

Microwave assisted synthesis using catalysts on controlled pore glass carriers

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Due to their beneficial features, TRISO[®]-controlled pore glass carriers are very well suited for the preparation of catalysts for application in technically important reactions, *e.g.*, C–C-coupling processes of the Suzuki-reaction type or highly selective hydrogenations. We describe here the development of first experiments with an effective and sustainable catalyst system in microwave-assisted syntheses. An essential advantage of porous catalysts prepared using microwave conditions is their reusability after reaction for further processes. The results are promising as regards the inception of a scalable reaction system for application in synthetic reactions using microwave energy.

Keywords: controlled pore glass, microwave energy, heterogeneous catalysis.

1. Introduction

Controlled pore glass is widely used as a carrier for solid phase synthesis [1]. Oligonucleotides as reference substances as well as pharmaceutically used anti-sense nucleotides or aptamers are manufactured using this support [2].

A matter of particular interest in industry and research is the broadening of the scope of applications of controlled pore glass [3]. Thus, introduction in the past few years of controlled pore glass in formulations of dental composites [4] and as carrier in affinity purification of antibodies are just a few typical applications.

Recently, we have become interested in evaluating the potential of our controlled pore glass products in microwave assisted synthetic reactions for the preparation of active pharmaceutical ingredients.

For a few years, energy entry by microwaves is used to initiate chemical reactions and processes. The hereby observed differences in both reaction time and yield and

partly in selectivity are often discussed in terms of the so-called non-thermal (or microwave) effect [5].

From evaluation of literature and comparison with our own published results we conclude that microwave irradiation promotes chemical reactions and proceeds only by means of dielectrical energy entry [6, 7]. The so-called non-thermal or specific effects, which are proposed in many publications, obviously have no or only a very limited impact. Typically, alleged “microwave effects” are intensively discussed where the reaction conditions are recorded only inaccurately or not at all or when the conditions applied are very different from the classical ones, respectively [6, 7].

Hence, the development and establishing of catalysts based on porous glass using microwave conditions is an attractive and new exciting field.

The Suzuki cross-coupling reaction is a technically important method to generate C–C bonds [8]. Metal-assisted and/or catalysed C–C-coupling reactions play an important role in syntheses of natural products, pharmaceuticals, speciality chemicals and organic photo- and electronic materials [9]. The reaction basically uses complex ligands coordinated with very expensive palladium catalysts [10].

Because of the high thermal stability of organic boron compounds, its low toxicity and its broad tolerance of functional groups, the Suzuki-reaction of arylboronic acids with arylhalogenides is one of the major preparative methods for the generation of aryl–aryl coupling products [8, 9, 11].

Disadvantages of Suzuki-reaction are the use of toxic solvents (*e.g.*, benzene) as well as the varying stability of catalysts in the presence of oxygen [10].

Mechanistically, the Suzuki-reaction proceeds via organo-palladium intermediates. Oxidative addition of organic halogenides via active palladium(0)-species leads to reactive palladium(II)-intermediates. The organic ligand is bound through a metal–carbon bond. The intermediates generated by oxidative addition in a transmetallation step react with unsaturated boron compounds. Reductive elimination leads to formation of new C–C bonds (Fig. 1).

Investigations of the Suzuki-reaction combined with microwave heating were done by WANG and SAUER [12]. So, an environmental and sustainable alternative for implementation of Suzuki-reaction is sought by various research groups [9, 13, 14].

A further example for the successful introduction of controlled pore glass is the hydrogenation of organic compounds. Heterogeneous methods play an important role in gas-phase-hydrogenation [15].

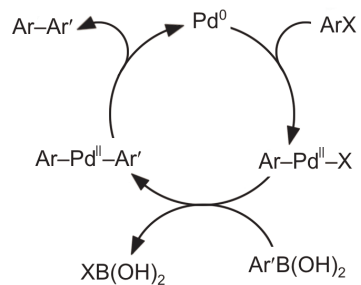


Fig. 1. Mechanism of the conventional Suzuki-reaction [9].

In heterogeneous operations, these catalysts are mostly fixed on a support such as activated carbon, aluminium oxide and silicon dioxide. This helps to avoid an erosion of the expensive components, *e.g.*, nickel, palladium, platinum, rhodium and their oxides, through high gas flows and high temperatures, respectively [15–17]. Solvents for heterogeneous catalytic liquid-phase-hydrogenations are, for instance, water, methanol, ethyl acetate, dioxane and mixtures of these. The choice of solvent depends on the solubility of the starting substance, unless it is used as solvent itself. Recently, new approaches in the field of heterogeneous hydrogenation are being studied, *e.g.*, in combination with alternative energy forms like microwave energy [18].

2. Experimental

2.1. Preparation of the catalyst system

In a typical experiment, Pd(OAc)₂ (0.09 mmol, 20.2 mg) is dissolved in 50 mL dichloromethane in a 100 mL round bottom flask. 1 g of TRISOPOR[®]/TRISOPERL[®] glass carrier (VitraBio GmbH, Steinach, Germany) is added and the solution evaporated to dryness. The impregnated glass is then calcinated in a microwave muffle furnace (MLS 1200 pyro, MLS Ltd. Leutkirch, Germany) for different periods of time (1, 2, 3 h) at 1000 W and 300°C.

2.2. Suzuki reaction of 4-bromophenol

In a typical reaction, 4-bromophenol (346.0 mg, 2 mmol), phenyl boronic acid (256 mg, 2.1 mmol), sodium carbonate (837.4 mg, 7.9 mmol), distilled water (4 mL) and 0.1 g of the catalyst system are transferred to a special glass tube for microwave applications. The tube is closed with a holder for a fibre optical sensor. The tube is put in a beaker and placed in the middle of the microwave equipment MLS ETHOS 1600. The fibre optical sensor is connected to the holder and the reaction mixture treated with microwave radiation for 10 min at 300 W and 150°C.

After that time the reaction mixture is extracted subsequently with 4 mL distilled water and 5 mL tert.-butyl-methyl-ether. The catalyst system is filtered off and dried at 50°C for 45 min. It is then ready for further reaction cycles. Aqueous and organic phases are separated and analysed by gas chromatography and inductively coupled plasma optical emission spectrometry (ICP-OES).

2.3. Hydrogenation of benzalacetophenone

15 mmol benzalacetophenone, 0.4 g catalyst (see above) and 60 mL ethyl acetate are mixed in a tube. The tube is closed with a glass valve, attached to a shaker and connected to the hydrogen source. The tube is filled with hydrogen and flushed three times with 400 mL hydrogen each. The reaction mixture is shaken at a frequency of 300 rpm. The hydrogen consumption is monitored periodically. Samples are taken at defined intervals and analysed by gas chromatography and mass spectroscopy. The reaction is finished when hydrogen consumption no longer increases. At the end

of the reaction, the catalyst is filtered off and subsequently dried at 105°C. The catalyst can be used for further reaction cycles.

3. Results and discussion

The basic concept to combine TRISO[®]-materials with catalysts was realised at the University in Jena.

As catalyst, palladium(II)-acetate was used [19]. TRISO[®]-material was treated with a solution of the palladium compound and immobilised on the surface of the porous glass by a calcination process using a microwave muffle furnace. The product shows a high reactivity as well as reusability and was tested in different reactions. Figure 2 and 3 show palladium-supported TRISOPERL[®]/TRISOPOR[®] porous glass carriers under the light optical microscope in the transmitted light mode. The bead-shaped TRISOPERL[®] which is a unique proprietary product is highly recommended for purification of fragile biomolecules (Fig. 2). Our granular carrier TRISOPOR[®] is an efficient and economical separation material for life sciences (Fig. 3).

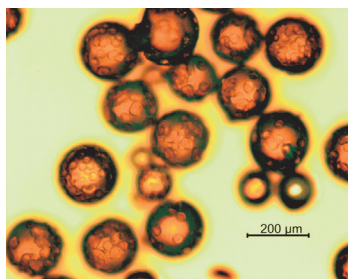


Fig. 2. TRISOPERL[®] with 2% Pd (transmitted light mode), pore size 50 nm, particle size 100–200 μm.

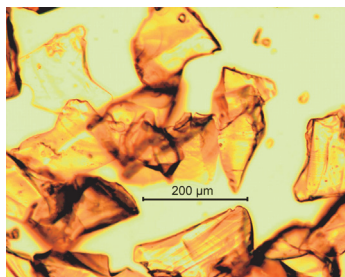


Fig. 3. TRISOPOR[®] with 2% Pd (transmitted light mode), pore size 50 nm, particle size 100–200 μm.

X-ray diffraction investigations of catalyst glass carrier show that the palladium particles are finely dispersed on the surface of the catalyst support (Fig. 4).

A first example of an application of our catalyst is the Suzuki-reaction. This is one of the most important preparative methods to generate aryl–aryl cross-coupling products. The reaction basically uses complex ligands coordinated with very expensive palladium catalysts. Further components required are different arylhalogenides, substituted boronic acids, bases and various solvents. Using controlled pore glass

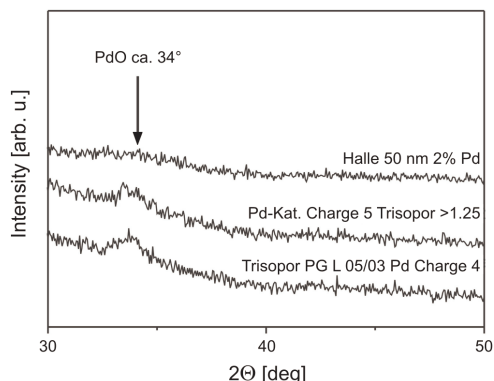


Fig. 4. XRD pattern of TRISOPOR® with 2% Pd.

carriers and microwave energy, we have tried to optimise the reaction. This can be effected on different levels: economising on solvent, introducing water as solvent, using alternative energy forms, using a supported palladium catalyst and using a ligand-free palladium catalyst.

For the new modification of the Suzuki-reaction presented here, no ligand is necessary and water can be used as solvent.

Feasibility of the reaction was demonstrated by conversion of 4-bromophenol and phenyl boronic acid into 4-phenylphenol (Fig. 5).

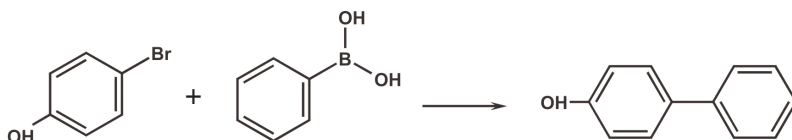


Fig. 5. Suzuki-reaction of 4-bromophenol with phenyl boronic acid into 4-phenylphenol.

Under the conditions shown in the experimental part, both high conversion and high yields of 4-phenylphenol were obtained (Fig. 5). The product (4-phenylphenol) is formed with high selectivity and the catalyst system was used after the reaction for further reaction batches. Even after 6 reaction cycles, high conversions and high yields are observed (see the Table).

T a b l e. Conversion of 4-bromophenol by the Suzuki-reaction (for conditions see Sec. 2).

Reaction batch	Conversion of 4-bromophenol [%]	Yield of 4-phenylphenol [%]
1	95.0	91.8
2	86.0	85.5
3	97.5	94.0
4	94.0	91.3
5	93.5	91.3
6	93.5	90.8

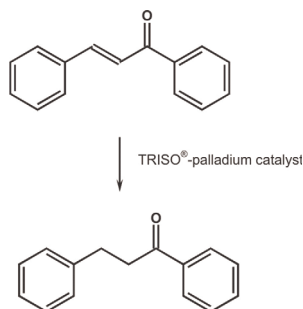
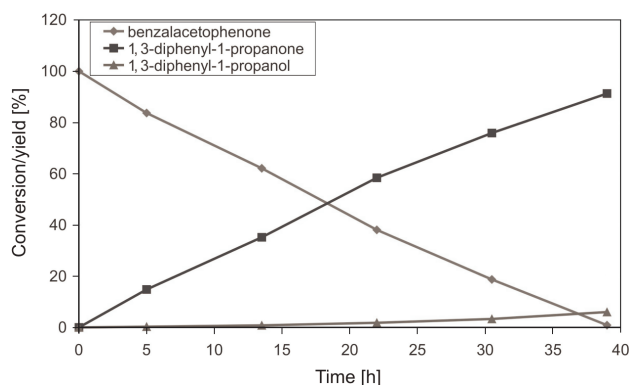


Fig. 6. Hydrogenation of benzalacetophenone.

Fig. 7. Conversion and yield of hydrogenation with TRISO[®]-palladium catalyst system of benzalacetophenone.

The new catalyst system also allows for highly advantageous reaction conditions, as no complex ligand on the catalyst is necessary and water can be used as solvent. Thus, we have in hand a sustainable reaction system in combination with alternative energy entry by microwave radiation.

Another successful introduction of controlled pore glass as a carrier in heterogeneous catalysis could be shown for the hydrogenation of organic compounds.

To investigate the role in selectivity and conversion, benzalacetophenone was used as test substance (Fig. 6). Figure 7 shows the results of hydrogenation with the TRISO[®]-palladium catalyst. After 40 hours, conversion of the starting material (benzalacetophenone) into 1, 3-diphenyl-propanone was nearly complete. A very small amount of the corresponding hydroxy derivative 1, 3-diphenylpropanol resulting from attack of the hydrogen on the carbonyl group indicates a high selectivity of the catalyst system towards the double bond.

A further example demonstrating the high selectivity of the catalyst system is the hydrogenation of isophorone (Fig. 8). This compound likewise offers two sites to bind hydrogen: the double bond and the carbonyl function. Conversion of isophorone using the TRISO[®]-palladium catalyst system exclusively gives one product, namely

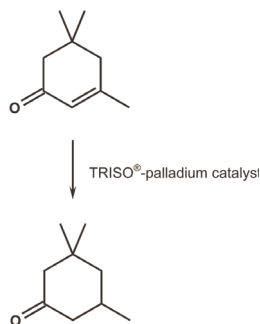
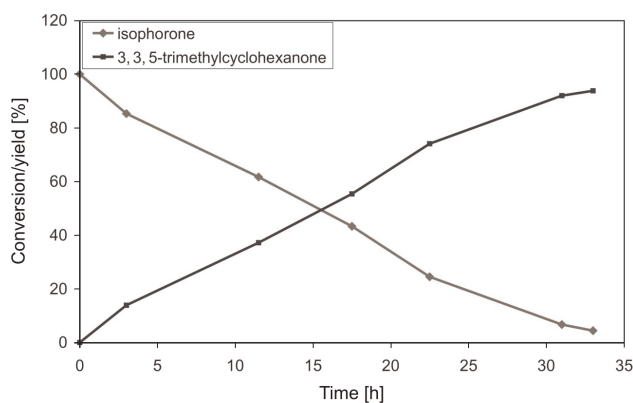


Fig. 8. Hydrogenation of isophorone.

Fig. 9. Conversion and yield of hydrogenation with TRISO[®]-palladium catalyst system of isophorone.

3,3,5-trimethylcyclohexanone (Fig. 9). Again, high selectivity combined with reusability of the catalyst is noteworthy result of this reaction. The properties and efficiency of catalysts are not affected in the course of the reaction.

4. Conclusions

Summing up, our preliminary experiments have shown the high potential of TRISO[®]-controlled pore glass products for versatile synthetic reactions. At first, with the development and preparation of the TRISO[®]-palladium catalyst system we have demonstrated an easy way of preparing an efficient catalyst using controlled pore glass. Second, the concept of combining TRISO[®]-carriers and alternative microwave energy was realized and successfully tested in technically relevant reactions such as the Suzuki reaction and catalytic hydrogenation. The extension of this promising concept to other catalyst systems and transformations is currently being tested.

Finally, using the approach demonstrated here in scaling-up catalyzed organic reactions will pave the way to important chemical specialties under environmentally safe conditions.

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