

Branched Tertiary Amines from Aldehydes and α -Olefins by Combined Multiphase Tandem Reactions

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Abstract: This study presents the transformation of olefins to branched amines by combining a hydroformylation/aldol condensation tandem reaction with the reductive amination in a combined multiphase system that can be recycled 9 times. The products are branched amines that are precursors for surfactants. Since the multiphase hydroformylation/aldol condensation system has already been studied, the first step was to develop the partial hydrogenation of unsaturated aldehydes together with a subsequent reductive amination. The rhodium/phosphine catalyst is immobilized in a polar polyethylene phase which separates from the product phase after the reaction. Reaction and catalyst recycling are

demonstrated by the conversion of the C₁₄-aldehyde 2-pentynal with the dimethylamine surrogate dimethylammonium dimethylcarbamate to the corresponding tertiary amine with yields up to 88% and an average rhodium leaching of less than 0.1% per recycling run. Furthermore, the positive influence of a Bronsted acid and carbon monoxide on the selectivity are discussed. Finally, the two PEG based systems have been merged in one recycling approach, by using the product phase of the hydroformylation aldol condensation reaction for the reductive amination reaction. The yields are stable during a nine recycling runs and the leaching low with 0.09% over the two recycling stages.

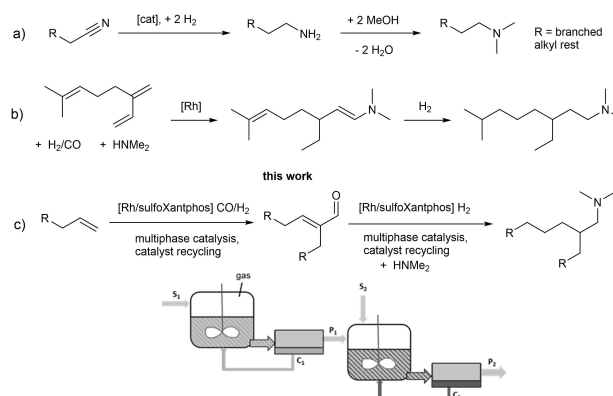
Introduction

Reductive amination is a great and efficient tandem reaction for the conversion of carbonyl compounds into primary, secondary, or tertiary amines.^[1] The reaction sequence starts with the condensation of an aldehyde or ketone with a non-tertiary amine to form an imine or enamine, followed by the consecutive reduction to the desired product. Amines that are formed by reductive amination represent highly valuable chemicals for applications such as pharmaceuticals, agrochemicals, polymers or surfactants.^[2] The importance of reductive amination is further reflected by many publications on this topic in recent years.^[3] When hydrogen is used as reducing agent, only water is formed as a by-product, which makes it a very sustainable procedure, especially considering that reductive amination is a one-pot reaction. One drawback of the reductive amination is the possibility of multiple aminations, which is why in industry reductive amination is mainly used for

the synthesis of secondary and tertiary amines. However, a couple of elegant solution for the selective formation of primary amines have been presented recently, too.^[4]

One important class of products that can be made from tertiary amines are surfactants, which have a wide range of application, for example, as detergents or food additives.^[5] A simple methylation of said amines that bear a large and branched alkyl backbone leads to ionic surfactants with a quaternary ammonium group for the hydrophilicity. Different methods have been developed to prepare long-chain branched amines, starting from basic chemicals such as alkenes or from biomass (Scheme 1).

A traditional synthesis involves the methylation of primary amines, which are produced by hydrogenation of nitriles (Scheme 1a). Starting from biomass, the hydroaminomethylation of terpenes was shown which is a tandem reaction consisting of hydroformylation and reductive amination



Scheme 1. Different routes to branched tertiary amines.

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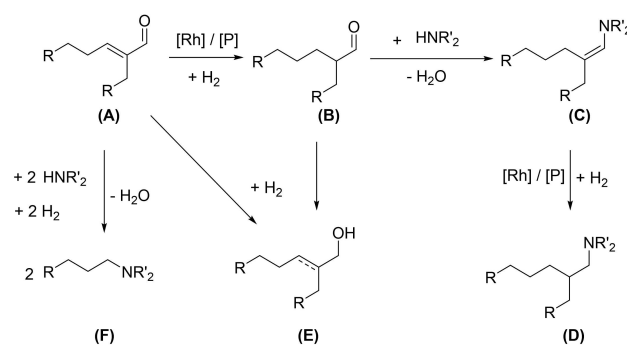
(Scheme 1b).^[6] One less explored route is the transformation of alpha-beta-unsaturated aldehydes, resulting from an aldol condensation to corresponding amines. This can be accomplished by the combination of a C=C hydrogenation with a consecutive reductive amination reaction, as shown in Scheme 1c. Hydrogenation of the double bond and reductive amination of the aldehyde can either be carried out in two separate steps^[7] or combined into a single step by means of tandem catalysis.^[8] The corresponding tandem reaction in this case is usually based on heterogeneous catalysts such as Pd/C or Pd/Al₂O₃.^[9] That homogeneous catalyst systems based on rhodium can also be applied for the reductive amination of saturated aldehydes was shown, too.^[1c,10] In addition, the combination of asymmetric hydrogenation and reductive amination of unsaturated aldehydes was also recently presented, for which a homogeneous rhodium-phosphine catalyst was used.^[11] However, the reaction systems were limited to the reaction with aromatic amines and no recycling of catalysts was discussed. In general, only few papers dealt with the catalyst recycling in homogeneously rhodium-catalyzed reductive aminations.^[12] For homogeneous catalysts based on expensive metals such as rhodium, catalyst recycling becomes especially important when thinking about applications so that the catalyst can be reused and is not lost. One elegant strategy for the recycling of organometallic catalysts is the use of multiphase systems, in which two immiscible liquid phases are used. The metal catalyst is dissolved in one of the two phases while the products form the other phase. This strategy allows an easy separation of catalyst and products.^[13]

In this work, we set out to develop a tandem hydrogenation/reductive amination reaction of alpha-beta-unsaturated aldehydes in a combination with a hydroformylation/aldol condensation reaction to yield branched amines from two intermeshed multiphase systems. First, a homogeneous catalyst system for the tandem hydrogenation/reductive amination reaction of alpha-beta-unsaturated aldehydes is developed. For this we used a multiphase system with special focus on catalyst recycling. In the tandem reaction, different unsaturated carbonyl compounds are first converted to the corresponding saturated analogous by rhodium catalyzed hydrogenation, followed by the acid supported reductive amination. Water and polyethylene glycol are investigated as solvents for the catalyst phase and the recyclability of both, the rhodium and the acid catalyst are demonstrated in recycling experiments. In addition, the combination of hydroformylation/aldol condensation and reductive amination is presented in a recycling experiment where the catalyst phases of both steps are recycled.

Results and Discussion

Reductive amination of 2-ethylhexenal (C₈-substrate)

Scheme 2 gives an overview of all species that were observed during this work and the proposed pathways leading to those molecules, starting from the unsaturated aldehyde (A). First, the double bond in (A) is hydrogenated to give the saturated



Scheme 2. Reaction network for the hydrogenation / reductive amination tandem reaction of 2-ethylhexenal. Displayed are the pathways to the desired amine product and the two major side products.

aldehyde (B). This can then condense with an amine to form the enamine (C). Finally, after hydrogenation of the enamine, the saturated tertiary amine (D) is formed. Typical side products are given by the alcohols (E), that form by hydrogenation of the aldehyde group. However, also the unexpected side product (F) could be observed which has only half the number of carbon atoms in the backbone compared to the starting material. The linear amine product (F) is only formed directly from the substrate (A) and most likely involves a retro-aldol fragmentation mechanism.

We started our investigations with the reaction of the model substrate 2-ethylhexenal – the aldol product of 1-butanal – and the secondary amines diethylamine and pyrrolidine. Water was selected as polar solvent for the catalyst phase to enable a multiphase catalyst recycling with substrates and products forming the non-polar phase. As the catalyst the well water-soluble species [RhH(CO)TPPTS₃] was chosen that can also be generated in situ by combining the rhodium-precursor [Rh(acac)(CO)₂] and the TPPTS-ligand. Due to the additional hydrogenation step of the double bond, the branched structure of the starting material and the occurrence of the side reaction towards the linear amine (F), the reaction was more challenging than the reductive amination of simple linear aldehydes. This was reflected by the unsuccessful reactions with diethylamine and pyrrolidine (amine yields < 60%). When diethylamine was used, either low conversions towards the products were observed at temperatures below 125 °C or catalyst deactivation by formation of nanoparticles at higher temperatures. Pyrrolidine, on the other hand, allowed high conversions at low temperatures of only 90 °C, but always showed a high selectivity (> 30%) towards the side product (F). Despite many attempts, it was not possible to improve the amine yield significantly (see Table S1).

Much better results could be achieved when dimethylamine (HNMe₂) was employed as reagent in the tandem reaction, with methyl groups also being the most common moieties attached to nitrogen in surfactants. Because our equipment did not allow the dosing of gaseous dimethylamine, the amine was introduced as an aqueous solution for the reaction instead, which delivered the solvent for the catalyst at the same time. At 90 °C,

a hydrogen pressure of 50 bar and a rhodium concentration of 0.5 mol% the substrate was completely converted and the desired amine formed with a good yield of 82% (Table 1, entry 1). While the separation of product and catalysts phase after the reaction worked as expected, it was not possible to test the recyclability of this system, since new addition of the amine would have changed the amount of water in the catalyst phase. Instead, a different source of dimethylamine was found in form of dimethylammonium dimethylcarbamate (DimCarb), which is the adduct of dimethylamine and carbon dioxide and appears as a liquid at room temperature. DimCarb was already successfully used as an amination reagent in the past.^[14] Under reaction conditions, DimCarb can release the amine and facilitates its reaction with the aldehyde. Unfortunately, a low conversion and therefore a low yield of the product (D) of only 13% was achieved, when DimCarb was used under otherwise identical conditions in the reaction with 2-ethylhexenal (Table 1, entry 2). The inhibition of the reaction is probably the result of a stabilization of DimCarb by water, so that dimethylamine is only released very slowly. To avoid this interaction between water and DimCarb, we thought about changing the solvent of the catalyst phase. In an earlier work from our group, we learned that polyethylene glycol with a low molecular weight (PEG-200) can be a suitable replacement for water in multiphase reactions.^[15] Being a very polar molecule,

PEG does not mix with a lot of non-polar substances and is moreover a green and cheap solvent.^[16] Indeed, it turned out that the reaction is not inhibited in PEG-200 and leads to full conversion of (A) with DimCarb as amine source (entry 3). Although the yield of (D) was with 72% lower than in the water

system, after some parameter changes, the yield could be optimized to 88% (entry 4). This optimization included a change of the catalyst species from [RhH(CO)TPPTS₃] to [RhCITPPTS₃] and the reduction of the DimCarb concentration and hydrogen pressure. We suspect that the improvement is mainly caused by the absence of CO as a ligand, which, as will be shown later, has a strong influence on the activity and selectivity of the rhodium complex.

With the optimized conditions in hand, we could conduct a first recycling experiment. Therefore, when the product phase and catalyst phase separated after the reaction (see Figure 1), the product phase was removed and replaced with new substrate for the second run. Unfortunately, the good yield of (D) from the first run could not be retained, as it dropped to only 29% while the yield of the short amine (F) increased significantly to 48% (entry 5). This decrease in the yield of the desired product was traced down to a deactivation of the rhodium catalyst. A ³¹P NMR spectrum of the catalyst phase after the reaction revealed that no phosphor ligand coordinated to the rhodium anymore, which was indicated by the absence of any doublet signals that are characteristic for the Rh–P coupling (see Figure S1). It was therefore concluded that during the reaction, the phosphine ligands dissociated from the metal center and were most likely replaced by amines. The poorly stabilized rhodium complexes then later formed either inactive clusters or nanoparticles, indicated by a black color of the catalyst phase, resulting in a lower activity in the recycling run. At the same time, the conditions that were successfully used for the conversion of the C₈-substrate (Table 1, entry 4) were also not suitable for the longer C₁₄-substrate, with which only 62% of the corresponding amine D were formed (entry 6).

Table 1. Hydrogenation / reductive amination of 2-ethylhexenal with different sources of dimethylamine and different solvents in a biphasic system.^[a]

Entry	Form of amine	B [%]	C [%]	D [%]	E [%]	F [%]
1	HNMe ₂ (aq)	7	3	82	1	6
2	DimCarb in H ₂ O	71	0	11	0	4
3	DimCarb in PEG	0	5	72	9	15
4	DimCarb in PEG ^[b]	0	2	88	6	4
5	DimCarb in PEG ^{[b][c]}	4	8	29	5	48
6	DimCarb in PEG ^{[b][d]}	7	7	62	5	6

[a] Conditions: 2-ethylhexenal (2 mmol), HNMe₂ (4 mmol), [RhH(CO)TPPTS₃] (0.5 mol%), H₂ (50 bar), solvent (0.4 mL), 90 °C, 16 h. Product yields were determined by GC-FID. [b] Optimized conditions: HNMe₂ (2 mmol), [RhCITPPTS₃] (0.5 mol%), H₂ (20 bar). [c] 2nd cycle. [d] 2-pentylnonenal (C₁₄) as substrate aldehyde.

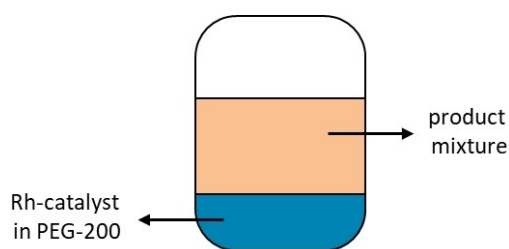


Figure 1. Phase separation after the reaction.

Reductive amination of C₁₄-substrate

The preliminary studies showed that the hydrogenation/reductive amination of the model substrate 2-ethylhexenal is possible when PEG-200 is used as the solvent and DimCarb as the dimethylamine source. Next, we focused on the conversion of the long-chain C₁₄-substrate 2-pentylnonenal, for which the reaction conditions had to be adjusted. The most important adjustment was to better stabilize the catalyst so that the formation of nanoparticles and clusters could be prevented. Two different options were considered for this: the use of a bidentate phosphine ligand and the addition of carbon monoxide (CO) to the gas phase. Bidentate phosphines such as SulfoXantphos (4,5-Bis(di-phenylphosphino)-9,9-dimethyl-2,7-disulfoxanthene disodium salt) bind more strongly to the metal center and thus are less likely replaced by amines compared to monodentate ligands. However, the use of SulfoXantphos instead of TPPTS as a ligand resulted also in a different product distribution in addition to its stabilization effect (Table 2). The comparison of the two ligands in the reductive amination of the C₁₄-substrate (2-pentylnonenal) at 130 °C showed that despite a similar yield of D of 49% and 53%, respectively, the yields of the side products differed greatly (Table 2, entries 1–2). While with TPPTS a large amount of (F) (21%) was formed, with

Table 2. Reductive amination of 2-pentylnonenal with SulfoXantphos as ligand, TsOH as co-catalyst and CO.^[a]

Entry	ligand	p (CO) [bar]	B+C [%]	D [%]	E [%]	F [%]
1	TPPTS	–	19	49	2	21
2	SulfoX.	–	2	53	41	2
3	SulfoX.	5	14	54	3	25
4	SulfoX.	2	7	68	4	18
5	SulfoX.	0.5	5	70	7	14
6 ^[b]	SulfoX.	0.5	4	82	9	3

[a] Conditions: 2-pentylnonenal (2 mmol), Dimcarb (1.5 mmol, \pm 3 mmol HNMe₂), [Rh(CO)₂(acac)] (0.5 mol %), sulfoXantphos (0.75 mol %), H₂ (50 bar), CO, PEG-200 (0.4 mL), 130 °C, 16 h. Product yields were determined by GC-FID. [b] Additionally TsOH (30 mol %).

SulfoXantphos the alcohols (E) (41 %) represented the main side products. The results can be explained by the fact that the use of SulfoXantphos leads to an increase in the hydrogenation activity of the system. (F) can be formed only from the unsaturated substrate, so its formation competes with the hydrogenation of the double bond. Therefore, if the hydrogenation to the unsaturated aldehyde is rapid, less of the short amine is formed, as was seen in the case of SulfoXantphos as a ligand. On the other hand, higher hydrogenation activity also leads to faster hydrogenation of the aldehyde group and thus to more alcohols as side products.

The addition of CO can also stabilize the rhodium complex, since CO is a strong ligand. However, it is also known that the presence of CO reduces the hydrogenation activity of rhodium-phosphine complexes; especially of C=C and C=O double bonds. Indeed, at a partial pressure of 5 bar CO a similar product distribution was observed as in the experiment with TPPTS as ligand and without CO (Table 2, entry 3). Reducing the CO partial pressure to 2 bar and 0.5 bar resulted in higher yields of D of 68 % and 70 %, respectively (entries 4–5). The yields of the two side products were intermediate between those of the experiments with 0 bar and 5 bar CO. The addition of a Brønsted acid as co-catalyst was described beneficial for the enamine formation.^[11,17] For this *para*-toluene sulfonic acid (TsOH) was chosen. With 30 mol % TsOH, the yield of D was increased to 82 % (Table 2, entry 6). Here, the increase of D by 12 percentage points compared to the experiment without acid resulted mainly from the reduction of the amount of side product (F) by suppressing the retro-aldol reaction.

After it was confirmed that the new conditions were beneficial for the tandem reaction, we wanted to check whether catalyst recycling was now also possible. For that we performed a recycling experiment over 8 runs with a shorter reaction time of 3 h (Figure 2). After each run the product phase was removed and the catalyst phase washed with pentane before new substrates were added to start the next run. We performed an additional recycling experiment without TsOH as co-catalyst for a comparison to verify if TsOH is successfully recycled, as well (Figure S2).

In the experiment with TsOH, a drop in the target product of nine percentage points was observed in the first three runs. This was accompanied by an increase in the yields of the

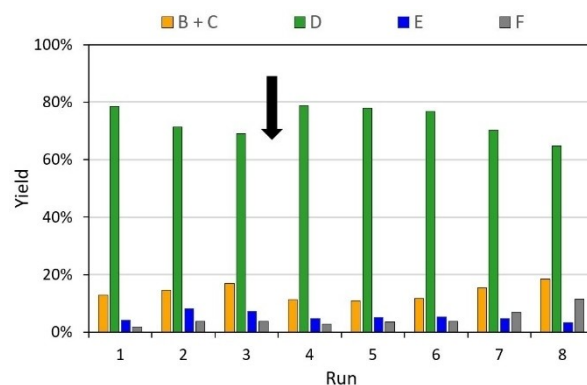


Figure 2. Recycling experiment of the hydrogenation / reductive amination of C14-Aldol with TsOH as co-catalyst in PEG. Conditions: 2-Pentylnonenal (2 mmol, 0.5 mL), DimCarb (1.0 mmol, 0.13 mL), PEG-200 (0.4 mL), [Rh-(acac)(CO)₂] (0.5 mol %), SulfoXantphos (0.75 mol %), TsOH (30 mol %), H₂ (50 bar), CO (0.5 bar), 125 °C, 3 h. From run 3 on (black arrow), the time on the vacuum after each run was increased from 1 min to 1 h to remove water.

intermediates and side products (Figure 2). However, in the fourth run, the product distribution of the first run was again achieved. This result can be attributed to a change in workup between runs. After each individual experiment, the product phase was separated, and the catalyst phase was washed with pentane and then briefly exposed to high vacuum (1×10^{-3} mbar) to remove air from the system and bring it back under argon. Since water is also formed as a by-product in the reductive amination, it can influence the catalytic performance. Therefore, in the workup of run 3 and subsequent runs, the time at vacuum was increased to also remove the water formed. The effect of this change was very clear, as in runs 4 and 5 the product distribution of the first run could be restored. A blind experiment verified that water can in fact be removed from a water/PEG mixture. This supported the hypothesis that the decrease in amine yield was due to the accumulation of water in the catalyst phase. Thus, it can be concluded that the recycling was very successful and both catalysts can be used at least 5 times without reduction of activity or selectivity. It is also important to note that although the starting substrate was fully converted in all runs (99 % conversion), full conversion was not achieved for the intermediates because only a reaction time of 3 h was selected.

In runs 6–8, a renewed drop in the yield of (D) could be observed, which was accompanied by an increase in (F) (Figure 2). Deactivation of the rhodium/phosphine catalyst, deactivation of the acid or leaching of one of the two catalysts were possible causes for this decrease. To check for possible deactivation or leaching of TsOH, the recycling experiment without addition of the acid was used (Figure S2). In contrast to the series of experiments with acid, an increased formation of alcohols (E) is observed here, but no significantly higher yield of (F). It can therefore be assumed that the drop in yield in the last runs of the first experiment (Figure 2) was not caused by deactivation or leaching of TsOH, since an increase in (F) up to 12 % was seen here. Rhodium leaching into the product phase was determined by ICP-MS measurements and found to be

1.7 ppm on average which corresponds to only a loss of 0.08% of the initial rhodium per run. A deactivation of the metal catalyst by oxidation of the SulfoXantphos ligand seems more likely, since complete oxygen exclusion between the individual runs could not be guaranteed. Since SulfoXantphos was used in excess relative to rhodium (1.5 eq), this could also explain why the deactivation is only noticeable at run 6.

After recyclability of our catalyst system was confirmed, we took a closer look at some specific parameters. Firstly, we looked at alternative Brønsted acids as co-catalysts for the reductive amination (Table S2). The comparison shows that 4-Cl-PhSO₃H performs best at 82% yield of (D). In addition, the formation of (F) did not occur with this acid and the amounts of intermediates were greatly reduced, indicating an overall faster reaction.

Furthermore, we investigated the influence of CO pressure on the reaction, which we already knew to be crucial (Figure 3). As it can be seen, there is a strong dependence of the product distribution on the amount of CO between 0 and 5 bar. As the pressure is increased from 0 to 1 bar, the yield towards the alcohol drops from 41% to only 1%, as the hydrogenation of the aldehyde group is slowed down more and more by the CO that coordinates to the rhodium. At the same time, the yield of the desired amine increases up to a maximum of 88% at 0.7 bar of CO.

At higher pressures the hydrogenation of the double bond in the substrate is suppressed, too, which leads to a reduction of conversion. The change in catalyst selectivity can also be observed visually after the reaction. The color of the catalyst phase turns red at 0.2 bar of CO, orange at 0.5 and 0.7 bar and yellow at higher amounts of CO. Furthermore, when the catalyst phase is exposed to air after the reaction, the color eventually turns back to red, as CO escapes from the solution. Notably when no CO is added to the reaction, the catalyst phase turns black, indicating a deactivation of rhodium. This confirms that CO not only shifts the selectivity towards the desired product but is also essential for the stabilization of the metal catalyst.

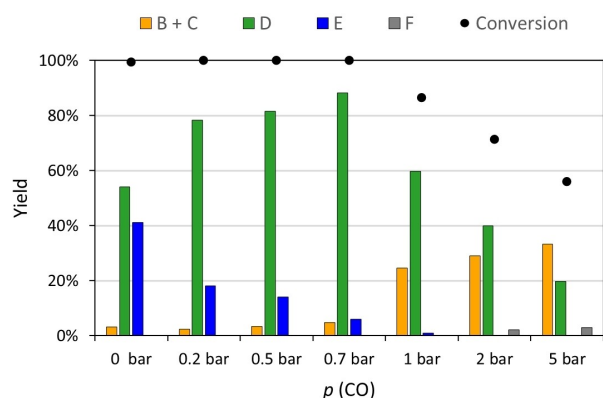


Figure 3. CO-pressure influence on the reductive amination of 2-pentylnonenal with DimCarb. Conditions: 2-Pentylnonenal (2 mmol, 0.5 mL), DimCarb (1.0 mmol, 0.13 mL), PEG-200 (0.4 mL), [Rh(acac)(CO)₂] (0.5 mol%), SulfoXantphos (0.75 mol%), 4-Cl-PhSO₃H (30 mol%), H₂ (50 bar), CO, 125 °C, 3 h.

We were also interested in expanding the catalyst system to other substrates, using shorter substrates and other amines. Figure 4 shows three products that were produced from 2-ethylhexenal and 2-butyloctenal. For this a CO-pressure of 1 bar was chosen, because the shorter substrates were easier converted to the alcohol.

Hydroformylation/aldol condensation + reductive amination

To go one step further, we wanted to combine reductive amination with another homogeneously catalyzed reaction to form a so-called cascade reaction. The aim was to carry out both reactions in succession in such a way that, apart from the recycling of the catalysts, no intermediate workup was necessary. Furthermore, a multiphase system was to allow recycling in both reaction steps (Figure 5).

In a recent publication we presented the multiphase hydroformylation/aldol condensation tandem reaction to convert linear olefins into unsaturated aldehydes.^[15] In combination with the reductive amination discussed in the present paper, it is possible to form branched, long-chain amines starting from simple olefins (Figure 6, a). To demonstrate that the two reaction stages can in fact be connected in series, a series of experiments was carried out in which the product solution of the hydroformylation/aldol condensation was used as the substrate solution for the second reaction. The catalyst phases

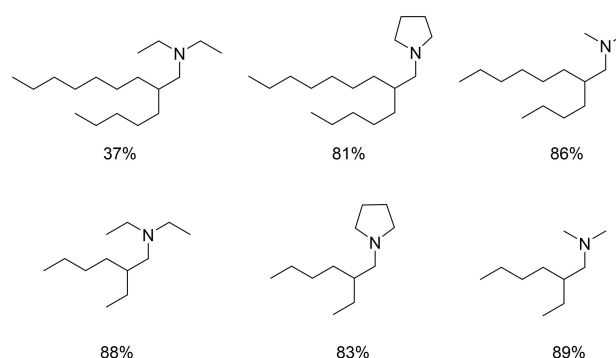


Figure 4. Substrate Scope. Yields were determined by GC analysis.

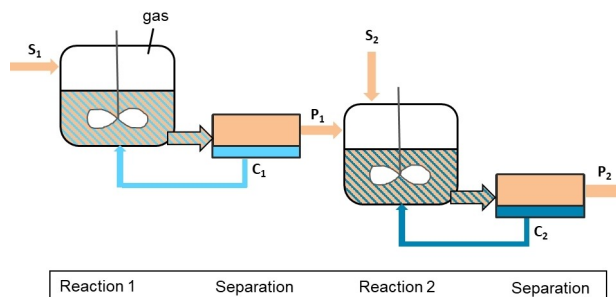


Figure 5. Schematic representation of a general cascade reaction with two multiphase partial reactions. The product phase is shown in orange and the catalyst phases in blue. S = substrate(s), P = product(s), C = catalyst(s).

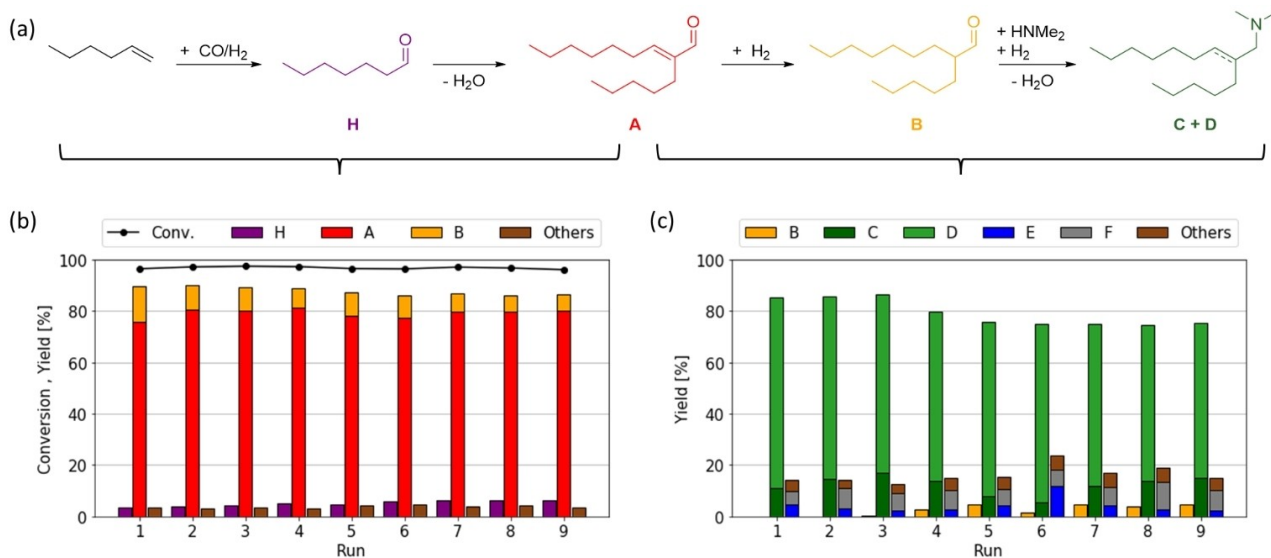


Figure 6. (a) Combination of hydroformylation/aldol condensation tandem reaction and hydrogenation/reductive amination tandem reaction. (b) Recycling experiment of the hydroformylation/aldol condensation of 1-hexene. Conditions: substrate: 1-Hexene (8 mmol, 1.0 mL), catalyst phase: PEG-200 (0.4 mL), [Rh(acac)(CO)₂] (0.1 mol%), SulfoXantphos (0.2 mol%), Cs₂CO₃ (2.5 mol%), additional parameter: H₂/CO (30 bar each), 5 h at 100 °C then 16 h at 125 °C. Others = hexane and heptanol. (c) Recycling experiment of the hydrogenation/reductive amination using the product mixture from the hydroformylation/aldol condensation as substrate. Substrate solution: 0.5 ml of the product solution of the corresponding run from experiment (b), catalyst phase: PEG-200 (0.4 mL), [Rh(acac)(CO)₂] (0.01 mmol), SulfoXantphos (0.015 mmol), 4-Cl-PhSO₃H (0.6 mmol), additional parameter: H₂ (50 bar), 125 °C, 3 h. Others = hexane, heptanol.

of both stages were recycled in each case and a total of nine runs were considered (Figure 6, b and c). The reaction conditions for hydroformylation and aldol condensation were chosen in a way that maximized the sum of the aldol product **A** and the saturated aldehyde **B**. For this purpose, the reaction solution was first stirred at 100 °C for 5 h to maximize the conversion of 1-hexene. Subsequently, the temperature was increased to 125 °C and stirred for another 16 h to ensure that the aldol condensation and, to some extent, the subsequent hydrogenation also proceeded as far as possible. As a result, a conversion of 96% and a combined aldehyde yield of 90% were achieved in the first run, with the saturated aldol accounting for 14% of the yield (Figure 6, b). The good conversion of hexene was also observed in the subsequent runs and ranged from 96% to 97% in each case. The combined aldehyde yield decreased only slightly across runs from the 90% of the first two to 86% in the final runs. At the same time, the amount of heptanal also increased from 3% to as high as 6%. The yields of the side products hexane and heptanol were between 3% and 4% in all runs.

The product solution after each run was used as substrate for the second reaction, hydrogenation, and reductive amination. Again, the catalyst phase after each run was recycled and reused. In addition to the usual products of the reaction, the side products, and unreacted intermediates of the first step were also found in the product mixture. Residual hexene had been thereby hydrogenated to hexane and *n*- and *iso*-heptanal aminated to the corresponding C₉-amines. In the first run of the recycling experiment, a 74% yield of the C₁₆ amine was observed (Figure 6, c). In addition, 11% of the enamine was

formed. Thus, most of the aldol products in the first stage were successfully converted to the aminated products. In the next two runs, the sum of amine and enamine was also 86% before dropping off from the fourth run. However, in runs 6 to 9, a constant yield of 75% of the aminated products was again established. The drop is likely the result of partial deactivation of the rhodium catalyst, as was also observed in the earlier recycling experiment (see Figure 2). Also, the changes in the product distribution of the hydroformylation/aldol condensation do not seem to be so pronounced as to be responsible for the drop of 10 percentage points. The decrease in yields of aminated products was offset by an increase in aldol product and saturated aldehyde (summarized under "Others"). Yields of C₁₄-alcohols and C₉-amines changed little across runs, ranging from 2%–4% and 5%–8%, respectively. Exceptions were the sixth run in which the alcohols increased to 11% and the eighth run in which the C₉-amines reached 11%. The deviations in the sixth run were probably caused by a too low CO pressure.

It can be stated that the two stages of the cascade reaction can be successfully connected in series. It is possible to achieve a total yield of C₁₆-amine and C₁₆-enamine of up to 86%. The leaching was found to be less than 0.09% of the initial rhodium per run from the overall system. Leaching of the first biphasic system is negligible since the leached catalyst can be used in the second conversion as well.

Conclusion

In conclusion, we developed a multiphase catalyst system for the hydrogenation/reductive amination tandem reaction based on a homogeneous rhodium/phosphine catalyst and a Brønsted acid in polyethylene glycol as solvent. This system was successfully applied to the reaction of the C₁₄-aldol product 2-pentylnonenal with the dimethylamine surrogate DimCarb giving the surfactant precursor molecule dimethyl-2-pentylnonaniline. The use of the bidentate phosphine ligand SulfoXantphos and the addition of small amounts of CO turned out to be crucial for the reaction, as both SulfoXantphos and CO stabilized the rhodium catalyst and thereby prevented deactivation. In addition, carbon monoxide suppressed the hydrogenation of the substrate to the alcohol and resulted in a higher yield of the desired amine of up to 88%. In a recycling experiment it was demonstrated that both the rhodium catalyst and the Brønsted acid could be recycled seven times and when the co-product water was removed after each run, the good yield of the target amine could be retained for at least the first six runs. By adjusting the CO-pressure, the catalyst system could also be applied to other substrate aldehydes and amines.

Furthermore, we showed the conversion of olefins to tertiary amines by connecting two tandem reactions in series. First, the previously discussed hydroformylation/aldol condensation reaction starting from 1-hexene gave a mixture consisting mainly of the saturated and unsaturated C₁₄-aldehydes. This product solution was subsequently subjected to the hydrogenation/reductive amination reaction to yield the branched tertiary amines. The catalyst systems of both tandem reactions could be recycled eight times, using the product solution of the first reaction as substrate for the second reaction after each run.

Experimental Section

Safety warning: High-pressure experiments with compressed H₂(g) must be carried out only with appropriate equipment and under rigorous safety precautions.

General: All reactions were carried out under argon inert gas atmosphere by using standard Schlenk-techniques or a glovebox. Chemicals were degassed before use and air-sensitive substances were stored under argon. Hydrogen (5.0) and carbon monoxide were supplied by Westfalen. All experiments including the use of gases were conducted in 10 mL stainless steel high-pressure autoclaves with glass inserts.

Analytics: Gas chromatography measurements were performed on a Shimadzu Chromatograph Nexis GC-2030 equipped with a CP Wax 52 CB column and an FID detector. Samples were prepared by diluting 0.1 mL of product solution with 1 mL heptane. The response factors of all compounds either were determined by calibration or estimated using Sternberg's effective carbon method.^[18]

¹H NMR spectra were recorded on a Bruker AV400 (400.2 MHz) spectrometer using CDCl₃ as solvent.

ICP-MS was used to determine rhodium leaching in recycling experiments. Measurements were performed using a Shimadzu

ICPMS-2030 instrument. For this purpose, the samples were digested with a microwave instrument (CEM Corp. Mars 6).

Synthesis of the starting material 2-pentylnon-2-enal: Heptanal (10 mL, 71 mmol) was dissolved in ethyl acetate (25 mL) and pyrrolidine (0.29 mL, 3.5 mmol) and benzoic acid (433 mg, 3.5 mmol) were added. The solution was stirred at 65 °C for 4 h to obtain complete conversion of the aldehyde. The product solution was washed with water (10 mL) and brine (10 mL) and dried over magnesium sulfate. After removal of the solvent, the crude yellow product was purified by filtration over silica and obtained as a colorless liquid.

Reductive amination: For a typical experiment, a glass insert was transferred to a 10-mL autoclave. If necessary, TsOH (116 mg, 0.6 mmol) was weighed in beforehand. Under inert gas, 0.4 mL of a preformed catalyst solution was added so that Rh(acac)(CO)₂ (0.01 mmol) and SulfoXantphos (0.015 mmol) were in the autoclave. Dimcarb (0.13 mL, 1 mmol) and aldehyde (2 mmol) were then added. The autoclave was then charged with H₂ (50 bar) and, if necessary, a small amount of CO (\leq 5 bar) and stirred at 125 °C for 6 h. In case of low CO-pressures, the gas mixtures of H₂ and CO were first prepared in a separate autoclave. For example, for a reaction pressure of 0.5 bar CO, 1 bar CO and 100 bar H₂ were mixed and then 50 bar of this mixture was forced onto the reaction autoclave.

Hydroformylation/aldol condensation recycling experiment: Cesium carbonate (0.4 mmol) was weighed into a glass insert, which was transferred to a 10 mL autoclave. Then 0.4 mL of a preformed catalyst solution in PEG-200 was added so that Rh(acac)(CO)₂ (0.008 mmol) and SulfoXantphos (0.016 mmol) were in the autoclave. After the addition of 1-hexene (1.0 mL, 8 mmol) the autoclave was pressurized with CO (30 bar) and H₂ (30 bar). The mixture was stirred for 5 h at 100 °C and additional 16 h at 125 °C. After completion of the reaction, the autoclave was cooled down to room temperature and both phases were separated. The catalyst phase was washed with pentane, dried at high vacuum, and reused for the next run. 0.5 mL of the crude product phase was used as substrate for the consecutive reductive amination step.

Reductive amination recycling experiments: Reactions were conducted as described above. After the reaction the autoclave was cooled down to room temperature and both phases were separated. The catalyst phase was washed with pentane, dried at high vacuum, and reused for the next run.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Keywords: amination · homogeneous catalysis · rhodium

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