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FULL PAPER

S-Benzylisothiourea complex of palladium on magnetic nanoparticles: A highly efficient and reusable nanocatalyst for synthesis of polyhydroquinolines and Suzuki reaction

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S-Benzylisothiourea complex of palladium supported on modified Fe_3O_4 magnetic nanoparticles (Pd-SBTU@Fe_3O_4) is reported for carbon–carbon coupling through the Suzuki coupling reaction. Also, the synthesis of polyhydroquinoline derivatives is reported in the presence of Pd-SBTU@Fe_3O_4 as nanocatalyst. The prepared nanoparticles were characterized using Fourier transform infrared spectroscopy, thermogravimetric analysis, scanning electron microscopy, vibrating sample magnetometry and inductively coupled plasma atomic emission spectroscopy. The nanocatalyst was easily recovered using an external magnet and reused several times without significant loss of its catalytic efficiency. The heterogeneity of Pd-SBTU@Fe_3O_4 was studied using hot filtration.

KEYWORDS

magnetic nanoparticle, palladium, polyhydroquinoline, Suzuki reaction

1 | INTRODUCTION

In green catalytic reactions, the recovery and reuse of catalysts is an important factor for ecological and economic demands.[1] Nanoparticles have recently emerged as recoverable and efficient supports for the immobilization of homogeneous catalysts.[2] However, particles with diameters of less than 100 nm are difficult to separate by filtration. In such cases, expensive ultracentrifugation is often the only way to separate product and catalyst.[3] This drawback can be overcome by using magnetic nanoparticles, which can be rapidly separated from a reaction mixture using an external magnet.[1] More importantly, magnetic separation is more effective and easier than filtration or centrifugation.[4] Fe_3O_4 magnetic nanoparticles are efficient, non-toxic, readily available, low cost, simply synthesized and of high surface area resulting in high catalyst loading capacity for immobilization of homogeneous catalysts.[5] Therefore, Fe_3O_4 nanoparticles are considered as ideal supports for the heterogenization of homogeneous catalysts.[6,7]

Therefore in the work reported here, a moisture- and air-stable catalyst of *S*-benzylisothiourea complex of palladium supported on modified Fe_3O_4 magnetic nanoparticles (Pd-SBTU@Fe_3O_4) was synthesized and characterized as a new organometallic catalyst for the synthesis of polyhydroquinoline derivatives and carbon–carbon coupling reactions. Carbon–carbon coupling reactions are used as an interesting method in modern synthesis of natural products, agrochemicals, pharmaceuticals, herbicides, biologically active compounds, polymers and advanced materials.[8–10] Also, polyhydroquinoline derivatives have a wide range of biological properties and pharmaceutical activities such as hepatoprotective, vasodilator, anti-atherosclerotic, anti-tumour, anti-diabetic, geroprotective and bronchodilator activities, and also they have the ability to modulate calcium channels.[11–15]

2 | EXPERIMENTAL

2.1 | Preparation of catalyst

The Fe_3O_4 nanoparticles modified with 3-choloropropyltriethoxysilane (CPr-Si@Fe_3O_4) were prepared according to our recently reported procedure.[16] Then CPr-Si@Fe_3O_4 (1 g) was dispersed in 25 ml of ethanol, and

S-benzylisothiourea (2 mmol) and K_2CO_3 (2 mmol) were added to the reaction mixture and stirred for 24 h under reflux. The resulting nanoparticles (SBTU@Fe_3O_4) were separated by magnetic decantation, washed with ethanol and dried at room temperature. Then, SBTU@Fe_3O_4 (0.5 g) was dispersed in ethanol, and $Pd(OAc)_2$ (0.25 g) was added and stirred for 20 h under reflux. Finally, $NaBH_4$ (0.5 mmol) was added to the reaction mixture and was allowed to run for another 2 h. The final nanoparticles (Pd-SBTU@Fe_3O_4) were separated by magnetic decantation, washed with ethanol and dried at room temperature.

2.2 | General procedure for suzuki reaction

A mixture of aryl halide (1 mmol), phenylboronic acid (1 mmol), K_2CO_3 (3 mmol) and Pd-SBTU@Fe_3O_4 (0.005 g) was added to a reaction vessel. The resulting mixture was stirred in poly(ethylene glycol) (PEG) at 60 °C. After completion of the reaction (monitored by TLC), the catalyst was separated using an external magnet and washed with ethyl acetate. The reaction mixture was extracted with water and ethyl acetate and dried over anhydrous Na_2SO_4 (1.5 g). Then the solvent was evaporated and pure biphenyl derivatives were obtained in good to excellent yields.

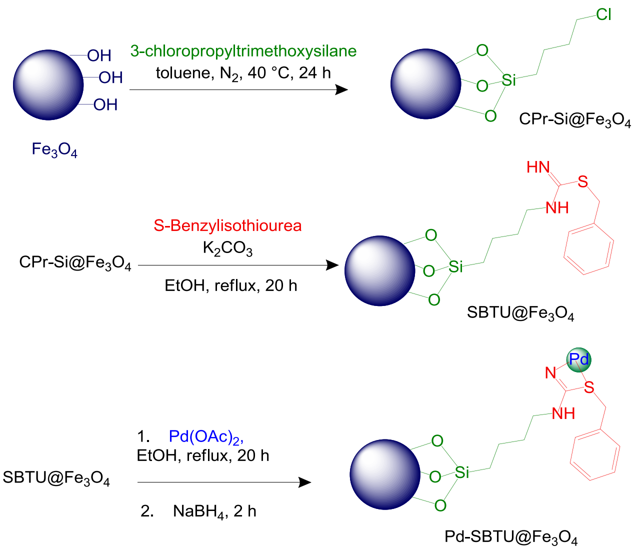
2.3 | General procedure for synthesis of polyhydroquinoline derivatives

A mixture of aldehyde (1 mmol), dimedon (1 mmol), ethylacetoacetate (1 mmol), ammonium acetate (1.2 mmol) and Pd-SBTU@Fe_3O_4 (0.01 g) was stirred in PEG at 80 °C and the progress of the reaction was monitored by TLC. After completion of the reaction, the catalyst was separated using an external magnet and washed with ethanol. Then, the solvent was evaporated and all products were recrystallized from ethanol. The pure polyhydroquinoline derivatives were obtained in good to excellent yields.

3 | RESULTS AND DISCUSSION

3.1 | Catalyst preparation

In continuation of our studies of the preparation of supported magnetic nanocatalysts,[17,18] herein we describe a new palladium complex immobilized on Fe_3O_4 as a reusable catalyst. Initially, CPr-Si@Fe_3O_4 was prepared according to a reported procedure[16] and, for the the preparation of SBTU@Fe_3O_4, *S*-benzylisothiourea was grafted on CPr-Si@Fe_3O_4 via substitution reaction of NH with terminal Cl groups. Finally, the catalyst was synthesized by reaction of SBTU@Fe_3O_4 with $Pd(OAc)_2$ (Scheme 1). This catalyst was characterized using Fourier transform infrared (FT-IR) spectroscopy, thermogravimetric analysis (TGA), scanning electron microscopy (SEM), vibrating sample magnetometry (VSM) and inductively coupled plasma atomic emission spectroscopy (ICP-OES).



SCHEME 1 Synthesis of Pd-SBTU@Fe_3O_4

3.2 | Catalyst characterization

The size and morphology of Pd-SBTU@Fe_3O_4 were studied using SEM. The SEM image of Pd-SBTU@Fe_3O_4 shows that the catalyst is formed of nanometre-sized particles, quasi-spherical, with an average diameter of about 20 ± 5 nm (Figure 1).

Also, we determined the exact amount of Pd on the magnetic nanoparticles using ICP-OES. The amount of Pd in Pd-SBTU@Fe_3O_4 is found to be 1.87×10^{-3} mol g^{-1}.

In order to investigate the presence of Pd complex on Fe_3O_4 magnetic nanoparticles, TGA/differential thermal analysis (DTA) was performed. The TGA curve of

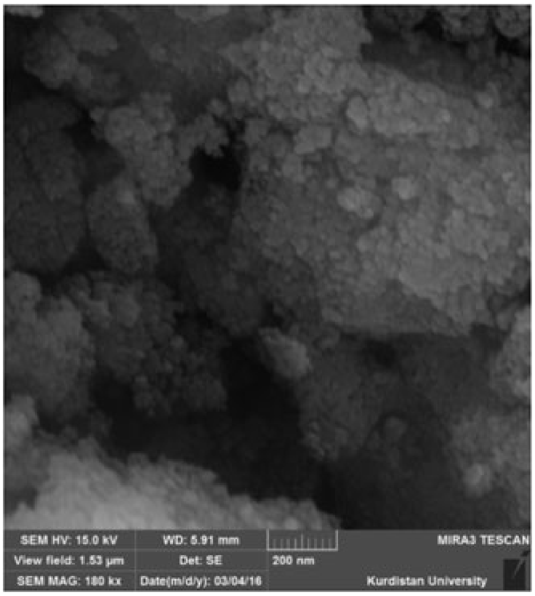


FIGURE 1 SEM image of Pd-SBTU@Fe_3O_4

Pd-SBTU@Fe_3O_4 shows a mass loss of the organic functional groups as it decomposes upon heating (Figure 2). The TGA curve shows a small amount of weight loss below 200 °C that is related to removal of adsorbed solvents. Also, a weight loss of about 9% from 200 to 500 °C is due to the decomposition of organic species on Fe_3O_4 surface. On the basis of this result, the good grafting of organic groups including the palladium complex on the Fe_3O_4 is verified.

Figure 3 shows the FT-IR spectra of Fe_3O_4 nanoparticles, CPr-Si@Fe_3O_4, SBTU@Fe_3O_4 and Pd-SBTU@Fe_3O_4. The FT-IR spectrum of Fe_3O_4 (Figure 3a) shows strong bands at 3393 cm^{-1}, which correspond to surface O—H bonds.[17] In all the FT-IR spectra, several peaks appear at 582 and 443 cm^{-1} which result from stretching vibration of Fe—O bonds in Fe_3O_4 nanoparticles.[11] In the FT-IR spectrum of CPr-Si@Fe_3O_4 (Figure 3b), the anchored 3-choloropropyltriethoxysilane is confirmed by C—H stretching vibrations at 2926 cm^{-1} and also O—Si stretching vibration modes at 1044 cm^{-1}.[17] In the FT-IR spectrum of SBTU@Fe_3O_4 (Figure 3c), the presence of the immobilized SBTU groups is indicated by C=N vibrations (1621 cm^{-1}). This band is shifted to lower frequency (1616 cm^{-1}) in the spectrum of Pd-SBTU@Fe_3O_4 (Figure 3d), which indicates the formation of the palladium complex on surface of functionalized nanoboehmite.[6]

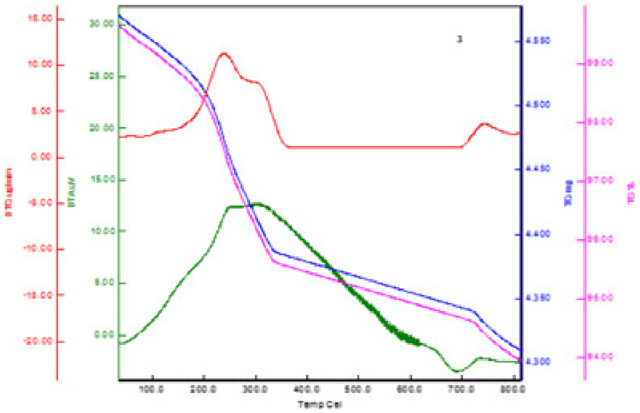


FIGURE 2 TGA/DTA curves of Pd-SBTU@Fe_3O_4

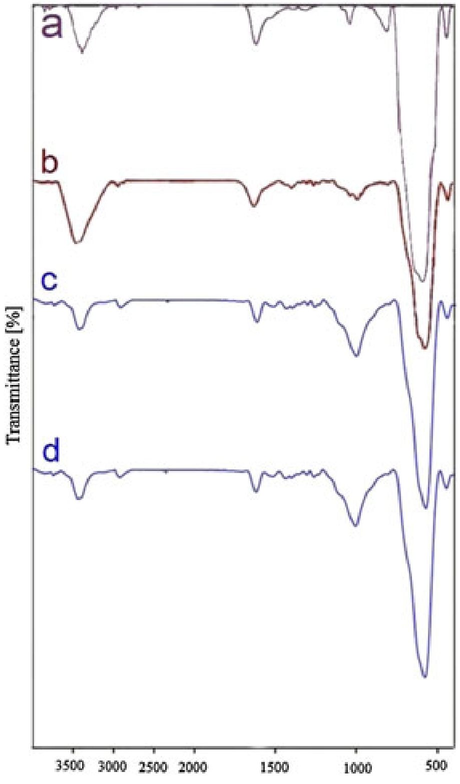


FIGURE 3 FT-IR spectra of (a) Fe_3O_4, (b) CPr-Si@Fe_3O_4, (c) SBTU@Fe_3O_4 and (d) Pd-SBTU@Fe_3O_4

The magnetic property of Pd-SBTU@Fe_3O_4 was studied using VSM. The room temperature magnetization analysis of the catalyst is shown in Figure 4. The magnetic measurement shows that Pd-SBTU@Fe_3O_4 has a saturation magnetization (M_s) value of 49.88 emu g^{-1}. The M_s value of the catalyst is lower than that of Fe_3O_4 nanoparticles, which is due to the organic layer and Pd complex on the surface of the Fe_3O_4 nanoparticles (39.1 emu g^{-1}).[11]

3.3 | Catalytic activity of Pd-SBTU@Fe_3O_4 in C—C coupling reactions

After synthesis and characterization of the catalyst, it was applied in carbon–carbon bond formation of the Suzuki reaction using the coupling of various aryl halides with phenylboronic acid (Scheme 2).

In order to optimize the reaction conditions, the coupling of 4-bromotoluene with phenylboronic acid in the presence of various amounts of Pd-SBTU@Fe_3O_4 was selected as a model reaction (Table 1, entries 1–6). The reaction does

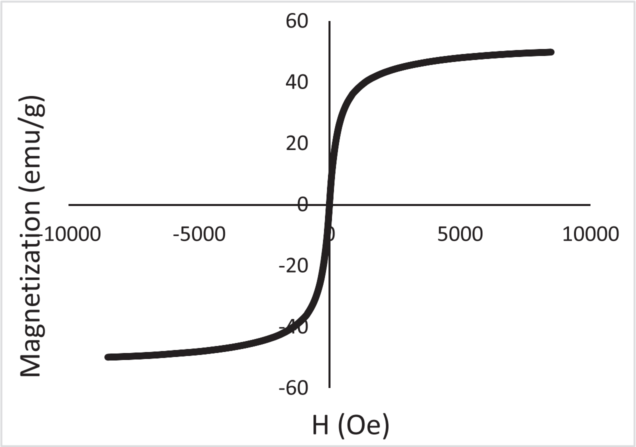
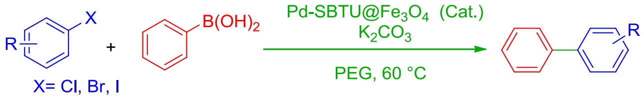


FIGURE 4 Magnetization curve for Pd-SBTU@Fe_3O_4 at room temperature



SCHEME 2 Pd-SBTU@Fe_3O_4-catalysed Suzuki reaction

TABLE 1 Optimization of reaction conditions for the C─C coupling reaction of 4-bromotoluene with $PhB(OH)_2$ in presence of Pd-SBTU@Fe_3O_4 at 60 °C

Entry	Catalyst (mg)	Solvent	Base	Amount of base (mmol)	Time (min)	Yield (%)[a]
1	—	PEG	K_2CO_3	3	100	—[b]
2	3	PEG	K_2CO_3	3	70	80
3	5	PEG	K_2CO_3	3	45	93
4	7	PEG	K_2CO_3	3	40	96
5	10	PEG	K_2CO_3	3	30	95
6	14	PEG	K_2CO_3	3	15	96
7	5	H_2O	K_2CO_3	3	45	26
8	5	DMF	K_2CO_3	3	45	37
9	5	PEG	NaOEt	3	45	69
10	5	PEG	Na_2CO_3	3	45	90
11	5	PEG	Et_3N	3	45	69
12	5	PEG	KOH	3	45	46
13	5	PEG	K_2CO_3	1.5	45	64

[a] Isolated yield.

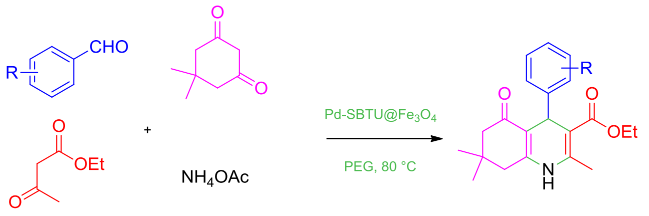
[b] No reaction.

not proceed in the absence of Pd-SBTU@Fe_3O_4 (Table 1, entry 1). Also the model reaction was examined in various solvents such as water, PEG and dimethylformamide (DMF) (Table 1, entries 6–8) and various bases such as K_2CO_3, NaOEt, KOH, Et_3N and Na_2CO_3 (Table 1, entries 9–12). As evident from Table 1, the best results are obtained using K_2CO_3 (3 mmol) in PEG-400 and in the presence 0.005 g of catalyst at 60 °C. Decreasing the amount of K_2CO_3 from 3 to 1.5 mmol leads to a decrease in yield of product from 93 to 69% (Table 1, entry 13).

After optimization of the reaction conditions, we examined the catalytic activity of Pd-SBTU@Fe_3O_4 for various aryl halides including chloride, bromide and iodide and the results are summarized in Table 2. The experimental method is simple and has the ability to tolerate a variety of electron-donating and electron-withdrawing functional groups such as CHO, NO_2, CN, OCH_3 and CH_3. Therefore, the results reveal that this procedure is effective for a wide range of aryl halides.

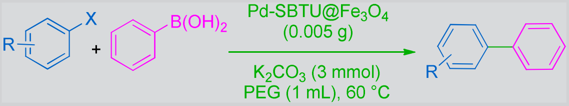
To extend the scope of our work, we next investigated the catalytic activity of Pd-SBTU@Fe_3O_4 for the synthesis of polyhydroquinoline derivatives (Scheme 3). In order to optimize the reaction conditions, the reaction of 4-chlorobenzaldehyde, dimedon, ethylacetoacetate and ammonium acetate (NH_4OAc) was selected as a model reaction. The effect of solvents and amount of Pd-SBTU@Fe_3O_4 were studied in the model reaction (Table 3). As evident from Table 3, 0.01 g of Pd-SBTU@Fe_3O_4 in PEG at 80 °C are found to be optimized reaction conditions for the outcome of the model reaction. While increasing the amount of catalyst (from 10 to 12 mg) has no significant effect on the model reaction.

Then, we extended the reaction to a variety of aldehydes with dimedon, ethylacetoacetate and ammonium acetate to confirm the generality of the present method.



SCHEME 3 Pd-SBTU@Fe_3O_4-catalysed one-pot synthesis of polyhydroquinoline derivatives

TABLE 2 Catalytic C─C coupling reaction of aryl halides with $C_6H_5B(OH)_2$ in presence of catalytic amounts of Pd-SBTU@Fe_3O_4



Entry	Aryl halide	Time (min)	Yield (%)[a]	Melting point (°C)
1	Iodobenzene	420	92	67–68
2	Bromobenzene	120	90	66–68
3	4-Iodotoluene	300	89	42–43
4	4-Bromotoluene	45	93	42–43
5	4-Bromobenzaldehyde	150	98	53–54
6	3-Bromobenzaldehyde	120	86	Oil
7	4-Iodoanisole	120	85[b]	83–85
8	4-Bromoanisole	180	90[b]	82–84
9	3-Bromoanisole	240	80[b]	Oil
10	4-Bromochlorobenzene	70	94	69–71
11	4-Chlorobenzonitrile	120	96	82–84
12	4-Bromonitrobenzene	120	99	113–115
13	4-Chloronitrobenzene	1440	50	108–111

[a] Isolated yield.

[b] Reaction conditions: aryl halide (1 mmol), Pd-SBTU@Fe_3O_4 (8 mg), $C_6H_5B(OH)_2$ (1 mmol) and K_2CO_3 (3 mmol) in PEG at 80 °C.

TABLE 3 Optimization of conditions for synthesis of polyhydroquinolines in presence of Pd-SBTU@Fe_3O_4

Entry	Solvent	Catalyst (mg)	Temperature (°C)	Time (min)	Yield (%)[a]
1	PEG	8	80	140	69
2	PEG	10	80	140	95
3	PEG	12	80	120	95
4	Ethanol	10	80	155	91
5	Ethyl acetate	10	80	140	55
6	H_2O	10	80	140	64
7	PEG	10	60	140	32

[a] Isolated yield.

TABLE 4 Synthesis of polyhydroquinolines catalyzed by Pd-SBTU@Fe_3O_4 in PEG

Entry	Aldehyde	Time (min)	Yield (%)[a]	Melting point (°C)
1	4-Methylbenzaldehyde	75	90	254–256
2	Benzaldehyde	160	92	216–218
3	4-Methoxybenzaldehyde	300	89	249–250
4	4-Ethoxybenzaldehyde	320	90	176–178
5	4-Bromobenzaldehyde	300	89	247–248
6	4-Fluorobenzaldehyde	150	94	184–186
7	4-Hydroxybenzaldehyde	150	90	230–232
8	3-Hydroxybenzaldehyde	420	90	228–230
9	3,4-Dimethoxybenzaldehyde	240	87	200–202
10	4-Chlorobenzaldehyde	140	95	235–237
11	3-Nitrobenzaldehyde	480	79	173–175

[a] Isolated yield.

Polyhydroquinoline derivatives are obtained in high yields. The results of this study are summarized in Table 4. As is evident, a variety of benzaldehydes bearing electron-donating and electron-withdrawing substituents are successfully employed to prepare corresponding polyhydroquinoline derivatives in excellent yields. Therefore, the results reveal that this methodology is effective for a wide range of aldehydes.

The Pd-SBTU@Fe_3O_4, as a magnetically recoverable and recyclable nanocatalyst, can be easily recovered from the reaction mixture and reused for the Suzuki reaction and synthesis of polyhydroquinoline derivatives. Therefore, recyclability of Pd-SBTU@Fe_3O_4 was studied for the synthesis of biphenyl (Table 4, entry 1) and ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 4, entry 10) under similar reaction conditions. As shown in Figure 5, the catalyst was recovered using an external magnet and recycled over five times without considerable decrease in activity.

3.4 | Comparison of catalyst

In order to describe the catalytic activity of Pd-SBTU@Fe_3O_4, we compared the results of the synthesis of ethyl 2,7,7-trimethyl-5-oxo-4-(*p*-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (Table 3, entry 1) in the presence of this catalyst with the results obtained using previously reported catalysts. As evident from Table 5, Pd-SBTU@Fe_3O_4 affords a better reaction time than the other catalysts. This new catalyst is comparable to or may be better in terms of non-toxicity, stability and ease of separation.

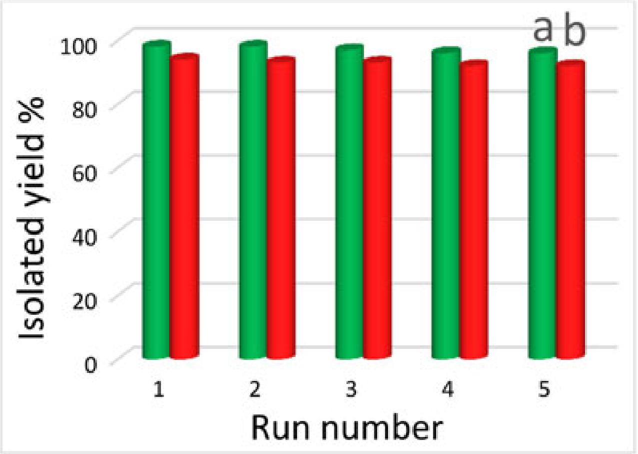


FIGURE 5 Recycling experiment of Pd-SBTU@Fe_3O_4 in synthesis of biphenyl (a) and ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (b)

TABLE 5 Comparison of Pd-SBTU@Fe_3O_4 for the synthesis of ethyl 2,7,7-trimethyl-5-oxo-4-(*p*-tolyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate with previously reported catalysts

Entry	Substrate	Catalyst	Time (min)	Yield (%)
1	4-Methylbenzaldehyde	Cu-SPATB/Fe_3O_4	240	91[11]
2	4-Methylbenzaldehyde	Boehmite-SSA	250	96[15]
3	4-Methylbenzaldehyde	GSA@MNPs	260	89 [19]
4	4-Methylbenzaldehyde	Triton X-100	120	92 [20]
5	4-Methylbenzaldehyde	Fe_3O_4-SA-PPCA	110	91 [21]
6	4-Methylbenzaldehyde	Pd-SBTU@Fe_3O_4	75	90 (this work)

[a]Isolated yield.

4 | CONCLUSIONS

In summary, a new type of magnetically recoverable nanocatalyst (Pd-SBTU@Fe_3O_4) was prepared and further applied as an excellent, highly reusable and air- and moisture-stable nanocatalyst for the Suzuki reaction and the synthesis of polyhydroquinoline derivatives in PEG-400 as a green solvent. The catalyst was characterized using SEM, VSM, ICP-OES, FT-IR spectroscopy and TGA. The catalyst could be reused five times without any significant loss of its activity.

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