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Advanced Synthesis & Catalysis

Rhodium-Catalysed Reductive Amination for the Synthesis of Tertiary Amines

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Abstract: A procedure for the synthesis of tertiary amines *via* reductive amination of aldehydes with molecular hydrogen as a reducing agent using homogeneous rhodium catalysis is presented. Using an amine to aldehyde ratio of 4/1 enabled the synthesis of tertiary amines from nine different aldehydes and nine different secondary amines with selectivities up to 99% and turnover frequencies (TOF) up to 7200 h^{-1}. The reaction showed a high tolerance against alcohol and ester functions allowing the formation of multifunctional molecules. In addition, secondary amines can also be produced by this synthesis. For all compounds, activities were determined by hydrogen gas-uptake. In order to increase the sustainability and efficiency of the procedure, a dosing strategy has been successfully developed. Using the determined reaction indicators enabled the stoichiometric use of aldehydes and amines without significant loss of selectivity.

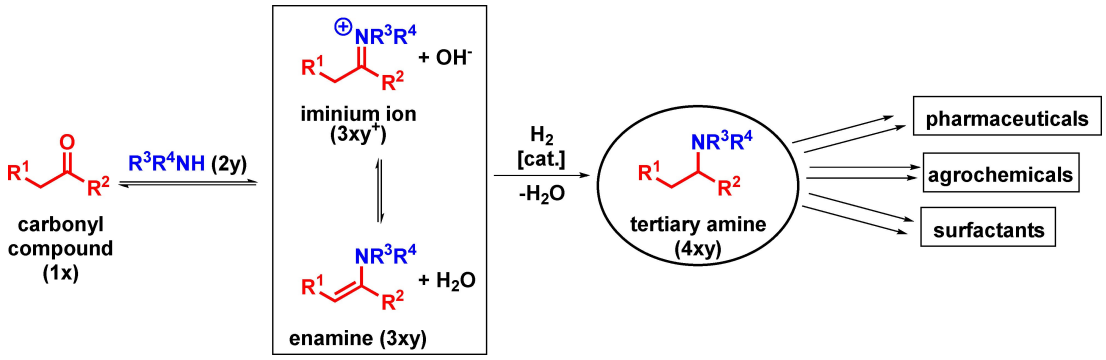
Keywords: Homogeneous Catalysis; Amines; Rhodium; Dosing; Aldehydes

1. Introduction

Tertiary amines are an important class of compounds in the chemical industry since they are used in pharmaceuticals, agrochemicals, biological systems or surfactants.[1,2] For their synthesis, both catalytic and non-catalytic routes exist; however, considering sustainability aspects, catalytic routes are clearly preferred. Alcohol amination, amination of alkyl halides or reductive amination of carbonyl compounds are typical representatives.[3] The reductive amination (RA) with molecular hydrogen (Scheme 1) is a very straightforward synthesis for tertiary amines since carbonyl compounds are easily available by hydroformylation (aldehydes) or oxidation (ketones) and only water is formed as co-product.[4]

The catalytic step of the reductive amination is the hydrogenation of either an enamine or an imine intermediate; in case of tertiary amines, it is the hydrogenation of an enamine. In the literature, it is intensively discussed whether the enamine or the iminium ion intermediate is finally reduced to an amine.[5,6] Since this is a simple hydrogenation reaction of a double bond, mainly heterogeneous catalysts are applied for this task.[3] However, also a range of homogeneous hydrogenation catalysts does exist. For instance, it is well-known that homogeneous rhodium catalysts show high activity in hydrogenation reactions such as Wilkinson's catalyst $[Rh(PPh_3)_3Cl]$.[7]

Surprisingly, only a few examples of RA for the synthesis of tertiary amines using homogeneous rhodium catalysts are reported despite their high activity in the hydrogenation of C=C double bonds. More frequently, the use of other metals such as ruthenium[8] or manganese[9] is reported, complemented by homogeneous catalysts for RA *via* transfer hydrogenation instead of using molecular hydrogen.[6,10] *Markó* and *Bakos* were the first to apply homogeneous rhodium catalysts in the reductive amination of aldehydes and ketones back in 1974. However, their focus was more



Scheme 1. Production of tertiary amines *via* reductive amination (RA) and their potential usage.

on hydroaminomethylation, which is a tandem reaction consisting of hydroformylation and reductive amination, and thus RA has been investigated under carbonylation conditions.[11] *Börner* and coworkers investigated the use of Rh(I) catalysts in the RA of aldehydes and ketones using different amines in the early 2000s. These investigations were performed at room temperature in methanol with molecular hydrogen at a pressure of 50 bar within 20 h reaction time and an amine excess of 2 equivalents referred to the aldehyde. The formation of alcohols from the carbonyl substrates revealed to be a major limitation of this reaction.[12,13] Recently, *Loginov et al.* synthesised different rhodium catalysts and proved their applicability in RA of aldehydes and ketones with different amines in water with carbon monoxide as reducing agent. A reaction time of 24–48 h and a catalyst loading of 1 mol% were necessary to reach yields up to 91%.[14]

Since for aldehydes the aldol condensation is a possible side reaction which significantly influences the selectivity, the efficient reductive amination of aldehydes seems to be more challenging than reductive amination of ketones. Our group recently reported on the continuous RA of undecanal with diethylamine, with a focus on catalyst separation by application of thermomorphic multiphase systems.[15] A homogeneous rhodium catalyst was used for the synthesis of primary amines *via* reductive amination of aromatic aldehydes with ammonia.[16] In addition, applications for the synthesis of asymmetric or chiral amines *via* RA using homogeneous rhodium catalysts have been reported.[17]

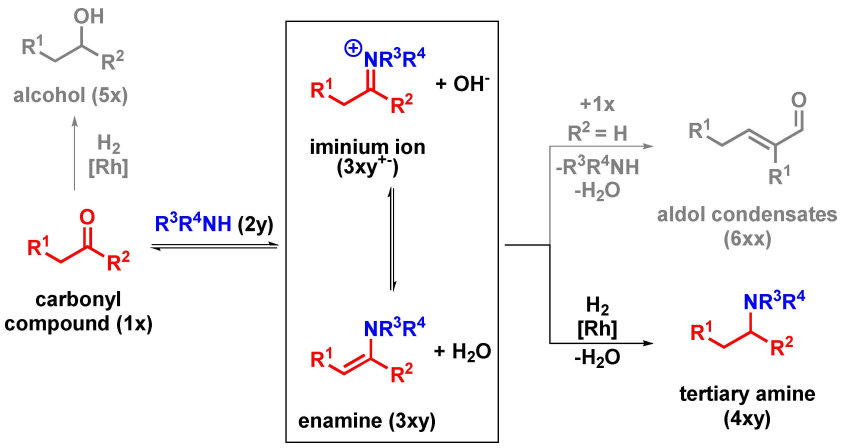
Moreover, rhodium has frequently been used in different hydroaminomethylation reactions.[18,19,20]

Our group has a strong interest in the development of sustainable amine syntheses enabled by homogeneous transition metal catalysts.[1,19,21] However, a general procedure for the selective and efficient production of tertiary amines *via* RA of aldehydes using highly active homogeneous rhodium catalysts is, to our surprise, not reported so far. In here we report on a procedure for the synthesis of tertiary amines which enables the application of various aldehydes and amines, even in the presence of functional groups. Since we used molecular hydrogen in this rhodium catalysed RA, reaction parameters can be determined by the gas-uptake of the reaction. Finally, a strategy to avoid the excess use of amines relative to the carbonyl compound and the associated waste production is presented.

2. Results and Discussion

As in all syntheses, for the synthesis of tertiary amines from aldehydes via reductive amination (RA, Scheme 2) a high selectivity to the product is essential. In principle, the hydrogenation of the enamine bears no selectivity issues. However, in RA of carbonyl compounds **1x**, the iminium ion **3xy**$^+$ respectively the enamine **3xy** is the essential intermediate, which is formed in a condensation of the carbonyl compound **1x** and the secondary amine **2y**. Selectivity issues can be caused by this condensation, especially in the case for aldehydes as substrates. Ideally, the enamine **3xy** is formed rapidly and subsequently hydrogenated to the tertiary amine **4xy** by a highly active rhodium catalyst. If the condensation does not proceed as fast, the remaining aldehyde **1x** might be hydrogenated to the alcohol **5x**. If the hydrogenation of the enamine does not proceed as fast, the simultaneous presence of both, aldehyde **1x** and enamine **3x**, can lead to increased formation of aldol condensates **6xx**.

Common homogeneous hydrogenation catalyst such as Wilkinson's catalyst[7] use monodentate ligands since no regioselectivity for the hydrogenation is required. Due to stability issues using monodentate ligands as triphenylphosphine and related reproducibility challenges in reductive amination experiments, we decided to use a bidentate ligand for the reductive amination. In particular, as catalyst system, a combination of Rh(acac)(cod) [acetylacetonato(1,5-cyclooctadiene)rhodium] as the precursor and Xantphos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene] as ligand has been chosen, since this system has already been reported to be active in RA.[22] This and similar catalyst



Scheme 2. Reductive amination of carbonyl compounds with secondary amines and side reactions to alcohols and aldol condensates.

systems with the solvent methanol have frequently been used in different reductive aminations and are also frequently reported in publications about hydroaminomethylation (hydroformylation with subsequent reductive amination) allowing high catalyst activities in these systems.[12,13,19,20,22,23] Moreover, Xantphos is a readily available bidentate ligand and offers the possibility of modification for more specialised applications such as catalyst recycling.[23,24] According to a small optimisation, we chose methanol as solvent, a temperature of 100 °C and H_2 pressure of 30 bar.

To reach high selectivities, the named side reactions need to be suppressed by shifting the equilibrium of the enamine formation to the product side. Therefore, the most common strategy described in the literature is to apply an excess of the amine.[12,13] Therefore initial experiments on the reductive amination of undecanal **1a** with diethylamine **2a** at ratios **2a/1a** of 2–4 (Figure 1) were conducted.

Under these conditions, nearly quantitative conversion and very high yields of the desired product amine **4aa** were already reached for all three amine/aldehyde ratios, the highest yield and selectivity of >99% is obtained for an amine/aldehyde ratio of 4/1.

Based on the promising results of the reaction system, a range of substrates will show whether the system is generally applicable for different aldehydes and amines. For a comparison between the different substrates, two indicators are determined in each case (Figure 6). These are TOF_{20} (turnover frequency at X = 20%) and the time to reach a conversion of X = 90%. These values could be determined with reasonable accuracy for all substrate combinations. Assuming high chemoselectivity, the reaction progress can be monitored by gas consumption. To this end, the hydrogen pressure drop in the reactor was monitored. At the end of the reaction conversion and selectivity

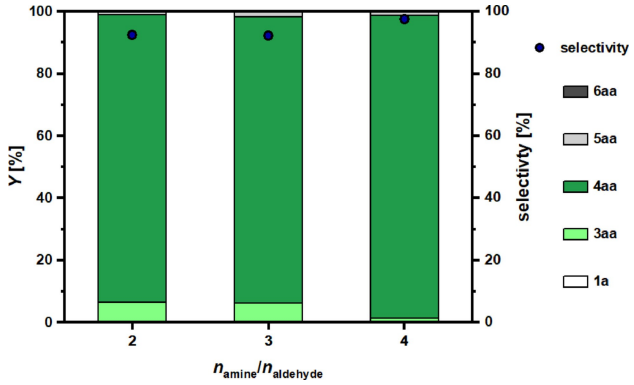


Figure 1. Reductive amination of undecanal **1a** with diethylamine **2a** at different substrate ratios. **Conditions**: $m_{total} = (m_{1a} + m_{2a} + m_{solvent}) = 100$ g, 0.25 mol% Rh(acac)(cod), 1 eq. Xantphos ($n_{Rh}/n_P = 1/2$), solvent: Methanol, $p_{H2} = 30$ bar, $T = 100$ °C, Preforming: Without undecanal **1a**, $t = 60$ min, $N = 500$ rpm. Reaction: Addition of 4 g **1a** *via* dropping funnel. Yield (Y) and selectivity (Y_{4aa}/X) determined by GC-FID with dibutyl ether as internal standard.

were determined by GC-FID. The pressure difference was then normalised with respect to the conversion and plotted versus time. The conversion vs time plot of the reaction of undecanal **1a** with diethylamine **2a** is presented in Figure 2.

From Figure 2, $t_{X=90\%}$ was determined at 6.5 min. A TOF_{20} of 7200 h^{-1} was obtained. Figure 3 shows the results of the RA with diethylamine of a range of aldehydes. For each reaction, conversion, yield, $t_{x=90\%}$ and TOF_{20} are presented.

The TOF_{20} was reached 7200 h^{-1} for **1a** and **1b** while the time to the reach 90% conversion (X = 90%) differs by 2.5 min. C_5-aldehydes such as pentanal, 2-methyl butyl aldehyde and 3-methyl butyl aldehyde (**1b-1d**) were investigated and TOFs between 4800 h^{-1} and 7200 h^{-1} were obtained, and the reactions

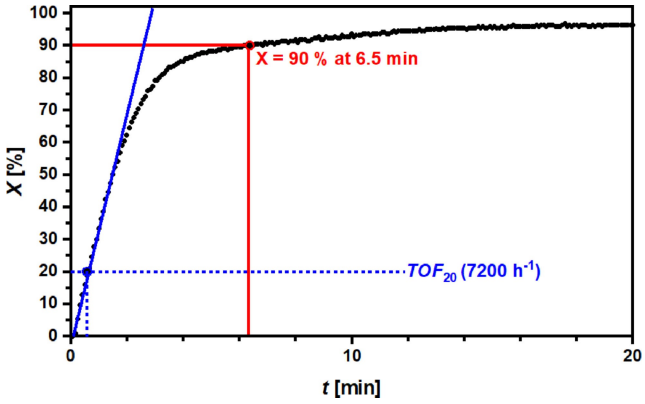


Figure 2. Progress of conversion (X) over time for the reductive amination of undecanal **1a** with diethylamine **2a. Conditions**: $m_{total}=(m_{1a}+m_{2a}+m_{solvent})=100$ g, $n_{1x}/n_{2a}=1/4$, 0.25 mol% Rh(acac)(cod), 1 eq. Xantphos ($n_{Rh}/n_{P}=1/2$), solvent: Methanol, $p_{H2}=30$ bar, $T=100$ °C, Preforming: Without undecanal **1a**, $t=60$ min, $N=500$ rpm. Reaction: Addition of 4 g **1a** *via* dropping funnel.Yield (Y) and selectivity (Y_{4aa}/X) determined by GC-FID with dibutyl ether as internal standard.

needed 8–9 min to reach a conversion of 90%. The overall activity seems to depend on the branching of the molecule, but the differences are relatively minor. The difference in TOF_{20} between **4ba** (7200 h^{-1}) and **4ca** (4800 h^{-1}) emerged due to a time difference of 10 s in which both reactions attained a value of X = 20%. Ketones seem not to be applicable under the chosen conditions because amine **4ea** was not obtained from ketone **1e**. Within 18 h of reaction time, a conversion of 30% was reached, and a range of byproducts was formed, which were not identified in the progress of this work. Furthermore, different cyclic and aromatic molecules were investigated (**1f–1i**). The progress of the reductive amination of cyclic aliphatic aldehydes is similar to that of aliphatic aldehydes. 90% of cyclohexane carboxaldehyde **1f** were converted within 6 min. and a TOF_{20} of 4800 h^{-1} was reached. Using cyclohexene carboxaldehyde **1g** revealed that there is no chemoselectivity for the hydrogenation of double bonds. Due to the hydrogenation of enamine and the additional double bond, this reaction reached a TOF_{20} of 4400 h^{-1} and the time to reach a conversion of 90% was determined at a time of 13 minutes. For benzaldehyde **1h**, the reaction time increased significantly to 35 min for X = 90% and led to a $TOF_{20}=3000$ h^{-1}. Due to the proximity to the phenyl group and the associated increased electron density, the electrophilicity of the carbonyl carbon is reduced. This impedes the nucleophilic attack of the secondary amine, causes a slower RA and enables the hydrogenation to benzyl alcohol. Since a small part of benzaldehyde is hydrogenated to the alcohol, the selectivity to the product only reaches 92%. Using 3-phenyl propionaldehyde **1i** with a larger distance between the carbonyl group and the aromatic ring, a higher TOF_{20} of 5200 h^{-1} was obtained. 90% conversion was reached after 5 min.

12-oxo-1-methyl dodecanoate **1j** is a bifunctional aldehyde ester and can be converted into a long-chain amine ester using this method. In comparison to undecanal, the ester function decreases the reaction time to reach 90% conversion from 9 min to 18 min. The TOF_{20} thus decreased from 7200 h^{-1} to 2200 h^{-1}. **1j** is synthesised by hydroformylation of methyl 10-undecenoate, which is made from castor oil.[24,25] This is a promising result for the conversion of other bifunctional aldehydes.

The GC yields and isolated yields differ significantly in most cases. All products were via vacuum distillation in order to transfer the general applicability of the reaction system also to the isolation of the respective component. For the model reaction of undecanal **1a** with diethylamine **2a**, the calibration of substrates, product **4aa** and possible byproducts such as the alcohol **5a** and the aldol condensate **6aa** were calibrated in the experimental matrix. Using this calibration, a yield of 99% of **4a** and no other byproducts were observed in the reaction mixture after the reaction. However, only 68% of **4a** were isolated. One reason for this is that a very low substrate loading was used. Since the product has a higher boiling point, the solvent methanol and diethylamine **2a** had to be removed initially by vacuum and thus carried out some small parts of the product. After this, the remaining mixture consisting of the product **4a** and the catalyst were separated by vacuum distillation. The catalyst was not stable under these conditions and thus caused that parts of the product remained in the mixture. These problems have occurred similarly for almost all formed products, and thus similar isolated yields were obtained in most cases.

Due to the high boiling compared to the other products point of **4ja**, the distillation turned out to be very challenging, and only 43% of the product could be isolated.

The developed method for synthesis of tertiary amines is generally applicable to various amines and therefore, a range of amines is applied in the reductive amination with undecanal **1a** (Figure 4).

To our delight, the conversion of undecanal was quantitative in all cases. First, differently substituted amines and the influence of branching on the reaction rate (**2a–2e**) were investigated. For dipropylamine **2b** and dibutylamine **3b** very similar reaction parameters were obtained. Time to reach 90% ($t_{X=90\%}$) conversion has been determined after 11 min and 13 min, respectively. The TOF_{20} shows a contrary trend (3300 h^{-1} to 3900 h^{-1}). However, the difference of 600 h^{-1} is related to a time difference of 17 seconds only and thus does not prove a significant difference. Selectivity is slightly decreasing with increasing size of the amine, and more

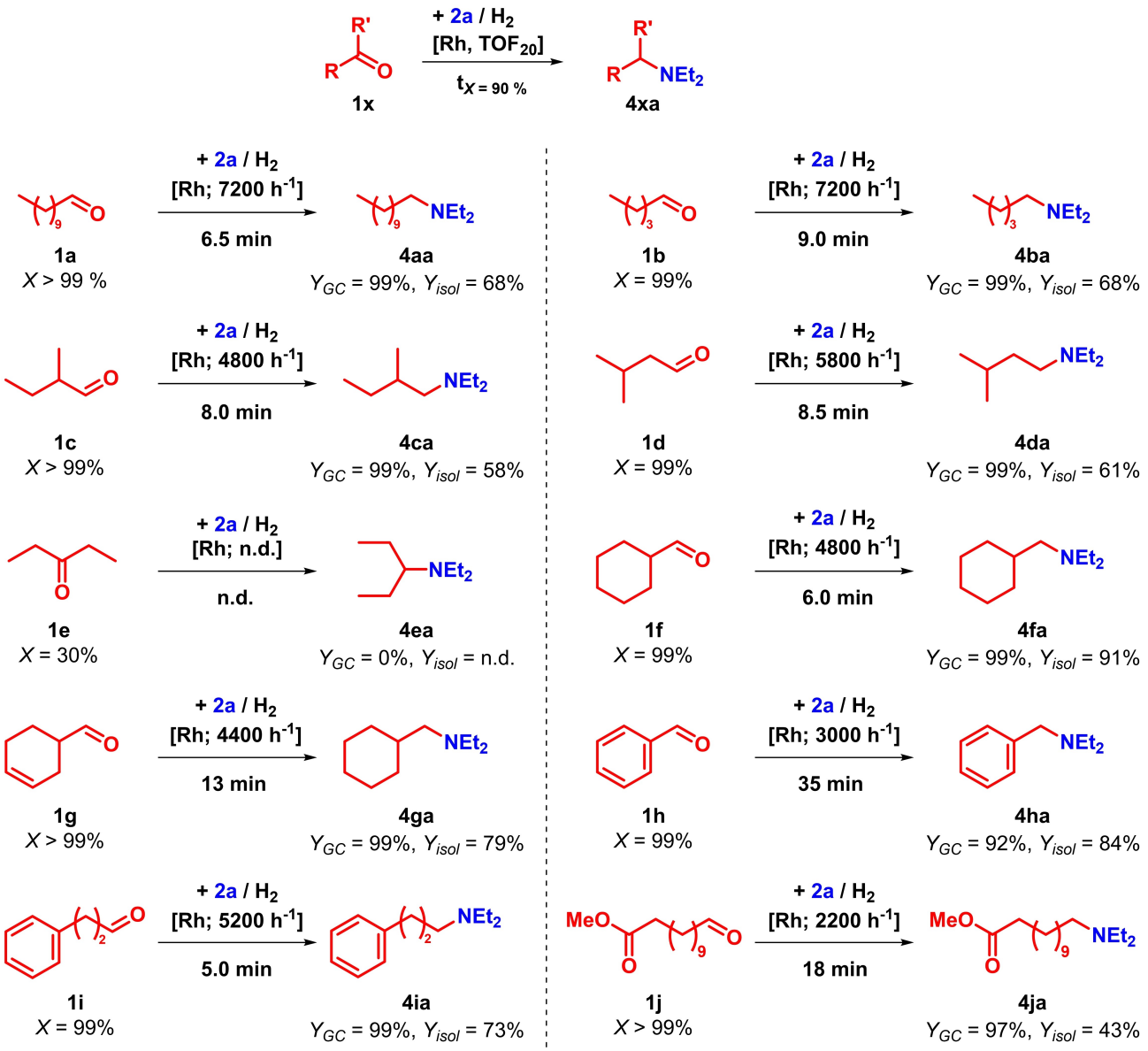


Figure 3. RA of different aldehydes with diethylamine. **Conditions**: $m_{total} = (m_{1x} + m_{2a} + m_{solvent}) = 100$ g, $n_{1x} / n_{2a} = 1/4$, 0.25 mol% Rh(acac)(cod), 1 eq. Xantphos ($n_{Rh} / n_P = 1/2$), solvent: Methanol, $p_{H2} = 30$ bar, $T = 100$ °C, Preforming: Without carbonyl compound **1x**, $t = 60$ min, N = 500 rpm. Reaction: Addition of 4 g **1x** *via* dropping funnel. Yield (Y_{GC}) was determined by GC-FID. Isolation of individual components (Y_{isol}) via vacumm distillation. For not determined yields, n.d. is indicated.

byproducts like aldol condensates and undecanol are formed in the presence of dipropyl- and dibutylamine, respectively. In addition, the branched amine diisopropylamine **2d** was significantly slower converted &bk, ($t_{X=90\%} = 130$ min) and also showed lower selectivity (80%) than the linear dipropylamine. If a sterically demanding amine such as dicyclohexylamine **2e** is used, the reaction time to reach 90% conversion is 110 min and TOF_{20} decreases to 300 h^{-1}. It seems that a longer hydrocarbon chain leads to a lower reaction rate and thus to lower selectivity of the reaction. This is consistent with the assumptions made for the conditions of the initial experiments (Figure 1).

By application of cyclic amines pyrrolidine **2f** and piperidine **2g**, 90% conversion is achieved after approx. 9 min and 6 min, which is comparable to the reaction with diethylamine (10 min). High TOF_{20} of 4600 h^{-1} (**2f**) and 5100 h^{-1} (**2g**) are obtained. For morpholine **2h**, the $t_{X=90\ \%}$ increases again to 17 min and thereby TOF_{20} decreases to 3200 h^{-1}. In principle, oxygen-containing functional groups appear to have a negative effect on the reaction rate, since they cause a lower nucleophilicity of the amine.

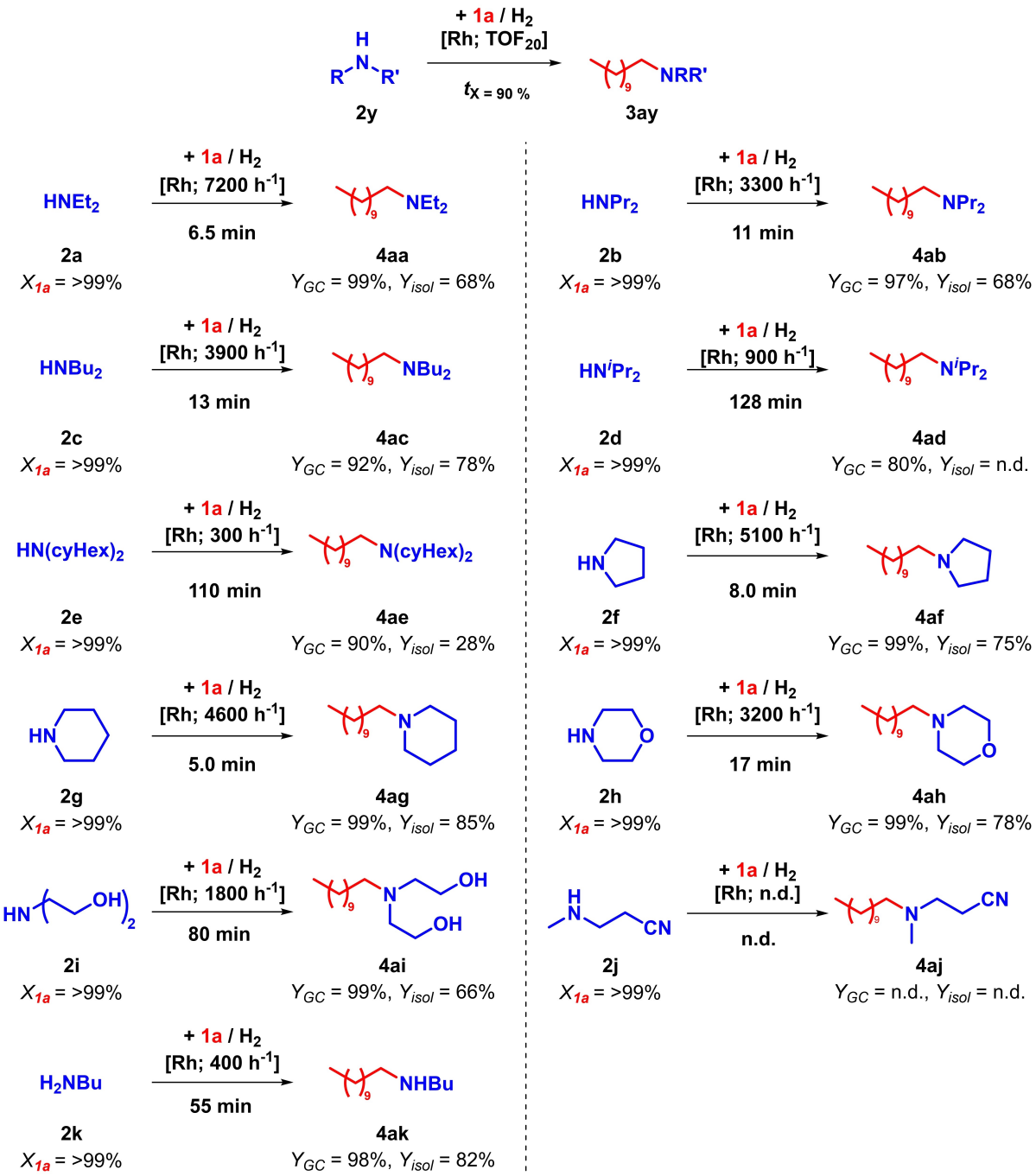


Figure 4. Different amines in reductive amination with undecanal. **Conditions**: $m_{total} = (m_{1a} + m_{2y} + m_{solvent}) = 100$ g, $n_{1a}/n_{2y} = 1/4$, 0.25 mol% Rh(acac)(cod), 1 eq. Xantphos ($n_{Rh}/n_P = 1/2$), solvent: Methanol, $p_{H2} = 30$ bar, $T = 100\,°C$, Preforming: Without carbonyl compound **1x**, $t = 60$ min, N = 500 rpm. Reaction: Addition of 4 g **1a** *via* dropping funnel. Yield (Y_{GC}) was determined by GC-FID. Isolation of individual components (Y_{isol}) via vacumm distillation. For not determined yields, n.d. is indicated.

The influence of other functional groups such as an alcohol group on the reaction has been investigated (**1i-1j**). With diethanolamine **2i**, approx. 80 min are needed for 90% conversion and a TOF_{20} of 1800 h^{-1} has been determined. In this case, a lower nucleophilicity of the amine is combined with a higher steric demand compared to other amines such as diethylamine (**2a**) which decreases the reaction rate significantly.

For 3-(*N*-methylamino)propionitrile **2j**, not only the resulting enamine but also the nitrile group is hydrogenated. In addition, a large number of different byproducts are produced by different side reactions such as the nitrile hydrogenation. The end of the

reaction by applying pressure uptake is therefore not valid in terms of conversion, and the isolation of the product was also not possible. Interestingly, secondary amines can also be produced selectively using the developed method. Finally, the primary amine *n*-butylamine **2k** was applied instead of a secondary amine to check if tertiary amines with two undecyl rests can be selectively produced by this method as well. Surprisingly, the secondary amine is formed instead with an excellent selectivity of 99%. In Comparison to di-*n*-butylamine **2c** ($TOF_{20} = 3900\ h^{-1}$), *n*-butylamine ($TOF_{20} = 400\ h^{-1}$) is less active in the reductive amination, which could be caused by a higher nucleophilicity of secondary amines compared to primary amines. Another reason could be that the intermediate product is an imine instead of an enamine/iminium ion in case of using primary amines as starting materials. Nevertheless, the resulting secondary amine **2ak** does not react, which may be caused by the low aldehyde loading in the reaction.

In case of the investigation of different amines, the GC yields and the isolated yields also differ due to the low used substrate loading. In the case of product **4ae**, the product decomposed partially within the distillation and only an isolated yield of 28% was reached. For product **4ad** the isolation via distillation was not possible. For future investigations, other isolation methods should be considered.

Overall, the concept presented is applicable to a wide variety of aldehydes and amines. The biggest limitations of the method are the high catalyst amount and the low loading of the aldehyde.

2.1. Dosing Strategy

As it has been shown before, a highly active and highly selective RA is possible using a homogeneous rhodium catalyst. However, a high amine/aldehyde ratio of 4/1 is necessary to suppress the byproduct formation. A higher aldehyde concentration would lead to the formation of alcohol **5a** or aldol condensate **6a**. An Experiment for the model reaction of undecanal **1a** and diethylamine **2a** was done, to prove this assumption and set a benchmark for further improvements. In this experiment, the initial undecanal (**1a**) loading (4 w%, 23 mmol) has been increased by a factor of five (20 w%, 117 mmol) and a stoichiometric amount of diethylamine **2a** (117 mmol) has been used. The complete amount of undecanal **1a** has been added in one step via dropping funnel to the reaction mixture containing amine, methanol, catalyst and ligand. In this experiment, a selectivity of only 12% to the amine **4aa** was reached at a conversion of 77% after a reaction time of 1 h. Mainly aldol condensate **6aa** is formed ($Y_{6aa} = 48\%$). The use of an excess of the amine with regard to the aldehyde seems unavoidable.

Obviously, the use of excess amine would result in a large amount of amine remaining at the end of the reaction. Occasionally, the dosing of the aldehyde has been reported to keep the aldehyde concentration low within the reaction.[26] To our knowledge, a proof of this concept is not reported, and a generally applicable instruction for the dosing has to be developed. For this, the reaction indicators obtained from the pressure uptake of the reaction were used. The aim was to adjust the dosing in such a way, that a higher amount of product could be produced with the same amount of catalyst. Moreover, a stoichiometric amount of diethylamine **2a** is to be used only without compromising selectivity. As it has been shown in Figure 2, the reaction needed 6.5 min to reach a conversion of 90%. To achieve high selectivities for higher undecanal **1a** loadings, this time value has been translated into a pump rate which means that over a time of 6.5 minutes, the same amount of undecanal **1a** (4 w%, 23.4 mmol) has been pumped into the reactor. This corresponds to a flow of 0.63 g/min which has been kept constant for 32.5 min. Thus, five times as much undecanal **1a** (20 w%, 117 mmol) as in the experiments before was fed into the reactor. Diethylamine **2a** in a 1/1 ratio (117 mmol) has been added in the reaction mixture before starting the dosing. Figure 5 shows the results of this experiment and the results of the benchmark reaction without using the dosing strategy.

The dosing strategy allows the production of almost five times as much amine **4aa** with the same amount of catalyst, corresponding to an improvement of the turnover number (TON) from 400 to 1860. A selectivity of 93% has been reached using a stoichiometric amount of diethylamine **2a**. Up to dosing of about 40 mmol undecanal **1a**, very high selectivities are reached. Subsequent, both alcohol **5aa** and aldol condensate **6aa** are formed in small amounts. The formation of byproducts was detected after 30 minutes and is related to a previous accumulation of undecanal **2a** due to a lower reaction rate of the RA. This decreasing reaction rate might be caused by the change in the amine/aldehyde ratio within the reaction progress. However, the pump ratio seems to be too fast to reach the selectivities shown before.

The application of dosing leads to a dramatically higher selectivity of 93% compared to 11% (without dosing) in case of stoichiometric substrate ratio, which proves the functionality of a dosing strategy for rhodium catalysed RA. To further improve the selectivity using a stoichiometric aldehyde/amine ratio, the aldehyde pump rate should be directly controlled by the hydrogen consumption. This could allow an almost complete conversion to the desired tertiary amine **4aa** using the shown method.

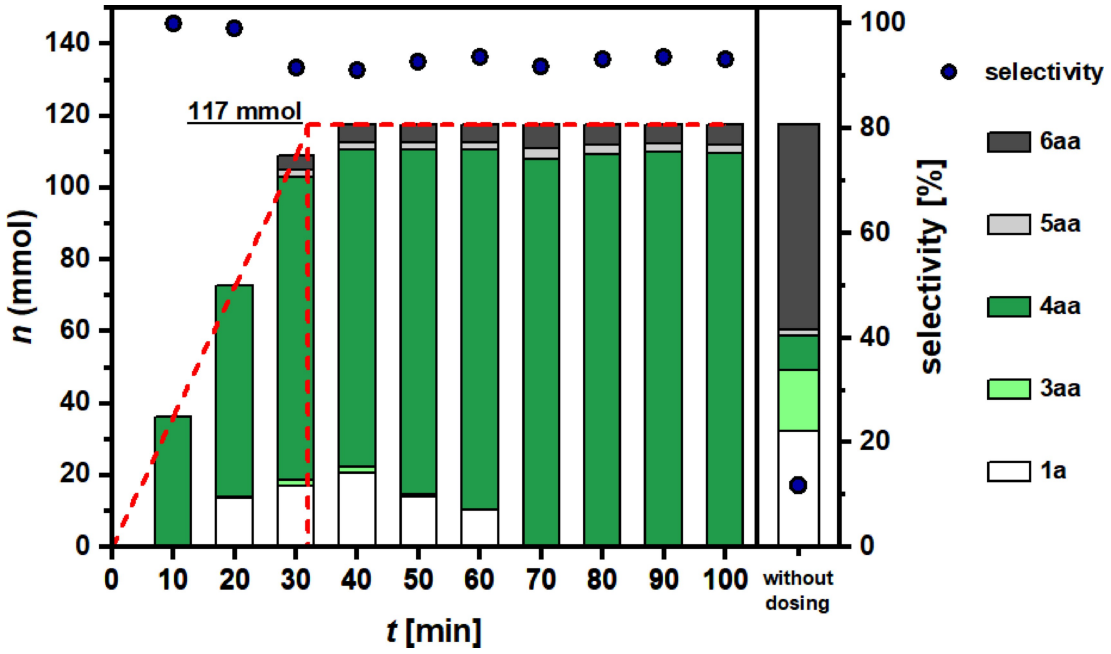


Figure 5. Reductive amination of undecanal **1 a** with diethylamine **2 a** with dosing of the aldehyde using a pump to achieve stoichiometric substrate ratio. **Conditions**: $m_{total} = (m_{1a} + m_{2a} + m_{solvent}) = 100$ g, $n_{1a}/n_{2a} = 1/1$, 0.25 mol% Rh(acac)(cod), 1 eq. Xantphos (n_{Rh} / $n_P = 1/2$), solvent: Methanol, $p_{H2} = 30$ bar, $T = 100\,°C$, Preforming: Without undecanal **1 a**, $t = 60$ min, N = 500 rpm. Reaction: Addition of 20 g **1 a** *via* HPLC-pump ($\dot{m}_{1a} = 0{,}63$ g/min). Yield (Y) and selectivity (Y_{4aa}/X) determined by GC-FID. The bar "without dosing" shows the experiment without the dosing strategy. Here the total amount of undecanal **1 a** has been added in one step into the reaction mixture. The reaction time was 60 minutes. The other reaction conditions were the same.

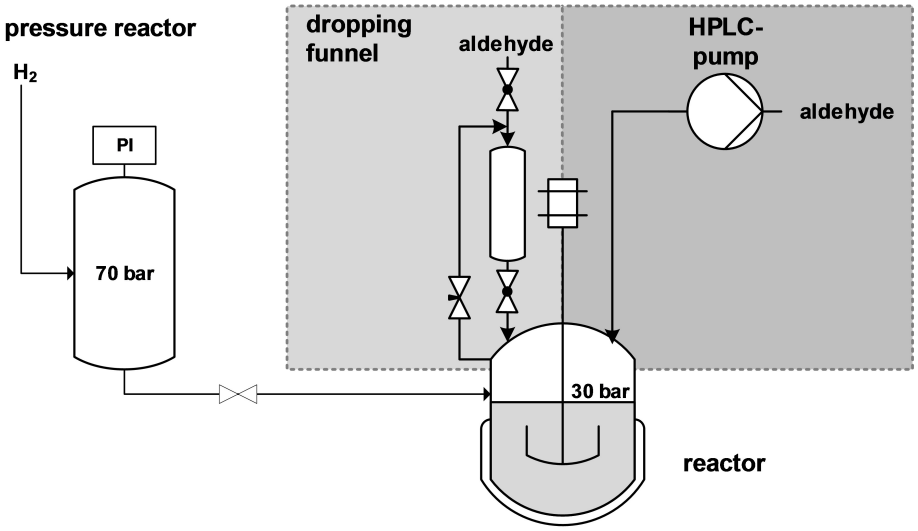


Figure 6. Reactor and equipment for reductive amination in a basic scheme.

3. Conclusions

The development of a generally applicable procedure for the synthesis of tertiary amines via rhodium-catalysed reductive amination of aldehydes is presented. An amine/aldehyde ratio of 4/1 enabled the conversion of nine different aldehydes and nine secondary amines to the corresponding tertiary amines with excellent yields and selectivities of up to 99% and TOF_{20} of up to 7200 h^{-1}. Limitations were only found for the use of the ketone butanone **1 e** and bifunctional amino nitriles **2 j**, which were not selectively convertible to the desired product. However, the reaction proved to be tolerant towards different functional groups such as alcohols, esters and aromatics. Surpris-

ingly, the synthesis of secondary amines was possible as well using di-*n*-butylamine **2 k** as amine compound. Currently, this reaction is under investigation in order to be utilised for the potential sequential synthesis of differently substituted amines.

These good results are maintained because the amine was used in excess amounts to the aldehyde. However, considering all collected knowledge about the control of selectivity, the excess amine can be avoided, and with specific dosing of the aldehyde at the previously determined reaction rate, similarly good selectivities but much higher productivities can be obtained with a stoichiometric amine/aldehyde ratio. The TON for the model reaction of undecanal **1 a** with diethylamine **2 a** was thus increased from 400 to 1860 with very good selectivities of up to 93%. This also facilitates an easier purification step after the reaction. In further research, the direct coupling of hydrogen gas consumption and feed-pump rate to increase the selectivity and its general applicability on other substrates will be investigated.

Experimental Section

Reactor and equipment

A 300 mL pressure autoclave was used for the experiments. To provide a continuous hydrogen pressure of 30 bar in the reactor, a pressure reactor ($V = 1$ L) was used. In order to reduce the pressure in the reaction, a pressure controller was used. For dosing of the aldehyde, two different options were available, a dropping funnel with pressure equilibration and an HPLC-pump.

General procedure of reductive amination using dropping funnel

To carry out the reaction, the catalyst (0.25 mol%) and ligand (0.50 mol%), the solvent and the used amine (4 eq.) were filled in the reactor. The autoclave was then closed and rinsed with argon. Afterwards, it was supplied with 5 bar hydrogen. After the reaction temperature of 100 °C had been reached, the hydrogen pressure was increased to 30 bar. After saturation of methanol with hydrogen and catalyst preforming of 1 h, the aldehyde (4 g) was then fed into the reactor via a valve using the dropping funnel. The total mass used for all experiments was 100 g. The pressure-time curves were recorded with the pressure sensor from BD Sensors, which was attached to the pressure reactor. After the reaction, the reactor has been cooled with an ice bath and carefully depressurised. A sample has been taken from the reaction mixture for GC-FID analysis.

Procedure of product purification

For purification, the resulting product solution containing the catalyst, methanol the substrate amine and product amine has been distilled under vacuum.

Procedure for reductive amination with aldehyde dosing

For the experiments with aldehyde addition, an HPLC pump was used. The pump is connected to the pressure autoclave *via* a valve. The autoclave was then closed and rinsed with argon. Afterwards, it was supplied with 5 bar hydrogen. Before the reaction, the pump tube was filled with the aldehyde. After the reaction temperature of 100 °C had been reached, the hydrogen pressure was increased to 30 bar. After saturation of methanol with hydrogen and catalyst preforming of 1 h, the aldehyde had been pumped into the reactor in different pump rates [ml/min]. Every ten minutes, a sample for the gas chromatography has been taken manually.

Synthesis of 12-oxo-1-methyl dodecanoate

For the synthesis, hydroformylation of methyl 10-undecenoate has been performed. 80 g cyclohexane were filled into the reactor with $Rh(acac)(CO)_2$ (0.05 mol%) and the ligand Biphephos ($n_{Rh}/n_L = 1/5$). After heating ($T = 90$ °C) and pressurising ($p_{CO/H2} = 20$ bar >, $CO/H_2 = 1$) the reactor, 30 g of methyl 10-undecenoate were filled into the reactor *via* dropping funnel. After the reaction, the product mixture was distilled, and 12-oxo-1-methyl dodecanoate has been obtained in a purity of about 95%.

Analytical Data

The analytical data is provided in SI.

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References

[1] T. A. Faßbach, T. Gaide, M. Terhorst, A. Behr, A. J. Vorholt, *ChemCatChem* **2017**, *9*, 1359.
[2] a) R. Tripathi, S. Verma, J. Pandey, V. Tiwari, *Curr. Org. Chem.* **2008**, *12*, 1093; b) D. Menche, S. Böhm, J. Li, S. Rudolph, W. Zander, *Tetrahedron Lett.* **2007**, *48*, 365.
[3] K. S. Hayes, *Appl. Catal. A* **2001**, *221*, 187.
[4] P. Roose, K. Eller, E. Henkes, R. Rossbacher, H. Höke in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2015**, pp. 1–55.
[5] a) P. Mattei, G. Moine, K. Püntener, R. Schmid, *Org. Process Res. Dev.* **2011**, *15*, 353; b) S. Tin, T. Fanjul, M. L. Clarke, *Catal. Sci. Technol.* **2016**, *6*, 677.

[6] D. Talwar, N. P. Salguero, C. M. Robertson, J. Xiao, *Chem. Eur. J.* **2014**, *20*, 245.
[7] J. F. Young, J. A. Osborn, F. H. Jardine, G. Wilkinson, *Chem. Commun. (London)* **1965**, 131.
[8] F. Christie, A. Zanotti-Gerosa, D. Grainger, *ChemCatChem* **2018**, *10*, 1012.
[9] D. Wei, A. Bruneau-Voisine, D. A. Valyaev, N. Lugan, J.-B. Sortais, *Chem. Commun.* **2018**, *54*, 4302.
[10] a) C. Wang, A. Pettman, J. Basca, J. Xiao, *Angew. Chem.* **2010**, *122*, 7710; b) D. Gnanamgari, A. Moores, E. Rajaseelan, R. H. Crabtree, *Organometallics* **2007**, *26*, 1226.
[11] L. Mark′o, J. Bakos, *J. Organomet. Chem.* **1974**, *81*, 411.
[12] V. I. Tararov, R. Kadyrov, A. Börner, T. H. Riermeier, *Chem. Commun.* **2000**, 1867.
[13] V. I. Tararov, R. Kadyrov, T. H. Riermeier, A. Börner, *Adv. Synth. Catal.* **2002**, *344*, 200.
[14] a) V. B. Kharitonov, E. Podyacheva, Y. V. Nelyubina, D. V. Muratov, A. S. Peregudov, G. Denisov, D. Chusov, D. A. Loginov, *Organometallics* **2019**, *38*, 3151; b) S. A. Runikhina, M. A. Arsenov, V. B. Kharitonov, E. R. Sovdagarova, O. Chusova, Y. V. Nelyubina, G. L. Denisov, D. L. Usanov, D. Chusov, D. A. Loginov, *J. Organomet. Chem.* **2018**, *867*, 106.
[15] a) K. U. Künnemann, J. Bianga, R. Scheel, T. Seidensticker, J. M. Dreimann, D. Vogt, *Org. Process Res. Dev.* **2020**, *24*, 41; b) J. Bianga, K. U. Künnemann, T. Gaide, A. J. Vorholt, T. Seidensticker, J. M. Dreimann, D. Vogt, *Chemistry (Weinheim an der Bergstrasse, Germany)* **2019**, *25*, 11586.
[16] T. Gross, A. M. Seayad, M. Ahmad, M. Beller, *Org. Lett.* **2002**, *4*, 2055.
[17] a) A. Levi, G. Modena, G. Scorrano, *J. Chem. Soc. Chem. Commun.* **1975**, 6; b) M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, *115*, 10125.
[18] a) T. Rische, P. Eilbracht, *Tetrahedron* **1999**, *55*, 1915–1920; b) P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, *Chem. Rev.* **1999**, *99*, 3329; c) S. Hanna, J. C. Holder, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2019**, *58*, 3368; d) A. Behr, T. Seidensticker, A. J. Vorholt, *Eur. J. Lipid Sci. Technol.* **2014**, *116*, 477; e) T. Vanbésien, E. Monflier, F. Hapiot, *Green Chem.* **2017**, *19*, 1940; f) A. J. Vorholt, S. Immohr, K. A. Ostrowski, S. Fuchs, A. Behr, *Eur. J. Lipid Sci. Technol.* **2017**, *119*, 1600211.
[19] B. Hamers, P. S. Bäuerlein, C. Müller, D. Vogt, *Adv. Synth. Catal.* **2008**, *350*, 332.
[20] P. Kalck, M. Urrutigoïty, *Chem. Rev.* **2018**, *118*, 3833.
[21] a) S. Fuchs, D. Lichte, T. Jolmes, T. Rösler, G. Meier, H. Strutz, A. Behr, A. J. Vorholt, *ChemCatChem* **2018**, *10*, 4126; b) S. Fuchs, T. Rösler, B. Grabe, A. Kampwerth, G. Meier, H. Strutz, A. Behr, A. J. Vorholt, *Appl. Catal. A* **2018**, *550*, 198; c) D. Vogelsang, T. A. Faßbach, P. P. Kossmann, A. J. Vorholt, *Adv. Synth. Catal.* **2018**, *360*, 1984; d) T. Seidensticker, J. M. Vosberg, K. A. Ostrowski, A. J. Vorholt, *Adv. Synth. Catal.* **2016**, *358*, 610.
[22] S. Kirschtowski, C. Kadar, A. Seidel-Morgenstern, C. Hamel, *Chem. Ing. Tech.* **2020**.
[23] J. Bianga, K. U. Künnemann, L. Goclik, L. Schurm, D. Vogt, T. Seidensticker, *ACS Catal.* **2020**, 6463.
[24] T. Gaide, J. M. Dreimann, A. Behr, A. J. Vorholt, *Angew. Chem. Int. Ed.* **2016**, *55*, 2924.
[25] a) J. Bianga, N. Herrmann, L. Schurm, T. Gaide, J. M. Dreimann, D. Vogt, T. Seidensticker, *Eur. J. Lipid Sci. Technol.* **2019**, *118*, 1900317; b) N. Herrmann, J. Bianga, M. Palten, T. Riemer, D. Vogt, J. M. Dreimann, T. Seidensticker, *Eur. J. Lipid Sci. Technol.* **2020**, *122*, 1900166.
[26] Sharples Chemicals Inc, GB615715A, **1945**.

