

Catalytic Study of 4-Bromoacetophenone in the Suzuki-Miyaura Cross-Coupling Reaction by Controllable, Effective and Reusable Magnetic Supported Palladium(II)-N₂O₂ Catalyst

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Supported catalysts growing a highly demand as they have the potentials to offer both the activity of molecular catalyst, and the convenience reusability of a catalyst in a different phase. The magnetic supported palladium(II)-N₂O₂ in the Suzuki-Miyaura C-C coupling reaction enables the facile recovery of the catalyst under optimised condition. An investigation was conducted by using 4-bromoacetophenone and phenylboronic acid as reactants with the variation of catalytic parameters, such as different of bases (NaHCO₃, NaOAc, Na₂CO₃, K₂CO₃ and Et₃N), catalyst loading (0.25 mmol%, 0.50 mmol% and 1.0 mmol%) and reaction temperatures (100 °C, 120 °C and 140 °C). The performances of catalytic reactions were monitored by GC-FID and the percentage conversion of product was calculated by determining the differences of initial and final peak areas. The catalyst showed an outstanding catalytic performance in the Suzuki-Miyaura C-C coupling reaction when Na₂CO₃ was used as a base and little catalyst usage (0.25 mmol%). The catalytic reaction was favoured at high temperature of 140 °C and longer reaction time, 24 hr. In addition, the catalyst could be separated conveniently from the reacting system with an external magnet, showed good catalytic performance even after being reused five times or more, indicating a good recyclability.

Keywords: Catalytic optimization; magnetic nanoparticles; supported catalyst; Suzuki-Miyaura reaction

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Suzuki-Miyaura reaction is one of the palladium (Pd)-catalysed carbon-carbon bond constructions in which the reaction occurs between aryl halides and arylboronic acid to form biaryl compounds, which mostly found in natural products, pharmaceuticals and herbicides [1]. Generally, homogeneous catalyst has been widely employed in Suzuki-Miyaura reaction due to their high activity, selectivity and tolerance towards poisons [2]. However, most of homogeneous catalysts suffer from its slow recovery and difficulty in separation from the reaction mixture [3]. Fortunately, the immobilisation of the homogeneous catalysts onto insoluble supports have been considered as a promising solution. Basically, heterogenising a homogeneous can be achieved by immobilising the metal complex on the surface of insoluble support (organic or inorganic supports) [4]. Several examples for the immobilisation of metal complex on various solid supports, such as zeolite, polymer, ferrite and

clay have been studied [5]. Over the past decades, the Suzuki-Miyaura reaction has been catalysed with various Pd(II) complexes anchored on different natural and synthetic supports in many cases with results similar to or even better than those provided by their homogeneous counterparts [6].

Lately, the use of ferrites nanoparticles as solid support for the development of magnetically separable catalysts has gained researchers' attention due to its simplicity in preparation, low cost and high surface area [7]. Magnetite nanoparticles (Fe₃O₄) specifically has superparamagnetism, low toxicity, easily synthesised and functionalised which make it potentially to be used in various fields, such as drug delivery and magnetic resonance [8-9]. A variety of magnetic supported palladium catalysts for Suzuki-Miyaura cross-coupling reaction have been identified and further outlined in **Table 1**.

Table 1. A variety of magnetic supported palladium catalysts for Suzuki-Miyaura cross-coupling reaction.

Entry	Catalyst	Year	Reference
1	Fe ₃ O ₄ @EDTA-PdCl ₂	2015	[10]
2	Fe ₃ O ₄ /IL/Pd	2017	[11]
3	Pd NPs@Fe ₃ O ₄ /CS-AG microcapsules	2019	[12]
4	Fe ₃ O ₄ -CS@tet-Pd(II)	2021	[13]
5	Fe ₃ O ₄ @SiNSB-Pd	2022	[14]

Heidari et al. (2017) reported a recoverable magnetite Pd catalyst was introduced for Suzuki-Miyaura cross-coupling reaction and found that the magnetically recoverable catalyst gave good yields and can be reused up to six times without drastic loss of catalytic activity [15]. Therefore, the literatures showed that the magnetic heterogeneous catalyst has an immense capability in solving the recoverability and recyclability challenges in catalytic systems [16]. In this study, we reported the catalytic activity of magnetic supported palladium(II)-N₂O₂ in the Suzuki-Miyaura reaction of 4-bromoacetophenone with phenylboronic acid using several parameters, including influence of bases, catalyst loading and various temperature in order to obtain the optimum reaction conditions.

EXPERIMENTAL

Chemicals and Materials

All the chemicals used were commercially available and used once received without further purification. The chemicals used in this study, including 4-bromoacetophenone, phenylboronic acid, sodium bicarbonate (NaHCO₃), sodium acetate (NaOAc), sodium carbonate (Na₂CO₃), potassium carbonate (K₂CO₃), and triethylamine (Et₃N) were purchased from Sigma-Aldrich and Fisher. While *N,N*-dimethylacetamide (DMA) was supplied by Merck.

General Procedure for Catalytic Suzuki-Miyaura by Magnetic Supported Palladium(II)-N₂O₂ Catalyst

The catalytic performance of magnetic supported palladium(II)-N₂O₂ catalyst was examined for Suzuki-Miyaura coupling reaction of 4-bromoacetophenone (1.0 mmol) with phenylboronic acid (1.5 mmol) as a model reaction. The reaction was carried out with the presence of certain amount of supported catalyst (1.0 mmol%), DMA solvent (5 mL), base (2.0 mmol) and the mixture was added in the Radley's 12-placed reaction carousel, refluxed at 100 °C for 24 hr. The absence of magnetic supported palladium(II)-N₂O₂ catalyst was also tested for control reaction and the result showed that the mixture did not produce any

coupling reaction and no coupling product was observed. The catalytic conversion was analysed by using GC-FID. Afterwards, the catalyst was magnetically separated from the catalytic mixture and rinsed with deionised (3 x 2 mL) water and ethanol (3 x 2 mL). The conversion percentage (%) of the reactant was calculated as in Equation (1), where $A_{initial}$ represents peak area of reactant before reaction, while A_{final} represents the peak area of reactant after the reaction.

$$\% \text{ conversion} = \frac{[A_{initial} - A_{final}]}{A_{initial}} \times 100 \quad (1)$$

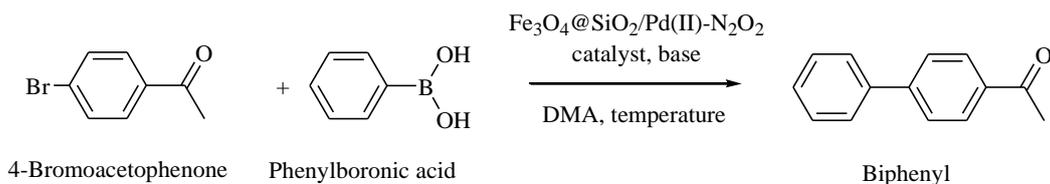
To obtain the optimum catalytic condition of Suzuki-Miyaura coupling reaction, several parameters were tested, such as the effect of bases (NaHCO₃, NaOAc, Na₂CO₃, K₂CO₃ and Et₃N), catalyst loading (0.25 mmol%, 0.50 mmol% and 1.0 mmol%) and reaction temperature (100 °C, 120 °C and 140 °C).

Recyclability of the Magnetic Supported Palladium(II)-N₂O₂ Catalyst

With the optimised conditions in hand, the versatility of catalytic system for magnetic supported palladium(II)-N₂O₂ catalyst was assessed through recycling cycles. The procedure described above was followed and the reaction was carried out for 24 hr. When the reaction had completed, the magnetic supported catalyst was decanted by an external magnetic field, dried in oven at 60 °C for 8 hr before dispersed to the next run.

RESULTS AND DISCUSSION

The performance of synthesised magnetic supported palladium(II)-N₂O₂ catalyst was tested in the heterogeneous catalysis of Suzuki-Miyaura cross-coupling reaction. In this study, 4-bromoacetophenone with phenylboronic acid (**Scheme 1**) were selected as reactants. With initial magnetic supported catalyst loading of 1.0 mmol%, 2.0 mmol of base at 100 °C, a complete conversion percentage was obtained after 24 hr. To optimise Suzuki-Miyaura catalytic reaction conditions, various of parameters need to be considered, giving a high yield of favourable product.



Scheme 1. Suzuki-Miyaura cross-coupling reaction of 4-bromoacetophenone and phenylboronic acid.

Initial optimisation of the reaction conditions began with the effect of different bases (**Table 2**). The presence of base essentials for cross-coupling reaction as the base increased the reactivity of the boronic acid towards the heterogenous catalytic system [17]. Preliminary tests with five different of bases, namely sodium bicarbonate (NaHCO₃), sodium acetate (NaOAc), sodium carbonate (Na₂CO₃), potassium carbonate (K₂CO₃) and ethylenediamine (Et₃N) indicated a good catalytic activity of cross-coupling. A remarkable product conversion was observed in the presence of Na₂CO₃ as a base with percentage of 94% (Table 2, Entry 1). Acceptable conversions were also observed for K₂CO₃, NaOAc and NaHCO₃ with the conversions percentage of 91%, 88% and 76%, respectively. It was noted that organic bases, such as Et₃N gave the lowest percentage conversions amongst these five bases with 35% probably due to insolubility in the reaction media [18].

Then, the catalytic studies were performed with

different catalyst loadings (**Table 3**). Increasing the catalyst amount in the catalytic reaction increased the conversion of cross-coupling product. The magnetic supported palladium(II)-N₂O₂ could be lowered to 0.25 mmol% without a significant loss of its efficiency in the catalytic system. By controlling the catalyst loading, the turnover number (TON) could be established. TON can be described as maximum catalytic conversions that can be achieved by the catalyst in one catalytic cycle [19]. **Table 3** shows the excellent TON corresponded to 288 was achieved when the catalyst loading used at 0.25 mmol% (Table 3, Entry 3). Therefore, 0.25 mmol% of catalyst loading was found to be sufficient to catalyse the Suzuki-Miyaura cross-coupling between 4-bromoacetophenone and phenylboronic acid. The Suzuki-Miyaura cross-coupling can be carried out with a small amount of expensive catalyst is the most efficient feature of catalytic reaction involving palladium metal.

Table 2. Optimization of different bases for the Suzuki-Miyaura cross-coupling reaction^a.

Entry	Base	Conversion (%) ^b
1	Na ₂ CO ₃	94
2	NaHCO ₃	75
3	K ₂ CO ₃	91
4	Et ₃ N	35
5	NaOAc	88

a. Reaction conditions: 4-bromoacetophenone (1.0 mmol), phenylboronic acid (1.5 mmol), supported catalyst (1.0 mmol%), bases (2.0 mmol), DMA (5 mL), 100 °C, 24 hours.

b. Percentage conversion determined by GC-FID.

Table 3. Optimization of catalyst loadings for the Suzuki-Miyaura cross-coupling reaction^a.

CC(=O)c1ccc(Br)cc1 + c1ccc(cc1)B(O)O
 $\xrightarrow[\text{DMA, 100 }^\circ\text{C, 24 h}]{\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{Pd(II)-N}_2\text{O}_2 \text{ catalyst, Na}_2\text{CO}_3}$
CC(=O)c1ccc(cc1)-c2ccccc2

4-Bromoacetophenone Phenylboronic acid Biphenyl

Entry	Catalyst loading (mmol%)	Conversion (%) ^b	Turnover number (TON) ^c
1	1.0	94	94
2	0.50	77	154
3	0.25	72	288

a. Reaction conditions: 4-bromoacetophenone (1.0 mmol), phenylboronic acid (1.5 mmol), 0.25 mmol% supported catalyst, Na₂CO₃ (2.0 mmol), DMA (5 mL), 24 hours.

b. Percentage conversion determined by GC-FID.

c. TON: mmol of product/mmol of catalyst used.

With the established optimum reaction conditions using Na₂CO₃ as a base and 0.25 mmol% catalyst loading, the performance of magnetic supported palladium(II)-N₂O₂ catalyst was further investigated at different reaction temperatures, 100 °C, 120 °C and 140 °C (**Table 4**). The reaction temperature played a vital role in the activation of aryl halides [20]. At low temperature, the aryl halide was found to be less reactive and probably leading to decreased in yield [21]. However, if the reaction temperature was too high, the formation of palladium black would affect the termination of catalytic cycle [22]. Therefore, the reaction temperature

required a meticulous control to avoid the formation of inactive palladium. In addition, the interface formed between magnetic palladium(II)-N₂O₂ supported catalyst and liquid phase reactants also imparted unique properties and required mass transfer considerations for cross-coupling conversion [23]. It was discovered that the increment of temperature had increased the conversion percentage in this study. The highest conversions were achieved 100% at 140 °C after 24 hr (Table 4, Entry 3). Both 72% and 85% conversion were observed when the reaction temperature were set at 100 °C and 120 °C, respectively.

Table 4. Optimization of the reaction temperature for the Suzuki-Miyaura cross-coupling reaction^a.

CC(=O)c1ccc(Br)cc1 + c1ccc(cc1)B(O)O
 $\xrightarrow[\text{DMA, temperature, 24 h}]{\text{Fe}_3\text{O}_4@\text{SiO}_2/\text{Pd(II)-N}_2\text{O}_2 \text{ catalyst, 0.25 mmol\%, Na}_2\text{CO}_3}$
CC(=O)c1ccc(cc1)-c2ccccc2

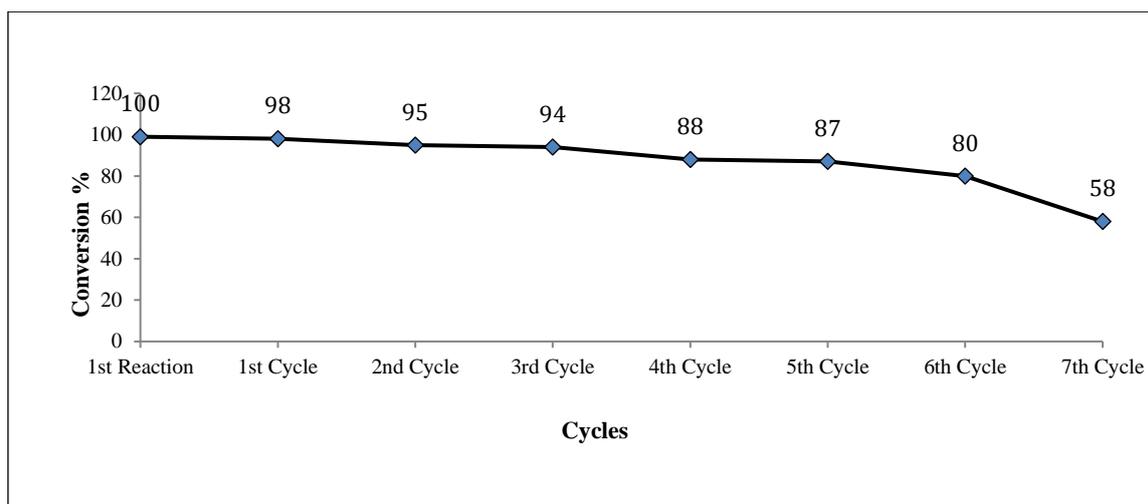
4-Bromoacetophenone Phenylboronic acid Biphenyl

Entry	Temperature (°C)	Conversion (%) ^b	Turnover number (TON) ^c
1	100	72	288
2	120	85	340
3	140	100	400

a. Reaction conditions: 4-bromoacetophenone (1.0 mmol), phenylboronic acid (1.5 mmol), 0.25 mmol% supported catalyst, Na₂CO₃ (2.0 mmol), DMA (5 mL), 24 hours.

b. Percentage conversion determined by GC-FID.

c. TON: mmol of product/mmol of catalyst used.



a. Reaction conditions: 4-bromoacetophenone (1.0 mmol), phenylboronic acid (1.5 mmol), 0.25 mmol% catalyst loading, Na₂CO₃ (2.0 mmol), DMA (5 mL), 140 °C.
b. Percentage conversion determined by GC-FID.

Figure 1. Recycling of magnetic supported palladium(II)-N₂O₂ in the Suzuki-Miyaura reaction^a.

A noteworthy application of a supported catalyst in the catalytic system is to be able to recycle the synthesised catalyst and reuse it for subsequent reactions [24]. Therefore, the recyclability of magnetic supported palladium(II)-N₂O₂ was conducted by using the optimised conditions for the Suzuki-Miyaura reaction of 4-bromoacetophenone with phenylboronic acid. As shown in **Figure 1**, the percentage conversion of products was remarkable for the first 6 cycles with the conversion percentage above 80% indicating the steadiness of magnetic supported palladium(II)-N₂O₂. After the seventh run, the conversion percentage fell to 58% probably due to the leaching of palladium from the magnetic support during catalytic process, apparently requiring a separate investigation.

CONCLUSION

In summary, the magnetic supported palladium(II)-N₂O₂ as a controllable, effective and reusable catalyst for 4-bromoacetophenone in the Suzuki-Miyaura cross-coupling reaction have been successfully investigated with very low 0.25 mmol% of palladium loading. The catalytic system showed a great tolerance and remarkable product conversion through the optimum conditions. The magnetic supported catalyst can be readily recovered and reused for further cross-coupling reaction up to sixth cycles with high efficiency. It is expected that the synthesised heterogeneous magnetic supported palladium(II)-N₂O₂ can be more broadly applied to Pd-catalysed reactions.

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