An Efficient Palladium-Thiourea Catalysed Heck Cross-Coupling Reaction for Molecular Electronic Interest

Wan M. Khairul [1*], Mohd Shahrul Shahmi Md Shariff[1], Rafizah Rahamathullah[1,2], Adibah Izzati Daud[1,2], Mustaffa Shamsuddin[3], and Siti Kamilah Che Soh[4]

1. School of Fundamental Science, Universiti Malaysia Terengganu, 21030 Kuala Terengganu, Terengganu, Malaysia
2. Faculty of Engineering Technology, University Malaysia Perlis (UniMAP), Padang Besar, 02100 Perlis, Malaysia
3. Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, 81310 Skudai, Johor, Malaysia
4. School of Marine Science and Environment, Universiti Malaysia Terengganu, 21030 Kuala Terengganu, Terengganu, Malaysia

*e-mail: wmkhairul@umt.edu.my

Abstract

The synthesis and utilization of C-C bonds formation are concerned about the key steps for the building of several conducting molecular electronics involving many asymmetric catalysts approached, which is an essential task that most researchers would ignore in preparing these materials to enhance the production yield of cross-coupling materials. Despite the enormous progress, there still remains a great demand for economic and practicable cross-coupling processes involving ultra-low catalyst loadings with high turnover numbers due to the employment of conventional metal catalyst. Thus, there has been an excessive interest to cultivate non-phosphine palladium catalysts for excellent achievement of activity, stability, and substrate tolerance which permit the coupling reactions to be conducted under mild reaction condition at ambient atmosphere. In this contribution, N-(4-nitrophenylcarbamothioyl)-N'-(4-methylbenzoyl) thiourea (**LT1**) and its metal complex of **MLT1** featuring Pd (II) have been successfully characterised via typical spectroscopic methods namely; Infrared (IR) spectroscopy, Ultraviolet-visible (UV-Vis) spectroscopy, CHNS elemental analysis, and Nuclear Magnetic Resonance (^{1}H and ^{13}C NMR). In turn, catalytic studies of palladium catalyst (**MLT1**) were tested for its homogenous catalytic activity in Heck cross-coupling reaction. The reaction was monitored by Gas Chromatography-Flame Ionisation Detector (GC-FID). Results reveal that **MLT1** exhibits 100% of conversion starting material into a cross-coupling product, which was alkene-based compound.

Abstrak

Palladium-Tiourea Yang Efisien Sebagai Katalis Reaksi Gandengan Silang Heck Untuk Molekul Elektronik. Sintesis dan penggunaan pembentukan ikatan C-C perlu diperhatikan sebagai langkah utama untuk membina beberapa molekul elektronik terkonduksi yang melibatkan banyak katalis-katalis asimetris, yang merupakan tugas yang sering diabaikan oleh kebanyakan peneliti dalam menyediakan bahan-bahan ini untuk meningkatkan pengeluaran hasil bahan gandengan silang. Meskipun telah banyak perkembangan dalam hal ini, masih ada permintaan yang tinggi untuk proses gandengan silang yang lebih ekonomis dan praktis yang hanya melibatkan pembekalan katalis yang sangat rendah dengan hasil perolehan yang tinggi dengan penggunaan katalis logam biasa. Oleh karena itu, terdapat banyak kepentingan untuk menghasilkan katalis paladium tanpa fosfina untuk pencapaian yang cemerlang dari segi aktivitas, kestabilan dan toleransi substrat yang membenarkan reaksi gandengan silang yang dijalankan dalam keadaan reaksi sederhana pada keadaan atmosfer tertentu. Dalam kajian ini, N-(4-nitrofenilcarbamotionil)-N'-(4-metilbenzoil) tiourea (**LT1**) dan kompleks logamnya yaitu **MLT1** menampilkan Pd(II) telah berhasil dicirikan melalui kaidah spektroskopi yang biasa yaitu spektroskopi sinar inframerah (IR), spektroskopi Ultra-Lembayung Sinar Nampak (UV-Vis), analisis unsur CHNS dan Resonan Magnetik Nukleus (^{1}H dan ^{13}C NMR). Selanjutnya, tindak balas ini dipantau menggunakan *Gas Chromatography-Flame Ionisation Detector* (GC-FID). Hasil penelitian menunjukkan **MLT1** memberikan 100% konversi bahan pemula menjadi produk gandengan silang yaitu senyawa berasaskan alkena.

Keywords: thiourea, catalyst, cross-coupling, Heck, alkene

1. Introduction

The palladium-catalyzed cross-coupling reaction is known to be as one of the most favorable reactions between aryl and vinyl electrophiles. It has been developed into a single operational method of a wide scope for the construction of C-C bond forming processes in the preparation of multifunctional derivatives towards the synthesis of electron-deficient alkynes [1-2], styrene [3-4], and stilbene derivatives [5] with numerous technology applications, which include natural products bioactive compounds, and active pharmaceutical drugs intermediate [6]. Recently, researchers are giving more attention regarding cross-coupling reaction due to its ability in the formation of C-C bonds with excellent yield. Since then, a large number of catalytic systems have been proposed to reduce the weaknesses associated with cross-coupling reaction, especially the involvement of phosphine as ligands in palladium catalyzed cross-coupling reactions [7-8].

The participation of palladium-phosphine complexes as a catalytic system for cross coupling reactions is well published. This is because palladium containing phosphine complexes are known to have an excellent catalytic activity for giving high yields, turnover number (TON), and turnover frequency (TOF) for various cross-coupling reactions [9-10]. However, most of these reactions have been carried out involving high cost metal catalyst, very reactive to air and moisture, and consequently, involving highly inert atmosphere conditions which are required to operate the catalyst for an efficient reaction work-up [11-12]. In addition, the oxidation of the phosphine to phosphine oxide and the cleavage of the P-C bond exhibit ligand dissociation, metal reduction, and termination of the catalytic cycle. In fact, most of the phosphorus ligands used in these reactions face the drawback of difficulty of synthetic work-up, very poor thermal, and air stability which become the key reasons for the growing interest in phosphine-free catalytic systems in every cross-coupling reaction. In the past few years, many attempts have been made to solve the existing problems, including the use of naturally occurring or semi-synthetic novel ligands/catalysts with the combination of low-toxic solvent, such as N,N'-dimethylformamide (DMF), tetrahydrofuran (THF), and dichloromethane (DCM) [13-14].

Therefore, in this study, thiourea derivatives are introduced to be used as ligand in palladium complexes because thiourea individually is known to be a versatile ligand which is widely used in organic synthesis. Thiourea acts as an ambidentate ligand that consists of two-toothed binds to the metal in which only one can attach to the metal. Thus, it should be able to do complexation with numerous metals. Inspired by the unique properties of thiourea derivatives in wide advanced material applications as well as previous reported structures of thiourea on several metal complexations [15-17], we report herein the design and synthesis of N-(4-nitrophenyl-carbamothioyl)-N'-(4-methylbenzoyl) thiourea (**LT1**) and their palladium complexation (**MLT1**) as homogenous catalyst cross coupling reaction (i.e. Heck cross coupling reaction). The role and behavior of this catalyst in the catalytic studies of Sonogashira cross-coupling reaction were further investigated. In this research, thiourea derivative and palladium (II) thiourea complexes were synthesized and fully characterized via several selected spectroscopic methods namely FTIR, UV-Vis, ^{1}H and ^{13}C NMR, and CHNS elemental analysis. In turn, the catalytic study was carried out to study the performance of palladium complex as a homogenous catalyst in the Heck reactions involving iodobenzene and 4-bromo-acetophenone.

2. Experiment

Materials and instrumentation All chemicals and solvents used in the experimental work-up were commercially purchased from standard suppliers namely Sigma Aldrich, Merck, Fisher Scientific and R&M Chemical. They were used as received without further purification and the reactions were carried out under an ambient atmosphere, and no special attention was taken to exclude air or moisture during experimental work-up. The infrared (IR) spectra were recorded on Perkin Elmer Spectrum 100 Fourier Transform Infrared Spectrometer by using potassium bromide (KBr) pellets or from neat liquids in the spectral range of 4000-400cm^{-1}. The UV-Vis spectroscopy was recorded in Spectrophotometer Shimadzu UV-1601PC in 1 cm path length quartz cell in methanolic solution with concentration 1×10^{-5}M for absorbance analysis. NMR spectra were recorded on Bruker Avance III 400 Spectrometer ^{1}H (400.11MHz) and ^{13}C (100.61MHz) using deuterated chloroform (CDCl$_3$) acting as the solvent and TMS an internal standard within the ranges between δ_H 0-15 ppm (^{1}H) and δ_C 0-200 ppm (^{13}C). In turn, Gas Chromatography Flame Ionization Detector (GC-FID) was used to verify the conversion starting material during catalytic activities. The percentage conversion of the products from the starting material was approximately calculated using the equation below.

GC-FID analysis conversion:

$$\% \text{ Convertion } = (A_{int} - A_{final})/ A_{int} \times 100 \qquad (1)$$

A_{int} : Peak area of reactant before reaction
A_{final}: Peak area of reactant after reaction

Synthesis of N-(4-nitrophenylcarbamothioyl)-N'-(4-methylbenzoyl) thiourea (LT1) The experimental details with regard to the synthesis of **LT1** have been reported previously in literatures [18]. However, some modifications in synthetic work and further characterization on the spectroscopic and analytical tasks were carried out and are discussed further in this report. A solution of

4-methylbenzoyl chloride (1 mmol), ammonium thio-cyanate (1 mmol), and 4-nitroaniline (1 mmol) in 50 mL acetone was put at reflux with constant and vigorous stirring for *ca.* 6 hours. Once the reaction was adjudged completion via a thin layer chromatography technique (TLC), the solution mixture was poured into a beaker containing ice blocks. The obtained yellow precipitate was filtered and purified via the recrystallization process from methanol to yield the title compound as **LT1** (77% yield). General synthetic pathway to afford **LT1** is as shown in Figure 1.

Complexation of N-(4-nitrophenylcarbamo thioyl) - N'-(4-methylbenzoyl) thiourea with palladium (II) chloride (MLT1) The reaction of palladium complexa-tion was carried out under an inert condition with continuous nitrogen flow. A solution of **LT1** (1 mmol) with palladium (II) chloride (1 mmol) in 30 ml acetonitrile was put at reflux with constant stirring for *ca.* 2 hours. The resulting grey precipitate obtained was then filtered

and washed with cold acetonitrile to yield the title compound as **MLT1**.

Catalytic testing on cross-coupling reaction (Heck system) Iodobenzene (1 mmol), methyl acrylate (2 mmol), triethylamine (2.5 mmol), and palladium cata-lyst of designated **MLT1** (1 mmol %) were mixed into Radley's 12-placed reaction carousel with the flow of nitrogen consistently under reflux condition (120 °C) for 24 hours. The progress of reaction was monitored by GC-FID as illustrated in Figure 2. Iodobenzene exhibits 100% of conversion.

In a similar manner as described above, 4-bromoa cetophenol (1 mmol, 0.2 g), methyl acrylate (2 mmol, 0.17 g), triethylamine (2.4 mmol, 2.42 g), and palladium catalyst of designated **MLT1** (1 mmol %) were mixed together in Radley's 12-placed reaction carousel whilst purged with nitrogen and heated to 120 °C for 24 hours. The reaction was monitored by GC-FID as shown in Figure 3. Conversion 4-bromoa-cetophenone: 83.88%.

Figure 1. The Synthetic Pathway for the Synthesis of LT1

Figure 2. Heck cross-coupling Reaction between Iodobenzene and Methyl Acrylate Catalyzed by MLT1

Figure 3. Heck cross-coupling Reaction between 4-bromoacetophenone and Methyl Acrylate Catalyzed by MLT1

3. Results and Discussion

Infrared (IR) Spectroscopy Analysis Infrared spectra of ligand LT1 and metal complex MLT1 revealed all the expected bands of interest namely v(N–H), v(C=O), v(C–N), and v(C=S) as shown in Figure 4 and 5. Two absorption bands of v(N-H) for LT1 in the secondary thioamide group can be observed at 3288 cm^{-1} to 3007 cm^{-1} while for MLT1 both v(N$_1$-H$_1$) and v(N$_2$-H$_2$) bands shifted to lower frequencies, 3117 cm^{-1} and 3011cm^{-1} which corresponded to symmetric and asymmetric stretching vibrations and have been examined to be the existence of C=O…H-N intramolecular hydrogen bond [19-20]. The stretching vibration for v(C=O) for LT1 was assigned at 1672 cm^{-1}, while for MLT1 the vibration signal has shifted to higher frequency, 1677 cm^{-1} suggesting formation of complexation of metal-thiourea between the ligand and the metal center at oxygen and attributed to π-back donation that occur between the thiocarbonyls and the metal center [21]. The v(C-N) band of LT1 can be observed at 1260cm^{-1}, while MLT1 was slightly shifted to higher frequencies, 1263cm^{-1}, as moderately strong bands which indicate the weakening of the C-N bond on coordination. Meanwhile, a strong band was observed at 746 cm^{-1} for free ligand LTU which attributed to v(C=S) stretching vibration, whereas for MLT1, the v(C=S) bands show slightly low frequency at 735 cm^{-1} that is in close agreement with a previously studied system [22]. The downshift frequency attributes to the formation of the Sulphur (S)-Metal (M) bond which leads to electron transfer from lone pair of Sulphur to the metal (M) [23].

Therefore, this has reduced the double bond character of the C=S bond. In addition, the empty π* orbital of the metal has been occupied and the interaction between (Pd-C-S) becomes stronger. Thus, the FTIR result shows the possible coordination of PdCl$_2$ with LT1 via oxygen atom in (C=O) and Sulphur atom in (C=S).

UV-Visible Spectroscopic Analysis. The UV-Vis spectrum of LT1 shows three important bands for the expected chromophores, namely phenyl, carbonyl (C=O) and thione (C=S) which exhibit $\pi \rightarrow \pi$* and $n \rightarrow \pi$* transitions as depicted in Figure 6. The strong absorption band observed at 258 nm can be suggested as phenyl and carbonyl group which is believed to undergo $\pi \rightarrow \pi$* and $n \rightarrow \pi$* transitions which involved the excitation of an electron in a nonbonding atomic orbital. Besides, broad and weak intensity of absorption band can be observed at 359 nm which was assigned to the transition involving thione portion (C=S) which is believed to exhibit $\pi \rightarrow \pi$* and $n \rightarrow \pi$* transitions. The broad absorption band observed in the region was due to π-conjugation of this compound with the phenyl rings (π - π* transition) and orbitals overlapping between C=O and C=S.

^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) Analysis The ^{1}H NMR spectrum for LT1 shows methyl resonance at δ_H 2.44 ppm because the hydrogen on the carbon attached to the phenyl ring were deshielded due to the contribution of electronegativity of the aromatic ring in the molecule as depicted in Figure 7. Meanwhile, the aromatic protons can be clearly observed as distinctive
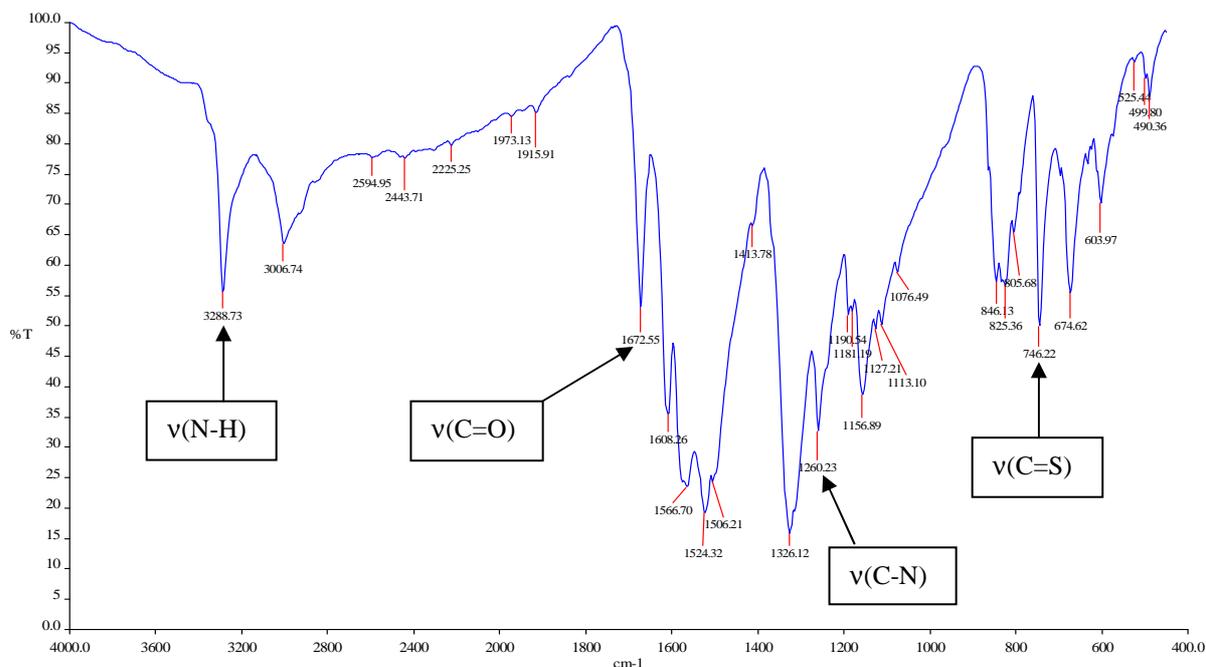

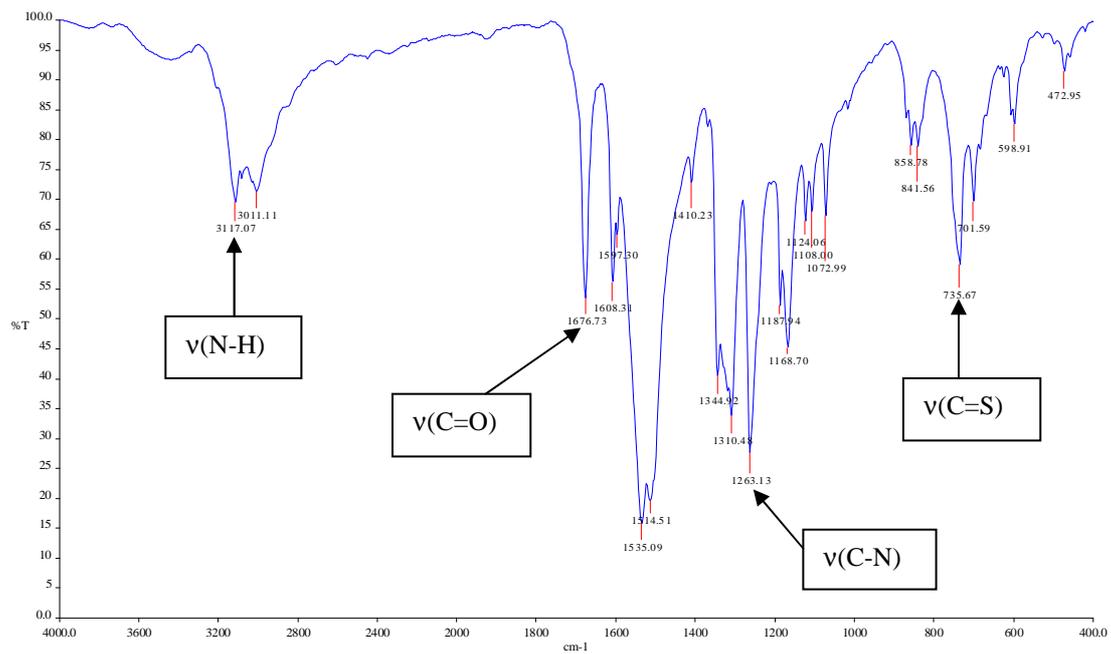**Figure 4. Infrared Spectrum of Ligand LT1**
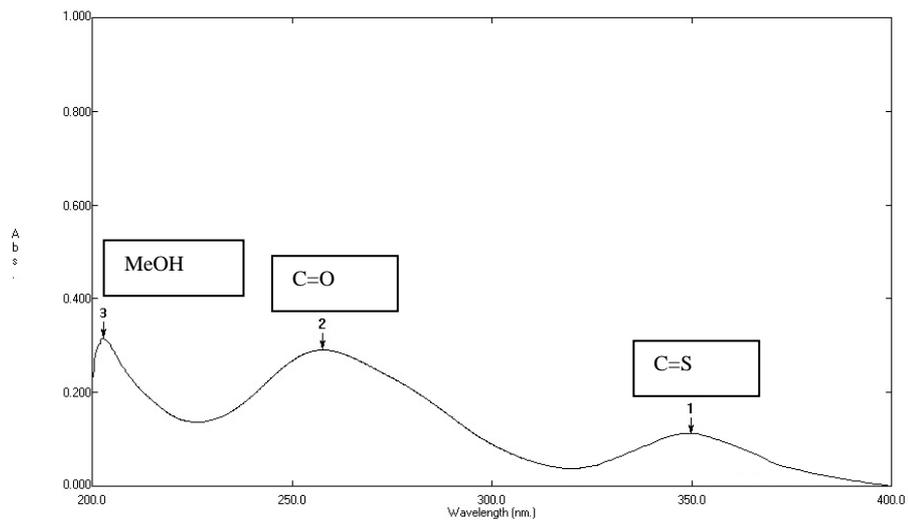
Figure 5. Infrared Spectrum of Metal Complex MLT1
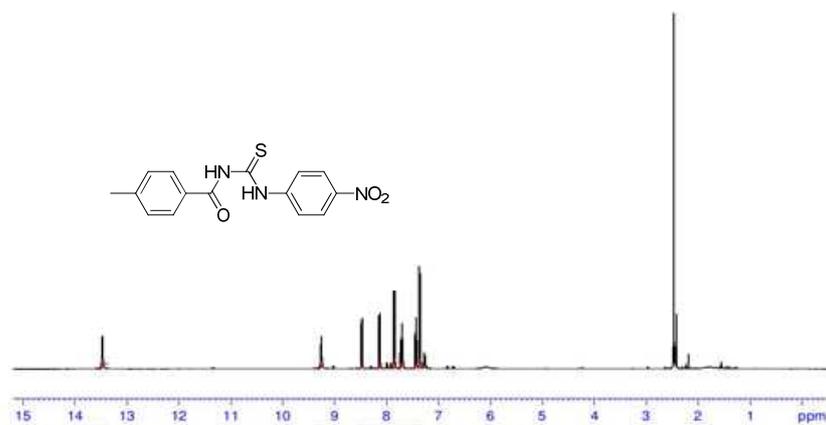

Figure 6. UV-Vis Spectrum of LT1

Figure 7. ^{1}H NMR Spectrum for LT1

pseudo-doublet resonances at around δ_H 7.42-8.49 ppm. These characteristics were strongly influenced by para-substitution of the aromatic rings in the molecule which were in agreement with the previous reports [24]. Two singlet resonances can be observed at δ_H 9.26 ppm and δ_H 13.47 ppm which attributed to NH group of NHC=O and NHC=S moiety respectively. The resonance for proton NHC=S, which bonded to thiocarbonyl and phenyl group, can be noticed at higher chemical shift compared to proton NHC=O that bonded to carbonyl and thiocarbonyl. These signals were different in terms of chemical shift due to the influences of the intra-molecular hydrogen bond in the molecule [25].

For ^{13}C NMR, **LT1** shows a resonance of methyl group at δ_C 21.72ppm due to the deshielding effect in the presence of aromatic rings that withdrew certain amount of electron density from the alkyl chain. This result reveals a good agreement with the previous reports on the similar systems [26]. Meanwhile, the resonances for both aromatic ring carbons were observed in the range of δ_C 125.20 to 145.04 ppm which corresponded to the phenyl rings in these compounds. Two individual resonances can be detected at δ_C 166.31ppm and δ_C 179.78 ppm which represented as C=O and C=S carbons respectively. These signals were slightly deshielded due to the formation of intramolecular hydrogen bonding in the molecule and increasing electronegativity of oxygen and Sulphur atoms. Figure 8 shows the ^{13}C NMR for **LT1**.

Catalytic Studies of Homogeneous Heck Reaction
The palladium complex MLT1 prepared in this study was tested as a homogenous catalyst in Heck cross-coupling reaction between iodobenzene with methyl acrylate and bromoacetophenone and methyl acrylate in

the presence of triethylamine at reflux temperature. The reaction was carried out in a Radleys 12-placed carousel reactor vessel, whilst continuously flushed with nitrogen gas. The reactor vessel was then heated at optimum temperature (120 °C) for *ca*.24 hours. The temperature was carefully controlled by a contact thermometer (±1 °C). In Heck cross-coupling reaction, the high tempera-ture—usually more than 100 °C—is needed to assist the activation of substrate such as iodobenzene. The reaction then was repeated between bromo acetophenone and methyl acrylate at the same time and condition. Catalytic loading was kept to 1.0 mol%, so as to give an expected turnover number of 100 if 100% conversion was achieved. The reaction was monitored by percentage (%) conversion of the aryl iodide and aryl bromide as starting materials by Gas Chromatography Flame Ionization Detector (GC-FID).

The data indicate that **MLT1** may be utilized as a homogenous catalyst in the Heck cross-coupling reaction as it gave a promising result around 80-100% conversion of starting materials into the desired Heck product of methyl cinnamate for iodobenzene and acid methyl ester for bromo acetophenone summarized in Table 1. The reaction using **MLT1** as a homogeneous catalyst exhibited 83.88% conversion for bromoacetophenone, while iodobenzene gave 100% conversion of starting materials into the desired Heck product. This is due to the selectivity and reactivity factors contributed by higher electronegativity of iodo than bromo as substituent. Thus, these preliminary results show the suitability of benzoyl thiourea as ligand in palladium catalyzed Heck cross coupling reaction.
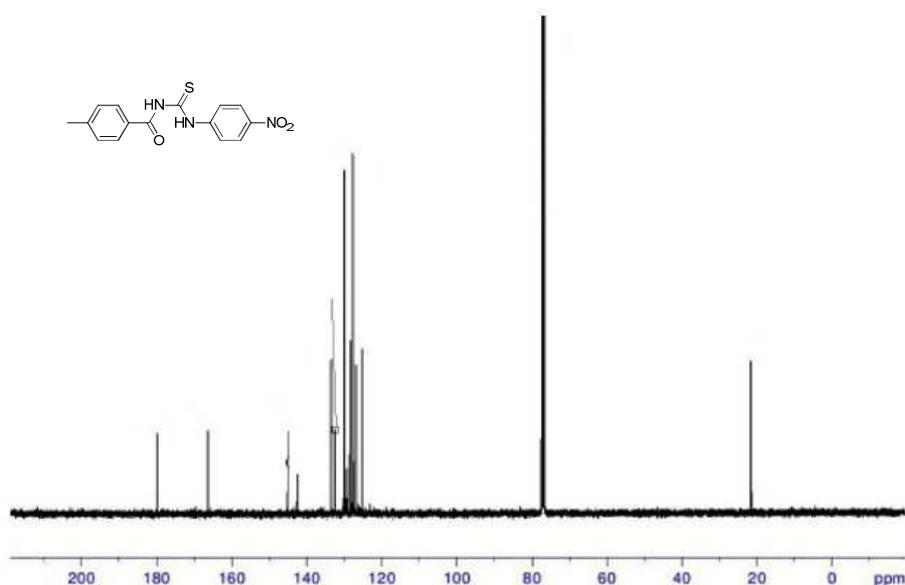

Figure 8. ^{13}C NMR Spectrum for LT1

Table 1. The Catalytic Activity and Performance of MLT1

Complex	Without catalyst	Synthesized **MLT1**
Catalyst loading	0.00 mml%	1.00 mmol%
Retention time	24 hours	24 hours
Temperature	120 °C	120 °C
Conversion of Iodobenzene	44.11%	100%
Convertion of bromo acetophenone	16.95%	83.88%

4. Conclusions

In conclusion, benzoylthiourea ligand namely *N*-(4-nitrophenylcarbamothioyl)-*N'*-(4-methylbenzoyl) thiourea (LT1) has been successfully synthesized and characterized via spectroscopic techniques and was undergone complexation to obtain palladium (II) thiourea complex (MLT1) which has been applied as a homogenous catalyst. The assessment on performance of benzoylthiourea as ligand in palladium catalyzed cross coupling reaction has afforded good to excellent results in catalytic activities which converted 80-100% of the starting materials into the coupled product.

Acknowledgement

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