The Suzuki Reaction revised – Simplification and Scale up in the Microwave Field

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Metal-catalysed reactions are ubiquitous in organic chemistry and represent a modern research area [1]. In the last years considerable progress was achieved in the field of palladium-catalysed C-C-coupling. A high number of publications as well as a great amount of reviews and books documented the progress and is reflected in name reactions names like Heck, Sonogashira, Stille or Suzuki [2]. Reactions of this type should reach high importance in case of technical und economical feasibility in the production of fine chemicals, pharmaceuticals and other high-level products. Also microwave irradiation was used for the activation of palladium-catalysed reactions. But only in a few cases deviations from the original composition of the reaction mixture are described, e. g. [3, 4].

A. m. reaction mixtures are very complex in the most of the described experiments. Depending on the type of reaction the starting material (e.g. aryl halide) is reacted with a substituent-supplying educt (e. g. olefins, acetylenes, boronic acids, siloxane derivates). However, further auxiliaries are necessary to adjust the reaction conditions. As a rule a base (e. g. triethyl amine, sodium carbonate), a metal compound (e. g. palladium acetate) and an additional complexing agent (e. g. triphenyl phosphine) are required beside a solvent (often DMF). The described reaction times are often very long, when the reaction is carried out at room temperature or slightly above. The resulting mixtures are worked up in the most cases by diluting with water and extraction with a water immiscible organic solvent (MTBE, dichloromethane).

We present here two concepts for the simplification of the Suzuki reaction, in which the entry of microwave energy plays important role in the reaction processing. Scale-up is also taken into consideration. Preliminary results are represented her.

I. Reactions on solid support (dry reaction)

The in this context presented investigations are only fragmentary and not systematically [5, 6]. A mixture of alumina and potassium fluoride has been described as support and simultaneous as solid base, s. formula 1 [7].

Formula 1:

$$12\ KF + Al_2O_3 + 3\ H_2O \rightarrow 2\ K_3AlF_6 + 6\ KOH$$

Under the preparing conditions potassium fluoride reacts very fast and exothermally with alumina and so a complex mixture with high concentrations of potassium hydroxide on the surface is formed.
The investigations presented here cover the variation of the experimental conditions, particularly the support composition and the reaction time as well as the educts. The palladium compound used reacts under the conditions very rapidly to metallic palladium. A great part of the educts react now immediately in an exothermic conversion. Additional microwave irradiation is only necessary for completion of the reaction. The experiments allow the synthesis of substituted biaryls from different bromoaryl compounds (tab. 1) in high yields and high selectivities (tab. 2). Scale-up of the dry reaction is also demonstrated.

Table 1: Bromoaryl derivates used in Suzuki reaction on solid support

entry	educt
A	bromobenzene
B	2-bromo-methoxybenzoate
C	1-bromonaphthalene
D	4-bromotoluene
E	4-bromoaniline
F	4-bromoacetophenone
G	4-bromonitrobenzene

In some cases the mechanochemical reaction in a planet mill is enough for a good yield (entry A, C, F, G in table 2). The additional microwave irradiation of the reaction mixture had only a small effect on the yield of the Suzuki product.
The Suzuki reaction of electro-rich aromatic compound (e. g. entry D) necessitates more energy, so that the yield increases in the using of microwave energy.

Table 2: Results of the different reaction methods in the Suzuki reaction in presence of a solid support (2.5 mmol bromoaryl derivate, 3 mmol phenyl boronic acid, 2 mol% $Pd(Ac)_2$, 5 g 40 % KF on Alumina)

entry	reaction conditions	product [area-%]
A-1	mixed with spatula, 30 min without energy entry	45
A-2	mixed with spatula + MW (15 min, 150 °C, 300 W)	93
A-3	after planet mill, without MW	92
A-4	after planet mill, MW (15 min, 150 °C, 300 W)	98
B-1	mixed with spatula, 30 min without energy entry	27
B-2	mixed with spatula + MW (15 min, 150 °C, 300 W)	24
B-3	after planet mill, without MW	20
B-4	after planet mill + MW (15 min, 150 °C, 300 W)	38
C-1	mixed with spatula, 30 min without energy entry	35
C-2	mixed with spatula + MW (15 min, 150 °C, 300 W)	73
C-3	after planet mill, without MW	62
C-4	after planet mill + MW (15 min, 150 °C, 300 W)	74
D-1	mixed with spatula, 30 min without energy entry	31
D-2	mixed with spatula + MW (15 min, 150 °C, 300 W)	82
D-3	after planet mill, without MW	36
D-4	after planet mill +MW (15 min, 150 °C, 300 W)	74
E-1	mixed with spatula, 30 min without energy entry	9
E-2	mixed with spatula + MW (15 min, 150 °C, 300 W)	66
E-3	after planet mill, without MW, extraction with MTBE	3
E-4	after planet mill + MW (15 min, 150 °C, 300 W), extraction with MTBE	6
F-1	mixed with spatula, 30 min without energy entry	55
F-2	mixed with spatula + MW (15 min, 150 °C, 300 W)	62
F-3	after planet mill, without MW	94
F-4	after planet mill + MW (15 min, 150 °C, 300 W)	94
G-1	mixed with spatula, 30 min without energy entry	51
G-2	mixed with spatula + MW (15 min, 150 °C, 300 W)	68
G-3	after planet mill, without MW	78
G-4	after planet mill + MW (15 min, 150 °C, 300 W)	80

The using of 4-bromoaniline (entry E) shows only small amounts of the Suzuki product. Main reaction is here the oxidation of the aniline derivate to an undefined mixture of dark coloured substances.
Under the used reaction conditions it is possible to describe a raw of reactivity of the used starting materials.
An important experience is that an intensive mixture (shaking, stirring or milling) of all components is very important for an effective realisation of the Suzuki reaction on solid support. Microwave irradiation is here only a secondary tool.
The scale up of the mechanochemical reactions was carried out in a 12 fold larger scale with the same results such as in the laboratory scale.

II. Reactions with support fixed palladium using water as solvent

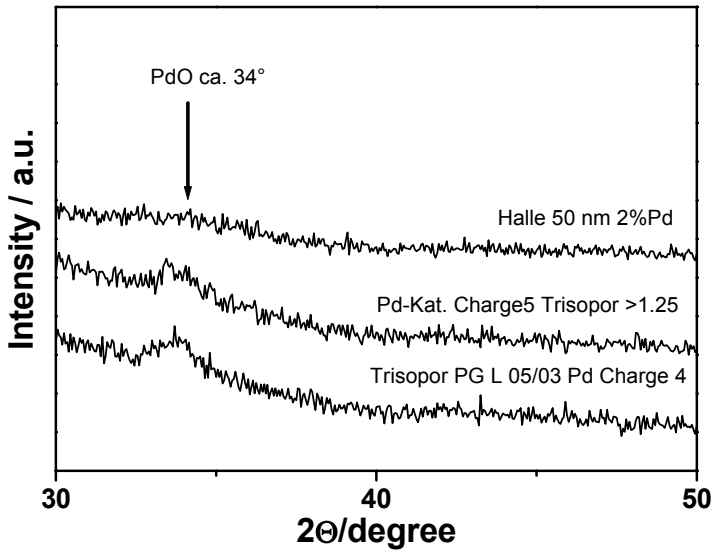
The use of water as solvent in organic reactions is a modern trend of sustainable chemistry, see [4, 8]. In most of reactions described up to now homogeneous reactions conditions are used and accepted the problems connected with recycling or loss of catalyst at the end of the reaction. Scale-up of Suzuki reactions is described only in few cases for this reason.
By using an exact defined porous glass (TRISOPOR®, VitraBio GmbH, Steinach, Germany) a microwave assisted fixation of palladium on the surface is possible. For preparation of palladium catalyst different amounts of a palladium-II-acetate are dissolute in dichloromethane and stirred with porous glass for 30 min. After distillation of dichloromethane in vacuum the raw catalyst is thermolysed in microwave field (MLS 1200 pyro, MLS GmbH Leutkirch, Germany). This preparation is possible up to 1 kg scale. Picture 1 shows a XRD-spectrum of the palladium compound on the catalyst support.
Theses catalysts with palladium concentrations of 0.001 mmol/g to 0.01 mmol/g are used for a heterogeneous Suzuki reaction in water. Some different examples are summarized in tab. 3.

Table 3: Suzuki reaction in water with palladium on porous glass in the microwave field (2 mmol bromo compound, 2.05 mmol phenyl boronic acid, 7.5 mmol sodium carbonate, 0.01 mmol palladium on porous glass, 0.2 mol water; ETHOS MR, MLS GmbH, Leutkirch, Germany; 10 min, 150 °C)

educt	conversion	yield
4-bromophenol	95	92
2-bromonaphthol	38	35
4-bromotoluene	99	97

In the cases of water insoluble substance (e. g 4-bromotoluene) the reactions were carried out in presence of a phase transfer catalyst.

Picture 1: XRD-spectrum of the palladium catalyst on the porous glass



The efficiency of the catalyst is demonstrated in a repeated Suzuki reaction of 4-bromophenol using water as solvent (tab. 4). The results shows that the catalyst is reusable several times without lost of reactivity.

Table 4: Repeated Suzuki reactions of 4-bromophenol with phenyl boronic acid. In all reactions the same catalyst was used (2 mmol 4-bromophenol, 2.05 mmol phenyl boronic acid, 7.5 mmol sodium carbonate, 0.01 mmol palladium on porous glass, 0.2 mol water; ETHOS MR, MLS GmbH, Leutkirch, Germany; 10 min, 150 °C)

reaction	conversion of 4-bromophenol	yield of 4-phenylphenol
1	95	92
2	86	86
3	98	94
4	94	91
5	94	91
6	94	91

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