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Ligand-free, recyclable palladium-functionalized magnetite nanoparticles as a catalyst in the Suzuki-, Sonogashira, and Stille reaction

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A magnetically reusable ligand-free Fe_3O_4 palladium functionalized catalyst system was successfully prepared without the use of reducing agents, but by making use of the reduction potential of magnetite. The stabilizer was variated depending on the investigated reaction, whereby poly(ethylene glycol) (PEG) stabilized nanoparticles were used for the Suzuki reaction, as it requires protic conditions, while oleic acid stabilized nanoparticles were used for the Sonogashira and Stille reaction. It was found that it was possible to perform the Suzuki reaction and the Sonogashira reaction resulting in good to excellent conversions under air. Despite the good results for the Suzuki and the Sonogashira reaction it was not possible to perform the Stille reaction using this easily synthesized catalyst system due to the poisoning of the reusable catalyst by the tin-compound. Furthermore, the reusable catalyst system was recycled and reused for five times, resulting in a separable, straightforward and less time-consuming catalyst system.

1. Introduction

Catalysts are an indispensable component for the majority of chemical processes, which makes them a key factor in the chemical research industry. More specifically, palladium-catalyzed cross-coupling reactions have attracted much interest over the last 30 years, because they unlocked valuable organic coupling pathways, not solely in academia but also for industrial applications [1–3]. Academically, the importance was recognized by awarding the 2010 Chemistry Nobel Prize to Richard F. Heck, Eiichi Negishi and Akira Suzuki for the development of "palladium-catalyzed coupling reactions in organic synthesis" [4,5]. The opportunity for a tolerable functionalization of aryl halides with boronic acids, acetylenes or tin compounds is the practical advantage for the use of Suzuki-, Sonogashira-, Stille- and many other cross-coupling reactions. In the past, these reactions were typically performed under homogeneous conditions using palladium and (phosphine) ligands as a catalytic system [6–9]. Nowadays, more innovative catalyst systems are used [10–13]. However, the separation and recovery of the catalyst represent major concerns for sustainable development. Generally, homogeneous palladium catalysts are popular for their high selectivity, activity, and resistance towards poisons, while heterogeneous catalysis offers the advantage of simplified product separation and recyclability of the catalyst [14–17]. Therefore, the immobilization of active homogeneous catalysts on solid supports has become a popular strategy to combine the advantages of both homo-and heterogeneous catalysis. Efforts have already been made to develop heterogeneous Pd catalysts for cross-coupling reactions [18–20] by the immobilization of Pd on various supports, such as silica nanoparticles [21–24], graphene [25,26], graphene oxide [27], cellulose [28,29], chitosan [30–35], Agar [36], bio-composite [37–39], starch [35,40], carbon nanotubes [41], dendrimers [42–45], polymers [46–50], metal oxides [51–53], graphene supported metal nanoparticles [54] and metal oxide nanoparticles [55–61], which can not only be used using conventional thermal heating but also using microwave assisted heating. These mentioned nanostructures can be separated into two groups based

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Abbreviations: PEG, Poly(Ethylene Glycol); ICP-AES, Inductively Coupled Plasma Atomic Emission Spectroscopy.
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on their method of separation. Nanoparticles can be separated by precipitation using a poor solvent (e.g. silica nanoparticles, polymer nanoparticles) or they can be separated by a magnet (e.g. magnetite nanoparticles) employing the superparamagnetic property of the nanoparticle. Due to the simplicity of the last method and ease of recovery, magnetite nanoparticles will be used during this study. The control of nanoparticle dimensions by modern synthetic techniques has enabled the production of catalysts with well-defined shapes, sizes, and compositions [62]. Because nanomaterials have well-defined dimensions, they can be applied in surface chemistry. For example, spherical nanoparticles with a size of 3 nm consist of 50% out of surface atoms, meaning a substantial proportion of the atoms are available for reaction [63]. Facile modification of the size of the particles alters the surface area ratio and consequently influences the activity. A dispersed nanoparticle can be considered as a cluster of atoms, that resembles the classical heterogeneous catalysts. Decreasing the particle size is beneficial because relatively more atoms become available for interaction at the surface. Therefore, the efficiency of the heterogeneous catalysts approximates the efficiency of homogeneous catalysts, which are distinct chemicals consisting of single molecules. Previous research already described the use of such heterogeneous catalysts which can be implemented in the Suzuki, Sonogashira, Stille or other cross-coupling reactions. Nonetheless, many of these reported processes with heterogeneous catalysts require prolonged reaction times, strict reaction conditions and time-consuming ligand synthesis [64–68]. These ligands can be present as an attached ligand onto the nanoparticle or as a ligand complexated to the Pd before the functionalization of the nanoparticle with Pd. In both cases it requires a longer and, consequently, more costly synthesis of the heterogeneous catalyst. Next to the ligand functionalized magnetite nanoparticles, core-shell nanoparticles consisting out of a magnetite core whereupon a SiO2 shell or Ag shell is attached has also been described in literature [69–72], which also results in a more times consuming catalyst preparation, just like the magnetically recyclable zeolite catalyst systems [73,74]. Nevertheless, it remains important to make use of stabilizing groups attached to the nanoparticle. This will prevent the nanoparticle to agglomerate as it will improve the reactivity of the immobilized catalyst system [75]. The deposition of Pd onto the magnetite surface using a reducing agent like $NaBH_4$ or hydrazine, resulting in a ligand-free immobilized Pd catalyst attached with or without stabilizing groups has been already reported [76–79]. The use of such reducing agents leads to a certain toxicity and dangerous reaction circumstances, which is deemed unnecessary. Therefore, our attempt is to make a catalyst system that provides the advantages of the presence of a stabilizer without the disadvantage of using a reducing agent. This can be achieved using the reducing nature and coordinating ability of the Fe_3O_4 support. Although already reported, no use was made of any stabilizing groups [80]. Our contribution is to combine both the advantage of the presence of a stabilized group and the absence of a reducing agent during synthesis. Through the use of poly(ethylene glycol) (PEG) or oleic acid as stabilizer for the nanoparticle together with a straightforwardly available Pd source like $Pd(OAc)_2$ and the reducing nature of the Fe_3O_4 support, it is possible to synthesize a less time consuming, cheap, non-toxic and reusable catalyst for the implementation in cross-coupling reactions. Despite the fact that such easily synthesized Pd functionalized magnetite nanoparticle was already used for the performance of a magnetically induced Suzuki reaction, improvement is still possible [81]. Due to the limitation of the heat generated by the magnetic field, the Suzuki reaction requires a prolonged reaction time of 4 h with average conversions, and the Sonogashira reaction does not lead to any conversion to the end-product. By using conventional thermal heating, it is possible to adapt the temperature to obtain high conversions with a short reaction time, using an as low as possible amount of valuable catalyst.

In this study straightforwardly synthesized Pd-functionalized magnetite nanoparticles are made starting from commercially available products in order to reduce the production time and increase the safety of the heterogeneous catalyst synthesis. The novel catalytic system is investigated for the Suzuki-, Sonogashira- and Stille-reactions. In consideration of the fact that these reactions require different solvent conditions (protic versus aprotic), several types of commercially available stabilizers are used to optimize the efficiency of the reactions. By making use of the superparamagnetic property of the Fe_3O_4 support it is possible to easily remove the heterogeneous catalyst system by the use of a magnet. Furthermore, the magnetite will act as a relative cheap support for the Pd catalyst. This in comparison to Pd nanoparticles, where only the surface of the nanoparticle can be used to catalyze the reaction, which means that the Pd present in the center can be seen as a waste and is an unnecessary cost. The use of a core-shell nanoparticle existing of a magnetite core surrounded by a golden shell will also be examined because this can combine the advantages of the use of Au in cross-coupling reactions [82] with the reusability of the catalyst system. Not only will the reactions be performed using an easily reusable catalyst, they will also be executed under air atmosphere using relative short reaction times, in order to facilitate these reactions.

2. Materials and methods

2.1. Experimental information

All reagents were purchased from TCI, Sigma-Aldrich, J&K Scientific and Acros Organics and used without further purification. ^1H NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer. The ultrasonication bath used in both functionalization of the magnetite nanoparticle and the core-shell synthesis was a Bransonic Model 5510 sonicator with a capacity of 10 L. The UV chamber used in the siloxane functionalization is equipped with 3 LEDs (365 nm) with an output power of 200 mW. For the TEM images, an 80 kV Zeiss EM-900 electron microscope was used in combination with 300 mesh Formvar coated copper grids from Ted Pella. For the inductively coupled plasma – atomic emission spectroscopy (ICP-AES) measurements, a Varian 720 ES was used with a A Varian patented vistachip CCD detector.

2.2. Pd functionalization of nanoparticles

Oleic acid stabilized Fe_3O_4 nanoparticles, PEG-silane stabilized Fe_3O_4 nanoparticles or gold-coated Fe_3O_4 nanoparticles in 1,4-dioxane were brought into a 100 mL flask. Its weight in palladium acetate was added accordingly, and the reaction mixture was stirred for four days after it was brought under argon atmosphere. The mixture was transferred to a tarred vial and the nanoparticles were isolated by a magnetic field and subsequently washed three times with 1,4-dioxane. The nanoparticles were dried under reduced pressure and the yield is determined gravimetrically. Thereafter dioxane is added to obtain a stock dispersion of nanoparticles. For more detailed information: see supplementary material.

2.3. General procedure for the Suzuki-Miyaura couplings

A two-necked flask was charged with, the aryl halide (0.180 mmol), the boronic acid-compound (0.270 mmol), K_2CO_3 (0.360mmol, 52.5 mg) and 1,3,5-trimethoxybenzene (0.180 mmol, 30.3 mg). A dispersion of Fe_3O_4/PEG/Pd nanoparticles in EtOH (0.500 mL, 0.100 mg/mL) was added to the two-necked flask, together with 0.500 mL H_2O. The reaction mixture was stirred for 1 h at 60 °C and the nanoparticles were isolated from the reaction mixture with a magnet. The conversion, with respect to the desired end-product, was determined by ^1H NMR of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard. For more detailed information: see supplementary material.

2.4. General procedure for the Sonogashira couplings

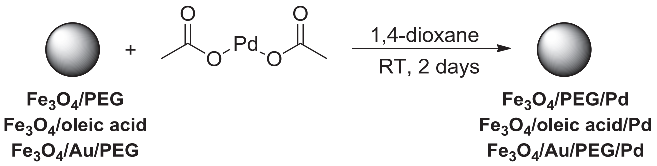
A two-necked flask was charged with, the aryl halide (0.180 mmol), 1,3,5-trimethoxybenzene (0.180 mmol, 30.3 mg) and KOAc (0.270 mmol, 26.5 mg). A dispersion of Fe_3O_4/oleic acid/Pd nanoparticles was made in DMSO-d_6 (1.00 mL, 2.00 mg/mL) and was added to the two-necked flask. The acetylene (1.80 mmol) was added and the mixture was stirred for 3 h under reflux at 100 °C. After stirring, the nanoparticles were isolated from the mixture with a magnet. The conversion, with respect to the desired end-product, was determined by ^1H NMR of the crude reaction mixture, using 1,3,5-trimethoxybenzene as an internal standard. For more detailed information: see supplementary material.

3. Results and discussion

In this study, a reusable catalyst system is created for different types of cross-coupling reactions. First, the Suzuki cross-coupling reaction is investigated, which is a typical example of a reaction that requires protic conditions [83,84]. Secondly, water-free reactions are performed and investigated by using the Sonogashira and Stille cross-coupling reaction. To produce relatively simple reusable catalysts, two types of nanoparticles are synthesized, one with a higher affinity for aprotic solvents, and one with a higher affinity for protic solvents. The affinity of the nanoparticle for the solvent can easily be changed by the use of different stabilizers. Nanoparticles stabilized with a poly(ethylene glycol) chain have a higher affinity for protic solvents compared to the oleic acid stabilized nanoparticles. The reason for using two types of nanoparticles instead of using one is due to the fact that the development of an easy-to-apply catalyst system was kept in mind. The synthesis of the oleic acid stabilized nanoparticles can be defined as a one-pot synthesis and is straightforward [85]. To obtain the PEG-silane stabilized nanoparticles, on the other hand, two synthesis steps are required consisting of, first, the synthesis of the nanoparticles with oleic acid as stabilizer and second, an exchange of this oleic acid stabilizer by PEG [86]. Therefore, PEG stabilized nanoparticles are harder to obtain and will only be used if necessary. Core-shell nanoparticles existing of a magnetite core surrounded by a golden shell will also be used to examine the influence of gold. Therefore, three catalyst systems will be used in this study: Pd functionalized magnetite nanoparticles stabilized with PEG (Fe_3O_4/PEG/Pd), Pd functionalized magnetite nanoparticles stabilized with oleic acid (Fe_3O_4/oleic acid/Pd) and, Pd functionalized core-shell nanoparticles stabilized with PEG (Fe_3O_4/Au/PEG/Pd).

3.1. Catalyst preparation

The different types of magnetite nanoparticles are prepared using known procedures. The magnetite nanoparticles stabilized with oleic acid are performed using the method of Chen et al. [85], while the water-soluble PEG stabilized magnetite nanoparticles are synthesized according to Bloemen et al. [86] The core-shell nanoparticles are synthesized and optimized by the procedure of Billen et al. [87] The functionalization of all nanoparticles with Pd is done by stirring $Pd(OAc)_2$ together with the nanoparticles in 1,4-dioxane for 4 days under argon atmosphere (Scheme 1). Uniquely, the functionalization is performed without the use of any reducing reagents or surface modification, but occurs due to the reducing nature and coordinating ability of the Fe_3O_4 support. Note that, in principle, it is possible to deposit any metal with a reduction potential more positive than that of Fe^{2+} (e.g., Co, Ni, Cu, Rh, Ru, Pd, Ag, Pt, and Au). This method was already reported in literature [80]. The amount of Pd present on the different types of catalyst systems was determined using inductively coupled plasma – atomic emission spectroscopy (ICP-AES) (Table 1). It should be mentioned that the amount of Pd on a PEG stabilized nanoparticle is higher compared to the oleic acid stabilized nanoparticle. This can be explained by the difference in stabilizer, where the palladium originating from Pd^{2+}, will be easier inserted inside the PEG stabilizer, due to the higher polarity of the PEG stabilizer compared to the oleic acid stabilizer, and by this making easier contact with the magnetite nanoparticle. The reason for the lower Pd content present on the Fe_3O_4/Au/PEG nanoparticle compared with the Fe_3O_4/PEG nanoparticle is twofold. Firstly, the size of the core-shell nanoparticles is larger compared with the magnetite nanoparticles, resulting in a lower surface to mass ratio, which results in a lower amount of Pd to mass ratio. Secondly, due to the coverage of the magnetite nanoparticle with the golden-shell, the magnetite is less available.



Scheme 1. Functionalization of the different types of nanoparticles with Pd.

3.2. Suzuki cross-coupling reactions

The Suzuki-Miyaura cross-coupling reaction is a main example of a Pd cross-coupling reaction in the presence of water. The reaction of 4-bromobenzoic acid with phenylboronic acid is used for initial studies as a model reaction and is carried out in the presence of aqueous K_2CO_3 [88–92]. The solvent chosen for this reaction was an EtOH/H_2O (1:1) mixture, which according to Zhou et al. results in optimal conditions [80]. The presence of water in the reaction mixture is the reason for the use of PEG-stabilized Pd-functionalized magnetite nanoparticles (Fe_3O_4/PEG/Pd). When oleic acid stabilized nanoparticles are used in this reaction, flocculation of the NPs occurs in the reaction mixture, but by the use of PEG as stabilizer a one-phase reaction mixture is obtained. As the Suzuki reaction is largely affected by the amount of catalyst and temperature, we set out to optimize the reaction conditions using the model reaction (Fig. 1).

As evident from Fig. 1, the use of a temperature of 60 °C with a catalyst amount of 0.05 mg of Fe_3O_4/PEG/Pd resulted in full conversion after 1 h. At room temperature, the yield of the target product decreases drastically when decreasing the catalyst amount, whereas a decrease in the catalyst amount at 60 °C resulted in only a small influence on the reaction yield. In summary, the best result is obtained at 60 °C during 1 h using 0.05 mg of Fe_3O_4/PEG/Pd. It should be mentioned that full conversion was also obtained at room temperature after 2 h with a catalyst loading of 0.3 mg of Fe_3O_4/PEG/Pd, resulting in an energy-efficient Suzuki reaction with short reaction times, and a low catalyst loading of only 1.3 10^{-3} mol % relative to the aryl halide.

To explore the scope and limitations of this protocol, a range of aryl halides and arylboronic acids were investigated (Table 2). It is

Table 1
ICP-AES results of Pd functionalized nanoparticles.

Nanoparticles	Amount of Pd (mg Pd/mg NPs)	Amount of Pd (10^{-4} mmol Pd/mg NPs)
Fe_3O_4/PEG/Pd	0.086	8.1
Fe_3O_4/oleic acid/Pd	0.014	1.3
Fe_3O_4/Au/PEG/Pd	0.051	4.8

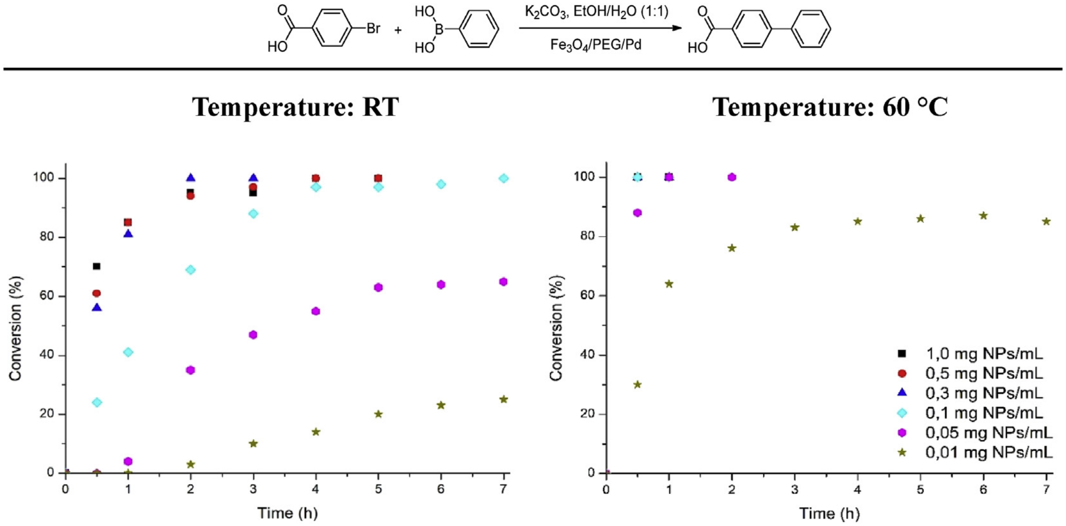
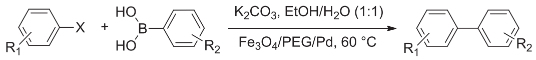


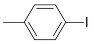
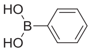
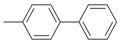
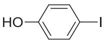
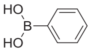
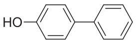
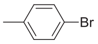
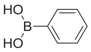
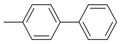
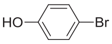
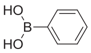
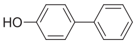
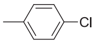
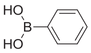
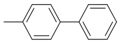
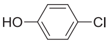
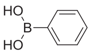
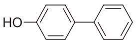
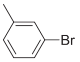
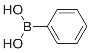
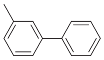
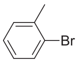
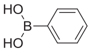
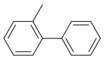
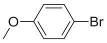
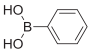
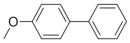
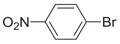
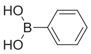
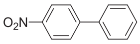
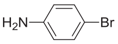
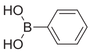
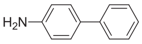
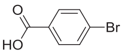
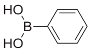
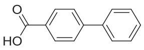
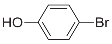
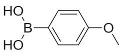
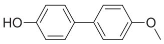
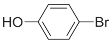
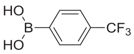
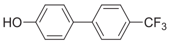
Fig. 1. Effect of the temperature and the amount of Fe_3O_4/PEG/Pd on the Suzuki cross-coupling. 4-bromobenzoic acid (0.18 mmol), phenylboronic acid (0.27 mmol), K_2CO_3 (0.36 mmol), Fe_3O_4/PEG/Pd, EtOH/H_2O (1:1) (1.0 mL), under air. Reaction was monitored by ^1H NMR. ^1H NMR conversions are calibrated using 1,3,5-trimethoxybenzene as an internal standard.

observed that aryl iodides and aryl bromides couple readily with phenylboronic acid to give significant results (Table 2), but that no reaction occurs for aryl chlorides (Table 2; entry 5 and 6). Interestingly, almost no difference in yield is noticeable between aryl iodides and aryl bromides. Generally speaking, a favorable effect of electron-withdrawing substituents on the halide is normally observed in palladium-catalyzed reactions. It is observed that aryl bromides containing electron-withdrawing groups couple readily with phenylboronic acid to give excellent yields (Table 2; entry 10 and 12). By introducing more steric hindrance on the aryl bromide, the yield decreases (Table 2; entry 3, 7 and 8). This was also noticed for the use of an electron-donating methoxy- or amine group (Table 2; entry 9 and 11). Very interesting results are obtained when a comparison is made between entry 4 and 9 (Table 2). Although all two halides have an electron-donating group, entry 4 leads to a higher conversion compared to entry 9. This leads to conflicting results, because due to the presence of K_2CO_3 the phenol-species is deprotonated to a phenoxide, resulting in a higher electron donation and thus a deactivation compared to the 4-bromoanisole. The reason for this opposite result is twofold. Firstly, this phenoxide has a high affinity for magnetite nanoparticles. Due to the interaction of the phenoxide with the nanoparticle, the substituent becomes a less electron-donating group compared to a “pure” alkoxide-species. Second and most importantly, due to the high affinity of the phenoxide for the nanoparticles, the binding brings the substrate in closer proximity to the catalytic system resulting in a higher yield compared to 4-bromoanisole for which no deprotonation can occur. The electronic nature of substituents of arylboronic acid was also investigated. The results show that arylboronic acids bearing either electron-donating groups or electron-withdrawing groups can provide the corresponding product (Table 2; entry 13 and 14). The use of an electron-donating substituent results in a higher yield compared to an electron-withdrawing group on the aryl boronic acid species.

Recovery and recycling of supported catalysts are very important issues from both the practical and environmental points of view. Therefore, catalyst recycling was performed at the optimized reaction conditions, to evaluate the reusability of the Fe_3O_4/PEG/Pd in the Suzuki reaction. After each cycle, when the reaction is finished, an external magnet is applied on the reaction vessel. Whereafter the separation of the catalyst is achieved and the resulting supernatant can be decanted, which minimizes the loss of catalyst during separation. The nanoparticle is then subsequently washed with 4 mL of 1,4-dioxane, 4 mL of water, 2 times 4 mL of ethanol and is dried under reduced pressure. The catalyst system was reused without further purification. As shown in Fig. 2 the catalyst can be reused at least 5 times, although with a loss in activity. At the 5th reaction, a conversion of only 18% was obtained. It should be mentioned that the loss in nanoparticles after each recovery was taken into account. This means that the amount of starting products, base and solvents are adapted to the amount of nanoparticles present after the recuperation. Due to this measure, the loss in activity can only be the cause of a change of the Fe_3O_4/PEG/Pd nanoparticle. By making use of ICP-AES the Pd-amount present in the crude end-product can be measured. As depicted in Fig. 2, there is a large loss in activity of the catalyst after the first cycle and is accompanied by a loss in Pd of 1.2%. After the 2nd, 3rd, and 4th, more moderate losses in conversions are observed and are accompanied by a respectively loss of 0.4%, 0.3% and 3.4% of Pd. It should be mentioned that the reaction is performed with only 0.22 10^{-3}mol% Pd. Therefore, it is understandable that even the leaching of a small quantity of Pd can cause a reduction in conversion. Transition electron microscopy (TEM) images of the Fe_3O_4/PEG/Pd

Table 2
The scope of Suzuki cross-coupling reactions with different substituents.



Entry	Reactant 1	Reactant 2	Product	Conversion[b]
1				73%
2				70%
3				76%
4				67%
5				0%
6				0%
7				14%
8				8%
9				20%
10				100%
11				25%
12				100%
13				55%
14				33%

[a]Reaction conditions: reactant 1 (0.18 mmol), reactant 2 (0.27 mmol).
K_2CO_3 (0.36 mmol), Fe_3O_4/PEG/Pd (0.05 mg), EtOH/H_2O (1:1).
(1.0 mL), temp: 60 °C, 1 h, under air.
[b] ^{1}H NMR conversions using 1,3,5-trimethoxybenzene as an internal standard.

nanoparticles before and after the reactions were recorded, in order to investigate the change in morphology of these nanoparticles as a result of the reaction (Fig. 3). According to Fig. 3, there is almost no difference in morphology between the nanoparticles before and after the reaction. Therefore there can be concluded that the decrease in conversion is probably due to the leaching of the Pd.

A comparison is made to other nanocatalysts reported in literature (Table 3). As seen in Table 3, the palladium functionalized magnetite nanoparticle show decent conversions compared to already existing systems. When the Fe_3O_4/PEG/Pd catalyst system is compared with other heterogeneous catalysts performed using thermal heating, there can be concluded that by using this catalyst system the reactions can be performed using a catalyst loading of over 2000 times lower compared to already existing systems with a longer reaction time. When this system is compared with a maghemite supported Pd catalyst, there can be concluded that the catalyst system obtained in this work was performed at much lower reaction temperatures. However, when this thermal induced reaction is compared with microwave induced reactions, using recyclable catalyst systems there can be observed that for the last one shorter reaction times are necessary, leading to similar conversions as the Fe_3O_4/PEG/Pd.

3.3. *Sonogashira cross-coupling reactions*

A second cross-coupling reaction investigated with the palladium-functionalized Fe_3O_4 catalyst is the Sonogashira reaction. This palladium catalyzed reaction is commonly performed in the presence of a copper(I) salt and an amine base, under an inert atmosphere [95,96]. When a terminal alkyne functionality is coupled to a substrate with a carbon-halide bond, copper has a dual role [97]. First, it interacts with the triple bond of the alkyne, lowering the Highest Occupied Molecular Orbital (HOMO), thereby increasing the acidity of the acidic proton of the alkyne. The second role of the copper is that it can bind to the deprotonated alkyne, generating a copper reagent that mediates the transmetalation step of the Sonogashira reaction. While a copper co-catalyst is added to the reaction to increase reactivity, the presence of copper can result in the formation of alkyne dimers [98,99]. This leads to the Glaser coupling reaction, which is an undesired formation of

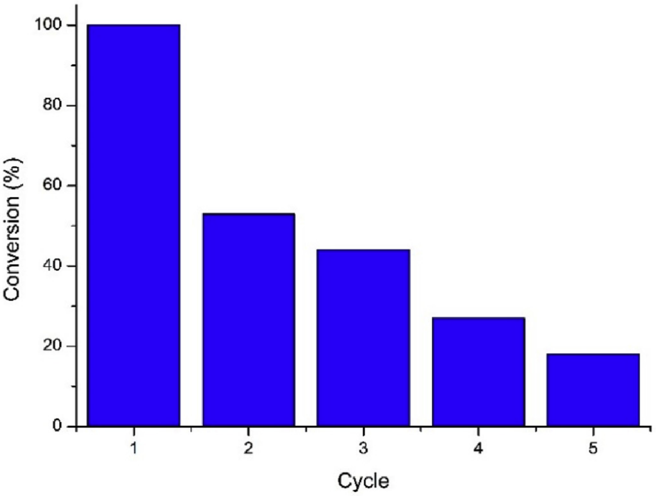


Fig. 2. The reusability of the Fe_3O_4/PEG/Pd NPs for the Suzuki reaction using 4-bromobenzoic acid and phenylboronic acids as substrates using 0.05 mg of nanoparticles/mL solvent (EtOH/H_2O 1:1) with adapting the amount of substrates to the amount of nanoparticles recycled after each cycle.

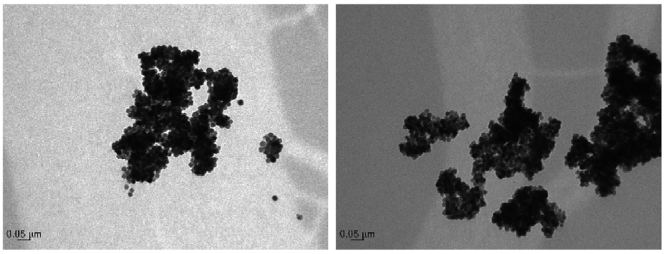


Fig. 3. TEM images of the Fe_3O_4/PEG/Pd nanoparticle catalysts before (left) and after (right) the Suzuki reaction.

homocoupling products of acetylene derivatives upon oxidation. As a result, when running a Sonogashira reaction with a copper co-catalyst, it is necessary to run the reaction in an inert atmosphere to avoid the unwanted dimerization. Copper-free variations to the Sonogashira reaction have been developed to avoid the formation of the homocoupling products and trace residues of Cu^+. A successful method of a recyclable catalyst for Cu-free Sonogashira reactions employs palladium nanoparticles on a pectin support, resulting in a recyclable catalyst using precipitation [100]. In the report by Khazaei and co-workers, complete conversion of starting material is obtained with short reaction times in DMF and using KOAc as a base, without the use of copper salts. In our approach, DMF is replaced by DMSO-d_6 for two reasons. Firstly, it is easier to monitor the reaction using ^1H NMR, and secondly, the use of DMSO as the solvent has a positive influence on the yield of the reaction [101]. Recyclable catalysts for the use in Sonogashira reactions have already been examined, resulting in a catalyst that can only be recycled using precipitation [100] or using a magnetite support which leads to reaction times up to 72 h [102]. Therefore, our attempt is to develop an easily recoverable catalyst using a magnetite support with short reaction times. For the investigation of the Sonogashira reaction an Fe_3O_4/oleic acid/Pd nanoparticles is used. The reason for using a different stabilizer compared to the Suzuki reaction is because of the simplicity of the nanoparticle synthesis. The synthesis of the Fe_3O_4/oleic acid nanoparticle requires just one step, while the synthesis of the Fe_3O_4/PEG nanoparticle requires two steps, and is in this way less straightforward because it will not result in any advantage for the Sonogashira reaction. Because side reactions tend to occur in the Sonogashira reaction with the use of copper in air and because, in our approach copper is absent, the Sonogashira reaction is attempted in air.

In a first step, the reaction is investigated and further optimized using the optimal conditions reported by Khazaei and co-workers [100]. Therefore, an equimolar reaction is chosen using 1-(*tert*-butyl)-4-iodobenzene and phenylacetylene in air (Scheme 2). The reaction progress is monitored by ^1H NMR of the crude reaction mixture. The conversion, with respect to the end-product, is illustrated in Fig. 4. It is observed that the conversion of the aryl iodide is 48% after 30 min, but the coupling reaction halts. With ^1H NMR is observed that the CH peak of the phenylacetylene has completely disappeared after this period. The disappearance of the phenylacetylene without complete conversion means the acetylene undergoes a side reaction. The peak of the phenylacetylene protons shifts to 7.62 ppm, and this corresponds to a homo coupled phenylacetylene.

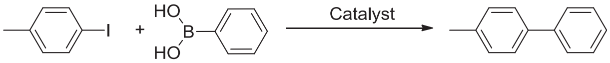
Therefore, the cause of the side-reaction is further investigated by heating phenylacetylene in the absence of the aryl iodide. This shows if the catalyst enables the side reaction and to what extent. In the first reaction identical conditions as the Sonogashira reaction are used without the aryl iodide (Scheme 3). The second reaction is similar to the first, but no KOAc is added. In the third reaction, unfunctionalized Fe_3O_4 nanoparticles are employed, these are of the same batch as the palladium functionalized catalyst but consist solely of magnetite. The fourth reaction is done without the addition of nanoparticles in the solvent and thus is performed in DMSO-d_6 with the addition of KOAc (Scheme 3).

As depicted in Fig. 5, the side reaction is catalyzed only by palladium, because no reaction occurs with unfunctionalized Fe_3O_4. The conversion of the reaction with the palladium catalyst and KOAc is 44% after 4 h, the reaction occurs to a smaller extent in the absence of a base. Hence, the homocoupling of phenylacetylene is an important side reaction to consider in the thermal Sonogashira reaction in an air atmosphere without a Cu^{+I} source. The phenylacetylene reacts with itself, preventing high conversions to be obtained in the cross-coupling reaction with the aryl halide. Because of the occurrence of the side reaction of phenylacetylene, a large excess (10 equivalents) of the phenylacetylene is used in next reactions. This results in high conversions. However, a reduction of the catalyst loading would be beneficial in the Sonogashira reaction. Therefore, the catalyst loading in the reaction is investigated by doing the reaction with various amounts of catalyst (Fig. 6). As expected, the conversion is the least for a catalyst loading of 0.1 mg. Little difference is noticeable between the use of 2 mg, 1 mg, 0.5 mg and 0.3 mg of nanoparticles, but full conversion is obtained using an amount of 2 mg of nanoparticles.

Further optimization was possible by investigating the temperature dependence of the reaction progress. For this, the reaction is done with the optimized catalyst loading at various temperatures. The temperatures investigated are 30 °C, 55 °C, 80 °C, 100 °C, and 120 °C (Fig. 7). The Fe_3O_4/oleic acid/Pd nanoparticles are isolated after each reaction and washed to prepare them for a second reaction at 100 °C (Fig. 8). This second reaction is done to determine the catalyst degradation at each temperature in the first catalytic reaction. A comparison of the conversions of starting material in the second reaction gives a measure for the deterioration of the catalyst and determines which temperature is optimal for the reaction.

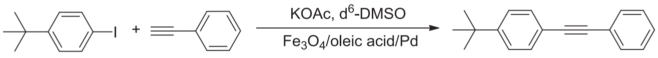
As depicted in Fig. 7, the reaction goes to completion the quickest at 120 °C. At this temperature, the conversion is already 92% after 30 min and 100% after 1 h. However, when the catalyst is recovered and reused at a temperature of 100 °C, it is observed that the catalyst has lost activity (Fig. 8). When the first reaction is

Table 3
Comparison between the catalytic performance of Fe_3O_4/PEG/Pd and different catalysts in the Suzuki cross-coupling reactions.



Catalyst	Solvent	T (°C)	Time	Pd content (mol %)	Yield[a] (%)	Ref
Chitosan-cellulose/Pd(II)	/	50 (MW)	5 min	0.015	63	[31]
OCMCS-SBL/Pd	/	50 (MW)	4 min	0.01	54	[32]
Chitosan-Ulva/Pd(II)	/	50 (MW)	4 min	0.02	47	[33]
OCMCS-3aPd	Toluene	100	48 h	0.04	51	[34]
Pd NPs@Fe_3O_4/CS-AG	/	50 (MW)	5 min	$1.5\ 10^{-5}$	80	[59]
Fe_3O_4@SiO_2–Pd(0)	H_2O/EtOH	85	26 min	0.03	93	[58]
Pd NPs@APC	/	50 (MW)	5 min	$1.8\ 10^{-6}$	67	[13]
AG-Pd	/	50 (MW)	6 min	$3.0\ 10^{-6}$	85	[36]
Pd NPs@CMC/AG	/	60 (US)	30 min	$1.0\ 10^{-5}$	75	[37]
CL-Gly-Pd	/	50 (MW)	7 min	$2.0\ 10^{-3}$	62	[28]
Chitosan/cellulose-Pd NP	/	50 (MW)	5 min	0.004	72	[12]
Pd@chitosan/starch	/	50 (MW)	6 min	0.005	75	[35]
ST-Shf-Pd(II)	/	50 (MW)	6 min	$2.0\ 10^{-3}$	72	[38]
Fe_3O_4-sporopollenin/Pd(II)	/	50 (MW)	5 min	$1.0\ 10^{-3}$	70	[57]
CS-NNSB-Pd(II)	/	50 (MW)	5 min	$6.0\ 10^{-3}$	38	[11]
OCS-NS-Pd(II)	/	50 (MW)	4 min	$5.0\ 10^{-3}$	66	[39]
CL-Sc-Pd(II)	/	50 (MW)	6 min	$5.0\ 10^{-3}$	64	[29]
Fe_3O_4/Ethyl-CN/Pd	H_2O/EtOH	25	30 min	0.2	98	[93]
ST-Sc-Pd(II)	/	50 (MW)	5 min	$4.0\ 10^{-3}$	68	[40]
γ-Fe_2O_3–Pd	H_2O/DMF	110	1 h	$0.1\ 10^{-4}$	90	[55]
Chitosan-pyridil-Pd(II)	/	50 (MW)	5 min	$5.0\ 10^{-3}$	69	[30]
Si–P–Pd	H_2O/MeOH	25	4 h	0.5	91	[94]
Fe@Fe_xO_y/Pd	H_2O/EtOH	25	2 h	0.5	84	[80]
Fe_3O_4/PEG/Pd	**H_2O/EtOH**	**60**	**1 h**	**$2.2\ 10^{-4}$**	**73**[b]	**This work**

MW = Microwave.
US = Ultrasonication.
[a] Isolated yield of the pure product.
[b] Conversion.



Scheme 2. Model reaction used for investigation of the Sonogashira reaction.

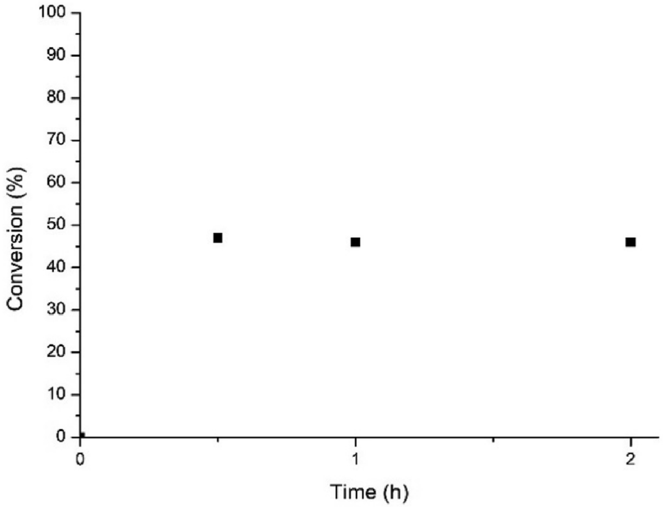
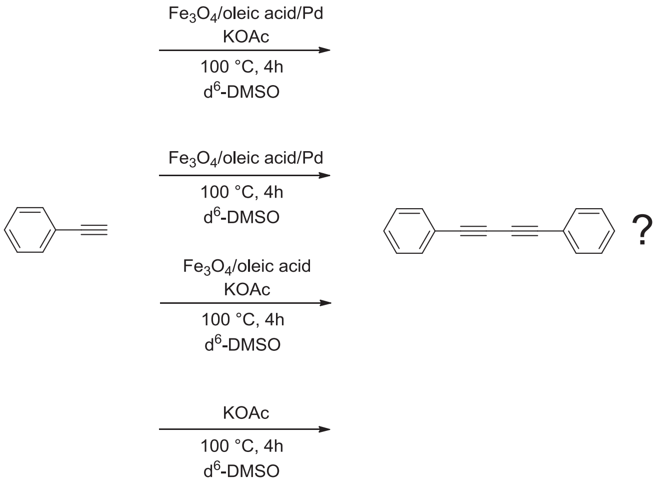


Fig. 4. Conversion in Sonogashira reaction with the substrates in equimolar amounts. Phenylacetylene (0.18 mmol), 1-(tert-butyl)-4-iodobenzene (0.18 mmol), KOAc (0.27 mmol), Fe_3O_4/oleic acid/Pd (2.0 mg), DMSO-d_6 (1.0 mL), temp: 100 °C, under air. Reaction was monitored by ^{1}H NMR. ^{1}H NMR conversions are calibrated using 1,3,5-trimethoxybenzene as an internal standard.

applied at a temperature of 100 °C or lower, the catalyst does not show a loss in activity in the second reaction applied at 100 °C (Fig. 8). This in combination with the fact when the first reaction applied at 100 °C, results in higher conversions compared to lower temperatures, an optimum is obtained at 100 °C. Therefore, further reactions are done with a reaction time of 3 h and a temperature of 100 °C.

To explore the scope and limitations of the optimized reaction conditions for the copper-free Sonogashira reaction in air, a range of aryl halides and phenylacetylenes were investigated (Table 4). In general, all of the coupling products are obtained in good to excellent yields using the optimal conditions. When a comparison is made between the Sonogashira and the Suzuki cross-coupling reaction, there can be observed that the Sonogashira reaction



Scheme 3. Investigation of the side-reaction of phenylacetylene with A) Fe_3O_4/oleic acid/Pd with base, B) Fe_3O_4/oleic acid/Pd without base, C) Fe_3O_4/oleic acid with base, D) DMSO-d_6 and base.

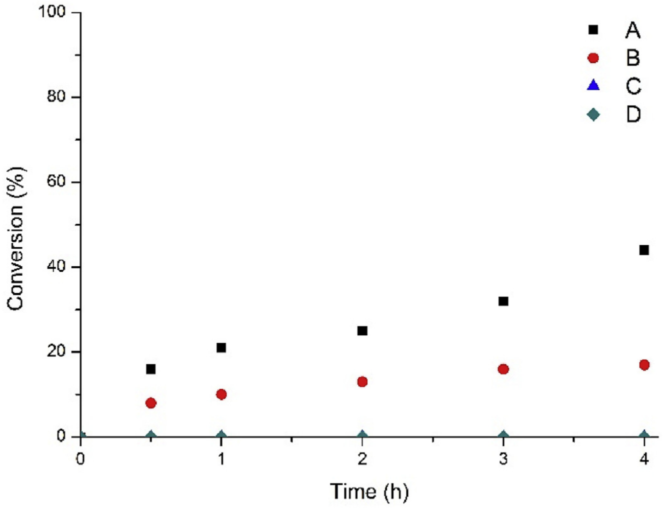


Fig. 5. The conversions of the reaction with phenylacetylene in function of time. A) Phenylacetylene (0.18 mmol), KOAc (0.27 mmol), Fe_3O_4/oleic acid/Pd (2.0 mg), DMSO-d_6 (1.0 mL), temp: 100 °C, under air. B) Phenylacetylene (0.18 mmol), Fe_3O_4/oleic acid/Pd (2.0 mg), DMSO-d_6 (1.0 mL), temp: 100 °C, under air. C) Phenylacetylene (0.18 mmol), KOAc (0.27 mmol), Fe_3O_4/oleic acid (2.0 mg), DMSO-d_6 (1.0 mL), temp: 100 °C, under air. D) Phenylacetylene (0.18 mmol), KOAc (0.27 mmol), DMSO-d_6 (1.0 mL), temp: 100 °C, under air. Reaction was monitored by ^{1}H NMR. ^{1}H NMR conversions are calibrated using 1,3,5-trimethoxybenzene as an internal standard.

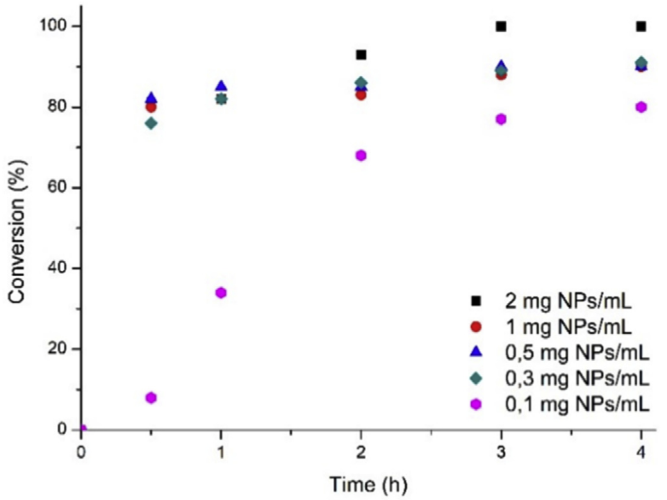


Fig. 6. Effect of the amount of Fe_3O_4/oleic acid/Pd on the Sonogashira cross-coupling. 1-(tert-butyl)-4-iodobenzene (0.18 mmol), phenylacetylene (1.8 mmol), KOAc (0.27 mmol), Fe_3O_4/oleic acid/Pd, DMSO-d_6 (1.0 mL), temp: 100 °C, under air. Reaction was monitored by ^{1}H NMR. ^{1}H NMR conversions are calibrated using 1,3,5-trimethoxybenzene as an internal standard.

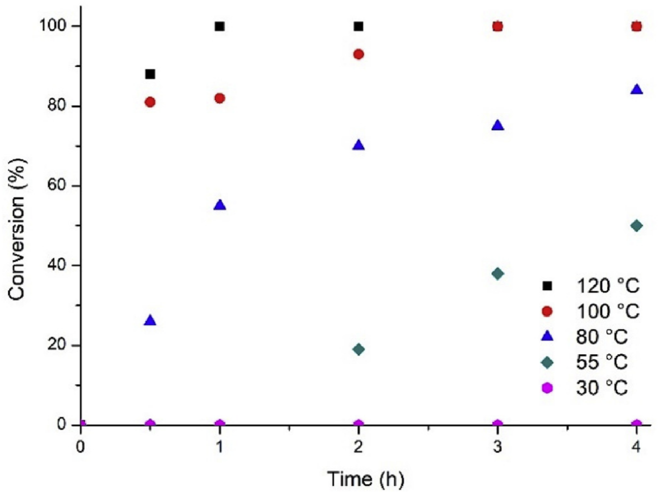


Fig. 7. Effect of the temperature on the Sonogashira cross-coupling. 1-(tert-butyl)-4-iodobenzene (0.18 mmol), phenylacetylene (1.8 mmol), KOAc (0.27 mmol), Fe_3O_4/oleic acid/Pd (2.0 mg), DMSO-d_6 (1.0 mL), under air. Reaction was monitored by ^{1}H NMR. ^{1}H NMR conversions are calibrated using 1,3,5-trimethoxybenzene as an internal standard.

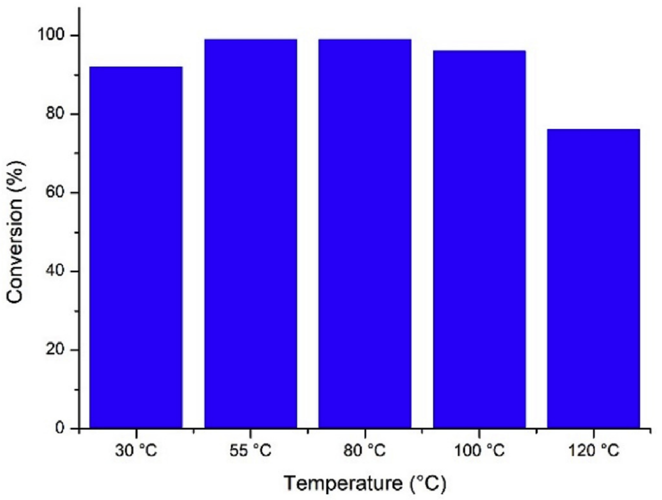
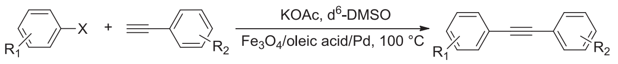


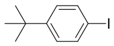
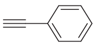
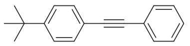
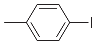
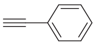
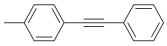
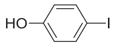
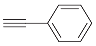
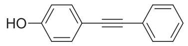
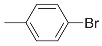
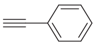
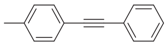
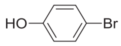
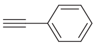
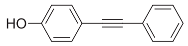
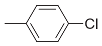
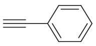
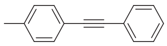
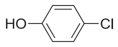
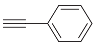
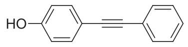
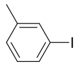
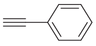
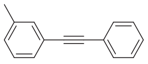
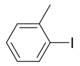
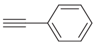
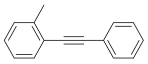
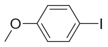
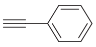
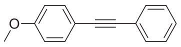
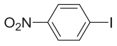
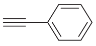
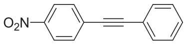
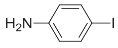
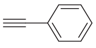
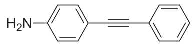
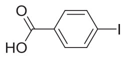
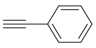
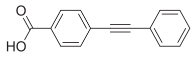
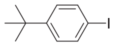
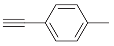
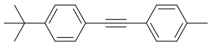
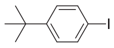
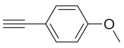
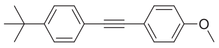
Fig. 8. Conversion at 100 °C after 4 h with recovered nanoparticles of the reactions at various temperatures.

demands harsher conditions. The Sonogashira reaction can only be performed at high temperatures and no conversion is obtained at 30 °C (Fig. 7), while for the Suzuki reaction full conversion was observed at room temperature with approximately the same Pd-loading. It is also observed that a six times larger Pd-loading is necessary to reach full conversion for the Sonogashira reaction alongside a reaction time, which is four times longer, at a higher temperature. It should also be mentioned that the Sonosgashira reaction is only possible for iodinated compounds, while the Suzuki reaction can also be performed using brominated compounds. Nevertheless, almost all end-products are obtained with a conversion of 100% using the optimized conditions in the Sonogashira reaction, while this is not observed for the Suzuki reaction. The only exception is the reaction performed with 4-iodoaniline, which only has a conversion of 62% in the Sonogashira reaction, due to its electron-donating character (Table 4; entry 12) [103]. Furthermore, the sterically hindered effect of substituent-bearing aryl iodides was also investigated. The results show that sterically hindered aryl iodides are also highly reactive using the optimized reaction conditions (Table 4; entry 8 and 9). It should be mentioned that in comparison with the Suzuki reaction, no influence of the phenoxide was observed. This results in an equal conversion of entry 3 and 10. The electronic nature of substituents of phenylacetylene is also investigated. To decrease the acidity of the acetylene proton, substrates with an electron-donating substituent are used. The results show that the phenylacetylenes couple readily with 1-(*tert*-butyl)-4-iodobenzene, resulting in full conversion (Table 4; entry 14 and 15).

The recyclability of the supported palladium catalyst was also surveyed. Catalyst recycling was performed, at the optimized

Table 4
The scope of Sonogashira cross-coupling reactions with different substituents.



Entry	Reactant 1	Reactant 2	Product	Conversion[b]
1				100%
2				100%
3				100%
4				0%
5				0%
6				0%
7				0%
8				100%
9				100%
10				100%
11				100%
12				62%
13				100%
14				100%
15				100%

[a] Reaction conditions: reactant 1 (0.18 mmol), reactant 2 (1.8 mmol).
KOAc (0.27 mmol), Fe_3O_4/oleic acid/Pd (2.0 mg), DMSO-d_6 (1.0 mL).
Temp: 100 °C, 4 h, under air.

[b] ^{1}H NMR conversions using 1,3,5-trimethoxybenzene as an internal standard.

reaction conditions, to evaluate the reusability of the Fe_3O_4/oleic acid/Pd in the Sonogashira reaction (Fig. 9). Therefore, after each cycle, an external magnet is applied to the reaction vessel separating the catalyst from the reaction mixture and the resulting supernatant can be decanted, which minimizes the loss of catalyst during separation. Despite the fact that another stabilizer is attached on the nanoparticle compared to the nanoparticle used for the Suzuki-Miyaura reaction, the magnetic separation occurs equally fast and is done in a few seconds. The catalyst system is then subsequently washed 2 times with 2 mL of DMSO and 2 times with 2 mL of 1,4-dioxane. After being dried, the catalyst system could be reused directly without further purification. As shown in Fig. 9 there is some loss of catalyst activity in the first reaction. In this first reaction, the conversion towards the end-product is 98%, which then declines to 94% in the second reaction with the catalyst. In the third reaction, the conversion decreases to 77%, a further drop in conversion is noticed in the fourth and fifth reaction with the recovered nanoparticles. It should be mentioned that the loss in nanoparticles after each recovery was again taken into account, similar as for the Suzuki reaction. TEM images of the Fe_3O_4/oleic acid/Pd nanoparticles before and after the reactions were recorded, in order to investigate the change in morphology of these nanoparticles as a result of the reaction (Fig. 10). According to Fig. 10, almost no difference in morphology was observed between the nanoparticles before and after the reaction. Therefore, there can be concluded that the decrease in conversion is not due to a change in morphology of the nanoparticles, but most probably due to the leaching of the palladium, which is investigated and confirmed by ICP-AES (Supplementary materials Table S2). When a comparison is made between the recyclability of the Suzuki cross-coupling reaction using Fe_3O_4/PEG/Pd nanoparticles and of the Sonogashira reaction using Fe_3O_4/oleic acid/Pd nanoparticles, a different trend is observed. While the conversion of the Suzuki reaction shows a fast decrease for the first recovery, the recovery performed for the Sonogashira reaction shows only a significant decrease in conversion after the 3rd cycle. It should also be mentioned that the leaching of Pd is 12.6%, 4.7%, 10.8%, 0.5 and 0.7% for the 1st, 2nd, 3rd, 4th, and 5th cycle respectively. When these values are compared to the Suzuki reaction, there can be observed that there is a much lower Pd-leaching for the Suzuki reaction. These dissimilar results can be explained by taken the total amount of Pd present in the reaction into account. While, for example, the total amount of Pd

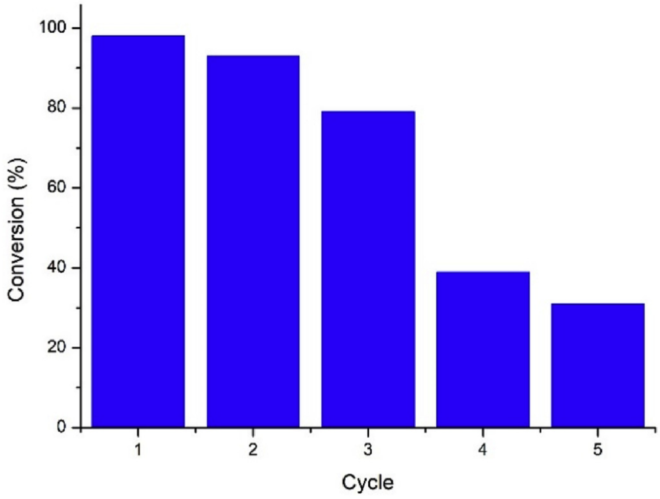


Fig. 9. The reusability of the Fe_3O_4/oleic acid/Pd NPs for the Sonogashira reaction using 1-(tert-butyl)-4-iodobenzene and phenylacetylene as substrates using 2.0 mg of nanoparticles/mL solvent (DMSO-d_6) with adapting the amount of substrates to the amount of nanoparticles recycled after each cycle.

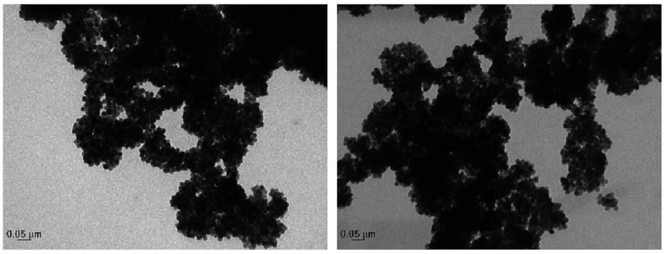


Fig. 10. TEM images of the Fe_3O_4/oleic acid/Pd nanoparticle catalysts before (left) and after (right) the Sonogashira reaction.

present in the second performed Sonogashira reaction exists out of 0.025 mg/mL, the total amount of Pd present in the second performed Suzuki reaction is only 0.0043 mg/mL. There should also be mentioned that a decrease of 50% in nanoparticle amount, resulting in a decrease of 50% of Pd, results in a decrease of only 10% of conversion (Fig. 6). Another possible explanation for the dissimilar results of the recuperation experiments between the Suzuki and the Sonogashira reaction is the possibility that the oleic acid stabilized nanoparticles have a higher stability in dry conditions compared to the PEG stabilized nanoparticles. Bringing the nanoparticles to the dry state is inevitable, so the correct amount of nanoparticles can be determined for the next cycle. Considering the results, it can be concluded that the catalyst can be employed up to three times without significant loss of activity.

3.4. *Stille cross-coupling reactions*

A third and last cross-coupling reaction investigated is the Stille reaction. The Stille coupling is an organometallic reaction that has the advantage of being tolerant to a lot of functional groups, without needing a base in the cross-coupling reaction but is notorious for its use of toxic tin reagents, that are hard to remove after the reaction [104,105]. Because no prior work was done with this catalyst in the Stille reaction, a first step in the investigation is finding optimal solvent conditions (Table 5). The reaction of 1-(*tert*-butyl)-4-iodobenzene with trimethyl(phenyl)stannane is used for initial studies as a model reaction. Because relatively short reaction times are optimal for the investigation, a predetermined reaction time of 4 h is used. A reaction temperature was chosen of 100 °C since this temperature is commonly used for the use in Stille reactions [6,106]. Although all reactions have similar low conversions, of the reactions in the different solvents, 1,4-dioxane has the highest conversion. Therefore, the following reactions are done in 1,4-dioxane (see Table 5).

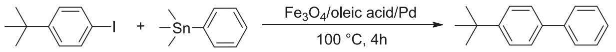
Because low conversions are obtained in the Stille reaction with 1-(*tert*-butyl)-4-iodobenzene as the substrate in the investigation of the solvent conditions, the substrate is changed to methyl-4-iodobenzoate. This aryl iodide contains an ester substituent in the *para* position, which results in an activated carbon-iodide bond. This is due to the stronger electron-withdrawing effect of an ester compared to the tertiary butyl group. Further, a longer reaction time is applied in order to investigate the progress of the reaction in time (Fig. 11), and to understand the low yield obtained after a reaction time of 4 h at 100 °C. The conversion was found to be approximately 15% higher compared with the less reactive 1-(*tert*-butyl)-4-iodobenzene but further conversion stagnates after 2 h. This stop in conversion could indicate that the catalyst degrades during the reaction or gets poisoned. To further investigate this behavior the catalyst is recovered and reused in an identical reaction. The nanoparticles are recovered with a magnet and washed 4 times with 2 mL 1,4-dioxane to remove all traces of the reaction mixture. The recovered nanoparticles are then dried under vacuum to prepare them for the next catalytic reaction. Adapting the quantity of the reactants to the mass of recovered catalyst, the reaction is repeated with the same nanoparticles. In the second reaction, there is no reaction occurring at all. The lack of any conversion of starting material clearly indicates that the Fe_3O_4 supported catalyst is degraded or poisoned in the first catalytic reaction. Therefore, the cause of the degradation is further investigated.

Because the conversion halts completely around 25% and does not increase after 2 h, it is speculated that the catalyst is poisoned either by trimethyl tin iodide, which is the by-product formed during the reaction or by the trimethyl(phenyl)stannane (Scheme 4). The poisoning is investigated by testing the two potential poisons. First, the Fe_3O_4/oleic acid/Pd nanoparticles are stirred at 100 °C for a period of 1 h in 1,4-dioxane with the addition of the potential poison (Scheme 4). Afterwards, the nanoparticles, that were stirred with one of the poisons, are recovered. To remove all traces of the tin compounds in the solvent, the nanoparticles are washed 3 times with 1,4-dioxane. Thereafter, the recovered nanoparticles are dried and, with adapting the scale of the solvent and reactants to the mass of the recovered nanoparticles, a Stille reaction is initiated. The conversion of the two reactions with the recovered nanoparticles is followed in time, and even after a reaction time of 5 h no conversion was obtained. The nanoparticles stirred both with trimethyl tin iodide as trimethyl(phenyl)stannane, have lost their catalytic activity. Therefore, the conclusion of the experiment is that both the tin reagent as the tin by-product, that is formed in the Stille reaction, are poisons for the catalyst. Because of this, it will be impossible to obtain optimal conditions in the Stille reaction using the Fe_3O_4/oleic acid/Pd catalyst. Because both the starting reagent and the product are a poison for the catalyst, the activity ceases before high conversion of the starting material is obtained and the catalyst is not suitable for reuse.

3.5. *The influence of Au on the catalytic activity*

The use of gold as co-catalyst in cross-coupling reactions has already widely been described in literature [82]. M.G. Speziali and co-workers are the only ones describing the influence of gold on the catalytic properties of a reusable Pd catalyst for the use in

Table 5
The effect of the solvent on the Stille reaction.



Entry	Solvent	Conversion[a]
1	Toluene	6%
2	Toluene/DMF (1:1)	6%
3	DMF	8%
4	1,4 Dioxane	10%

[a] H NMR conversions using 1,3,5-trimethoxybenzene as an internal standard.

Suzuki-reactions [107]. Knowing the importance and positive effect of gold present as Au(III) or Au(I) together with Pd in the Sonogashira reaction [82,108–110], our goal is to combine this effect with the advantage of a reusable catalyst. Therefore, a core-shell nanoparticle was made consisting of a magnetite core surrounded by a golden shell, stabilized with PEG and functionalized with Pd. The reason for the use of PEG as stabilizer is the result of the fact that the bonding of oleic acid to the golden shell of the nanoparticle is much weaker compared to a thiolated PEG-chain. Second, the synthesis of the Fe_3O_4/Au core-shell nanoparticle is performed using ascorbic acid as stabilizer, therefore it is not possible to attach a group as for example oleic acid, which has an approximately equal binding energy. It should also be mentioned that the structure of the PEG-ligands protects the core-shell nanoparticles from aggregation through steric hindrance. Due to the presence of the magnetite core, it is possible to reuse the catalyst system in the Sonogashira reaction as described in the previous section (Fig. 9). Because it is aimed to investigate the influence and the possible improvement on the yield of the reaction, reaction conditions are used resulting in a yield of 0%. Therefore, the reaction of 1-(*tert*-butyl)-4-iodobenzene with phenylacetylene at a temperature of 30 °C and a reaction time of 3 h is used (Fig. 7). The influence of gold on the catalytic activity is investigated by testing the two catalytic systems in parallel for three times (Fig. 12). The catalyst systems used are the already described and investigated Fe_3O_4/oleic acid/Pd and, second, the gold/magnetite core-shell nanoparticle functionalized with Pd (Fe_3O_4/Au/PEG/Pd). To investigate the influence of the gold, the same amount of Pd is used, resulting in the use of 2 mg Fe_3O_4/oleic acid/Pd and 0.56 mg Fe_3O_4/Au/PEG/Pd (see fig. 12).

As depicted in Fig. 12, the presence of gold has indeed a positive influence on the yield of the reaction and activity of the catalyst. Due to this, it is not only possible to perform Sonogashira reactions at a shorter reaction time, but also at much lower reaction temperatures, resulting in a more time- and energy-efficient reaction.

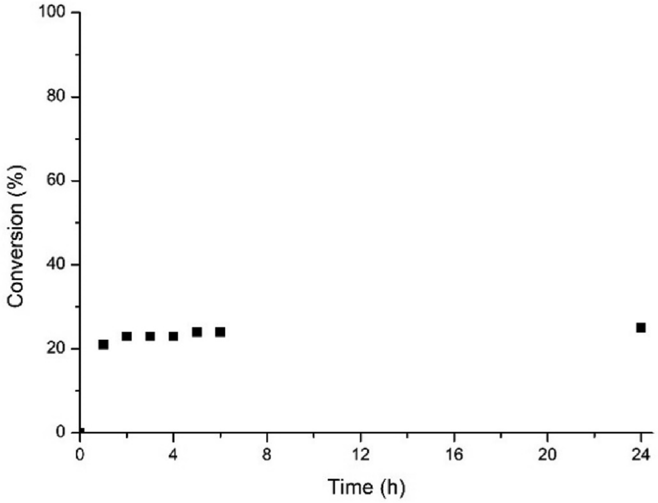
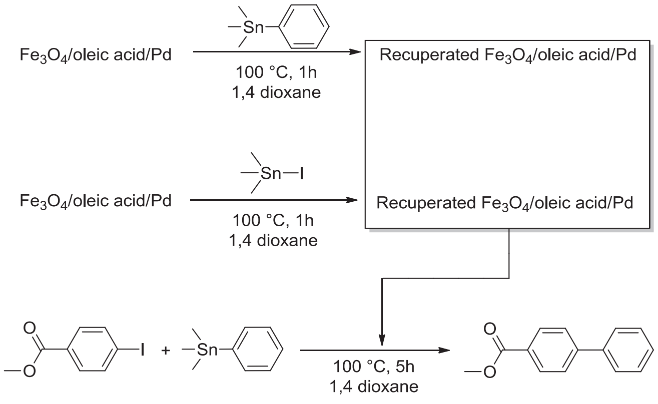


Fig. 11. Conversion of the Stille reaction in function of time at “optimal” solvent conditions. Methyl 4-iodobenzoate (1.44 mmol), trimethyl(phenyl)stannane (1.73 mmol), Fe_3O_4/oleic acid/Pd (8.0 mg), 1,4-dioxane (8.0 mL), temp: 100 °C, under argon atmosphere. ^{1}H NMR conversions are calibrated using 1,3,5-trimethoxybenzene as an internal standard.



Scheme 4. Experiments for investigation of catalyst poisoning with A) trimethyl(phenyl)stannane B) trimethyltin iodide.

4. Conclusion

In summary, it is possible to synthesize a less time consuming recyclable Pd catalyst by the use of commercially available stabilizers and Pd-sources, and without the use of toxic reducing agents. It is found that ligand-free palladium functionalized magnetite nanoparticles can be used in Suzuki cross-coupling reactions as well as in Sonogashira reactions under ligand-free and aerobic conditions. By varying the stabilizer present on the magnetite nanoparticle it is possible to make a nanoparticle that is suitable for the implementation in a reaction making use of an aprotic solvent, like the Sonogashira reaction, as well as it is possible to make them useable in a Suzuki reaction, which is a reaction using protic solvents. By analyzing the scope of the Suzuki reaction, it can be concluded that a substituent with a high affinity for the magnetite

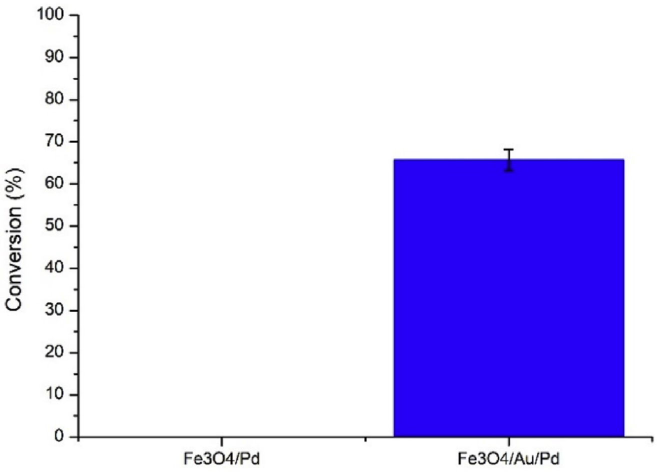


Fig. 12. Conversion obtained using Fe_3O_4/Pd compared with Fe_3O_4/Au/Pd using the model Sonogashira reaction. 1-(tert-butyl)-4-iodobenzene (0.18 mmol), phenylacetylene (1.8 mmol), KOAc (0.27 mmol), Pd functionalized nanoparticles, DMSO-d_6 (1.0 mL), temp: 30 °C, 4 h, under air. ^{1}H NMR conversions are calibrated using 1,3,5-trimethoxybenzene as an internal standard.

nanoparticle has a positive influence on the yield of the reaction. This phenomenon was not observed for the Sonogashira reaction. It should be noticed that although excellent yields are obtained in the Sonogashira reaction, harsh reaction conditions are necessary in comparison with the Suzuki reaction, resulting in higher temperatures and a higher catalyst loading. Although good yields were obtained in the Suzuki- and Sonogashira-reaction it can be concluded that it is not possible to use the as described Pd-functionalized nanoparticles in the Stille reaction. This was found to be due to poisoning of the catalytic system by the tin-reagent as by the tin by-product. The supported catalyst developed in the study also had the advantage of being recoverable with the simple application of a magnetic field. Furthermore, the influence of Au as co-catalyst is described and leads to a positive influence in the yield of the Sonogashira reactions, resulting in a reusable catalyst with short reaction times and low reaction temperatures. All these advantages make this an eco-friendly and economic catalyst for the use in Suzuki reactions and Sonogashira reactions with added value in achieving green chemistry goals.

Declaration of competing interest

The paper is not under consideration in any other journal. There is no declaration of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jorganchem.2019.121005.

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