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Palladium(II)-Pivaloyl Thiourea Complexes: Synthesis, Characterisation and Their Catalytic Activity in Mild Sonogashira Cross-Coupling Reaction

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ABSTRACT

We report herein the synthesis of Pd(II) complexes featuring pivaloylthiourea derivatives to investigate their catalytic behaviour in Sonogashira cross-coupling reactions as the homogenous catalyst. The SN_2 reactions have resulted in pivaloyl thiourea derivatives ligands with general formula $(CH_3)_3C(O)NHC(S)NHR$ introducing different substituent groups of NO_2 (**L1**), OCH_3 (**L2**), and H (**L3**) prior to form complexation with Pd(II) (**MC1**, **MC2**, and **MC3** respectively). All synthesised compounds were characterised *via* typical selected spectroscopic and analytical methods. Hence, catalytic screening activity revealed that Pd(II)-pivaloyl thiourea catalysed, featuring **MC3,** is the best catalyst as it gave a high conversion rate up to 99%.

Keywords: pivaloyl-thiourea; spectroscopic; Sonogashira; Pd-catalyst; phosphine-free

1. Introduction

The uprising research in transition metal-catalysed carbon-carbon cross-coupling reactions has attracted the highest intention among researchers in the practice of organic synthesis in the last two decades [1,2] due to its recognition as convenient one-step methods for the construction of carbon-carbon bonds. The chemistry and significance of alkynes derivatives are directly related with their existence in various natural product interest especially as biologically active substances [3,4] as well as for the production and development of materials for advanced materials application namely, organic light-emitting diode (OLED) [5,6] organic photovoltaic solar cells [7-9] non-linear optical devices [10,11] and liquid crystals properties [12]. Thus, the prominence development of methods for incorporating carbon-carbon triple bonds into the desired molecular framework remains an important research area to date. Besides, one of the prominent monoligated precatalyst backbones is to carry out the reaction under air-stable palladacycles that can be activated by deprotonation under mild reaction conditions to obtain the monoligated Pd(0)complex *via* reductive elimination of the intramolecular amine–aryl group from the pivaloyl-thiourea ligand [13,14].

Conventionally, the catalytic reaction of Sonogashira cross-coupling reaction is performed by palladium complexes in combination with phosphine based, copper iodide (CuI) as co-catalyst and a significant excess of tertiary amines such as triethylamine. However, problems associated with phosphine ligands are air and moisture sensitive in which involved high cost, demand for the inert environment. They arise with toxicity issues, which, to some extent, would limit any large scale of industrial applications. The presence of excess phosphine also can lead to the high toxicity of the reaction as well as can slow down the reaction rate due to the presence of steric hindrance [15]. The importance of ligands in modern homogeneous transition metal catalysis cannot be exaggerated. The coordination of ligand can change the structure and reactivity of a metal catalyst, in which it inherently changes the activation energy of elementary steps in a given catalytic process.

Therefore, there has been a great interest in the line to develop a non-phosphine catalyst for the higher achievement of activity, stability, and substrate tolerance,

which may allow the coupling reaction to be conducted under mild reaction conditions or at ambient environment. Thus, among a variety of synthesised ligands, thiourea derivatives seem to be very interesting due to the easily synthesised and able to form complexes with various transition metals, especially palladium [16]. The low cost of starting materials and insensitivity towards air and humidity have made thiourea a perfect ligand of choices. Previously, we also have reported our work related to thiourea derivative featuring propionic acid moiety coordinated to Pd(II) for Heck cross-coupling reaction and gave promising 100% conversion rate [17].

In a continuation of our research directions on the use of a palladium catalyst in cross-coupling reactions, herein, we report an efficient and mild catalytic system featuring pivaloylthiourea reacted with various amines of choice, namely, 4-nitroaniline, 4-methoxyaniline, and aniline. The selection of these ligands is due to their distinctive advantages such as a simple approach to synthesis ligands and their corresponding complexes, as well as they have never been utilised as ligands and catalysts in any reported cross-coupling reactions. Besides, the presence of various substituents strength either as an electron-donating or electron-withdrawing group gives a significant contribution to catalytic activity. The choice of palladium as a metal center in compounds attributed to its high stability, selectivity, and reactivity. Therefore, the suitability and performance of synthesised Pd(II) pivaloylthiourea complexes as a homogenous catalyst have been evaluated in Sonogashira cross-coupling reactions of phenylacetylene and various bromo-halides.

2. Materials and Characterisation

All chemicals used in this study were purchased from standard commercial suppliers and used as received without further purification. The Infrared (IR) spectra were recorded on Perkin Elmer Spectrum 100 Fourier Transform-Infrared (FTIR) Spectrometer by using KBr disc in the range between 4000 cm^{-1} to 400 cm^{-1}. UV-Vis spectra were recorded using Shimadzu UV-Vis Spectrophotometer in the range between 200 to 600 nm by using methanol as a solvent in a quartz cell (1 cm^3). The proton (^1H) 400.11 MHz and carbon-13 (^{13}C) 100.61 MHz Nuclear Magnetic Resonance (NMR) spectra were obtained on Bruker Avance III 400 spectrometer in

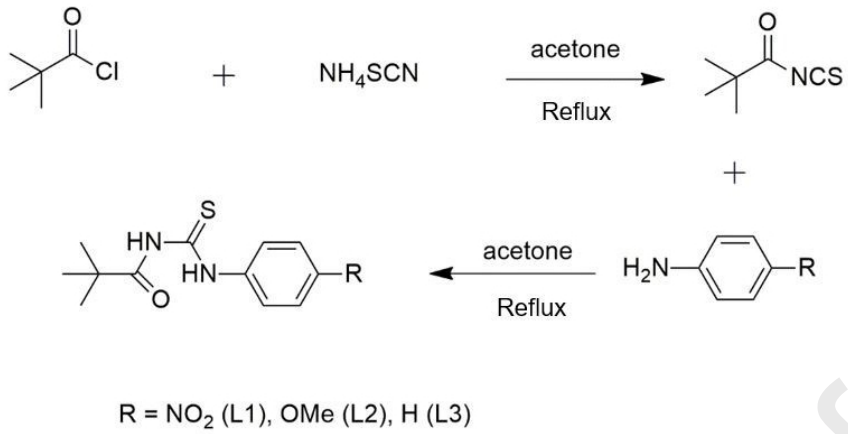
deuterated chloroform ($CDCl_3$) as solvent at room temperature in the range between δ_H 0-13 ppm and δ_C 0-190 ppm, respectively. Furthermore, Gas Chromatography (GC-Hewlett Packard-5890 series II) was used to determine the product conversions from catalytic testing using Flame Ionization Detection (FID) method. The microliter samples were injected at 50 °C. The temperature increment was set at 30 °C per minute, and the final temperature was at 280 °C. 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.

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

3. Methodology

3.1 Preparation of N-(4-nitrophenyl)-N'-pivaloylthiourea (L1)

A solution of pivaloyl chloride (5.87 g, 48.7 mmol) in 30 mL acetone was added dropwise into a solution of ammonium thiocyanate (3.70 g, 48.7 mmol) in 50 mL acetone in 250 mL three-necked round bottom flask. The reaction mixture was stirred continuously and put at reflux for *ca.* 2 hours until the colourless solution turned into light yellow with the formation of white precipitate. The progress of the reaction was monitored by thin-layer chromatography (TLC) in 7:3 (dichloromethane: hexane). Then, equivalent molar of 4-nitroaniline (6.21 g, 48.7 mmol) in 50 mL acetone was added into the solution and put at reflux for *ca.* 4 hours. After adjudged completion, the reaction mixture was cooled into room temperature and filtered before the addition of ice cubes to the filtrate. The precipitate formed was then filtered and recrystallised from methanol to afford yellow crystalline solid of the title product, **L1** (5.5 g, 19.55 mmol, 44%). The schematic pathway to the synthesis of pivaloylthiourea derivatives (**L1-L3**) is, as shown in Scheme 1.



Scheme 1. The synthetic pathway to the synthesis of pivaloylthiourea derivatives (**L1**-**L3**).

3.2 Preparation of N-(4-methoxyphenyl)-N'-pivaloylthiourea (L2)

In a similar manner to the synthesis of **L1**, a brownish-purple precipitate of title compound **L2** (6.60 g, 24.80 mmol, 51%) afforded from the reaction of pivaloyl chloride (5.87 g, 48.70 mmol), ammonium thiocyanate (3.70 g, 48.70 mmol) and 4-methoxyaniline (6.00 g, 48.70 mmol).

3.3 Preparation of N-(4-phenyl)-N'-pivaloylthiourea (L3)

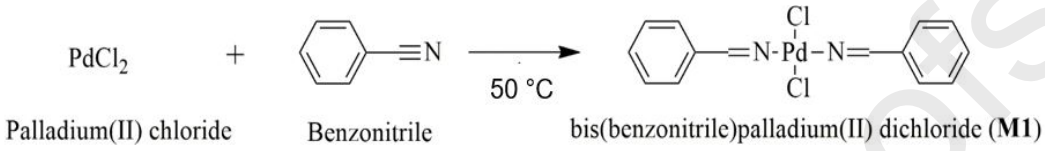
In a similar manner to the synthesis of **L1**, the white precipitate of **L3** (4.80 g, 20.26 mmol, 42%) afforded from the reaction between pivaloyl chloride (5.87 g, 48.70 mmol), ammonium thiocyanate (3.70 g, 48.70 mmol) and aniline (4.54 g, 48.70 mmol).

3.4 Preparation of palladium(II) complexes

*3.4.1 Preparation of bis(benzonitrile)palladium(II) dichloride (**M1**)*

The experimental details concerning the synthesis of Pd(II)-thiourea derivatives had already been reported in the previous literature [18]. A solution of benzonitrile (15 mL) was added dropwise to $PdCl_2$ (0.50 g, 2.82 mmol) in 100 mL three-necked round bottom flask. The reaction mixture was heated (50 °C) in an oil bath for *ca.* 8

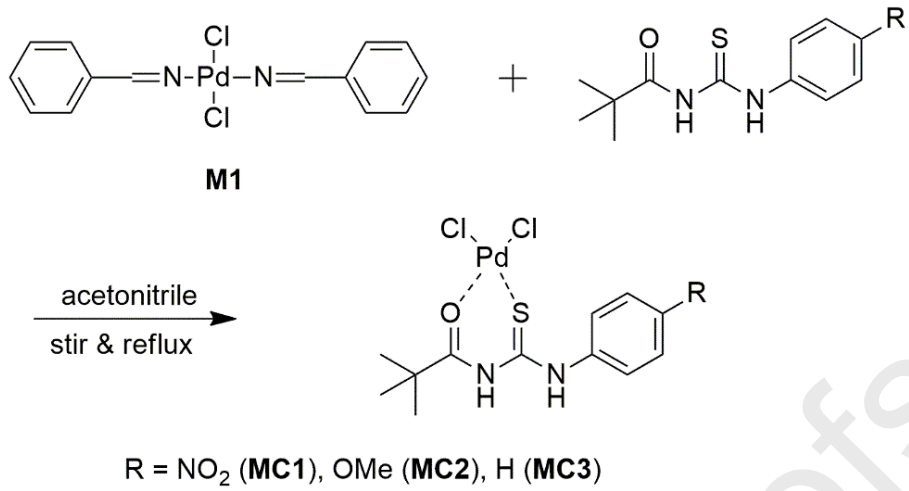
hours. The change of solution colour was observed from reddish to dark reddish-brown after 5 hours of heating. The reaction mixture was then left undisturbed at room temperature overnight to allow the formation of a red-orange crystalline precipitate. The solid was collected by vacuum filtration to give a product of **M1** (0.10 g, 20%). Scheme 2 illustrates the schematic pathway to the synthesis of Pd(II) complex.



Scheme 2. the schematic pathway to the synthesis of Pd(II) complex.

*3.4.2 Preparation of dichloro [N-(4-nitrophenyl)-N'-pivaloylthiourea-κ²S,O] palladium(II) (**MC1**)*

A solution of L1 (0.10 g, 0.36 mmol) in 3 mL acetonitrile was added dropwise into a solution of M1 (0.14 g, 0.36 mmol) in 8 mL acetonitrile in a three-necked round bottom flask. Then, the reaction mixture was put at reflux and stirred continuously for *ca.* 3 hours under dry-nitrogen flow. The colour of the solution changed from light red-brick to brownish solution after 3 hours of reaction. The precipitate formed was filtered, and the solvent removed *in-vacuo*. The synthetic approach applied to the synthesis of Pd(II) complexes is as shown in **Scheme 3**. The green-brownish solid formed labelled as MC1 (0.10 g, 64%).



Scheme 3. The synthetic approach to the synthesis of Pd(II)-pivaloyl thiourea complexes.

*3.4.3 Preparation of dichloro [N-(4-methoxyphenyl)-N'-pivaloylthiourea-κ²S,O] palladium(II) (**MC2**)*

In a similar manner to the synthesis of **MC1**, an orange-brown precipitate of **MC2** (0.10 g, 82%) was obtained from the reaction of **M1** (0.17 g, 0.44 mmol) and **L2** (0.12 g, 0.44 mmol) in acetonitrile as solvent.

*3.4.4 Preparation of Dichloro [N-(4-phenyl)-N'-pivaloylthiourea-κ²S,O] palladium(II) (**MC3**)*

In a similar manner to the synthesis of **MC1**, a brown precipitate of **MC3** (0.14 g, 74%) was obtained from the reaction of **M1** (0.30 g, 0.79 mmol) and **L3** (0.18 g, 0.79 mmol) in acetonitrile as solvent. (0.14 g, 74%).

3.5 General procedure for the Sonogashira cross-coupling reaction

Aryl bromides (1.00 mmol) and terminal alkynes (1.10 mmol) were charged to a mixture of 1.00 mol% Pd(II) pivaloylthiourea derivatives (**MC1-MC3**), CuI (1.00 mol%), and triethylamine as a base (2 mmol) in 5 mL N, N'-dimethylformamide (DMF) in a tube of Radley's 12-placed carousel. The mixture was heated (60 °C) with constant nitrogen flow for 24 hours. The aliquot was taken out after 24 hours

and analysed by GC-FID to investigate the percentage of product conversion. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate and water. The collected organic layer was acidified with 2% hydrochloric acid (HCl) to yield white-brownish precipitate. The precipitate was filtered and dried *in-vacuo* to give a brown solid cross-coupling product.

4. Results and discussion

4.1 Spectroscopic studies

4.1.1 Infrared spectroscopy analysis of L1-L3

The presence of different vibrational modes of functional groups in all synthesised ligands (**L1**-**L3**) was determined by using Fourier-Transform Infrared (FT-IR) spectroscopy in the range 400-4000 cm^{-1}. From the experimental data, it showed five major absorption bands of interest, namely, ν(N-H), ν(C=O), ν(C=N), ν(C-N) and ν(C=S). Two absorption bands of ν(N-H) in the secondary thioamide group can be observed at 3290 to 3123 cm^{-1} and 3149 to 3036 $cm^{-1,}$ which represent asymmetric and symmetric stretching vibration respectively. These assignments were supported by previous studies, which stated that ν(N-H) could be seen above 3000 cm^{-1} due to the occurrence of intramolecular hydrogen bonding [19, 20]. Influential absorption band, which is accredited to carbonyl stretching vibration ν(C=O), appears at about 1678 to 1666 cm^{-1} in synthesised ligands, apparently decreasing in frequencies compared to the ordinary carbonyl absorption, 1710 cm^{-1} [21,22]. This resulted from its conjugated resonance with the phenyl ring and the formation of intramolecular hydrogen bonding with N-H in the -C(O)NHC(S)NH- moiety.

The existence of intramolecular hydrogen bonds led to an increase in their polarity, which decreases the strength of the double bond and thus, moves the absorption to a lower wavenumber as reported. The most crucial changes were observed for the presence of the C=S stretching frequency at 741-760 cm^{-1}. The frequencies for ν(C=S) were found at low frequency due to the decrease of double-bond character and the lower nucleophilic character of the sulfur atom in the C=S

moiety of the synthesised materials. The infrared spectra for all synthesised ligands **L1-L3** are illustrated in supporting information (**Fig. S.I 1 – Fig. S.I 3**).

*4.1.2 Infrared spectroscopy analysis of **MC1** – **MC3***

Three palladium complexes have been successfully synthesised by the reaction between ligand **L1**, **L2**, and **L3**, respectively, with bis(benzonitrile)palladium(II) dichloride (M1) to afford corresponding palladium complexes labelled as **MC1**, **MC2**, and **MC3**. Due to the unsuccessful single crystals growth for single-crystal X-ray Diffraction analysis, the molecular structures of the complexes were suggested from the spectroscopic results of FTIR, NMR, and electronic transition analyses. From FTIR spectra, the frequencies of essential bands of interest namely $\nu(N_1\text{-}H_1)$, $\nu(N_2\text{-}H_2)$, ν(C=O), ν(C-N) and ν(C=S) are evaluated and compared between the free ligands and its corresponding metal complexes. Both $\nu(N_1\text{-}H_1)$ and $\nu(N_2\text{-}H_2)$ bands shifted to lower frequencies at ca. 132 to 137 cm^{-1} and 108 to 173 $cm^{-1,}$ respectively, in complexes of **MC1** and **MC3** rather than their designated ligands. However, **MC2** complex reported higher frequency shifting at around 7.83 cm^{-1} in $\nu(N_1\text{-}H_1)$ and slightly shifted to lower wavenumber in $\nu(N_2\text{-}H_2)$ at approximately 8.77 cm^{-1} in comparison to their free ligand.

According to previously reported literature [23], the stretching of N-H vibrations is usually observed in lower frequencies and form a weak and broad band at approximately 2900-3200 cm^{-1} in complexes relative to their ligands which suggest the alteration of the double bond and single bond character of **L1**, **L2** and **L3** due to the complexation with palladium(II) [24,25]. Besides, an upward shift of ν(C=O) is identified from 1666 to 1678 cm^{-1} in the spectra of the free ligands to 1686 to 1695 cm^{-1} in the complexes of **MC1**, **MC2**, and **MC3**, which might be attributed to π back donation that occur between the thiocarbonyls and the metal centre. Besides, the ν(C-N) stretching vibration of **L1** has shifted to lower frequencies at approximately 10 cm^{-1} upon coordination to palladium, but surprisingly, in **MC2** and **MC3**, the ν(C-N) bands are shifted by ca. 23 to 25 cm^{-1} to higher frequencies, as a moderately strong band. The changes towards a higher shift of C-N bands indicate the weakening of the C-N or C=S bonds on coordination. The C=S bond tends to lose its double bond character while the C-N gains electron density, raising its bond character. Table 1 indicates the comparison of vibrational analyses between

free ligands **L1-L3** and their complexation with Pd(II) (**MC1-MC3**). The infrared spectra for all synthesised ligands MC1-MC3 are illustrated in supporting information (**Fig. S.I 4 – Fig. S.I 6**).

Table 1. Comparison of vibrational analyses of all synthesized ligands and complexes.

Compounds	FTIR absorption bands (cm^{-1})				
	$\nu(N_1\text{-}H_1)$	$\nu(N_2\text{-}H_2)$	ν(C=O)	ν(C-N)	ν(C=S)
L1	3284	3149	1678	1325	737
MC1	3147	2977	1695	1314	732
L2	3123	3036	1666	1324	743
MC2	3131	3027	1688	1349	724
L3	3290	3149	1676	1326	736
MC3	3159	3041	1686	1349	764

4.1.3 NMR analysis of L1-L3

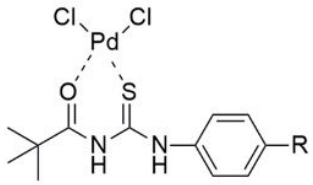
For structural elucidation, both ^{1}H and ^{13}C NMR of **L1-L3** are consistent with the expected molecular structures. Two singlet resonances were observed at deshielded region at two different environments δ_H 8.58-8.63 ppm and δ_H 12.33-13.00 ppm accordingly in which were allocated for the appearance of NH-C=O and NH-C=S moieties due to the anisotropic effect from aromatic moieties and intramolecular hydrogen bonding (N-H···O) from the *trans-cis* conformation of thiourea derivatives [26,27], N-H resonances for **L1** shifted further downfield to δ_H 8.64 and 13.00 ppm due to the presence of a strong electron-attracting group, $-NO_2$ which leads to stronger interaction of hydrogen bonding compared to the existence of the electron-donating group, -OMe (**L2**) and H (**L3**). The distinctive multiplet resonance presence in the range of δ_H 6.50-8.00 ppm attributed to the presence of aromatic protons. For ^{13}C NMR, two signals within shielded region δ_C 26.9-27.0 ppm and δ_C 39.9-40.1 ppm represent methyl carbons and quaternary carbons, respectively. Meanwhile, the aromatic carbons resonances can be found in between δ_C 114.0-158.0 ppm for all compounds. The carbonyl and thione carbons can be observed within range δ_C 178.5-179.8 ppm at the most deshielded region due to the

formation of intramolecular hydrogen bonding and the presence of electronegative atoms of oxygen and sulfur. The signal of thione carbon (C=S) appears at the highest values δ_C 179.8 ppm due to the lower excitation energy of n→π*, which suggests the existence of very strong electron-withdrawing substituent that reduce the nucleophilic character of the C=S group. The spectra for ^1H and ^{13}C NMR for all synthesised ligands **L1-L3** illustrated in supporting information (**Fig. S.I 7 – Fig. S.I 12**).

*4.1.4 NMR analysis of **MC1-MC3***

In ^1H NMR analyses of all complexes, the N-H signals became less intense as well as shifted towards the downfield region upon coordination with palladium. The resonance for N_1-H_1 proton exhibited the most significant shift towards the downfield area from δ_H 8.58-8.64 ppm (**L1-L3**) to δ_H 11.10-11.30 ppm upon complexation. Besides, the proton for N_2-H_2 experience slightly changes from δ_H 12.33-13.00 ppm (**L1-L3**) to δ_H 12.46-13.05 ppm in their corresponding complexes, **MC1-MC3**. The substantial downfield shifting is affected by the reduced electron density around N_1-H_1 due to the effect from the metal ion, which resulted in a reduction of the π-electron character of thione and thiocarbonyl and decreasing the number of unshared pairs of electrons from two to one prior coordination with Pd(II). From this fact, this indicates that the synthesised ligands **L1-L3** are coordinated to palladium (II) *via* thione and thiocarbonyl moieties. In addition, the proton resonances of the phenyl ring in free ligands are attributed around δ_H 6.90-8.27 ppm, while, for the formation of complexes, the resonances are assigned around δ_H 6.94-8.36 ppm. The most crucial shift in all compounds **MC1-MC3** is on carbonyl and thione moieties, which may arise due to coordination towards the metal centre. The signal for carbonyl slightly shifted upfield while thione has shifted towards the downfield region. Moreover, the carbons on the phenyl rings also shifted towards the upfield and downfield region compared to their corresponding values in the free ligands. This may be attributed to the fact that coordination of oxygen and sulfur atoms through their lone pairs may lead to two opposing effects which are, the presence of the electron-withdrawing effect of Pd(II) through σ-bonding and NO_2 substituent on the phenyl ring, would decrease the electron density around C=S and carbon atoms of the ring. Additionally, a π-back bonding occurs

through d_{π}-p_{π} interaction between Pd(II) and a π* orbital of C=O which able to accept electrons from the metal, thereby increasing the electron density at the carbon atoms of carbonyl, hence, shifted the δ_C value to the higher field. Based on the results obtained from FTIR, ^{1}H, and ^{13}C NMR can be concluded that the ligands are coordinated to the metal centre, Pd(II) through C=O and C=S. The suggested molecular structures of all complexes obtained are as illustrated in Fig. 1. The spectra for ^{1}H and ^{13}C NMR for all synthesised metal complexes (**MC1**-**MC3**) shown in supporting information (**Fig. S.I 13** – **Fig. S.I 18**).



Where R = NO_2 (**MC1**), OMe (**MC2**), H (**MC3**)

Fig. 1. General molecular structure for Palladium(II)-Pivaloyl thiourea complexes.

4.1.5 Electronic analysis

The electronic transition of **L1**-**L3** shows two influential bands represent chromophores for carbonyl (C=O) and thione (C=S), which exhibit mixed transitions of n→π* and π→π*. The broad and weak intensity of absorption bands observed at 231-261 nm represent the carbonyl group, which is believed to exhibit n→π* and π→π* transitions. These n→π* transitions involve the excitation of an electron in a nonbonding atomic orbital such as unshared electrons on O, N, S, or a halogen atom, to an antibonding π* orbital. However, from the absorption of C=O, a hypsochromic shift occurred due to the presence of auxochrome methoxy and hydrogen in the compound. Besides, the broad and weak intensity of the absorption band can be observed at 269-294 nm is assigned to the transition involving the mixed transition of n→π* and π→π* in thione moiety (C=S). The π→π* transition involves molecules that contain double or triple bonds or aromatic rings having π electron is excited to an antibonding π* orbital. A presence of NO_2 band is observed in the UV spectrum of **L1** with maximum absorption observed at 334 nm. The appearance of a shoulder or weak band is attributed to a highly conjugated system in every synthesised compound. After complexation occurred, a valuable shift of these

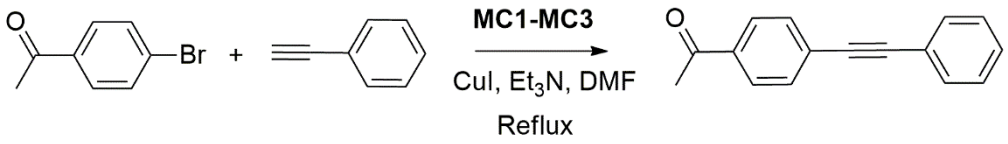
bands to the low frequency is observed, which indicates the participation of functional groups in coordination to the metal centre. UV-Vis experimental results revealed that new absorption bands or a "hump" appeared in region 400 – 682 nm that could be assigned as charge transfer (CT) of ligand to metal, O→Pd(II) and S→Pd(II) as well as Pd(II) d-d bands. These observations are associated with the participation of the ligand C=O and C=S groups in coordination to the central metal ion. However, in this study, the d-d bands are not well resolved as observed in the spectra of complexes, in which the bands attributed as weak shoulder and low molar absorptivity, which may occur because of the charge transfer (CT) transition of the ligand is overlapped with d-d transitions. The significant electronic absorption bands for the ligands and their complexes are given in Table 2. The electronic transition spectra for all synthesised ligands **L1-L3** and their metal complexes, **MC1-MC3** are illustrated in supporting information (**Fig. S.I 19** – **Fig. S.I 24**).

Table 2. UV-Vis data for the ligands (**L1-L3**) and their corresponding complexes (**MC-MC3**).

Compound	Absorption λ/nm (Extinction Coefficient ε/ M^{-1} cm^{-1})/	Possible Assignment
L1	231.2 (14011)	n→π* and π→π*
	269.4 (17700)	n→π* and π→π*
	334.6 (13206)	n→π* and π→π*
L2	261.0 (12043)	n→π* and π→π*
	285.6 (8568)	n→π* and π→π*
L3	247.6 (14825)	n→π* and π→π*
	294.2 (11430)	n→π* and π→π*
MC1	237.5 (5040)	n→π* and π→π*
	270.5 (4022)	n→π* and π→π*
	345.5 (4659)	n→π* and π→π*
	470.0 (674)	CT and d-d
MC2	258.0 (11107)	n→π* and π→π*
	327.5 (7833)	n→π* and π→π*
	435.0 (563)	CT and d-d
MC3	277.0 (18371)	n→π* and π→π*
	459.0 (747)	CT and d-d

4.2 Catalytic activity of Pd(II)-pivaloyl thiourea derivatives (MC1-MC3) in Sonogashira cross-coupling reactions

The use of metal transition complexes as a catalyst has given a considerable revolution in this field of cross-coupling reactions between a terminal alkyne and aryl halides, in which they are widely used for the rapid and efficient synthesis of alkyne derivatives. The catalytic activity of the homogenous **MC1**-**MC3** catalysts was investigated in the Sonogashira cross-coupling on the model reaction of 4-bromoacetophenone with phenylacetylene catalysed by 1.00 mol% catalysts **MC1**-**MC3**, copper (I) iodide as co-catalyst, triethylamine as a base in 5 mL N-N'-dimethylformamide (DMF) as solvent under constant nitrogen flow at 60 °C for 24 hours (Scheme 4). A control reaction was conducted by following the same procedure in the absence of Pd-catalysts. After 24 hours of reaction, each of the reaction mixtures was analysed by GC-FID to determine the percentage conversion of catalytic activity obtained by the **MC1**-**MC3** catalyst. The remaining mixture was then cooled to room temperature prior to extraction. As shown in Table 3, **MC3** gave an excellent performance with almost 99% of product conversion, followed by **MC2** and **MC1,** which exhibit 35% and 27% of product conversion, respectively. Apparently, without any metal-catalysed, the control reaction gave only a 22% conversion of limiting reactant into the product. **MC3** and **MC2** act as the most significant catalyst due to the presence of electron-donating substituent, **MC2** (OCH_3), and **MC3** (H), which can donate more electrons and can facilitate better in transmetallation process [28].



Scheme 4. The general protocol for Sonogashira cross-coupling reaction.

Table 3. [a]The effect of different catalyst **MC1-MC3** on the Sonogashira cross-coupling reaction.

Entry	Cat.	Base	Solvent	Yield (%)[b]
1	-	Triethylamine	DMF	22
2	**MC1**	Triethylamine	DMF	27
3	**MC2**	Triethylamine	DMF	35
4	**MC3**	Triethylamine	DMF	99

[a]Reaction conditions: 4-bromoacetophenone (1.00 mmol), phenylacetylene (1.10 mmol), catalyst (1.00 mol %), CuI (1.00 mol %), base (2.00 mmol), solvent (5 mL), 60 °C, 24 h.
[b]GC yield against calibrated internal standard.

4.3 Optimisation of catalytic activity

The presence of the base is one of the essential roles in defining the rate of reaction and product formation in the Sonogashira cross-coupling reaction. Without a base, only 15% of the targeted product was produced [29, 30]. Various types of bases such as organic base, namely triethylamine (Et_3N) and inorganic bases, for example, sodium carbonate (Na_2CO_3), sodium hydrogen carbonate ($NaHCO_3$) and sodium acetate (NaOAc)were screened in the reaction model of 4-bromoacetophenone with phenylacetylene to assess their catalytic activity. Amongst them, Et_3N was found to be the most efficient base in terms of product yield, which gave almost 99% of product conversion, while inorganic bases such as NaOAC and $NaHCO_3$ exhibit an acceptable percentage of product conversion 76% and 72% respectively. The least capable base for the reaction model is Na_2CO_3, which only gave 26% of product conversion (Table 4). The usage of Et_3N as a base has resulted in a remarkably higher yield in the Sonogashira reaction, which might occur due to its high solubility in the reaction mixture. Based on previously reported literature, it was reasonable to suggest that the improvement of base solubility in the solvent would lead to the acceleration of the reaction rate [31, 32]. Results indicated that organic amines are more efficient than inorganic base because they efficiently trap hydrogen halide formed in the reaction. Thus, it proves that the use of Et_3N helps in the enhancement of catalysis as well as in the absorption of hydrogen halide.

The amount of catalyst loading in the catalytic system is another critically important in the Sonogashira cross-coupling reaction as it may affect the efficiency of overall catalytic activity. In this study, four different palladium catalysts loading, which is 0.25, 0.50, 1.00, and 1.50 mol%, were used to study the effect of catalyst loading on the conversion of 4-bromoacetophenone at 60 °C. As expected, the model reaction gave the lowest product conversion in the absence of catalyst, and most of the starting material remained intact (Table 3, entry 1). From the results obtained in Table 5, the conversion of 4-bromoacetophenone increases with increasing catalyst loading. However, as can be seen from Table 5, using a higher amount of the catalyst has not resulted in further enhancement in the effectiveness of reaction (Table 5, entry 4). When 1.50 mol% of catalyst loading was used, the percentage of conversion decreased to give poor yield. Thus, at higher catalyst loadings, the intrinsic catalytic activity is lower. This implicates the formation of large unreactive Pd(0) clusters, formed *via* aggregation, at higher catalyst loadings, which may serve as a reservoir for the reactive Pd(0), possibly a mononuclear, catalytic species [33]. Meanwhile, the highest turnover number (TON) value of 100 was achieved when using 1.00 mol% of catalyst loading for 24 hours reaction. Thus, the choice of 1.00 mmol% catalyst loading is suitable as it gave the highest TON after the same period of reaction time compared to other catalyst loadings. From the observations tabulated in Table 3-Table 5, we conclude that 1.00 mol% of the catalyst (**MC3**), Et_3N (1.00 mmol) as the base in DMF at 60 °C, is the appropriate reaction parameters for this product synthesis in Sonogashira cross-coupling reaction.

Under the optimised reaction conditions, all the complexes (**MC1**-**MC3**) were tested for a variety of activated and un-activated aryl bromides (Table 6). As shown in Table 6, **MC1**-**MC3** catalysts gave a high yield under optimum reaction conditions, proving their wide substrate tolerance. From the results obtained, high catalytic activity with good to excellent yields was observed in the coupling of electron-deficient aryl bromides possessing an electron-withdrawing group such as 4-bromoacetophenone (Table 6, entry 1). On the other hand, the reaction efficiency of non-substituted bromobenzene and electron-rich aryl bromides with electron-donating (4-bromoanisole) in (Table 6, entry 2 and 3) were low probably due to the

possible homo-coupling of alkynes in association with the decrease reaction rate in the oxidative addition step of carbon-bromo bonds to the palladium metal while using deactivated aryl bromides [34, 35]. As expected, the reactants of aryl bromides consist of electron-withdrawing or electron-donating groups exhibited a noticeable alteration in reactivity, indicating that the reaction was sensitive to the electronic characteristics of the substituent under the present reaction conditions. In this Sonogashira cross-coupling reaction, we believe that the pivaloyl thiourea derivatives associated with Pd(II) complexes (**MC1**-**MC3**) provide the synergetic steric and electronic effects to confer the appropriate properties to the metal centre to optimise it for the critical steps of the catalytic cycles. Therefore, the proposed mechanism for the Sonogashira cross-coupling reaction [29] is demonstrated in Scheme 5. The first step of oxidative-addition involved the activation of the catalyst to yield the chloride-free catalytic species before the addition of aryl bromide to this active site of the complex. The next step is the addition of phenylacetylene and formation of a Pd-acetylide complex *via* the transmetallation route. The final step is the formation of the product *via* a reductive–elimination process and liberating the catalyst for the next catalytic cycle.

Table 4. [a]Effect of bases on Sonogashira reaction of phenylacetylene and 4-bromoacetophenone.

Entry	Base	Catalyst	Solvent	Yield (%)[b]
1	Et_3N	**MC3**	DMF	99
2	Na_2CO_3	**MC3**	DMF	26
3	$NaHCO_3$	**MC3**	DMF	72
4	NaOAc	**MC3**	DMF	76

[a]Reaction condition: [substrate]= 1.00 mmol; [base]=2.00 mmol; [catalyst loading]= 1.00 mol%; [CuI] = 1.00 mol%, DMF=5 mL; temperature 60 °C; time = 24 hours.
[b]GC yield against calibrated internal standard.

Table 5. [a]Effect of catalyst loading on the Sonogashira reaction of phenylacetylene and 4-bromoacetophenone.

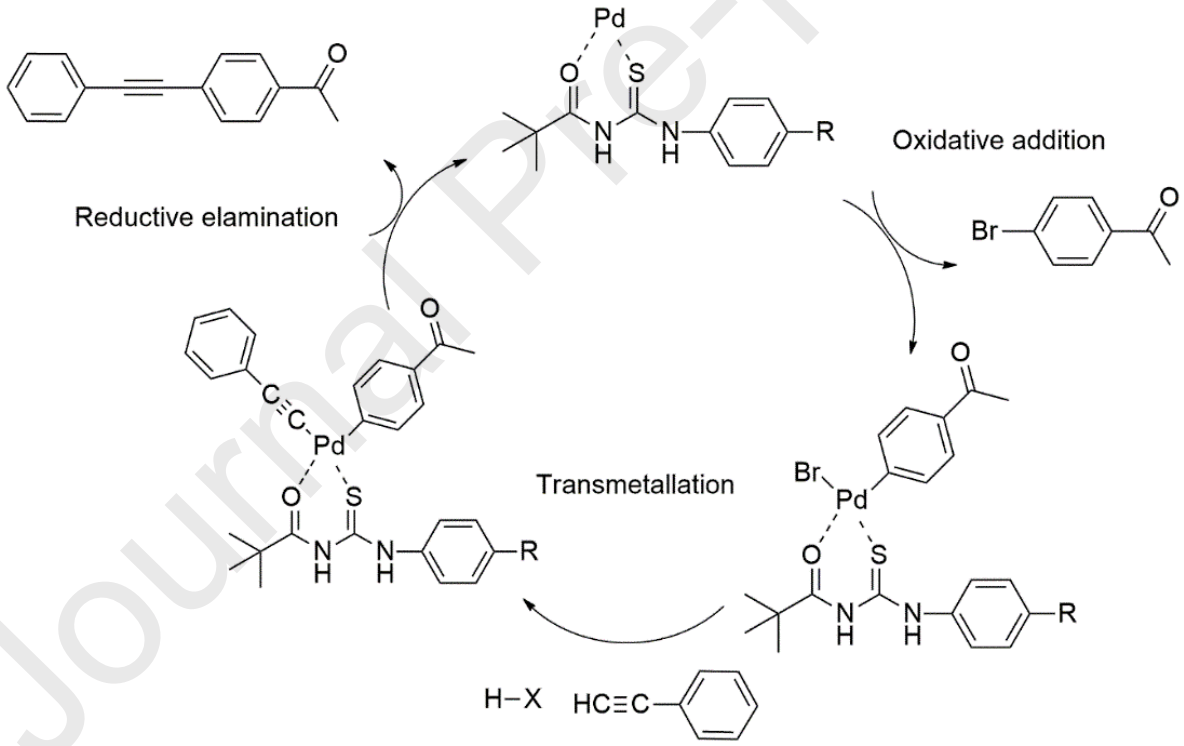
Entry	Base	Catalyst	Catalyst loading (%)	Solvent	Yield (%)[b]
1	Et_3N	**MC3**	0.25	DMF	17 (68)
2	Et_3N	**MC3**	0.50	DMF	28 (56)
3	Et_3N	**MC3**	1.00	DMF	99 (100)
4	Et_3N	**MC3**	1.50	DMF	18 (12)

[a]Reaction condition: [substrate] = 1.00 mmol; [CuI] = 1.00 mol%, [Et_3N] = 2.00 mmol; DMF = 5 mL; temperature 60 °C; time = 24 hours; Turn over number (TON) = mmol product/ mmol catalyst used.
[b]GC yield against calibrated internal standard.

Table 6. [a]Sonogashira reaction of several aryl bromides with phenylacetylene.

Entry	Aryl Bromides	Conversion of Aryl Bromides (%)[b]			
		Control	**MC1**	**MC2**	**MC3**
1	4-bromoacetophenone	22	27	35	99
2	4-bromoanisole	9	19	17	20
3	bromobenzene	13	26	19	39

[a]Reaction condition: [substrate] = 1.00 mmol; [catalyst] = 1.00 mol%, [CuI] = 1.00 mol%, [Et_3N] = 2.00 mmol; DMF = 5 mL; temperature 60 °C; time = 24 hours.
[b]GC yield against calibrated internal standard.



Scheme 5. The proposed mechanism for the Sonogashira cross-coupling reaction.

5. Conclusions

We have synthesised three derivatives of palladium-pivaloylthiourea complexes. This Pd (II) complexes have been employed as catalysts in Sonogashira cross-

coupling reactions. For the Sonogashira coupling reaction, **MC3** exhibited efficient catalytic activity under copper(I) iodide co-catalyst in the Et_3N base and DMF solvent in an inert atmosphere. In this work, palladium complexes have been employed to act as a homogeneous catalyst in the Sonogashira cross-coupling reaction in which the compounds were tested as a homogeneous catalyst in the reaction model of phenylacetylene and 4-bromoacetophenone. The performances of all catalysts were investigated by using less reactive substrates of aryl bromides such as 4-bromoanisole and bromobenzene. Based on the experimental results obtained, these catalysts are effective for activated aryl bromides that possess an electron-withdrawing group. The activity follows in the order $COCH_3$>H>OMe.

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Disclosure statements

No potential conflict of interest was reported by the author(s).

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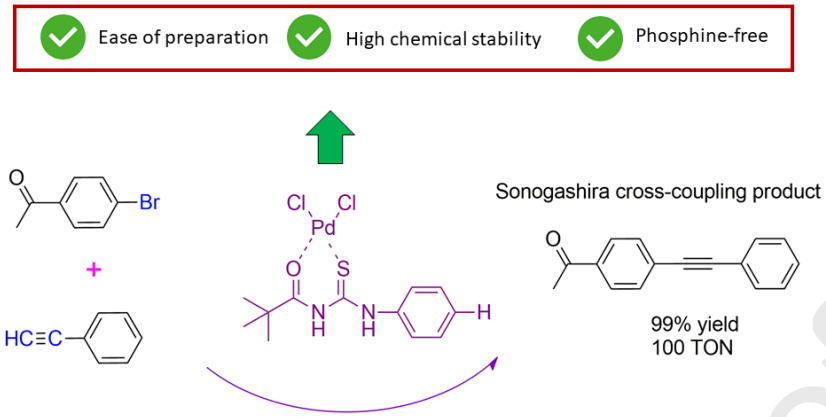
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



Highlights

include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

- Palladium(II)-Pivaloyl thiourea complexes successfully synthesized and characterized.
- The Pd(II) complexes gave significant results in the Sonogashira catalytic activity.
- **MC3** with no substitution exhibit the best catalyst as it gave a high conversion rate.