Chapter 10
Hydroamination and Telomerisation of *β*-Myrcene

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10.1 Introduction

In this chapter, the scale-up of the hydroamination (see Chap. 4) and telomerisation (see Chap. 5) of the industrially available renewable resource *β*-myrcene (hereafter simply called myrcene) from batch to a continuous process is discussed in detail. The terpenyl amines produced by these reactions could be used as plasticisers, as precursors for surfactants or even as fragrances, depending on the substrate combination. This enables an alternative route to these interesting products. The variety of products that can be generated from the renewable starting material myrcene is depicted by Behr and Hu [1, 2].

The hydroamination is an atom-economical reaction for the synthesis of alkyl amines via formation of a C–N bond. The hydroamination can be carried out intramolecularly, resulting in heterocycles or intermolecularly, when amine and unsaturated compound are separate molecules (Fig. 10.1). This offers an alternative route to alkyl amines apart from the common paths such as oxidation of the unsaturated compound and condensation with an amine [2].

While the reaction of an alkene with an amine is thermodynamically feasible, it suffers from a very high activation barrier. This is caused by the repelling effect of the π-electron cloud of the alkene with the free electron pair of the amine [4]. However, without a catalyst the application of higher temperatures to overcome this activation barrier results in a shift in the chemical equilibrium towards the starting materials, thus limiting the total conversion of the reaction. At this point, a highly active catalyst is needed to lower the activation barrier and to facilitate the hydroamination at lower temperatures.

The hydroamination can be catalysed by a wide variety of catalysts, including acid/base-catalysts, metal and late transition metal catalysts as well as alkali and rare earth metals. A good overview about the scope of hydroamination catalysts and substrates is given by Müller et al. [5]. The *Takasago* process, one of the rare realisations of the hydroamination on industrial scale (5000 t/a (-)-menthol),
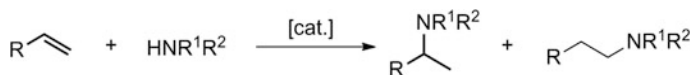
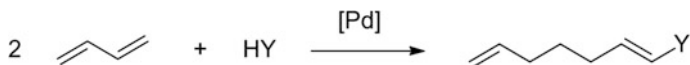**Fig. 10.1** Hydroamination of an alkene with an amine [3]

Fig. 10.2 Telomerisation reaction of a diene (exemplified by butadiene)

incorporates the lithium-catalysed hydroamination of myrcene with diethylamine to *N,N*-diethylgeranylamine [6]. Late transition metals like palladium or platinum combined with phosphorus or carbene ligands feature greatly improved catalytic activity [5], but require an efficient catalyst recycling as a result of higher catalyst prices. The hydroamination of myrcene with morpholine to the desired terpenyl amines is shown in detail in Fig. 10.3 (see Chap. 4).

In contrast to the hydroamination, the telomerisation incorporates two diene molecules and one molecule of the nucleophilic component. The telomerisation is defined as a diene oligomerisation with the incorporation of a nucleophile. Like the hydroamination, it is an atom-economic coupling reaction leading to the desired terpenyl amines, but with two molecules of the diene incorporated into the final product (Fig. 10.2).

Like the hydroamination, the telomerisation can be catalysed by transition metals, for example, palladium, platinum, or nickel [7]. An overview of the wide catalyst and substrate spectrum used in the telomerisation is given by Behr et al. [7, 8]. The telomerisation reaction and the scope of possible substrates and nucleophiles are
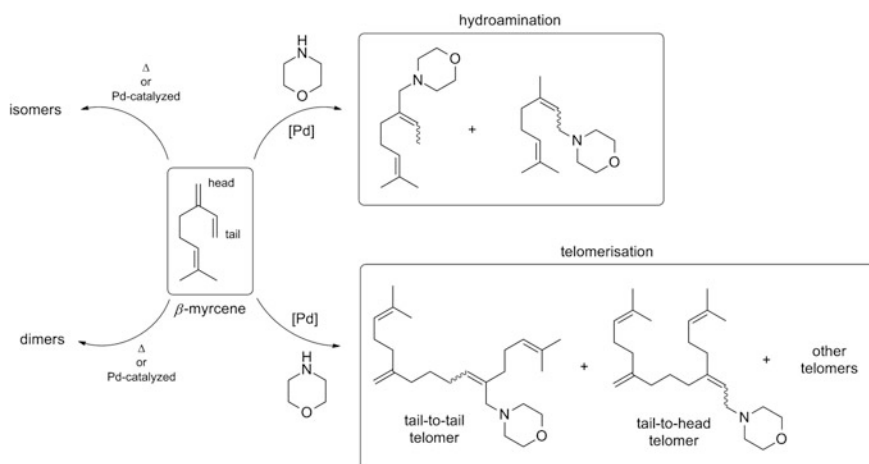

Fig. 10.3 Product spectrum of the hydroamination and telomerisation of β-myrcene

described in detail in Chap. 5. Figure 10.3 shows the hydroamination and telomerisation of myrcene with morpholine as well as the isomerisation and dimerisation side-reactions.

It has to be noted that both reactions can be catalysed by the same or similar catalytic system and incorporate the same substrates, so the path of the reaction has to be controlled by the reaction parameters.

10.2 Laboratory Experiments

10.2.1 Control of Reaction Pathways

The desired pathways of hydroamination and telomerisation as well as the side-reactions isomerisation and dimerisation are illustrated in Fig. 10.3. It has to be noted that both side-reactions can either be favoured by heat or the palladium complex. Compared to the main reactions, these reaction pathways can in most cases be suppressed by not exceeding a certain temperature level.

The hydroamination and telomerisation can be catalysed by the same catalytic system, so the control of the reaction pathways is of great concern. Johnen conducted an extended catalyst screening for the hydroamination of myrcene with morpholine as well as the telomerisation of myrcene with diethylamine. All experiments have been carried out using toluene as the solvent. The best catalytic activity for the hydroamination is achieved by fluorinated palladium precursors as $(Pd(tfa)_2$ or $Pd(hfacac)_2)$ in combination with diphosphine ligands (DPPB, DPEPhos) [9]. The telomerisation of myrcene can be catalysed by the same precursor/ligand systems as the hydroamination, but also non-fluorinated precursors $([Pd(MeCN)_4](BF_4)_2)$ and monodentate ligands like triphenylphosphine (TPP) have proven to be active [10].

Apart from the catalytic system, the product spectrum can be influenced by the temperature as well. Johnen varied the reaction temperature for the hydroamination of β-myrcene using $Pd(tfa)_2$/dppb as the catalytic system and points out that good yields of hydroamination products (1,4-adducts) can be achieved at 100–120 °C. However, the dimerisation and isomerisation side-reactions occur in substantial amounts, when a reaction temperature of at least 120 °C is applied (Fig. 10.4, [9]). This concurs with a partial deactivation of the catalyst resulting in the formation of palladium black as a precipitate. This limits the maximum reaction temperature of this catalyst system to 110 °C.

In general, the hydroamination is favoured by high catalyst and ligand concentrations as well as high amine/myrcene ratios. This effect is due to the probability of two myrcene molecules coordinating simultaneously at the active catalytic complex, so that before mentioned conditions shift the reaction system towards the hydroamination products (Table 10.1).

Fig. 10.4 Influence of
temperature on the
hydroamination of β-myrcene
using Pd(CF$_3$CO$_2$)$_2$/dppb [9].
Conditions: 0.2 mol%, Pd
(CF$_3$CO$_2$)$_2$, DPPB, Pd/P 1:8,
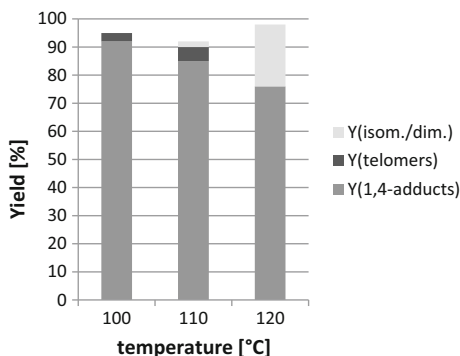t = 5 h, 500 rpm,
c(substrates) = 0.17 mol/l,
toluene, p(argon) = 5 bar

Table 10.1 Influencing parameters/reaction conditions on reaction pathway

Parameter	Hydroamination [9]	Telomerisation [10]
Catalyst concentration	0.4 mol% (high)	0.05 mol% (low)
Phosphor:metal ratio	8:1 (high)	≤ 4:1 (low)
Amine:myrcene ratio	≥ 1:1	≤ 1:2
Catalyst	Fluorinated palladium precursors (Pd(tfa)$_2$, Pd(hfacac)$_2$)	Palladium precursors ([Pd(MeCN)$_4$](BF$_4$)$_2$, Pd(tfa)$_2$)
Ligands	Bidentate (DPPB, DPEPhos)	Bidentate or monodentate (DPPB, TPP, Carbene)

The most significant factor to shift the reaction between hydroamination and telomerisation is the catalyst to substrate ratio. An increase in the catalyst concentration leads directly to an increase in hydroamination products (Fig. 10.5).

Fig. 10.5 Influence of
catalyst concentration on
hydroamination and
telomerisation product
distribution [9]. Conditions:
Pd(CF$_3$CO$_2$)$_2$, DPPB,
Pd/P 1:8, T = 100 °C,
t = 5 h, 500 rpm,
c(substrates) = 0.17 mol/l,
toluene, p(argon) = 5 bar
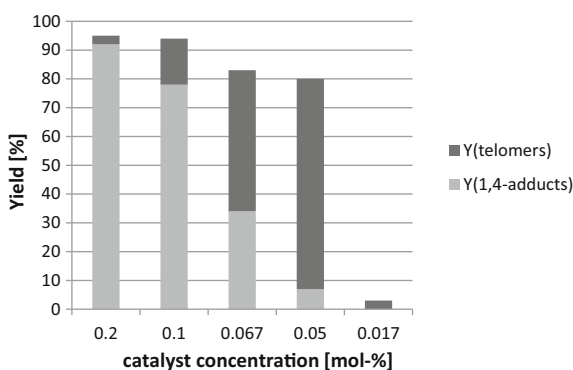
10.2.2   Catalyst Recycling

As mentioned in the previous paragraph, the recycling of the homogeneous transition metal catalyst is important for the realisation of the hydroamination and telomerisation on a technical scale. In this case, thermal processes cannot be applied, either because of the product properties (high boiling point, polarity) or catalyst instability at separation temperature. A lot of promising alternative concepts have been developed in recent years to recycle homogeneous catalysts [3]. Especially, thermomorphic solvent systems offer a number of advantages in comparison with multiphase systems. TMS-systems utilise the temperature-dependant miscibility gap between solvents of different polarity. This way the reaction can be performed at elevated temperatures in homogeneous conditions, while the catalyst separation occurs at biphasic conditions at lower temperatures.

The two main aspects for the successful development of a TMS-system are catalysis and phase properties. Johnen investigated two TMS recycling systems for the hydroamination (acetonitrile/*n*-heptane, dimethylformamide/*n*-heptane) and one system for the telomerisation of myrcene (methanol/*n*-octane) in detail. The solvent scope for the polar solvent was then further extended for the hydroamination. For all experiments, *n*-heptane was used as the non-polar phase, while the polar solvent was modified. A wide range of solvents was tested and those solvents, which successfully formed a TMS-system in a suitable temperature range, were applied and tested in the hydroamination reaction. Figure 10.6 shows the influence of the polar solvent on the catalytic activity for the selected solvents.

This exemplifies the impact the choice of solvent can have on the performance of a catalytic system. Acetonitrile, methanol, and *N*,*N*-dimethylformamide (DMF) are active in the hydroamination with decreasing conversion; however, some telomerisation products are formed when using DMF as polar solvent. When methanol is used as the catalyst solvent, the precipitation of palladium black can be observed
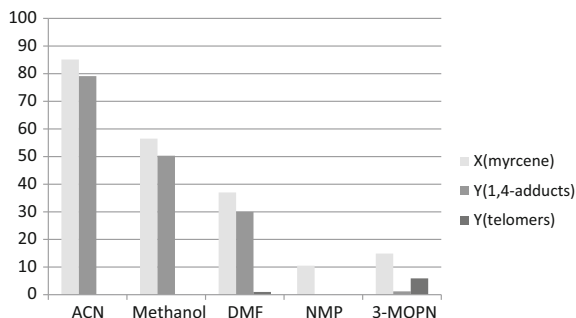

Fig. 10.6 Effect of polar solvent on hydroamination and telomerisation. Conditions: Pd(CF$_3$CO$_2$)$_2$/DPPB, $c_{cat.}$ = 0.4 mol%, *M/P* = 1:8, p_{Ar} = 5 bar, *T* = 110 °C, c(substrates) = 0.1667 mol/l, 450 rpm, *t* = 3 h; *ACN* acetonitrile, *DMF* dimethylformamide, *NMP* *N*-Methyl-2-pyrrolidone, 3-*MOPN* 3-Methoxypropionitrile

after the reaction. As a result, methanol was excluded for the continuous experiments and acetonitrile and DMF were selected for the continuous miniplant experiments.

10.3   Miniplant Investigations

10.3.1   Choice of Reactor

After the catalytic system has been screened in the laboratory, the reaction was transferred into a continuous process in order to look at catalyst recycling and scale-up effects. A very important decision is the correct choice of the chemical reactor. Continuously operated chemical reactors can in most cases be traced or seen as a combination of the two ideal reactor types: continuous stirred-tank reactor (CSTR) and plug-flow reactor (PFR). Each of these reactor types has its specific benefits and disadvantages.

A CSTR would not be suited for a reaction system with consecutive reactions, as the constant presence of all reactants would lead to considerable by-product formation. The hydroamination and telomerisation do not require excessive mixing (homogeneous solution) or gas supply (no gaseous reactants), so a continuous CSTR would not be beneficial, as this would also reduce the overall yield as a result of the continuous dilution by the reaction feed. A CSTR-cascade would compensate this drawback, but also increase the investment costs (multiple reactors, process control equipment) and the costs of operation.

The reactor for the realisation of hydroamination and telomerisation would possess plug-flow behaviour to achieve high yields of the desired terpenyl amines. However, preliminary studies in miniplant-scale have shown that a PFR was not the best option as a result of the low volumetric flow (~ 120 ml/h). This low flow rate leads to a very small velocity in the PFR resulting in extreme boundary effects. These effects lead to a very broad residence time distribution and would require a very long reactor (40 m) to reach the desired product yield, resulting in high instrument costs and challenging process operation (heating, cleaning). Higher flow rates on the other hand would increase the costs of the miniplant operation.

A very promising reactor concept to solve this conflict is the so-called Taylor-Couette reactor (TCR). This reactor type combines the advantages of PF and CST reactors and achieves plug-flow like behaviour even at low flow rates.

10.3.2   The Taylor-Couette Reactor

Apart from the "standard"-reactor types, a variety of reactors exists that feature characteristics in between these ideal reactor types (e.g. cascade, loop reactor).

A very promising and versatile reactor is the so-called Taylor-Couette reactor (TCR). It combines the specific advantages of a CSTR (mixing properties) and PFR (plug flow profile). The TCR exhibits a hydrodynamic behaviour closely related to a CSTR-cascade with a very high number of reactors in series, but with the possibility to change the hydrodynamic properties independent of the flow rate. This way the reactor can be tailored to the demands of a specific reaction without changing the reactor hardware (Fig. 10.7).

The TCR consists of two concentric cylinders, which rotate in relation to each other. In most cases the outer cylinder remains static, while the inner one rotates at a certain velocity. This movement results in a number of flow regimes in the annular gap. This creates an additional degree of freedom in comparison with a plug-flow reactor, because the flow conditions can be modified independently of the feed rate.

Apart from a cylindrical rotor, other geometries have been discussed in the literature. Kraushaar-Czarnetzki et al. developed a ribbed rotor that exhibits an even narrower residence time distribution than the standard rotor by "locking" the vortices in place, only allowing for very small mass transfer between the individual reaction volumes [11]. Sorg et al. modified the TCR with a lobed rotor geometry for application as a bioreactor, minimising the hydrodynamic stress in the reaction medium [12].

The advantages of low back-mixing, good heat dissipation, and low shear stress while still remaining good mixing, lead to a variety of possible applications for this reactor type. Among others, its use in polymerisation [13], electrochemical [14], photochemical [15], and enzymatic [11] reactions as well as gas–liquid reactions [16] has already been investigated. The possibility to create a PFR-like flow profile

**Fig. 10.7** Taylor-Couette reactor with cylindrical rotor (*left*) and ribbed rotor (*right*)
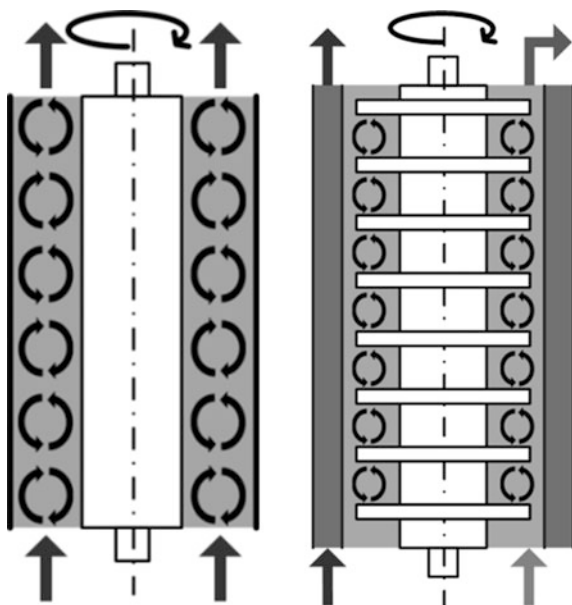
in a well-mixed reactor with good heat transfer makes this reactor a promising concept for the application in homogeneous catalysis as well.

10.3.3 Design Aspects and Construction

The main focus of this work is the transfer of a homogeneous process from laboratory batch experiments to a continuously operated process. As a result, the optimisation of the TCR was not the main goal; instead the main focus lied upon the application of this reactor concept in the field of homogeneous catalysis. Basis of the reactor development were the works of Richter and Liu, which conducted extensive research in the field of Taylor-Couette reactor development and its use for polymer synthesis [11, 13, 17]. Based on these works we scaled-up and developed a TCR with a ribbed rotor, which was specifically tailored towards our demands in homogeneous catalysis. The final technical drawing of the TCR is shown in Fig. 10.8. The reactor features a pipe-in-pipe heating system with an external thermostat. It can be operated up to a pressure of 5 bar, which is needed for the inert atmosphere and to keep the organic solvents in the liquid phase at reaction temperature. The bearing of the rotor is achieved by a fixed/floating bearing system in the upper part of the reactor, sealed by two graphite-filled Teflon-seals. The rotor is connected to a magnetic coupling on top of the reactor which is driven by an electric motor.

After construction of the TCR residence time measurements were made to verify the flow characteristics of the reactor. Experiments with varying flow rate and

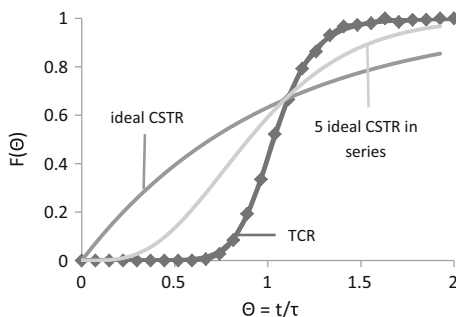**Fig. 10.8** Technical drawing of the constructed Taylor-Couette reactor
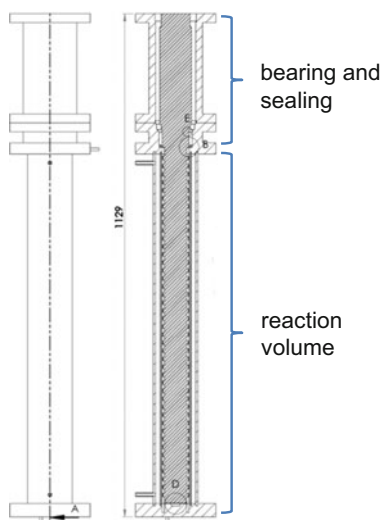
Fig. 10.9 Taylor-Couette reactor flow characteristics

rotational speed showed that the flow characteristics were similar to a CSTR-cascade with a high number of reactors in series (Fig. 10.9).

10.3.4   Batch Experiments

After the flow characteristics of the TCR were examined, the performance in homogeneously catalysed reactions had to be investigated. The reactor was mounted and connected to two high precision HPLC pumps for dosing of the liquid components. The hydroamination was carried out in a homogeneous solution with toluene as solvent (no TMS-system), as it showed the best results in the laboratory screening experiments [9]. The catalytic system (Pd(tfa)$_2$/DPPB) was used as a benchmark system. This system was developed by *Johnen* and already showed high catalytic activity in the hydroamination of myrcene. Figure 10.10 shows a comparison of the hydroamination in a laboratory batch reactor (*Parr* pressure autoclave) and the Taylor-Couette reactor under similar reaction conditions.

The Taylor-Couette reactor is able to reproduce the batch experiments with comparable hydroamination yields (X(myrcene) = 97%, Y(1,4-adducts) = 87%). The slight increase in side-product formation is most likely a result of the non-ideal temperature distribution along the length of the reactor. As a result, the TCR tempering jacket was retrofitted with guide plates to achieve a more even temperature distribution.
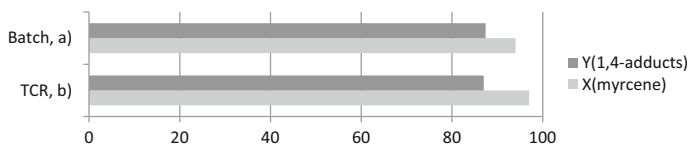

Fig. 10.10 Results of the hydroamination in batch- and Taylor-Couette reactor. Conditions: *solvent* toluene, Pd(CF$_3$CO$_2$)$_2$/DPPB, c(cat.) = 0.454 mol%, M/P = 1:8, p(argon) = 5 bar, T = 110 °C, c(substrates) = 0.1667 mol/l, (**a**) TCR: 100 rpm, τ = 4 h; (**b**) batch: 450 rpm, t = 3 h, V(solvent) = 100 ml

10.3.5   *Miniplant Concept*

After the catalytic activity of the TCR in the hydroamination has been tested, the reactor was integrated into the miniplant and connected to the peripherals. A simplified version of the process flow chart is shown in Fig. 10.11 and illustrates the necessary process equipment for the continuous operation of the reactor and the continuous recycling of the catalyst using TMS-systems. The miniplant is equipped with a process monitoring system (*National Instruments* CompactRIO) to monitor the necessary process parameters (p, T, m) with *NI* LabVIEW.

Fluid transport is achieved by HPLC pumps for the precise dosing of the substrates and a diaphragm pump for the non-polar solvent. The catalyst phase is placed in the phase separator at the beginning of the reaction and dosed by a HPLC pump. All the liquid components (solvent, substrates, and catalyst phase) are fed into a heated mixing unit that homogenises the mixture, but operates below reaction temperature. This way a precise ratio of catalyst to substrates can be set, as *Johnen* already showed that the catalyst to myrcene ratio is one of the key factors to shift the reaction system between hydroamination and telomerisation [18]. The homogenous solution is fed into the Taylor-Couette reactor and the reaction proceeds ($T_{reaction}$ = 100–110 °C). After the specified residence time, the mixture leaves the reactor at the top and flows gravity-driven into the cooled phase separator (T = 10 °C), where the mixture splits into the polar catalyst phase, which is fed back into the reactor and the non-polar product-rich phase which is continuously
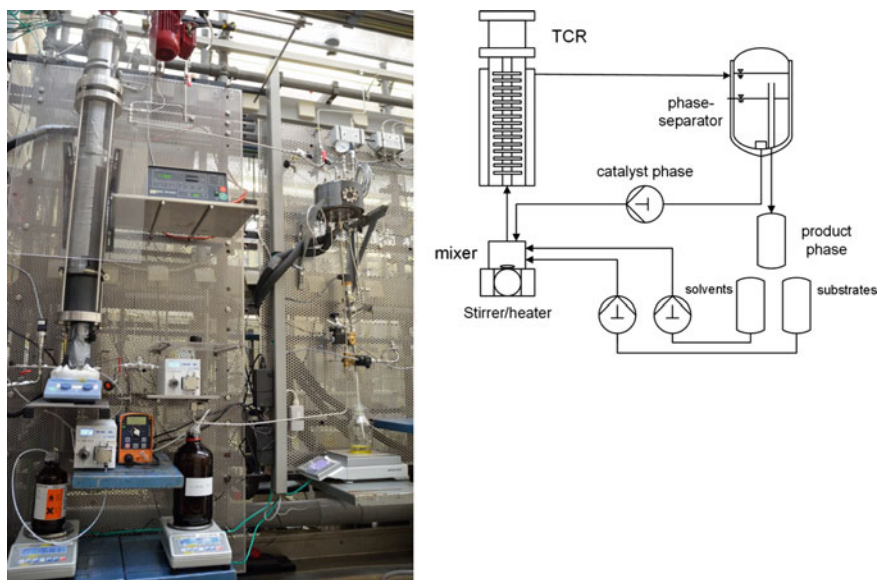

Fig. 10.11 Integration of Taylor-Couette reactor and miniplant peripherals

discharged by an autonomous system and weighed. The product phase can then be analysed by GC-chromatography.

10.3.6   Continuous Experiments

Two main TMS-systems for hydroamination and telomerisation were first briefly tested by Johnen and later optimised. The TMS-systems acetonitrile (ACN)/*n*-heptane and dimethylformamide (DMF)/*n*-heptane were both active and showed low catalyst leaching (Table 10.2) but differed in the selectivity towards hydroamination and telomerisation. These two systems were then tested in continuous experiments in the miniplant. The results are shown in Figs. 10.12 and 10.13.

Table 10.2 Average catalyst leaching into the non-polar product phase during miniplant operation

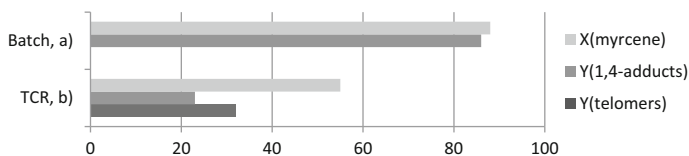| Element	TMS-system catalyst leaching	
	Acetonitrile/*n*-heptane	Dimethylformamide/*n*-heptane
Pd [ppm]	3(0.6%)	2(0.5%)
P [ppm]	6(0.9%)	4(0.5%)

Fig. 10.12 Comparison of batch and miniplant experiments (TMS-System: ACN/*n*-heptane). Conditions: *TMS-System* acetonitrile/*n*-heptane (40:60), $Pd(CF_3CO_2)_2$/DPPB, c(cat.) = 0.454 mol%, M/P = 1:8, p(argon) = 5 bar, T = 110 °C, c(substrates) = 0.1667 mol/l, (**a**) TCR: 100 rpm, T = 4 h; (**b**) batch: 450 rpm, t = 3 h
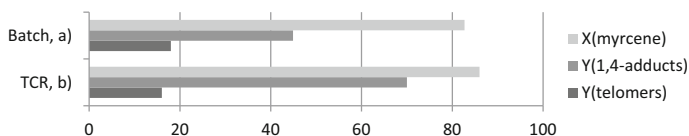

Fig. 10.13 Comparison of batch and miniplant experiments (TMS-System: DMF/n-heptane). Conditions: *TMS-System* dimethylformamide/*n*-heptane (40:60), $Pd(CF_3CO_2)_2$/DPPB, c(cat.) = 0.454 mol%, M/P = 1:8, p(argon) = 5 bar, T = 110 °C, c(substrates) = 0.1667 mol/l, (**a**) TCR: 100 rpm, T = 4 h; (**b**) batch: 450 rpm, t = 3 h

The results of the ACN/*n*-heptane system differ significantly from the laboratory results. The catalyst activity and selectivity towards the hydroamination products are very low. However, large amounts of telomerisation products are formed, which is a strong indicator, that either the ligand concentration in the catalyst phase or the overall catalyst concentration is too low. This controlling effect was also observed by *Johnen* and in previous laboratory experiments (Fig. 10.5). The reaction system can be shifted between hydroamination and telomerisation by catalyst and ligand concentrations, where low concentrations favour the telomerisation [9, 10]. During miniplant operation, the precipitation of ligand could be observed at the interface between the two solvents in the phase separator. It was conducted that the solubility of the ligand DPPB in the solvent acetonitrile is too low, so precipitation occurs when the catalyst phase is cooled down after the reaction. This behaviour was not observed in the laboratory because of the different preparation procedures and temperatures. As a result the alternative system DMF/*n*-heptane was tested, as the polar solvent DMF possesses significantly better solubility for the catalyst system. The results of the miniplant experiment with the TMS-system DMF/*n*-heptane are shown in Fig. 10.13. Only the polar solvent was changed in comparison with the previous experiment, all other process parameters remained unchanged.

The activity of the system is significantly increased in comparison with the acetonitrile-based TMS-system. With a myrcene conversion of 86 and 70% yield of hydroamination products, the performance of the laboratory experiments can be reproduced and even be exceeded. The formation of small amounts of telomers is a result of the coordinating nature of the polar solvent DMF, which can also act as a ligand in the catalytic system and was also observed in batch experiments (Fig. 10.6). The comparison of both TMS-systems illustrates the importance of the solvent for the performance of the catalyst.

Another important aspect of every continuous process is the loss of the catalyst into the product phase (catalyst leaching). It has a massive impact on the economy of a process and can determine if a process is realised or rejected. Both TMS-systems tested in the continuous hydroamination and telomerisation show low catalyst leaching (Table 10.2) which shows that TMS-systems can be a demanding but effective tool for catalyst recycling. However, the TMS-system has to be tailored to the demands of each chemical reaction (polarity, effects on catalysis) and not all effects can be determined in batch experiments. This shows the importance of continuous experiments in the development of new catalytic processes with renewable resources.

10.4 Conclusion and Outlook

The transfer of a chemical reaction from batch to continuous scale poses a great challenge as a result of the variety of influencing factors that have to be considered. In addition to the catalysis, aspects such as solubility, catalyst recycling and handling have to be taken into consideration. The combination of hydroamination and

telomerisation of the renewable *β*-myrcene with TMS-systems allows the atom-efficient synthesis of terpenyl amines and the efficient recycling of the precious transition metal catalyst.

For the production of terpenyl amines, a Taylor-Couette reactor has been implemented into a miniplant with continuous catalyst recycling by thermomorphic multicomponent solvent systems. High yields of the desired products (70% 1, 4-adducts, and 16% telomers) were generated while maintaining a leaching of only 2/4 ppm Pd/P in the TMS-system DMF/*n*-heptane. This shows that the TCR is a promising reactor concept for homogeneous catalysis, as it combines the advantages of CSTR (good mixing) and PFR (plug-flow behaviour with low back-mixing).

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