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Magnetically induced Suzuki and Sonogashira reaction performed using recyclable, palladium-functionalized magnetite nanoparticles



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1. Introduction

Cross-coupling reactions are powerful and versatile tools in modern organic synthesis for the formation of mainly carboncarbon bonds. More specifically, palladium-catalyzed crosscoupling reactions have become of great importance over the last decades [1-3]. The importance was recognized by awarding the 2010 Chemistry Nobel Prize for "palladium-catalyzed cross couplings in organic synthesis" [4,5]. Over the past decades, significant progress has been achieved using a variety of homogeneous catalysts. Generally, homogeneous palladium catalysts are popular for their high selectivity, activity, and resistance towards poisons, but are difficult to recover and reuse. To overcome the fact that such catalysts cannot be used in large-scale synthesis for environmental and economic concerns, the application of reusable heterogeneous catalysts has attracted much attention due to the increasing momentum for the development of environmental friendly reactions. In this context, a lot of efforts have been made to synthesize

ABSTRACT

A magnetically reusable, ligand-free palladium functionalized Fe₃O₄ catalyst system was successfully prepared. To overcome current problems such as the recyclability of the nanoparticle and the control and safety of the reaction, full advantage of the magnetite support was used. The palladium functionalized magnetite nanoparticle was removed by precipitation using a permanent magnet, while local heating, around the catalytic site, was induced using an external magnetic field. It was found that it was possible to perform the Suzuki reaction resulting in good to excellent conversions under air, with a magnetic field strength of 210 G and a frequency of 160 kHz. Despite the good results for the Suzuki reaction, it was not possible to perform the Sonogashira reaction magnetically due to an insufficient heat generation around the catalytic site. Further, the reusable catalyst system was recycled and reused for five times, resulting in a separable and straightforward catalyst system with the advantage of having full control of the reaction. © 2019 Elsevier B.V. All rights reserved.

recoverable catalysts, but despite the many applications and various examples of such catalysts, a lot of improvement is still possible. The most important examples are Pd nanoparticles [6-8]and Pd immobilized on silica nanoparticles [9–12], carbon nanotubes [13,14], polymers [15–19], dendrimers [20–23] and graphene [24,25]. Furthermore, Pd has also been immobilized on metal oxides [26-28] and metal oxide nanoparticles [29-32]. Improvement of such heterogeneous catalysts has also been performed using halloysite nanotubes [33,34]. This system does not only show a high catalytic activity, but also exhibited excellent recyclability and low Pd leaching. One of the most used metal oxide nanoparticles are magnetite nanoparticles. By performing reactions with Pd functionalized magnetite nanoparticles and using its superparamagnetic property, it is easy to recover the catalyst by a magnet. This is in contrast with other nanoparticles, like silica or polymer nanoparticles, which can only be recovered by precipitation. A lot of the Pd functionalized magnetite nanoparticles make use of a difficult and time-consuming ligand synthesis [35-38]. To obtain an as easy as possible catalyst preparation, no ligands will be used. Palladium functionalized magnetite nanoparticles were used in previous work for the performance of Suzuki- and Sonogashirareactions. From this study it was concluded that the Suzuki reaction reached a conversion of 67% after 4 h at 60 °C, while the Sonogashira reaction was completed after 3 h at 100 °C. Nonetheless, many

Abbreviations: PEG, Poly(Ethylene Glycol); ICP-AES, Inductively Coupled Plasma Atomic Emission Spectroscopy.

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of these reported processes with heterogeneous catalysts require relatively elevated reaction temperatures resulting in the disadvantage of having poor control of the reaction. This disadvantage can be solved by making use of a local heating procedure, which can be achieved using magnetic induced heating. Magnetic induced heating can be achieved by applying an AC magnetic field onto a reaction mixture containing a Pd functionalized magnetite catalyst system. The local temperature at the catalytic site can be straightforwardly adjusted by changing the magnetic field. This allows full control of the reaction rate, which is an asset for production regulation, but also leads to a valuable safety feature as it prevents runaway reactions. In the case of magnetic local heating, runaway reactions can be stopped by simply switching off the magnetic field. The local temperature at the catalytic site will then drop rapidly below the required catalytic temperature aided by efficient cooling by the much colder reaction medium. In this way, full advantage is obtained using the superparamagnetic property of the Fe₃O₄ nanoparticles, at which the nanoparticle not only induce an easy way to recover the catalyst but also implements a heating procedure which is not only efficient but also provides a higher control and safety of the reaction. To study this effect, a ligand-free Pd functionalized magnetite nanoparticle will be implemented in the Suzuki- and the Sonogashira-reaction using magnetic induced heating, performed at relative low temperatures. As a reference a thermal reaction will be performed at the temperature obtained in the magnetic reactor. This comparison leads to the proof of principle of the magnetic induced reaction and by this result in a safe and excellent controlled reaction together with the advantage to recuperate the valuable Pd catalyst and make this protocol a valid candidate towards the goal of green chemistry. It should be mentioned that such study has never been performed using a low cost reusable catalyst resulting in an alternative heating method using an AC magnetic field. Not only will the reactions be performed using an easily reusable catalyst combined with an alternative heating source, they will also be executed under air in order to facilitate these reactions.

2. Experimental

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. Infrared spectra were recorded on a Bruker Alpha FT-IRspectrometer equipped with a Platinum ATR single reflection diamond ATR module. The ultrasonication bath used for the functionalization of the magnetite nanoparticle 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. For the magnetically induced reaction, an in-house built magnetic setup was used.

2.2. Pd functionalization of nanoparticles

Oleic acid stabilized Fe₃O₄ nanoparticles or poly(ethylene glycol) (PEG)-silane stabilized Fe₃O₄ nanoparticles in 1,4-dioxane are brought into a 100 mL flask. Its weight in palladium acetate is added accordingly, and the reaction mixture is brought under argon atmosphere. After stirring for four days, the mixture is transferred to a tarred vial. The nanoparticles are isolated by the influence of a magnetic field and subsequently washed three times with 1,4dioxane. The nanoparticles are 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 Information.

2.3. General procedure for the Suzuki-Miyaura couplings

To a 8 mL glass vial, the aryl halide (0.180 mmol), the boronic acid-compound (0.270 mmol), K_2CO_3 (0.360 mmol, 52.5 mg) and 1,3,5-trimethoxybenzene (0.180 mmol, 30.3 mg) are added. A dispersion of Fe₃O₄/PEG/Pd nanoparticles is made in EtOH (0.500 mL, 0.200 mg/mL) and this is added to the glass vial. After the addition of 0.500 mL H₂O, the reaction mixture is stirred for 4 h at 210 G with a frequency of 160 kHz. After stirring, the nanoparticles are isolated from the mixture with a magnet and the conversion, in respect to the desired end-product, is determined by ¹H NMR of the crude reaction mixture. 1,3,5-trimethoxybenzene is used as internal standard. For more detailed information: see Supplementary Information.

3. Results and discussion

3.1. Catalyst preparation

To produce the catalyst system, 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) (PEG) chain have a higher affinity for protic solvents compared to the oleic acid stabilized nanoparticles. It is known that Suzuki cross-coupling reactions perform better in the presence of water and require protic conditions [39], while Sonogashira crosscoupling reactions are performed in aprotic solvents. Therefore, polv(ethylene glycol) (PEG) stabilized nanoparticles will be used in the Suzuki reaction and oleic acid stabilized nanoparticles will be used in the Sonogashira reaction. The magnetite nanoparticle stabilized with oleic acid are synthesized using the method of Chen et al. [40] The PEG-silane stabilized magnetite nanoparticles are also synthesized using a procedure found in literature resulting in monodisperse and water-soluble nanoparticles [41]. Both type of nanoparticles are characterized using Transmission Electron Microscopy (TEM) (Fig. 1). As depicted in Fig. 1 the PEG stabilized magnetite nanoparticles as well as the oleic acid stabilized have a size of approximately 20 nm and show a relative low size distribution. Statistical analysis of the oleic acid stabilized nanoparticles are included in Fig. S1 and result in a mean size of 19.1 ± 1.7 nm. In addition, to prove the presence of the stabilizer on the nanoparticle, FT-IR spectra were recorded of the oleic acid and PEG stabilized



Fig. 1. TEM image of oleic acid (left) and PEG (right) functionalized iron oxide nanoparticles.

nanoparticles together with the corresponding stabilizer (Fig. 2 and Fig. 3). From Figs. 2 and 3 there can be derived that the stabilizer, which are respectively oleic acid and PEG, are attached onto the magnetite nanoparticle. The functionalization of these nanoparticles with Pd is done using the same procedure for all types of nanoparticles (Scheme 1). Therefore, Pd(OAc)₂ is stirred together with the nanoparticles in 1.4-dioxane for 4 days under argon atmosphere. Note that our approach does not use any reducing reagents or surface modification employing the reducing nature and coordinating ability of the Fe₃O₄ support [39]. The amount of Pd present on the different types of catalyst systems is determined using inductively coupled plasma - atomic emission spectroscopy (ICP-AES), (Table 1) resulting in 0.080 mg Pd/mg Fe₃O₄/PEG/Pd nanoparticles and 0.014 mg Pd/mg Fe₃O₄/oleic acid/Pd nanoparticles. It should be mentioned that the amount of Pd varies with the type of nanoparticle used. The fact that the amount of Pd on a PEG stabilized nanoparticle is higher compared to the oleic acid stabilized nanoparticle can be explained by the difference in the stabilizer. The Pd, originating from Pd²⁺, will be easier inserted



Fig. 2. FT-IR spectrum of Fe_3O_4 nanoparticles functionalized with oleic acid (Fe_3O_4 / oleic acid NPs) (black) and oleic acid (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



Fig. 3. FT-IR spectrum of Fe_3O_4 nanoparticles functionalized with PEG-silane (Fe_3O_4 / PEG NPs) (black) and PEG-silane (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)



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

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 ₃ O ₄ /PEG/Pd	0.080	7.5
Fe ₃ O₄/oleic acid/Pd	0.014	1.3

inside the PEG stabilizer and by this making more direct contact with the magnetite nanoparticle due to the higher polarity of the PEG stabilizer. This in contrast with the oleic acid stabilizer which explains the difference in Pd amount present on the nanoparticle.

3.2. Suzuki cross-coupling reactions

The reaction of 4-bromophenol with phenyl boronic acid is used for initial studies as a model reaction and is carried out in the presence of K_2CO_3 , which is a base resulting in a high conversion and is applied in many Suzuki reactions (Scheme 2) [42–46].

The reason for the choice of 4-bromophenol as substrate is because in the previous study there has been concluded that, due to the presence of K₂CO₃, 4-bromophenol is deprotonated resulting in a phenolate. This phenolate has a high affinity for the magnetite nanoparticle, resulting in a higher conversion compared to a similar electron-donating group like methoxy (4-bromoanisole). Due to this effect, it is possible that a large difference can be depicted between the magnetically induced reaction and the corresponding thermal reaction. Because, when the hypothesis is correct, the substrate will not only be closer to the catalyst but also closer to the heating source, resulting in an even higher conversion for the magnetically induced reaction compared to the corresponding thermal reaction, which is performed at the same temperature as measured inside the reaction vial during the magnetic reaction. The solvent chosen for this reaction was an EtOH/H₂O (1:1) mixture, which according to Vienot et al. result in optimal conditions [39]. The presence of water in the reaction mixture is the reason for the use of PEG-stabilized Pd-functionalized magnetite nanoparticles (Fe₃O₄/PEG/Pd).

First, the proof of principle is given using the magnetically induced model reaction together with the thermal reaction, performed at the same temperature as that of the bulk during the magnetically induced reaction in function of time (Fig. 4).

As is depicted in Fig. 4, the magnetically induced reaction tends to stop after 4 h, and a difference of 44% of conversion is displayed between the magnetic induced and the corresponding thermal contribution. The thermal contribution is obtained performing a reaction under the same conditions as the magnetic reaction, but using the temperature measured inside the reaction vial of the magnetically induced reaction, which was 32 °C, but without the



Scheme 2. Model reaction used for investigation of the magnetic induced Suzuki reaction.



Fig. 4. Conversion in function of time for the magnetic induced Suzuki reaction (black) and the thermal contribution (red). 4-Bromophenol (0.18 mmol), phenylboronic acid (0.27 mmol), K₂CO₃ (0.36 mmol), Fe₃O₄/PEG/Pd (0.2 mg), EtOH/H₂O (1:1) (1.0 mL), under air. Applied frequency: 160 kHz, applied magnetic field: 210 G (black). Reaction temperature: $32 \degree C$ (red). The reaction was monitored by ¹H NMR. ¹H NMR conversions were determined using 1,3,5-trimethoxybenzene as an internal standard. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

presence of an external magnetic field. This means that the use of an external magnetic field resulted in an increase of approximately 7 °C inside the reaction vial. To obtain stronger evidence of this principle, the magnetic induced and the corresponding thermal reaction is performed in triple and error bars are added resulting in an average difference of 49% of conversion (Fig. 5).

As the Suzuki reaction is largely affected by the amount of catalyst, the reaction conditions are optimized using the model reaction (Fig. 6). Since no conventional heat is used during the magnetically induced reaction, not the influence of the temperature will be examined but the influence of the magnetic field and the applied frequency (Fig. 7).

As evident from Fig. 6, a catalyst loading of 0.1 mg of $Fe_3O_4/PEG/Pd$ nanoparticles in 1 mL is optimal and will be used in future reactions. It is depicted that there is only a small influence of catalyst loading using magnetically induced heating with a magnetic field



Fig. 5. Proof-of-principle of the magnetic induced Suzuki reaction and the thermal contribution.



Fig. 6. Effect of the amount of Fe₃O₄/PEG/Pd on the magnetic induced Suzuki crosscoupling. 4-Bromophenol (0.18 mmol), phenylboronic acid (0.27 mmol), K₂CO₃ (0.36 mmol), Fe₃O₄/PEG/Pd, EtOH/H₂O (1:1) (1.0 mL), under air. Applied frequency: 160 kHz, applied magnetic field: 210 G. The reaction was monitored by ¹H NMR. ¹H NMR conversions were determined using 1,3,5-trimethoxybenzene as an internal standard.



Fig. 7. Influence of the magnetic field strength and frequency on the magnetic Suzuki reaction (black) and the thermal contribution (red). 4-Bromophenol (0.18 mmol), phenylboronic acid (0.27 mmol), K_2CO_3 (0.36 mmol), $Fe_3O_4/PEG/Pd$ (0.1 mg), EtOH/H₂O (1:1) (1.0 mL), under air. The reaction was monitored by ¹H NMR. ¹H NMR conversions were determined using 1,3,5-trimethoxybenzene as an internal standard. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of 210 G and a frequency of 160 kHz. Although a drop in conversion is observed when a catalyst loading is applied lower than 0.05 mg of nanoparticles in 1 mL and it should also be mentioned that a catalyst loading of 0.05 mg of nanoparticles in 1 mL results in a conversion decrease of 10% compared to 0.1 mg of nanoparticles. Therefore, using an amount of 0.1 mg of Fe₃O₄/PEG/Pd nanoparticles, a Pd amount is present of only 0.42 10^{-3} mol% in the reaction mixture.

In Fig. 7 the influence is given of the magnetic field strength and the frequency of the magnetic field on the reaction yield. The contribution of the thermal effect is also depicted. It can be concluded that by increasing the strength and/or the frequency of the magnetic field an increase in reaction yield is observed. Despite this increase, a higher contribution of the thermal effect is noticed when either one or both parameters are increased. This can be due to two factors. Firstly, by increasing the strength of the frequency or the magnetic field, the coil will heat up by a few degrees, which has a direct result in a higher temperature inside the reaction vial. Secondly, it can also increase the temperature generated by the nanoparticle, resulting in a higher temperature of the reaction medium due to the thermal convection of the heat generated at the nanoparticle to the reaction mixture. The optimal conditions resulting in a high conversion with a low contribution of the thermal effect are obtained using a magnetic field strength of 210 G with a frequency of 160 kHz. To examine the magnetically induced Suzuki reaction, these conditions are used, resulting in a high difference between the magnetically induced reaction and the thermal contribution.

With the optimized conditions in hand, the magnetically induced reaction performance of Fe₃O₄/PEG/Pd for various substrates is investigated. All the reactions were carried out at 210G and 160 kHz under air using K₂CO₃ as the base and EtOH/H₂O (1:1) as the reaction medium, with a catalyst loading of 0.1 mg of nanoparticles, resulting in a Pd amount of 0.42 10^{-3} mol%. The

results are summarized in Table 2.

The cross-coupling reactions of aryl halides with phenyl boronic acids afforded mostly the desired biaryls. The only exceptions are the chlorinated substrates and the highly sterically hindered 2bromotoluene (Table 2; Entry 5, 6 and 8). It should be mentioned that not all substrates result in an as efficient reaction as the reaction using 4-bromophenol. By introducing more steric hindrance on the arvl bromide the yield decreases (Table 2: Entry 3, 7 and 8). This was also noticed for the use of an electron-donating methoxyor amine group (Table 2; Entry 9 and 11). Very interesting results are shown when a comparison is made between entry 4 and 9 (Table 2). All two are strong electron donating groups but there is a large difference in conversion between these groups. Actually, by the presence of the base, the phenol is deprotonated to the phenoxide and is even more electron donating, which should result in an even lower conversion. 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

Table 2

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

$R_1 \xrightarrow{HO} X + HO = R_2 \xrightarrow{HO} R_2 O_4/PEG/Pd \xrightarrow{R_2O_3.EtOH/H_2O(1:1)} R_1$					
Entry	Reactant 1	Reactant 2	Magnetic conversion ^b	Thermal conversion ^b	
1		HO B HO	21%	0%	
2	но-	HO B HO	72%	24%	
3	——————————————————————————————————————	HO B HO	15%	0%	
4	HO-	HO HO	74%	24%	
5	<->-ci	HO B	0%	0%	
6	HO-CI	HO B-	0%	0%	
1	Br	HO B-	5%	0%	
8	Br	HO B HO	0%	0%	
9	O-Br	HO HO	1%	1%	
10	O ₂ N-	HO B HO	87%	8%	
11	H ₂ N-	HO B HO	8%	0%	
12	HO HO	HO B HO	42%	13%	
13	HO-Br		69%	24%	
14	HO	HO B-CF ₃ HO	5%	υ%	

^aReaction conditions: reactant 1 (0.18 mmol), reactant 2 (0.27 mmol).

K₂CO₃ (0.36 mmol), Fe₃O₄/PEG/Pd (0.1 mg), EtOH/H₂O (1:1).

(1.0 mL), magnetic field strength: 210 G, frequency: 160 kHz, 4 h, under air. ^{b1}H NMR conversions were determined using 1,3,5-trimethoxybenzene as an internal standard. nanoparticles, the binding brings the substrate in closer proximity to the catalytic system and to the heating source resulting in a higher yield compared to 4-bromoanisole for which no deprotonation can occur. Because the substrate is not only closer to the catalyst system, but also closer to the heating source, an even higher conversion is obtained for the magnetic heating compared to the thermal contribution. The electronic nature of substituents of aryl boronic acid was also investigated. The results show that aryl boronic acids bearing either electron-donating groups or electronwithdrawing 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 electronwithdrawing group on the aryl boronic acid species. This results in an opposite effect compared to the aryl halide.

Recycling of the heterogeneous catalyst system is important from both the economic and environmental points of view. The reusability of the Fe₃O₄/PEG/Pd nanoparticles is examined using the optimized model reaction at 210 G and 160 kHz with a reaction time of 4 h. The results are illustrated in Fig. 8. The catalyst was used for five runs, in which each run the conditions are kept identical. After each run, the catalyst was separated by an external magnet, and the resulting supernatant can be decanted. This minimizes the loss of catalyst during separation. The catalyst system is then subsequently washed 3 times with 2 mL ethanol and 1 time with water. After being dried, the catalyst system could be reused directly without further purification. As shown in Fig. 8 the catalyst can be reused at least 5 times, although with a linear loss in activity over the various cycles. At the 5th reaction, a conversion of only 27% was obtained. It should be mentioned that the amount of nanoparticles after each recuperation was taken into account. This means that the amount of starting reagents and solvents are adapted to the amount of nanoparticles present after the recuperation step. Due to this procedure, the loss in conversion cannot be the cause of the loss of Fe₃O₄/PEG/Pd nanoparticles during the recuperation step, but can only be due to a change in the composition of the Fe₃O₄/PEG/Pd nanoparticles. This means that the loss in activity is the result of Pd leaching of the catalyst system, which is confirmed using ICP-AES measurements after each run (Supplementary Information Table S1).

To get a better insight of the temperature at the catalytic site, a comparison is made between the conversion obtained using



3.3. Sonogashira cross-coupling reaction

A second cross-coupling reaction investigated with the palladium-functionalized Fe_3O_4 catalyst is the Sonogashira reaction. In previous work a method was developed using a Cu-free and aerobic reaction, resulting in a reaction time of only 3 h possible for a wide range of substrates (Scheme 3).

Therefore, the same conditions are used for the examination of the Sonogashira reaction performed with a magnetic field as the same Pd functionalized oleic acid stabilized Fe_3O_4 catalyst is used. As already mentioned, the magnetic reactor has an adaptable frequency of the magnetic field. Also, each frequency has a certain magnetic field strength range. To determine whether the reaction has a possibility to succeed, a maximum magnetic field was used at different frequencies, thus generating maximum heat around the nanoparticle. Accordingly, the same reaction, using 1-(*tert*-butyl)-4-iodobenzene and phenylacetylene in air, with KOAc as a base and DMSO- d_6 as solvent, is attempted for various frequencies, each time at the maximal magnetic field strength obtainable with the magnetic reactor. These results are shown in Table 3.

The results of the reactions with altering the frequency and magnetic field show that the catalysis by magnetic heating is not accomplished. The reaction with a frequency of 107 kHz at the highest magnetic field gives no conversion. A frequency of 160 kHz with a magnetic field of 210 G are the optimal conditions for our nanoparticles, as this gave the best results in the Suzuki reaction, but the reaction at this frequency gives no adequate results. Also, no conversion to the end-product is detected in the reactions conducted at a frequency of 240 kHz and 350 kHz at maximum







Fig. 9. Comparison between the conversion using magnetic induction (black) and thermal heating (red). 4-Bromophenol (0.18 mmol), phenylboronic acid (0.27 mmol), K_2CO_3 (0.36 mmol), $Fe_3O_4/PEG/Pd$ (0.1 mg), EtOH/H₂O (1:1) (1.0 mL), under air. The reaction was monitored by ¹H NMR. ¹H NMR conversions were determined using 1,3,5-trimethoxybenzene as an internal standard. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Scheme 3. Model reaction used for investigation of the magnetic induced Sonogashira reaction.

Table 3

Magnetic induced Sonogashira reaction with different magnetic field strength and frequency.

Frequency (kHz)	Magnetic field (G)	Conversion ^b
350	170	0%
230	210	0%
160	210	0%
106	260	0%

^aKOAc (0.27 mmol), Fe₃O₄/oleic acid/Pd (2.0 mg), DMSO-*d*₆ (1.0 mL), 4 h, 1-(*tert*butyl)-4-iodobenzene (0.18 mmol), phenylacetylene (1.8 mmol).

^{b1}H NMR conversions were determined using 1,3,5-trimethoxybenzene as an internal standard.

magnetic field. Although all possible frequencies attainable with the magnetic reactor are investigated, no reaction is achieved with local heating by magnetic induction.

Knowing that there is indeed an effect of the substrate in the Suzuki cross-coupling reaction, 4-iodophenol is used as substrate to examine the possibility for the magnetic induced Sonogashira reaction (Scheme 4). Therefore, 4-iodophenol and phenylacetylene are used, with KOAc as a base and DMSO- d_6 as reaction medium. Although no positive results are obtained for the Sonogashira reaction and resulted in a conversion of 0%.

The employed frequencies and magnetic field strengths are not sufficient to generate a temperature high enough at the catalytic site. Consequently, the catalysis by magnetic induction is impossible with the use of the magnetically recoverable particles for Sonogashira reactions. The reason for this large difference between the Suzuki and the Sonogashira reaction can be derived from our previous work. From these results, it can be concluded that the Sonogashira reaction needs a much higher temperature compared to the Suzuki reaction. The Suzuki reaction was already possible at room temperature, while the Sonogashira reaction only reached full conversion at 100 $^\circ\text{C}$ after a reaction time of 3 h, and no conversion was detected at low temperatures. This indicates that Sonogashira reactions requires much harsher conditions compared to the Suzuki reaction using our catalyst system. Combining the results obtained in this work and previous work it can be concluded that insufficient high temperatures were created at the substrate, resulting in a limitation of reactions dependent on their required reaction temperature.

4. Conclusion

In summary, it is found that an alternating magnetic field can efficiently enhance the performance of a Pd functionalized magnetite nanoparticle in the Suzuki reaction, while keeping the reaction medium at relatively low temperatures. This results in the applicable advantage of increasing the control and safety of the reaction. Furthermore, due to the magnetite nanoparticle, the catalyst can easily be recovered and reused. It is found that an optimal result was achieved using a magnetic field of 210 G with a



Scheme 4. Investigation of the magnetic induced Sonogashira reaction using 4-iodophenol.

frequency of 160 kHz and that a temperature of around 60 °C was reached at the catalytic site. Although, it should be mentioned that not all substrates give rise to high conversions. Only substrates having an affinity for a magnetite nanoparticle result in high conversion. Despite the results obtained for the Suzuki reaction, it can be concluded that no magnetically induced reaction is possible for the Sonogashira reaction, which can be explained by the fact that Sonogashira reactions are only possible at high temperatures using our catalyst system.

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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.2019.120905.

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