

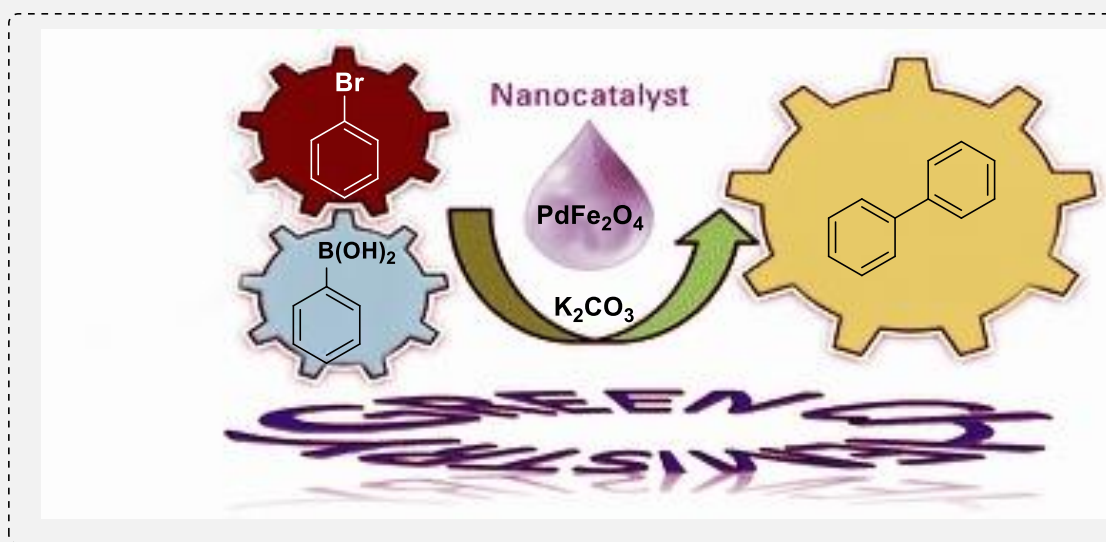
A Method for Palladium-Catalyzed Asymmetric Couplings of Bromobenzene Derivatives: Suzuki Reactions Catalyzed by Pd Fe₂O₄

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ABSTRACT: In the synthesizing of unsymmetrical biaryl compounds, palladium is the most effective metal catalyst. The high cost of the product limits its application on a wide scale. A good approach for reducing noble metal needs is to use nanoscale particles as active catalysts. Using magnetic nanocores as a support, precious nanoparticles can be loaded on magnetic nanocores, and catalysts can be recycled and repurposed. When applied to an external magnetic field, magnetic nanoparticles have a superparamagnetic property that allows them to collect supported catalysts quickly and easily from reaction milieus. An immobilized palladium catalyst on Fe₂O₄ magnetic nanoparticles was synthesized in the present study. An FT-IR spectrometer, thermogravimetric analysis, X-ray diffraction, and ICP were then used to characterize the catalyst. A high level of activity was observed in the Suzuki–Miyaura cross-coupling reaction between phenylboronic acid and aryl halides when the catalyst was prepared. Several aspects of the catalyst were investigated, including activity, Pd loading, reusability, and Pd leaching. A simple external magnetic field can be used to completely recover the supported catalyst, as evidenced by the results.



KEYWORDS: Unsymmetrical, Nanocores, Fe₂O₄ Magnetic, Suzuki–Miyaura.

■ Introduction

Among the many applications of carbon-carbon reactions is the synthesis of complex compounds from simpler raw materials [1]. The fact that these reactions can be used in organic chemistry in this way made them a powerful tool in recent years. In terms of efficiency, Sonogashira, Heck, and Suzuki's reactions are the most effective [2]. The main reasons for the remarkable progress of Suzuki's response are: 1- The Suzuki reaction can be performed for a wide range of precursors and many functional groups under mild reaction conditions [3]. Therefore, this reaction is used for the synthesis of many complex pharmaceutical molecules [4]. 2- Boronic acids, which are the raw materials of the Suzuki reaction, are stable in thermal conditions and are ineffective against water and oxygen [5]. As a result, their use does not require dry environment and solvents [6]. These compounds are easily available and have low toxicity and can be easily separated from the reaction medium [7]. The Suzuki reaction is usually catalyzed by soluble palladium complexes, with different ligands in organic solvents, and finally in aqueous media [8]. At first, scientists used homogeneous catalysts in the field of carbon-carbon bond formation reactions, including the Suzuki reaction, which have high activity and selectivity [9]. But despite the many advantages of homogeneous catalysts, their use has limitations [10]. The main problem of homogeneous catalysts is their separation from the reaction environment. Since the majority of palladium catalysts have a high price and therefore their reuse in a chemical process is very important from an economic point of view [11]. On the other hand, the contamination of synthesized products, especially pharmaceutical compounds, with a small amount of palladium is another problem that must be solved [12]. In order to solve these problems, chemists used heterogeneous catalysts. Heterogeneous palladium catalysts are easily separated from the reaction environment and are used many times, also the prepared products have high purity [13,14].

Due to palladium's high price, its separation and recovery are important factors in these reactions since they use palladium salts or palladium complexes with different ligands [15]. Palladium catalysts with homogeneous surfaces cannot be recovered, but to increase their efficiency, adding additives like phosphine is necessary [16]. The project is therefore unprofitable from an economic standpoint. Different substrates can be stabilized to improve the catalytic properties and increase the recyclability of metal complexes [17]. Because of their high surface-to-volume ratio, nano substrates can be more stable than other substrates, resulting in heterogeneous catalysts with higher activity than those synthesized on non-nano substrates [18]. Generally, smoothing or centrifugation is used to separate heterogeneous catalysts. Separation methods such as these require a great deal of time and waste some catalyst [19]. To solve this problem, metal magnetic nanoparticles have been introduced as a suitable nano substrate in recent years [20]. A simple external magnetic field such as a magnet can be used to separate heterogeneous nanomagnetic catalysts synthesized on a nanomagnetic substrate [21]. The loss of catalyst is lower in this separation method compared to other methods, and it is also more environmentally friendly and economically beneficial [22].

In this paper, we synthesized a novel palladium catalyst immobilized on Fe₂O₄ magnetic nanoparticles. Here, we gathered the advantages of heterogeneous catalysis, thermal stability, oxygen insensitivity, air and moisture stability, magnetic separation, and enhanced catalytic activity of palladium without adding phosphine ligands to synthesize a new catalyst for the Suzuki cross-coupling reaction.

Results and Discussion

The first step involves the synthesis of highly stable palladium ferrite nanoparticles. The catalyst was prepared by combining sonochemical techniques and co-precipitation in an aqueous environment without using any surfactant or coating agent. The nanostructure of PdFe₂O₄ nanoparticles has been well characterized using FT-IR, X-ray diffraction (XRD) and ICP techniques. Crystallization and phase purity of PdFe₂O₄ nanoparticles were investigated by XRD measurements. As shown in **Fig. 1**, strong and sharp reflections peak in the XRD patterns of the dried precipitate, which is mainly composed of tetragonal PdFe₂O₄ with good crystallinity (JCPDS card N034-0425). The average particle size was calculated to be 38 nm using Scherer's formula,

$$D = 0.94 \lambda / \beta \cos \theta$$

where D is the average size of the particles, λ is the wavelength of the incident X-ray, θ is the Bragg angle (in degrees), β is the full width (in radians) subtended by the half-maximum intensity width of the powder peak, expressed in units of 2θ .

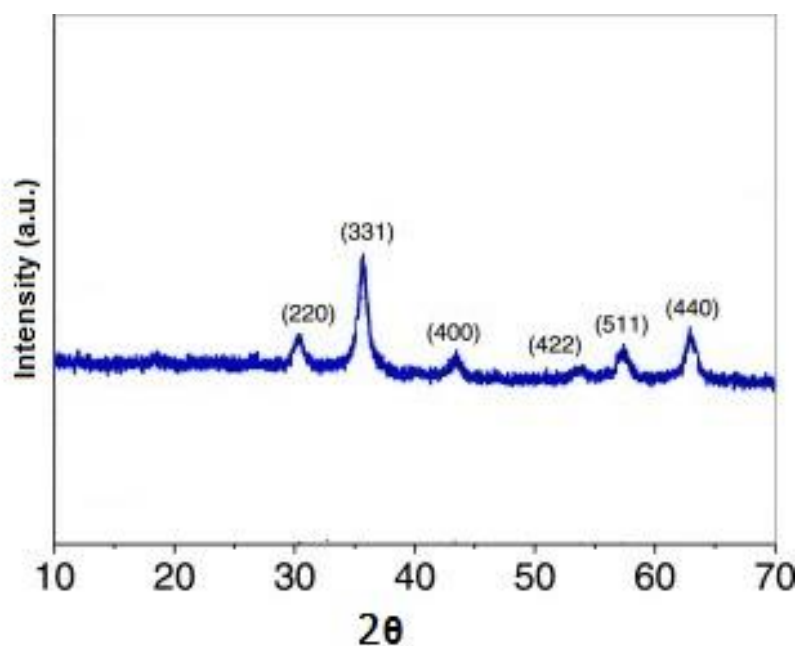


Figure 1. XRD spectrum of native PdFe₂O₄ catalyst.

The FTIR spectra (**Fig. 2**) of the PdFe₂O₄ nanoparticles indicate the presence of two absorption bands at 560 cm⁻¹ and 480 cm⁻¹. These intense absorption bands are attributed to the stretching vibration of Fe–O in the tetrahedral complexes and Pd–O in the octahedral complexes respectively. The positions of these bands confirm the existence of Pd ions entirely in the octahedral sites and the Fe³⁺ ions in tetrahedral ones.

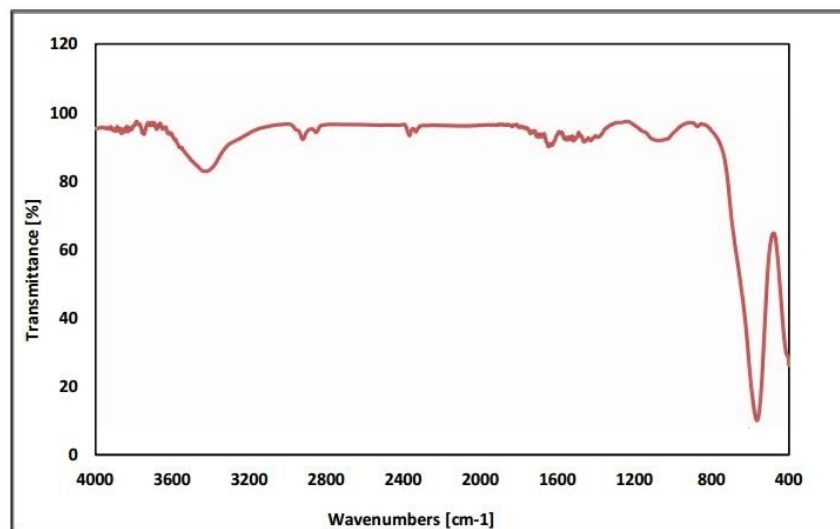


Figure 1. FT-IR spectra for PdFe₂O₄ catalyst.

After identifying the palladium catalyst stabilized on the substrate, its catalytic activity in the Suzuki-Miyaura reaction was investigated. The optimization of the effective factors was done according to the following method, while all the factors are constant in the reactions, the reaction was done with different amounts of one of the variables such as the amount of catalyst, type of base and solvent. In this way, a reasonable approximate value has been chosen for each of the effective factors. The value of the variable related to the best efficiency was selected as the optimal value and kept constant in the next reactions, thus all the variables were optimized and the optimization results are presented in **Table 1**. The best conditions for the combination of potassium carbonate as a base and methanol and water as a solvent is the PdFe₂O₄ catalyst amount of 20 mg, which was determined in the carbon-carbon bonding reaction of bromobenzene and phenylboronic acid as a model reaction.

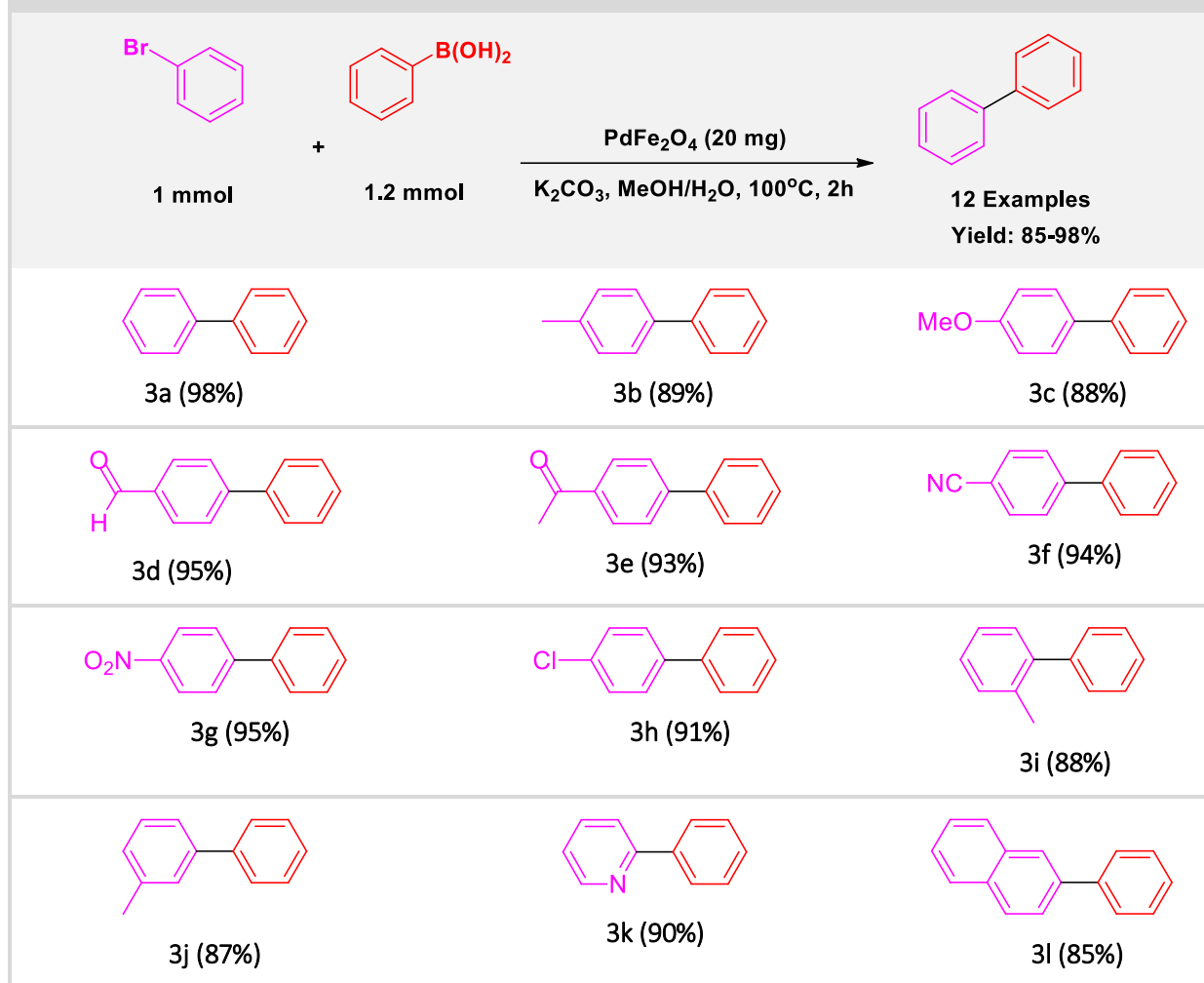
Table 1. Optimization parameters for the Suzuki reaction of phenylboronic acid with bromobenzene in the presence of PdFe₂O₄ nanocatalyst ^a

Entry	Catalyst (mg)	Base	Solvent (Tem °C)	Time (h)	Yield (%) ^a
1	--	K ₂ CO ₃	MeOH/H ₂ O	4	No
2	5	K ₂ CO ₃	MeOH/H ₂ O	2	51
3	10	K ₂ CO ₃	MeOH/H ₂ O	2	63
4	15	K ₂ CO ₃	MeOH/H ₂ O	2	77
5	20	K ₂ CO ₃	MeOH/H ₂ O	2	98

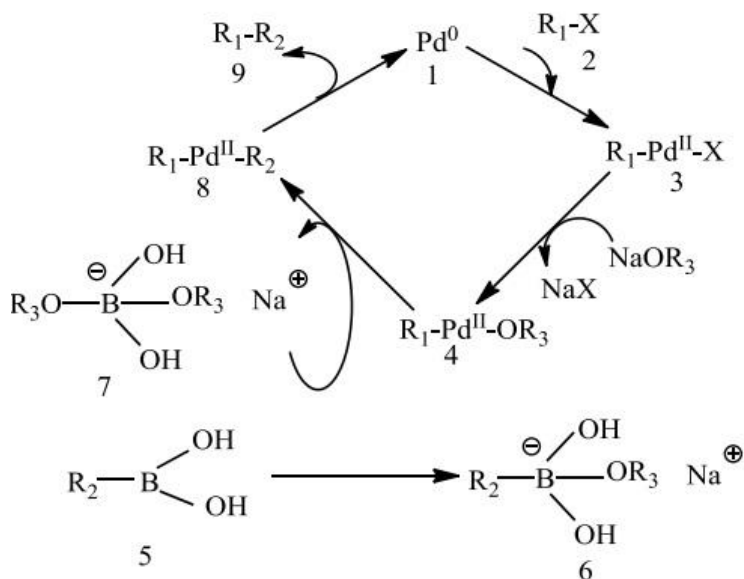
6	20	K ₂ CO ₃	THF	2	80
7	20	K ₂ CO ₃	DMF	2	70
8	20	K ₂ CO ₃	DMSO	2	58
9	20	t-BuONa	MeOH/H ₂ O	2	39
10	20	DBU	MeOH/H ₂ O	2	65
11	20	NaOH	MeOH/H ₂ O	2	71
12	20	Et ₃ N	MeOH/H ₂ O	2	55
13	20	Na ₂ CO ₃	MeOH/H ₂ O	2	52
14	20	KOH	MeOH/H ₂ O	2	89

After optimizing the reaction conditions of various aryl bromides with electron-withdrawing or electron-donating substituent groups on the benzene ring with phenylboronic acid, the Suzuki-Miura reaction was successfully performed under optimal conditions, the results of which are presented in **Table 2**. The results showed that the reaction with electron withdrawing groups has a higher yield.

Table 2. Scope of Suzuki reactions of phenylboronic acids with bromobenzene in the presence of PdFe₂O₄ nanocatalyst ^a



The catalytic cycle of the Suzuki reaction consists of three main stages as shown in **Scheme 1**. In the first step, which is called oxidative addition, the palladium species becomes palladium arylhalide complex by activating the carbon-halogen bond of arylhalide. In the oxidative increase stage, palladium zero may be removed from the substrate and the palladium (II) complex is dissolved in solution, and then all subsequent steps of the Suzuki reaction are performed in the solution. After the oxidative increase, the negatively charged base reacts with arylboronic acid and becomes an intermediate 4 is created. In the second step, which is called the metal transfer step, the metal exchange between complexes 4 and 6 is performed and the palladium-diaryl complex 8 is synthesized. The final step is the reductive elimination step of intermediate 8, which finally returns zero palladium to the catalytic cycle and the biaryl product is obtained.



Scheme 1. Plausible mechanism.

Because the possibility of recycling and reusing the catalyst is one of the important factors in the success of solid catalytic systems. Experiments were conducted to check the reusability of this catalyst. For this purpose, after the completion of the reaction, the catalyst was separated from the reaction medium by filtering. Then it was washed with ethyl acetate and after drying it was used for the next steps. As shown in **Fig. 3**, the palladium-stabilized catalyst is stable and reusable and can be reused up to eight times without significant reduction in efficiency.

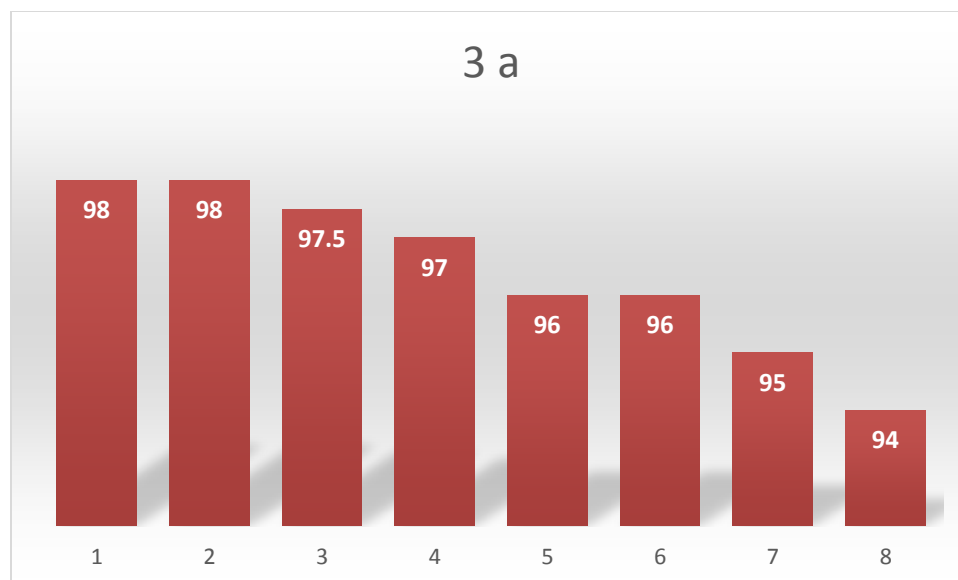


Figure 3. Reusability of PdFe₂O₄ catalyst in the synthesis of product 3a

■ Conclusion

In this research, the design and synthesis of palladium catalyst stabilized on the Fe₂O₄ substrate was reported. The structure and physical and chemical properties of PdFe₂O₄ were determined using various spectroscopic analysis technologies such as XRD and ICP. Then its catalytic activity in the Suzuki-Miura reaction was investigated and it was found that the PdFe₂O₄ nanocatalyst is very efficient in this process. The studied palladium nanocatalyst (PdFe₂O₄) can be recycled for eight consecutive times without any significant decrease in catalytic activity. High yield, stability and reusability, low amount of catalyst and high reaction speed in mild reaction conditions are the characteristics of the method presented in this article.

■ Experimental

All the chemicals used were of research grade and were used without further purification. The melting points of all compounds were determined on a Toshniwal apparatus. The purity of compounds was checked on thin layers of silica Gel– G coated glass plates and n-hexane: ethyl acetate (8 : 2) as eluent. IR spectra were recorded on a Shimadzu FT IR–8400S spectrophotometer using KBr pellets. ¹H and ¹³C NMR spectra were recorded in CDCl₃ using TMS as an internal standard on a Bruker spectrophotometer at 300 and 75 MHz respectively. Mass spectra of representative compounds were recorded on JEOL-SX-102 mass spectrometer at 70 eV. Elemental microanalyses were carried out on a Carlo-Erba 1108 CHN analyzer. Single crystal X-ray diffraction was performed on a Bruker Kappa Apex II instrument.

Synthesis of Catalyst

Preparation PdFe₂O₄ nanoparticles

In the presence of sodium hydroxide, Pd(NO₃)₂ and Fe(NO₃)₃ were thermally decomposed to produce PdFe₂O₄ nanoparticles. In total, 3 g (75 mmol) of NaOH dissolved in 15 mL of water was added at room

temperature over 10 minutes to a solution containing $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (3.34 g, 8.2 mmol) and $\text{Pd}(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$ (1 g, 4.1 mmol). A reddish-black precipitate was formed after the addition of NaOH. Afterward, the reaction mixture was heated to 90 °C and stirred under ultrasonic irradiation for two hours. A magnetic separator was used to separate the magnetic particles formed after cooling to room temperature for 2 hours. An air oven at 80 °C was used to dry the catalyst overnight after it was washed with water (36 mL). In the next step, the catalyst was ground in a mortar pestle and kept at 700 °C for 5 hours (step up temperature 20 °C min⁻¹) before being cooled to room temperature. Magnetic PdFe_2O_4 particles with a size range of 30–50 nm were obtained from 940 mg of PdFe_2O_4 particles.

General Procedure for Synthesis of biphenyl Derivatives 3(a-l)

For this purpose, the coupling reaction of Suzuki phenylboronic acid (1.2 mmol) with bromobenzene (1 mmol) in the presence of PdFe_2O_4 catalyst (20 mg) and potassium carbonate base (1.5 mmol), in a 10 ml flask liter and at a temperature of 100 °C and in 5 ml of methanol and water solvent mixture was investigated. The progress of the reaction was followed by gas chromatography. After the completion of the reaction, the obtained mixture was first cooled to room temperature and after being filtered, it was washed by water and ethyl acetate. In the next step, the recycled catalyst was effectively reused eight times under the same conditions as mentioned.

Supporting Information

4-Methoxybiphenyl (3c) White solid, m.p.: 86 – 87 °C. ¹H NMR (400 MHz, CDCl_3) δ (ppm): 7.58 – 7.55 (m, 4H, Ar-H), 7.44 – 7.41 (m, 2H, Ar-H), 7.36 – 7.32 (m, 1H, Ar-H), 7.05 – 6.99 (m, 2H, Ar-H), 3.85 (s, 3H, OCH₃). ¹³C NMR (100 MHz, CDCl_3) δ (ppm): 158.2, 141.8, 133.7, 128.4, 128.1, 126.3, 126.2, 114.7, 55.3.

2-Phenylpyridine (3k) Slight yellow liquid. ¹H NMR (400 MHz, CDCl_3) δ (ppm): 8.71 – 8.67 (m, 1H, Py-H), 8.05 – 7.99 (m, 2H, Ar-H), 7.52 – 7.50 (m, 2H, Ar-H), 7.48 – 7.37 (m, 1H, Ar-H, 2H, Py-H), 7.25 – 7.17 (m, 1H, Py-H). ¹³C NMR (100 MHz, CDCl_3) δ (ppm): 157.2, 149.8, 139.2, 136.5, 129.7, 128.1, 126.3, 122.7, 120.3.

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