

**Sol-gel processes in catalysis: catalyst synthesis,  
application, recycling and combination to tandem  
reactions in microemulsions**

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Whether women are better than  
men I cannot say - but I can say  
they are certainly not worse

**Golda Meier**

## Abstract

Palladium, rhodium and manganese catalysts were immobilized on hydrophilically and hydrophobically modified silica by sol-gel method and applied in a variety of reactions in aqueous solutions e.g. microemulsions or aqueous-micellar solutions. In this context more environmentally friendly and less expensive reaction processes were developed. On the one hand aqueous solutions with surfactants and organic solvents as additives represent a greener alternative to conventional solvents. On the other hand the application of heterogeneous sol-gel immobilized catalysts in the process allows the catalyst recovery and reuse after reaction and easy product separation from the reaction mixture. In dependency of catalyst precursor and immobilization method different activities and stabilities of the catalysts were obtained. The overall efficiency of the catalyst in desired reactions was expressed by catalyst efficiency  $\eta$  which was estimated from recycling and immobilization efficiencies, number of catalytic runs, comparison to homogeneous reaction and pore efficiency (diffusion limitations).

Heck coupling reaction was catalyzed by sol-gel immobilized palladium catalysts in aqueous one phase microemulsion consisting of mainly water/ surfactant and propanol as cosurfactant. A variety of haloarene and styrene or acrylic acid and derivatives were used as reactants for the synthesis of pharmaceutically important *trans*-stilbene products. Especially the reaction of iodo- and bromobenzene with styrene was applied for kinetic investigations with palladium acetate immobilized on hydrophobic phenyl-modified silica. The obtained microporous catalyst could be recycled up to 6 times without leaching and full conversion was achieved after 6-8 hours with >99% selectivity. Also palladium, manganese and a mixture of palladium-manganese catalysts were immobilized on silica by the same method and applied in epoxidation of styrene and *trans*-stilbene in microemulsion. Both reactions could be combined to a tandem process with one or more different catalysts present from the beginning of the reaction.

Enantioselective hydrogenations of itaconic acid and derivatives were catalyzed by a  $[\text{Rh}(\text{cod})\text{Cl}]_2/(2S,4S)\text{-BPPM}$  catalyst-ligand complex in methanol and aqueous-micellar solutions at  $1.1 \cdot 10^5$  Pa hydrogen pressure. It was shown that not only the support material and the catalyst influences the reaction but also the type of substrate. Catalysts immobilized on hydrophilic surfaces are preferred for the reactions with hydrophilic substrates e.g. itaconates and vice versa. The immobilization of the catalyst in the presence of a ligand is more difficult because of catalyst deactivation during the immobilization process and air sensitivity of the complex.

At least the recycling process with the sol-gel immobilized palladium catalysts discussed before was compared with catalyst and product recycling from a three phase microemulsion system with a homogeneous catalyst. As model reaction the Suzuki coupling of 4-chlorobenzenboronic acid and 1-chloro-2-nitrobenzene to 4'-chloro-2-nitrobiphenyl as important intermediate for Boscalid<sup>®</sup> synthesis was chosen. The reaction was carried out in aqueous water/CTAB/propanol or three phase heptan/water/Novel8 microemulsion system with PdSPhos and PdTPPTS complexes as catalysts.

## *Zusammenfassung*

Palladium-, Rhodium- und Mangankatalysatoren wurden auf hydrophil und hydrophob modifizierten Silika mittels der Sol-Gel Methode immobilisiert und in einer Vielfalt von Reaktionen in wässrigen Lösungen angewendet. In diesem Zusammenhang wurden umweltfreundlichere und kostensparendere Konzepte zur Reaktionsführung entwickelt. Einerseits wurden tensidhaltige wässrige Lösungen mit organischen Zusatzstoffen eingesetzt, welche eine grüne Alternative zu konventionellen Lösungsmittelsystemen darstellen. Andererseits ermöglicht der Einsatz von Sol-Gel immobilisierten Katalysatoren das Wiederverwenden der Katalysatoren nach der Reaktion und eine leichte Abtrennung des Produktes. Je nach Art des Precursors und der Immobilisierungsmethode wurden unterschiedliche Katalysatoraktivitäten und Stabilitäten erhalten. Die Nutzung des Katalysators für die gewünschte Reaktion lässt sich durch die Katalysatoreffizienz  $\eta$  ausdrücken, die aus der Recycling- und Immobilisierungseffizienz, Anzahl der Reaktionen, aus dem Vergleich mit der homogenen Reaktion und dem Porennutzungsgrad (Diffusions-limitierung) abgeschätzt wird. Die Heck Kupplungsreaktion wurde mit Sol-Gel immobilisierten Palladium Katalysatoren in wässriger einphasiger Mikroemulsion bestehend zum größten Teil aus Wasser, Tensid und Propanol als Cotensid durchgeführt. Eine große Vielfalt von Reaktanden wie Haloarene und Styrol oder Acrylsäure und deren Derivate wurden für die Synthese von pharmazeutisch wichtigen *trans*-Stilben Produkten eingesetzt. Speziell die Reaktion von Iodo- oder Bromobenzol mit Styrol, katalysiert durch das hydrophobe Sol-Gel-immobilisierte Palladium acetat wurde ausführlich kinetisch untersucht. Der entstandene mikroporöse Katalysator wurde sechsmal ohne Katalysatorverlust (Leaching) wiederverwendet, voller Umsatz und Selektivität wurden nach 6-8 Stunden erhalten. Auch Palladium-, Mangan- und Palladium-Mangankatalysatoren wurden mit der gleichen Methode immobilisiert und in der Epoxidierung von Styrol und *trans*-Stilben in Mikroemulsion eingesetzt. Beide Reaktionen wurden zu einem Tandemprozess mit einem oder mehreren Katalysatoren, die von Anfang an in der Reaktionslösung vorhanden waren, kombiniert. Die enantioselektive Hydrierung von Itaconsäure und Derivaten wurde mit dem Sol-Gel immobilisierten  $[\text{Rh}(\text{cod})\text{Cl}]_2/(2S,4S)$ -BPPM Komplex in Methanol und wässrig-mizellaren Lösungen bei  $1.1 \cdot 10^5$  Pa Wasserstoffdruck durchgeführt. Es wurde gezeigt, dass nicht nur der Katalysator und das Trägermaterial, sondern auch das Edukt eine entscheidende Rolle bei der Reaktionsführung spielen. Katalysatoren, immobilisiert auf hydrophilen Oberflächen, werden bevorzugt in Reaktionen mit hydrophilen Stoffen eingesetzt und umgekehrt. Die Immobilisierung des Katalysators mit Liganden ist wegen der Luftempfindlichkeit und Katalysatordeaktivierung während des Immobilisierungsprozesses viel schwieriger. Zuletzt wurde die Katalysator- und Produktabtrennung mithilfe des Sol-Gel immobilisierten Katalysators mit der Abtrennung aus dem dreiphasigen Mikroemulsionssystem verglichen, am Beispiel der Suzuki Kupplung von 4-Chlorophenylboronsäure und 1-Chloro-2-Nitrobenzol zum Zwischenprodukt der Boskalidsynthese, 4'-Chloro-2-nitrobiphenyl. Die Reaktion fand in ein- und dreiphasigen Mikroemulsionen mit homogenen PdSPhos oder PdTPPTS Komplexen als Katalysator statt.

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# 1 Introduction and Motivation

The recent trends in the modern chemical research are on the one side the development of greener processes to avoid the pollution of the environment and on the other side a search for new alternative energy sources because of the natural resources deficit in the next 10-20 years and also the invention of new drugs e.g. against cancer, HIV etc.

More environmentally friendly processes can be realized for example by reusing of solvents, catalysts and organic components after each reaction to reduce the costs of the process and the pollution of the atmosphere, by applying of green solvents (e.g. water or ionic liquids) in the reaction process and by synthesis of the desired products in tandem reactions (atom economy). For this purpose the use of sol-gel immobilized catalysts may be highly beneficial. Sol-gel process is a method applied in material science for the production of stable solid materials e.g. silicon or titanium oxides from metal alkoxides precursors. Sol-gel materials have many applications in different areas of human life, for example in production of drugs and fine chemicals as well as in wastewater treatment.

One of the important fields of the sol-gel applications is in catalysis: e.g. the synthesis of heterogeneous catalysts through the entrapment of metal precursors (homogeneous catalysts) into silica or titanium matrix by a sol-gel method. The materials synthesized in such a way are very stable, can be applied in a variety of reactions and can be easily removed from the reaction mixture by filtration and reused several times in the next reaction steps.

The aim of this work is the application of the sol-gel immobilized catalysts in a variety of reactions e.g. hydrogenations, epoxidations and coupling reactions and the combination of these reaction steps in tandem reactions for the production of pharmaceutically important precursors. The reactions should be carried out not in conventional organic solvents, but in aqueous-micellar solutions or microemulsions for greener process management. The general mechanism of the sol-gel process is well known, but the influence of the immobilization of different metals in the silica matrix was studied only on the examples of selected reactions. In this work we try to find out which parameters influence the activity and stability of sol-gel immobilized catalysts and to quantify the efficiency of these catalysts in comparison to homogeneous catalysts gained by recycling and reuse of the catalyst after several reaction steps, loss of metal precursor from silica surface after catalyst synthesis and reaction as well as by reactivity of the heterogeneous

catalyst. Also the influence of diffusion limitations on the heterogeneous reactions has to be investigated and the advantages and disadvantages of using of the microemulsions and aqueous-micellar solutions as green solvents have to be studied.

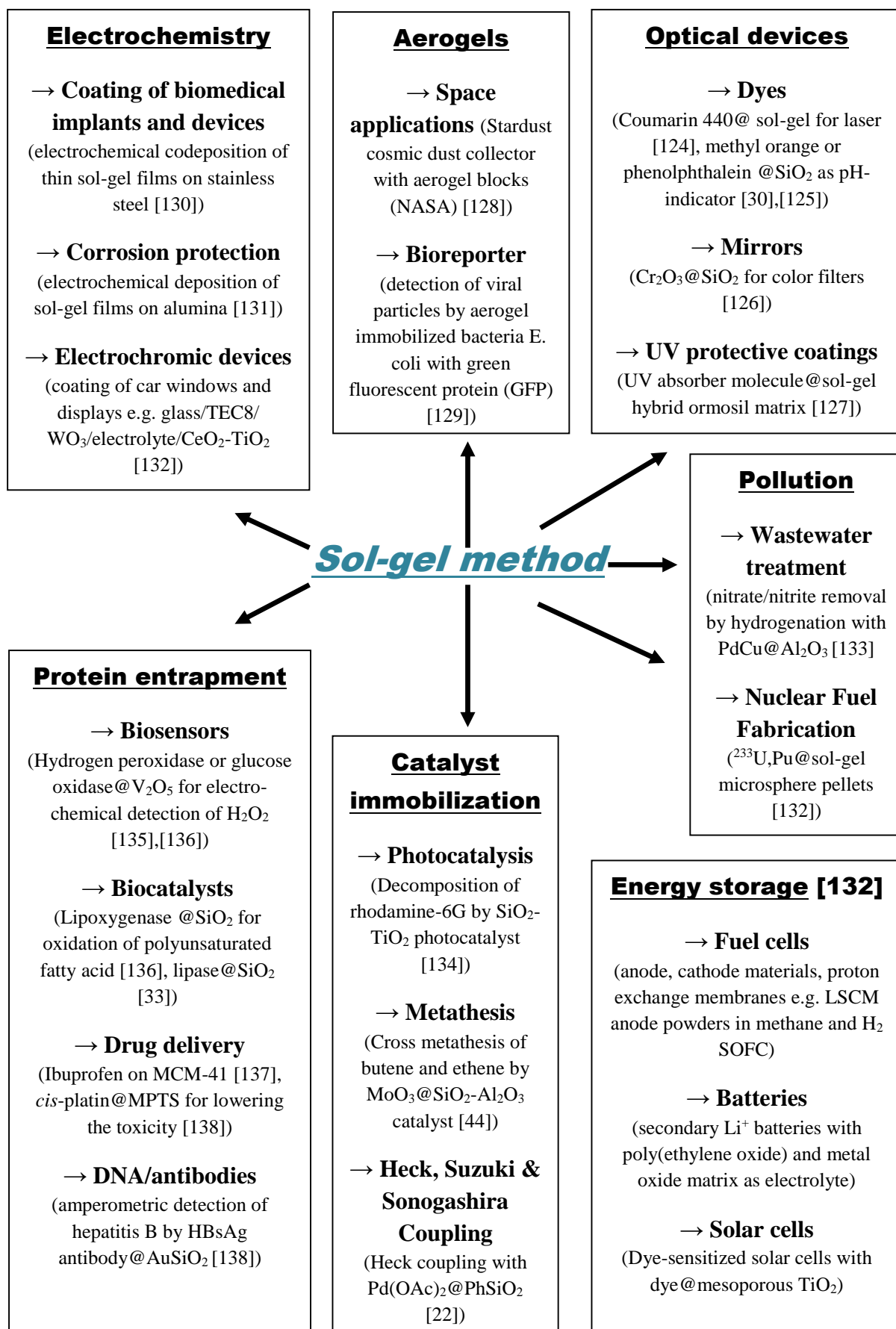
## 2 Theoretical background

### 2.1 Sol-gel technology

Many definitions of sol-gel processes exist. In material science a sol-gel process is a method for the production of porous solid materials (ceramics) from small molecules e.g. metal alkoxides, nitrides or sulfides by colloidal route. This method cannot be defined as a single technique because a broad variety of procedures exist. A distinction is drawn between aqueous and non aqueous routes with similar order of steps [1]: (a) Conversion of dissolved molecular precursors to the reactive state; (b) Polycondensation of activated molecular precursors into nanoclusters (Formation of colloidal solution or sol); (c) Gelation; (d) Aging; (e) Washing and (f) Drying/Stabilization. Different factors can affect the sol-gel chemistry: pH of the solution, additives, solvents, temperature and catalysts.

Applications of these materials in human life prepared by sol-gel methods are shown in Scheme 1. The first significant industrial products of sol-gel technology were mixed oxide powders of radioactive elements such as uranium and thorium for nuclear fuel fabrication and for radiation protection. The second example of industrial application areas is in the production of coatings for glasses and windows, self-cleaning and anti-reflective (UV-protecting) coatings on the mirrors of cars as well as for corrosion protection of metals and very stable protection materials in space applications. Materials produced by sol-gel method found also application in medicine (coatings for biomedical implants, biosensors for the detection of viral particles) and in pharmacy (entrapment of drugs into sol-gel matrix e.g. Ibuprofen or *cis*-platin).

More actual example of the technological application of sol-gel materials are in the field of catalysis, which will be introduced and discussed as a part of this scientific work. Metal precursor e.g. palladium, rhodium and manganese can be immobilized on silica support materials by sol-gel method and the heterogeneous catalysts formed in this way can be applied in a variety of reactions with further recycling opportunities.



**Scheme 1:** Applications of the sol-gel process

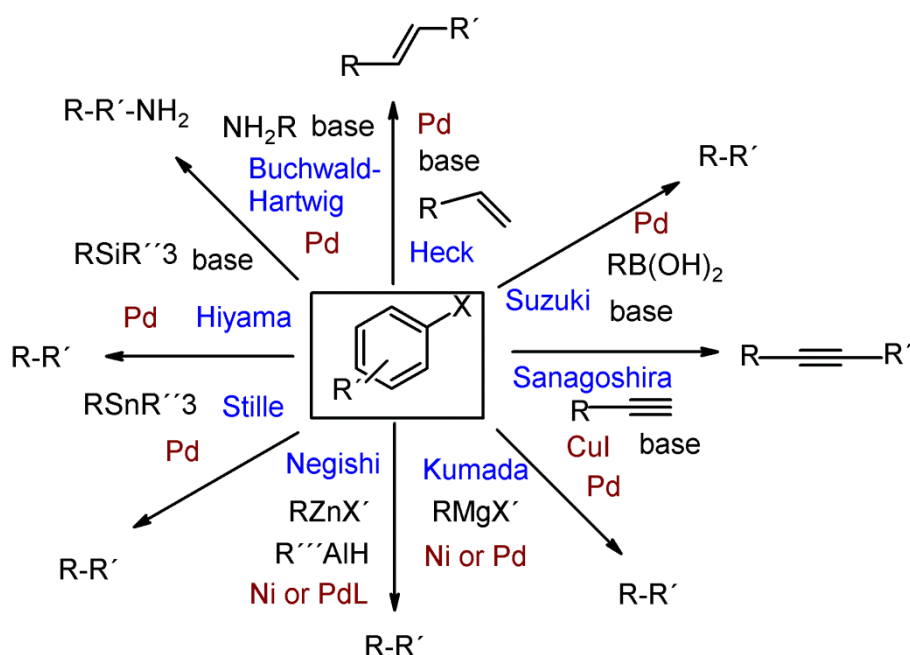
## 2.2 Catalytic reactions

A catalytic reaction is a chemical reaction which is accomplished via a substance called catalyst. The catalyst as a species increases the rate of the chemical reaction due to decreasing its activation energy. The catalyst is a part of the reaction but is not consumed during the process and can be deactivated or destroyed by some additives (catalyst poisons) during the reaction. Catalytic reactions are classified in homogeneous and heterogeneous. Catalytic reaction in one phase e.g. liquid phase are called homogeneous catalysis and reactions in two or more different phases e.g. two gases react with a solid catalyst are called heterogeneous catalysis. Both concepts are also subdivided in several terms which depend on the catalysts. The most reactions used in industry are carried out with heterogeneous catalysts. These catalysts can be synthesized for example from homogeneous catalyst precursors and a support material and can be reused several times after the reaction. Homogeneous catalysts can be codissolved in a reaction medium with the reactants. These catalysts can also be separated and reused after the reaction e.g. through extraction or ultrafiltration, but the separation process is much more difficult to handle.

## 2.3 Cross-coupling reactions

Coupling reactions are reactions in organic chemistry where two hydrocarbon compounds are coupled via metallic catalyst. An organic electrophilic halide  $R'X$  reacts with mostly metallic nucleophilic compound  $RM$  with a formation of a carbon-carbon bond to a product  $R'R$ . There are two types of coupling reactions: cross couplings between two different reaction partners, for example, Heck coupling and homocouplings between two identical reactions partners, for example, coupling of two iodobenzene to biphenyl.

E. Nigishi, R. F. Heck and A. Suzuki have received the Nobel Prize in Chemistry in 2010 for their research about palladium catalyzed coupling reactions in organic chemistry. Most of the cross coupling reactions are catalyzed by a palladium catalysts, but nickel (e.g.  $Ni(dppb)Cl_2$  in *Kumada* coupling or  $Ni(PPh_3)_4$  in *Negishi* coupling) or copper catalysts (e.g.  $CuI$  in *Sonogashira Coupling*) are also common. The broad variety of coupling reactions is presented in Scheme 2:



**Scheme 2:** A variety of cross coupling reactions

In the last years more different types of coupling reactions were invented. 1998 Fukuyama et al. presented palladium catalyzed transformation of thioesters and organozinc compounds to ketones (*Fukuyama coupling*). 2000 the *Liebeskind-Srogl coupling* was presented as a palladium catalyzed reaction of boronic acids and thioesters to ketones.

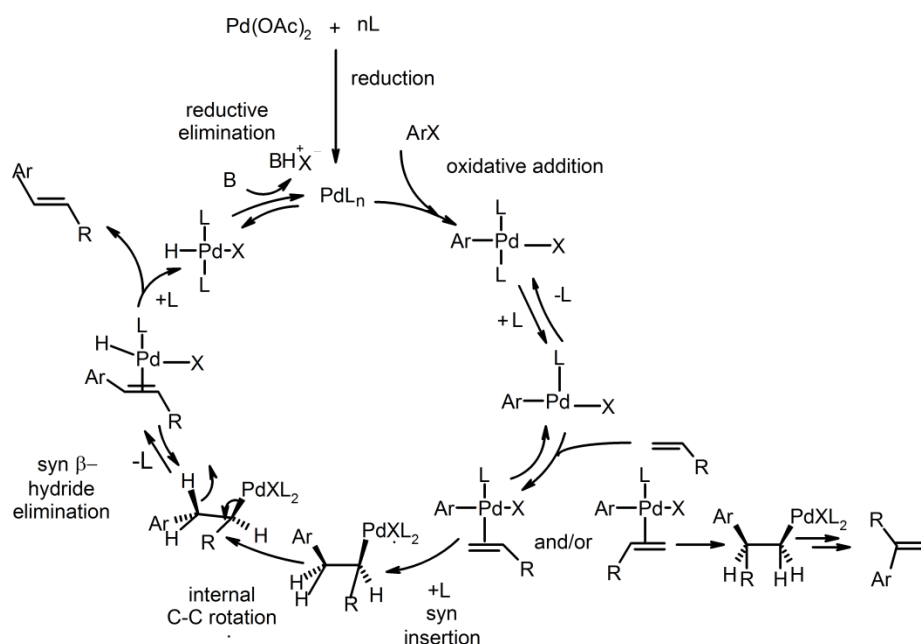
Cross-coupling reactions are one of the most important reactions in the pharmaceutical industry, synthesis of fragrances, synthesis of sun screening agents and the production of fine chemicals. 1995 Danishevsky et al. [2] published the synthesis of Paclitaxel (Taxol®), which is now one of the most frequently applied anticancer drugs. The most important step of this reaction is the ring closing intramolecular *Heck reaction*. 1996 Dawson et al. [3] published the first stereospecific synthesis of Michellamin B, which is one of the strongest tetrahydroisochinoline alkaloids (anti-HIV viral replication inhibitors). The main step of this synthesis is the formation of three aryl-aryl bonds via *Suzuki coupling*. Also the herbicide Prosulfuron<sup>TM</sup>, antiasthma agent Singulair<sup>TM</sup> and analgesic drug Naproxen [4] are synthesized from styrene derivatives via Heck coupling by palladium acetate catalyst.

One of the benefits of the Heck coupling reaction is the production of *trans*-products. The catalytic cycle for the Heck reaction was proposed 1974 by H.A. Dieck/ R.F. Heck and involves a series of transformations around the palladium catalyst. The palladium (0) compound required in this cycle is generally prepared in situ from a palladium (II) precursor, for example

through the reduction by monophosphine ligand  $\text{PPh}_3$ . Also the reduction of the catalyst by alkenes, amines or ammonium salts is possible.

The mechanism of the Heck coupling reaction is shown in Scheme 3. First step of the catalytic cycle is the *oxidative addition* of aryl halide  $\text{Ar-X}$  to the  $\text{Pd}^0\text{L}_2$  catalyst and the formation of  $\delta$ -aryl-palladium (II) halide (*trans*- $\text{ArPdL}_2\text{X}$  complex). The second step is the addition of the second reaction partner after the dissociation of one ligand and the formation of a  $\pi$ -palladium (II)-complex. This reaction, also called *carbopalladation*, is responsible for the *trans*-regioselectivity of Heck couplings. Then the alkene inserts (*syn-insertion*) into the palladium-carbon bond and the  $\delta$ -intermediate complex is build. The next step is *syn- $\beta$ -hydride elimination* with the formation of a  $\pi$ -hydrido-palladium-complex and the separation of the alkene. This complex reacts with a base and is regenerated in the next reversible step by a *reductive elimination* to palladium (0). The role of the base in this reaction is to shift the equilibrium towards the  $\text{Pd}(0)$  catalyst.

In comparison to Heck coupling reaction the general mechanism of other couplings is very simple. The first step is also the oxidative addition of the aryl halide to  $\text{Pd}(0)$  complex and the formation of  $\text{Pd}(\text{II})$  complex. Then the mechanism of the coupling differs through a second step (*transmetallation* with the second edukt e.g.  $\text{XPhB}(\text{OH})_2$  in *Suzuki coupling*) and the formation of  $\text{ArPdL}_2\text{R}'$  complex. There are also no *syn*-addition and  $\beta$ -hydride elimination steps. The third step can be the *rearrangement* of  $\text{R}'$  from *trans*- to *cis*- position (e.g. *Negishi coupling*) followed by the reductive elimination. Or the product is directly separated after the second step and the catalyst complex is regenerated through the *reductive elimination* step (e.g. *Suzuki coupling*).



**Scheme 3:** Proposed mechanism of the Heck coupling reaction when the palladium acetate precursor and the monophosphine ligand L is used [5].

## 2.4 Hydrogenation and epoxidation reactions

### 2.4.1 Hydrogenation

*Hydrogenations* are reactions where the C-C, C-O and C-N- bonds of substrates are treated with hydrogen. Molecular hydrogen  $\text{H}_2$  acts as hydrogen source, produced by the steam reforming process from hydrocarbons. It can also be generated from hydrogen-donors e.g. hydrazine, dihydronaphthalene and formic acid (transfer hydrogenation).

A distinction is drawn between homogeneously and heterogeneously catalyzed hydrogenation reactions. Asymmetric homogeneous hydrogenations are often used for the production of pharmaceutically important products and will be explained in the next chapter. Heterogeneous catalysts are commonly used in industry: in petrochemical processes (hydrocracking of heavy residues to diesel), processing of vegetable oils (converting of vegetable oils to margarine compounds), coal hydrogenation to hydrocarbons for use in synthetic fuel (Bergius process) and the most famous example the Haber-Bosch process for ammonia production from hydrogen and nitrogen via iron catalyst. The mechanism of the heterogeneously catalyzed hydrogenation [6] differs from homogeneously catalyzed hydrogenation. First the reactant (e.g. ethene) and hydrogen gas pass through a catalyst bed into the pores of the catalyst. Then hydrogen molecules and concurrently reactants are adsorbed on the transition metal surface. After this, two hydrogen atoms are transferred to each C-atom of the reactant (*syn*-addition) and a  $\delta$ -bound

is formed from a C-C double bond. Finally the catalyst-carbon bond breaks and the product formation occurs through desorption from catalyst surface.

#### 2.4.2 Enantioselective hydrogenation

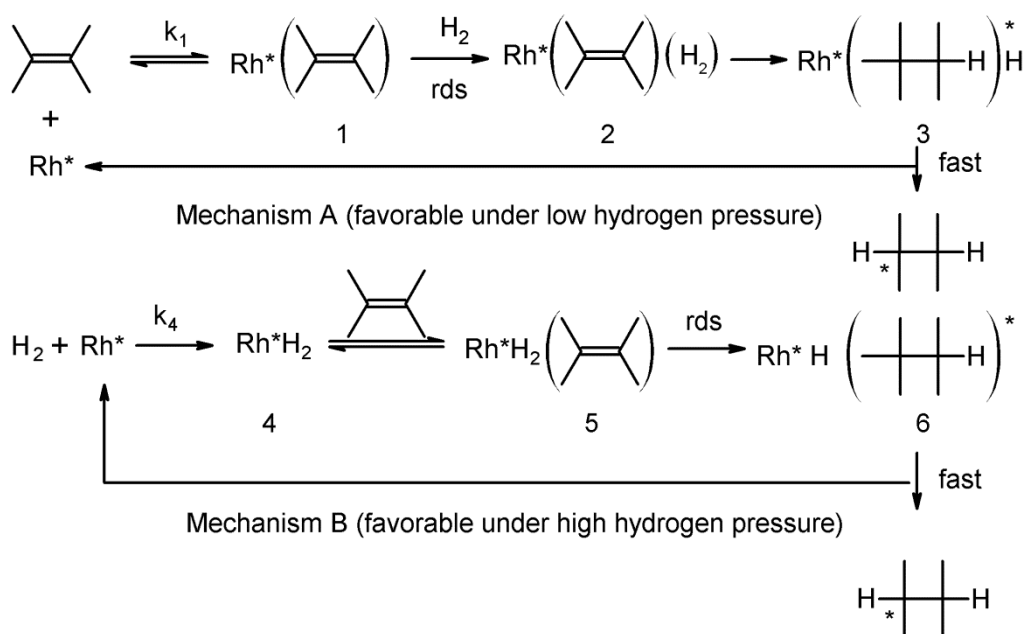
Rhodium is one of the first noble metals, which were used in a homogeneous catalysis. Despite the high price of this metal, it is very often applied in many industrial processes like hydrogenations and hydroformylation reactions.

Hydrogenations reactions are also often used for the production of fine chemicals and in pharmaceutical industry. For the synthesis of many chemicals the *asymmetric hydrogenation* catalyzed by homogeneous enantioselective transition metal-ligand complexes [7] is necessary. The synthesis of *L-Dopa* (3,4-Dihydroxyphenylalanine), which is an important medicine for the therapy of Parkinson disease, was the first metal catalyzed asymmetric hydrogenation with  $[\text{Rh}(\text{DIPAMP})(\text{cod})]^+\text{BF}_4^-$  catalyst used in industry, developed by W.S. Knowles (Monsanto company). *Aspartame* (*L*-Aspartyl-*L*-phenylalanine-1-methylester) is a sweetening agent and was synthesized by Aventis Company through a hydrogenation with the  $[\text{Rh}/\text{DeguPHOS}]$  catalyst. The hydrogenation reactions are very important steps in the synthesis of HIV-protease inhibitor *Indinavir* (Merck company), antibiotic *Carbapeneme* ( $\beta$ -Lactam), *Biotin* (Vitamin H) and agrochemical (*S*)-*Metolachlor* (Novartis company).

There are different types of transition metal catalysts which are applied in enantioselective and not enantioselective hydrogenation reactions. The *Wilkinson's catalysts* e.g. chloro(triphenylphosphine)rhodium(I)  $\text{RhCl}(\text{PPh}_3)_3$  or  $\text{RuCl}_2(\text{PPh}_3)_3$  contain the catalyst metal and the monodentate phosphorus ligands (one bound to a central metal atom in coordination complex) and a chlorine ligands. This type of catalysts is often used in the hydrogenations of alkene, but has to be hydrogenated by  $\text{H}_2$  (oxidative addition) before the reaction to transform the complex into the hydride complex. *Transition metal hydride complexes* e.g.  $\text{Rh}(\text{CO})(\text{PPh}_3)_2\text{H}$  are also applied in the hydrogenations of alkenes and can be used without activation by hydrogen before the reaction. The chelate complexes (hydrogenation catalysts or *Noyori-type catalysts*) consists of bidentate or polydentate ligands e.g. BINAP and can be applied in asymmetric hydrogenations. Also ionic transition metal complexes are used in asymmetric catalysis, they can be cationic e.g.  $[\text{Rh}(\text{cod})(\text{PPh}_3)_2]^+$  or anionic  $[\text{CoH}(\text{CN})_5]^{3-}$ . The mechanism with cationic rhodium complex was already described for the hydrogenation of ethene [7] and consists of alkene addition to the rhodium-ligand complex, oxidative addition of

hydrogen (rate limiting step), insertion and ethane elimination followed by catalyst complex regeneration.

To test the different ligands and catalysts and to investigate the reaction kinetics, some typical *model substances* can be applied. These substrates were often analyzed in a variety of reactions by different research groups. For the enantioselective hydrogenation of C-C double bonds 2-acetamidoacrylic acid or derivatives, itaconic acid or derivatives or  $\alpha$ -acetamidocinnamic acids are often used as model substances. The general mechanism of the asymmetric hydrogenation of acids and esters catalyzed by rhodium complexes containing  $[\text{Rh}(\text{cod})\text{Cl}]_2$  or  $[\text{Rh}(\text{cod})^+\text{ClO}_4^-]$  as catalyst precursor and chiral BPPM or PPPM ligand is similar to the mechanism described above for the hydrogenation of ethene and was showed first 1980 by Ojima et al. [8] for the asymmetric hydrogenation of itaconic acid and  $\alpha$ -(acylamino) acrylic acid at low and high hydrogen pressure:

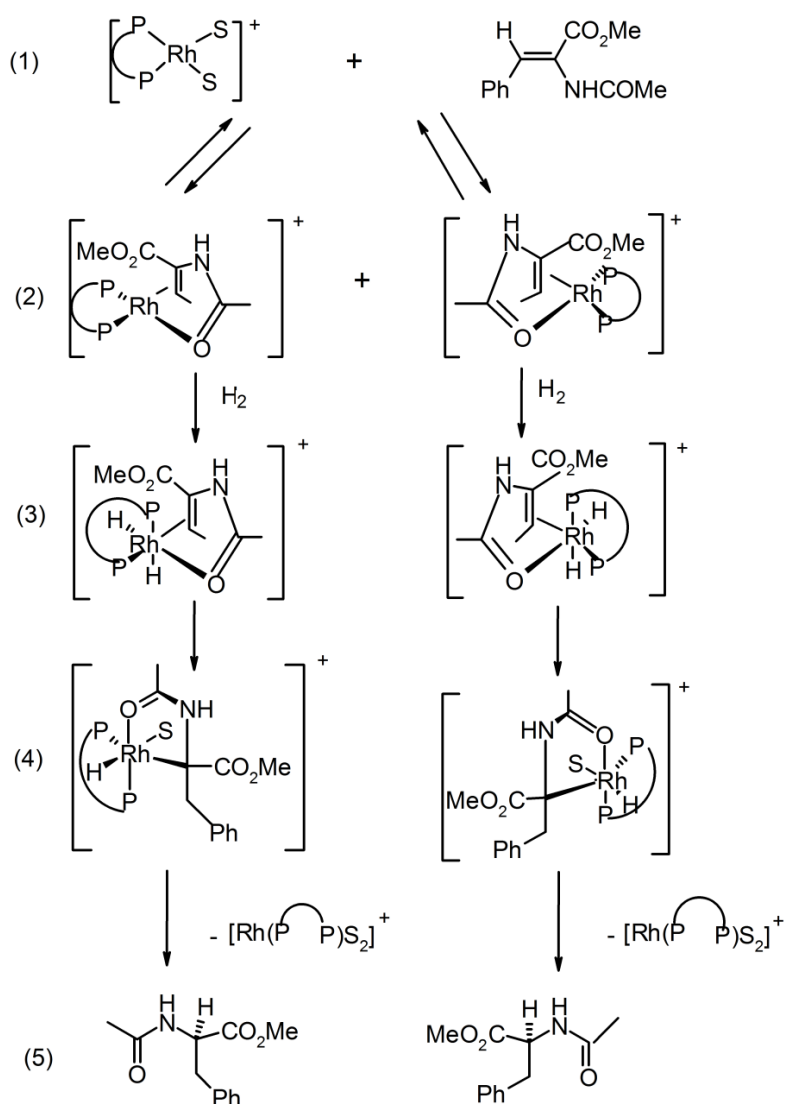


**Scheme 4:** General mechanism of the enantioselective hydrogenation of olefins to saturated hydrocarbons with rhodium complexes at low and high pressure (rds= rate determining step) [8].

At low pressure the rate limiting step is the oxidative addition of hydrogen to the rhodium-substrate intermediate and at higher pressure the limiting step is hydrogen migration giving the rhodium hydride intermediate. Hydrogen pressure has a high influence on the enantioselectivity of the reaction. At higher pressure the enantioselectivity of the favored product decreases and the production of other isomer is preferred e.g. hydrogenation of (*Z*)- $\alpha$ -benzamidocinnamic acid

in ethanol with  $[\text{Rh}(\text{cod})^+\text{ClO}_4^-]/\text{BPPM}$  complex yields 83.8 ee% of R-isomer at 1 atm and 21.2 ee% at 20 atm.

To understand the preferred formation of only one product, a more detailed view inside the mechanism of the reaction is necessary (Scheme 5). In the first step the catalyst complex containing rhodium precursor e.g.  $[\text{Rh}(\text{cod})\text{Cl}]_2$ , chiral ligand e.g. (2*S*,4*S*)-BPPM and 2 solvent molecules (S) e.g. methanol reacts with the substrate to the square-planar complex. The solvent molecules in rhodium complex are displaced by the substrate, which bonds to the complex by a double bond and an oxygen atom. Two diastereomers are possible in dependency of the coordination of the olefin to rhodium (major Re or minor Si isomer). After the oxidative addition of the hydrogen (rate limiting step), the isomers are transformed into the octahedral dihydrides. The coordinated olefins insert into Rh-H bonds and  $\delta$ -complexes are formed. After the reductive elimination of the complexes, the enantioselective products are produced: R-product (left side) from major R-isomer and S-product (right side) from minor S-isomer. The product formed from minor isomer predominates because of higher reactivity (Minor-major principle).

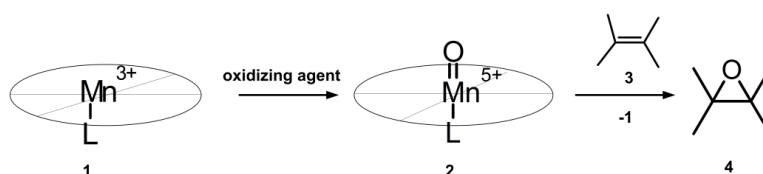


**Scheme 5:** ‘Unsaturated’ mechanism of the hydrogenation of Methyl (Z)- $\alpha$ -acetamidocinnamate with rhodium-ligand complex [9]

### 2.4.3 Epoxidation

*Epoxidation* is a reaction of alkenes with oxidizing agents to epoxides (oxirane) and is one of the most important methods for the formation of C-O bonds. As oxidizing agent's a variety of chemical substances can be used e.g. *meta*-chloroperbenzoic acid (mCPBA) or other peracids for the epoxidation of alkene and olefine (*Prilezhaev Reaction*). Also potassium peroxymonosulfate  $\text{KHSO}_5$  (oxone) is an oxidizing agent in enantioselective *Shi-epoxidation* of alkene with fructose derived catalyst as well as hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) or TBHP in *Sharpless epoxidations* of prochiral allylic alcohols with  $\text{Ti}(\text{OiPr})_4$  catalysts and asymmetric tartrate ligands. Other oxidizing agents are sodiumperiodate  $\text{NaIO}_4$ , oxygen  $\text{O}_2$  and  $\text{NaOCl}$  (bleach) in *Jacobsen-Katsuki epoxidation* for the formation of *cis*-substituted olefins via Mn-salen catalyst.

The function of the oxidizing agent is an oxygen transfer to the double bond of the olefine as shown in Scheme 6, at the example of the Jacobsen-Katsuki epoxidation. First the  $\text{Mn}^{\text{III}}$  catalyst e.g. manganese (III) acetylacetonate has to be oxidized to Oxo- $\text{Mn}^{\text{V}}$  species and then the oxygen has to be transferred to the substrate and the product formation is occurred. The transfer from the metal complex to the substrate is still under discussion: a concerted mechanism, via radicals or via a manganaoxetane intermediate is possible:

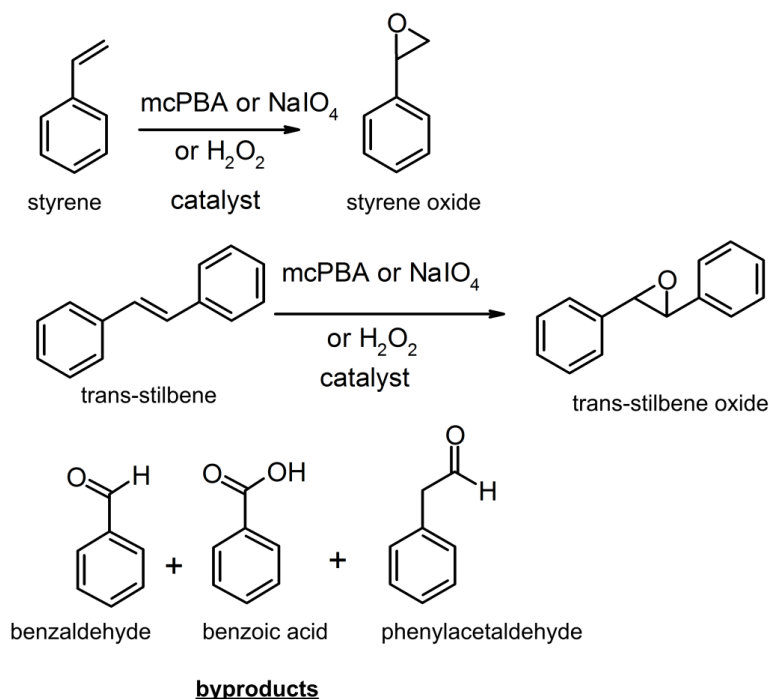


**Scheme 6:** Mechanism of a Jacobsen-Katsuki epoxidation [10]

Many epoxidation reactions are commonly catalyzed by manganese catalysts. Manganese species were found in many active centers of enzymes, which are responsible for selective epoxidation reactions. The manganese containing Monooxygenase enzymes catalyze the styrene epoxidation to carcinogen acting styrene oxide in human body.

Also reactions of the  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/\text{L}$  catalyst with hydrogen peroxide and different substrates [11] are reported in the literature.  $\text{Mo}(\text{CO})_6$ ,  $\text{MoO}_3$ ,  $\text{W}(\text{CO})_6$  are usually used for the epoxidation of cyclohexane with tert. butyl hydroperoxide TBHP as oxidizing agent [12] or vanadyl acetylacetonate for the oxidation of styrene with hydrogen peroxide [13] .

The disadvantage of the epoxidation reactions is the high amount of by-products (aldehyde, diol, ketone and acids) because of further oxidations of substrates and products as can be seen from Scheme 7. In the reaction of the more hydrophobic *trans*-stilbene hardly any byproducts can be obtained because of sterical hindrance. In comparison to *trans*-stilbene, the epoxidation of styrene yields a large spectrum of byproducts [14].



**Scheme 7:** Epoxidation of styrene and *trans*-stilbene

## 2.5 Catalyst immobilization

Catalyst immobilization processes can be explained as a binding of the molecular catalyst inside the inorganic support without substantial changes caused by the formation of insoluble solid structures. There is a variety of methodologies for the immobilization of catalysts inside porous materials. A distinction is drawn between different types of catalyst precursor and support interactions [15,16]: adsorption (van der Waals forces), encapsulation, covalent binding and electrostatic or ionic interaction.

The most frequently used method is the immobilization through covalent binding which allows the production of most stable heterogeneous catalysts whereas another distinction is drawn between the sequential and convergent approach. The catalyst can be immobilized on micro- or mesoporous silica by sol-gel method e.g. Heck reaction with palladium acetate immobilized on silica [17]. Another alternative is the immobilization of catalysts on the surface of mesoporous silica during the hydrothermal synthesis e.g. synthesis of palladium acetate on MCM-41 in the presence of cetyltrimethylammonium bromide as template followed by calcination in order to remove the template [18].

In comparison to this, the adsorption method is disadvantageous because of weak van der Waals interactions and resulting high amount of leaching. The stability of the catalyst can be improved

by modifying the surface of the support or the catalyst to allow hydrogen bonding to occur. For example enantioselective hydrogenation of dimethylitaconate or methyl- $\alpha$ -(acetamido)acrylate was catalyzed by chiral rhodium phosphine catalyst immobilized on silica by interaction between silanol groups of the support and H-atoms of sulfonic acid counter ion of ligand.

Encapsulation of the catalyst is a relatively complex process and does not require any physical interactions between support and catalyst and also no changes in catalyst structure can happen. The catalyst should be larger than the pores of the support material. The heterogeneous catalyst can be prepared by either formation of the support material around the catalyst or by assembling the catalyst within the pores of support material (ship-in-a-bottle synthesis). This method is widely used for the immobilization of metal salen complexes inside the supercages of zeolite e.g. for the epoxidation of styrene catalyzed by (*R,R*)-(salen)Mn-complex immobilized in zeolite [15].

Immobilization via electrostatic interaction (ion exchange) is a simple method for the entrapment of ionic catalysts. Clays, zeolites or ordered mesoporous silicates are surface-charged and can act as ion exchangers and bind metal cations and complexes as stable heterogeneous catalysts e.g. in enantioselective hydrogenation of dimethyl itaconate catalyzed by cationic diphosphine rhodium complex  $[\text{Rh}(\text{cod})\text{Cl}]_2/(\text{S,S})\text{-Me-Duphos}$  supported on Al-containing MCM-41, prepared by impregnation method [19].

## 2.6 Heterogeneously catalyzed reactions

The heterogeneously catalyzed reactions with inorganic supports are preferred in comparison to homogeneous reactions mainly because of the reusability of the catalysts and decreasing of the process costs. Although the following important critical factors often determine the viability of the desired process: stability of the catalyst (heterogeneity, metal and ligand leaching), catalyst reactivity (activity of the active species immobilized into the support), productivity of the process, easy separation, price and availability of the catalyst.

*Zeolites* are microporous framework aluminosilicate minerals e.g. NaY containing  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$  or  $\text{Mg}^{2+}$  ions. They are not only used in catalysis as support materials, but also as adsorbents, molecular sieves for molecule sorting by a size, in nuclear reprocessing and in production of laundry detergents. The advantages of using zeolite are their high surface areas and availability in nature (analcime  $\text{NaAlSi}_2\text{O}_6 \cdot \text{H}_2\text{O}$ , natrolite  $\text{Na}_2\text{Al}_2\text{Si}_3\text{O}_{10} \cdot 2\text{H}_2\text{O}$  or stilbite  $\text{NaCa}_4(\text{Si}_{27}\text{Al}_9)\text{O}_{72} \cdot 28\text{H}_2\text{O}$  minerals). One of the applications of zeolites in chemical reactions

is for example arylation of acrolein diethyl acetal with  $\text{Pd}(\text{NH}_3)_4$ , immobilized on zeolite NaY as catalyst [20], or Heck coupling reaction with basic  $\text{PdCl}_2$ , immobilized on CsX as catalyst [21].

*Mesoporous silica* is the most used support material for catalyst immobilization. The pores of the materials are larger than of microporous sol-gel materials in the range of 5-50 nm and the surface areas are about 1000  $\text{m}^2/\text{g}$ . The most common mesoporous silica are MCM-41 (Mobil crystalline materials or Mobil composition of material No 41), MCM-48 and Santa Barbara amorphous type SBA-15 with hexagonal array of pores [22]. The synthesis of these materials can be done by the preparation of silica frameworks by *sol-gel method* with surfactant as templates. After the process the template has to be removed by calcination. The catalyst can be used e.g. in epoxidation of *trans*-stilbene with Mn-MCM-41 [23] or Heck coupling reactions [24]. The other applications of these materials are in drug delivery or as biosensors filled with fluorescent dye.

The application of *activated charcoal* as support material is beneficial, because of the high activity of the formed immobilized catalysts. But this high activity can also cause by-reactions e.g. hydrodehalogenation of aromatic compounds in Heck coupling reactions.

Another catalyst type is *magnetic nanoparticles* which are synthesized from desired catalyst precursor and magnetic  $\text{Fe}_3\text{O}_4$  particles. After the reactions the catalysts can be separated by using an external magnetic field (*magnetofiltration*). There are different methods for the catalyst preparation. For example palladium can be impregnated into  $\text{Fe}_3\text{O}_4$  and used in Suzuki coupling reactions or hydrogenation of nitroarene [25]. Another option is the preparation by a sol-gel method for the immobilization of di(benzonitrile)dichloropalladium(II) with tetraethyl orthosilicate for Suzuki coupling reactions of bromobenzene and phenylboronic acid [26]. The more complex structure of the catalyst can be obtained by mixing of the  $\text{Fe}_3\text{O}_4\text{-NH}_2$  powder and  $\text{Pd}(\text{OAc})_2$  and reducing with  $\text{KBH}_4$  [27], this catalyst is commonly used in the Heck coupling reactions.

Homogeneous catalysts can also be immobilized into polymers, e.g. polyethylene glycol PEG, polystyrene or polyureas. For example  $\text{Mo}(\text{CO})_6$  catalyst was immobilized in polystyrene-bound Schiff base ligand and used in the epoxidation of alkene with *tert*.-butyl hydroperoxide (TBHP) [28],[29].

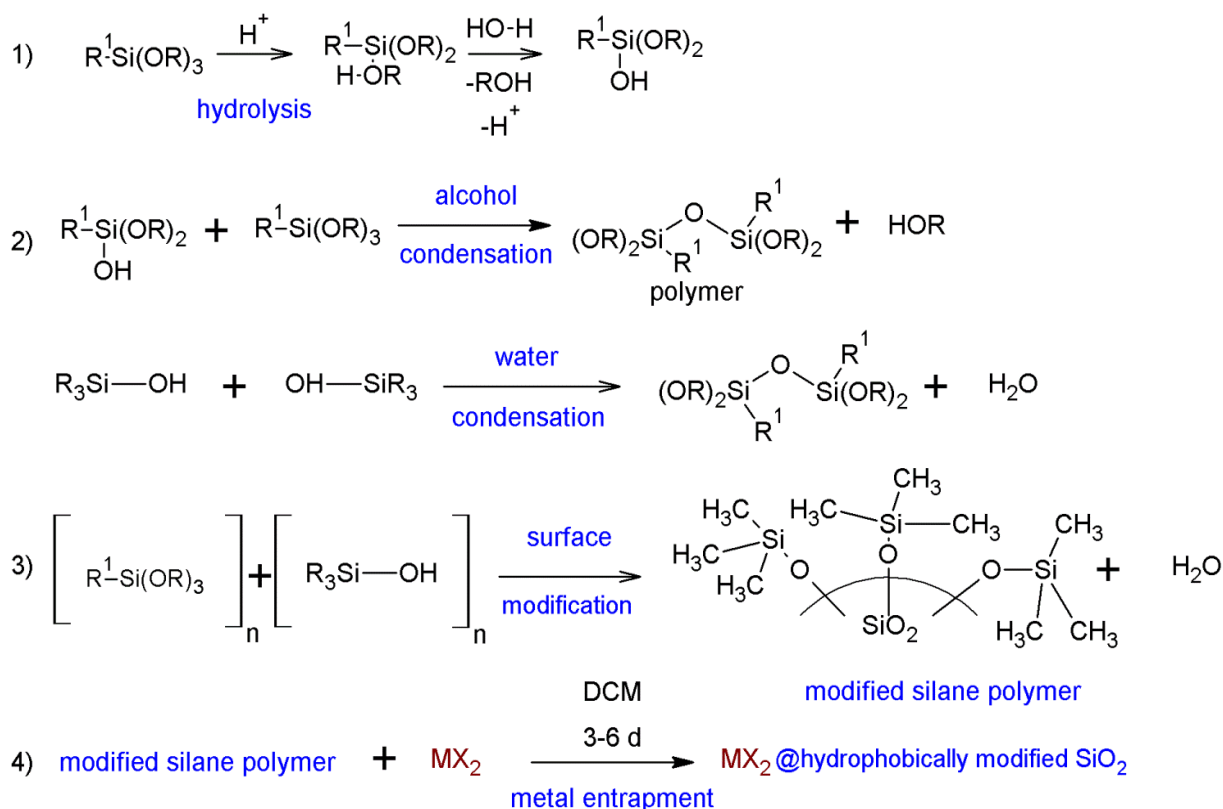
## 2.7 Preparation of the catalysts by sol-gel method

A general trend in catalysis is the transformation of homogeneous catalytic reactions into heterogeneous processes in which the active species are immobilized on solid support material, making the catalyst easy to recover from reaction mixtures, to reuse and to minimize waste. The entrapment of organic and organometallic compounds into sol-gel matrices is one of important techniques of catalyst immobilization. It can be used for different applications, e.g. photochemistry, chemical sensing and optics [30], biochemistry and enzyme technology [31],[32],[33]. Furthermore, this technique allows the immobilization of homogeneous catalysts in order to overcome the major drawback of homogeneous catalysis, the difficult separation of the products and catalysts after the reaction.

Sol-gel process can be described as the formation of an oxide network by polycondensation of different precursors in liquid. It was already applied in 60's for the synthesis of new materials in nuclear industry e.g. for the preparation of fuel elements containing  $^{233}\text{UO}_2\text{-ThO}_2$  [34]. Many scientific articles as in the *Journal of Sol-Gel Science and Technology*, *Chemistry of Materials* and *Journal of Non-Crystalline Solids* were published since this time containing the research in the field of silica compounds. In early 90's a sol-gel process was finally applied in catalysis for the synthesis of heterogeneous catalysts. At this time R. Gomez and T. Lopez et al. studied the synthesis of the sol-gel immobilized catalysts for the reforming of n-butane or n-hexane with  $\text{Pt-Sn@Al}_2\text{O}_3$ , hydrogenation of phenylacetylene by  $\text{Pt@TiO}_2$  or  $\text{Pd@SiO}_2$ , CO oxidation by  $\text{Cu@MgO-SiO}_2$  etc.

The sol-gel process was studied in more details since 1993 by D. Avnir and J. Blum et al. (Hebrew University of Jerusalem/Israel) and tested for a large variety of catalytic reactions. Catalysts entrapped into sol-gel matrices can be used for different reactions: ligand-free Heck and Suzuki coupling reactions of aromatic compounds with  $\text{Pd}(\text{OAc})_2$  as catalyst [17,35],  $\text{RhCl}_3\cdot\text{H}_2\text{O}/\text{Aliquat 336}$  catalyzed isomerization of hydrophobic allylarenes [36], hydroformylation of styrene derivatives by  $[\text{Rh}(\text{cod})\text{Cl}]_2$  [37], hydrogenation of itaconic acid and derivatives by  $[\text{Rh}(\text{cod})\text{Cl}]_2/\text{BPPM}$  catalyst [38], transfer hydrogenation by  $\text{Pd}(\text{OAc})_2$  [39] and disproportionation of dihydroarenes by  $\text{RhCl}_3\cdot\text{H}_2\text{O}/\text{Aliquat 336}$  or  $\text{Pd}(\text{OAc})_2$  as catalysts [40]. The immobilization of the in situ generated complexes within sol-gel materials allows a better and easier separation of these catalysts from solution and facilitates their reuse, which greatly improves the productivity of the catalyst.

The common mechanism of the *hydrolytic* sol-gel process was described in detail by C.J Brinker in the book “Sol-gel Science: The Physics and Chemistry of Sol-Gel Processing” [41]. The simplified mechanism of this process is shown in Scheme 8 and consists of several steps [42]. The sol-gel process is initiated by an acid catalyzed or neutral hydrolysis of silicon alkoxide precursors e.g. tetramethyl orthosilicate  $\text{Si}(\text{OMe})_4$ , triethoxyphenylsilane  $\text{PhSi}(\text{OEt})_3$  or trimethoxy(octyl)silane  $\text{OcSi}(\text{OMe})_3$  to silanol and alcohol (*substitution*) [43]. This step is followed by alcohol and water condensation and formation of H- and O-bonds between the sol particles (*polymer siloxane network formation*). The silica surface can be modified by mixing of two different silane precursors for example triethoxyphenylsilane and tetramethyl-orthosilicate in step 3, followed by metal entrapment into the silica polymer in step 4. All steps except metal entrapment are reversible. The stability and reactivity of the sol-gel immobilized catalyst depends on the type of silica and metal precursor, solvent ratio (alcohol and water), gelation time, catalyst drying technique and involvement of acid or base in the process.



**Scheme 8:** Immobilization of a catalyst by a sol-gel method

The other option to prepare the immobilized catalysts is the *nonhydrolytic* (without water addition) sol-gel route. In this synthesis, water is not acting as O-donor and is not part of the process. Instead of water ether or alkoxides e.g.  $^i\text{Pr}_2\text{O}$  are applied and chlorides or alkoxides

e.g.  $\text{SiCl}_4$  are used as precursor. Sol-gel immobilized catalysts prepared in this way are often applied in oxidations and as photocatalysts [44,45]: for example olefin epoxidation with iodosylbenzene catalyzed by  $\text{Co@Al}_2\text{O}_3$  prepared from  $\text{CoCl}_2$  (catalyst precursor),  $\text{AlCl}_3$  (chloride precursor) and  $^i\text{Pr}_2\text{O}$  (solvent and O-donor). Not only silica but also other *inorganic oxides* are often applied as support materials in sol-gel processes for catalyst synthesis. The activity of the immobilized catalysts depends not only on the support material but also on the type of reaction. The activity of immobilized Pd catalyst in Heck coupling reaction of bromobenzene with styrene was:  $\text{TiO}_2 > \text{ZrO}_2 > \text{MgO} > \text{ZnO} > \text{SiO}_2$  [46] and in coupling of iodobenzene and acrylonitrile in the presence of  $\text{PPh}_3$  ligand it was:  $\text{MgO} > \gamma\text{-Al}_2\text{O}_3 > \text{CaCO}_3 > \text{SiO}_2$  [47]. The difference between silica and other metal precursors is the hydrolysis time: e.g.  $\text{Ti(OR)}_4$  hydrolysis is  $10^5$  times faster than silicium alkoxide because metal alkoxides are stronger Lewis acids and promote the nucleophilic attack of water. That's why silica supports are sometimes more preferred than more stable and active  $\text{TiO}_2$  supports. Because of the low hydrolysis rate they can be modified with for example enantioselective ligands, modified silica supports or imine and amine [22].

The detailed structure of the silica materials prepared by a sol-gel processes can be characterized by different spectroscopic techniques e.g. FT-IR, Raman and  $^{29}\text{Si}$ -NMR spectroscopy.

## 2.8 Efficiency of an immobilized catalyst

The efficiency of an immobilized catalyst in comparison to the homogeneous one can be limited by different factors. The catalyst can be deactivated by some reaction partners (catalyst poisoning), can leaches into the reaction solution (catalyst stability) and there could be also transport limitations through the pores of the immobilized catalyst (diffusion limitations). The heterogeneously catalyzed reaction consists of several steps [48]:

- (1) Diffusion of reactants through the boundary layer surrounding the catalyst particles
- (2) Diffusion of the reactants into the pores of the catalyst
- (3) Adsorption of the reactants onto active sites in the pores of the catalyst
- (4) Reaction
- (5) Desorption of the products from active sites
- (6) Diffusion of the products through the pores
- (7) Diffusion of the products through the boundary layer surrounding the catalyst particles

This complex mechanism is demonstrated in Scheme 9, where we can look inside the porous catalyst. The active sites (catalyst precursor particles intercalated into support material) are situated inside the pores of the catalyst where the chemical reaction takes place.

To examine the influence of the diffusion of the reactants inside the catalyst pores on the rate of the reaction, the ratio of the reaction time constant and the diffusion time constant is estimated, expressed as *Weisz modulus*  $\Psi$ . This is a characteristic parameter for mass transfer limitations on heterogeneously catalyzed reactions. It can be calculated by using the Weisz-Prater criterion [36,49]:

$$\Psi = L_{cat}^2 \cdot \frac{n+1}{2} \cdot \frac{r \cdot \rho_{cat}}{c_0 \cdot D_{eff,reactant}} \quad \text{Eq 1}$$

In Equation 1 there are  $L_{cat}$ = radius of the catalyst nanoparticles,  $n$ =reaction order,  $r$ =reaction rate:  $r = c_0 \cdot \frac{dx}{dt}$ ,  $\rho_{cat}$ = density of the catalyst,  $c_0$ =initial concentration of the dearth compound and  $D_{eff,reactant}$ = effective diffusion coefficient. For  $\Psi \leq 1$  no diffusion limitation influences the reaction.

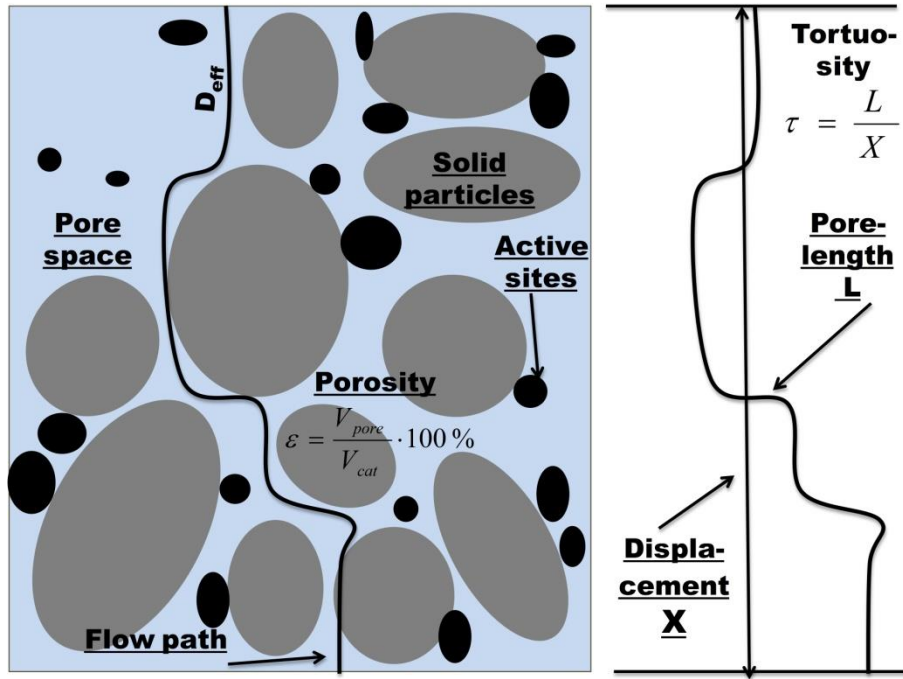
The effective diffusion coefficient  $D_{eff,reactant}$  can be calculated from the measured diffusion coefficient  $D_{eff,tracer}$ :

$$D_{eff,reactant} = D_{M,reactant} \cdot \frac{\varepsilon}{\tau} \quad \text{Eq 2}$$

$$\frac{\varepsilon}{\tau} = \frac{D_{eff,tracer}}{D_{M,tracer}} \quad \text{Eq 3}$$

The diffusion coefficients can be measured by different methods. For this purpose the immobilized catalysts or porous materials have to be impregnated with a tracer, for example a salt ( $Ni^{2+}$ ,  $K^+$ , and  $Sr^{2+}$ ). Then the change in concentration of tracer in an aqueous solution (diffusion of the tracer from the pores of the catalyst) as a function of time can be measured by UV-Vis spectrometer [50],[51], fluorescence, NMR [52] or conductivity measurements.

In Equation 3,  $\varepsilon$  is defined as porosity of the immobilized catalyst or the ratio of pore volume to bulk volume of the catalyst.  $\tau$  is defined as tortuosity or sinuousness of the transport ways in the pores of the porous materials. In Scheme 9 the diffusion of the reactant-product flow inside the pores of the catalyst is shown:



**Scheme 9:** Flow in the pores of an immobilized catalyst

The overall efficiency of the porous catalyst  $\eta$  will be estimated and discussed for different sol-gel immobilized catalysts within the scope of this work:

$$\eta = \eta_{\text{immobilisation}} \cdot \eta_{\text{intercalation}} \cdot \eta_{\text{pore}} \cdot (>N_{\text{cycle}}) \cdot (>\eta_{\text{recycling}}^N) \quad \text{Eq 4}$$

In this equation  $\eta_{\text{immobilisation}}$  and  $\eta_{\text{recycling}}$  are defined as leaching ratios (from ICP measurements) of the metal precursor from the immobilized catalyst after the synthesis and N recycling experiments.

$$\eta_{\text{recycling}} > 1 - \left( \frac{m_{\text{leaching}}}{m_{\text{initial}}} \right)^N \quad \text{Eq 5}$$

$$\eta_{\text{immobilization}} = \frac{m_{\text{metal catalyst, immobilized}}}{m_{\text{metal catalyst, initial}}} \quad \text{Eq 6}$$

$\eta_{\text{intercalation}}$  is the efficiency of the immobilized catalysts compared to the homogeneous catalyst and is estimated from the associated reaction rates.

$$\eta_{\text{intercalation}} = \frac{r_{\text{heterogeneous}}}{r_{\text{homogeneous}}} \quad \text{Eq 7}$$

The pore efficiency of the immobilized catalysts,  $\eta_{\text{pore}}$ , describes the decrease of the reaction rate by pore diffusion and depends from the reaction order:

$$\eta_{pore} = \frac{r_{eff}}{r_0} \quad \text{Eq 8}$$

The pore efficiency can be calculated from the Weisz-Prater criterion  $\Psi$  for various reaction orders [53]:

For  $\Psi < 1$   $\eta_{pore} = 1$  (no diffusion limitations)

And for  $\Psi > 1$   $\eta_{pore} = \Psi^{-1}$  (diffusion limited reaction).

Catalyst efficiencies  $\eta \geq 1$  are typical for very stable and active catalysts and demonstrate that these catalysts immobilized by sol-gel method are a good alternative to homogeneous one. In comparison to these results, catalysts with high amount of leaching and low reactivity show smaller efficiencies and the overall efficiency of the catalyst would be  $\ll 1$ .

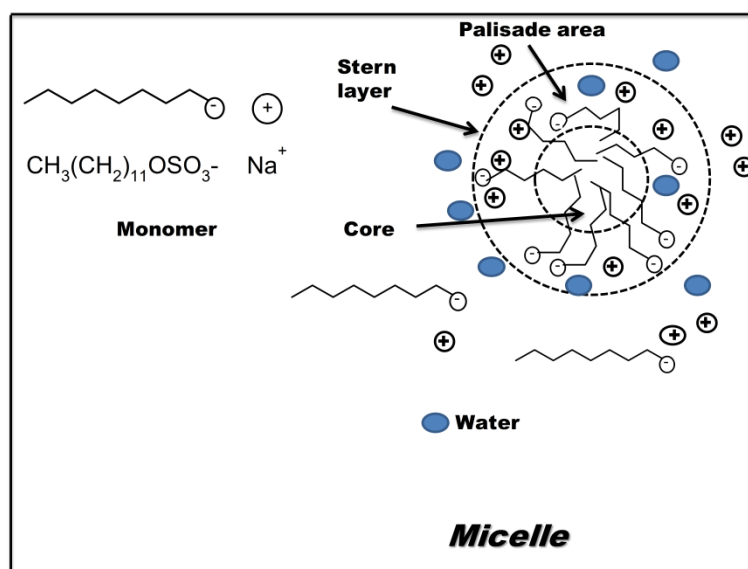
## 2.9 Microemulsions and aqueous micellar solutions

Most organic transformations are performed in solutions. It brings the reactants and catalysts together and delivers the thermal energy needed for the reaction. The choice of solvent affects the activation energy, the reaction rate and the selectivity. In addition the choice of the solvent is also important from the environmental point of view, costs, safety, handling and product isolation. Paul Anastas (Environmental Protection Agency USA) has formulated some simple rules for how sustainability can be achieved in the production of chemicals. The most crucial of them are to avoid waste, atom economy or efficiency, use of less toxic chemicals, energy efficiency, avoids derivatization and use of renewable primary products.

Besides using the immobilized catalyst as was described in last chapters, also the replacement of organic solvents by more environmentally friendly media is recommended. Using water as solvent makes the reaction process greener, but decreases the solubility of aromatic and aliphatic hydrophobic compounds. That's why the addition of small amount of organic solvent or/and a surfactant or ionic liquid is necessary for such a type of reactions.

Surfactants are amphiphilic substances, which consist of hydrophilic head and hydrophobic hydrocarbon-containing tails. They lower the surface tension of a liquid and increase the solubility of chemical compounds in aqueous solutions. There are different types of surfactants: cationic e.g. cetyltrimethylammonium bromide CTAB, nonionic e.g. octyl phenyl ethoxylate Triton X-100 and anionic e.g. sodium dodecyl sulfate SDS. Their properties can be

characterized by *HLB* values (hydrophilic-lipophilic balance or a ratio of hydrophilic to lipophilic region in the molecule) described by W.C. Griffin in 1949 for nonionic surfactants and by J.T. Davies in 1957 for ionic surfactants. The *HLB* value decreases with increasing hydrophobicity and indicates the ability of the surfactant to solubilize the oil. At surfactant concentrations higher than *cmc* (critical micelle concentration), the surfactant monomers form *micelles*. The *cmc* values of different surfactants can be calculated from the change of their physical properties at increasing surfactant concentrations e.g. absorbance, conductance for ionic surfactants or surface tension measurements. The formed micelles consist of hydrophobic cores, where the catalyst and hydrophobic substrates can be intercalated and the hydrophilic outer region (Palisade area) as shown in Scheme 10. The size of the micelles or hydrodynamic radius  $r_h$  is in the range of few nanometers and can be measured for example by dynamic light scattering experiments (DLS).



**Scheme 10:** An idealized model of a spherical micelle of SDS surfactant [54].

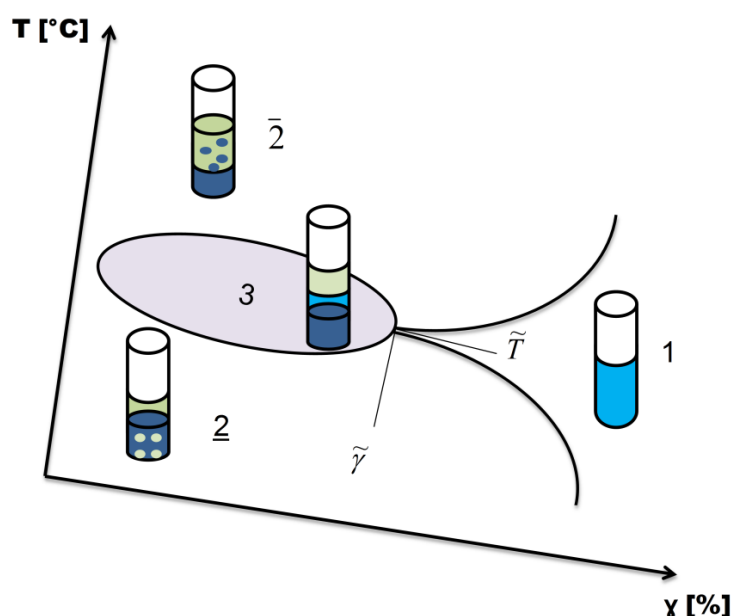
The regions where the different substrates are located in the micelles can be estimated from partition coefficient measurements [55].

First reactions in aqueous-micellar solutions were studied by G. Oehme et al. at Leibniz institute of organic catalysis in Rostock/Germany in the nineties: enantioselective hydrogenation of model substances like methyl-(*Z*)-2-*N*-acetylaminocinnamate [56] and (*Z*)-methyl- $\alpha$ -acetamidocinnamate [57],[58] by rhodium(I)biphosphane catalysts e.g.  $[\text{Rh}(\text{cod})_2]\text{BF}_4/\text{BPPM}$ .

Later also the Heck coupling reaction of styrene and acrylate catalyzed by  $\text{PdCl}_2$  [59] and Suzuki coupling catalyzed by  $\text{PdPPh}_3$  [60] were studied in aqueous-micellar solutions.

For more hydrophobic aromatic substrates e.g. *trans*-stilbene the application of aqueous-micellar solution is not enough, because of the limited storage capacity of the micelle aggregates. The other option is the use of microemulsions as a solvent. *Microemulsions* are liquid mixtures of oil, water and surfactant, which can also be combined with cosurfactant e.g. an alcohol. Four types of microemulsion systems were first classified by P. Winsor in 1948 [61].

Their behavior at different temperatures can be understood by using phase prisms and Gibbs diagrams. By changing the temperature in dependency of surfactant ratio  $\gamma$  at constant oil/water ratio  $\alpha=50\%$ , a vertical section of phase prism can be obtained. This diagram is also called a *fish* because of the fishlike shape [62]:



**Scheme 11:** Fish diagram ( $\alpha=\text{constant}$ )

The fish body at lower surfactant concentrations is characteristic for a three phase region (3): the lower aqueous and upper organic phases are in equilibrium with middle phase containing oil, water and surfactant (*Winsor Type III*). A fish tail at higher surfactant concentrations indicates the formation of homogeneous one phase mixture containing solubilized oil, water and surfactant (*Winsor Type IV*). At lower temperatures the 2-phase region (2) or oil-in-water microemulsion (*Winsor Type I*) is formed, containing water-surfactant phase with small amount

of solubilized oil and an upper oil phase. At higher temperatures above the fish body the 2-phase region ( $\bar{2}$ ) of water-in-oil or oil-rich microemulsion is formed (*Winsor Type II*), containing an aqueous solution and an upper oil phase with small amount of solubilized aqueous phase [61,63]. This variable phase behavior is useful for the separation of homogeneous catalysts and products after chemical reactions.

The heterogeneously catalyzed reactions, for example Heck or Suzuki couplings with sol-gel immobilized palladium catalysts [17],[35] can already be carried out in aqueous one phase microemulsion at higher surfactant concentrations. The catalysts can be separated through the filtration and reused. The product separation can be done by extraction with organic solvent followed by solvent evaporation.

The product and catalyst separation after homogeneously catalyzed reaction is much more difficult. The separation of the catalyst from the one phase microemulsion is possible through the dead-end or continuous cross-flow ultra- or nanofiltration. This method was studied considerably by D. Vogt (University of Eindhoven/Netherlands) et al. [64]. The method was modified for the separation of catalysts from the aqueous-micellar solution by R. Schomäcker et al. [65],[66] and is called the micellar-enhanced ultrafiltration (MEUF). It was used to separate Rh/BPPM catalyst after the enantioselective hydrogenation of itaconates. For this filtration method the catalyst is intercalated into large micelles, which can be filtrated and held back (*retentate*), it can be returned to a reactor and reused for the next reaction. The product in an aqueous solution passes the membrane (*permeate*) and can be separated after the reaction.

The other option is to arrange the reaction process in multiphase solutions. The water soluble catalyst-ligand complexes were already separated after the Suzuki coupling with Pd(OAc)<sub>2</sub>/TPPTS or Pd(OAc)<sub>2</sub>/SPhos catalyst in water/heptan/Marlipal 24/70 three-phase microemulsion [67]. The middle phase of the three-phase microemulsion was used again for the following coupling reaction. The produced product was separated from the upper organic phase by a rotary evaporator and the surfactants could be separated from the lower aqueous phase.

## 2.10 Non-conventional green solvent systems

*Ionic liquids*(IL) also called 'designer solvents' are understood as salts, with melting points below the boiling point of water and ionic-covalent structure e.g. imidazolium, pyridinium or alkylphosphonium cation and Cl<sup>-</sup>, BF<sub>4</sub><sup>-</sup>, AlCl<sub>4</sub><sup>-</sup> anion [7]. Through the variation of anion and cation, the melting point of the IL can be 'designed'. They increase the solubility of catalyst

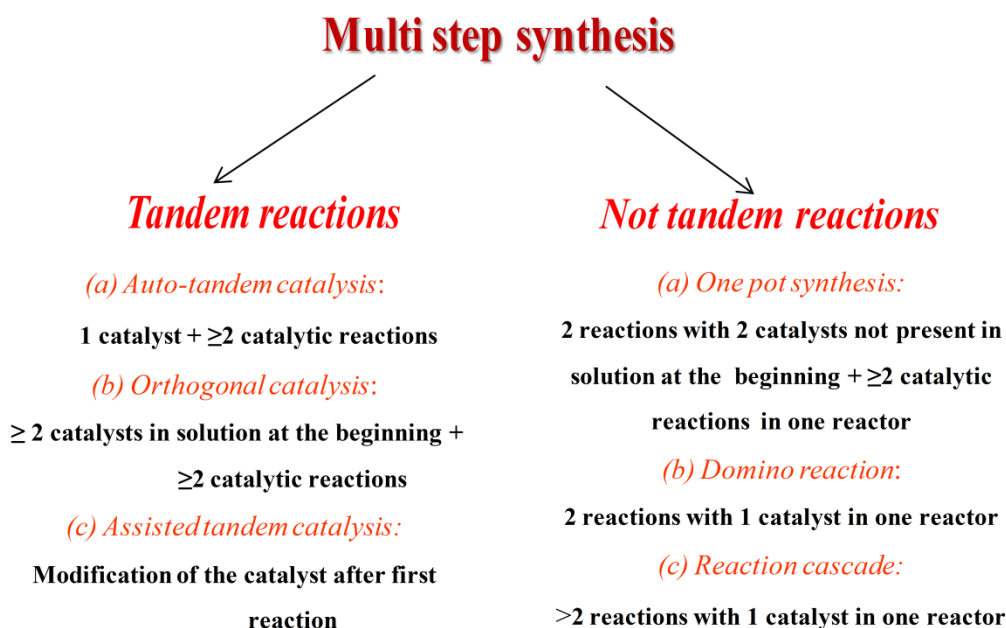
precursors, stabilize them and allow the recovering of the homogeneous catalysts after the reaction because of non miscibility with organic solvents (two-phase behavior). The most famous examples of using IL are the BASIL-Process (BASF) for the synthesis of diethoxyphenylphosphine and DIFASOL-Process (Y. Chauvin and H. Olivier-Bourbigou) for the nickel catalyzed dimerization of propenes.

Generally supercritical fluids (water, CO<sub>2</sub>) are substances, with properties different from normal fluids; they exist at temperature higher than the critical temperature  $T_c$  and critical pressure  $p_c$ . *Supercritical CO<sub>2</sub>* ( $T_K=31^\circ\text{C}$ ,  $p_K=73.8$  bar) is a non toxic, environmentally friendly, inexpensive and non-flammable solvent. The solubility of different compounds in scCO<sub>2</sub> and the density of the solution can be tuned by pressure and temperature; in addition it facilitates the separation of products and catalysts by two-phase formation with other organic solvents [68].

*Fluorous solvents* (non-toxic perfluoroalkenes, perfluorodialkyl ethers and amines) have also lower miscibility with organic solvents and can form a two-phase system for catalyst separation at lower temperature after reaction. The disadvantages of these solvents are high costs for synthesis and a slow biodegradability.

## 2.11 Tandem reactions

*Tandem catalysis* can be described as a multicomponent reaction catalyzed by one, two or several catalysts (multifunctional catalysis), differentiated by tandem reaction and not-tandem reaction types. The advantage of tandem reactions is their atom-efficiency. 2004 D.E. Fogg and E.N. dos Santos [69] defined different types of multicomponent reactions as shown in Scheme 12.



**Scheme 12:** Classification of tandem and not tandem reactions

*Tandem reactions* are defined as sequences of two or more coupled reactions, which proceed with different catalytic mechanisms: For example ring opening metathesis (RCM) catalyzed by ruthenium followed by Heck coupling with palladium catalyst (orthogonal catalysis). These reactions are also subdivided in auto-tandem, orthogonal and assisted tandem catalysis. Auto-tandem reaction is for example a *hydroaminomethylation* (HAM) with only one rhodium catalyst. This reaction sequence consists of a hydroformylation of an alkene with CO/H<sub>2</sub> (synthesis gas) to an aldehyde, followed by imineformation with R<sub>2</sub>NH and hydrogenation of imine to amine product. The other famous example of the auto-tandem catalysis is the combination of cobalt catalyzed hydroformylation of propene and synthesis gas to n- and isobutanale followed by hydrogenation to n- and isobutanol in the *Shell-Process*. Orthogonal catalysis can be achieved with two or more catalysts e.g. allylic alkylation to enine by Pd<sub>2</sub>dba<sub>3</sub>/dppb catalyst and Pausand-Khand reaction with [RhCl(CO)dppb]<sub>2</sub> to cyclopentanone. Tandem reactions are also often applied in polymerizations. For example the dimerization of ethene with nickel catalyst to 1-butene followed by copolymerization to poly(ethylene-co-butene) by Ti catalyst. If the catalyst has to be modified after the first reaction, then the reaction is called the assisted tandem catalysis. After the bromoallylation by PdBr<sub>2</sub>(NCPh)<sub>3</sub> catalyst, the active species has to be modified with CuI, PPh<sub>3</sub> and amine for the application in *Sonogashira coupling*.

*Not tandem reactions* are sub-classified in one pot synthesis, domino and cascade reactions. For the one pot synthesis the second catalyst has to be added after the reaction e.g. Heck coupling reaction by  $\text{Pd}(\text{OAc})_2$  and epoxidation by  $\text{Mn}(\text{AcAc})_2$  catalyst. Domino reactions contain all components at the beginning of the reaction process: Cycloheptenestyreneether metathesis to chromane by a Ru catalyst or cycloisomerization of a polyenyne to polyspirane by a Pd catalyst. In comparison to the domino reaction, the reaction cascade or zipper mode cascade is a series of intramolecular organic reactions in one reactor. The Banert cascade is an organic reaction used in alkynes chemistry in which NH-1,2,3-triazoles are synthesized from propargyl chloride with  $\text{NaN}_3$ .

The advantages of tandem reactions are high efficiency because of elimination of intermediate work up steps and use of only one catalyst for several reactions e.g. domino or auto-tandem reaction. Potential problems could be negative interactions between different catalytic species and inhibition by by-products of the reactions. Because of formation of the products with low purity, low conversions and selectivity's in the following steps can be obtained. Also the recovery of two or more catalytic species after the tandem reaction can be a problem.

## 3 Experimental Part

### 3.1 Materials

4-Biphenylboronic acid, 2-bromobenzonitrile, chloro(1,5-cyclooctadiene)rhodium(I) dimer  $[\text{Rh}(\text{cod})\text{Cl}]_2$ , 4-chlorophenylboronic acid, 2-chlorotoluene, dimethyl itaconate (DMI), iron (II,III) oxide  $\text{Fe}_3\text{O}_4$ , methylcinnamate, *trans*- $\alpha$ -methylstilbene, palladium 5wt% on silica powder (Pd@Si), palladium(II) bromide ( $\text{PdBr}_2$ ) and 2-dicyclohexylphosphino-2,6'-dimethoxy-1,1'-biphenyl (SPhos) were purchased from *abcr GmbH Co. KG* Karlsruhe/Germany. 1-(Tetradecyl)trimethylammonium bromide (TTAB) was obtained from *Alfa Aesar Company* Karlsruhe/Germany. Sodium dodecyl sulfate (SDS) was obtained from *AppliChem GmbH* Darmstadt/Germany. 30 mol-% 3,3',3''-Phosphinidynetris(benzenesulfonic acid) trisodium salt solution (TPPTS) was obtained from *Celanese Corporation* Irving/USA. Cinnamic acid (CA), 4,4'-dichlorobiphenyl (PCB), 2-ethylhexylacrylate, phenylboronic acid, styrene and triethylamine ( $\text{NEt}_3$ ) were purchased from Fluka. Acrylic acid (AA), polyoxyethylen (23) lauryl ether (Brij®35) and commercial 10wt% palladium on activated carbon (Pd@C) for hydrogenations and coupling reactions were ordered from *Merck KGaA* Darmstadt/ Germany. Acetonitril, dimethyl formamide and water (HPLC Gradient) were purchased from *Carl Roth GmbH+ Co. KG* Karlsruhe/ Germany. Marlipal 24/60, Marlipal 24/70 and Novel 8 were provided from *Sasol Germany GmbH* Marl/Germany.  $\alpha$ -Methylstyrene, benzaldehyde (BA), benzoic acid, biphenyl, 4-bromoacetophenone, bromobenzene (PhBr), 4-bromobenzylamine, 1-bromo-4-iodobenzene (IPhBr), (2*S*,4*S*)-1-tert-butoxycarbonyl-4-diphenylphosphino-2-(diphenylphosphinomethyl) pyrrolidine (BPPM), *tert*.-butylmethacrylate, 4-chloroacetophenone, chlorobenzene (PhCl), 2-chlorobenzonitrile, 2-chloro-1,3-dimethylbenzene, 1-chloro-2-nitrobenzene, 3-chloroperbenzoic acid (mCPBA), 4-chlorostyrene, *trans*-4-chlorostilbene, 1,2-diphenylethane, dodecyltrimethylammonium bromide (DTAB), hexadecyltrimethylammonium bromide (CTAB), 30wt% hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) solution in  $\text{H}_2\text{O}$ , 2-hydroxyethylmethacrylate, IGEPAL CA-520, iodo-benzene (PhI), itaconic acid (IA), manganese (II) acetylacetonate ( $\text{Mn}(\text{AcAc})_2$ ), manganese/ phosphorus/ palladium/ rhodium ICP standard solutions, methacrylic acid, methylacrylate,  $\alpha$ -methylcinnamic acid, methylmethacrylate, methyl- $\alpha$ -methylcinnamate, palladium 1wt% on alumina powder (Pd@ $\text{Al}_2\text{O}_3$ ), palladium (II) acetate ( $\text{Pd}(\text{OAc})_2$ ), phenyl acetaldehyde, poly(4-vinylpyridine) (PvyPy), potassium carbonate ( $\text{K}_2\text{CO}_3$ ), sodium periodate ( $\text{NaIO}_4$ ), *trans*-stilbene oxide, styrene oxide (STO), tetraethyl orthosilicate (TEOS), tetramethyl orthosilicate

(TMOS), *trans*-stilbene, triethoxyphenylsilane ( $\text{PhSi}(\text{OEt})_3$ ), trimethoxy(octyl) silane ( $\text{OcSi}(\text{OMe})_3$ ), (trimethylsilyl)diazomethane solution, dioctyl sodium sulfosuccinate (DSS), Triton X-100 (TX-100) and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) were obtained from *Sigma-Aldrich Company* Munich/Germany. *Trans*-4-bromostilbene, 4-bromobenzeneboronic acid, *trans*-4-chlorostilbene, diethyl itaconate (DEI) stabilized with trichlorobenzene (TCB) and dibutyl itaconate (DBI) were purchased from *TCI Europe* Eschborn/Germany.

## 3.2 Synthesis of the catalysts by a sol-gel method

### 3.2.1 Preparation of the rhodium catalysts for the hydrogenation of itaconate

The  $[\text{Rh}(\text{cod})\text{Cl}]_2/(2S,4S)\text{-BPPM}$  (Rh/BPPM) catalysts were entrapped into the silica by a sol-gel method under  $\text{N}_2$  using different gel building agents. In every case, after the preparation of the catalysts, they were dried for 24 h in a vacuum oven under a reduced pressure of  $10^3$  Pa and a temperature of  $30^\circ\text{C}$ , washed carefully 3 times with 10 mL boiling water and dried again. The washing liquids were analyzed for their rhodium and phosphorous contents (catalyst leaching into washing solution) by ICP-OES. The structures of the catalyst precursor and ligand are shown in Scheme 14.

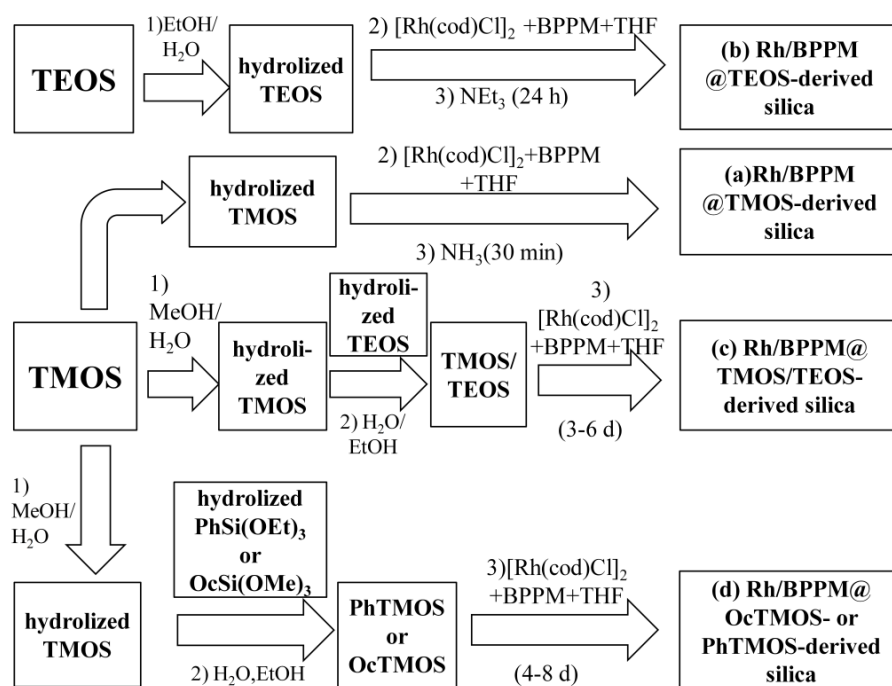
The entrapment of the Rh/BPPM catalyst into the *hydrophilic gel* was catalyzed by hydrochloric acid. The procedure was described first by Gelman et al [70]. A mixture of 2.50 mL TMOS (16.92 mmol) in 3.50 mL methanol and 0.78 mL hydrochloric acid (prepared from 0.1 mL of 1.1 N HCl and 9.9 mL  $\text{H}_2\text{O}$ ) was stirred for 10 minutes at  $25^\circ\text{C}$ . Separately the Rh/BPPM catalyst was formed in situ from 11 mg  $[\text{Rh}(\text{cod})\text{Cl}]_2$  (0.022 mmol) and 24 mg BPPM (0.044 mmol) dissolved in 0.78-5 mL tetrahydrofuran. The hydrolyzed TMOS solution was mixed with the activated catalyst and 0.83 mL ammonia solution (0.1 N). The gelation occurred after 20-30 minutes.

The entrapment of the Rh/BPPM catalyst in the *hydrophilically modified support* could be realized with TEOS or a mixture of TMOS and TEOS. After the hydrolysis of 1.58 mL TEOS (9.88 mmol) in 5.60 mL ethanol and 0.40 mL of distilled water for 24 h, the solution was added to the catalyst solution (prepared similarly as described before). Then a small amount of concentrated triethylamine (3-5 drops) was added to the mixture to catalyze the gelation process. The gelation of the catalyst occurred after about 24 h.

For the preparation of the *mixed TMOS/TEOS* immobilized catalyst, the hydrolyzed TMOS solution (3.6mL TMOS (23.0 mmol), 2.4 mL methanol and 2.0 mL water) was added to the hydrolyzed TEOS solution.

The procedure for the immobilization of the catalyst in *hydrophobically modified support* is comparable to the immobilization of a palladium catalyst for the Heck coupling reaction as was shown by Rozin-Ben Baruch et al. [17]. A mixture of 2.1 mL trimethoxy(octyl) silane (9.88 mmol) or 1.61 mL triethoxyphenylsilane (6.68 mmol) was stirred for 24 h in 4.2 mL ethanol and 0.4 mL distilled water. Then the hydrolyzed tetramethyl orthosilicate solution was added and stirred for 20 minutes. The combined solutions were mixed with Rh/BPPM in tetrahydrofurane and the gelation was completed within 4-8 days.

Different preparation routes of the catalysts are summarized in Scheme 13:



**Scheme 13:** Preparation of sol-gel immobilized Rh/BPPM catalysts

### 3.2.2 Preparation of the immobilized palladium and manganese catalysts

The immobilization procedure of the palladium or manganese catalysts on silica is comparable to the procedure reported by Rozin-Ben Baruch [17]. All catalysts were prepared from a mixture of a catalyst and hydrolyzed silane. After the entrapment the solutions were shaken until the gelation occurred. Thereafter, the catalyst was first dried for 4-8 h at 80°C and then dried further for 8-12 h in a vacuum oven at 80°C and 10<sup>3</sup> Pa to remove the solvents. Then the catalyst was

washed carefully with boiling dichloromethane and dried again at 80°C and 10<sup>3</sup> Pa for 8-10 h. After the immobilization procedure about 2.2-2.4 g of black solid catalyst were obtained. Immobilized palladium, manganese and palladium-manganese catalysts were applied in Heck coupling, hydrogenation of *trans*-stilbene, Suzuki coupling, epoxidation of *trans*-stilbene and styrene and in tandem reactions.

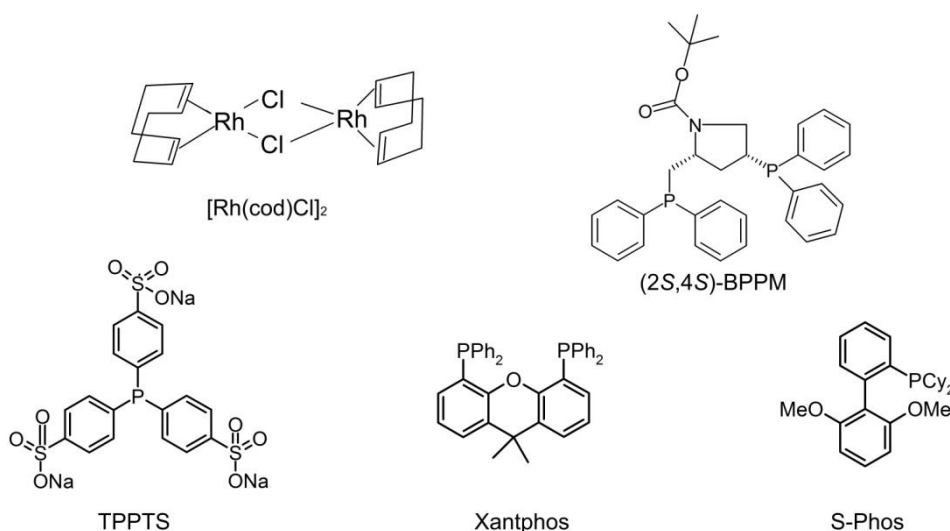
For the preparation of the catalysts on a *hydrophobically modified surface*, the solution of a 2.1 mL trimethoxy(octyl)silane (9.877 mmol) or 1.612 mL triethoxyphenylsilane (6.680 mmol) in 0.4 mL water and 4.25 mL methanol or ethanol was hydrolyzed for 24 h. Then separately a solution of 3.6 mL tetramethyl orthosilicate (TMOS) (22.961 mmol) in 2.4 mL methanol and 2 mL water was stirred for 20 min. Both solutions were combined and stirred for another 30 minutes. Then 30 mg of homogeneous *palladium(II) acetate* or 35 mg of *palladium(II) bromide* or 33 mg *manganese(II) acetylacetonate* (0.134 mmol) was dissolved in 4 mL dichloromethane and stirred for 20 minutes, after this they were combined with the solution of the hydrophobically modified silane.

The *hydrophilic* immobilized *palladium (II) acetate* catalyst was prepared without adding trimethoxy(octyl)silane or triethoxyphenylsilane to the solution of hydrolyzed tetramethyl orthosilicate.

For the immobilization of the catalyst/ligand complex (Scheme 14), *palladium (II) bromide* or *palladium (II) acetate* or *manganese (II) acetylacetonate* catalyst precursors (0.134 mmol) were added to the 30.420 mg of *Xantphos* ligand (0.134 mmol) in 4 mL dichloromethane or 0.135 g *SPhos* ligand (0.27 mmol) in 8 mL H<sub>2</sub>O or 1.24 g of 30% *TPPTS* ligand in water (0.640 mmol) and were stirred for 12 h.

Also a mixture of *palladium-manganese* catalyst was immobilized on hydrophobically modified silica by mixing of *palladium acetate* or *bromide* and *manganese acetylacetonate* with and without *Xantphos* ligand, the molar amounts of the catalysts and ligands were described before.

For the immobilization of *palladium*, *palladium-manganese* and *manganese catalyst* on double or triple amount of hydrophobic PhSiO<sub>2</sub> support, double and triple amounts of hydrolyzed TMOS and PhSi(OEt)<sub>3</sub> solutions were prepared.



**Scheme 14:** Structures of the catalyst precursor and ligands

### 3.2.3 Preparation of the magnetic palladium catalyst

For the preparation of the magnetic palladium nanoparticles, the same procedure was used as in Chapter 3.2.2 except the addition of 0.1-1 g of magnetic *iron (II,III) oxide* ( $Fe_3O_4$ ) to the solution of palladium acetate in dichloromethane.

## 3.3 Catalyst characterization

### 3.3.1 Surface area measurements (BET)

$N_2$ -BET specific surface area A, pore volume and pore size distribution measurements of sol-gel immobilized catalysts and commercial catalysts were obtained by a Micromeritics Gemini 1325 instrument. All catalysts were treated for 24 h under  $N_2$  at 300°C before the measurements.

### 3.3.2 Microwave decomposition and ICP-OES measurements

The removing of palladium or rhodium from silica support was carried out by microwave decomposition ( $p=20 \cdot 10^5$  Pa,  $t=35$  min and  $T=200^\circ\text{C}$ ) with a CEM Discover SP-D (Sample Preparation Digestion) instrument (CEM GmbH, Camp-Lintfort/Germany). Before this procedure, the catalysts were ball milled and then mixed with 12 mL of a  $HNO_3/HCl/H_2SO_4$  solution (2eq/6eq/4eq). After the microwave treatment, the solid white silica was removed by filtration and the residue solution was analyzed for palladium, rhodium or/and phosphorus content using a Varian 715-ES Optical Emission Spectrometer (ICP-OES). Calibration of the instrument was performed with commercial palladium, rhodium and phosphorus standards. Also the leaching of the catalyst into the reaction solution was determined by ICP-OES.

Calibration of the instrument was performed with a commercial manganese, palladium, phosphorus and rhodium standards.

### 3.3.3 Transmission Electron Microscopy (TEM)

Transmission electron microscopy (TEM) was performed in ZELMI/TU Berlin (Zentraleinrichtung Elektronenmikroskopie) with a conventional LaB<sub>6</sub>-TEM Tecnai G<sup>2</sup>20 S-TWIN instrument (FEI Company, USA) operated at 200 kV and equipped with EDAX-EDS for identification of elemental compositions.

### 3.3.4 X-ray diffraction (XRD)

The size of palladium particles and the structure of the palladium acetate@PhSiO<sub>2</sub> were determined by X-ray diffraction measurement (XRD) in X-ray apparatus (D8 Bruker Advance) with KFL Cu 2k x-ray tube as source and Lyux Eye Detector. The samples were previously dried and crunched to a powder.

### 3.3.5 Conductivity measurements (determination of diffusion coefficients)

Conductivity measurements were performed in a glass reactor by a method used for the determination of the diffusion coefficients in saturated brick materials in the construction chemistry [71]. Immobilized catalysts were stored in an aqueous SrCl<sub>2</sub> solution for 24 hours under N<sub>2</sub>. Then they were filtered off, and placed in a glass reactor with pure water. The increase in conductivity  $\kappa(t)$  due to diffusion of the Sr<sup>2+</sup> salt ions from the pores of the catalyst in the solution was measured at 25°C. The measured diffusion coefficient  $D_{eff, tracer}$  was calculated from the slope  $m$  of the line with  $r$  as the radius of the catalyst particles:

$$m = \frac{d \ln \left( \frac{\kappa(t) - \kappa_{end}}{\kappa_0 - \kappa_{end}} \right)}{dt} \quad \text{Eq 9}$$

$$D_{eff, tracer} = \frac{m \cdot r^2}{\pi^2} \quad \text{Eq 10}$$

## 3.4 Reaction procedure

### 3.4.1 Enantioselective hydrogenation

The set up of the hydrogenation apparatus [72] is shown in Scheme 15. About 1.0-1.4 g of the yellow-orange sol-gel immobilized rhodium catalyst containing 11 mg [Rh(cod)Cl]<sub>2</sub> (0.022 mmol) and 24 mg BPPM (0.044 mmol), a desired amount of substrate and 95 mL of solvent (methanol, water or aqueous-micellar solution) were added to a stirred tank reactor and stirred

at 400 rpm under N<sub>2</sub>-atmosphere at the desired reaction temperature for 30 min. The N<sub>2</sub> was replaced by H<sub>2</sub> (p=1.1·10<sup>5</sup> Pa) without stirring and the reaction was started by turning the stirrer on at 800 or 1200 rpm again. The reactions were performed in semi-batch mode with hydrogen being permanently added to the stirred tank reactor to achieve a constant total pressure of 1.1·10<sup>5</sup> Pa inside the reactor. The cumulative hydrogen consumption and the pressure during the reaction were recorded using a Bronkhorst flow meter and pressure controller (Bronkhorst Mättig GmbH, Kamen/Germany), respectively. The sensitivity of measured hydrogen consumption was ±0.4 mL. The pressure and the hydrogen flow during the reaction were registered and analyzed on a PC. From these results the substrate concentration  $c_{\text{substrate}}$  and conversion  $X$  were calculated:

$$c_{IA}(t) = \frac{n_{IA}}{V} = \frac{n_{IA,0} - n_{IA,consumption}}{V} = \frac{n_{IA} - \left( \frac{p \cdot V_{H_2(t)}}{R \cdot T} \right)}{V} \quad \text{Eq 11}$$

$$X(t) = \frac{V_{H_2}(t)}{V_{H_2,complete}} = \frac{V_{H_2}(t)}{\left( \frac{n_{IA,0} \cdot R \cdot T}{p} \right)} \quad \text{Eq 12}$$

The concentrations of reactants and products at the end of the reaction were measured by gas chromatography. The leaching of rhodium and phosphorus into the solution after the reaction was detected by ICP-OES measurements.

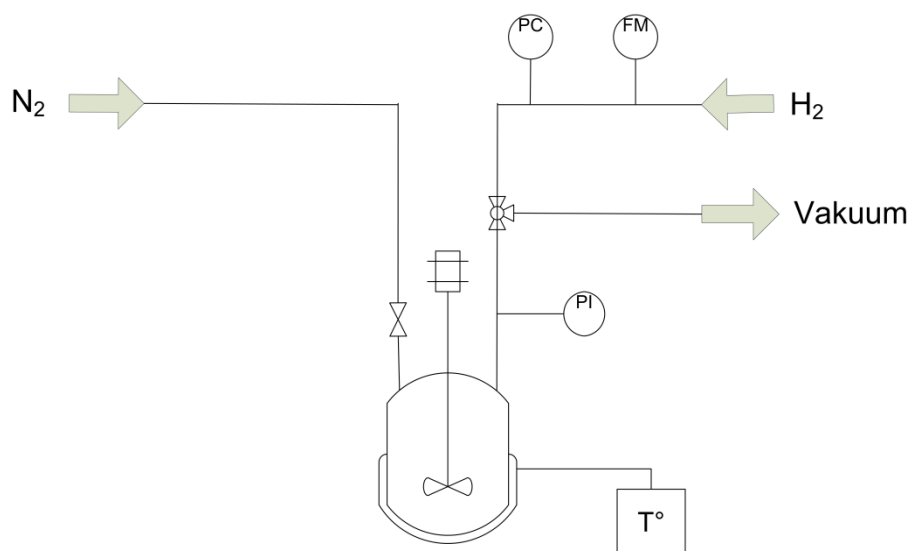
To compare different substrates and catalysts, turnover frequencies (catalyst efficiency) were calculated:

$$TOF = \frac{TON}{t} = \frac{\frac{n_{product}}{n_{metal catalyst}}}{t} \quad \text{Eq 13}$$

For sol-gel immobilized catalysts the amount of immobilized and leached rhodium catalyst was determined from the microwave decomposition measurements followed by ICP analysis.

Enantiomeric excess values, ee%, of *S*-product were calculated from GC measurements:

$$ee\% = 100 \cdot \frac{c_{S,product} - c_{R,product}}{c_{S,product} + c_{R,product}} \quad \text{Eq 14}$$



**Scheme 15:** Hydrogenation set-up (PI = pressure indicator, PC = pressure controller, FM = flow meter, T°= thermostat)

### 3.4.2 Suzuki and Heck Coupling

Typical *Heck coupling reactions* were performed in a double walled stirred glass reactor with reflux condenser at ambient pressure (Scheme 16) and typical *Suzuki coupling reactions* were performed in double walled stirred glass reactor under nitrogen (Scheme 17).

The reaction progress was monitored by measuring the reactant and product concentrations by HPLC. From these results the conversions of reactants and the selectivity's of the products were calculated using following equations:

$$\text{conversion } X(t) = \frac{c_0 - c_t}{c_0} \cdot 100 \quad \text{Eq 15}$$

$$\text{selectivity } Y(t) = \frac{\frac{c_{t,\text{product}}}{M_{\text{product}}}}{\frac{c_{0,\text{educt}}}{M_{\text{educt}}}} \cdot 100 \quad \text{Eq 16}$$

The reaction rate was determined from the concentration change during the reaction process:

$$r = -\frac{dc}{dt} \quad \text{Eq 17}$$

The amount of catalyst and ligand leached into the solution was measured by ICP-OES after reaction. The formed products were separated by extraction of the microemulsion with heptane or dichloromethane, followed by solvent evaporation.

For the *Heck coupling* procedure, alkene e.g. 153  $\mu\text{L}$  styrene (1.34 mmol) and aryl halide e.g. 158  $\mu\text{L}$  iodobenzene (1.50 mmol) were dissolved in 46 mL of organic solvent or aqueous microemulsion in the presence of 0.276 g  $\text{K}_2\text{CO}_3$  (2.00 mmol) as base. For *Suzuki coupling* 469.10 mg of 4-chlorobenzeneboronic acid (3.00 mmol) and 472.65 mg of 1-chloro-2-nitrobenzene (3.00 mmol) were added to 100 mL organic solvent, one or three phase microemulsion in the presence of 0.553 g  $\text{K}_2\text{CO}_3$  (4.00 mmol) as base under nitrogen.

The one phase aqueous microemulsion used in Heck coupling consists of 1.510 g CTAB as surfactant (5.235 mmol, 3.3 wt %), 3.020 g 1-propanol (50.25 mmol, 6.6 wt %) as cosurfactant and 40,855 g of  $\text{H}_2\text{O}$  (2269 mmol, 89.3 wt %) and organic substrates e.g. iodobenzene and styrene (2.84 mmol, 0.8 wt %). For Suzuki coupling a double amount of all compounds was added.

The oil (substrate) fraction in the microemulsion was  $\alpha = 0.9\%$  for Heck coupling reaction and  $\alpha = 1.1\%$  for Suzuki coupling reaction

$$\alpha = \frac{m_{oil}}{m_{oil} + m_{H_2O}} \quad \text{Eq 18}$$

The surfactant fraction was  $\gamma = 9.9\%$

$$\gamma = \frac{m_{surfactant} + m_{cosurfactant}}{m_{surfactant} + m_{cosurfactant} + m_{H_2O} + m_{oil}} \quad \text{Eq 19}$$

The cosurfactant fraction was  $\delta = 66.7\%$

$$\delta = \frac{m_{cosurfactant}}{m_{surfactant} + m_{cosurfactant}} \quad \text{Eq 20}$$

Three phase microemulsion applied in Suzuki coupling consists of 44.02 g heptane (732 mmol, 48 wt %) and educts (6 mmol, 1.03 wt %) as oil phase, 2.7231 g Novel 8 (9.442 mmol, 2.97 wt %) as surfactant and 44.02 g water (2446 mmol, 48 wt %). The oil fraction was  $\alpha = 50.3\%$ , the surfactant fraction was  $\gamma = 2.9\%$ .

1.2-1.4 g of the immobilized catalyst containing 15 mg of  $\text{Pd}(\text{OAc})_2$  (0.0668 mmol) on silica support was added to the reaction mixture and the reaction was started. For the homogeneous Suzuki coupling 15 mg of palladium (II) acetate (0.0668 mmol) was added with and without 67.97 mg PdSPhos (0.1337 mmol) or 0.625 g 30% PdTPPTS/ $\text{H}_2\text{O}$  (0.3342 mmol) as ligand.



**Scheme 16:** Experimental set-up of Heck coupling, epoxidation and tandem reaction ( $T^\circ$ = thermostat, S= stirrer, RC= batch reactor with magnetic stirring bar, C= reflux condenser)



**Scheme 17:** Experimental set-up of Suzuki coupling ( $T^\circ$ = thermostat, S= stirrer, RC= batch reactor with magnetic stirring bar, NG=nitrogen access, V= vacuum access, C= reflux condenser, B= bubble counter)

### 3.4.3 Hydrogenation and epoxidation of *trans*-stilbene

The *hydrogenation reactions* were done at 40°C with 0.483 g of *trans*-stilbene (2.368 mmol), homogeneous or heterogeneous catalyst containing 30 mg palladium acetate (0.1336 mmol) in methanol or aqueous microemulsion (water/propanol/CTAB:  $\gamma=10\%$ ,  $\delta=66\%$ ,  $\alpha=0,58\%$ ) in the hydrogenation reactor ( $V=100$  mL, 800 rpm,  $1.1 \cdot 10^5$  Pa  $H_2$ ) shown in Scheme 15. The concentrations of reactants and products were measured by HPLC at the end of the reaction and also monitored on a PC as was shown in chapter 3.4.1.

The *epoxidation* experiments were carried out in a stirred tank reactor shown in Scheme 16. The epoxidations of 0.2415 g *trans*-stilbene (1.34 mmol) or 0.1395 g styrene (1.34 mmol) were carried out in aqueous microemulsion (water/propanol/CTAB:  $\gamma=10\%$ ,  $\delta=66\%$ ,  $\alpha=0,58\%$ ) at 70-80°C with required amount of oxidizing agent (mCPBA,  $H_2O_2$ ,  $NaIO_4$ ), homogeneous or heterogeneous catalyst containing 15 mg palladium, 17 mg manganese catalyst or mixed Pd-Mn catalyst (0.0668 mmol) and total volume  $V=46$  mL. The leaching of the catalyst into the reaction mixture was detected by ICP-OES measurements.

### 3.4.4 Tandem reactions

All tandem reactions combining *Heck coupling reaction* and *epoxidation* were carried out in a stirred tank reactor, as shown in Scheme 16. The experimental set-up of the Heck reaction was carried out as described in chapter 3.4.2. After the Heck procedure, a desired amount of oxidizing agent and catalyst were added to the microemulsion and the epoxidation process was traced by HPLC analysis.

For the tandem reaction including *hydrogenation* the reaction set-up showed in Scheme 15 was used. First the *Heck* procedure was carried out as described before ( $V=100$  mL) in stirred tank reactor. Then the reaction mixture was transferred to the hydrogenation reactor and the *hydrogenation* reaction was started by adding  $1.1 \cdot 10^5$  Pa  $H_2$  gas. The concentrations of reactants and products were measured by HPLC at the end of reaction. The reaction progress was recorded as was showed in chapter 3.4.1. The leaching of the catalyst was detected by ICP-OES measurements.

### 3.5 Concentration measurements

#### 3.5.1 High pressure liquid chromatography (HPLC)

**Table 1:** HPLC calibrations

substances	t [min]	$\lambda$ [nm]	calibration
<b><u>Heck coupling</u></b>			
acrylic acid	1.500	225	$y=16.0720x$
benzoic acid	1.700	225	$y=39.8580x$
$\alpha$ -methylcinnamic acid	1.700	225	$y=23.7120x$
cinnamic acid	2.500	225	$y=95.5600x$
methacrylic acid	2.634	225	$y=7.3128x$
methylacrylate	3.225	225	$y=1.1808x+1.9104$
methylmethacrylate	3.639	225	$y=7.3548x+44.9795$
2-hydroxyethylmethacrylate	4.545	225	$y=0.0366x-2.6358$
methylcinnamate	4.674	225	$y=26.6123x+118.4129$
styrene	5.36	225	$y=25.1746x+37.0682$
4-chlorostyrene	5.473	225	$y=14.8095x+13.9769$
methyl- $\alpha$ -methylcinnamate	5.830	225	$y=19.0602x+139.7222$
tert.-butylmethacrylate	5.909	225	$y=20.0356x+12.5898$
ethylhexylacrylate	11.403	225	$y=0.9640x+1.5969$
2-chlorobenzonitrile	4.256	225	$y=36.2743x+103.3429$
2-bromobenzonitrile	4.272	225	$y=27.6083x+37.3183$
4-chloroacetophenone	4.506	225	$y=9.0025x+6.0063$
4-bromoacetophenone	4.740	225	$y=7.1434x-12.9704$
chlorobenzene	5.468	225	$y=3.0156x+52.1422$
bromobenzene	5.819	225	$y=14.3033x+8.7098$
iodobenzene	6.516	225	$y=29.6146x+198.4535$
2-chlorotoluene	6.760	225	$y=5.8775x+70.5812$
2-chloro-1,3-dimethylbenzene	8.630	225	$y=9.3425x+51.6087$
1-bromo-4-iodobenzene	9.100	225	$y=20.0315x-1.4166$
<i>trans</i> -stilbene	9.724	225	$y=65.2863x-129.9284$
1,2-diphenylethane	9.762	225	$y=8.0317x+23.6157$
<i>trans</i> -4-bromostilbene	12.946	225	$y=79.6602x-496.2526$
cinnamic acid	2.500	275	$y=287.9700x$
styrene	5.800	275	$y=4.3748x+2.4131$
iodobenzene	6.442	275	$y=0.7632x-0.4959$
$\alpha$ -methylstyrene	6.818	275	$y=10.7919x+43.7619$
4-chlorostyrene	7.053	275	$y=6.1589x-0.3511$
<i>trans</i> -stilbene	9.906	275	$y=78.5455x-46.2976$
<i>trans</i> - $\alpha$ -methylstilbene	11.977	275	$y=16.1024x-67.4308$
<i>trans</i> -4-bromostilbene	14.452	275	$y=95.0744x-478.4399$
<b><u>Suzuki coupling</u></b>			
4-chlorobenzeneboronic acid	2.8	225	$y=51.1865x-2.6375$
phenylboronic acid	2.789	225	$y=24.2373x+91.0107$
4-chlorobenzeneboronic acid	3.145	225	$y=35.0299x-77.2933$
4-bromobenzeneboronic acid	3.263	225	$y=32.2091x+80.7563$
1-chloro-2-nitrobenzene	3.9	225	$y=18.0722x+5.3133$
4-biphenylboronic acid	4.1	225	$y=5.9876x$
4-chloro-2-nitrobiphenyl	5.75	225	$y=38.5886x+6.968$
4-acetylbiphenyl	5.992	225	$y=18.7180x+7.5612$
biphenyl	7.483	225	$y=7.1432x$
4,4'-dichlorobiphenyl	11.573	225	$y=10.3616x-13.1813$
<b><u>epoxidation</u></b>			
phenyl acetaldehyde	3.020	225	$y=4.0689x+13.2249$
benzaldehyde	3.524	225	$y=13.3894x-20.8641$
styrene oxide	4.35	225	$y=15.7776x-16.9201$
<i>trans</i> -stilbene oxide	6.957	225	$y=55.2641x+325.1597$

The conversions of reactants and the selectivity of the products obtained in Heck and Suzuki coupling reactions, epoxidations, hydrogenations and tandem reactions were determined by high performance liquid chromatography (HPLC) using an Agilent instrument 1200 series with 250×4 mm chromatographic column Multospher 120 RP18-5μ from Ziemer Chromatographie Langerwehe/Germany. A mixture of acetonitrile/water (70 vol% /30 vol%) was used as eluent with a flow rate of 1 mL/min, T=25 °C, λ=225 or 275 nm, injection volume=10 μL, p=110-114 bar and t=11 min. All samples were dissolved in acetonitrile or dimethyl formamide (F=25).

### 3.5.2 Gas chromatography (GC)

The conversions X and the enantiomeric excess ee% of the enantioselective hydrogenation of IA, DMI, DEI and DBI were obtained by gas chromatography using a Hewlett-Packard model HP 5710 equipped with a Lipodex E column (Macherey-Nagel GmbH & Co. KG, Düren/Germany). Following conditions were used for the analysis: T<sub>injector</sub>=200°C, T<sub>detector</sub>=250 °C, T<sub>oven</sub>= 80 °C and p<sub>column</sub>=60·10<sup>3</sup> Pa, carrier gas=N<sub>2</sub>. For the analysis of itaconic acid (IA), the sample was treated with (trimethylsilyl)diazomethane and then analyzed the same way as described for DMI.

## 4 Results and Discussion

### 4.1 Catalyst characterization

#### 4.1.1. Sol-gel immobilized catalysts

Besides of the already mentioned applications, the sol-gel silica materials can be applied for the synthesis of heterogeneous catalysts. Various metal precursors with or without ligand can be entrapped into the hydrophilic or hydrophobically modified silica matrix and applied in the required reaction. A series of these catalysts (Figure 1) were prepared in this way and applied in different reaction steps:



**Figure 1:** Variety of sol-gel immobilized catalysts

For the enantioselective hydrogenation of itaconates yellow  $[\text{Rh}(\text{cod})\text{Cl}]_2$  or  $[\text{Rh}(\text{nbd})\text{Cl}]_2$  metal precursor and enantioselective ligand BPPM (Figure 1 exemplar 3-4) or commercial RhFerrotane complex (Figure 1 exemplar 5) immobilized on silica were applied. The catalyst and ligand forms a complex which is incorporated in the pores of white silica support e.g.  $\text{OcSiO}_2$  (Figure 1 exemplar 2).

For the coupling reactions red  $\text{Pd}(\text{OAc})_2$  catalyst precursor immobilized on silica or a mixture of magnetic  $\text{Fe}_3\text{O}_4$  and silica can be used. During the sol-gel process the red Pd(II) catalyst is

reduced to black Pd(0) nanoparticles (Figure 1 exemplar 1, 6-7) which are involved in the catalytic reaction. Characteristic binding energy peaks were obtained from X-ray photoelectron spectroscopy (XPS) measurements [39] at 336.8 and 342.11 eV before catalyst entrapment and 335.55 and 340.81 eV after the entrapment. These signals are characteristic for Pd(II) and Pd(0) species, respectively.

The epoxidations were performed with palladium catalysts described before, a light pink manganese (II) acetylacetonate complexes or a mixture of palladium and manganese catalyst precursors were immobilized on silica (Figure 1 exemplar 8-9).

Following particle size distribution was obtained for the immobilized palladium, rhodium and manganese catalysts and was determined by sieving method: about 60% was smaller than 200  $\mu\text{m}$ , only about 13 % of particles were between 400-715  $\mu\text{m}$  and 715-850  $\mu\text{m}$  and about 6 % were between 200-300  $\mu\text{m}$  and 300-400  $\mu\text{m}$ . The larger particles were reduced to smaller pieces during the reaction.

In Table 2 the stabilities of all immobilized catalysts after the preparation and the loading of metal precursors on silica supports are shown. The stability of the catalyst (metal and ligand leaching) after the preparation was determined from the analysis of washing solutions by ICP-OES. The metal precursor loading in the silica material is the ratio of the mass of metal precursor entrapped into support material and the mass of the whole immobilized catalyst. The mass of metal precursor entrapped into silica matrix should be identical to the initial weight of the metal precursor applied in the sol-gel procedure if no metal leaching after the preparation was detected. The metal content was determined by microwave decomposition method and ICP-OES. There the metal precursor and ligand were removed from the support material into solution and the concentrations of the compounds in these solutions were measured by ICP-OES.

**Table 2:** Catalyst stability after the immobilization (leaching) and metal loading on silica support

catalyst	support	metal precursor loading on support (wt%) <sup>a</sup>	leaching after preparation of intended loading (%)
[Rh(cod)Cl] <sub>2</sub> /BPPM	SiO <sub>2</sub>	0.92 (0.91 <sup>f</sup> )	0.47-2.3% [Rh(cod)Cl] <sub>2</sub> (0.72% BPPM)
[Rh(cod)Cl] <sub>2</sub> /BPPM	EtSiO <sub>2</sub>	0.92 (0.91 <sup>f</sup> )	0.36% [Rh(cod)Cl] <sub>2</sub> (0.42% BPPM)
[Rh(cod)Cl] <sub>2</sub> /BPPM	SiO <sub>2</sub> /EtSiO <sub>2</sub>	0.92 (0.91 <sup>f</sup> )	1.8% [Rh(cod)Cl] <sub>2</sub>
[Rh(cod)Cl] <sub>2</sub> /BPPM	PhSiO <sub>2</sub>	0.92	0.04% [Rh(cod)Cl] <sub>2</sub> (0.14% BPPM)
[Rh(cod)Cl] <sub>2</sub> /BPPM	OcSiO <sub>2</sub>	0.92 (0.8 <sup>f</sup> )	12% [Rh(cod)Cl] <sub>2</sub> (31.89% BPPM)
Pd(OAc) <sub>2</sub>	PhSiO <sub>2</sub>	1.25	0
Pd(OAc) <sub>2</sub>	2PhSiO <sub>2</sub>	0.07	0
Pd(OAc) <sub>2</sub>	3PhSiO <sub>2</sub>	0.49	0
Pd(OAc) <sub>2</sub> <sup>b</sup>	PhSiO <sub>2</sub>	1.25 (0.43 <sup>f</sup> )	14% Pd(OAc) <sub>2</sub>
Pd(OAc) <sub>2</sub> <sup>c</sup>	PhSiO <sub>2</sub>	1.25 (1.1 <sup>f</sup> )	0.07% Pd(OAc) <sub>2</sub>
Pd(OAc) <sub>2</sub> <sup>d</sup>	PhSiO <sub>2</sub>	1.25 (1.2 <sup>f</sup> )	0.33% Pd(OAc) <sub>2</sub> (2.3% SPhos)
Pd(OAc) <sub>2</sub>	OcSiO <sub>2</sub>	1.25	0
Pd(OAc) <sub>2</sub>	SiO <sub>2</sub>	1.25	0
PdBr <sub>2</sub>	PhSiO <sub>2</sub>	1.25	0
Pd <sup>e</sup>	SiO <sub>2</sub>	1.25	0
Pd <sup>e</sup>	charcoal	1.25	0
Pd <sup>e</sup>	Al <sub>2</sub> O <sub>3</sub>	1.25	0
Pd(OAc) <sub>2</sub>	0.1 PhSiO <sub>2</sub> Fe <sub>3</sub> O <sub>4</sub>	1.21	0
Pd(OAc) <sub>2</sub>	0.3 PhSiO <sub>2</sub> Fe <sub>3</sub> O <sub>4</sub>	1.22	0
Pd(OAc) <sub>2</sub>	0.5 PhSiO <sub>2</sub> Fe <sub>3</sub> O <sub>4</sub>	1.21	0
Pd(OAc) <sub>2</sub>	1PhSiO <sub>2</sub> Fe <sub>3</sub> O <sub>4</sub>	0.83	0.01
Mn(AcAc) <sub>2</sub>	1PhSiO <sub>2</sub>	1.47	0.52
Mn(AcAc) <sub>2</sub>	2PhSiO <sub>2</sub>	0.74	0.04
Mn(AcAc) <sub>2</sub>	3PhSiO <sub>2</sub>	0.51	0.19
Mn(AcAc) <sub>2</sub> -PdBr <sub>2</sub>	1PhSiO <sub>2</sub>	1.06% PdBr <sub>2</sub> / 1.20% Mn(AcAc) <sub>2</sub>	0.029% Mn(AcAc) <sub>2</sub>
Mn(AcAc) <sub>2</sub> -PdBr <sub>2</sub>	2PhSiO <sub>2</sub>	0.65% PdBr <sub>2</sub> / 0.74% Mn(AcAc) <sub>2</sub> (0.6% Mn(AcAc) <sub>2</sub> <sup>f</sup> )	3.68% Mn(AcAc) <sub>2</sub>
Mn(AcAc) <sub>2</sub> -PdBr <sub>2</sub>	3PhSiO <sub>2</sub>	0.44% PdBr <sub>2</sub> / 0.49% Mn(AcAc) <sub>2</sub>	0
Mn(AcAc) <sub>2</sub> -PdBr <sub>2</sub> -Xantphos	PhSiO <sub>2</sub>	1.06% PdBr <sub>2</sub> / 1.47% Mn(AcAc) <sub>2</sub> (1.1% Mn(AcAc) <sub>2</sub> <sup>f</sup> )	0.01% PdBr <sub>2</sub> / 6.69% Mn(AcAc) <sub>2</sub>
Mn(AcAc) <sub>2</sub> -Pd(OAc) <sub>2</sub>	PhSiO <sub>2</sub>	1.38% Pd(OAc) <sub>2</sub> / 1.57% Mn(AcAc) <sub>2</sub>	0.21% Pd(OAc) <sub>2</sub> / 0.67% Mn(AcAc) <sub>2</sub>
Mn(AcAc) <sub>2</sub> -Pd(OAc) <sub>2</sub> -Xantphos	PhSiO <sub>2</sub>	1.39% Pd(OAc) <sub>2</sub> / 1.58% Mn(AcAc) <sub>2</sub>	0.71% Mn(AcAc) <sub>2</sub>

<sup>a</sup> calculated from initial weight of the catalyst; <sup>b</sup> TPPTS; <sup>c</sup> Xantphos; <sup>d</sup> SPhos; <sup>e</sup> commercial catalyst; <sup>f</sup> calculated from microwave decomposition and ICP-OES measurements

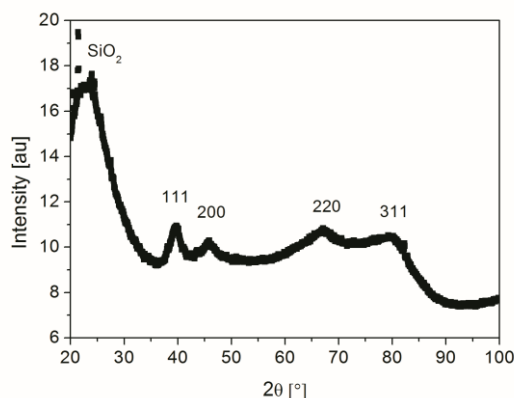
From the amount of the leached metal during the catalyst washing (entrapment process) and also from microwave decomposition and ICP-OES measurements (Table 2), the amount of metal precursor immobilized on silica could be obtained. From these results the immobilization efficiency  $\eta_{\text{immobilisation}}$  was calculated. The determined values describe the stability of the prepared catalyst before reaction:

$$\eta_{\text{immobilisation}} = \frac{m_{\text{metal catalyst,immobilized}}}{m_{\text{metal catalyst,initial}}} \quad \text{Eq 6}$$

Most stable catalysts were sol-gel immobilized and commercial palladium complexes with  $\eta_{\text{immobilization}}=1$ , between 0.3-1% leaching of catalyst precursor and ligand was obtained for immobilized rhodium catalysts and  $\eta_{\text{immobilization}}$  was 0.977-0.996. As also already known from the literature heterogeneous manganese catalysts are not very stable and difficult to immobilize. The immobilization efficiency was 0.9948 for  $\text{Mn}(\text{AcAc})_2@\text{PhSiO}_2$  with 0.52%  $\text{Mn}(\text{AcAc})_2$  leaching and 0.999 % for mixed  $\text{PdBr}_2\text{Mn}(\text{AcAc})_2@\text{PhSiO}_2$  catalyst with 0.029%  $\text{Mn}(\text{AcAc})_2$  leaching.

#### 4.1.2. XRD measurements

The crystallographic structure of the sol-gel immobilized catalyst  $\text{Pd}(\text{OAc})_2@\text{PhSiO}_2$  was analyzed by X-ray diffraction measurement (XRD).



**Figure 2:** XRD measurement of an immobilized Pd catalyst after the Heck reaction (2.72 wt% palladium acetate on  $\text{PhSiO}_2$ )

The observed size of crystals was 2.7-3.4 nm.  $\text{Pd}(\text{II})$  species were reduced to metallic  $\text{Pd}(0)$  through the sol-gel process and metallic fcc palladium phase with (111), (200), (220) and (311) crystallographic planes were obtained in the XRD patterns of the sample (Figure 2). Also a large amorphous peak characteristic to  $\text{SiO}_2$  support can be seen from this diffractogram.

#### 4.1.3. BET measurements

As can be seen from the subsequent tables, the surface areas of pure support materials were comparable to the surface areas of catalysts immobilized on these supports. The surface areas of rhodium catalysts were in the range of 320-380 m<sup>2</sup>/g. Palladium acetate and bromide immobilized on hydrophilic and hydrophobic silica with and without addition of magnetic iron (II,III) oxide had a specific surface area A between 200-300 m<sup>2</sup>/g, except the catalysts immobilized in the presence of ligands. These results are comparable to the surface areas of commercial palladium catalysts immobilized on silica. For the palladium acetate catalyst immobilized on PhSiO<sub>2</sub>, which was mainly used in this work, also the poresize was measured to be  $d_{\text{pore}} \leq 2$  nm, which is characteristic for microporous catalysts. The surface areas of manganese and mixed palladium-manganese catalyst were mostly between 400-500 m<sup>2</sup>/g.

**Table 3:** Specific surface areas A of immobilized [Rh(cod)Cl]<sub>2</sub>/BPPM catalysts and support materials applied in enantioselective hydrogenation of itaconates

catalyst	support	A [m <sup>2</sup> /g]
-	SiO <sub>2</sub>	397.3
-	EtSiO <sub>2</sub>	467.4
-	PhSiO <sub>2</sub>	249.7
Rh/BPPM	SiO <sub>2</sub>	382.8
Rh/BPPM	EtSiO <sub>2</sub>	224.8
Rh/BPPM	PhSiO <sub>2</sub>	327.1
Rh/BPPM	OcSiO <sub>2</sub>	326.5

**Table 4:** Specific surface areas A of supported palladium catalysts applied in Heck and Suzuki coupling reaction, hydrogenation, epoxidation and tandem reactions

catalyst	support	A [m <sup>2</sup> /g]
Pd(OAc) <sub>2</sub> <sup>a</sup>	PhSiO <sub>2</sub>	263.2
Pd(OAc) <sub>2</sub>	2PhSiO <sub>2</sub>	219.9
Pd(OAc) <sub>2</sub>	3PhSiO <sub>2</sub>	104.5
Pd(OAc) <sub>2</sub> <sup>b</sup>	PhSiO <sub>2</sub>	110.2
Pd(OAc) <sub>2</sub> <sup>c</sup>	PhSiO <sub>2</sub>	66.7
Pd(OAc) <sub>2</sub>	OcSiO <sub>2</sub>	22.8
Pd(OAc) <sub>2</sub>	SiO <sub>2</sub>	338.2
PdBr <sub>2</sub>	PhSiO <sub>2</sub>	216.3
Pd <sup>d</sup>	SiO <sub>2</sub>	254.7
Pd <sup>d</sup>	charcoal	792.6
Pd <sup>d</sup>	Al <sub>2</sub> O <sub>3</sub>	160.9

<sup>a</sup> Porevolume=0.176cm<sup>3</sup>/g,  $d_{\text{pore}} \leq 2.45$ nm, <sup>b</sup> TPPTS,

<sup>c</sup> Xantphos, <sup>d</sup> commercial catalyst

**Table 5:** Specific surface areas A of magnetic Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub>Fe<sub>3</sub>O<sub>4</sub> catalysts used in Heck reaction

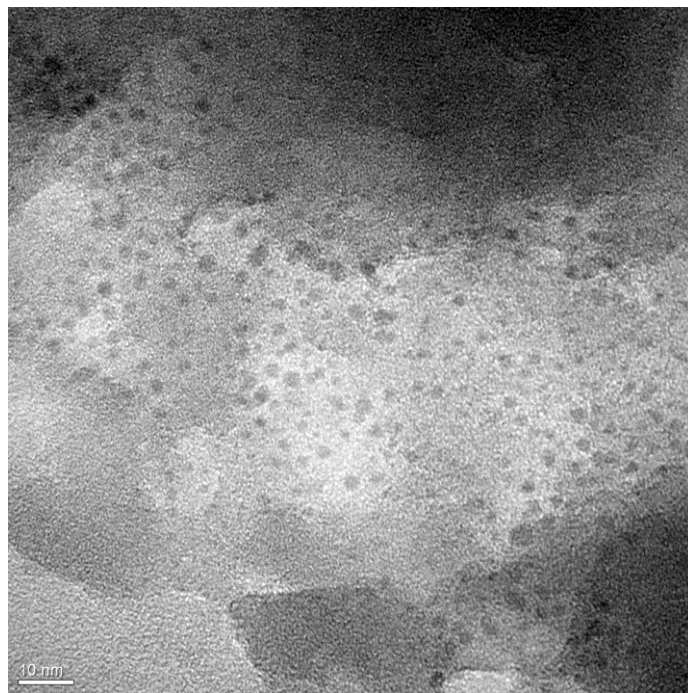
<b>Fe<sub>3</sub>O<sub>4</sub> amount [g]</b>	<b>A [m<sup>2</sup>/g]</b>
0.1	188.9
0.3	215.1
0.5	168.3
1	249.1

**Table 6:** Specific surface areas A of Mn and Mn-Pd catalysts immobilized on PhSiO<sub>2</sub> applied in Heck coupling, epoxidation and tandem reactions

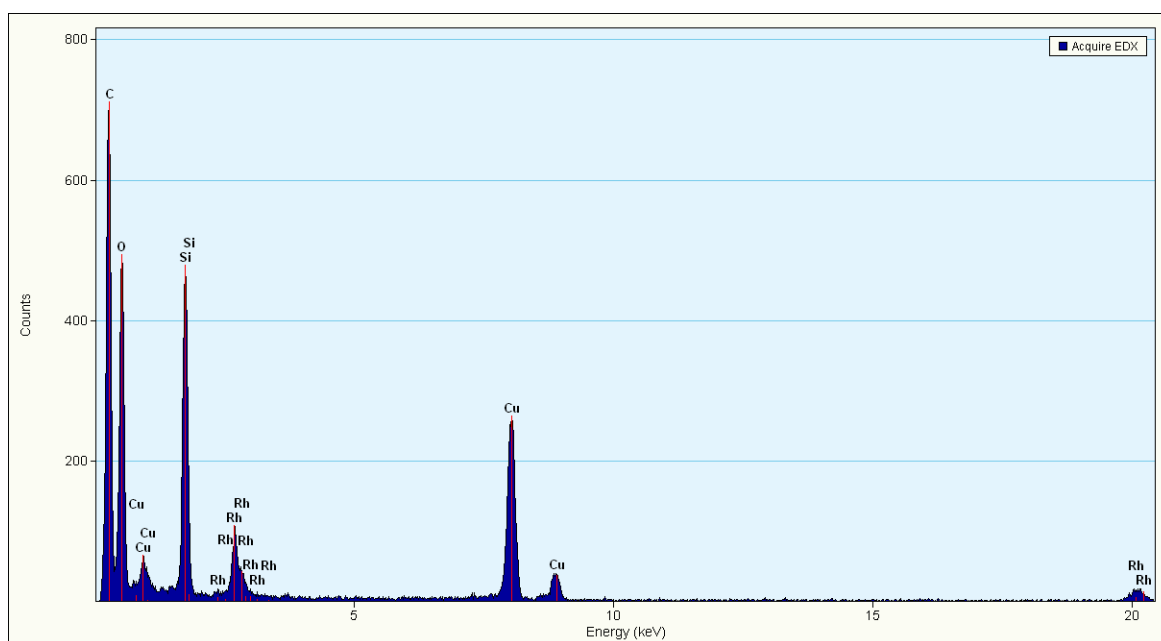
<b>catalyst</b>	<b>support</b>	<b>A [m<sup>2</sup>/g]</b>
Mn(AcAc) <sub>2</sub>	PhSiO <sub>2</sub>	551.9
Mn(AcAc) <sub>2</sub>	2PhSiO <sub>2</sub>	572.2
Mn(AcAc) <sub>2</sub>	3PhSiO <sub>2</sub>	588.0
Mn(AcAc) <sub>2</sub> -PdBr <sub>2</sub>	PhSiO <sub>2</sub>	151.8
Mn(AcAc) <sub>2</sub> -PdBr <sub>2</sub>	2PhSiO <sub>2</sub>	437.6
Mn(AcAc) <sub>2</sub> -PdBr <sub>2</sub>	3PhSiO <sub>2</sub>	348.4
Mn(AcAc) <sub>2</sub> -PdBr <sub>2</sub> -Xantphos	PhSiO <sub>2</sub>	557.9
Mn(AcAc) <sub>2</sub> -Pd(OAc) <sub>2</sub>	PhSiO <sub>2</sub>	433.1
Mn(AcAc) <sub>2</sub> -Pd(OAc) <sub>2</sub> - Xantphos	PhSiO <sub>2</sub>	336.9

#### 4.1.4. TEM and EDX measurements

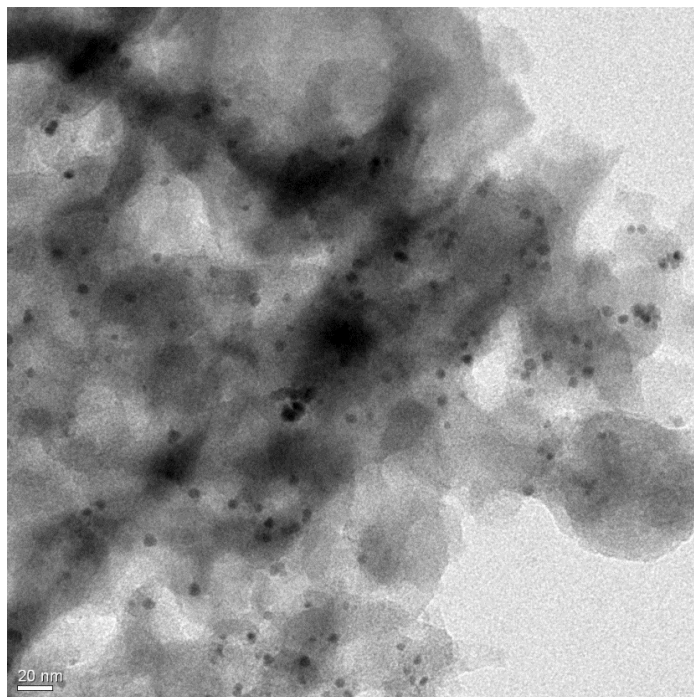
The transmission electron microscopy measurements (TEM) of palladium acetate catalyst immobilized on PhSiO<sub>2</sub> and applied in Heck and epoxidation reactions and also of [Rh(cod)Cl]<sub>2</sub>/BPPM catalyst immobilized on SiO<sub>2</sub> and used in enantioselective hydrogenation of itaconates show a highly porous structures with micropores of about 1-3 nm. There were no difference between the catalyst structure before and after the reactions, that's why only the TEM images of the immobilized catalysts after the reactions were shown. These pore sizes are comparable to the pore size determined for Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> catalyst from the BET measurement in Chapter 4.1.3. Inside the small pores the black particles are seen, which are characteristic for active metallic compounds intercalated in the pores. This prediction was confirmed by the detection of metallic rhodium and palladium particles inside the pores by energy-dispersive X-ray spectroscopy (EDX).



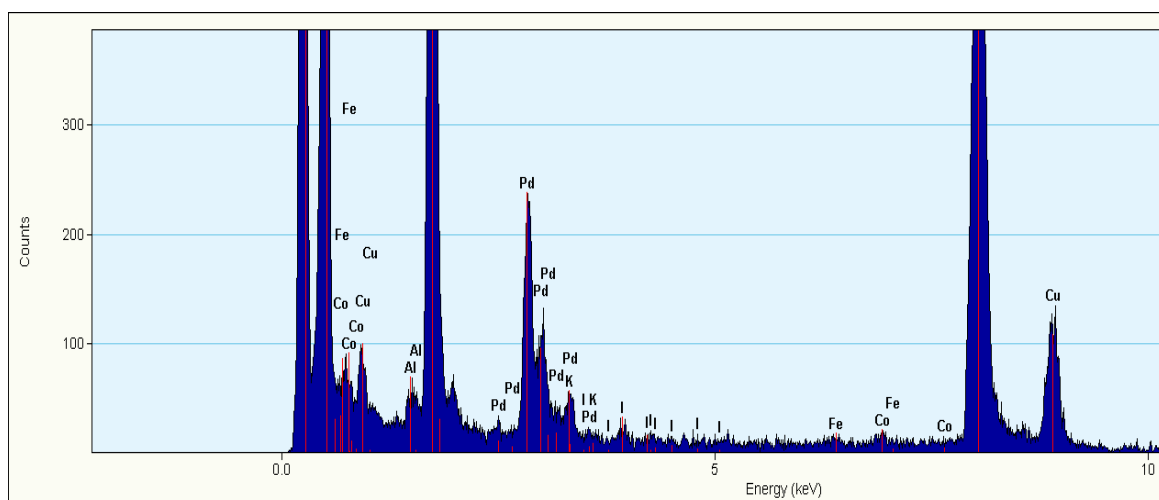
**Figure 3:** TEM image of a typical Rh/BPPM@SiO<sub>2</sub> catalyst after the hydrogenation of itaconic acid in methanol (poresize=1-4nm)



**Figure 4:** EDX spectrum of Rh/BPPM@SiO<sub>2</sub>



**Figure 5:** TEM image of a typical Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> catalyst after Heck reaction (poresize=1-3nm).

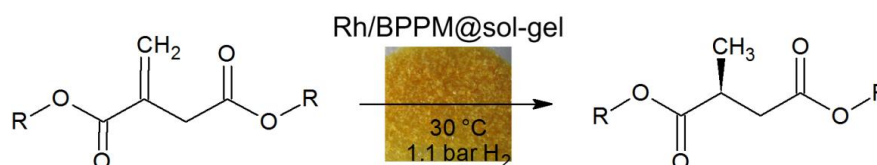


**Figure 6:** EDX spectrum of Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub>

## 4.2 Enantioselective Hydrogenation of itaconic acid and derivatives

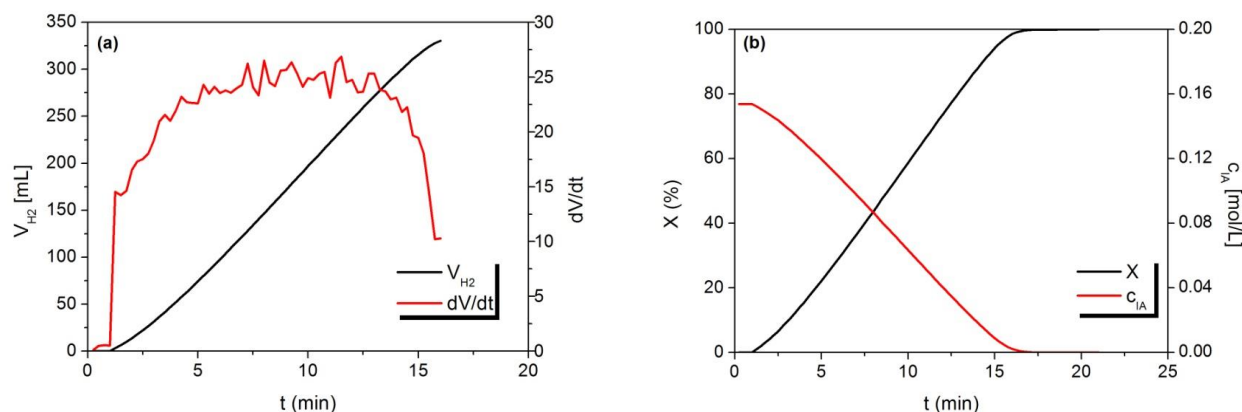
### 4.2.1. Reaction

Homogeneous enantioselective hydrogenation of itaconic acid to (*S*)-(+)-2-methylsuccinic acid was extensively studied in the last years with the accent on evaluation of new chiral catalysts. Itaconic acid is preferred as model substance for this reaction because of high solubility (hydrophilicity) in organic solvents and water and also because of good reactivity with a variety of catalysts. As catalyst we have chosen an in situ generated catalyst-ligand complex, which was formed from commercially available neutral chloroolefin rhodium complex [Rh(cod)Cl]<sub>2</sub> (synthesized from RhCl<sub>3</sub> and 1,5-cyclooctadiene) and chiral (2*S*,4*S*)-BPPM ligand. The complex allows the formation of the desired (*S*)-product with high enantiomeric excess, ee%, because of the coordination of the substrate on the catalyst complex only from the one side. The complex was entrapped into the hydrophilic silica support prepared from tetramethyl orthosilicate by sol-gel method aiming to decrease the air sensibility of the catalyst and to reuse it in subsequent reaction steps. The enantioselective reaction (Scheme 18) was carried out in methanol and aqueous-micellar solutions of different surfactants at 30°C and 1.1·10<sup>5</sup> Pa H<sub>2</sub> pressure:



**Scheme 18:** Hydrogenation of itaconic acid and derivatives

A typical reaction profile of the enantioselective hydrogenation is shown in Figure 7 for the homogeneously catalyzed hydrogenation of itaconic acid in methanol. The itaconic acid consumption  $c_{IA}(t)$  was calculated from the amount of hydrogen  $V_{H_2}$  (Figure 7a) added during the reaction and the conversion  $X$  was determined from this concentration decrease (Figure 7b). The results could be compared to the results obtained by GC analysis at the end of the reaction. In all cases the results should be comparable except the situation when the reactor would not be leak proof.

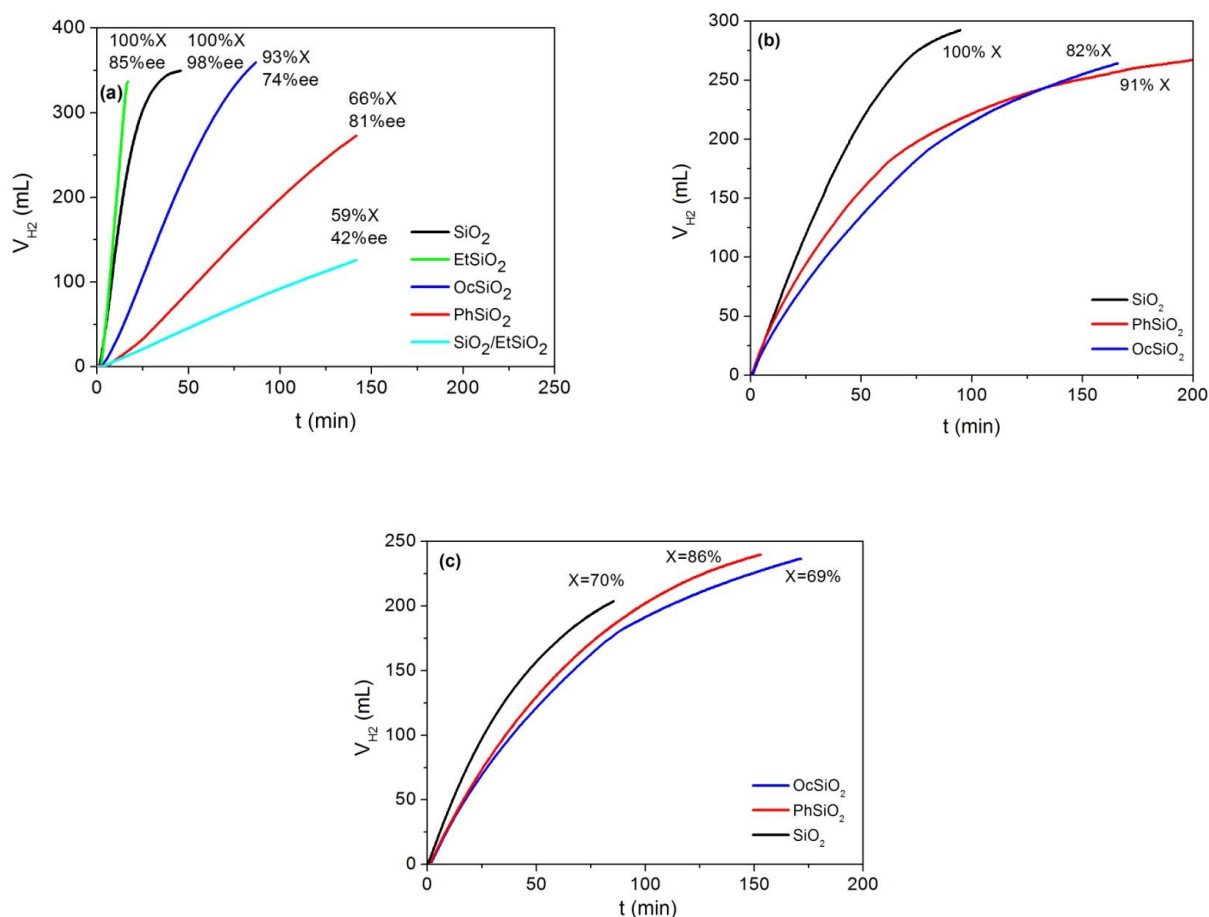


**Figure 7:** Reaction profile of the homogeneous hydrogenation of itaconic acid in methanol (a) cumulative hydrogen consumption  $V_{H_2}$  and hydrogen flow ( $dV/dt$ ); (b) conversion of itaconic acid  $X$  and substrate concentration  $c_{IA}$  (15.4 mmol IA, 0.022 mmol  $[Rh(cod)Cl]_2$ , 0.044 mmol BPPM, 100 mL MeOH,  $1.1 \cdot 10^5$  Pa  $H_2$ , 800 rpm, 30 °C).

#### 4.2.2. Choice of the catalyst

Besides the hydrophobic character of the substrate, the polarity of the catalyst surface also influences the rate of the hydrogenation reaction. The catalysts were prepared with different hydrophilic and hydrophobic sol-gel building agents: hydrophilic tetramethyl orthosilicate ( $SiO_2$ ), tetraethyl orthosilicate ( $EtSiO_2$ ), a mixture of tetramethyl and tetraethyl orthosilicate ( $SiO_2/EtSiO_2$ ) and hydrophobically modified silica's ( $PhSiO_2$  and  $OcSiO_2$ ). The entrapment of the catalyst precursor into the hydrophilic  $SiO_2$  or  $EtSiO_2$  matrix was catalyzed by an acid. In addition to the activity of the catalyst the gelation speed increases through the addition of a base at the end of the process: ammonia ( $NH_3$ ) to tetramethyl orthosilicate and triethylamine ( $NEt_3$ ) to tetraethyl orthosilicate.

The hydrogenations of IA, DMI and DBI were carried out with sol-gel supported Rh/BPPM catalysts immobilized on these different hydrophobic surfaces and the reaction profiles are shown in Figure 8:



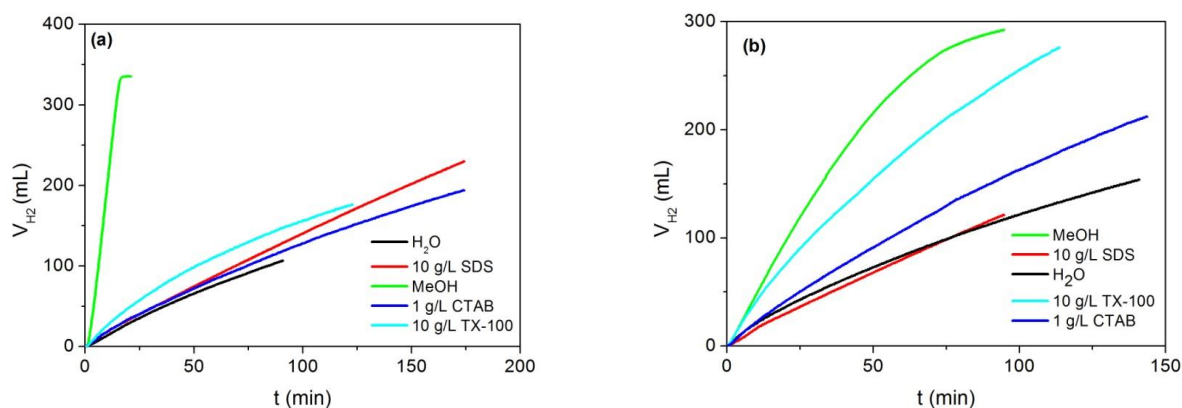
**Figure 8:** Effect of the silica support on the reaction behavior (a) IA, (b) DMI, (c) DBI (15.4 mmol substrate, 0.022 mmol [Rh(cod)Cl]<sub>2</sub>, 0.044 mmol BPPM, 100 mL MeOH, 1.1 · 10<sup>5</sup> Pa H<sub>2</sub>, 800 rpm, 30 °C)

The reaction rate of the hydrogenation of more hydrophilic substrates (IA, DMI) increases if catalysts immobilized on hydrophilic surfaces were applied (SiO<sub>2</sub>, EtSiO<sub>2</sub>). The reaction rate was quite the same in the hydrogenation of more hydrophobic DBI with the catalyst immobilized on hydrophobic support. The use of Rh/BPPM catalyst immobilized within hydrophobically modified silica is preferred in reactions with more hydrophobic substrates for example DBI because of hydrophobic attractive interactions or absorption between the substrate and the catalyst surface. The same effect was seen in Heck reaction with immobilized Pd(OAc)<sub>2</sub> catalyst and aromatic substrates and will be discussed in the next chapters. Further advantages of the catalysts immobilized on hydrophobically modified surfaces were already shown in literature. Catalysts immobilized on these surfaces were more stable and no leaching into the reaction mixture was observed because of more branched silica structure inside the support material [32]. From our results it is also clear that the catalyst immobilized in a more branched

matrix is more stable: about 2-3 wt%  $[\text{Rh}(\text{cod})\text{Cl}]_2$  and 4-7 wt% BPPM leaching during the reaction was obtained by using  $\text{Rh/BPPM@OcSiO}_2$  or  $\text{@PhSiO}_2$  catalyst and 10-14 wt%  $[\text{Rh}(\text{cod})\text{Cl}]_2$  and 17-30 wt% BPPM leached into the solution by applying  $\text{Rh/BPPM@SiO}_2$  or  $\text{@EtSiO}_2$  as catalyst.

#### 4.2.3. Effect of reaction medium

Most homogeneously catalyzed reactions are carried out in conventional organic solvents, but the use of water as solvent allows more environmentally friendly process management. The main problem of using water as reaction medium is that many substrates are hydrophobic and cannot be solubilized completely in water. The addition of surfactants with concentrations higher than the critical micelle concentration (*cmc*) results in the formation of micelles, which are able to store the substrates in their cores. Depending on the partition coefficient, the substrates are stored in the cores of micelles (hydrophobic substrates) or in the palisade layer (hydrophilic substrates) as was shown in Scheme 10 (Page 22) [55]. By increasing the surfactant concentration, the solubility of the substrates can be improved. In Figure 9a the reaction profiles for the hydrogenation of itaconic acid in methanol, water and in aqueous-micellar solutions of different surfactants are shown.



**Figure 9:** Effect of the solvent (a) IA, (b) DMI (15.4 mmol substrate, 0.022 mmol  $[\text{Rh}(\text{cod})\text{Cl}]_2$ , 0.044 mmol BPPM, 100 mL solvent,  $1.1 \cdot 10^5$  Pa  $\text{H}_2$ , 800 rpm, 30 °C)

As expected, because of the higher solubility of hydrogen in methanol (about 5 times higher), the reaction is faster in methanol than in aqueous media and the addition of surfactants to water did not improved the reaction rate of this hydrophilic substrate. In the aqueous-micellar solutions the hydrogenation reactions proceed with a similar rate as in water, because of the high solubility of itaconic acid in water (ca. 40 g/L). That's why the addition of surfactants is

not required for the solubilization and hydrogenation of IA. For the hydrogenation of DMI, the use of more hydrophobic nonionic Triton TX-100 surfactant (HLB=13.5) or cationic cetyltrimethylammonium bromide CTAB (HLB=12) with lower HLB value (hydrophilic lipophilic balance) is advisable. The reaction rates is higher than for the reaction only in water or aqueous solution of hydrophilic SDS surfactant (HLB=40) as shown in Figure 9b.

The reaction rates of the hydrogenation of dimethyl itaconate in methanol and in aqueous-micellar solution with Triton TX-100 surfactant are comparable. But the main disadvantage of using the micellar solutions for this reaction with heterogeneous catalysts is the decreased enantioselectivity (Table 7). Only the reactions in aqueous-micellar solutions with homogeneous catalysts proceed with high enantioselectivities (entry 8 and 10), because the immobilized rhodium complexes are not protected against contact with water by embedding them in the hydrophobic cores of the micelles. This was also shown to be important in a variety of hydrogenation reactions with homogeneous rhodium catalysts [56,57,73]. The same phenomenon was reported by J. Jamis et al. [74,75] for the hydrogenation of  $\alpha$ -acetamidocinnamic acid and itaconic acid with catalyst immobilized on silica by sol-gel method or on hexagonal mesoporous silica (HMS) in water. Only 20% ee was reported for the hydrogenation of IA in water catalyzed by Rh/BPPM on HMS and 24% ee with sol-gel (EtSiO<sub>2</sub>) immobilized Rh/BPPM.

In our process the addition of methanol to an aqueous solution (1:1) (entry 6) or the use of cyclohexane/Triton TX-100/water/1-pentanol microemulsion (entry 12), reported by [76] as alternative reaction media, has increased the reaction rate because of the involvement of organic solvent in the reaction process and increasing the solubility of the hydrogen, but it did not improved the enantioselectivity. A successful application of this concept is an EST process (emulsion-solid transport), which has already been reported in [77] for the Suzuki and Heck coupling reactions with sol-gel immobilized palladium catalysts in microemulsions.

**Table 7:** Conversions, enantiomeric excess (ee) and turnover frequencies (TOF) for hydrogenation reactions in methanol and in aqueous-micellar solutions with homogeneous and supported Rh/BPPM catalysts <sup>[a]</sup>.

entry	catalyst	subst-rate	X (%) <sup>[c]</sup>	ee (%) <sup>[c]</sup>	TOF (1/h) <sup>[b]</sup>	support	solvent
1	[Rh(cod)Cl] <sub>2</sub>	IA	100	99	6132	-	methanol
2	[Rh(cod)Cl] <sub>2</sub>	IA	100	98	2390	SiO <sub>2</sub>	methanol
3	[Rh(nbd)Cl] <sub>2</sub>	IA	100	99	3947	-	methanol
4	[Rh(nbd)Cl] <sub>2</sub>	IA	100	98	4426	SiO <sub>2</sub>	methanol
5	[Rh(cod)Cl] <sub>2</sub>	IA	25	37	126	SiO <sub>2</sub>	water
6	[Rh(cod)Cl] <sub>2</sub>	IA	44	35	201	SiO <sub>2</sub>	H <sub>2</sub> O/ methanol
7	[Rh(cod)Cl] <sub>2</sub>	IA	100	2	111	SiO <sub>2</sub>	H <sub>2</sub> O/SDS <sup>[d]</sup>
8	[Rh(cod)Cl] <sub>2</sub>	IA	100	95	377	-	H <sub>2</sub> O/CTAB <sup>[e]</sup>
9	[Rh(cod)Cl] <sub>2</sub>	IA	100	23	163	SiO <sub>2</sub>	H <sub>2</sub> O/CTAB <sup>[e]</sup>
10	[Rh(cod)Cl] <sub>2</sub>	IA	100	88	565	-	H <sub>2</sub> O/TX-100 <sup>[d]</sup>
11	[Rh(cod)Cl] <sub>2</sub>	IA	45	30	195	SiO <sub>2</sub>	H <sub>2</sub> O/TX-100 <sup>[d]</sup>
12	[Rh(cod)Cl] <sub>2</sub>	IA	100	2	251	SiO <sub>2</sub>	microemulsion <sup>[f]</sup>
13	[Rh(cod)Cl] <sub>2</sub>	DMI	100	61	592	-	methanol
14	[Rh(cod)Cl] <sub>2</sub>	DMI	56	12	398	SiO <sub>2</sub>	methanol
15	[Rh(nbd)Cl] <sub>2</sub>	DMI	100	63	964	-	methanol
16	[Rh(nbd)Cl] <sub>2</sub>	DMI	100	5	369	SiO <sub>2</sub>	methanol
17	[Rh(cod)Cl] <sub>2</sub>	DMI	53	2	121	SiO <sub>2</sub>	water
18	[Rh(cod)Cl] <sub>2</sub>	DMI	79	20	464	-	H <sub>2</sub> O/SDS <sup>[d]</sup>
19	[Rh(cod)Cl] <sub>2</sub>	DMI	62	10	235	SiO <sub>2</sub>	H <sub>2</sub> O/SDS <sup>[d]</sup>
20	[Rh(cod)Cl] <sub>2</sub>	DMI	96	33	508	-	H <sub>2</sub> O/TX-100 <sup>[d]</sup>
21	[Rh(cod)Cl] <sub>2</sub>	DMI	63	10	300	SiO <sub>2</sub>	H <sub>2</sub> O/TX-100 <sup>[d]</sup>

<sup>[a]</sup> reaction conditions: 15.4 mmol substrate, 0.022mmol [Rh(cod)Cl]<sub>2</sub>, 0.044 mmol BPPM, 100mL solvent, 1.1 · 10<sup>5</sup> Pa H<sub>2</sub>, 800rpm, 30 °C

<sup>[b]</sup> Rh content from ICP measurements

<sup>[c]</sup> GC measurements

<sup>[d]</sup> 10 g/L surfactant

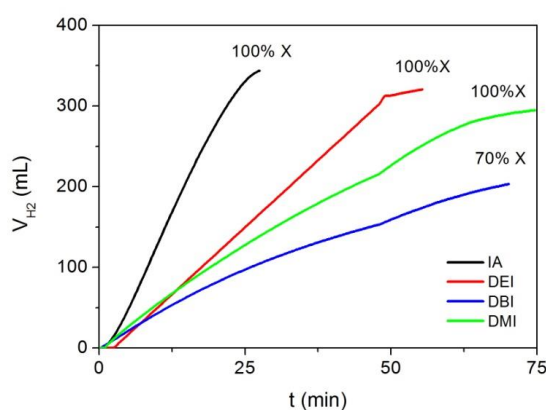
<sup>[e]</sup> 1 g/L surfactant

<sup>[f]</sup> microemulsion: 77wt% cyclohexane, 5wt% water, 9wt% Triton TX-100 and 9wt% pentanol [73]

The conversions and enantioselectivities obtained for the hydrogenation of itaconic acid and derivatives with sol-gel immobilized Rh/BPPM catalysts in methanol solution are comparable with results obtained with homogeneous catalysts and also with rhodium catalysts immobilized on mesoporous silica e.g. MCM-41 or SBA-15. Some of the catalyst could be recycled about 4-8 times without loss in activity and enantioselectivity [19,78,79]. The hydrogenation reactions in aqueous solutions are not very common and the main challenge here is still to obtain high enantioselectivities.

#### 4.2.4. Substrate variation

The enantioselective hydrogenation catalyzed by  $[\text{Rh}(\text{cod})\text{Cl}]_2/\text{BPPM}@\text{SiO}_2$  was performed with different itaconic acid derivatives in methanol solution. The cumulative hydrogen consumptions for the hydrogenation of hydrophilic water soluble itaconic acid (IA), dimethyl itaconate (DMI), diethyl itaconate (DEI) and hydrophobic dibutyl itaconate (DBI) are shown in Figure 10:



**Figure 10:** Hydrogenation of itaconic acid and derivatives with  $\text{Rh}/\text{BPPM}@\text{SiO}_2$  (15.4 mmol substrate, 0.022 mmol  $[\text{Rh}(\text{cod})\text{Cl}]_2$ , 0.044 mmol BPPM, 100 mL MeOH,  $1.1 \cdot 10^5$  Pa  $\text{H}_2$ , 800 rpm, 30 °C)

The reaction with itaconic acid as substrate was very fast and full conversion was achieved within 25 minutes with 98% ee. For the hydrogenations of dimethyl itaconate and diethyl itaconate, full conversions were achieved only within 50-80 minutes, but interestingly, the reaction with diethyl itaconate was faster than with dimethyl itaconate. The hydrogenation of hydrophobic dibutylitaconate was more slowly, the conversion after 70 minutes was only 70%. From these results it is clear that the conversion of the reaction increases with decreasing hydrophobicity of the substrates (decreasing C-chain length). The comparison to the same

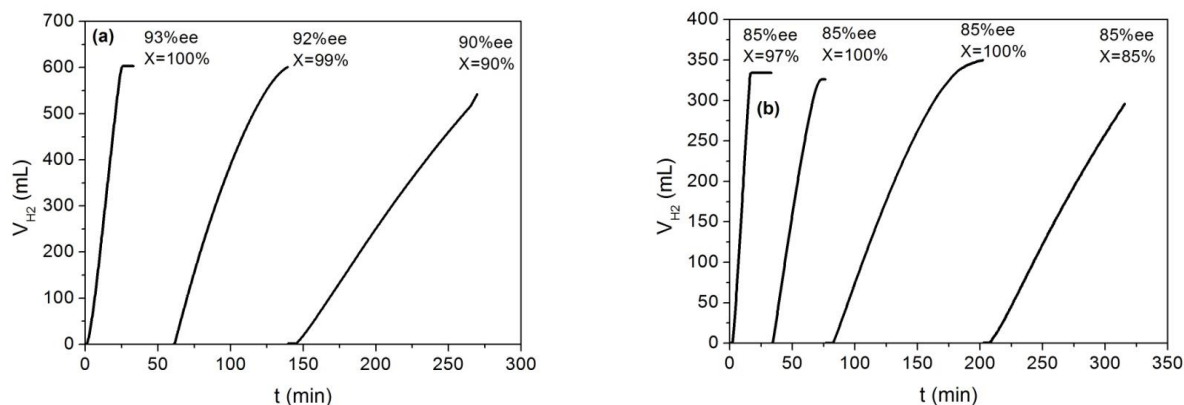
reactions with a homogeneous catalyst also shows that the difference is caused by the reactivity of the substrates [38,66]. The hydrogenations catalyzed by Rh/BPPM@SiO<sub>2</sub> with dimethyl (12 ee %), diethyl and dibutyl itaconates were not enantioselective. The reasons for such a bad selectivities could be changes in the structure of the complex because of the immobilization process (e.g. deactivation of rhodium catalyst to black inactive rhodium (0) particles). Screening for other immobilized catalyst-ligand complexes should improve these bad results. But it is well known that heterogeneous catalysts have limited success in enantioselective reactions.

#### *4.2.5. Efficiency and stability of an immobilized catalyst*

To estimate if the enantioselective hydrogenation catalyzed by sol-gel immobilized Rh/BPPM complexes is a good and a less expensive alternative to the homogeneous reaction, the activity and stability of the heterogeneous catalysts were studied. The stability of the catalysts can be estimated from the number of recycling steps and amount of metal leaching during the catalyst synthesis and preparation. The activity of the heterogeneous catalysts was compared to the unsupported homogeneous catalysts and the diffusion limitations of the reactions were determined.

##### **a) Catalyst recycling**

The replacement of homogeneous molecular catalysts by sol-gel immobilized catalysts allows their reuse and also decreases the costs of the process. In case of an air sensitive in situ formed Rh/BPPM complex the recycling procedure of the catalyst is not very easy. As can be seen in the Figure 11a and b the catalyst could be immobilized on silica support from tetramethyl orthosilicate and tetraethyl orthosilicate as gel building agents, and recycled 3 and 4 times with small loss in activity and enantioselectivity due to the leaching and catalyst deactivation. About 0.1 mg Rh or 0.48 mg [Rh(cod)Cl]<sub>2</sub> (4 wt% of initial amount) and about 0.4 mg P or 7.1 mg (2*S*,4*S*)-BPPM (30 wt% of initial amount) were leached into the solution during the recycling experiments. One part of the catalyst is converted to small black inactive particles which decrease the activity, reaction rate and enantioselectivity. All recycling experiments were carried out under N<sub>2</sub> atmosphere to avoid the deactivation of the catalyst by contact to the oxygen from air.



**Figure 11:** Catalyst recycling (a) Rh/BPPM@SiO<sub>2</sub> (b) Rh/BPPM@ EtSiO<sub>2</sub> (15.4 mmol IA, 0.022 mmol [Rh(cod)Cl]<sub>2</sub>, 0.044 mmol BPPM, 100 mL MeOH, 1.1·10<sup>5</sup> Pa H<sub>2</sub>, 800 rpm, 30°C)

From the recycling experiments with Rh/BPPM@SiO<sub>2</sub> and Rh/BPPM@EtSiO<sub>2</sub> the determined amounts of metal leaching were quantified and the recycling efficiency could be determined:

$$\eta_{recycling} > 1 - \left( \frac{m_{leaching}}{m_{initial}} \right)^N \quad \text{Eq 5}$$

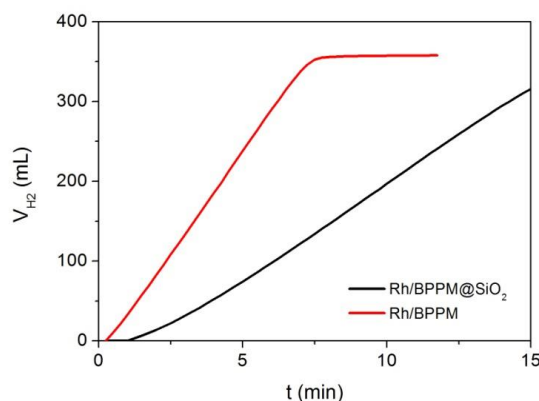
The values of  $\eta_{recycling}$  depend on amount of catalyst leaching during the recycling experiments and on the number of recycling steps  $N$ . For rhodium catalysts immobilized on SiO<sub>2</sub> and EtSiO<sub>2</sub> the recycling efficiency was >0.9936-0.9744 with 4% [Rh(cod)Cl]<sub>2</sub> leaching and >3 and >4 recycling steps.

### b) Catalyst efficiency

Not only good recycling of the catalyst but also a comparable activity to homogeneous not immobilized catalysts is essential for high efficiency of a heterogeneous catalyst. The hydrogenation of itaconic acid was carried out with homogeneous molecular Rh/BPPM catalyst and with sol-gel immobilized Rh/BPPM catalyst. The reaction rate in methanol with heterogeneous Rh/BPPM catalyst was slower than with homogeneous catalyst (Figure 12), but the same enantiomeric excess was obtained (ee=90-97%).

The turnover frequency (TOF) for the sol-gel immobilized Rh/BPPM catalyst was ~2400/h and by about a factor of 3 lower than for the homogeneous catalyst (TOF~6100/h). Possible reasons for such a difference could be mass-transport limitations within the pores of the heterogeneous sol-gel material or a decrease in activity of the catalyst due to its encapsulation inside the silica

material. Both turnover frequencies TOF are typical for an efficient industrial synthesis of small-volume products (TOF>500/h).



**Figure 12:** Homogeneously and heterogeneously catalyzed hydrogenation of IA (15.4 mmol IA, 0.022 mmol [Rh(cod)Cl]<sub>2</sub>, 0.044 mmol BPPM, 100 mL MeOH, 1.1 · 10<sup>5</sup> Pa H<sub>2</sub>, 800 rpm, 30 °C).

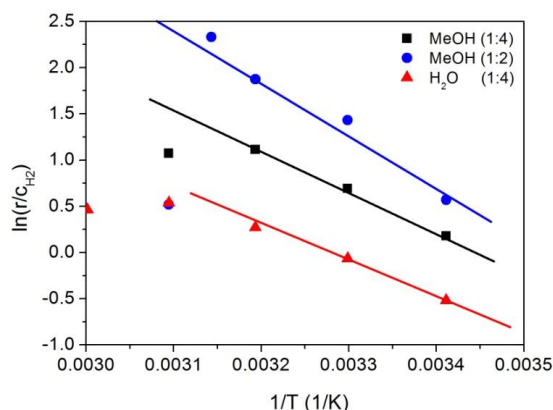
From the comparison of heterogeneously and homogeneously catalyzed reaction, the efficiency of the sol-gel immobilized catalyst  $\eta_{intercalation}$  can be estimated:

$$\eta_{intercalation} = \frac{r_{heterogeneous}}{r_{homogeneous}} \quad \text{Eq 7}$$

The comparison of reaction rates determined from itaconic acid consumption or hydrogen addition  $V_{H_2}$  shows that  $\eta_{intercalation}=0.45$  for Rh/BPPM@SiO<sub>2</sub> and also Rh/BPPM@EtSiO<sub>2</sub>.

In order to check for mass transport limitations, the temperature dependency of the hydrogenation reaction were studied (Figure 13).

The reaction rate increases with increasing temperature as expected:



**Figure 13:** Arrhenius plots of the hydrogenation of itaconic acid in water and methanol with Rh/BPPM@SiO<sub>2</sub> (15.4 mmol IA, 0.022 mmol [Rh(cod)Cl]<sub>2</sub>, 0.044 or 0.088 mmol BPPM (1:2 or 1:4 catalyst: ligand ratio), 100 mL solvent, 1.1 · 10<sup>5</sup> Pa H<sub>2</sub>, 800 rpm)

From the slope of the regression line in the Arrhenius plot, the activation energy  $E_A$  of the chemical reaction was calculated (Table 8):

**Table 8:** Activation energy  $E_A$  (hydrogenation of itaconic acid)

[Rh(cod)Cl] <sub>2</sub> : Ligand ratio	solvent	$E_{A, \text{heterogeneous}}$ [kJ/mol]	$e_{\text{heterogeneous}}$ %	$E_{A, \text{homogeneous}}^{[a]}$ [kJ/mol]	$e_{\text{homogeneous}}^{[b]}$ %
1:4	methanol	33.4	98		
1:2	methanol	50.5	98	49,9	95
1:4	water	24.4	37	33 <sup>[c]</sup>	38 <sup>[c]</sup>

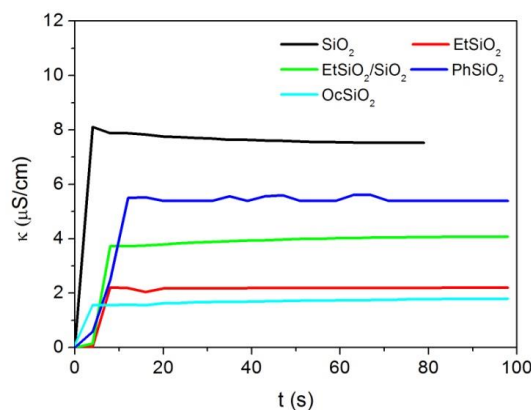
<sup>[a]</sup> Rh(cod)<sub>2</sub>SO<sub>3</sub>CF<sub>3</sub>/BPPM [72]

<sup>[b]</sup> [Rh(cod)Cl]<sub>2</sub>/BPPM

<sup>[c]</sup> H<sub>2</sub>O/SDS

For the hydrogenation of itaconic acid in methanol solution the reaction rate is higher than in water due to the higher solubility of hydrogen in methanol. Also the hydrogenation reaction using the catalyst with 1:2 [Rh(cod)Cl]<sub>2</sub>: BPPM molar ratio is much faster than with 1:4 molar ratio. The activation energies  $E_A$  of the hydrogenation with heterogeneous catalyst in methanol and also in water or aqueous-micellar solutions are comparable with the activation energies when using a homogeneous catalyst (1Rh(cod)SO<sub>3</sub>CF<sub>3</sub>:2BPPM) [72]. That means that there is only small mass transport limitations and the decrease of the reaction rate can be explained mainly by the partial deactivation of the catalyst or encapsulation in silica material. An influence of pore diffusion on the reaction rate would be indicated by a strong decrease in the activation energy  $E_A$ . Also the variation of stirring rates between 600-1200 rpm in homogeneous and heterogeneous reactions shows no increase of reaction rate with increasing

stirring intensity. That means that the hydrogenation is not limited through the transport between the gas and the liquid phase. Only the reactions with stirring rates below 600 rpm were transport limited. As it was shown before by comparison of activation energies of homogeneous and heterogeneous reactions in water and methanol, the enantioselective hydrogenation of itaconic acid is not really mass transport limited. But the determination of activation energies is not a sufficient criterion for the confirmation of these results. That's why the determination of effective diffusion coefficients  $D_{\text{eff,IA}}$  (diffusion in porous media) is also recommendable. Diffusion coefficients were calculated from conductivity measurements (Figure 14) as it was explained in chapter 3.4.6 (Eq 16-17). The diffusion time  $t$  of the  $\text{Sr}^{2+}$  ions from the pores of the heterogeneous catalyst depends on its effective diffusion coefficients. The conductivity  $\kappa$  increases with time because of the diffusion of  $\text{Sr}^{2+}$  ions into the aqueous solution. After certain period of time the conductivity stays constant because all tracer species have migrated into the solution.



**Figure 14:** Conductivity measurements of sol-gel immobilized Rh/BPPM catalysts

As can be seen from Figure 14 the diffusion time of the tracer is very short ( $t=10-20\text{s}$ ) in comparison to average reaction time ( $t=10-15\text{ min}$ ) and this is an indication for a not diffusion limited reaction process. For the further discussion the effective diffusion coefficients  $D_{\text{eff,IA}}$  were calculated from the measured coefficients (equation 2 and 3) considering the molecular diffusion coefficients of  $\text{SrCl}_2$  (tracer) and itaconic acid at ambient temperature in water ( $D_{\text{M,tracer}}=\text{SrCl}_2=1,4\cdot 10^{-4}\text{cm}^2/\text{s}$  [80] and  $D_{\text{M,IA}}=\text{itaconic acid}=1,3\cdot 10^{-5}\text{cm}^2/\text{s}$  [81]). The results of the diffusion coefficients in different supported Rh/BPPM catalysts are shown in table 9:

**Table 9:** Diffusion coefficients and Weisz-Modulus  $\Psi$  of immobilized Rh/BPPM catalysts

<b>Material</b>	<b><math>D_{eff, tracer}</math> [cm<sup>2</sup>·s<sup>-1</sup>]</b>	<b><math>D_{eff, IA}</math> [cm<sup>2</sup>·s<sup>-1</sup>]</b>	<b><math>r_0</math> [mol·l<sup>-1</sup>·s<sup>-1</sup>]</b>	<b>Weisz- Modulus <math>\Psi</math></b>
Rh/BPPM@SiO <sub>2</sub>	2.07·10 <sup>-6</sup>	1.92·10 <sup>-7</sup>	1.1·10 <sup>-4</sup>	1.8
Rh/BPPM@EtSiO <sub>2</sub>	1.33·10 <sup>-6</sup>	1.23·10 <sup>-7</sup>	1.5·10 <sup>-4</sup>	3.8
Rh/BPPM@EtSiO <sub>2</sub> /SiO <sub>2</sub>	5.46·10 <sup>-6</sup>	5.05·10 <sup>-7</sup>	1.0·10 <sup>-5</sup>	0.1
Rh/BPPM@OcSiO <sub>2</sub>	6.22·10 <sup>-7</sup>	5.75·10 <sup>-8</sup>	3.3·10 <sup>-5</sup>	1.7
Rh/BPPM@PhSiO <sub>2</sub>	1.05·10 <sup>-7</sup>	9.75·10 <sup>-9</sup>	1.5·10 <sup>-5</sup>	4.6

In the next step the Weisz-prater criteria or Weisz-modulus  $\Psi$  (Table 9) is determined from the comparison of effective diffusion coefficients  $D_{eff, IA}$  and reaction rate  $r_0$  (Eq 1). The size of particles was  $L_{cat}=200\mu m$ , catalyst density  $\rho_{cat}=1.9\text{ g/cm}^3$ , initial concentration of itaconic acid  $c_{0, IA}=0.155\text{ mol/L}$  and reaction order  $n=1$ . As can be seen from the table the reaction rate  $r_0$  decreases with increasing hydrophobicity of the support and the diffusion coefficients are similar for all catalysts except Rh/BPPM on aromatic support. The comparison between the diffusion and reaction rate, the Weisz-modulus, indicates the diffusion limitation of the reaction. In our case the Weisz-Modulus  $\Psi$  was  $\leq 1$  for all catalysts applied in the enantioselective hydrogenation of itaconic acid except rhodium immobilized on phenyl modified silica and ethyl modified silica. These results are characteristic for not diffusion limited reaction and confirm our hypothesis.

The porosities  $\varepsilon$  of the Rh/BPPM catalysts were calculated from the ratio of pore volume  $V_{pore}$  obtained from BET measurements to the volume of whole catalyst with pore diameter  $d=1-2\text{ nm}$  and pore volume  $V_{pore}=0.175\text{ cm}^3/\text{g}$ :

$$\varepsilon = \frac{V_{pore}}{V_{cat}} = 33.4\% \quad \text{Eq 21}$$

The tortuosities  $\tau$  were determined by rearranging of Eq 3 and describe the diffusion way of the substrate flow through the pores of the catalyst:

$$\tau = \frac{\varepsilon \cdot D_{eff, tracer}}{D_{eff, IA}} \approx 3.6 - 4.3 \quad \text{Eq 22}$$

From Weisz-modulus  $\Psi$  the pore effectiveness factor  $\eta_{pore}$  of the heterogeneous catalysts can be determined. The hydrogenation of itaconic acid with sol-gel immobilized Rh/BPPM catalysts was supposed to be a first order reaction [53]. Pore efficiency increases with decreasing Weisz-modulus, for  $\Psi < 1$  there were no diffusion limitations and full pore

efficiencies (95-100 %) could be obtained. For the hydrogenation of itaconic acid catalyzed by Rh/BPPM@SiO<sub>2</sub> or EtSiO<sub>2</sub>,  $\eta_{\text{pore}}$  was 0.52 and 0.38, respectively.

The overall efficiency  $\eta$  of porous Rh/BPPM catalyst immobilized on SiO<sub>2</sub> and EtSiO<sub>2</sub> was estimated from the different efficiencies, which were calculated in last chapters, by multiplication of all factors:

$$\eta = \eta_{\text{immobilisation}} \cdot \eta_{\text{intercalation}} \cdot \eta_{\text{pore}} \cdot (>N_{\text{cycle}}) \cdot (>\eta_{\text{recycling}}^N) \quad \text{Eq 4}$$

In this equation  $\eta_{\text{immobilisation}}$  and  $\eta_{\text{recycling}}$  are rhodium leaching fractions into the solution after the catalyst synthesis and after N recycling experiments and were determined from ICP measurements.  $N_{\text{cycle}}$  is the number of recycling experiments.  $\eta_{\text{intercalation}}$  is the efficiency of the immobilized catalysts compared to the homogeneous catalysts and was estimated from the comparison of reaction rates. The pore efficiency  $\eta_{\text{pore}}$  was calculated from the Weisz-Prater criterion  $\Psi$  for the first order reaction.

$$\eta_{\text{RhBPPM@SiO}_2} = 0.977 \cdot 0.4516 \cdot 0.52 \cdot (>3) \cdot (>0.9978^3) = (>0.68)$$

$$\eta_{\text{RhBPPM@EtSiO}_2} = 0.9964 \cdot 0.4541 \cdot 0.38 \cdot (>4) \cdot (>0.9935^4) = (>0.67)$$

Because no further deactivation and leaching of the catalyst after third and fourth step was seen, further application of the catalyst in much more recycling steps can be predicted. That's why the number of the recycling steps was estimated to be  $\gg 4$ .

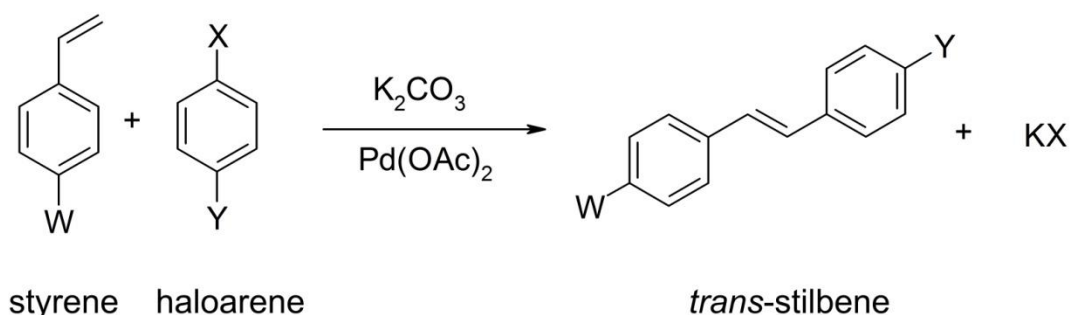
Catalyst efficiencies  $\eta > 1$  are typical for very stable and active catalysts. In comparison to these results, the catalyst with high amount of leaching and low reactivity show much lower overall efficiency of the catalyst. Rhodium immobilized on EtSiO<sub>2</sub> or SiO<sub>2</sub> by sol-gel method has an overall catalyst efficiency of only  $\eta \approx 0.7$ . Obviously is the immobilization of homogeneous catalysts disadvantageous in comparison to homogeneous catalysts because of diffusion limitations and decrease in reactivity due to deactivation of the entrapped catalyst and metal leaching. The main challenge in the immobilization of Rh/BPPM catalyst is the deactivation of catalyst-ligand complex to inactive Rh(0) particles, which decreases the reaction rate of the heterogeneous reaction. But on the other side the possibility to recycle the catalysts more than 3-4 times increases the efficiency of sol-gel immobilized catalysts enormously and reduces the cost of the complete process. With more than 5 for Rh/BPPM@SiO<sub>2</sub> ( $\eta > 1.13$ ) and 7 recycling steps for Rh/BPPM@EtSiO<sub>2</sub> ( $\eta > 1.15$ ), the catalyst would become more efficient than the

homogeneous analogue. The Turnover Number would increase from TON=598 for one run up to TON=1790 after 3 runs for both catalysts.

In order to improve the stability of the immobilized rhodium catalysts and to avoid the deactivation of the complex through the oxygen, a continuous process is recommended. More stable complexes immobilized on support can be achieved by improvement of the immobilization method e.g. ligand immobilization by covalent bond before metal complex is inserted [82].

### 4.3 Heck coupling: synthesis of *trans*-stilbene

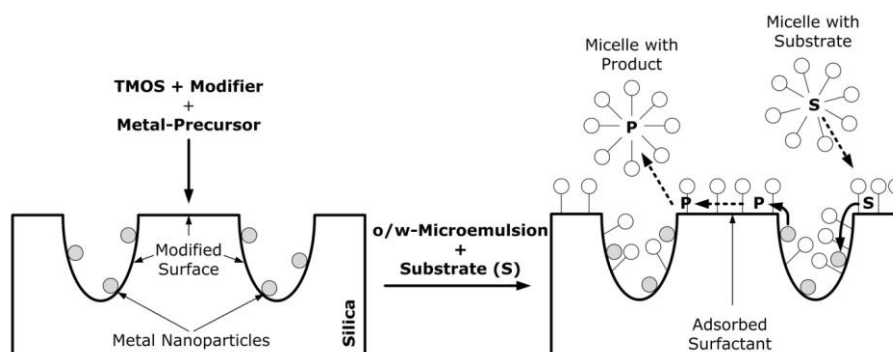
Heck coupling as a reaction for the formation of carbon-carbon bond between substrates was the first example of a coupling between two compounds. *Trans*-stilbene occurs as a main product of the reaction and can be widely used for example in fine chemistry and production of drugs in pharmacy. One of the important derivatives of *trans*-stilbene is stilbenoid resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) which was found in the skin of red grapes and in the roots of Japanese knotweed. It attracts attention because of the anti-tumor application. For example the O-methylated stilbene derivative DMU-212 can be synthesized by Heck coupling with palladium catalyst [83]. *Trans*-stilbene is also an important intermediate in the tandem reaction for the synthesis of polycyclic aromatic substances like distyrylbenzene or styrylbiphenyl which can be used as fluorescent dopands, organic light emitting diodes, in laser [84], etc. Heck coupling reaction is shown in Scheme 19:



**Scheme 19:** Heck coupling

#### 4.3.1. Mechanism of sol-gel immobilized catalytic reaction in microemulsion

Heterogeneous Heck reaction takes place in the pores of the immobilized catalyst where the metallic palladium particles are located as was already described in Chapter 4.1.4 from the TEM images of the catalyst. The proposed mechanism of the reaction in a microemulsion as reaction medium is shown in Scheme 20:



**Scheme 20:** Mechanism of the sol-gel immobilized catalytic reaction in microemulsion

From this scheme it can be derived that primarily the structure of the sol-gel immobilized catalyst influences the rate of the reaction. The structure depends on the choice of the metal precursor and the gel building silica agent as well as on the modification of the support surface. Additionally the choice of the solvent (surfactant, cosurfactant) and substrate is crucial for the optimization of reaction conditions. The interactions between all these parameters have an effect on the reaction performance and will be discussed in the next Chapters.

#### 4.3.2. Choice of the catalyst

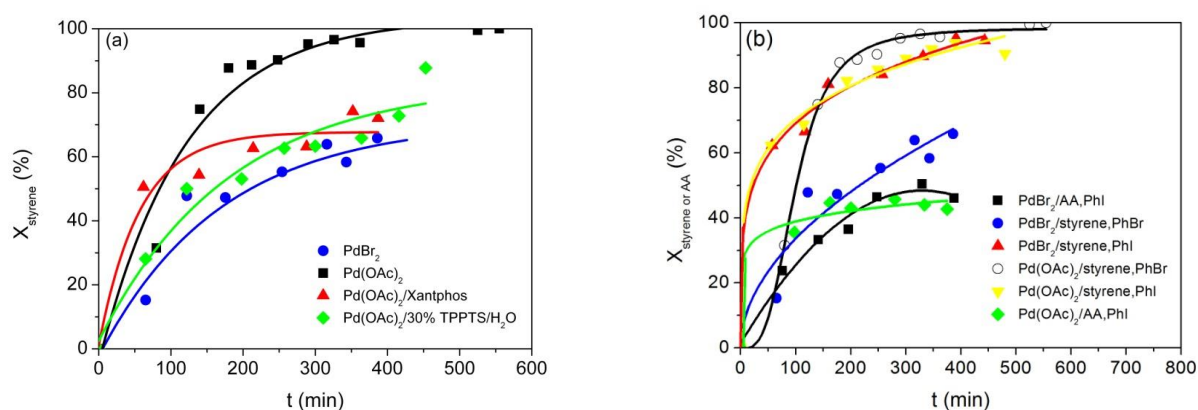
All components of the immobilized catalyst can influence its performance as described in the following paragraphs.

##### a) Catalyst precursor

Coupling reactions are proceeding with Pd(II) catalyst precursors, which are reduced during the reaction to Pd(0) intermediate according to the mechanism of Heck or Suzuki coupling described before. In our research we used  $\text{PdBr}_2$  and  $\text{Pd}(\text{OAc})_2$  and also a mixture of  $\text{Pd}(\text{OAc})_2$  as catalyst precursor and Xantphos or water soluble TPPTS salt as ligands.

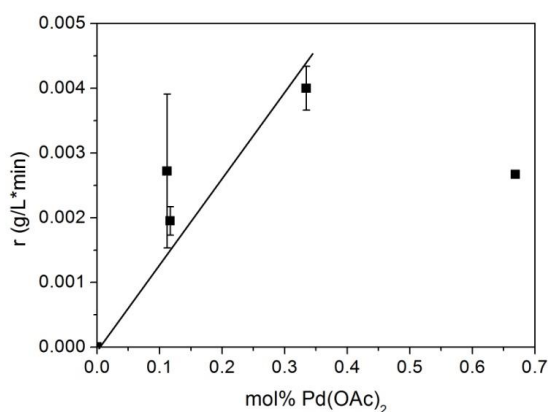
From the rate of the reaction with catalyst-ligand complexes we realized that the addition of the ligand is not necessary for this type of the reaction. During the preparation the air sensitive ligands can be oxidized and also a large amount of catalyst and ligand can leach into the solution after the reaction. In comparison to this only 0.011-0.012 % of  $\text{Pd}(\text{OAc})_2$ , 0.031-0.077% of  $\text{PdBr}_2$  leaching after reaction was measured. In comparison to this, about 0.062%  $\text{Pd}(\text{OAc})_2$  (5.475% TPPTS) and 0.068%  $\text{Pd}(\text{OAc})_2$  (7.800% Xantphos) leaching was detected, also after the preparation of catalyst-ligand complex a large amount of leaching was obtained as was reported in Table 2 before. The activity of  $\text{PdBr}_2$  precursor is comparable to that of  $\text{Pd}(\text{OAc})_2$  but only for the reactive substrates like iodobenzene (PhI) or acrylic acid (AA). The reaction

rate for the less active bromobenzene decreases by a factor of about two by using of  $\text{PdBr}_2$  as catalyst precursor.



**Figure 15:** Choice of the catalyst precursor (a) coupling of bromobenzene and styrene with catalyst/ligand precursor@ $\text{PhSiO}_2$  (b) catalyst precursor-substrate interactions (1.34 mmol alkenes, 1.5 mmol  $\text{PhX}$ , 2 mmol  $\text{K}_2\text{CO}_3$ , catalyst@ $\text{PhSiO}_2$ : 0.0668 mmol  $\text{PdX}_2$ /catalyst: ligand ratio=1:1(Xantphos) and 1:5 (TPPTS), 46 mL microemulsion, 80°C).

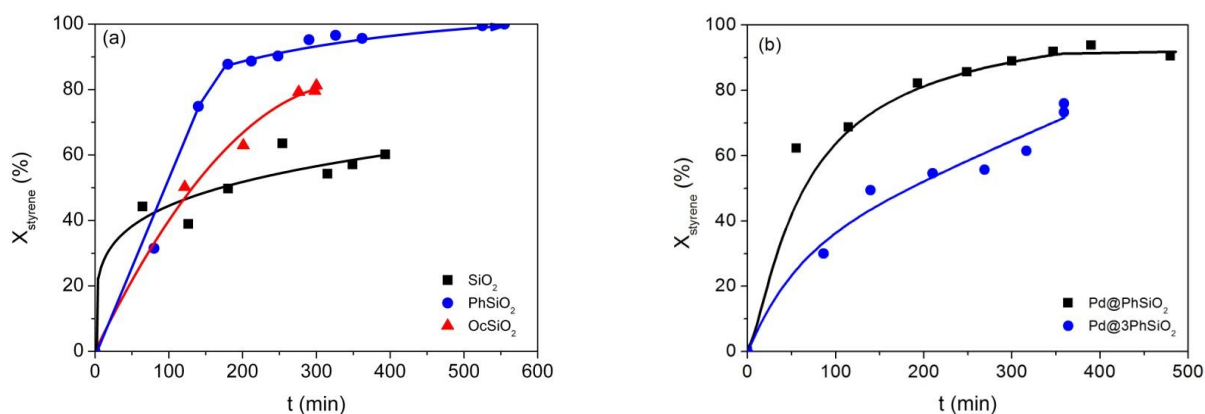
The reaction rate increases with increasing amount of catalyst precursor until the full loading of the silica surface with palladium precursor is obtained. In contrast to this, the leaching of catalyst into the solution increases with increasing amount of catalyst. That's why our following experiments were carried out with catalyst loading of 0.335mol%=15 mg  $\text{Pd}(\text{OAc})_2$  on 1.2 g  $\text{PhSiO}_2$  support.



**Figure 16:** Reaction rate dependency on amount of the catalyst precursor (1.34 mmol styrene, 1.5 mmol bromobenzene, 2 mmol  $\text{K}_2\text{CO}_3$ ,  $\text{Pd}(\text{Ac})_2$ @ $\text{PhSiO}_2$ , 46 mL microemulsion, 80°C).

### b) Catalyst support

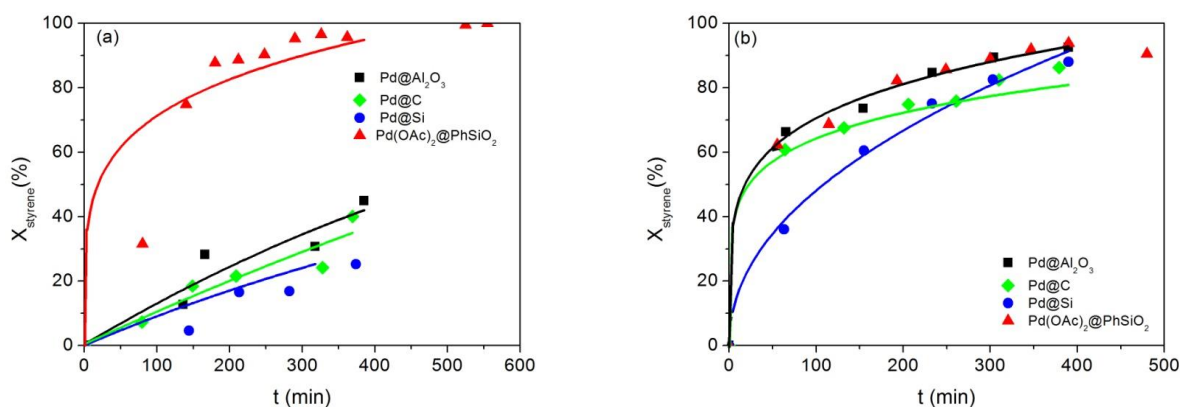
$\text{Pd}(\text{OAc})_2$  catalysts were immobilized on three different silica modified support materials prepared from hydrophobically substituted octyl or phenyl silane or hydrophilic tetramethyl orthosilicate. The adsorption and the reaction rate of the aromatic compounds used in the reaction are stronger by using the hydrophobic support materials than with hydrophilic silica because of the similarities in the structure of the support and the substrates (attractive interactions) as shown in Figure 17a. The amount of leaching of  $\text{Pd}(\text{OAc})_2$  from  $\text{SiO}_2$  and  $\text{OcSiO}_2$  support into the solution after the reaction was comparable to that of  $\text{Pd}(\text{OAc})_2@ \text{PhSiO}_2$ . The inverse adsorption effect was already reported in previous chapter for the enantioselective hydrogenation of itaconic acid and derivatives [38]. The hydrogenation of hydrophilic substrates is favored with  $\text{Rh}/\text{BPPM}$  catalysts immobilized on hydrophilically modified sol-gel materials, whereas the reaction is very slow if it is catalyzed by complexes immobilized on hydrophobically modified surfaces. To minimize the leaching of the catalyst, we also increased the amount of support up to 3 times ( $\text{Pd}(\text{OAc})_2@3\text{PhSiO}_2$  with catalyst loading of 0.49 wt%) in order to stabilize the entrapment of the catalyst precursor into the pores of the catalyst as was shown in Scheme 20 before. In comparison to  $\text{Pd}(\text{OAc})_2@ \text{PhSiO}_2$  also only a small amount of leaching (about 0.02 wt%  $\text{Pd}(\text{OAc})_2$ ) was obtained for this immobilized catalyst. As can be seen from the Figure 17b the reaction rates of both catalysts were comparable.



**Figure 17:** Modification of silica support (a) surface modification, (b) amount of support (1.34 mmol styrene, 1.5 mmol (a) bromobenzene and (b) iodobenzene, 2 mmol  $\text{K}_2\text{CO}_3$ , 0.0668 mmol palladium acetate@support, 46 mL microemulsion,  $80^\circ\text{C}$ ).

### c) Comparison with commercial catalysts

The commercial catalysts tested in this coupling reaction were very stable and no leaching was detected, but the coupling of inactive bromobenzene and styrene with these catalysts was very slow in comparison to the sol-gel immobilized catalysts (Figure 18a). Those commercial catalysts are commonly applied for the hydrogenations of unsaturated substrates. They are not very suitable for the coupling reactions because the support material do not allow the required access of all components of the reaction to the palladium inside the catalyst pores, because they are optimized in their structure for the transport and reaction of unsaturated hydrocarbons and hydrogen. Next, the same catalysts were tested for the coupling of more reactive iodobenzene and styrene. The results are shown in Figure 18b. Here we found that the reaction rates with commercial catalysts are much higher than in the Heck coupling of bromobenzene and styrene. The reaction rate with Pd@Al<sub>2</sub>O<sub>3</sub> catalyst was comparable to the sol-gel immobilized catalyst. So, the commercial catalysts can also be applied in this reaction type, but the rate depends on the substrate type (inactive substrates e.g. bromo- or chlorobenzene are not preferred) and is lower than that with hydrophobically modified sol-gel catalyst. The strong difference in the behavior of the commercial catalysts with certain substrates is unexpected and very difficult to predict.



**Figure 18:** Comparison of Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> to commercial catalysts (a) bromobenzene, (b) iodobenzene (1.34 mmol styrene, 1.5 mmol PhX, 2 mmol K<sub>2</sub>CO<sub>3</sub>, 1wt% palladium on support, 46 mL microemulsion and 80°C).

### 4.3.3. Effect of reaction medium

#### a) Choice of the solvent

For the coupling of iodo- or bromobenzene with styrene the amount of inorganic base was equivalent to the amount of the reactant. The addition of higher amounts of the base blocks the reaction progress. The role of the inorganic base is clear from the reaction mechanism showed in theoretical chapter. Without this additive the reaction was not possible or only small amounts of products could be obtained. But the disadvantage of using inorganic salts is the necessity to proceed the reaction in aqueous solution or at higher temperatures ( $>100^{\circ}\text{C}$ ) because of bad solubility of the base in organic solvent as can be seen from the Table 10. An alternative to increase the reactivity is the use of organic but maybe more toxic salts in the reaction. Very small conversions were obtained for the Heck coupling of bromobenzene and styrene in methanol and dimethylformamide with  $\text{K}_2\text{CO}_3$  at  $80^{\circ}\text{C}$  with  $\text{Pd}(\text{OAc})_2 @ \text{PhSiO}_2$  as catalyst.

**Table 10:** Variation of the solvent

solvent	X [%]	t [min]
MeOH	10	438
MeOH <sup>a</sup>	31	380
DMF	30	433
$\text{DMF}/\text{K}_2\text{CO}_3/\text{PdCl}_2 @ \text{zeolite}/153^{\circ}\text{C}$ [21]	74	150
$\text{NMP}/\text{K}_2\text{CO}_3/\text{Pd} @ \text{hydroxyapatite}/130^{\circ}\text{C}$ [85]	94	1440
DMF <sup>a</sup>	17	1335
DMF <sup>b</sup>	2	1334
ACN/ $\text{H}_2\text{O}$ (1:1)	45	420
$\text{H}_2\text{O}$	88	420
$\text{H}_2\text{O}$ iodobenzene/ styrene/ Pd@polystyrene/KOH/ $90^{\circ}\text{C}$ [86]	10	1320
10g/L CTAB/ $\text{H}_2\text{O}$	100	420
70 g/L SDS/ $\text{H}_2\text{O}$	50	360
CTAB/ $\text{H}_2\text{O}$ iodobenzene/styrene/Pd@C/ $\text{K}_2\text{CO}_3/80^{\circ}\text{C}$ [87]	60	240
CTAB/propanol/ $\text{H}_2\text{O}$ microemulsion	100	420
TX-100/ $\text{H}_2\text{O}$ /[BMIM]PF <sub>6</sub> microemulsion	81	120
iodobenzene/styrene/NEt <sub>3</sub> /PdCl <sub>2</sub> / $100^{\circ}\text{C}$ [88]		

<sup>a</sup> TPPTS

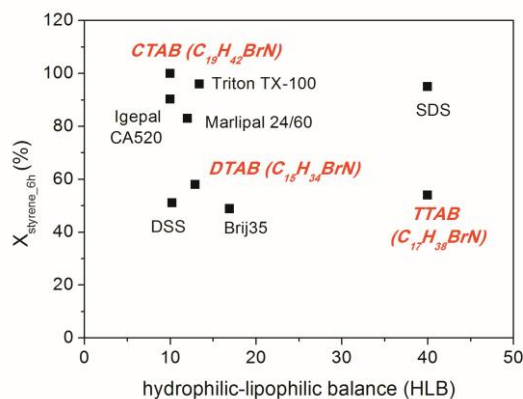
<sup>b</sup> Xantphos

Similar reactions were carried out by the other research groups at higher temperatures and excellent results were obtained. The addition of water to the acetonitrile solution (1:1) increased the conversion of the reaction up to 45 %. As can be seen from the Table the reactions in aqueous-micellar solutions of CTAB or SDS are also preferred, but not the whole amount of substrates could be solubilized in this mixture during the reaction. The best results and full conversion were obtained for the reaction in a microemulsion. Also similar results but with more additives (ionic liquids or polyethylene glycol PEG) were already reported by Zhang et

al. for the coupling in TX-100/H<sub>2</sub>O/ionic liquid microemulsion at 100°C and by Jiang et al. [89] for the ligandfree coupling in TX-10/heptane/butanol/H<sub>2</sub>O/propanol/PEG microemulsion.

#### **b) Formation of the microemulsion**

As was shown in Scheme 20, beside the parameters determined by the preparation of the sol-gel immobilized Pd catalyst also the solvent selection is important. In 4.3.2 we have studied the influence of the Pd precursor and silica support, and we found optimal conditions with respect to the catalyst synthesis. For the solubilization of the hydrophobic reactants in aqueous environment surfactants have to be added. The interactions between the silica support and the formed micellar aggregates will also govern the reaction rate. Therefore, Heck reaction was investigated in aqueous microemulsion with different anionic, nonionic and cationic surfactants, which can be characterized by their structures, critical micellar concentrations *cmc* and the average diameter of the micelles ( $d_{\text{micelle}}$ ) or hydrophilic lipophilic balance values *HLB*. The reaction mixtures with DSS and Igepal CA-520 as surfactants were not transparent. As can be seen from Figure 19, a broad variety of surfactants can be applied for the microemulsion formulation. As was reported by Rosin Ben-Baruch et al. the reaction with sol-gel immobilized catalyst is possible in microemulsion with surfactants with not too large micelle aggregates, because of the difficult accessibility to the catalyst pores. Full conversion was obtained after 6-7 h with cationic CTAB, nonionic Triton TX-100 and anionic SDS as surfactants. The conversion increases with increasing C-chain length, decreasing HLB-value (hydrophilic-lipophilic balance) and decreasing *cmc* if homologue series of cationic surfactants CTAB, TTAB and DTAB were used:  $C_{16} >> C_{14} \approx C_{12}$ . The most hydrophobic surfactant CTAB is preferred because of the more hydrophobic micelle cores ( $d_{\text{micelle}}$ ) and largest storage capacity for the substrates ( $d_{\text{micelle}} = 5.39 \text{ nm} > 3.840 \text{ nm} > 3.34 \text{ nm}$  [90]). Prediction cannot be done for the behavior of the other not homologue surfactants in this coupling reaction because of their different structures. There is also no dependence between the type of the surfactant and the reaction rate.



**Figure 19:** Influence of hydrophilic lipophilic balance values (HLB) and the type of surfactants on the reaction behavior (1.34 mmol styrene, 1.5 mmol bromobenzene, 2 mmol K<sub>2</sub>CO<sub>3</sub>, 0.0668 mmol Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub>, 46 mL microemulsion, 80°C).

#### 4.3.4. Substrates

The type and the concentration of the substrates are also expected to influence the rate of the coupling reaction strongly.

##### a) Substrate variation

To extend the scope of the protocol we applied the conditions to screen a wide variety of substrates. A screening of aryl halides Y-Ph-X shows that this catalytic system is suitable for all kinds of aryl halide. It results in the expected ranking with higher reactivity of iodobenzene than bromobenzene, 1-bromo-4-iodobenzene (with 4-bromo-*trans*-stilbene as product) and lowest reactivity of less active chlorobenzene with palladium(II) acetate immobilized on hydrophobically modified silica as can be seen from Table 11. These results are typical for the reaction of aryl halide with styrene (Entry 17-20), acrylic acid (Entry 1-4) and methacrylic acid (Entry 9-10). Because of the mechanistic aspects of Heck coupling, *trans*-products are favored. It is well known that haloarenes with substituents (leaving group) with more positive inductive effect (+I) are less reactive.

The reactivity of styrene is higher than that of 4-chlorostyrene and  $\alpha$ -methylstyrene (with terminal olefins as by products 1:1) as shown in Table 11 (Entry 30-33) for the reaction with iodo- and bromobenzene.

Also different aromatic ortho- and para- substituted aryl halides Y-Ph-X react with styrene to *trans*-stilbene derivatives. The reactivity decreases if the para-substituted substrates (e.g. para-iodobromobenzene) are applied in the reaction (Table 11 Entry 21-29) and is very small with

the ortho-substituted substrates (e.g. ortho-methylchlorobenzene). The reaction rate depends not only on the position of the substituent, but also on the substituent type. Substituents with electron withdrawing groups (e.g. cyano or acetyl group) are more active than these with electron donating groups (e.g. methoxy or methyl group).

The nonaromatic acrylic acid shows good reactivity with iodobenzene and its reactivity is comparable to aromatic styrene. The more sterically hindered methacrylic acid and derivatives were less reactive (Table 11 entry 5-16) and side-products were formed. The arylation of medically interesting 1,1-substituted olefins like methacrylate or  $\alpha$ -methylstyrene can afford different products in dependency of the direction of the  $\beta$ -H-elimination: the main desired product  $\alpha$ -methylcinnamate with *E*- or *Z*-stereochemistry or a by-product  $\alpha$ -benzylacrylate with a terminal double bond [91]. The product and by-product ratio was 1:1. This product seldom undergoes a further arylation. The ratio of product and by-product depends on the substituents.

All substrates tested in Heck coupling reaction in aqueous microemulsions show similar reactivity as in commonly used organic solvents e.g. dimethylformamide or acetonitrile at higher temperatures. For the following investigations only the reactions of styrene and iodo- or bromobenzene to *trans*-stilbene were applied.

**Table 11:** Substrate variation in Heck coupling reactions in aqueous microemulsion<sup>a</sup>

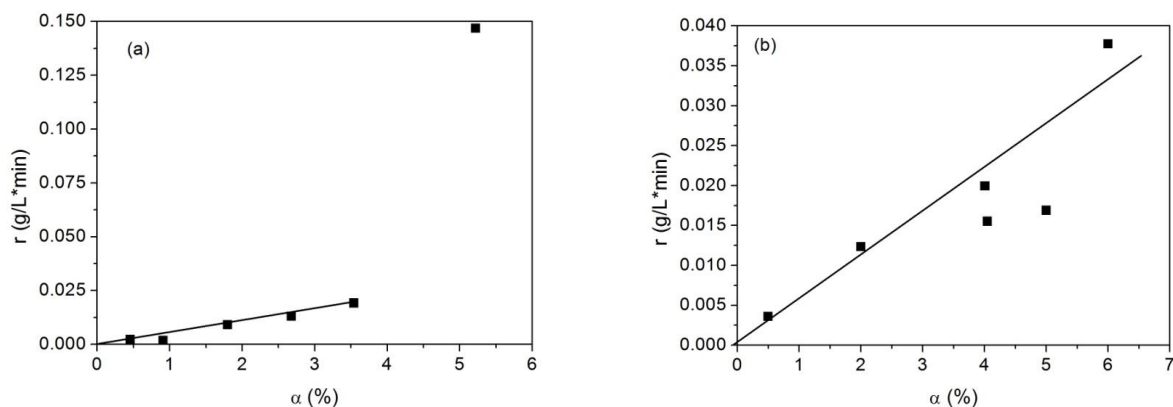
entry	compound 1	compound 2	product	reaction time t (min)	conversion (%)
1	chlorobenzene	acrylic acid	cinnamic acid	429	70
2	bromobenzene	acrylic acid	cinnamic acid	396	76
3	iodobenzene	acrylic acid	cinnamic acid	359	98
4	4-iodobromobenzene	acrylic acid	4-bromocinnamic acid	513	77
5	bromobenzene	methylacrylate	<i>trans</i> -methyl- cinnamate	372	45
6	iodobenzene	methylacrylate	<i>trans</i> -methyl- cinnamate	407	72
7	bromobenzene	2-ethylhexyl- acrylate	2-ethylhexyl- cinnamate	359	64
8	iodobenzene	2-ethylhexyl- acrylate	2-ethylhexyl- cinnamate	451	82
9	bromobenzene	methacrylic acid	$\alpha$ -methylcinnamic acid	389	64
10	iodobenzene	methacrylic acid	$\alpha$ -methylcinnamic acid	477	62
11	bromobenzene	methylmeth- acrylate	methyl-( <i>E</i> )- $\alpha$ - methylcinnamate	339	46 <sup>b</sup>

12	iodobenzene	methylmethacrylate	methyl-( <i>E</i> )- $\alpha$ -methylcinnamate	435	54 <sup>b</sup>
13	bromobenzene	<sup>t</sup> butylmethacrylate	( <i>E</i> )- <sup>t</sup> butyl-2-methyl-3-phenylacrylate	387	45
14	iodobenzene	<sup>t</sup> butylmethacrylate	( <i>E</i> )- <sup>t</sup> butyl-2-methyl-3-phenylacrylate	422	89
15	bromobenzene	2-hydroxyethylmethacrylate	2-hydroxyethyl-( <i>E</i> )- $\alpha$ -methylcinnamate	407	50
16	iodobenzene	2-hydroxyethylmethacrylate	2-hydroxyethyl-( <i>E</i> )- $\alpha$ -methylcinnamate	485	70
17	chlorobenzene	styrene	<i>trans</i> -stilbene	327	62
18	bromobenzene	styrene	<i>trans</i> -stilbene	555	100
19	iodobenzene	styrene	<i>trans</i> -stilbene	480	94
20	4-iodobromobenzene	styrene	4- <i>trans</i> -bromostilbene	398	89
21	2-bromobenzylamine	styrene	4-[(1 <i>E</i> )-2-(phenyl)ethenyl]-benzene-methanamine	458	57
22	2-chlorobenzonitrile	styrene	2- <i>trans</i> -cyano-stilbene	433	41
23	2-bromobenzonitrile	styrene	2- <i>trans</i> -cyano-stilbene	393	59
24	2-chlorotoluene	styrene	<i>trans</i> -2-methylstilbene	477	44
25	2-chloro-1,3-dimethylbenzene	styrene	2,6- <i>trans</i> -dimethylstilbene	367	55
26	4-chloroacetophenone	styrene	4- <i>trans</i> -acetylstilbene	444	65
27	4-bromoacetophenone	styrene	4- <i>trans</i> -acetylstilbene	446	60
28	4- <i>trans</i> -chlorostilbene	styrene	distyrylbenzene	419	0
29	4- <i>trans</i> -bromostilbene	styrene	distyrylbenzene	448	20
30	bromobenzene	4-chlorostyrene	4- <i>trans</i> -chlorostilbene	371	50
31	iodobenzene	4-chlorostyrene	4- <i>trans</i> -chlorostilbene	415	92
32	bromobenzene	$\alpha$ -methylstyrene	$\alpha$ -methylstilbene	377	32 <sup>b</sup>
33	iodobenzene	$\alpha$ -methylstyrene	$\alpha$ -methylstilbene	318	65 <sup>b</sup>

<sup>a</sup> reaction conditions: 1.5 mmol olefine (compound 1), 1.34 mmol RX (compound 2), 2 mmol K<sub>2</sub>CO<sub>3</sub>, 1.25 wt% Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> (0.067 mmol Pd(OAc)<sub>2</sub>), 46 mL microemulsion (3.3 wt% CTAB, 89.3 wt% H<sub>2</sub>O, 6.6 wt% propanol), 80°C  
<sup>b</sup> 1:1  
product: terminal olefine

### b) Substrate concentration

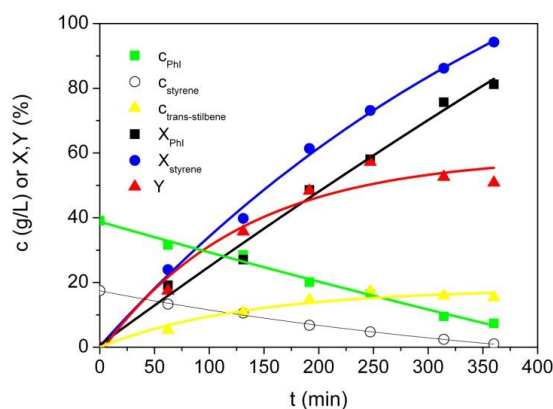
Water-oil (substrate) ratio  $\alpha$  of the microemulsion was increased from 0.5 wt% (standard laboratory conditions of the Heck reaction) up to 5 and 6 wt% as shown in Figure 20 for the reaction of (a) bromobenzene and (b) iodobenzene with styrene.



**Figure 20:** Influence of substrate amount on reaction rate (a) bromobenzene, (b) iodobenzene (styrene: haloarene=1.34:1.5, 2 mmol  $K_2CO_3$ , 0.0668 mmol  $Pd(OAc)_2@PhSiO_2$ , 46 mL microemulsion, 80°C).

In all reactions no change in phase behavior was observed and a one phase aqueous microemulsion region was obtained. The reaction rate increases with increasing oil fraction and the conversion decreases. Also the same trend in reactivity of bromo-and iodobenzene was obtained as was described in the last chapter. The reaction is slower with less active bromobenzene as with iodobenzene. That means that more time is necessary to obtain the full conversion of the reaction if higher amounts of educts are applied.

An example of successful increase of the amount of reactants is demonstrated in Figure 21 for the Heck coupling of iodobenzene and styrene with oil fraction of  $\alpha=5\%$ .



**Figure 21:** Increase of the reactants concentrations (6.728 mmol styrene, 7.449 mmol iodobenzene, 2 mmol  $K_2CO_3$ , 0.0668 mmol  $Pd(OAc)_2@PhSiO_2$ , 46 mL microemulsion, 80°C,  $\alpha=5\%$ ).

#### 4.3.5. Efficiency and stability of an immobilized catalyst

In the last chapters we have seen that Heck reactions with sol-gel immobilized catalysts in aqueous microemulsions yield good results in comparison to commercial catalysts and also only small amount of catalyst leaching into the solution was obtained after preparation of the catalyst and after the reaction. In order to check if the use of these catalysts is recommendable we have also looked for the real heterogeneity of the catalyst and compared the catalyst efficiency between homogeneous and heterogeneous catalysts and looked for reasons of lower reaction rate for the heterogeneously catalyzed reactions.

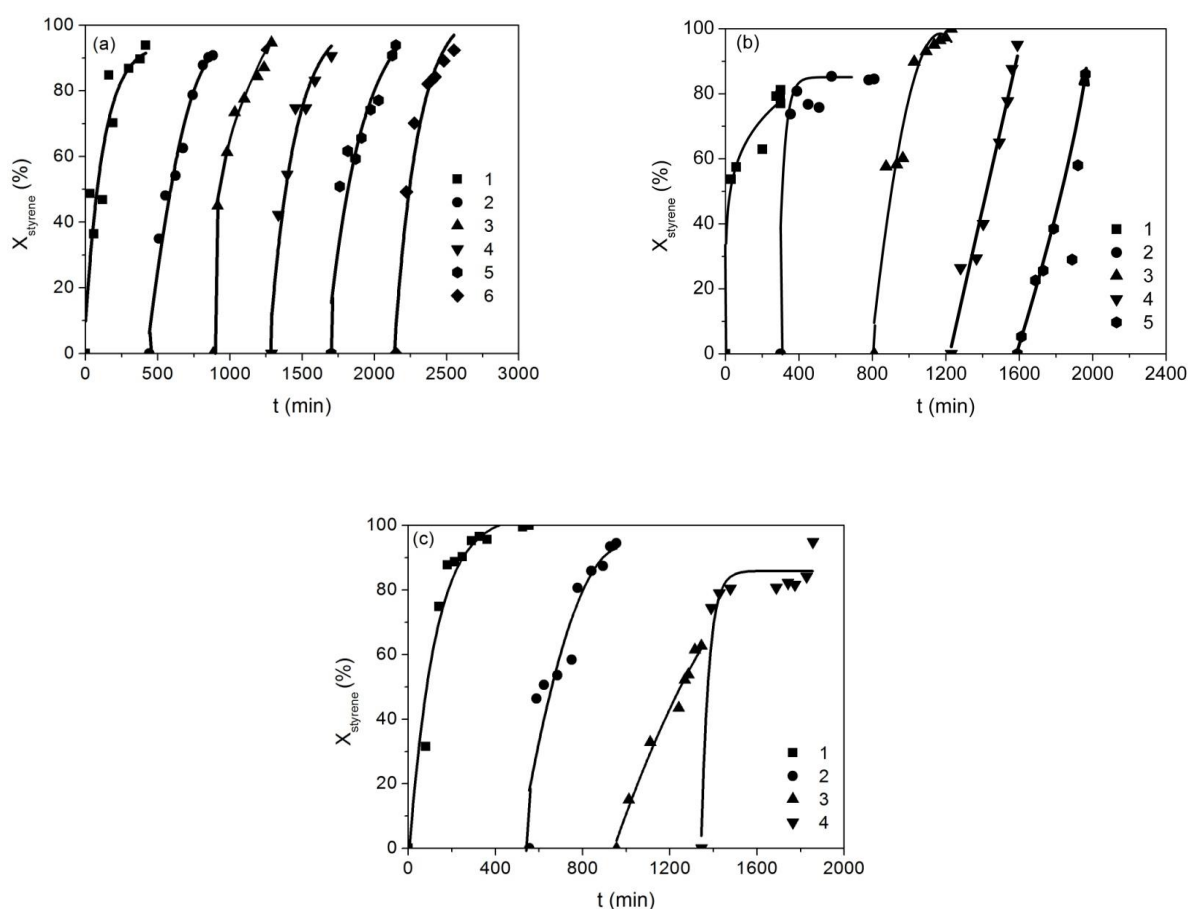
##### a) Catalyst recycling

The main motivation for the use of the immobilized catalysts in chemical reactions is their recovery (e.g. by filtration) after each reaction and the reuse in the next reaction. The recycling experiments were carried out for the coupling of bromobenzene or iodobenzene with styrene to *trans*-stilbene. Palladium (II) acetate catalysts immobilized on hydrophobically octyl or phenyl modified silica support materials could be recycled 6 times without decrease in activity (Figure 22). Only little amount of leaching of palladium into the solution was detected by ICP measurements after each reaction. Only about 0.01-0.02 wt% of Pd(OAc)<sub>2</sub> leached from the support after the first reaction and no leaching was detected after the following recycling steps.

From these results the recycling efficiency of the sol-gel immobilized catalyst  $\eta_{\text{recycling}}$  can be estimated. For mostly applied Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> only 0.01% palladium acetate leaching after the first reaction and no further metal leaching was detected. That's why the recycling efficiency  $\eta_{\text{recycling}}$  of the catalyst can be estimated from Equation 5 to be 0.9999 with N>6 runs.

Some reactions can be carried out with only very small amounts of the homogeneous catalyst. That's why a variety of investigations called "heterogeneity tests" should be performed to check if the catalytically active species applied in this reaction is really heterogeneous or if the catalyst leached into the solution influences the reaction rate. Also if the following reactions will be applied in the production of fine chemicals or in pharmaceutical industry, the catalyst used here should not poison the produced drugs. As was shown before the catalyst could be recycled several times and only very small amount of palladium leached into the reaction solution. The hot filtration test of the catalyst after obtaining a conversion of about 50% was done. Thereafter the reaction was continued with the residual solution. No further conversion was observed in the reaction as a proof that no homogeneous catalyst was present in the reaction mixture. There

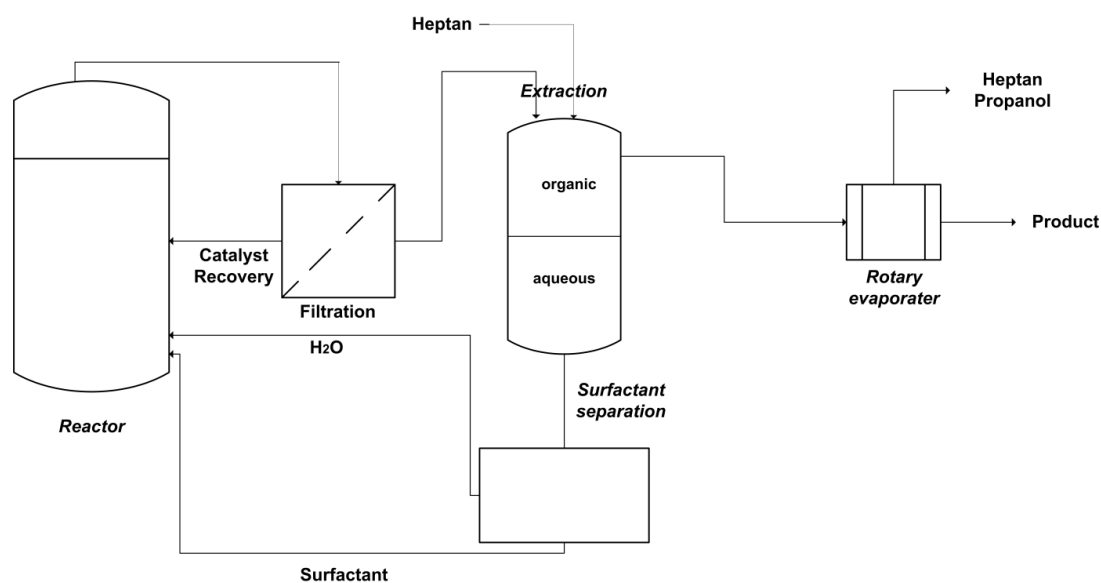
are several substances which act as poisons for soluble catalysts [92], they decrease the rate of the reaction and deactivate the catalytic species. In this context they can be used for the investigation of catalyst heterogeneity. There are many catalyst poisons for homogeneous palladium (II) species: Hg(0) used in Mercury test, CS<sub>2</sub>, cross-linked poly(vinylpyridine) and Quadrapure TU metal scavenger. A poisoning test was done with 300 eq of highly cross linked poly(4-vinylpyridine) [93–95]. This substance can bind to homogeneous Pd(II) species and poisons it, followed by a decrease in reaction rate. The reaction with heterogeneous catalyst (Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub>) showed no decrease in reactivity upon the addition of poly(4-vinylpyridine).



**Figure 22:** Recycling experiments (a) iodobenzene, Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub>, (b) bromobenzene, Pd@OcSiO<sub>2</sub>, (c) bromobenzene, Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> (1.34 mmol styrene, 1.5 mmol haloarene, 2 mmol K<sub>2</sub>CO<sub>3</sub>, 0.0668 mmol Pd(OAc)<sub>2</sub>@support, 46 mL microemulsion, 80°C).

From these experiments we conclude that no homogeneous catalyst is involved in the Heck coupling with sol-gel immobilized catalyst in microemulsion as reaction medium. After the

reaction the catalyst was separated by filtration and the product separation was done by extraction with organic solvent followed by solvent evaporation as can be seen from Scheme 21. The residual aqueous phase includes the surfactants which have to be separated from water to arrive at a greener process management. Both surfactant and water can be reused for this process or applied in other context. In dependency on the surfactant type there are different separation techniques which are commonly used in industry for waste water treatment. The surfactants can be separated by a membrane by micellar enhanced ultrafiltration (MEUF) [96]. The cloud point extraction method can be applied for the separation of nonionic surfactants. At the certain temperature (cloud point temperature) the phase separation into concentrated phase containing micelles and in water phase containing only small amount of surfactants occurred [97,98]. The phase separation is accelerated by centrifugation. The other commonly used technique is adsorption of anionic surfactants through for example silica gel, clay, MCM-41 or granite sand [99].



**Scheme 21:** Process management of the organic synthesis with sol-gel immobilized catalysts in microemulsion

### b) Catalyst efficiency

The coupling of styrene with bromobenzene or iodobenzene is known to be a second order reaction [89,100]. In our studies the reaction rate increases linearly with the concentrations of both reactants. The distinction has to be drawn between homogeneously (insitu formed palladium (0) nanoparticles) and heterogeneously catalyzed reaction ( $\text{Pd}(\text{OAc})_2$  immobilized on silica). In comparison to the homogeneously catalyzed reaction, the coupling with sol-gel

immobilized catalyst (1.2 wt% Pd(OAc)<sub>2</sub> on modified silica support material) was slower at the beginning as can be seen from the conversion  $X(t)$  measurements at 80°C shown in Figure 23a, but finally reaches a higher conversion than the homogeneous palladium catalyst. This experiment was repeated for temperatures between 50-90°C for both catalysts. From the slopes of Arrhenius plots in Figure 23b the activation energies  $E_A$  were determined for the Heck reaction of bromobenzene and styrene with homogeneous and heterogeneous catalysts according to Eq 23:

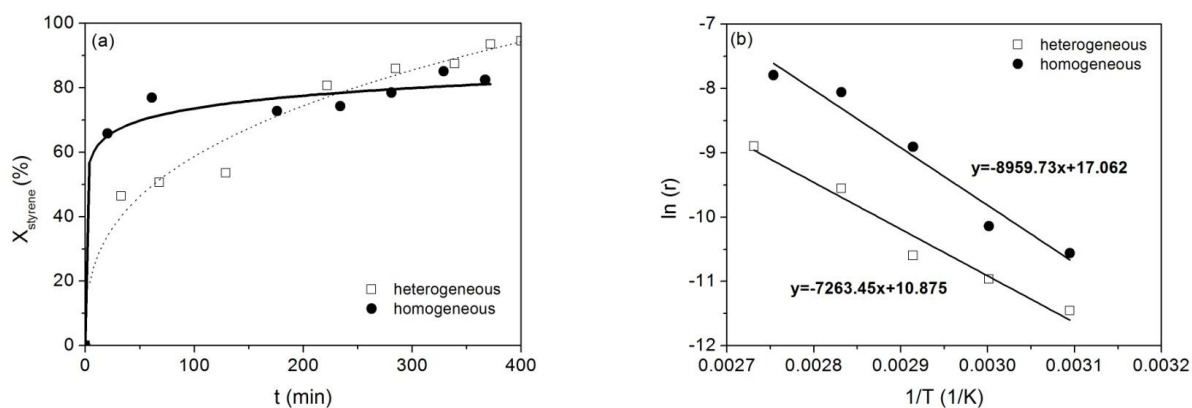
$$\ln(k) = -\frac{E_A}{R \cdot T} + \ln(k_\infty) \quad \text{Eq 23}$$

Where reaction rate constant  $k \sim$  reaction rate  $r = -\frac{dc_{\text{styrene}}}{dt}$

$$E_{A, \text{heterogeneous}} = 60.4 \text{ kJ} \cdot \text{mol}^{-1}$$

$$E_{A, \text{homogeneous}} = 74.5 \text{ kJ} \cdot \text{mol}^{-1}$$

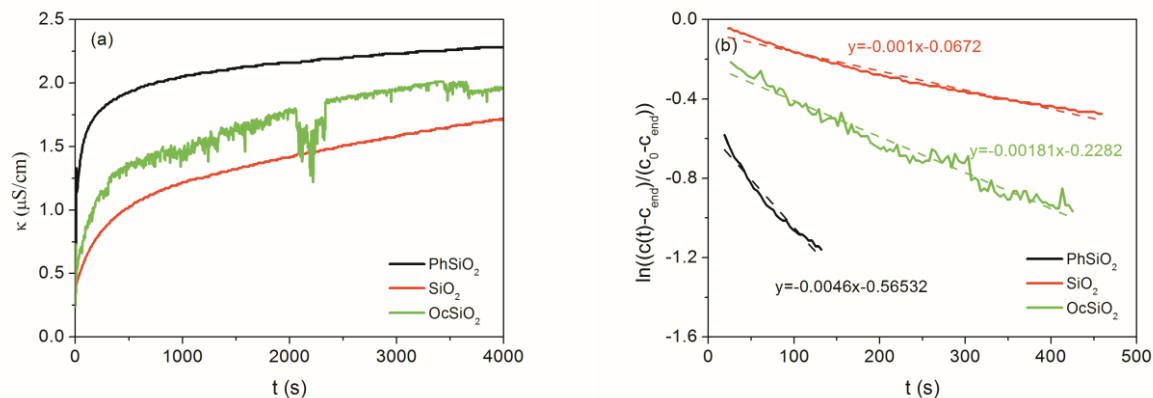
The activation energy  $E_A$  of the heterogeneous reaction is a little lower than that of the homogeneous reaction. No catalyst deactivation or leaching was obtained after several reactions, so the only possible reason for such a difference could be the diffusion limitation that is much less temperature sensitive than the chemical reaction itself.



**Figure 23:** Comparison of homogeneously and heterogeneously catalyzed Heck reactions in microemulsion (a)  $X_{\text{styrene}}-t$ -curve (80°C), (b) Arrhenius plot (1.34 mmol styrene, 1.5 mmol PhBr, 0.276 g K<sub>2</sub>CO<sub>3</sub>, 0.0668 mmol Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> or homogeneous Pd(OAc)<sub>2</sub>, 46 mL microemulsion).

From the comparison of reaction rates of heterogeneously and homogeneously catalyzed Heck coupling reaction,  $\eta_{\text{intercalation}}$  can be estimated (Equation 7) to be  $\eta_{\text{intercalation}} = 0.805$ .

The diffusion coefficients  $D_{\text{eff,tracer}}$  in  $\text{Pd}(\text{OAc})_2$  immobilized on phenyl and octylmodified silica or in hydrophilic silica were calculated from the conductivity measurements with  $\text{SrCl}_2$  as tracer (Equation 9-10):



**Figure 24:** Diffusion measurements at immobilized palladium catalysts (a)  $\kappa$ - $t$  plot (b) determination of diffusion coefficients  $D_{\text{eff,tracer}}$

For our discussion the effective diffusion coefficients  $D_{\text{eff,styrene}}$  were calculated from the measured values (equation 2 and 3) considering to the molecular diffusion coefficients of  $\text{SrCl}_2$  (tracer) and styrene at ambient temperature in water ( $D_{\text{M,tracer}}=\text{SrCl}_2=1,4\cdot 10^{-4}\text{cm}^2/\text{s}$  [80] and  $D_{\text{M,styrene}}=1\cdot 10^{-5}\text{cm}^2/\text{s}$  [101]):

**Table 12:** Diffusion coefficients and Weisz-Modulus for the  $\text{Pd}(\text{OAc})_2$  catalysts immobilized on silica

Material	$D_{\text{eff,tracer}}$ [ $\text{cm}^2\cdot\text{s}^{-1}$ ]	$D_{\text{eff,styrene}}$ [ $\text{cm}^2\cdot\text{s}^{-1}$ ]	$r_0$ [ $\text{mol}\cdot\text{l}^{-1}\cdot\text{s}^{-1}$ ]	Weisz-Modulus $\Psi$
$\text{Pd}(\text{OAc})_2@\text{SiO}_2$	$8.1\cdot 10^{-9}$	$6.0\cdot 10^{-10}$	$7.5\cdot 10^{-7}$	4
$\text{Pd}(\text{OAc})_2@\text{PhSiO}_2$	$4.7\cdot 10^{-8}$	$1.2\cdot 10^{-9}$	$2.3\cdot 10^{-6}$	3
$\text{Pd}(\text{OAc})_2@\text{OcSiO}_2$	$1.5\cdot 10^{-8}$	$3.6\cdot 10^{-9}$	$3.0\cdot 10^{-6}$	5

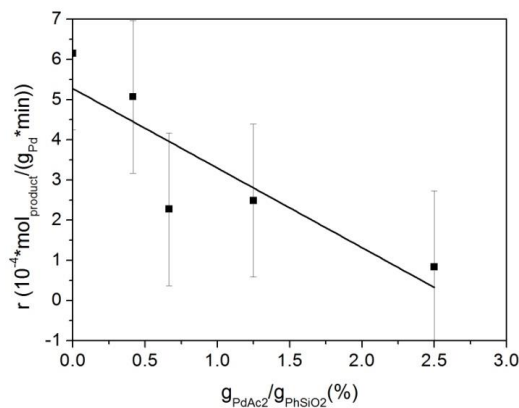
The measured diffusion coefficients of the tracer and effective diffusion coefficients of styrene listed in Table 12 for the catalyst immobilized on hydrophobically modified silica are larger than that on hydrophilic silica.

The Weisz-Modulus  $\Psi$  provides information about the diffusion limitations of selected reactions. For  $\Psi \leq 1$  no diffusion limitation influences the reaction. The Weisz-Modulus can be calculated from equation 1. The initial rates  $r_0$  of the reactions with different catalysts were determined from the consumption of styrene ( $-dc_{\text{styrene}}/dt$ ) during the reaction. The average particle size  $L$  of 200 μm and catalyst density  $\rho_{\text{cat}}$  of 1.9 g/cm<sup>3</sup> was considered for all

calculations. The values of  $\Psi$  vary between 3-5, this is an indicator of a reaction rate limitation by diffusion of reactants inside silica pores. These results were also supported by the comparison of the temperature dependence of the heterogeneous and the homogeneous catalysts as discussed before for the Heck coupling with  $\text{Pd}(\text{OAc})_2@ \text{PhSiO}_2$  and homogeneous  $\text{Pd}(\text{OAc})_2$  catalyst. With this diffusion limitation of the reaction the utilization of the palladium can be estimated from the pore effectiveness factor  $\eta_{\text{pore}}$  of the catalyst to be about 40%. The porosity of  $\text{Pd}(\text{OAc})_2@ \text{PhSiO}_2$  can be calculated from the ratio of pore volume  $V_{\text{pore}}$  (BET measurement) to the volume of catalyst and is  $\varepsilon=33.4\%$  with pore diameter  $d=1-2$  nm. The tortuosity  $\tau$  describes the way of the diffusion in the pores of the catalyst and can be determined from Equation 3 ( $\tau=4.7$ ).

R. Takahashi and S. Sato [50,52,102] measured  $D_{\text{eff}}=5 \cdot 10^{-9} \text{cm}^2 \cdot \text{s}^{-1}$  and  $\tau=100$  for wet mesoporous silica gel ( $d_{\text{pore}}=2.1$  nm) and  $\tau=2.76$  for mesoporous silica ( $d_{\text{pore}}=4$ nm). The tortuosity  $\tau$  decreases, the porosity  $\varepsilon$  increases and the diffusion coefficient increases (lower diffusion limitations) if catalysts with larger pores ( $d_{\text{pore}}=12$ nm) are used:  $\varepsilon=66\%$ ,  $\tau=1.2$ ,  $A=269 \text{ m}^2 \cdot \text{g}^{-1}$ ,  $D_{\text{eff}}=6.43 \cdot 10^{-6} \text{m}^2 \cdot \text{s}^{-1}$ .

Due to the high porosity and the strongly branched pore systems (high tortuosity) of the sol-gel materials the diffusivity of small reactant molecules inside the pore systems is not very high. To obtain a good utilization of the active noble metal immobilized in the support material the loading should be limited to an amount that still guarantees a high effectiveness factor of the composite catalysts. By decreasing the  $\text{Pd}(\text{OAc})_2$  loading of the silica material from 1.2 % to 0.5 %, the specific productivity of the palladium was increased by a factor of 2 from  $2.5 \cdot 10^{-4}$  to  $5 \cdot 10^{-4} \text{ mol/g}_{\text{Pd}} \cdot \text{min}$ :



**Figure 25:** Reaction rate dependency on the  $Pd(OAc)_2$  loading of the catalyst (1.34 mmol styrene, 1.5 mmol PhBr, 0.276 g  $K_2CO_3$ ,  $Pd(OAc)_2@PhSiO_2$ , 0%  $g_{Pd(OAc)_2}/g_{PhSiO_2}$  for homogeneous  $Pd(OAc)_2$ , 46 mL microemulsion).

At last the overall efficiency  $\eta$  of porous  $Pd(OAc)_2$  catalyst immobilized on  $PhSiO_2$  was estimated from the different efficiencies, which were calculated in the last chapters by multiplication of all factors:

$$\eta = \eta_{\text{immobilisation}} \cdot \eta_{\text{intercalation}} \cdot \eta_{\text{pore}} \cdot (>N_{\text{cycle}}) \cdot (>\eta_{\text{recycling}}^N) \quad \text{Eq 4}$$

$$\eta = 1 \cdot 0.805 \cdot 0.4 \cdot (>6) \cdot (>0.999^6) = (>1.92)$$

Catalyst efficiencies  $\eta \gg 1$  are typical for very stable and active catalysts and demonstrate that palladium acetate immobilized on hydrophobically modified silica by sol-gel method is a very good alternative to homogeneous one. The catalyst could be recycled more than 6 times without visible leaching and deactivation. In comparison to a homogeneously catalyzed reaction, heterogeneous reaction is a bit slower due to diffusion limitation. But the costs of the process can be lowered and easier catalyst, product and aqueous phase separation can be achieved.

The Turnover Number TON and Turnover frequency TOF provides the information about the activity and efficiency of the catalyst:

$$TOF = \frac{TON}{t} = \frac{\frac{n_{\text{product}}}{n_{Pd(OAc)_2}}}{t} = \frac{\frac{1.34 \text{ mmol}}{0.0668 \text{ mmol } Pd(OAc)_2}}{6 \text{ h}} = \frac{20.1}{6 \text{ h}} = \frac{3.34}{h} \quad \text{Eq 13}$$

For the most often used  $Pd(OAc)_2@PhSiO_2$ , the TON is 20 and TOF is 3.3/h for the reaction of iodobenzene and styrene. For the  $Pd(OAc)_2$  catalyzed homogeneous reaction the same results would be obtained. TOF should be  $>500/h$  ( $TON > 1000$ ) for industrially usable catalysts [7]. In

Figure 22 we have shown, that  $\text{Pd}(\text{OAc})_2@\text{PhSiO}_2$  could be recycled more than 6 times without loss in activity. Considering these results the TON would be  $>501$  after 25 runs, which is useful for industrial application. In Figure 21 we have also shown, that the reactant concentration can be increased up to 5 times, which would increase the Turnover Number to  $\text{TON}=100$  after one run up to  $\text{TON}>1000$  for 10 runs.

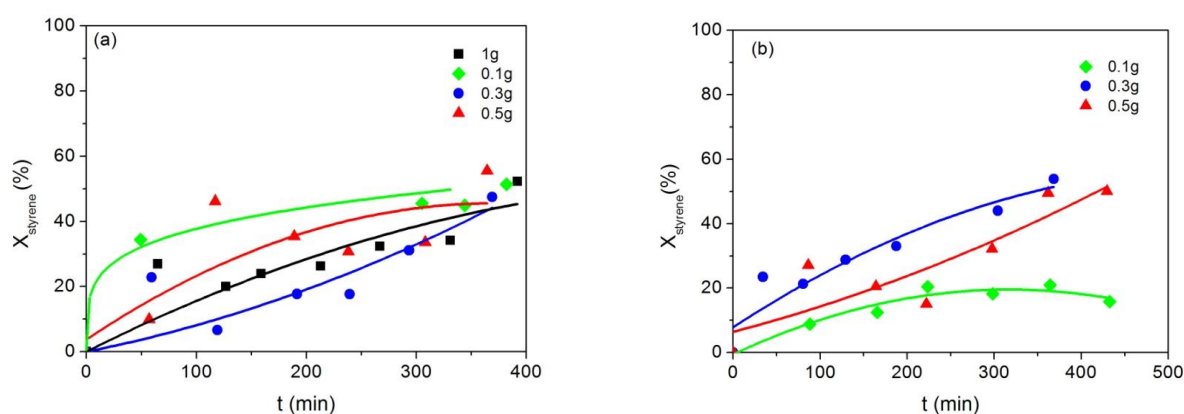
#### 4.3.6. Heck coupling with other heterogeneous catalysts

In addition Heck coupling reaction was also carried out with sol-gel immobilized manganese and a mixture of palladium-manganese catalysts. Also the option of the catalyst recycling by magnetofiltration through the application of sol-gel immobilized  $\text{Pd}(\text{OAc})_2@\text{Fe}_3\text{O}_4\text{PhSiO}_2$  catalysts was presented.

##### a) Magnetic $\text{Pd}@\text{Fe}_3\text{O}_4\text{PhSiO}_2$ catalyst

The further improvement in recycling of the heterogeneous catalyst can be achieved by using the magnetic particles, which can be synthesized by a sol-gel method described before with the addition of small amounts of magnetic  $\text{Fe}_3\text{O}_4$  to the palladium precursor. After the reaction the magnetic catalyst particles can be separated filtration-free by using the external magnetic field. The advantage of this method is that no particles have to be removed from the reactor and no catalyst gets lost.

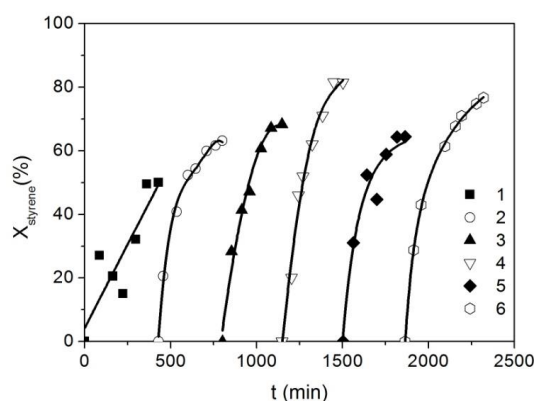
Magnetic nanoparticles with different loadings of  $\text{Fe}_3\text{O}_4$  were tested for the Heck reaction of iodo- and bromobenzene with styrene to *trans*-stilbene:



**Figure 26:** Activity of  $\text{Pd}(\text{OAc})_2@\text{PhSiO}_2\text{Fe}_3\text{O}_4$  catalyst (a) bromobenzene, (b) iodobenzene (1.34 mmol styrene, 1.5 mmol PhX, 0.276 g  $\text{K}_2\text{CO}_3$ , 0.0668 mmol  $\text{Pd}(\text{OAc})_2@\text{PhSiO}_2\text{Fe}_3\text{O}_4$ , x g  $\text{Fe}_3\text{O}_4$ , 46 mL microemulsion,  $80^\circ\text{C}$ )

The reaction rates for the coupling of iodo- and bromobenzene were comparable. The reactions with the catalysts containing 0.3 and 0.5 g of  $\text{Fe}_3\text{O}_4$ , respectively, yield the best results and also the catalyst stabilities were similar (0.7 wt%  $\text{Pd}(\text{OAc})_2$  and no  $\text{Fe}_3\text{O}_4$  leaching into the reaction mixture). The catalyst immobilized with 1 g  $\text{Fe}_3\text{O}_4$  was not very stable because of too high amount of  $\text{Fe}_3\text{O}_4$ : 0.5 wt%  $\text{Pd}(\text{OAc})_2$  and 0.4 wt%  $\text{Fe}_3\text{O}_4$  leach into the reaction solution. The disadvantages of the catalyst immobilized with 0.1 g  $\text{Fe}_3\text{O}_4$  were on the one side too small iron amount (bad catalyst separation because of weak magnetic forces in the catalyst) and on the other side too slow catalyst activation during the reaction and small catalyst activity.

For the recycling experiments the most active and stable catalyst was selected:  $\text{Pd}(\text{OAc})_2$  immobilized on 0.5 g  $\text{Fe}_3\text{O}_4/\text{PhSiO}_2$ . Magnetic palladium nanoparticles could be recycled 6 times without loss in activity and with only 0.01 % palladium leaching after the first run, no iron leaching was detected. Also, as an interesting observation we have found that the catalyst activity increases with increasing number of catalytic runs, which is an identification of slowly catalyst activation during the reaction (induction period).



**Figure 27:** Recycling experiments (1.34 mmol styrene, 1.5 mmol PhI, 0.276 g  $\text{K}_2\text{CO}_3$ , 0.0668 mmol  $\text{Pd}(\text{OAc})_2/\text{PhSiO}_2/\text{Fe}_3\text{O}_4$ , 0.5 g  $\text{Fe}_3\text{O}_4$ , 46 mL microemulsion, 80°C).

Also hot filtration test was done to prove the catalyst heterogeneity. After the filtration of the heterogeneous catalyst the reaction progress was monitored in the residue solution and no further increase in conversion was obtained. So, the catalyst used in this reaction can be identified as truly heterogeneous.

In comparison to  $\text{Pd}(\text{OAc})_2$  immobilized on  $\text{PhSiO}_2$  magnetic palladium catalyst is less active because of longer induction period of the catalyst activation and more palladium leaching into the reaction mixture was obtained, but the catalyst could be also recycled 6 times without

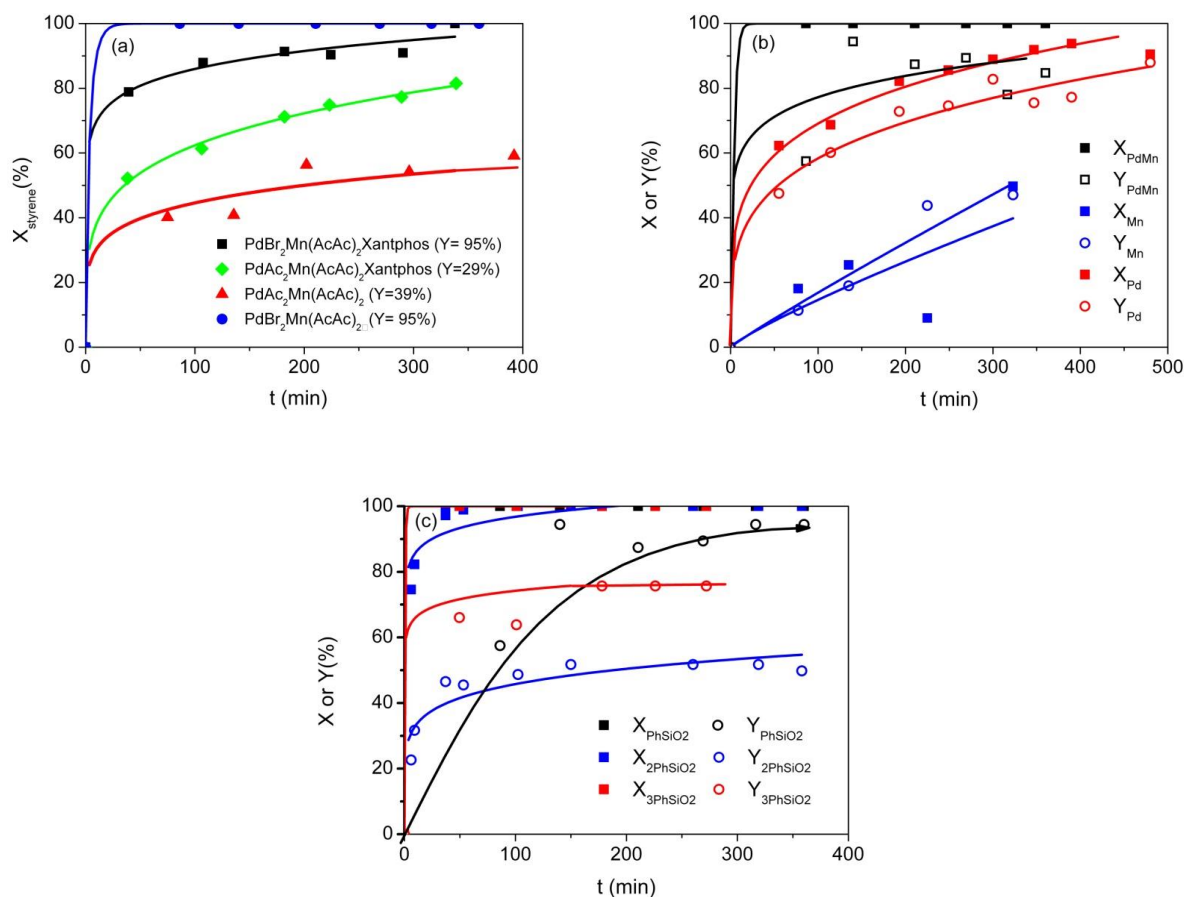
palladium leaching and decrease in activity. The biggest advantage of such an immobilization method is a faster catalyst separation by external magnet and no mass loss.

#### **b) PdMn@PhSiO<sub>2</sub> and Mn@PhSiO<sub>2</sub> catalysts**

As was reported before, the aim of this work is the research in the field of sol-gel immobilized catalysis especially for coupling reactions. Different or the same reaction steps can be combined to tandem reactions with fine chemicals as products e.g. Heck coupling reaction followed by epoxidation with manganese or palladium catalysts. In this context we prepared new sol-gel immobilized catalysts from manganese (II) acetylacetonate precursor or a mixture of palladium (II) bromide or acetate and manganese (II) acetylacetonate with and without ligands.

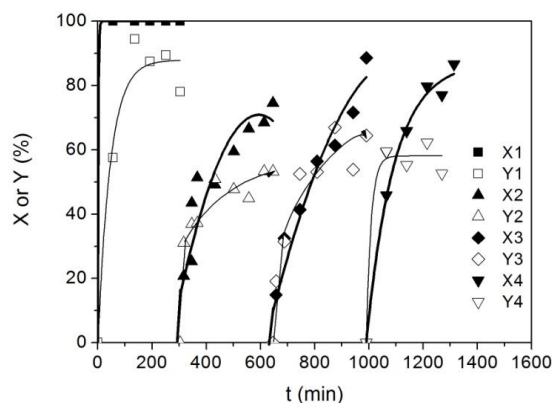
The highest yield was detected for the reaction with sol-gel immobilized PdBr<sub>2</sub>-Mn(AcAc)<sub>2</sub> catalyst with and without addition of Xantphos ligand (Figure 28a). Then the results were compared with commonly used Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> catalyst. As can be seen from Figure 28b a synergistic effect between palladium and manganese species is observed. The reaction rate with manganese catalyst, which is seldom applied in couplings, is very low in comparison to palladium and increases by using a bimetallic sol-gel immobilized catalyst.

Similar effects were already reported in literature for the arene hydrogenation with sol-gel immobilized [Rh(cod)Cl]<sub>2</sub>-Pd(OAc)<sub>2</sub> catalyst [103] and oxidative carbonylation of amine with polymer supported PdCl<sub>2</sub>-MnCl<sub>2</sub> catalyst [104]. The advantages of using these catalysts is atom and costs economy (applying of one catalyst in tandem reactions), but the largest challenge is to find the right synthesis method to produce stable heterogeneous catalysts. PdBr<sub>2</sub>-Mn(AcAc)<sub>2</sub> was immobilized with a double and threefold amount of hydrolyzed silica precursors to stabilize the catalyst-silica matrix. The same activities were measured (Figure 28c), but no improvement in the catalyst stability was obtained: for all Pd-Mn catalysts about 0.3-0.6 % Mn(AcAc)<sub>2</sub> and 3-4% PdX<sub>2</sub> leaching was detected by ICP measurements.



**Figure 28:** Heck coupling with sol-gel immobilized Pd-Mn catalysts (a) choice of Pd-Mn catalyst precursor, (b) synergic effect, (c) silica amount in  $\text{PdBr}_2\text{Mn}(\text{AcAc})_2@\text{PhSiO}_2$  (1.34 mmol styrene, 1.5 mmol PhI, 0.276 g  $\text{K}_2\text{CO}_3$ , catalyst:  $\text{Pd}=\text{Pd}(\text{OAc})_2@\text{PhSiO}_2$ ,  $\text{Mn}=\text{Mn}(\text{AcAc})_2@\text{PhSiO}_2$ ,  $\text{PdMn}=\text{PdBr}_2\text{Mn}(\text{AcAc})_2@\text{PhSiO}_2$  [0.0668 mmol  $\text{PdX}_2$ , 0.0668 mmol  $\text{Mn}(\text{AcAc})_2$ ,  $\text{PdX}_2:\text{Xantphos}=1:1$ ], 46 mL microemulsion,  $80^\circ\text{C}$ ,  $X=\text{conversion}_{\text{styrene}}$ ,  $Y=\text{yield}_{\text{trans-stilbene}}$ ).

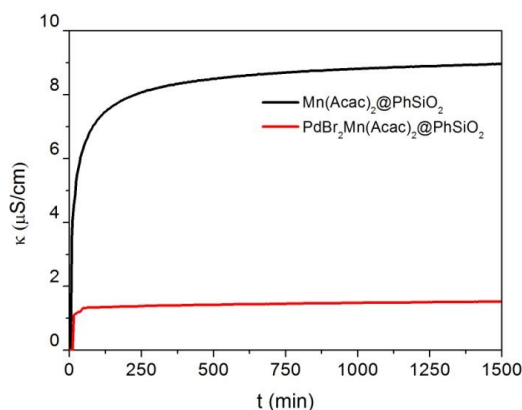
Pd-Mn catalyst with highest activity containing  $\text{PdBr}_2$  and  $\text{Mn}(\text{Acac})_2$  catalyst precursors was recycled 4 times, as expected a loss in activity after the first run was obtained due to high palladium and manganese leaching into the reaction mixture. The catalyst activity stayed constant in the following runs and only 0.1%  $\text{MnAc}_3$  and 0.7%  $\text{PdBr}_2$  leaching after second run and no leaching in following runs was detected.



**Figure 29:** Recycling experiments with PdMn@PhSiO<sub>2</sub> catalyst (1.34 mmol styrene, 1.5 mmol PhI, 0.276 g K<sub>2</sub>CO<sub>3</sub>, PdBr<sub>2</sub>Mn(AcAc)<sub>2</sub>@PhSiO<sub>2</sub>, 0.0668 mmol PdBr<sub>2</sub>, 0.0668 mmol Mn(AcAc)<sub>2</sub>, 46 mL microemulsion, 80°C, X=conversion<sub>styrene</sub>, Y=yield<sub>trans-stilbene</sub>).

From the recycling experiments with PdBr<sub>2</sub>-Mn(Acac)<sub>2</sub>@PhSiO<sub>2</sub> the recycling efficiency  $\eta_{\text{recycling}}$  was estimated to be >0.94 after N>4 runs with about 5% overall loss of palladium and manganese.

Diffusion coefficients  $D_{\text{eff,tracer}}$  for the sol-gel immobilized manganese (II) acetylacetonate and PdBr<sub>2</sub>Mn(Acac)<sub>2</sub> catalysts used in Heck coupling reactions were determined from conductivity measurements:



**Figure 30:** Conductivity measurements of sol-gel immobilized Mn(Acac)<sub>2</sub> and PdBr<sub>2</sub>-Mn(Acac)<sub>2</sub> catalysts

Effective diffusion coefficients  $D_{\text{eff,styrene}}$  were calculated from  $D_{\text{eff,tracer}}$  (equation 2 and 3) considering the molecular diffusion coefficients of SrCl<sub>2</sub> (tracer) and styrene at ambient temperature in water ( $D_{\text{M,tracer}} = \text{SrCl}_2 = 1.4 \cdot 10^{-4} \text{ cm}^2/\text{s}$  [80] and  $D_{\text{M,styrene}} = 1 \cdot 10^{-5} \text{ cm}^2/\text{s}$  [101]):

**Table 13:** Diffusion coefficients and Weisz-Modulus for the sol-gel immobilized manganese and palladium-manganese catalysts

Material	$D_{eff, tracer}$ [cm <sup>2</sup> ·s <sup>-1</sup> ]	$D_{eff, styrene}$ [cm <sup>2</sup> ·s <sup>-1</sup> ]	$r_0$ [mol·l <sup>-1</sup> ·s <sup>-1</sup> ]	Weisz- Modulus $\Psi$
Mn(Acac) <sub>2</sub> @PhSiO <sub>2</sub>	4.35·10 <sup>-7</sup>	3.1·10 <sup>-8</sup>	3.5·10 <sup>-7</sup>	0.5
PdBr <sub>2</sub> Mn(Acac) <sub>2</sub> @PhSiO <sub>2</sub>	2.85·10 <sup>-7</sup>	2.0·10 <sup>-8</sup>	2.1·10 <sup>-6</sup>	4.4
Pd(OAc) <sub>2</sub> @PhSiO <sub>2</sub>	4.70·10 <sup>-8</sup>	1.2·10 <sup>-9</sup>	2.3·10 <sup>-6</sup>	3

The Weisz-Modulus was calculated from the equation 1 with initial rates  $r_0$  determined from the consumption of styrene ( $-dc_{styrene}/dt$ ) during the reaction, average particle size  $L$  of 200  $\mu m$  and catalyst density  $\rho_{cat}$  of 1.9 g/cm<sup>3</sup>. The values of  $\Psi$  vary between 3 and 4 for palladium and palladium manganese catalyst, which is an indication of a reaction rate limitation by diffusion of reactants inside the silica material pores. The pore effectiveness factor  $\eta_{pore}$  of the sol-gel immobilized palladium and palladium-manganese catalysts was estimated to be about 40% for Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> and 30% for PdBr<sub>2</sub>Mn(Acac)<sub>2</sub>@PhSiO<sub>2</sub> for the second order reaction. Weisz-Modulus  $\Psi$  was  $\ll 1$  for sol-gel immobilized manganese catalyst because of very low reaction rate (small activity of the catalyst). Pore effectiveness factor of this catalyst was estimated to be  $\eta_{pore}=85\%$ . In comparison to homogeneous reaction, the heterogeneously catalyzed Heck coupling reaction is slower due to some diffusion limitation and  $\eta_{intercalation}$  (Equation 7) was estimated to be 0.83. The overall efficiency of the PdBr<sub>2</sub>-Mn(Acac)<sub>2</sub>@ PhSiO<sub>2</sub> was determined from recycling, immobilization, intercalation and pore efficiency (Equation 4):

$$\eta = \eta_{immobilisation} \cdot \eta_{intercalation} \cdot \eta_{pore} \cdot (>N_{cycle}) \cdot (>\eta_{recycling}^N) \quad \text{Eq 4}$$

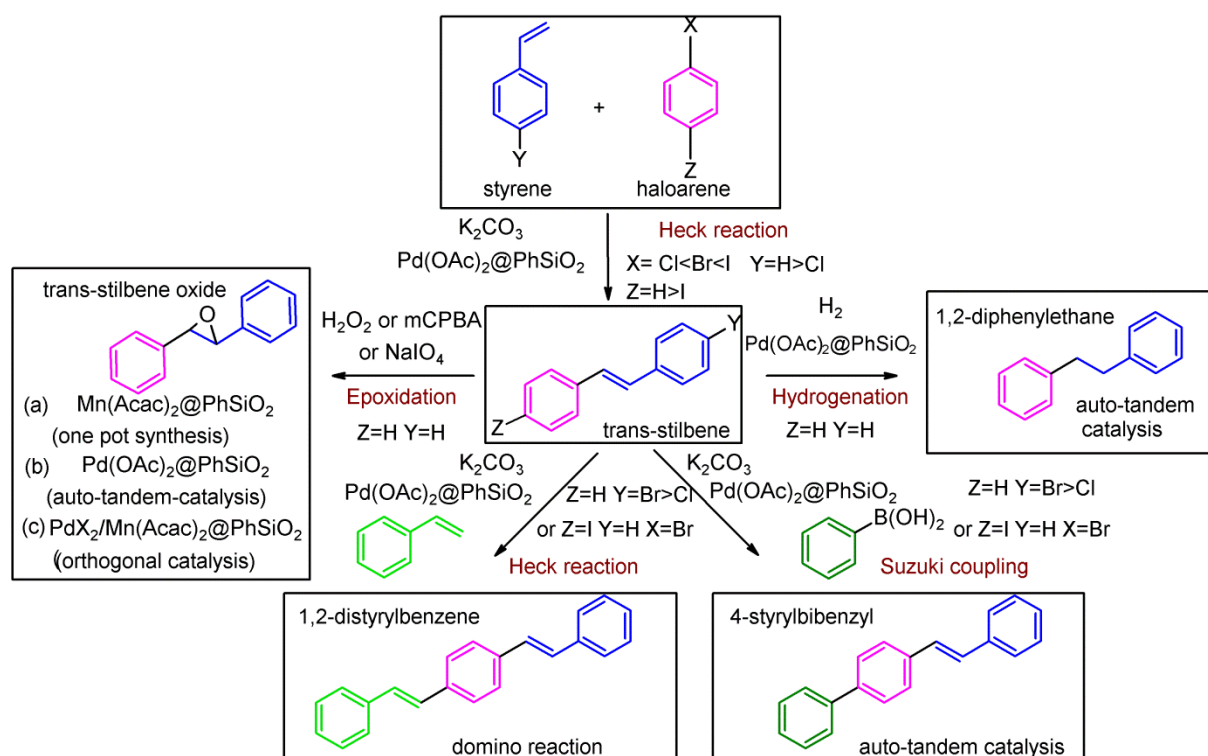
$$\eta = 0.9997 \cdot 0.8306 \cdot 0.3 \cdot (>4) \cdot (>0.9839^4) = (>0.934)$$

In comparison to palladium acetate prepared by the same method, a mixed palladium-manganese catalyst is more active due to the synergistic effect between both metallic species (TON=20 and TOF=14/h). The overall efficiency was  $\eta \approx 1$  after 4 runs and would increase up to  $\eta > 2.1$  after 10 runs. The main disadvantage of this catalyst was higher amount of manganese and palladium leaching and lower pore efficiency.

#### 4.4. Tandem reactions with sol-gel immobilized catalysts

After the synthesis of different sol-gel immobilized rhodium, manganese, palladium and a mixture of manganese-palladium catalysts, they were applied in different tandem reactions: enantioselective hydrogenation, epoxidation and Heck coupling reactions. The factors

influencing the catalyst activity and stability were determined and the heterogeneity of the immobilized catalysts was tested. The main advantage of using immobilized catalyst is of course the recycling and reusability in several reactions. The other opportunity to use these catalysts is to combine different reaction steps to tandem processes and to apply only one or two heterogeneous catalysts in several reaction steps (atom economy). The difficulty of such a process design could be the adverse interactions between different catalysts applied in this process (catalyst poisoning) and also of not pure enough intermediates, which would decrease the reaction rate of following steps. *Trans*-stilbene is an important intermediate in the synthesis of stilbene derivatives, which are commonly applied in pharmacy because of their hormone-like, fluorescent and medicative effects. In Scheme 22 different subsequent processing steps of *trans*-stilbene in tandem reactions with sol-gel immobilized palladium and manganese catalysts are shown, that were tested in microemulsions as reaction media:

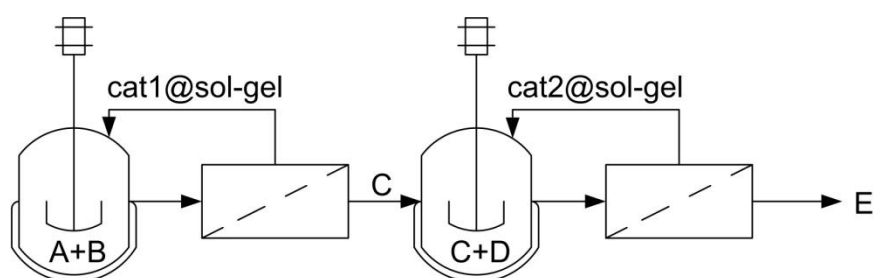


**Scheme 22:** Tandem reactions with sol-gel immobilized catalysts with *trans*-stilbene as intermediate product

*Trans*-stilbene prepared from iodobenzene and styrene via Heck coupling was converted to different derived products: fluorescence active 1,2-distyrylbenzene (*domino* Heck/Heck reaction via one  $\text{Pd}(\text{OAc})_2 @ \text{PhSiO}_2$  catalyst and one mechanism) and 4-styrylbibenzyl (*auto-tandem* Heck/Suzuki catalysis via one  $\text{Pd}(\text{OAc})_2$  catalyst and two reaction mechanisms namely

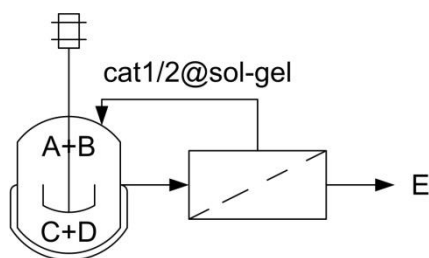
Heck and Suzuki coupling); 1,2-diphenylethane (via *auto-tandem* Heck/hydrogenation reaction) and epoxidation to *trans*-stilbene oxide via *one pot synthesis* with  $\text{Mn}(\text{Acac})_2@\text{PhSiO}_2$  (two different catalysts and reaction steps), *auto-tandem catalysis* with  $\text{Pd}(\text{OAc})_2@\text{PhSiO}_2$  (one catalyst, two different reaction steps) or *orthogonal catalysis* with  $\text{PdX}_2\text{Mn}(\text{Acac})_2@\text{PhSiO}_2$  (two different catalysts at the beginning of the process and two different reaction steps).

In dependency of the reaction type the concept could be realized in two sequenced reactors (Scheme 23), where the first catalyst was filtered off and reused and the product C was transferred into the second reactor. There the second reactant D and the second sol-gel immobilized catalyst were added to produce the final product E. For example for the preparation of 1,2-diphenylethane the transfer of the reaction mixture after the Heck reaction with *trans*-stilbene as intermediate product C, microemulsion and  $\text{Pd}(\text{OAc})_2@\text{PhSiO}_2$  as cat1@sol-gel) from stirred tank reactor into the hydrogenation reactor and the addition of hydrogen (educt D) was necessary.



**Scheme 23:** Two sequenced reactor concept for the performance of tandem reaction

In many cases use of only one reactor is sufficient (Scheme 24). For example, for the performance of Heck/Heck tandem reaction, only the addition of styrene after the first reaction step is necessary to obtain 1,2-distyrylbenzene as product E. After the process, one or several catalysts can be recovered by filtration and applied in the next synthesis of product E.



**Scheme 24:** Tandem reaction with sol-gel immobilized catalyst in one reactor

#### 4.4.1. Heck coupling and Hydrogenation

As first example of the tandem reaction concept, the synthesis of 1,2-diphenylethane from *trans*-stilbene as intermediate by Heck/hydrogenation reaction (Auto-tandem catalysis) was developed. 1,2-Diphenylethane is an important intermediate in organic synthesis. Aryl substituted 1,2-diphenylethane acts as intermediate for the synthesis of potential anti cancer agents [105] e.g. 2-hydroxyethanone or 1,2-ethanedione, which are inhibitors for Retinoic acid-metabolizing enzyme. The other application is the synthesis of aminoalkoxybibenzyl compounds as therapeutic agents for glaucoma treatment (EP0695545).

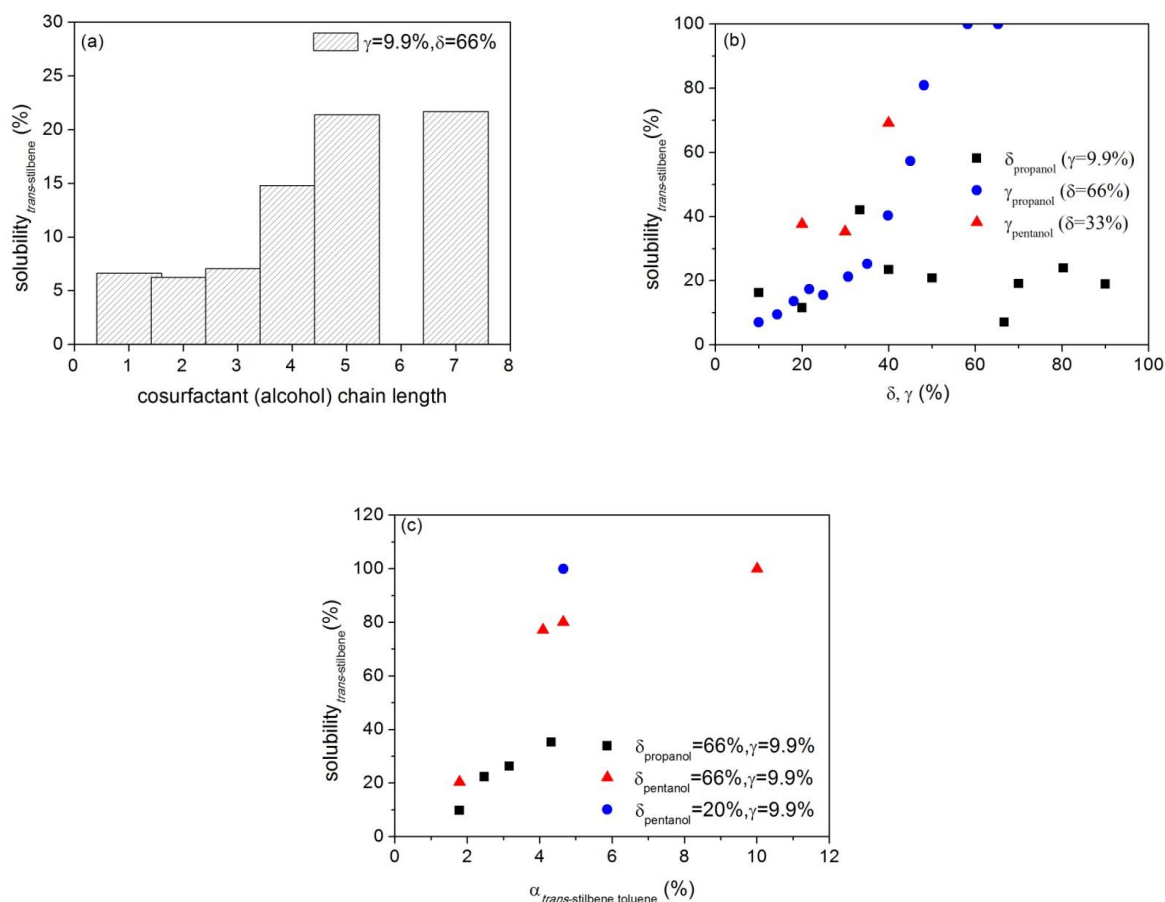
In Chapter 4.2 we described the enantioselective hydrogenation of itaconic acid and derivate with sol-gel immobilized Rh/BPPM complex. For the non enantioselective hydrogenation reaction of *trans*-stilbene no adaption of enantioselective ligand into the metal complex is necessary. Commonly used catalysts for the hydrogenation of olefins are insoluble mainly heterogeneous metal catalysts like Pd/C, Raney-Ni (Ni-Al alloy) or PtO<sub>2</sub>. The tandem process can also be carried out with only one palladium catalyst immobilized on silica by sol-gel method, which was already been applied in Heck coupling reaction and was a very stable and active heterogeneous catalyst.

##### a) Hydrogenation of *trans*-stilbene

Before starting the tandem Heck-hydrogenation reaction, benchmark experiments with *trans*-stilbene were done. *Trans*-stilbene obtained from Sigma-Aldrich Company was hydrogenated to 1,2-diphenylethane in methanol and in aqueous microemulsion with homogeneous and sol-gel immobilized palladium catalysts.

First, *trans*-stilbene was hydrogenated in methanol with heterogeneous and homogeneous Pd(OAc)<sub>2</sub> catalysts (Figure 32a). After 10-20 minutes the full conversion was achieved, as expected the reaction rate of the heterogeneous reaction was a little slower because of diffusion limitations. As can be seen in Figure 32b, *trans*-stilbene also reacts in aqueous microemulsion with homogeneous and sol-gel immobilized palladium catalysts. The reaction rate is slower because of lower hydrogen solubility in water than in methanol (about 5 times). In standard water/propanol/CTAB microemulsion ( $\gamma$ =10%,  $\delta$ =66%,  $\alpha$ =0.58%) at 40°C *trans*-stilbene was not completely soluble and also the reaction rates were very slow (reaction time about 400 min). Increasing of the temperature to 80°C increased the solubility of the substrate, but not completely. That's why a further solubilization experiments (phase investigations) were carried

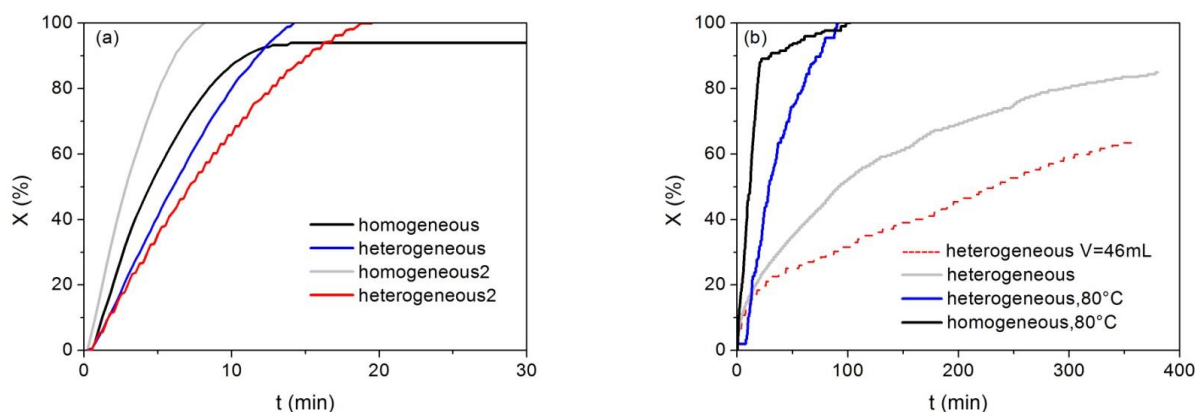
out with constant concentration of *trans*-stilbene ( $\alpha=0.58\%$ ) with different microemulsion compositions at  $80^\circ\text{C}$  to improve the low solubility as shown in Figure 31:



**Figure 31:** Solubility measurements with *trans*-stilbene at  $80^\circ\text{C}$  (a) choice of cosurfactant (alcohol), (b) surfactant ratio  $\gamma$  and cosurfactant ratio  $\delta$ , (c) influence of toluene ( $\alpha_{\text{trans-stilbene, toluene}}$ ).

The variation of cosurfactant chain length from methanol and ethanol up to 1-heptanol in  $\text{H}_2\text{O}/\text{CTAB}/\text{alcohol}$  microemulsions ( $\gamma=9.9\%$ ,  $\delta=66\%$ ,  $\alpha=0.58\%$ ) increases the solubility of *trans*-stilbene in the case of pentanol to about 20% (Figure 31a). The solubility was calculated as a ratio of initial concentration of *trans*-stilbene to the concentration of *trans*-stilbene dissolved in microemulsion obtained from HPLC measurements. Also increasing the amount of cosurfactant (decreasing  $\delta$ ) and increasing of surfactant ratio  $\gamma$  promotes the solubility (Figure 31b). Full solubilization of *trans*-stilbene was obtained for surfactant ratio  $\gamma>40\%$  with pentanol or propanol as cosurfactant. Because of trying to make the process more environmentally friendly, the addition of surfactants with  $\gamma>15\%$  is not reasonable and another solution of this problem has to be found. In Figure 31c a small amount of toluene (co-solvent)

was added to *trans*-stilbene and the oil fraction was increased up to 10 %. Complete solubility was obtained in H<sub>2</sub>O/CTAB/pentanol/toluene microemulsion ( $\gamma=9.9\%$ ,  $\delta=20\%$ ,  $\alpha=4.6\%$ ). The obtained microemulsion was applied in hydrogenation experiments at 80°C (Figure 32b) and full conversion was obtained after 60-80 min with homogeneous as well as sol-gel immobilized palladium catalysts.

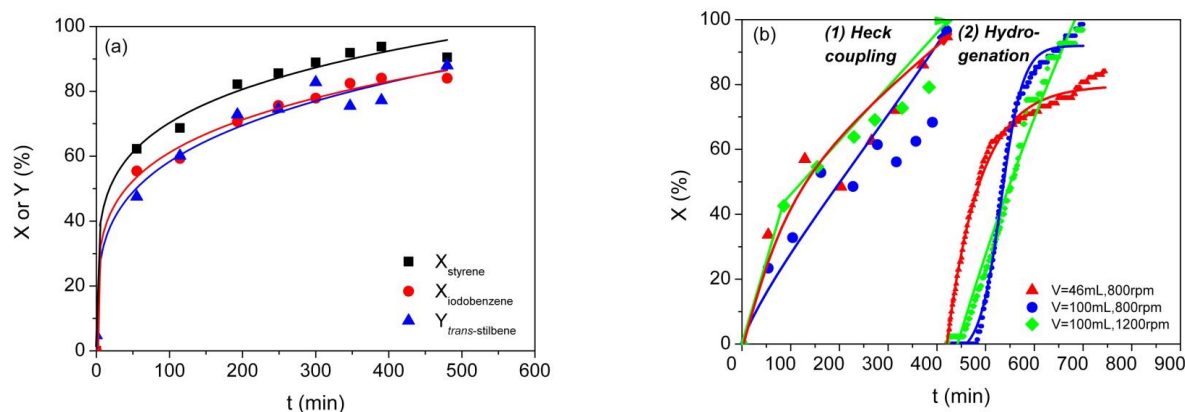


**Figure 32:** Hydrogenation of *trans*-stilbene in (a) methanol at 40°C, (b) microemulsion ( $X=V_{H_2,added}/V_{H_2}$ , 2.68 mmol *trans*-stilbene, 1.1 bar H<sub>2</sub>, 800rpm, 1.25 wt% Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> or Pd(OAc)<sub>2</sub> (0.1334 mmol Pd(OAc)<sub>2</sub>), 100 mL microemulsion (81.7 g H<sub>2</sub>O/3 g CTAB/ 6.04 g propanol) at 40°C:  $\gamma=10\%$ ,  $\delta=66\%$ ,  $\alpha=0.58\%$  or 100 mL microemulsion (83.45g H<sub>2</sub>O/ 6.14g CTAB/ 1.57 g pentanol/ 3.52 g toluene) at 80°C:  $\gamma=8\%$ ,  $\delta=20\%$ ,  $\alpha=4.6\%$ ).

#### ***b) Combination to a tandem process***

Heck reaction (chapter 4.3) of iodobenzene and styrene to *trans*-stilbene in aqueous microemulsion (Figure 33a) was successfully combined with the hydrogenation reaction of *trans*-stilbene to 1,2-diphenylethane to a tandem reaction shown in Figure 33b. Both reactions were carried out with only one Pd(OAc)<sub>2</sub> catalyst immobilized on PhSiO<sub>2</sub>.

The results obtained for the hydrogenation of intermediate product *trans*-stilbene (Figure 33b) at 800 rpm or 1200 rpm stirring speed ( $V=100\text{mL}$ ) were comparable to the results obtained for the hydrogenation with commercially available *trans*-stilbene (Figure 32b). No leaching of palladium from support material was detected ( $<0.004\%$  Pd(OAc)<sub>2</sub>).



**Figure 33:** (a) Heck coupling, (b) Tandem reaction (1) Heck (2.68 mmol styrene, 3 mmol iodobenzene, 4 mmol  $K_2CO_3$ , 0.1336 mmol  $Pd(OAc)_2@PhSiO_2$ , 100 mL microemulsion (81.7 g  $H_2O$ / 3 g CTAB/ 6.04 g propanol),  $80^\circ C$ ) (2) Hydrogenation (1.1 bar  $H_2$ ,  $60^\circ C$ , 800rpm) with X= conversion of (1) styrene and (2) *trans*-stilbene.

#### 4.4.2. Heck coupling and epoxidation

The second example of a tandem reaction is Heck coupling followed by epoxidation for the synthesis of *trans*-stilbene oxide as final product with *trans*-stilbene as intermediate. *Trans*-stilbene oxide inhibits the drug-metabolizing enzymes like epoxide hydratase [106], glutathione *S*-transferase [107] and nuclear epoxide hydrolase [108]. It can also be applied for the production of different products by ring opening reaction with nitrogen containing reagents, oxygen or sulfur nucleophiles: for example synthesis of antihypertensive drug (R/S)-1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol or Metoprolol ( $\beta_1$  receptor blocker) from epoxide and isopropyl amine catalyzed by zinc tetrafluoroborate hydrate [109].

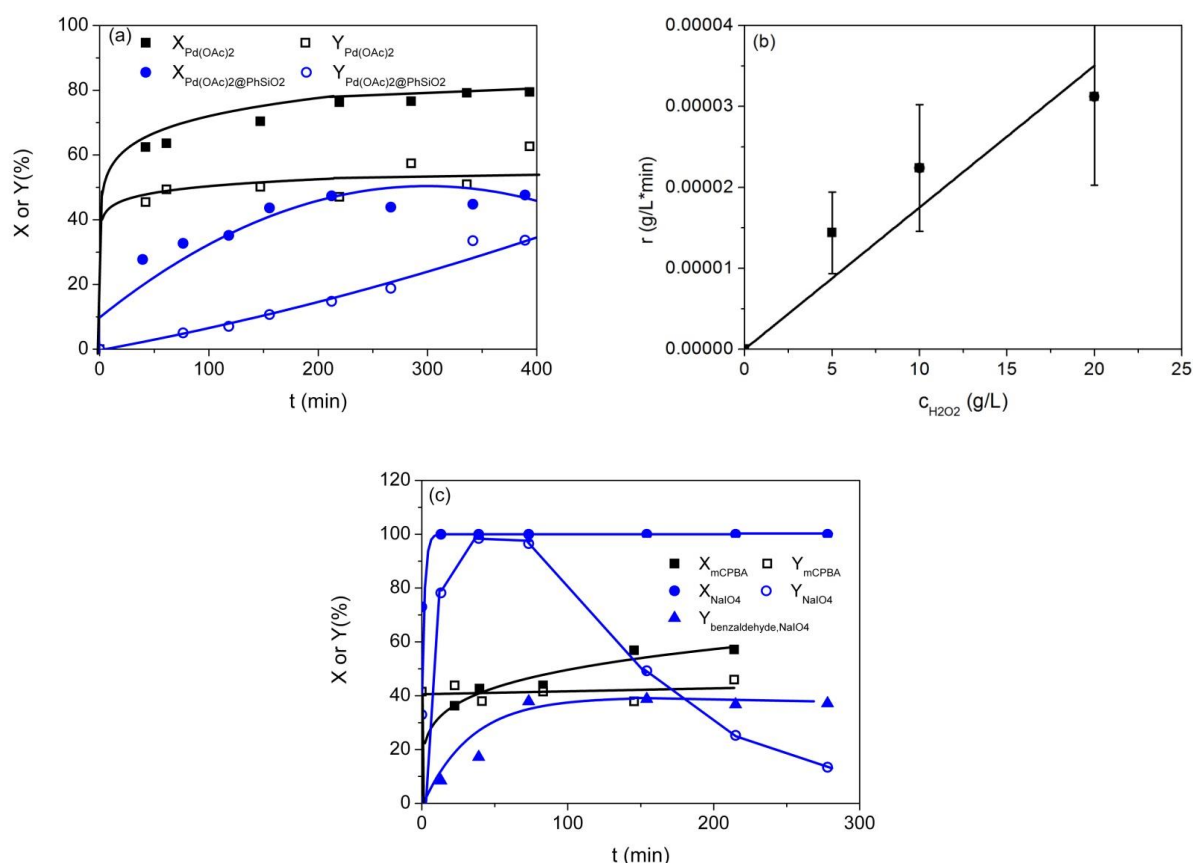
The epoxidation can be catalyzed by a variety of heterogeneous catalysts. In dependency of catalytic species applied in this process different tandem reaction classifications are used: auto-tandem catalysis with only one  $Pd(OAc)_2@PhSiO_2$  catalyst and two different reaction mechanisms, one pot synthesis with two catalysts ( $Pd(OAc)_2@PhSiO_2$  for Heck coupling and  $Mn(Acac)_2@PhSiO_2$  for epoxidation) and orthogonal catalysis with two metal precursors present from the beginning of the reaction ( $Pd(OAc)_2Mn(Acac)_2@PhSiO_2$ ).

##### a) Epoxidation of styrene and *trans*-stilbene with palladium catalyst

Before starting the tandem Heck-epoxidation tandem reaction, at first a suitable oxidizing agent, reaction conditions and catalyst for the epoxidation of *trans*-stilbene as intermediate of the tandem reaction had to be selected. *Trans*-stilbene is a very aromatic hydrophobic substrate

with low reactivity and solubility in water. For this reason primarily some test reactions catalyzed by homogeneous and sol-gel immobilized palladium acetate catalysts were carried out with less hydrophobic styrene at 70°C in aqueous CTAB/propanol/H<sub>2</sub>O microemulsion.

As oxidizing agents commonly used non toxic reactive species were selected: hydrogen peroxide H<sub>2</sub>O<sub>2</sub>, meta-chloroperbenzoic acid mCPBA and sodium periodate NaIO<sub>4</sub>:



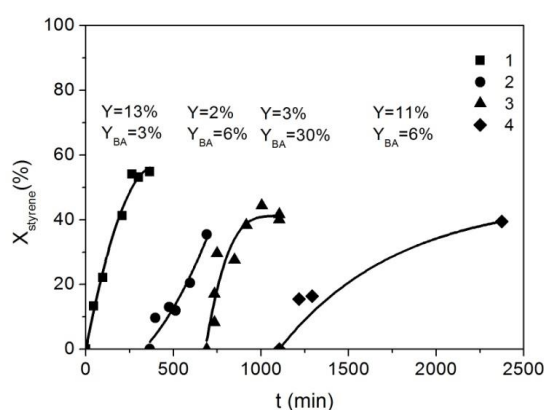
**Figure 34:** Choice of oxidizing agent (a) 10 mmol H<sub>2</sub>O<sub>2</sub>, (b) CH<sub>2</sub>O<sub>2</sub>, (c) 2.38 mmol mCPBA or NaIO<sub>4</sub> (1.34 mmol styrene, oxidizing agent, 0.0068 mmol Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub>, 46mL micro-emulsion, 70°C, X=conversion<sub>styrene</sub>, Y=yield<sub>styrene oxide</sub>)

Hydrogen peroxide is less reactive than the other oxidizing agents and can also decompose to water at higher temperatures. The advantage of using hydrogen peroxide is that this oxidizing agent is more environmentally friendly and also that reactions with hydrogen peroxide proceed without the formation of by-products (Figure 34a). In comparison to the reaction with homogeneous Pd(OAc)<sub>2</sub> the reaction with sol-gel immobilized palladium catalyst was slower because of catalyst leaching into the reaction mixture and diffusion limitations. From comparison of reaction rates for homogeneous and heterogeneous epoxidation with palladium

acetate@PhSiO<sub>2</sub> and hydrogen peroxide as oxidizing agent (Figure 34a) the intercalation efficiency of the catalyst was determined (Equation 7) to be only  $\eta_{\text{intercalation}} = 0.1709$ .

The addition of more hydrogen peroxide increases the reactivity to be only with respect to the formation of less favorable by-products e.g. benzoic acid and benzaldehyde (Figure 34b). Highest yields were obtained for the epoxidation with sodium periodate (Figure 34c), but after certain time styrene oxide was oxidized to benzaldehyde.

The sol-gel immobilized palladium catalyst, which was already successfully applied in Heck reactions, was recycled 4 times after epoxidation of styrene with 10 mmol hydrogen peroxide as oxidizing agent. As can be seen from Figure 35, the catalyst was not very stable and the reaction rate and product selectivity decreases with increasing number of runs. About 4.5 % Pd(OAc)<sub>2</sub> was leached after first run, 0.5% after the second, 0.8 after the third and 0.6 after the fourth run. In comparison to the Heck coupling reaction the catalyst was not really stable and such a strong leaching of palladium from the support material can only be caused by a strong oxidizing agent.

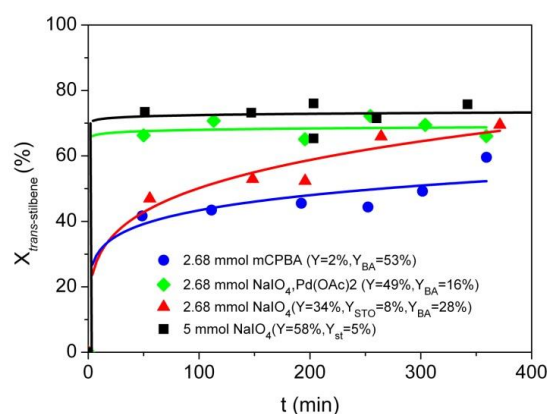


**Figure 35:** Recycling experiments (1.34 mmol styrene, 10 mmol H<sub>2</sub>O<sub>2</sub>, 0.0068 mmol Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub>, 46 mL microemulsion, 70°C, Y= yield<sub>styrene oxide</sub>, Y<sub>BA</sub>= yield<sub>benzaldehyde</sub>)

From these results the recycling efficiency was determined (Equation 5) to be  $\eta_{\text{recycling}} > 0.832$  for N>4 runs and 6.4% palladium acetate leaching.

Similar experiments were carried out with less reactive *trans*-stilbene at 80°C. A lower amount of byproducts was formed in comparison to the epoxidation of styrene. *Trans*-stilbene was not completely soluble in microemulsion and only after 1-2 hours the reaction mixture became clearer because of formation of better soluble *trans*-stilbene oxide as product.

Hardly any product was formed with hydrogen peroxide as oxidizing agent, with meta-Chloroperbenzoic acid the yield was <5% and mostly benzaldehyde as by-product was obtained. The best oxidizing agent was again sodium periodate as in the case of styrene (Figure 36). For the epoxidation of *trans*-stilbene a higher amount of NaIO<sub>4</sub> (5 mmol) was required because of low reactivity of this substrate. In the case of the epoxidation of *trans*-stilbene the catalyst was also not very stable and about 3-6% Pd(OAc)<sub>2</sub> leaching into the reaction mixture was detected.



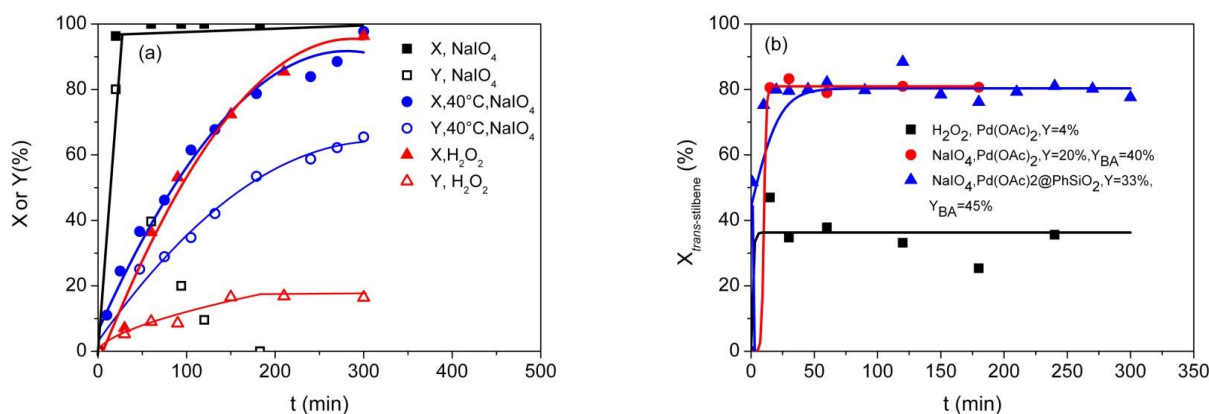
**Figure 36:** Epoxidation of *trans*-stilbene (1.34 mmol *trans*-stilbene, oxidizing agent, 0.0068 mmol Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> or Pd(OAc)<sub>2</sub>, 46mL microemulsion, 80°C, Y=yield<sub>*trans*-stilbene oxide</sub>, Y<sub>BA</sub>=yield<sub>benzaldehyde</sub>, Y<sub>STO</sub>=yield<sub>styrene oxide</sub>, Y<sub>st</sub>=yield<sub>styrene</sub>)

#### b) Epoxidation of styrene and *trans*-stilbene with Mn and Pd-Mn catalysts

Pd(OAc)<sub>2</sub> immobilized on silica by a sol-gel method is a very stable and frequently investigated catalyst. In many cases it was applied as catalyst for coupling reactions and hydrogenations but it is not commonly used for oxidations e.g. epoxidations of olefins because of low reactivity in comparison to other metals. Only few examples are known from the literature e.g. epoxidation of olefine with t-BuOOH by Pd(OAc)<sub>2</sub> at 0°C [110]. Usually manganese (II) species e.g. manganese (II) porphyrine complexes were used as catalysts for the variety of epoxidation reactions, but the immobilization of manganese catalyst is still challenging, because of strong leaching and low availability of commercial catalysts. Lane et al. [111] reported a simple and cheap method to catalyze epoxidation reactions in dimethylformamide by homogeneous MnSO<sub>4</sub> or MnAc<sub>2</sub> catalyst with hydrogen peroxide as oxidizing agent.

In our case we oxidized styrene with homogeneous manganese (II) acetylacetonate in aqueous microemulsion with sodium periodate or hydrogen peroxide as oxidizing agent (Figure 37a).

As expected and was already seen for the same reaction with palladium acetate, hydrogen peroxide was the worse oxidizing agent than sodium periodate. Styrene was completely transferred to styrene oxide and then reacts to the secondary product benzaldehyde, if sodium periodate was applied. Lowering the reaction temperature to 40 °C decreases the reactivity of the oxidizing agent and the amount of formed by-products.

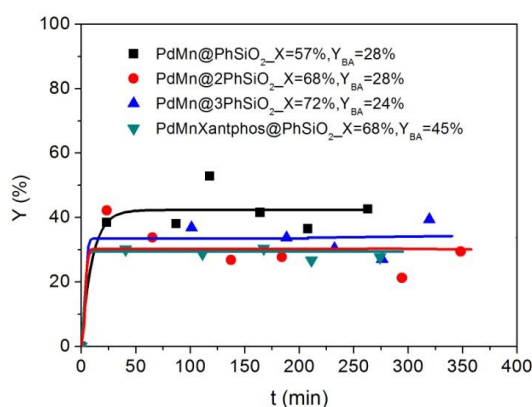


**Figure 37:** Epoxidation of (a) styrene at 70°C with Mn(AcAc)<sub>2</sub> and (b) *trans*-stilbene at 80°C with Mn(AcAc)<sub>2</sub>@PhSiO<sub>2</sub> (1.34 mmol substrate, 2.68 mmol NaIO<sub>4</sub> or 20 mmol H<sub>2</sub>O<sub>2</sub>, 0.0068 mmol Mn(AcAc)<sub>2</sub>, 46 mL microemulsion, X=conversion<sub>*trans*-stilbene</sub>, Y=yield<sub>product</sub> (a) styrene oxide or (b) *trans*-stilbene oxide), Y<sub>BA</sub>=yield<sub>benzaldehyde</sub>)

The epoxidation of less reactive *trans*-stilbene (Figure 37b) at 80°C is accompanied with high amount of by-products and the best results were obtained for the reaction with sodium periodate as oxidizing agent. There was no difference in activity between homogeneous and sol-gel immobilized manganese catalyst. About 55% of manganese leaching after the reaction was detected by ICP measurements. The catalyst was not really heterogeneous because the active species in this reaction consists mostly of leached manganese catalyst. From the comparison of reaction rates of homogeneously and heterogeneously catalyzed reaction (Figure 37a) it is clear that the intercalation efficiency  $\eta_{\text{intercalation}}=1$  (Equation 7), but the sol-gel immobilized manganese catalyst is not really heterogeneous.

The sol-gel immobilized catalyst was recycled 4 times after the epoxidation of *trans*-stilbene with sodium periodate. The conversion of *trans*-stilbene decreases from 80 to 68% during the runs because of high catalyst leaching (55% Mn(Acac)<sub>2</sub> after first run and up to 90% Mn(Acac)<sub>2</sub> after 3-4 runs). In all runs the amount of by-product benzaldehyde was about 10-20%, but surprisingly the yield of product increases from 33 up to 60% after fourth run. The recycling

efficiency of the heterogeneous manganese catalyst was very low:  $\eta_{\text{recycling}} > 0.185$  with  $N > 4$  runs and 95%  $\text{Mn}(\text{Acac})_2$  leaching. In summary it is well seen that manganese catalyst is not recommended as heterogeneous catalyst for the epoxidation because of its low stability. In comparison to this, heterogeneous palladium acetate yields better results and was the more stable catalyst. That's why we tried in the next step to combine the usually used not stable manganese (II) with palladium (II) species to obtain a new sol-gel immobilized catalyst with better properties (Figure 38). Sol-gel immobilized palladium-manganese catalysts were already applied in Heck coupling in Chapter 4.3.5 and a synergistic effect between palladium (II) bromide and manganese (II) acetylacetonate was found. The palladium acetate precursor was not suitable because of unfavorable interactions with manganese acetylacetonate. Typical yield curves are shown in Figure 38 for the epoxidation of *trans*-stilbene: a very fast increase of product yield and reactant conversion and after certain time (about 50 minutes) no further progress in the reaction was seen. In comparison to homogeneously catalyzed reaction, the reaction rate for the epoxidation with sol-gel immobilized catalyst was similar and  $\eta_{\text{intercalation}}$  was estimated to be 0.89.



**Figure 38:** Epoxidation of *trans*-stilbene with Pd-Mn catalysts (1.34 mmol *trans*-stilbene, 2.68 mmol  $\text{NaIO}_4$ ,  $\text{PdMnX@nPhSiO}_2$ , 0.0068 mmol  $\text{PdBr}_2$  and 0.0068 mmol  $\text{Mn}(\text{AcAc})_2$ ,  $\text{PdBr}_2$ : Xantphos ligand 1:1, 46 mL ME,  $80^\circ\text{C}$ ,  $X = \text{conversion}_{\text{trans-stilbene}}$ ,  $Y = \text{yield}_{\text{trans-stilbene oxide}}$ ,  $Y_{BA} = \text{yield}_{\text{benzaldehyde}}$ )

The epoxidation was also catalyzed by Pd-Mn catalysts immobilized on double and triple amount of silica and also with addition of the Xantphos ligand to improve the stability of the catalyst and to avoid the leaching problem. The catalyst activities were similar in all cases. Only 0.04%  $\text{Mn}(\text{AcAc})_2$  and 2%  $\text{PdBr}_2$  leaching was detected after the reaction with  $\text{PdMn-Xantphos}$  complex. No improvement in catalyst stability was seen by immobilization of the catalyst

precursors in higher amount of silica, catalyst leaching was between 6-9% for both  $\text{PdBr}_2$  and  $\text{Mn}(\text{AcAc})_2$ . The recycling efficiency was estimated to be  $\eta_{\text{recycling}} > 0.98$  after  $N > 1$  run and 2% catalyst leaching.

For manganese, palladium and palladium-manganese catalysts applied in the epoxidation of *trans*-stilbene the effective diffusion coefficients  $D_{\text{eff}, \text{trans-stilbene}}$  and Weisz-Modulus  $\Psi$  were calculated:

**Table 14:** Diffusion coefficients and Weisz-Modulus for the sol-gel immobilized palladium, manganese and palladium-manganese catalysts

material	$D_{\text{eff}, \text{tracer}}$ [ $\text{cm}^2 \cdot \text{s}^{-1}$ ]	$D_{\text{eff}, \text{trans-stilbene}}$ [ $\text{cm}^2 \cdot \text{s}^{-1}$ ]	$r_0$ [ $\text{mol} \cdot \text{l}^{-1} \cdot \text{s}^{-1}$ ]	Weisz-Modulus $\Psi$	$\eta_{\text{pore}}$ (%)
$\text{Mn}(\text{Acac})_2 @ \text{PhSiO}_2$	$4.35 \cdot 10^{-7}$	$1.0 \cdot 10^{-8}$	$4.9 \cdot 10^{-7}$	1	75
$\text{PdBr}_2 \text{Mn}(\text{Acac})_2 @ \text{PhSiO}_2$	$2.85 \cdot 10^{-7}$	$6.8 \cdot 10^{-9}$	$1.8 \cdot 10^{-6}$	7	10
$\text{Pd}(\text{OAc})_2 @ \text{PhSiO}_2$	$4.70 \cdot 10^{-8}$	$1.1 \cdot 10^{-9}$	$1.8 \cdot 10^{-7}$	4	30

$D_{\text{eff}, \text{trans-stilbene}}$  was calculated from measured diffusion coefficients  $D_{\text{eff}, \text{tracer}}$  (Figure 29) with  $D_{\text{M}, \text{trans-stilbene}} = 0.333 \cdot 10^{-5} \text{ cm}^2/\text{s}$  [112] and  $D_{\text{M}, \text{tracer}} = \text{SrCl}_2 = 1.4 \cdot 10^{-4} \text{ cm}^2/\text{s}$ . Weisz-Modulus  $\Psi$  was determined from a comparison between reaction rate and effective diffusion rate (Equation 1). The values were 4 and 7, respectively, for the reaction with sol-gel immobilized palladium and palladium manganese catalysts, which is characteristic for strongly diffusion limited reactions. From the Weisz-Prater criteria  $\Psi$ , the pore efficiencies  $\eta_{\text{pore}}$  of used catalysts were calculated (Table 14). However a large amount of metal leaching was detected during the reaction and that's why the results are not really trustable. The initial reaction rate  $r_0$  calculated from the *trans*-stilbene consumption during the reaction is partly caused from homogeneous palladium and manganese species in the reaction mixture. Metal leaching could also change the structure of the immobilized catalyst which affects the values of the diffusion coefficients.

Finally the overall catalyst efficiency  $\eta$  could be determined from kinetic and diffusion measurements with palladium, manganese and palladium-manganese catalyst immobilized on  $\text{PhSiO}_2$  by sol-gel method:

$$\eta = \eta_{\text{immobilisation}} \cdot \eta_{\text{intercalation}} \cdot \eta_{\text{pore}} \cdot (>N_{\text{cycle}}) \cdot (>\eta_{\text{recycling}}^N) \quad \text{Eq 4}$$

$$\eta_{\text{Mn}(\text{Acac})_2 @ \text{PhSiO}_2} = 0.9948 \cdot 1 \cdot 0.75 \cdot (>4) \cdot (>0.656^4) = (>0.5521)$$

$$\eta_{\text{Pd}(\text{OAc})_2 @ \text{PhSiO}_2} = 1 \cdot 0.1709 \cdot 0.3 \cdot (>4) \cdot (>0.955^4) = (>0.171)$$

$$\eta_{\text{PdBr}_2\text{Mn}(\text{Acac})_2@\text{PhSiO}_2}=0.9997\cdot0.8923\cdot0.1\cdot(>1)\cdot(>0.98^1)=(>\mathbf{0.0874})$$

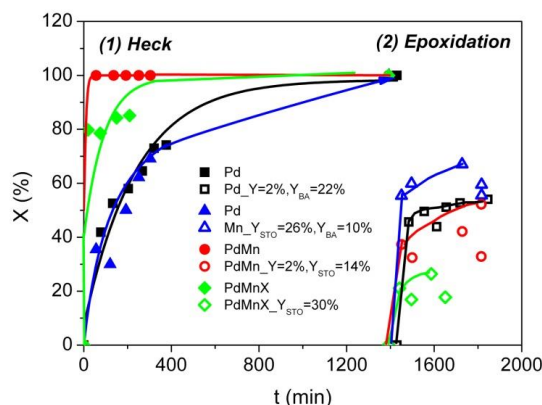
The efficiencies of palladium and palladium-manganese catalysts were very low because of diffusion limitations and low reactivities in comparison to homogeneous reactions (TON=20 and TOF=3/h for both catalysts). But only small amounts of catalyst leaching were detected and the overall efficiency would increase to  $\eta \gg 1$  after 20 runs for  $\text{Pd}(\text{OAc})_2@\text{PhSiO}_2$  and after 16 runs for  $\text{PdBr}_2\text{Mn}(\text{Acac})_2@\text{PhSiO}_2$ .

Manganese catalyst immobilized on  $\text{PhSiO}_2$  had a good reactivity (TON=23 and TOF=4), but almost 95% of catalyst leached into the solution and this catalyst can be characterized as almost homogeneous. The immobilization and reuse of manganese catalyst on silica for the applications in epoxidation reactions is not a recommendable method. In comparison to the palladium catalyst, the catalyst efficiency of immobilized manganese catalyst would decrease below  $\eta < 0.1$  after 10 runs.

### c) Combination to tandem reactions

Heck coupling with *trans*-stilbene as product was combined with the epoxidation to a tandem reaction. Different palladium, manganese and palladium-manganese catalyst precursors immobilized by sol-gel method on silica were used to study various types of tandem reactions shown in Figure 39:

- 1) *One pot reaction (not tandem catalysis)* with two catalysts not present in solution at the beginning:  $\text{Pd}(\text{OAc})_2@\text{PhSiO}_2$  for Heck coupling and  $\text{Mn}(\text{Acac})_2@\text{PhSiO}_2$  for epoxidation
- 2) *Orthogonal catalysis (tandem reaction)* with two catalysts present in solution at the beginning:  $\text{PdBr}_2\text{Mn}(\text{Acac})_2@\text{PhSiO}_2$  or  $\text{PdBr}_2\text{Mn}(\text{Acac})_2\text{Xantphos}@\text{PhSiO}_2$
- 3) *Auto-tandem catalysis (tandem reaction)* with only one catalyst without modification present in solution at the beginning:  $\text{Pd}(\text{OAc})_2@\text{PhSiO}_2$



**Figure 39:** Tandem Heck/epoxidation ( $\text{Pd}(\text{OAc})_2@ \text{PhSiO}_2$  (**Pd**),  $\text{PdBr}_2\text{Mn}(\text{Acac})_2@ \text{PhSiO}_2$  (**PdMn**),  $\text{Mn}(\text{Acac})_2@ \text{PhSiO}_2$  (**Mn**) or  $\text{PdBr}_2\text{Mn}(\text{Acac})_2\text{Xantphos}@ \text{PhSiO}_2$  (**PdMnX**) with  $\text{PdBr}_2\text{:Xantphos}$  1:1, 46 mL microemulsion, 80°C, 0.0068 mmol metal precursor (1) *Heck coupling* (1.34 mmol styrene, 1.5 mmol iodobenzene, 2 mmol  $\text{K}_2\text{CO}_3$ ) (2) *Epoxidation* (1.34 mmol *trans*-stilbene, 2.68 mmol  $\text{NaIO}_4$ ,  $X$ = conversion of (1) styrene and (2) *trans*-stilbene,  $Y$ =yield<sub>*trans*-stilbene oxide</sub>,  $Y_{\text{STO}}$ =yield<sub>styrene oxide</sub>,  $Y_{\text{BA}}$ = yield<sub>benzaldehyde</sub>))

In Chapter 4.3.2 and 4.3.5 we have shown that the best sol-gel immobilized catalysts for Heck coupling reaction are palladium (II) acetate and a mixture of palladium (II) bromide and manganese (II) acetylacetonate with and without stabilizing Xantphos ligand. Palladium acetate was the most stable catalyst and could be recycled several times without leaching and palladium-manganese catalyst shows the highest activity of all prepared catalysts.

The preparation of appropriate catalyst for the epoxidation reaction is more difficult because of the influence of oxidizing agent on the stability of the immobilized catalyst. In this chapter we have studied epoxidations with sodium periodate as oxidizing agent with sol-gel immobilized palladium, manganese and palladium-manganese catalysts.

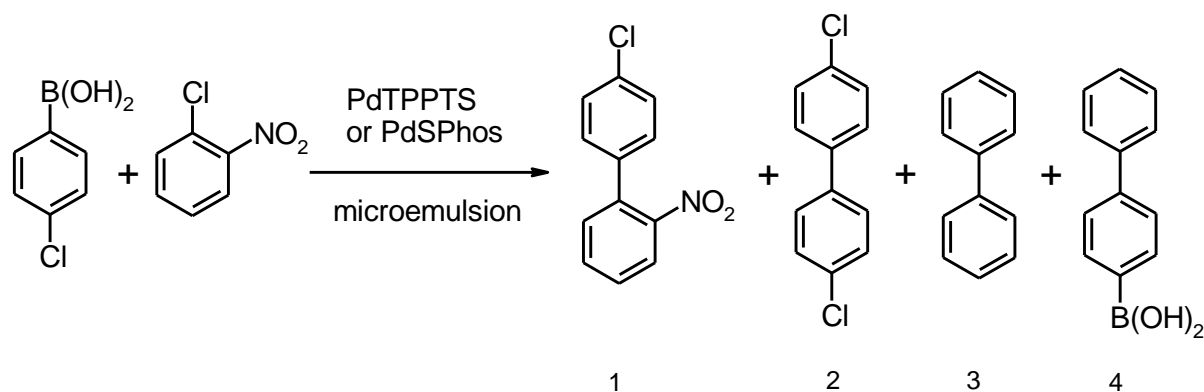
As can be seen from Figure 39, the yields of desired product *trans*-stilbene oxide obtained by tandem reaction were in all cases very low ( $Y=1\text{-}2\%$ ) and mainly benzaldehyde and styrene oxide as by-products were obtained. In comparison to this results 35-50% *trans*-stilbene oxide (Figure 38) were obtained for the epoxidation with commercial *trans*-stilbene catalyzed by  $\text{PdBr}_2\text{Mn}(\text{Acac})_2@ \text{PhSiO}_2$  with and without Xantphos, 33% with  $\text{Mn}(\text{Acac})_2@ \text{PhSiO}_2$  (Figure 37) or with  $\text{Pd}(\text{OAc})_2@ \text{PhSiO}_2$  (Figure 36). The decreasing activity of the catalyst in tandem reaction in comparison to benchmark experiments can be explained by high catalyst leaching during the reaction and also by low purity of the intermediate product *trans*-stilbene.

Increasing of *trans*-stilbene purity through separation and cleaning after Heck reaction would increase the yield and selectivity of *trans*-stilbene oxide. Also the development of more stable sol-gel immobilized catalysts with selective ligands would be recommended. Epoxidations with more stable heterogeneous MoO<sub>3</sub> or WO<sub>3</sub> catalysts [12,113,114] immobilized on MCM-41 could be an alternative to the commonly used manganese catalysts.

#### 4.5. Comparison of immobilization concepts for a Suzuki coupling reaction

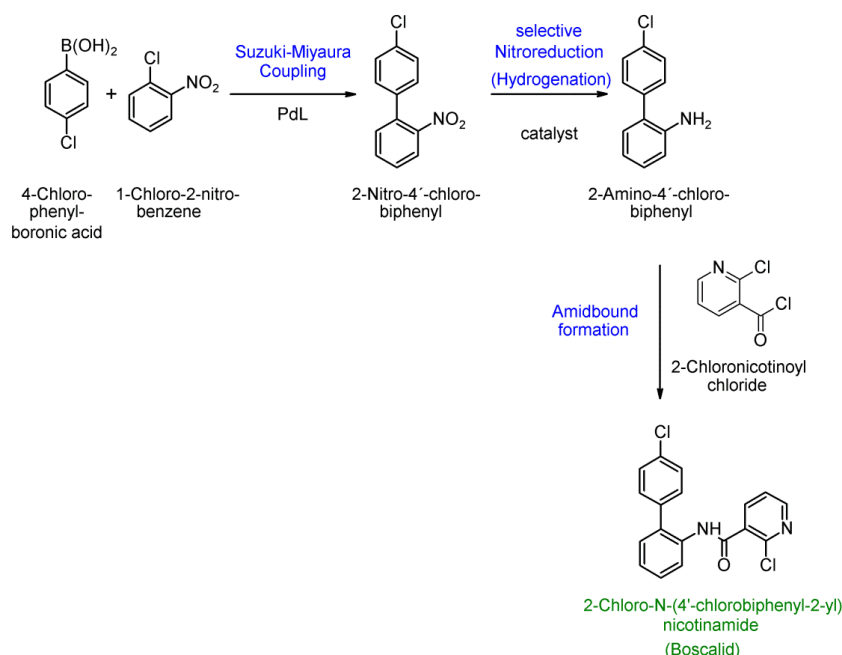
A comparison of different immobilization and catalyst recycling concepts will be done in this chapter at the example of homogeneous and sol-gel immobilized palladium catalysts for Suzuki coupling reaction.

In comparison to Heck coupling reaction, Suzuki coupling reaction is coupling of haloarene with aromatic boronic acid and not with activated alkene e.g. styrene. 4-Chlorobenzeneboronic acid reacts with 1-chloro-2-nitrobenzene in the presence of K<sub>2</sub>CO<sub>3</sub> as base to 4'-chloro-2-nitrobiphenyl (**1**) and different homo-coupling products can occur e.g. 4,4'-dichlorobiphenyl (**2**), biphenyl (**3**) and 4-biphenylboronic acid (**4**) :



**Scheme 25:** Suzuki coupling of 4-chlorobenzeneboronic acid and 1-chloro-2-nitrobenzene

This coupling reaction was chosen as a model reaction because of high interest in the synthesis of this product. The product of this Suzuki coupling reaction is an important intermediate in the synthesis of 2-chloro-*N*-(4'-chlorobiphenyl-2-yl)nicotinamide (Boscalid®) [115,116] which is an important fungicide applied to control the range of plant pathogens in agricultural industry. For the Boscalid synthesis Suzuki coupling is followed by hydrogenation of the nitro group to an amine group (aniline) and then in the final step an amide bond formation occur with 2-chloronicotinoyl chloride:



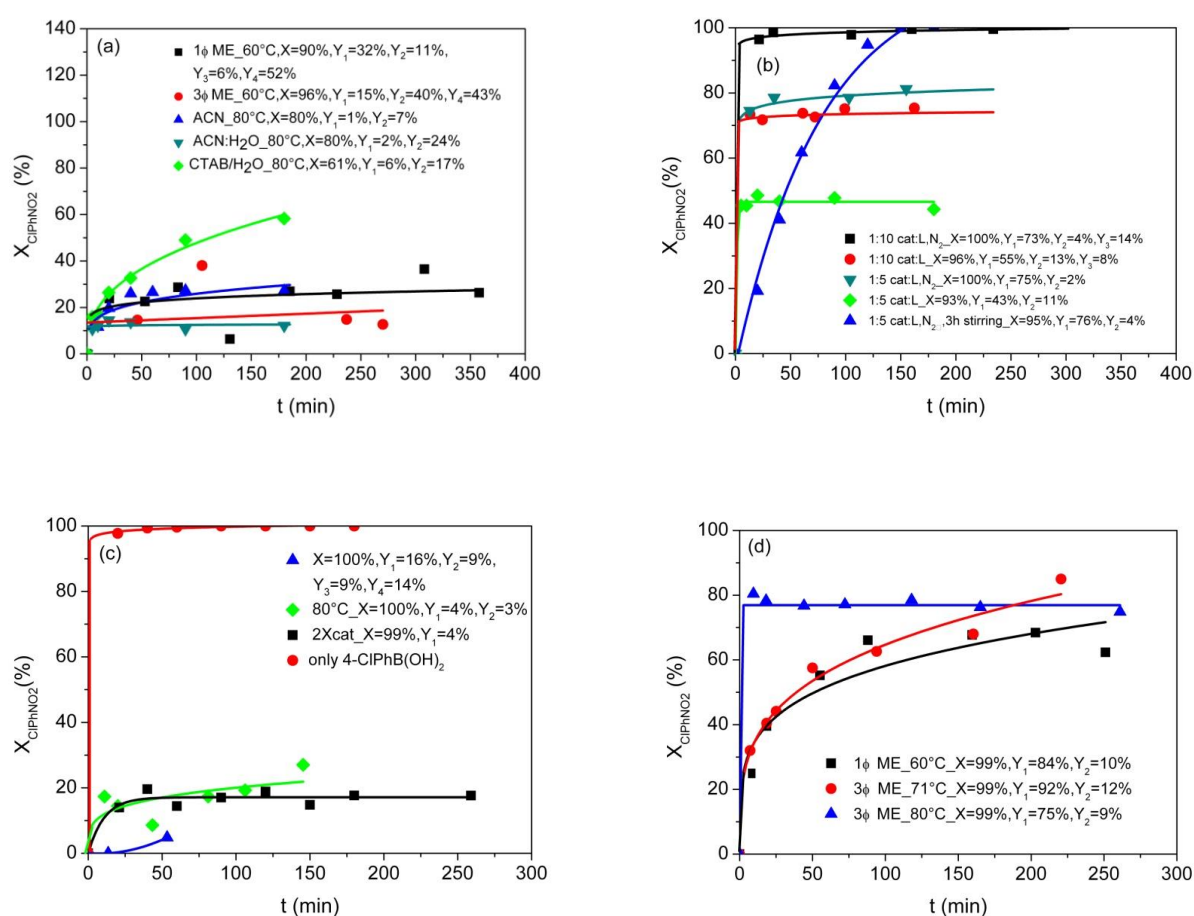
**Scheme 26:** Boscalid<sup>®</sup> synthesis [115,116]

Because of the low reactivity of both reactants of the Suzuki coupling reaction caused by less reactive chloride substituents and sterical hindrance of ortho substituents, the addition of selective ligands is recommended. Also, performing the reaction only with palladium (II) catalyst enables the formation of majority undesired homocoupling products: biphenyl, 2,2'-dichlorobiphenyl (PCB) or 2-biphenylboronic acid as was shown in Scheme 25. For the reactions in aqueous solutions e.g. microemulsions the catalyst-ligand complex should be well soluble in water, that's why we have chosen water soluble salts 3,3',3''-phosphanetriyltris-(benzenesulfonic acid) trisodium salt (TPPTS) and 2-dicyclohexyl-phosphino-2',6'-dimethoxybiphenyl sodium salt (SPhos) [117,118] as ligands.

Different concepts for the recycling and reuse of the catalyst-ligand complexes were developed and evaluated on the example of this Suzuki coupling. On the one side the catalyst recycling and reuse can be arrived by filtration of heterogeneous sol-gel immobilized palladium acetate or bromide catalysts or palladium-ligand complexes after reaction, as was shown for Heck coupling, hydrogenation and epoxidation reactions in last chapters. On the other side, homogeneous water soluble catalyst-ligand complexes can be separated and reused after the Suzuki coupling reaction from the middle phase of three phase microemulsion. This multiphase microemulsion (Scheme 11) can be obtained by increasing the oil ratio up to 50 % through the addition of organic solvent e.g. heptane and using of nonionic surfactants.

#### 4.5.1. Separation of homogeneous catalyst-ligand complex from three phase microemulsion

Before starting the reaction in multiphase microemulsion systems, the Suzuki coupling reaction was carried out in conventional solvents e.g. acetonitrile or water with homogeneous palladium (II) acetate as catalyst (Figure 40a). Of course the use of homogeneous catalyst without selective ligand is attendant with very low selectivity's and high amount of undesired byproducts. Because of high solubility of boronic acids in water, use of aqueous solutions or water/alcohol mixtures is preferred. Best results were obtained for the reaction in one phase CTAB/H<sub>2</sub>O/propanol ( $\alpha=1.1\%$ ,  $\gamma=9.9\%$ ,  $\delta=66.8\%$ ) and in three phase heptane/H<sub>2</sub>O/Novel 8 ( $\alpha=50\%$ ,  $\gamma=3\%$ ) microemulsions.



**Figure 40:** Suzuki coupling with homogeneous catalysts (a) Pd(OAc)<sub>2</sub>, (b) PdTPPTS, 1 $\phi$  ME, 60°C (c) PdTPPTS, 3 $\phi$  ME, 71°C (d) PdSPhos (3 mmol 2-NO<sub>2</sub>PhCl, 3 mmol 4-ClPhB(OH)<sub>2</sub>, 4 mmol K<sub>2</sub>CO<sub>3</sub>, 0.0068 mmol Pd(OAc)<sub>2</sub>, 1:2 Pd(OAc)<sub>2</sub>:Sphos, 1:5 Pd(OAc)<sub>2</sub>:TPPTS, 100 mL solvent, 1 $\phi$  CTAB/H<sub>2</sub>O/propanol ME ( $\alpha=1.1\%$ ,  $\gamma=9.9\%$ ,  $\delta=66.8\%$ ), 3 $\phi$  H<sub>2</sub>O/Novel8/heptane three phase ME ( $\alpha=50\%$ ,  $\gamma=3\%$ ), N<sub>2</sub>, X=conversion 4-chlorobenzeneboronic acid, Y<sub>i</sub>=yield<sub>products</sub> Scheme 25)

Addition of water soluble phosphine ligands increases the activity of the catalysts and product selectivity. As ligands TPPTS (Figure 40b-c) and SPhos (Figure 40d) were added to the palladium catalyst and the reactions were carried out first in one phase and then in three phase microemulsions. One phase microemulsions are usually applied in heterogeneous catalysis because of simple catalyst and product separation after reaction. In our case we have performed the reactions in one phase microemulsion with homogeneous catalysts as a reference to heterogeneous catalysts. For the separation of the product and recycling of homogeneous catalyst a three phase microemulsion is necessary.

Before starting the reaction, the mixture of catalyst and ligand dissolved in organic solvent has to be stirred about 10-20 hours to allow the formation of the catalyst-ligand complex. Similar final results were obtained for Suzuki coupling reactions with fresh PdTPPTS catalyst (stirring time  $t=3$  h), but the reaction was associated with a long induction period.

As can be seen from Figure 40b operation without nitrogen causes deactivation of the catalyst-ligand complex which is associated with decrease in selectivity and reaction rate. In dependency of ligand type different catalyst-ligand ratios has to be applied in the catalyst synthesis process: 1:3 up to 1:10 for Pd(OAc)<sub>2</sub>: TPPTS because of three phosphorus atoms coordinated on palladium [119] and 1:2 Pd(OAc)<sub>2</sub>:SPhos because of two phosphorus atoms coordinated on palladium [120]. The reactions in one phase CTAB/H<sub>2</sub>O/propanol microemulsion with both ligands show good selectivity's, only 10-15% of undesired products were obtained (Figure 40b,d).

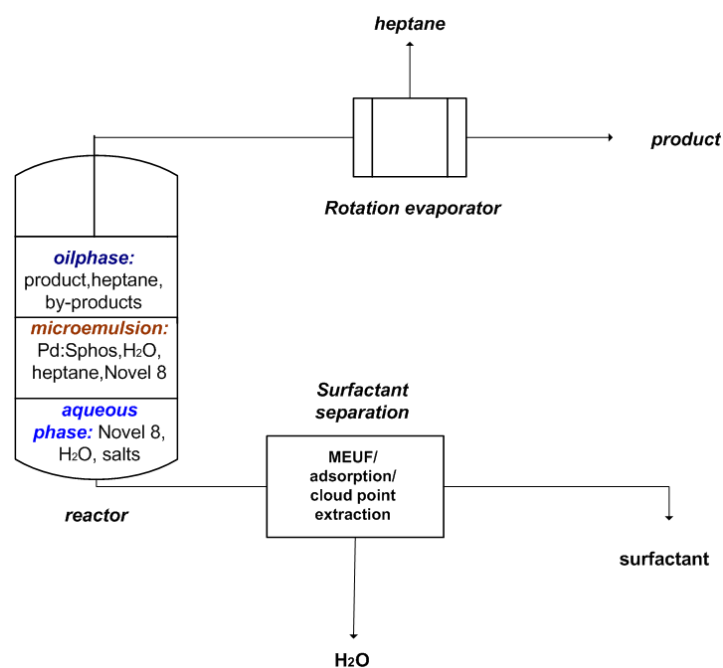
For operating of reactions in multiphase system, especially three phase microemulsions, first the phase behavior has to be investigated and optimal temperature region for a complete phase separation has to be found. Phase behavior of microemulsions depends on different factors: type of reactants, hydrophobicity of surfactants (chain length), type of catalyst and ligand and organic solvent.

The reaction in H<sub>2</sub>O/Novel8/heptane three phase microemulsion with 1-chloro-2-nitrobenzene and 4-chlorophenylboronic acid was started in  $\bar{2}$  phase microemulsion (water/oil microemulsion) at 71°C and also 80°C (3 phase region between 54-56°C). After addition of PdSPhos (3 phase microemulsion between 75-84°C) or PdTPPTS (3 phase microemulsion between 70-73°C) catalyst the reaction was started and the phase behavior changed. After the reaction the phase separation was occurred after several minutes.



**Scheme 27:** Phase separation after the coupling of 1-chloro-2-nitrobenzene and 4-chloro-phenylboronic acid catalyzed by PdSPhos ( $T=79^{\circ}\text{C}$ )

The catalyst could be recycled from the middle phase and reused in further reactions, product was separated from upper organic heptane phase by solvent evaporation and surfactant can be separated from lower aqueous phase by e.g. micellar enhanced ultrafiltration (MEUF), cloud point extraction or adsorption.

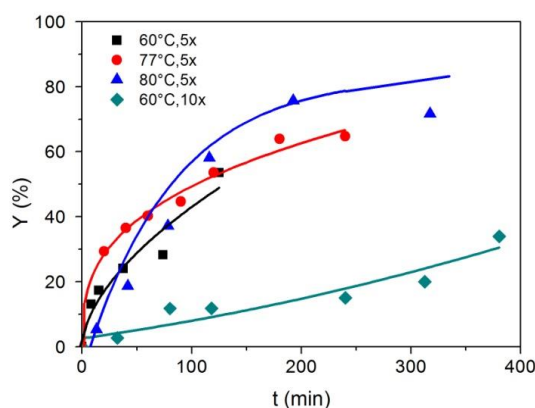


**Scheme 28:** Separation of the homogeneous PdSPhos complex, product and surfactant from three phase (Novel 8/ $\text{H}_2\text{O}$ /heptane) microemulsion

Unfortunately the reaction in three phase microemulsion was only selective with PdSPhos as catalyst. Synthesis with PdTPPTS catalyst shows a complete decomposition of 4-chloro-benzeneboronic acid (Figure 40c) to boronic acid salts.

#### 4.5.2. Reaction scale up and recycling of homogeneous PdSPhos catalyst

For the further application in Boscalid<sup>®</sup> synthesis, higher amounts (5-10 times) of 4'-chloro-2-nitrophenyl product were produced in three phase microemulsion with PdSPhos as catalyst at different temperatures:

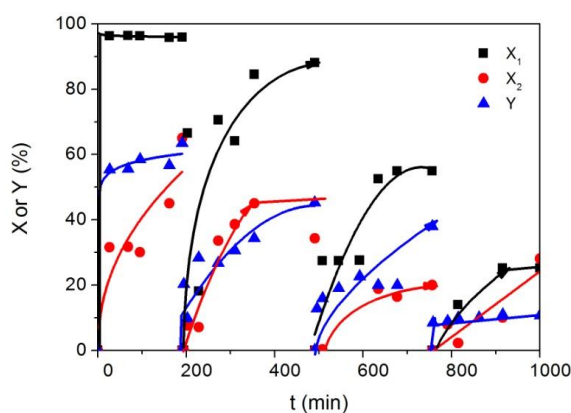


**Figure 41:** Reaction scale up in 3 $\phi$  microemulsion (**5X**: 15 mmol 2-NO<sub>2</sub>PhCl/15 mmol 4-ClPhB(OH)<sub>2</sub>/20 mmol K<sub>2</sub>CO<sub>3</sub>, **10X**: 30 mmol 2-NO<sub>2</sub>PhCl/30 mmol 4-ClPhB(OH)<sub>2</sub>/40 mmol K<sub>2</sub>CO<sub>3</sub>, 0.0068 mmol Pd(OAc)<sub>2</sub>, 1:2 Pd(OAc)<sub>2</sub>:Sphos, 100 mL 3 $\phi$  H<sub>2</sub>O/Novel8/heptane three phase ME ( $\alpha=50\%$ ,  $\gamma=3\%$ ), N<sub>2</sub>, Y=yield<sub>product</sub>)

The reaction rate and yield of the product increase with increasing temperature and decrease with increasing amount of educts. About 7% of undesired byproduct PCB was obtained for every reaction. After the reaction, product and catalyst have to be separated from three phase microemulsion for further application of product in the synthesis of Boscalid<sup>®</sup> and for catalyst reuse in the Suzuki coupling reaction. In Chapter 4.5.1 we have studied the reaction in three phase microemulsion system with Novel 8 as surfactant, which was only possible with PdSPhos as catalyst between 70-80°C. Clear three phases were obtained by phase separation in a very close temperature region between 76-77°C. Phase behavior changes if higher amounts of reactants are applied and the three phase region shifts to lower temperatures: 53-56°C for double, 43-45°C for fivefold and 33-36°C for tenfold amount of reactants. Performing the reactions at such a low temperatures doesn't work because of the high activation energy. That's why the reactions were carried out at higher temperatures like 60-80°C and after that the three

phase system was obtained by lowering the temperature. 95-99% of product and small amounts of formed by-products and not consumed 1-chloro-2-nitrobenzene were located in the upper organic phase and could be separated from heptane by rotary evaporation. The lower aqueous phase consists of surfactant and small amounts of not consumed boronic acid and the boronic acid salts, which are formed during the reaction. Surfactants and salts can be separated from water by different methods e.g. micellar enhanced ultrafiltration (MEUF) as was described in Chapter 2.9 and cleared solution can be reused for further coupling reactions. The middle, catalyst containing phase was left in reactor under nitrogen and applied in next Suzuki coupling reactions.

As can be seen from Figure 42, the PdSPhos catalyst could be applied in Suzuki coupling at 77°C and recycled 4 times from three phase microemulsion. Phases were separated at 65°C, 82°C, 84°C and 84°C, respectively after each reaction. The three phase region changes to higher temperatures because of increasing amount of surfactant and changing microemulsion composition. The activity of the catalyst decreases a lot with increasing number of recycling steps.



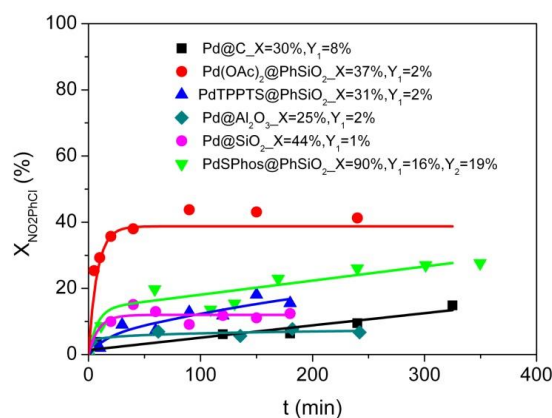
**Figure 42:** Catalyst recycling in 3 $\phi$  microemulsion (3 mmol 2-NO<sub>2</sub>PhCl (**X**<sub>2</sub>), 3 mmol 4-ClPhB(OH)<sub>2</sub> (**X**<sub>1</sub>), 4 mmol K<sub>2</sub>CO<sub>3</sub>, 0.0068 mmol Pd(OAc)<sub>2</sub>, 1:2 Pd(OAc)<sub>2</sub>:Sphos, 100 mL H<sub>2</sub>O/Novel8 /heptane three phase ME ( $\alpha=50\%$ ,  $\gamma=3\%$ ), N<sub>2</sub>, 77°C)

On the one hand the catalyst-ligand complex is very air sensitive and deactivates partly to black inactive palladium particles. On the other hand, a small part of the catalyst leaches into the organic phase and gets lost after reaction. Also small amounts of educts and product which were present in a middle phase can disturb the reaction. To improve this difficult recycling process the phase composition has to be analyzed more in detail, especially the consistence of the

middle phase. Also a better phase separation with less catalyst leaching has to be achieved e.g. by using more stable and less air sensitive catalyst-ligand complexes.

#### 4.5.3. Suzuki coupling with sol-gel immobilized palladium catalysts

As alternative recycling method, reactions with heterogeneous sol-gel immobilized catalyst were carried out in one phase CTAB/H<sub>2</sub>O/propanol microemulsions. Activities of self-made immobilized palladium catalysts with and without ligands were compared with commonly used commercial catalysts. Both sol-gel immobilized and commercial catalysts are inapplicable for this type of reaction. Indeed the catalyst leaching was low (0.1-0.3 % Pd for commercial catalysts, 1.2% Pd(OAc)<sub>2</sub> and 3.3% SPhos, 2% Pd(OAc)<sub>2</sub> and 0.012% TPPTS), anyhow the activity and selectivity of the catalyst was very bad (Y=2-16 %).



**Figure 43:** Suzuki coupling with heterogeneous catalysts (3 mmol 2-NO<sub>2</sub>PhCl, 3 mmol 4-ClPhB(OH)<sub>2</sub>, 4 mmol K<sub>2</sub>CO<sub>3</sub>, 0.0068 mmol Pd(OAc)<sub>2</sub>, 1:2 Pd(OAc)<sub>2</sub>:Sphos, 1:5 Pd(OAc)<sub>2</sub>:TPPTS, 100 mL 1φ CTAB/H<sub>2</sub>O/propanol ME (α=1.1%, γ=9.9%, δ=66.8%), 60°C, N<sub>2</sub>, X=conversion, Y<sub>i</sub>=yield (products Scheme 25))

The preparation of selective heterogeneous catalysts is still a challenge because of air-sensitivity of the catalyst and loss of enantioselective ligands through the immobilization process. Otherwise Suzuki coupling reactions with more active substrates can also be carried out with heterogeneous catalysts in one phase microemulsion. In this case the addition of ligands to the palladium acetate is not necessary and catalyst can be recycled several times without leaching [35].

**Table 15:** Suzuki coupling with more active substrates

substrate <sup>a</sup>	X <sub>1</sub> (%)	X <sub>2</sub> (%)	Y (%)	t (min)
4-bromoacetophenone and phenylboronic acid	90	85	85 (6% biphenyl)	301
bromobenzene or 1-bromo-4-chlorobenzene and phenylboronic acid	99	99	96-99 [35]	420

<sup>a</sup> reaction conditions: 60°C, 1.34 mmol substrate1, 1.5 mmol substrate2, 100 mL CTAB/H<sub>2</sub>O/propanol microemulsion ( $\alpha$ =1.1%,  $\gamma$ =9.9%,  $\delta$ =66.8%), 2mmol K<sub>2</sub>CO<sub>3</sub>, 0.0068mmol Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub>

## 5. Conclusion and Outlook

In the present work different sol-gel immobilized catalysts were synthesized and applied in a variety of reactions in microemulsions or aqueous-micellar solutions as alternative green reaction media. Different product isolation and catalyst recycling methods were compared with each other and the best method for certain reaction types was selected. The catalyst efficiency was investigated by estimation of catalyst stability and reactivity. Also the influence of different factors on the activity of an immobilized catalyst and kinetics of the reaction was shown: support material, concentrations of reactants, temperature, composition of microemulsion etc.

The overall efficiency's  $\eta$  of all important catalysts synthesized in this work were calculated from Equation 4 and are shown in Table 16:

$$\eta = \eta_{\text{immobilisation}} \cdot \eta_{\text{intercalation}} \cdot \eta_{\text{pore}} \cdot N_{\text{cycle}} \cdot (\eta_{\text{recycling}})^N \quad \text{Eq 4}$$

The estimation of the overall efficiency of immobilized catalysts which were used in different reaction depends on several factors as can be seen from Equation 4. It depends on reaction type and reactants and compounds applied in the process because some of them can deactivate or destroy the catalyst. Also catalyst stability becomes important. Metal leaching from support material during immobilization and recycling process influences the long term catalyst activity. Kinetic measurements e.g. diffusion limitation of the reaction, described as pore efficiency factor, and comparison of the activity of heterogeneous catalysts to homogeneous catalysts provide information for the selection of suitable catalysts.

Overall catalyst efficiency  $\eta > 1$  were obtained for very stable and active catalysts like Pd(OAc)<sub>2</sub> and PdBr<sub>2</sub>Mn(Acac)<sub>2</sub> immobilized on hydrophobically modified silica, which were applied in Heck coupling reactions of haloarene with styrene to *trans*-stilbene. The catalysts could be recycled 6 and 4 times after reactions without remarkable catalyst loss.

**Table 16:** Efficiency of sol-gel immobilized catalysts

catalyst	reaction	$\eta_{\text{immobilisation}}$	$\eta_{\text{intercalation}}$	$\Psi$	$\eta_{\text{pore}}$	$N_{\text{cycle}}$	$\eta_{\text{recycling}}$	$\eta$
Pd(OAc) <sub>2</sub> @PhSiO <sub>2</sub>	Heck coupling	1	0.805	3	0.40	6	0.999	1.920
PdBr <sub>2</sub> Mn(Acac) <sub>2</sub> @PhSiO <sub>2</sub>	Heck coupling	0.9997	0.831	4.4	0.30	4	0.938	0.934
Pd(OAc) <sub>2</sub> @PhSiO <sub>2</sub>	Epoxidation <sup>a</sup>	1	0.171	4.2	0.30	4	0.820	0.171
Mn(Acac) <sub>2</sub> @PhSiO <sub>2</sub>	Epoxidation <sup>b</sup>	0.9948	1	1.3	0.75	4	0.185	0.552
PdBr <sub>2</sub> Mn(Acac) <sub>2</sub> @PhSiO <sub>2</sub>	Epoxidation <sup>b</sup>	0.9997	0.892	7.0	0.10	1	0.980	0.087
Rh/BPPM@SiO <sub>2</sub>	Hydrogenation	0.9770	0.452	1.8	0.52	3	0.994	0.689
Rh/BPPM@EtSiO <sub>2</sub>	Hydrogenation	0.9964	0.454	3.8	0.38	4	0.974	0.688

<sup>a</sup>H<sub>2</sub>O<sub>2</sub><sup>b</sup>NaIO<sub>4</sub>

As was shown in Chapter 4.3.5 the possibility to recycle Pd(OAc)<sub>2</sub>@PhSiO<sub>2</sub> more than 6 times increases the Turnover Number TON from 20 to TON<sub>>25runs</sub>>500. With a fivefold increased concentrations of reactants the Turnover Number would be extrapolated up to TON>100 in one run and TON>1000 after 10 runs.

**Table 17:** Efficiency  $\eta$  and turnover number TON of sol-gel immobilized catalysts

catalyst	reaction	$\eta$	N	TON 1 run	N <sub>extrap</sub>	$\eta_{\text{extrap}}$	TON extrap
Pd(OAc) <sub>2</sub> @PhSiO <sub>2</sub>	Heck coupling	1.920	6	20	10	3.188	200
PdBr <sub>2</sub> Mn(Acac) <sub>2</sub> @PhSiO <sub>2</sub>	Heck coupling	0.934	4	20	10	2.117	140
Pd(OAc) <sub>2</sub> @PhSiO <sub>2</sub>	Epoxidation <sup>a</sup>	0.171	4	20	20	1.005	200
Mn(Acac) <sub>2</sub> @PhSiO <sub>2</sub>	Epoxidation <sup>b</sup>	0.552	4	23	10	0.110	226
PdBr <sub>2</sub> Mn(Acac) <sub>2</sub> @PhSiO <sub>2</sub>	Epoxidation <sup>b</sup>	0.087	1	20	16	1.033	201
Rh/BPPM@SiO <sub>2</sub>	Hydrogenation	0.689	3	597	5	1.135	2985
Rh/BPPM@EtSiO <sub>2</sub>	Hydrogenation	0.688	4	597	7	1.150	4178

<sup>a</sup>H<sub>2</sub>O<sub>2</sub><sup>b</sup>NaIO<sub>4</sub>

Heck coupling of iodobenzene and styrene catalyzed by sol-gel immobilized palladium (II) acetate represents a good alternative to the commonly used homogeneous e.g. Pd(dba)<sub>2</sub>/phosphoramidite catalyzed coupling of iodobenzene and styrene in dimethylformamide at 80°C (TOF=315/h) [121]. Also heterogeneous catalyzed reactions e.g. Heck coupling of styrene and 4-bromofluorobenzene catalyzed by palladium immobilized on zeolite at 140°C in dimethyl acetamide (TOF[Pd(0)]-NaY=20/h and TOF[Pd(OAc)<sub>2</sub>]-NaY=2000/h) [122] or reactions under biphasic conditions e.g. PdCl<sub>2</sub>(bipy) catalyzed coupling of iodobenzene and styrene in n-octane/*p*-xylene/ethylene glycol at 150°C (TOF=227/h) [123] were already showed by other research groups. The reactions in conventional solvents at high temperatures, which were already reported in the literature, had higher Turnover Frequencies. For example Heck coupling

catalyzed by Pd/C in NMP at 150°C [47] had a TOF>18000/h. By lowering the reaction temperature the Turnover Frequency would decrease below  $\text{TOF}_{80^\circ\text{C}}=8\text{-}140/\text{h}$ . On the other hand, a more environmentally friendly process management on the example of Heck coupling in microemulsion with >90% of water at lower temperatures could be showed. In addition to this, the catalyst and product recycling was enabled. Also we have showed in Table 16-17, that the catalyst efficiency and Turnover Numbers will be increased by increasing the number of recycling runs and concentration of reactants.

We have also shown that not only the stability is crucial for the catalyst selection, but also in which type of reaction it will be applied. Catalysts used in hydrogenation reaction of *trans*-stilbene were very stable, but in epoxidation with highly active oxidizing agents:  $\text{NaIO}_4$ , mCPBA or  $\text{H}_2\text{O}_2$  a lot of metal leached into the solution because of destroying effect of oxidizing species.

Some of the catalysts were not really applicable for the sol-gel synthesis. After immo-bilization of manganese acetylacetonate and using it in Heck or epoxidation reaction, the major amount of metal was removed from the support. On the other hand the immobilization of catalyst-ligand complexes was challenging because of air sensitivity and deactivation during the synthesis of the catalyst.

To improve the metal entrapment into the silica support the hydrophobizing of the surface was necessary. This happened by addition of hydrophobic octyltrimethoxysilane or phenyltriethoxysilane to tetramethylorthosilicate during the sol-gel process. The surface structure changes and more branched pore structures were obtained. Except hydrogenation of more hydrophilic itaconic acid and derivatives this concept was very advantageous. For the enantioselective hydrogenation of itaconates the immobilization of Rh/BPPM catalyst in  $\text{SiO}_2$  and  $\text{EtSiO}_2$  was most suitable because of attractive interactions between hydrophilic substrates and surface.

Generally it is clear that the nanoparticles formed from metal precursor by a sol-gel method e.g.  $\text{Pd}(\text{OAc})_2@\text{PhSiO}_2$  applied in Heck coupling, represent a very stable heterogeneous catalyst. In comparison to these results, a molecular catalyst e.g.  $\text{Rh/BPPM}@\text{SiO}_2$  applied in enantioselective hydrogenation of itaconates is less stable and reactive because of air sensitivity and changes of its structure during the preparation process.

From the other point of view we have shown that the reactions in water e.g. microemulsions or aqueous-micellar solutions were more environmentally friendly than in commonly used organic solvents. The other benefits of using of microemulsions as solvents are the possibility to separate and to reuse the homogeneous catalysts after the reaction. For example Suzuki coupling of less reactive 1-chloro-2-nitrobenzene with 4-chlorobenzenboronic acid could be only carried out with catalyst-ligand complex. Use of three phase microemulsions allows easy catalyst reuse and product separation from organic phase.

At least different reaction steps with one or more sol-gel immobilized catalysts were successfully combined to tandem reactions for the production of pharmaceutically important products e.g. Heck coupling to *trans*-stilbene followed by epoxidation, hydrogenation or further coupling steps.

Main challenge in the synthesis of sol-gel immobilized catalysts is to produce catalysts with similar activities as homogeneous catalysts. Sol-gel immobilized catalysts are microporous ( $d < 2$  nm) structures which allow a good entrapment of metal in the pores of the support material. Because of such as small pore size the diffusion of molecules within the pores is hindered and the investigated reactions are partly diffusion limited.

Of course is the immobilization of homogeneous catalysts disadvantageous in comparison to homogeneous catalysts, due to diffusion limitations and decrease in reactivity. But on the other hand the possibility to recycle the catalysts several times increases the efficiency of sol-gel immobilized catalysts enormously and reduces the cost of the complete process (Table 17).

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## Symbols and Acronyms

### Acronyms

A	m <sup>2</sup> /g	surface area
AA		acrylic acid
Aliquat 336		<i>N</i> -methyl- <i>N,N</i> -dioctyloctan-1-ammonium chloride
atm		atmosphere
B		bubble counter
BA		benzaldehyde
BET		Brunauer–Emmett–Teller
BINAP		2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BPPM		butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine
c	g/L	concentration
C		reflux condenser
cat		catalyst
cmc	g/L	critical micelle concentration
CTAB		cetyltrimethylammonium bromide
DIPAMP		ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane]
d	nm	catalyst diameter
D	cm <sup>2</sup> /s	diffusion coefficient
DBI		dibutyl itaconate
DEI		diethyl itaconate
DSS		dioctyl sodium sulfosuccinate
DLS		dynamic light scattering
DMI		dimethyl itaconate
DTAB		dodecyltrimethylammonium bromide
dppb		1,4-bis(diphenylphosphino)butane
E <sub>A</sub>	kJ/mol	activation energy
EDX		energy dispersive X-ray spectroscopy
ee%		enantiomeric excess
EST		emulsion/sol-gel transport
fcc		face-centered cubic
FM		flow meter
FT-IR		Fourier transform infrared spectroscopy
g		gram
GFP		green fluorescent protein
GC		gas chromatography
HAM		Hydroaminomethylation
HIV		human immunodeficiency virus
HLB		hydrophilic lipophilic balance
HMS		hexagonal mesoporous silica
HPLC		high pressure liquid chromatography
IA		itaconic acid
ICP		inductively coupled plasma
IL		ionic liquid
L		ligand
L <sub>cat</sub>	nm	catalyst radius

LSCM		lanthanum strontium chromites manganese
m	g	mass
MCM-41,		mobile crystalline materials
MCM-48		
mCPBA		meta-chloroperbenzoic acid
ME		microemulsion
MEUF		micellar-enhanced ultrafiltration
MPTS		3-methacryloxypropyltrimethoxysilane
n		reaction order
N		number of recycling cycles
NG		nitrogen access
NMR		nuclear magnetic resonance
OES		optical emission spectroscopy
p	Pa	pressure
Pa		Pascal
PC		pressure controller
PCB		polychlorinated biphenyl
PEG		polyethyleneglykole
PI		pressure indicator
PvyPy		poly(4-vinyl)pyridine
r	g/L·min	reaction rate
R	J/mol·K	gas constant
RC		reactor
RCM		ring closing metathesis
rds		rate determining step
rpm		revolutions per minute
S		stirrer
SBA-15		Santa Barbara Amorphous type mesoporous silica
scCO <sub>2</sub>		supercritical carbon monoxide
SDS		sodium dodecyl sulfate
SOFC		solid oxide fuel cell
Sphos		2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
STO		styrene oxide
t	min	time
T	°C	temperature
T°		thermostat
TBHP		tert. butyl hydroperoxide
TCB		trichlorobenzene
TEOS		tetraethyl orthosilicate
TEM		transmission electron microscopy
TMOS		tetramethyl orthosilicate
TOF	1/h	Turnover Frequency
TON		Turnover Number
TPPTS		tris(3-sulfophenyl)phosphine trisodium salt
Triton X-100		polyethylene glycol p-(1,1,3,3-tetramethylbutyl)phenyl ether
TTAB		tetradecyltrimethylammonium bromide
UV-VIS		ultraviolet-visible spectroscopy
V	mL	volume

wt	%	weight percent
X	%	conversion
Xantphos		4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPS		x-ray photoelectron spectroscopy
XRD		x-ray diffraction
Y	%	selectivity

## Symbols

1		one phase microemulsion
$\bar{2}$		water in oil phase
$\underline{2}$		oil in water phase
3		three phase microemulsion
$\alpha$	%	oil ratio
$\gamma$	%	surfactant ratio
$\delta$	%	cosurfactant ratio
$\varepsilon$	%	porosity
$\eta$	%	efficiency
$\theta$	°	scattering angle
$\kappa$	$\mu\text{S}/\text{cm}$	conductivity
$\lambda$	nm	wave length
$\rho$	$\text{g}/\text{cm}^3$	density
$\tau$	%	tortuosity
1 $\phi$		one phase microemulsion
3 $\phi$		three phase microemulsion
$\Psi$		Weisz-Prater Criterion

## **Publications**

- Volovych I.; Kasaka Y.; Schwarze M.; Nairoukh Z.; Blum, J.; Fanun M.; Schomäcker R. “ Heck catalyzed coupling reaction using sol-gel immobilized palladium catalysts under aqueous microemulsion conditions for the synthesis of *trans*-stilbenes” in preparation
- Volovych I.; Schwarze M.; Nairoukh Z.; Blum, J.; Schomäcker R. “Sol-gel immobilized catalytic system for tandem transformations with trans-stilbene as intermediate” in preparation
- Volovych, I.; Hamerla, T.; Schwarze, M.; Blum, J.; Schomäcker, R. “Enantioselective hydrogenation of itaconic acid and its derivatives with sol-gel immobilized Rh/BPPM catalysts” J. Mol. Catal. A: Chem. 366 (2013) 359-367
- Batarseh, C.; Nairoukh Z.; Volovych, I.; Schwarze, M.; Schomäcker, R.; Fanun, M.; Blum, J. „Catalytic transfer hydrogenation of hydrophobic substrates by water-insoluble hydrogen donors in aqueous microemulsions“. J. Mol. Catal. A: Chem. 366 (2013) 210-214
- Schwarze, M.; Volovych, I.; Wille, S.; Mokrushina, L.; Arlt, W.; Schomäcker, R. „Partition Coefficients of Itaconates in Aqueous-Micellar Solutions: Measurements and Predictions with COSMO-RS” Ind. Eng. Chem. Res. 51(4) (2012) 1846–1852

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- Volovych I.; Schwarze M.; Blum J.; Schomäcker R. “Hydrogenation of itaconates with sol-gel immobilized rhodium catalysts“ **8<sup>th</sup> European Congress of Chemical Engineering** in Berlin/Germany, 26-29 Sept. 2011

## **Poster**

- Volovych, I.; Kasaka, Y.; Schwarze, M.; Blum, J.; Schomäcker, R. „Sol-gel immobilized palladium catalysts: synthesis, recycling and applications in tandem reactions” XVII International Sol-gel Conference in Madrid/Spain, 25-30 Aug. 2013
- Volovych, I.; Hamerla, T.; Schwarze, M.; Blum, J.; Schomäcker, R. „The Hydrogenation of itaconic acid and derivatives with sol-gel immobilized Rh/BPPM catalysts” International Symposium on Relations between Homogeneous and Heterogeneous Catalysis XVII International Sol-gel Conference in Madrid/Spain, 25-30 Aug. 2013
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- Volovych, I.; Blum, J.; Schomäcker, R. „Heck coupling with sol-gel immobilized palladium catalysts“ AIChE Annual Meeting in Pittsburgh/USA, 28 Okt.-2 Nov. 2012

- Volovych, I.; Schomäcker, R. „Heck coupling with sol-gel immobilized palladium catalysts“ 15th International Congress on Catalysis in Munich/ Germany, 1-6 July 2012
- Volovych, I.; Schwarze, M.; Blum, J.; Schomäcker, R. „Sol-gel Katalysatoren für Tandemreaktionen“ Jahrestreffen Reaktionstechnik in Würzburg/Germany, 14-16 Mai 2012
- Volovych, I.; Blum, J.; Schomäcker, R. „The hydrogenation of itaconic acid and derivatives with sol gel immobilized Rh/BPPM catalysts“ 45 Jahrestreffen deutscher Katalytiker in Weimar/Germany, 14-16 March 2012
- Volovych, I.; Blum, J.; Schomäcker, R. „Heck reaction with sol-gel immobilized palladium catalysts“ International Symposium on Relations between Homogeneous and Heterogeneous Catalysis ISHHC XV in Berlin/Germany, 11-16 Sept. 2011
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