International Journal of Advanced Research in Chemical Science (IJARCS)
Volume 2, Issue 3, March 2015, PP 14-20
ISSN 2349-039X (Print) & ISSN 2349-0403 (Online)
www.arcjournals.org

Synthesis of Palladium N-Heterocyclic Carbene Complexes and the Assessment and Implications of the Use of these Complexes as Catalysts for Alkoxycarbonylation Reactions

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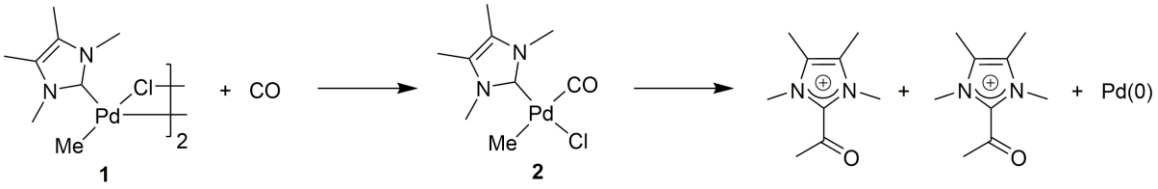
Abstract: *A number of palladium N-heterocyclic carbene (NHC) complexes are prepared and their synthesis discussed in terms of the product isomers formed and the implications on catalytic activity. The use of the Pd-NHC complexes in alkoxycarbonylation reactions is probed. There has been some debate about the use of Pd-NHC complexes in reactions involving carbon monoxide, some reports showing that NHC ligands are non-innocent in the presence of CO, and some claiming that complexes bearing these ligands are catalytically active. Our results suggest that Pd-NHC complexes are poisoned by carbon monoxide, forming metallic palladium and organic byproducts. This adds further credence to the assertion that Pd-NHC complexes have limited use as catalysts for reactions involving carbon monoxide as a reagent.*

Keywords: *Catalysis, Carbene, Palladium, Carbonylation, Organometallic Chemistry.*

1. INTRODUCTION

Nucleophilic *N*-heterocyclic carbenes (NHCs), especially the imidazol-2-ylidenes, have attracted considerable attention as possible alternatives for widely used phosphine ligands in homogeneous catalysis.[1,2] As ligands, NHCs are strong σ-donors which lack any appreciable ability for π-acceptor back-bonding, and in this respect resemble donor phosphines.[3] In catalysis, the key role of the carbene is one of stabilising and activating a zerovalent metal centre toward oxidative addition of the organic substrate.[4] An additional advantage of carbene ligands is that the metal complexes formed are extraordinarily stable towards heat and the M-NHC bond shows high dissociation energies. This means that it is possible to overcome some of the disadvantages of phosphine-ligated metal complexes. NHC complexes of palladium have found particular use in cross-couplings, examples being the Suzuki and Sonogashira reactions.[5] In the field of palladium catalysis, some work in our laboratories has focused particularly on alkoxycarbonylation reactions.[6] When using NHC complexes for reactions involving carbon monoxide, the literature is mixed as to the results.[7] In 2000 McGuinness and Cavell reported that CO inserts in to the Pd-Me bond of methylpalladium-NHC dimer $[PdMe(tmiy)(\mu\text{-}Cl]_2$ (**1**) (tmiy = 1,3,4,5-tetramethylimidazolin-2-ylidene).[8] The resultant complex, [PdMeCl(tmiy)CO] (**2**), decomposes to yield the 1,2,3,4,5-pentamethylimidazolium ion along with a trace of the 2-acyl-1,3,4,5-tetramethylimidazolium ion (Scheme 1). This was seen to portend a possible disadvantage of the use of Pd-NHC complexes for reactions involving carbon monoxide as a reagent, and confirmed a report from the previous year[9] suggesting that these complexes are modest at best as copolymerization catalysts using CO. However, subsequent to this, a combination of $Pd(OAc)_2$ and NHC ligands has been shown to very effectively catalyze the coupling of diazonium salts with boronic acids to yield ketones[10] or amides[11] in the presence of CO or CO/ammonia, respectively. Benzothiazole-derived carbene-ligated Pd complexes have been used for the carbonylation of aryl halides.[12] Oxidative carbonylations can also be carried out using NHC ligands. For example, phenol can be converted to diphenyl carbonate,[13] and amines can be transformed to ureas.[14] In light of these mixed results, we decided to prepare and screen a range of these complexes for the alkoxycarbonylation of aryl halides. We present and discuss our results here, showing that NHC ligands are non-innocent.

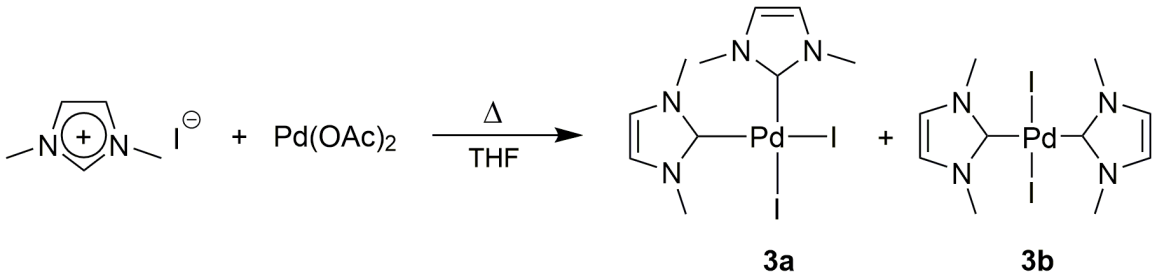


Scheme1. *Decomposition of Pd-NHC complex **1** upon reaction with CO*

2. RESULTS AND DISCUSSION

2.1. Synthesis of Palladium NHC Complexes

The starting point for our work was to prepare palladium complexes bearing 1,3-dimethylimidazolin-2-ylidene ligands. The precursor, 1,3-dimethylimidazolium iodide, was synthesised by alkylation of *N*-methylimidazole following Grätzel's method[15] but using toluene as solvent instead of 1,1,1-trichloroethane as better yields have been reported using this modification.[16] The palladium-carbene complex, *bis*(1,3-dimethylimidazolin-2-ylidene) palladium (II) diiodide, **3**, was initially prepared by heating a DMSO solution of 1,3-dimethylimidazolium iodide and palladium(II) acetate at 50 °C for 4 h, but yields of pure product were repeatedly low.[17] Performing the reaction in THF at reflux for 30 min gave pure product in higher yields (Scheme 2).



Scheme2. *Synthesis of Pd-NHC complex **3***

Independent of the synthetic method used, we obtained a mixture of *cis*- (**3a**) and *trans*- (**3b**) isomers of the palladium complex; the *trans*- predominating in all cases (3:1 ratio). The assignment of the signals appearing in the ^{1}H NMR spectra of each isomer was undertaken by reference to literature reports where crystals of the *cis*-isomer had been obtained and the corresponding NMR spectrum recorded. For the *cis*-isomer, two singlets appear at δ 7.24 and 3.92 ppm.[17] We observed these but also found signals at δ 6.86 and 3.94 ppm which we attribute to the *trans* isomer (**3b**). The mixture of **3a** and **3b** gives elemental analysis results and a mass spectrum exactly corresponding to that expected for $C_{10}H_{16}I_2N_4Pd$, confirming that the two are indeed isomers.

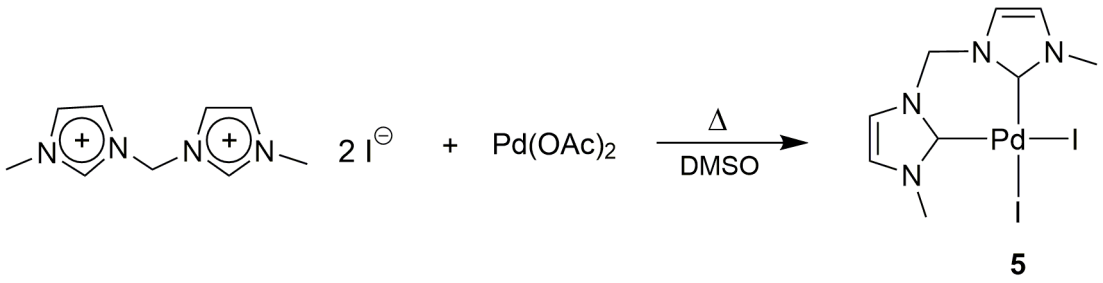
As the synthesis of only **3a** was reported previously, and its crystal structure presented with no reference to the formation of **3b**,[17] we wanted to see if **3b** isomerises to **3a** over time at room temperature. To probe this, the ^{1}H NMR spectrum of a freshly prepared sample of the mix of isomers was recorded and compared to one obtained after allowing the same sample to stand in solution for three days. The spectra showed no variation in the relative ratio of both isomers. Hence, it seems that there is no interconversion between the isomers in solution over this time at room temperature.

The cis isomer (**3a**) is an active catalyst for the Heck reaction.[17] To see whether the isomer mixtures formed in our synthesis of **3** were equally catalytically active, we screened them in the Heck reaction carried out in the same conditions as reported in the literature. When coupling 4-chlorobenzaldehyde and *n*-butyl acrylate in *N*,*N*-dimethylacetamide, only a 50% yield of (*E*)-4-formylcinnamate was obtained, which is significantly lower than the 99% yield reported in the literature using **3a**.[17] This points towards the *trans*-isomer (**3b**) being catalytically less active or inactive, the majority (or all) of the activity being from the **3a** in the mixture.

Of interest is that, upon standing overnight,a dichloromethane solution of **3a** and **3b** readily forms a dimeric complex, di-μ-iodobis(1,3-dimethylimidazolin-2-ylidene)-diiododipalladium(II) (**4**) in approximately 30% yield. This dimer is also formed if a solution of **3a** and **3b** is heated at 50 °C

for a period of 2-3 h. Evidence for the formation of **4** comes from comparison of spectral data with that in the literature,[18] and elemental analysis.

To avoid the problem of isomer formation when preparing Pd-NHC complexes like **3**, 1,1'-dimethyl-3,3'-methylenediimidazoline-2,2'-diylidene)palladium(II) diiodide (**5**) was synthesised from 1,1'-dimethyl-3,3'-methylenediimidazolium-diiodide using a modified literature procedure.[19] A THF solution of *N*-methylimidazole and diiodomethane was refluxed for 2 days generating the bidentate NHC ligand, which was reacted with palladium acetate in DMSO to give **5** in modest yield (Scheme 3).



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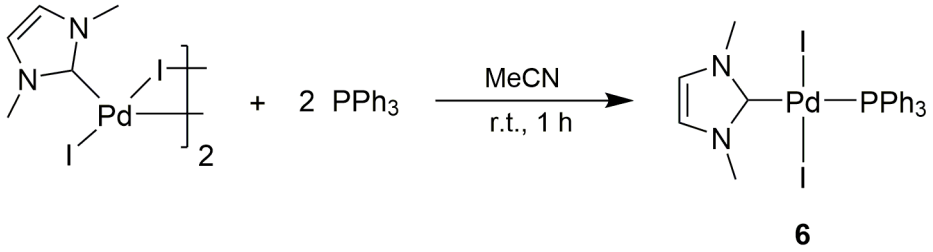
Scheme3. *Synthesis of Pd-NHC complex **5***

As well as Pd-NHC complexes, a mixed NHC / phosphine palladium (II) complex was prepared. This class of complex can have advantages over *bis*-phosphine or *bis*-NHC complexes due to the ability of the carbene to bind tightly to the metal centre while the phosphine ligand is more labile, favoring elementary steps during which one of the ligands has to dissociate while the other stays attached to the palladium in order to stabilise the active catalyst. Diiodo(1,3-dimethylimidazolin-2-ylidene)(triphenylphosphino)palladium(II) (**6**) was prepared in acetonitrile from dimer **3** by stirring it at room temperature with triphenylphosphine (Scheme 4).



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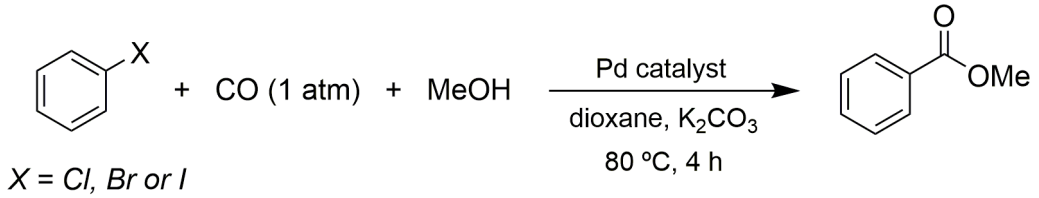
Scheme4. *Synthesis of mixed NHC / phosphine complex **6***

2.2. Screening the Palladium NHC Complexes in Alkoxycarbonylation Reactions

The palladium-catalyzed carbonylation of aryl halide derivatives constitutes a powerful method for the synthesis of various aromatic compounds, most importantly carboxylic acid derivatives and unsymmetrical biaryl ketones.[20] The low cost of carbon monoxide and the variety of accessible carbonylation products that can be derived by simply choosing the appropriate nucleophile, Nu-H, turns this reaction into a powerful synthetic tool. When screening our Pd-NHC complexes, initial reaction conditions were chosen based those used for other carbon-carbon bond forming protocols, such as Suzuki reactions, in which palladium-NHC complexes have been employed, as well as those for alkoxycarbonylation reactions using palladium salts as catalysts. We used methanol as the nucleophile, 1,4-dioxane as the solvent, potassium carbonate as the base, and opted to perform the reaction at 80 °C under an atmosphere of carbon monoxide for 4 h. In an attempt to assess the scope of the reaction, different catalysts were employed as well as different aryl halides as substrates. The results obtained are shown in Table 1.



Scheme5. *Alkoxycarbonylation of aryl halides*

The phosphine complex $PdCl_2(PPh_3)_2$ (**7**) was screened as a catalyst in order to benchmark our results with others in the literature.[21] Using **7**, good yields of methyl benzoate were obtained using iodo- and bromobenzene but no product was formed when chlorobenzene was used as the substrate. Using **3** as the catalyst, the yield of the desired product was low when bromobenzene was used and scarcely any methyl benzoate was produced from chlorobenzene, even with longer reaction times. The same was true with **4** and **5**. Mixed NHC-phosphine complex **6** was also screened and lower yields were obtained compared to those using **3** and **7**. Finally, *in situ* reduction of **3** prior to use in the alkoxycarbonylation reaction was attempted but no methyl benzoate was obtained.

In attempts to increase the activity of the catalyst mixture, a range of different reaction conditions were screened using chlorobenzene as the aryl halide. As the reaction proceeds only in the presence of a base, the influence of different bases was examined. However, no advantage was found using triethylamine, sodium acetate, or potassium phosphate as the base. Likewise, different solvents, reaction times, and reaction temperatures were screened but with no improvement.

To probe the reaction in more detail, we decided to study further the reaction of **3** with CO. We dissolved **3** in dry THF and stirred it at room temperature for 1 h while bubbling carbon monoxide through the solution. Within a few minutes, the deep red solution of **3** turned brown. Decomposition then occured rapidly with significant precipitation being observed. We attempted to monitor the progress of the reaction using IR spectroscopy. The IR spectrum of the brown solution formed within a few minutes of starting the reaction showed one band in the ν_{CO} region of the spectrum at 2086 cm^{-1} indicating that some form of metal carbonyl species is generated. We tentitively assign this as **8**, an analog of **2** (Figure 1). The ^{1}H and ^{13}C NMR spectra of the final reaction mixture shows evidence for the formation of a carbonyl-containing organic product which, by inference, must derive from a reaction between the NHC and carbon monoxide. We have no firm structural evidence for the organic product formed in the reaction but these results clearly indicate that, as with **1**,[8] the carbene ligands in **3** are non-innocent, reacting with CO leading to poisoning of the catalyst. This explains the low yields of product obtained in the alkoxycarbonylation reaction and adds further credence to the assertion that Pd-NHC complexes have limited use as catalysts for reactions involving carbon monoxide as a reagent.

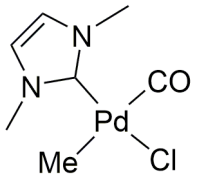


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Figure1. *The proposed structure of 8.*

Table1. *Alkoxycarbonylation of aryl halides catalyzed by Pd-NHC complexes*

Aryl halide	**Catalyst**	**Time (h)**	**Yield (%)**
Iodobenzene	$PdCl_2(PPh_3)_2$	4	78
Bromobenzene	$PdCl_2(PPh_3)_2$	4	84
Chlorobenzene	$PdCl_2(PPh_3)_2$	4	0
Bromobenzene	**3**	4	23
Chlorobenzene	**3**	4	5
Chlorobenzene	**3**	16	4
Chlorobenzene	**4**	5	0
Chlorobenzene	**5**	4	0
Bromobenzene	**6**	3.5	16
Chlorobenzene	Zn / **2**	4	0

3. CONCLUSION

In conclusion we have shown that, at least in the Heck reaction, although the cis-isomer of bis(1,3-dimethylimidazolin-2-ylidene)palladium (II) diiodide (**3**) is catalytically active in a range of reactions as reported in the literature previously, the trans-isomer is less catalytically active or

inactive. The reason for this could be that the trans-isomer (**3b**), is readily converted to dimeric complex **4** upon heating. Our attempts to use Pd-NHC complexes as catalysts for the alkoxycarbonylation of aryl halides have met with limited success. The Pd-NHC complexes are poisoned by carbon monoxide, forming Pd(0) and organic byproducts. This adds further credence to the assertion that Pd-NHC complexes have limited use as catalysts for reactions involving carbon monoxide as a reagent.

4. EXPERIMENTAL SECTION

4.1. Materials and Measurements

All experiments were run using dry distilled solvents and under anaerobic conditions unless noted otherwise. All chemicals were used as received without any further purification. 1H and 13C NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are given in ppm relative to TMS. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer. Elemental analyses were run by Medac Ltd, Brunel Science Park, UK.

4.2. Synthesis

The following compounds were prepared following literature procedures: 1,3-dimethylimidazolium iodide,[15] 1,1'-dimethyl-3,3'-methylenediimidazolium diiodide,[21] 1,1'-dimethyl-3,3'-methylenediimidazoline-2,2'-diylidene)palladium(II) diiodide (**5**),[21] diiodo(1,3-dimethylimidazolin-2-ylidene)(triphenylphosphino)palladium(II) (**6**).[18]

*Bis(1,3-Dimethylimidazolin-2-ylidene)palladium (II) diiodide (**3**).* Procedure A: A stirred DMSO solution (5 mL) of 1,3-dimethylimidazolium iodide (207 mg, 0.92 mmol) and $Pd(OAc)_2$ (100 mg, 0.45 mmol) was heated at 50 ºC for 4 h. The solvent was then removed under vacuum and the residue obtained dissolved in dichloromethane and filtered. After removal of the solvent, a mixture of *cis*- and *trans*-isomers of (**3**) in a relative ratio of 1:3, was obtained as orange solids (152 mg, 30% yield). ^{1}H NMR ($CDCl_3$) δ 7.21 (s, 4H, NCH= cis-isomer), 6.87 (s, 4H, NCH= trans-isomer), 4.09 (s, 6H, CH_3*cis*-isomer), 3.94 (s, 6H, CH_3*trans*-isomer). Anal. Found: C, 21.95; H, 3.01; N, 10.20; I, 46.49 %; Pd, 18.07. Calc. for $C_{10}H_{16}I_2N_4Pd$ (552.75): C, 21.74; H, 2.92; N, 10.14; I, 45.94; Pd, 19.26 %. m/z = 552.

Procedure B: A tetrahydrofuran (50 mL) solution of Pd $(OAc)_2$ (200 mg, 0.89 mmol) and 1,3-dimethylimidazolium iodide (404 mg, 1.80 mmol) was heated under reflux for 30 min, changing its colour from brown to yellow. After evaporation to dryness under vacuum, the residue was washed with diethyl ether (3 $\times$ 20 mL), taken up into dichloromethane (50 mL) and the solution layered with hexane. The yellow- orange precipitate that appeared was filtered off and dried under vacuum. The metal complex was purified using column chromatography (silica as the stationary phase, dichloromethane as the eluent), yielding **3** as a yellow powder (310 mg, 63% yield). Again a mixture of *cis*- and *trans*-isomers of **3**, in a relative ratio of 1:3, was obtained.

*Di-µ-iodobis (1,3-dimethylimidazolin-2-ylidene)-diiododipalladium(II) (**4**).* A dichloromethane solution of **3** was allowed to stand overnight. Dark red crystals were seen to form. Analysis of these showed that they were **4** by comparison with literature data.[17]

4.3. General Procedure for Alkoxycarbonylation Reactions

A solution of the palladium complex (0.05 mmol), base (5 mmol), aryl halide (1 mmol), and methanol (5 mL) were added to a flask fitted with a reflux condenser, a septum inlet, and a magnetic stirring bar. After evacuating the flask and flushing with nitrogen, solvent (10 mL) was added and then carbon monoxide was bubbled through the reaction mixture and regulated at a rate of approximately, 1 bubble/sec. The reaction mixture was then heated to the desired temperature. At the end of the allotted reaction time, the mixture was filtered, the solvent removed in vacuo and the residue obtained dissolved in diethyl ether (50 mL). This was then washed with water (50 mL), the ether layer dried over anhydrous $MgSO_4$ and the solvent removed. The product mixture was analysed by IR and NMR spectroscopy.

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Dr Maria Marco was born in Madrid, Spain, and obtained her B. Sc. in Organic Chemistry from the Complutense University of Madrid in 1999. She spent a year working for GlaxoWellcome in Madrid as a graduate trainee, before moving to King's College London to carry out her Ph.D. on the development of new synthetic methodologies for metal- mediated organic synthesis under the supervision of Dr Nicholas E. Leadbeater. On completion of her Ph. D., she started working for GlaxoSmithKline in Tres Cantos, Spain in the antimalarial research field as a medicinal chemist. Recently, the focus of her research interests has moved to other Neglected Diseases, such as Human African Trypanosomiasis, Chagas and Leishmaniasis working in collaboration with other institutions in the discovery of novel antikinetoplastida drugs.

Dr Nicholas E. Leadbeater is currently an Associate Professor at the University of Connecticut in the USA. A native of the United Kingdom, he received his Ph.D. from the University of Cambridge. After a further three years in Cambridge as a College Research Fellow he moved to King's College London where he was a Lecturer from 1999 until his move to Connecticut in 2004. The overarching theme of his research group is the development of new methods for preparative organic chemistry. The group's current hot topics are clean, green oxidation methods using oxoammonium salts, the selective incorporation of fluorine into organic molecules, and the application of microwave heating and continuous-flow processing in synthetic chemistry.