Journal of Molecular Catalysis A: Chemical 404 (2015) 74–82

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Synthesis of primary amines from the renewable compound citronellal via biphasic reductive amination

A. Behr*, A. Wintzer, C. Lübke, M. Müller

Department of Biochemical and Chemical Engineering, Laboratory of Technical Chemistry – Chemical Process Development, Emil-Figgestr. 66, D-44227 Dortmund, Germany

ARTICLE INFO

Article history:
Received 12 January 2015
Received in revised form 10 April 2015
Accepted 13 April 2015
Available online 14 April 2015

Keywords:
Amination
Terpenes
Homogeneous catalysis
Renewables
Biphasic

ABSTRACT

The reductive amination of the natural product citronellal with ammonia is presented as a new and atom economic way to its primary amine derivatives. The aqueous ammonia phase contains the homogeneous catalytic system $[Rh(cod)Cl]_2$/TPPTS in a biphasic solvent system, whereas the starting material and the products remain in the apolar solvent phase. This concept supresses side reactions effectively, achieving a high yield of primary amines of up to 87%. Systematic investigations demonstrate that the cleavage of the secondary imine as an undesired by-product is necessary in achieving high selectivites, which can be controlled by the reaction conditions. Surfactants, ionic liquids or native cyclodextrins and their derivates prove to be useful phase transfer agents for optimising the interaction between the organic and the aqueous phase. The use of the ionic liquid [DecMIM]Br and the cyclodextrin derivative methyl-β-cyclodextrin provided especially fast and accurate phase separation.

1. Introduction

Citronellal (3,7-dimethyloct-6-en-1-al) is a monoterpenoid that contains an aldehyde function. As a natural resource, it is well known as a flavoring agent and insect repellent. Citronellal exists in the form of two possible enantiomers: the (*R*)-isomer is typically found in citronella [1] while the (*S*)-isomer appears mainly in the essential oil of kaffir lime [2] (Fig. 1).

In addition to that, citronellal as a racemate is among many essential oils that are derived from the fruits and leaves of citrus plants. Essential oils can be extracted from these plants by means of steam distillation. Apart from the natural way of producing citronellal, it can be synthesised from the monoterpene β-pinene. β-Pinene itself is in large part the turpentine oil from conifers. After pyrolysis to β-myrcene, amination, isomerisation and hydrolysis, citronellal is produced as a racemate ($1.000\,t\,a^{-1}$) [3a,b]. Alternative synthesis routes include the dehydrogenation of citronellol [4] or the selective hydrogenation of citral [5a–c]. Citronellal is used for the production of isopulegol and menthol, as well as vitamins A and E at an industrial scale [6]. A review describes well-established synthesis routes based on citronellal.[7]

The reductive amination is a tandem reaction that consists of a condensation and a hydrogenation step (Scheme 1). Reductive aminations are possible with ketones, aldehydes, and even alcohols as starting materials. They react with an amine substrate in a condensation reaction, which results in an aldimine, imine or enamine in the initial step. In the second step, the intermediate is hydrogenated catalytically under the same reaction conditions, which results in primary, secondary or tertiary amines depending on which amine is used.

Reductive aminations of aldehydes with ammonia were first described in a general sense in relation to the Borch-reduction [8]. Bhattacharyya et al. investigated the reductive amination in two steps including the combination of ammonia with titanium(IV) isopropoxide and a consecutive reduction with sodium borohydride [9]. With benzaldehyde as substrate, a 77% yield of the primary amine was achieved. Later, Timmer et al. developed an alternative process using sodium cyanohydridoborate in combination with ammonium acetate and ammonia [10]. The best yield was reached in the reduction of n-nonanal to its analogous primary amine at 98%. Late transition metals have also been used for the reductive amination of aldehydes, mainly in combination with the model substrate benzaldehyde [11–13]. Beller et al. transformed benzaldehyde to benzylamine with a 96% yield by raising the reaction temperature to 135 °C [12]. A catalytic system consisting of a rhodium precursor and water-soluble phosphine ligand was used in a biphasic solvent system. Liu et al. described an iridium-catalysed alternative

* Corresponding author. Tel.: +49 231 755 2310.
E-mail address: arno.behr@bci.tu-dortmund.de (A. Behr).

http://dx.doi.org/10.1016/j.molcata.2015.04.006
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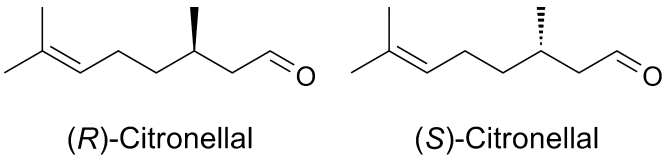
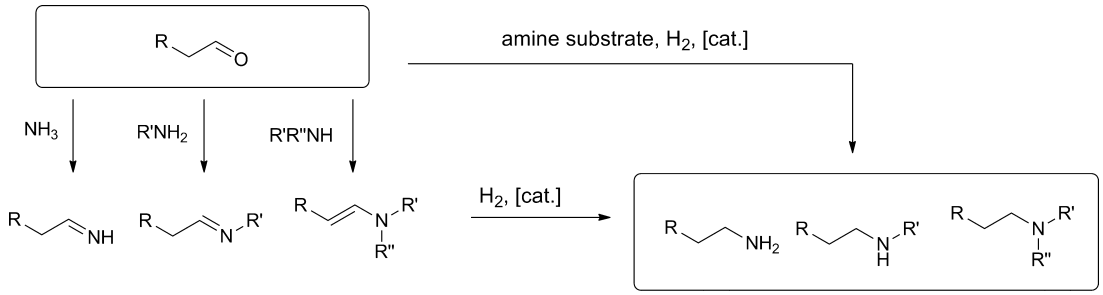


Fig. 1. The two natural isomers of citronellal.



Scheme 1. Reaction scheme of the reductive amination of an aldehyde with different amine substrates.

that required an additional reducing agent (triethylsilane) to produce a 40% yield of benzylamine [13]. Heterogeneous alternatives have been described by Peters et al., [14] Bayer AG [15] and OXEA [16]. Articles reviewing reductive amination in a general sense have been written by Hartwig et al. [17] and Maschmeyer et al. [18]. Implementation on an industrial scale is known from the heterogeneously catalysed reductive amination of alcohols using ammonia. It results in a product mixture of primary, secondary, and tertiary amines. [19]

To the best of our knowledge, the functionalisation of citronellal with ammonia leading directly to primary amines has not been described until now. The main product, citronellyl amine, was synthesised from the analogous oxime, [20] amide [21] and from geranylnitrile [22]. Published examples of the transition metal catalysed reductive amination of aldehydes with ammonia demonstrated the need to suppress side reactions in order to achieve high primary amine yield. The use of an efficient working biphasic solvent system is an alternative to the subsequent cleavage of secondary amines [23]. Aqueous biphasic reaction systems like the one used in this reaction often require phase transfer agents to reduce transport limitations. Important examples include the use of surfactants, [24] cyclodextrins [25] or ionic liquids [26], predominantly known for their use in hydroformylation and hydrogenation reactions. We compared these potential means of reductive amination of citronellal with ammonia in order to identify an optimal catalytic system that provides ample opportunities for catalyst separation.

2. Experimental

2.1. Typical synthetic procedure

All reactants, catalysts and solvents were commercially available and were used without further purification. In a typical experiment Chloro(1,5-cyclooctadiene) rhodium(I) (0.03 mmol 14.8 mg), triphenylphosphine trisulfonate (TPPTS, aq. saturated, 0.12 mmol, 68.2 mg) and hexadecyltrimethylammonium chloride (CTAC, aq. 25%, 0.031 mol, 60.7 mg) were dissolved in an aqueous ammonia solution (28%, 216.0 mmol, 13.14 g NH_3). Nexy, toluene (5.0 ml, 4.3 g) and citronellal (6.0 mmol, 925.5 mg) were added to the solution, which was sonicated for 5 min. The solution was transferred to an evacuated stainless steel autoclave with a volume of 70 ml (Parr Instrument Company). The autoclave was pressurised at 60 bar of H_2, mechanically stirred with 800 rpm and heated up to 130 °C. At the end of the reaction time, the autoclave was allowed to cool to room temperature, the pressure was released, the two layers were separated using a separating funnel, and the solution was analysed by gas chromatography.

2.2. Characterisation

Citronellyl amine **4** (see Scheme 2) is known from the synthesis of the analogous oxime. Analytical data is in accordance with published data [22].

MS (70 eV, EI): m/z (%): 155 (M^+, 1%), 138 (2), 123 (6), 112 (3), 109 (3), 95 (17), 81 (29), 70 (100), 55 (52).

For the characterisation of amine **5**, a mixture of amines **4** and **5** was hydrogenated, which resulted in compound **5** exclusively.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.86 ppm (d, ^{3}J(H,H) = 6.6 Hz, 6H, 2 x -CH_3), 0.89 (d, ^{3}J(H,H) = 6.6 Hz, 3H, CH_3), 1.15 (m, 6H, 3 x -CH_2), 1.37 (m, 2H, -CH_2), 1.58 (m, 2H, 2 x -CH-) 2.80 (m, 2H, -CH_2), 3.68 (m, 2H, NH_2).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 19.92, 22.87, 22.95, 25.00, 28.31, 29.85, 37.70, 39.58, 40.33, 41.58.

MS (70 eV, EI): m/z (%): 157 (M^+, 6), 140 (11), 125 (4), 114 (43), 100 (26), 84 (21), 70 (80), 55 (100)

The observed side products are identified by comparing the analytical data with the pure substance (citronellol **2**) or by mass spectrometry.

Citronellol **2**

MS (70 eV, EI): m/z (%): 156 (M^+, 1), 138 (2), 123 (9), 109 (7), 95 (31), 81 (50), 69 (100), 55 (92).

3,7-Dimethyloct-6-en-1-imine **3**

MS (70 eV, EI): m/z (%): 154 (M^+, 1%), 139 (3), 121 (12), 111 (8), 95 (33), 93 (13), 91 (11), 84 (16), 79 (27), 77 (22), 69 (100), 67 (74), 65 (19), 63 (7), 55 (90), 83 (74), 51 (28).

(E)-N-(3,7-dimethyloct-6-en-1-ylidene)-3,7-dimethyloct-6-en-1-amine **6**

MS (70 eV, EI): m/z (%): 291 (M^+, 1%), 276 (7), 248 (41), 234 (8), 222 (11), 208 (49), 194 (5), 180 (6), 166 (100), 152 (15), 138 (9), 124 (26), 110 (16), 98 (28), 84 (43), 69 (69), 55 (42).

Bis(3,7-dimethyloct-6-en-1-yl) amine **7**

MS (70 eV, EI): m/z (%): 293 (M^+, 2%), 278 (5), 250 (1), 236 (2), 224 (2), 208 (100), 168 (25), 152 (4), 138 (2), 126 (24), 112 (7), 98 (18), 93 (2), 81 (18), 69 (100), 65 (4), 55 (57), 51 (2).

(E)-N,N-Bis(3,7-dimethyloct-6-en-1-yl)-3,7-dimethylocta-1,6-diene-1-amine **8**

MS (70 eV, EI): 346 (2), 180 (2), 152 (2), 124 (2), 109 (4), 95 (6), 82 (12), 77 (2), 69 (100), 55 (57), 51 (1).

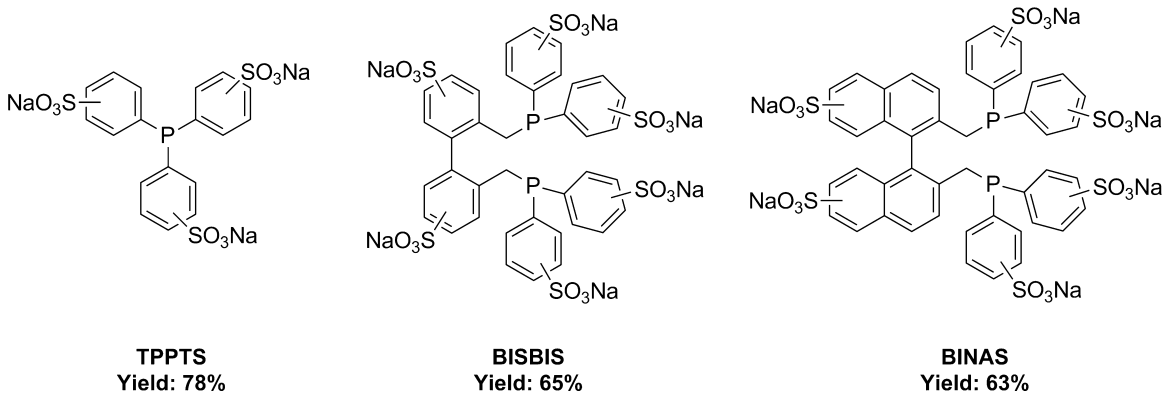


Fig. 2. Molecular structure of selected sulfonated phosphine ligands.

Tris(3,7-dimethyloct-6-en-1-yl) amine **9**

MS (70 eV, EI): 346 (2), 304 (1), 236 (1), 180 (1), 152 (2), 138 (2), 109 (4), 95 (8), 82 (11), 77 (3), 69 (100), 65 (2), 55 (53), 51 (1).

3. Results and discussion

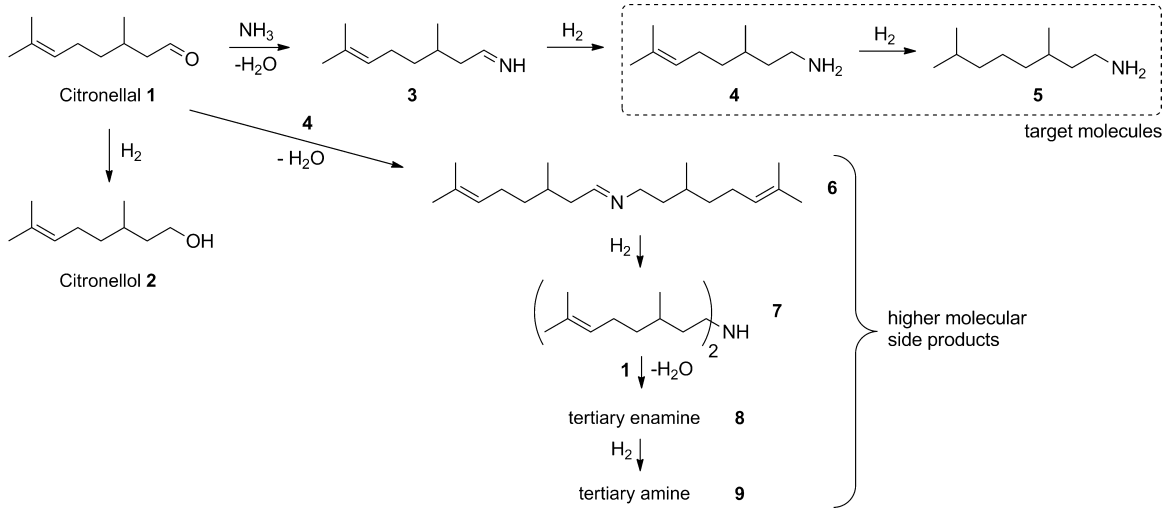
Apart from the condensation of starting material **1** with ammonia, the hydrogenation to citronellol **2** occured as side reaction (Scheme 2). Condensation between ammonia and citronellal **1** followed by hydrogenation of the resulting aldimine **3** to citronellyl amine **4** was identified as the other pathway. We could demonstrate that over long reaction times, **4** was further hydrogenated to form the other primary amine **5**. Another undesired side reaction was the condensation of **4** with the remaining citronellal **1** which resulted in imine **6**. This secondary product has two possibilities for further reaction: One pathway is the hydrogenation to secondary amine **7**, which condenses further with the remaining citronellal **1** to form tertiary product **8** and **9** after subsequent hydrogenation. Products **6**–**9** are declared as higher molecular side products. The desired pathway is the most important step in this cascade: imine **6** showed to be converted back to the primary products, which will be discussed later in detail. This cleavage of secondary imines has not been described in other research, though Beller et al. have described a ruthenium system for the catalytic cleavage of secondary amines.[23] After the dehydrogenation of the secondary amine, the imine is cleaved to one molecule of primary amine and one molecule of aldimine via a nucleophilic attack of ammonia. Hydrogenation catalysts then convert the aldimine into another primary amine molecule.

In the results, main products **4** and **5** as well as secondary (**6** and **7**) and tertiary (**8** and **9**) side products are combined. Unless otherwise indicated, the conversion was quantitative.

Due to the complexity of the reaction network, a catalytic system that was very active in imine hydrogenation and less active in aldehyde hydrogenation was needed. Rhodium and iridium based systems with water soluble phosphine ligands are described as active for the synthesis of a primary amine via reductive amination [12,13] and were tested in combination with the ligand TPPTS (Table 1).

The data showed that iridium complexes had a higher hydrogenation activity, which resulted in the formation of more citronellol **2**. Especially with $[Ir(cod)Cl]_2$ 40% yield of **2** were observed (entry 2), whereas the rhodium analogon $[Rh(cod)Cl]_2$ leads to the formation of 11% **2** and 77% of the primary amines **4** and **5** (entry 1). Higher hydrogenation activity of rhodium precursors, for example of the Wilkinson catalyst, also resulted in the formation of citronellol as well as the unwanted secondary amine **7** (entries 3-5).

Bidentate ligands were tested and compared to TPPTS, a mono-dentate ligand. BINAS (sulfonated 2,2′-bis(diphenylphosphino-methyl)-1,1′-binaphthylene) and BISBIS (sulfonated 2,2′-bis(diphenylphosphinomethyl)-1,1′-biphenyl), both chelating phosphine ligands (Fig. 2), produced desirable results in the biphasic hydroformylation of higher alkenes [27].



Scheme 2. Complete reaction scheme from the reductive amination of citronellal with ammonia.

Table 1
Influence of the precursor on the product distribution in the reductive amination of citronellal.

Nr.	Precursor	Y (main products) [%]			Y (side products) [%]		
		4	5	4+5	2	6+7	8+9
1	$[Rh(cod)Cl]_2$	51	26	77	11	9	3
2	$[Ir(cod)Cl]_2$	36	3	39	40	13	6
3	$[Rh(PPh_3)_3Cl]$	33	0	33	21	42	0
4	$[Rh(cod)_2]BF_4$	29	1	30	17	46	5
5	$[Rh(CO)H(PPh_3)_3]$	29	0	29	12	45	11
6	$[Ir(CO)H(PPh_3)_3]$	25	0	25	19	49	4

Reaction conditions: 6 mmol citronellal, 144 mmol NH_3, 0.5 mol% precursor, 4.0 mol% TPPTS, 0.5 mol% CTAB (Cetyltrimethylammonium bromide), 5 ml toluene, 60 bar H_2, 130 °C, 800 rpm, 6 h.

Table 2
Various precursor/phosphine ratios in comparison for two different ligands.

Nr.	Ligand / precursor/ligand ratio	Y (main products) [%]			Y (side products) [%]		
		4	5	4+5	2	6+7	8+9
1	TPPTS / 1:4	35	43	78	9	12	1
2	TPPTS / 1:8	51	26	77	11	9	3
3	BINAS / 1:4	35	25	60	10	24	6
4	BINAS / 1:8	48	15	63	10	23	5

Reaction conditions: 6 mmol citronellal, 144 mmol NH_3, 0.5 mol% $[Rh(cod)Cl]_2$, 0.5 mol% CTAB, 5 ml toluene, 60 bar H_2, 130 °C, 800 rpm, 6 h.

Especially in terms of the *n*/*iso* ratio, the chelating ligands showed improved yield compared to TPPTS. There was no need to improve the *n*/*iso* ratio for the reductive amination of citronellal.

Therefore, the bidentate ligands were unable to increase the yield of the primary amines. Apart from that, it can be said that they provided faster phase separation. Due to its simple structure and therefore lower cost, the TPPTS ligand was selected as the more economic choice. Experimental investigations showed that the ratio of the dimeric precursor and the monodentate sulfonated triphenylphosphine can be reduced to a molar ratio of 1:4 for a precursor concentration of 0.5 mol% based on the starting material (Table 2). In this way, costs can be reduced additionally whereas the ligand excess is high enough to provide sufficient catalyst stabilisation and activity.

The principle of micellar catalysis uses the formation of spheric aggregates which act as amphoteric compounds for the interaction between two unsoluble phases. Changing the surfactant or using a derivative can lead to another form of micelle formation. Using CTAC (Cetyltrimethylammonium chloride) instead of CTAB (Cetyltrimethylammonium bromide) in this investigation improved the yield of this reductive amination slightly to 81% (Table 3).

Shortening the apolar chain of the surfactant using TTAB (Tetradecyltrimethylammonium bromide) did not lead to changes in the product yield. A useful way to avoid the use of sulfonated ligands was demonstrated by using the anionic surfactant SDS (sodium dodecyl sulfate). The coordination of the sulfate functionality to the active metal centre generated an amphoteric catalyst system, which interacted in the apolar phase with the starting material. The compound is also able to stabilise the catalytic system. Although the yield decreased to 58%, it proved to be a highly effective method of combining the amphoteric properties of a surfactant with the metal-coordinating functionality of a ligand. In addition, tests were performed to determine whether the reaction could take place without any surfactant. Still, a moderate yield of 45% of the primary amines was achieved. The amount of imine **6** as part of the secondary products increased to 33% (entry 5), indicating a lower hydrogenation activity as a result of decreased phase interaction. This showed that transport limitations were low enough to provide proper phase interaction without the use of a phase transfer agent in the biphasic citronellal + toluene and water + ammonia + catalyst system.

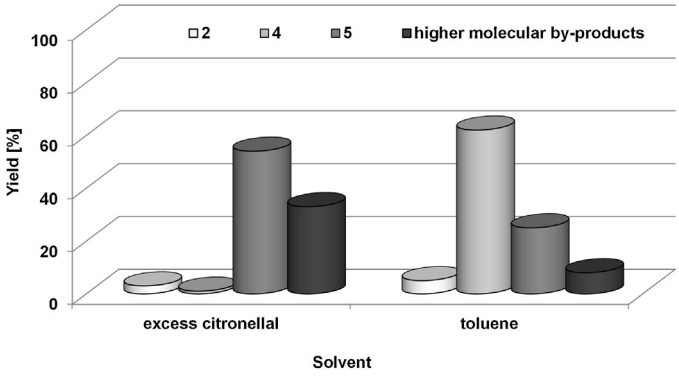


Fig. 3. Reaction conditions: 6 mmol citronellal, 144 mmol NH_3, 0.5 mol% $[Rh(cod)Cl]_2$, 2.0 mol% TPPTS, 0.5 mol% CTAC, 5 ml solvent, 60 bar H_2, 130 °C, 800 rpm, 6 h.

In addition to toluene, the organic solvents cyclohexane and 1-decane were also suitable for this reaction. The yield dropped to 75% using cyclohexane and to 67% using decane. When the structural properties of the starting material citronellal were compared to the organic solvents, it became clear that citronellal itself presented an adequate solvent as an organic phase. In fact, using a large excess of citronellal rather than an additional solvent led to a lower primary amine yield of 55% at a 97% conversion rate (Fig. 3). With respect to the rules of "green" chemistry it is desirable to minimise the use of solvents in chemical syntheses [28]. This environmentally-friendly method resulted in lower primary amine yield, which could pose a suitable compromise for an upscaled process. In a continuous process this would imply recycling the excess citronellal after the separation step.

Further on, different reaction parameters were varied within the established catalytic system to investigate their effects on product distribution. In an initial step, the substrate ratio of citronellal to ammonia proved ideal when a large excess of ammonia was used (Table 4). Using a ratio of 1:12, the yield dropped to 68% compared to a ratio of 1:24 (81%). When the excess of ammonia was increased to a ratio of 1:36 the yield was improved to 87%. Increasing the ratio even more to 1:48 showed with 82% no further improvement in yield. Comparing the yield of the secondary products (15% at 1:12 and 8% at 1:36) indicated that a larger aqueous ammonia phase

Table 3
Influence of the specific surfactant on the product distribution in the reductive amination of citronellal.

Nr.	Phase transfer agent	Y (main products) [%]			Y (side products) [%]		
		4	5	4+5	2	6+7	8+9
1	CTAC	36	45	81	7	11	0
2	CTAB	35	43	78	9	12	1
3	TTAB	45	34	79	9	13	0
4	SDS[a]	39	19	58	8	22	12
5	–	40	5	45	9	38	9

Reaction conditions: 6 mmol citronellal, 144 mmol NH_3, 0.5 mol% $[Rh(cod)Cl]_2$, 2.0 mol% TPPTS, 0.5 mol% surfactant, 5 ml toluene, 60 bar H_2, 130 °C, 800 rpm, 6 h. [a] without the use of TPPTS.

Table 4
Comparison of different citronellal/ammonia ratios.

Nr.	citronellal/NH_3 ratio [mol/mol]	Y (main products) [%]			Y (side products) [%]		
		4	5	4+5	2	6+7	8+9
1	1:12	56	12	68	10	15	0
2	1:24	36	45	81	7	11	0
3	1:36	62	25	87	5	8	0
4	1:48	49	33	82	9	9	0

Reaction conditions: 6 mmol citronellal, 0.5 mol% $[Rh(cod)Cl]_2$, 2.0 mol% TPPTS, 0.5 mol% CTAC, 5 ml toluene, 60 bar H_2, 130 °C, 800 rpm, 6 h.

had a controlling effect, which was expected to work as cleavage instrument for imine **6**.

The reaction temperature and hydrogen pressure were other important process parameters in terms of the imine cleavage. The primary amine yield was controlled with ease by varying these factors. A maximum yield of 87% (Fig. 4), was achieved within a temperature range of 130–150 °C. There were only traces of imine **6** at a reaction temperature of 130 °C, while a reaction temperature of 150 °C provided no improvement.

Decreasing the temperature to 110 °C resulted in a higher yield of secondary imine **6** at 20%, indicating insufficient imine cleavage. This trend became even more clear when the reaction was performed at 90 °C. 47% of imine **6** was produced, whereas the primary amine yield decreased to 30%. These results clearly demonstrated that temperatures of at least 130 °C are necessary for the cleavage of the imine to the primary products. The cleavage of secondary amines via the imine as an intermediate as described previously was performed under similar reaction conditions.[23] For example, dicyclohexylamine was cleaved more effectively at a reaction temperature of 150 °C (87% yield) than at a temperature of 130 °C (49% yield). It should be noted that the ammonia catalysed cleavage of a secondary imine to the primary compounds is more efficient at high reaction temperatures.

Compared to the reaction temperature, the effects of varying the hydrogen pressure showed a similar behaviour: a pressure of 60 bar afforded a yield of 87% (Fig. 5). In general, a slight increase of primary amine yield from 80% to 87% was observed within a range between 20 bar and 60 bar. In terms of atom economy, keeping the hydrogen pressure at 20 bar proved to be the most reasonable value. Further pressure drops to 10 and 2 bar resulted in higher secondary product yields of 19% and 52%, respectively. In the latter case, the secondary products consisted of imine **6** only. High hydrogen pressure provides the best conditions for cleavage of the undesired secondary imine.

These experimental results demonstrated the possible ways of reaction control quite simply, but to investigate especially the transformation of imine **6** to the primary products in more detail, a conversion-time plot was determined (Fig. 6). The reaction was very fast; after one hour the conversion was quantitative. Surprisingly, imine **6** was formed analogously to the conversion curve. This indicated that the condensation of citronellal **1** with ammonia and the following hydrogenation of aldimine **3** to amine **4**, as well as the condensation to imine **6** took place very quickly. It should be noted that the autoclave was heating up during this period (reaching 130 °C after 45 min), which indicated that these reactions were carried out at even lower temperatures than 130 °C. After one hour,

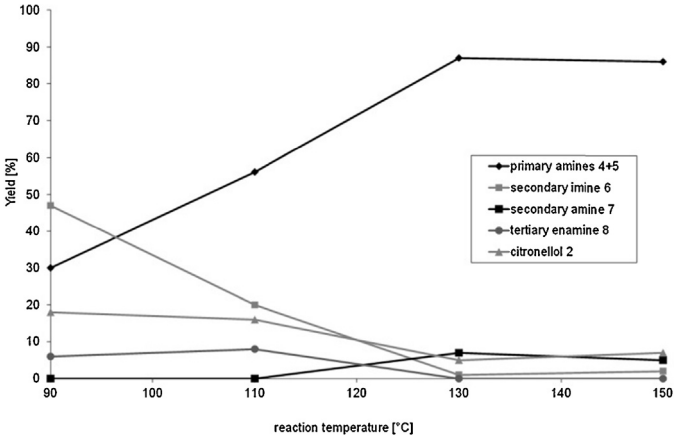


Fig. 4. Impact of the reaction temperature on the imine cleavage; data points are connected to result in a better comparison. Reaction conditions: 6 mmol citronellal, 216 mmol NH_3, 0.5 mol% $[Rh(cod)Cl]_2$, 2.0 mol% TPPTS, 0.5 mol% CTAC, 5 ml toluene, 60 bar H_2, 800 rpm, 6 h.

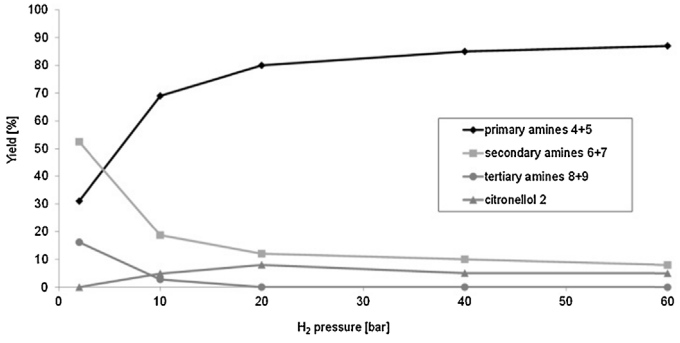


Fig. 5. Impact of the hydrogen pressure on the product distribution in the reductive amination of citronellal; data points are connected to result in a better comparison. Reaction conditions: 6 mmol citronellal, 216 mmol NH_3, 0.5 mol% $[Rh(cod)Cl]_2$, 2.0 mol% TPPTS, 0.5 mol% CTAC, 5 ml toluene, 130 °C, 800 rpm, 6 h.

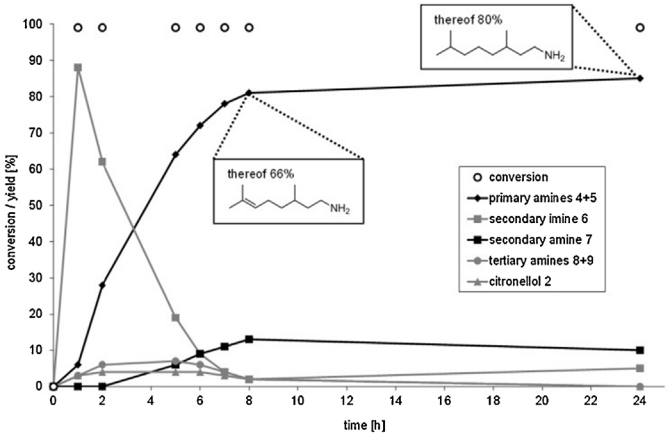


Fig. 6. Conversion-time plot of the reductive amination of citronellal with ammonia. Reaction conditions: 6 mmol citronellal, 216 mmol NH_3, 0.5 mol% $[Rh(cod)Cl]_2$, 2.0 mol% TPPTS, 0.5 mol% CTAC, 5 ml toluene, 60 bar H_2, 130 °C, 800 rpm.

the yield of imine **6** reached 88%. As time passed, the imine yield decreased while amine **4** was formed in increasing amounts. After 5 h, a yield of 58% for amine **4** and 19% for imine **6** was observed. The highest yield of primary amine **4** was achieved after 8 h at 66%. The internal double bound of **4** was hydrogenated as time passed, leading to a yield of 80% of amine **5** and 3% of amine **4** after 24 h. It has been described before that specific parameters are crucial for a low amount of higher molecular by-products such as imine **6**. While **6** results from a condensation of **1** with **4**, the depletion over the reaction time is an interesting observation. In general, imines like **6** can be hydrolysed to give an amine and an aldehyde, although this is more likely for acidic systems.

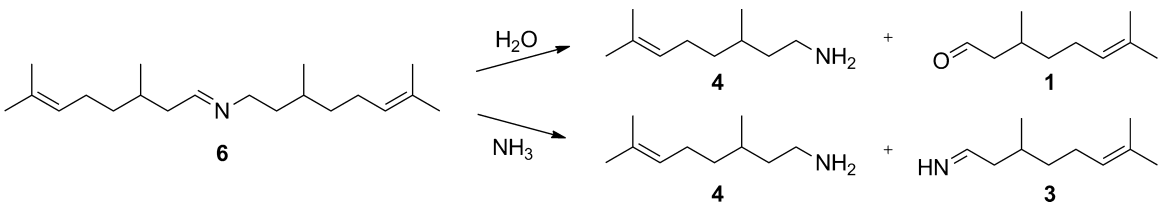
Another possible mechanism is the cleavage by ammonia, which would result in two amine products and does not require acidic reaction conditions (Scheme 3). This way of reaction has been also described by Beller et al. with and without the use of water [23]. As we cannot exclude that hydrolysis is involved in the reaction mechanism, it is likely that ammonia is necessary to shift the equilibrium which results from reversible hydrolysis. An exceptional hydrolysis would not result in a decreasing, rather than in a stabilising imine yield. Therefore we believe that ammonia acts as a cleavage instrument which is responsible for a high primary amine yield.

The use of phase transfer agents in biphasic aqueous solvent systems can enhance the interaction between the substrates and the catalyst. Their use can also negatively impact the phase separation of the reaction system which would lead to a lower space-time yield and therefore to a less economical process. It is well-established that typical surfactants like CTAB offer suitable properties in terms of reaction rate. In this point of view, the critical micelle concentration (CMC) is responsible for the occurring micellar catalysis which is described for several reactions by Oehme et al [29]. But the use of surfactants can also lead to the formation of emulsions in biphasic aqueous solvent systems [26a]. In fact, we observed the formation of an emulsion phase between the aqueous and toluenic layer in the tested reaction system. This led to a very slow separation process that occurred overnight. In certain cases, it even complicated or interfered with the separation of the product phase from the catalyst phase. In this case, the capacity of a production plant would decrease dramatically. Therefore, we searched for alternative phase transfer agents. Suitable examples from biphasic aqueous hydroformylation reactions of alkenes are well established. Ionic liquids, especially imidazolium derivatives, were used by Hamilton et al. for the hydroformylation of 1-hexene, 1-octene and 1-decene. Phase separation occurred with the matching agent within a few minutes and resulted in a very accurate interface [26a–b].

These imidazolium based ionic liquids can be varied in form of the chain length and in the type of the anion. As the results achieved by Hamilton et al. indicated a correlation between the chain length of the ionic liquid and the starting material in order to secure a suitable interaction between the phases,[26b] imidazolium derivatives with a side chain with a carbon number of 8, 10 and 12 were chosen for this experiment (Fig. 7). Aside from the ionic liquids 1-methyl-3-octylimidazolium bromide ([OctMIM]Br), 1-decyl-3-methylimidazolium bromide ([DecMIM]Br) and 1-dodecyl-3-methylimidazolium bromide ([DodMIM]Br), another class of ionic liquids was selected to test its properties as a phase transfer agent. These so-called Ammoeng molecules are quarternary ammonium compounds with chains from fatty acids and polyethylene glycol of different chain lengths. Their potential has been shown in the production of biodiesel [30] and the exploitation of crude oil [31].

Compared to the use of surfactants, all of the tested ionic liquids provided fast and accurate phase separation. A clear phase separation was achieved in a matter of minutes, which demonstrated the potential of ionic liquids as efficient phase transfer agents. Regarding the yield of the primary amines **4** and **5**, the ionic liquids generated different results (Table 5).

A maximum yield of 82% was achieved using [DecMIM]Br. Using imidazolium bromides with the octyl and dodecyl chain, higher amounts of citronellol **2** (20%, entry 1) and secondary products **6**



Scheme 3. Potential cleavage mechanisms of imine 6 to produce primary products.

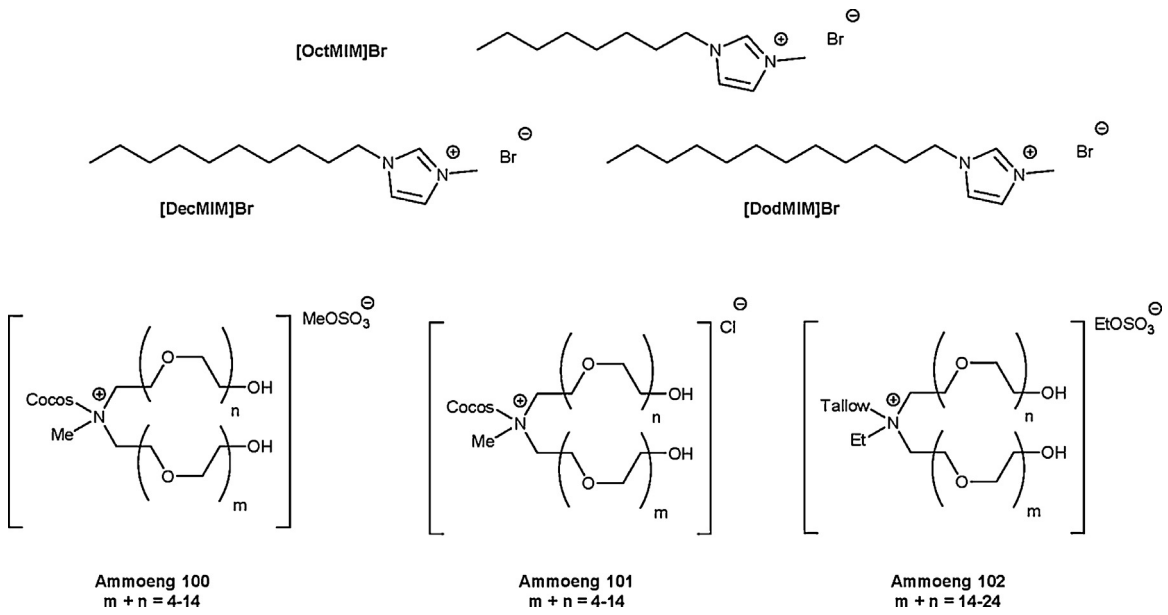


Fig. 7. Structures of the used ionic liquids as phase transfer agents for the reductive amination of citronellal.

Table 5
Comparison of ionic liquids as phase transfer agents in the reductive amination of citronellal.

Nr.	Phase transfer agent	Y (main products) [%]			Y (side products) [%]			
		4	5	4+5	2	3	6+7	8+9
1	[OctMim]Br	41	2	43	20	21	15	0
2	[DecMIM]Br	81	1	82	8	8	1	0
3	[DodMim]Br	27	2	29	0	0	71	0
4	Ammoeng 100	73	6	79	8	8	4	0
5	Ammoeng 101	40	4	44	14	14	27	0
6	Ammoeng 102	0	20	20	0	0	80	0

Reaction conditions: 6 mmol citronellal, 216 mmol NH_3, 0.5 mol% $[Rh(cod)Cl]_2$, 2.0 mol% TPPTS, 5 mmol ionic liquid, 5 ml toluene, 60 bar H_2, 800 rpm, 130 °C, 6 h.

and **7** (71%, entry 3) were formed, which resulted in a lower primary amine yield. Using the Ammoeng compounds, comparable results to the imidazolium species were generated (entries 4–6). Ammoeng 100 in particular, which contains fatty acid chains from coconut oil, led to high amounts of the primary amines **4** and **5** at 79%. For the most part, unsaturated amine **4** was observed, with the exception of Ammoeng 102 (entry 6). Using this species, which has fatty acid chains from tall oil, led to the selective formation of saturated primary amine **5** and imine **6** without observing secondary amine **7**. Similar results are obtained for [DodMim]Br with 70% of imine **6** (entry 3). Both species represent longer chained examples for phase transfer agents which do not seem suitable for this biphasic reaction system.

The use of native cyclodextrines and their derivatives as phase transfer agents in aqueous biphasic reaction systems were described in detail by Monflier et al. and reviewed [25g]. Randomly methylated β-cyclodextrin (RAME-β-CD) in particular proved its ability to perform homogeneously catalysed reactions in biphasic solvent systems. It was tested and compared with the native cyclodextrins α-cyclodextrin (α-CD), β-cyclodextrin (β-CD) and γ-cyclodextrin (γ-CD) as well as hydroxypropyl-β-cyclodextrin (HP-β-CD), another derivative of β-CD for the reductive amination of citronellal with ammonia (Table 6).

The influence of the ring size of these molecules showed only slight increases of primary amines using α-CD. Using the larger γ-CD, the primary amine yield dropped from 61% to 52%. Secondary products were observed within a range between 39% and 48% in all cases. The yield of the side products was supressed using RAME-β-CD (entry 4). Secondary product yield decreased to 4% whereas a high yield of the primary amines was observed at 79%. In contrast to the native cyclodextrins where no citronellol **2** was detected, alcohol was observed at a low yield of 8%. This indicated adequate

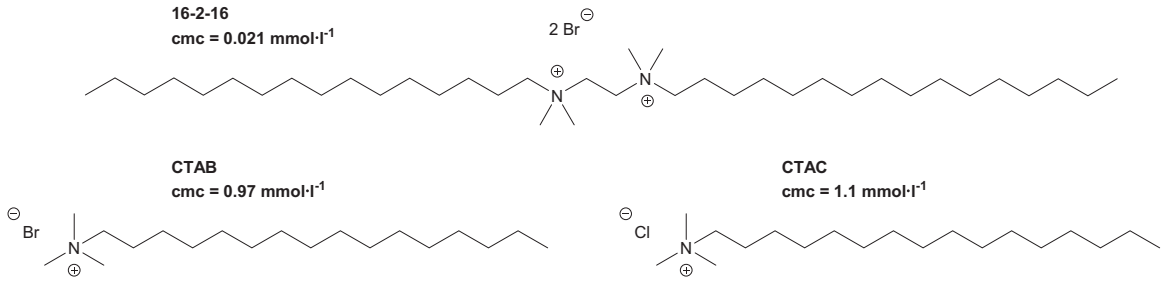


Fig. 8. Structural comparison of typical surfactants with the gemini surfactant 16-2-16.

Table 6
Comparison of cyclodextrins as phase transfer agents in the reductive amination of citronellal.

Nr.	Phase transfer agent	Y (main products) [%]			Y (side products) [%]		
		4	5	4+5	2	6+7	8+9
1	α-CD	54	7	61	0	39	0
2	β-CD	52	7	58	0	42	0
3	γ-CD	48	4	52	0	48	0
4	RAME-β-CD	73	6	79	8	4	0
5	HP-β-CD	59	5	64	0	36	0

Reaction conditions: 6 mmol citronellal, 216 mmol NH_3, 0.5 mol% $[Rh(cod)Cl]_2$, 2.0 mol% TPPTS, 0.54 mmol cyclodextrin, 5 ml Toluol, 60 bar H_2, 800 rpm, 130 °C, 6 h.

interaction between the phases, as citronellal came into contact with the catalyst and hydrogenated to citronellol **2**. A lower primary amine yield was observed for HP-β-CD (entry 5, 64%), which indicated that the polarity of the molecules is the most important factor in improving phase interaction.

Gemini surfactants are a special type of surfactants. They differ from typical surfactants due to their specific structure: two polar headgroups, each connected to an apolar chain, are linked by one spacer. This can lead to much lower critical micell concentrations (CMC) compared to surfactants such as CTAC. [32] Using a gemini surfactant with a low CMC in the biphasic solvent system was expected to lower the surfactant concentration in comparison to CTAC. Therefore, phase separation was expected to improve due to decreased emulsion formation. We decided to use the gemini surfactant hexadeca-diylbis(dimethylethylammonium) bromide (16-2-16). With a CMC of 0.021 mmol l^{-1}, [33] it provides a much smaller CMC than the surfactant CTAC (1.10 mmol l^{-1}) [34] (Fig. 8).

Performing the reaction with the gemini surfactant reduced the formation of emulsions, thus offering improved phase separation compared to CTAC. At the same time, high primary amine yield at a rate of 79% was achieved, indicating micellar catalysis was carried out successfully in this catalytic system as well.

4. Conclusions

Reductive amination of citronellal with ammonia was investigated as a selective one-step synthesis of primary amines from a renewable material. Using aqueous ammonia as substrate, a two phase solvent system was created to prevent side reactions. In addition, a conversion-time plot showed that the cleavage of the undesired secondary imine is the most important step in this tandem reaction, which was also indicated by temperature and pressure variations. We compared a variety of phase transfer agents, combining surfactants, ionic liquids and cyclodextrins with a water soluble homogeneous rhodium catalyst. Ionic liquids and cyclodextrins provided particularly fast and accurate phase separation, yielding the primary amines at a maximum yield of 82% at full conversion. Using gemini surfactants as an alternative was also investigated, which provided extremely low CMC. Therefore, no formation of emulsion was observed. In addition, the products were isolated from the catalyst with ease by separating the aqueous from the organic layer.

Acknowledgements

This work was financially supported by the DFG (Deutsche Forschungsgemeinschaft). The authors thank Umicore AG & Co. KG for the donation of precursors.

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