined by studying the IR frequencies of the CO stretch vibrations in the particular rhodium-carbonyl complexes. For two ligands, the corresponding selenides were synthesised. The NMR coupling constant J_{Se-P} can be used as a measure for the σ-donor ability of a ligand. Furthermore, the coordination behaviour of the ligands was investigated by high pressure NMR and IR spectroscopic measurements under actual

hydroformylation reaction conditions. The ligands have been compared to the diphosphine ligand Xantphos, which performs very well in regioselective hydroformylations. An X-ray crystal structure was determined for a rhodium complex with Xantphos.

Although the hydroaminomethylation reaction is a promising and atom-efficient alternative for the classical production process towards amines, this reaction has not been applied on a large scale in industry to date. On the other hand, in recent (patent) literature, more and more publications concerning this interesting reaction can be found. The near absence of hydroaminomethylation in industry might be explained by the fact that most publications mention rhodium, which is a very expensive metal. Moreover, no chemo- and regioselective synthesis of linear primary amines via hydroaminomethylation with NH_3 has been reported up to now. Most probably, this reaction will first be applied in fine chemical or pharmaceutical industry, since smaller product volumes and higher added value are common practice in these industries. For bulk chemical application, this reaction needs further optimisation for which intensive and challenging research is necessary. **Chapter 6** deals with these possibilities and the future of hydroaminomethylation. Hydroaminomethylation with protected amines and the opportunities of primary amine protection by using ammonium carbamate as a combined substrate/dynamic protection group has been presented.

Samenvatting

Amines zijn belangrijke bouwstenen of zelfs eindproducten in een breed scala aan consumentenartikelen in het dagelijks leven, zoals polymeren, airbags, textiel, insecticides en geneesmiddelen. De traditionele synthesemethode voor de productie van amines leidt vaak tot grote hoeveelheden afval, en dan voornamelijk anorganische zouten. Eén van de meest veelbelovende nieuwe reacties met betrekking tot atoomefficiëntie, activiteit, selectiviteit en toepasbaarheid voor de productie van amines, is de hydroaminomethylering van alkenen waarbij water het enige nevenproduct is. De mogelijkheid om primaire amines atoomefficiënt te kunnen synthetiseren uitgaande van goedkope alkenen en ammoniak door gebruik te maken van de bovengenoemde hydroaminomethylering, zorgt ervoor dat dit een interessante reactie is vanuit een industrieel oogpunt. Hoewel deze reactie al in 1949 ontdekt werd door Reppe bij BASF is het meeste onderzoek met betrekking tot deze reactie uitgevoerd gedurende de laatste twee decennia. In **Hoofdstuk 1** is de meest relevante literatuur aangaande de hydroaminomethylering beschreven en samengevat.

Hoofdstuk 2 beschrijft het katalysator-hergebruik in een tweefasensysteem met een ionische vloeistof. Hydroaminomethyleringsreacties zijn met succes uitgevoerd in een ionische vloeistof, gebaseerd op imidazolium en gebruikmakend van een rhodium/Sulfoxantphos-systeem, door piperidine te laten reageren met verschillende *n*-alkenen. Opbrengsten van meer dan 95% van het gewenste amine in combinatie met een turnover-frequentie van 8400 h^{-1} en regioselectiviteiten (verhouding lineair/vertakt amine) van 78 amine zijn behaald. Tevens blijken katalysator- en productscheiding en kwantitatief katalysator-hergebruik door middel van een snelle fasenscheiding bijzonder goed mogelijk te zijn. De productverdeling in het reactiemengsel is in de tijd gemeten bij verschillende temperaturen, zowel in een organisch oplosmiddel alsook in de ionische vloeistof. Dit om de vorming en verdere reactie van (neven)producten en tussenproducten in deze reacties te onderzoeken. Aanvullend hierop is aangetoond dat de aard van de Rh-prekatalysator een significante invloed heeft op de activiteit en selectiviteit in de reactie. Protische organische oplosmiddelen en ionische vloeistoffen met een acide C-H binding in het imidazolium-gedeelte hebben een gunstige invloed op de hydrogeneringsactiviteit van de katalysatorsystemen.

In **Hoofdstuk 3** wordt de bijzonder snelle en selectieve hydroaminomethylering met een nieuwe ligandklasse beschreven. Om de activiteit te verhogen en een goede selectiviteit te behouden in de hydroaminomethyleringsreactie is een nieuw π-acide ligand, bis-[(dipyrrolyl)phosphino]xantheen, gesynthetiseerd. Dit ligand geeft, in combinatie met rhodium, buitengewoon hoge activiteiten en selectiviteiten, een turnover-frequentie van 6200 h^{-1} en opmerkelijk hoge lineair/vertakt-verhoudingen die de 200 overschrijden. Bovendien is aangetoond dat de pKa-waarde van het gebuikte alcohol in het oplosmiddelmengsel een sterke invloed heeft op de werking van het katalytische systeem. Zure oplosmiddelen verhogen de activiteit terwijl de meer basische oplosmiddelen de regio- en chemoselectiviteit alsook de isomerisatiegraad juist beïnvloeden.

Hoofdstuk 4 is gewijd aan de rhodium-gekatalyseerde hydroaminomethylering van interne alkenen richting lineaire amines, gebruikmakende van amino-gefunctionaliseerde liganden. Starre en bulky substituenten zijn geïntroduceerd en de ruggengraat van het ligand is gefunctionaliseerd met een (bis-indolyl)phosphine-groep om de regioselectiviteit in het proces te verhogen. Desalniettemin blijkt het bis-[(dipyrrolyl)phosphino]xantheen, geïntroduceerd in Hoofdstuk 3, ook hier het best presterende ligand te zijn. Ondanks dat de reactie langzamer verloopt dan in het geval van *n*-alkenen, zijn katalysator-activiteiten ook hier redelijk hoog. De invloed van katalysator-preformatie, reactietemperatuur, oplosmiddelmengsel en synthesegas-verhouding worden beschreven. Tevens is het effect van de toevoeging van een monodentaat fosfor-ligand aan het reactiemengsel beschreven. De regioselectiviteit wordt aanzienlijk hoger bij toevoeging van trifenylfosfine aan het katalysatormengsel. Dit kan worden verklaard door de veranderde isomerisatiesnelheid in relatie tot β-waterstof eliminatie door deze toevoeging.

De coördinatiechemie van de in Hoofdstuk 3 en 4 geïntroduceerde katalysator-systemen met rhodium en platinum is beschreven in **Hoofdstuk 5**. Deze verbindingen vertonen interessante katalytische resultaten in de hydroaminomethylering met rhodium als het metaal. De coördinatiechemie is onderzocht om de structuur-resultaat relatie op te helderen. De eigenschappen van de liganden met betrekking tot de structuur zijn onderzocht met NMR-spectroscopie van de corresponderende platinum en rhodium complexen, terwijl de electronische eigenschappen zijn onderzocht door de IR-frequenties van de CO-rekvibraties in de corresponderende rhodium-carbonyl complexen te onderzoeken. Voor twee

liganden zijn ook de corresponderende selenides gesynthetiseerd. De NMR-koppelingsconstante J_{Se-P} kan worden gebruikt als een maat voor de σ-donor capaciteit van een ligand. Verder zijn de coördinatie-eigenschappen van de verschillende liganden onderzocht met gebruikmaking van hoge druk NMR- en IR-spectroscopische metingen onder reactiecondities van een hydroformyleringsreactie. De liganden zijn vergeleken met het difosfine-ligand Xantphos, dat goede resultaten geeft in regioselectieve hydroformyleringsreacties. De kristalstructuur voor een rhodiumcomplex met Xantphos is bepaald.

Ondanks het feit dat de hydroaminomethyleringsreactie een veelbelovend en atoomefficiënt alternatief voor het traditionele productieproces van amines is, is deze reactie tot op heden niet toegepast in de chemishe industrie op grote schaal. Desondanks kan men meer en meer publicaties met betrekking tot deze reactie terugvinden in de huidige (patent)literatuur. Het feit dat de hydroaminomethyleringsreactie zo goed als niet toegepast is in de chemische industrie kan worden verklaard door de bijzonder hoge kostprijs van rhodium, dat meestal als het gebruikte metaal in deze katalytische reactie wordt gerapporteerd. Bovendien zijn chemo- en regioselectieve syntheses van lineaire, primaire amines via hydroaminomethylering met ammoniak tot op heden niet gerapporteerd. Hoogstwaarschijnlijk zal de hydroaminomethyleringsreactie dan ook als eerste worden toegepast in de fijnchemische of farmaceutische chemie, aangezien in deze branche de productievolumes kleiner en de toegevoegde waarde van het product groter zijn. Verdere optimalisatie van deze reactie door intensief en uitdagend onderzoek is nodig voor de toepassing avn de hydroaminomethylering in de bulkchemische industrie. **Hoofdstuk 6** beschrijft deze mogelijkheden en de toekomst van de hydroaminomethylering. Hydroaminomethylering met beschermde amines en de mogelijkheden met betrekking tot het beschermen van door hydroaminomethylering gesynthetiseerde primaire amines met ammonium carbamaat als een gecombineerd substraat/beschermgroep is gepresenteerd.

Curriculum Vitae

Bart Hamers werd op 28 september 1981 geboren te Born. In 1999 behaalde hij zijn gymnasium-diploma aan het Serviam College te Sittard waarna hij in datzelfde jaar de studie Scheikundige Technologie begon aan de Technische Universiteit te Eindhoven. Tijdens deze studie werd het certificaat Technisch Management aan de faculteit Technische Bedrijfskunde van de Technische Universiteit te Eindhoven behaald. Na het uitvoeren van een halfjaarlijkse bedrijfsstage bij DSM Pharma Chemicals te Venlo en het afronden van het afstudeeronderzoek in de vakgroep Macromoleculaire en Organische Chemie bij prof. dr. Bert Meijer en prof. dr. Rint Sijbesma werd de ingenieursstudie in december 2004 voltooid. Daarna begon hij half april 2005 met zijn promotieonderzoek naar de mogelijkheden van hydroaminomethyleringsreacties in de vakgroep Homogene Katalyse en Coördinatiechemie bij prof. dr. Dieter Vogt aan de Technische Universiteit te Eindhoven. De belangrijkste resultaten van dit onderzoek zijn beschreven in dit proefschrift. Vanaf september 2009 is hij werkzaam als proces-chemicus bij Evonik Oxeno GmbH te Marl, Duitsland.

Bart Hamers was born in Born, the Netherlands, on the 28th of September 1981. In 1999 he graduated from the Serviam College in Sittard and started the study Chemical Engineering and Chemistry at the Eindhoven University of Technology. During this study he obtained the Certificate Management Technology at the Faculty of Technology Management at the Eindhoven University of Technology. After carrying out an internship at DSM Pharma Chemicals in Venlo and finalising his graduation project in the group of prof. dr. Bert Meijer and prof. dr. Rint Sijbesma in the field of marcomolecular and organic chemistry, he graduated in December 2004. In April 2005 he started his PhD research on the possibilities of hydroaminomethylation reactions in the laboratory of Homogeneous Catalysis and Coordination Chemistry of prof. dr. Dieter Vogt at the Eindhoven University of Technology. The most important results of this research are described in this thesis. In September 2009 he started as a process chemist at Evonik Oxeno GmbH in Marl, Germany.

List of Publications

B. Hamers, P. S. Bäuerlein, C. Müller, D. Vogt, "Hydroaminomethylation of *n*-Alkenes in a Biphasic Ionic Liquid System", *Adv. Synth. Catal.* **2008**, *350*, 332-342.

B. Hamers, E. Kosciusko-Morizet, C. Müller, D. Vogt, "Fast and Selective Hydroaminomethylation Using Xanthene-Based Amino-Functionalized Ligands", *ChemCatChem* **2009**, *1*, 103-106.

M. C. C. Janssen, L. Bini, B. Hamers, C. Müller, M. A. Siegler, A. L. Spek, D. Vogt, "Tetraphenol-based diphosphite ligands in the rhodium catalyzed hydroformylation of octenes", *under review from the industrial partner*.

L. Bini, M. C. C. Janssen, B. Hamers, C. Müller, D. Vogt, "Hydrocyanation of 3-pentenenitrile with tetraphenol-based ligands: formation of η^3-allyl and σ-alkyl intermediates", *under review from the industrial partner*.

B. Hamers, E. Kosciusko-Morizet, C. Müller, D. Vogt, "Hydroaminomethylation of Internal and Terminal Alkenes by Xanthene-Based Amino-Functionalised Ligands", *manuscript in preparation*.

B. Hamers, C. Müller, D. Vogt, "Coordination Chemistry with Pyrrole-Functionalised Ligands", *manuscript in preparation*.

B. Hamers, C. Müller, D. Vogt, "Transition Metal Catalysed Hydroaminomethylation", *manuscript in preparation*.

Dankwoord

Een interessante en in velerlei opzichten leerzame onderzoeksperiode van zo'n vier jaar zit er bijna op. Een goed moment om terug te kijken en de mensen te bedanken zonder wie deze expeditie lang niet zo enerverend of zelfs mogelijk zou zijn geweest.

Allereerst wil ik mijn promotor Dieter Vogt en co-promotor Christian Müller bedanken. Dieter, bedankt voor de mogelijkheid die je me geboden hebt om aan deze promotie-expeditie in jouw lab te beginnen en de navigatiehulp en verhelderende discussies op momenten dat het pad in nevelen gehuld was. Jouw kennis, enthousiasme en energie zijn erg motiverend en waardeer ik dan ook zeer! Christian, jouw adviezen en correcties met betrekking tot wetenschappelijke teksten, presentaties en posters kwamen altijd zeer snel. Ik heb hiervan veel geleerd! Erik, ik heb moeten wennen aan jouw, in bepaalde opzichten, bijzondere handelswijze. Dit heeft me echter de ogen ook verder geopend. Bedankt hiervoor! Furthermore, I am very grateful to the promotion committee for their willingness to correct the manuscript and take part in this committee.

Vanwege het feit dat mijn project gefinancierd werd door ACTS-Aspect heb ik veel mensen in een veelheid aan vakgebieden leren kennen. De halfjaarlijkse meetings waren altijd leerzaam en gezellig waarvoor ik mijn Aspect-collega's wil bedanken. Rudy Parton en Jim Brandts wil ik bedanken voor hun bijdrage aan dit project. De discussies en opmerkingen met betrekking tot dit onderzoek waren van groot belang voor mij. Rudy wil ik in het bijzonder bedanken voor de bereidheid om zitting te nemen in mijn promotiecommissie. Ook wil ik Dorine Keusters en Arlette Werner bedanken voor de afhandeling van alle Aspect gerelateerde zaken.

Patrick, ruim vier jaren hebben we het kantoor en het lab gedeeld en dus ook alle wetenschappelijke hoogte- en dieptepunten. Op momenten dat het iets minder ging had je altijd advies of in ieder geval een luisterend oor paraat, vooral ook tijdens onze vele gezamenlijke (en soms bijzondere lange) treinreizen. Ik ben dan ook blij de mogelijkheid te hebben gekregen jou te leren kennen. Hopelijk kunnen we de gezellige momenten die we buiten het lab hebben gehad ook voortzetten nu we iets verder van elkaar vandaan wonen. Veel succes boven de grote rivieren!

Ook mijn andere kantoorgenoten, Jarno en Leandra, wil ik bedanken. Bedankt voor de vele wetenschappelijke discussies en uitwisseling van de laatste roddels. Door jullie toedoen was de sfeer op kantoor uitstekend! Leandra, veel succes in het Noord-Limburgse en Jarno veel succes met het africhten van je phosphinines.

Laura, veel tijd hebben we al kokend naast elkaar verbracht en zo onze successen en mislukkingen gedeeld. Bedankt voor de tips, adviezen en opbeurende woorden op de momenten dat het nodig was! Ik hoop dat mijn fluitconcerten jou ook af en toe hebben kunnen opvrolijken…

Ondanks dat we geen kantoor of lab deelden, kon ik bij Michèle altijd terecht voor advies, het printen van een poster, een wetenschappelijk praatje, een serieus praatje, een gezellig praatje, et cetera. Dank hiervoor! Ik wens je veel succes met de laatste maanden van je promotie!

Jarl, onze gezamenlijke tijd in Eindhoven was slechts beperkt, maar er is toch een goede band ontstaan en ik heb in deze korte periode veel van je geleerd. Ik denk dan ook met plezier terug aan de wetenschappelijk en minder wetenschappelijke gesprekken die we hebben gevoerd binnen en buiten het lab. Bedankt ook dat je zitting wil nemen in mijn promotiecommissie.

I have been lucky enough to get the chance to guide an internship student in our laboratories. Etienne, the planning of your arrival was far from perfect because of a conference and the holiday period, but I've been very happy with your help in my project. It was a pleasure to see that you got the hang of Schlenk techniques and that you enjoyed what you were doing. In the end, it turned out that this work was the start of further research which even led to a publication!

There has been a number of other (PhD) students who joined our group for a limited period of time. Tiina, Carolina, Julie and Christine, good luck with finishing your PhD and good luck in the future! Matthijs en Patrick A., veel plezier en succes in jullie baan en William, veel succes met afstuderen!

Verder een bijzonder woord van dank aan Ton. Jouw hulp bij de verschillende analyse-technieken en autoclaven-opstellingen en vooral ook jouw rustige werkwijze zijn voor mij heel waardevol geweest. Hierbij wil ik ook meteen Wout en Hendawy bedanken voor hun hulp op het lab of bij bepaalde opstellingen. Elize en Marion wil ik bedanken voor de vele administratieve zaken waarbij jullie dagelijks van grote waarde zijn geweest in de afgelopen jaren.

Vele andere mensen hebben ook hun steentje bijgedragen aan de sfeer in de groep tijdens conferenties, pauzes, NIOK-cursus, (kerst)borrels, SKA uitjes, HomCat-weekenden of op enigerlei andere wijze. Ruben, Katharina, Jos, Dennis, Andreas, Gijsbert, Arjen, Gilbère, Evgeny, Tiny, Freek, Maarten, Adelaida en Niels, bedankt en veel succes verder!

Ook buiten het lab zijn er vele mensen die ik wil bedanken. Allereerst wil ik Bart, Sandra, Tim en Margriet bedanken voor de interesse in mijn project en de vele gezellige momenten samen. Ondanks de afstand, hoop ik dat we deze gezellige ontmoetingen en uitstapjes nog lang kunnen voortzetten! Veel succes in jullie baan en bij het afronden van jullie PhD of Master. Bart en Sandra, bijzondere dank aan jullie dat jullie mijn paranimfen willen zijn!

Muziek is een goede uitlaatklep na een week stevig doorwerken. Mijn muziekvrienden en in het bijzonder mijn collega-trompettisten bij de fanfare van Buchten wil ik hiervoor dan ook bedanken. Dank ook aan mijn collega-bestuursleden wanneer ik weer eens te laat bij een vergadering aansloot of helemaal afwezig was. Bijzondere dank aan Rosemarie, Anita, Ilse, Thijs, Annemiek, Chantalle, Johan, Anique en Sander voor de gezellige momenten tijdens, concerten, vakanties, concoursen en avondjes samen en jullie interesse in mijn werkzaamheden! Een bijzonder woord van dank aan Anique. Ik vind het erg leuk dat je de kaft van dit proefschrift hebt ontworpen. Ik ben er heel erg blij mee!

Ook sport is een prima activiteit om de geest van het werk af te leiden, vooral op de momenten dat het allemaal wat minder gaat. De judotraining op maandagavond was dan ook een goed moment om helemaal af te schakelen. Linda, Claudia, Bart, Paul, Jo, Nancy, Sean, Etienne, Jules, Jakob, Joyce, Sanne en Lotte wil ik bedanken voor de stevige, maar gezellige trainingen. Ik vind het dan ook jammer dat ik de trainingen niet meer kan bijwonen nu ik in Duitsland woon. Bart, bedankt voor de effectieve trainingen samen en je bereidheid om (meerdere keren zelfs) mijn valpartner te zijn bij het 2^{e} Dan-examen! Veel succes verder met je (toch wel bijzondere) baan!

Ook mijn familieleden zijn van grote betekenis en steun gebleken in de afgelopen vier jaren. Jullie wil ik bedanken voor de vele gezellige momenten tijdens feestjes, Kerst, Nieuwjaar en willekeurige andere momenten, en de interesse en steun in mijn onderzoek ondanks het feit dat ik niet altijd helemaal duidelijk kon maken wat mijn onderzoek precies inhield en wat ik zoal deed de hele dag.

Zonder de steun van mijn ouders zou ik nooit zijn gekomen, waar ik nu ben. Jo en Anjes, jullie hebben me altijd onvoorwaardelijk gesteund in velerlei opzichten tijdens mijn

studie en promotie en altijd vertrouwen gehad in wat ik deed. Jullie hebben me geleerd het leven te waarderen en van elke dag te genieten. Ik kan jullie nooit genoeg bedanken hiervoor!

Nicole, jij hebt me laten inzien hoe mooi het leven kan zijn. Ondanks dat het afgelopen jaar niet altijd eenvoudig is geweest vanwege onze lange werkdagen, hebben we onze energie gehaald uit de vele goede momenten samen. Je hebt me altijd gesteund bij mijn onderzoek en samen zijn we door de dalen gegaan en hebben we de successen gevierd. Opnieuw hebben we niet de eenvoudigste weg gekozen. Ik heb dan ook enorm veel respect voor je sterke persoonlijkheid en ben heel blij dat je me steunt in mijn keuze om in Duitsland te gaan werken. Ik ben ervan overtuigd dat we nog heel veel mooie momenten zullen delen!

Bedankt allemaal!

Bart