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UNVEILING HOMOGENEOUS CATALYTIC PERFORMANCE OF *N,N'*-BIS-(3,5-DI-*TERT*-BUTYLSALICYLIDENE)-2,2-DIMETHYLPROPANE-1,3-DIAMINEPALLADIUM(II) IN THE MIZOROKI-HECK REACTION

(Menyingkap Prestasi Pemangkinan Homogen *N,N'*-bis-(3,5-di-*tert*-butilsalisilidena)-2,2-dimetilpropana-1,3-diaminapaladium(II) dalam Tindak Balas Mizoroki-Heck**)**

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Abstract

Efficient Mizoroki-Heck coupling reactions were obtained using a homogeneous catalyst of symmetrical square planar *N,N'*-bis-(3,5-di-*tert*-butylsalicylidene)-2,2-dimethylpropane-1,3-diaminepalladium(II), Pd-L_{DDP}. The variables of time (3 and 6 hours), temperature (100, 120 and 140 °C), amount of catalyst loading (0.5, 1.0, 1.5 and 2.0 mmol%), and type of bases (Et_3N, $NaHCO_3$, methyl acrylate. Catalytic results exhibited that the Pd-L_{DDP}/NaOAc/0.5 mmol%/140 °C catalyst system gave the optimum condition and achieved high performance for a wide range of electron withdrawing aryl bromides with the conversion of up to 85% in 6 hours of reaction time. Thus, the proposed phoshine-free catalyst, which is more stable towards air and moisture, significantly provided access towards the organic transformation of Mizoroki-Heck coupling reaction.

Keywords: N_2O_2-tetradentade ligand, palladium(II) complex, Mizoroki-Heck reaction

Abstrak

Tindak balas gandingan Mizoroki-Heck yang efisien telah dihasilkan menggunakan mangkin homogen bersimetri segi empat planar, *N,N'*-bis-(3,5-di-*tert*-butilsalisilidena)-2,2-dimetilpropana-1,3-diaminapaladium(II), Pd-L_{DDP}. Pembolehubah masa (3 dan 6 jam), suhu (100, 120 dan 140 °C), jumlah muatan mangkin yang digunakan (0.5, 1.0, 1.5 dan 2.0 mmol%), dan jenis bes (Et_3N, $NaHCO_3$, Na_2CO_3 dan NaOAc) telah dioptimumkan untuk memberikan hasil yang sangat baik bagi produk gandingan Mizoroki-Heck 4-bromoasetofenon dengan metil akrilat. Hasil kajian pemangkinan menunjukkan sistem mangkin Pd-L_{DDP}/NaOAc/0.5 mmol%/140 °C telah memberikan keadaan yang optimum serta mencapai prestasi tinggi bagi pelbagai aril bromida berpenarik elektron dengan penukaran hasil sehingga 85% dalam masa tindak balas selama 6 jam. Oleh itu, cadangan mangkin bebas-fosfina yang lebih stabil terhadap udara dan kelembapan secara signifikan telah menyediakan capaian terhadap transformasi organik dalam tindak balas gandingan Mizoroki-Heck.

Kata kunci: ligan tetradentat-N_2O_2, kompleks paladium(II), tindak balas Mizoroki-Heck

Introduction

The palladium catalysed Mizoroki-Heck reaction provides a promising route for the formation of C-C bonds in organic synthesis as these coupling reactions are significantly used for the preparation of materials [1], natural products [2], biologically active compounds [3] conducting polymers, and pharmaceutical intermediates [4, 5]. The reaction was discovered by Mizoroki and Heck in year 1972 through independent research which could replace the combination of metalated arenes and reoxidants, thus giving rise to the form of catalytic reaction practised today [6]. Mannepalli et al., reported that palladium is arguably the most versatile and achieved the status of an indispensable tool for organic transformations [7]. There is no doubt that other transition metals cannot compete with the versatility of palladium. The ready accessibility of two stable oxidation states, 0 and +2, as well as the availability of Pd-containing species simultaneously, are mainly responsible for the rich chemistry enjoyed by the palladium complex in the catalytic system.

The improvement of catalytic efficiency also strongly relies on the reactivity of palladium catalyst attached with efficient supporting ligands. Recently, much efforts have been made to search for powerful ligands that could replace common type homogeneous palladium-phosphine complexes which are often air and moisture sensitive [8]. P-C bond degradation sometimes occurs at elevated temperatures, leading to the decomposition of the catalyst and this phenomenon strongly affects the catalytic conversion as well as selectivity [9-11]. In this regard, the development of simple, mild, efficient, and more environmentally N-, O- donor Schiff base ligands have emerged as phosphine-free ligands. Schiff bases have been extensively studied and proved suitable for the palladium species. In an attempt to evaluate the phosphine-free system in the Mizoroki-Heck reaction, tetradentate N_2O_2 chelated palladium(II) complex was chosen for this purpose due to its facile approach, relative tolerance, readily adjusted ancillary ligand, and electronic environment on the metal centre [12].

Inspired by these properties, the tetradentate N_2O_2 chelated palladium (II) complex often act as a catalyst. This study aims to investigate the performance of the synthesised catalyst to be potentially used for carbon cross-coupling reaction. Then, the catalytic of this synthesised complex was evaluated using the Mizoroki-Heck reaction to produce trans alkene with excellent yields. Notably, the use of palladium(II) complex derived from bulky 3,5-di-*tert*-butylsalicylidene has a positive influence on the Mizoroki-Heck reaction which conserved leading to an inexpensive alternative and provide a magical boosting of catalytic activity and efficiency [13].

Materials and Methods

Chemicals and reagents

All reactants, reagents and solvents were of synthetic grade, purchased from various commercial sources and used without prior treatment unless stated otherwise. Chemicals namely sodium acetate (NaOAc), sodium carbonate (Na_2CO_3), sodium bicarbonate ($NaHCO_3$), and triethylamine (Et_3N) were obtained from R&M Supplier, United Kingdom. In addition, 4-bromoacetophenone and methyl acrylate were procured from Sigma-Aldrich (Malaysia) Sdn Bhd. N,N-dimethylacetamide (DMAc) and other solvents were supplied by Merck Sdn Bhd, Malaysia.

Characterisation techniques

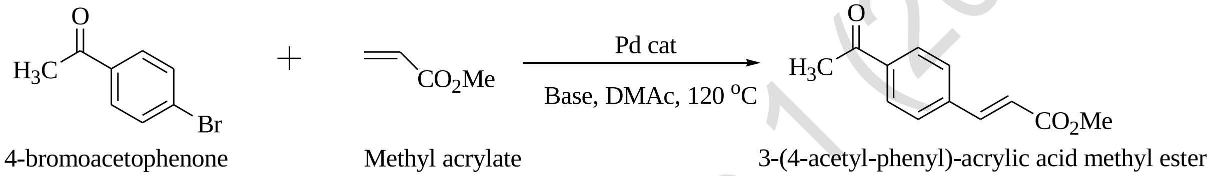
The catalytic Mizoroki-Heck reaction was analysed using a gas chromatography (GC-Hewlett Packard-5890 Series II) with ULTRA-1.0.05, 100% dimethylpolysiloxane capillary column (30 m length and 0.25 mm diameter), and flame ionization detector. The microliter (1 μL) samples were injected at 50 °C and the temperature increment was set at the rate of 15 °C per minute. The final temperature of the analyses was fixed at 300 °C. The catalytic conversion of reactant percentage was calculated using Equation 1:

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

The structure of the isolated catalytic product was elucidated with FTIR, ^1H and ^{13}C NMR spectroscopies.

General procedure for catalytic Mizoroki-Heck reaction

The catalytic tests were conducted under a nitrogen atmosphere using Carousel 12 Plus reaction station. In a typical Mizoroki-Heck reaction (Scheme 1), a mixture of 4-bromoacetophenone (1.0 mmol), methyl acrylate (1.5 mmol), base (2.4 mmol), catalyst (approximately 0.5-2.0 mmol%), and DMAc (2.5 mL) was stirred and heated for a given time (3 and 6 hours) and at a given temperature (100, 120 and 140 °C). After the desired reaction time, a small fraction (1 μL) of the liquid sample was taken and analysed by GC-FID. Then, the product was acidified with 2% hydrochloric acid (HCl) solution [14]. The percentage of product conversion was calculated based on the amount of 4-bromoacetophenone consumed. The purified product was determined by Perkin Elmer Spectrum One FTIR spectrometer and Bruker Avance 400 MHz NMR spectroscopy.



Scheme 1. The palladium (II) complex catalysed Mizoroki-Heck reaction

Results and Discussion

The synthesised complex, namely *N,N'*-bis-(3,5-di-*tert*-butylsalicylidene)-2,2-dimethylpropane-1,3-diaminepalladium(II) (**Pd-L$_{\mathbf{DDP}}$**) was successfully obtained in 76% yields as orange crystals by the reaction according to the previous methods [15, 16]. The spectroscopic characterisations of the ligand are agreed with literature values [17, 18]. As a preliminary study, the complex was explored as a homogeneous catalyst for the Mizoroki-Heck coupling of 4-bromoacetophenone with methyl acrylate. DMAc was used in this catalytic reaction as polar aprotic solvents give faster reaction rates compared to polar protic and nonpolar solvents [19, 20]. DMAc with a high boiling point has a strong influence on the solubilisation and stabilisation of the palladium catalyst [21, 22]. Reaction conditions were optimised using different types of bases, catalyst loading, and temperature [23, 24]. With the optimised conditions in hand, the catalytic reaction was further investigated for a variety of aryl bromides and the results obtained from the Mizoroki-Heck cross-coupling reaction are discussed in the following section.

Influence of different bases

Inorganic and organic bases were tested in the catalytic Mizoroki-Heck reaction. It should be noted that the choice of the base has been found to have a crucial effect on the rate and the conversion of Mizoroki-Heck product [25, 26]. A study by Dounay and Overman, reported that base plays a significant role in the reductive elimination of hydrogen bromide from the palladium(II) centre in the last step of the Mizoroki-Heck catalytic cycle and also to regenerate the palladium(0) catalyst [27]. Initially, four types of different bases (NaOAc, Na_2CO_3, $NaHCO_3$ and Et_3N) were selected for screening (Figure 1). It was observed that all the bases encouraged yields in the presence of polar DMAc and the increase of reaction time. Notably, NaOAc gave the highest conversion of the coupling product of up to 85% in 6 hours of reaction time. The effectiveness of using NaOAc for Mizoroki-Heck reaction was also reported previously [28]. Other inorganic bases such as $NaHCO_3$ and Na_2CO_3 recorded conversion percentage of 61% and 24%, respectively, due to the relative insolubility effects of the inorganic bases in the organic transformation reaction [29].

However, it is noteworthy that acceptable percentage product conversion of 35% was achieved when Et_3N was used as the base, and this could be explained due to the ligating properties of an organic base that may compete with the substrates and in part to block off free coordination sites on the palladium centre [30].

Influence of catalyst loading

Encouraged by the results of the different bases effect, the catalytic behaviour of palladium(II) complex was further investigated using various catalyst loading. The coupling of 4-bromoacetophenone with methyl acrylate in the presence of DMAc as the solvent, NaOAc as the base at 120 °C were set out in this study. The volume of the solvent, base, temperature, and time was also kept constant. The experiments were repeated for 0.5, 1.5 and 2.0 mmol% of the amount of catalyst used, respectively. As observed in Table 1, by increasing the amount of the palladium catalyst, the conversion percentage also increased [29]. This suggests that palladium functions as an active site for the cross-coupling reaction and the catalyst loads of 1.0 mmol% typically required to achieve a quantitative conversion of the substrates. The amount of catalyst loading tremendously affects the overall catalytic performance and selectivity patterns [1]. It was apparent that 0.5 mmol% recorded the highest TON occurred with 66% of product conversion (Table 1, entry 2). Thus, by controlling the amount of catalyst, an excellent TON was expected to maximise the conversion percentage of the desired products. The Mizoroki0Heck catalytic reaction that can be carried out with a small amount of expensive catalyst is the most efficient feature of synthetic reactions involving palladium(II) complex.

Influence of reaction temperature

After the optimisation of catalyst loading, the experiments with various reaction temperature revealed that the best reaction temperature was found to be at 140 °C, which was suitable for the activation of aryl bromide using the synthesised **Pd-L$_{DDP}$**. It could be seen that no conversion of the product was formed when the reaction was carried out at room temperature (Table 2, entries 1 and 5), but as the temperature increased, the constant reaction rate increased due to the increase in average kinetic energy of molecules and more collisions per unit time [19]. The conversion of 4-bromoacetophenone increased from 53% to 90% under the same reaction time. Thus, showed that the **Pd-L$_{DDP}$** exhibited stability at high temperature. The high temperature used in the catalytic reaction should be carefully controlled to prevent the possible decomposition of **Pd-L$_{DDP}$** by the formation of palladium black, thereby the catalytic cycle of Mizoroki-Heck could be terminated immediately.

Different and diversely substituted aryl bromides

To show the performance efficiency of **Pd-L$_{DDP}$,** the catalytic Mizoroki-Heck was further investigated using different substrates (Scheme 2). With the favourable results in hand, the optimal reaction conditions: (**Pd-L$_{DDP}$** (0.5 mmol), aryl bromides (1.0 mmol), methyl acrylate (1.5 mmol), NaOAc (2.4 mmol), DMAc (5 mL) under thermal conditions at 140 °C, four aryl bromides were tested to study the natural effect of substituents containing electron-donating and electron-withdrawing groups. The activated aryl bromides which have electron-withdrawing groups (Table 3, entries 1 and 2) were beneficial and gave excellent conversion percentage at the reaction time of 6 hours. However, no desirable coupled products were obtained until the end of the reaction for deactivated electron-donating aryl bromides (entries 3 and 4).

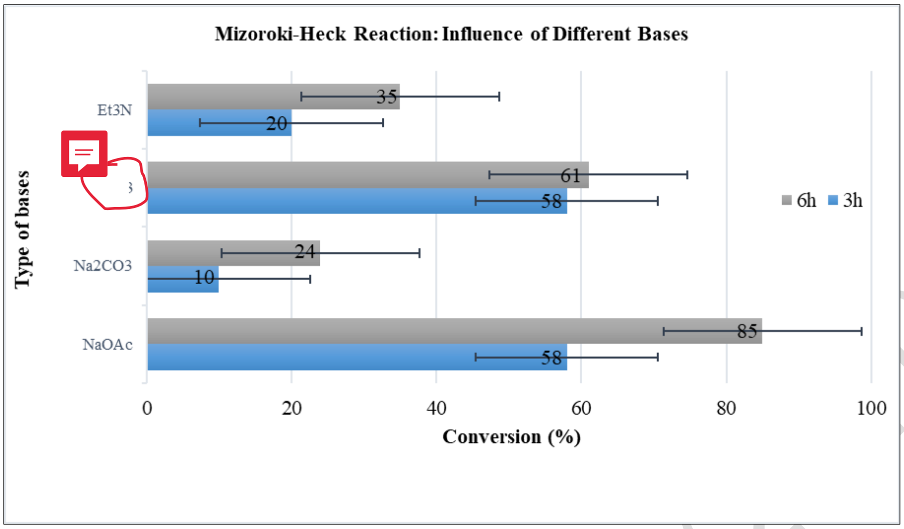


Figure 1. Results obtained for Mizoroki-Heck reaction with a different type of bases

Table 1. Results obtained for Mizoroki-Heck reaction with the effect of different catalyst loading

Entry	**Catalyst (Pd-L_{DDP}) (mmol%)**	**Reaction Time (h)**	**Reaction Temperature (°C)**	**Product Conversion[b] (%)**	**TON[c]**
1	0.5	3	120	46	92
2	0.5	6	120	66	132
3	1.0	3	120	58	58
4	1.0	6	120	85	85
5	1.5	3	120	62	41
6	1.5	6	120	88	59
7	2.0	3	120	71	36
8	2.0	6	120	92	46

[a] Reaction conditions: 4-bromoacetophenone (1.0 mmol), methyl acrylate (1.5 mmol), NaOAc (2.4 mmol), 5 mL DMAc, Pd(II) catalyst.

[b] Determined by GC-FID.

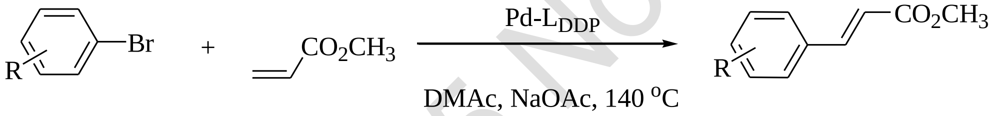
[c] Turnover number (TON) calculated at the completion of the reaction (mmol of 4-bromoacetophenone transformed/mmol of catalyst used).

Table 2. Results obtained from Mizoroki-Heck reaction with the effect of different reaction temperature

Entry	Catalyst (Pd-LDDP) (mmol%)	Reaction Time (h)	Reaction Temperature (°C)	Product Conversion[b] (%)
1	0.5	3	room temp.	0
2	0.5	3	100	31
3	0.5	3	120	46
4	0.5	3	140	79
5	0.5	6	room temp.	0
6	0.5	6	100	53
7	0.5	6	120	66
8	0.5	6	140	90

[a]Reaction conditions: 4-bromoacetophenone (1.0 mmol), methyl acrylate (1.5 mmol), NaOAc (2.4 mmol), 5 mL DMAc, Pd(II) catalyst

[b]Determined by GC-FID



Scheme 2. Mizoroki-Heck reaction of aryl bromides

Table 3. Results obtained from the Mizoroki-Heck reaction with diversity substituted aryl bromides

Entry	R (mmol%)	Reaction Time (h)	Product Conversion[b] (%)
1	4-COMe	6	90
2	4-NO_2	6	85
3	4-OMe	6	No conversion
4	H	6	No conversion

[a]Reaction conditions: aryl halide (1.0 mmol), methyl acrylate (1.5 mmol), NaOAc (2.4 mmol), 5 mL DMAc, Pd(II) catalyst

[b]Determined by GC-FID

Conclusion

The **Pd-LDDP** was successfully tested as a homogeneous catalyst in the Mizoroki-Heck reaction. The catalyst demonstrated good catalytic performances in the Mizoroki-Heck coupling reaction, in which the high conversion of products was obtained. Remarkably, only small amounts of **Pd-LDDP** (0.5 mmol%) were required to perform the catalysed reaction at a high temperature of 140 °C. Optimised conditions resulted in up to 80% of product conversion for activated electron-withdrawing groups. Also, the electronic nature of aryl bromides had a dominating effect on the conversion of the product. The activated aryl bromides reacted nearly quantitatively compared to other substituents. We believe these findings were found to be optimum are beginning to merge as set of conditions for **Pd-L$_{DDP}$** catalyst which could be the starting point for most substrates.

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