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Hydroaminomethylation in Aqueous Solvent Systems – An Efficient Pathway to Highly Functionalized Amines

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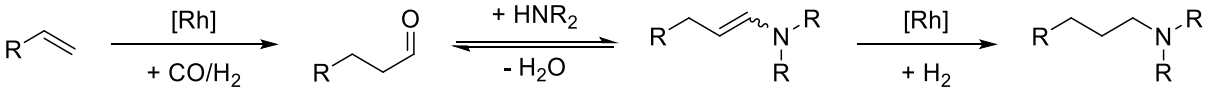
Abstract: Tandem-catalyzed hydroaminomethylation is a useful tool for synthesizing linear amines from olefins and amines in an atom-efficient manner. To enable the coupling of highly functionalized, hydrosoluble amines with non-water-soluble olefins, this reaction must be transferred to aqueous biphasic solvent systems. In this work, we systematically evaluate reaction conditions to provide a selective hydroaminomethylation of 1-octene with diethanolamine as model substrates. Although water is both the condensation side product and the solvent, yields of 79% were achieved using a catalytic system consisting a rhodium precursor and a sulfonated diphosphine ligand. This approach was applied to other functionalized amines, proving this concept is a suitable tool for the catalytic alkylation of highly functionalized amines.

Introduction

Linear amines are of great importance in the production of pharmaceuticals, agrochemicals or surfactants.[1,2] There are numerous ways to synthesize amines, *e.g.* the Buchwald-Hartwig amination.[3,4] Hydroaminomethylation provides another means of catalytic synthesis of higher amines and is a term that describes a tandem catalyzed reaction consisting of a hydroformylation and a subsequent reductive amination (Scheme 1).[5,6]



Scheme 1: General hydroaminomethylation reaction sequence.

Hydroformylation and hydrogenation, which are both transition metal catalyzed reaction steps, are irreversible. The enamine condensation step in between is an equilibrium. This means that high amounts of water and/or enamine hamper the reaction in a whole.

In general, rhodium catalysts are used, as they show high activities for both the hydroformylation and the hydrogenation step under mild conditions.[7] Since the hydroformylation step can be adjusted to ensure high selectivities to the linear aldehyde, it is an efficient method for synthesizing anti-Markovnikov products. Identifying catalytic conversions that enable linear amination is among the most challenging tasks in chemistry research.[8]

The olefin and the amine are typically dissolved in the same phase, maintaining high reaction rates, especially for the condensation reaction.[9,10] Highly polar amines, *e.g.* amines functionalized with carboxylic acids or hydroxyl groups, cannot generally be coupled with olefins in this way. Amines other than relatively short alkyl amines are thus rarely reported in the literature. Thermomorphic solvent systems (TMS)[11] provide an elegant solution to this issue, though these have to be developed for every single substrate combination specifically and are often limited to amines of medium polarity.[12]

The use of aqueous solvent systems in the hydroaminomethylation could enable hydrocarbons to be coupled to highly polar amines. The spectrum of products that result could include pharmaceuticals or surfactants. However, the enamine condensation is a reversible reaction that incorporates the formation of water, which poses a great challenge. Accordingly, working in aqueous solutions that shift the equilibrium of that reaction to the aldehyde intermediate is crucial. The first hydroaminomethylation of ammonia with olefins in aqueous solvent systems was reported by *Beller*. Using sulfonated diphosphines and an

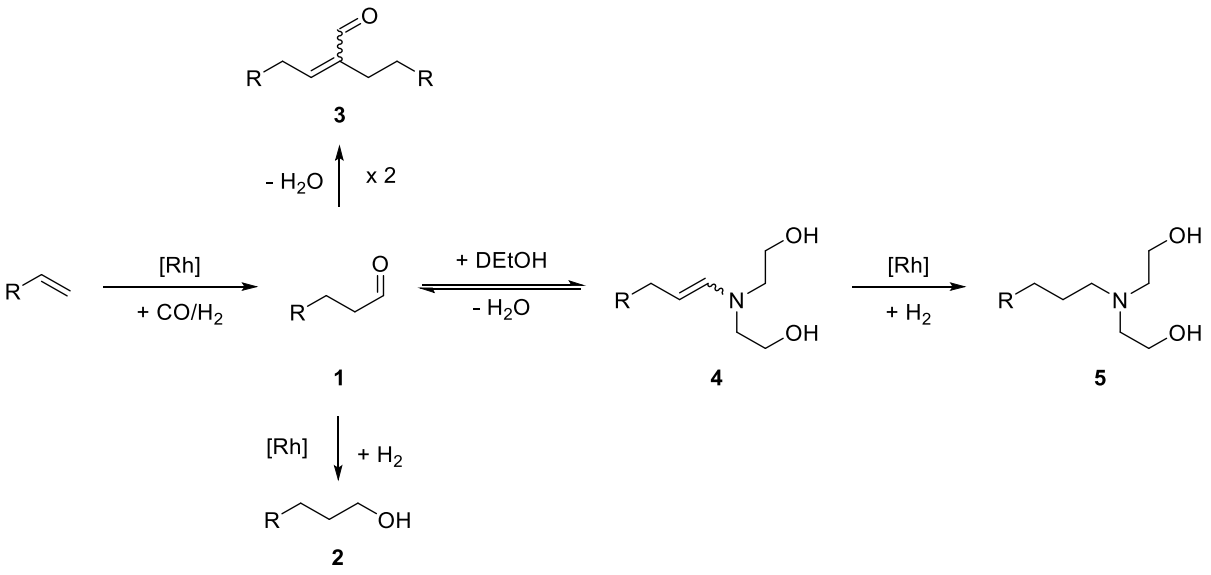
iridium co-catalyst, olefins up to the chain length of 1-pentene were converted to the respective primary amine.[13] Another example for this is the hydroaminomethylation of isoprene.[14].

The approach for the hydroaminomethylation of higher olefins in aqueous solvent systems was only realized using additional surfactants, such as quaternary ammonium compounds.[15] *Weberskirch* took this approach a step further, using triphenylphosphine functionalized poly(2-oxazoline)s as ligands for the substrates 1-octene and dimethylamine to react inside micelles with a bimetallic catalytic system.[16] The conversion of substrates with strongly opposing polarities without additives has yet to be described in the literature.

This work presents the development of an efficient hydroaminomethylation of water-soluble amines with non-polar olefins that focuses on a simple, viable procedure. Crucial factors for achieving this goal include the condensation equilibrium and the sufficient mixing of the substrates. The influence of temperature and substrate ratios on these crucial factors are investigated systematically. Selecting a proper solvent is an important precondition for these factors. These investigations are carried out using 1-octene and diethanolamine as model substrates with strongly opposing polarities. At the end a set of reaction conditions is put together and then transferred to other amines.

Results and Discussion

To find a suitable catalytic system as well as a solvent system that enables the conversion of water-soluble amines and olefins, which are insoluble in water, the model substrates diethanolamine and 1-octene were chosen. Diethanolamine is a functionalized and highly water-soluble amine.[17] On the other hand, 1-octene is insoluble in water (4.1 mg/L, 25 °C)[18] and a widely investigated substrate for hydroaminomethylations. The reaction sequence that follows from these model compounds is depicted in Scheme 2.



Scheme 2: Hydroaminomethylation of a 1-alkene with diethanolamine (only the linear hydroformylation pathway is shown).

The first step in this particular sequence is the rhodium catalyzed hydroformylation of 1-octene to nonanal **1**. The formation of the *iso*-product 2-methyl-octanal occurs as a side product (this pathway is omitted in Scheme 2). The resulting *n*-nonanal (**1**) can undergo three different reactions under these conditions: since rhodium is active as a hydrogenation catalyst, the formation of alcohol **2** is possible. This reaction has been observed, especially in the presence of amines.[19–21] Another side reaction - irreversible under these reaction

conditions - is the aldol condensation, leading to α,β-unsaturated branched aldehydes **3**. This reaction is important as it can be catalyzed by secondary amines under hydroformylation conditions.[22,23]

The condensation of nonanal with diethanolamine yields the corresponding enamine **4**. This reaction is an equilibrium, which means that it is not favored in aqueous systems. Consequently, the hydrogenation reaction to the desired amine **5** must occur quickly. The yields ($\mathbf{Y_x}$) for the mentioned (intermediate) products are discussed, as well as the selectivity for the desired amine ($\mathbf{S_5}$). In this context, the *n*- and *iso*-products are summarized and branched products that would result from a hydroformylation of internal double bonds were not observed over the course of our investigations.

Water and 1-butanol proved to be a good choice along with the sulfonated Xantphos ligand for the hydroformylation in aqueous biphasic systems (Figure 1).[24] The rhodium precursor $[Rh(cod)Cl]_2$ has shown to be active in many reported hydroaminomethylations[11,14,15,25] and was employed with the Xantphos ligand in the first evaluations of the organic solvent (Table 1).

Since the functionalized amine diethanolamine is highly water-soluble (log $P_{oct/wat}$ = -1.43[17]) and the employed alkene (1-octene) is not, the choice of the organic co-solvent for the aqueous system is of great importance both in terms of conversion and selectivity. It must ensure the availability of substrates to the catalyst and provide for sufficient mixing of the amine and the aldehyde formed. If too little amine is present in the phase containing the aldehyde, aldol condensation is favored.[26] For this purpose, several short-chain alcohols were employed (Table 1).

Table 1: Results using different organic co-solvents.

Entry	Organic solvent	Y_1	Y_2	Y_3	Y_4	Y_5	S_5
1.1	-/-	0	0	0	0	0	-/-
1.2	1-butanol	4	16	5	0	30	55
1.3	2-butanol	8	5	6	0	34	64
1.4	*tert*-butanol	9	9	4	0	34	61
1.5	*iso*-propanol	4	7	9	0	30	60
1.6	ethanol	1	2	17	0	9	31

Reaction conditions: *c*($[Rh(cod)Cl]_2$)=0.2 mol%, *n*(1-octene)=6 mmol, ligand=Xantphos, M/P=1/5 *n*(diethanolamine)=12 mmol, *V*(Co-solvent)=2.5 mL, *V*(H_2O)=2.5 mL, *p*(CO/H_2)=40 bar, CO/H_2=1/1, *T*=140 °C, *t*=6 h, 500 rpm. Yields (Y) are given in % based on 1-octene. $S_5=Y_5/(Y_1+Y_2+Y_3+Y_4+Y_5)$. Results determined by GC-FID using dodecane as internal standard.

Without any additional solvent the reaction did not take place (Entry 1.1), which can be explained by the insufficiently dissolved 1-octene in the aqueous phase. Ethanol (Entry 1.6) showed a different influence, with significantly higher amounts of aldol condensation product formed, which led to decreased selectivity. This could be because it is the only applied organic solvent that maintained one homogeneous phase after the reaction. When butanols were used as a solvent (Entry 1.2 – 1.4), phase separation took place. It was reported that the solvent system consisting of water and 1-butanol is not completely homogenous, even at elevated temperatures of 140 °C and above, meaning this system constitutes a “narrow TMS” (TMS= thermomorphic solvent system).[24] This finding was verified for the substrates present under reaction conditions using a reactor equipped with a sight-glass. Because the conversion using 1-butanol was the highest, subsequent investigations were carried out using this solvent system. The aldol condensation, however, was still an important side reaction, reducing the selectivity to 55% (Entry 1.2). This side reaction was affected by the amine/aldehyde ratio, which was set at the beginning with a proper alkene/amine ratio (Table 2).

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Table 2: Results of the investigations regarding the substrate ratio

Entry	Alkene/amine	Y_1	Y_2	Y_3	Y_4	Y_5	S_5
2.1	1/0.5	11	8	5	0	21	47
2.2	1/1	3	3	31	0	30	45
2.3	1/1.5	6	3	4	0	33	72
2.4	1/3	4	7	7	0	35	66
2.5	1/4	1	3	3	0	18	72

Reaction conditions: *c*([Rh(cod)Cl]$_2$)=0.2 mol%, *n*(1-octene)=6 mmol, ligand=Xantphos, M/P=1/5, *V*(1-butanol)=2.5 mL, *V*(H_2O)=2.5 mL, *p*(CO/H_2)=40 bar, CO/H_2=1/1, *T*=140 °C, *t*=6 h, 500 rpm. Yields (Y) are given in % based on 1-octene. $S_5=Y_5/(Y_1+Y_2+Y_3+Y_4+Y_5)$. Results determined by GC-FID using dodecane as internal standard.

As expected, the selectivity for **5** employing sub-stoichiometric and stoichiometric amounts of amine was very low (Entry 2.1 and 2.2). Once an excess of amine is present, selectivity increases (Entry 2.3 – 2.5). It was shown that the aldol condensation is favored in hydroaminomethylations if low amounts of amines are present, whereas high amounts of amine, as compared to aldehydes, tend to form enamines.[26] The highest yield for amines (35%) was achieved at an alkene to amine ratio of 1/3. Since the amount of diethanolamine affects phase behavior and, more importantly, the tendency to form aldol condensates, subsequent investigations were conducted using this substrate ratio.

Since the tandem catalyzed reaction sequence involves two different catalytic processes, hydroformylation and hydrogenation, the temperature is crucial in terms of adjusting the two reactions as desired. Temperature also has a strong influence on the miscibility of all compounds, substrates and solvents. The results achieved at different temperatures are summarized in Table 3.

Table 3: Results of the investigations regarding the temperature

Entry	*T* [°C]	Y_1	Y_2	Y_3	Y_4	Y_5	S_5
3.1	80	14	5	5	0	76	76
3.2	100	5	3	<1	0	53	85
3.3	110	5	1	8	0	52	79
3.4	120	7	<1	7	0	28	67
3.5	130	5	3	6	0	36	72
3.6	170	4	15	3	0	29	57

Reaction conditions: *c*([Rh(cod)Cl]$_2$)=0.2 mol%, *n*(1-octene)=6 mmol, *n*(diethanolamine)=18 mmol, ligand=Xantphos, M/P=1/5, *V*(1-butanol)=2.5 mL, *V*(H_2O)=2.5 mL, *p*(CO/H_2)=40 bar, CO/H_2=1/1, *t*=6 h, 500 rpm. Yields (Y) are given in % based on 1-octene. $S_5=Y_5/(Y_1+Y_2+Y_3+Y_4+Y_5)$. Results determined by GC-FID using dodecane as internal standard.

For instance, a higher temperature increases the miscibility of the liquid phases, whereas the solubility of gaseous compounds decreases. Temperature also strongly affects the reaction rates of hydroformylation and hydrogenation. Hydroformylation starts at lower temperatures than hydrogenation, whereas hydrogenation benefits from higher temperatures more than hydroformylation does.[6] Surprisingly, the yield of the desired amines was highest (76%) at a low temperature of 80 °C (Entry 3.1). The highest selectivity observed (85%) was achieved at 100 °C (Entry 3.2), at which point on, selectivity and conversion rates decrease (Entry 3.3 – 3.5). At 170 °C (Entry 3.6) black precipitation indicates that the rhodium catalyst is irreversibly deactivated. In the present case, lower temperatures seem to favor the desired reaction pathway. This is most probably due to the temperature-dependent solubility of hydrogen and carbon monoxide in water.[27]

Comparing the Henry's law constants of the gaseous compounds in water, solubility decreases strongly as temperature increases (for details see SI). With temperatures higher than 50 °C hydrogen is more soluble than CO in the aqueous phase. This is favorable, because more hydrogen is consumed than carbon monoxide during the reaction. Comparing the solubility of H_2 and CO at 140 °C with their solubility at 100 °C, an increase of 16% for

hydrogen and 44% for CO is given at the lower temperature, which explains the better results at lower temperatures. This effect only seems possible because of the phase-mediating butanol that makes the olefin substrate available in the aqueous phase.
Taking the considerations from the temperature-dependent solubilities of the syngas components into account, an excess of hydrogen in the syngas mixture may be advantageous for the reaction. The selectivity as well as the yield for the desired amines was the highest using a threefold excess of hydrogen in the syngas mixture (Table 4, Entry 4.2) though there is no clear trend in selectivity.

Table 4: Results of the investigations on syngas composition

Entry	CO/H_2	Y_1	Y_2	Y_3	Y_4	Y_5	S_5
4.1	1/2	6	7	3	0	23	58
4.2	1/3	3	3	1	0	23	77
4.3	1/4	3	8	1	0	20	63
4.4	1/5	7	4	0	0	4	27

Reaction conditions: *c*([Rh(cod)Cl]$_2$)=0.2 mol%, *n*(1-octene)=6 mmol, *n*(diethanolamine)=18 mmol, ligand=Xantphos, M/P=1/5, *V*(1-butanol)=2.5 mL, *V*(H_2O)=2.5 mL, *T*=140 °C, *p*(CO/H_2)=40 bar, CO/H_2=1/1, *t*=6 h, 500 rpm. Yields (Y) are given in % based on 1-octene. $S_5=Y_5/(Y_1+Y_2+Y_3+Y_4+Y_5)$. Results determined by GC-FID using dodecane as internal standard.

Having tested different pressures, 50 bar was shown to increase conversion rates. Finally, the amount of rhodium, as well as the metal/ligand ratio was investigated (Table 5). Both are important factors that affect conversion and selectivity rates within the reaction, as they determine the structure and composition of the metal complexes in solution.

Table 5: Results of different precursor concentrations.

Entry	$[Rh(cod)Cl]_2$	M/P	Y_1	Y_2	Y_3	Y_4	Y_5	S_5
5.1	0.06 mol%	1/5	2	2	21	0	27	52
5.2	0.13 mol%	1/5	3	2	20	0	33	57
5.3	0.2 mol%	1/5	4	16	5	0	30	55
5.4	0.2 mol%	1/2	3	1	4	0	27	77
5.5	0.2 mol%	1/7	3	1	6	0	21	66
5.6	0.2 mol%	1/15	<1	6	6	0	12	50
5.7	0.4 mol%	1/5	2	3	8	0	20	61

Reaction conditions: *n*(1-octene)=6 mmol, ligand=Xantphos, *n*(diethanolamine)=12 mmol, *V*(1-butanol)=2.5 mL, *V*(H_2O)=2.5 mL, M/P=1/5, *p*(CO/H_2)=40 bar, CO/H_2=1/1, *T*=140 °C, *t*=6 h, 500 rpm. Yields (Y) are given in % based on 1-octene. $S_5=Y_5/(Y_1+Y_2+Y_3+Y_4+Y_5)$. Results determined by GC-FID using dodecane as internal standard.

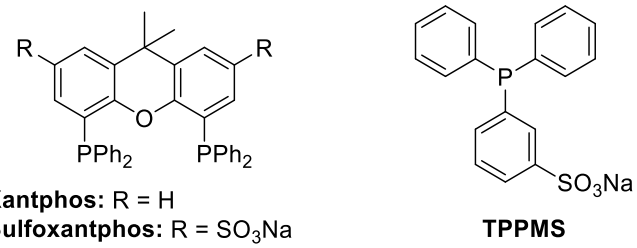
Low rhodium concentrations (Entry 5.1) achieved only low conversions, whereas high amounts of catalyst led to increased aldol condensation (Entry 5.3). Going further, the hydrogenation of the formed aldehyde to alcohol was observed (Entry 5.3). Since both reactions, hydroformylation and hydrogenation, are catalyzed by the same metal catalyst and ligand but with different complexations[28], the metal to ligand ratio plays an important role in selectivity. Typically, with high metal/ligand ratios, the hydroformylation is favored, whereas low ligand excesses favor hydrogenation.[9,29] Investigations on the metal/ligand ratio showed no definitive trend in terms of reactivity. In general, the amine yield was higher for lower amounts of phosphorous (Entry 5.4). Higher amounts of ligand lead to decreasing yields (Entry 5.5 and 5.6). The selectivity was highest (77%) at a metal/phosphorous ratio of 1/2 (Entry 5.4).
Previous investigations of the influence of different reaction parameters led to new reaction conditions, which can be considered optimized for hydroaminomethylation in aqueous solvent systems (Table 6). A precursor concentration of 0.13 mol% ensures high conversion. Apart from that, transition metal catalyzed side reactions, for example the hydrogenation of aldehydes to alcohols, are low. This is also maintained by a low ligand excess (M/P=1/2), which enables both hydroformylation of the olefin and hydrogenation of the enamine. As

stated before, high amounts of hydrogen are necessary for the desired reaction pathway. One way to ensure this is the syngas composition (CO/H_2=1/3) and pressure (50 bar). Furthermore, a temperature of 100 °C enables fast catalytic conversion and high solubility of the gaseous compounds.

Table 6: Chosen reaction conditions based on previous investigations

Parameter	Value
c([Rh(cod)Cl]$_2$	0.13 mol%
Metal/phosphorous	1/2
Co-Solvent	1-butanol (*V*/*V*=1/1)
Syngas pressure	50 bar
CO/H_2	1/3
Olefin/amine	1/3
Temperature	100 °C

Taking these reaction conditions into account, the choice of the ligand was re-evaluated. The sulfonated Xantphos analog Sulfoxantphos as well as the mono-sulfonated triphenylphosphine was tested (TPPMS, both see Figure 1). TPPMS have been shown to be beneficial for homogeneously catalyzed reactions in aqueous biphasic reaction mixtures.[30] In general, sulfonated and thus hydrosoluble ligands may enable recycling of the precious metal catalyst because the product accumulates in the organic phase.



Xantphos: R = H
Sulfoxantphos: R = SO_3Na

TPPMS

Figure 1: Structure of employed ligands

As can be seen in Table 7, the product yield was slightly higher using Sulfoxantphos (Entry 7.2) compared to the non-sulfonated ligand (Entry 7.1). Interestingly, there was some aldehyde left, which could still be converted to the desired product. The TPPMS ligand showed lower activity than the Xantphos ligands.

Table 7: Results with different ligands under optimized reaction conditions

Entry	Ligand	Y_1	Y_2	Y_3	Y_4	Y_5	S_5
7.1	Xantphos	1	5	9	0	62	81
7.2	Sulfoxantphos	13	2	5	0	64	76
7.3	TPPMS	16	<1	3	0	51	73

Reaction conditions: *c*([Rh(cod)Cl]$_2$)=0.13 mol%, *n*(1-octene)=6 mmol, *n*(diethanolamine)=18 mmol, M/P=1/2, *V*(1-butanol)=2.5 mL, *V*(H_2O)=2.5 mL, *T*=100 °C, *p*(CO/H_2)=50 bar, CO/H_2=1/3, *t*=6 h, 500 rpm. Yields (Y) are given in % based on 1-octene. $S_5=Y_5/(Y_1+Y_2+Y_3+Y_4+Y_5)$. Results determined by GC-FID using dodecane as internal standard.

A yield-time plot was recorded for these reaction parameters to obtain a deeper understanding for the course of the reaction. The resulting plot is depicted in Figure 2.

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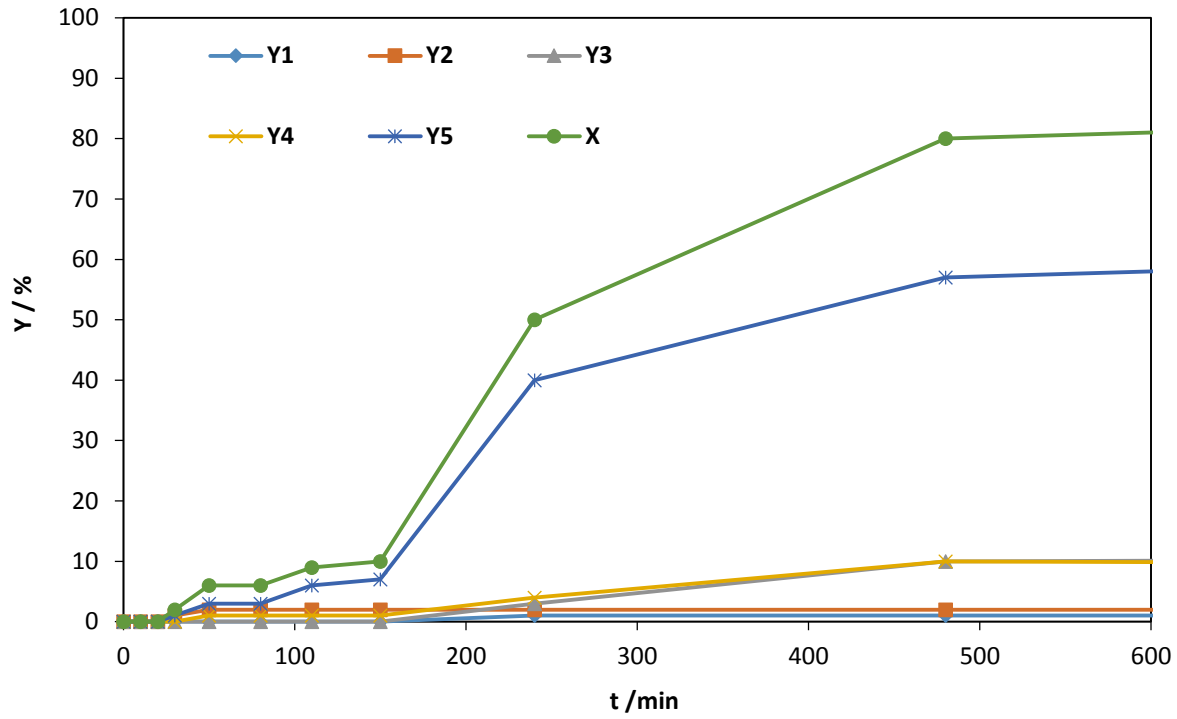

Figure 2. Yield-time plot under chosen reaction conditions.

Reaction conditions: *c*([Rh(cod)Cl]$_2$)=0.13 mol%, *n*(1-octene)=6 mmol, *n*(diethanolamine)=18 mmol, ligand=Sulfoxantphos, M/P=1/2, *V*(1-butanol)=2.5 mL, *V*(H_2O)=2.5 mL, *T*=100 °C, *p*(CO/H_2)=50 bar, CO/H_2=1/3, 500 rpm. Yields (Y) are given in % based on 1-octene. X=Y_1+Y_2+Y_3+Y_4+Y_5. Results determined by GC-FID using dodecane as internal standard.

Interestingly, the first 30 minutes pass without any olefin conversion. This might be explained by the formation of the catalytically active complex. But after this time conversion takes place rather slowly over the next two hours. This might be due to insufficient mixture between the catalyst, which is most probably located in the aqueous phase, and the olefin, which solubilizes in the organic phase. At this point, a yield of only 7% of the desired amine (**Y_5**) and an overall conversion of the olefin at 10% was observed. The conversion rate increased significantly afterwards, leading to an overall yield of 40% after four hours and 50% after eight hours. It should be stated that at no point was a significant amount of the enamine **4** detected. This is rather exceptional for the time profile of hydroaminomethylations[26,29]. Usually, the enamine is formed instantaneously from the aldehyde produced and the subsequent hydrogenation to the saturated amine takes place successively. On the one hand, the enamine is not very stable in aqueous media and, consequently, only the hydrogenated amine, which is no longer in equilibrium, is detected. On the other hand, the respective aldehyde is not detected in large amounts either. This indicates fast hydrogenation under these conditions and the hydroformylation step is decisive in determining the rate. This differentiates the reaction under aqueous biphasic conditions substantially from hydroaminomethylation, which is typically conducted in one homogenous phase. In the latter case the hydroformylation is very fast.

It would thus be of interest to use the Sulfoxantphos ligand due to its selectivity and reactivity, while avoiding the lengthy catalyst formation time. Preformation provided a suitable workaround, whereby the catalyst was preformed three hours in advance without the olefin in a syngas atmosphere. This was conducted at room temperature and at reaction temperature (T=100 °C). After three hours, the olefin was added *via* a reservoir with syngas pressure. The results of the following reaction (t=8 h) differ clearly (Figure 3).

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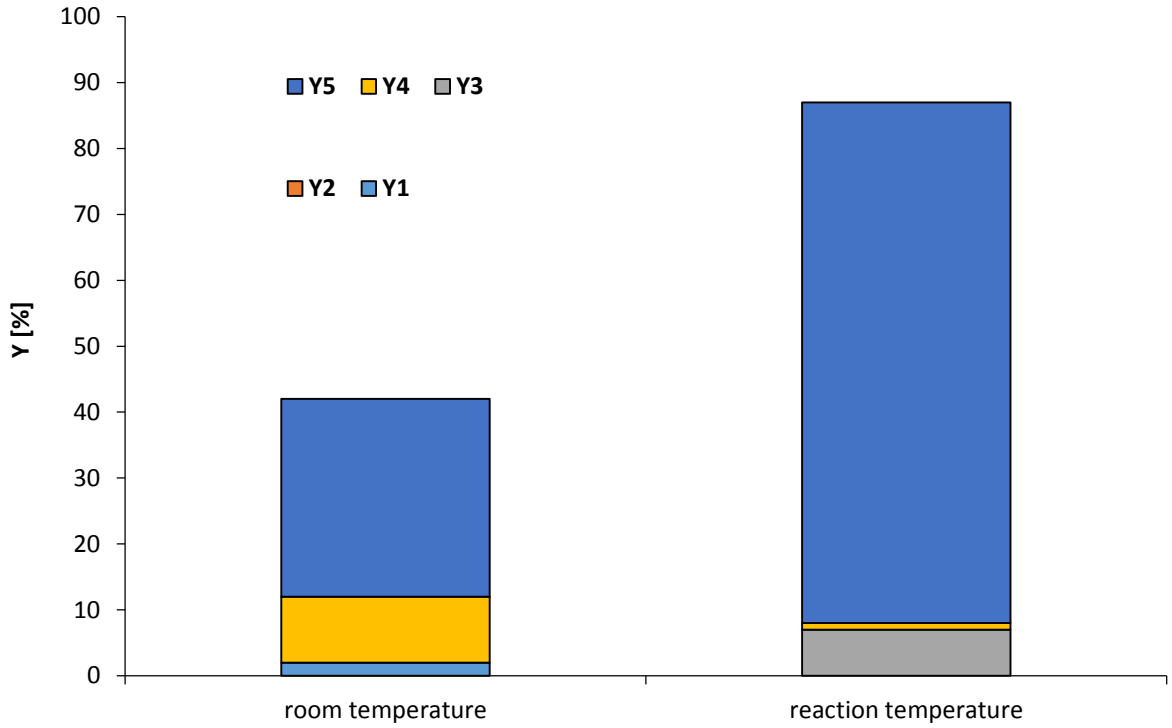


Figure 3. Comparison of the results using catalyst preforming under room temperature and reaction temperature

Reaction conditions: *c*([Rh(cod)Cl]$_2$)=0.13 mol%, *n*(1-octene)=6 mmol, *n*(diethanolamine)=18 mmol, ligand=Sulfoxantphos, M/P=1/2, *V*(1-butanol)=2.5 mL, *V*(H_2O)=2.5 mL, *T*=100 °C, *p*(CO/H_2)=50 bar, CO/H_2=1/3, 500 rpm. Yields (Y) are given in % based on 1-octene. Results determined by GC-FID using dodecane as internal standard.

Preforming the catalyst at reaction temperature significantly enhances the reactivity of the catalytic system. After eight hours a yield of 79% of the desired amines was achieved, constituting the best result of the investigations presented. The active catalyst is not only formed from the rhodium precursor and the phosphine ligand but also from syngas to form a rhodium carbonyl hydride complex, as described in the literature.[31] To form this catalytically active species, higher temperatures and syngas pressure are required, especially with regard to phase behavior and the availability of carbon monoxide and hydrogen in the liquid phases. Since the reaction mixture is biphasic after the reaction has taken place, the experiment procedure was altered slightly to evaluate the potential for catalyst recycling. In particular, the phase separation time was shortened to a few minutes to avoid catalyst deactivation (see Experimental section). Since non-converted octene is completely dissolved in the product phase (1-butanol) it was completely replenished after each reaction. The amine is employed in a threefold excess and as a consequence, only a third of the original amount is complemented. The results are shown in Figure 4.

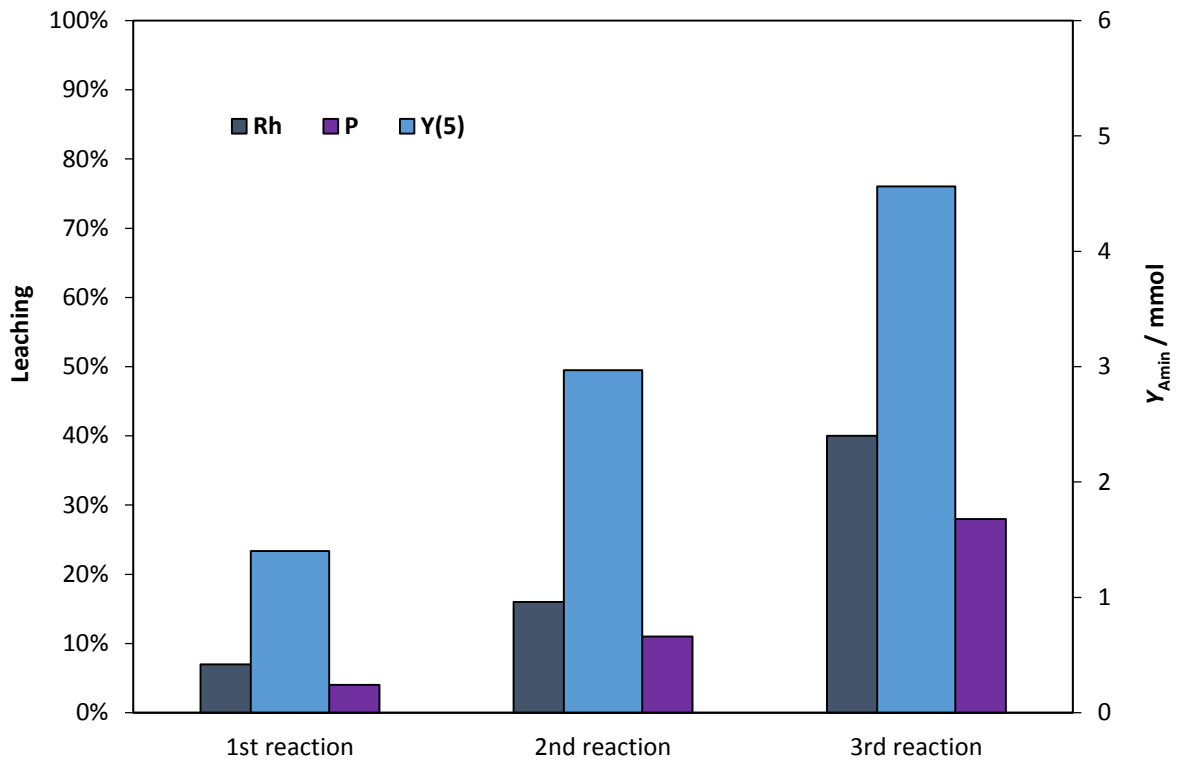
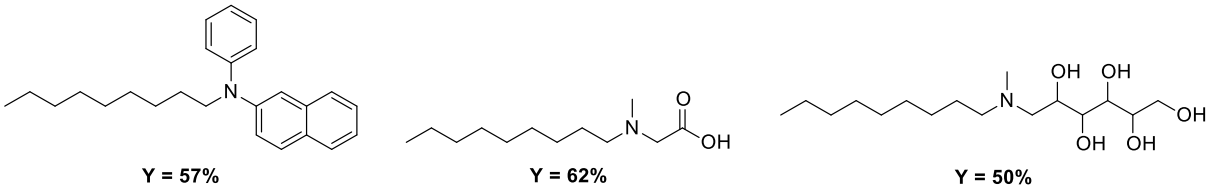


Figure 4. Reaction yields and leaching of the catalyst in recycling experiments.

Reaction conditions: *c*([Rh(cod)Cl]$_2$)=0.13 mol%, *n*(1-octene)=6 mmol, *n*(diethanolamine)=18 mmol, ligand=Sulfoxantphos, M/P=1/2, *V*(1-butanol)=2.5 mL, *V*(H_2O)=2.5 mL, *T*=100 °C, *p*(CO/H_2)=50 bar, CO/H_2=1/3, 500 rpm. Yields (Y) are given in mmol. Results determined by GC-FID using dodecane as internal standard.
Recycling conditions: Recovered aqueous phase, *n*(1-octene)=6 mmol, *n*(diethanolamine)=6 mmol, *V*(1-butanol)=2.5 mL, *T*=100 °C, *p*(CO/H_2)=50 bar, CO/H_2=1/3, 500 rpm. Leaching determined by ICP-OES and is given as a percentage of the initial amount. Yields (Y) are given in mmol. Results determined by GC-FID using dodecane as internal standard.

It can be seen that the yield in the first reaction (23%) is significantly lower than in the corresponding batch experiment (64%). This is most probably due to the shortened phase separation period, leading to incomplete product extraction in the organic phase. Catalyst leaching into the organic phase in this reaction was measured at 7% and 4% for rhodium and phosphorous, respectively. While this is not sufficient at an industrial scale, the catalyst can still be reused in the next cycle, as shown. The yield of the second reaction increases (50%), though at this point this could be product from the first reaction. Unfortunately, catalyst leaching increases. At the start of the third reaction, a maximum of 76% of the initial amount of rhodium and 85% of the phosphorous was left. It should be mentioned that neither the metal nor the ligand were replenished at any time. The third reaction resulted in a yield of 75%, which surely consists of product left from the first two cycles. Nevertheless, the catalyst was used 2.3 times more efficiently as compared to the batch experiment (Table 7, Entry 7.2). After the third reaction less than half of the catalyst compounds are likely to be present in the reaction mixture. Furthermore, after the fourth reaction, phase separation did not take place. A possible explanation for this behavior might be the accumulated 1-butanol in the aqueous phase. Since the aqueous catalyst phase was not analyzed and the phase separation was shortened, the amount of leached organic solvent was not determined. Complete replenishment then leads to an accumulation of 1-butanol, which results in an outright miscibility of all compounds.
Potential optimizations of this recycling scheme should include a detailed mass balance of all involved compounds, especially the solvents. Organic solvent that leaches into the aqueous

phase interferes with the intended phase behavior and the amount of water formed during condensation may be an important factor after numerous recycling runs.
Differently functionalized amines were employed to ultimately verify this approach for conducting hydroaminomethylation in aqueous solvent systems to successfully convert olefins to functionalized amines (Figure 5).



Reaction conditions: c([Rh(cod)Cl]$_2$)=0.13 mol%, n(1-octene)=6 mmol, n(amine)=18 mmol, ligand=Sulfoxantphos, M/P=1/2, V(1-butanol)=2.5 mL, V(H_2O)=2.5 mL, T=100 °C, p(CO/H_2)=50 bar, CO/H_2=1/3, 500 rpm. Yields (Y) are given in % based on 1-octene. Results determined by GC-FID using dodecane as the internal standard.

Figure 5. Substrate scope with different amines

The amino polyol *N*-methylglucamine is produced by the reductive amination of sucrose and is a promising building block for creating non-ionic surfactants. Enabling the hydroaminomethylation with this substrate may yield interesting new non-ionic surfactants that are partially based on a renewable feedstock. Under the conditions mentioned in Table 6, a 50% yield of *N*,*N*-methyl-nonyl glucamine was achieved. Employing *N*-methyl glycine, a synthetic amino acid, led to yields of 62%. This means that in general, polar amino acids can be functionalized using the approach presented. In the case of *N*-methyl glycine the resulting long chain substituted amino acid could be further functionalized to obtain betaines. To stress this concept, a highly non-polar amine, *N*,*N*-phenyl-naphthyl amine, was employed as well. This leads to 57% yield, demonstrating that this concept also works with amines that are not soluble in water.

Conclusion

To produce long chain substituted and highly functionalized amines, it is of interest to employ water-soluble amines in the hydroaminomethylation. With the model substrates 1-octene and diethanolamine crucial reaction parameters, *i.e.* temperature, pressures and concentrations, were investigated systematically. The investigations demonstrate that hydroaminomethylation can be conducted efficiently in aqueous solvent systems, though it incorporates a condensation reaction, forming water. Fast hydrogenation of the intermediate enamine ensures high yields of the desired amines. For this, a comparably low temperature is favorable, which is uncommon for hydroaminomethylations. The use of the water-soluble Sulfoxantphos ligand enables high yields and selectivities, but shows a long catalyst formation. This can be overcome by preforming the catalyst in the absence of the olefin at reaction temperature. Finally, this model was applied to amino acids and amino polyols (*N*-methyl glycine and *N*-methyl glucamine). Because *N*-methylglucamine in particular is difficult to dissolve in organic solvents, a conversion in aqueous solvent systems is highly beneficial. Phase separation after the reaction was successfully used for catalyst recycling, although leaching of solvent and catalyst in the product phase occurs.
The investigations will be extended to different alkenes and terpenes. Furthermore, other water-soluble amines could be employed.

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Experimental Section

Chemicals were purchased from *Acros Organics* (Geel, Belgium), *Sigma-Aldrich* (Steinheim, Germany) and *TCI* (Tokyo, Japan).
The catalyst and ligand were weighed directly into the reaction vessel. The amine was employed as a stock solution in water, the 1-octene as a stock solution in the organic solvent. The reactor was closed and pressurized with syngas. The reaction was terminated by cooling the reactor in an ice-bath. The reaction mixture was transferred to culture tubes and phase separation took place over night. The product phase was then removed and analyzed using GC-FID analytics. In addition, the aqueous phase was analyzed by GC-FID, but no products and/or substrates could be found in any of the samples collected.
Several identical reactions were started in individual reactors and terminated after the given time to produce the yield-time plot.
In the course of the experiment, all reaction compounds, except the 1-octene, were added separately to the reaction vessel. As with the previously-mentioned method, the vessel was closed, treated with syngas and stirred for 3 hours at the desired temperature. After the reactor was cooled down in an ice-bath, the syngas was devolatilized, and the reaction solution was stored in an argon atmosphere to insert the 1-octene. Further reaction steps were performed as described.
The recycling experiments were conducted as mentioned above with slight alterations. In order to avoid catalyst decomposition, phase separation was conducted in an argon-flushed schlenk tube and the phase separation time was limited to a few minutes. The product phases from the recycling experiments were also investigated to evaluate catalyst leaching (rhodium and phosphorous) using ICP-OES. The replacement of the removed phase was realized in the form of a stock solution consisting of the alkene, amine and organic solvent.
All products were purified by silica gel column chromatography and calibrated for GC-FID analysis with the internal standard. Routine gas chromatographic analyses were performed on an *Agilent* 7890B instrument (Santa Clara, USA) equipped with a flame ionization detector (FID) and a HP-5 capillary column (30 m, diameter 0.32 mm, film thickness 0.25 µm) connected to an auto sampler (7693) and an injector (G4513A). GC-MS analyses of the products were carried out on an Agilent 5977A MSD (70 eV).
NMR spectra were recorded on *Bruker* DRX spectrometers. $CDCl_3$ was used as solvent and standard for chemical shifts, purchased from *Deutero*.
Spectroscopic data for the main product of these investigations (**5**):
^{1}H-NMR (400 MHz, d_4-MeOH): ppm (δ) = 4.20 – 3.98 (m, 1H), 3.92 – 3.78 (m, 2H), 3.75 – 3.57 (m, 3H), 3.30 – 3.12 (m, 1H), 2.91 – 2.76 (m, 2H), 2.73 – 2.35 (m, 4H), 1.64 – 1.00 (m, 12H), 0.98 - 0.76 (m, 4H). **^{13}C-NMR** (100 MHz, d_4-MeOH): ppm (δ) = 96.82, 64.27, 61.16, 60.18, 55.19, 51.77, 50.96, 34.29, 32.01, 29.70, 25.17, 22.80, 14.25. **EI-MS:** m/z = 230 ($[M]^+$, < 1%), 201 (13), 200 (100), 118 (32), 88 (70), 74 (19), 58 (5), 57 (6), 56 (14), 55 (8).
The spectroscopic data of all other products can be found in the supplementary information.

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