Aqueous Biphasic Hydroaminomethylation Enabled by Methylated Cyclodextrins: Sensitivity Analysis for Transfer into a Continuous Process

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Abstract:

Hydroaminomethylation (HAM) is a highly efficient homogeneously catalyzed auto-tandem reaction converting alkenes into valuable amine products with water being the only co-product. This work reports for the first time the scale-up of the highly regioselective HAM of 1-decene with diethylamine for a potential continuous process application in a green and sustainable aqueous biphasic medium. The catalytic system Rh/SulfoXantphos and randomly methylated β-cyclodextrin (RAME-β-CD) were herein dissolved in the plain aqueous phase. The addition of cyclodextrins as green mass transfer agent remarkably increases the reaction rate as well as the selectivity towards linear amines, but they can also support solid content precipitation in this reaction system due to up-scaling effects. Therefore, parameters such as catalyst concentration, organic volume fraction, cyclodextrin concentration and recyclability were investigated regarding the stability and activity of the system. Especially the organic volume fraction had decisive influence on the solid content precipitation. High regio- and chemoselectivities of 35 respectively 82 % at nearly full conversion were achieved towards the linear product amine. The catalytic system was further recycled in batch and scaled-up into a 2100 ml autoclave without loss in activity and selectivity. Finally, a continuous process concept was proposed for an extensive investigation regarding long-term stability of the catalytic system.

Introduction

Hydroaminomethylation (HAM), discovered by REPPE[1] in 1949, represents an atom-economic and efficient one-pot process for the synthesis of amines from alkenes, syngas and primary or secondary amines. This catalytic auto-tandem reaction, nowadays typically catalyzed by homogeneous Rh-complexes, consists of an initial hydroformylation of an alkene to an aldehyde and subsequent formation of an enamine (or imine) followed by a hydrogenation.[2] From both, economic and environmental points of view, this direct preparation process of amines from low-cost feedstock is superior to traditional procedures, which are mostly multi-step and less atom-efficient with a number of by-products.[3,4] HAM has been used in many examples for the production of all kinds of amines from different unsaturated starting materials.[5–9] However, to fully exploit the inherent advantages of homogeneous auto-tandem catalytic hydroaminomethylation and prove its competitiveness among larger-scale aliphatic amine syntheses, an efficient separation and subsequent recycling of the catalyst in its active form is crucial. Various concepts have been presented in the last decades for the separation and recovery of homogenous catalysts for batch and flow processes in general.[10–17] In 2018 KALCK & URRUTIGOITY[2] examined these methods and several reaction pathways more closely for the hydroaminomethylation. Key reaction and separation systems discussed, were, among others, thermomorphic solvent systems[18], super critical CO_2 and ionic liquids.[19–21] In addition, biphasic systems were discussed as topic of interest. Especially, since water is formed as co-product in the hydroaminomethylation, aqueous separation concepts were reviewed as a potential green alternative. Particularly for the synthesis of higher aliphatic amines, the immobilization of the catalyst in a polar liquid phase has been frequently used as promising energy efficient method, due to the high boiling points of the formed products.[2] 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.[22] The first hydroaminomethylation in aqueous biphasic systems was reported by BELLER ET AL. using sulfonated diphosphines and an iridium co-catalyst together with rhodium. [23] Alkenes up to the chain length of 1-pentene were converted with ammonia to the respective primary amines. Another example for this was the hydroaminomethylation of isoprene.[24] The approach for the hydroaminomethylation of higher alkenes in aqueous solvent systems was yet only realized for a few selected examples in small scale by using additional surfactants,[25–28] such as quaternary ammonium compounds,[26] a co-solvent such as 1-butanol,[29] macro ligands to form a micellar system,[30] rhodium nano particles[31,32] or mass transfer agents (MTA) such as cyclodextrins (CD).[33] These examples are compared in more detail together with the results of this work in Table 7.

Herein, we further investigate the use of the mass transfer agent RAME-β-CD for the aqueous biphasic hydroaminomethylation. Chemically modified CDs are cyclic oligosaccharides composed of (α-1,4)-linked α-D-glucopyranose units, which are obtained from the enzymatic conversion of starch.[34,35] These compounds allowed to achieve the catalytic functionalization of numerous substrates in an aqueous/organic two-phase system due to formation of inclusion complexes at the aqueous/organic interface (Figure 1).[36] Just recently, we presented for the first time the successful scale-up and transfer of these MTAs into a continuous process for an aqueous biphasic hydroformylation mediated by RAME-β-CD.[37] High chemo- and regioselectivity, very low catalyst leaching and excellent long-term stability were presented. By combing the process development knowledge from that reaction with first experience in the HAM of Eugenol using a similar catalytic system[33] we considered a transfer of the hydroaminomethylation mediated by CDs into a continuous process would be eventually a big step forward for an efficient and sustainable conversion of higher alkenes to valuable amine products. Especially, since up to now only two continuous processes (thermomorphic multiphase system[38] + ionic liquid[21]) have ever been reported for the HAM and none of them were based on an aqueous solvent system. Therefore, we optimized and scaled-up for the first time the catalytic system

Rh(acac)$(CO)_2$/SulfoXantphos/RAME-β-CD for the aqueous biphasic hydroaminomethylation. For proper comparison with the other aqueous systems (Table 7) and the recent scale-up of this catalytic system for the hydroformylation,[37] we chose 1-decene and diethylamine (DEA) as model substrates. The functionalization of long chain alkenes is also of great interest, because of the high industrial importance of the resulting aliphatic tertiary amines.[39] To elaborate potential barriers for an application in a continuous process the promising small scale batch results[33] of this multiphase reaction are first scaled-up into a 300 ml batch autoclave and various parameters are investigated systematically, such as: catalyst concentration, organic volume fraction, cyclodextrin and diethylamine concentration as well as H_2/CO ratio. In particular, the organic volume fraction is an important key parameter in terms of phase separation efficiency for a proper catalyst recycling in a miniplant process. Therefore, a first recycling of this system is conducted in batch and eventually the catalytic system is further scaled-up into a 2100 ml autoclave to compare reaction performances for a transfer and to verify the obtained results. In the end an extended continuous process for the cyclodextrin based hydroaminomethylation is proposed to get a profounder understanding of catalytic stability, activity and leaching behavior.

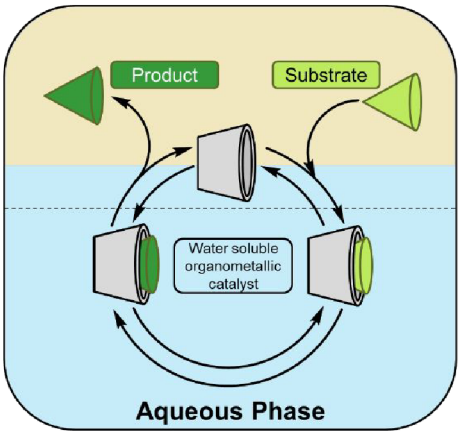

Figure 1: Principle of aqueous biphasic organometallic catalysis mediated by modified cyclodextrins (adapted from BRICOUT ET AL.[40])

Experimental Section

General methods and reagents

All the reaction experiments were carried out under inert argon atmosphere. Chemicals and reagents were procured from Alfa Aesar (1-decene 96%, diethylamine >99%), Sigma Aldrich (methyl-β-Cyclodextrin 98%), Messer Industriegase (syngas 99%, argon 99%, nitrogen 99%), Umicore (Rh(acac)(CO_2)) and Molisa (SufloXanthphos). All experiments were carried out either in 300 ml pressure Parr autoclave or a 2100 ml pressure Büchi autoclave. Reagents (deionized water and 1-decene, not DEA) are degassed via frit in an ultrasonic bath for 30 minutes using dispersed argon. Ligand and cyclodextrin were dissolved in the deionized and degassed water using an ultrasonic bath tempered to 40 °C. Preforming (overnight, >12 h) was conducted at 20 bar syngas pressure, reaction temperature and stirring. The reaction process was monitored by gas chromatography for liquid samples on an Agilent Technologies equipment type 7890A equipped with a flame ionization detector with a capillary column HP-5 (30 m x 0.32 mm x 0.25 µm). For analysis, 0.05 g di-n-butyl ether as internal standard, 0.35 g sample and 0.6 g n-hexane were used. Another 7890A Agilent Technologies gas chromatograph was also used to analyze on-line gas samples which is equipped with three consecutive columns and a thermal conductivity detector. The first two columns are used to protect the separation column from liquid and CO_2. A HP-Plot Molesieve column (30 m x 0.53 mm x 0.5 µm) is used as the separation column for H_2 and CO. It uses a carrier gas pressure of 1.3214 bar, an injection temperature of 150 °C, an injection volume of 250 µl, a spilt ratio of 2:1, a carrier gas volume flow of 20 ml/min, a reference volume flow of 10 ml/min, an oven temperature of 40 °C and a detector temperature of 200 °C. Rhodium and phosphorous leaching results were determined by ICP-OES (Analytic Jena Plasma Quant PQ 9000).

Typical procedure for aqueous biphasic HAM in the pressure autoclaves

The 300 ml pressure autoclave was first inertized using Schlenk technique. The catalyst solution (deionized water, Rh precursor, ligand) and diethylamine were added next. The reactor was then sealed pressure-tight and again flushed with argon. Preforming was carried out overnight. At start of reaction syngas was in most cases continuously fed into the reactor at 30 bar. All experiments in the 300 ml pressure autoclaves were carried out with a pitched blade stirrer at a speed of 800 rpm. After the reaction time has expired, continuous gassing was stopped, and the reactor was cooled down with ice water to room temperature (≤ 20 °C). Subsequently stirring was stopped, the reactor was depressurized and flushed several times with argon. The reactor was opened to separate the phases and to do the corresponding analyses, in the end the reactor was cleaned with isopropanol. Separation of organic phase (product rich) and aqueous phase (catalyst rich) was done by using a separation funnel and the corresponding analyses were carried out afterwards for each phase. For the reaction profile experiments, samples were taken at defined intervals from the reactor directly into a GC-vail via capillary line and needle valve. Also, the recycle experiments were conducted as described before, but at the end of each experiment, the aqueous phase was separated from the organic phase in separation funnel and reused in the cleaned reactor for a further batch run. The reacted diethylamine was replaced and the reactor was sealed pressure tight. Subsequently, 20 bar of syngas was pressed onto the reactor and afterwards heated up to 125 °C. As soon as the reaction temperature was reached, the next recycle run was started. Preforming was carried out only for the initial run and not for each recycle run.

The 2100 ml pressure autoclave was also first inertized using Schlenk technique. Catalyst solution (deionized water, Rh precursor, ligand) and diethylamine were added afterwards. The experiments were carried out with hydrogen and carbon monoxide (1:1) at 40 bar without continuous gassing of

syngas, since it was not technically possible at that apparatus to that time. After the reaction time has expired, the reactor was cooled to room temperature (≤ 20 °C). Stirring was stopped, the reactor was depressurized and flushed several times with argon. The reactor was emptied via a bottom valve, the phases were separated via separation funnel and the corresponding analyses were carried out. Finally, isopropanol was drawn into the reactor via vacuum for cleaning. A Rushton turbine was used at for these experiments

Results & Discussion

Within the presented study, the aqueous biphasic hydroaminomethylation of 1-decene with diethylamine (DEA/Et_2NH) mediated by the mass transfer agent RAME-β-Cyclodextrin is discussed (Figure 2). The main reaction is divided into hydroformylation of 1-decene **1** to the linear aldehyde undecanal ***l*-2** and the reductive amination, which itself consists of the condensation of the aldehyde with diethylamine to the linear enamine ***l*-3** and subsequent reduction of the latter to the desired linear amine *N,N*-diethylundecylamine ***l*-4**. Besides, the methyl branched products of the hydroformylation ***iso*-2** can be converted in a reductive amination via *iso*-enamine ***iso*-3** to the corresponding *iso*-amine ***iso*-4**. Other by-products are *iso*-decenes ***iso*-1** formed by C=C double bond isomerisation, *n*-decane **5** from hydrogenation of **1** and undecanols **6** from hydrogenation of the intermediate aldehydes, as well as aldol condensation products **7** and their hydrogenation products (not shown in figure 2). The formation of aldol condensates are mainly influenced by the concentration of the formed enamines, however it can also be formed directly from the corresponding aldehydes.

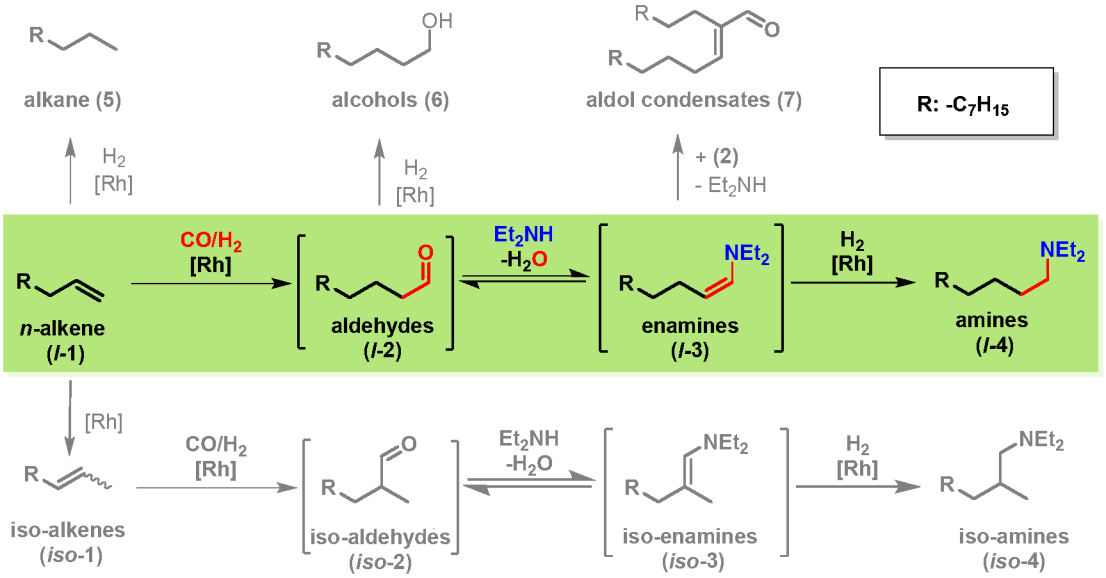

Figure 2: A simplified reaction network of the hydroaminomethylation of 1-decene and diethylamine

In the following, this work is divided in five sub-sections with the goal to scale-up the aqueous HAM for a continuous process application. At first a sensitivity analysis is conducted in a 300 ml batch autoclave regarding several important parameters for the scale-up. In the next step the optimized parameters are used to determine the reaction profile of the reaction which is necessary for a proper comparison of the catalytic activity and successful transfer of the optimized parameter into a larger autoclave. Also, a batch recycling of the catalytic system is conducted to get first information about the recyclability of the system. With all the data in hand the system is scaled-up into a 2100 ml batch

autoclave. Again, a reaction profile is taken to not only compare the activity of the catalytic system with the 300 ml autoclave but also to determine the optimal residence/reaction time for a continuous process. In the end a potential miniplant process is proposed (which is these days under construction) to conduct the first aqueous biphasic HAM in continuous operation.

Sensitivity analysis

Parameters (such as temperature, pressure etc.) for the sensitivity analysis were chosen based on earlier work on continuous hydroformylation[37] and hydroaminomethylation of eugenol[33] using RAME-β-CD as mass transfer agent. Since in the HAM of eugenol a 100 ml pressure autoclave was used, we decided to perform further screening experiments in larger autoclaves with the size of 300 ml to better represent changes in phase behavior and to evaluate further occurring effects. One of these effects which we haven't expected before hand is the amount of potential solid material which will be inadvertently formed in the upcoming experiments. This effect never showed up in smaller experimental batches and shows, inter alia, the necessity of a scale-up. This solid material has been analyzed by NMR, MALDi-TOF and IR (supporting information – Figure S1-S4). The solids are composed of RAME-β-Cyclodextrin and hydroaminomethylation products of the reaction. The amount of solid material will be in the following graded as the level of solid content precipitation (SCP). In particular, the SCP level is one of the major criteria in the following screening to decide whether a certain parameter change is useful for a scale-up or not. The different SCP levels that can occur in the following investigations are shown in Figure 3. No solid content (N) is the preferred alternative for transferring the catalytic system into a continuous process. The SCP level is used amongst other, such as the selectivity towards the linear amine product and the sum of yields for the intermediates and main product (aldehyde ***l*-2** enamine ***l*-3** + amine ***l*-4**) to determine efficient reaction parameters.

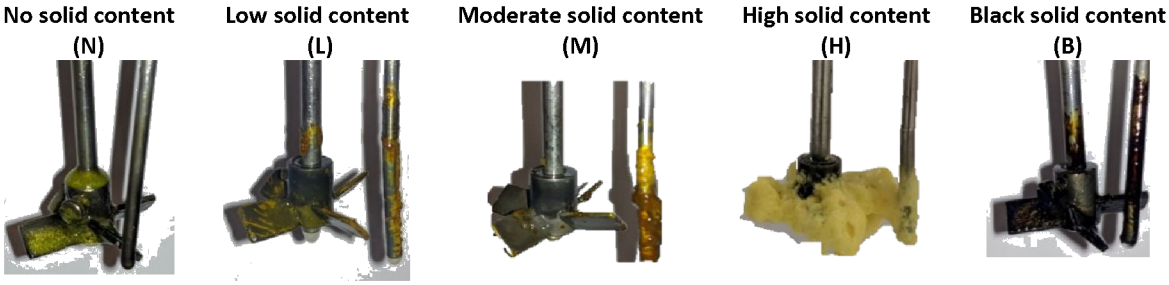

Figure 3: Level of solid content precipitation (SCP) after reaction in the HAM.

Substrate/catalyst ratio

The substrate/catalyst ratio has a decisive influence on the selectivity, conversion and efficiency of the hydroaminomethylation. Therefore, based on knowledge from the continuous hydroformylation[37] and the hydroaminomethylation of eugenol,[33] a catalyst/substrate ratio between 500 and 1000 was tested. The results (Table 1) show that increasing the ratio decreases the yield of main products by 20% (entry 1 and 3; $\sum Y_{MP}$). Especially, the change of from 750 (entry 2) to 1000 (entry3) shows a striking increase in by-product formation from 16% to 28% and hence, a decreased product selectivity of 55%. However, the catalyst concentration has no noticeable influence on the solid content precipitation (SCP) as in all cases a constant moderate SCP level occurred. Since the yield of the main products is highest at substrate/catalyst ratio of 500 it was chosen for further parameter screening with respect to decrease

the SCP level. However, in terms of a continuous larger scale application this ratio of 500 is rather low, which would need further optimization for an industrial application.

Table 1: Variation of catalyst concentration for the aqueous biphasic HAM of 1-decene and diethylamine. Further data are presented in the supporting Information.

#	$c_{Cat.}$ [mmol/l]	$n_{1\text{-decene}}/n_{Cat.}$	SCP	$\sum Y_{MP}$[%]	$\sum Y_{BP}$[%]	S4 [%]	Y4 [%]	Y3 [%]	Y2 [%]
1	2.6	500	**M**	**81**	14	70	68	0	13
2	1.8	750	**M**	**71**	16	75	70	0	2
3	1.3	1000	**M**	**61**	28	55	52	1	8

MP = Main products (aldehyde **2** + enamine **3** + amine **4**); BP= By-products (alkanes **5** + alcohol **6** + aldol condensates **7**)

Reaction conditions: $n_{SXP}/n_{Cat.}$: 2.5, $n_{CD}/n_{Cat.}$: 12, $n_{DEA}/n_{1\text{-decene}}$: 1, organic volume fraction ϕ: 0.2, T: 125 °C, p: 30 bar, t: 30 h, n: 800 rpm with pitched blade stirrer, all experiments carried out once.

Organic volume fraction

The organic volume fraction ϕ is defined as the ratio between organic (substrate rich) phase and aqueous (catalyst rich) phase in the reactor. Its variation can have a two-fold influence on the reaction system. On the one hand, it can affect the catalytic turnover as an increasing organic volume fraction generally supports a higher turnover number due to the availability of more substrate, provided the catalyst concentration is kept constant. On the other hand, for an efficient phase separation a ϕ between 0.1-0.9 is favorable, as too high or too small organic volume fractions need technically advanced or larger scale separation units in a continuous process to guarantee an optimal phase separation and to compensate potential process variations. Therefore, different organic volume fractions are tested (Table 2). As a catalyst/substrate ratio of 500 showed the most promising results in the first experiments (Table 1), this ratio is kept constant while varying ϕ. As a result, the catalyst concentration (c_{cat}) increased with increasing organic volume fraction ϕ. For that reason, we expected no major deviations in each of the experiments regarding the turnover numbers of the substrate. Accordingly, the catalyst concentrations and the catalyst activity (TOF) are specifically shown in Table 2 supporting this assumption since the TOF in all experiments is nearly constant at about 12 h^{-1}. The respective yields are also listed and show no great deviation. Therefore, the results are again primarily evaluated according to the level of solid content precipitation (SCP), which increases with increasing ϕ. However, at an organic volume fraction of 0.6 or greater (entry 8) no solid content precipitated anymore, since these fractions form three stable phases instead of only two (supporting information – Figure S5). The three phases remain stable in a separating funnel for several days, which is not favorable for a continuous phase separation in terms of time and flow regimes. Because of that no further increase of ϕ was investigated. The yields and selectivities at ϕ varied slightly with increasing organic volume fraction from 0.1 to 0.4 between 75- 81% and 70-78% (except entry 4). Due to the low SCP level and high yields towards the main products, further experiments were conducted using lower organic volume fractions of 0.1 (entry 4) or 0.2 (entry 5).

Table 2: Variation of organic volume fraction ϕ for the aqueous biphasic HAM of 1-decene and diethylamine. Further data are presented in the supporting Information.

#	ϕ	$c_{Cat.}$ [mmol/l]	SCP	$\sum Y_{MP}$[%]	$\sum Y_{BP}$[%]	TOF [h^{-1}]	S4 [%]	Y4 [%]	Y3 [%]	Y2 [%]
4	0.1	1.2	**L**	**75**	20	8	47	47	0	28

5	0.2	2.6	**M**	**81**	14	12	70	68	0	13
6	0.25	3.5	**M**	**78**	17	12	73	71	0	6
7	0.4	7.0	**H**	**75**	15	12	78	74	0	1
8	0.6	15.8	*	**75**	16	12	77	74	0	1

MP = Main products (aldehyde **2** + enamine **3** + amine **4**); BP= By-products (alkanes **5** + alcohol **6** + aldol condensates **7**); *stable three phasic conditions

Reaction conditions: $n_{1\text{-decene}}/n_{Cat.}$: 500, $n_{SXP}/n_{Cat.}$: 2.5, $n_{CD}/n_{Cat.}$: 12, $n_{DEA}/n_{1\text{-decene}.}$: 1, T: 125 °C, p: 30 bar, t: 30 h, n: 800 rpm pitched blade stirrer, all experiments carried out once.

Cyclodextrin/ catalyst ratio

The cyclodextrin (CD)/catalyst ratio is a parameter with a decisive influence on contacting the substrate in the organic phase with the catalyst complex in the aqueous phase. Therefore, different ratios from 6 to 15 are investigated. The results show that for a cyclodextrin/catalyst ratio smaller than 12 (entry 9 and 10; Table 3), selectivities of only about 46% occur. A very low *l/b* ratio of only 1 that does not correspond to the usually high regioselectivity for SulfoXantphos and a very dark colored organic phase also indicate that a substantial amount of rhodium has been transferred as unmodified $HRh(CO)_4$ into the organic phase reacting there non-selectively. Noticeably the cyclodextrin/catalyst ratio also has an influence on the solid content precipitation (SCP). Black solid content precipitates at a ratio of less than 12. In addition, with increasing cyclodextrin/catalyst ratio, both the SCP level decreases and the yield and selectivity of the product amine ***l*-4** increase slightly (entry 11 and 12). This indicates that higher cyclodextrin concentration not only supports a higher mass transfer rate between the organic and aqueous phase, but it seems that higher CD concentration also supports the stability of the active catalyst complex. Accordingly, further experiments are continued with a cyclodextrin/catalyst ratio greater 12.

Table 3: Variation of CD concentration for the aqueous biphasic HAM of 1-decene and diethylamine. Further data are presented in the supporting Information.

#	$n_{CD}/n_{Cat.}$	SCP	$\sum Y_{MP}$[%]	$\sum Y_{BP}$[%]	*l/b*	S4 [%]	Y4 [%]	Y3 [%]	Y2 [%]
9	6	**B**	**46**	47	1	47	46	0	0
10	9	**B**	**44**	47	1	46	44	0	0
11	12	**M**	**81**	14	33	70	68	0	13
12	15	**L**	**80**	16	30	74	72	0	8

MP = Main products (aldehyde **2** + enamine **3** + amine **4**); BP= By-products (alkanes **5** + alcohol **6** + aldol condensates **7**)

Reaction conditions: $c_{Cat.}$: 2.6 mmol/l, $n_{1\text{-decene}}/n_{Cat.}$: 500, $n_{SXP}/n_{Cat.}$: 2.5, $n_{DEA}/n_{1\text{-decene}.}$: 1, ϕ: 0.2, T: 125 °C, p: 30 bar, t: 30 h, n: 800 rpm with pitched blade stirrer, all experiments carried out once.

Diethylamine/ catalyst ratio

In principle, diethylamine (DEA) as co-substrate is present in both the organic product phase and the aqueous catalyst phase. Therefore, the hypothesis was that higher DEA concentration should improve the conversion towards the product amine, as more DEA will be available in the organic phase next to 1-decene. In Table 4 it can be seen that a DEA/1-decene ratio of 1 results in significant amounts (28%) of linear undecanal (**Y2**) at a low organic volume fraction (ϕ:0.1, entry 13) at the end of the reaction, whereas for the higher organic volume fraction (ϕ:0.2; entry 17) the amount of linear undecanal (**Y2**, entry 17) is only at about 13%. DEA/1-decene ratio >1 (entry 14-16 and 19) show in most cases the

highest yield and selectivity towards the product amine (**Y4**), proving also the initial hypothesis. This is explained by the shift of the equilibrium in the condensation reaction towards the linear enamine, which is then hydrogenated to the product amine (**Y4**) due to the long reaction time of 30 hours. In addition, having a DEA/1-decene ratio >1 completely prevents solid content precipitation (SCP, Table 4). Therefore, in the following we will continue working with an organic volume fraction of 0.2 and a DEA/1-decene ratio of 1.5, as no solid content precipitated and the highest selectivity of 78% towards the product amine occurred.

Table 4: Variation of DEA concentration for the aqueous biphasic HAM of 1-decene and diethylamine for an organic volume fraction of φ: 0.1 and φ: 0.2. Further data are presented in the supporting Information.

#	ϕ	$n_{DEA}/n_{1\text{-decene}}$	$n_{CD}/n_{Cat.}$	SCP	$\sum Y_{2+3+4}$[%]	$\sum Y_{BP}$[%]	S4 [%]	Y4 [%]	Y3 [%]	Y2 [%]
13	0.1	1	12	**L**	**75**	20	47	47	0	28
14	0.1	1.5	12	**L**	**76**	13	76	70	0	6
15	0.1	1.5	15	**L**	**76**	20	75	74	0	2
16	0.1	2	12	**N**	**70**	15	75	68	0	2
17	0.2	1	12	**M**	**81**	14	70	68	0	13
18	0.2	1	15	**L**	**80**	16	74	72	0	8
19	0.2	1.5	15	**N**	**76**	16	78	76	0	0
20	0.2	2	12	**N**	**69**	20	69	67	1	1

MP = Main products (aldehyde **2** + enamine **3** + amine **4**); BP= By-products (alkanes **5** + alcohol **6** + aldol condensates **7**)

Reaction conditions: $c_{Cat.}$: 1.2 mmol/l, $n_{1\text{-decene}}/n_{Cat.}$: 500, $n_{SXP}/n_{Cat.}$: 2.5, T: 125 °C, p: 30 bar, t: 30 h, n: 800 rpm with pitched blade stirrer, *all experiments carried out once.*

H2/CO gas ratio

The H_2/CO ratio is investigated as the hydroaminomethylation requires two equivalents of H_2 and one equivalent of CO by only considering the stoichiometry. However, several research groups presented in literature[25,29–31,33] that a H_2/CO ratio of 2:1 for the HAM often does not show the best results regarding product yield and selectivity. In these examples an H_2/CO ratio of 1:1 often showed the best results. This can have various reasons starting by the type of autoclave used (e.g. flow reactor vs batch reactor), the procedure to pressurize the autoclave (e.g. batch vs continuous), how the H_2/CO ratio is established (e.g. pressure regulator vs mass flow controller), the used phase system and substrates (regarding the solubility of H_2/CO) and the ratio of liquid volume (substrates etc.) to gas volume (H_2/CO) inside the autoclave. Therefore, we considered it quite difficult to find a general statement about the optimal H_2/CO ratio for the HAM, especially in batch autoclaves. To underline the complex interaction between all these parameters for an aqueous biphasic system, we tested three different H_2/CO ratios (0.5, 1 and 2) in a batch autoclave. The liquid volume to gas volume was 1:2 in all cases. The experiments with the syngas ratio of 0.5 (entry 21, Table 5) and the ratio of 2 (entry 23, Table 5) were completely tested in batch mode, while the ratio 1 (entry 22, Table 5) was tested in semi-batch mode, continuously supplying syngas to the reactor during reaction. Since a pressure loss during reaction was expected for experiments 21 and 23, the reactions were started at an initial pressure of 40 bar and then re-pressurized to 40 bar at a pressure loss of 20 bar (after approx. 6 h) to minimize the influence of a pressure drop. In comparison, the experiments 1-20 (Table 1 - Table 3) were all conducted with a continuous gas feed at 30 bar.

Table 5: Variation of H_2/CO ratio for the aqueous biphasic HAM of 1-decene and diethylamine. Further data are presented in supporting Information.

#	H_2/CO	SCP	$\sum Y_{MP}$[%]	$\sum Y_{BP}$[%]	p_{End} [bar]	S 4 [%]	Y 4 [%]	Y 3 [%]	Y 2 [%]
21	0.5	**N**	**74**	14	12	78	71	0	3
22	1	**N**	**76**	16	-	78	76	0	0
23	2	**H**	**77**	21	33	73	71	0	6

MP = Main products (aldehyde **2** + enamine **3** + amine **4**); BP= By-products (alkanes **5** + alcohol **6** + aldol condensates **7**)

Reaction conditions: $c_{Cat.}$: 2.6 mmol/l, $n_{1\text{-decene}}/n_{Cat.}$: 500, $n_{SXP}/n_{Cat.}$: 2.5, $n_{CD}/n_{Cat.}$: 15, $n_{DEA}/n_{1\text{-decene}.}$: 1.5, ϕ: 0.2, T: 125 °C, p_{Start}: 40 bar, t: 30 h, n: 800 rpm with pitched blade stirrer, *all experiments carried out once.*

The results in Table 5 show that there is no significant difference between the three experiments in the selectivity (73%-78%) towards the product amine ***l*-4** or in the general yields towards the main products (71%- 76%). So, the results fit well to the already published data for other HAM reactions in different aqueous systems. The reason for these similar results in this particular case we consider in the excess supply of H_2/CO in all experiments, due to a high pressure of 40 bar and a gas volume which is twice as large as the substrate liquid volume. To support this argument, we established a method to measure the H_2/CO ratio during reaction via gas chromatography, while continuously supplying syngas to the reactor at the same time. The observation of the H_2/CO ratio with continuous syngas feed (1:1; entry 22) showed a gradual accumulation of CO in the gas phase (Figure 4), due to which the H_2/CO syngas ratio decreases until reaction rate slows down after approximately 12 hour. This data fits well to the reaction profile shown in Figure 5. On the one hand that is exactly the effect we anticipated from the stoichiometry of the reaction, since the reaction needs two equivalents of hydrogen. On the other hand it also shows that after 30 hours there is still enough hydrogen in the autoclave so that no significant effects regarding the limitation of one of the gaseous components can be seen in the yield or selectivity of the product amine ***l*-4**. In addition, the solubility of hydrogen in water is slightly higher than the solubility of carbon monoxide in water at temperatures higher than 50 °C when comparing the Henry's law constants (supporting information – Table S2).

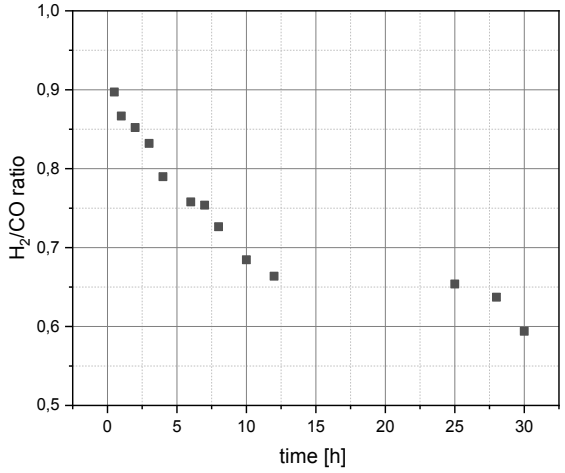

Figure 4: Change of the H_2/CO ratio over time of reaction for the HAM of 1-decene and diethylamine with continuous syngas (1:1) supply. The reaction took place overnight and was not stopped during that time.

Reaction conditions: $c_{Cat.}$: 2.6 mmol/l, $n_{1\text{-decene}}/n_{Cat.}$: 500, $n_{SXP}/n_{Cat.}$: 2.5, $n_{CD}/n_{Cat.}$: 15, $n_{DEA}/n_{1\text{-decene.}}$: 1.5, ϕ: 0.2, T: 125 °C, p_{Start}: 40 bar, t: 30 h, n: 800 rpm with pitched blade stirrer.

The accumulation of CO in the gas phase can also be observed in experiment 21. Due to the lower H_2/CO start ratio of 0.5 at the beginning of reaction, the amount of hydrogen decreases in that case to about 15%, but still shows no significant influence on the selectivity or yield. Overall, the continuous gassing with syngas (H_2/CO ratio of 1) shows for the semi-batch application a slightly higher yield and selectivity compared to the H_2/CO ratio of 0.5. In both experiments (21 and 22) no solid content precipitation occurred compared to experiment 23 in which high SCP level arose (Table 5). The continuous gassing with syngas (ratio 1) is therefore continued to determine the reaction profile and the recycling experiments to also be consistent with all the previously shown experiments. However, these results show that simple batch investigations do not give sufficiently reliable results regarding the optimal syngas ratio. For this reason, continuous flow applications might be more reliable as the thermodynamic and chemical equilibrium can easier be adjusted and optimized.

Reaction profile in 300ml autoclave

With optimized reaction conditions (Table 6) obtained from the sensitivity analysis a reaction profile of the aqueous biphasic hydroaminomethylation was determined (Figure 5). The optimized conditions were reproduced three times to ensure the quality of the data (supporting information; Table S3). This gives a precise benchmark for the upcoming scale-up experiments in the 2100 ml pressure autoclave to compare if one the sub-reactions of the hydroaminomethylation decelerate in the larger autoclave.

Table 6: Optimized reaction conditions for the HAM of 1-decene and diethylamine

Reaction conditions	Values
Temperature	125 °C
Pressure (constant)	30 bar
Stirrer speed	800 rpm
$\mathbf{c_{Cat}}$	2.6 mmol/l
$\mathbf{n_{SXP}/n_{Cat.}}$	2.5
$\mathbf{n_{1\text{-decene}}/n_{Cat.}}$	500
$\mathbf{n_{CD}/n_{Cat.}}$	15
$\mathbf{n_{DEA}/n_{1\text{-decene}}}$	1.5
Organic volume fraction ϕ	0.2
H_2/CO	1:1

In the first four hours yields of the aldehyde ***l*-2** and enamine ***l*-3** increasing considerably since first the hydroformylation and the subsequent condensation reaction takes place (see reaction network, Figure 2). Followed by an increase in the yield of the product amine ***l*-4** due the hydrogenation of enamine to approx. 60% after 10 hours. Already after 12 hour the course of the amine starts to flatten out After 24 hours, both yields of the aldehyde ***l*-2** and enamine ***l*-3** drop to nearly 0 and product amine yield (***l*-4**) increases only slowly in the following hours, since almost full conversion has already been reached. Overall, an expected yield and chemoselectivity of 80%, a TOF of 13 h^{-1} and an *l/b* ratio of 32 is achieved after 30 h and full conversion. In addition, no solid content precipitation occurred. With that in hand, also a first approximation can be made for the continuous process regarding the necessary residence time inside the reactor, which should be at least 12 hours to ensure a high conversion of aldehyde ***l*-2** and enamine ***l*-3**.

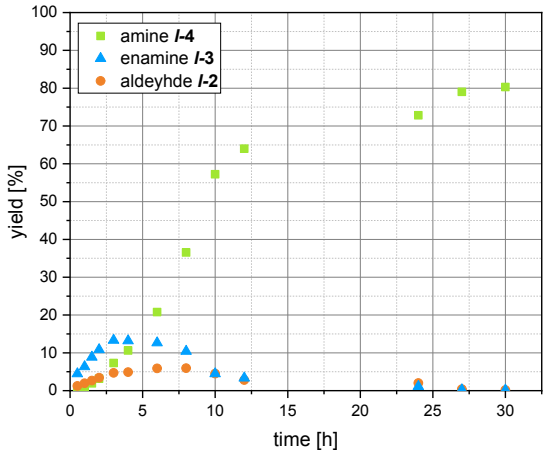

Figure 5: Reaction profile for the HAM of 1-decene and diethylamine under optimized conditions in 300 ml autoclave.

Reaction conditions: $c_{Cat.}$: 2.6 mmol/l, $n_{1\text{-decene}}/n_{Cat.}$: 500, $n_{SXP}/n_{Cat.}$: 2.5, $n_{CD}/n_{Cat.}$: 15, $n_{DEA}/n_{1\text{-decene}}$: 1.5, ϕ: 0.2, T: 125 °C, p: 30 bar, t: 30h, n: 800 rpm with pitched blade stirrer.

Recycling experiments

To show the feasibility of a continuous catalyst recycling a set of batch recycling experiments were conducted. The initial experiment 0 (Figure 6) reached a selectivity towards the product amine ***l*-4** of about 72% and a high *l/b* ratio of 26, but with a moderate solid content precipitation. Compared to the reaction profile (Figure 5) the recycle experiments used a slightly higher organic volume fraction (0.25 vs 0.2) to ensure an easier phase separation in the batch autoclave, which decreased the selectivity by 10% towards the product amine ***l*-4**. However, already the first recycling run has a way lower *l/b* ratio of about 6 compared to the initial run 0, but constant yield and selectivity towards the product amine ***l*-4**. A moderate solid content precipitation also occurred in this run. The leaching of rhodium and phosphorus into the organic phase are about 1% for the initial run 0 and recycle run 1 (supporting information – Figure S7). However, in recycle run 2 black solid content precipitation occurred to our surprise. Furthermore, both the organic and the catalyst phase were dark colored, which also reflects a much higher rhodium and phosphorus leaching of about 5%. This is consistent with a lower product selectivity of 39% and a low l/b ratio of 2. With respect to the results of the previous 24 batch experiments and the results from literature[33,37], we concluded that the system has the potential for an effect catalyst recycle, however a proper batch recycling of the catalytic system is not feasible in the existing set-up. Since a fully inert transfer of the catalyst phase is not possible and no additional preforming for each recycle run took place. Therefore, we concluded that the recyclability should be tested under constant process condition in order to obtain more reliable results, which can be obtained best in a continuous process. The benefits in this attempt are that the catalyst separation takes places under constant reaction pressure and inert process conditions, which allows an enhanced statement about the long-term recyclability of the aqueous catalytic system for the hydroaminomethylation.

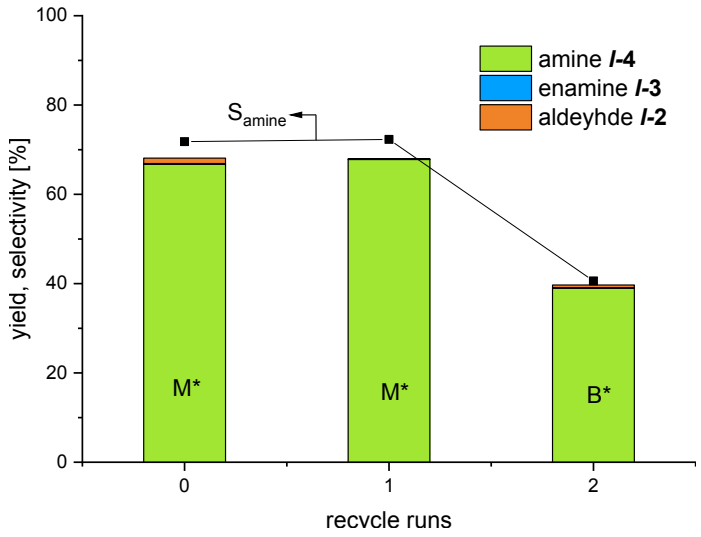

*Figure 6: Recycle experiments for the HAM of 1-decene and diethylamine under optimized conditions.*solid content precipitation*

Reaction conditions: $c_{Cat.}$: 2.6 mmol/l, $n_{1\text{-decene}}/n_{Cat.}$: 500, $n_{SXP}/n_{Cat.}$: 2.5, $n_{CD}/n_{Cat.}$: 12, $n_{DEA}/n_{1\text{-decene}}$: 1.5, ϕ: 0.25, T: 125 °C, p_{Start}: 30 bar, t: 30 h, n: 800 rpm with pitched blade stirrer, all experiments carried out once.

Scale-up in 2100 ml autoclave

Before the aqueous biphasic hydroaminomethylation can be transferred into a continuous operation a first scale-up of the reaction has to be realized. As the reactor unit in the continuous operated process is more than 6x larger than the used batch autoclaves, mixing behavior and heat transfer can differ. This has an decisive influence on multiphase reaction systems as we have recently shown at the example of the continuous hydroformylation supported by cyclodextrins.[37] Therefore, we performed the HAM as shown in Figure 5 under optimized conditions (Table 6) in a 2100 ml pressure autoclave. In contrast to the 300 ml batch experiments a Rushton turbine stirrer was used in his experiment due to availability in the larger autoclave. Experimental data for the aqueous biphasic hydroformylation supported by cyclodextrin have shown no significant difference between Rushton turbine and pitched blade stirrer under similar reaction conditions in terms of product yield (supporting information – Figure S8 and Figure S9) as the gas diffusion is supposed to be much faster than the speed of reaction. The reaction profile taken was than compared with the reaction profile from the 300 ml autoclave (Figure 5). Fortunately, the catalytic performance was successfully kept on the same level and *l/b* ratio and TOF were even slightly increased. Overall, a yield and chemoselectivity of 80%, a TOF of 14 h^{-1} and an *l/b* ratio of 34 was achieved after 30 h at full conversion of 1-decene. In addition, no solid content precipitation occurred. The residence time for the reaction solution was determined to be at least 12 hours inside the reactor of the continuous process, to ensure a high conversion of the intermediate products (aldehyde ***l*-2** and enamine ***l*-3**).

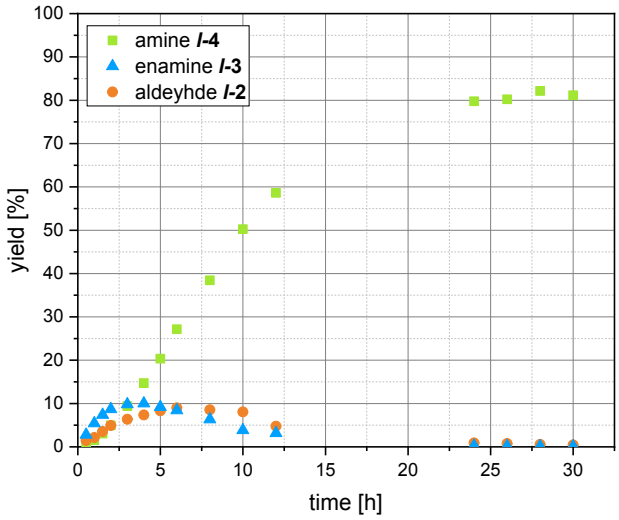

Figure 7: Reaction profile for the HAM of 1-decene and diethylamine under optimized conditions in 2100 ml autoclave and φ: 0.2.

Reaction conditions: $c_{Cat.}$: 2.6 mmol/l, $n_{1\text{-decene}}/n_{Cat.}$: 500, $n_{SXP}/n_{Cat.}$: 2.5, $n_{CD}/n_{Cat.}$: 15, $n_{DEA}/n_{1\text{-decene}}$: 1.5, ϕ: 0.2, t: 30 h, T: 125 °C, p_{Start}: 40 bar, n: 800 rpm with Rushton turbine.

Process concept for continuous HAM with CD

To verify the recyclability, long-term stability and the potential industrial relevance of an aqueous biphasic hydroaminomethylation mediated by cyclodextrins the system needs to be tested in continuous operation under the optimized reaction conditions (Table 6). Therefore, we constructed in the past a miniplant for multiphase catalysis applications[41] which we recently used for the first continuous hydroformylation of 1-decene mediated by cyclodextrin[37]. The miniplant set-up (Figure 8) consists of a reactor (B1) and phase separator unit (B2) with an integrated catalyst recycling loop. Since the hydroaminomethylation is a more advanced reaction with a second liquid substrate (diethylamine) next to 1-decene and water as co-product, an extend miniplant process is now proposed for the aqueous HAM. First, for the second substrate another feed pump must be installed. Second, the co-product water needs to be removed from the process as it will accumulate over time in the aqueous catalyst (blue) recycle stream. Even though the batch experiments have shown (Table 2) that more water in the reaction system is not instantly harmful to the catalytic activity. However, an accumulation of water in a long-term operating process will nevertheless face difficulties regarding the catalytic activity (e.g. due to dilution effects) and phase separation efficiency. To prevent this problem from start, a second separation unit (grey box) must be implemented into the recycle loop to eject the excess water. Because of high water concentrations in the system, moderate system pressure and energy efficiency organic solvent nanofiltration was selected as separation technique. All the technical changes at the miniplant are in progress these days, as well as a membrane screening for an efficient water separation. Results from the membrane screening and further investigations regarding the continuous operation of the reaction will follow in an additional publication.

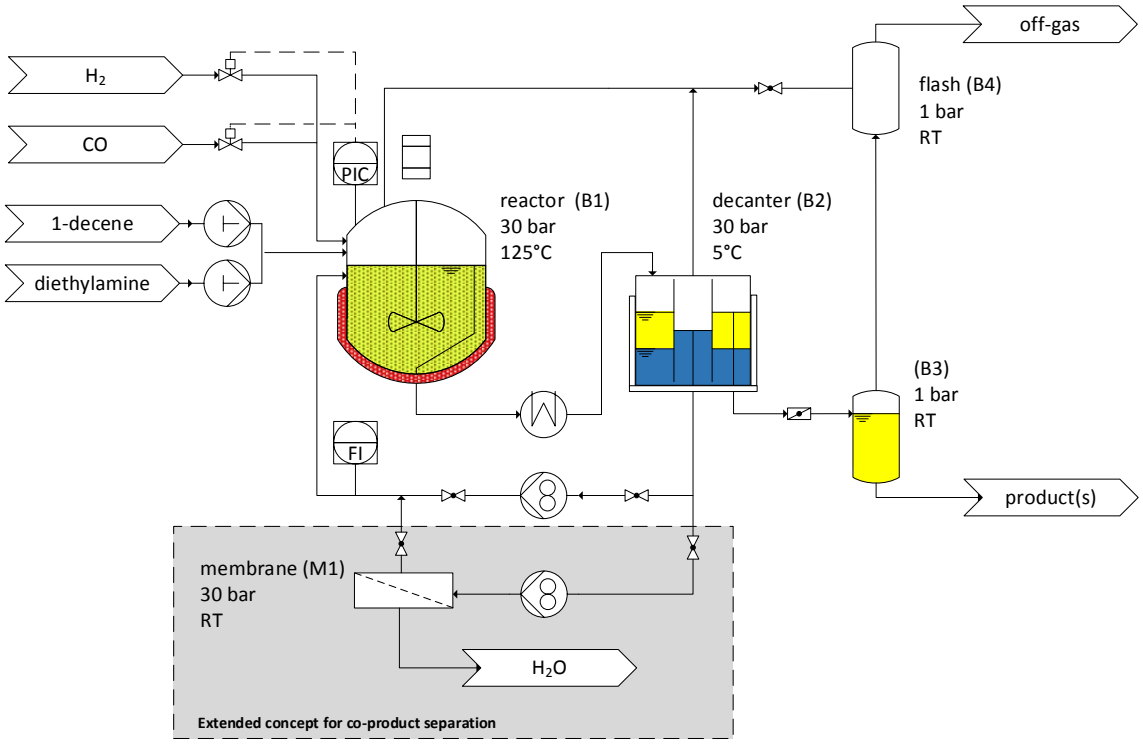

Figure 8: Process concept for the continuous HAM of 1-decene and diethylamine mediate by methylated-β-cyclodextrins.

Conclusions

The Rh-catalyzed aqueous biphasic hydroaminomethylation of 1-decene with diethylamine was investigated for a potential transfer into a continuous process using solely water as environmentally friendly solvent and RAME-β-CD as green mass transfer agent. It is the second time (entry 5; Table 7) that the use of cyclodextrin is reported in the hydroaminomethylation and for the first time a scale-up with a parameter screening was conducted to show potential barriers for a transfer of the catalytic system into a continuous process. Significant parameters such as catalyst concentration, organic volume fraction, cyclodextrin and diethylamine concentration as well as H_2/CO ratio with continuous pressurization were systematically investigated in 300 ml batch autoclaves. Especially the unexpected effect of solid content precipitation (SCP) in many experiments showed the necessity of a general scale-up investigations before a potential transfer into continuous process is possible at all. Reasons for SCP can be manifold, but in this system the concentration of cyclodextrin and DEA, as well as the phase ratio between organic and aqueous phase, are decisive for a successful reaction without creating solid material.

However, high regio- and chemoselectivities of 33 respectively 80% at nearly full conversion of 1-decene were successfully achieved towards the linear amine product with low rhodium and phosphorus leaching of 1% (entry 6; Table 7). First recycling experiments with 2 recycle runs of the catalytic system were conducted showing also limitations in the batch recycling of that system and the necessity of validation in a continuous process under constant recycling conditions. Eventually the catalytic system was scaled-up into 2100 ml autoclave (entry 7; Table 7) without losing any activity. Therefore, an extended continuous process based on a set-up presented in earlier publication[37] is herein proposed for the hydroaminomethylation to get an insight of long-term catalytic stability, activity and leaching behavior. Experiments regarding a deeper understanding why the solids are formed in this reaction system, membrane selection to eject the co-product water, as well as first continuous experiments are in preparation these days and will be discussed in an additional publication. All in all, the results show that these system can compete with other aqueous based systems for the conversion of higher alkenes with secondary amines (Table 7) in terms of moderate reaction conditions and chemoselectivities, although having a comparably slow reaction rate. However, it outperforms every other presented system by factor of 3 in terms of *l/b* ratio and it is the first aqueous based reaction system for the hydroaminomethylation which was successfully scaled-up for a continuous process application.

Table 7: Comparison of various aqueous based hydroaminomethylation reaction systems for the conversion of higher alkenes with secondary amines

#	System	Cat.	Alkene/Amine (Substrate)*	T [°C]	p (CO:H_2) [bar]	X [%]	S [%]	l/b [-]	t [h]	Rec.	Reactor size
1	Micellar **(Macro ligands)**[30]	Rh/Ir	1-C8en/DMA	130	50 (1:2)	39	62h	11	7	no	300 ml
2	Co-solvent **(1-butanol)** [29]	Rh	1-C8en/DOLA	100	50 (1:3)	88	90[#]	-	6	yes	<100 ml[#]
3	Surfactant **(CTAB*)**[25]	Rh/Ir	1-C10en/DMA	130	30 (1:1)	94	69	9	5	no	60 ml
4	Nanoparticles[31]	Rh	1-C12en/DPA	120	60 (1:1)	99	97	4	5	yes	75 ml
5	MTA (CD)[33]	Rh	Eugenol/Piperidine	80	30 (1:1)	92	79	-	8	yes	100 ml
6	MTA (CD) **-this work-**	Rh	1-C10en/DEA	125	40 (1:1)	99	80	33	30	yes	300 ml
7	MTA (CD) **-this work-**	Rh	1-C10en/DEA	125	40 (1:1)	97	84	34	30	No	2100 ml

*DMA = Dimethylamine; DPA = Dipropylamine, DOLA = Diethanolamine; MTA = Mass transfer agent; DEA = Diethylamine; CTAB = cetyltrimethylammonium bromide; 1-C8en= 1-octene; 1-C10en= 1-decene, 1-c12en= 1-dodecene; Rec.= Recycling
#Not given in original reference; calculated/estimated by authors

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Conflict of interest

The authors declare no conflict of interest.

Supporting Information

Additional information about l/b ratio and TOF for all 23 batch experiments, Figures regarding solid content precipitation; Henry's law constants for CO/H_2; Further data for recycling and scale-up experiments.

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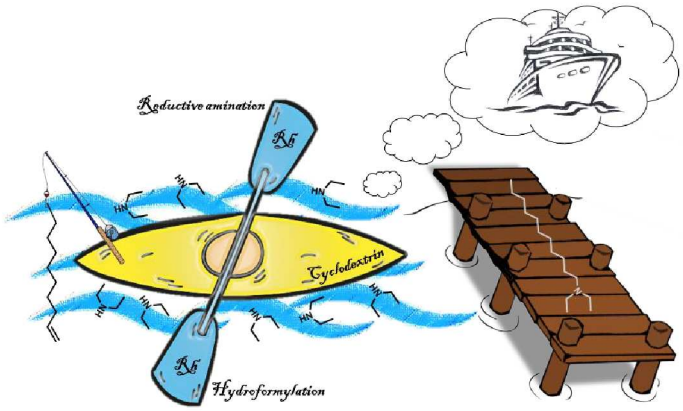

Synopsis: Scale-up of a homogenous tandem reaction in an aqueous biphasic media for the efficient and sustainable production of tertiary amines.