EVALUATION OF LIGAND MODIFIED PALLADIUM CATALYSTS IN THE WACKER OXIDATION OF ALKENES

A thesis submitted in accordance with the requirements for the

DOCTOR OF PHILOSOPHY

In the Faculty of Natural and Agricultural Sciences

Department of Chemistry

At the

UNIVERSITY OF FREE STATE

BY

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AUGUST 2012

ACKNOWLEDGEMENTS

The author wishes to express her deepest gratitude to

- Prof B. C. B. Bezuidenhoudt – for supervising the project, his wisdom and patience, guidance and understanding as well as support financially and otherwise. The many fruitful conversations about chemistry and life were invaluable.
- Dr C. M. Marais – for all the hard work that went into editing and proof-reading the thesis.
- Dr Mukut Gohain – for his mentorship, wisdom and friendship. Many valuable life and chemistry lessons shared were highly appreciated.
- Mr Johannes van Tonder and Mr Bradley Miller – for putting their best foot forward as colleagues and assisting with technical aspects of the project when needed the most.
- Ms Ellan Kuo, Mr L. Shunhuang, Mr R. Swart and previous colleagues Ms Vanina mende and Mr Charles Enow– for their kindness, warmth and generosity as colleagues and friends.
- Ms Mandy Moleme and Ms Enkosi Mpondo – for their friendship, sisterhood, unwavering support and being the biggest fans.
- Mr M. Mutisya and Ms Mary-Faith Saku – for being a pillar of strength, unwavering love, kindness, warmth, support, generosity and for being the biggest fans!
- Mr and Mrs P. Saku – for being great parents, their prayers, faith and consistent encouragement; offering their unwavering support, patience and understanding throughout.
- SASOL – Funding

DECLARATION

“I, DUDUETSANG SAKU, declare that the dissertation hereby handed in for the qualification DOCTOR OF PHILOSOPHY, in the Faculty of Natural and Agricultural Sciences, Department of Chemistry, at the University of the Free State; is my own independent work and that I have not previously submitted the same work for a qualification at/in another University/faculty.”

I, also give copyright consent to the University of Free State for the dissertation submitted towards fulfilment of the DOCTOR OF PHILOSOPHY degree.

ABBREVIATIONS

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atm	atmosphere
Ac_2O	acetic anhydride
n-BuLi	*n*-butyllithium
cat.	catalyst
CH_3CN	acetonitrile
$CDCl_3$	deuterated chloroform
°	degree
DCM	dichloromethane
DMA	dimethylacetamide
DMAP	N, N'-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Eq.	equivalent(s)
J	coupling constant
H_2O_2	hydrogen peroxide
IR	infra red
Lit.	literature
M^+	parent molecular ion
MeOH	methanol

Min(s)	minute(s)
M.p.	melting point
NEt_3	triethylamine
NMR	Nuclear magnetic resonance
Ph	Phenyl
PPh_2Cl	chlorodiphenylphosphine
ppm	parts per million
r.t.	room temperature
TBHP	tert-butylhydrogen peroxide
THF	tetrahydrofuran
TOF	turnover frequency
TON	turnover number
w.r.t.	with respect to

ABSTRACT

The industrial application of Wacker oxidation of terminal olefins in aqueous aerobic mixtures with $PdCl_2$ and $CuCl/CuCl_2$ has largely been limited to shorter chain alkenes, that is, ethylene. As the alkene chain length increases, so do the challenges that render the reaction inapplicable for large scale production. Longer chain alkenes tend to isomerize due to the limited solubility in organic-aqueous mixtures. More so, the use of co-oxidants such as CuCl or $CuCl_2$ in stoichiometric amounts results in the formation of toxic chlorinated by-products which make the system corrosive. Pd^0 aggregation from the Pd^{II} active state, is also pertinent in these reactions hence the use of large amounts of a co-oxidant. Small TONs and TOFs have subsequently been reported. As one of the approaches to curb these challenges, ligand support and modification has recently been viewed with interest because it promises efficient stabilization of Pd^0, wherein the efficiency of O_2 to re-oxidize the Pd^0 species is relied upon thereby avoiding Pd^0 aggregation. Ligand support can also be used to alter the electronic environment of the Pd^{II} centre thereby affecting its activity and selectivity.

The application of phosphorus-palladium complexes in this study is not only a new approach in Wacker oxidation but the utilization of the π-accepting and or σ-donating abilities of phosphorus compounds was also advantageous in altering the Pd^{II} electronic environment. No co-oxidants were used in this study w.r.t. the oxidation of 1-octene and the complexes evaluated were comparable to those reported in literature with $PdCl_2$/DMA systems under similar conditions. Since oxygen is the preferred oxidant in all oxidation reactions because of its natural abundance, its reported enhanced selectivity and ease of separation from products, it was decided to evaluate the utilization of this reagent as first choice in the current investigation of ligand supported palladium catalysts in the Wacker oxidation.

Due to the fact that the phosphite based palladium catalyst, $PdCl_2[P(OPh)_3]_2$, is readily soluble in DMA, it was determined that no pre-stirring as for $PdCl_2$ was required for this catalyst. In order to obtain the optimum reaction conditions for oxygen as oxidant with this catalyst, conditions like solvent, reaction temperature, O_2 pressure and water, catalyst, and substrate concentration were varied. The optimized conditions were determined to be 0.5 mol% of catalyst in DMA:H_2O (6:1) under 9 atm of O_2 at 80°C, while the optimum substrate concentration was found to be 0.2M.

$PdCl_2[P(OPh)_3]_2$ showed the highest activity of the catalysts evaluated and gave a TOF of >1370 (mol/mol/hr), which compared favourably with other known catalysts like $PdCl_2$, $PdCl_2(CH_3CN)_2$ $Pd(OAc)_2$, and $Pd(CF_3SO_3)_2$ where TOF's of 1429, 1420, 817 and 524 respectively, were obtained under the conditions optimized for $PdCl_2[P(OPh)_3]_2$. While the palladium metallocycle $[Pd(u\text{-}Cl)(C_6H_4O)(OC_6H_6)_2]_2$ gave TOF's (1380 mol/mol/hr) virtually the same as $PdCl_2[P(OPh)_3]_2$, total conversion for the latter catalyst was only 93%, so it can be regarded as the second best of all the catalysts evaluated. The monomers thereof, $PdCl[(C_6H_4O)(C_6H_6O)_2P(OPh_3)]$ and $PdCl[(C_6H_4O)(C_6H_6O)_2(PPh_3)]$, revealed the least basic $P(OPh_3)$ to be more reactive (TOF >900 mol/mol/hr) than the TPP containing analogue, where the latter showed no activity within the first hour of reaction. While all the active catalysts showed good selectivities of >80%, the metallocycle $[Pd(u\text{-}Cl)(C_6H_4O)(OC_6H_6)_2]_2$ proved to be the best with a selectivity of 89%. Catalyst recyclability was also observed to at least 3 cycles, with selectivities maintained above 80%. No Pd^0 'fall-out' or aggregation was observed with any of the catalysts evaluated.

For the palladium phosphinite catalysts $1,2\text{-}Ph(OPPh_2)_2PdCl_2$ and $1,3\text{-}Ph(OPPh_2)_2PdCl$ it was found that both were active in the Wacker oxidation of 1-octene albeit with very low rates for the latter complex ($1,3\text{-}Ph(OPPh_2)_2PdCl$). The low reactivity of $1,3\text{-}Ph(OPPh_2)_2PdCl$ was similar to that of the phosphines $(PPh_3)_2PdCl_2$ and $(3,5\text{-}CF_3\text{-}PPh_2Cl)_2PdCl_2$ where $(PPh_3)_2PdCl_2$ showed some conversion only after 3 hours and $(3,5\text{-}CF_3\text{-}PPh_2Cl)_2PdCl_2$ gave only 53% conversion after an hour. Through a comparison of the reactivity of $1,2\text{-}Ph(OPPh_2)_2PdCl_2$ with that of the hydrolyzed equivalent $[\mu\text{-}ClPd(PPh_2OH)(PPh_2O)]_2$, it seemed as if the phosphinite catalysts are prone to hydrolysis under the prevailing conditions as the final conversion of both these catalysts were almost the same (85 and 79% respectively).

Hydrogen peroxide and *tert*-butylhydroperoxide (TBHP) were also evaluated as alternative oxidants with $PdCl_2[P(OPh)_3]_2$ as catalyst and H_2O_2 was found to be the better of the two oxidants with conversion (99%), selectivity (86%), and TOF (1220) almost as good as those found for oxygen (100, 82% and 1370 respectively). In addition, the catalyst could also be recycled three times although degradation of the H_2O_2 was observed and additional peroxide (12 eq.) had to be added with each cycle of substrate. TBHP, however, suffered from moderate selectivities of only 60-65%, while the catalysts was deactivated during the first oxidation cycle and could therefore not be recycled at all.

Although all phosphite catalysts promoted isomerization to internal 1-octene isomers to some extent, the cyclopalladated $[Pd(u\text{-}Cl)(C_6H_4O)(OC_6H_6)_2]_2$ catalysts proved to be the best in this aspect of the reaction w.r.t. oxygen as oxidant and led to very low quantities of isomerised products being observed

(3 - 4%). It was also evident that the type and amount (for H_2O_2 and TBHP) of oxidant played a crucial role in enhancing or suppressing isomerization and hydrogen peroxide (at only 2% isomerization) was found to be the best oxidant in this regard followed by oxygen (13%).

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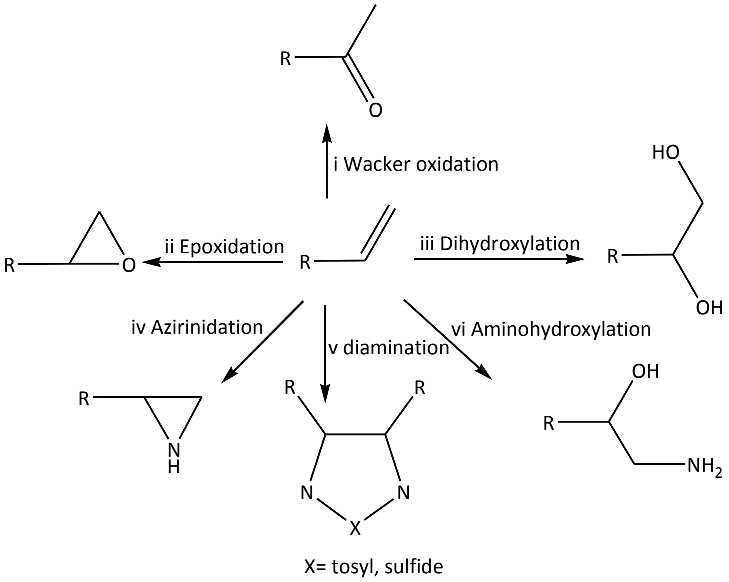
CHAPTER ONE

Introduction

1.1 Wacker Oxidation

Due to our association with industry and their abundance of alkene by-products from processes such as Fischer-Tropsch, functional group convergence of alkenes to value-added products is pivotal. A range of organic reactions for functionalization of alkenes do exist, namely, Wacker oxidation, dihydroxylation, azirinidation, aminohydroxylation, diamination, and epoxidation (Scheme 1.1).[1]



Scheme 1.1: Transition-metal catalyzed functionalization of alkenes.

Oxidation products, as shown in Scheme 1.1, are highly valuable in the pharmaceutical and chemical industries as biological intermediates or as intermediates in the synthesis of surfactants and other industrial products. The global demand of such products is therefore huge. To meet these demands, industries have to develop feasible processes which are both economically and environmentally sound. As much as there has been great success with applications that has moved from laboratory to industrial scale, some remain limited to laboratory use and warrant ongoing investigation and development. One such reaction that is of primary interest and the focus of this investigation is the Wacker oxidation reaction.

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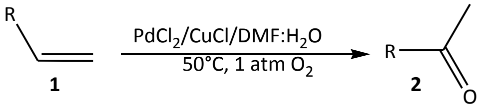
[1] S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan, D. H. Brown Ripin, *Chem. Rev.*, **2006**, *106*, 2943; A. Arcadi, *Chem. Rev.*, **2008**, *108,* 3266.

The Wacker oxidation reaction is a transition-metal catalyzed transformation of a terminal alkene **1** into a methyl ketone **2** in aqueous medium. The only successful industrial application of the Wacker oxidation to date is found in the conversion of ethene to acetaldehyde.[2] Classical Tsuji conditions of 10 mol% $PdCl_2$, CuCl and oxygen in dimethylformamide (DMF) and water (4:1) at 50°C (Scheme 1.2) have been used over the years as a benchmark in Wacker oxidation developments.[3]



Scheme 1.2: Classical Tsuji-Wacker oxidation of terminal alkenes.

The limitation to the industrial utilization of this reaction has been its application to longer chain olefins, which become increasingly insoluble in aqueous medium and consequently suffer from isomerization to internal olefins and other side reactions at the higher temperatures required.

In addition, the use of a co-oxidant, copper chloride, in stoichiometric quantities and often in large excess is required to afford reasonable turnovers.[4] This is cumbersome as it generates a lot of corrosive chlorinated by-products which are very undesirable. High catalyst loading of the palladium chloride catalyst, which cannot be recovered and recycled as it 'falls out' of the catalytic cycle as aggregated Pd^0 is also a serious concern. Low TONs of a few 100 to 1000s in Wacker oxidation is also a problem that limits the industrial use of the Wacker oxidation.[4]

Many developments to curb these shortfalls ranging from the utilization of alternative oxidants such as *tert*-butyl hydroperoxide (TBHP), H_2O_2 or benzoquinone; inorganic salts and inorganic supports or immobilization of catalysts; different solvent media and ligand modulated palladium catalysts have been reported.[4] Although studied to some extent, ligand modification of the palladium species in Wacker oxidation applications have not received much attention, so it was decided to make this approach the focus of the current investigation, which will be broken down into two parts.

The first part entails the utilization of a bimetallic catalyst system comprising of copper and palladium attached to the same organic ligand. In the second part, palladium systems that would allow the omission of copper and/or chloride would be investigated.

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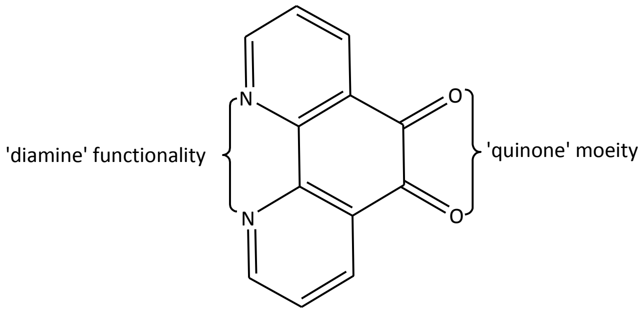
[2] R. Jira*, Angew. Chem. Int. Ed.*, **2009**, *48,* 9034.
[3] J. Tsuji, H. Nagashima, H. Nemoto, *Org. Synth*., **1984**, *62*, 9.
[4] J. M. Takacs, X. Jiang, *Curr. Org. Chem*., **2003**, *7*, 369.

1.2 Bimetallic copper-palladium catalyst system

With its diamine functionality that can coordinate metals and Lewis acids and the redox active *o*-quinone which could be used to coordinate metals in a low oxidation state,[5,6,7] 1,10-phenanthroline-5,6-dione **3** (Figure 1.1) was identified as organic ligand in the preparation of potential bimetallic copper-palladium catalyst systems.



3

Figure 1.1: 1,10-Phenanthroline-5,6-dione **3**.

Electronic communication in a Pd-Cu bimetallic system could be efficient enough for copper to facilitate re-oxidation of the Pd metal in a 'through-bond' effect as well as avoid stoichiometric or excess amounts of copper which are normally required to combat palladium aggregation and 'fall-out'.

1.3 Ligand modulated Wacker oxidation

In order to be able to attach both the copper and palladium to the same ligand system, the possibility and efficiency of ligand bound palladium in the Wacker oxidation had to be established first. Impetus as to the fact that ligand bound palladium might actually be an effective catalyst in the Wacker oxidation was found in the work of Sigman.[8]

Kaneda *et al*. discovered that with a dimethylacetamide (DMA)-water solvent system, terminal ketones could be obtained successfully from the corresponding alkenes at elevated temperatures (80°C) and

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[5] L. Calucci, G. Pampaloni, C. Pinzino, A. Prescimone, *Inorg. Chim. Acta*, **2006**, *359*, 3911.

[6] W. Paw, R. Einsberg, *Inorg. Chem*., **1997**, *36*, 2287.

[7] E. K. Brechin, L. Calucci, U. Englert, L. Margheriti, G. Pampaloni, C. Pinzino, A. Prescimone, *Inorg. Chim. Acta*, **2008**, *361*, 2375.

[8] C. N. Cornell, M. S. Sigman, *Org. Lett*., **2006**, *8*, 4117.

pressure (6 atm O_2) with 0.5-1mol% $PdCl_2$ without copper chloride, but with a $PdCl_2$(-)-sparteine catalyst **4** (Figure 1.2), Sigman *et al*. obtained similar yields of methyl ketones with baloon oxygen, only at longer reaction times.[8,9]

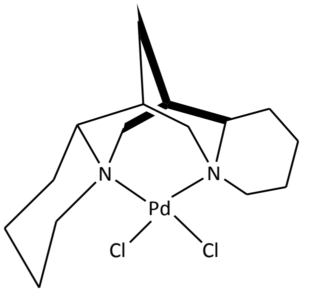

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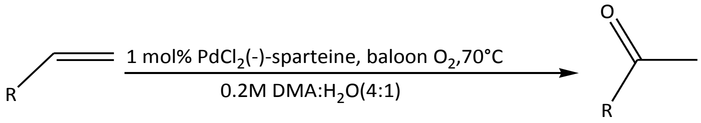
Figure 1.2: $PdCl_2$(-)-sparteine **4**.

The Sigman group continued their investigation by studying the potential use of ligands in Wacker oxidation reactions (Scheme 1.3) as a way of stabilizing the active Pd(II) species thereby avoiding aggregation and fine tuning the metal centre to effect superior reactivity.



Scheme 1.3: $PdCl_2$(-)-sparteine **4** catalyzed Wacker oxidation.

This approach also eliminated the use of copper salts which might get involved in ligand-exchange reactions and allowed direct use of oxygen or peroxides as sole oxidant. The use of abundant oxygen or cheap benign peroxides, which give off water as by-products, is very attractive as it would meet another industrial demand of a cost efficient and benign oxidation system.

In more recent work, Kaneda reported the Wacker oxidation of internal alkenes such as 2-, 3-, and 4-octenes using 5 mol% $PdCl_2$ in dimethylacetamide (DMA) without added ligand at 3 atm O_2 over a period of 10 hours.[10] Sigman however reported shorter reaction times for the oxidation of 1-octene with a

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[9] T. Mitsudome, T. Umetani, T. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem. Int. Ed*., **2006**, *45*, 481.

[10] T. Mitsudome, K. Mizumoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem. Int. Ed*., **2010**, *49*, 1238.

quinox-based [2-(2-quinolinyl)oxazoline] (quinox) ligand **5** (Figure 1.3) and $PdCl_2$ catalyst (**5** in large excess) and TBHP as oxidant in dichloromethane.[11]

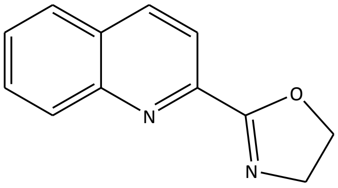

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Figure 1.3: **[**2-(2-quinolinyl)oxazoline] (Quinox) **5**.

The challenge is then to find ligands which are stable enough to keep the complex intact, but still display adequate reactivity to be used in Wacker oxidation.

1.4 Ligand Choice

For this study phosphorus-based compounds have been identified as potential ligands for application in Wacker oxidation. According to the HASB rule, phosphorus as a soft Lewis base readily forms strong bonds with the soft palladium centre and would therefore be a better atom to investigate than the borderline hard-soft nitrogen atom.

Phosphorus has the potential to provide the necessary or required stability to the palladium centre thereby avoiding aggregation and precipitation of Pd^0.

In this regard, Weiss *et al.* used a palladium peroxo-catalyst and on varying the substituents on their carboxylate ligand, observed that a decrease in electron density on palladium by electron withdrawing groups attached to the ligand, increased the reactivity and selectivity of the system to MEK (methyl ethyl ketone).[12] The addition of PPh_3 furthermore prevented the oxidation of the substrate. It was therefore clear that a good phosphorus ligand system for Wacker oxidation, would have to be less nucleophilic than sp^3 PR_3 (R = alkyl or aryl) ligands. Furthermore, to the best of our knowledge, phosphorus ligands on palladium have not been explored in Wacker oxidations.

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[11] B. W. Michel, A. M. Camelio, C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc.,* **2009**, *131*, 6076.

[12] H. Mimoun, R. Chapentier, A. Mitschler, J. Fischer, R. Weiss, *J. Am. Chem. Soc*., **1980**, *102*, 1047.

1.5 Aim and objective

The aim of the current study was therefore to firstly prepare a 1,10-phenanthroline-5,6-dione **3** bimetallic copper-palladium catalyst system for Wacker oxidations with the prospect of establishing electronic communication between the metals in order for copper to facilitate re-oxidation of the Pd metal in a ‘through-bond’ effect and secondly to prepare simple phosphorus ligands and evaluate their influence on the reactivity of palladium in the Wacker oxidation of a few selected common alkene substrates of industrial importance. Both scenarios were considered to have the potential to allow the omission of stoichiometric or excess amounts of copper which are normally required to combat palladium aggregation and ‘fall-out’.

CHAPTER TWO

Literature Review

2.1 Introduction

Palladium, platinum, iridium, osmium, rhenium, and ruthenium all have similar chemical properties and are collectively referred to as the platinum group metals.[13,14] Palladium exists as the second most abundant of these metals, occurring as 6 natural isotopes, that is, ^{102}Pd (0.8% relative abundance), ^{104}Pd (9.3%), ^{105}Pd (22.6%), ^{106}Pd (27.2%), ^{108}Pd (26.8%), ^{110}Pd (13.5%). Pt is often compared to Pd because of the similarities in their chemistry, but Pd is more reactive.

Pd has potentially six oxidation states, that is, Pd^{0}, Pd^{I}, Pd^{II}, Pd^{III} ,Pd^{IV} and Pd^{V}. While extensive research has been done on Pd^{0}, Pd^{I}, Pd^{II} and Pd^{IV}; Pd^{III} and Pd^{V} oxidation states do exist but reported complexes remain very rare.

Pd is classified as a class *b* soft metal, which according the Hard-Soft Acid-Base theory, will bind strongly to soft bases such as phosphorus and sulphur.[15] Complexes with oxygen and a borderline hard base, such as nitrogen compounds, do however also exist. In cases where metal-halide complexes in high oxidation states are used, a common feature with all Pt group metals is that a metal hydride (M-H) will form upon reduction of that metal halide.[16] An important aspect related to metal hydrides of the transition metals of group 8 to 10, is their propensity towards causing double bond isomerization of terminal alkenes. Such isomerizations might occur *via* either a metal hydride addition-elimination mechanism which involves the insertion of an alkene into a M-H bond, followed by *β*-hydride elimination (Scheme 2.1, eq. 1) or, alternatively, metal coordination to the alkene, followed by a 1,3-hydrogen shift *via* a *π*-allyl metal hydride complex (Scheme 2.1, eq. 2).[16,17] For addition-elimination metal hydride reactions a vacant coordination site and *syn*-coplanar arrangement of the metal centre, *α*- and *β*-carbons as well as the *β*-hydrogen is required.[16]

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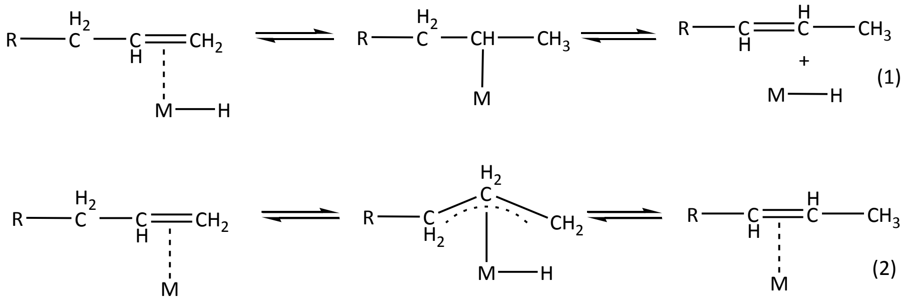
[13] C. F. J. Barnard, M. J. H. Russel, Palladium, Organometallic Chemistry, Johnson Matthey Technology Centre, Reading, UK, 1099.
[14] F. A. Cotton, G. Wilkinson, P. L. Basic Inorganic Chemistry, 3rd Edn., John Wiley & Sons, Inc., New York, **1995**, 597.
[15] T. -L. Ho, *Chem. Rev.,* **1975**, *75*, 1.
[16] T. C. Morrill, C. A. D'Souza, *Organometallics*, **2003**, *22,* 1626.
[17] D.V. McGrath, R.H. Grubbs, *Organometallics*, **1994**, *13*, 224.



Scheme 2.1: Isomerisation of terminal alkenes *via* metal hydride addition-elimination (eq. 1) or π-allyl metal hydride (eq. 2) mechanisms.

The preferred geometry of Pd^0 when coordinated to other molecules (ligands) is square planar, accommodating a maximum of four ligands, giving it a d^{10} configuration. Several of these complexes have been characterised, the most common being *tetrakis*(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] and *tris*(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) **6** (Figure 2.1).[18]

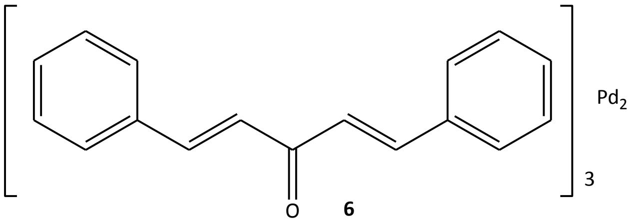


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Figure 2.1: *Tris*(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) **6**.

Pd^I complexes take on a d^9 configuration, are commonly dimeric or oligomeric in nature, and are diamagnetic.[13] These exist as complexes of type [PdL_n] (n=2,4) with phosphines as common ligand. Pd^{III} complexes such as the dithiolenes **7** and **8** (Figure 2.2) have been reported while indications of Pd^V in complexes such as $(O_2)[PdF_6]$ (or $O_2^+PdF_6^-$) and $Na[PdF_6]$ have also been found.[13]

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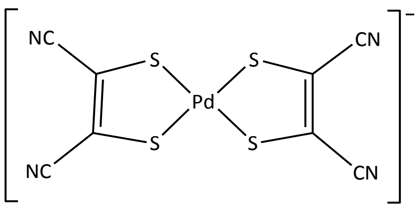
[18] P. Wothers, N. Greeves, S. Warren, J. Clayden, Organic Chemistry, Oxford University Press Inc., New York, **2001**, 1320.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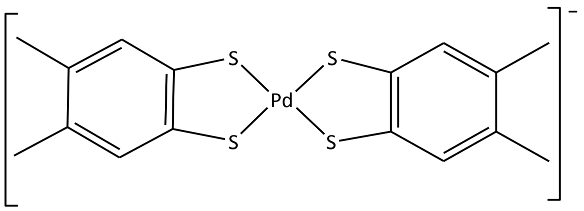
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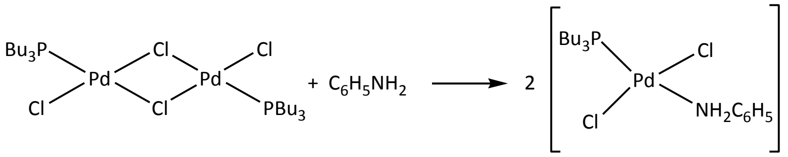
Figure 2.2: Dithiolene Pd^{III} complexes **7** and **8**.

Pd^{IV} is very unstable and readily reverts back to Pd^{II} which is regarded as the most stable oxidation state of palladium. Pd^{II} is also diamagnetic, taking on a low spin d^8 configuration. Common Pd^{II} complexes are $PdCl_2$ and $Pd(OAc)_2$, obtainable through chlorination for the former and acetylation of a Pd sponge with acetic acid in HNO_3 for the latter. Pd^{II} and Pt^{II} exist as square or five co-ordinate complexes in the form of ML_4^{2+}, ML_5^{2+}, ML_2X_2 (*cis*- and *trans*-), MX_4, and ML_3X_2 where L is a neutral nonlabile ligand and X is a labile ion.[19] Bridged dinuclear Pd species such as **9** are common and are cleaved to the corresponding mononuclear complexes **10** through the action of coordinating or donor compounds (Scheme 2.2).



9 **10**

Scheme 2.2: Formation of a mononuclear complex **10** from a dinuclear Pd complex **9**.

The role of ligands in square planar complexes can in many instances be explained by the so-called *trans*-effect,[19] which is defined as the effect that nonlabile ligands (L) in ML_2X_2 complexes have on the rate of substitution of a leaving group X that are in the *trans* position. Studies of the ability of ligands to direct rapid substitution *trans* to themselves has led to what is known as the *trans* series (Scheme 2.3).

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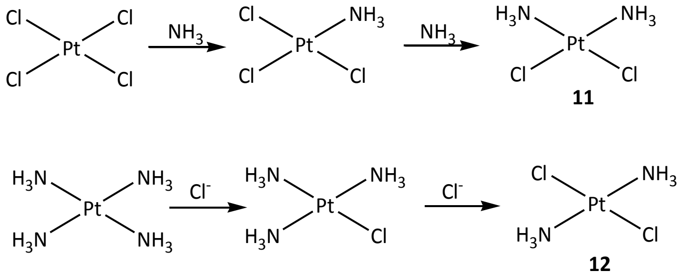
[19] F. A. Cotton, G. Wilkinson, P. L. Gauss, Basic Inorganic Chemistry, 3rd Edn., John Wiley & Sons, Inc., New York, **1995**, 201.

Trans series:
H_2O, OH^-, NH_3, py(NC_5H_5) < Cl^- < Br^-, SCN^-, I^-, NO_2^-, $C_6H_5^-$, $SC(NH_2)_2$, CH_3^- < H^-, PR_3 < C_2H_4, CN^-, CO

Scheme 2.3: *trans* series in order of increasing *trans* influence.

The *trans* effect is more pronounced in Pt complexes than in Pd and can be useful in explaining why some complexes form and why some will not form. For example, *cis*- **11** and *trans*- **12** isomers of $[Pt(NH_3)_2Cl_2]$ are generated through different Pt sources because of the *trans*-effect (Scheme 2.4).



Scheme 2.4: The *trans* effect: *cis*- **11** and *trans*- **12** isomers of $[Pt(NH_3)_2Cl_2]$.

Two pathways describe substitutions at metals centres, namely the associative and dissociative mechanisms.[20] In the associative mechanism, a concerted displacement of the ligand by the substrate takes place, while in a dissociative mechanism the ligand dissociates from the metal, leaving behind a 'vacant' site which gets temporarily occupied by a solvent molecule before it makes way for the substrate. Square planar Pt and Pd complexes in general react *via* an associative mechanism. In aqueous solutions, the rate law **14** for the reaction **13** (Scheme 2.5), suggest that there are two steps in this reaction which both go *via* an associative interchange (I_a) mechanism.

$PtL_3X + Y \longrightarrow PtL_3Y + X$ **13** (L = non-labile ligand, X = labile ligand, Y = incoming ligand)

$\text{rate} = k_1[PtL_3X] + k_2[PtL_3X][Y]$ **14**

Scheme 2.5: The rate law for aqueous $PtL_3X + Y$ reaction.

The rate constant k_1 describes a rate-determining step where X is first displaced by a solvent molecule like water in this instance.

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[20] P.W.N.M. van Leeuwen, Homogeneous Catalysis: Understanding the art, Kluwer Academic Publishers **2004**, 32.

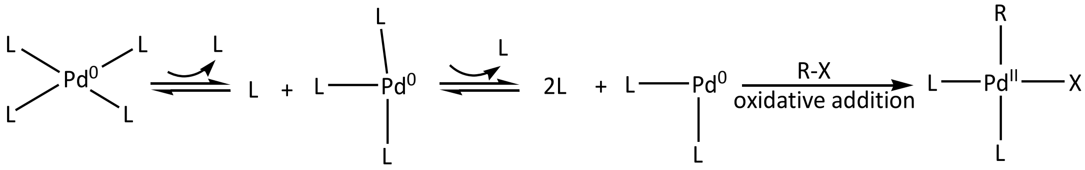
This is then followed by a fast displacement, through a five coordinate complex, of the water by the incoming Y ligand.

If an associative mechanism is followed, steric crowding present in the incoming ligand Y retards substitution at the metal centre, while substitution is enhanced by increased nucleophilicity of the ligand. A series that has been developed in this regard reveal that alkenes for example have a higher propensity for the metal centre than H_2O but less than phosphines (PR_3) (Scheme 2.6).

$$F^- \sim \mathbf{H_2O} \sim OH^- < Cl^- < Br^- \sim NH_3 \sim \textbf{alkenes} < C_6H_5NH_2 < C_5H_5N < NO_2^- < N_3^- < I^- < SCN^- \sim \mathbf{PR_3}$$

Scheme 2.6: Nucleophilicity of incoming ligands towards metal centres in square planar complexes.

Apart from direct displacement of ligands, Pt group metals can also be attached to organic molecules through the process of oxidative addition to halides or triflates (R-X, R = aryl, alkyl, vinyl; X = Br, I) (Scheme 2.7).



Scheme 2.7: Oxidative addition to Pd^0.

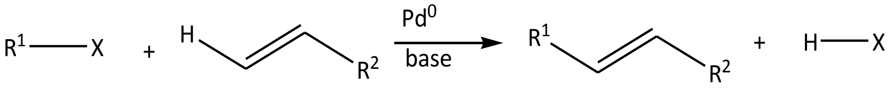
During this process an organic molecule interacts with the metal by cleaving a σ-bond (R-X), resulting in the addition of R and X ligands, both bearing a formal negative charge, onto the metal. Since two new σ-bonds to the metal are formed; the oxidation state of the metal is increased by two, i.e. from 0 to II in the case of palladium. Reactions that follow after this oxidative addition step are reductive elimination, migratory insertion, and β-hydride elimination. These characterize Pd^0 catalysis through name reactions such as the Heck, Suzuki and Stille reactions, as well as Sonogashira coupling.

2.2 Palladium(0) catalyzed C-C bond forming reactions

Transition metals afford transformations of organic molecules into useful or more powerful intermediates or products through carbon-carbon (C-C) bond forming reactions that would otherwise not have been possible with traditional organic methods. At the forefront of these developments were researchers like Richard F. Heck, Ei-ichi Negishi and Akira Suzuki, who received the recent the 2010 Nobel Prize in Chemistry for their significant contribution and developments in the field of Pd catalyzed reactions over the last 30-40 years.[21] The Heck, Negishi, and Suzuki couplings were named after these Nobel laureates and others such as the Stille and Sonogashira couplings are also widely used. These coupling reactions and many others have found numerous applications in organic synthesis, pharmaceutical, agrochemical, and material science. There is extensive literature that covers these reactions more elaborately, giving more detailed information as to the mechanisms, effect of ligands, heterogenous supports, nanoparticles, and other aspects related to the afore mentioned reactions.[22,23,24,25] Herein, only a few selected examples to showcase the role that Pd^0 and ligands have on Heck, Stille, Suzuki, and Sonogashira C-C couplings, are given.

2.2.1 Heck reaction

The Heck reaction comprises C-C bond formation between an alkyl entity containing a leaving group like halide or triflate R^1-X (X= halide or triflate) and an alkene (Scheme 2.8).



Scheme 2.8: The Heck reaction.

Despite its wide applicability, the Heck reaction has one serious limitation in that the nature of the R^1 group in R^1-X, should not allow β-hydride elimination after oxidative addition and before reaction with

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[21] D. Astruc, *Anal. Bioanal. Chem.*, **2011**, *399*, 1811.

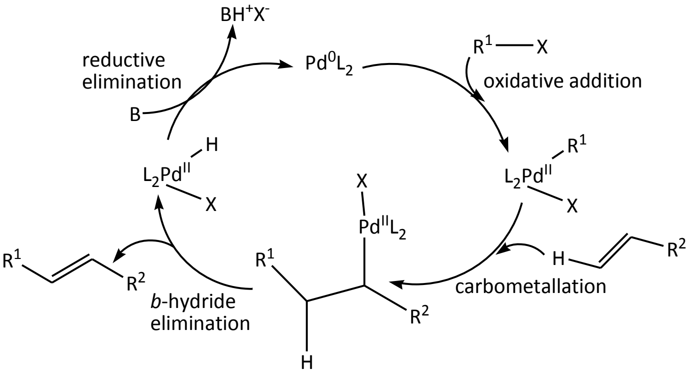
[22] V. Farina, *Adv. Synth. Catal.*, **2004**, *346*, 1553; M. Shibasaki, E. M. Vogl, T. Ohshima, *Adv. Synth. Catal.*, **2004**, *346*, 1533.

[23] J. -P. Corbet, G. Mignani, *Chem. Rev.*, **2006**, *106*, 2651.

[24] R. Chinchilla, C. Nájera, *Chem. Rev.*, **2007**, *107*, 874.

[25] M. Lamblin, L. Nassar-Hardy, J. -C. Hierso, E. Fouquet, F. -X. Felpin, *Adv. Synth. Catal.*, **2010**, *352*, 33.

the alkene substrate.[26] R^1 groups therefore are limited to aryl, vinyl, benzyl, *tert*-alkyl and other alkyl groups with no β hydrogens. This would allow a slow carbometallation (Pd-C) step where the alkene is inserted into the weak Pd-R^1 bond after oxidative addition (Scheme 2.9).



Scheme 2.9: Mechanistic pathway of the Heck reaction with Pd^0.

The alkylpalladium(II) intermediate generated in this way subsequently undergoes β-hydride elimination giving off the C-C coupled product and a Pd^{II} hydride ($Pd^{II}L_2H$) species. Reductive elimination from the palladium hydride species, to afford the required Pd^0 (Pd^0L_2), would lead to the formation of an acid. As such, a base **B** is usually added to the reaction mixture to regenerate the active Pd^0.

Since Pd^{II} species are more stable and easier to handle than Pd^0, Pd^{II} compounds can be used to generate Pd^0 *via* an *in situ* reduction process using ligands or compounds such as amines, phosphines, alkenes, or organometallic compounds like DIBAL-H, butyllithium or trialkyl aluminium.[26]

While early developments of the Heck reaction centered on the utilization of phosphine ligands, other ligands were evaluated in more recent investigations. The dipalladium complex **15** (Figure 2.3, n=2,3,4) based on a di-*N*-heterocyclic (NHC) ligand for example, has been shown to give good selectivities (66-77%) and conversions (92-98%) during the formation of stilbene through a reaction of styrene with bromobenzene.[27] The improved reactivity of these catalysts was attributed to the increased steric bulk by NHC ligands, together with their higher electron density which would have a stabilizing effect on the Pd^0 catalytic species.

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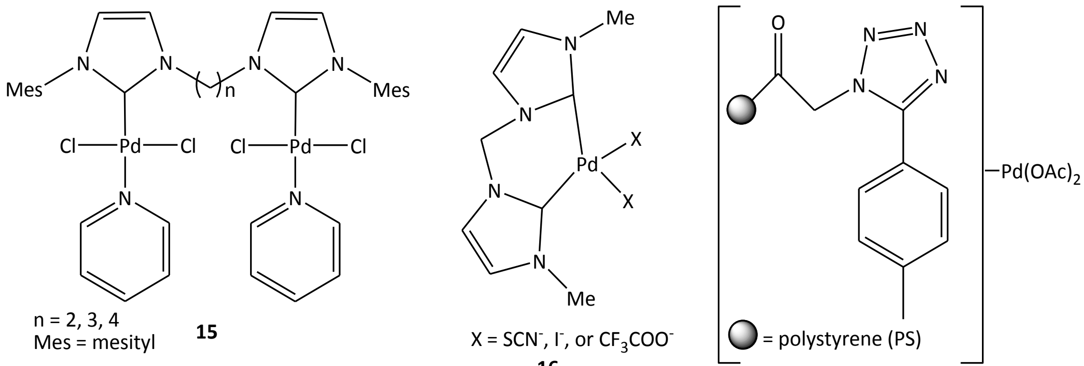
[26] J. Clayden, N. Greeves, S. Warren, P. Wothers, Organic Chemistry, Oxford University Press Inc., New York, **2001**, 1321.

[27] C. Cao, Y. Zhuang, J. Zhao, Y. Peng, X. Li, Z. Shi, G. Pang, Y. Shi, *Inorg. Chim. Acta*, **2010**, *363*, 3914.

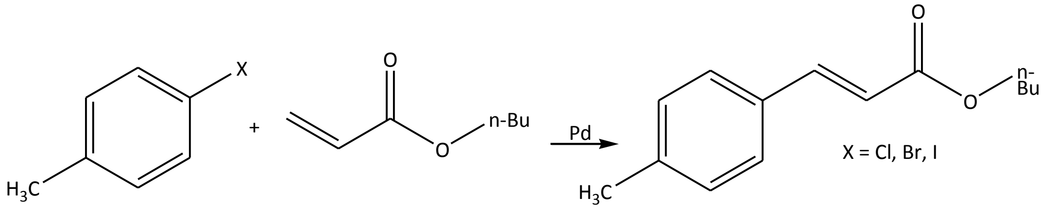


15 **16** **17**

Figure 2.3: Palladium^{II} complexes **15**-**17** used for Heck reactions.

With the NHC palladium^{II} complex **16** (Figure 2.3), the role of counterions was highlighted in the reactions of arylbromides and chlorides with *tert*-butylacrylates.[28,29] In these reactions the best yield of 97% was obtained with the CF_3COO^- counterion at 1 mol% catalyst concentration in DMF. Along the same lines it was found that a Pd^{II} catalyst tethered to a polystyrene tetrazole support **17** (Figure 2.3) showed increased stability affording a wide range of products in up to 98% yield.[30]

The influence of electronic factors on the reactivity of the catalyst has also been a subject of investigation wherein yields of up to 99% could be obtained during the coupling of butylacrylates with arylhalides (Scheme 2.10) through the utilization of bulky phosphite ligands such as **18** (Figure 2.4).[31]



Scheme 2.10: Heck reaction of arylhalides and butylacrylates with Pd(OAc)$_2$ and phosphite **18**.

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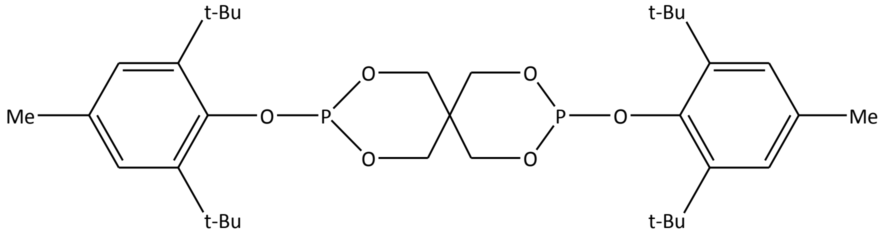
[28] A. D. Yeung, P. S. Ng, H. V. Huynh, *J. Organomet. Chem.*, **2011**, 112.

[29] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.*, 2000, 100, 3009.

[30] Y. He, C. Cai, *Transition Met. Chem.*, **2011**, *36*, 113.

[31] E. Jung, K. Park, J. Kim, H. –T. Jung, I. –K. Oh, S. Lee, *Inorg. Chem. Comm.*, **2010**, *13*, 1329.



18

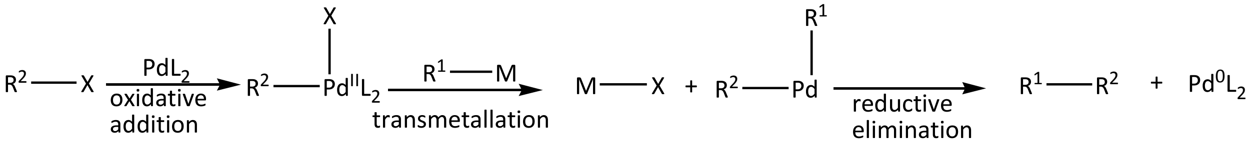
Figure 2.4: A phosphite ligand **18**.

As bulky air-stable π acceptors, phosphites are thought to be better σ donors than phosphines, thus leading to enhanced reactivity of the palladium catalyst.

Although the best yields (99%) during this study were realized with K_2CO_3 as base, the specific base did not seem to have a significant effect on yields. Cs_3CO_3, Na_2CO_3 and K_3PO_4 also afforded high yields of 97%, 94% and 90% respectively.

2.2.2 Suzuki cross coupling

Suzuki, Stille and Sonogashira coupling reactions differ slightly from the Heck reaction as they all involve substitution of the halogen or triflate attached to the palladium upon oxidative addition, by an organometallic component (R^1-M) (Scheme 2.11).[32] This additional step that is not present in Heck coupling is referred to as the transmetallation step.



Scheme 2.11: A general cross-coupling mechanism.

Reductive elimination step is faster than β-hydride elimination. R^1 in this instance is not restricted to groups without β-hydrogens. R^2, however, still is, because transmetallation is slower than β-hydride elimination. The metal **M** in these reactions may be Mg, Zn, Cu, Sn, Si, Zr, Al, or B.

The Suzuki C-C coupling, named after Akira Suzuki, involves the reaction of boronic acids or derivatives with aryl or vinyl halides or triflates (Scheme 2.12).

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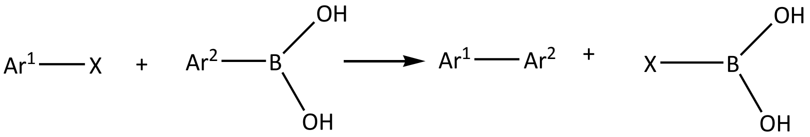
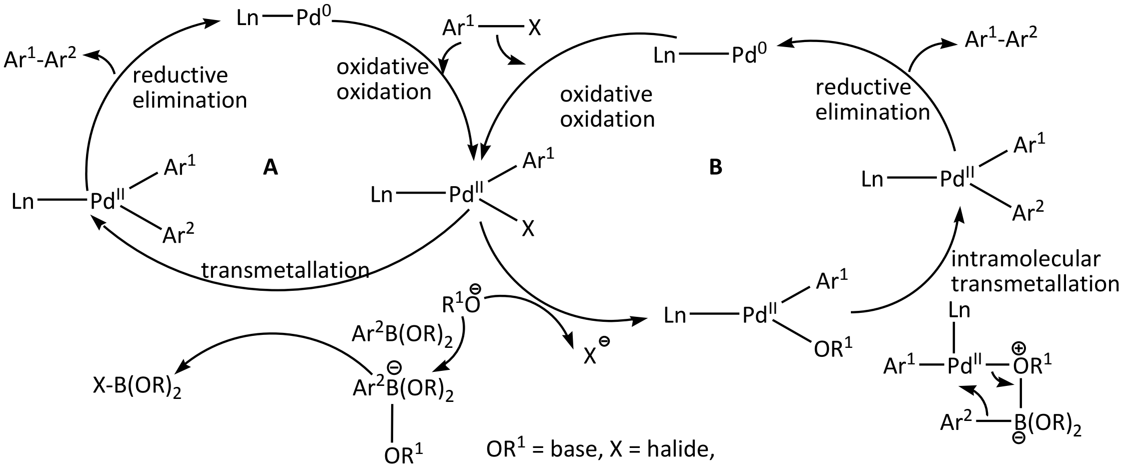
[32] J. Clayden, N. Greeves, S. Warren, P. Wothers, Organic Chemistry, Oxford University Press Inc., New York, **2001**, 1321.



Scheme 2.12: Suzuki cross coupling.

In this reaction the transmetallation step is proposed to follow two possible mechanistic routes **A** and **B** (Scheme 2.13).[33] In path **A**, the base, usually K_3PO_4 or K_2CO_3, converts the mild boronic acid ($Ar_2B(OR)_2$) to a more reactive boronate ($Ar_2XB^{-}(OR)_2$) species that can speed up the transmetallation step. Reductive elimination then affords the coupled Ar^1-Ar^2 product and Pd^0 which can re-enter the catalytic cycle. Alternatively, the oxidative step can be followed by displacement of the halide on the arylpalladium (II) species by the base (Path **B**, Scheme 2.13), which then interacts with the boronic acid to form the boronate. Through intramolecular transmetallation facilitated by the Pd^{II} centre, both aryl groups add to the metal. Reductive elimination affords the product and Pd^0.



Scheme 2.13: A Proposed Suzuki cross-coupling mechanism.

The Suzuki reaction proceeds well under mild conditions, with great stability of boronic acids in the presence of heat, water and oxygen.[34] A wide range of functional groups are tolerated and separation of boron by-products comes with ease. These features make it a popular choice for carbon-carbon bond

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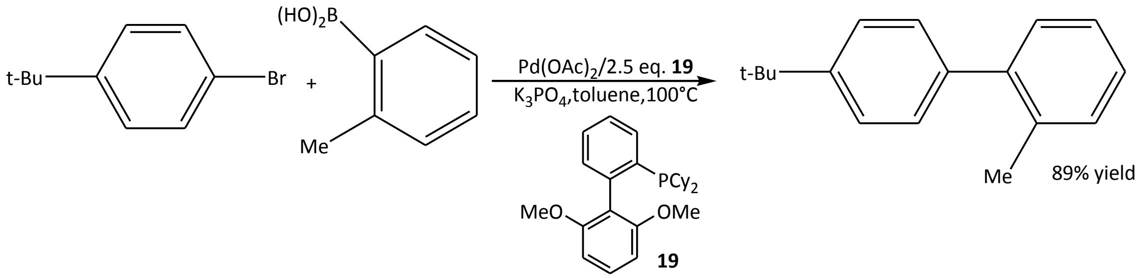
[33] R. Martin, S. L. Buchwald, *Acc. Chem. Res.*, **2008**, *41*, 1461.

[34] M. Lamblin, L. Nassar-Hardy, J. -C. Hierso, E. Fouquet, F. –X. Felpin, *Adv. Synth. Catal.*, **2010**, *352*, 33.

formation and since efficiency in these reactions has been realized with ligand modification, ongoing work is still focused on that.

Buchwald *et al*. attribute the success of the coupling reaction between a methylboronic acid and an arylhalide to the remarkable properties of the bulky, electron-rich diaryldialkyl phosphine **19** (Scheme 2.14) as an additive to $Pd(OAc)_2$.[35]



Scheme 2.14: Suzuki cross-coupling reaction with $Pd(OAc)_2$ and a diaryldialkyl phosphine **19**.

Martin and Buchwald attributed the superior activity of biarylphospines to a combination of electronic and steric effects which facilitates the formation of monoligated L_1Pd intermediates, thus enhancing oxidative addition, transmetallation and reductive elimination by firstly stabilizing the monoligated intermediate, secondly by increasing the rate of oxidative addition to this species compared to higher coordinated intermediates (e.g $L_2Pd(0)$) due to reduced steric interactions with the approaching substrate, and thirdly by increasing the rate of transmetallation and reductive elimination for related steric reasons.[35] *o*-Substituents on the non-phosphorylated ring make a further contribution towards the steric bulk of the ligand. Biarylphosphines with *ortho*-OMe groups are superb ligands which in addition to the above mentioned, stabilize the oxidative addition intermediate as two rotameric species where Pd interacts with the *ipso* carbon in one rotamer or the OMe oxygen in the other.

The influence of the steric bulk and electron donating properties of ligands on the activity of the Pd catalyst also finds a precedent in other systems. $P(t\text{-}Bu)_3$, for example, is more electron donating and

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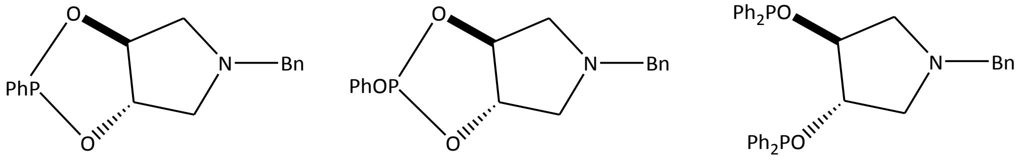
[35] R. Martin, S. L. Buchwald, *Acc. Chem. Res.*, **2008**, *41*, 1461.

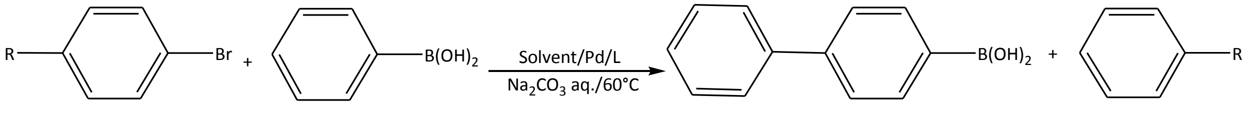
bulkier than $P(Cy)_3$ and performed better as a ligand in coupling reactions of arylchlorides, bromides and iodides with arylboronic acids.[36]

In a recent study the effect of the electronic nature of the phosphorus ligand, *i.e.* it being a phosphonite **20**, phosphite **21**, or diphosphinite **22** (Figure 2.5), on the reaction of the very reactive 1-bromo-4-trifluoromethylbenzene with phenylboronic acid over $PdCl_2COD$ was investigated (Scheme 2.15).[37]



20 **21** **22**

Figure 2.5: Phosphonite **20**, phosphite **21**, diphosphinite **22**.



R = CF_3, OMe

Scheme 2.15: 1-bromo-4-trifluoromethylbenzene and 1-bromo-4-methoxybenzene with phenylboronic acid over $PdCl_2COD$ and ligands L = **20**, **21** and **22**.

While all ligands displayed activity, the electron withdrawing effects of the CF_3 group showed overall higher conversions than the electron donating OMe group across all ligands. Similar activity between **21** and **22** were observed, giving 98% and 91% conversion respectively with R = CF_3, while 20 resulted in 80% conversions.

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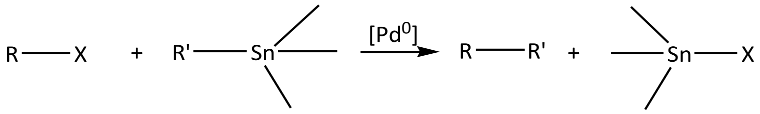
[36] G. C. Fu, *Acc. Chem. Res.*, **2008**, *41*, 1555.

[37] M. V. Escárcega-Bobadilla, E. Teuma, A. M. Masdeu-Bultó, M. Gómez, *Tetrahedron*, **2011**, *67*, 421.

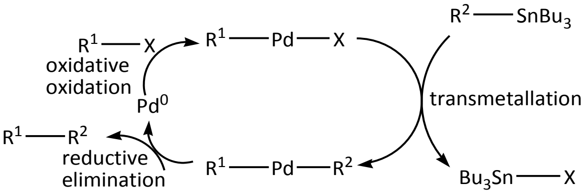
2.2.3 Stille cross-coupling

The Stille cross-coupling differs from the Suzuki coupling in that an organostannane compound rather than an alkyl boron reagent is involved in the transmetallation step (Scheme 2.16).[38]



Scheme 2.16: Stille cross-coupling.

The fact that trialkyl organotin species are readily available, quite air and moisture stable, and tolerant to many functional groups renders the Stille coupling one of the most popular reactions in modern organic synthesis and it has been used in the synthesis of numerous complex organic molecules. The stability and other properties of organotin compounds are mostly due to the low polarity of the C-Sn bond, when compared to those of other transmetallating species like Grignard reagents.[38] Since the oxidative-addition and reductive–elimination steps in the catalytic cycle of the Stille coupling (Scheme 2.17) resembles that of other palladium catalyzed C-C bond forming reactions (Heck, Suzuki, and other coupling reactions) to a large extent, ligand systems and active catalyst species for all of these reactions are very similar.



Scheme 2.17: Stille coupling of stannanes and organic electrophiles.

While the first and last steps (oxidative-addition and reductive–elimination) in the catalytic cycle of the Stille coupling is well understood and resembles, to a large extent, those of the Heck and Suzuki reactions, the mechanism of the transmetallation part of the reaction is, despite it being a simple ligand substitution on a Pd^{II}, complex in nature and may follow an associative or dissociative pathway.[39,40]

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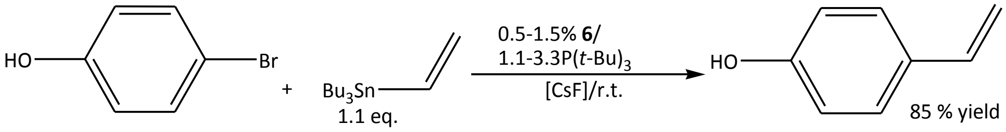
[38] P. Espinet, A. M. Echavarren, *Angew. Chem. Int. Ed.*, **2004**, *43*, 4704.

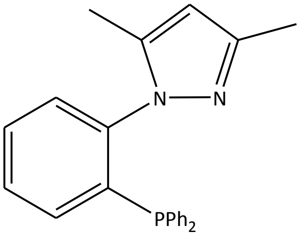
[39] R. Cross, *Adv. Inorg. Chem.*, **1989**, *34*, 219.
[40] R. Romeo, *Comments Inorg. Chem.*, **1990**, *11*, 21.

Although additives like halide ions or bases are not required in the catalytic cycle of the Stille coupling reaction, it has been found that the addition of compounds like LiCl[41] and CsF have an accelerating effect on reactions between less reactive aryl substrates (chloro or triflate derivatives) and alkylstannanes.[42,43] In this regard, it was demonstrated that the reaction rate for reactions with Pd/PBu_3^t catalyst systems could be enhanced significantly by the addition of CsF (Scheme 2.18).

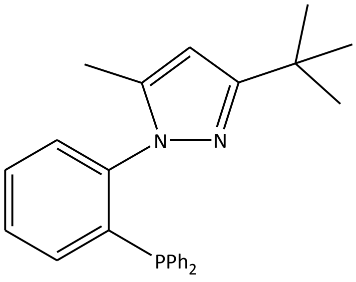


Scheme 2.18: Stille cross-coupling of 4-bromophenol with an allylstannane.

Furthermore, CsF was found to be superior to basic additives like Cs_2CO_3 or K_3PO_4 in coupling reactions of phenyltributyltin with 4-bromoanisole using pyrazole-phosphine ligands **23** and **24** (Figure 2.6) and Pd_2dba_3 as catalyst.[44]



23



24

Figure 2.6: Pyrazole-phosphine ligands **23** and **24**.

The accelerating role of CsF is attributed to the fluoride anion's ability to activate the tin compound through the formation of a pentacoordinated tin species. The less polarized R'-Sn bond is therefore activated towards transmetallation.

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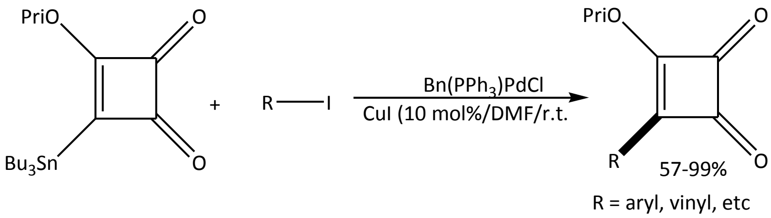
[41] A. L. Casado, P. Espinet, A. M. Gallego, J. M. Martinez-Ilarduya, *Chem. Commun.*, **2001**, 339.

[42] E. Fouquet, A. Rodriguez, *Synlett*, **1998**, 1323.

[43] P. Espinet, A. M. Echavarren, *Angew. Chem. Int. Ed.*, **2004**, *43*, 4704.

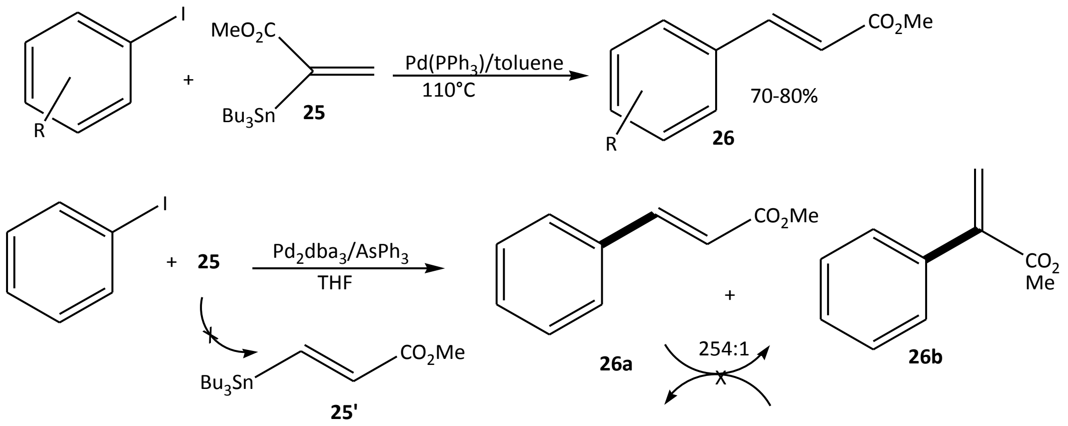
[44] A. Pal, R. Ghosh, N. N. Adarsh, A. Sarkar, *Tetrahedron*, **2010**, *66*, 5451.

A remarkable phenomenon in the Stille coupling reaction is found in the addition of copper (I) salts to couplings catalyzed by PdL_4 systems.[45] The first so-called 'copper effect' (Scheme 2.19), which manifested itself in the enhancement of yields in the coupling reactions of vinylstannanes with aryl or vinyl halides, was rationalized in terms of the copper capturing the neutral ligand released during the oxidative addition of the alkylhalide to the palladium catalyst.



Scheme 2.19: The Cu effect in Stille cross-coupling: early days.

More recently it was also found that copper could be used to suppress the formation of *cine* coupled products, like **26**, in the reaction of sterically hindered stannanes **25** (Scheme 2.20 & 2.21).[46]



Scheme 2.20: C*ine* substitution of methyl *α*-(tributylstannyl)acrylate **25**.

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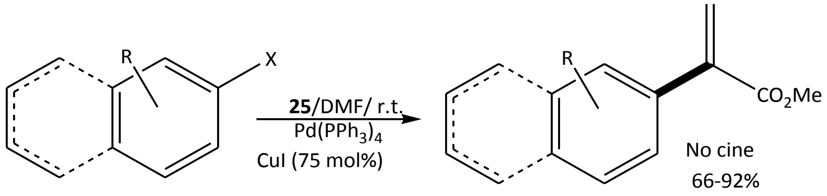
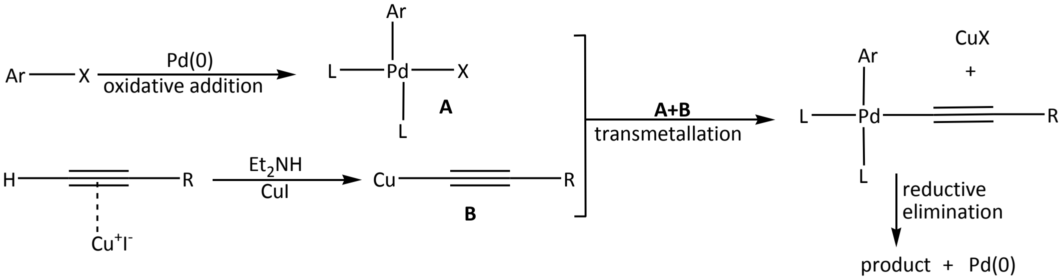
[45] V. Farina, S. Kapadia, B. Krishnan, C. Wang, L. S. Liebeskind, *J. Org. Chem.*, **1994**, *59*, 5905.
[46] Y. Peng, W. -D. Z. Li, *Eur. J. Org. Chem.*, **2010**, 6703.



Scheme 2.21: No *cine*, *ipso* selective synthesis of methylaryl acrylates.

2.2.4 Sonogashira coupling

While conditions for the oxidative addition step in the Sonogashira coupling are the same as for the Heck, Stille and Suzuki reactions, this coupling reaction is distinguished by a transmetallation step that uses copper acetylide (copper salt of a terminal alkyne). The alkyne is usually activated for transmetallation by copper iodide in the presence of a base (Scheme 2.22). The transmetallation step is followed by reductive elimination to form the product and Pd^0.



Scheme 2.22: Sonogashira coupling.

In the Sonogashira reaction vinylic halides are generally more reactive than aryl halides with the order of reactivity of the leaving groups being the expected I > OTf > Br >> Cl.[47] For successful oxidative addition, electron withdrawing substituents on the aryl group are needed in order to activate the C-X bond. Typical reaction conditions of Sonogashira coupling require high catalyst loading of 5 mol% with large quantities of copper and common Pd-phosphine salts such as $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$. In reactions with 3 mol% $PdCl_2(PhCN)_2$/6 mol% $P(Bu_3^t)$, room temperature Sonogashira coupling across a wide range

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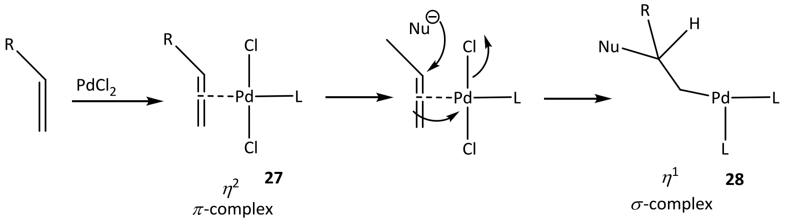
[47] T. Hundertmark, A. F. Littke, S. L. Buchwald, G. C. Fu, *Organic Lett.*, **2000**, *2*, 1729.

of alkynes and the least reactive arylbromides which normally require temperature of at least 80°C, was reported to proceed successfully at room temperature.

Having evaluated ligands such as PPh_3, P(*o*-tolyl)$_3$, dppf, PCy_3 and $P(Bu_3^t)$, the nature of the ligand appeared to have a tremendous effect on the efficiency of the reactions, with all the four ligands but $P(Bu_3^t)$ giving virtually no yield in product (<2%).

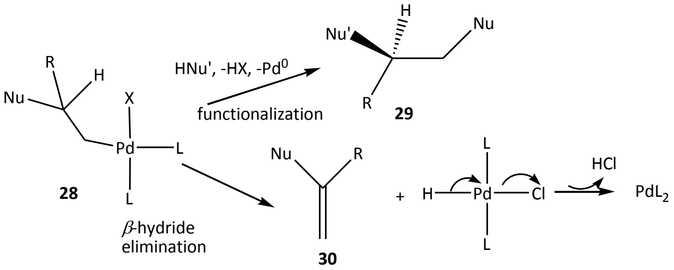
2.3 Pd (II) catalysis in alkene functionalization

Pd^{II} may act as Lewis acid; it therefore promotes the addition of a nucleophile across a rather inert double bond. During this process the π-electrons of the alkene are, upon coordination and formation of a η^2 complex **27**, utilized in the formation of a very unstable η^1 σ-alkyl palladium intermediate **28** (Scheme 2.23).[48]



Scheme 2.23: Addition of a nucleophile across a palladium bound alkene.

This alkyl intermediate **28** plays a key role in the product formed from the reaction as it may be decomposed in either of two ways (Scheme 2.24);



Scheme 2.24: Decomposition of alkylpalladium intermediate into a 'hydro' (Nu = H_2O, X = Cl) **30** or di-functionalized **29** species.

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[48] K. H. Jensen, M. S. Sigman, *Org. Biomol. Chem.*, **2008**, *6*, 4083; K. H. Jansen, T. P. Pathak, Y. Zhang, M. S. Sigman, *J. Am. Chem. Soc.*, **2009**, *131*, 17074.

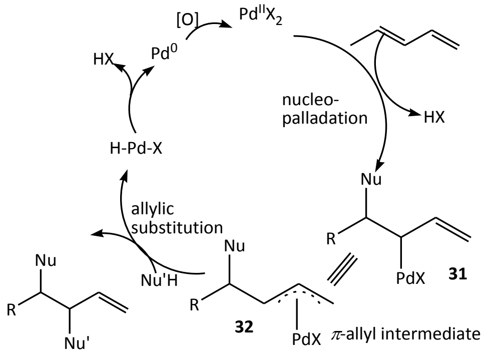
When treated with a second nucleophile it may give rise to a 1,2-disubstituted alkane product **29** (Scheme 2.24) or the double bond may be re-generated through *β*-hydride elimination leading to overall substitution of the leaving group by the incumbent nucleophile to give product **30** (Scheme 2.24).[48]

Difunctionalization is successful only if the *β*-elimination route is intercepted or suppressed through further stabilization of **28**. This can be afforded by using alkenes that have a functional group that can stabilize the alkylpalladium species through coordination with Pd or by converting it to a more stable intermediate that will allow the second addition of a nucleophile. As such, reactions such as diamination, diacetoxylation, dihydroxylation, and aziridination have been reported.

2.3.1 Palladium catalysed diamination

Diamines are present in many biologically active molecules and also make good ligands in organotransition metal synthesis. The latter attribute is but what makes their preparation extremely challenging as the diamine itself, once formed, can coordinate to the transition metal used in the preparation and deactivate it.[49]

Diamination of olefins is a relatively new field with the first transition-metal catalyzed reaction reported in 2005.[49,50] Proceeding through a *π*-allyl intermediate, dienes have been identified as compounds to suppress *β*-hydride elimination, and in the presense of amines, afford diamination. The proposed mechanism involves nucleopalladation through the first double bond to the palladium metal, generating an alkylpalladium species **31** (Scheme 2.25).



Scheme 2.25: Proposed mechanism for the diene stabilization *π*-allyl intermediate **32**.

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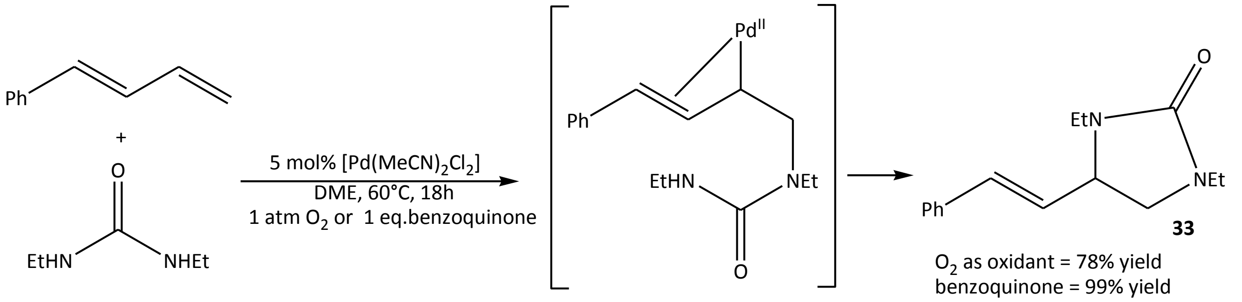
[49] R. M. de Figueiredo, *Angew. Chem. Int. Ed.*, **2009**, *48*, 1190.

[50] G. L. J. Bar, G. C. Llyod-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.*, **2005**, *127*, 7308.

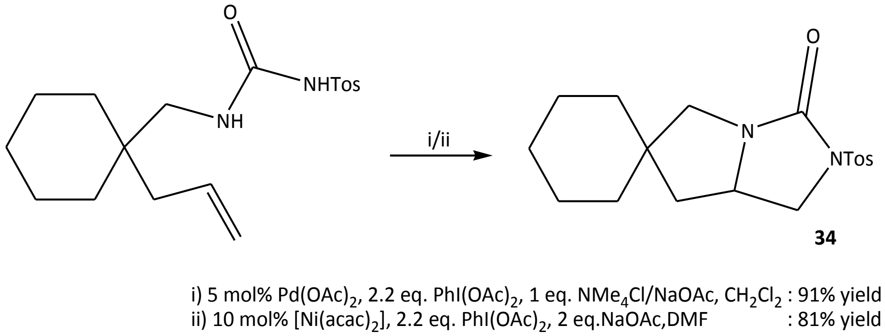
This rearranges to a more stable π-allyl intermediate **32**, which is electrophilic enough for a second attack by a nucleophile (Scheme 2.25).[51]

Milburn *et al.* used 1,3-butadiene and the less reactive alkyl ureas to direct the amination regioselectively to the terminal alkene; affording the diaminated compound **33** in 78 to 99% yield (Scheme 2.26).[50]



Scheme 2.26: Transition-metal catalyzed diamination of olefins.

Using a similar strategy, Muniz *et al.* achieved intramolecular diamination of a ω-alkenyl-substituted urea with the formation of bicyclic guanidines as products **34** (Scheme 2.27). In this instance the authors used iodobenzene diacetate as oxidant and found the reaction to be rather limited in scope as well as poor in selectivity.[52]



Scheme 2.27: Intramolecular diamination of a ω-alkenyl-substituted urea with Pd(OAc)$_2$ or Ni(acac)$_2$.

Further developments on diamination methodology saw the utilization of *tert*-butyldiaziridinone **35** as source of the nitrogen atoms (Scheme 2.28). In this instance the reaction is initiated by oxidative

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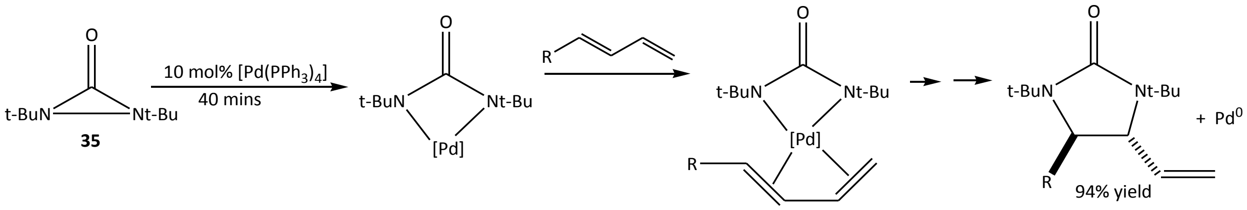
[51] K. H. Jensen, M. S. Sigman, *Org. Biomol. Chem.*, **2008**, *6*, 4083.

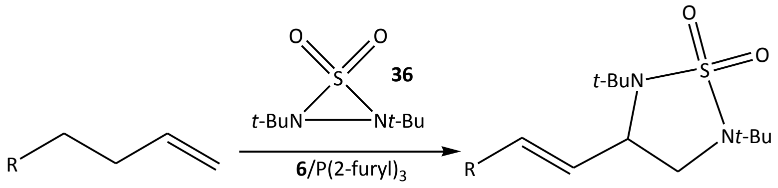
[52] J. Streuff, C. H. Hövelmann, M. Nieger, K. Muñiz, *J. Am. Chem. Soc.*, **2005**, *127*, 14586.

addition of a Pd^0 source to the nitrogen-nitrogen bond of the aziridine **35** (Scheme 2.28).[53] Regioselectivity is maintained, that is, the internal double bond still reacts preferentially.



Scheme 2.28: Diamination of a range of dienes and trienes with Pd^0 [$Pd(PPh_3)_3$] and *tert*-butyldiaziridinone **35**.

Dehydrogenative diaminination has been proposed in order to explain the different product obtained in diamination of terminal olefins when a different nitrogen source *N,N*-di-*tert*-butylthiadiaziridine 1,1-dioxide **36** was used together with different phosphine ligand, P(2-furyl)$_3$ (Scheme 2.29).[54]



Scheme 2.29: Dehydrogenative diamination of terminal olefins with *N,N*-di-*tert*-butylthiadiaziridine 1,1-dioxide **36**.

Triphenyl phosphine (PPh_3) was found to catalyze diamination of funtionalized alkenes such as chalcone **37** in reactions with *N,N*-dichloro-*p*-toluenesulfonamide ($TsNCl_2$) **38** and acetonitrile (CH_3CN) (Scheme 2.30).[55]

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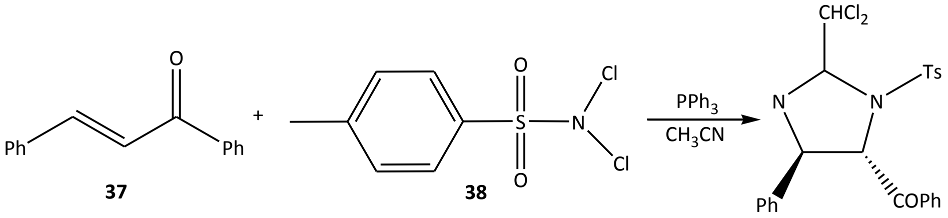
[53] H. Du, B. Zhao, Y. Shi, *J. Am. Chem. Soc.*, **2007**, *129*, 14542; H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.*, **2007**, *129*, 11688.

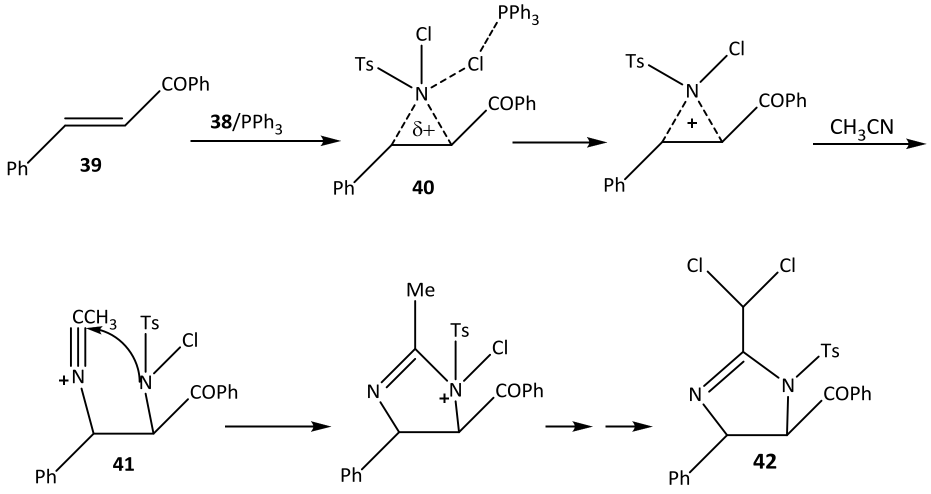
[54] B. Wang, H. Du, Y. Shi, *Angew. Chem. Int. Ed.*, **2008**, *47*, 8224.

[55] H. Wu, X. Ji, H. Sun, G. An, J. Han, G. Li, Y. Pan, *Tetrahedron*, **2010**, *66*, 4555.



Scheme 2.30: Diamination of chalcone **37** with PPh_3 and **38** in CH_3CN.

It is proposed that the role of PPh_3 was to activate **38** which then reacts with chalcone **39** forming a 3-membered ring **40** which goes through a [2+3] cycloadditon with CH_3CN for a second diamination (**41**, Scheme 2.31). This collapses the ring to form a 5-membered ring, which after a series of steps affords a diaminated product **42**.



Scheme 2.31: A proposed mechanism for PPh_3 activation of **38**.

Although the reaction was slow (30 hours), good yields (>70%) together with ee's of over 95% were obtained for a range of electron donating and electron withdrawing substituents on the chalcone skeleton.

2.3.2 Epoxidation

A recent literature account of the progress made in the palladium-catalyzed epoxidation reaction, indicate that the metals, oxidants, substrate, ligands and solvents play a significant role in the success of the reaction, both catalytically and with stoichiometric reagents.[56]

Several stoichiometric oxidants, like *tert*-butylhydroperoxide (THBP) **43**, iodosylbenzene (PhIO) **44**, 2,6-dichloropyridine-*N*-oxide (Cl_2PyNO) **45**, hydrogen peroxide (H_2O_2) **46**, peracids **47** (Figure 2.7), and the ultimate industrial oxidant, molecular oxygen, have all been utilised and evaluated in the epoxidation of a variety of substrates.

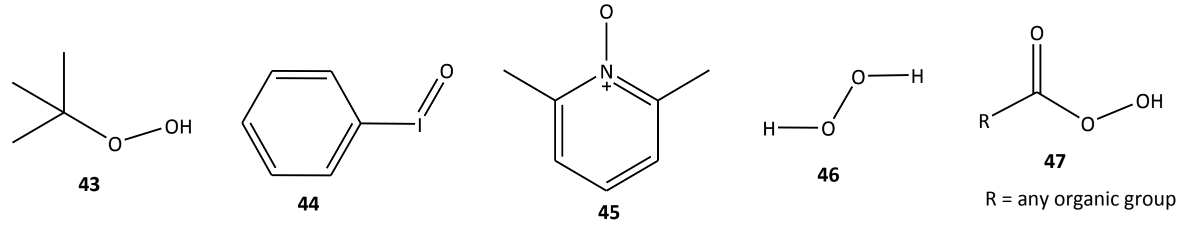
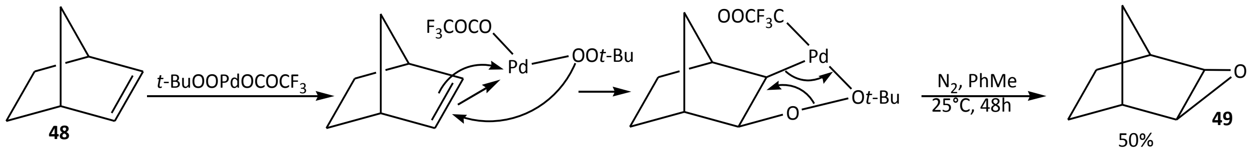


Figure 2.7: Some stoichiometric oxidants **43**-**47** used in epoxidation.

In the presence of **43**, for example, the (t-BuOOPdOCOCF$_3$)$_4$ complex generated from **43** and $Pd(OCOCF_3)_2$, was proposed as the active species in the epoxidation of norbornene **48** with 1 equivalent of $Pd(OCOCF_3)_2$ (Scheme 2.32) leading to *exo*-epoxynorbornene **49** in 50% yield.[57]



Scheme 2.32: Epoxidation of norbornene **48** with $Pd(OCOCF_3)_2$.

With 1 equivalent of $ClPdNO_2(MeCN)_2$[58], obtainable *via* a reaction of $PdCl_2(CH_3CN)_2$, silver nitrite ($AgNO_2$) and acetonitrile (CH_3CN), a different intermediate **50** (Scheme 2.33) has been proposed for the formation of *exo*-epoxynorbornene **49** (90% yield).[59]

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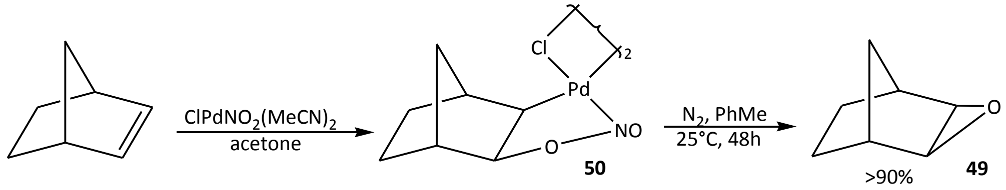
[56] J. Muzart, *J. Mol. Cat. A: Chemical*, **2007**, *276*, 62.

[57] H. Mimoun, R. Charpentier, A. Mitschler, J. Fischer, R. Weiss, *J. Am. Chem. Soc.*, **1980**, *102*, 1047.

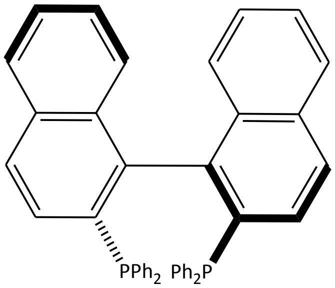
[58] M. A. Andrews, K. P. Kelly, *J. Am. Chem. Soc.*, **1981**, *103*, 2894.

[59] M. A. Andrews, C. –W. F. Chang, *J. Am. Chem. Soc.*, **1982**, *104*, 4268.

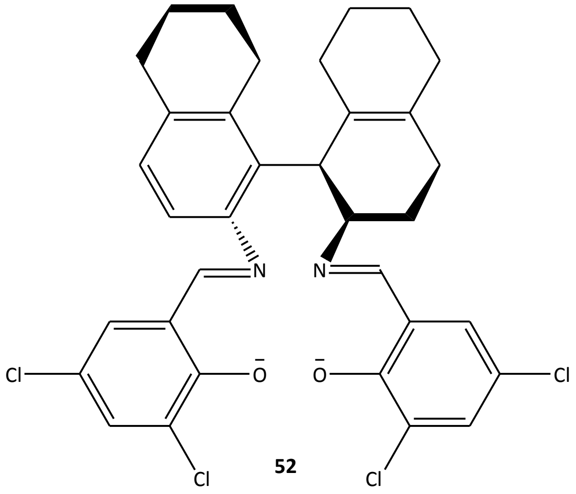


Scheme 2.33: Epoxidation of **48** with ClPdNO$_2$(MeCN)$_2$.

Utilizing a **(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)** BINAP **51** derived ligand **52** (Figure 2.8), Che *et al*. investigated the potential of different stoichiometric oxidizing agents in Pd catalyzed epoxidation reactions.[60]



51



52

Figure 2.8: A BINAP derived ligand **52** used in a Pd-catalyzed epoxidation of styrene and its derivatives.

For styrene type substrates, **43** was found to be superior over **44** and Cl$_2$PyNO **42** leading to yields of 70-76 and 27% respectively for styrene and *p*-fluorostyrene. The formation of allylic *tert*-butoxides were however found to be competing reactions (Scheme 2.34). For aliphatic substrates like **48** 82% yield of **49** was obtained.

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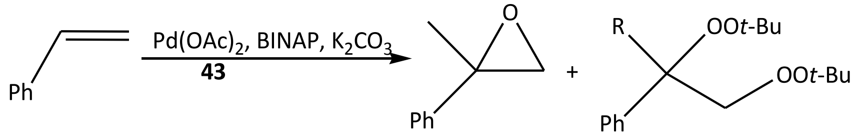
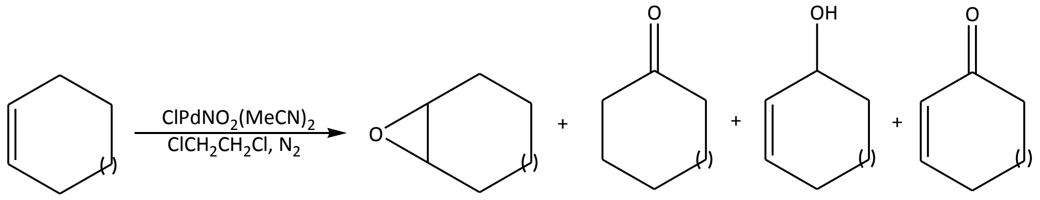
[60] X. –G. Zhou, J. –S. Huang, X. –Q. Yu, Z. –Y. Zhou, C. –M. Che, *J. Chem. Soc., Dalton Trans.*, **2000**, 1075.



Scheme 2.34: Allylic *tert*-butylperoxidation of styrene.

As is evident from the previous paragraphs, the structure of a substrate plays a paramount role in its ability to be epoxidised. Thus, linear alkenes could not be epoxidized with $ClPdNO_2(MeCN)_2$, while epoxidation of cycloheptene and cyclohexene was met with competing reactions, which afforded alkenols, ketones and enones (Scheme 2.35).[56] $Pd(OCOCF_3)_2$ produced cycloheptenol, cycloheptenone, and cycloheptanone in 11, 33, and 1% respectively from cycloheptene.



n = 0,	4%	3%	27%	1%
n = 1	0%	3%	34%	5%
n = 2	21%	4%	2%	32%

Scheme 2.35: Epoxidation of cyclohexene (n = 0), cycloheptene (n = 1) and cyclooctene (n = 2) with $ClPdNO_2(MeCN)_2$.

Furthermore, substrate concentration also appears to have a significant influence on the outcome of the epoxidation reaction. At a norbornene concentration of 0.04M and catalytic $ClPdNO(MeCN)_2$, the ratio of the epoxide to the tetrahydrofuran by-product **53** (Figure 2.9) was 98:2.[61] Increasing the norbornene concentration to 0.4M led to a ratio of 2:98 in favour of the tetrahydrofuran derivative.

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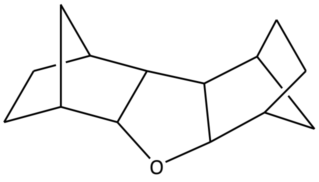
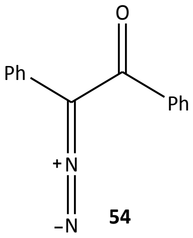
[61] P. K. Wong, M. K. Dickson, L. L. Sterna, *J. Chem. Soc., Chem. Comm.*, **1985**, 1565.



53

Figure 2.9: Tetrahydrofuran derivative **53** obtained at high concentration of norbornene.

Since oxygen cannot be used as stoichiometric oxidant in any system that contains allylic hydrogens, several co-oxidants/additives have been exploited in order to avoid allylic oxidation during the epoxidation of these systems. In this regard, azibenzil **54** (Figure 2.10) has been used to form a carbene-palladium species that is capable of reacting with O_2 to epoxidize alkenes.[62]



54

Figure 2.10: Azibenzil **54**.

A large excess (20 eq.) of azibenzil is however required to achieve decent yields. Since aldehydes can be converted to peracids by the action of oxygen, these compounds have been used as sacrificial oxidants in the palladium catalyzed epoxidation of many alkenes. Although yields of between 89 and 91% were obtained with aldehydes like isobutyraldehyde and benzaldehyde in the epoxidation of (*E*)-2-octene, cyclohexene and 1-decene with palladium salts ($PdCl_2$, $Pd(OAc)_2$)[63] as well Pd/C and Pd/SiO_2[64]; these reactions are complicated by the formation of the acid corresponding to the aldehyde which has to be disposed of.

While hydrogen peroxide is, from an environmental point of view, one of the best epoxidizing agents available, it is rather expensive to produce, explosive in high concentrations, and therefore has the

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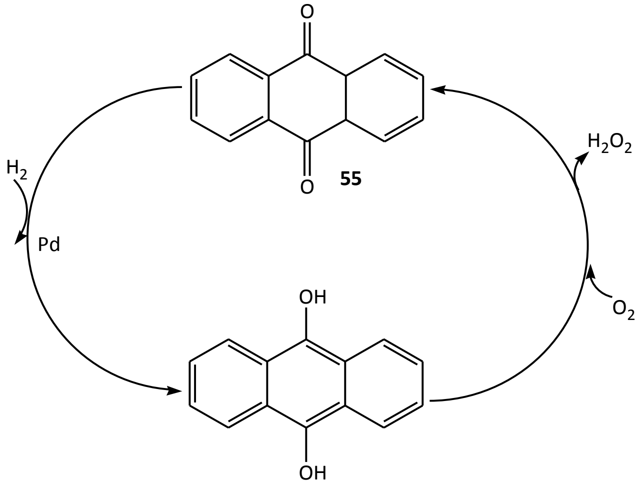
[62] H. –S. Ryang, C. S. Foote, *J. Am. Chem. Soc.*, **1980**, *102*, 2129.

[63] A. Atlamsani, E. Pedraza, C. Potvin, E. Duprey, O. Mohammedi, J. –M. Brégeault, *C. R. Acad. Sci. Paris, Série II*, **1993**, *317*, 757.

[64] H. Gao, R. J. Angelici, *Synth. Commun.*, **2000**, *30*, 1239.

added disadvantage that large quantities of water (at least 50%) has to be transported with it. Large industrial use thereof has to be with extreme caution. This aspect of hydrogen peroxide has led to numerous attempts towards the *in situ* production of it. Beckman *et al.* used a palladium catalyst to react H_2 and O_2 in the presence of liquid CO_2 to generate H_2O_2, thus avoiding the less economical route of going *via* anthraquinone **55** (Scheme 2.36).[65] The H_2O_2 formed in this way also reacts with CO_2, giving off a percarbonate ion which has been demonstrated to epoxidize hydrophilic alkenes with no catalyst present.[66] Nonetheless, epoxidation of cyclohexene was possible with H_2O_2 prepared by reaction of hydrogen with oxygen in CO_2 over **6** (Figure2.1).



Scheme 2.36: Production of H_2O_2 *via* anthraquinone **55**.

Other peroxy compounds like *α*-silylalkyl peroxybenzoate **56** (Scheme 2.36) have also been utilized in the epoxidation of a series of alkenes, including *α*,*β*-unsaturated substrates, in 4 to 88% yields.[67] Based on ^{18}O-labelling experiments and isolated products, a Pd^{IV} species **59** (Scheme 2.36) has been proposed in epoxidations that involve direct addition of the *in situ* formed Pd reagent to the substrate. The formation of the side products, 1-cyclopropylethanone **57** and *tert*-butyldimethylsilylbenzoate **58**, from the reaction of stilbene with **56**, could be explained through rearrangement of the peroxybenzoate on coordination to $Pd(OAc)_2$ (Scheme 2.37).

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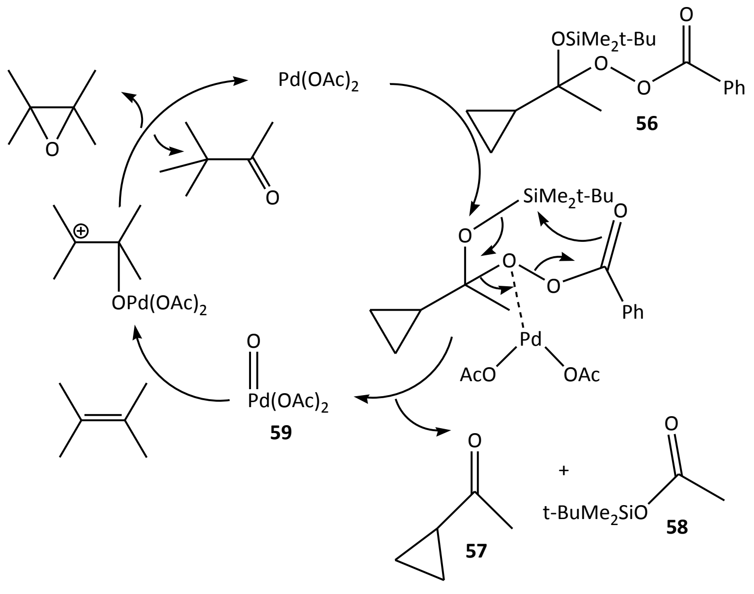
[65] D. Hâncu, J. Green, E. J. Beckman, *Ind. Eng. Chem. Res.*, **2002**, *41*, 4466.
[66] D. E. Richardson, H. R. Yao, K. M. Frank, D. A. Bennett, *J. Am Chem. Soc.*, **2000**, *122*, 1729.
[67] J. Muzart, *J. Mol. Cat. A: Chem*., **2007**, *276*, 62.



Scheme 2.37: A proposed mechanism for the epoxidation of alkenes with *α*-silylalkylperoxybenzoate **56**.

The application of heterogeneous catalysts to epoxidation reactions is perhaps best demonstrated in studies with peroxo-polyoxometallates. In this regard Che *et al*. demonstrated that a polyoxometallate, $[(C_6H_{13})N_3]\{PO_4[W(O)(O_2)]_4\}$ or THA-PW_4, together with $Pd(OAc)_2$ and O_2 could be used for the epoxidation of propylene in moderate conversion (42.7%) but good selectivity (82%).[68] Similar reactions were observed with other polyoxometallates such as $[(C_6H_{13})_4N]_2\{HPO_4[W(O)(O_2)_2]_2\}$ (abbreviated THA-PW_2).[69]

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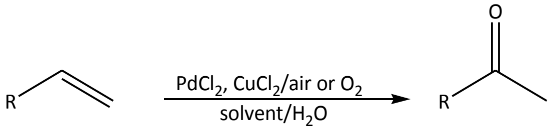
[68] Y. Liu, K. Murata, M. Inaba, N. Mimura, *Appl. Catal. B: Environmental*, **2005**, *58*, 51.

[69] Y. Liu, K. Murata, M. Inaba, *Green Chem*., **2004**, *6*, 510.

2.4 Wacker Oxidation

2.4.1 Introduction

The Wacker oxidation entails a palladium catalyzed oxidation of alkenes, in particular terminal alkenes to methyl ketones (Scheme 2.38).[4,70,71] It is a one-step route towards the introduction of a ketone or sometimes an aldehyde functionality and is preferred over the two-step process involving hydration of alkenes with subsequent dehydrogenation to the corresponding carbonyl compound.



Scheme 2.38: Wacker oxidation of terminal alkenes.

The only commercial process to date is that for the production of acetaldehyde from ethylene. The conventional method for Wacker oxidation involves the use of a Pd^{II} species under aerobic aqueous conditions with stoichiometric amounts of copper (I/II) chloride ($CuCl/CuCl_2$) as a co-catalyst and DMF as common solvent (Scheme 2.38). Since the Pd catalyst is reduced to Pd^0 during the process and Pd^{II} is required at the beginning of the catalytic cycle, re-oxidation of the Pd^0 is critical and represents one of the major challenges in the application of Wacker methodology to the synthesis of ketones. The common approach to this problem has been to include a co-catalyst of very low oxidation potential, such as copper chloride, as part of the catalytic cycle.[72] This however, introduces unwanted chlorinated by-products and renders the systems toxic and corrosive. Due to miscibility problems, the use of water also limits the scope and application of the reaction as longer chain olefins rather isomerize to internal alkenes.

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[70] a) P. H. Espeel, G. de Peuter, M. C. Tielen, P. A. Jacobs, *J. Phys. Chem*., 1994, *98*, 11588; b) J. M. Takacs, X.-T. Jiang, *Curr. Org. Chem*. **2003**, *7*, 369; c) K. M. Gligorich, M. S. Sigman, *Chem. Comm*., **2009**, 3854; d) A. B. Smith, Y. S. Cho, G. K. Friestad, *Tetrahedron Lett*., **1998**, *39*, 8765.

[71] C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc*., **2005**, *127*, 2796.

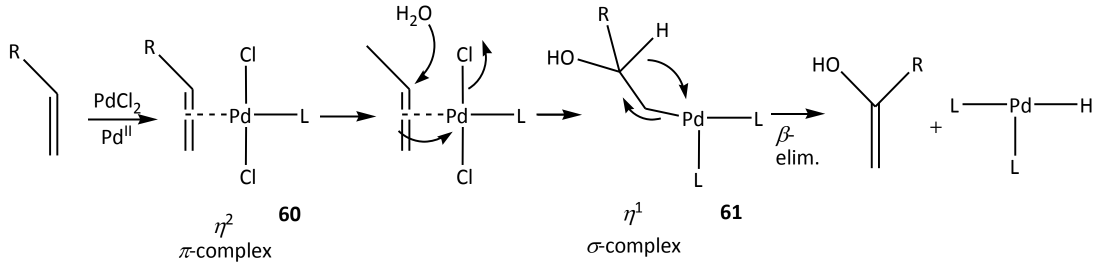
[72] D. S. Helfer, J. D. Atwood, *Organometallics*, **2004**, *23*, 2412.

The predominant problem associated with the Wacker oxidation, however, is found in low turnover numbers (TON's), which usually vary between a few hundreds and a thousand at the standard reaction conditions developed by Tsuji (10 mol% $PdCl_2$, 1 equivalent of $CuCl_2$, room temperature).

In many instances this limitation have been addressed by using stoichiometric quantities of palladium (up to 5 equivalents), which also rendered the use of the copper co-catalyst unnecessary.[4] For industrial applications, high concentrations of chlorides limit their use as they render the system too corrosive. Recent developments are centered on curbing these shortcomings through ligand modification, heterogenizing the palladium catalyst, alternative metals and the addition of additives and/or different oxidants such as oxygen, benzoquinone, and peroxides (H_2O_2 & TBHP). In order to get a better understanding of the role of the different reagents and to optimize reaction parameters, the Wacker oxidation has thus been constantly the subject of many mechanistic studies with a lot of controversy.

2.4.2 Mechanism/catalytic cycle

As depicted in Scheme 2.39, the mechanism of the Wacker oxidation could be simplified to the formation of a η^2 π-complex **60** between the Lewis acidic Pd^{II} reagent and the alkene. This step is followed by nucleophilic water attack on the otherwise inert double bond with the formation of a η^1 σ-complex **61**, which subsequently undergoes a β-hydride elimination leading to the enol form of the product ketone.



60

61

Scheme 2.39: π- **60** and σ- **61** Pd^{II} intermediates in the Wacker oxidation.

Although the initially proposed simplified mechanism could explain the formation of the products in the Wacker oxidation, several questions regarding the exact nature of the different steps in the process remained unanswered by this version of the mechanism:

1. Does the oxidation go through a π- and σ- Pd^{II} complex or only a σ- Pd^{II} complex?
2. What is the mode of the nucleophilic addition of the water? Is the water/hydroxide transferred from the palladium or does it entail a direct attack onto the alkene fragment of the transition state complex?
3. What is the effect of Cl$^-$ ion concentration on the mode of water addition?

Through a study involving the $PdCl_2$ catalyzed oxidation of ethylene under classical Tsuji aqueous conditions, Henry and co-workers convincingly postulated as early as 1964, that the Wacker oxidation does indeed proceed *via* both π- and σ- Pd^{II} complexes. Kinetic studies revealed the oxidation to be first order in ethylene, while a second order inhibition by chloride was also found. These results led to the mechanistic proposal in Scheme 2.40 wherein formation of an aquo Pd^{II} π-complex **63** after alkene coordination to the tetrachloropalladate complex $(PdCl_4)^{2-}$ **62**, was proposed. The $PdCl_4$ complex was found to be the resting state of $PdCl_2$ at the relevant experimental conditions.[73]

$$\underset{\mathbf{62}}{[PdCl_4]^{2-}} + C_2H_4 \rightleftharpoons \underset{\mathbf{63}}{[PdCl_3C_2H_4]^-} + Cl^-$$

$$\mathbf{63} + H_2O \rightleftharpoons \underset{\mathbf{64}}{[PdCl_2(H_2O)C_2H_4]} + Cl^-$$

$$\mathbf{64} + H_2O \rightleftharpoons \underset{\mathbf{65}}{PdCl_2(OH)C_2H_4]^-} + H_3O^+$$

$$\mathbf{65} \longrightarrow \underset{\mathbf{66}}{Cl\text{-}Pd\text{-}CH_2\text{-}CH_2\text{-}OH} + Cl^-$$

$$\underset{\mathbf{66}}{Cl\text{-}Pd\text{-}CH_2\text{-}CH_2\text{-}OH} \longrightarrow HCl + Pd^0 + \underset{\mathbf{67}}{CH_3CHO}$$

Scheme 2.40: Proposed reaction intermediates for ethylene oxidation to acetaldehyde in aqueous $PdCl_2$.

Using isotopic labeling and the stereochemistry of the intermediate formed (substituted 66 equivalent), Henry *et al*. proposed a *cis* intramolecular water attack to lead to the final product **67** (Scheme 2.41).[74,75]

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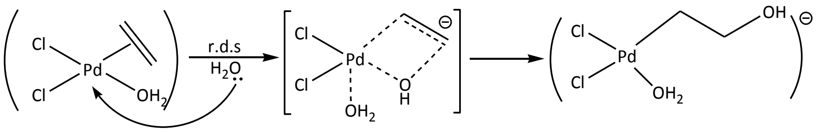
[73] J. A. Keith, P. M. Henry, *Angew. Chem. Int. Ed.*, **2009**, *48*, 9038.

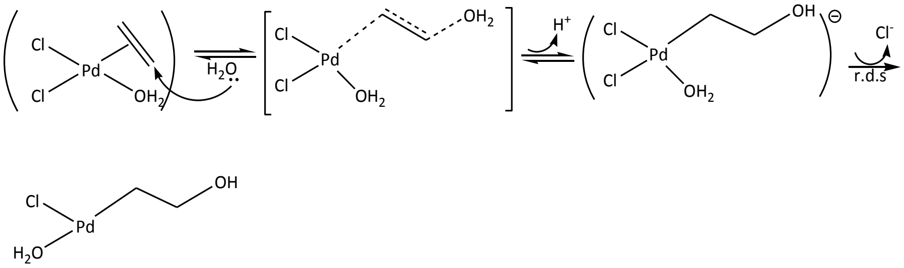
[74] P. M. Henry, *J. Am. Chem. Soc.*, **1966**, *88*, 1595; P. M. Henry, *J. Org. Chem.*, **1973**, *38*, 1681.

[75] D. J. Nelson, R. Li, C. Brammer, *J. Am. Chem. Soc.*, **2001**, *123,* 1564.



Scheme 2.41: Intramolecular *syn*-addition of water on a palladium bound alkene.

Backvall *et al*. on the other hand, proposed a *trans* intermolecular addition of water (Scheme 2.42) to a palladium bound alkene based on kinetic studies at high chloride concentration, while Stille used ethylene isotopic labeling to reach the same conclusion.[76,77]



Scheme 2.42: Intermolecular *trans*-addition of water to a palladium-bound alkene.

Recently, Goddard *et al*. summarised the now generally accepted mechanism for the Wacker oxidation reaction as involving two competing pathways; namely, the 'inner sphere' *syn*- pathway and the 'outer sphere' *anti*-.pathway[78]

In this mechanism, **62** (Scheme 2.43) loses one chloride to create a vacant site for alkene (ethylene) binding, generating a π complex **68**.

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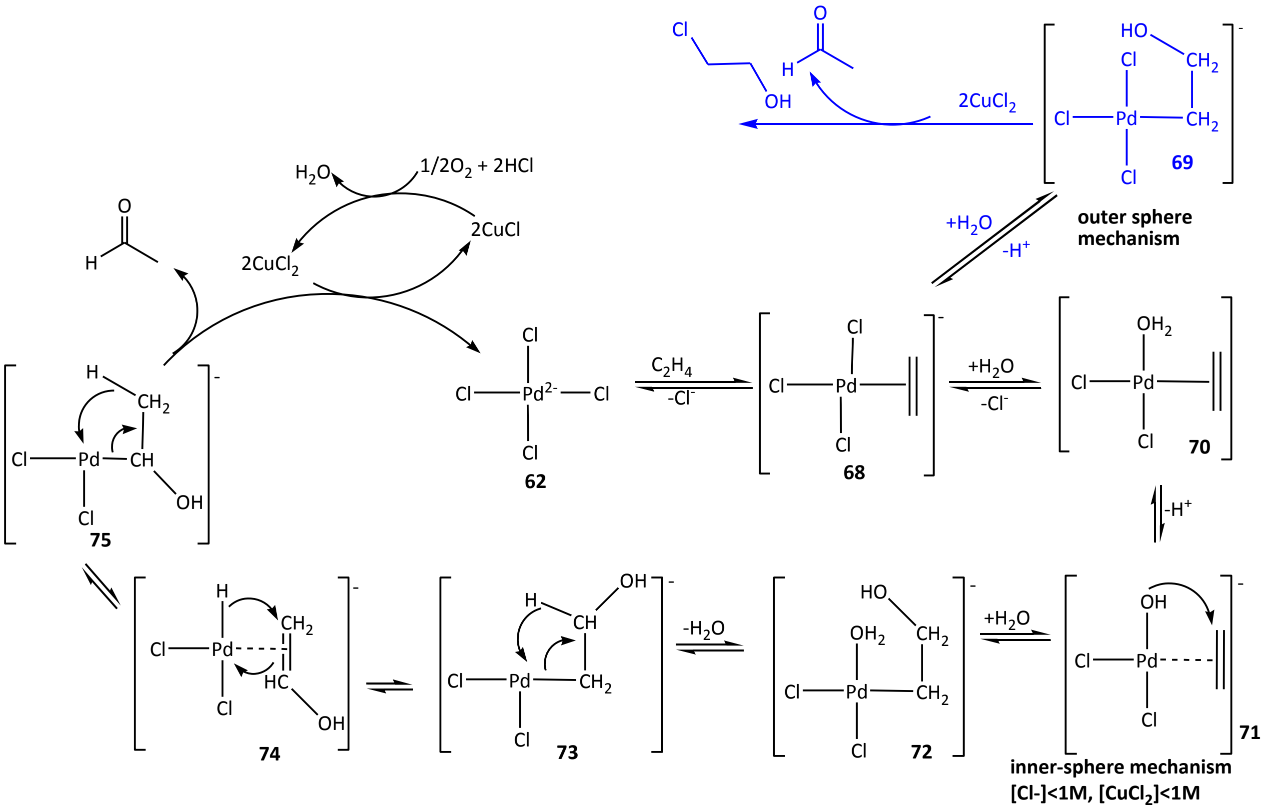
[76] J. E. Backvall, E. A. Heumann, *J. Am. Chem. Soc.*, **1986**, *108*, 7107.
[77] J. K. Stille, R. Divakaruni, *J. Organomet. Chem.*, **1979**, *169*, 239.
[78] J. A. Keith, R. J. Nielsen, J. Oxgaard, W. A. Goddard, *J. Am. Chem. Soc.*, **2007**, *129*, 12342.



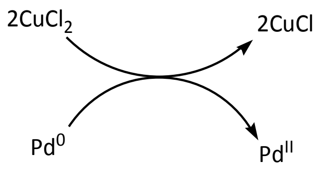
Scheme 2.43: The generally accepted Wacker 'outer' and 'inner' sphere mechanisms.

At high chloride and copper concentrations, an 'outer-sphere' or '*anti*-addition' rate-limiting pathway ('outer sphere mechanism') is proposed whereby a water molecule attacks **68** intermolecularly, generating intermediate **69** (Scheme 2.43) upon deprotonation of the bound water molecule. The aldehyde product and the by-product, 2-chloroethanol are then eliminated.

Alternatively, at low chloride (< 1M) and copper chloride (< 1M) concentrations, a second Cl$^-$ may make way for a nucleophilic attack of a water molecule, affording a neutral intermediate **70** through an 'inner-sphere' mechanism. After deprotonation of the bound water molecule, a *syn* intramolecular hydroxide transfer to the Pd bound alkene in **71** affords hydroxypalladation through a second rate-determining addition of water to Pd, generating a β-alkylhydroxypalladium intermediate **72**. Two hydride shifts (**73**-**75**), lead to the product and **62** after water-assisted reductive elimination of HCl and regeneration of Pd(II) by CuCl$_2$.

2.4.3 Co-oxidants

Since the reductive elimination step in the mechanism of the Wacker oxidation results in a Pd^0L_2 species being formed and Pd^{II} is required to continue the catalytic cycle, co-oxidants that are capable of re-oxidizing the Pd^0 to Pd^{II} are essential in order to reach a viable catalytic process (Scheme 2.44).



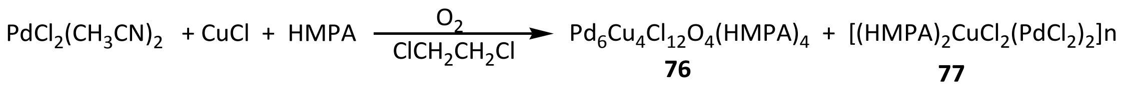
Scheme 2.44: Re-oxidation of Pd^0 to Pd^{II} by $CuCl_2$.

Common co-oxidants include copper salts such as CuCl, $CuCl_2$, and $Cu(OAc)_2$ but other inorganic salts such as heteropolyacids have also recently emerged useful in this regard.

2.4.3.1 Copper salts

The classic Tsuji Wacker conditions are based on the use of CuCl with $PdCl_2$ in aqueous aerobic conditions with DMF as a solvent. The problem with CuCl, as highlighted in the mechanism, is its contribution towards high [Cl^-] because it is often used in stoichiometric or excess amounts, thus giving rise to chlorinated by-products.

Murahashi *et al*. have shown that the involvement of copper in the catalytic cycle could be more complex than that shown in Scheme 2.42.[79] They propose that the Pd-Cu heterometallic complex $Pd_6Cu_4Cl_{12}O_4(HMPA)_4$ **76** (Scheme 2.45), isolated by reacting $PdCl_2(CH_3CN)_2$, CuCl, and O_2 in anhydrous $Cl_2CH_2CH_2Cl$ and hexamethylphosphoramide (HMPA), is the actual active species in Wacker oxidation.



$$PdCl_2(CH_3CN)_2 + CuCl + HMPA \xrightarrow[ClCH_2CH_2Cl]{O_2} \underset{\mathbf{76}}{Pd_6Cu_4Cl_{12}O_4(HMPA)_4} + \underset{\mathbf{77}}{[(HMPA)_2CuCl_2(PdCl_2)_2]n}$$

Scheme 2.45: Formation of a Pd-Cu complex using $PdCl_2(CH_3CN)_2$, CuCl and O_2 in $ClCH_2CH_2Cl$ and HMPA.

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[79] T. Hosokawa, M. Takano, S. –I. Murahashi, *J. Am. Chem. Soc*., **1996**, *118*, 3990.

It was further proposed that coordinating solvents (L) such as HMPA react with CuCl and O_2 to give a polymeric $CuCl_2(L)_n$ species and an μ-peroxocopper complex, L-Cu-O-O-Cu-L.

Four moles of the μ-peroxocopper species with 4 moles of $PdCl_2$ forms **76**, while reaction of the polymeric $CuCl_2(L)_n$ with $PdCl_2$ forms **77**. The role of **76** was proven in the oxidation of 1-decene which afforded 2-decanone in >99% yield under argon conditions in $ClCH_2CH_2Cl$. Under an oxygen atmosphere the yield of 2-decanone turned out to be 360% based on Pd. Another Pd-Cu complex, $[(PdCl_2)_2(CuCl_2(DMF)_4]_n$, was isolated by the same group, after reacting $PdCl_2(CH_3CN)_2$ with $CuCl_2$ in DMF under an O_2 atmosphere.[80] This complex also catalyzed the oxidation of 1-decene in aqueous DMF under O_2. The yield of 2-decanone was 200% (based on Pd) when 0.2ml of water was used and 720% with 5 mmol of water.

Internal olefins are almost impossible or rather difficult to oxidize under classic aqueous aerobic Wacker conditions (10 mol% $PdCl_2$/10mol% CuCl/DMF/O_2). Kaneda *et al*. recently offered a possible explanation for this phenomenon based on their experimental findings.[81] They found that *trans*-4-octene could be oxidized to 4-octanone in 91% yield over 10 hours using 5 mol% $PdCl_2$ using a more powerful coordinating solvent like dimethylacetamide (DMA) under an oxygen atmosphere without CuCl. Addition of 10 mol% CuCl, however, decreased the yield to 68% and even further to ca. 20% with the addition of more CuCl or even $Cu(OAc)_2$. These authors inferred that a Pd-Cu complex similar to that postulated by Muharashi *et al*. $\{[(PdCl_2)_2(CuCl_2(DMF)_4]_n\}$ could be the active species in reactions with CuCl, its steric bulk preventing access of the hindered internal olefin to the metal centre. In contrast, the oxidation of terminal olefins such as 1-octene to 2-octanone gradually increase with an increasing CuCl concentration.

Increased chloride concentration may lead to the formation of large quantities of unwanted corrosive side products, although increased reactivity was observed in 1-octene with an increase in copper chloride concentration. Realizing the importance of co-oxidants as well as their detrimental effects, one of the approaches towards decreasing or eliminating $[Cl^-]$ has led to the investigation of alternative, non-chloride based salts as co-oxidants.

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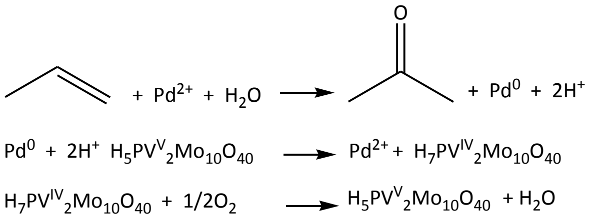
[80] T. Hosokawa, M. Takano, S. –I. Murahashi, *J. Organomet.Chem.,* **1998***, 55, 387.*

[81] T. Mitsudome, K. Mizumoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem. Int. Ed*., **2010**, *49*, 1238.

2.4.3.2 Alternative salts

Polyoxometallates or heteropolyacids (HPA x) of the type $H_{3+x}PV_xMo_{12-x}O_{40}$ (HPA-x) (x=2-6) were found to be viable alternatives to copper chloride and have been proven efficient as co-catalysts in alkene oxidation reactions.[82,83,84,85]

HPA-x is a reversible oxidant; it is able to regenerate the active Pd(II) species needed in the catalytic cycle through transfer of electrons ($V^{IV} \rightarrow V^{V}$) to the palladium (Scheme 2.46).[85]



Scheme 2.46: Reaction sequence in the oxidation of an alkene using a Keggin-type heteropolyacid $H_{3+x}PV_xMo_{12-x}O_{40}$ (HPA-x) (x=2-6) HPA-x.

Matveev *et al*. proposed a dimeric Pd species to be involved in the oxidation of propene to acetone and 1-butene to butanone with HPA-x and $PdSO_4$ (selectivity: > 99% and >98% respectively).[84] HPA was also found to be effective in stabilizing Pd^0 species, but only in the absence of oxygen or air, which represents the drawback of this method.

In molybdovanadophosphate (NPMoV) over carbon (C), utilizing O_2 and $Pd(OAc)_2$, slow addition of cyclopentene improved its selective oxidation to cyclopentanone although addition of methanesulfonic acid ($MeSO_3H$) was necessary to prevent Pd^0 precipitation.[82] Polyethylene glycol (PEG) proved to be a stabilizing solvent in oxidations with $PdCl_2$ and $H_5PV_2Mo_{10}O_{40}$ under O_2.[85] Although high conversion of propene was obtained with this system, isomerization was very prominent in higher alkenes such as 1-octene and 1-decene, leading to not more than 20% yield of the desired product. Stability of the catalyst was however evident as the catalyst solution could be recycled 3 times with loss of <5% activity.

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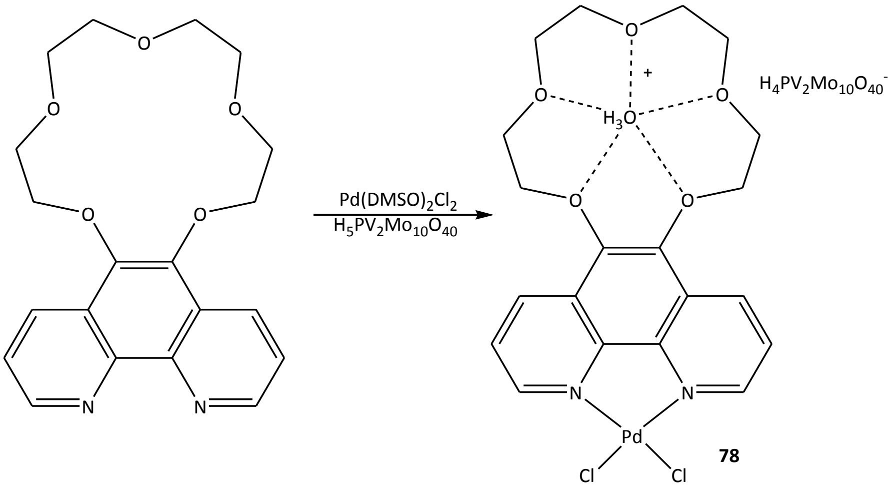
[82] A. Kishi, T. Higashino, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett*., **2000**, *41*, 99.
[83] T. Yokota, A. Sakakura, M. Tani, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett*., **2002**, *43*, 8887.
[84] E. G. Zhizhina, M. V. Simonova, V. F. Odyakov, K. I. Matveev, *Appl. Catal. A.: Gen*., **2007**, *319*, 91.
[85] A. Haimov, R. Neumann, *Chem. Comm*., **2002**, 876.

Neuman *et al*. utilized the known dipole induced interaction between an ether and the hydronium cation on a polyoxometallate (POM) ($H_4PV_2Mo_{10}O_{40}^-$) to prepare a 1,10-phenanthroline (Phen) crown ether Pd^{II} polyoxometallate (POM) ($H_4PV_2Mo_{10}O_{40}^-$) catalyst **78** (Scheme 2.47).[86]



Scheme 2.47: Preparation of a polyoxometallate ($H_4PV_2Mo_{10}O_{40}^-$) Phen-$PdCl_2$ catalyst.

This catalyst allowed oxygen to be replaced by the environmentally benign nitrous oxide as terminal oxidant in the Wacker oxidation and gave only the ketone products in > 99% yield during the oxidation of C_6-C_{10} olefins. Although the exact mechanism of the reaction with **78** is not clear, the authors proposed that the oxidation of the alkene proceeds *via* a typical Wacker type mechanism where oxidative addition of water to the alkene leads to the ketone and a Pd^0 species. Re-oxidation of the palladium is effected by the N_2O (and not O_2 formed from it) and catalyzed by the polyoxometallate ($H_5PV_2Mo_{10}O_{40}$).

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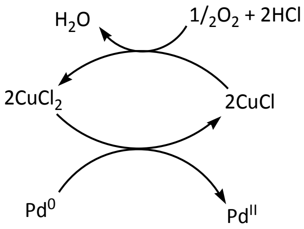
[86] J. Ettedgui, R. Neumann, *J. Am. Chem. Soc.*, **2009**, *131*, 4.

2.4.4 Oxidants

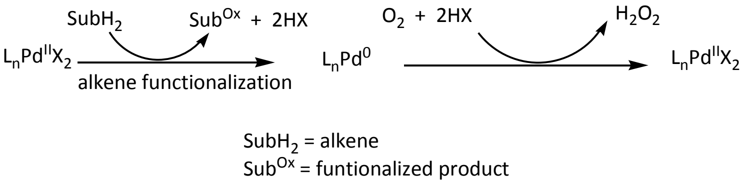
2.4.4.1 Oxygen

The role of stoichiometric oxidants such as oxygen in the traditional Tsuji aqueous Wacker oxidation reaction ($PdCl_2/CuCl_2$-DMF/H_2O) is to re-oxidize the CuCl, obtained from converting Pd^0 to Pd^{II} (Scheme 2.48).



Scheme 2.48: Re-oxidation of CuCl by O_2.

More recently, oxygen has been explored as the sole oxidant, that is, without the use of co-catalysts like CuCl.[87,88,89] Under these conditions the role of oxygen can be described by two distinct half reactions. In the first half reaction the alkene is oxidized by the Pd^{II} to generate L_nPd^0 and the oxidized substrate, while the second half reaction involves O_2–coupled regeneration of the active Pd^{II} species together with water formation from decomposition of hydrogen peroxide (Scheme 2.49).[89]



Scheme 2.49: Alkene functionalization with O_2 as sole oxidant.

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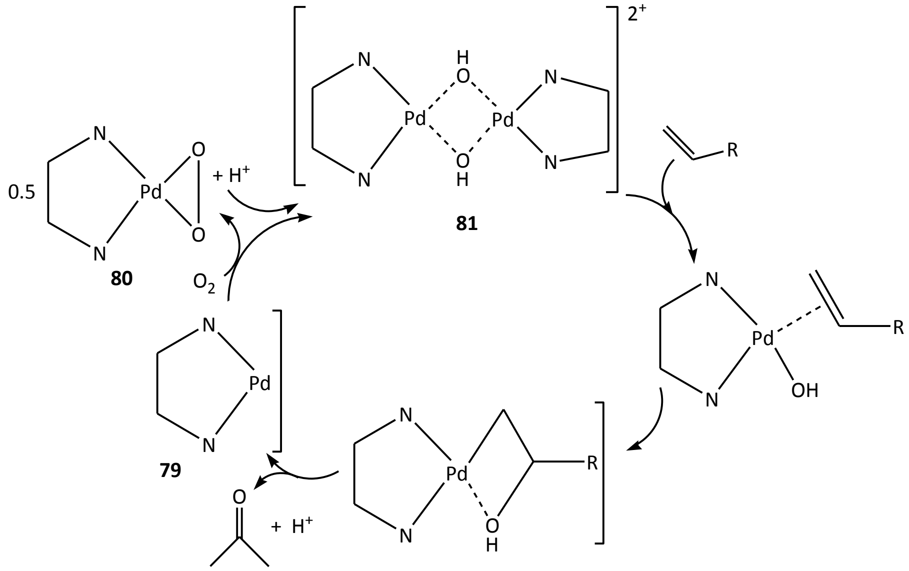
[87] T. Mitsudome, T. Umetani, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem. Int. Ed.*, **2006**, *45*, 481.

[88] C. N. Cornell, M. S. Sigman, *Inorg. Chem.*, **2007**, *46*, 1903.

[89] K. M. Gligorich, M. S. Sigman, *Chem. Comm.*, **2009**, 3854; K. M. Gligorich, M. S. Sigman, *Angew. Chem. Int. Ed.*, **2006**, *45*, 6612.

In this regard, Kaneda *et al*. reported successful Wacker oxidations of terminal alkenes such as 1-hexene, 1-octene and 1-dodecene to the 2-ketones in 78, 83, and 85% yield respectively, using 0.5-1 mol% $PdCl_2$ in DMA-H_2O (6:1) at 80°C under 6atm O_2 pressure without any co-catalyst.[87] A ligand based palladium salt, Pd[(-)-sparteine]Cl_2, afforded reactions under mild oxygen pressure (balloon O_2 pressure) with 1 mol% catalyst at 70°C to afford, for example, 85% yield of dodecan-2-one after 18 hours of reaction time.[88]

In both these studies a solvent effect was observed which will be discussed at a later stage. Sheldon *et al*. proposed a different role for O_2 in the re-oxidation of their water-soluble bathophenanthroline disulfonate (PhenS*)Pd$(OAc)_2$ catalyst in aqueous solvents.[90] The mononuclear Pd^0 species **79** (Scheme 2.50) is re-oxidized by O_2 to the active dimeric complex **81** via a peroxopalladium species **80**. Oxidation of 1-hexene with 1 mol % of (PhenS*)Pd$(OAc)_2$ at rather harsh conditions (100°C and oxygen pressures of 30 bar) with an added equivalent of sodium acetate and water, yielded only 45% of the product after 10 hours.



Scheme 2.50: A proposed formation of a binuclear water-soluble cationic Pd complex in aqueous oxidations.

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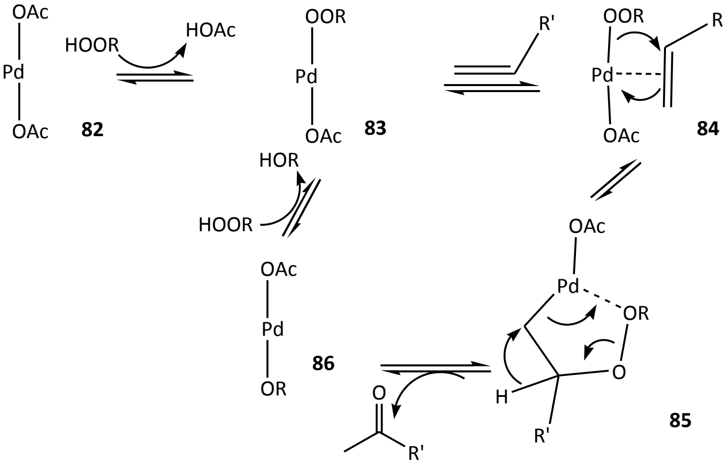
[90] G. -J. ten Brink, I. W. C. E. Arends, G. Papadogianakis, R. A. Sheldon, *Appl. Catal. A: Gen*., **2000**, *194*, 435.

2.4.4.2 Peroxides

TBHP, in aqueous and anhydrous medium, and H_2O_2 are common peroxides utilized as stoichiometric oxidants in Wacker type oxidations.[91,92,93]

In an anhydrous process with TBHP as oxidant and palladium carboxylate catalysts, Mimoun *et al*. found that the reactivity and selectivity towards methyl ketone formation increased with decreasing electron density on the palladium, *i.e.* with increasing acid strength of the carboxylic acid of which the anion is attached to the palladium.[93] Using isotopic labeling ($^{18}OH_2$) they proved that the oxygen in the peroxide ends up in the carbonyl group of the ketone. A ligand exchange process between the acetate in $Pd(OAc)_2$ **82** and the peroxide was proposed as the initial step in the oxidation reaction (Scheme 2.51).



Scheme 2.51: A proposed peroxide-mediated Wacker oxidation mechanism.

The palladium-peroxo species **83** was therefore activated for olefin coordination and *via* a π-allyl complex **84** and formed a 5-membered peroxopalladacyclic intermediate **85** (Scheme 2.51). Cleavage of the O-O bond is then facilitated by an α-hydride shift. The active peroxypalladium intermediate **83** could thereafter be regenerated in the presence of peroxide without going through Pd^0. A large excess of peroxide was necessary to regenerate **83** from **86** (Scheme 2.51) and to avoid hydroxypalladation of the olefin which would ultimately lead to Pd^0 formation, aggregation, and no ketone product.

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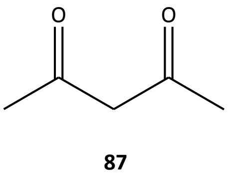
[91] J. M. Escola, J. A. Botas, A. D. P. Serrano, C. Vargas, M. Bravo, *Appl. Cat. A.: Gen.*, **2008**, *335*, 137; J. M. Escola, J. A. Botas, C. Vargas, M. Bravo, *J. Catal.*, **2010**, *270*, 34.

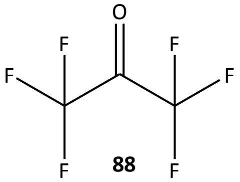
[92] B. W. Michel, A. M. Camelio, C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc.*, **2009**, *131*, 6076.

[93] M. Roussel, H. Mimoun, *J. Org. Chem.*, **1980**, *45*, 5387.

Water and the nature of the palladium salt seemed to have no effect on the rate of the reaction although in alcoholic solvents, coordinating ligands such as acetylacetone **87** (Figure 2.11) and hexafluoroacetylacetone **88** (Figure 2.11), inactivated the catalyst.



87



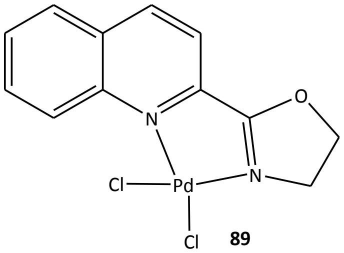
88

Figure 2.11: Acetylacetone **87** and hexafluoroacetone **88.**

In the presence of water, the reaction probably follows a more classical Wacker mechanism with the TBHP only re-oxidizing the Pd^0.[92]

A similar mechanism to Scheme 2.50 was proposed for the oxidation of dodecene to dodecan-2-one, where TBHP was found to be more efficient than H_2O_2, leading to fewer isomerized products in acetonitrile than in isopropanol.[91]

A peroxide mediated oxidation of decene with a Quinox based palladium salt, $Pd(Quinox)Cl_2$ **89** (Figure 2.12), and a silver salt $AgSbF_6$ in CH_2Cl_2, afforded 2-decanone in 86% yield over 20 minutes at room temperature.[92]

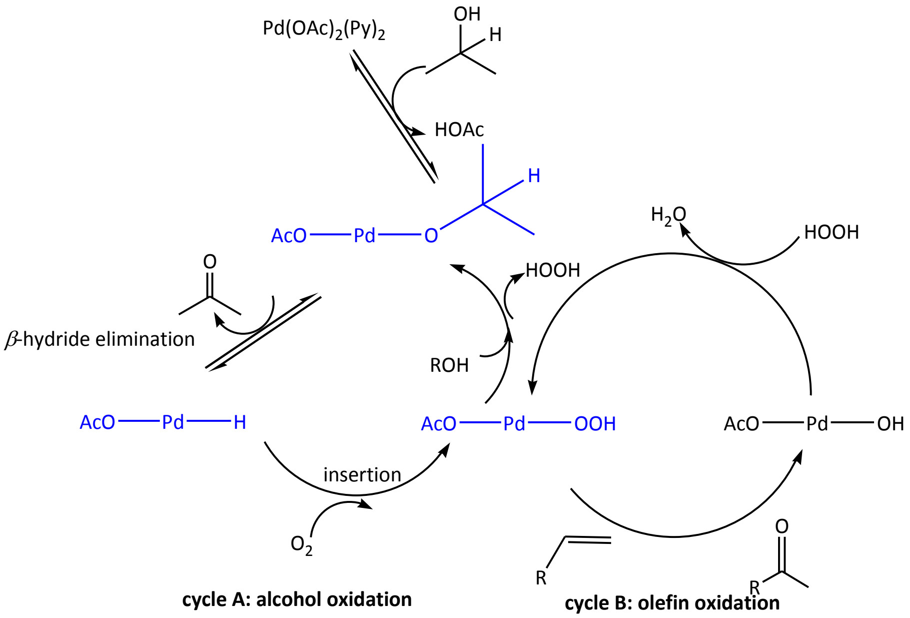


89

Figure 2.12: $Pd(Quinox)Cl_2$ **89**.

Metal peroxo species can also be formed *in situ* in the presence of palladium hydride and oxygen. Evidence of this was seen during alcohol oxidation and used by Uemura and coworkers in their proposal of a mechanistic pathway for oxidation of olefins in alcoholic solvents with no added peroxides (Scheme 2.52).[94]

During this reaction a palladium-hydride species is formed after *β*-hydride elimination from the Pd-alcohol complex. Subsequent oxygen insertion into the palladium-hydride forms a peroxo-palladium species like **85** (in Scheme 2.51) which will oxidize the incoming olefin.



Scheme 2.52: Alcohol oxidation (cycle A) and peroxide-mediated (cycle B) olefin oxidation.

2.4.6 Other Metals in Wacker oxidations

First-row transition metals are notorious for auto-oxidation free radical pathways which are uncontrollable and result in oxidatively cleaved products and polymeric materials.[95] In contrast, second and third row transition metals often afford selective oxidation of olefins. Apart from palladium, which has been investigated extensively in Wacker oxidations, Rh, Ir, Pt, and the first row element, Co, have been studied as catalysts in these reactions.[4]

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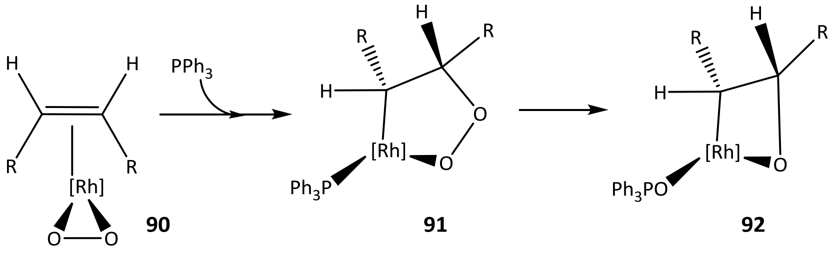
[94] T. Nishimura, N. Kakiuchi, T. Onoue, K. Ohe, S. Uemura, *J. Chem. Soc.*, *Perkin Trans. 1*, **2000**, 1915.

[95] J. E. Lyons, *Adv. Chem. Ser.*, **1974**, *132*, 64.

Rhodium catalysts that were found to be active in the oxidation of alkenes are $RhCl(PPh_3)_3$ and $RhCl_3$, but interestingly, although a Wacker-type mechanism has been proposed, the usual Wacker co-catalysts generally showed an inhibiting effect on the aerobic oxidation of alkenes.[96] Addition of CuCl to $RhCl_3$, for example, inhibits catalytic activity, while addition of salts like $Cu(NO_3)$ or $CuOCl_4$ led to quantitative yields in the oxidation of 1-hexene to 2-hexanone.

Interestingly, the presence of water in the reaction mixture reduces the activity of the $RuCl_3$-$Cu(ClO_4)_2(HMPA)_4$ catalyst tested, while it has also been found that coordinating solvents have a deactivating effect on the Rh catalysts. For reactions involving Wilkinson's catalyst, $[RhCl(PPh_3)_3]$, it is proposed that the Rh^I binds to both the alkene and oxygen resulting in one oxygen atom ending up in the ketone product and the other forming an oxidized Rh^{III}-oxo species. In $RhCl(PPh_3)_3$ systems over O_2, a peroxometallocycle intermediate **90** has been proposed (Scheme 2.53).[97,98]



Scheme 2.53: A proposed mechanism of a phosphine based Rh catalyst in the Wacker oxidation of an olefin.

Coordination of an additional triphenylphosphine (PPh_3) results in a 5-membered peroxomatallocycle **91** wherein oxygen transfer to the PPh_3, decomposes **91** to a 4-membered oxo-intermediate **92** and with a coordinated PPh_3O. *β*-Hydride elimination ultimately facilitates the ketone product and a Rh species.

Other effective Rh catalysts include alumina bound RhO_2 (with no ligand support), which catalyzes the epoxidation of **48** (Scheme 2.32) and styrene to **49** (Scheme 2.32) and acetophenone respectively as shown by the mass spectral data (no yields reported).[99,100]

Most ruthenium (Ru) systems for Wacker oxidation have been explored using phase-transfer catalysts (PTCs) such as cetyltrimethylammoniumbromide and tributylammoniumhydrogensulfate.[101]

---

[96] H. Mimoun, M. M. P. Machirant, I. S. de Roch, *J. Am. Chem. Soc.*, **1978**, *100*, 5437.

[97] G. Read, *J. Mol. Cat.*, **1988**, *44*, 15.

[98] M. Krom, R. G. E. Coumans, J. M. M. Smits, A. W. Gal, *Angew. Chem. Int. Ed. Engl.*, **2001**, *40*, 2106.

[99] J. W. McMillan, H. E. Fischer, J. Schwartz, *J. Am. Chem. Soc.*, **1991**, *113*, 4014.

[100] X. Xu, C. M. Friend, *J. Am. Chem. Soc.*, **1991**, *113*, 8572; X. Xu, C. M. Friend, *J. Am. Chem. Soc.*, **1990**, *112*, 4571.

The nature of the PTC and Ru source both played a role as poor activity was observed in the oxidation of 1-decene with cetyltrimethylammoniumbromide using $RuCl_3$ (13% yield 2-decanone), while $RuCl_2(PPh_3)$ afforded 2-octanone in 64% yield.[101] The combination of tributylammoniumhydrogensulfate and $RuCl_2(PPh_3)_3$ however resulted in a decrease in yield of 2-decanone (28%). In contrast to the Rh systems discussed above, an aqueous HCl-$RuCl_3$ system was found to be effective in the oxidation of 1-hexene giving 2-hexanone in 54% yield.[102]

The cobalt (II) Schiff-base complex **93** (Figure 2.13) has also been explored in the oxidation of a range of olefins. Selectivity towards methyl ketones was, however, found to be low and 2-alcohols were obtained as major products.[103]

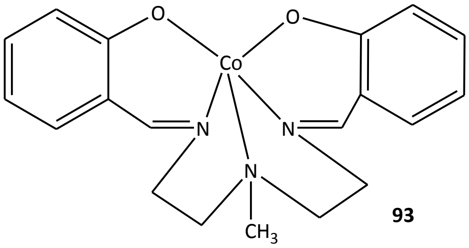
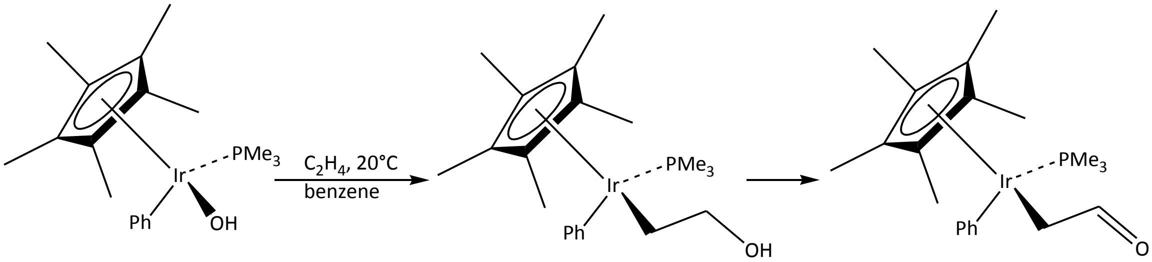

93

Figure 2.13: [Bis(salicylidene-γ-iminopropyl)-methylamine]cobalt(II) (CoSMDPT) **93**.

During their oxidation studies with iridium complexes, Bergman *et al*. found that the Ir complex **94** (Scheme 2.54) is able to bind ethylene and produce [Ir]CH_2CH_2OH **95** which could subsequently be transformed into an aldehyde bound Ir species **96**.[104]



94 **95** **96**

Scheme 2.54: Iridium based oxidation of ethylene.

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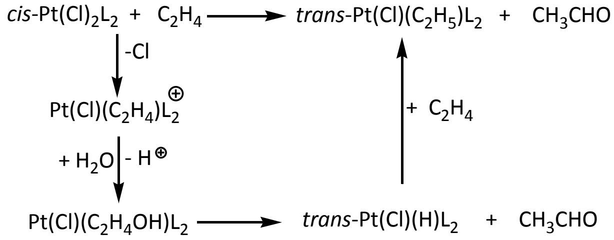
[101] K. Januszkiewicz, H. Alper, *Tetrahedron Lett.*, **1983**, *24*, 5163.
[102] M. M. Taquikhan, A. P. Rao, *J. Mol. Cat.*, **1999**, *44*, 95.
[103] A. Zombeck, D. E. Hamilton, R. S. Drago, *J. Am. Chem. Soc.*, **1982**, *104*, 6782; D. E. Hamilton, R. S. Drago, A. Zombeck, *J. Am. Chem. Soc.*, **1987**, *109*, 374.
[104] K. A. Woerpel, R. G. Bergman, *J. Am. Chem. Soc.*, **1993**, *115*, 7888; J. C. M. Ritter, R. G. Bergman, *J. Am. Chem. Soc.*, **1997**, *119*, 2580.

A water soluble platinum-phosphine complex $PtCl_2(TPPTS)_2$ (TPPTS = P(*m*-$C_6H_4SO_3Na)_3$) was reported as active in the oxidation of ethylene, propene and 1-hexene.[105] At 60°C, 5 TONs were obtained over 18 hours, while at 75°C and 95°C, the TON increased to 15 and 90 respectively.

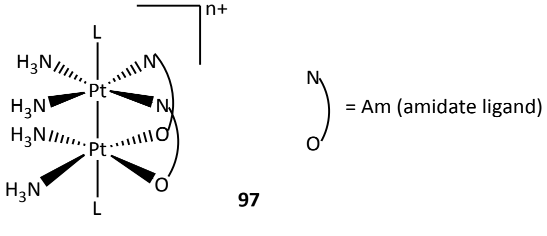
Based on ^{31}P NMR studies, a *trans*-$Pt(Cl)(C_2H_5)(TPPS)_2$ species was identified as intermediate in the reaction which probably follows a reaction mechanism as depicted in Scheme 2.55 for the production of acetaldehyde. Application of this catalyst system to the reaction of propylene and 1-hexene in aqueous solution at room temperature led to the formation of acetone and 2-hexanone.



Scheme 2.55: A proposed pathway in the oxidation of ethylene, propene and 1-hexene with $PtCl_2(TPPTS)_2$ (TPPTS = P(*m*-$C_6H_4SO_3Na)_3$).

Matsumoto *et al*. used an amidate-bridged Pt^{III} dinuclear complex **97** (Figure 2.12) on a range of olefins including 1-hexene, 1-octene, and 1-decene, to produce ketones.[106] TONs for these substrates were between 2 and 23. More challenging substrates such as *α*- and *β*-methylstyrene gave no reaction, whereas in the case of cycloalkenes epoxides co-formed as main products alongside ketones.

Due to its solubility in water, **97** (Figure 2.14) would be attractive from an environmental point of view but this catalyst operates in an acidic-biphasic $ClCH_2CH_2Cl$-H_2O solvent system, which reduces its applicability from an environmental point of view.



97

Figure 2.14: Amidate-bridged Pt^{III} dinuclear complex **97**.

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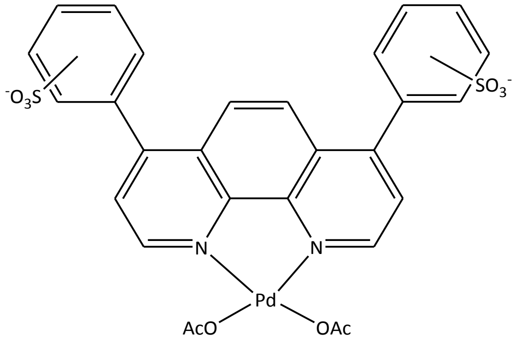
[105] D. S. Helfer, J. D. Atwood, *Organometallics*, **2004**, *23*, 2412.

[106] K. Matsumoto, Y. Nagai, J. Matsunami, K. Mizuno, T. Abe, R. Somazawa, J. Kinoshita, H. Shimura, *J. Am. Chem. Soc.*, **1998**, *120*, 2900.

2.4.7 Solvents

2.4.7.1 Water

The classical Wacker oxidation takes place in an aqueous environment where water acts as nucleophile. Although the aqueous solvent can be viewed as positive with respect to environmental issues, the presence of $PdCl_2$ and $CuCl_2$, which lead to a lot of toxic and corrosive by-products, make the process less attractive. In an attempt to circumvent the necessity of the $CuCl_2$ co-oxidant and aggregation of Pd^0, a water soluble bathophenanthroline sulfonate $Pd(OAc)_2$ **98** (Figure 2.15) was used in water as the only solvent to catalyze the oxidation of 1-hexene to 2-hexanone.[107]



98

Figure 2.15: A water soluble bathophenanthroline sulfonate $Pd(OAc)_2$ **98**.

Maximum conversion (50%) to 2-hexanone was obtained after 10 hours at which point the rate started decreasing. Catalyst degradation was not observed in that regard but an increase in the amount of 1-hexene saw a constant rate for a longer time.

Since many longer chain alkene substrates show very limited solubility in water, general organic solvents have been probed in Wacker oxidation and although not ideal, have shown to play a significant role in addressing the challenges of isomerization during utilization of the classical Tsuji conditions.

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[107] G. -J. ten Brink, I. W. C. E. Arends, G. Papadogianakis, R. A. Sheldon, *Applied Cat. A: General*, **2000**, *194*, 435.

2.4.7.2 Organic Solvents

The limited solubility of longer chain alkenes, such as 2-dodecene, in aqueous organic solvents, inevitably results in reduced yield in product, possibly as a result of competing isomerization of 2-dodecene due to extended reaction times.[108] In an attempt to circumvent the problem of miscibility between water and higher alkenes, water miscible solvents such as THF, DMF, DMA and HMPA have often been investigated as solvents in the Wacker oxidation. These solvents, however, are σ-donor solvents and as such may compete with the substrate olefin for coordination to the palladium catalyst. Hosokawa *et al*. obtained crystal structures of solvated Pd^{II} complexes to prove this. Still, their catalyst system was able to catalyze the oxidation of 1-decene.[109]

Fahey *et al*. on the other hand, observed $PdCl_2$ poisoning through formation of a $PdCl_2(NHMe_2)_2$ complex which probably originated from hydrolysis of the DMF solvent used in the reaction.[110] *N*-methylpyrrolidinone (NMP) and 3-methylsulfolane were found to be better solvents in this instance, with the latter resulting in 91% yield of 3,3,dimethylbutan-2-one from 3,3-dimethylbut-1-ene in 1.4 hours under aqueous conditions (organic solvent : water 50 : 7 v/v). DMA (*N*,*N*-dimethylacetamide) has recently been found to be superior to NMP in the oxidation of longer chain alkenes such as 1-decene, affording 2-decanone in 84% yield in 6 hours under aqueous conditions (organic solvent : water 50 : 3 v/v) with 0.005 mmol $PdCl_2$ without copper as co-oxidant.[111]

Since the oxidation potential of Pd^0 in DMA is more negative than that of NMP and DMF (DMA: -0.26V, NMP: -0.20V, and DMF: -0.12V), these authors concluded that the re-oxidation of Pd^0 by oxygen in DMA is faster than in the other solvents, so the need for a co-catalyst is completely eliminated by the utilization of this solvent. More recently, the efficiency of DMA as solvent was further demonstrated on internal olefins when *trans*-4-octene could be oxidized to 4-octanone in 91% yield over 10 hours under aqueous conditions with 0.05 mmol $PdCl_2$ at 80°C without co-catalyst at 3 atm O_2.[112] The oxidation of this substrate, although attainable in other solvents such as NMP and DMF as well but were low-yielding at 76% and 12% respectively, under the same conditions.

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[108] W. H. Clement, C. M. Selwitz, *J. Org. Chem*., **1964**, *29*, 241.

[109] T. Hosokawa, T. Nomura, S. –I. Murahashi, *J. Organomet. Chem*., **1998**, *551*, 387.

[110] D. R. Fahey, E. A. Zuech, *J. Org. Chem*., **1974**, *39*, 3276.

[111] T. Mitsudome, T. Umetani, N. Nosaka, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem. Int. Ed*., **2006**, *45*, 481.

[112] T. Mitsudome, K. Mizumoto, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Angew. Chem. Int. Ed*, **2010**, *49*, 1238.

Alcohols such as methanol, ethanol, *tert*-butanol and isopropanol have also been investigated as solvents in Wacker oxidation reactions and at times have had an enhancing effect on reactions.[113]

Terminal olefins such as 1-hexene and 1-octene can be oxidized in 1-propanol to the corresponding methylketones in yields as high as 97% at temperatures of 30°C with 0.02M $PdCl_2$ and 0.1M $CuCl_2.2H_2O$ with little or no water present.[114] Conversions of up to 30% were obtained in the oxidation of cyclohexene to cyclohexanone in ethanol at 90°C.

DMA seems to be the solvent of choice[8,9,10,111,112] for Wacker oxidations with the added advantage of facile separation of products from the catalyst mixture through hexane extraction. A more environmentally benign solvent is however needed.

2.4.7.3 'Green' Solvents

Water is a non-toxic, naturally abundant and inexpensive solvent that makes it attractive as solvent for reactions from an environmental point of view.[115] Given the limited solubility of organic substrates in water, biphasic liquid-liquid systems could be an alternative as was shown for the Pt-amidate catalyst **97** (Figure 2.14) in $ClCH_2CH_2Cl$-H_2O. The chlorinated solvent in this case makes this system undesirable. Supercritical carbon dioxide ($scCO_2$), ionic liquids (ILs), fluorous biphasic systems or dialkyl carbonates, where the substrate would reside in the organic phase and the catalyst in the aqueous phase, would offer a better alternative to these biphasic systems.[116]

2.4.7.3.1 Supercritical carbon dioxide ($scCO_2$)

Supercritical fluids (scFs) as alternative to organic solvents offer an environmentally benign solution to most toxic chlorinated organic solvents and as such the interest in the use of catalyst systems compatible with these liquids has grown considerably.[117] Supercritical fluids have densities which can be manipulated over a wide range and change with small changes in pressure; making them accessible to

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[113] T. T. Wenzel, *J. Chem. Soc., Chem. Comm.*, **1993**, 862.

[114] W. G. Llyod, B. J. Luberoff, *J. Org. Chem.*, **1969**, *34*, 3949.

[115] R. A. Sheldon, *Green Chem.*, **2007**, *9*, 1273.

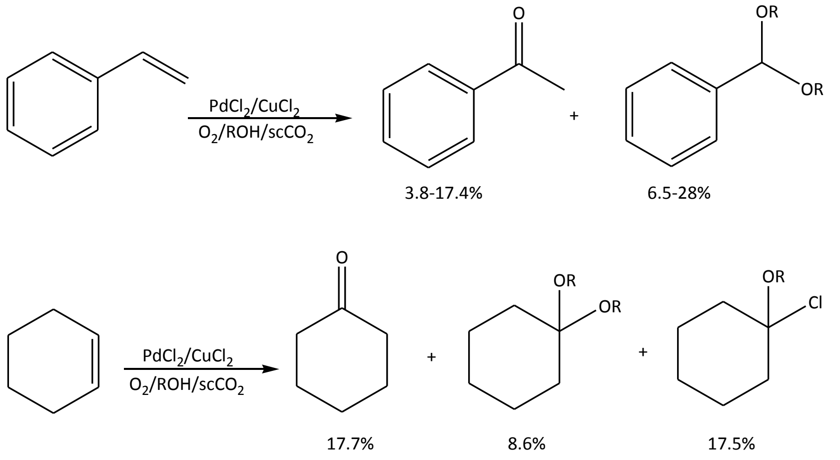
[116] R. A. Sheldon, *Green Chem.*, **2004**, *7*, 267.

[117] S. Campestrini, U. Tonellato, *Curr. Org. Chem.*, **2005**, *9*, 31.

tuning and enhanced solubilization of many compounds. $scCO_2$ is often a scF of choice as it encompasses many other desirable properties of an scF with only minor drawbacks such as limited solubilities of substrates, which are often circumvented through the utilization of co-solvents. Since the solubility of O_2 in $scCO_2$ is relatively high, this compound represents the solvent of choice for oxidation reactions involving oxygen. Furthermore, CO_2 has the added advantage that it is stable towards further oxidation.

Oxidation of 1-octene with $PdCl_2$ and $CuCl_2$ in $scCO_2$ for 48 hours afforded moderate selectivity towards 2-octanone (62%), which was accompanied by a mixture of 3- and 4-octanone (11%).[118] Similar conditions in methanol gave 2-octanone in 60% yield together with 13% of the 3- and 4- ketone isomers and octanal 1,1-dimethylacetal (1.9%) after 24 hours. A combination of the two solvents, however, resulted in increased selectivity towards 2-octanone to 85.5% and even 90% at increased $scCO_2$ pressures.

Although isomerization could be limited to less than 1% in this system, formation of the octanal by-product (5%) was unaffected. For challenging substrates like styrene and cyclohexene, the same system however resulted in the desired ketones being accompanied by the acetals (28.0% for styrene, 8.6% for cyclohexene) as well as a chlorinated ether by-product (17.5%) for the latter substrate (Scheme 2.56).



Scheme 2.56: $ScCO_2$/methanol solvent system for styrene and cyclohexene.

An environmentally benign solvent, polyethylene glycol (PEG), was also investigated as a co-solvent in the oxidation of 1-octene and styrene.[119] Selectivity towards 2-octanone in the PEG/$scCO_2$ solvent system was much higher (95%) compared to the MeOH/$scCO_2$ (62%) (*vide supra*). Oxidation of styrene,

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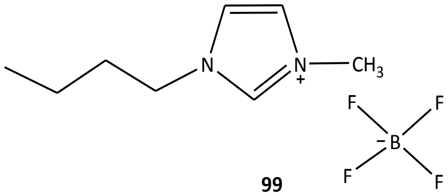
[118] H. Jiang, L. Jia, J. Li, *Green Chem.*, **2000**, *2*, 161.
[119] J. –Q. Wang, F. Cai, L. –N. He, *Green Chem.*, **2005**, *9*, 882.

which proved to be difficult in MeOH/scCO_2 was successful with PEG/scCO_2 (91% selectivity towards the ketone was obtained), while the palladium catalyst could be recycled up to 5 times without significant loss in activity (80% yield on 5th cycle). Even in pure PEG, good selectivity towards the desired ketone was observed (87% *vs* 60% in MeOH). It seems that the PEG's ability to interact with metal salts, its amenable change in viscosity and consequently diffusion rates, together with the increased versatility of the scCO_2, makes the PEG/scCO_2 system superior to other liquid-liquid biphasic solvent systems.

2.4.7.3.2 Ionic liquids

Ionic liquids (ILs) are salts that are liquid at room temperature and made up of *N*,*N'*-dialkylimidazolium, alkylammonium, alkylphosphonium or *N*-alkylimidazolium cations with poorly coordinating ions such as BF_4^- or PF_6^-.[120] What makes these compounds very attractive as environmetally friendly solvents is the fact that they are non-volatile and because of immiscibility with organic solvents, have the potential of being used in biphasic systems affording better separation of products and the catalyst mixture.

In the oxidation of styrene with $PdCl_2$ in [bmim][BF_4] **99** (Figure 2.16) and H_2O_2 at 60°C, acetophenone was obtained in 79% yield within 3 hours compared to 56% with 4 equivalents of H_2O_2 in similar studies without ILs.



99

Figure 2.16: 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) **99**.

Higher yields of acetophenone (up to 90%) was realized with a water:**99** (2:1) solvent system, although at slightly longer reaction times (24 hours) and with $CuCl_2$ as co-catalyst.[121]

Longer chain alkenes such as 1-octene, undecene, and dodecene were oxidized to the corresponding methyl ketones in between 60 and 70% yield, but longer reaction times were required (40-50 hours) and the ketones were accompanied by 7.5-13.6% of aldehyde products. Recyclability of the catalyst in **99**

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[120] V. V. Namboodiri, R. S. Varma, E. Sahle-Demessie, U. R. Pillai, *Green Chem*., **2002**, *4*, 170.
[121] I. A. Ansari, S. Joyasawal, M. K. Gupta, J. S. Yadav, R. Gree, *Tetrahedron lett*., **2005**, *46*, 7507.

was demonstrated in oxidation reactions of 4-methylstyrene, dropping only from 96% in the 1st cycle to 85% in the 5th cycle. The effect of combining ILs with $scCO_2$ has been investigated in a study using 1-hexene in a $PdCl_2/CuCl_2$ system with methanol as co-solvent.[122]

Selectivity towards 2-hexanone (91.9%) was found to be higher in a [bmim][PF_6]-$scCO_2$ mixture than in pure $scCO_2$ (70.5%) or pure [bmim][PF_6] (64.2%). Selectivity (63.2%) was hardly affected by the absence of the co-solvent in the [bmim][PF_6] system but greatly enhanced by increased CO_2 pressure. Reduced isomerization was attributed to the IL. 1-Hexene is thought to gradually enter the IL liquid/catalyst phase and as a result does not saturate the catalyst phase. Additionally, $scCO_2$ increases mass transfer as it mixes with the IL phase, enhancing reaction rate, thereby limiting isomerization. ILs and $scCO_2$ seem to have complimentary features wherein the $scCO_2$ keeps the amount of substrate limited in the IL phase but at increased pressures, miscibility of the two phases is greatly enhanced and improves selectivity.

2.4.7.3.3 Fluorous biphasic

A fluorous biphasic system consists of a perfluorinated solvent layer (bromofluoroctane) containing the catalyst and the solvent in another layer, for example, benzene, containing the reagents.[123] These layers become monophasic at optimum temperatures (60°C), allowing the reaction to take place efficiently. Upon cooling to room temperature, the system reverts back to two phases, allowing for facile separation. Oxidation of polyfunctional olefins was successful at 5 mol% palladium catalyst using TBHP (1.5-3.5 eq.) and bromofluorooctane and benzene as solvent.[123] Acetophenone was obtained from styrene in 97% yield within 5 hours and phenyl benzyl ketone in 73% yield from yet another difficult substrate, stilbene. Ethyl cinnamate was oxidized to the corresponding 1,3-ketoester in 59% yield. Oxidation of aliphatic alkenes however needed longer reaction times with a larger excess of TBHP (3.5 eq.). Recyclability was tested using 4-methoxystyrene and up to 78% yield of product was obtained even after the 8th run. Stability of a catalyst is crucial to obtaining longevity of the active catalytic species and one other solvent system that has similar potential to other green solvents is organic carbonates.

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[122] Z. Hou, B. Han, L. Gao, T. Jiang, Z. Liu, Y. Chang, X. Zhang, J. He, *New J. Chem.*, **2002**, *26*, 1246.

[123] B. Betzemeier, F. Lhermitte, P. Knochel, *Tetrahedron Lett.*, **1998**, *39*, 6667.

2.4.7.3.4 Organic carbonates

Organic or dialkyl carbonates exist in the form of ROCOOR’ or RR’CO_3 where R and R’ can be cyclic or acyclic. Not much attention has been given to organic carbonates, but cyclic carbonates have shown potential as green solvents in Wacker oxidation.[124] Organic carbonates have low vapour pressure and low toxicities. The high boiling point thereof allows for safer use at elevated temperatures. In the oxidation of 1-dodecene in ethylene carbonate (EC) and $PdCl_2$/NaOAc at 60°C, dodecan-2-one was obtained in 74% yield in just 6 hours.

EC was found to be superior to other solvents such as DMF, DMA, NMP which afforded dodecan-2-one in 3, 15 and 22% yield, respectively. With diethylene carbonate and dimethyl carbonate, no product was formed at all. Water had a positive effect on the reaction rate and NaOAc as additive proved to be essential as well since reactions were retarded without it.

Isomerization was non-detectable, but the formation of palladium nanoparticles was observed. EC was seen as having a stabilizing effect on Pd^0 species by preventing them from ‘falling out’ of the solution as Pd^0 aggregates. Instead of distillation to isolate the product, extractions with hexane enables separation of the product with the hexane phase and catalyst being contained in the EC layer.

2.4.8 Other systems

2.4.8.1 Montmorillonites

A typical montmorillonite structure consists of cationic species sandwiched between negatively charged silicate $(SiO_4)^{4-}$ layers (Figure 2.17).

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[124] J. L. Wang, L. –N. He, C. –X. Miao, Y. –N. Li, *Green Chem.*, **2009**, *11*, 1317.

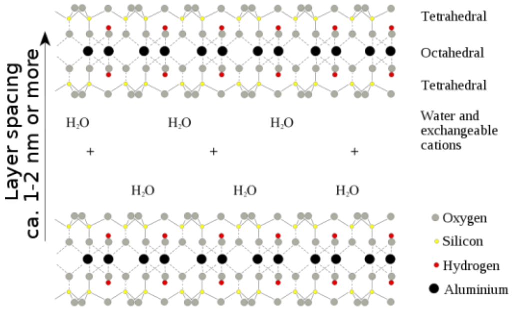

Figure 2.17: A typical structure of a montmorillonite species.

Through ion-exchange methods, different metal ions (Al, Fe, Mg) can be introduced into the interlayers as Kaneda *et al*. did in their preparation of Pd montmorillonite (Pd-mont) which was then applied to catalyze oxidation of terminal olefins.[125]

This approach allows for an acid-free system which will not only avoid corrosion of reactors, but seems to promote selectivity towards formation of the ketone, which is often a problem in acidic medium. 2-Decene was selectively oxidized to 2-decanone (85% yield) in DMA/H_2O, Pd-Mont/CuCl/O_2 at 80°C. In this study DMA proved to be the best solvent over NMP, DMF, EtOH, CH_3CN, and DMSO.

$CuCl_2$ was a superior co-catalyst compared to $Cu(OAc)_2$ and $Cu(NO_3)_2$ which resulted in 0% yield of the desired ketone. At 50% conversion, leaching of the Pd catalyst into the organic solvent containing products and unreacted substrate was minimal (<1 ppb, by ICP). 2nd and 3rd catalyst cycles still maintained high yield of 2-decanone (84%) and conversion of 1-decene (84-85%) with TON of 2400 and 6000 for 1-hexene. Although still considerably low for a catalytic reaction, these TONs are by far superior to the generally reported TON for Wacker oxidation (a few 100s). A few selected olefins from this work are given in Table 2.1, showing percentage conversion and yield of different olefins.

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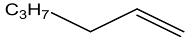
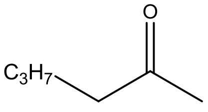
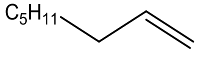
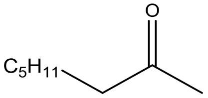
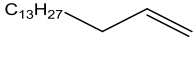
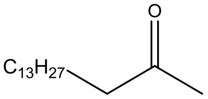
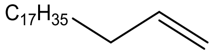
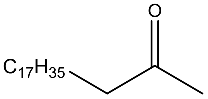
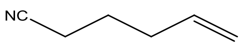
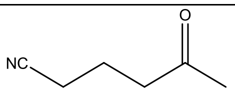
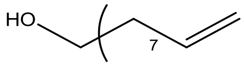
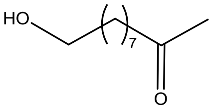
[125] T. Mitsudome, T. Umetani, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Tetrahedron Lett*., **2006**, *47*, 1425.

Table 2.1: Wacker oxidation of olefins with Pd-Mont (0.05g, Pd: 0.004 mmol), 1 mmol substrate, $CuCl_2$ (0.016 mmol), H_2O (0.5 ml), DMA (3 ml), 80°C, O_2 (1 atm).

	Time (h)	Conversion (%)	Product	Yield (%)
	3	82		81
	3	82		82
	3	88		85
	3	82		81
	15	75		73
	4	92		91

2.4.8.2 Polymer support

In the oxidation of ethylene, 1-hexene and cyclohexene with polymer supports such as polypropyleneglycol, (PPG), polyvinylalcohol (PVA) and polyethyleneglycol on silica support; PEG was found to be the best to be used with a $PdCl_2/CuCl_2/LiCl$ system.[126] Acetaldehyde and 2-hexanone were obtained with good selectivity while no product was observed with cyclohexene.

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[126] M. Okamoto, Y. Taniguchi, *J. Catalysis*, **2009**, *61*, 195.

2.4.8.3 *β*-Cyclodextrins and Calixarenes

The applicability of a water soluble catalyst is limited by the efficiency of the transfer of the olefin into the aqueous catalyst phase.[127] Surfactants, cyclodextrins (CDs) and calixarenes, just to name a few, are often employed for this purpose.

CDs are cyclic oligomers with a hydrophobic cavity that encourages the formation of a host-guest inclusion complex with organic compounds, thereby acting as a phase transfer catalyst between the aqueous and organic layers of a reaction medium.[128,129] This hydrophobic cavity can be modified to become specific for certain substrates. These oligomers exist as 6, 7 or 8 units wherein the CD is consequently named *α*-, *β*-, and *γ*-cyclodextrin (Figure 2.18), respectively, and take on a 'cylindrical' shape.[130]

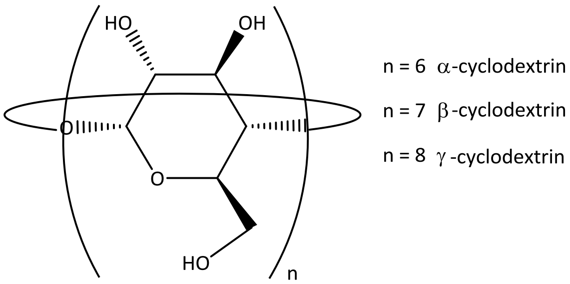

Figure 2.18: A typical *α*, *β*, and *γ* cylodextrin (CD) molecule.

CDs have thus been employed in enhancing the efficiency of water-soluble catalyst in a biphasic medium. Higher terminal olefins (C_8-C_{16}) were oxidized in yields greater than 90% using a biphasic system comprising of an organic olefin layer and an inorganic layer containing per(2,6-di-*O*-methyl)-*β*-cyclodextrins (DMCD) and $PdSO_4/H_9PV_6Mo_6O_{40}/CuSO_4$.[131,132,133]

The yield and selectivity of the product ketone were affected by the nature of the CD employed, with, as such, DMCD showing overall better performance than the *β*-CD and 2-hydroxypropyl-*β*-CD (HPCD), for example. In an attempt to further improve on these results, modification of the hydrophobic core is

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[127] E. Karakhanov, T. Buchneva, A. Maximov, M. Zavertyaeva, *J. Mol. Cat. A: Chem*., **2002**, *184*, 11.
[128] E. Karakhanov, A. Maximov, A. Kirillov, *J. Mol. Cat.: Chem*., **2000**, *157*, 25.
[129] E. Karakhanov, A. L. Maksimov, E. A. Runova, Y. S. Kardasheva, M. V. Terenina, T. S. Buchneva, A. Y. Guchkova, *Macromol. Symp*., **2003**, *204*, 159.
[130] H. Bricout, F. Hapiot, A. Ponchel, S. Tilloy, E. Monflier, *Sustainability*, **2009**, *1*, 924.
[131] E. Monflier, S. Tilloy, G. Fremy, Y. Barbaux, A. Mortreux, *Tetrahedron Lett*., **1995**, *36*, 387.
[132] E. Monflier, S. Tilloy, E. Blouet, Y. Barbaux, A. Mortreux, *J. Mol. Cat. A.: Chem*., **1996**, *109*, 27.
[133] S. Tilloy, F. Bertoux, A. Mortreux, E. Monflier, *Catalysis Today*, **1999**, *48*, 245.

often targeted and in this instance, a CD with nitrile groups in the hydrophobic cavity, that is, *β*-CD-CN were tested on 1-octene using a $PdCl_2/CuCl_2$ system. Only 20% yield of 2-octanone was obtained after 2 hours with no real significance between the *β*-CD and the *β*-CD-CN. The system was enhanced with the use of a heteropolyacid (HPA= $H_{3+n}[PV_nMo_{12-n}O_{40}]$, n= 1,2 3) as co-oxidant, giving 2-octanone in 50% yield with *β*-CD and 73% yield with *β*-CD-CN.

An increase in temperature saw an increase in yield to 94% after 6 hours. In the presence of *β*-CD-CN, $Pd(CH_3CN)_3(Cl_2)/CuCl_2$ was rated as the most active catalyst investigated, followed by $PdSO_4/CuSO_4$ and then $PdCl_2/CuCl_2$/HPA system. A *β*-CD can be generated in a reaction medium with or without an olefin present.[129] It was found that in the latter approach, the rate of oxidation was compromised. The former approach saw the rates go up to four times for dodecene and 5.5 times for hexadecane.

Calixarenes are also cyclic oligomeric compounds, but unlike the carbohydrate units within a CD molecule, they are made up of phenol derived fragments arranged in a 'bowl' shape.[129]

Water soluble calixarenes have been explored in the Wacker oxidation of terminal olefins using the $PdSO_4/CuCl_2$ catalyst system.[127] The most efficient calixarene over a range of olefins, CN-calix[4]arene-SO_3Na, was found to be specific for 1-hexene conversion to 2-hexanone (90% yield within 2 hours).[127] 1-Heptene, 1-octene and 1-dodecene gave yields of the corresponding ketones in yields of 15, 20 and 3%, respectively, under these conditions.

In curbing isomerization, calixarenes have an added advantage of a hydrophobic core that can be modified to target incoming substrate which will have the rest of its molecule 'hidden' in the cavity where the reaction doesn't take place [129]

Typical pressures of between 0.5MPa-8MPa of O_2, which are extremely high, in addition to HPAs as co-oxidants which are necessary to enhance the system, do however render the system less desirable from an industrial point of view.

Dendrimers make use of the many cores, branches and periphery of their highly branched repetitive macromolecules (or monomers) to immobilize metals ions. Their many 'chain-ends' results in their high solubility in organic solvents making them highly applicable where a homogenous system is required.[134]

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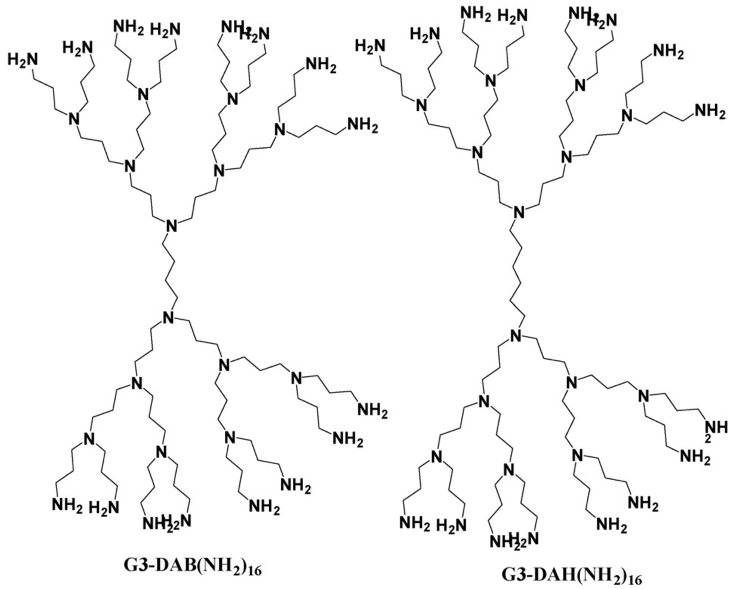
[134] E. A. Karakhanov, A. L. Maximov, B. N. Tarasevich, V. A. Skorkin, *J. Mol. Cat. A: Chem*., **2009**, *297*, 73.

To distinguish between the sizes of dendrimers, an increase in the branched macromolecules is referred to as a ‘generation’ where the smallest is 0 and the largest can be up to a 10th generation dendrimer, adopting a ‘ball-like’ structure the higher the generation.[135] In aqueous alcohol systems, 3rd generation polypropyleneimine (PPI) dendrimers G$_3$-DAB(NH$_2$)$_{16}$ **100** (Figure 2.19) were used with Pd(II)(CN)$_4$ and $CuCl_2$ to generate, *in situ*, a bimetallic complex for the oxidation of C_6-C_{12} terminal alkenes.



G3-DAB(NH$_2$)$_{16}$ G3-DAH(NH$_2$)$_{16}$ **100**

Figure 2.19: Generation 3 (G$_3$) diaminobutane (DAB) (NH$_2$)$_{16}$ and diaminohexane (DAH) (NH$_2$)$_{16}$ dendrimers.

High isomerization of terminal olefins was observed and that was attributed to the known rapid isomerization of olefins in aqueous alcoholic solvents. The shortfall of dendrimers, that is, the negative dendritic effect of a decrease in activity with increasing dendrimer generation was observed. This dependency on dendrimer generation was also observed with methyl ketone selectivity.

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[135] B. Klajnert, M. Bryszewska, *Acta Biochim. Pol.*, **2001**, *48*, 199.

2.4.8.4 Ligands

Organic ligands are known to provide good support or stabilization for transition metals during catalysis, allowing for fine-tuning of the ligand environment towards increased rates and selectivity. Since ligands can get involved in ligand-exchange reaction with $CuCl/CuCl_2$, their investigation in Wacker oxidation reactions does not involve copper salts.[88] This consequently provides a ligand system with lowered [Cl^-].

Nonetheless, in the investigation of neutral ligands, Henry *et al.*, used $CuCl_2$ and a neutral ligand, pyridine, with $PdCl_3$(pyridine) and found that even at low Cl^- concentrations, chlorinated by-products such as 2-chloroethanol were favored and that the reaction rate was reduced.[136] This was attributed to the pyridine ligand that makes the hydroxypalladated intermediate too stable, allowing $CuCl_2$ to react to form a chlorinated by-product.

In the investigation towards attaining a copper free catalyst system through an efficient ligand system for palladium, Sigman *et al*. have come up with two catalysts, one bearing a bulky *N*-heterocyclic carbene ligand (NHC) in a binuclear Pd catalyst, $[Pd\text{-}(IiPr)Cl_2]_2$ **101** (Figure 2.20), the other an acetate based Pd catalyst, $Pd(IiPr)(OAc)_2.H_2O$ **102** (Figure 2.20).[71]

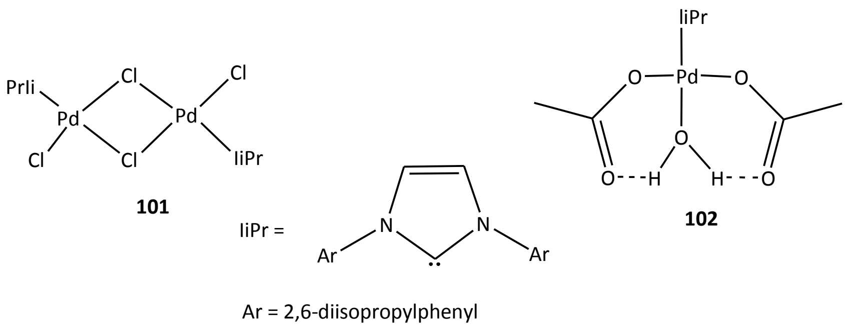

Figure 2.20:$[Pd\text{-}(IiPr)Cl_2]_2$ **101** and $Pd(IiPr)(OAc)_2.H_2O$ **102**.

Even for a substrate prone to polymerization and oxidative cleavage like styrene, Wacker oxidation was accomplished without copper additives with little or no oxidative cleavage. In the presence of TBHP, a 1,2-hydride shift mechanism similar to that discussed in Scheme 2.50 was proposed.[137]

Oxidation of styrene under aerobic conditions with 2.5 mol% of **101** in methanol gave 95% conversion to acetophenone within 24 hours, with a 10 hour induction period. In their optimization efforts, dicationic

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[136] J. W. Francis, P. M. Henry, *J. Mol. Cat. A*: *Chem*., **1995**, *99*, 77.
[137] C. N. Cornell, M. S. Sigman, *J. Am. Chem. Soc*., **2005**, *127*, 2796.

complexes of **101** and **102** with counterions OTf$^-$, OTs$^-$ and BF_4^- were explored. A reduced induction time from 10 to 2 hours was observed with OTf$^-$ as the counterion. This suggested that a cationic species was the active catalyst. Addition of 5.5 eq. of TBHP resulted in no induction period and the O-atom source in the product was proved with ^{18}O-labelling to be TBHP. When **98** was used in the oxidation of decene under similar anaerobic conditions with TBHP and AgOTs salt, a mixture of 2-, 3-, and 4-decanone was obtained.[8] Such olefin isomerization of terminal olefins is a challenge in Wacker oxidation and since the rate of oxidation of terminal olefins is faster than that of internal olefins, the true nature of isomerization is often not reflected in the results. A change to a bidantate amine ligand, (-)-sparteine, in **4** (Figure 1.2) in direct O_2 coupled Wacker oxidation still led to isomerization until a different solvent was employed.[8] DMF suppressed isomerization of decene, but afforded no decanone. In DMA or NMP, 8 mol% of **4** catalyzed the oxidation of decene at 70°C over 24 hours, with 99% conversion of decene in the presence of 5 eq. TBHP and air, with no isomerization. To prove that the sparteine ligand was still significant despite the influence of the solvent, oxidation of decene was carried out with a $Pd(CH_3CN)_2Cl_2$ system in DMA/H_2O. Isomerization of decene, as well as formation of palladium 'black' which aggregated out of solution, was observed.

In the oxidation of allylic alcohols with **4**, regioselectivity was observed giving moderate to high yield (69-87%) of one ketone product with only 2 mol% **4** over 24-48 hours with balloon oxygen only.[8]

An *in-situ* generation of an active catalyst species from 6 mol % of **5** (Figure 1.3) with 5 mol % $Pd(CH_3CN)_2Cl_2$ and 12 mol% of $AgSbF_6$ in dichloromethane also catalyzed the Wacker oxidation of protected allylic alcohols to the corresponding methylketones.[138]

Typically, protected allylic alcohols under classical Tsuji conditions give both Markovnikov and anti-Markovnikov products **103** and **104** (Scheme 2.57) through a proposed interaction of an oxygen atom of the alcohol and the electrophilic palladium centre during alkene coordination **A**.[139] This interaction then allows for the formation of both the Markovnikov and *anti*-Markovnikov products (Scheme 2.57, **A**).

It is envisaged that the reason why this was not observed when a bidantate ligand together with TBHP were used, was because along with an incoming alkene, a coordinatively saturated species **B** (Scheme 2.57) is formed, with no site for the OH-oxygen to bind. This then led to the formation of the Markovnikov product.

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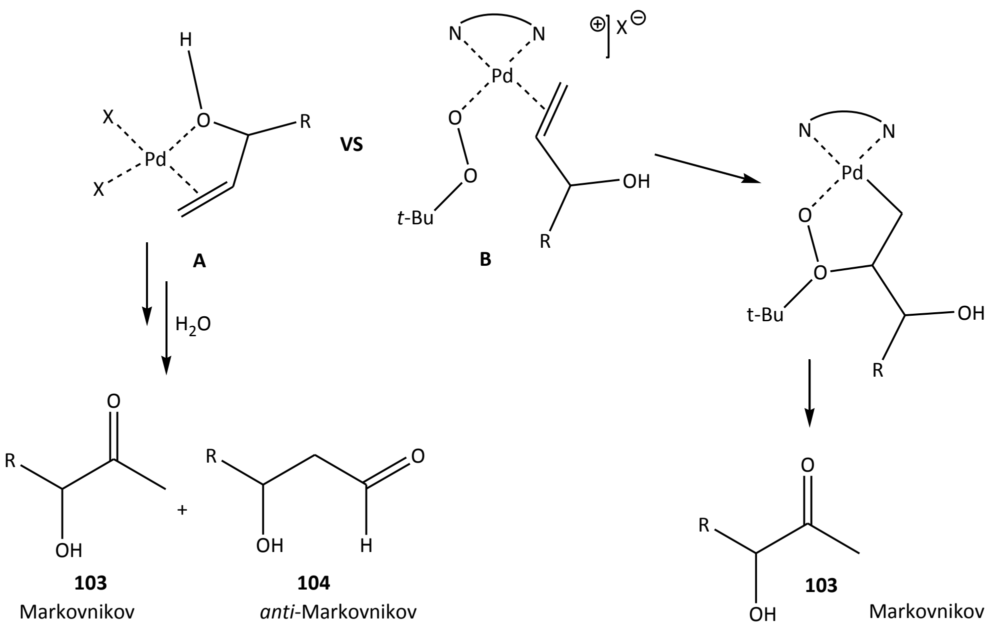
[138] J. R. McCombs, B. W. Michel, M. S. Sigman, *J. Org. Chem*. **2011**, *76*, 3609.
[139] J. R. McCombs, B. W. Michel, M. S. Sigman, *J. Am. Chem. Soc*. **2011**, *133*, 8317.



Scheme 2.57: Hypothesis into the binding of allylic alcohols in monodentate **A** without TBHP *versus* bidentate ligands with TBHP in **B**.

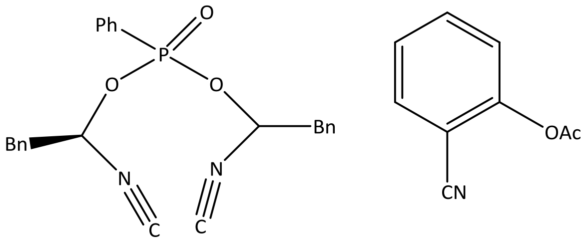
1-Decene, as well as styrenes, was also oxidized with little isomerization, although highly electron-deficient styrenes still gave low yields of the ketone, for example only 60% yield of *m*-nitro benzophenone from *m*-nitro-styrene (1 mmol) after 17 hours compared to 4-methylstyrene (3 mmol) where 88% yield of the benzophenone derivative was obtainable within 50 minutes. Lower catalyst loadings (5 mol%) compared to 10 mol% under classical conditions were employed, without use of co-oxidants.

When other solvents such as methanol or DMA were investigated with **5** (Figure 1.3) as a ligand on $PdCl_2(CH_3CN)_2$,oxidation of alkene substrates was not observed.[11] A range of other *N*-donor ligands, both mono- and bidentate which were investigated and found to be ineffective with this system are bipyridine, TMEDA, (-)-sparteine and pyridine, all with conversions and yields below 20%.

The role of a nitrogen-based bidantate phenanthroline ligand in **98** (Figure 2.15) reported by Sheldon *et al*. was hypothesized to decrease the oxidation potential of the Pd^{II}/Pd^{0} redox couple, thereby effecting a much faster re-oxidation of Pd^{0} back to the active Pd^{II} and lowering the Pd^{0} aggregation.[140]

In addition, the steric bulk of the ligand was thought to bring further stabilization to the Pd^{0}. The use of water in this system was limiting as many substrates were not miscible with water and this limited the reaction and led to decreased yields. Kinetic studies on **98** showed a first order rate dependence on catalyst concentration and oxygen pressure.

A bis(isonitrile) **105** (Figure 2.21) and monodentate nitrile ligand **106** (Figure 2.21) have also been explored as good σ donors for Pd in the Wacker oxidation.[141] Reactions with 1-octene and 4-methylstyrene, for example, resulted in overall >98% conversion of 1-octene (24 hours) and > 99% conversion for 4-methylstyrene (70 hours) using 5 mol% $PdCl_2$/**105** under 1 atm O_2 at 70°C. The reactivity of the bidentate **105** (10 mol%)/$PdCl_2$(5 mol%) compared the monodentate **106** (10 mol%)/$PdCl_2$ (5 mol%) was slightly higher, resulting in conversion of 98% with 0.2M 1-octene while the same conversion was realized with only 0.125M 1-octene for the latter.



105 **106**

Figure 2.21: Bis(isonitrile) ligand **105** and monodentate nitrile ligand **106**.

The need to produce enantiomerically pure products still gives chiral ligands a pivotal place in transition metal-catalyzed asymmetric catalysis.[142]

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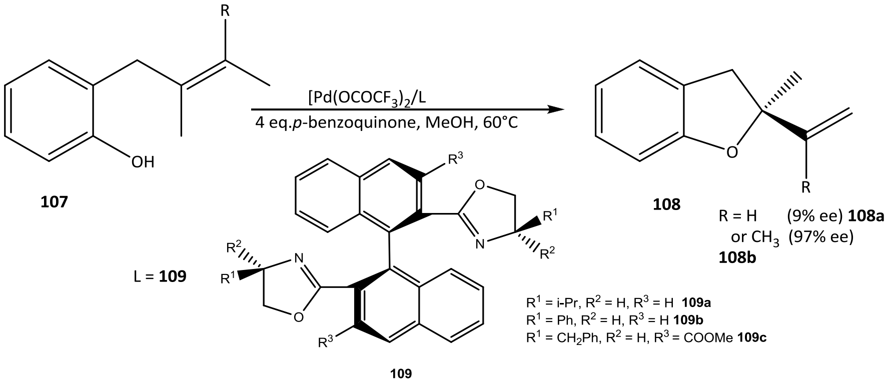
[140] G. –J. ten Brink, I. W. C. E. Arends, G. Papadogianakis, R. A. Sheldon, *Chem. Comm*., **1998**, 2359; G. –J. ten Brink, I. W. C. E. Arends, G. Papadogianakis, R. A. Sheldon, *Appl. Catal. A*, **2000**, *194*, 435.

[141] A. Naik, L. Meina, M. Zabel, O. Reiser, *Chem. Eur. J*., **2010**, *16*, 1624.

[142] a) Y. Uozomi, K. Kato, T. Hayashi, *J. Am. Chem. Soc*., **1997**, *119*, 5063; b) Y. Uozumi, K. Kato, T. Hayashi, *J. Org. Chem*., **1998**, *63*, 5071; c) Uozumi, H. Kyota, K. Kato, M. Ogasawara, T. Hayashi, *J. Org. Chem*., **1999**, *64*, 1620; d) F. Wang, Y. J. Zhang, G. Yang, W. Zhang, *Tetrahedron Lett*., **2007**, *48*, 4179; e) Y. J. Zhang, F. Wang, W. Zhang, *J. Org. Chem*., **2007**, *72*, 9208; f) F. Wang , G. Yang, Y. J. Zhang, W. Zhang, *Tetrahedron*, **2008**, *64*, 9413.

As such, it comes as no surprise that chiral ligands have been probed in the synthesis of optically active dihydrobenzofurans **108** for example, *via* an intramolecular Wacker-type cyclization of *o*-allylphenols **107** (Scheme 2.58).



Scheme 2.58: Wacker cyclization of *o*-allylphenol **107**.

A bulky optically active 2,2'-bis(oxazolyl,-1,1'-binapthyl (*S,S*-ip-boxax) **109a** (Scheme 2.58) was used together with palladium bis(trifluoroacetate) (PdOCOCF$_3$)$_2$, to afford **108** in ees of up to 97%.[142a] Herein, the binapthyl moiety was superior compared to where bis(oxazoline) ligands **110** and **111** (Figure 2.22) were used by itself, affording ees of 18% and 35%, respectively.

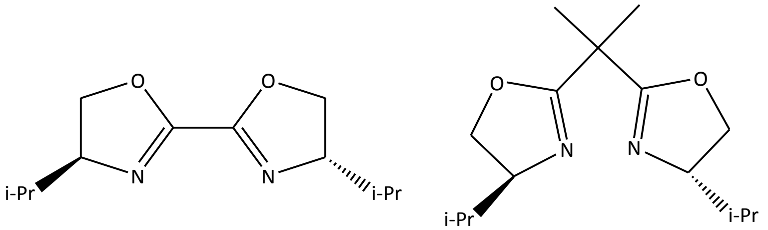


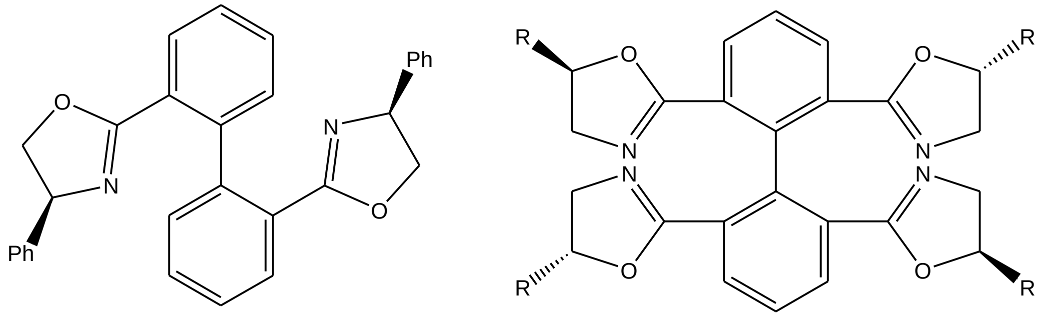
Figure 2.22: (*S*)-2,2'-bioxazoyl **110** and (*S*)-2,2-bis(oxazolyl)propane **111**.

Further probes into the anionic ligands, exploring counterions such as chlorides in PdCl$_2$/**109a**, which were unreactive, still left the Pd(OCOCF$_3$)$_2$/**109a** as the best catalyst sytem.[142b]

A switch to a more electrophilic dicationic complex of **109a** obtained from Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ with 2 equivalents of **109a**, did however see a great increase in catalytic activity. Synthesis of **108a** was achieved in 91% yield in 98% ee in only 50 minutes using 10 mol% [Pd(CH$_3$CN)$_4$](BF$_4$)$_2$ catalyst and 2 equivalents of **109a** in benzoquinone and methanol at 60°C. With 1-2 mol% catalyst the catalyst was still active enough to give 45% yield of **108a** in 94% ee, where an increase to 75% yield and 96% ee where achieved under reflux conditions.

Continuing with highly active dicationic complexes of **109**, the effect of steric bulk of the substituents on the oxazoline moiety was investigated.[142c] Alkyl groups (*i*-Pr, *t*-Bu, CH_2Ph, Ph) were introduced to the oxazoline moiety where the isopropyl was found to be the most effective. Functional groups at the C3 and C3' positions also seemed to influence enantioselectivity as absence of such gave lower ees.

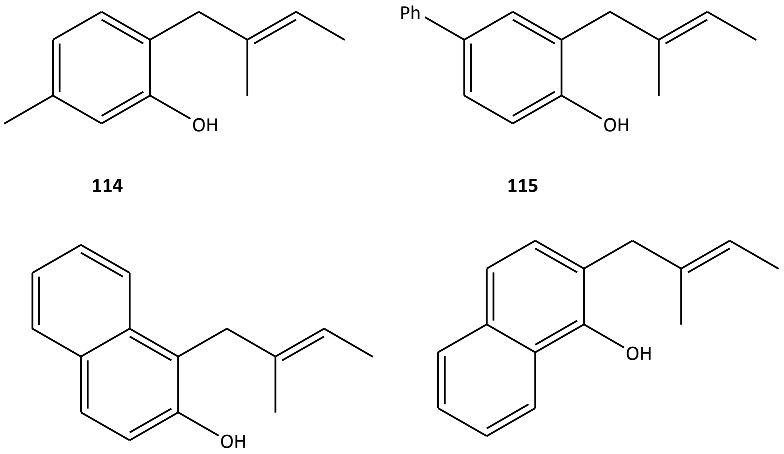
The higher the ratio of the ligand to the palladium, the higher the enantioselectivity; 1, 2 and 3 equivalents of ligand to palladium gave 8, 67 and 86% ee respectively.[142c] While temperature played a role, substituents on the catalyst also influenced the enantioselectivity and catalyst activity with a high dependence on the nature of the substrate; a highly substituted alkene worked better with a less bulky ligand system. On catalyzing the synthesis of **108** with a $Pd(OCOCF_3)_2$ derived bisoxazoline ligand that has a biphenyl moiety **112** (Figure 2.23), high enantioselectivities of up to 98% ee were obtained.[142d]



112 **113**

Figure 2.23: Axis-unfixed biphenyl bisoxazoline ligands **112** and **113**.

The $Pd(CF_3COO)_2$ and bisoxazoline ligand **113** catalyst system did not bring about any major changes except for maintaining high catalytic activities and enantioselectivities of between 93 and 99%.[142e] Perhaps a bit different from all the work done in this regard, is the substrate scope, proving that the system is applicable over a wide range of substrates, including *o*-allylphenols **114-116** (Figure 2.24).

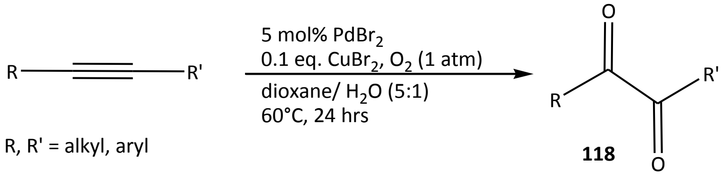


114 **115** **116** **117**

Figure 2.24: *o*-allylphenols **114-117** in Wacker oxidation with Pd($CF_3COO)_2$-bisoxazoline ligand **113**.

2.4.8.5 General organic reactions

The great functional group tolerance and great selectivity of the Wacker oxidation has made it widely applicable in the synthesis of biologically active compounds. It has already been discussed how the selectivity and enantiomeric excess in Wacker-type cyclization (Scheme 2.58) can be influenced using different asymmetric ligands.[140,142] Other reactions include deoxybenzoin **118** (Scheme 2.59) synthesis *via* alkynes, with up to 97% yield of product obtained using 5 mol% $PdBr_2$ and 10 mol% $CuBr_2$ under 1 atm oxygen at 60°C in a dioxane/H_2O solvent system.[143]



Scheme 2.59: Synthesis of deoxybenzoin **118**.

A “chemically sensitive *cis*-keto-enol” **120** which is a key component in biologically active natural products, was regioselectively synthesized from a precursor **119** in a multistep reaction *via* Wacker oxidation using classical Tsuji conditions ($PdCl_2$/CuCl, DMA:H_2O, O_2, 50°C) (Scheme 2.60).[144]

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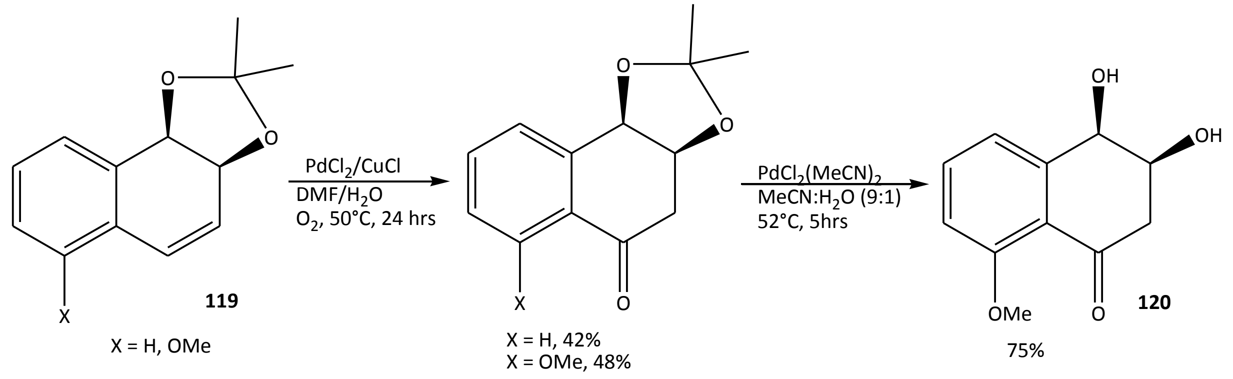
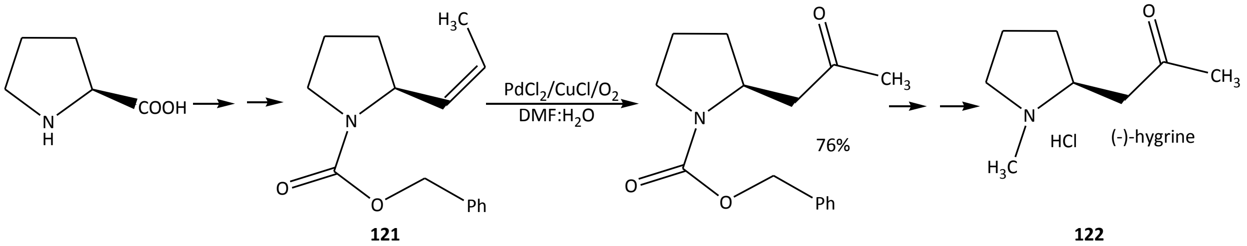
[143] W. Ren, Y. Xia, S. –J. Ji, Y. Zhang, X. Wan, J. Zhao, *Organic Lett.*, **2009**, *11*, 1841.
[144] P. Mukherjee, S. J. S. Roy, T. K. Sarkar, *Organic Lett.*, **2010**, *12*, 2472.



Scheme 2.60: Regioselective synthesis of *cis*-keto diol biologically active intermediate **120**.

Using the same conditions, synthesis of an important alkaloid, (-)-hygrine **122** was also achieved regioselectively in a multistep synthesis *via* a Wacker oxidation reaction on the corresponding olefinic precursor **121** (Scheme 2.61).[145]



Scheme 2.61: Regioselective synthesis of (-)-hygrine **122**.

Further applications include synthesis of methyl branched pheromone components 6-methyl-2-octadecanone **123**, 14-methyl-2-octadecanone **124**, 6,14-dimethyl-2-octanedecanone **125** (Scheme 2.62),[146] as well as the selective oxidation of allyllic phthalamides **126** (Scheme 2.63) .[147]

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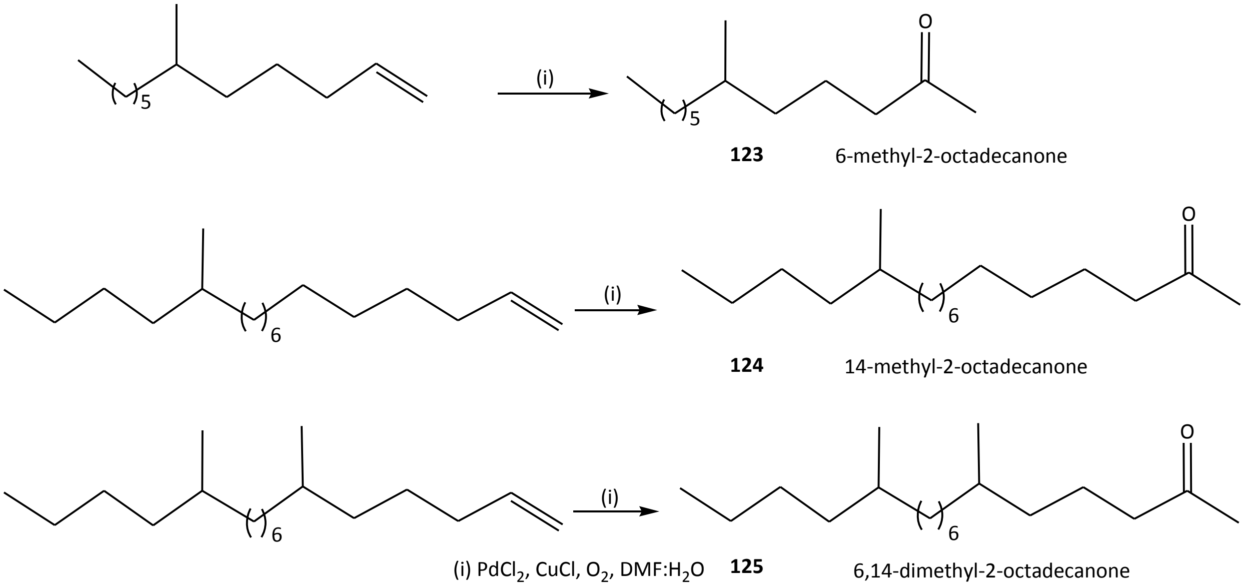
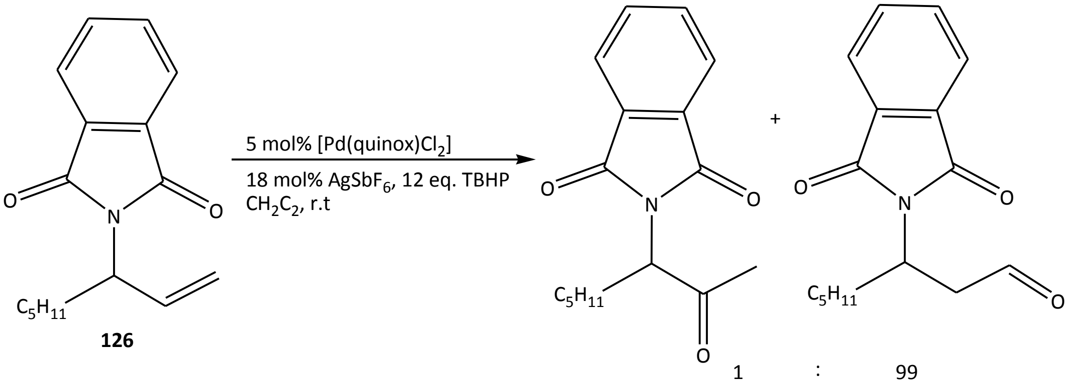
[145] M. S. Majik, S. G. Tilve, *Tetrahedron Lett*., **2010**, *51*, 2900.

[146] T. Taguri, R. Yamakawa, Y. Adachi, K. Mori, T. Ando, *Biosci. Biotechnol. Biochem*., **2010**, *74*, 119.

[147] B. Weiner, A. Baeza, T. Jerphagnon, B. L. Feringa, *J. Am. Chem. Soc*., **2009**, *131*, 9473.



Scheme 2.62: Branched pheromones **123-125** via Wacker oxidation.



Scheme 2.63: Synthesis of allylic phthalamides *via* Wacker oxidation.

2-Methylquinolines were afforded in 19% yield over 36 hours in a challenging aza-Wacker-type cyclization of a hydroxyaniline wherein 10 mol% $Pd(OAc)_2$ was the best Pd salt amongst $PdCl_2$, $PdCl_2(CH_3CN)_2$ and $Pd(PhCN)_2$ and the best solvent methanol in a range of solvents including THF, EtOH, CH_2Cl_2 and CH_3CN (Scheme 2.64).[148]

Improved yields were obtained with 20 mol% of added ligands such as 1,10-phenanthroline (87%), pyridine (67%), DMAP (42%) and 2,2'-bipyridine (65%), but ligands such as triphenylphoshine and imidazole led to only trace amounts of product.

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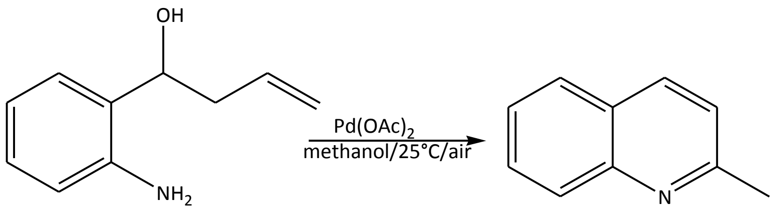
[148] Z. Zhang, J. Tan, Z. Wang, *Org. Lett.*, **2008**, *10*, 173.



Scheme 2.64: Aza-Wacker-type cyclization of hydroxyanilines with $Pd(OAc)_2$ in air.

The Wacker oxidation reaction is indeed a versatile organic reaction applicable over a wide range of organic substrates and great industrial potential. In order to meet industrial standards of low toxicity, high TONs and TOFs, the many factors which govern its reaction dynamics, that is, substrate solubility, solvents, ligands, oxidants and or co-oxidants as well as the central metal; have to be carefully manipulated to obtain optimum results. As highlighted in this study, it remains a challenge.

Chapter 3

Phenanthroline type catalysts

3.1 Introduction

The industrial application of the Wacker oxidation is hampered by factors such as substrate isomerisation to internal olefins, especially when applied to longer chain olefins, as well as the generation of large quantities of corrosive chlorinated by-products originating from reaction with the copper chloride employed as co-oxidant under standard reaction conditions. The reaction is furthermore associated with low turn-over numbers (TONs), since the palladium catalyst often 'falls out' of the catalytic cycle as aggregated Pd^0 (*cf* paragraph 1.1). While many efforts to address these problems and improve on the TONs and yields have been reported (chapter 1, ref. 4), ligand modification of palladium catalysts in Wacker oxidations has received little attention and as such selected in the current study as an approach to investigate towards improving this reaction.

In this regard it was envisaged that the utilization of a bimetallic catalyst system comprising of copper and palladium attached to the same organic ligand could lead to improved TONs and may lead to less Pd 'fall-out'.

1,10-Phenanthroline-5,6-dione **127** (Figure 3.1) has been utilized in oxidation reactions before and has a potential to accept two (different) metals in a bidentate mode; it was selected as a starting point in the development of a heterobimetallic type of catalyst for the Wacker oxidation reaction. [149,150,151,152]

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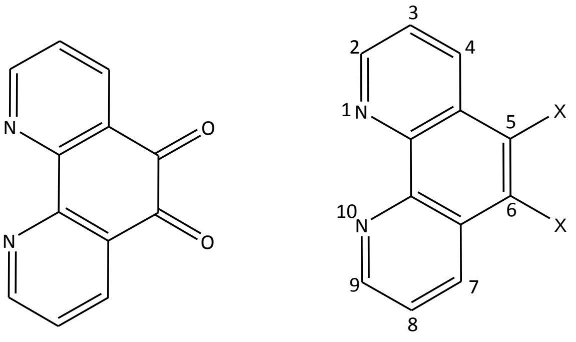
[149] C. R. Luman, F. N. Castellano, *Phenanthroline Ligands*, Bowling Green State University, Ohio, USA, pg 25.
[150] A. Y. Girgis, Y. S. Sohn, A. L. Balch, *Inorg. Chem*., **1975**, *14*, 2327.
[151] C. A. Goss, H. D. Abruňa, *Inorg. Chem*., **1985**, *24*, 4263.
[152] G. A. Fox, S. Bhattacharrya, C. G. Piepont, *Inorg. Chem*., **1991**, *30*, 2895.

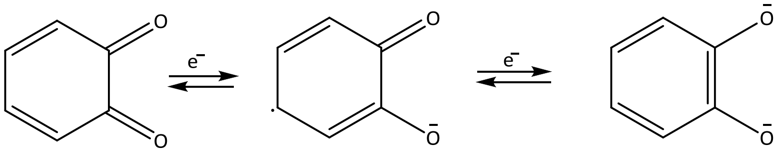


127

128a X = H
128b X = O or other hetero atom)

Figure 3.1: 1,10-Phenanthroline-5,6-dione **127** and 1,10-phenanthroline derivatives **128**.

Furthermore, quinones are known for the fact that they are prone to reversible multiple step one-electron redox reactions leading to three distinct forms, *i.e*. benzoquinones (BQ), semiquinones (SQ), and catecholates or hydroquinones (HQ) (Scheme 3.1).[153]



BQ **SQ** **HQ**

Scheme 3.1: Redox states of quinones, *i.e.*benzoquinone (**BQ**), semiquinone (**SQ**), and hydroquinones (HQ).

As a result, quinones have often been used to facilitate electrochemical activity and it was envisaged that if the copper and palladium could be attached to the different sides of the molecule, intramolecular redox activity could lead to the required re-oxidation of the palladium after reaction with an olefin. If the second metal could not be attached to the dione moiety, **127** could be converted to a 5,6-disubstituted analogue better suited for binding to the two metals as well as having a preference for binding palladium on one side and copper on the other one.

Further impetus as to the utilization of these types of phenanthroline based ligands (**127** and **128b**) came from the work of Girgis *et al*. who demonstrated the preparation of a platinum complex **129**

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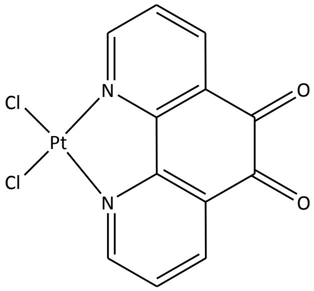
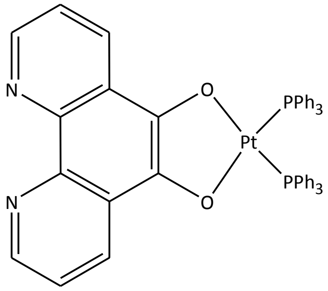
[153] R. M. Buchanan, J. Claflin, C. G. Pietpont, *Inorg. Chem*., **1983**, *22*, 2552.

through binding with the N atoms (leaving the O atoms of the benzoquinone uncoordinated) as well as complexation to the oxygens, generating the bipyridine equivalent **130** (Fig 3.2).[150]



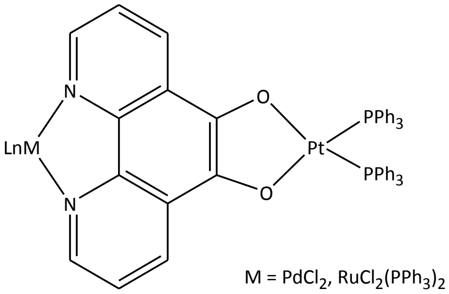
129



130

Figure 3.2: Platinum benzoquinone equivalent **129** and the bipyridine platinum complex **130**.

Fox *et al.* showed that **129** and **130** can in fact be reacted further through either the *o*-quinoid or bipyridyl moiety to generate a polynuclear complex **131** (Fig 3.3).[152]



131

Figure 3.3: Binuclear platinum complex **131**.

3.2 Results and discussion - Synthesis of a bimetallic palladium-copper complex of type 131

Girgis *et al*. described the first step of the synthesis of **131** as an oxidative addition of **127** to a low valent platinum complex, *tetrakis*platinumtriphenylphosphine ($Pt(PPh_3)_4$). It was thought that a similar approach could thus be used for the preparation of the palladium analogue **131**.[150] *Tetrakis*palladiumtriphenylphosphine ($Pd(PPh_3)_4$) was obtained as a yellow solid in 92% yield by heating under reflux a mixture of palladium chloride ($PdCl_2$), triphenylphosphine (6 equivalents), and hydrazine sulfate (4 equivalents) according to a well described literature procedure.[154] Although **127** is available commercially, it is expensive, and was obtained in 95% yield from **128a** in an oxidation process using a mixture of H_2SO_4/HNO_3 and KBr under reflux.[155]

The presence of the CO functionality in the product was confirmed by a carbonyl stretching frequency at 1703 cm^{-1} in the IR spectrum of **127** (Plate 1). The ^1H NMR spectrum of **127** (Plate 2) had three doublet of doublets in the aromatic region at δ_H 9.11, 8.50 and 7.59 ppm. The three signals instead of the four observed in the starting material, indicated di-substitution with the symmetry in the molecule being retained. The ^1H NMR chemical shifts were found to be identical to values reported in literature.[155]

The ^{13}C NMR spectrum (Plate 3) also displayed a downfield signal at δ_C 178.7 ppm, indicating the presence of a carbonyl group.

Having confirmed the identity of **127**, the synthesis of **132** was subsequently attempted by heating under reflux a mixture of **127** (120 mg, 0.6 mmol, 1.2 eq.) and $Pd(PPh_3)_4$ (610 mg, 0.5 mmol) in anhydrous dichloromethane (Scheme 3.2).

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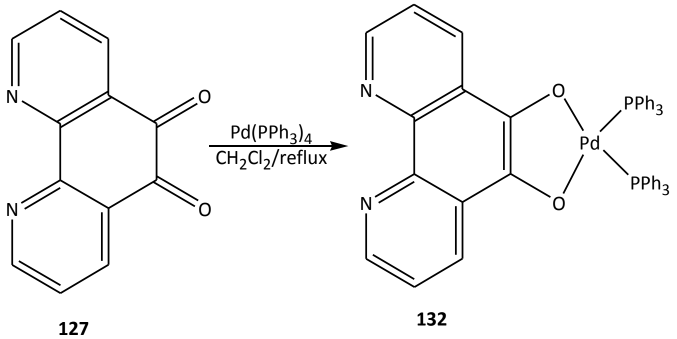
[154] L. S. Hegedus, B. H. Lipshutz, *Organometallic in Synthesis – A manual*, 2nd Ed (M. Schlosser, Ed.), John Wiley & Sons, New York. **2002**,

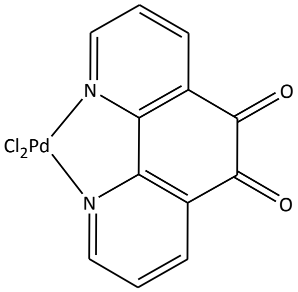
[155] W. Paw, R. Einsberg, *Inorg. Chem*., **1997**, *36*, 2287.



127 **132**

Scheme 3.2: The reaction of **127** with Pd(PPh$_3$)$_4$.

A small quantity of Pd^0 black was filtered off (leaving a very thin black layer on the filter paper)and the solvent removed to give a brown solid, which was found to have limited solubility in common organic solvents (DCM, THF, DMF, DMA, and DMSO). Since the brown solid product seemed to be insoluble, proper characterization of the product by NMR etc. proved to be impossible at this stage. However, since very little palladium was recovered and both **127** and Pd(PPh$_3$)$_4$ are soluble in DCM, it can be concluded that some reaction had occurred and that palladium must either be attached to the two oxygens or by means of the pyridine nitrogens at the back side of the molecule as shown in Figure 3.4.

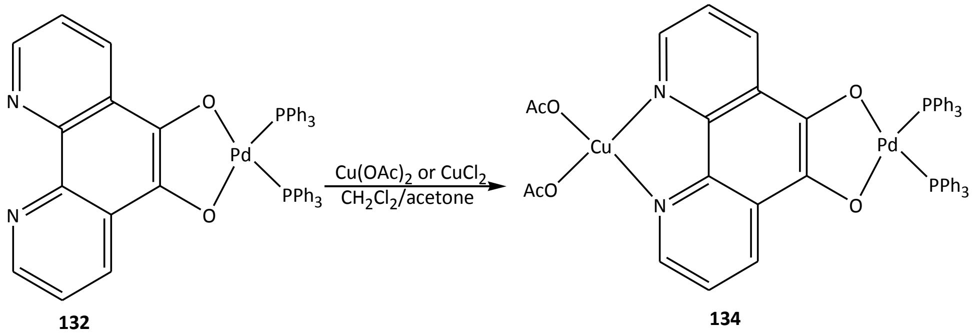


133

Figure 3.4: PdCl$_2$ derivative **133** reported in literature.

The nitrogen bound palladium complex **133** has, however, been reported in literature as a **yellow** complex insoluble in dichloromethane.[150] Since the material obtained in the current study was brown in colour and C=O stretching frequencies were absent in the solid IR spectrum, it was concluded that the carbonyl moieties of the substrate had been reacted away. Further impetus as to the palladium being bound to the oxygen atoms came from a broad peak at 3425.4 cm^{-1}in the spectrum, indicating bonded oxygen atoms are present in the molecule.

Although the structure of the product from the reaction could not be proved beyond doubt, it was decided to continue with the preparation of the bimetallic catalyst **134**. A suspension of the crude brown solid in DCM was therefore treated with a solution of copper acetate in ethanol.[156] Since quantifiable product could not be isolated from this procedure, the reaction was repeated with acetonitrile as solvent,[157] but isolable material was only obtained in very small quantites. When the copper acetate was dissolved in acetone, as in the silica bound copper-bipyridine complexes prepared by Likhar *et al.*, a brown solid was obtained (Scheme 3.3).[158]



Scheme 3.3: Reaction of presumed **132** with $Cu(OAc)_2$.

Since this product also proved to be rather insoluble in organic solvents it was decided to determine the metal content by ICP-OES. While the results from analytical procedure confirmed the presence of copper, no Pd could be detected. It was therefore concluded that the palladium was either displaced by copper in a ligand exchange reaction leading to a complex containing two copper ions or that the brown solid thought to be complex **132** was in fact something else and never contained any palladium.

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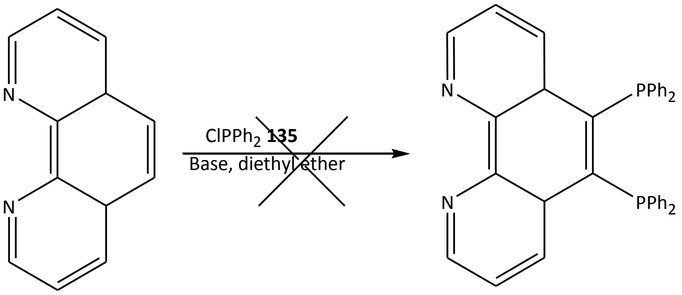
[156] H.–L. Kwong, W.–S. Lee, W. –H. Chiu, W. –T. Wong, *J. Chem. Soc., Dalton Trans.*, **1998**, 1043.
[157] M. Barquin, M. J. G. Garmendia, L. Larrainga, E. Pinilla. M. R. Torres, *Inorg. Chim. Acta*, **2009**, *362*, 2334.
[158] P. R. Likhar, S. Roy, M. Roy, M. L. Kantam, R. L. De, *J. Mol. Cat. A: Chem.*, **2007**, *271*, 57.

3.3: Functionalization of 1,10-phenanthroline at the 5- and 6- positions.

Since the palladium-oxygen bonds in the synthesis of **134** were being replaced by copper-oxygen bonds, it was felt that the problem could be solved by changing the hard oxygen nucleophiles into the much softer phosphorous analogues, which would show a preference for palladium over copper. Compound **128** was therefore treated with pyridine/DMAP and chlorodiphenylphosphine (Ph_2PCl) **135**, but the desired product, 5,6-*bis*(triphenyl-phosphino)phenanthroline **136** could not be isolated from the reaction mixture (Scheme 3.4).[159]



128

136

Scheme 3.4: Phosphination of **128**.

When the reaction was repeated with bases such as pyridine/DMAP, NEt_3, 2,6-lutidine or *n*-BuLi[160], indications of phosphine attachment to the phenanthroline moiety were also not found. Performing the reactions under reflux, at 0°C and below or at longer reactions times (up to 10 days) did not yield any wanted product either.

In order to establish the integrity of the *n*-BuLi solution used and determine whether the electrophiles could in fact be directed towards the desired 5- and 6- positions on the phenanthroline, the substrate was again treated with *n*-BuLi, followed by quenching with 2 eq. acetic anhydride (Scheme 3.5).[161] When the amount of Ac_2O used was decreased to 1 equivalent in order to prevent overacetylation, **137** could still not be isolated and only a decrease in the yield of isolated bands of the reaction mixture was found.

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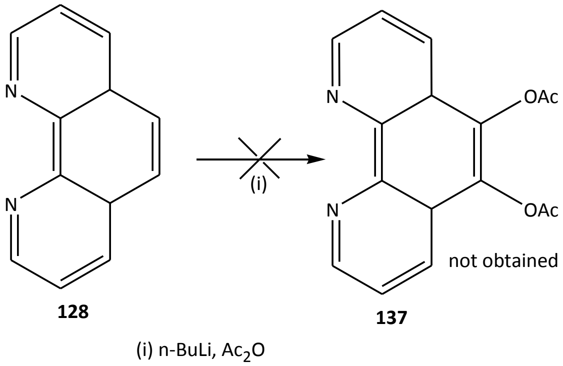
[159] D. S. Clyne, Y. C. Mermet-Bouvier, N. Nomura, T. V. RajanBabu, *J. Org. Chem*., **1999**, *64*, 7601.

[160] C. J. Chapman, C. G. Frost, M. F. Mahon, *Dalton Trans.*, **2006**, 2251.

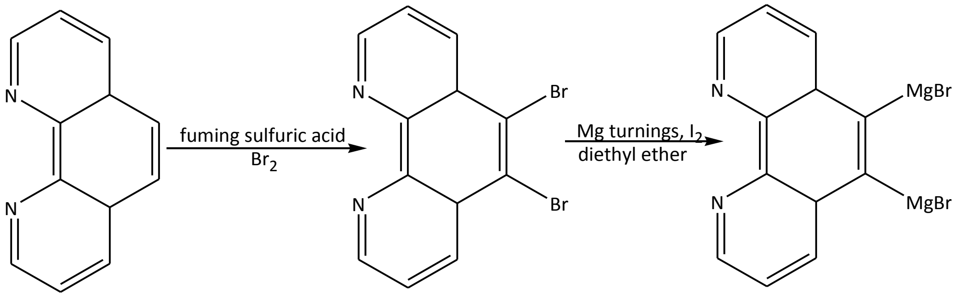
[161] R. J. Ferrier, J. C. S. Perkin I, **1978**, *8*, 1098.



Scheme 3.5: Synthesis of 1,10-phenanthroline-5,6-diacetate from **128**.

^{1}H NMR analysis of the isolated products which were separated by TLC, indicated multiple signals in the aliphatic region collectively integrating for more than six protons, suggesting multiple acetylations.

Since the failure of the reaction could probably be ascribed to non-selective deprotonation of the phenanthroline nucleus, it was decided to prepare the 5,6-dibromoderivative **138** and generate the anion to be reacted with the **135** through formation of the Grignard reagent **139** or transmetallation (Scheme 3.6).



128 **138** **139**

Scheme 3.6: Dibromination of **128**.

Bromination of **128** in the 5- and 6- positions was therefore attempted by reacting it with bromine in fuming sulfuric acid at 120°C (Scheme 3.6).[162]

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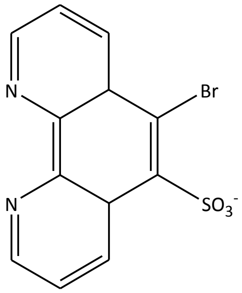
[162] M. Feng, K. S. Chang, *Organometallics*, **2002**, *21*, 2743.

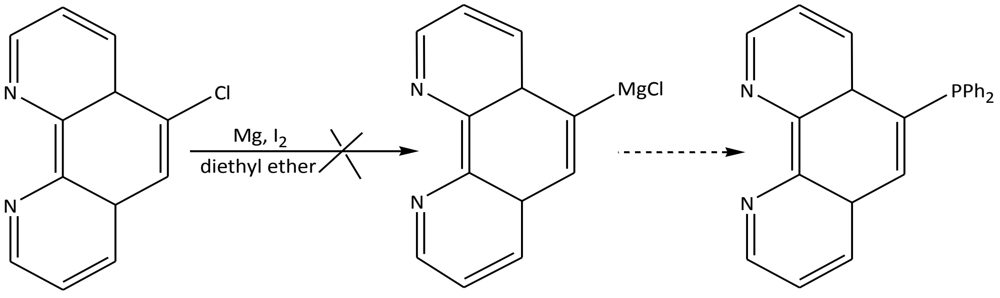
While the ^1H NMR spectrum of **138** showed a downfield shift for the phenanthroline protons with molecular symmetry largely intact, MS(EI) indicated the product to be the mono-brominated derivative **140**, (Figure 3.5) with a SO_3^- group remaining in the position that was to be occupied by the second bromine.



140

Figure 3.5: A by-product in the dibromination of **128**.

Since it is reported that very high temperatures are necessary for both initially added SO_3^- groups to be substituted by bromines, this result was attributed to a too low reaction temperature (only 120°C). When the reaction was repeated in a sealed glass tube at 140°C, the desired product **138** was obtained in 44% yield. The correct m/z value was obtained (338 M^+ +1) and the ^1H and ^{13}C NMR spectra (Plate 4&5) were similar to the reported literature value with three sets of multiplets at δ_H 9.20-9.19, 8.77-8.76 and 7.68-7.62 ppm each integrating for two protons in the ^1H NMR spectrum and the corresponding carbon signals in the ^{13}C spectrum. With the dibromo derivative in hand, attention was turned towards forming the Grignard reagent **139** and reaction thereof with **135**. Despite several attempts including standardization of the prepared Grignard reagent, all attempts at reacting **138** with **135** failed. It was thus decided to subject the commercially available model substrate, 5-chlorophenanthroline **141**, to these reaction conditions (Scheme 3.7).

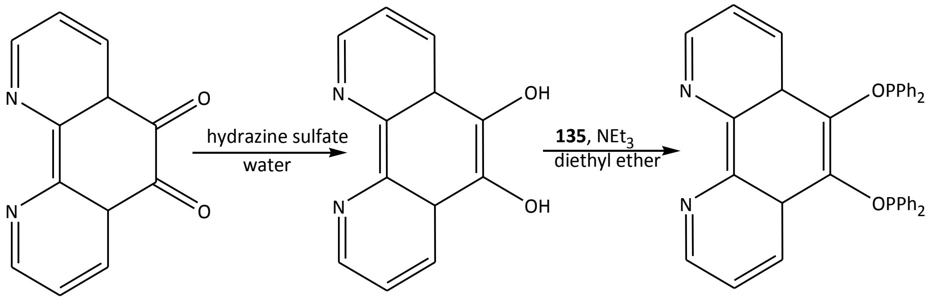


141

Scheme 3.7:Mono-phosphinationof Grignard reagent generated from 5-chlorophenanthroline **141**.

Compound **141** nonetheless failed to dissolve in any of the solvents traditionally used for Grignard reactions and the reaction once again proved to be unsuccessful.

All efforts towards preparing the **136** failed, it was thus decided to generate a diol **142** from **127** and then transform it into a phosphinite **143** (Scheme 3.8) and rather use that as a ligand in the bimetallic process. Subsequent hydrazine sulfate reduction of **127** in water afforded the diol **142** as a yellow solid in 80% yield.[163]



127 **142** **143**

Scheme 3.8: Attempted synthesis of a bisphosphinite **143** from **127** *via* **142**.

The IR spectrum of **142** clearly showed the disappearance of the C=O functionality (of **127**) and presence of the OH groups (ν_{max} 3279 cm^{-1}).

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[163] J. –Z. Wu, H. Li, J. –G. Zhang, J. –H. Xu, *Inorg. Chem. Comm.*, **2002**, *5*, 71; A. S. Denisova, M. B. Degtyareva, E. M. Dem'yanchuk, A. A. Simanova, *Russ. J. Org. Chem.*, **2005**, *41*, 1690.

The symmetry in the molecule was expected to show in the ^{1}H NMR spectrum (Plate 6) with only four protons integrated for, including one OH proton. A multiplet at δ_H 9.06-9.06 and 8.63-8.60 each integrating for one proton, as well as a doublet of doublets at δ_H 7.59 ppm, also integrating for one proton was thus observed. A broad signal observed at δ_H 6.91 ppm integrating for one proton was assigned to the OH group in **142**.

Attaching the phosphorous moieties to the hydroxy groups, however, turned out to be much more challenging and could not be achieved despite several attempts with a range of bases such as *n*-BuLi, NEt_3, and pyridine/DMAP.

Due to the fact that, to the best of our knowledge, oxygenated phosphorous analogues like phosphinites and phosphites have not been utilized as ligands for palladium catalyzed Wacker oxidations, it was decided to leave the synthesis of **143** at this point and first evaluate the potential of simple examples of these types of compounds in the Wacker oxidation. If it can be proved that palladium catalysts carrying phosphinite or phosphite ligands are capable of affecting the Wacker oxidation reaction, further attempts towards preparation of **143** could then be embarked upon.

Chapter 4

4.1 Phosphorus based ligands

4.1.1 Properties of organophosphorus compounds

Phosphorus (III) or tervalent organophosphorus with their available lone pair of electrons, are able to form strong bonds not only with 'soft' transition metals, but have an affinity for atoms such as oxygen, generating phosphorus compounds of different basicity.[164] Phosphine (PR_3, R = any alkyl or aryl) is regarded as the most basic of these compounds and thereafter basicity decreases with each new P-O bond present, making phosphites ($P(OR)_3$, R = any alkyl or aryl) the least basic and less likely to be oxidized (Figure 4.1).[165]

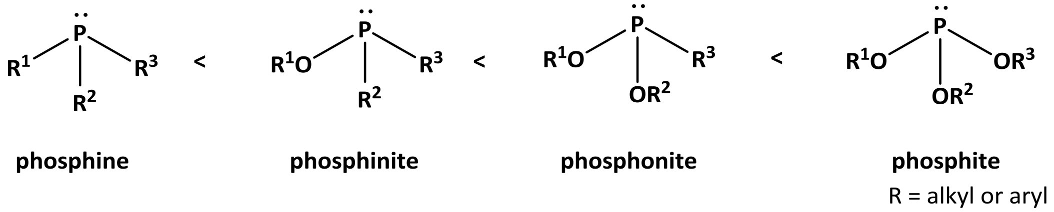

Figure 4.1: General structure for phosphorus (III) compounds.

If oxidized, P^{III} compounds form pentavalent phosphorus compounds (P^{V}), which then coordinate through the oxygen atom and not the phosphorous atom any more. With oxygen being a 'harder' atom, a more labile system would be created on coordination with Pd for example, which for purposes of stabilizing Pd^0 through the P atom would be compromised. Phosphorus-Carbon (P-C) bond cleavage in tertiary phosphines ligands has mainly been reported in hydrogenation and hydroformylation reactions where a shift towards more stable bulky phosphite ligands as early as the late 60s has been reported as a way of curbing this.[166,167]

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[164] J. H. Downing, M. B. Smith, Phosphorus Ligands, Loughborough University, UK, pg 253.

[165] D. E. C. Corbridge, Phosphorus. An Outline of its Chemistry, Biochemistry and Technology, Elsevier Science Publishers, Amsterdam, **1990**, pg 886.

[166] P. E. Garrou, *Chem. Rev*. **1985**, *85*, 165.

[167] P. W. N. M. Leeuwen, C. Claver, Rhodium Catalyzed Hydroformylation, Kluwer Academic Publishers, Netherlands, **2000**, pg 7.

It has been demonstrated by Pacchioni *et al*. in their study of $P(CH_3)_3$, PH_3, $P(OCH_3)_3$ and PF_3 ligands that although the degree of basicity changes, all ligands acted as both σ-donors and π- acceptors but the metal attached to them and surrounding ligands in a complex further affects their basicity and thereby the extent or dominance of their σ-donating and π- accepting abilities.[168] In a different study, a phosphoryl P-O bond, three models have been proposed to explain the interaction of orbitals between P and O (Figure 4.2).[165] The first model depicted, explained the two π-bonds to be a result of a back donation from the oxygen lone pairs into the σ^*-acceptor orbitals on phosphorus (Figure 4.2 left). Molecular modeling studies, however, were in support of the Ω-model (middle) and triple back bonding (right) models (Figure 4.2).

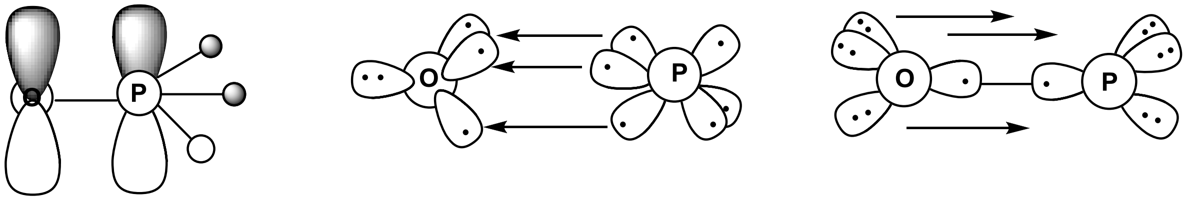

Figure 4.2: Phosphoryl PO bond models; π-backbond (left), Ω-model (middle), triple back bond (right).

A more practical approach to 'measure' phosphorus as a π-acceptor or σ-donor has been through infra-red (IR) spectroscopy using carbon monoxide metal complexes of nickel and chromium.[169] Since CO is known to be a strong 'back donating' molecule with metals, it has often been used to determine the effect that other ligands might have on the metal centre. Lower IR stretching frequencies indicate a stronger CO back donation to the metal, which suggests that electron density is directed towards the metal from the phosphorus or other ligand (σ donor).[169] High IR frequencies therefore indicate a reduced electron density at the metal centre, a consequence of weak 'back donation', indicating that electron density is directed towards phosphorus which now acts as a π acceptor. Organophosphites, as π acceptors, can form stable complexes with transition metal complexes as well as use their σ donor abilities to form stable complexes with high valent metals. In the case of lower valent metals, phosphites still show strong bonding.

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[168] G. Pacchioni, P. S. Bagus, *Inorg. Chem*., **1992**, *31*, 4391.

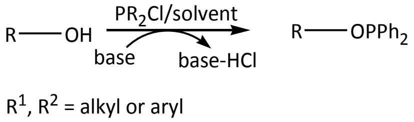
[169] P. W. N. M. Leeuwen, Homogenous Catalysis: Understanding the Art, Kluwer Academic Publishers, Netherlands, **2004**, pg 11.

This property has led to conclusions that the σ^*-orbitals of carbon, in phosphorus-carbon compounds (phosphines), and oxygen in phosphorus-oxygen compounds (phosphites), might be acting as π acceptors on the phosphorus atom.[169] The coordination chemistry of phosphorus-palladium complexes is diverse and it includes *mono*- or *bis*- compounds, *mono*- or dimeric palladacycles and heteroligand systems that encompass our ligands of interest, phosphinites and phosphite molecules.

4.1.2 Phosphinites and Phosphites

4.1.2.1 *Mono*- and b*is*phosphinites

In general, monophosphinites (PR_2OR) can be prepared by reacting alcohols (R-OH, R = any alkyl or aryl group) with phosphorus compounds bearing a leaving group. Commonly used for this purpose is chlorodialkylphosphines (PR_2Cl) which is reacted with the alcohol in the presence of bases such as pyridine/dmap (N,N-dimethylaminopyridine) or triethylamine in THF or toluene (Schemes 4.1) under rigorously dry and inert conditions.[170,171,172]



Scheme 4.1: Synthesis of phosphinites from alcohols.

Using the same approach, *bis*alkyl/aryl-, heteroamino- or diaminophosphinites (X = O, Y = NR) can be obtained by reacting the glycol, 1,2-aminoalcohol or 1,2-diamine, respectively, with the phosphorous(III) electrophile (Scheme 4.2).[173]

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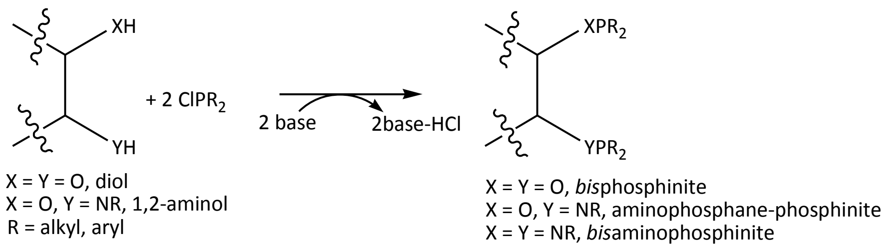
[170] R. B. Bedford, S. L. Samantha, M. E. Limmert, *Organometallics*, **2003**, *22*, 1364.

[171] I. Pryjomska, H. Bartosz-Bechowski, Z. Ciunik, A. M. Treciak, *J. Ziółkowski*, **2006**, 213.

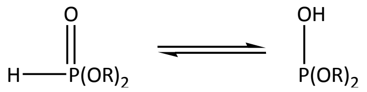
[172] P. Bergamini, V. Bertalasi, M. Cattabriga, V. Ferretti, U. Loprieno, N. Mantovani, L. Marvelli, *Eur. J. Org. Chem.*, **2003**, 918.

[173] P. Bergamini, V. Bertalasi, F. Milani, *Eur. J. Org. Chem.*, **2004**, 1277.



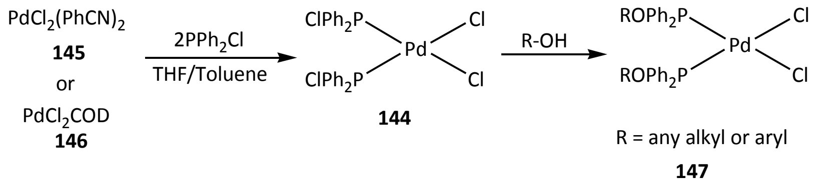
Scheme 4.2: Different types of 1,2-*bis*phosphorus/amine compounds.

The preparation of phosphinites is not as facile as demonstrated in the schemes above because it is often met with hydrolysis even under the most stringent of measures in keeping to anhydrous conditions. Oxidation of P^{III} to multiple P^{V} species has been reported in that regard, and these species are often detected as hydrogen phosphonates, existing in two tautomeric forms as depicted below (Scheme 4.3).[171,173]



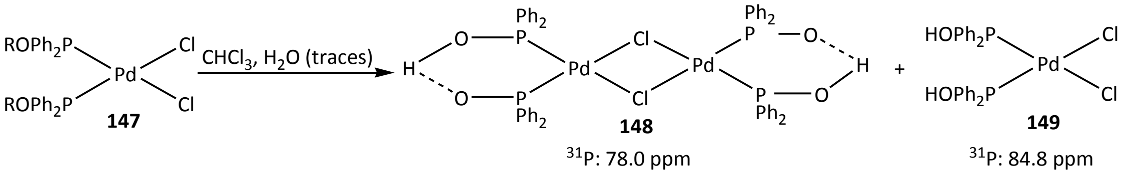
Scheme 4.3: A tautomeric form of a P^{v} species, hydrogen phosphate from a hydrolyzed P^{III}.

These challenges led to the exploration of the ease of the reaction between phosphorous electrophiles and nucleohpiles in the preparation of phosphinites enroute to their Pd complexes and entail the *in situ* displacement of the chlorides from the phosphorous atoms, which is already bound to palladium chloride. $PdCl_2(PPh_2Cl)_2$ **144** would be first generated from a typical Pd source such as $PdCl_2(PhCN)_2$ **145** or $PdCl_2COD$ **146** and PPh_2Cl and its formation confirmed by a disappearance of the PPh_2Cl signal (δ_P 82.5 ppm) and the appearance of a new signal at δ_P 96.0 ppm in the ^{31}P NMR spectrum (Scheme 4.4).[172,173]



Scheme 4.4: Preparation of Pd phosphinites *via* $PdCl_2(PPh_2Cl)_2$ **144**.

This approach, however, is also prone to hydrolysis even if only trace amounts of water is present and leads to dimeric chlorobridged species [μ-ClPd(PPh_2OH)(PPh_2O)]$_2$ **148** (Scheme 4.5), detectable by a ^{31}P NMR signal at δ_P 78.0 ppm, and in some instances, a palladium phosphinic acid $PdCl_2[PPh_2(OH)]_2$ **149** (δ_P 84.8 ppm) (Scheme 4.5).[171,172]

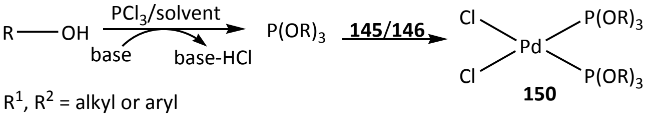


Scheme 4.5: Hydrolysis of Pd phosphinites in trace amounts of water.

Once successfully formed, Pd phosphinite complexes are, however, reported to be stable compounds that could be handled in air and left in solutions for days without evidence of hydrolysis or any decomposition.[171,172,173]

4.1.2.2 *Mono*- and *bis*phosphites

In order to have three alkoxy groups attached to the phosphorous atom, a different phosphorus source *i.e.* PCl_3 is generally employed. Under conditions similar to those described for the phosphinite preparation (Scheme 4.6), phosphites can be prepared when treating PCl_3 with three moles of alcohol. Subsequent reaction of the phosphite with $PdCl_2(PhCN)_2$ **145** or the palladium dichloride-COD complex **146** would lead to the desired Pd phosphite complex **150** (Scheme 4.6).



Scheme 4.6: Preparation of phosphites and Pd complexes thereof.

Although more stable than phosphinites, phosphites are also prone to hydrolysis during the synthesis of their Pd complexes, so preparations are often carried out *in situ*.[171]

4.1.2.3 Palladacycles

A palladacycle is a type of organopalladium complex that involves coordination of at least one carbon atom as well as at least one heteroatomic donor atom of the same molecule to the metal (Figure 4.3).

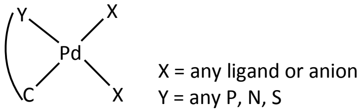
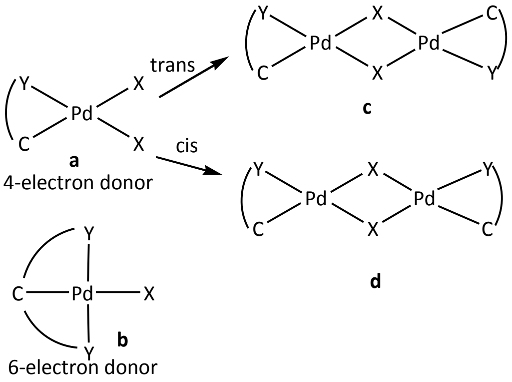


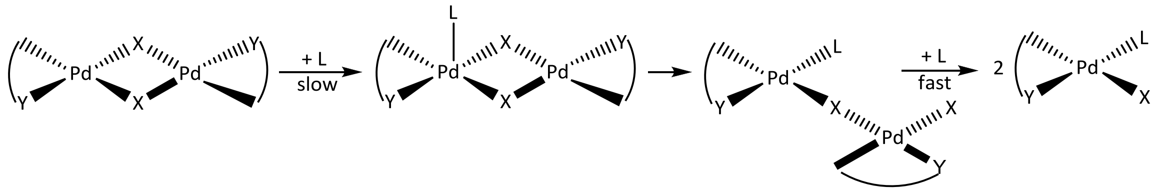
Figure 4.3: A typical palladacycle molecule.

Two types of palladacycles have been identified, that is, an anionic four donor species (Scheme 4.7, **a**) or a six-electron donor species (Scheme 4.7, **b**). The former can exist as a monomeric entity (Scheme 4.7, **a**) or dimeric (neutral) *bis*cyclopalladated species in *trans*-(**c**) or *cis*- (**d**) form (Scheme 4.7).



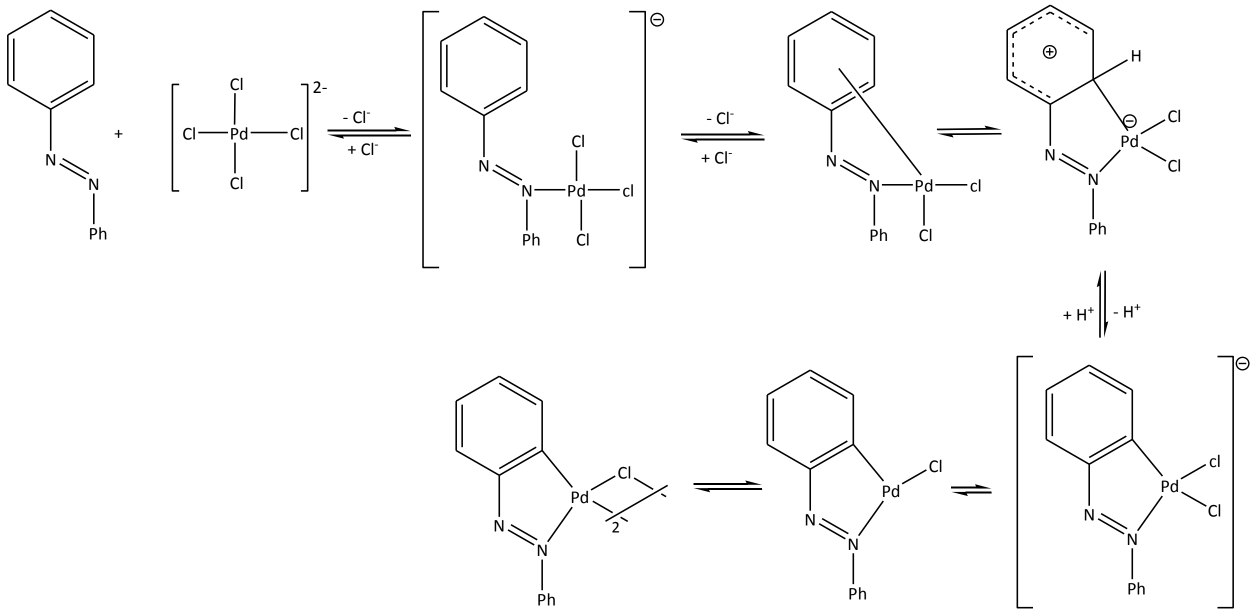
Scheme 4.7: Types of palladacycle; **a**) 4-electron donor, **b**) 6-electron donor, **c**) dimeric *trans*, **d**) dimeric *cis*

The dimeric palladacycle may exist as *cis*- or *trans*-isomers where the latter is the favoured crystalline form. The *trans*- ligand effect is more pronounced from the cyclometallated carbon than it is through the donor atom Y. During formation of a palladated monomer from an existing palladated dimer, an incoming ligand **L** (phosphine, pyridine) however, predominantly attacks *cis*- to the metallated carbon (Scheme 4.8).



Scheme 4.8: Proposed mechanism of a ligand (**L)** splitting a halo-bridged cyclopalladated species.

Palladacycles are accessible through a variety of methods, some of which include C-H bond activation or orthometallation, oxidative addition, and transmetallation.[174] During orthometallation, a tetra-chloropalladate salt with a base or palladium acetate with acetic acid is commonly used to generate the Pd-C bond. Although many mechanisms have been proposed, aromatic derivatives are generally formed *via* electrophilic aromatic substitution involving the aromatic ring and one of the chlorides on palladium followed by de-aromatization and finally elimination of hydrogen (Scheme 4.9).[174]



Scheme 4.9: Proposed mechanism for the cyclopalladation of aromatic compounds.

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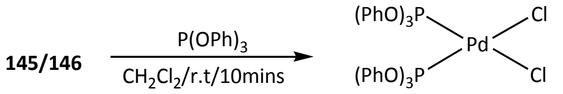
[174] J. Dupont C. S. Consorti, J. Spencer, *Chem. Rev.*, **2005**, *105*, 2527.

4.2 Synthesis and Characterization – Phosphite based palladium complexes

4.2.1 Synthesis

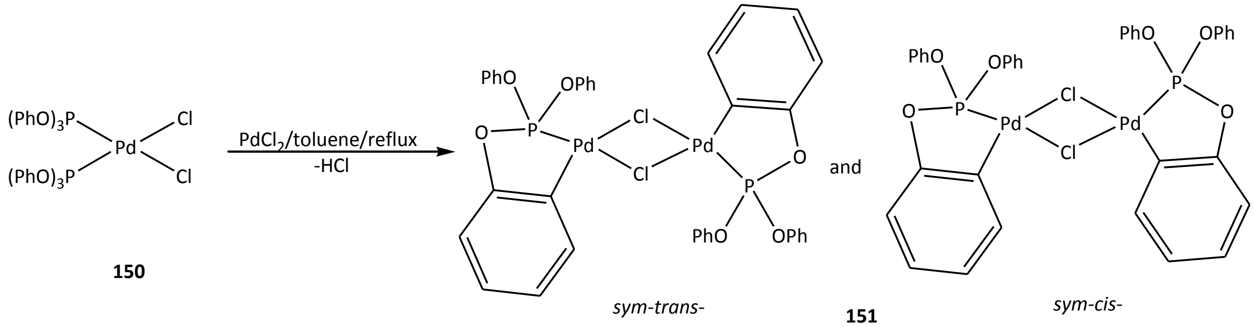
The basic phosphite palladium (II) dichloride complex ($PdCl_2[P(OPh)_3]_2$) **150** that was selected as starting point in the investigation of ligand bound palladium complexes as catalysts in the Wacker oxidation was prepared by Albinati before for utilization in other applications.[175] ($PdCl_2[P(OPh)_3]_2$) **150** was therefore prepared by reacting 2 equivalents of triphenylphosphite ($P(OPh)_3$) with *bis*(benzonitrile)palladium(II) dichloride ($PdCl_2(PhCN)_2$) **145** following Albinati's procedure or, alternatively, with **146** in CH_2Cl_2, affording **150** in 82 and 86% yield, respectively (Scheme 4.10).



150 82-86% yield

Scheme 4.10: Preparation of **150** *via* reaction of $PdCl_2(PhCN)_2$ **145** or $PdCl_2COD$ **146** with $P(OPh)_3$.

Proceeding from **150**, the cyclometallated dimeric species **151** was prepared by stirring under reflux a solution of **150** in toluene with 1 equivalent of $PdCl_2$ (Scheme 4.11), with a gentle purge of argon to drive off the HCl that was liberated.[175] The solution obtained was treated with hexane and afforded a mixture of cyclometallated dimeric isomers **151** as a pale yellow solid in 72% yield.



150

151
72% yield

Scheme 4.11: Synthesis of the dinuclear cyclopalladated Pd(II) complex **151** from **150**.

In the presence of coordinating ligands, a typical halo-bridged dinuclear Pd(II) complex such as **151** will break down into a mono-nuclear Pd(II) species.[175]

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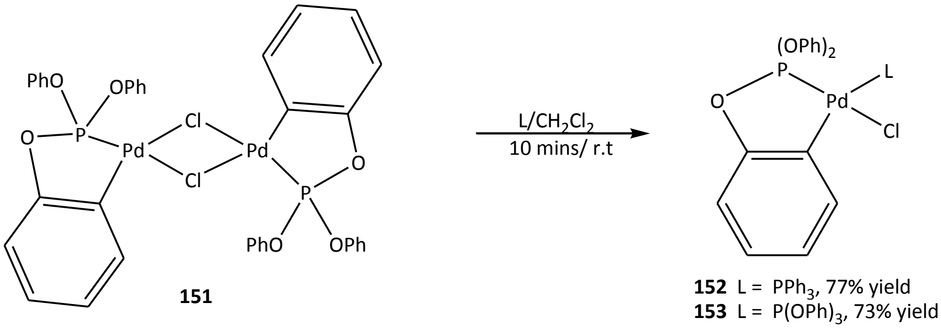
[175] A. Albinati, *Organometallics*, **1990**, *9*, 379.

Complexes **152** and **153** were thus prepared by treating a solution of **151** in CH_2Cl_2 with 2 moles of neat $P(OPh)_3$ or PPh_3 ligand and obtained in 77 and 73% yield, respectively. When DMA or H_2O was utilized as ligand, only starting material (complex **151**) could be recovered, even after extended reaction periods (5 hours) or stirring under reflux for 24 hours (Scheme 4.12).[176]

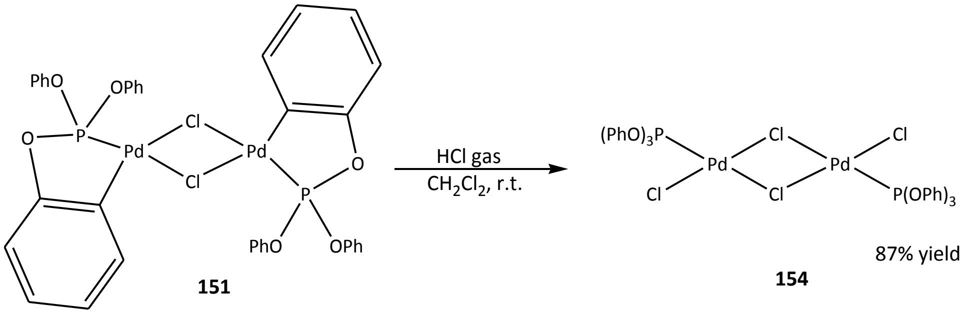


151

152 L = PPh_3, 77% yield
153 L = $P(OPh)_3$, 73% yield

Scheme 4.12: Synthesis of monocuclear cyclopalladated Pd(II) complex **152** and **153**.

The acyclic metallated dinuclear complex **154** was prepared by treating **151** with anhydrous HCl and was obtained as an orange solid in 87% yield (Scheme 4.13).[177]



151

87% yield

154

Scheme 4.13: Synthesis of dinuclear diphosphite complex **154**.

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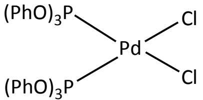
[176] R. B. Bedford, M. Betham, S. J. Coles, P. N. Horton, M. –J. López-Sáez, *Polyhedron*, **2006**, *25*, 1003.

[177] R. B. Bedford, S. L. Hazelwood, M. E. Limmert, D. A. Albisson, S. M. Draper, P. N. Scully, S. J. Coles, M. B. Hursthouse, *Chem. Eur. J.*, **2003**, *9*, 3216.

4.2.2 Characterization

The expected singlet in the ^{31}P NMR spectrum of the *cis-bis*triphenylphosphite palladium dichloride complex **150** (Figure 4.4, Plate 7) appeared at δ_P 83.6 ppm in good comparison to the reported value of δ_P 83.7 ppm.

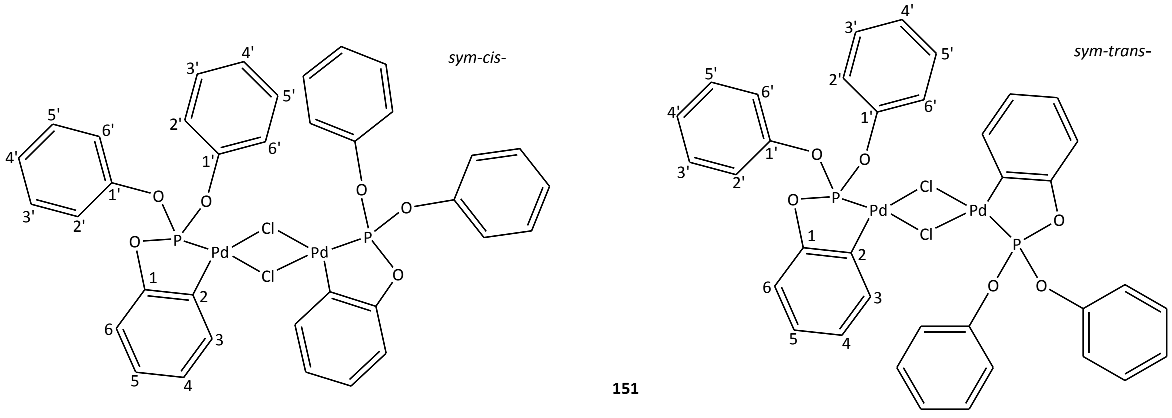


150

Figure 4.4: $PdCl_2[P(OPh)_3]$ **150**.

The 'free' $P(OPh)_3$ that has a ^{31}P NMR signal which typically resonates at δ_P 128.0 ppm as determined from an authentic sample, was not present in the spectrum of **150**. Two overlapping multiplets [δ_{1H} 7.33-7.20 (18H) and 7.17-7.15 ppm (12H)] in the ^1H NMR spectrum of *cis*-$PdCl_2(P(OPh)_3)_2$ **150** (Plate 8), integrated for the expected number of aromatic protons. The four carbon signals at δ_C 150.5, 130.0, 125.9 and 120.7 ppm in the ^{13}C NMR spectrum (Plate 9) were in regions similar to that reported in literature, giving further credence to the allocated structure.[175]

The ^{31}P NMR spectrum of the dinuclear palladacycles **151** (Figure 4.5, Plate 10) had two broad signals at δ_P 125.2, 122.9 ppm, indicative of a *cis-trans* mixture of **151** in a 7:3 ratio, the downfield signal of the two being the most dominant.



151

Figure 4.5: Cyclometallated (C1-C6) and uncyclometallated (C1'-C6') structures of *sym-cis* and *sym-trans-* **151**.

These signals were also similar to those reported in literature (δ_P 124.6 and 122.3 ppm).[175] In the ^{1}H NMR spectrum of the *cis-trans* mixture of palladacycles **151** (Plate 11), two protons less, were expected in the aromatic region when compared to **150** due to cyclometallation of two of the aromatic rings. In accordance with this, the five multiplets observed collectively integrated for 28 protons.

Since cyclometallation 'destroyed' the element of symmetry in the aromatic ring involved in the metallacycle, carbons C-1 to C-6 gave six distinctly different signals in the ^{13}C NMR spectrum of **151** (Plate 12), while the carbons of the phenyl groups (C-1' to C-6') are still symmetrical resulting in four carbon resonances. The chemical shifts of the observed ten carbon resonances (Table 4.1) were furthermore in agreement with those reported by Albinati, with the lower field resonances of C-1 to C-4 relative to that of C-1' to C-6' giving further credence to the presence of a palladacycle that allows the metal to deshield these carbons through the inductive effect.[175] Broad ^{13}C signals were also observed for most carbon atoms except C-1 (155.7 and 155.4 ppm) and C-6 (111.4 and 111.2 ppm); these indicated the presence of isomers but because of overlapping, these signals could not be assigned to the major and minor products. The structures of *sym-cis* and *sym-trans*-**151** were unambiguously confirmed by MS (EI) where the expected *m/z* value of 901.1 [M$^+$, 46.4%] was detected.

Table 4.1: ^{13}C NMR chemical shifts of carbon atoms of the *sym-trans* and *sym-cis* **151**.

Carbon	δ_c (CDCl$_3$)	
	Isomer **a**	Isomer **b**
C-1	155.7	155.4
C-2	133.1 (broad)	
C-3	136.8 (broad)	
C-4	123.2 (broad)	
C-5	127.8 (broad)	
Carbon	Isomer **a**	Isomer b
C-6	111.4	111.2
C-1'	149.4 (broad)	
C-2'	121.7 (broad)	
	129.9 (broad)	
C-4'	126.3 (broad)	

The ^{31}P NMR spectrum of mononuclear palladacycle **152** (Plate 13) confirmed the two expected phosphorous signals in the regions typical for phosphites (δ_P 129.9 ppm) and phosphines (δ_P 17.7 ppm) respectively and were similar to that previously reported for this compound (δ_P 129.9 and 17.8 ppm).[175] The 29 aromatic protons observed in the ^{1}H NMR spectrum of **152** (Plate 14) (Figure 4.6) confirmed successful coordination of the PPh$_3$ ligand to the palladium. Since the ^{1}H NMR spectrum displayed a one proton multiplet at a relatively far downfield position (δ_H 8.49-8.44 ppm), it could be concluded that the metallacycle remained intact and that the remaining chloride attached to the palladium was orientated towards the ring associated with the metallacycle as this proton experiences the strongest deshielding effect due to the Cl-ligand close by.[175]

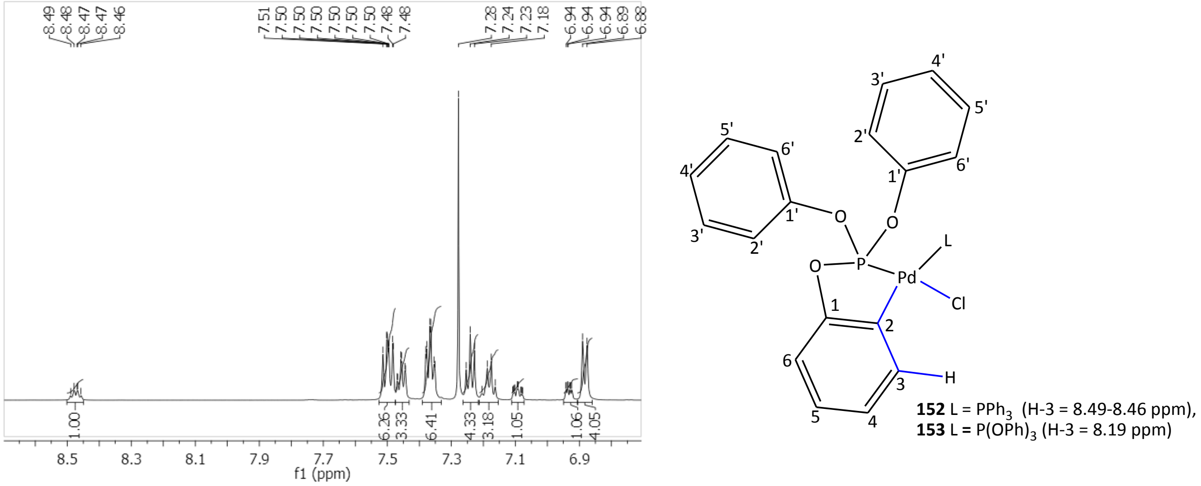


Figure 4.6: ^{1}H NMR spectrum of **152**.

The ^{13}C NMR spectrum of **152** (Plate 15) displayed the expected four carbon signals originating from the PPh$_3$ moiety as well as the six carbon atoms from the cyclometallated ring (C-1 to C-6) and another four from the phenoxy rings (C-1' to C-6'). These signals, with the most downfield one from C-1 (δ_C 156.2 ppm), were in good agreement with those reported for the same compound.[175] 2D NMR experiments (COSY, NOESY, HMQC, HMBC, Plate 16-19) enabled carbon - proton correlations and thus assignment of carbon atoms to resonances in the spectrum of **152**.

The ^{31}P NMR spectrum of **153** (Plate 20) on the other hand displayed two phosphorous signals at δ_P 128.4 and 109.6 ppm as expected for the two different P moieties present, with the phosphorous of the coordinated phosphite resonating upfield from the orthometallated [P(OPh)$_2$O] moiety in accordance with a study by Stewart *et al*.[178]

The ^{1}H NMR spectrum of **153** (Plate 21) showed a close resemblance to that of **152** and also displayed the expected number of protons (29) in the aromatic region with the signal from H-3 (δ_H 8.22-8.19 ppm) slightly upfield to the one in the spectrum of **151** (δ_H 8.21-8.17 ppm). The expected 14 carbon resonances in the ^{13}C NMR spectrum of **153** (Plate 22) were also observed. Similar to that in **152** (δ_C 156.2), the most downfield carbon signal (δ_C 156.7 ppm) in the spectrum of **153** could again be allocated to H-3. 2D NMR experiments (COSY, HMQC, HMBC, Plates 23-26) again allowed for assignment resonances to carbon atoms, which were in good agreement to values reported in literature.[175]

Successful de-orthometallation of **151** to **154** (Figure 4.7) was supported by a phosphorous signal resonating upfield at δ_P 56.7 ppm in the ^{31}P NMR spectrum (Plate 27) of **154**, which is a value typical of *chloro*-bridged phosphites and different to δ_P 125.2 and 122.9 ppm observed for **151** and δ_P 83.6 ppm for **150**.[179] In the ^{1}H NMR spectrum (Plate 28) of **154**, two multiplets, integrating in a two to three ratio, appeared in the aromatic region (δ_H 7.40-7.37 and 7.28-7.29 ppm), while the ^{13}C NMR spectrum (Plate 29) contained four resonances (Table 4.2) confirming the presence of P(OPh)$_3$ rings. The chemical shift of the C-1 signal in the spectrum of **154** (δ_C 150.3 ppm) was almost identical to those of the equivalent carbon in the spectrum of **150** (δ_C 150.7 ppm) and very similar to that observed for the corresponding carbon (C-1’) in the non-metallated rings of **151** (δ_C 149.4 ppm), giving further credence to the absence of cyclometallation.

The chemical shift values of the remaining carbon resonances in the ^{13}C NMR spectrum of **153** were very close, but not identical to those of **150** (Table 4.2). Final confirmation of the dinuclear arrangement in the structure of **154** came from treatment with excess P(OPh)$_3$ which led to the formation of a complex having a signal at δ_P 83.6 ppm in the ^{31}P NMR spectrum identical to that obtained for **150**.

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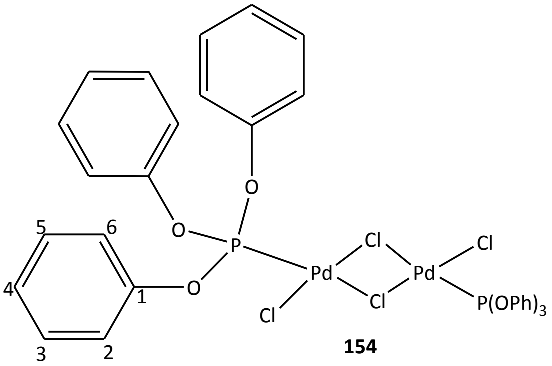
[178] R. P. Stewart, Jr., L. R. Isbrandt, J. J. Benedict, *Inorg.Chem.*, **1976**, *15*, 2011.

[179] R. B. Bedford, S. L. Hazelwood (néeWelch), M. E. Limmert, D. A. Albisson, S. M. Draper, P. N. Scully, S. J. Coles, M. B. Hursthouse, *Chem. Eur. J.*, **2003**, *9*, 3216.



154

Figure 4.7: De-orthometallated **151**.

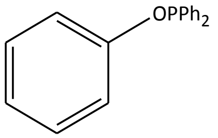
Table 4.2: ^{13}C NMR chemical shifts for uncyclometallated ring in **154** *versus* **151** and the cyclometallated **150**.

δ_c ($CDCl_3$) **150**	$\delta_{c'}$ ($CDCl_3$) **154**	$\delta_{c'}$ ($CDCl_3$) **151**
C-1 150.7	**C-1** 150.3	**C-1’** 149.4
C-2 121.0	**C-2** 120.6	**C-2’** 121.7
C-3 130.2	**C-3** 130.1	**C-3’** 129.9
C-4 126.4	**C-4** 126.2	**C-4’** 126.3

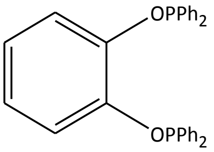
4.3 *Mono*- and *bis*phenylphosphinites

4.3.1 Direct Synthesis of *mono*- and *bis*phenylphosphinites

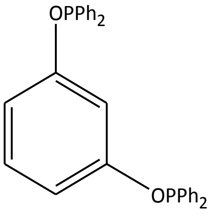
The investigation into phosphinite ligands was started with the preparation of phenoxydiphenylphosphine **155**, 1,2-*bis*(diphenylphosphinoxy)benzene **156**, and 1,3-*bis*(diphenylphosphinoxy)benzene **157** (Figure 4.8).



155



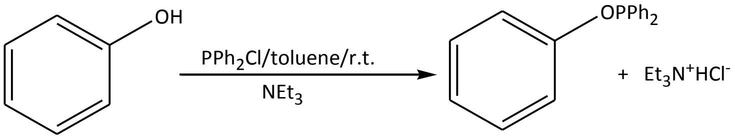
156



157

Figure 4.8: Phosphinite ligands **155**-**157** to be investigated.

Phosphinite **155** was prepared through the literature procedure of mixing a solution of phenol **158** in toluene with PPh_2Cl, followed by dropwise addition of triethylamine (NEt_3) in toluene at room temperature (Scheme 4.14).[180] The base facilitated the formation of $Et_3N^+HCl^-$, which could be filtered off and the solvent removed by distillation under reduced pressure leading to the crude product **155** in 119% yield.



158 **155**

Scheme 4.14: Preparation of phenoxydiphenylphosphine **155**.

The identity of the crude **155** was confirmed by ^{31}P NMR spectroscopy (Plate 30) where a distinct singlet at δ_H 110.5 ppm was observed in the spectrum. The proposed structure was further supported by mass spectrometry (EI), which displayed the molecular ion at *m/z* 278.10 (M^+ +1). All attempts to purify the product were, however, met with the formation of unidentified phosphorus compounds (^{31}P NMR), which was to be expected as purification of phosphinites are often avoided as they are prone to hydrolysis.[180,181] The crude product was therefore used as such in subsequent reactions (par. 4.3.2).

Milani *et al*. published the only existing report on the *in situ* synthesis of the palladium catechol-phosphinite **159**, which could be made from catechol **160** and a palladium intermediate, $PdCl_2[PPh_2Cl)_2$ **144**, generated from PPh_2Cl and a palladium-COD complex **145** (Scheme 4.15).[182]

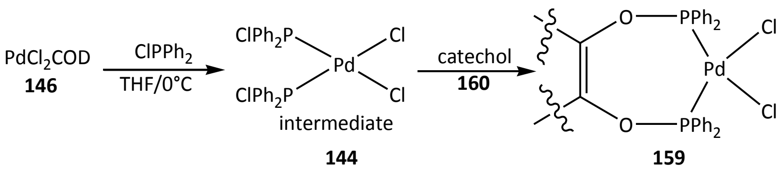
From ^{31}P NMR studies of the reaction mixture, the phosphorous atoms of **156** and the Pd-complex thereof, **159,** resonates at δ_P 114.1 and 122.0 ppm, respectively.

---

[180] R. B. Bedford, S. L. Hazelwood, P. N. Horton, M. B. Hursthouse, *Dalton Trans.*, **2003**, 4157.

[181] B. H. G. Swennenhuis, R. Chen, P. W. N. M. Van Leeuwen, J. G. De Vries, P. C. J. Kramer, *Eur. J. Org. Chem.*, **2009**, 5796.

[182] P. Bergamini, V. Bertolasi, F. Milani, *Eur. J. Inorg. Chem.*, **2004**, 1277.



Scheme 4.15: Preparation of Pd-complex **159** *via* $PdCl_2(PPh_2Cl)_2$.

Although intermediate **144** could be generated successfully as a yellow solid in 91% yield [^{31}P NMR signal at δ_P 95.3 ppm *vs* lit.[182] 96 ppm and ^1H NMR] by utilizing Milani's protocol, addition of catechol **160** to the reaction mixture led to the formation of multiple unidentified phosphorus compounds as was evident from several signals in the ^{31}P NMR specrum as well as resonances at δ_P 114.0 and 122.1 ppm attributable to **156** and **159**, respectively. Attempts to purify and isolate **159** all failed.

As the ultimate goal was to prepare **159**, an alternative approach of first generating **156** by using the methodology applied to the preparation of **155** (Scheme 4.13), was followed. Unfortunately, even after 48 hours of reaction time only a very small signal indicative of the formation of **156** (δ_P 114.0 ppm) could be detected by ^{31}P NMR. The desired resonance was accompanied by signals from other unknown phosphorus adducts between δ_P 35 and -35 ppm which are typical of P^v species resulting from the oxidation of PPh_2Cl.[182] Longer reaction times led to even more of these unwanted phosphorus adducts being formed. In an attempt to improve on the reaction procedure and obtain workable quantities of the product, a method reported by Zhang *et al*. for the preparation of arylphosphinites[183] was subsequently investigated and different bases, *i.e.* NaH, 2,6-lutidine, K_2CO_3 and pyridine/dimethylaminopyridine (DMAP), added to the reaction mixture, but only catalytic quantities of

DMAP in pyridine at 0°C led to the formation of the desired product after 24 hours of reaction time. Since the pyridine took several hours to remove through a vacuum distillation process, trace amounts of water present in the system reduced the yield of the phosphinite **155** through the formation of its oxide (as determined by ^{31}P NMR), dramatically. Changing the base to NEt_3 and using toluene as solvent with drop-wise addition of a mixture of catechol and NEt_3 in toluene to PPh_2Cl in toluene at 0°C (Scheme 4.16), however, led to the formation of appreciable quantities of the product without any decomposition to P^v adducts.

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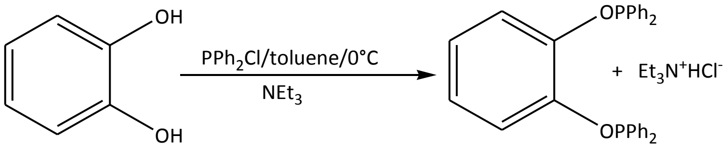
[183] G. Zhu, X. Zhang, *J. Org. Chem*., **1998**, *63*, 3133.

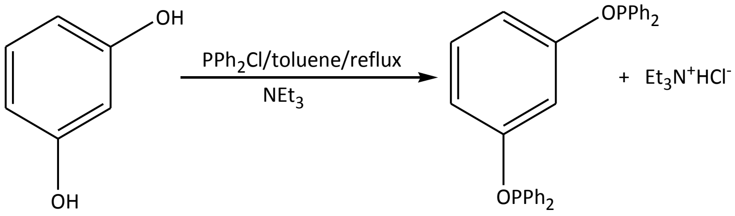


160 **156**

Scheme 4.16: Preparation of 1,2-*bis*(diphenylphosphinoxy)benzene **156** from catechol and PPh_2Cl.

Apart from the signal at δ_P 114.0 ppm in the ^{31}P NMR spectrum (Plate 31), the structure of the product was confirmed to be **156** by MS (EI) as a molecular ion with *m/z* 477 (M^+) could be observed (Table 4.3). This crude product (99% yield) was also used in subsequent steps without further purification, except for filtering off of the triethylammonium chloride salt.

Since the preparation of the resorcinol phosphinite **157** was reported to involve the stirring of resorcinol **161** and PPh_2Cl in toluene with drop-wise addition of NEt_3 followed by refluxing the solution for 18 hours, this method was utilized as first attempt towards the preparation of **157** (Scheme 4.17).[184]



161 **157**

Scheme 4.17: Preparation of 1,3-*bis*(diphenylphosphinoxy)benzene **157** from resorcinol and PPh_2Cl.

Due to the low solubility of resorcinol in toluene, the procedure was changed to mixing of the resorcinol and PPh_2Cl in toluene before the mixture was brought to reflux and the NEt_3 added. The ^{31}P NMR spectrum of the reaction mixture, however, showed one distinct singlet at δ_P 111.0 ppm (Plate 32), in the same region as the reported literature value of 111.2 ppm.[185]

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[184] R. B. Bedford, S. M. Draper, P. N. Scully, S. L. Welch, *New J. Chem.*, **2000**, *24*, 745.

[185] R. B Bedford, M. Betham, M. E. Blake, S. J. Coles, S. M. Draper, M. B. Hursthouse, P. N. Scully, *Inorg. Chim. Acta*, **2006**, *359*, 1870.

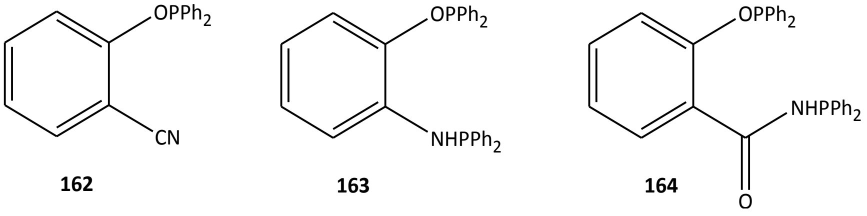
Athough a clean ^{1}H NMR spectrum (Plate 33) of resorcinol phosphinite **157** could not be obtained, the major triphenylphosphine peaks integrated for ca 24 protons, indicating that at least a bi-substituted compound was formed. Mass spectrometric analysis (EI) of the reaction mixture showed a molecular ion at *m/z* 477 indicating the presence of at least some of the correct product **157** (Table 4.3).

Table 4.3: MS (EI) and ^{31}P NMR values of ligands **155**-**157**.

Phosphinites	***m/z* (EI)**	**^{31}P NMR (δ ppm)**
155	278 (M^{+} +1, 39%), 277 (M^{+}, 100%)	110.5
156	477 (M^{+}, 30%)	114.0
157	477 (M^{+}, 54%)	111.2

4.3.2 Heteroamino phosphinites

In order to investigate the electronic effects of hetero-bidentate 1,2-ligands in the Wacker oxidation, it was decided to introduce a nitrogen functionality into the 2-position of the phosphinite type ligands and evaluate the catalytic properties of these compounds. In this regard compounds such as 2-(diphenylphosphinoxy)benzonitrile **162**, 1-(N-diphenylphosphino)-2-(diphenylphosphinoxy)aniline **163** and *N*-(diphenylphosphino)-2-(diphenylphosphinoxy)benzamide **164** were selected as target ligands to be evaluated (Figure 4.9).

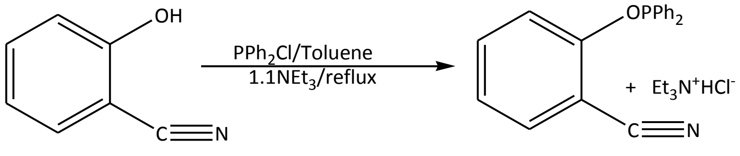


162 **163** **164**

Figure 4.9: 2-(diphenylphosphinoxy)benzonitrile **162**, 1-(N-diphenylphosphino)-2-(diphenylphosphinoxy)aniline **163** and *N*-(diphenylphosphino)-2-(diphenylphosphinoxy)benzamide **164**.

Since literature references to the synthesis of these compounds could not be found, it was decided to apply the methods utilized for the preparation of **155**-**157** as first attempt towards the synthesis thereof. With regard to **162**, an upfield signal in the phosphinite region to δ_P 115.7 ppm and some P^{v} adducts in the ^{31}P NMR spectrum of the reaction mixture was only observed when 1 equivalent of

PPh_2Cl in toluene was added to a stirred solution of 2-hydroxybenzonitrile **165** and NEt_3 in toluene and the mixture heated under reflux (Scheme 4.18).

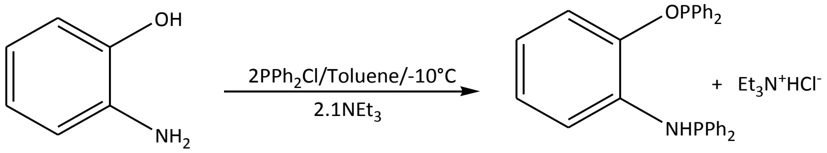


165 **162**

Scheme 4.18: Reaction of 2-hydroxybenzonitrile with PPh_2Cl and NEt_3 in toluene.

This was assigned to the phosphinite moiety. The Maldi-TOF MS spectrum of the reaction mixture, however, did not give any indication of the expected molecular ion (*m/z* 303). An ion with *m/z* 490 was observed instead, which indicated a possible second PPh_2 moiety to be attached to the substrate. In an attempt to prevent this and the formation of P^V adducts, different methods of combining the reagents as well as changes to the reaction temperature, were investigated. Finally, a stirred mixture of PPh_2Cl in toluene at 40°C which was treated with a mixture of **165** and NEt_3 in toluene and the resulting mixture refluxed for four hours afforded the desired product **162** [singlet at δ_P 115.7 ppm in the ^{31}P NMR spectrum (Plate 34), with no indication of P^V adducts.

The method used in the synthesis of the catechol phosphinite **156** was successfully applied to the convertion of 2-aminophenol **173** into its phosphinite-aminophosphinite product **163** only at -10°C (Scheme 4.19).

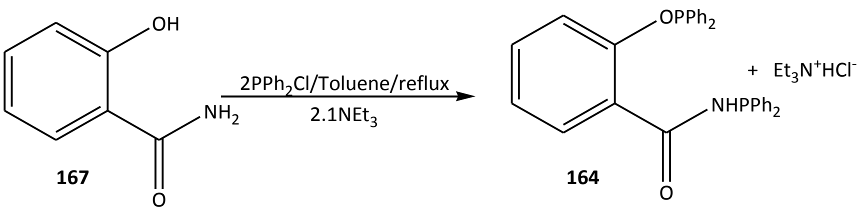


166 **163**

Scheme 4.19: Reaction of 2-aminophenol **166** with PPh_2Cl and NEt_3 in toluene.

This approach resulted in two signals being observed in the phosphinite region at δ_P 115.5 and 26.5 ppm in the ^{31}P NMR spectrum (Plate 35) of the product.

Finally the phosphination of **167** was attempted by reacting it with 2 equivalents of PPh_2Cl and NEt_3 in toluene with salicylamide under reflux conditions (Scheme 4.20).



Scheme 4.20: Reaction of salicylamide **167** with PPh_2Cl and NEt_3.

Phosphorous signals at δ_P 116.2 and 24.9 ppm (Table 4.4) in the ^{31}P NMR spectrum (Plate 36) of the reaction mixture indicated the formation of the desired amidophosphinite, with the latter signal being assigned to the amidophosphino moiety.[186]

Table 4.4: ^{31}P NMR values of ligands **162-164**.

Phosphinites	**^{31}P NMR (ppm)**
162	115.8
163	115.5, 26.5
164	116.3, 24.9

As mentioned before, none of the phosphinites could be purified and were therefore reacted with Pd immediately in order to avoid decomposition to the corresponding oxides. This proved to be a tedious exercise since the preparation of phosphinites **155**-**157** and **162**-**164** were difficult to control and often not reproducible. In an attempt to circumvent these problems, it was decided to resort to a protection/deprotection strategy in order to allow for purification and longer storage without decomposition of the protected phosphinites and do the deprotection as needed just before utilization in the Pd catalyst preparation.

4.3.3 Protection as boranes: Synthesis of Phosphinite boranes

Two routes for protection of phosphines, *i.e.* by formation of the borane complexes with either BH_3-THF or $BH_3{\cdot}SMe_2$ or conversion into phosphorus-oxides with H_2O_2 (Scheme 4.21) have found general application in the synthesis of various phosphorous based compounds.[187,188,189]

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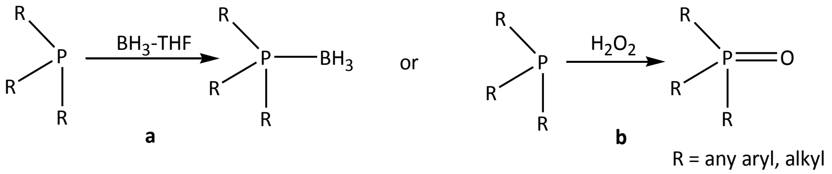
[186] A. Roucoux, L. Thieffry, J.-F. Carpentier, M. Devocelle, C. Me´liet, F. Agbossou, A. Mortreux, *Organometallics* **1996**, *15,* 2440.



Scheme 4.21: Protection of phosphorus (III) compounds *via* boranes (**a**) or by oxide formation (**b**).

Once formed, borane complexes are stable towards purification by column chromatography and the borohydride can be removed through treatment with secondary amines such as morpholine, diethylamine or DABCO or, as reported by Eycken *et al.*, by heating the complexes under reflux in ethanol.[190,191,192]

Phosphinites **155**-**157** and **162**-**164** in toluene were thus treated with a slight excess (1.5 eq.) of a $BH_3{\cdot}SMe_2$ solution at room temperature (Scheme 4.24) and the reaction monitored by ^{31}P NMR to completion, upon which the excess borane was destroyed with methanol. Purification was carried out on TLC with mixtures of ethyl acetate:hexane (V/V). A broadening of the original phosphinite signal or slightly shifted broad signal was taken as indication of the successful synthesis of the protected phosphinites.[188]

4.3.3.1 Characterization of boranes derivatives by NMR and MS (EI)

Borane protection of **155** with of $BH_3{\cdot}SMe_2$ solution (1.5 eq.) at room temperature gave **168** as a white solid in 73% yield (Scheme 4.22).

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[187] T. Imamoto, T. Oshiki, T. Onazawaj, T. Kusmoto, K. Sato, *J. Am. Chem. Soc.*, **1990**, *112*, 5244.

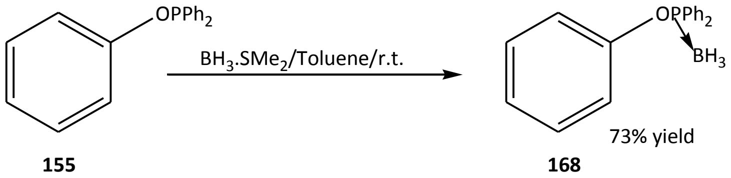
[188] G. Keglevich, H. Szelke, A. Kerényi, T. Imre, K. Ludányi, J. Dukai, F. Nagy, P. Arányi, *Heteroatom Chemistry*, **2004**, *15*, 459.

[189] Ö. Sarıöza, O. Serindaĝb, M. İ. Abdullaha, *Phosphorus, Sulfur, and Silicon*, **2009**, *184*, 1785.

[190] L. Palais, I.S. Mikhel, C. Bournaud, L. Micouin, C. A. Falciola, M. Vuagnoux-d Augustin, S. Rosset, G. Bernardinelli, A. Alexakis, *Angew. Chem.*, **2007**, *119*, 7606.

[191] A.Grabulosa, J. Granell, G. Muller, *Coord. Chem. Rev.*, **2007**, *251*, 25.

[192] M. Van Overschelde, E. Vervecken, S. G. Modha, S. Cogen, E. Van der Eycken, J. Van der Eycken, *Tetrahedron*, **2009**, *65*, 6410.



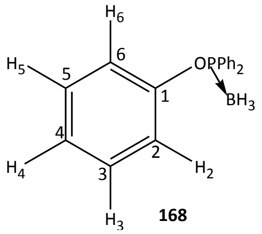
Scheme 4.22: Borane protection of **155** with $BH_3{\cdot}SMe_2$.

In the ^{31}P NMR spectrum of **168** (Plate 37), the broad phosphorous signal resonated slightly up-field to that observed for **155** (δ_P 107.2 *versus* 110 ppm, Plate 30).

The ^1H NMR spectra of all the borane protected phosphinites were expected to have a multiplet originating from the BH_3 moiety between δ_H 0.8 and 1.29 ppm, integrating for either three for *mono*- or six for *bis*-borane protected compounds. As such, the multiplet observed between δ_H 1.29 and 0.87 ppm in the ^1H NMR spectrum of **168** (Plate 38) provided further evidence of a BH_3 group in support of the ^{31}P NMR.

The ten protons expected in the aromatic region were observed as three sets of multiplets at δ_H 7.90-7.86, 7.59-7.57 and 7.53-7.52 ppm (Plate 38), integrating for four, two and four protons respectively. The 'core' phenyl ring structure was furthermore confirmed by the presence of a doublet of doublets at δ_H 7.26 ppm integrating for two protons, a multiplet integrating for one proton at δ_H 7.15-7.13 ppm and another multiplet at δ_H 7.05-7.04 ppm integrating for two protons, thus making up the total number of the five expected protons. The seven ^{13}C NMR signals (Plate 39) supported the proton assignments of a symmetrical molecule. 2D COSY, NOESY, HMQC and HMBC experiments (Plate 40-43) allowed assignment of the proton and carbon atoms of the core ring structure (Table 4.5).

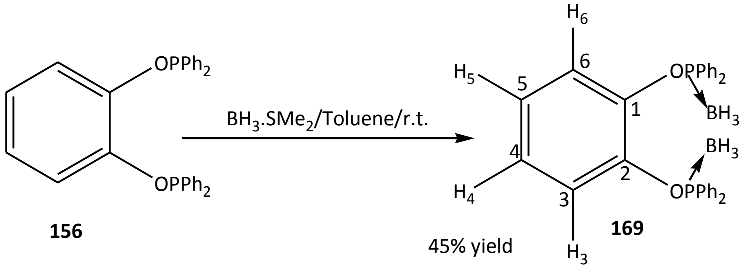
Table 4.5: ^1H and ^{13}C chemical shifts of 168 in $CDCl_3$ (600 MHz).



168

^1H NMR (δ_H, ppm)	^{13}C NMR (δ_C, ppm)
7.05-7.04 (2H, m, H-2, H-6)	121.1 (C-2, C-6)
7.15-7.13 (1H, m, H-4)	124.7 (C-4)
7.28-7.25 (2H, m, H-3, H-5)	129.3 (C-3, C-5)
7.53-7.52 (4H, m, Ar-H)	128.6
7.59-7.57 (2H, m, Ar-H)	132.2
7.90-7.86 (4H, m, Ar-H)	131.5
	152.3 (C-1)

Extending borane protection (reaction with $BH_3{\cdot}SMe_2$) to the pure catechol phosphinite **156** led to the isolation of the protected phosphinite **169** as a white solid (Scheme 4.23).

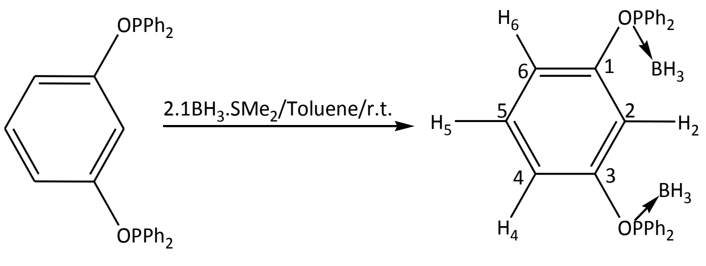


Scheme 4.23: Protection of **156** with $BH_3{\cdot}SMe_2$.

A broad signal at δ_P 114.0 ppm in the ^{31}P NMR spectrum (Plate 44) was accepted as indication that borane was attached to the phosphinite **156**. Confirmation of two borane groups present in molecule **169** came from the ^{1}H NMR spectrum (Plate 45) where the multiplet at δ_H 1.29-0.87 ppm integrated for six protons compared to resonances from twenty protons at δ_H 7.79-7.76, 7.53-7.51 and 7.40-7.38; originating from the two PPh_2O- moieties and another four protons at δ_H 7.01-6.99 and 6.94-6.92 ppm belonging to the 'core' catechol ring.

The structure of the product was further confirmed by ^{13}C NMR spectroscopy where seven carbon signals, three from the core ring and four from the phosphinite rings, were evident in the spectrum (Plate 46).

Reaction of the resorcinol phosphinite **157** with $BH_3{\cdot}SMe_2$ (Scheme 4.24) afforded a product **170** in 74% yield with a broad signal at δ_P 111.3 ppm in the ^{31}P NMR spectrum (Plate 47) indicative of successful protection of the phosphorous entity in the molecule.

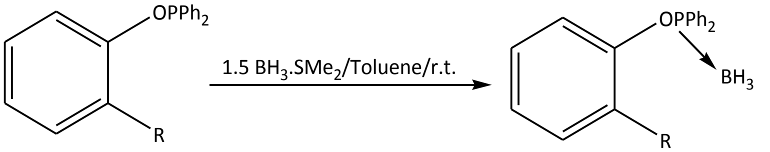


157 **170**

Scheme 4.24: Borane protection of **157** $BH_3{\cdot}SMe_2$.

The expected six proton- multiplet in the borane region of the ^{1}H NMR spectrum of **170** (Plate 48) was accompanied by signals from twenty protons from the PPh_2O- groups (δ_H 7.79-7.77, 7.56-7.55 and 7.50-7.49; as well as three multiplets from the four protons attached to the resorcinol ring (δ_H 7.12-7.09, 6.83-6.81 and 6.79-6.78 ppm). The ^{13}C NMR spectrum (Plate 49) of **170** displayed eight carbon signals arising from the four resorcinol carbons, as well as the four symmetrical PPh_2O- carbons. The 2D COSY, NOESY, HMBC and HMQC and ^{13}C-DEPT corroborated these assignments (Plate 50-55). Final confirmation of the structure of **170** came from the MS (EI) spectrum where a molecular ion of *m/z* 506 (M^+ +1) was observed.

Borane protection of the nitrogen containing phosphinites, **162** and **163** by reaction with borane-dimethylsulfide complex was also successful and led to the isolation of the protected phosphinites **171** and **172** in 69 and 71 yields respectively (Schemes 4.25).



162 R = CN
163 R= $NHPPh_2$

171 R = CN, 69% yield
172 R = $NHP(BH_3)Ph_2$, 71% yield

Scheme 4.25: Borane protection of **162** and **163** by reaction with $BH_3{\cdot}SMe_2$.

The ^{31}P NMR spectra (Plates 56 and 63) of the two products (**171** and **172**) contained broad singlets at δ_P 109.8 (in the spectrum of **171**) and δ_P 113.4 and 53.3 ppm (in the spectrum of **172**) clearly indicating the presence of a single protected phosphorous atom in the case of **171** and a two protected different P-atoms for **172**. Protection of the phosphorous atoms in both compounds were confirmed by the typical borane multiplet at δ_H 1.29-0.86 ppm integrating for 3 and 6 hydrogens respectively in the ^{1}H NMR spectra (Table 4.6 and 4.7; Plates 57 and 64) of **171** and **172**. The 2D COSY, NOESY, HMBC and HMQC of both **171** (Plate 58-62) and 172 (Plate 65-69) further supported the proton assignments.

Table 4.6: ^{1}H and ^{13}C NMR assignments of the benzonitrile ring in **171**.

^{1}H NMR (δ_H, ppm) 171	**^{1}C NMR (δ_C, ppm) 171**	
7.11-7.08 (1H, m, H-3)	130.0 (C-3)	
6.62-5.59 (2H, m, H-4, H-5)	113.5 (C-4, C-5)	156.3 (C-2)
6.57-6.56 (1H, m, H-6)	108.7 (C-6)	153.1 (C-1)

Table 4.7: ^{1}H NMR assignments of **172**.

7.84-7.81 (4H, m, Ar-H)	6.91-6.89 (1H, m, H-4)
7.71-7.68 (4H, m, Ar-H)	6.80-6.76 (2H, m, H-5, H-6)
7.59-7.57 (2H, m, Ar-H)	6.71-6.68 (1H, m, H-3); 5.05 (1H, bs, N-H)
7.50-7.49 (6H, m, Ar-H)	
7.46-7.43 (4H, m, Ar-H)	

4.3.2.2 Deprotection of phosphinite boranes

Since the procedure reported by Eycken *et al*. seemed to be very mild, simple, and efficient, this approach was followed for the deprotection of **168**-**172**.[20] The borane protected phosphinites were therefore refluxed in ethanol, and only the ^{31}P NMR chemical shifts were recorded, indicating the smooth removal of the borane entity as was evident from broad borane signals to the original singlets in the phosphinte region.

While all of the reactions proceeded smoothly, removal of the residual borate salts from the reaction mixture proved to be problematic, although reported by the authors to be possible at higher temperature under vacuum. Even at temperatures of over 200°C, trace amounts of borate salts still seemed to be present as detected by Pd^{0} formation during a test reaction with PdCl$_2$COD. Despite several purification methods, 'fall-out' of Pd^{0} could not be prevented. Since Williams *et al*. reported that borate by-products from de-protection reactions can be extracted into an aqueous phase and the deprotected phosphorus compounds recovered in the organic layer,[193] This approach was subsequently followed in order get rid of the remaining borate salts.

As such, after de-protection of **168** by ethanol under reflux, the solvent was removed under reduced pressure and the residue taken up in ethyl acetate. Several washes with water appeared to be efficient in removing even trace amounts of borate as the recovered phosphinites could be used to further prepare palladium-phosphinite complexes without any evidence of Pd^0 formation.

4.4. Preparation of Palladium complexes

4.4.1 Palladium phosphinite complexes

Initial preparation of the palladium complexes of phosphinites **155** and **156** were attempted by adding a dichloromethane solution of the phosphinite-triethylammonium chloride mixture to a DCM solution of one of the common palladium complexes like $PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$ or $PdCl_2COD$[180] as was reported by Pryjomska *et al*.[171]

This approach led to the products co-precipitating with the triethylammonium hydrochloride salt. According to literature, this problem could be circumvented by taking the reaction mixtures up in an organic solvent and removing the salts through a water wash. Application of this method, however, led to multiple new phosphorous compounds being formed, as was evident from several additional signals in the ^{31}P NMR spectrum of the reaction mixture, and very small amounts of the desired products being obtained. Changing to the Bedford[194] approach, *i.e.* adding two moles of phosphinite **155** in dichloromethane to $PdCl_2(CH_3CN)_2$ in DCM and allowing the reaction mixture to stir for 1 hour, yielded an orange solid in 13% yield (Scheme 4.26).

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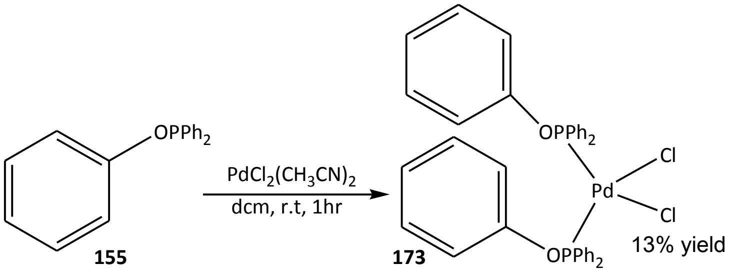
[193] D. B. G. Williams, H. Lombard, M. van Niekerk, P. P. Coetzee, C. W. Holzapfel, *Phosphorus, Sulfur and Silicon*, **2002**, *177*, 2799.

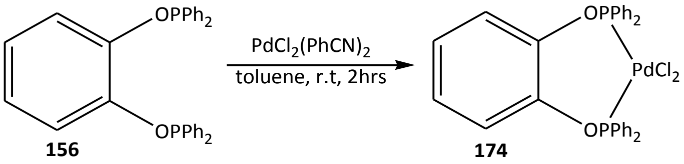
[194] R. B. Bedford, S. L. Hazelwood, M. E. Limmert, *Organometallics*, **2003**, *22*, 1364.



Scheme 4.26: Preparation of phenyl diphenylphosphinite palladium dichloride from phosphinite **155**.

The ^{31}P NMR spectrum (Plate 70) of this product displayed a resonance at δ_P 110.3 ppm. The ^{1}H NMR spectrum (Plate 71) of **173** had several multiplets between 7 and 6 ppm integrating for a total of 15 protons. This was expected because of the symmetry in the molecule leading to half the expected protons. Although the ^{1}H NMR pointed towards the proposed structure and in agreement with the literature values, the ^{31}P NMR was not well corroborated by the same source which reported a value of 101.1 ppm.[194]

The synthesis of **174** was subsequently attempted along the route used for **173**, so one equivalent of **156** in toluene was added to a stirred solution of $PdCl_2(PhCN)_2$ **145** in toluene (Scheme 4.27) and the reaction monitored by ^{31}P NMR.



Scheme 4.27: Synthesis of 1,2-*bis*(diphenylphosphinito)benzene palladium dichloride **174** from **156** and $PdCl_2(PhCN)_2$.

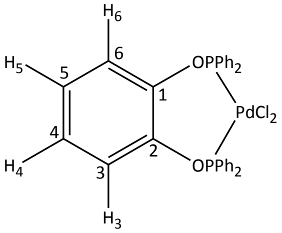
After one hour of reaction time, it was evident that the substrate was completely consumed (no signal at δ_P 114.0 ppm remaining) and a singlet at ca. δ_P 121.8 ppm was observed. Since the chemical shift of the 'new' resonance was different to those expected for the hydrolysis derived palladium dimer product **148** or, palladium phosphinic acid **149** (δ_P 78.0 ppm or δ_P 84.8 ppm respectively), and in agreement with the literature value, it was accepted that formation of the desired product was completed and the reaction was therefore stopped.

Isolating the product from the reaction mixture, however, proved to be very challenging as precipitation by pentane addition, led to the formation of some of the dimer product **148** (δ_P 78 ppm). Attempts to separate the two products by re-precipitation were unsuccessful and only led to continued formation of the dimeric product. Since this could be due to trace amounts of water being present in the pentane, anhydrous pentane was subsequently used, but it proved to be insufficient in avoiding the formation of the hydrolysis product. Finally, it was decided to just filter off the precipitate that was formed during the reaction and wash with a portion of dry pentane. The pale yellow solid recovered in 31% yield was dried overnight under vacuum and was found to be sufficiently pure to be evaluated as catalyst as was indicated by only one singlet at δ_P 121.8 ppm in the ^{31}P NMR spectrum (Plate 72). This value was in agreement with the only reported characterization in literature for **174** at δ_P 122.0 ppm.[182]

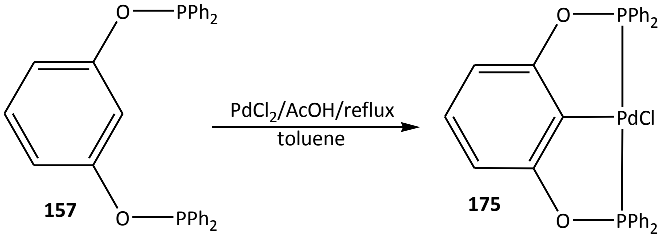
The ^{1}H NMR spectrum (Plate 73) of compound **174** displayed three sets of multiplets in the downfield phenyl region (> 7 ppm, Table 4.8) that integrated for a total of twenty protons relative to two multiplets (δ_H 6.85-6.83 and 6.06-6.04) integrating for two protons each in the δ_H 6 to 7 ppm (phenolic) area, confirming the presence of four phenyl rings and a catechol moiety respectively.

Table 4.8: ^{1}H NMR chemical shifts of proton signals and **174**.

^{1}H NMR (δ_H, ppm) 174
8.06-8.03 (8H, m, Ar-H)
7.62-7.59 (4H, m, Ar-H)
7.52-7.49 (8H, m, Ar-H)
6.85-6.83 (2H, m, H-4, H-5)
6.06-6.04 (2H, m, H-3, H-6)



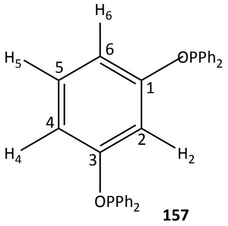
Palladation of phosphinite **157** was attempted by treatment of the phosphinite with either $PdCl_2(PhCN)_2$ **144** or $PdCl_2COD$ **145** in dichloromethane or toluene, but both reactions in both solvents only led to a white insoluble precipitate being obtained. Since the preparation of the palladium complex of **157** seemed to be very challenging, it was decided to rather make the orthopalladated derivative **175**. Application of a modified literature procedure (Scheme 4.28)[195] subsequently led to the smooth conversion of **157** to the desired orthopalladated derivative **175**, which was characterised by a singlet at δ_P 143.7 ppm in the ^{31}P NMR spectrum (Plate 75).



Scheme 4.28: Synthesis of 2,6-*bis*(diphenylphosphinito)benzene palladium chloride **175**.

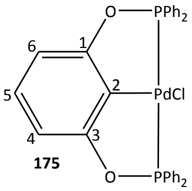
The chemical shift of the observed signal in the phosphorous NMR spectrum of the product, 2,6-bis(diphenylphosphinito)benzene palladium chloride, **175** was in agreement with the reported literature value of δ_P 144 ppm. Confirmation of structure **175** for the cyclopalladated product also came from the ^1H NMR spectrum of **175** (Plate 76), where the signal (δ_H 6.37 ppm) from the *m*-coupled proton (H-2) on the resorcinol ring of the starting material disappeared in the spectrum of the product (Table 4.11).

Table 4.9:^1H NMR spectra of **157**[195] and **175**.



157

^1H NMR (δ_H, ppm) 157	**^1H NMR (δ_H, ppm) 175**
7.63 (8H, m, Ar-H)	8.01-7.98 (8H, m, Ar-H)
7.44 (12H, m, Ar-H)	7.53-7.49 (12H, m, Ar-H)
7.14 (1H, m, Ar-H)	7.11 (1H, m, H-5)
7.02 (1H, s, Ar-H)	6.77 (2H, d, *J* = 7.65, H-4, H-6)
6.84 (2H, m, Ar-H)	



175

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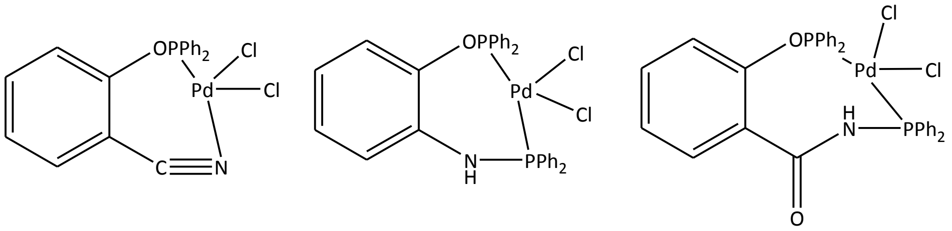
[195] R. B. Bedford, S. M. Draper, P. N. Scully, S. L. Welch, *New J. Chem.*, 2000, **24**, 745.

The ^{1}H NMR chemical shifts of **175** were also distinctly different from those reported for **157** (Table 4.9), with the protons on the $OPPh_2$ moiety shifted more downfield and the core ring protons upfield to the corresponding protons in **157**.

Palladation of the nitrogen containing mixed phosphinites, **162** – **164** (Figure 4.10), was also attempted by application of the procedure that was used for the synthesis of **174**. Treatment of the starting materials with $PdCl_2(PhCN)_2$ led to indications (^{31}P NMR chemical shifts of products – Table 4.10) of the palladated products **176** – **178** having been formed, but isolation and full characterization was found to be impossible due to rapid hydrolysis during isolation attempts, leading to a product that was identified as the hydrolysis dimer **148** (^{31}P NMR chemical shift 78.0 ppm). When $PdCl_2COD$ was used as the Pd source, only the hydrolysis product **148** was observed in the reaction mixtures.



176 **177** **178**

Figure 4.10: Proposed Pd complexes **176**, **177**, **178** from $PdCl_2(PhCN)_2$ and the respective phosphinites.

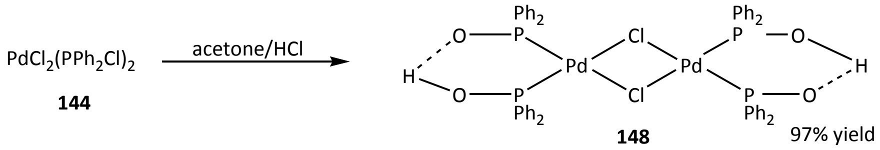
Table 4.10: ^{31}P NMR chemical shifts for palladated and metal-free phosphinites **152-153**, **155-157**.

Phosphinite	Metal-free (δ, ppm)	Palladated product (δ, ppm)
173	110.3	110.5
174	114.5	122.0
175	111.2	143.7
176	115.7	111.9,
177	114.6, 26.5	110.6, 110.3 (*J*(P,P) = 326.28Hz); 64.7, 64.5 (*J*(P,P) = 28.9Hz)
178	116.3, 24.9	112.9, 104.5

Since preparation of the mixed nitrogen–oxygen phosphinite complexes **176**-**178** were not successful, it was decided to shifted attention towards a comparison of the catalytic properties of the prepared phosphites and phosphinites with that of simple phosphine complexes $PdCl_2[(PPh_3)]_2$ **179** and the dimeric hydrolysis phosphinite palladium species **148**.

4.4.2 Hydrolysed Palladium phosphinite complex

Since palladium phosphinites are known to be prone to hydrolysis with the formation of chloro-bridged species such as $Pd_2Cl_2\{(PPh_2PPh_2O(OH)\}_2$ **148**, it was decided to prepare compound **148** for purposes of identification of such products if formed during the Wacker oxidation. Following literature procedures, **148** was prepared by suspending **144** in acetone with dropwise addition of concentrated HCl and precipitation of the product with water (Scheme 4.29).[196]



Scheme 4.29: Hydrolysis of **144**.

Analogous to that obtained in literature, the ^{31}P NMR spectrum (77) of **148** displayed a single P resonance at δ_P 78.3 ppm with no presence of the palladiumphosphinic acid **149** (δ_P 84.8 ppm, Scheme 4.5, pg 88). No signals were observed in the phosphorus oxide region, indicating that hydrolysis of **144** did not go all the way even after 1 hour of stirring in a 1:1 mixture of acetone and water. In the ^1H NMR spectrum (Plate 78) of the product **148**, the chemical shift of the aromatic multiplets (δ_H 7.58, 7.40 and 7.27 ppm) were also shifted from that of the starting material **144** (δ_H 7.92-7.86, 7.60-7.55 and 7.55-7.49 ppm) thus confirming that we no longer had **144**.

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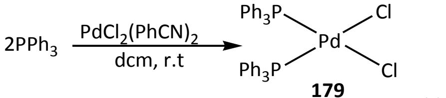
[196] E. H. Wong, F. C. Bradley, *Inorg. Chem.*, **1981**, *20*, 2333.

4.4.3 Palladium phosphine complexes

The $PdCl_2$ complex of triphenylphosphine (PPh_3), $PdCl_2[(PPh_3)]_2$ **179** is well documented in literature and as such prepared using reported methods of reacting the ligand with $PdCl_2(PhCN)_2$ **145** $PdCl_2COD$ or **146** in dichloromethane. The reaction was monitored by ^{31}P NMR to completion (1 hour) and the precipitated complex filtered off to give a yellow solid in 76 % yield (Scheme 4.30).



179

Scheme 4.30: Preparation of $PdCl_2(PPh_3)_2$ **179**.

The structure of the product **179** was confirmed by a downfield shift of the phosphorous resonance in the ^{31}P NMR spectrum (Plate 80) from δ_P -5.40 ppm of the starting material PPh_3, to δ_P 23.5 ppm in the spectrum of the product.

The chemical shift of the signal from the phosphorous atom in the product was in good agreement with literature values of δ_P 24.4 ppm and completely different from that of triphenylphosphine oxide ($O=PPh_3$), which typically resonates at δ_P 27.3 ppm ($CDCl_3$, 85% H_3PO_4).[197,198]

Further confirmation of the structure of the palladium triphenylphosphine complex **179** came from the ^1H NMR spectrum (Plate 81) where the one broad singlet at δ_H 7.38 ppm in the spectrum of PPh_3 was replaced by three multiplets at δ_H 7.75-7.72, 7.47-7.45 and 7.42-7.39 ppm integrating for two, one and two protons respectively and four carbon signals in the ^{13}C NMR spectrum (Plate 82).

To evaluate the effect that an electron withdrawing group attached to the phenyl rings would have on the activity of a palladium phosphine catalyst, it was decided to synthesize the Pd complex of *bis*[3,5-di(trifluoromethyl)phenyl]chlorophosphine **180**, which is available commercially. Thus, following the same procedure as for the preparation of **144**, a yellow solid was obtained in 72% yield after precipitating the product by hexane addition (Scheme 4.31).

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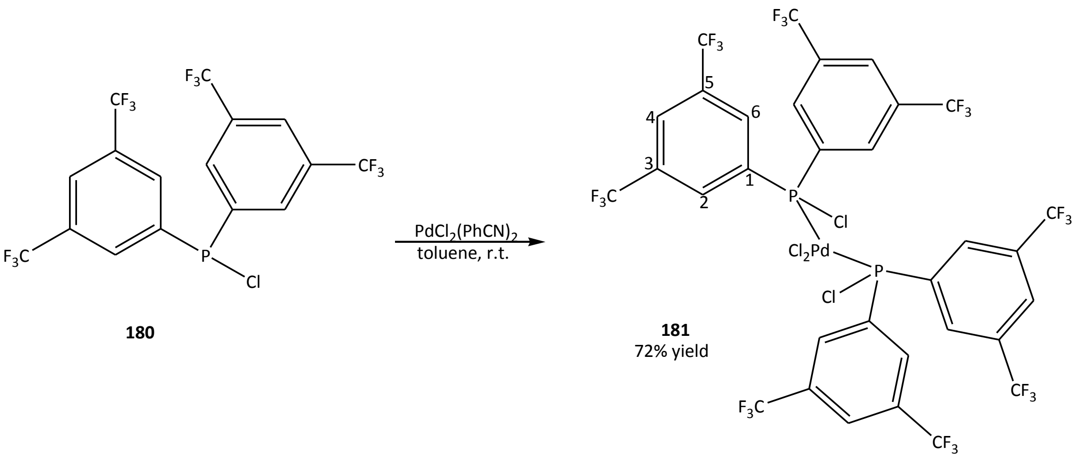
[197] Y. Cabon, I. Reboule, M. Lutz, R. J. M. K. Gebbink, B. Deelman, *Organometallics*, **2010**, *29*, 5904.

[198] A. Romerosa, C. López-Magańa, M. Saoud, S. Mańas, *Eur. J. Inorg. Chem.*, **2003**, 348.



Scheme 4.31: Preparation of $PdCl_2\{[3,5-(CF_3)_2C_6H_3]_2PCl\}_2$ **181**.

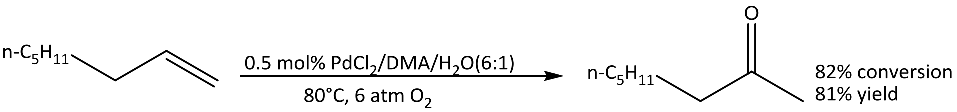
A singlet at δ_P 84.5 ppm in the ^{31}P NMR spectrum (Plate 83) of **181,** which appeared ca. 13 ppm downfield to that of the starting material **180** (δ_P 70.9 ppm), gave an indication of the formation of the desired product. The difference is similar (ca. 13.3 ppm) to that observed between PPh_2Cl (δ_P 82.0 ppm) and **144** (δ_P 95.3 ppm). Electron withdrawing groups on P would decrease its σ-donating ability and at the same time increase its π-accepting capabilities. This means that Pd-P back-bonding would be favored and that the electron density coming from the Pd metal would effectively 'quench' the anticipated electron withdrawing effects on P, resulting in overall similar difference in magnitudes of P vs Pd-P in **144** and **180**. ^1H NMR spectrum (Plate 84) of **181** had a multiplet at δ_H 8.46-8.44 ppm and a broad singlet at 8.29 ppm, downfield from those observed in the starting material at δ_H 8.38, 8.19 and 8.06 ppm. A ^{13}C NMR spectrum (Plate 85) gave carbon signals at δ_C 135.6, 132.4 (broad), 126.6, 123.9 and 119.6 ppm in similar regions for trifluoromethylbenzene for example.

CHAPTER 5

Wacker oxidation of 1-octene with phosphorus-based catalysts

5.1 Introduction

The series of phosphorus-containing palladium catalysts, prepared in this study, were evaluated for activity in the Wacker oxidation of 1-octene. In an effort to find an efficient catalyst system, factors such as solvent, catalyst concentration, reaction temperature, oxygen pressure, water content, and 1-octene concentration were explored. The optimum conditions employed by Kaneda *et al*. in which 81% yield were obtained with 0.5 mol% $PdCl_2$ (0.005 mmol) as catalyst in a DMA:H_2O (6:1) solvent system at 80°C and 6 atm of O_2 pressure in 3 hours (Scheme 5.1) were used as starting point for the current investigation.[9]



Scheme 5.1: Wacker oxidation of 0.3M 1-octene with 0.5 mol% $PdCl_2$, DMA:H_2O (6:1), 80°C, 6 atm O_2.

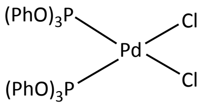
In order to validate the published experimental procedure, the reaction on 1-octene was repeated following the exact literature procedure, which involved pre-stirring of the catalyst in the DMA:H_2O mixture for 1 hour at room temperature under 9 atm of O_2 before the substrate was added and the reaction mixture stirred at 80°C under 6 atm of O_2 pressure for another 3 hours. Since a 94% overall conversion with a 2-octanone yield of 80% were obtained, it was evident that the reported values could be reproduced and these results were therefore used as benchmark in the catalyst screening reactions performed during the current investigation.

5.2 $PdCl_2[P(OPh)_3]_2$ as catalyst (*cis*-isomer 150)

5.2.1 Oxygen as oxidant

5.2.1.1 Benchmark reaction

The investigation was started by subjecting 1-octene to the *cis*-isomer of the phosphite based $PdCl_2$-catalyst $\{PdCl_2[P(OPh)_3]_2\}$ **150** (Figure 5.1) at 0.5 mol% under the above mentioned reaction conditions.



150

Figure 5.1: $\{PdCl_2[P(OPh)_3]_2\}$ **150**.

Overall conversions of 96% with 79% 2-octanone were found, which were comparable to those obtained with only $PdCl_2$ under the benchmark conditions mentioned above (Table 5.1).

Table 5.1: Summary of results obtained with 0.5 mol% $PdCl_2$ and **150** in the oxidation of 0.3M 1-octene under 6 atm of O_2 at 80°C in DMA:H_2O (6:1) over 3 hours.

Catalyst	Conversion (%)	Yield (%)	Selectivity (%)	TON (mol/mol)	TOF (mol/mol/hr)
$PdCl_2$	98	81	82	160 009	888
$PdCl_2[P(OPh)_3]_2$	96	79	82	155 534	864

Since no product could be detected in the absence of **150**, the possibility of a non-metal centred oxidation could be excluded. It is known that reduced electron density on a Pd centre increases reactivity and selectivity towards methyl ketone formation.[88,12] As such, the performance of **150** relative to $PdCl_2$ was expected to be enhanced. These preliminary results indicated a very similar activity for the two catalysts compared (Table 5.1).

The optimum catalytic activity of **150** was subsequently investigated by varying solvents, temperature, oxygen pressure, catalyst, and substrate concentration as well as the water to solvent ratio.

5.2.1.2 Solvents

The effect of solvents like DMA, DMF, THF, CH_3CN, CH_2Cl_2, MeOH, *t*-BuOH, *i*-PrOH, and DMSO on the reactivity of **150** was investigated under the benchmark conditions mentioned above. Based on the conversion of 1-octene to 2-octanone, as well as isomerization to internal olefins, DMA proved to be the solvent of choice for this oxidation, followed by DMF and THF. No 2-octanone formation could be detected with the rest of the solvents investigated. Heterogeneous mixtures which did not homogenize, along with unreacted 1-octene and isomerization to internal octenes were observed (GC) for these solvents. The superiority of DMA as solvent in Wacker oxidation reactions has been attributed to its more negative redox potential that results in a more negative redox potential for Pd^0.[8] The Pd^0 centre can therefore easily be re-oxidized by oxygen thus enhancing the rate of the reaction. As determined by cyclovoltammetric experiments by Sigman *et al.*, DMA (E_{ox} = -0.26V) was found to have a more negative redox potential when compared to other common solvents like N-methylpyrrolidone (NMP, E_{ox} = -0.20V), N-,N-dimethylformamide (DMF, E_{ox} = -0.12V), and acetonitrile (MeCN, E_{ox} = 0.10V) (Table 5.2).

Table 5.2: Redox potentials (E_{red}/E_{ox} in Volts) of different solvents in the oxidation of 1-decene (0.5 mmol) with $PdCl_2$ (0.005 mmol) in 6:1 (solvent:H_2O) under 1 atm of O_2 at 80°C over 6 hours. SCE = Saturated Calomel Electrode, NMP = N-methylpyrrolidone, DMPA = N, N-dimethylpropionamide.

Solvent	**Yield**	**E_{red} [V vs. SCE]**	**E_{ox} [V vs. SCE]**
DMA	84	-0.70	-0.26
NMP	74	-0.69	-0.20
DMPA	33	-0.57	-0.13
DMF	Trace	-0.50	-0.12
EtOH	Trace	-0.10	0.19
MeCN	Trace	-0.40	0.10

Having found DMA to be the best solvent, the optimum temperature for the oxidation reactions with **150** in DMA was subsequently determined.

5.2.1.3 Temperature

In their reported research Mitsudome *et al.*, pre-stirred the $PdCl_2$ in DMA at room temperature for 1 hour in order to completely dissolve the $PdCl_2$.[10] Although this pre-treatment would be unnecessary for phosphite catalyst **150**, as it was readily soluble in DMA, the effect of pre-treatment was nevertheless investigated. While the subsequent reactions were performed over 3 hours under the benchmarks conditions of 6 atm O_2 and 80°C in DMA:H_2O (3:1), the pre-stirring treatment was done at different temperatures of 50, 60, 70, and 80°C respectively. The plot of conversion and yield of 2-octanone showed that as the temperature of the pre-stirring treatment increased, so did the rate of the reaction (Figure 5.2).

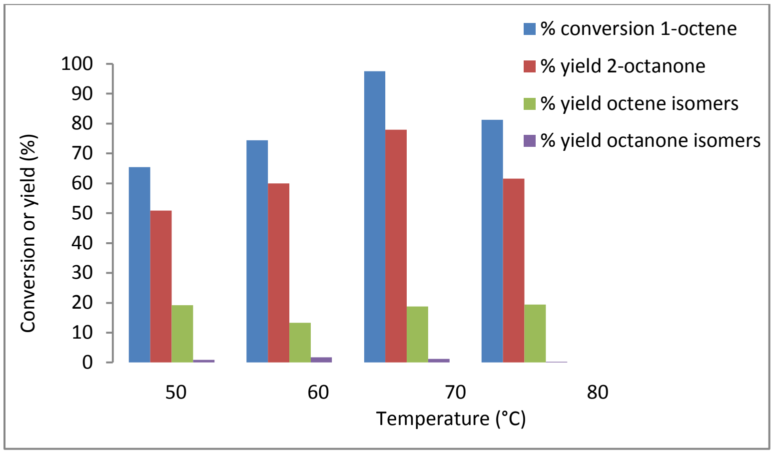


Figure 5.2: Oxidation of 1-octene with 0.5 mol% **150** at different catalyst pre-stirring temperatures at 9 atm of O_2 over the first 1 hour and a maintained reaction temperature of 80°C and 6 atm O_2 over 3 hours.

The conversion and yield of octanone increased steadily in increments of approximately 10% reaching a maximum of 96 and 78% respectively at 70°C, before it dropped down again to 81% and 60% respectively at 80°C (Figure 5.2). Although isomerization to the internal olefins 2-, 3-, and 4-octene proved to be significant (between 13 and 19%), oxidation of those internal olefins were negligible (less than 2%).

Pre-stirring of **150** was then eliminated and the reaction repeated at 6 atm of O_2 pressure and 80°C over 3 hours in DMA:H_2O (6:1). About 50 % conversion of 1-octene was obtained with 31% yield of 2-octanone within the first hour of the reaction. After 2 hours, the yield of 2-octanone had doubled and the conversion increased to 89%, before a maximum yield of 71% with 98% conversion was reached after 3 hours (Table 5.3).

Table 5.3: Comparison of pre-stirred and not pre-stirred solution of catalyst **150** under the same reaction conditions of 80°C under 6 atm of O_2 after 3 hours. (Prestirring at room temperature for 1 hour under 9 atm O_2).

	Conversion (%)	**Yield of 2-octanone (%)**	**Selectivity (%)**	**Yield of octene isomers (%)**	**Yield of octanone isomers (%)**
$PdCl_2[P(OPh)_3]_2$ not pre-stirred	98	71	80	16	1.6
$PdCl_2[P(OPh)_3]_2$ pre-stirred	81	62	76	19	0.3
$PdCl_2$ pre-stirred	98	80	82	17	1.2

Since a comparison of pre-stirred with not pre-stirred reaction sequences (Table 5.3) indicated the not pre-stirred reaction to be better than the pre-stirred one, the rest of the investigation with **150** was carried out **without pre-stirring treatment** of the catalyst mixture. To confirm the optimum reaction temperature without catalyst pre-stirring, the reaction was repeated at 6 atm of O_2 pressure in DMA:H_2O between 50 and 80°C over a period of 3 hours and it was determined that the optimum reaction temperature under these conditions was in fact 80°C (96% conversion, 82% selectivity) (Figure 5.3).

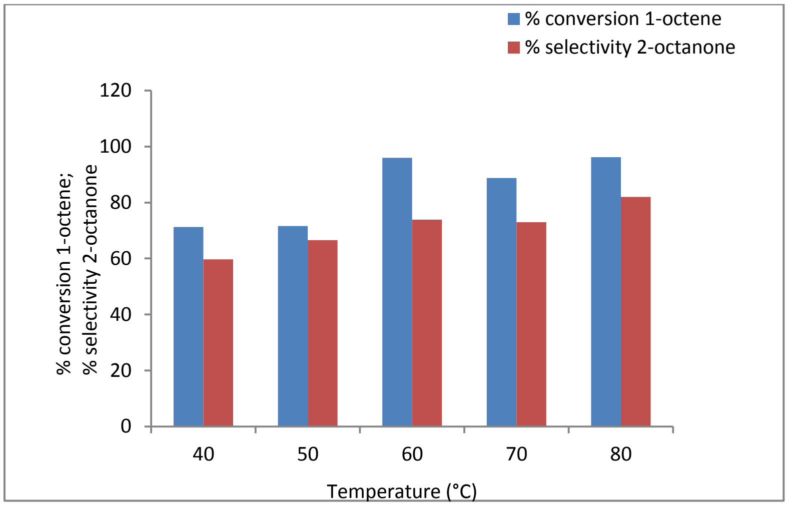


Figure 5.3: Reaction profile of 1-octene at various temperatures with 0.5 mol% **150** and 6 atm of O_2 pressure in DMA:H_2O (6:1) after 3 hours without catalyst pre-treatment.

Although it is known that water concentration has an enhancing effect on reaction rates, it could also influence catalyst activity and stability.[8] The effect of the amount of water relative to DMA in the reaction mixture was therefore subsequently investigated.

5.2.1.4 Water concentration

Phosphite ligands are known to be prone to hydrolysis; when bound to a metal the cleavage of the phosphorus-carbon (P-C) bond is often also realised by metal catalyzed reactions.[199] It was therefore expected that too much water in the DMA would lead to hydrolysis of the ligands with the formation of phosphorous acid derivatives and therefore increased Pd^0 'fall-out', so the presence of aggregated Pd^0 was carefully monitored. The amount of water relative to DMA was varied between 1:24 and 1:3 and after monitoring each reaction for 2 hours, a ratio of 1:6 was found to be the optimum for catalyst **150** (Figure 5.4). No Pd^0 aggregation at the optimum conditions of 1:6, *i.e.* 0.5 ml of water in 3 ml DMA, was observed.

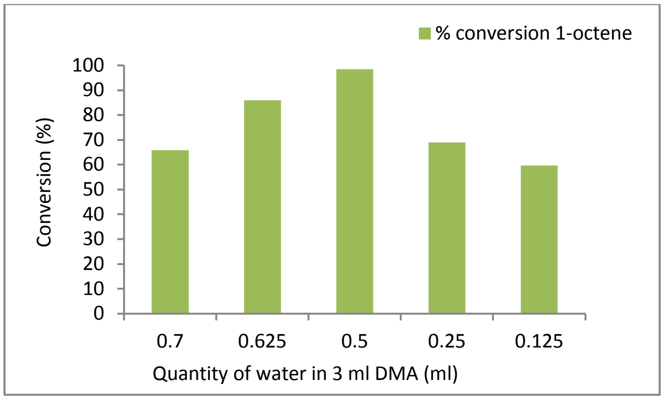


Figure 5.4: 1-Octene conversion at different quantities of water in DMA.

5.2.1.5 Oxygen pressure

An investigation into the effect of O_2 pressure (between 1 and 9 atm) on the reaction revealed an increase in activity of **150** with increasing O_2 pressure, reaching 96% conversion and 76% 2-octanone yield at 9 atm (Table 5.4).

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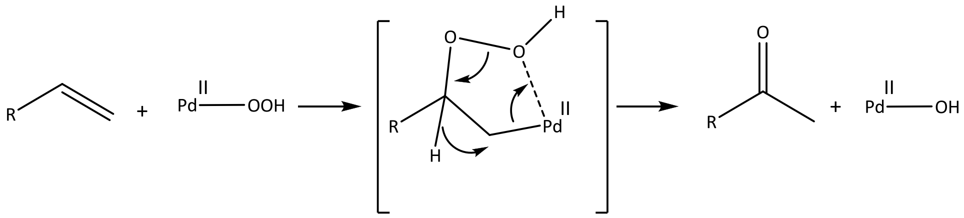
[199] P.W.N.M. van Leeuwen, *Appl. Cat. A: Gen.*, **2001**, *212*, 61.

Table 5.4: Effect of O_2 pressure on conversion and yield of 2-octanone at 0.5 mol% of **150** and 80°C in DMA:H_2O (6:1) over 1 hour.

O_2 pressure (atm)	Conversion (%)	Selectivity (%)	Yield of 2-octanone (%)	Internal isomers (%)	Octanone by-products (%)
1	28	37	11	13	0.8
3	63	69	43	16	1.1
5	70	71	49	16	0.7
7	91	78	71	15	2.3
9	96	79	76	17	1.5

Selectivity towards 2-octanone seemed to be unaffected by the increases in O_2 pressure with the amount of internal octenes and 3- and 4 octanone isomers remaining almost constant between 3 and 9 atm. (Table 5.4).

It has been suggested that O_2 can insert into a Pd-H bond during re-oxidation for maintaining a Pd^{II} state (Scheme 5.2).[200]



Scheme 5.2: Proposed 5-membered pseudocyclic peroxypalladium intermediate for oxygen transfer to alkenes.

Kaneda *et al.,* through ^{18}O isotope labelling, convincingly showed that the oxygen in the product ketone originated from water and not the oxygen.[10]

The increased reactivity at higher O_2 pressures could therefore be attributed to a higher oxygen concentration in the solution and thus more efficient re-oxidation of the palladium.

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[200] T. Hosokawa, S.–I. Muharashi, *Acc. Chem. Res.*, **1990**, *23*, 49.

Since the oxidation of 1-octene with **150** in the absence of water did not yield any 2-octanone under an O_2 environment nor under an argon atmosphere in the presence of water, results from the current investigation confirmed Kaneda's proposal for the role of water also when **150** is used as catalyst.

5.2.1.6 Catalyst and substrate concentration

Having determined the best conditions w.r.t. solvent, water concentration, and oxygen pressure, attention was subsequently turned towards establishing optimum catalyst loading, keeping in mind that high catalyst concentrations may lead to palladium (Pd^0) aggregation and thus 'fall-out'. Catalyst concentration was therefore varied between 0.125 and 2 mol% (Table 5.5). Although Pd^0 aggregation was not observed even at 2 mol%, the higher reaction rates at high catalyst loadings were accompanied by higher levels of 1-octene isomerization to internal olefins (ca. 29% at 2 mol%). Since reasonable conversions (73 %) with moderate isomerization (15%) were obtained at 0.5 mol% catalyst loading, this catalyst concentration, which was comparable to literature values found with $PdCl_2$,[9] was decided upon as the condition to be used during subsequent investigations.

Table 5.5: Reactivity of 1-octene at various concentrations of **150** in DMA:H_2O (6:1) at 80°C.

Mol% of 150	Conversion (%)	Selectivity (%)	2-Octanone yield (%)	Internal isomers (%)	Octanone by-products (%)
0.125	31	67	21	6	0.1
0.25	53	77	41	8	0.8
0.5	73	72	52	15	2.4
1	78	68	53	21	1.6
2	94	63	59	29	1.4

The concentration of 1-octene was also varied from 0.1M to 0.5M and monitored over 1 hour reaction periods (Table 5.6). At low 1-octene concentrations (0.1 and 0.2M), the % conversions were ca. 96 and 100% respectively with increased selectivity from 75% (at 0.1M) to 82% (0.2M) (Table 5.6). A decrease in the reactivity of **150**, as well as isomerization and the formation of by-products, was, however, observed for concentrations of 0.3M and higher. As such, the poor reactivity could possibly be attributed to some phase separation occurring at the higher octene concentrations.

Table 5.6: Reactivity of **150** at different concentrations of 1-octene in DMA:H_2O (6:1) at 80°C under 9 atm O_2.

[1-octene] (M)	Conversion (%)	Selectivity (%)	Yield of 2-octanone (%)	Internal isomers (%)	Octanone by-products (%)
0.1	96	75	72	21	1.3
0.2	**100**	**82**	**82**	**13**	**1.4**
0.3	73	72	52	15	2.4
0.4	74	67	50	12	0.6
0.5	68	65	45	8	0.7

The best operating conditions for catalyst **150** was thus established as 0.2M 1-octene and 0.5 mol% Pd in DMA:H_2O (6:1) at 80°C and 9 atm of O_2 pressure, which were subsequently used to determine overall TON (turn-over number) and TOF (turn-over frequency) during the first hour of the reaction (Table 5.7).

Table 5.7: Overall reactivity of **150** for Wacker oxidation of 1-octene (0.2M) in DMA:H_2O (6:1) under 9 atm O_2 at 80°C over a period of 1 hour.

Conversion (%)	Selectivity (%)	Yield of 2-octanone (%)	Internal isomers (%)	Octanone by-products (%)	TON (mol/mol)	TOF (mol/mol/hr)
100	82	**82**	**13**	**1.4**	82 362	1 372

In order to assess the ability/stability of the phosphite catalyst **150** w.r.t. recycling, three additional batches of 1-octene were added sequentially to the reaction mixture after completion of the oxidation of the initial quantity of 1-octene. Catalyst **150** showed excellent recyclability properties under the optimized reaction conditions with conversions and selectivities of >95% and >82% respectively being maintained even during the third cycle of substrate addition.

To compare the activity of phosphite catalyst **150** with other common palladium salts/complexes reported for Wacker oxidation, 1-octene was subjected to reactions with $Pd(CF_3SO_3)_2$, $PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$, and $PdCl_2$ under the optimum conditions as determined for catalyst **150** (*vide supra*) (Table 5.2). Based on TOFs, the overall best catalyst was **$PdCl_2$**, followed closely by $PdCl_2(CH_3CN)_2$ then, **150**, $PdCl_2(PhCN)_2$, $Pd(OAc)_2$, and lastly $Pd(CF_3SO_3)_2$ (Table 5.8).

Table 5.8: The activity of various Pd catalysts in comparison to **150** at 0.5 mol% in the oxidation of 0.2M 1-octene in DMA:H_2O (6:1) at 80°C and 9 atm O_2 pressure over 1 hour.

Palladium compound	**Conversion (%)**	**Selectivity (%)**	**TON (mol/mol)**	**TOF (mol/mol/hr)**
$PdCl_2$	**98**	**87**	**85 749**	**1 429**
$Pd(CF_3SO_3)_2$	47	67	31 475	524
$PdCl_2(CH_3CN)_2$	99	86	85 247	1 420
$PdCl_2(PhCN)_2$	83	86	71 952	1 199
$Pd(OAc)_2$	55	90	49 050	817
$PdCl_2[P(OPh)_3]_2$	100	82	82 362	1 372

In order to determine the activity of **150** with alternative oxidants such as H_2O_2 or TBHP, which have been reported for the oxidation of terminal alkenes to ketones[71] and gave activities very similar to oxygen with $PdCl_2$, it was decided to also investigate the oxidant effects of these reagents, if any, on the activity of the phosphite based catalyst **150**.

5.2.2 $PdCl_2[P(OPh)_3]_2$ with H_2O_2 and TBHP as oxidants

Wacker oxidation of 1-octene with **150** was thus investigated with the two most common alternative oxidants, *tert*-butylhydroperoxide (TBHP) and H_2O_2. The major drawback of these two liquid oxidants is they both have a relatively low 'active' O_2 content of 17.8 and 47 wt%, respectively.[201]

As such, large quantities are often employed to reach reasonable activities. Nonetheless, improved reaction rates have been reported with either oxidant when used together with $PdCl_2$ for example. While TBHP is often used in large excess (5-12 equivalents),[71] H_2O_2 can be used in relatively small excess quantities (1.1 equivalents), but large amounts are sometimes necessary to avoid decomposition of the active catalytic species.[120]

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[201] Y. Shi, Modern Organic Methods, 1st Ed., J.-E. Bäckvall, Wiley-VCH, **2004**, 18.

5.2.2.1 Oxidant concentration

The concentration of these oxidants was varied between 5 and 12 mol equivalents to 0.5 mol% of **150**, maintaining the concentration of 1-octene at 0.2M in DMA:H_2O (6:1) under an air atmosphere and the reactions monitored for 1 hour.

While the amount of H_2O_2 did not seem to effect the reactivity of **150** as the conversion remained virtually unchanged (ca 80%) from 5 to 12 mol equivalents, the selectivity, however, increased (from ca 53 to 69%) with increasing quantities of oxidant (Figure 5.5). For TBHP on the other hand, a sharp increase in the conversion from ca 68 to 79% was observed from 8 to 12 mol equivalents, while the selectivity also increased from about 47% to 54% between 8 and 12 mol equivalents (Figure 5.5).

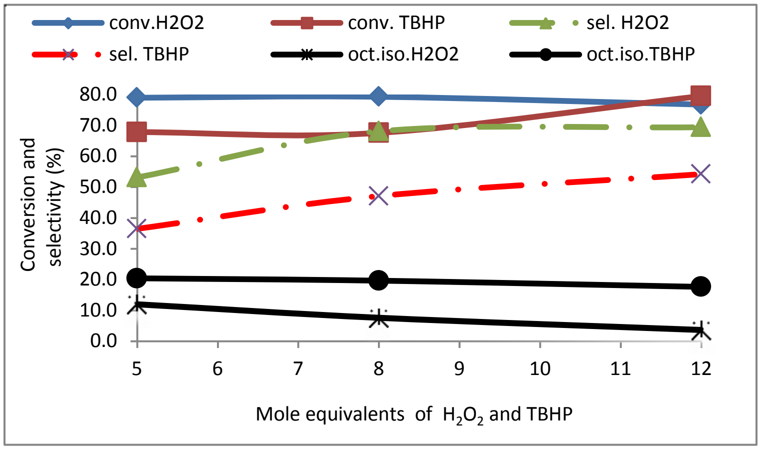

Figure 5.5: Reactivity of 1-octene (0.2 M solution) with H_2O_2 or TBHP at various mol equivalents, with 0.5 mol % of **150** in DMA:H_2O (6:1) at 80°C.

Overall, H_2O_2 appeared to be better than TBHP in enhancing the rate of the reaction, albeit reaching similar conversion of least ca 77% after 1 hour. The role of the oxidant also affected the degree of isomerization of 1-octene to internal octene isomers as more isomerization was observed with TBHP (18% internal octane isomers) than H_2O_2 (4% internal octane isomers) (Figure 5.5). Furthermore, H_2O_2 also led to reduced quantities of internal octene isomers (3.6%) when compared to what was observed with O_2 as oxidant (13.4%) (Table 5.9). While no 3- and 4-octanones were observed with H_2O_2, the use of TBHP resulted in at least 0.4 % of these ketones being formed. Under the reaction parameters of 0.5 mol % of **150** in DMA:H_2O (6:1) at 80°C, the highest activity and selectivity of **150** was therefore observed with O_2.

Table 5.9: A comparison of the activity of **150** with oxidants O_2 (9 atm), H_2O_2 (12 eq.), and TBHP (12 eq.) after 1 hour in DMA:H_2O (6:1) at 80°C with a 0.2M 1-octene solution.

Oxidant	**Conversion (%)**	**Selectivity (%)**	**Internal octene isomers (%)**	**Octanone by-products (%)**
O_2	100	82	13	1.4
H_2O_2	77	69	4	0.0
TBHP	80	54	18	0.4

5.2.2.2 Water concentration

Since the peroxides used are only available as aqueous solutions (70% w/w for TBHP and 30% for H_2O_2) and it was found with oxygen as oxidant that too much water in the reaction mixture can lead to a decrease in conversion and yield (paragraph 5.1.3), it was felt that perhaps the low conversion (only 80%) and selectivity (54 and 69% respectively) found with these oxidants could be due to excess water present in the reaction mixtures. The reactions with aqueous solutions of both these oxidants were therefore repeated at 12 equivalents of oxidant, but with the DMA:H_2O ratio of the prepared solvent mixture being varied from 6:1 to 3:1. The results obtained indicated that an increased water content was more desirable with the best conversions and selectivities obtained at a 3:1 DMA:H_2O ratio for both H_2O_2 and TBHP (Figure 5.6).

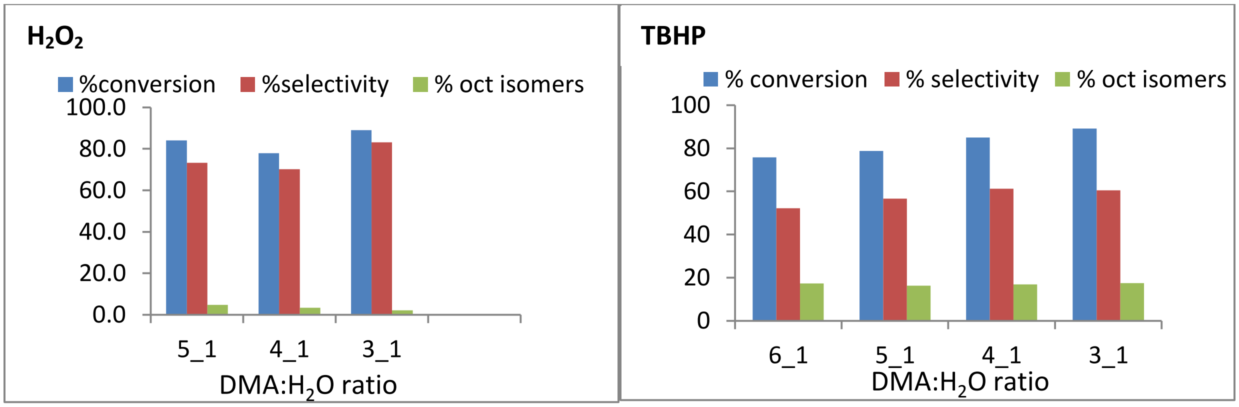

Figure 5.6: Conversion, selectivity and internal octene isomer formed at various DMA:H_2O ratios with H_2O_2 or TBHP.

The selectivity for H_2O_2 improved significantly to about 83% in contrast to TBHP where the selectivity only reached about 60% after an hour at a 3:1 DMA:H_2O ratio (Table 5.10). Isomerization to internal octene isomers with H_2O_2 was slightly reduced to ca. 2.1% in a 3:1 DMA:H_2O solution, but remained unchanged with TBHP at ca. 18% (Table 5.10).

Table 5.10: Activity of 0.5 mol% of **150** with H_2O_2 and TBHP at 6:1 and 3:1 DMA:H_2O ratio

DMA: H_2O	**Conversion (%)**	**Selectivity (%)**	**Internal octene isomers (%)**
6:1 (H_2O_2)	78	67	3.6
3:1 (H_2O_2)	**89**	**83**	**2.1**
6:1 (TBHP)	76	57	18
3:1 (TBHP)	**89**	**60**	**18**

When the water added to the DMA was eliminated, *i.e.* the reaction performed in DMA only with the aqueous oxidants, a significant effect in the percentage conversion and selectivity was observed. At 0.5 mol% of **150**, the conversion in 3:1 DMA:H_2O with TBHP was 89%, but it decreased to ca. 35% in DMA only. Conversion observed with H_2O_2 was also lower at 36% in absence of additional water compared to the 89% observed in DMA:H_2O (3:1) reaction mixture. Likewise, the selectivity with both oxidants was lower to ca. 40 and 37% respectively for TBHP and H_2O_2 (Table 5.11).

Table 5.11: Absence of additional water on the reaction rate and selectivity with aqueous TBHP or H_2O_2 as oxidants with 0.5 mol % of **150** at 80°C over 1 hour.

	Conversion (%)		Selectivity (%)	
	Aq.TBHP	Aq.H_2O_2	Aq.TBHP	Aq.H_2O_2
DMA:H_2O (3:1)	86	89	60	83
DMA (neat)	**35**	**36**	**40**	**37**

These results suggested that even at 12 equivalents of oxidant the water concentration is still too low for a proper reaction with the 1-octene to occur when no additional water is added to the DMA and is in agreement with what was found with oxygen as oxidant where water concentrations of below 0.5 ml in 3 ml gave poor conversions. This confirms that the oxygen atom in the final product comes from a water molecule, supporting the proposals by Kaneda *et al.* in O_2 oxidations where similar conclusions were drawn.[9]

5.2.2.3 Catalyst loading

To investigate the activity of **150** with TBHP or H_2O_2 as stoichiometric oxidants, the concentration of **150** in the reaction mixture was varied between 0.5 and 2 mol%. The selectivity of **150** with H_2O_2 remained virtually unchanged between 0.5 and 2 mol% (at ca. 83%), but the reactivity increased dramatically (to > 99% conversion at 2 mol%) accompanied by an increased in the formation of internal olefins from 2.1% to 13.2% (Table 5.12).

Table 5.12: Activity of **150** with H_2O_2 and TBHP at different concentrations in DMA:H_2O (3:1) at 80°C over a period of 1 hour.

Oxidant	**Catalyst loading (mol %)**	**Conversion (%)**	**Selectivity (%)**	**Internal octene isomers (%)**
H_2O_2	0.5	**89**	**83**	**2.1**
H_2O_2	1.0	91	83	6.5
H_2O_2	2.0	>99	84	13
TBHP	0.5	**89**	**60**	**18**
TBHP	1.0	99	64	31
TBHP	2.0	99	63	32

With TBHP on the other hand, conversion, selectivity and internal olefin formation reached a maximum at 1 mol% (ca 99, 64, and 31% respectively) after 1 hour. Oxidation of the internal olefins to ketones remain at less than 1% for both oxidants from 0.5 to 2 mol% of **150**.

5.2.2.4 Temperature effect

In order to determine whether temperature had any effect on the rate of isomerization at higher catalyst loadings, temperatures were varied from 40 to 80°C with 2 mol% of **150**. The rate of isomerization was observed to decrease with increasing temperature using TBHP, but no trend could be detected in the rate of isomerization when H_2O_2 was used (Table 5.13).

Table 5.13: Temperature effect on the degree of isomerization of 1-octene with 2 mol% of **150** using 12 eq. H_2O_2 or TBHP under an air atmosphere in DMA:H_2O (3:1).

Temperature (°C)	**Internal octene isomers (%)**	
	H_2O_2	**TBHP**
40	7	42
50	4	39
60	14	36
70	18	32
80	13	32

While the selectivity with H_2O_2 increased from 61% at 40°C to 84% at 80°C (Figure 5.7), that of the reaction with THBP showed only a slight increase (from ca 54 to 62%). The conversion with both oxidants remained uneffected by temperature at >99% after an hour.

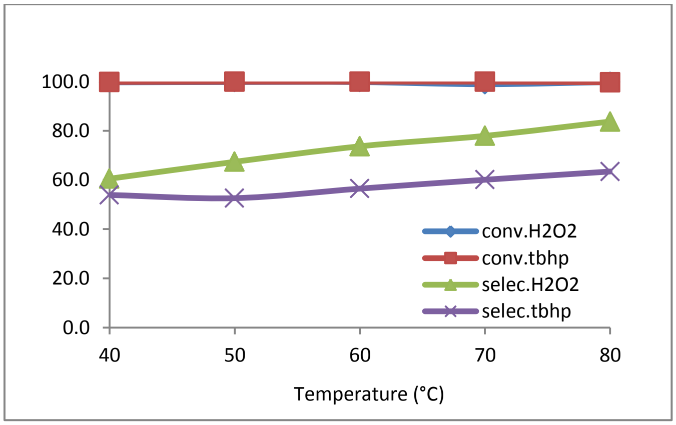

Figure 5.7: Conversion and selectivity of **150** (2 mol%) in the Wacker oxidation of 1-octene (at 0.2M) with H_2O_2 or TBHP at various temperatures over 1 hour in DMA:H_2O (3:1) under an air atmosphere.

5.2.2.5 Octene concentration

Since it has been determined that 1-octene concentration had a profound effect on the conversion and yield with molecular oxygen as oxidant (*cf* table 5.6), this aspect of the reaction with hydrogen peroxide and TBHP was subsequently investigated and 1-octene concentration varied between 0.1-0.4M. While a similar decrease in activity (conversion) and selectivity with increasing substrate concentration was expected, reactions with H_2O_2 were somewhat inconclusive and no clear trend in both conversion and selectivity were found despite three consecutive repetitions of each of the reactions at 0.4 and 0.5 mol (Figure 5.8).

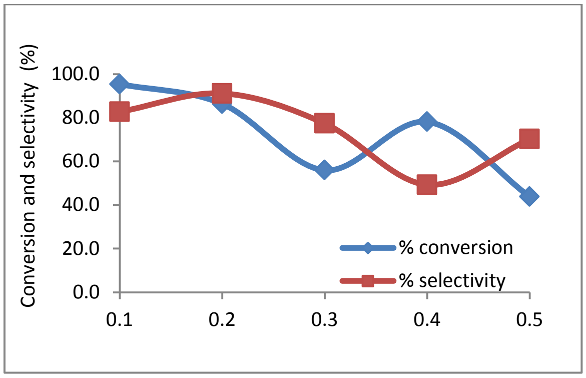

Figure 5.8: Effect of substrate concentration on the activity of **150** (2 mol%) using 12 eq. of H_2O_2 under air atmosphere over a period of 2 hours.

For TBHP the reactivity and selectivity remained virtually unchanged over the concentration range of 0.1-0.4M 1-octene (Figure 5.9).

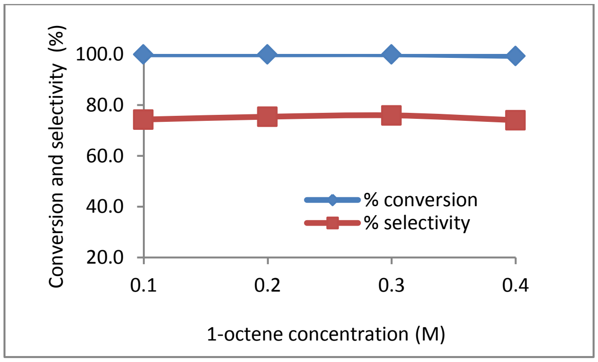

Figure 5.9: The activity of **150** (2 mol%) in DMA:H_2O (3:1) using 12 eq. of TBHP at 80°C at different concentrations of 1-octene over a period of 2 hours.

5.2.2.6 Relative catalyst activity with different oxidants

Since the reactivity and selectivity with TBHP as oxidant remained relatively unchanged over the concentration range of 1-octene, this oxidant was chosen as a model to test **150** against $PdCl_2$ with the alternative oxidants.

While similar reactivities were observed for $PdCl_2$ and **150** with $PdCl_2$ being slightly superior, with oxygen as oxidant (*cf* Table 5.8), it was determined that the phosphite catalyst **150** performed slightly better than $PdCl_2$ w.r.t. conversion and TON with TBHP as oxidant (Table 5.14) at 0.1M 1-octene over 1 hour. Isomerization to internal octenes was, however, more profound with **150** than with $PdCl_2$.

Table 5.14: Comparison of the activity of $PdCl_2$ and **150** (both at 1 mol%) to oxidize 1-octene (0.1 M) with TBHP (12 eq.) in DMA:H_2O (3:1) at 80 °C over 1 hour.

Catalyst	**Conversion (%)**	**Selectivity (%)**	**Internal octene isomers (%)**	**TON (mol/mol)**	**TOF (mol/mol/hr)**
$PdCl_2$	76	80	5.3	60 825	1 014
150	100	74	18	73 486	1 225

5.2.2.7 Catalyst recyclability and deactivation

Since **150** showed excellent recyclability properties with oxygen as oxidant this aspect of the catalyst w.r.t. H_2O_2 and TBHP was subsequently investigated. After the initial quantity of 1-octene was completely reacted away, a second batch of octene was added to the reaction mixture containing 1 mol% of catalyst **150** to see if the reaction would continue. No oxidation of the second batch of reactant could, however, be detected.

Since H_2O_2 is known to disproportionate to water and oxygen (Scheme 5.3), especially in presence of even trace amounts of transition metals;[202] degradation of the H_2O_2 after the first catalytic cycle could not be ruled out as the cause of the inability of the catalyst to effect further oxidation.[94]

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[202] F. A. Cotton, G. Wilkinson, P. L. Gaus, Basic Inorganic Chemistry, 3rd Edn, John Wiley & Sons, Inc, **1995**, 441.

$$2H_2O_2 \longrightarrow H_2O + O_2$$

Scheme 5.3: Disproportionation of H_2O_2.

In this regard, Pillai *et al*. also found rapid decomposition of H_2O_2 at temperatures >80°C in the oxidation of styrene and good conversions and selectivities were only possible at 60°C.[120] It was proposed that the decomposition of H_2O_2 can be associated with the rather unstable Pd^{II}-OOH entity that can be formed upon 'attack' of H_2O_2 on Pd^{II} which might be responsible for oxygen transfer to the alkene when H_2O_2 is used as oxidant.[93] A large quantity of H_2O_2 is needed to regenerate the required Pd^{II}-OOH from Pd^{II}-OH (the Pd species after oxygen transfer) and at low levels, the Pd-OH species undergoes a second hydroxypalladation step with an olefin, eliminating insoluble Pd^0 and the ketone.[93] Since reactions during the current investigation were performed at 80°C, and some release of gas was observed with 1-octene concentrations of 0.3 and 0.4M, it was concluded that a possible explanation for the lack of recyclability could be depletion of the H_2O_2 oxidant despite it being present at the start of the reaction at 12 equivalents.

Due to these two possibilities, the recycling experiment was repeated and more H_2O_2 (12 eq.) was added together with 1-octene at the start of the second cycle and formation of 2-octanone was resumed. It was therefore concluded that the active catalytic species was still present at the end of the first cycle and that insufficient H_2O_2 was the cause of the presumed inactivity of the catalyst during the second cycle.

With the addition of H_2O_2 (12 eq.) together with 1-octene at the beginning of each cycle, 3 oxidation cycles could be completed and conversion and selectivity of 85 and 80% respectively reached without additional catalyst being required. No Pd^0 aggregation was observed.

Recycling phosphite catalyst **150** using TBHP oxidant, as was performed with O_2 and H_2O_2, was, however, not attainable despite addition of extra TBHP (12 eq.) together with 1-octene at the beginning of each cycle. This result is contrary to some literature reports where it is claimed that $PdCl_2$ can be recycled 3 times in reactions with TBHP during the oxidation of 1-dodecene in MeCN at 80°C.[91]

5.2.3 Summary

Since the phosphite based palladium catalyst **150** is readily soluble DMA, it was determined that no pre-stirring as for $PdCl_2$ was required. For oxygen as oxidant, optimized reactions conditions were determined to be 0.5 mol% of **150** in DMA:H_2O (6:1) under 9 atm O_2 at 80°C, while the optimum substrate concentration was found to be 0.2M. Application of the optimized conditions gave conversion, selectivity towards 2-octanone, and TON's (Table 5.16) comparable to those found for $PdCl_2$ and $PdCl_2(CH_3CN)_2$ and better than what was found for other catalysts like, $PdCl_2(PhCN)_2$, $Pd(OAc)_2$, and $Pd(CF_3SO_3)_2$, while it was also determined that the catalyst could be recycled at least three times.

With H_2O_2 and TBHP 2 mol% of **150** was found to be required for the best conversions and selectivity, while a large excess of oxidant (12 eq) was needed to keep the palladium in its higher oxidation state. Since both H_2O_2 and TBHP were available as aqueous solutions the DMA:water ratio had to be changed to 3:1 and substrate concentration lowered to 0.1M for best conversions and selectivities for both these oxidants. Of the peroxides, H_2O_2 performed the best and afforded conversion, selectivity, and TON's almost as good as those found for O_2 as oxidant (Table 5.15). In addition, the catalyst could also be recycled three times when hydrogen peroxide was used as oxidant, but no recycling was possible with TBHP. Although isomerization to internal octenes was observed for all three oxidants, it was almost negligible with H_2O_2 (2.1%) followed by oxygen (13,4%) and TBHP (17,5%). Fortunately, internal isomers were not oxidized rapidly, resulting in less than 3% of 3- and 4-octanones being formed from reactions with all three oxidants.

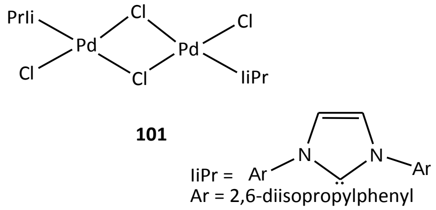
Table 5.15: Activity of **150** with O_2 (0.5 mol% **150**, DMA:H_2O/6:1, 9 atm.), TBHP (2 mol% **150**, DMA:H_2O/3:1) and H_2O_2 (2 mol% **150**, DMA:H_2O/3:1) at 80°C over a period of 1 hour.

Oxidant	**Conversion (%) [Substrate conc. (M)]**	**Selectivity (%)**	**TON (mol/mol)**	**TOF (mol/mol/hr)**
O_2	100 [0.2]	82	82 362	1 372
H_2O_2	> 99 [0.1]	86	73 373	1 223
TBHP	> 99 [0.1]	60	60 113	1 002

5.3 Other phosphite based catalysts

5.3.1 Phosphites containing a metallocycle moiety

Since dinuclear catalysts have led to remarkable increases in TON (up to 10^5) in Heck reactions and a ligand-modulated Wacker oxidation using the NHC-dinuclear palladium catalyst **101** (Figure 5.10) has been reported for oxidation of styrene to acetophenone;[71] it was decided to evaluate the mixture of *sym-cis* & *sym-trans* dinuclear Pd complexes **151** (Figure 5.10) as catalyst in the Wacker oxidation of 1-octene. While this catalyst, that could easily be prepared from **151**, still has the phosphite ligand present as in **151**, it also has a metallocycle moiety, which would render it different w.r.t. electron donating nature.



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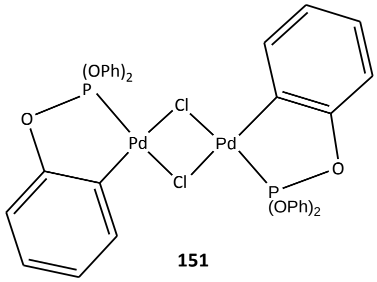


151

Figure 5.10: Dinuclear palladium NHC catalyst **101** and the cyclometallated $[Pd(\mu\text{-}Cl)(P(OPh)_2)(OC_6H_4)]_2$ complex **151**.

The investigation with **151** was started with the optimized conditions determined for **150**, *i.e.* 0.5 mol% catalyst, 80°C, 9 atm of O_2 pressure, and a 6:1 mixture of DMA and water as solvent. The reaction was monitored in short time intervals over 1 hour and compared to that of **150**. The conversion observed with **151** within the first 5 minutes (60%) was higher than what was found with **150** (43%) (Figure 5.11).

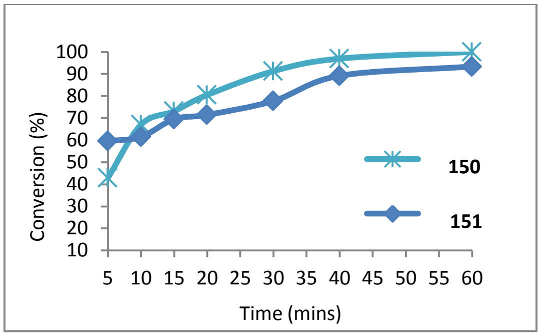


Figure 5.11: Conversion of 1-octene (0.2M) with 0.5 mol% of both **150** and **151** in DMA:H_2O (6:1) under 9 atm of O_2 at 80 °C.

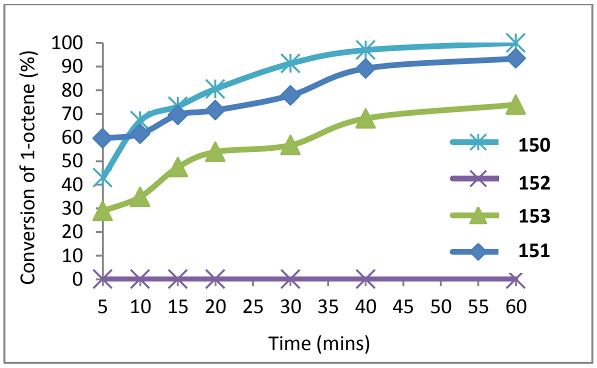
After 5 minutes, however, the reaction rate for **150** exceeded that of **151**, reaching 67% conversion while **151** only reached 62% after 10 minutes. Overall conversion after 1 hour was therefore higher with **150** (100%) compared to **151** (93%) (Table 5.16), but the selectivity for **151** was slightly better (89 vs 82%) than with **150**. W.r.t. the level of isomerization to internal isomers, **151** also appeared to be a much better catalyst as only 2.9% of internal octenes were observed compared to the 13.4% with **150** (Table 5.16).

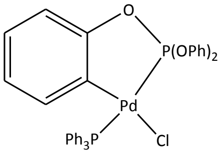
Table 5.16: The reactivity of **151** in comparison to **150** in the oxidation of 0.2M 1-octene in DMA:H_2O (6:1) under 9 atm of O_2 at 80 °C over a period of 1 hour.

Catalyst	**Conversion (%)**	**Selectivity (%)**	**Internal octene isomers (%)**	**TON (mol/mol)**	**TOF (mol/mol/hr)**
150	100	82	13	82 362	1 372
151	93	89	4	82 937	1 382

As they are known to 'break' down into mononuclear complexes in presence of excess ligand, complexes of type **151** have often been viewed as precursors to the actual catalytic species involved in these reactions. In order to assess whether the dimer or monomeric species were in fact the active catalyst, monomers **152** and **153** (Figure 5.12), accessible from the dimeric compounds by treatment with PPh_3 and $P(OPh)_3$ respectively, were also tested as catalysts in the oxidation of 1-octene under the same reaction conditions as **150** and **151.**

The strongly σ-donating PPh_3 ligand appeared to have a significant influence on the activity of **152** as no conversion of 1-octene was observed within the first hour. Catalyst **153**, however, followed almost the same reaction path w.r.t. conversion than **151**, although the final conversion proved to be ca 20% lower. In terms of selectivity and isomerization to internal octenes, **153** showed some improvement over **150**, but was not as good as **151** (Figure 5.12 and Table 5.17).





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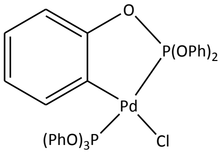


153

Figure 5.12: Comparison of the reactivity of **150**, **151**, **152** and **153** at 0.5 mol% in DMA:H_2O (6:1) under 9 atm of O_2 at 80°C.

Table 5.17: Comparison of the activity of 0.5 mol% of **153**, **151**, and **150** in the oxidation of 0.2M 1-octene in DMA:H_2O (6:1) under 9 atm of O_2 at 80°C over a 1 hour period.

Catalyst	**Conversion (%)**	**Selectivity (%)**	**Internal octene isomers (%)**	**TON (mol/mol)**	**TOF (mol/mol/hr)**
153	74	86	3	73 668	1 228
151	93	89	4	82 937	1 382
150	100	82	13	82 362	1 372

Since the amount of water in the reaction mixture had an influence on the reactivity of catalyst **150,** this aspect of the reaction with **151** and **153** was subsequently investigated. A DMA:H_2O ratio of (3:0.7, v/v) was found to be the optimum for catalyst **151** with 60% conversion already observed within the first 5 minutes of the reaction (Figure 5.13).

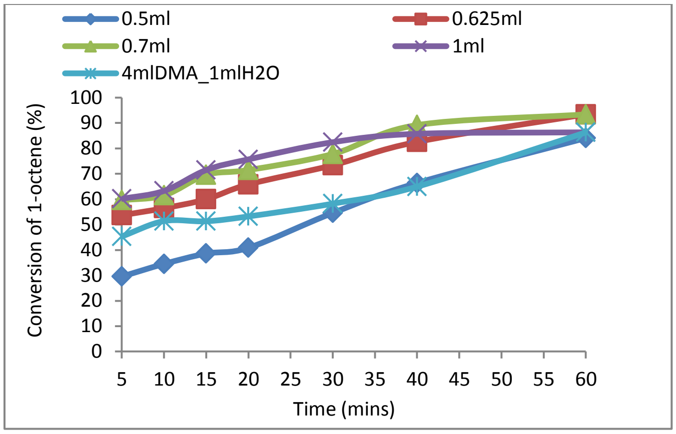


Figure 5.13: The effect of water content on the activity of **151**. (Volume of water in 3 ml of DMA)

From Figure 5.13 and Table 5.18 it also appeared that the water content of the reaction mixture only has a significant effect in initial reaction rates as the conversion only changed dramatically within the first 5 minutes of the reaction when the amount of water is increased from 0.5 ml to 0.625 ml for example.

Table 5.18: The effect of H_2O concentration on reaction rates and isomerization levels in the oxidation of 1-octene (0.2M) in DMA:H_2O under 9 atm of O_2 at 80°C over a 1 hour period at 0.5 mol% of **151**. (^{a} conversion at 5 minutes; ^{b} conversion/selectivity after 1 hour).

DMA:H_2O/v:v (ml)	**Conversion (%)**	**Selectivity (%)**	**Internal octene isomers (%)**
3:1	$60^a/82^b$	87^b	4.5^b
3:0.7	$60^a/93^b$	89^b	4.0^b
3:0.625	$61^a/88^b$	83^b	3.3^b
3:0.5	$30^a/80^b$	87^b	2.9^b

An increase in water, however, also led to a slight increase in isomerization to internal octene isomers; with 2.9% at a DMA:H_2O ratio (v:v) of 3:0.5 and up to 4.5% at a 3:1 DMA:H_2O (v/v) ratio.

Having observed the highest conversion (93%) with **151** at a water concentration of 0.7ml in 3 ml of DMA, the same water content and reaction conditions were extended to the evaluation of catalyst **153**.

In this instance, however, higher water content resulted in a decrease of ca 25% in conversion in going from 0.5 ml to 0.7 ml after 5 minutes (Figure 5.14, Table 5.19). Overall conversion after 1 hour was also lower 74% with 0.7 ml of water compared to the 91% observed with 0.5 ml of H_2O (Figure 5.14, Table

5.19), while selectivity and isomerization to internal octenes showed a slight improvement with increased water concentration (Table 5.19).

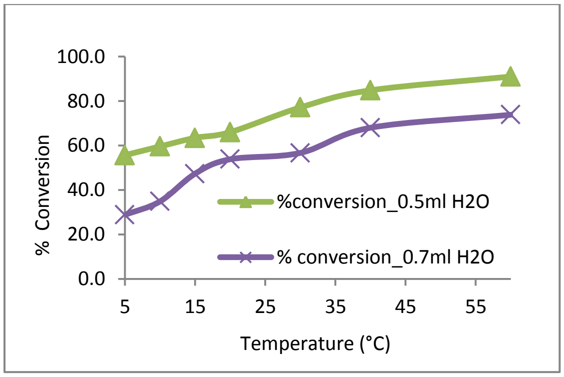


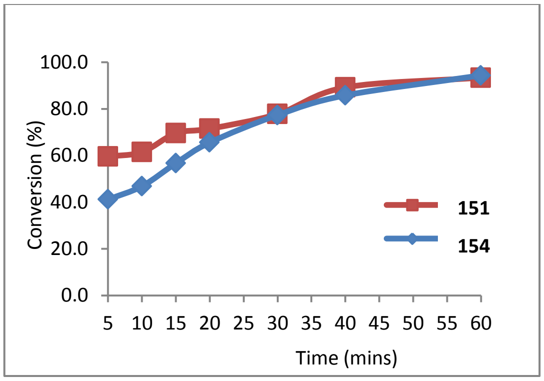
Figure 5.14: Conversion of 1-octene (0.2M) using 0.5 mol% of **153** with 0.5 and 0.7ml of H_2O in 3ml DMA under 9 atm O_2 at 80°C.

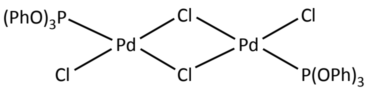
Table 5.19: A comparison of the activity of 0.5 mol% of **153** using 0.5 and 0.7 ml of H_2O to 3ml of DMA with 0.2M 1-octene under 9 atm O_2 at 80°C over a 1 hour period ([a]: after 5 minutes; [b]: after 1 hour).

DMA:H_2O/v:v (ml)	**Conversion (%)**	**Selectivity (%)**	**Internal octene isomers (%)**
3:0.5	55[a]/91[b]	81[b]	6.9[b]
3:0.7	29[a]/74[b]	86[b]	3.0[b]

5.3.2 Dimeric chloro-bridged phosphite catalyst

The influence of the metallocycle moiety on the properties of **151** was established by subjecting 1-octene to reactions with the dimeric phosphite **154** where the metallacycle bond was replaced by a dichloride bridge. Apart from the initial stages of the reaction where **151** showed the higher activity (60% conversion, Figure 5.15), the two catalysts were, however, found to be almost identical; both giving a final conversion of ca 93%.





154

Figure 5.15: Conversion of 1-octene (0.2M) with 0.5 mol% of **151** and **154** at a DMA:H_2O ration of 6:1 under 9 atm of O_2.

5.3.3 Summary

For the cyclopalladated phosphite catalysts **151** and **153** it was found that water concentration had a profound effect on the conversion of 1-octene at the start of the oxidation reaction (first 5 to 10 min.). While this effect persisted over the whole of the reaction period for **153**, water content became less important w.r.t. conversion towards the end of the reaction for catalyst **151**. The optimum water content in the DMA was nevertheless determined to be 0.7 ml and 0.5 ml in 3 ml DMA for catalysts **151** and **153** respectively.

When compared to the acyclic phosphite catalyst **150**, the conversions observed for the dimeric equivalent **154** and cyclopalladated dimeric species **151** were found to be very similar (94 and 93%), but somewhat lower than **150** (100%). The cyclopalladated monomeric phosphite **153** were the least reactive (74% conversion) of the series tested (Table 5.21). W.r.t. selectivity towards 2-octanone formation **151** and **153** were found to be almost equal (89 and 86% respectively), but superior to **150** and **154** (82 and 79% respectively), with the worst selectivity being observed for **154**. On the last parameter determining the quality and usefulness of the series of catalysts, *i.e*. isomerization to internal octenes, **151** and **153** gave very similar results (4 and 3% respectively) and outperformed both **150** and **154** by ca 9% (Table 5.20).

Table 5.20: Relative activity of **150**, **151**, **153,** and **154** towards the oxidation of 1-octene (0.2M) in DMA:H_2O under 9 atm of O_2 at 80°C over a 1 hour period.

Catalyst (DMA:H_2O)	**Conversion (%)**	**Selectivity (%)**	**Internal octene isomers (%)**	**TON (mol/mol)**	**TOF (mol/mol/hr)**
154 (6:1)	94	79	13	74 214	1 237
153 (6:1)	74	86	3.0	57 229	954
151 (3:1)	93	89	4.0	82 937	1 382
150 (6:1)	100	82	13	82 362	1 372

5.4 Palladium phosphinites and phosphines

Having the phosphinite complexes **174** and **175** available, it was decided to also evaluate these catalysts in the Wacker oxidation of 1-octene under conditions optimized for **150**. While no activity was observed with **175** within the first hour, 85% conversion was obtained with **174** (Figure 5.16). A % conversion (84%) similar to that obtained with **174** was, however, obtained with **175** after 8 hours of reaction time. Less than 3% internal octene isomers were observed with **174** and even less than 1% with **175**.

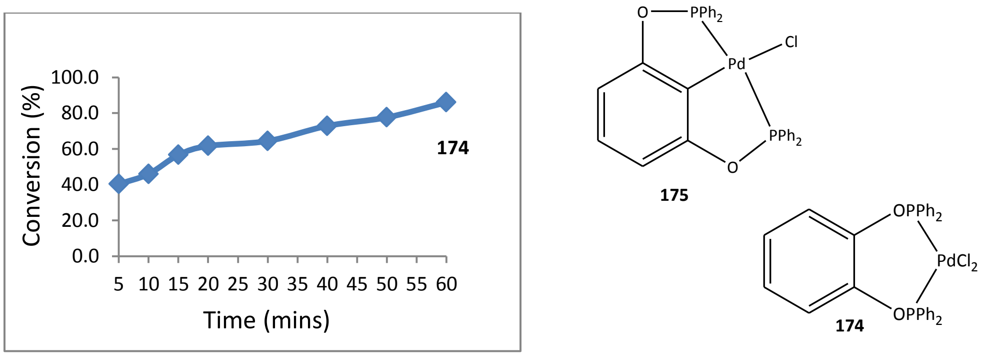
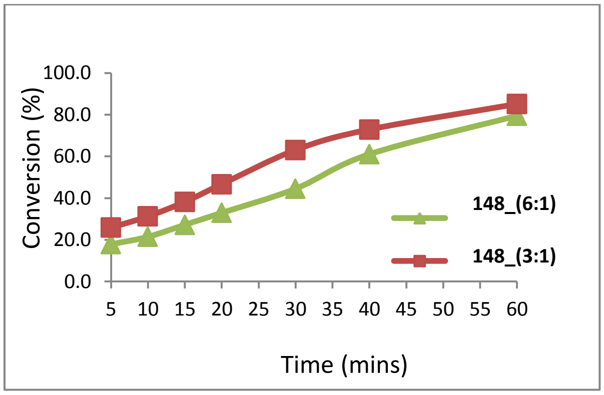
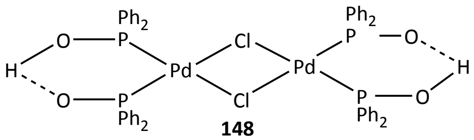


Figure 5.16: Conversion of 1-octene (0.2M) with 0.5 mol% of catalyst **174** vs **175** at a DMA:H_2O ratio of 6:1 under 9 atm of O_2.

The partially hydrolysed dimer **148**, obtained during the synthesis of **174** was also investigated as catalyst in the Wacker oxidation of 1-octene (0.2M) under conditions of 6:1 and 3:1 DMA:H_2O and 0.5

mol% catalyst at 80°C under 9 atm of O_2. It was found that this complex also showed some activity towards the Wacker oxidation of 1-octene. As observed with dinuclear metallocycle **151**, more water in the solvent system showed an increase in the rate of the reaction, at least within the first 5 minutes, from 18% (6:1) to 26% (3:1) respectively (Figure 5.17). The almost parallel slopes between 5 and 20 minutes did however suggest that the reaction proceeded at moderate and similar rates, reaching overall conversions of 79 and 85% respectively after 1 hour.

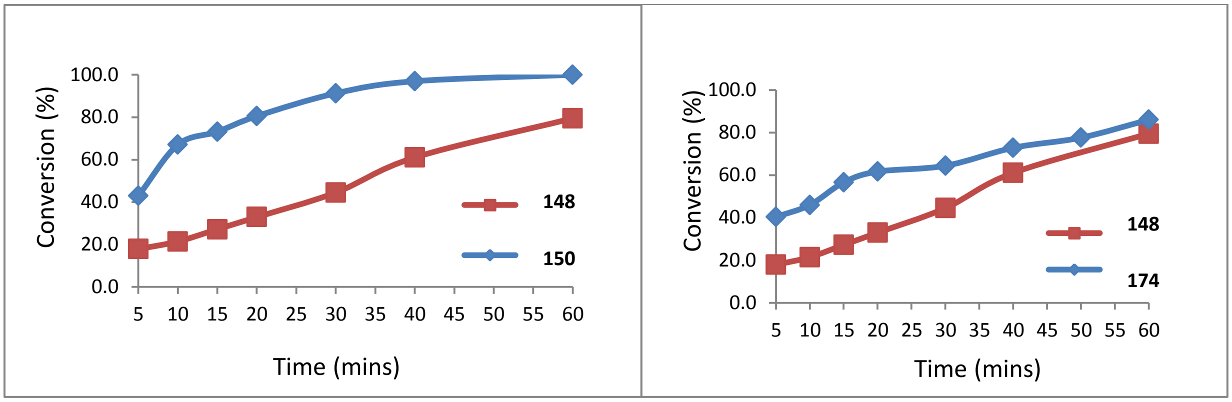


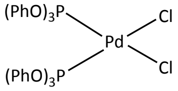


148

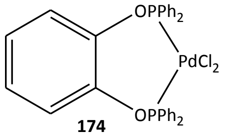
Figure 5.17: A comparison of the activity of **148** in 6:1 vs 3:1 DMA:H_2O.

Since all phosphites and phosphinites are prone to hydrolysis under aqueous conditions and since the hydrolysis product **148** showed some activity towards the Wacker oxidation of 1-octene, it was decided to determine if the activity observed from the different phosphite and phosphinite catalysts could not be attributed to the hydrolysis product **148** only. The catalytic activity of phosphite **150** and phosphinite **174** were therefore compared to that of **148** under conditions of 6:1 DMA:H_2O and 0.5 mol% catalyst at 80°C under 9 atm of O_2. While the reactivities of **150** and **174** were almost the same during the initial stages (first 20 min) of the reaction (Figure 5.18), these catalysts gave conversions of ca 40 to 30 % better than what was observed for **148** during the same period of the process. Since the slope of the plot of conversion *vs* time for catalyst **174** levelled out between 20 and 30 minutes as well as the fact that both **174** and **148** gave virtually the same final conversion (79 and 85%), it could be concluded that hydrolysis of **174** to a species similar to **148** during the 20 - 30 min. period, might be a real possibility. The phosphite **150**, however, proved to be much more reactive over the whole reaction period giving a final conversion of 100%, so the chances of it being hydrolysed during the process can be regarded as very slim.





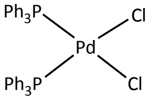
150



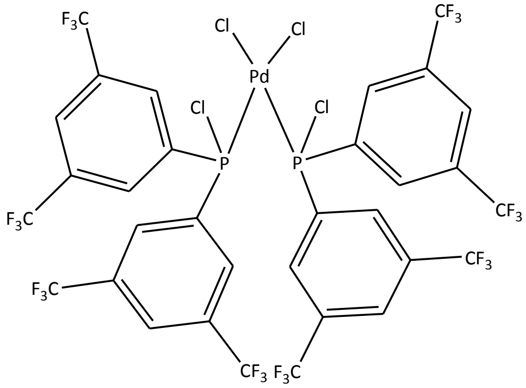
174

Figure 5.18: Relative catalytic activity of **150, 174** and **148** under conditions of 6:1 DMA:H_2O and 0.5 mol% catalyst at 80°C under 9 atm of O_2.

Finally, in order to verify the assumption that the Wacker oxidation would require/be enhanced by electron-withdrawing ligands attached to the palladium, the activity of the triphenylphosphine based catalyst **179** was compared to that of and its chloro and fluoride containing analogue **181** (Figure 5.19**).**



179



181

Figure 5.19: Phosphine complexes **179** and **181**.

Thus 0.2M solutions of 1-octene in DMA:H_2O (6:1) was reacted over 0.5 mol% of the catalysts under 9 atm of O_2 at 80°C for a 1 hour period. No activity was observed with **179** after one hour, while **181** gave 53% conversion confirming the assumption that additional electron-withdrawing substituents would enhance the π-accepting abilities of the P atom, which could lead to enhanced electrophilicity of the Pd atom and thus increased rates of reaction.

5.5 Conclusion

This study has demonstrated for the first time that phosphite-based palladium catalysts have great potential as catalysts in the Wacker oxidation of alkenes. All the phosphite based catalysts tested (**150-154)** except the phosphine analogue (**152**) were active in the oxidation of 1-octene within 1 hour. With oxygen as oxidant, the most active catalysts were the monodentate phosphite **150** and dinuclear cyclopalladated equivalent **151** (TOF's > 1300), followed by the chloro-bridged dimeric analogue **154** (TOF > 1200). It was also interesting to note that replacing the phosphite ligand on the mononuclear cyclopalladated catalyst **153** with a phosphine moiety resulted in a catalyst (**152**) that was completely inactive under the optimum conditions as determined for the other catalysts. When compared to the known $PdCl_2$ in DMA system, it was noticed that no pre-stirring of the phosphite catalysts were necessary since all of them are easily soluble in the DMA, while the activity of **150** proved to be only slightly worse than that of $PdCl_2$ (TOF: ca 1400 vs 1370) under the same conditions with oxygen as oxidant. Catalyst **150** also outperformed a number of other palladium catalysts, *i.e.* $PdCl_2(PhCN)_2$, $Pd(OAc)_2$, and $Pd(CF_3SO_3)_2$, that have been reported for the Wacker oxidation. It was also determined that one of the phosphite catalysts (**150**) could be recycled at least 3 times without considerable loss in activity (conversions remaining > 95%) and selectivity towards 2-octanone (82%).

W.r.t. hydrogen peroxide and TBHP as oxidants, the activity of only **150** was evaluated and it was determined that 12 equivalents of oxidant was needed to reach decent conversions. H_2O_2 performed the best and afforded conversion (99%), selectivity (86%), and TOF (1220) almost as good as those found for oxygen as oxidant (100, 82% and 1370 respectively). In addition, the catalyst could also be recycled three times when hydrogen peroxide was used as oxidant, but no recycling was possible with TBHP.

Although all phosphite catalysts promoted isomerization to internal 1-octene isomers to some extent, the cyclopalladated mono **153** and dinuclear **151** catalysts proved to be the best in this aspect of the reaction w.r.t. oxygen as oxidant and led to very low quantities of isomerised products being observed (3 and 4% respectively). It was also evident that the type and amount (for H_2O_2 and TBHP) of oxidant played a crucial role in enhancing or suppressing isomerization and hydrogen peroxide (at only 2% isomerization) was found to be the best oxidant in this regard followed by oxygen (13%).

No induction period was observed with any of the phosphite catalysts, suggesting that the formation of the active catalytic species was rapid as anticipated. It was also determined that the reactivity of **150** was considerable high than that of the hydrolyzed complex **148**. The phosphite moieties therefore appeared to provide the necessary stabilization for palladium as no Pd^0 aggregation was observed with all catalysts, although recyclability was limited to only O_2 and H_2O_2.

For the palladium phosphinite catalysts **174** and **175** it was found that both were active in the Wacker oxidation of 1-octene albeit with very low rates for the latter complex (**175**). The low reactivity of **175** was similar to that of the phosphines **179** and **181** where **179** showed some conversion only after 3 hours and **181** gave only 53% conversion after an hour. Through a comparison of the reactivity of **174** with that of the hydrolyzed equivalent **148**, it seemed as if the phosphinite catalysts are prone to hydrolysis under the prevailing conditions as the final conversion of both these catalysts were almost the same (85 and 79% respectively).

Finally, ample evidence to support the assumption that additional electron-withdrawing substituents on the phosphorous atom of ligands that would enhance the π-accepting abilities of the P atom and thus electrophilicity of the palladium which would lead to increased activity of catalysts (when compared to phosphines) in the palladium catalysed Wacker oxidation of alkenes, has been found.

CHAPTER 6 - EXPERIMENTAL

6.1 General remarks

Solvents were dried according to standard procedures (Table 6.1) and handled under an inert atmosphere of nitrogen or argon using standard purification and drying methods (Table 6.1).[203] Except where specific temperatures are specified, all reactions were performed at room temperature.

Table 6.1: General drying agents for solvents

Solvent	Drying agent
Acetonitrile	CaH_2, 4 Å molecular sieves
Diethyl ether, chlorodiphenylphosphine	Na wire
Dichloromethane, pentane, hexane	CaH_2
Dimethylformamide	Silica gel, basic alumina, molecular sieves (4 Å)
Pyridine	KOH
Tetrahydrofuran, toluene	Na, benzophenone
Methanol, ethanol	Mg turnings, I_2

All solvents unused were stored over appropriate molecular sieves or sodium wire and sealed with a septum. All glassware, syringes and all the equipment used were thoroughly cleaned and oven-dried (>150°C) before use. Except where specific temperatures are specified, all reactions were performed at room temperature. Sensitive manipulations were carried out in a Schlenk apparatus that was supplied with a positive flow of argon.

Column chromatography was conducted either on silica gel 60, particle size 0.063 mm – 0.200 mm (70 – 230 mesh ASTM) or neutral alumina, particle size 0.063 mm – 0.200 mm (70 – 230 mesh

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[203] B. S. Furniss, A. J. Hannaford, P. W. G. Smith, A. R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, 5th Edn., Longman Group UK Ltd., **1989**, pg 395.

ASTM). Columns were generally prepared with 1:100 ratio of product to chromatographic material. Solvents used for chromatography were of analytical grade and used without further purification.

Unless stated otherwise, all precipitations were performed at room temperature. If more than one solvent was used in this regard, two different annotations are used, e.g., dichloromethane/hexane denotes that a mixture of two solvents was used, whereas dichloromethane-hexane denotes that dichloromethane was used to dissolve the solid and that slow addition of hexane resulted in precipitation.

6.2 Instrumentation

Melting points were determined on a Stuart SMP3 melting point apparatus by Barloworld Scientific Limited, and are uncorrected.

NMR spectra were recorded on a Bruker AM 300 or a Bruker 600 MHz FT spectrometer at ambient temperatures. ^{1}H NMR spectra were referenced internally using residual protons in the deuterated solvent ($CDCl_3$: δ 7.28 at 300 MHz and δ 7.26 at 600 MHz) and values reported relative to an internal standard, tetramethylsilane (δ 0.00). ^{13}C NMR spectra were similarly referenced internally to the solvent resonance ($CDCl_3$: δ 77.0) with values reported relative to tetramethylsilane (δ 0.00). An external standard, 85% H_3PO_4 (δ 0.00, 121.489 MHz), was used in collecting ^{31}P NMR spectra. A singlet at *ca*. 1.56 ppm on the ^{1}H NMR spectra is recognized as residual moisture.[204] All ^{1}H and ^{13}C assignments were confirmed by COSY-2D, NOESY-2D, HMQC/HSQC-2D, HMBC-2D and ^{13}C DEPT experiments. All NMR values are given in 'ppm' and coupling constants (*J*) in 'Hz'. $Pd(PPh_3)_4$, $PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$ and $PdCl_2COD$ were prepared following literature methods of stirring $PdCl_2$ with PPh_3, CH_3CN, PhCN and COD respectively.[205]

Gas chromatography (GC) was conducted on a Shimadzu GC-2010 fitted with a PONA column (50.0m x 0.20mm x 0.50) and FID detector. Nitrogen was used as carrier gas.

Mass Spectrometry (MS) and GC-MS were performed *via* Electron Impact (EI) ionization on a Shimadzu GC-MS QP-2010 gas chromatograph-mass spectrometer. Alternatively, a Bruker Microflex LRF20 MALDI-TOF mass spectrometer was used to obtain MS of some compounds.

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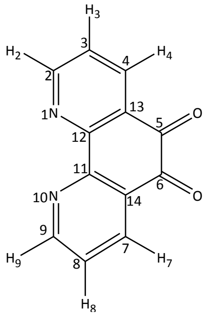
[204] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem*., **1997**, *62*, 7512.

[205] L. S. Hegedus, B. H. Lipshutz, *Organometallics in Synthesis: A Manual*, **2002**, 2nd Edition (M. Schlosser, Ed.), John Wiley & Sons, New York.

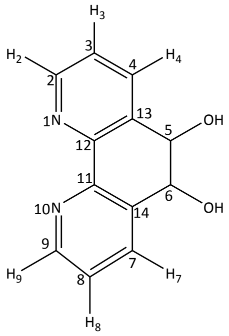
6.3 Phenanthrolines

6.3.1 1,10-phenanthroline-5,6-dione (127).[155]



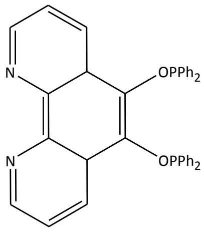
An ice-cold mixture of concentrated sulfuric acid (40 ml) and nitric acid (20 ml) was added to 1,10-phenanthroline **128a** (4000 mg, 22 mmol) and potassium bromide (4000 mg, 33 mmol, 1.5 eq.). The mixture was heated under reflux for 3 hours. The hot yellow solution was then added to ice (500 ml) and neutralized to a slightly acidic pH with sodium hydroxide. The organic layer was thus taken up in dichloromethane and dried over anhydrous sodium sulfate. The solvent was subsequently removed under vacuum and the yellow solid residue further purified by recrystallization from ethanol. The yellow product was identified as 1,10-phenanthroline-5,6-dione **127** (4500 mg, 95%); ^{1}H NMR δ_H (600 MHz CDCl$_3$) 9.11 (dd, 2H, dd, *J* = 4.6, 1.5 Hz, H-2), 8.50 (dd, 2H, *J* = 7.8, 4.6 Hz, 2H, H-4), 7.59 (dd, 2H, *J* = 7.8, 4.6 Hz, H-3); ^{13}C NMR δ_C (150.963 MHz, CDCl$_3$) 178.7 (C-5, C-6), 156.4 (C-2), 152.9, 137.3 (C-4), 128.1, 125.6 (C-3); IR (KBr cm^{-1}) ν_{max} 3061.4, 1703.2, 1685.1, 1575.9, 1560.8, 1460.1, 1414.3, 1314.9, 1292.9, 1205.6, 1115.7, 1083.8, 1061.4, 1010.4, 925.3, 816.6, 738.8, 668.6.

6.3.2 1,10-phenanthroline-5,6-diol (142).[163]



1,10-Phenanthroline-5,6-dione **127** (1100 mg, 5.2 mmol) and hydrazine sulfate (500 mg, 3.8 mmol, 1.3 eq.) were mixed with water (15 ml) and heated over a water bath until the gas evolution had ceased (*ca*. 5 minutes). The orange solid obtained was washed with copious amounts of ethanol and dried under vacuum to give 1,10-phenanthroline-5,6-diol **142** as a yellow solid (902 mg, 80%); ^{1}H NMR δ_H (600 MHz DMSO-d$_6$) 9.06-9.05 (m, 2H, Ar-H), 8.63-8.60 (m, 2H, Ar-H), 7.92-7.87 (m, 2H, Ar-H), 6.91 (2H, s, O-H); IR (KBr cm^{-1}) ν_{max} 3279, 3183.8, 3036.5, 2772.8, 2562.7, 1644.0, 1611.6, 1600.2, 1496.4, 1474.1, 1342.8, 1326.1, 1186.4, 1110.3, 1061.3, 1029.2, 963.1, 910.2, 804.3, 719.7, 619.5.

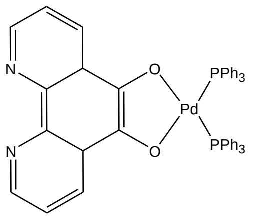
6.3.3 1,10-phenanthroline-5,6-diol and chlorodiphenylphosphine (143).[180]



1,10-Phenanthroline-5,6-diol **142** (200 mg, 0.9 mmol) was suspended in diethyl ether (5 ml) and chlorodiphenylphosphine (0.33 ml, 1.8 mmol, 2 eq.)

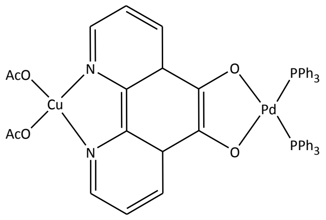
added. The temperature of the mixture was brought down to 0°C and triethylamine (0.27 ml, 1.9 mmol, 2.1 eq.) in diethyl ether (1 ml) added dropwise. The reaction mixture was left to stir at 0°C for two hours, then left to warm up to room temperature and stirred overnight. The yellow precipitate was filtered off, washed with diethyl ether and the solvent reduced under vacuum. No product was obtained.

6.3.4 $(PPh_3)_2$Pd-(*O'*,*O*-1,10-phenanthroline-5,6-dione) (132).[150]



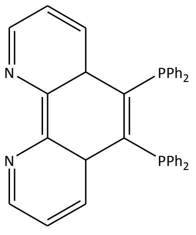
$Pd(PPh_3)_4$ (610 mg, 0.49 mmol) and **127** (120 mg, 0.57 mmol, 1.2 eq.) were added as solids to boiling dichloromethane (15 ml). After filtration, *n*-hexane (20 ml) was added to the filtrate and the solvent removed by distillation until a solid began to appear. The brown product was removed by filtration and purified by reprecipitation from dichloromethane-hexane to give **(**$PPh_3)_2$Pd-(*O'*,*O*-1,10-phenanthroline-5,6-dione) **132** (490 mg, 89%).

6.3.5 $(PPh_3)_2$Pd-(*O'*,*O*-1,10-phenanthroline-5,6-dione-*N'*,*N*)Cu$(OAc)_2$ (134)[158]



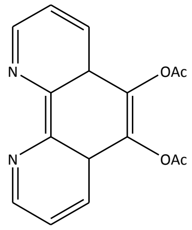
$(PPh_3)_2$Pd-(*O'*,*O*-1,10-phenathroline-5,6-dione) **132** (12 mg, 0.014 mmol) in anhydrous dichloromethane (1 ml) was added dropwise to a solution of copper acetate (2.6 mg, 0.014 mmol, 1 eq.) in absolute ethanol (1 ml). The solution was heated under reflux overnight. The reaction mixture was cooled, the precipitate filtered off and diethyl ether (5 ml) added. The brown solution was left overnight in the fridge and the precipitate that formed filtered off to give a brown solid.

6.3.6 1,10-phenanthroline and chlorodiphenylphosphine (136).[160]



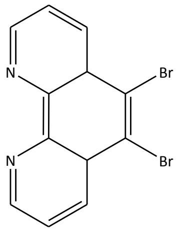
(*Modified literature procedure*): 1,10 Phenanthroline **128a** (200 mg, 1.1 mmol) was suspended in diethyl ether (2 ml) and the mixture cooled to 0°C. Chlorodiphenylphosphine (0.32 ml, 2.3 mmol, 2.1 eq.) and chlorodiphenylphosphine (0.4 ml, 2.2 mmol, 2 eq.) were then added and the reaction mixture allowed to stir at 0°C for 2 hours then allowed to warm up to room temperature and left to stir overnight. The reaction mixture was filtered off over celite and the solvent removed under vacuum. The crude mixture was taken for ^{31}P NMR analysis which contained multiple signals in the phosphine region. No product was isolated. Other bases tried were 2,6-Lutidine, n-BuLi (-78°C), pyridine/dmap.

6.3.7 1,10-phenanthroline and Ac_2O (137).[161]



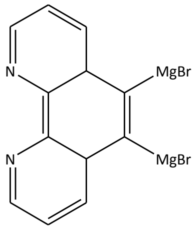
1,10-Phenanthroline **128a** (200 mg, 1.1 mmol) in THF (1.5 ml) was added at once to an n-BuLi (0.9 ml, 2.3 mmol, 2.1 eq., 2.5M in hexane) solution in THF which was cooled to -70°C. The reaction mixture turned to a red-brown suspension which was left to stir at -70°C for 15 minutes then at room temperature for 30 minutes. Acetic anhydride (2.1 ml, 2.2. mmol, 2 eq.) was then added in portions over 5 minutes. The red-brown mixture turned to orange and this was left to stir overnight at room temperature. The reaction mixture was then poured onto ice and the organic layer extracted with ethyl acetate (3 x 10ml). The combined organic extracts were washed with aqueous sodium bicarbonate (1N) and dried over sodium sulfate. The solvent was then reduced under vacuum and the yellow oil residue taken up in preparative TLC. No product was isolated.

6.3.8 1,10-phenanthroline and Br_2 (138).[162]



1,10-phenanthroline **128a** (900 mg, 5 mmol) was added to a stainless steel tube which was then cooled to -40°C. Fuming sulphuric acid (7 ml, 30% SO_3) was then added and the mixture left to cool at -40°C. Bromine (0.3 ml, 1 mmol, 0.2 eq.) was then added and the reactor sealed and immersed in an oil bath at 140°C. The reaction was left to stir for 12 hours, cooled and the mixture poured onto ice water. The product was precipitated from this mixture by slow addition of ammonium hydroxide to pH 3. The yellow solid recovered was filtered and re-precipitated from ethanol (150 mg, 44%); ^{1}H NMR δ_H (600 MHz $CDCl_3$) δ_H 9.20-9.19 (2H, m, Ar-H), 8.77-8.76 (2H, m, Ar-H) and 7.68-7.62 (2H, m, Ar-H); ^{13}C NMR δ_C (150.963 MHz, $CDCl_3$) 151.1, 144.8, 137.4, 128.2, 124.9, 124.5.

6.3.9 1,10-phenanthroline-5,6-dibromo and Mg/I_2 (139).[206]



Magnesium turnings (29 mg, 1.2 mmol) and I_2 were stirred in diethyl ether and after H_2 evolution had ceased, 1,10-phenanthroline-5,6-dibromo (100 mg, 2.9 mmol) was added in portions, allowing a gentle reflux. The reaction was then left to stir until no gas evolution was observed. The reaction mixture was allowed to settle while a standardization set-up was prepared.

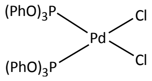
Standardization:[206] In a dry 3-necked flask under a positive flow of argon was added 1,10-phenanthroline in benzene. 1M of butanol in p-xylene was prepared and added to a burette set on a 3-necked flask. The Grignard reagent (0.5 ml) was then transferred into this three-necked flask and the butanol mixture titrated against the stirred mixture of the Grignard reagent until a red-brown colour was obtained. Using the relation that 1 mol butan-2-ol is equivalent to 1 mol of organometallic reagent, the concentration of the Grignard reagent was determined to be 0.25M.

6.3.10 1,10-phenanthroline-5,6-dibromo Grignard reagent with chlorodiphenylphosphine (136).

To the Grignard reagent (2 ml, 0.25M) at 0°C was added dropwise chlorodiphenylphosphine (0.18 ml, 1 mmol, 2 eq.) in diethyl ether (1 ml). The reaction mixture was allowed to stir for 2 hours at 0°C and then allowed to warm up to room temperature and stirred overnight. The reaction mixture was filtered off over celite and the solvent removed under vaccum. The yellow residue was taken up in preparative TLC plates with ethyl acetate:hexane (7:3). No product was obtained. Similarly, 5-chloro-1,10 phenthanthroline was attempted. No Grignard reagent could be generated.

6.4 Synthesis of Aryl phosphites

6.4.1 *cis*-$PdCl_2[P(OPh)_3]_2$ (150).[175]



$PdCl_2(PhCN)_2$ **145** (98 mg, 0.2 mmol) was dissolved in dichloromethane (2 ml) and to the resulting red solution was added triphenylphosphite (0.1 ml, 0.5 mmol, 2 eq.) at once.

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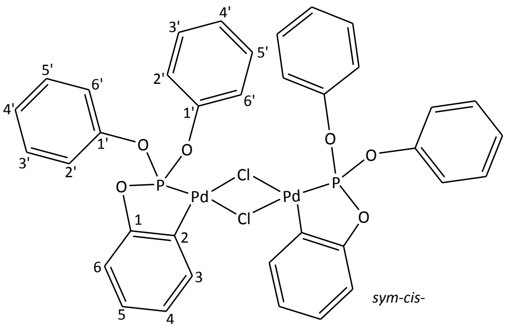
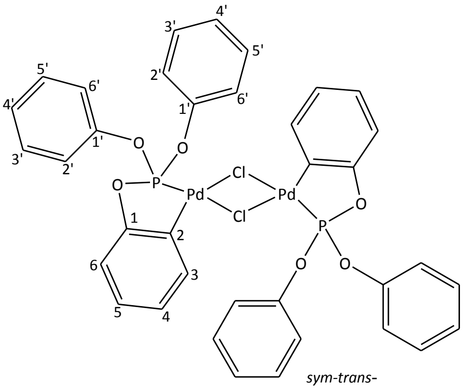
[206] B. S. Furniss, A. J. Hannaford, P. W. G. Smith, A. R. Tatchell, Vogel's Textbook of Practical Organic Chemistry, 5th Edn., Longman Group UK Ltd., 1989, pg 443.

The red solution immediately turned to a clear pale yellow colour and was left to stir for 10 minutes. Pentane (20 ml) was then added, precipitating a white product which was filtered off and precipitated from dichloromethane-pentane to afford the title compound as a white solid (176 mg, 86% yield); m.p. 175.9-176.1°C (lit.[175] m.p. 174 – 176 °C); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 83.6 (lit.[175] 83.0); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.33-7.20 (18H, m, Ar-H), 7.17-7.15 (12H, m, Ar-H); ^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 150.48, 130.02, 125.89, 120.73.

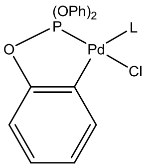
6.4.2 [Pd(*μ*-Cl)(P(OPh)$_2$(OC$_6$H$_4$))]$_2$ (151).[175]





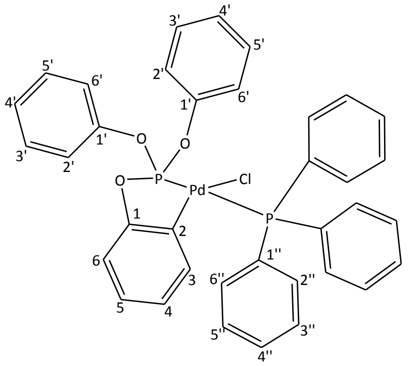
cis-PdCl$_2$[P(OPh)$_3$]$_2$ **150** (146 mg, 0.2 mmol) was suspended in toluene (10 ml) and palladium(II)dichloride (34 mg, 0.2 mmol, 1 eq.) was then added. The reaction mixture was heated under reflux with a stream of argon purging through the mixture to drive out HCl gas. The reaction was stopped once all the PdCl$_2$ had dissolved and the HCl emission had ceased (*ca.* 5 hours). The mixture was allowed to cool to room temperature and filtered through Celite which was then washed with portions of dichloromethane (3 x 5 ml). The solvent was reduced under vacuum and the resulting crude solid precipitated from dichloromethane-pentane to afford the title compound as a pale yellow solid (119 mg, 72%); m.p. 174.8-175.0°C; ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P (*cis*-) 125.2 (lit.[175] 124.6), (*trans*-) 122.9 (lit.[175] 122.3); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.47-7.45 (2H, m, Ar-H), 7.36-7.24 (13H, m, Ar-H), 7.15-7.07 (10H, m, Ar-H), 6.98-6.97 (1H, m, Ar-H), 6.91-6.87 (2H, m, Ar-H); ^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 155.7 (C-1), 149.4 (C-1'), 136.8 (C-3), 133.1 (C-2), 121.7 (C-2'), 127.8 (C-5), 123.2 (C-4), 111.4 (C-6), 129.9 (C-3'), 126.3 (C-4') (allocation of ^{13}C signals as published by Albinati).

6.4.3 General procedure for the preparation of PdCl(P(OPh)$_2$(OC$_6$H$_4$))(L) (L= PPh$_3$, P(OPh)$_3$).[175]



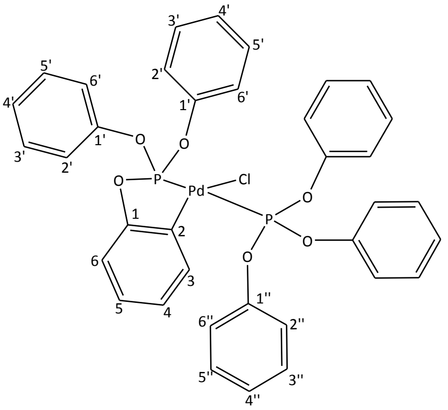
[Pd(μ-Cl)(P(OPh)$_2$(OC$_6$H$_5$))]$_2$ **151** (90 mg, 0.7 mmol) was dissolved in dichloromethane (2 ml) and **L** (2 eq.) added neat. The reaction mixture was allowed to stir for 10 minutes and the solvent removed under vacuum. The resulting crude solid was re-precipitated from dichloromethane-pentane/hexane (1:10, V/V).

6.4.3.1 PdCl(P(OPh)$_2$(OC$_6$H$_4$))(PPh$_3$) (152).[175]



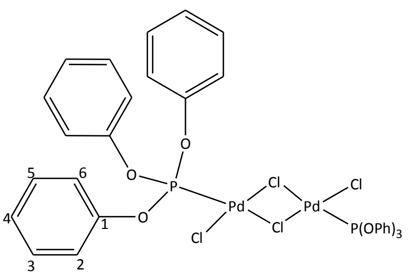
[Pd(μ-Cl)(P(OPh)$_2$(OC$_6$H$_4$))]$_2$ **151** (90 mg, 0.7 mmol) and triphenylphoshine (53 mg, 0.2 mmol, 2 eq.). White solid obtained, (110 mg, 77%); m.p. 186.2-187.4°C (Lit.[175] m.p. 184 °C (dec)); ^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 129.9, 17.7 (Lit.[175] δ_P 129.9, 17.8); ^{1}H NMR (600 MHz, CDCl$_3$) δ_H 8.49-8.44 (1H, m, H-3), 7.50-7.45 (6H, m, H-3'',H-5''), 7.47-7.44 (3H, m, H-4''), 7.38-7.33 (6H, m, H-2'', H-6''), 7.24-7.22 (4H, m, H-3', H-5'), 7.19-7.16 (3H, m, H-4', H-5), 7.10-7.08 (1H, m, H-4), 6.93-6.92 (1H, m, H-6), 6.88-6.87 (4H, m, H-2', H-6'); ^{13}C NMR (150.963 MHz , CDCl$_3$) δ_C 156.2, 149.9, 142.8, 142.0, 134.7, 134.7, 134.6, 131.7, 131.4, 130.5, 129.8, 128.4, 128.2, 125.3, 123.5, 120.3.

6.4.3.2 PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$) (153).[175]



[Pd(μ-Cl)(P(OPh)$_2$(OC$_6$H$_5$))]$_2$ **151** (55 mg, 0.061 mmol) and triphenylphosphite (0.03 ml, 0.12 mmol, 2 eq.); White solid (69 mg, 73%); m.p. 140.3-140.5°C (Lit.[175] m.p. 142 °C); ^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 128.4, 109.6 (Lit.[175] 127.9, 108.9); ^{1}H NMR (600 MHz, CDCl$_3$) δ_H 8.21-8.17 (1H, m, H-3), 7.27-7.25 (9H, m, 3x(H-3", H-4", H-5")), 7.21-7.19 (8H, m, 2x(H-4'), 3x(H-2", H-6")), 7.17-7.15 (5H, m, 2x(H-3', H-5'), H-6), 7.09-7.08 (4H, m, 2x(H-2', H-6')), 7.03-7.00 (1H, m, H-4), 6.93 (1H, m, H-5); ^{13}C NMR (150.963 MHz, CDCl$_3$) δ_C 156.6, 150.5, 150.1, 142.4, 141.1, 136.9, 130.1, 129.8, 128.6, 125.8, 125.4, 123.5, 123.4, 121.1, 120.4, 111.1, 110.9.

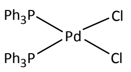
6.4.4 $Pd_2Cl_4[P(OPh)_3]_2$ (154).[177]



A solution of $[Pd(\mu\text{-}Cl)(P(OPh)_2(OC_6H_5))]_2$ **151** (200 mg, 0.2 mmol) in dichloromethane (5 ml) was treated with anhydrous HCl that was generated from H_2SO_4 and NaCl and the reaction monitored to completion by ^{31}P NMR. The orange-red solution was then concentrated under vacuum and the desired product precipitated from dichloromethane-pentane as an orange solid (189 mg, 87%); m.p. 164.1-164.5 °C; ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 56.7 ppm; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.40-7.37 (6H, m, H-3, H-5), 7.28-7.29 (9H, m, H-2, H-6, H-4); ^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 150.2, 130.1, 126.2, 120.6.

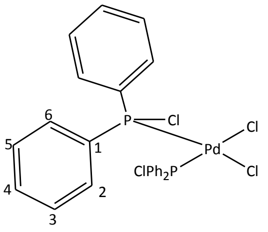
6.5 Palladium arylphosphines

6.5.1 $PdCl_2(PPh_3)_2$ (179).[197]



Triphenylphosphine (138 mg, 0.5 mmol, 2.5 eq.) was added to a stirred suspension of $PdCl_2(PhCN)_2$ **145** (98 mg, 0.2 mmol) in dichloromethane (2 ml). The reaction mixture was filtered off over celite and the filtrate reduced under vacuum and the yellow oily residue washed with copious amounts of hexane. The yellow solid recovered filtered off, washed with hexane and re-dissolved in dichloromethane for re-precipitation by hexane to obtain a yellow solid (136 mg, 76%); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 23.5 ppm; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.75-7.72 (2H x6, m, Ar-H), 7.47-7.45 (1H x6, m, Ar-H), 7.42-7.39 (2H x6, m, Ar-H); ^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 135.1, 130.5, 129.8, 128.1.

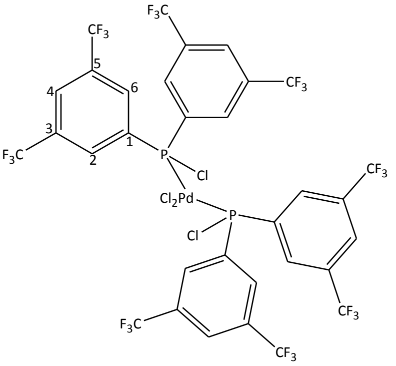
6.5.2 $PdCl_2(PPh_2Cl)_2$ (144).[173]



Chlorodiphenylphosphine (0.20 ml, 1.0 mmol, 2 eq.) in toluene was added dropwise to an orange solution of $PdCl_2(PhCN)_2$ **145** (200 mg, 0.5 mmol) in toluene (5 ml). The orange solution turned yellow and was allowed to stir for 30 minutes. Hexane (20 ml) was then added and the yellow precipitate that formed filtered off, washed repeatedly with hexane (3 x 10 ml) and dried under vacuum to give the title compound as a yellow solid (295 mg, 91%); ^{31}P NMR (121.489

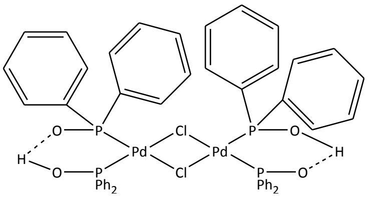
MHz, $CDCl_3$) δ_P 95.3; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.92-7.86 (8H, m, H-5, H-3), 7.60-7.55 (4H, m,H-4), 7.55-7.49 (8H, m, H-2, H-6).

6.5.3 $PdCl_2\{[3,5\text{-}(CF_3)_2C_6H_3]_2PCl\}_2$ (181).[173]



Similarly, bis[3,5-di(trifluoromethyl)phenyl]chloro-phosphine **180** (205 mg, 0.4 mmol) and $PdCl_2(PhCN)_2$ (80 mg, 0.2 mmol, 0.5 eq.) a yellow solid (110 mg, 72%); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 81.9; ^1H NMR (600 MHz, $CDCl_3$) δ_H 8.29 (2H, m, H-2, H-6), 8.17 (1H, m, H-5); compounds precipitates out of $CDCl_3$ during a ^{13}C experiment.

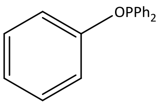
6.5.4 $Pd_2Cl_2\{(PPh_2OPPh_2(OH)\}_2$ (148).[173]



$(PPh_2Cl)_2PdCl_2$ **144** (200 mg, 0.3 mmol) was suspended in acetone (1 ml) and concentrated HCl (1 ml) was added dropwise with stirring. The clear yellow solution was concentrated and water added to induce precipitation. The yellow amorphous solid obtained was filtered off and dried under vacuum (343 mg, 97%); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 78.3 ppm; ^1H NMR (600 MHz, $CDCl_3$) δ_H 7.58 (16H, m, Ar-H), 7.40 (8H, m, Ar-H), 7.27 (16H, m, Ar-H); ^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 135.5, 135.2, 135.0, 132.0, 131.0, 128.0.

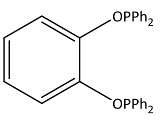
6.6 Arylphosphinites

6.6.1 $PPh_2(OC_6H_5)$ (155).[180]



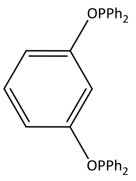
Phenol **158** (200 mg, 2.1 mmol) was suspended in toluene (5 ml) and chlorodiphenylphosphine (0.4 ml, 2.0 mmol, 1 eq.) added at room temperature. triethylamine (0.3 ml, 2.3 mmol, 1.1 eq.) was subsequently added dropwise to the stirred solution over 15 minutes and the reaction mixture allowed to stir under reflux overnight. The reaction mixture was then allowed to cool and filtered through Celite which was washed with THF (3 x 15 ml) and the solvent removed under vacuum. The yellow oil recovered was used in subsequent steps without further purification; (crude - 7025 mg); ^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 110.6; *m/z* (EI) 277.05 (M$^+$).

6.6.2 $PPh_2(2-OC_6H_4OPPh_2)$ (156).



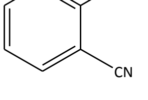
Chlorodiphenylphosphine (0.8 ml, 2.0 mmol, 2 eq.) in toluene (5 ml) was cooled to 0°C and a mixture of catechol **160** (200 mg, 1.8 mmol) and triethylamine (0.4ml, 2 mmol, 2.1 eq.) in toluene (2 ml) was added dropwise. The reaction mixture was allowed to stir at 0°C for 2 hours then left to stir overnight at room temperature. The reaction mixture was subsequently filtered through Celite which was then washed with toluene (3 x 10 ml). The solvent was then reduced under vacuum and the *yellow-brown oil* recovered used in subsequent steps without further purification (crude- 8654 mg); ^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 114.0; *m/z* (EI) 477.20 (M$^+$).

6.6.3 $PPh_2(3-OC_6H_4OPPh_2)$ (157).[184]



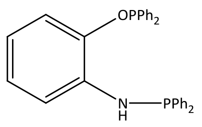
Resorcinol **161** (200 mg, 1.8 mmol) was suspended in toluene (5 ml) and chlorodiphenylphosphine (0.6 ml, 3.6 mmol, 2 eq.) added at room temperature. Triethylamine (0.5 ml, 3.8 mmol, 2.1 eq.) was added dropwise to the stirred solution over 15 minutes and the reaction mixture allowed to stir under reflux overnight. The reaction mixture was then allowed to cool and filtered through Celite which was washed with THF (3 x 15 ml) and the solvent removed under vacuum. The yellow oil recovered was used in subsequent steps without further purification (crude - 9730 mg); ^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 111.2.

6.6.4 $PPh_2(2-OC_6H_4CN)$ (162).



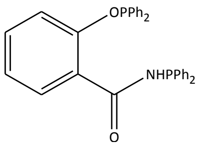
Chlorodiphenylphosphine (0.2 ml, 0.9 mmol, 1 eq.) in toluene (5 ml) was stirred at 40°C and treated with a mixture of 2-hydroxybenzonitrile **165** (200 mg, 0.8 mmol) and triethylamine (0.1 ml, 0.9 mmol, 1.1eq.) in toluene (2 ml). The reaction mixture was allowed to stir under reflux over 4 hours. Upon cooling, the mixture was filtered through Celite, which was washed with toluene (3 x 15 ml) and the solvent removed *in vacuo*. The *orange oil* recovered was used without further purification (crude - 8324 mg); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 115.7.

6.6.5 $PPh_2(2\text{-}OC_6H_4NHPPh_2)$ (163).



Chlorodiphenylphosphine (0.7 ml, 3.6 mmol, 2 eq.) in toluene (5 ml) was cooled to -10°C and treated with a mixture of 2-aminophenol **166** (200 mg, 1.8 mmol) and triethylamine (0.5 ml, 3.8 mmol, 2.1 eq.) in toluene (5 ml). The mixture was stirred for 10 hours at -10°C the left to stir at room temperature overnight. The mixture was filtered through Celite, which was washed with THF (3 x 5 ml). The solvent was concentrated *in vacuo* to give a *pale yellow oil* which was used in subsequent steps without further purification(crude - 9888 mg); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 114.6, 26.6.

6.6.6 $PPh_2(2\text{-}OC_6H_4CONHPPh_2)$ (164).

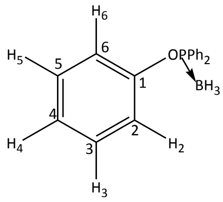


Same procedure as in **5.5.6.2**: salicylamide **167** (200 mg, 1.5 mmol), NEt_3 (0.4 ml, 3.1 mmol, 2.1 eq.), Chlorodiphenylphosphine (0.5 ml, 2.9 mmol, 2 eq.) to give a *pale yellow oil* (9355 mg); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 116.2, 24.9.

6.7 General procedure for protection with borane dimethylsulfide

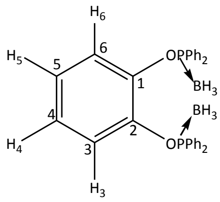
An unpurified phosphinite (500 mg) was dissolved in toluene (20 ml) and borane dimethylsulfide (0.1M in THF, 0.5 eq. with regard to starting R-OH) added all at once. The reaction mixture was stirred at room temperature overnight. Methanol (1 ml) was then added slowly to destroy the excess borane. The solvent was reduced under vacuum and the pale yellow oil residue passed through a silica-gel column (ethyl acetate:hexane 3:7, V/V), followed by further purification by preparative TLC (ethyl acetate:hexane 3:7, V/V).

6.7.1 $PPh_2(OC_6H_5).BH_3$ (168).



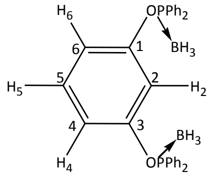
White plate-like flakes (383 mg, 73%, with regard to phenol); m.p. 91.7-92.2°C; R_f 0.8 (ethyl acetate:hexane, 3:7, V/V); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 107.2 (bs); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.90-7.86 (4H, m, Ar-H), 7.59-7.57 (2H, m, Ar-H), 7.53-7.52 (4H, m, Ar-H), 7.28-7.25 (2H, m, H-3, H-5), 7.15-7.13 (1H, m, H-4), 7.05-7.04 (2H, m, H-2, H-6), 1.29-0.87 (3H, m, BH_3); ^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 152.1 (C-1), 143.9, 132.2, 131.7, 131.6, 131.5, 131.1, 129.3 (C-3, C-5), 128.6, 124.7 (C-4), 121.8 (C-2, C-6); *m/z* (EI) 291.10 (M^+, 94.4%), 225.0 (24.1%), 185.0 (100%), 122.10 (24.0%).

6.7.2 $PPh_2(2\text{-}OC_6H_4OPPh_2).(BH_3)_2$ (169).



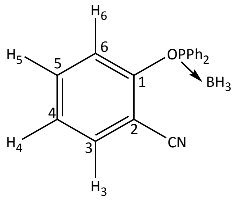
White solid (240 mg, 45%); R_f 0.40 (ethyl acetate:hexane, 8:2, v/v); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P bs 114.2; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.90-7.86 (m, 4H, Ar-H), 7.79-7.76 (m, 2H, Ar-H), 7.53-7.51 (m, 4H, Ar-H), 7.40-7.38 (m, 8H, Ar-H), 7.01-6.99 (m, 2H, H-4, H-5), 6.94-6.92 (m, 2H, H-3, H-6), 1.29-0.87 (6H, m, BH_3);^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 143.9, 132.2, 131.7, 131.1, 128.8, 124.7, 121.8.

6.7.3 $PPh_2(3\text{-}OC_6H_4OPPh_2).(BH_3)_2$ (170).



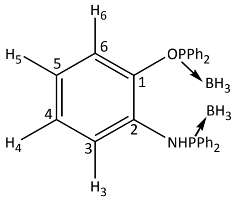
White waxy solid (394 mg, 74%); R_f 0.60 (dichloromethane:hexane, 6:5, v/v); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P bs 111.3; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.79-7.77 (8H, m, Ar-H), 7.56-7.55 (4H, m, Ar-H), 7.50-7.49 (8H, m, Ar-H), 7.12-7.09 (1H, m, H-5), 6.80 (2H, m, H-4, H-6), 6.76 (1H, s, H-2), 0.76-1.27 (6H, m, BH_3); ^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 152.7, 132.3, 131.6, 131.5, 131.4, 131.0, 129.7, 128.8; *m/z* (EI) 506.25 ($M^{+\cdot}$, 7.86%), 498.15 (10.8%), 477.15 (54.0%), 370.15 (32.6%), 318.10 (18.6%), 308.15 (12.0%), 307.10 (62.0%), 306.10 (68.8%), 304.15 (19.2%), 303.10 (10.8%), 278.10 (19.9%), 276.10 (20.3%), 230.05, (11.5%), 189.05 (55.2%), 188.05 (10.5%),185.05 (90.4%), 183.00 (100%), 182.05 (10.5%).

6.7.4 PPh$_2$(2-OC$_6$H$_4$CN).BH$_3$ (172).



Pale yellow oil (366 mg, 69%); R$_f$ 0.72 (ethyl acetate:hexane 3:7); ^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P bs 109.8; ^{1}H NMR (600 MHz, CDCl$_3$) δ_H 7.86-7.83 (4H, m, Ar-H), 7.59-7.56 (2H, m, Ar-H), 7.53-7.50 (4H, m, Ar-H), 7.11-7.08 (1H, m, H-3), 6.62-5.59 (2H, m, H-4, H-5), 6.57-6.56 (1H, m, H-6), 1.29-0.86 (3H, m, BH$_3$); ^{13}C NMR (150.963 MHz, CDCl$_3$) δ_C 156.3 (C-2), 153.1 (C-1), 132.3, 131.6, 131.3, 130.0 (C-3), 128.8, 113.5 (C-4, C-5), 108.7 (C-6).

6.7.5 PPh$_2$(2-OC$_6$H$_4$NHPPh$_2$).(BH$_3$)$_2$ (173).s



Pale yellow oil (286 mg, 54%); R$_f$ 0.72 (ethyl acetate:hexane 3:7); ^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P bs 113.4, bs 53.3; ^{1}H NMR (600 MHz, CDCl$_3$) δ_H 7.84-7.81 (4H, m, Ar-H), 7.71-7.68 (4H, m, Ar-H), 7.59-7.57 (2H, m, Ar-H), 7.50-7.49 (6H, m, Ar-H), 7.46-7.43 (4H, m, Ar-H), 6.90 (1H, m, H-6), 6.80-6.76 (2H, m, H-4, H-5), 6.71-6.68 (1H, m, H-3), 5.05 (1H, d, bs, N-H), 1.29-0.86 (6H, m, 2XBH$_3$); ^{13}C NMR (150.963 MHz, CDCl$_3$) δ_C 133.7, 132.6, 132.0, 131.7, 131.6, 131.1, 130.6, 129.7, 129.3, 129.1, 128.9, 124.8, 121.1, 120.7, 118.3.

6.8 General procedure for borane deprotection.[193]

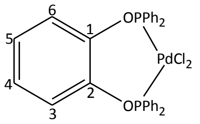
A borane phosphinite (50 mg, x mmol), in ethanol (1 ml), was heated under reflux and the deprotection followed to completion by ^{31}P NMR (30 minutes). The solvent was reduced under vacuum, the concentrate taken up into dichloromethane (1 ml) and washed with water (2 x 2 ml). The organic layer was then dried over sodium sulfate and the solvent reduced under vacuum to give the respective oils which could be characterized as the deprotected phosphinites **5.5.1**-**5.5.6**.

6.9 Palladium phosphinites

6.9.1 Ph(OPPh$_2$)$_2$ PdCl$_2$ (173).[194]

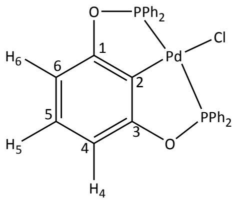
PdCl$_2$(CH$_3$CN)$_2$ (23 mg, 0.1 mmol) was dissolved in dichloromethane (1 ml) and **Ph(OPPh$_2$)$_2$ 155** (50 mg, 0.2 mmol, 2 eq.) in dichloromethane (1 ml) added at once. The reaction mixture was allowed to stir at room temperature for 1 hour. The solvent was reduced under vacuum and the orange residue dissolved in a minimum amount of dichloromethane. An equal amount of ethanol was added to induce precipitation. The precipitate was then filtered off, washed with portions of cold ethanol (3 x 2 ml) and dried under vacuum to give a pale orange solid (45 mg, 34%); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 110.3; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.67-7.64 (8H, m, Ar-PPh_2), 7.47-7.44 (4H, m, Ar-PPh_2), 7.33-7.31 (8H, m, Ar-PPh_2), 7.15-7.12 (4H, m, Ar-H), 7.11-7.08 (2H, m, Ar-H), 6.61-6.60 (2H, m, Ar-H).

6.9.2 1,2-Ph(OPPh$_2$)$_2$PdCl$_2$ (174).[173]



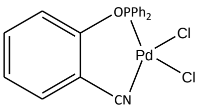
To a solution of $PdCl_2(PhCN)_2$ **145** (174 mg, 0.4 mmol) in dichloromethane (1 ml) was added **1,2-Ph(OPPh$_2$)$_2$ 156** (0.5 mmol, 1 eq.) in dichloromethane. The reaction mixture was then left to stir at room temperature and monitored to completion by ^{31}P NMR (2 hours). The solvent was then reduced and the orange oil washed repeatedly with pentane to induce precipitation. The yellow solid that formed was further washed with pentane and precipitated from dichloromethane/ethanol (1:1) The *pale yellow* precipitate was filtered off and washed with diethyl ether and dried under vacuum(66 mg, 31%); ^{31}P NMR (121.489 MHz, $CDCl_3$) 121.8 (Lit 122.0); ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.06-8.03 (8H, m, Ar-H), 7.62-7.59 (4H, m, Ar-H), 7.52-7.49 (8H, m, Ar-H), 6.85-6.83 (2H, m, H-4, H-5), 6.06-6.04 (2H, m, H-3, H-6); ^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 142.8, 133.7, 133.6, 132.7, 131.6, 131.3, 131.1, 130.9, 128.5, 128.4, 126.3, 123.9.

6.9.3 1,3-Ph(OPPh$_2$)$_2$ PdCl (175).[185]



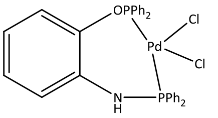
Resorcinol **157** (50 mg, 0.5 mmol), chlorodiphenylphosphine (0.1 ml, 1 mmol, 2.2 eq.) and $PdCl_2$ (81 mg, 0.5 mmol, 1 eq.) were stirred together in toluene at room temperature and $ClPPh_2$ (0.2 ml, 0.9 mmol, 2 eq.) in toluene (1 ml) added dropwise. An excess amount of acetic acid (0.5 ml, 9.1 mmol, 20 eq.) was then added dropwise. The reaction mixture was allowed to heat under reflux overnight. The reaction mixture as cooled, the solvent reduced under pressure and the residue taken up dichloromethane and purified by PLC (dichloromethane) to give the target compound as white powder (122 mg, 41%); ^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 143.7; ^{1}H NMR (600 MHz, $CDCl_3$) δ_H 8.01-7.98 (8H, m, Ar-H), 7.53-7.49 (12H, m, Ar-H), 7.11 (1H, m, H-5), 6.79 (2H, d, J = 7.65 Hz, H-4, H-6); ^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 164.5 (C-1, C-3), 133.4, 133.3, 133.1, 132.0, 131.7, 131.6 (C-2) , 129.0, 128.9 (C-5), 107.3 (C-4, C-6).

6.9.4 2-Ph(OPPh$_2$)(CN) PdCl$_2$ (176).



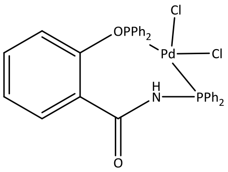
Similar procedure as **174** with **165** as starting material; ^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 111.9; only hydrolysis product **148** (δ_P 78.3 ppm) recovered upon isolation.

6.9.5 2-Ph(OPPh$_2$)(NHPPh$_2$) PdCl$_2$ (177).



Similar procedure as **174** with **166** as starting material; ^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 110.6, 110.3 (J(P,P) = 326.28Hz); 64.7, 64.5 (J(P,P) = 28.9Hz) obtained *in-situ*; only hydrolysis product **147** (δ_P 78.3 ppm) recovered upon isolation.

6.9.6 2-Ph(OPPh$_2$)(CONHPPh$_2$) PdCl$_2$ (185).



Similar procedure as **174** with **167** as starting material; ^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 112.9, 104.5 obtained *in-situ*; only hydrolysis product **147** (δ_P 78.3 ppm) recovered upon isolation.

6.10 Wacker oxidation

6.10.1 O$_2$ oxidations[9]

A Pd catalyst was transferred quantitatively with DMA into a stainless steel reactor cooled to 0°C. Water was then added, followed by a mixture of naphthalene (internal standard) and 1-octene in DMA such that the total volume in the reactor gave a resultant required ratio of 6:1 DMA:H$_2$O for example. The reaction mixture was then immersed into an oil bath set at 80°C, sealed and pressurized with O$_2$.

The mixture was then cooled to 0°C, the O$_2$ pressure released slowly and ca. 0.2 ml of the reaction mixture was taken during sampling and passed through a short silica pad which was then washed with ethyl acetate.

6.10.2 TBHP and H_2O_2 oxidations[8]

A Pd catalyst was transferred quantitatively with DMA into a stainless steel reactor cooled to 0°C. Water was then added, followed by the oxidant then a mixture of naphthalene (internal standard) and 1-octene in DMA such that the total volume in the reactor gave a resultant required ratio of 6:1 DMA:H_2O for example. The reaction mixture was then immersed into an oil bath and the reactor sealed. The mixture was then cooled to 0°C, the O_2 pressure released slowly and ca. 0.2 ml of the reaction mixture was taken during sampling and passed through a short silica pad which was then washed with ethyl acetate. Sampling proceeded as mentioned in O_2 oxidations.

The GC program used was as follows;

Initial temperature was set at 60°C and ramped to 120°C at 30°C/min. The rate was reduced to 0.5°C/min between 120°C and 122°C and then ramped at 30°C/min to 172°C and set to 1°C/min from 172°C-174°C, then at 70°C/min to 250°C and that temperature held from 1 min. Total run time was 11 minutes 75 seconds. 1-octene as determined by an aunthentic sample had a retention time (R_t) of ca. 5.9 minutes, 2-octanone at ca. 8.3 minutes and naphthalene at 11.2 minutes.

<u>Response factors</u>:

1-octene (0.1 ml) and naphthalene (internal standard) (1 eq.) in DMA (1 ml) were prepared in 3 different vials and the samples thereof run on a GC. The response factor of 1-octene was then calculated with the equation

$R_f = A_r \times M_i/A_i \times M_r$ where R_f = response factor

A_i = Peak area of the internal standard (naphthalene)

A_r = Peak area of reactant (1-octene)

M_i = Moles of internal standard (naphthalene)

M_r = Moles of reactant (1-octene)

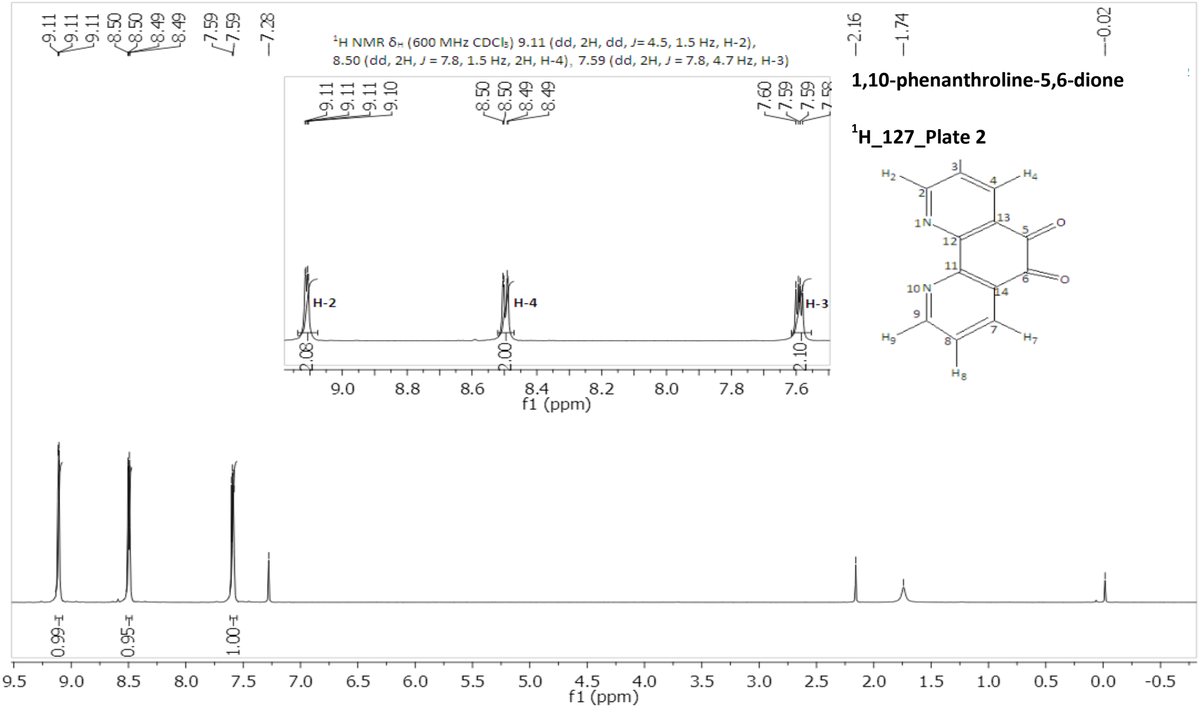
The R_f of 1-octene was thus determined to be 0.98.

<u>% Conversion</u>:

From the equation $R_f = A_r \times M_i/A_i \times M_r$

The % conversion of 1-octene would therefore be $M_r = A_r \times M_i/A_i \times R_f$

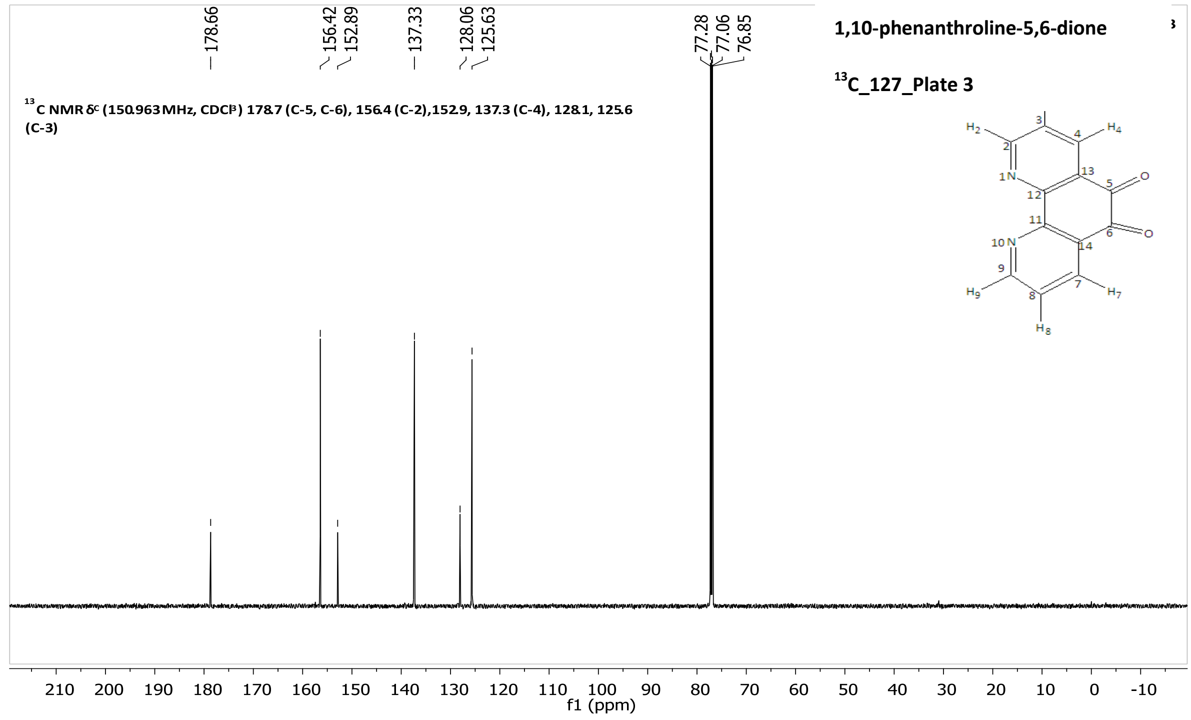
APPENDIX



^{1}H NMR δ_H (600 MHz CDCl$_3$) 9.11 (dd, 2H, dd, J= 4.5, 1.5 Hz, H-2), 8.50 (dd, 2H, J = 7.8, 1.5 Hz, 2H, H-4), 7.59 (dd, 2H, J = 7.8, 4.7 Hz, H-3)

1,10-phenanthroline-5,6-dione

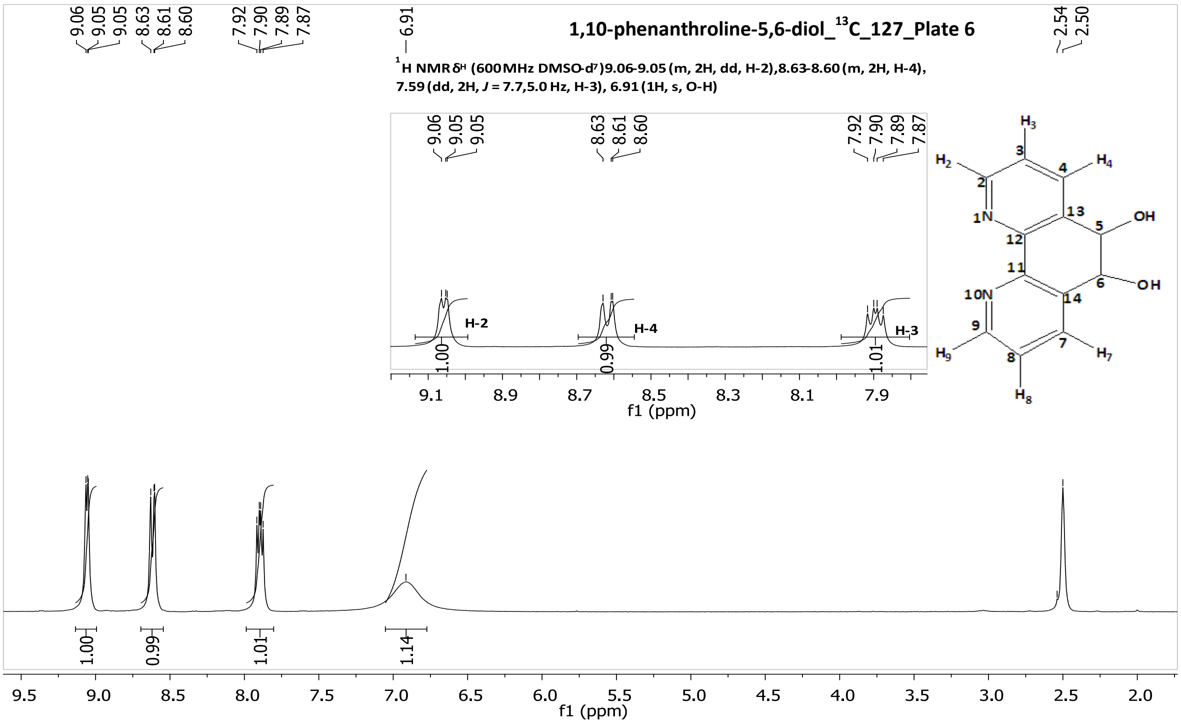
^{1}H_127_Plate 2



^{13}C NMR δ_C (150.963 MHz, CDCl$_3$) 178.7 (C-5, C-6), 156.4 (C-2),152.9, 137.3 (C-4), 128.1, 125.6 (C-3)

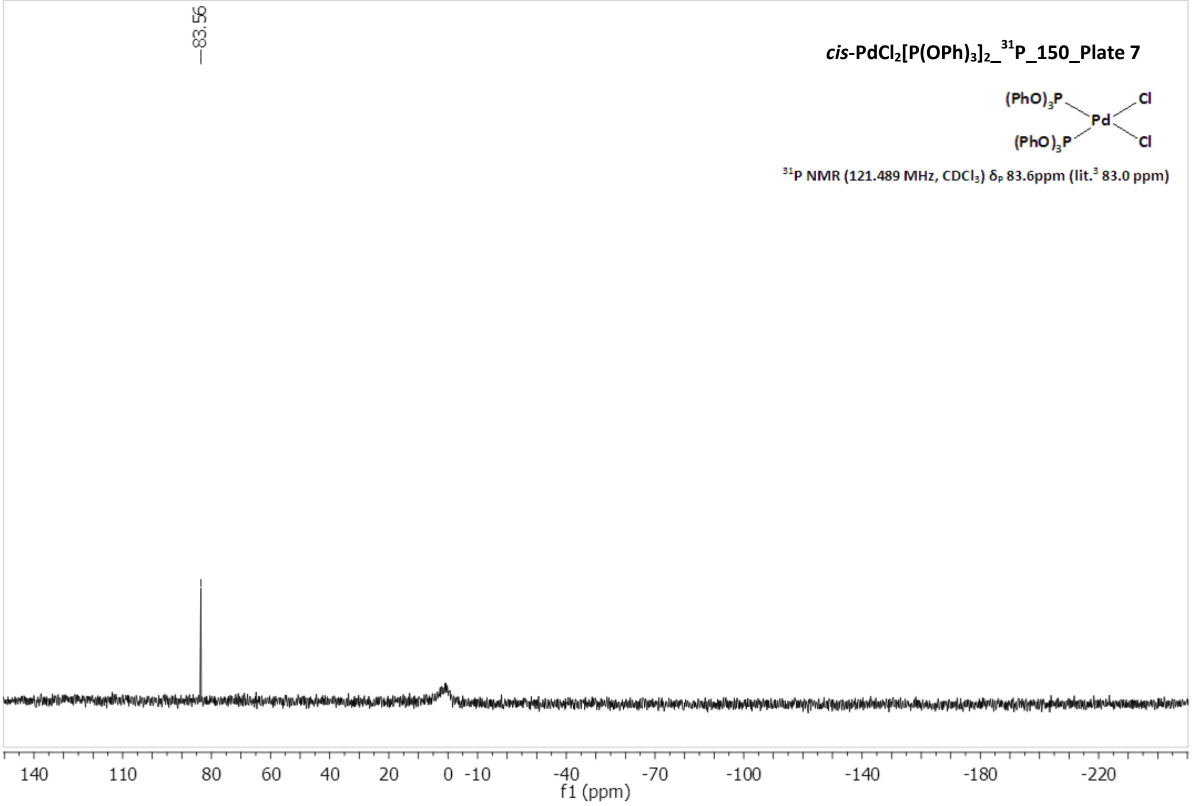
1,10-phenanthroline-5,6-dione

^{13}C_127_Plate 3



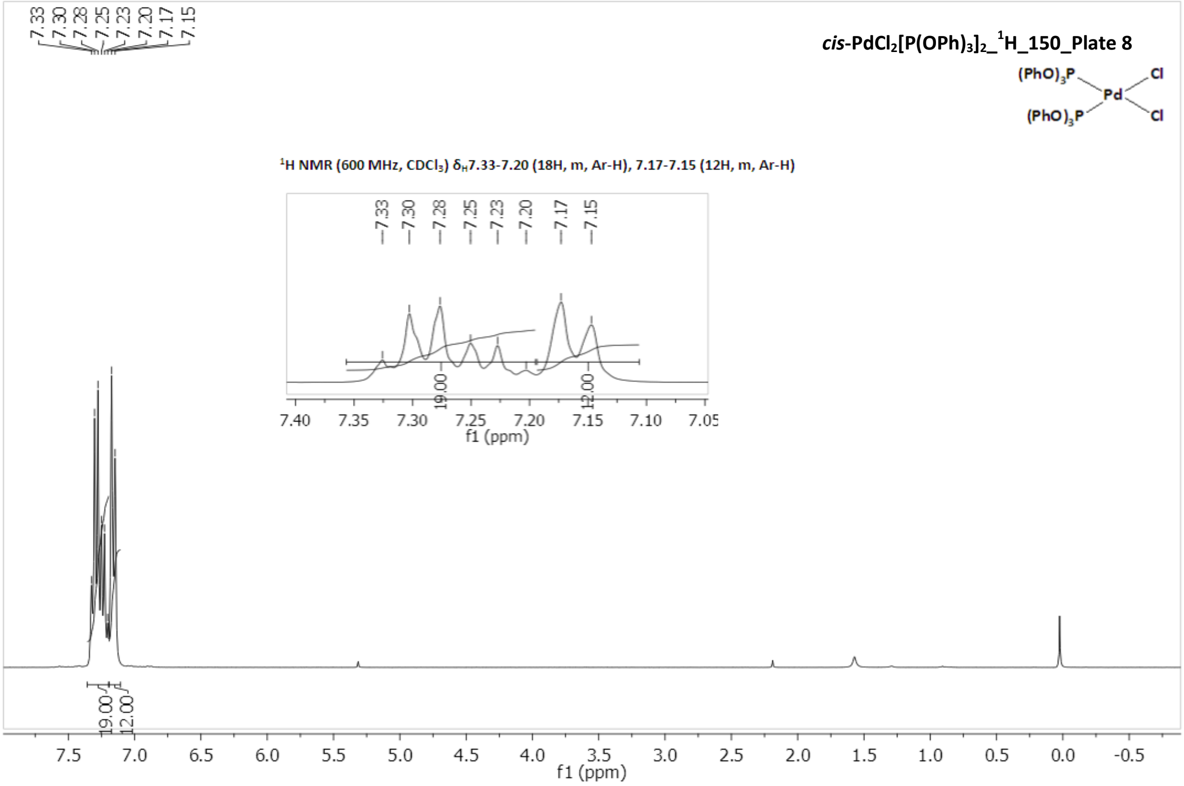
1,10-phenanthroline-5,6-diol_^{13}C_127_Plate 6

^{1}H NMR δ^H (600MHz DMSO-d^7)9.06-9.05 (m, 2H, dd, H-2),8.63-8.60 (m, 2H, H-4), 7.59 (dd, 2H, *J* = 7.7,5.0 Hz, H-3), 6.91 (1H, s, O-H)



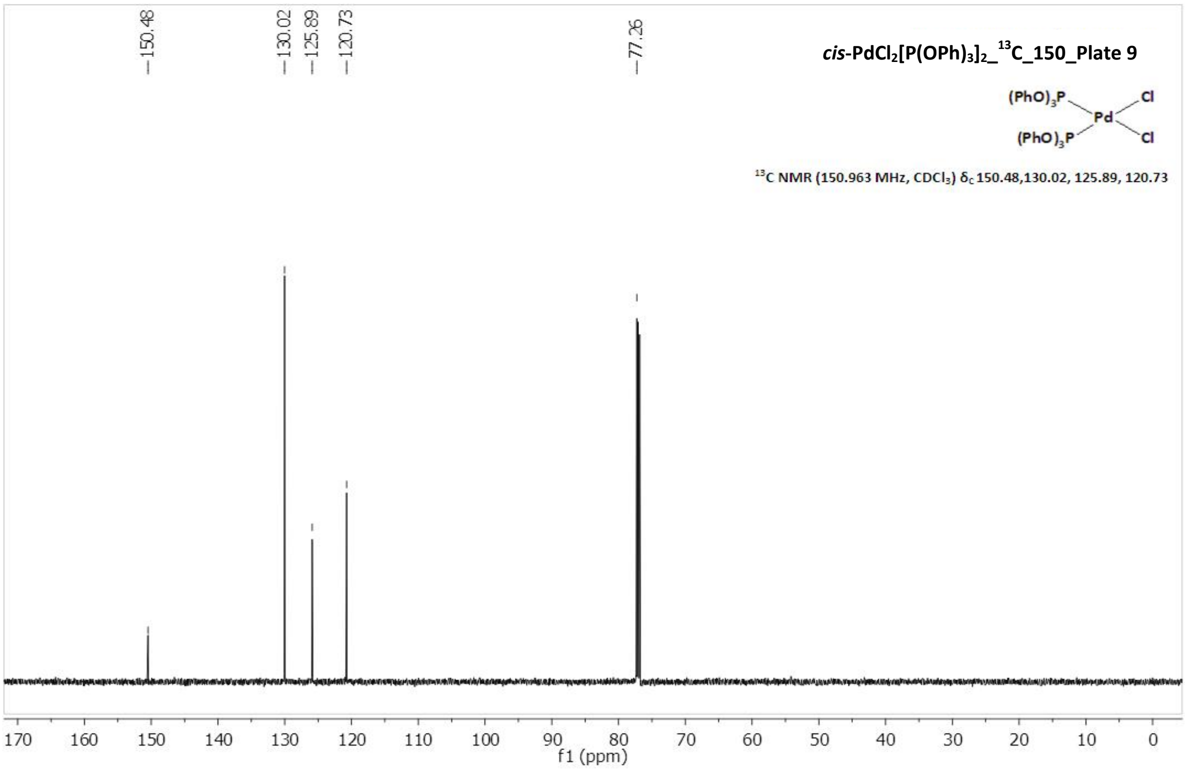
***cis*-PdCl$_2$[P(OPh)$_3$]$_2$_^{31}P_150_Plate 7**

^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 83.6ppm (lit.^{3} 83.0 ppm)



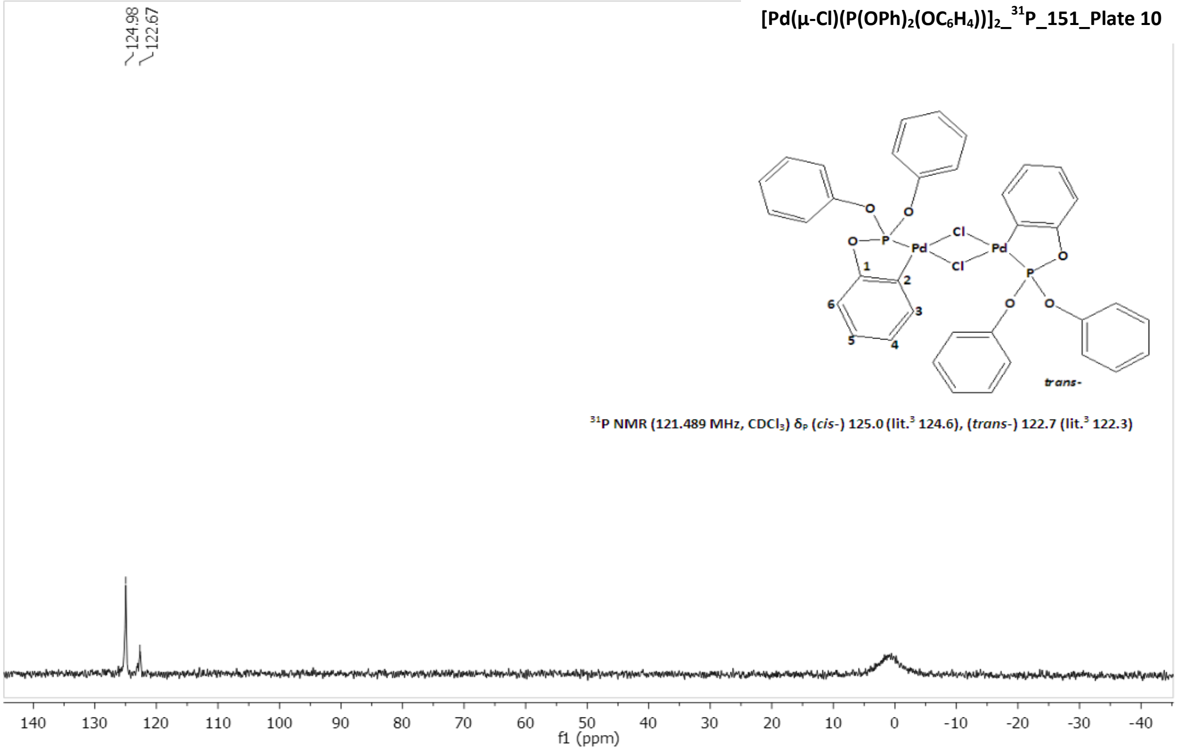
***cis*-PdCl$_2$[P(OPh)$_3$]$_2$_^{1}H_150_Plate 8**

^{1}H NMR (600 MHz, CDCl$_3$) δ_H 7.33-7.20 (18H, m, Ar-H), 7.17-7.15 (12H, m, Ar-H)



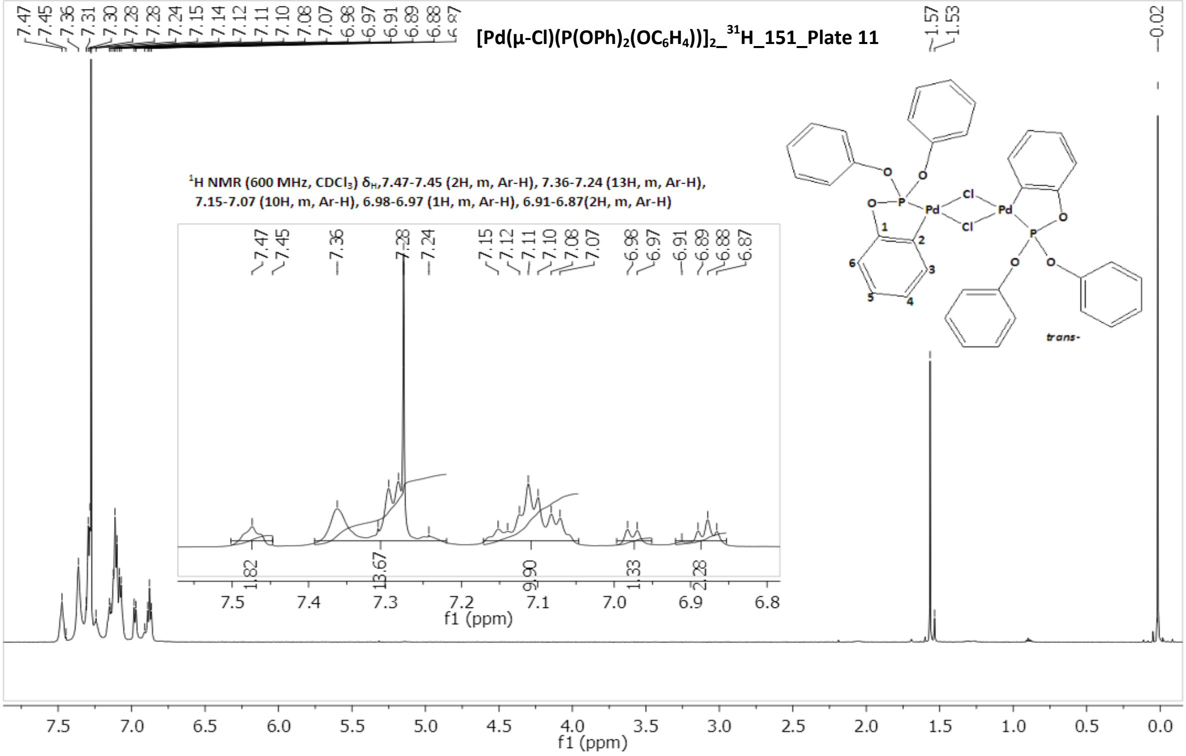
***cis*-PdCl$_2$[P(OPh)$_3$]$_2$_^{13}C_150_Plate 9**

^{13}C NMR (150.963 MHz, CDCl$_3$) δ_C 150.48,130.02, 125.89, 120.73



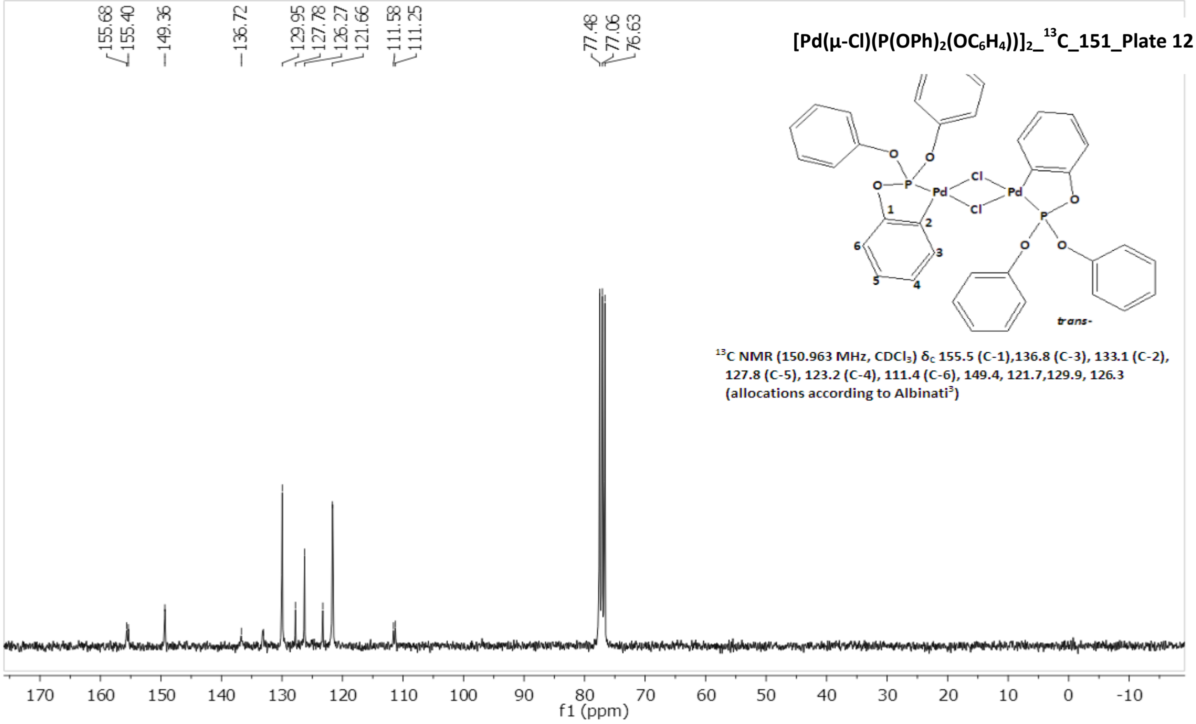
[Pd(μ-Cl)(P(OPh)$_2$(OC$_6$H$_4$))]$_2$_^{31}P_151_Plate 10

^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P (*cis*-) 125.0 (lit.^{3} 124.6), (*trans*-) 122.7 (lit.^{3} 122.3)



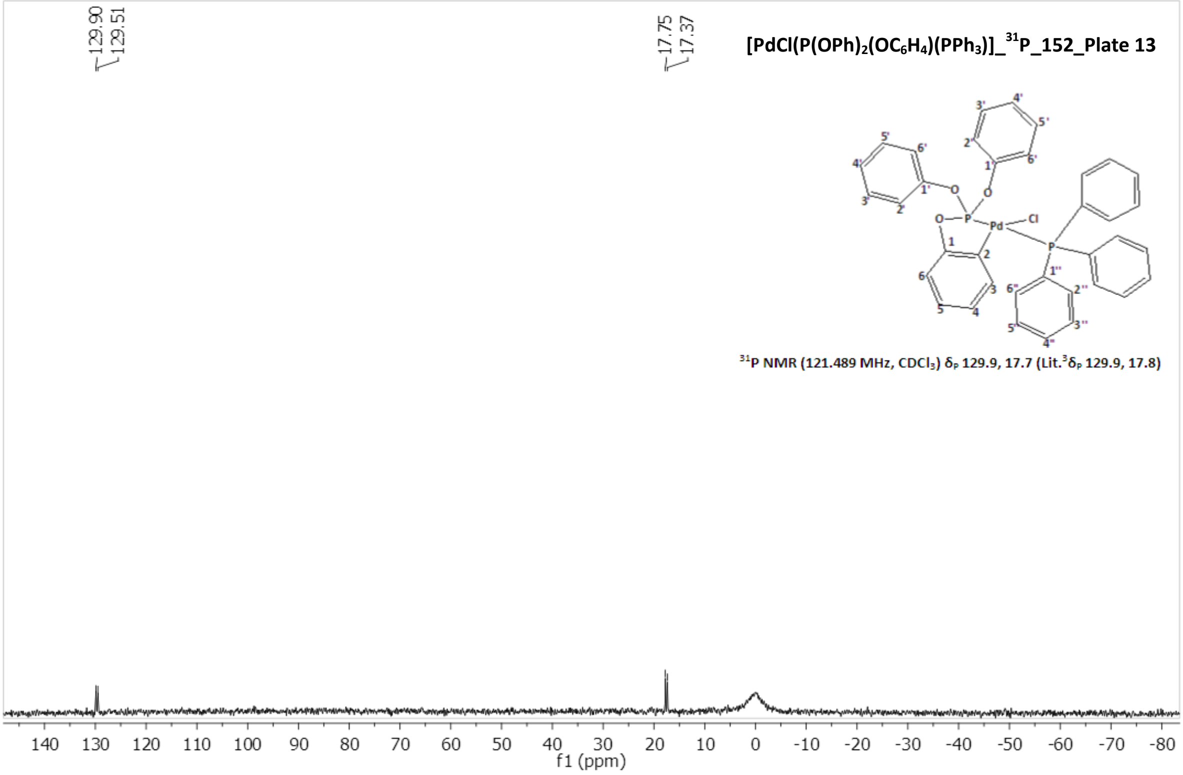
[Pd(μ-Cl)(P(OPh)$_2$(OC$_6$H$_4$))]$_2$_^{31}H_151_Plate 11

^{1}H NMR (600 MHz, CDCl$_3$) δ_H,7.47-7.45 (2H, m, Ar-H), 7.36-7.24 (13H, m, Ar-H), 7.15-7.07 (10H, m, Ar-H), 6.98-6.97 (1H, m, Ar-H), 6.91-6.87(2H, m, Ar-H)



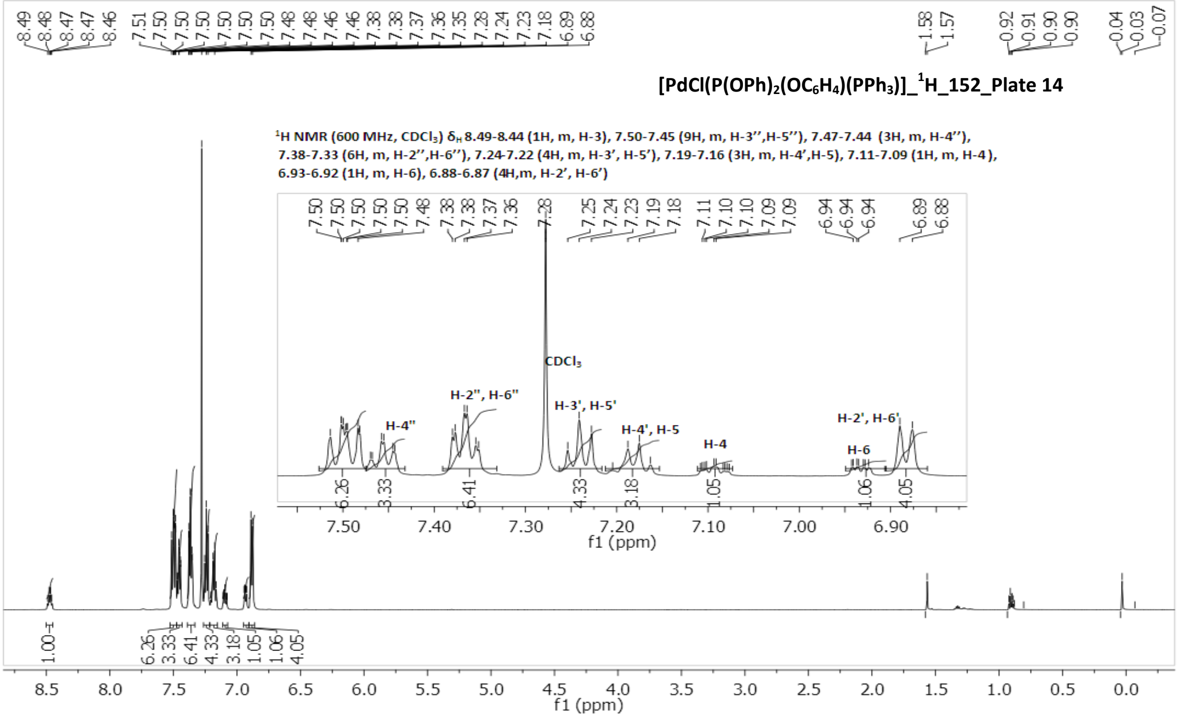
[Pd(μ-Cl)(P(OPh)$_2$(OC$_6$H$_4$))]$_2$_^{13}C_151_Plate 12

^{13}C NMR (150.963 MHz, CDCl$_3$) δ_C 155.5 (C-1),136.8 (C-3), 133.1 (C-2), 127.8 (C-5), 123.2 (C-4), 111.4 (C-6), 149.4, 121.7,129.9, 126.3 (allocations according to Albinati[3])



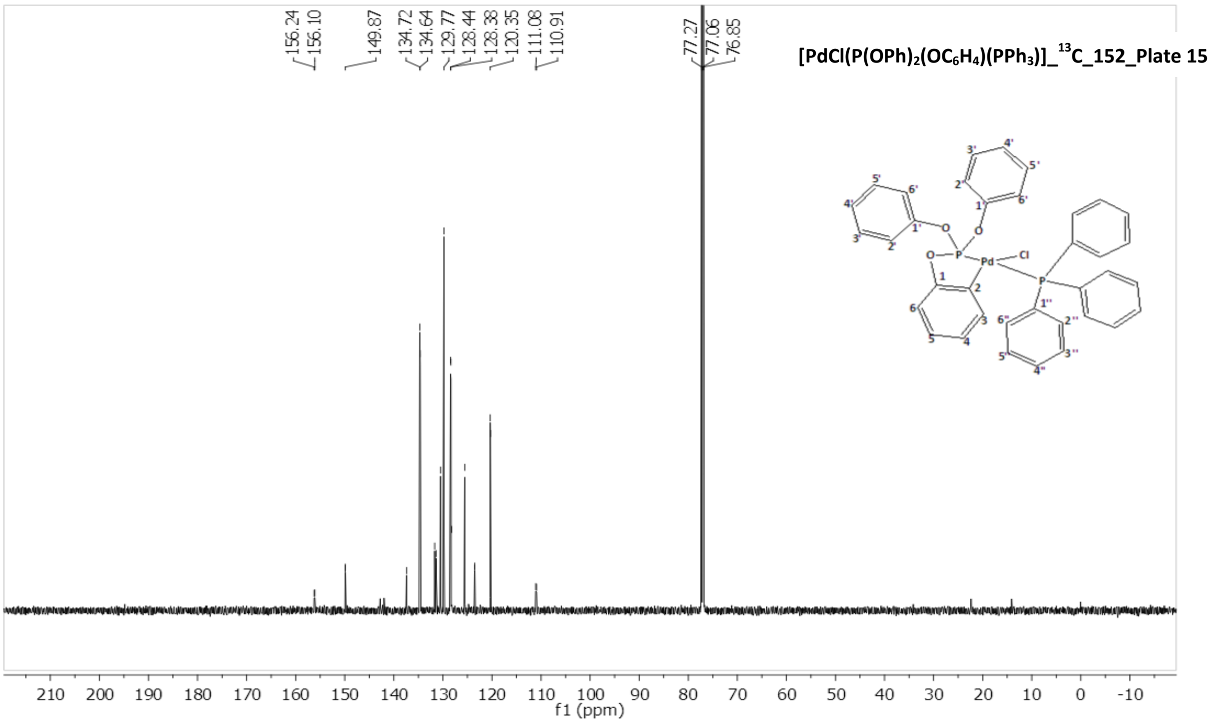
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(PPh$_3$)]_^{31}P_152_Plate 13

^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 129.9, 17.7 (Lit.[3] δ_P 129.9, 17.8)

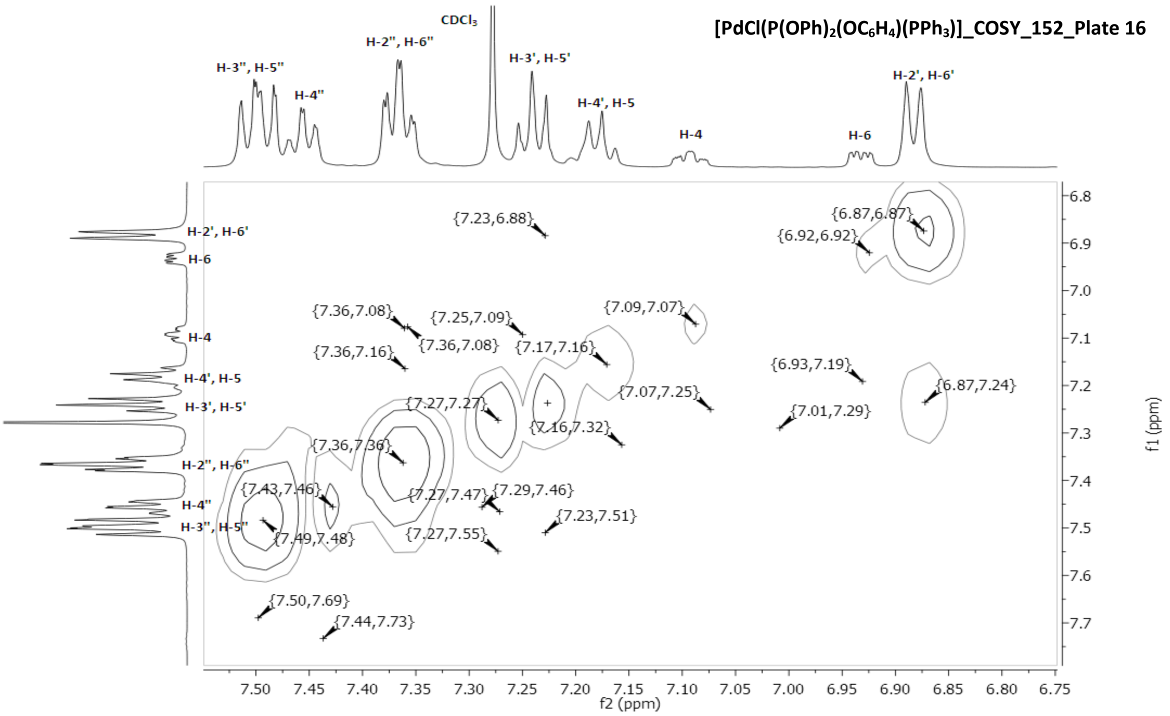


[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(PPh$_3$)]_^{1}H_152_Plate 14

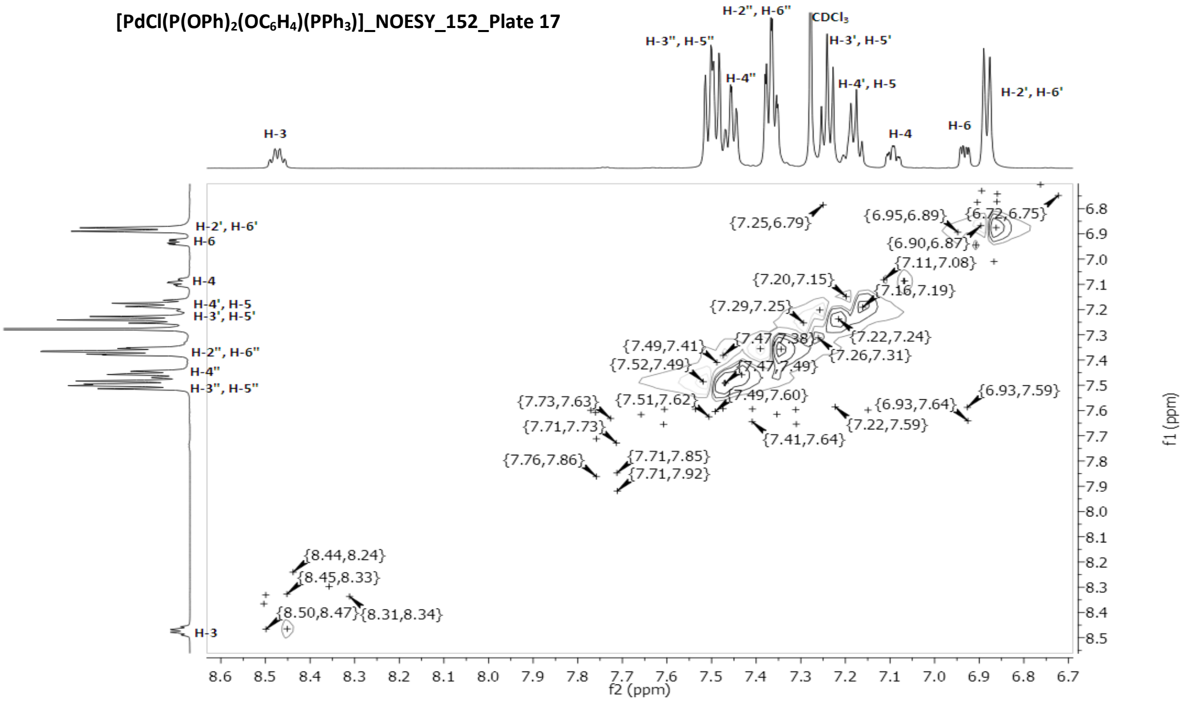
^{1}H NMR (600 MHz, CDCl$_3$) δ_H 8.49-8.44 (1H, m, H-3), 7.50-7.45 (9H, m, H-3'',H-5''), 7.47-7.44 (3H, m, H-4''), 7.38-7.33 (6H, m, H-2'',H-6''), 7.24-7.22 (4H, m, H-3', H-5'), 7.19-7.16 (3H, m, H-4',H-5), 7.11-7.09 (1H, m, H-4), 6.93-6.92 (1H, m, H-6), 6.88-6.87 (4H,m, H-2', H-6')



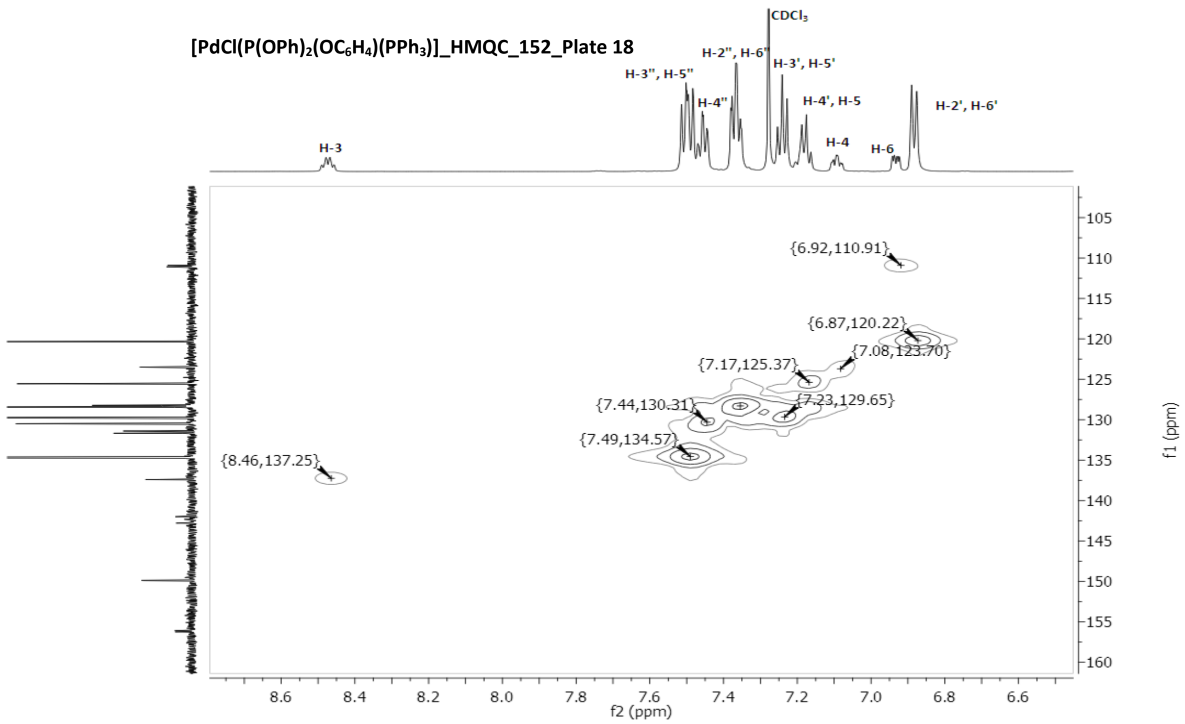
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(PPh$_3$)]_^{13}C_152_Plate 15


[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(PPh$_3$)]_COSY_152_Plate 16

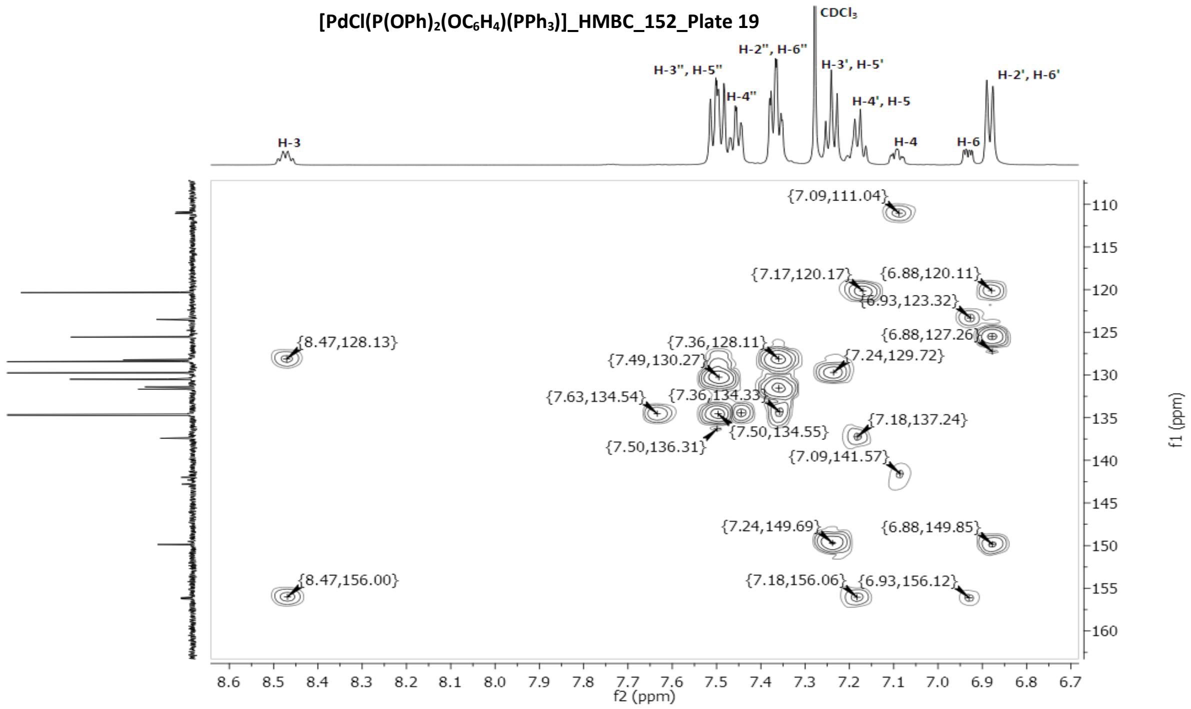
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(PPh$_3$)]_NOESY_152_Plate 17

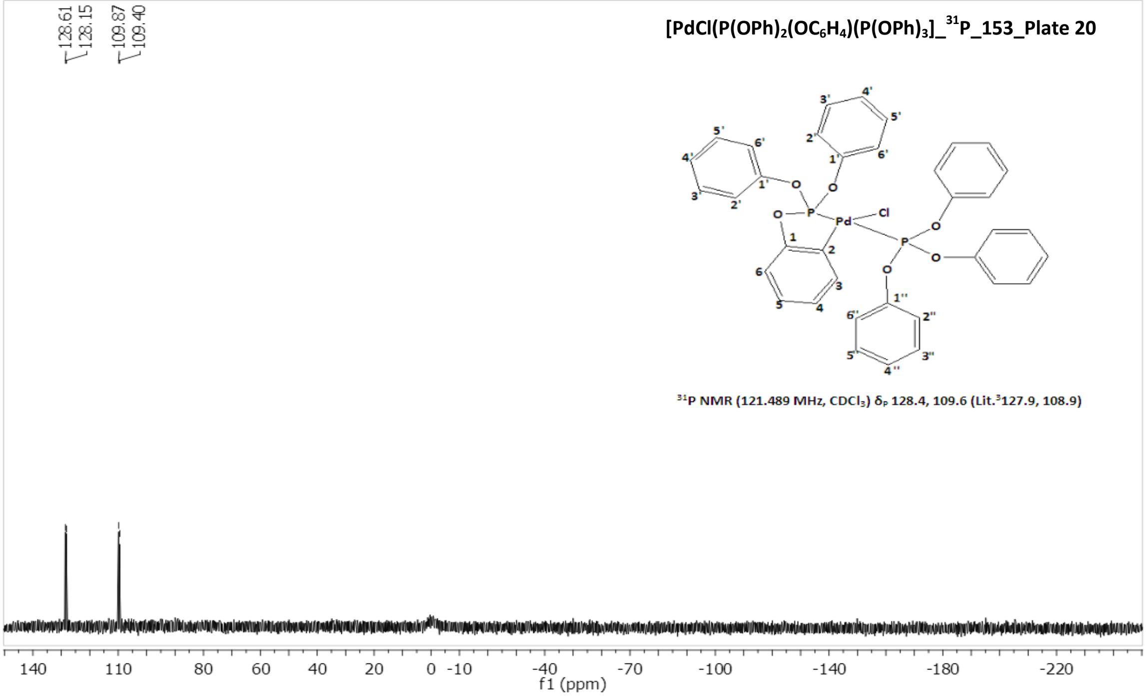


[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(PPh$_3$)]_HMQC_152_Plate 18



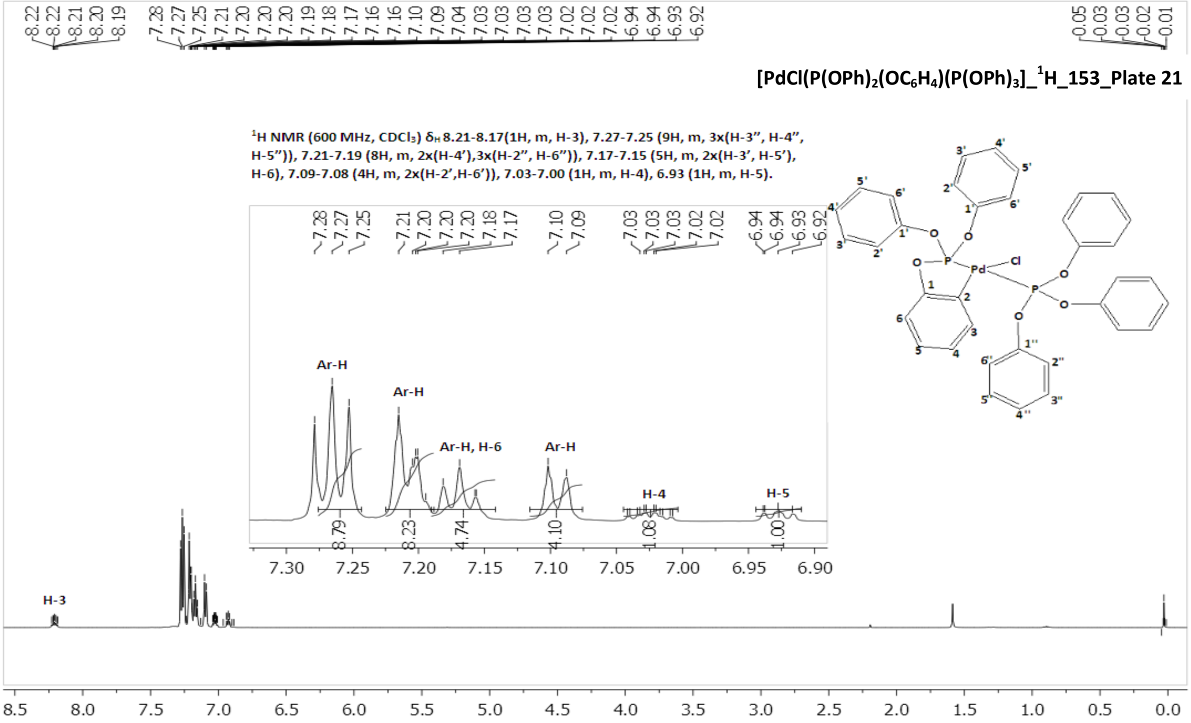
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(PPh$_3$)]_HMBC_152_Plate 19





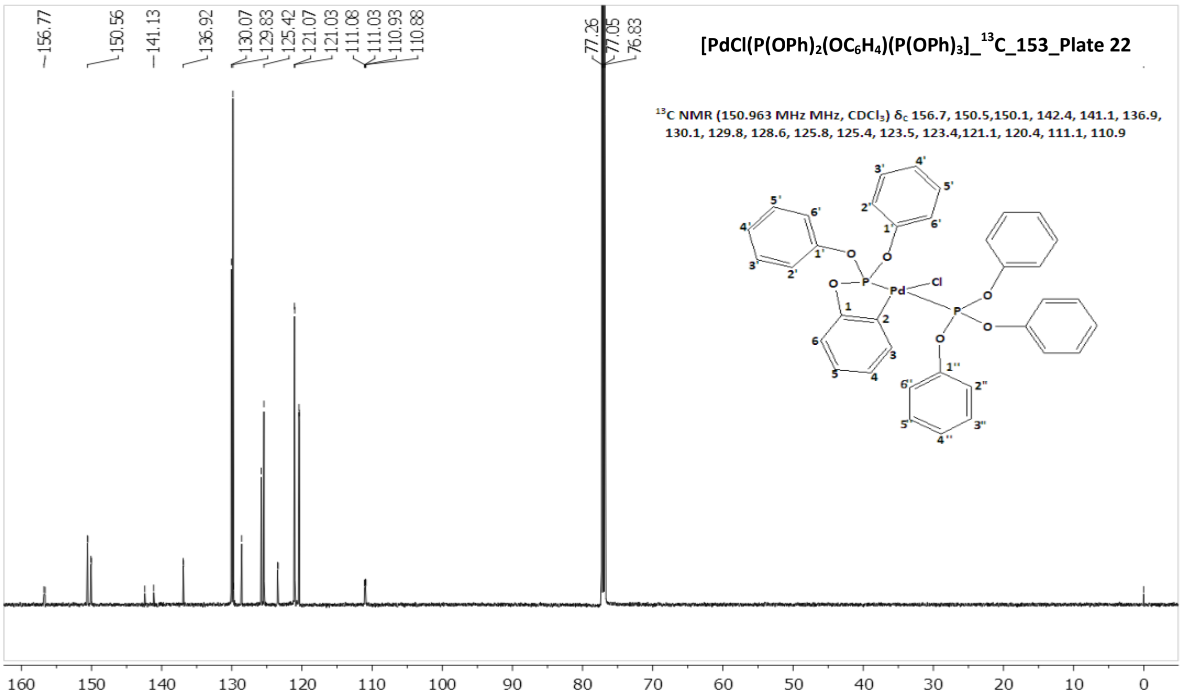
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$)]_^{31}P_153_Plate 20

^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 128.4, 109.6 (Lit.[3]127.9, 108.9)



[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$]_^{1}H_153_Plate 21

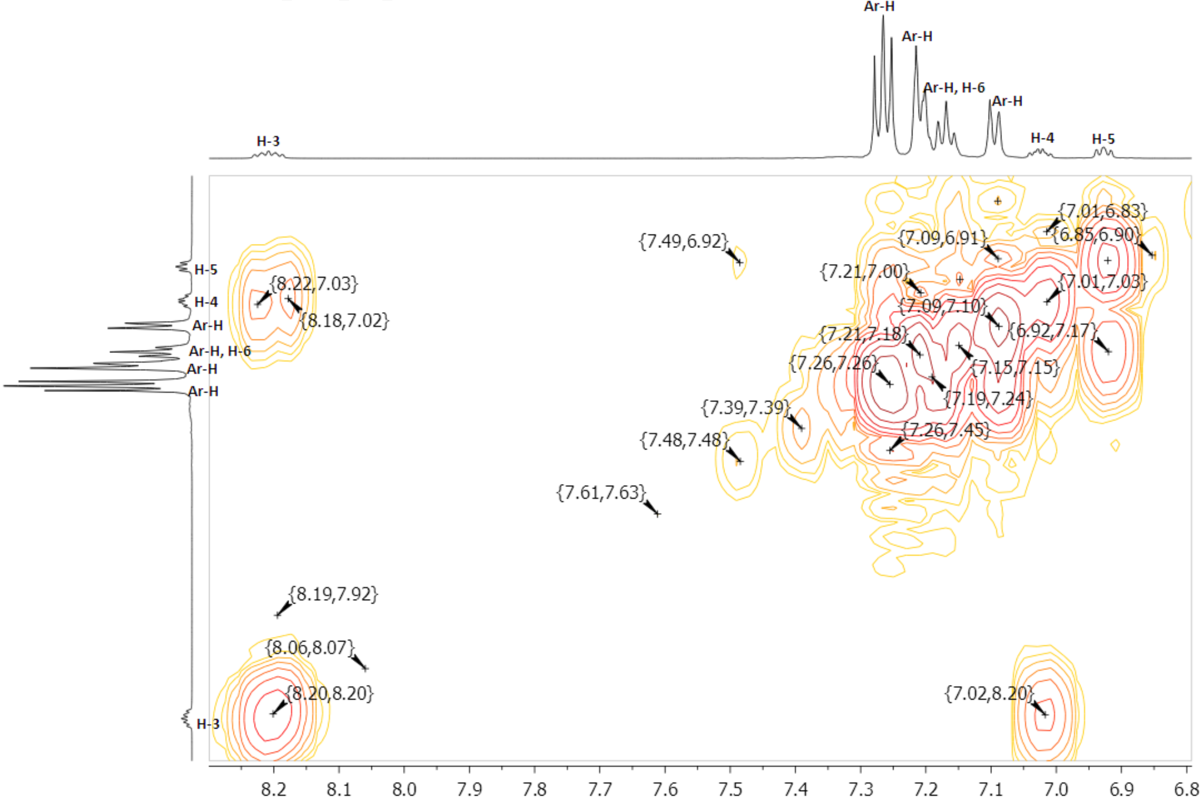
^{1}H NMR (600 MHz, CDCl$_3$) δ_H 8.21-8.17(1H, m, H-3), 7.27-7.25 (9H, m, 3x(H-3'', H-4'', H-5'')), 7.21-7.19 (8H, m, 2x(H-4'),3x(H-2'', H-6'')), 7.17-7.15 (5H, m, 2x(H-3', H-5'), H-6), 7.09-7.08 (4H, m, 2x(H-2',H-6')), 7.03-7.00 (1H, m, H-4), 6.93 (1H, m, H-5).



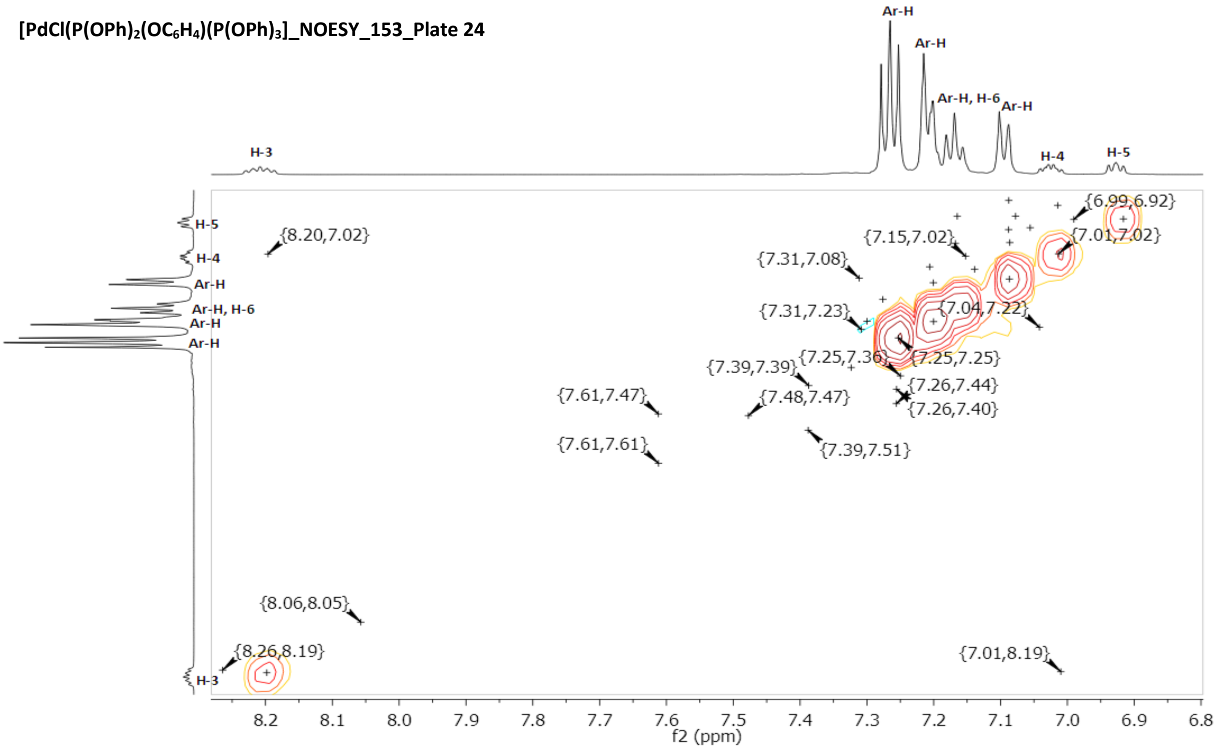
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$]_^{13}C_153_Plate 22

^{13}C NMR (150.963 MHz MHz, CDCl$_3$) δ_C 156.7, 150.5,150.1, 142.4, 141.1, 136.9, 130.1, 129.8, 128.6, 125.8, 125.4, 123.5, 123.4,121.1, 120.4, 111.1, 110.9

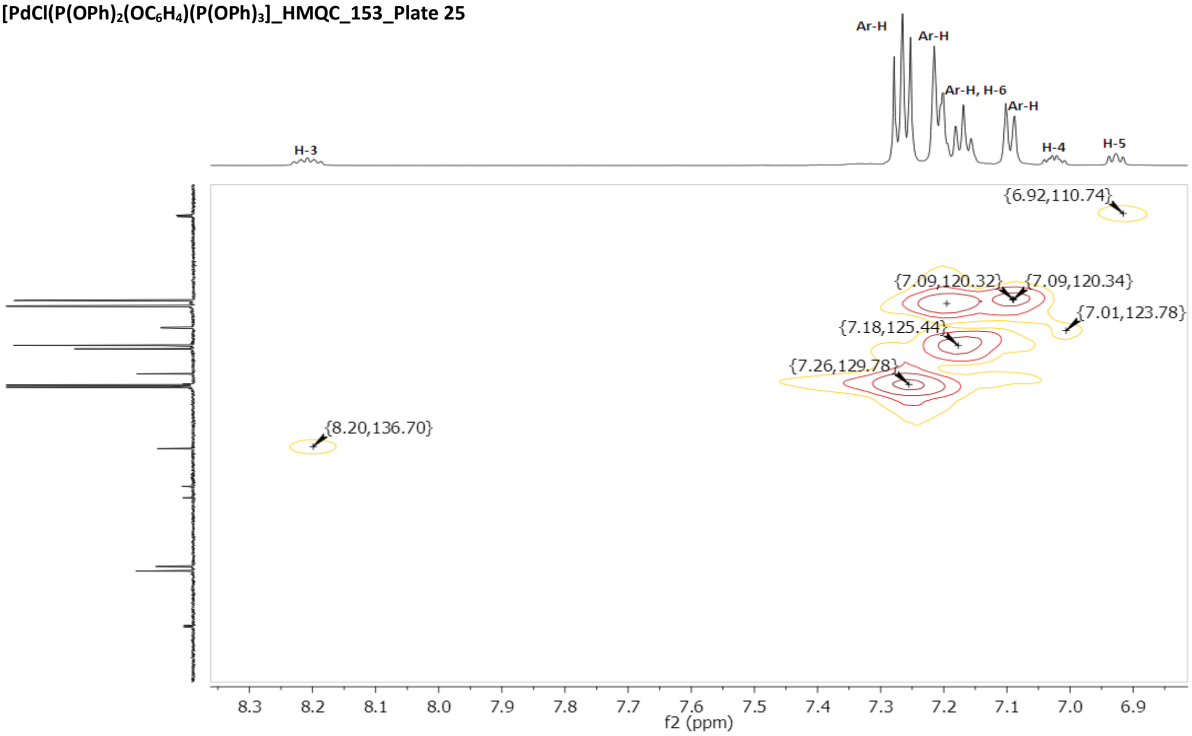
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$]_COSY_153_Plate 23



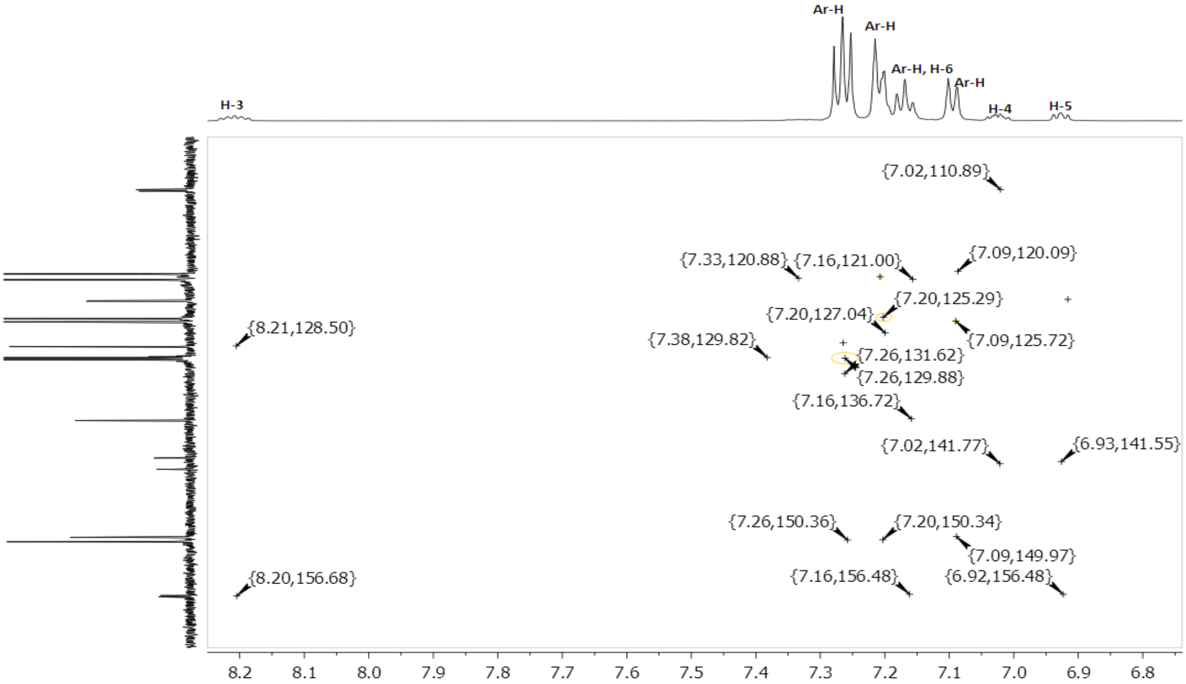
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$)]_NOESY_153_Plate 24



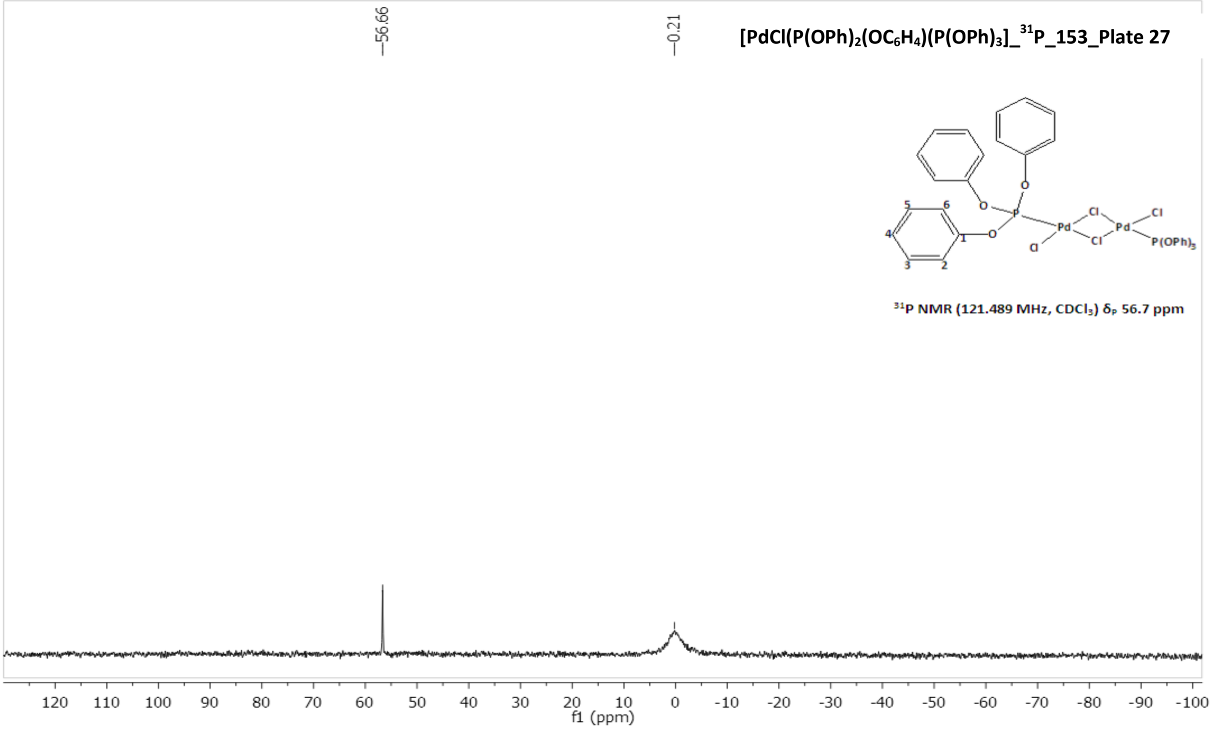
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$)]_HMQC_153_Plate 25



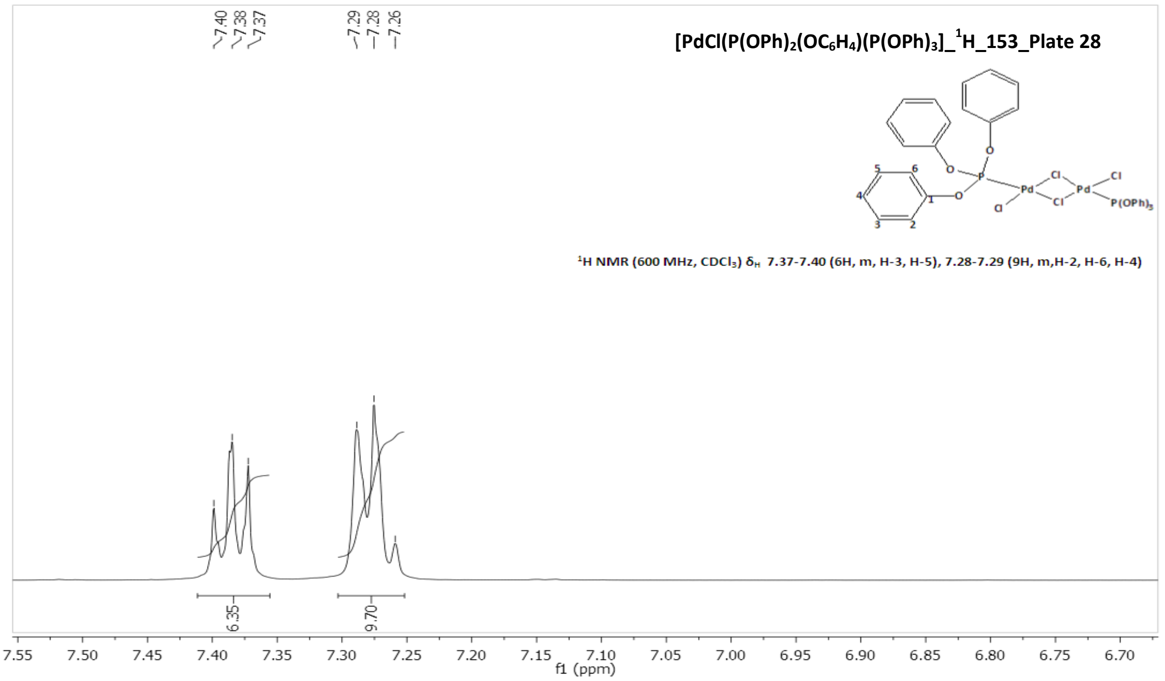
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$]_HMBC_153_Plate 26



[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$]_^{31}P_153_Plate 27

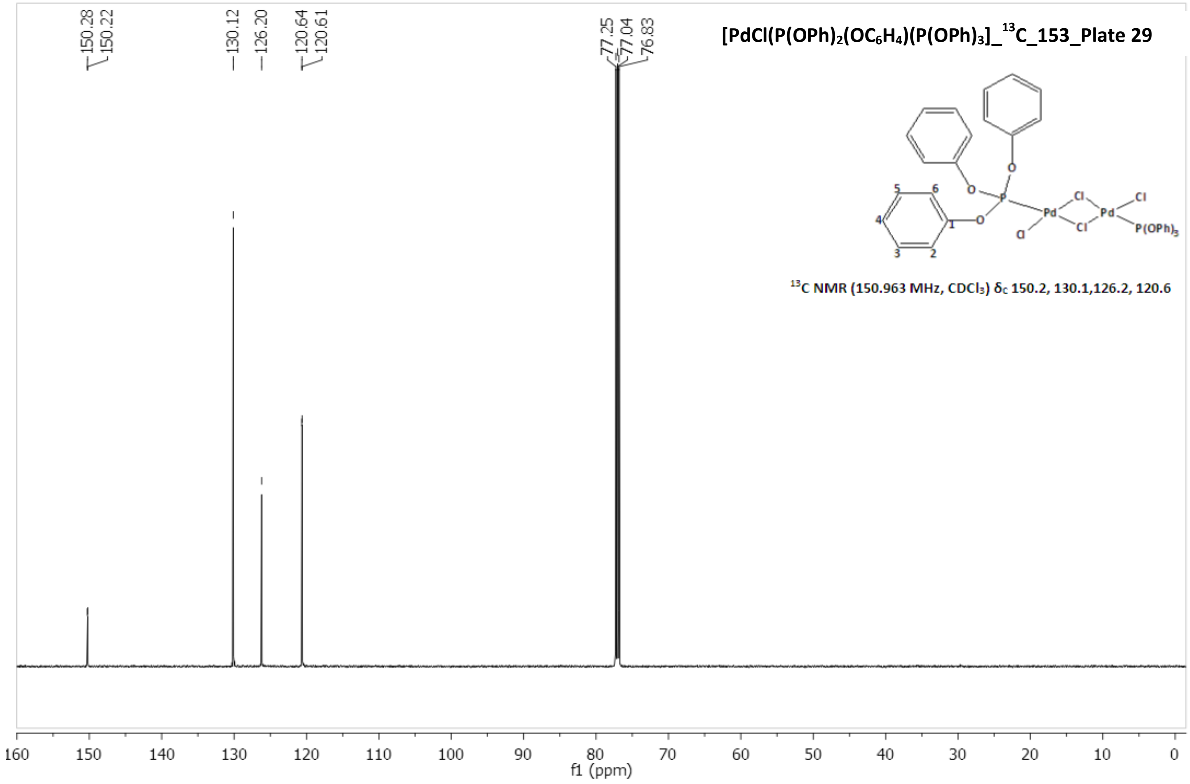


^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 56.7 ppm



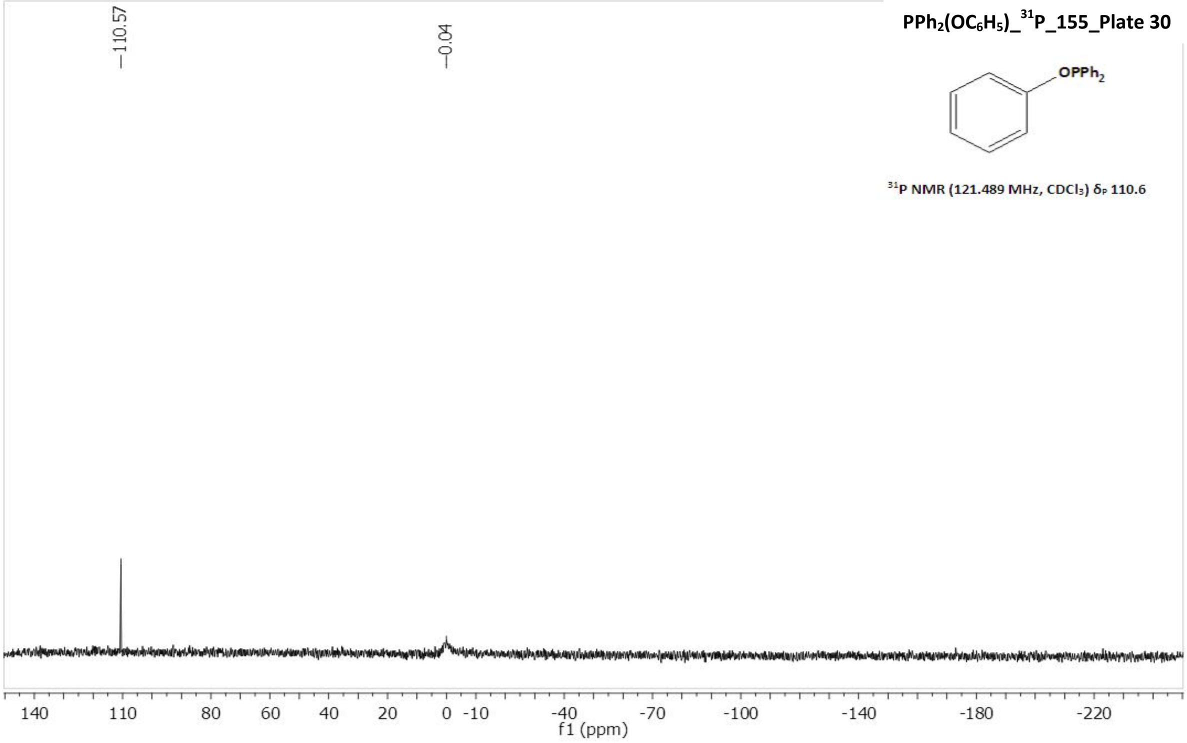
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$)]_^{1}H_153_Plate 28

^{1}H NMR (600 MHz, CDCl$_3$) δ$_H$ 7.37-7.40 (6H, m, H-3, H-5), 7.28-7.29 (9H, m,H-2, H-6, H-4)



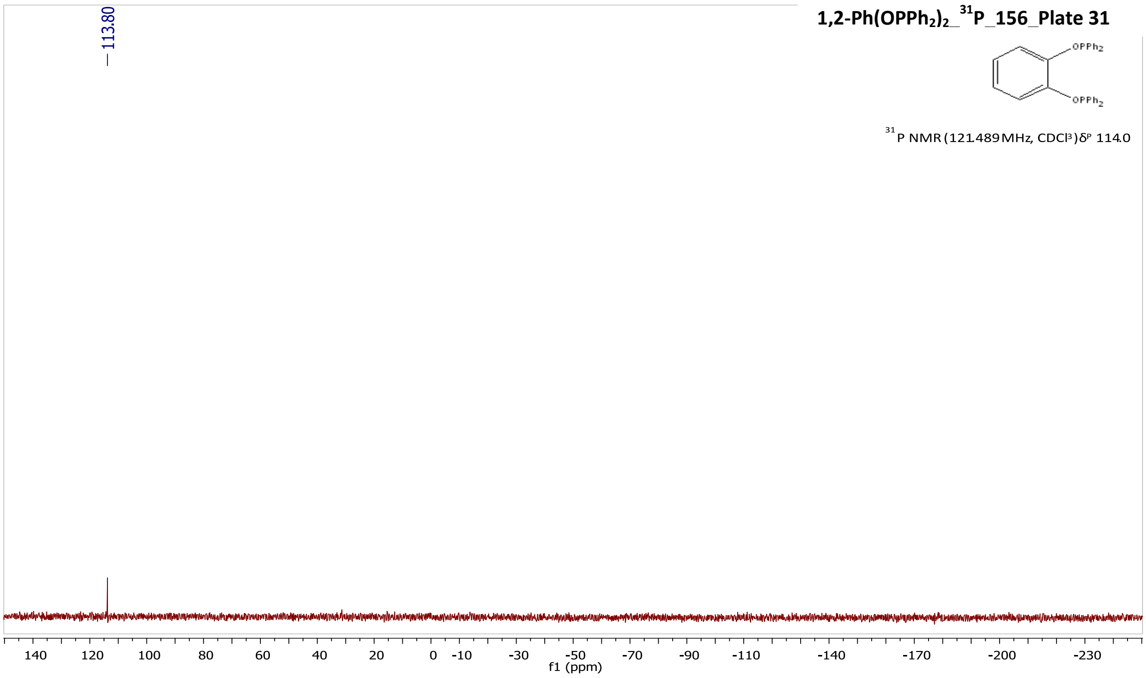
[PdCl(P(OPh)$_2$(OC$_6$H$_4$)(P(OPh)$_3$)]_^{13}C_153_Plate 29

^{13}C NMR (150.963 MHz, CDCl$_3$) δ$_C$ 150.2, 130.1,126.2, 120.6



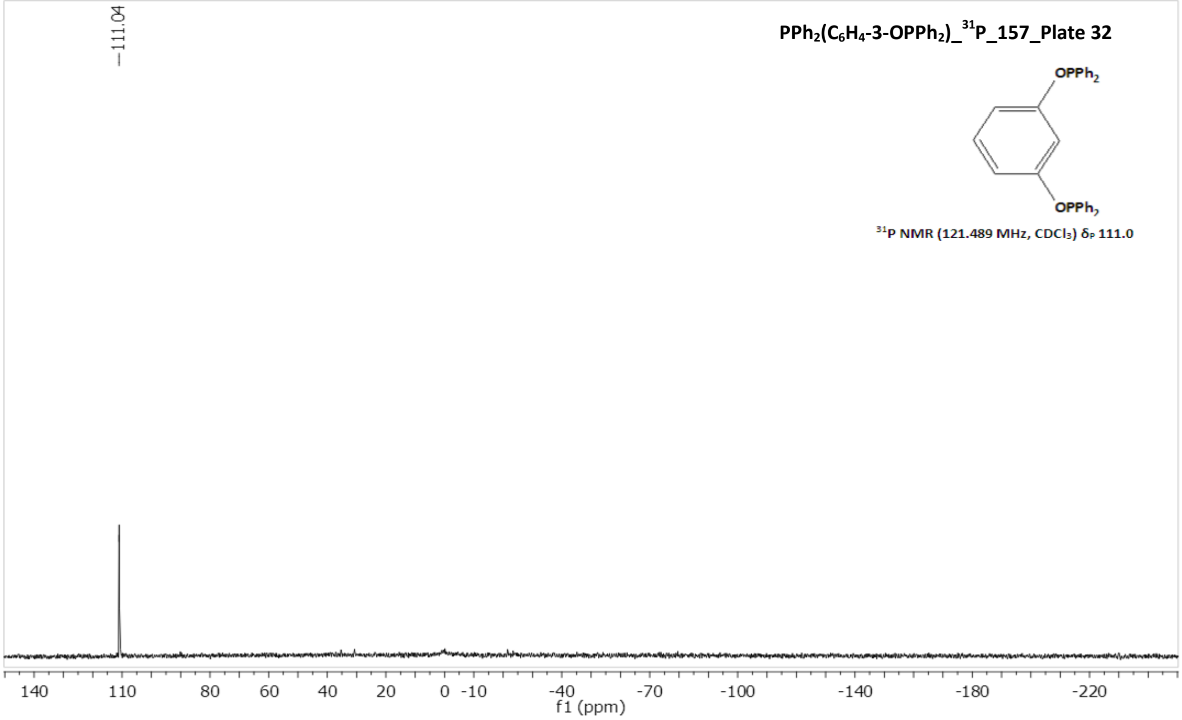
$PPh_2(OC_6H_5)$_^{31}P_155_Plate 30

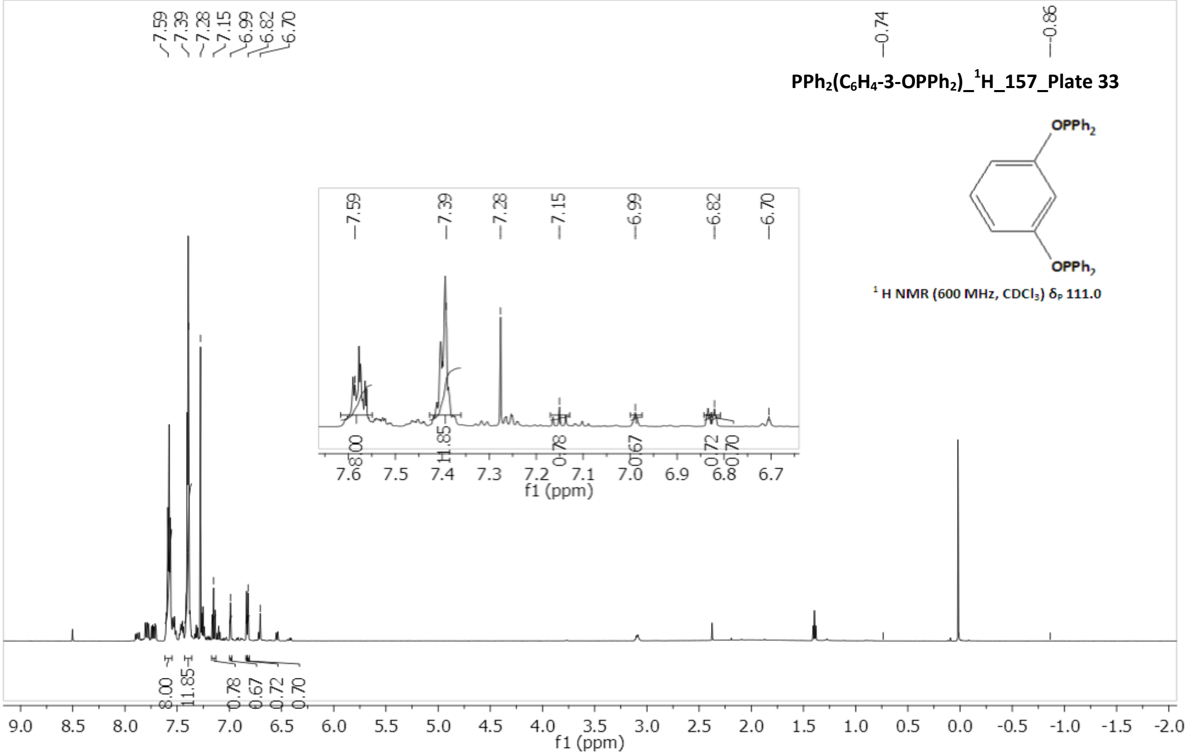
^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 110.6

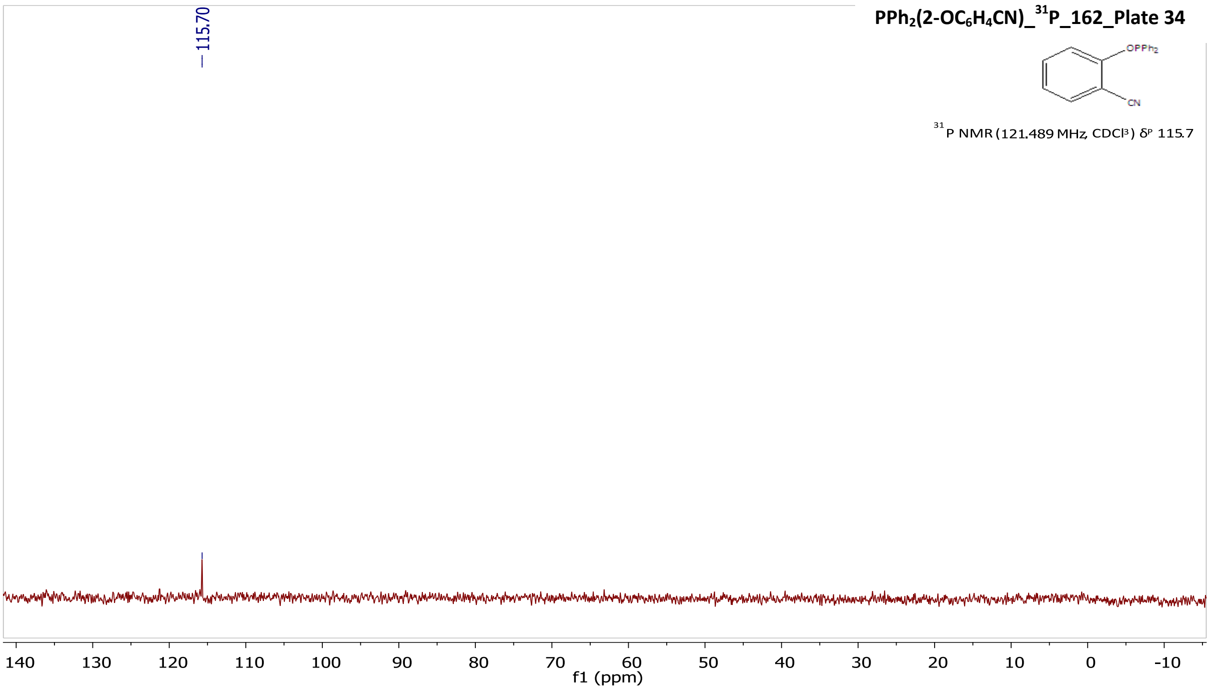


1,2-$Ph(OPPh_2)_2$_^{31}P_156_Plate 31

^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P 114.0

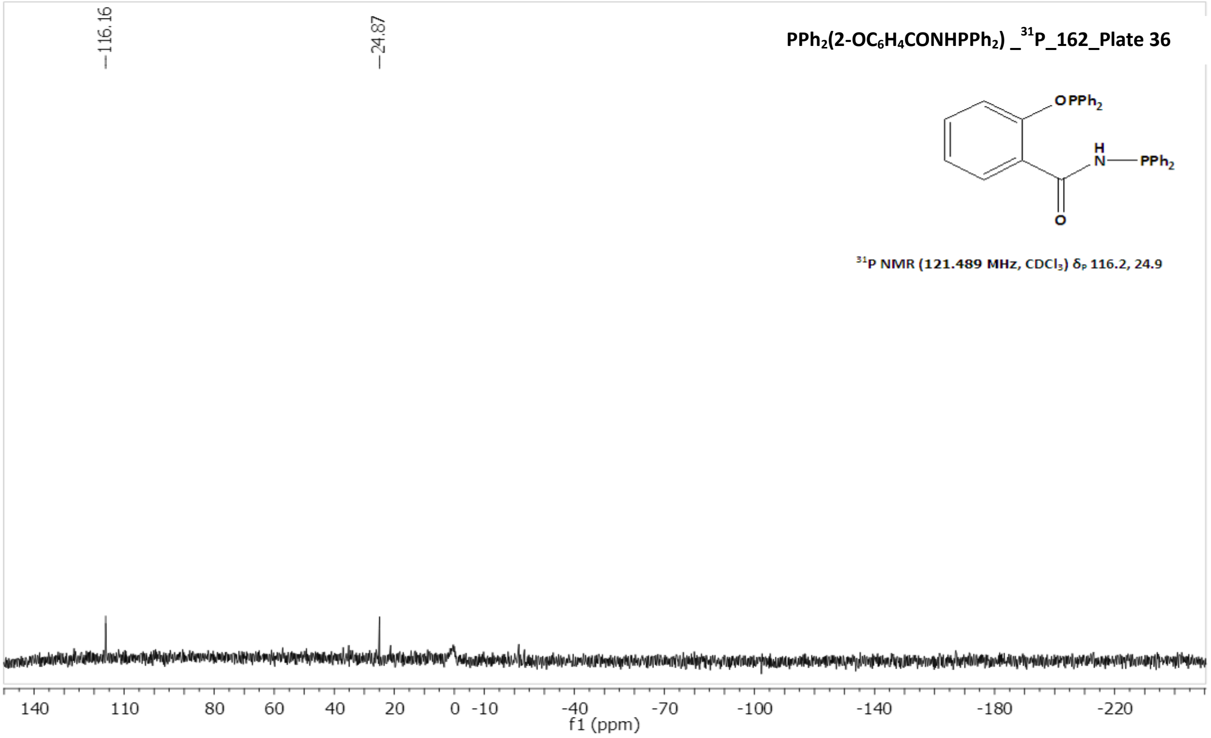

—111.04
PPh2(C6H4-3-OPPh2)_31P_157_Plate 32
OPPh2
OPPh2
31P NMR (121.489 MHz, CDCl3) δP 111.0
140 110 80 60 40 20 0 -10 -40 -70 -100 -140 -180 -220
f1 (ppm)


7.59
7.39
7.28
7.15
6.99
6.82
6.70
—0.74
—0.86
PPh2(C6H4-3-OPPh2)_1H_157_Plate 33
OPPh2
OPPh2
1 H NMR (600 MHz, CDCl3) δP 111.0
8.00
11.85
0.78
0.67
0.72
0.70
7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7
f1 (ppm)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0
f1 (ppm)



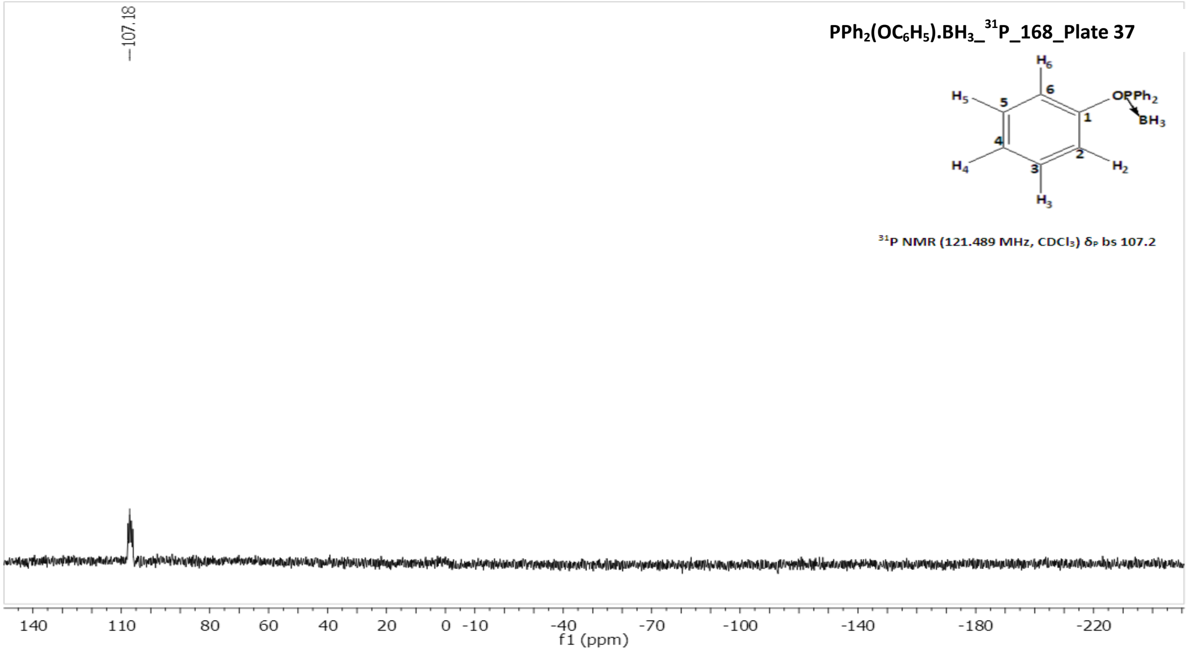
PPh$_2$(2-OC$_6$H$_4$CN)_^{31}P_162_Plate 34

^{31}P NMR (121.489 MHz, CDCl^3) δ^P 115.7



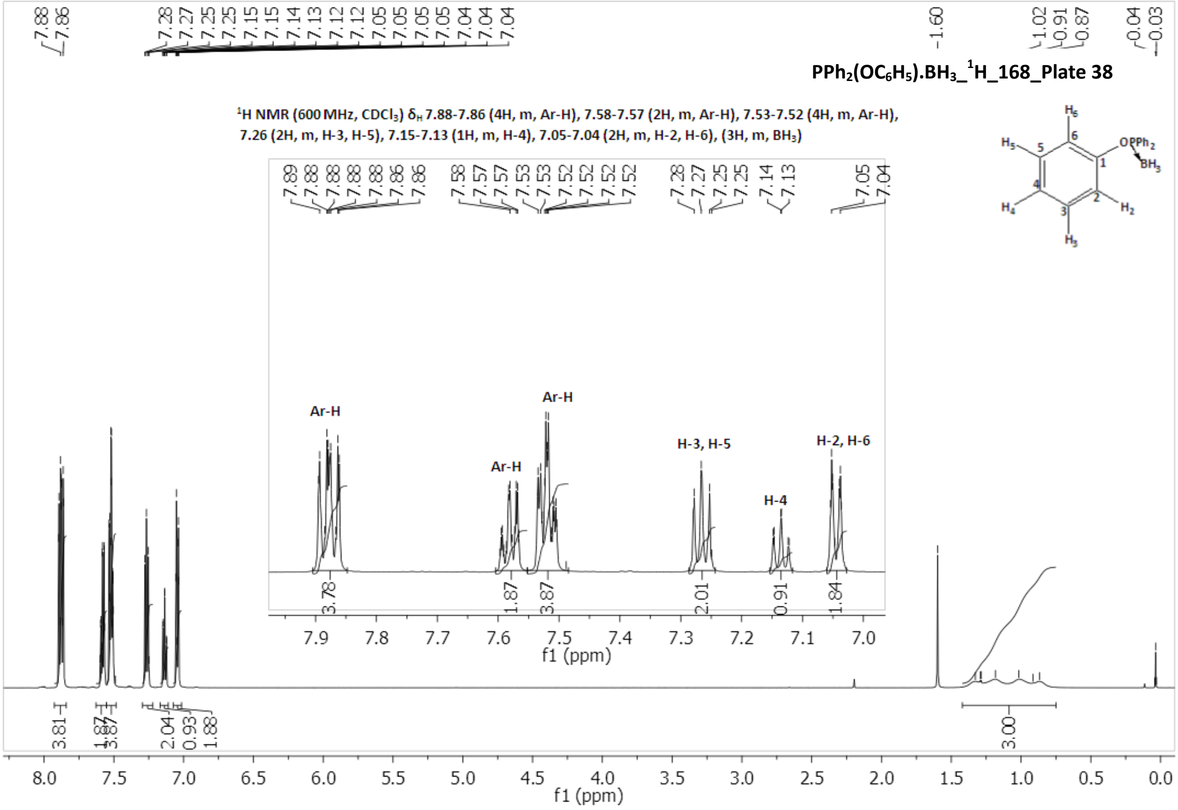
PPh$_2$(2-OC$_6$H$_4$CONHPPh$_2$) _^{31}P_162_Plate 36

^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 116.2, 24.9



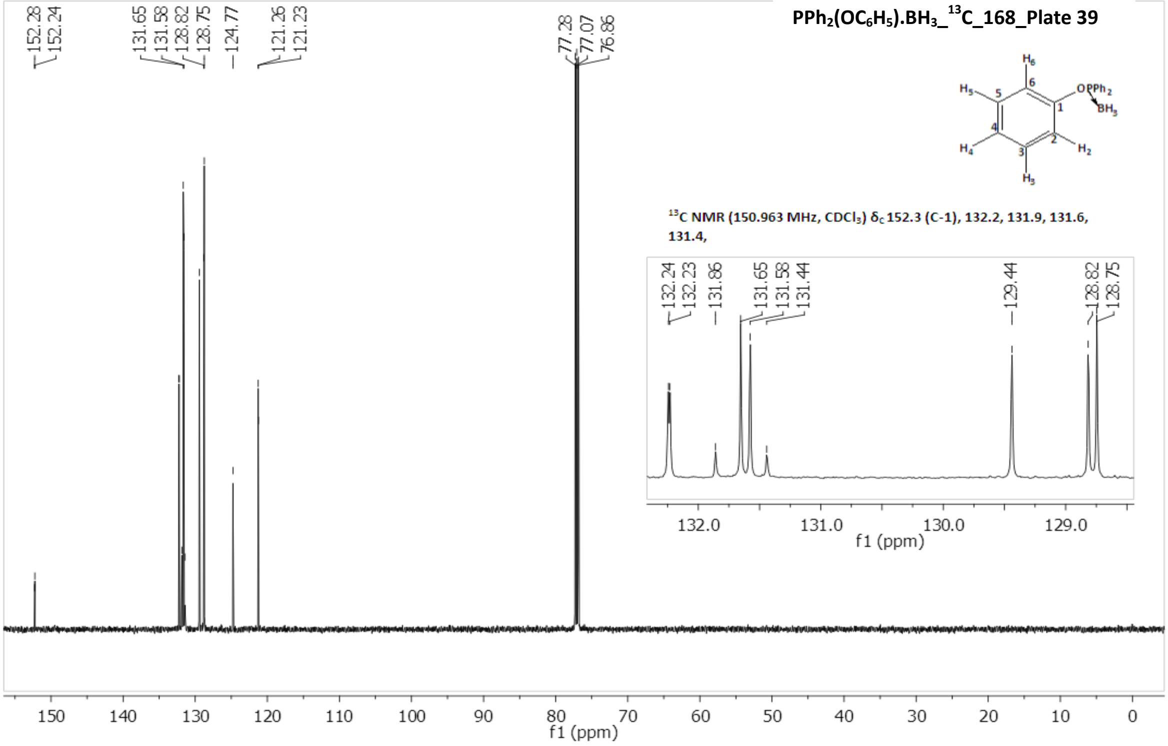
$PPh_2(OC_6H_5).BH_3$_^{31}P_168_Plate 37

^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P bs 107.2



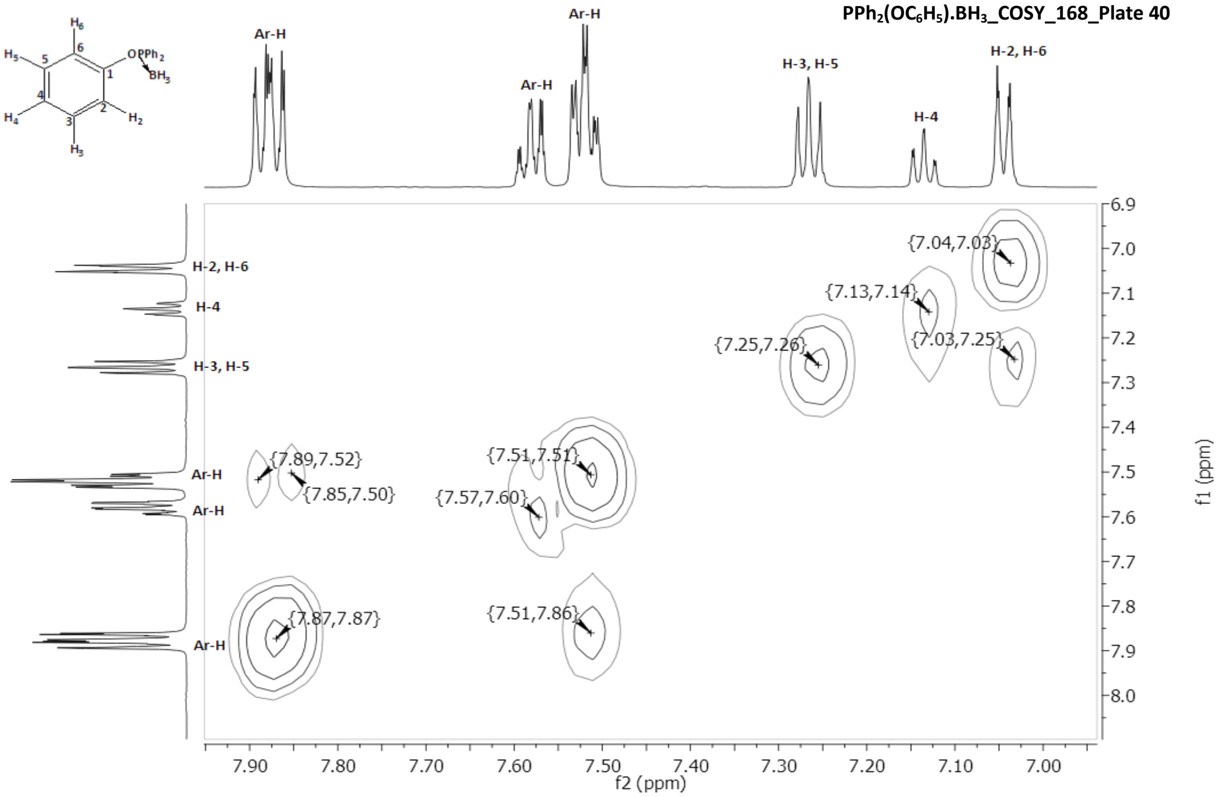
$PPh_2(OC_6H_5).BH_3$_^{1}H_168_Plate 38

^1H NMR (600 MHz, $CDCl_3$) δ_H 7.88-7.86 (4H, m, Ar-H), 7.58-7.57 (2H, m, Ar-H), 7.53-7.52 (4H, m, Ar-H), 7.26 (2H, m, H-3, H-5), 7.15-7.13 (1H, m, H-4), 7.05-7.04 (2H, m, H-2, H-6), (3H, m, BH_3)

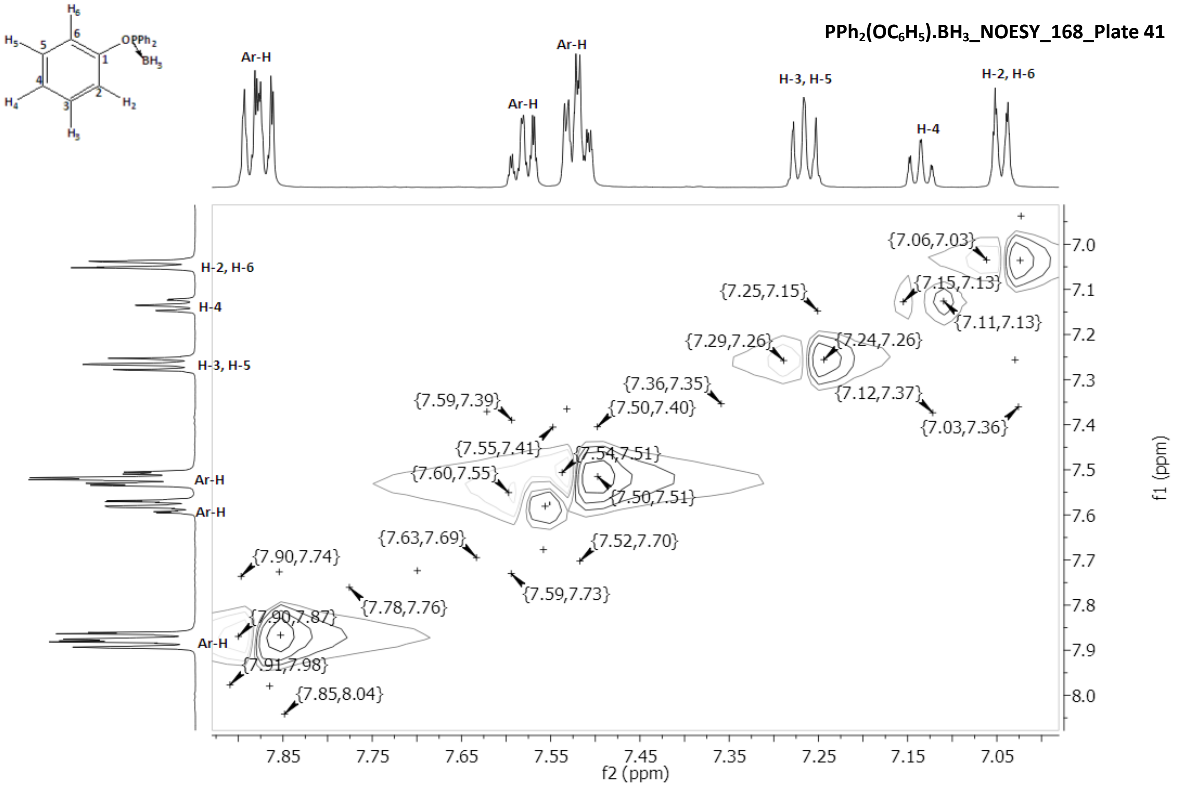


$PPh_2(OC_6H_5).BH_3$_^{13}C_168_Plate 39

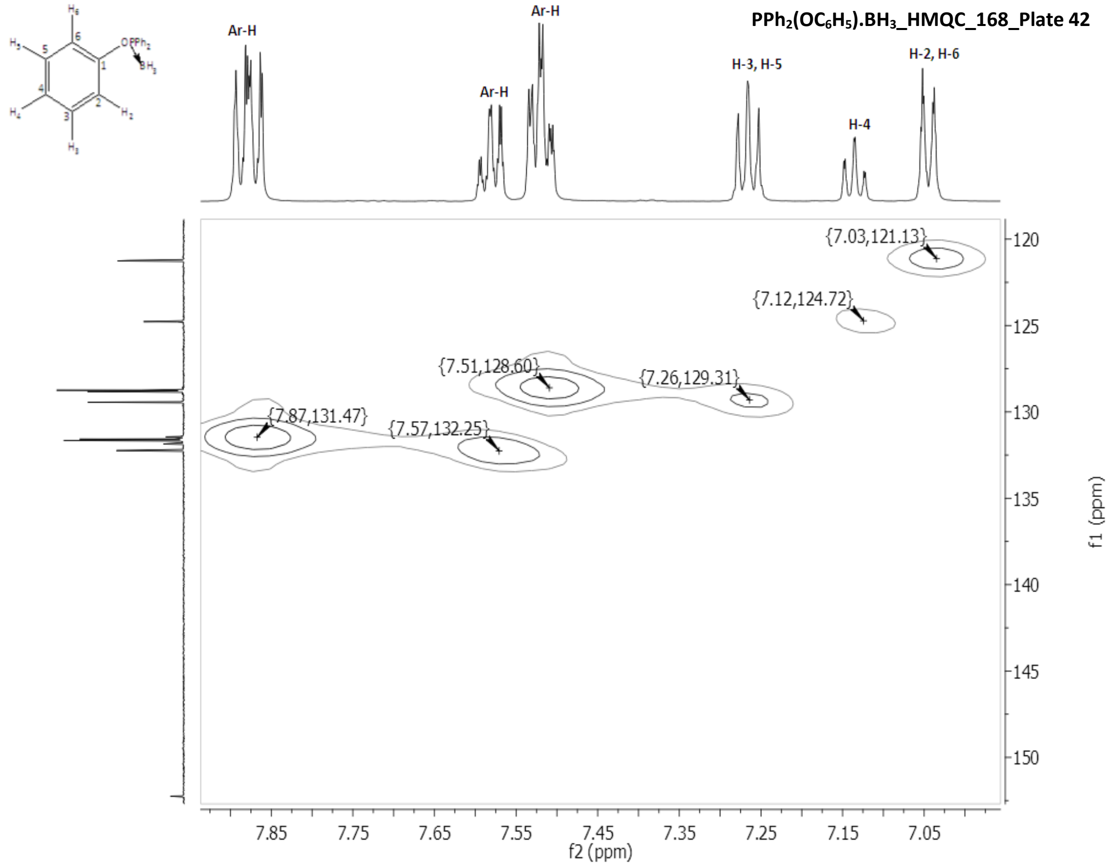
^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 152.3 (C-1), 132.2, 131.9, 131.6, 131.4,



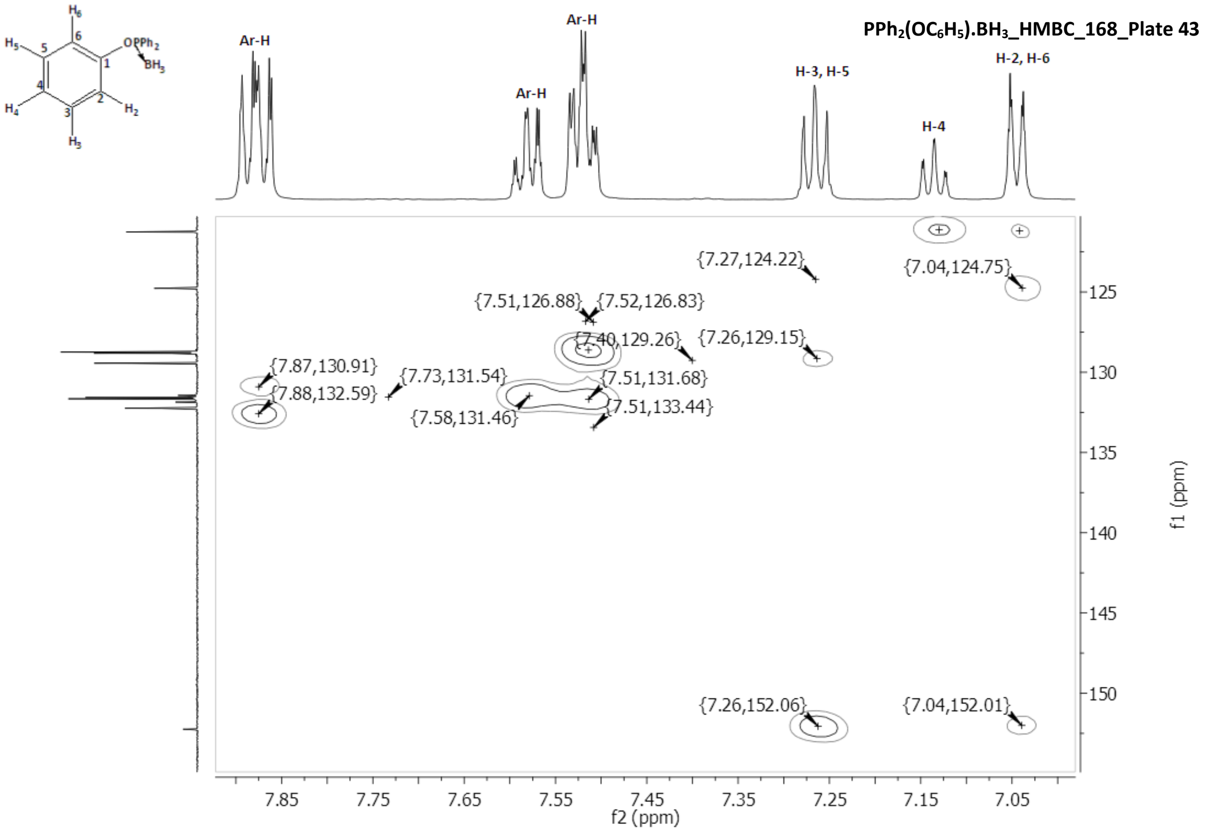
$PPh_2(OC_6H_5).BH_3$_COSY_168_Plate 40



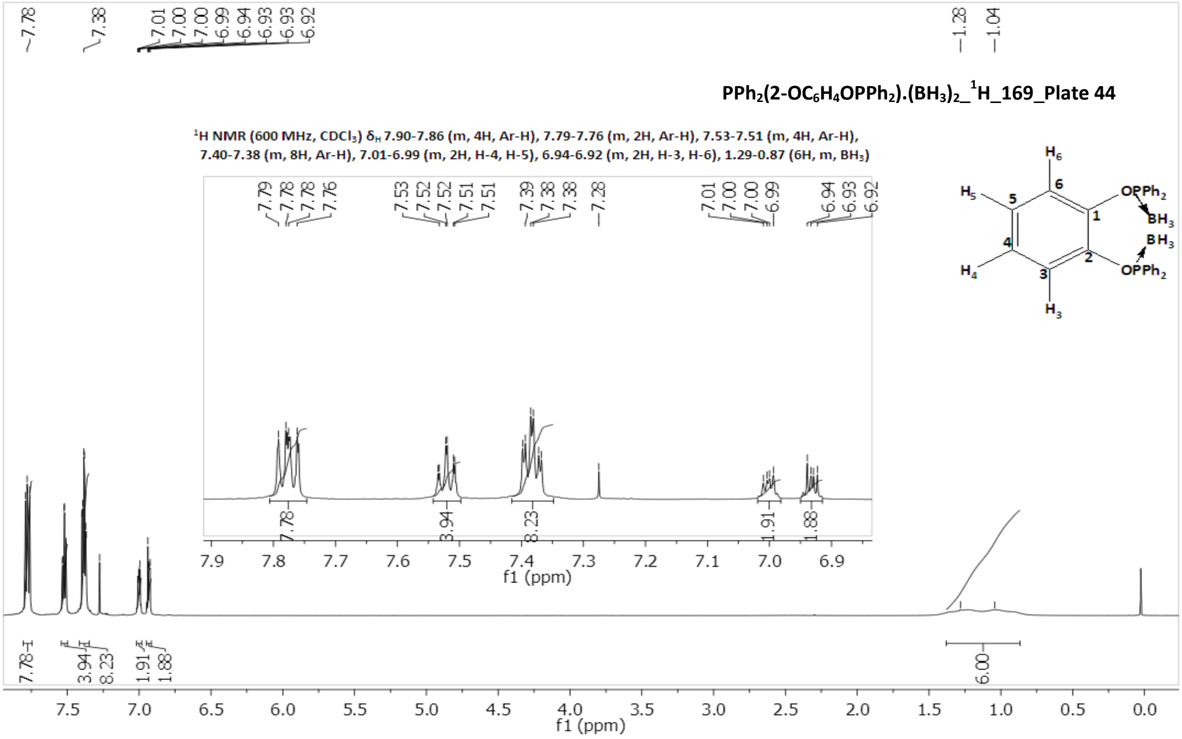
$PPh_2(OC_6H_5).BH_3$_NOESY_168_Plate 41



$PPh_2(OC_6H_5).BH_3$_HMQC_168_Plate 42

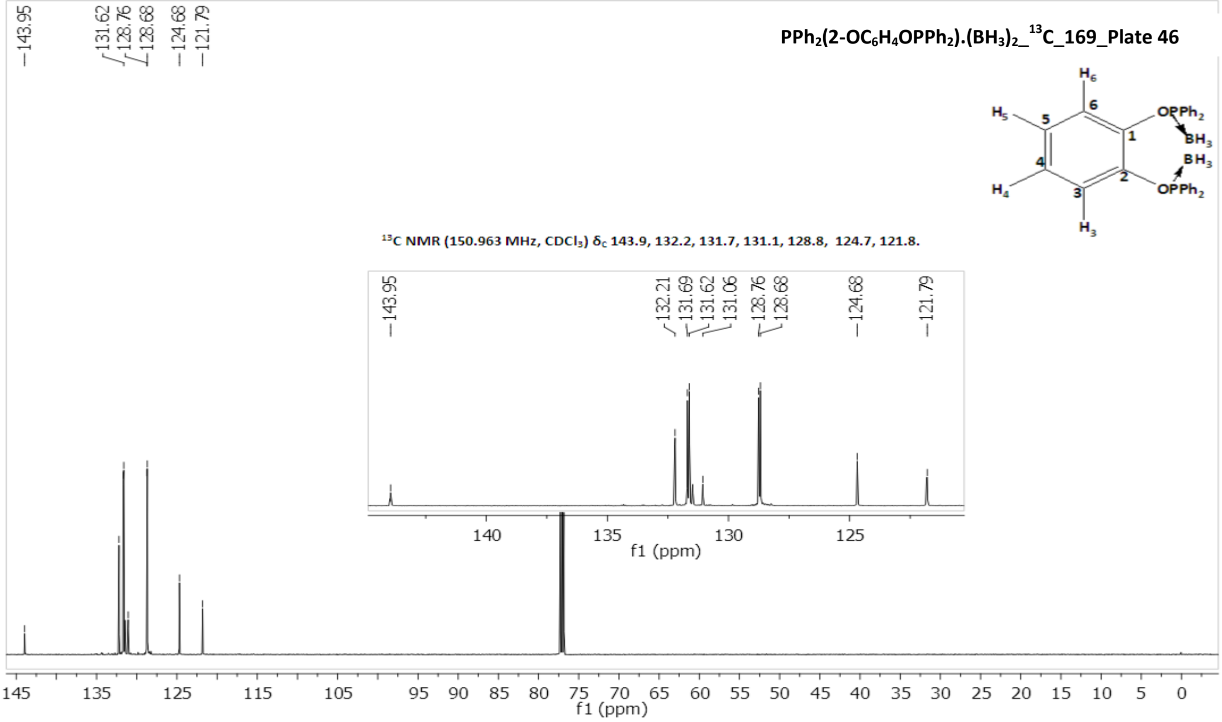


$PPh_2(OC_6H_5).BH_3$_HMBC_168_Plate 43



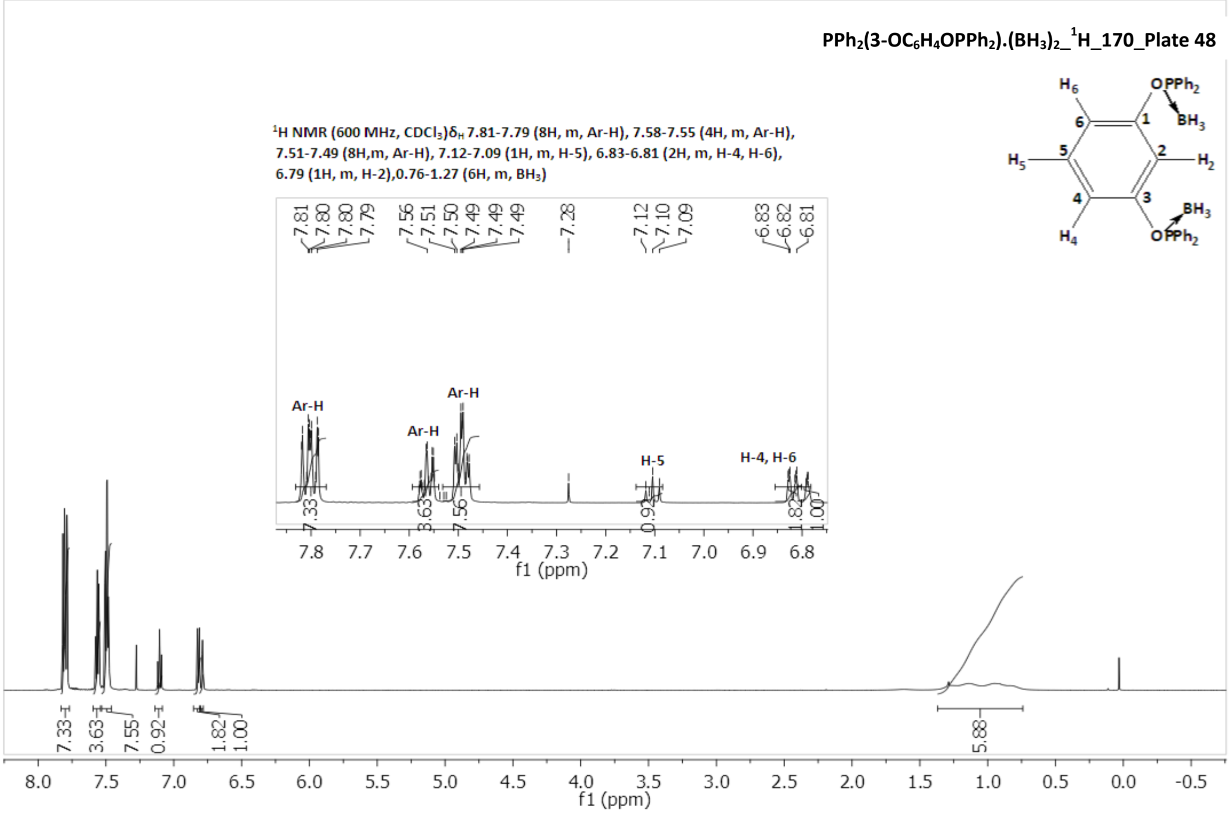
$PPh_2(2\text{-}OC_6H_4OPPh_2).(BH_3)_2$_^{1}H_169_Plate 44

^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.90-7.86 (m, 4H, Ar-H), 7.79-7.76 (m, 2H, Ar-H), 7.53-7.51 (m, 4H, Ar-H), 7.40-7.38 (m, 8H, Ar-H), 7.01-6.99 (m, 2H, H-4, H-5), 6.94-6.92 (m, 2H, H-3, H-6), 1.29-0.87 (6H, m, BH_3)



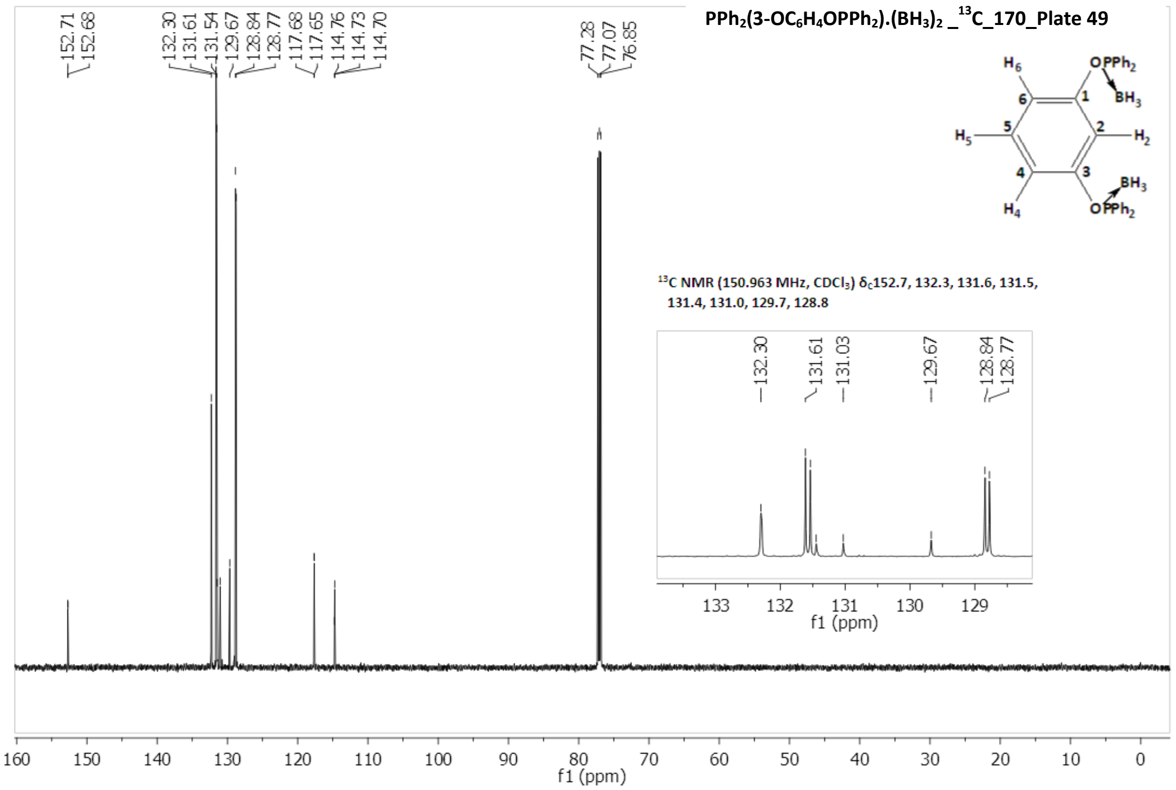
$PPh_2(2-OC_6H_4OPPh_2).(BH_3)_2$_^{13}C_169_Plate 46

^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C 143.9, 132.2, 131.7, 131.1, 128.8, 124.7, 121.8.



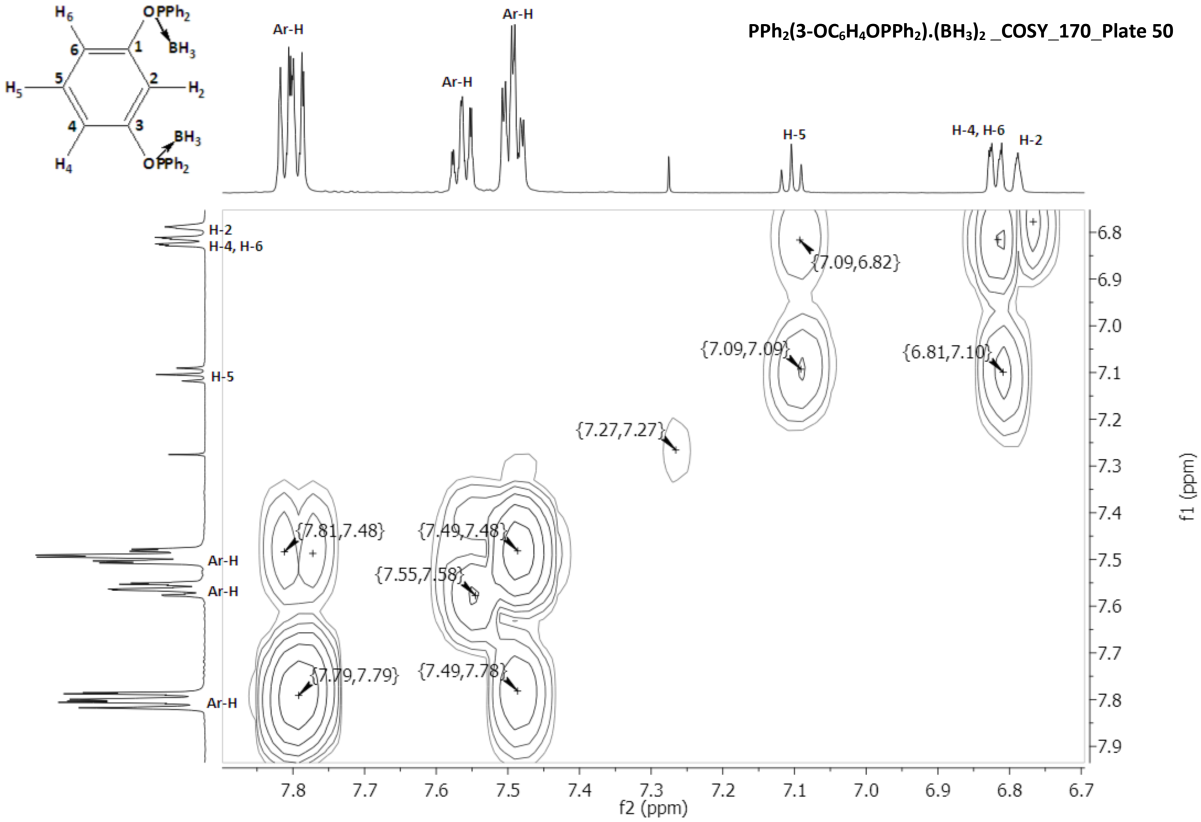
$PPh_2(3-OC_6H_4OPPh_2).(BH_3)_2$_^{1}H_170_Plate 48

^{1}H NMR (600 MHz, $CDCl_3$)δ_H 7.81-7.79 (8H, m, Ar-H), 7.58-7.55 (4H, m, Ar-H), 7.51-7.49 (8H,m, Ar-H), 7.12-7.09 (1H, m, H-5), 6.83-6.81 (2H, m, H-4, H-6), 6.79 (1H, m, H-2),0.76-1.27 (6H, m, BH_3)

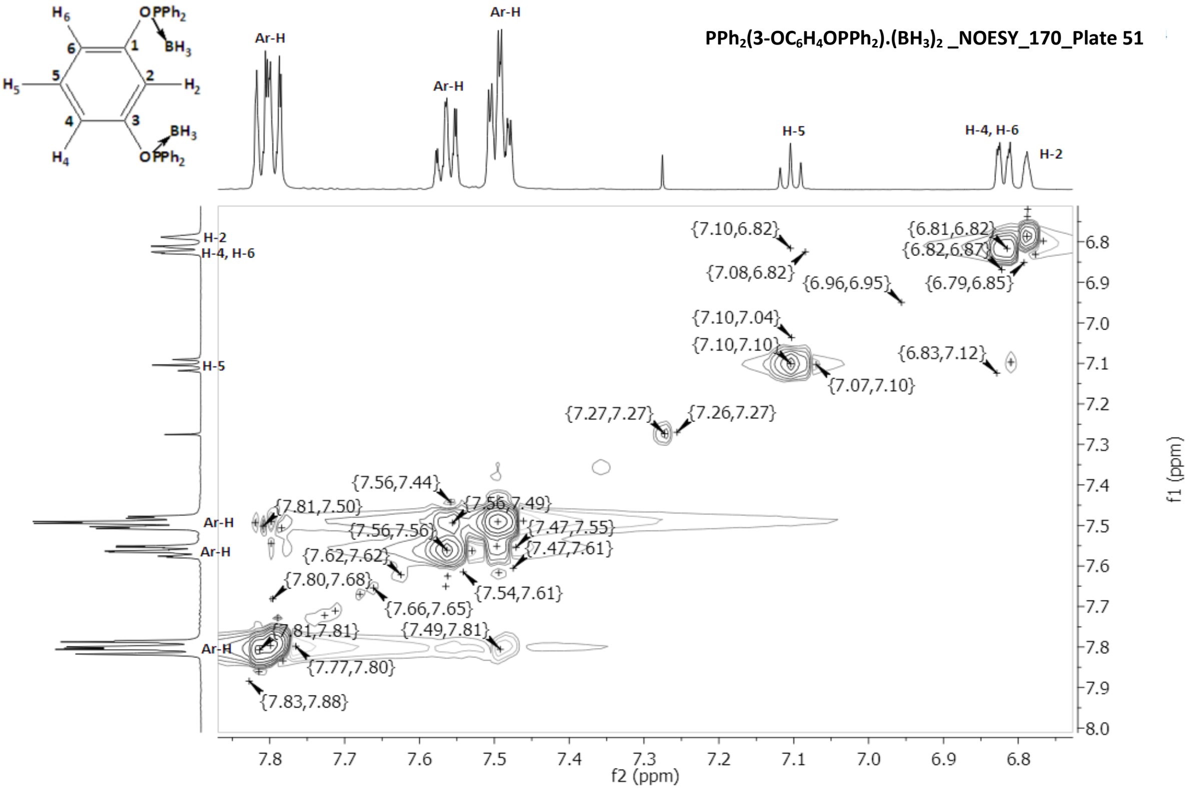


$PPh_2(3\text{-}OC_6H_4OPPh_2).(BH_3)_2$ _^{13}C_170_Plate 49

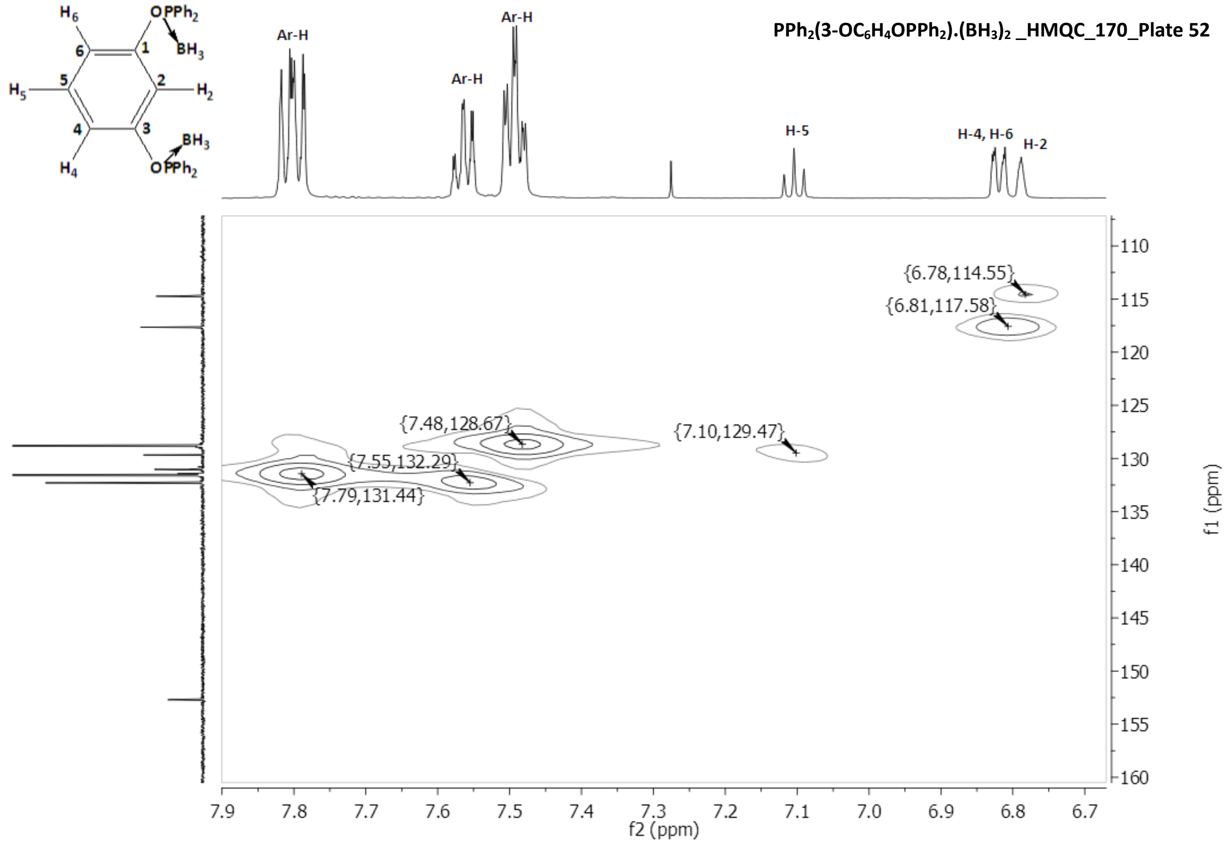
^{13}C NMR (150.963 MHz, $CDCl_3$) δ_C152.7, 132.3, 131.6, 131.5, 131.4, 131.0, 129.7, 128.8



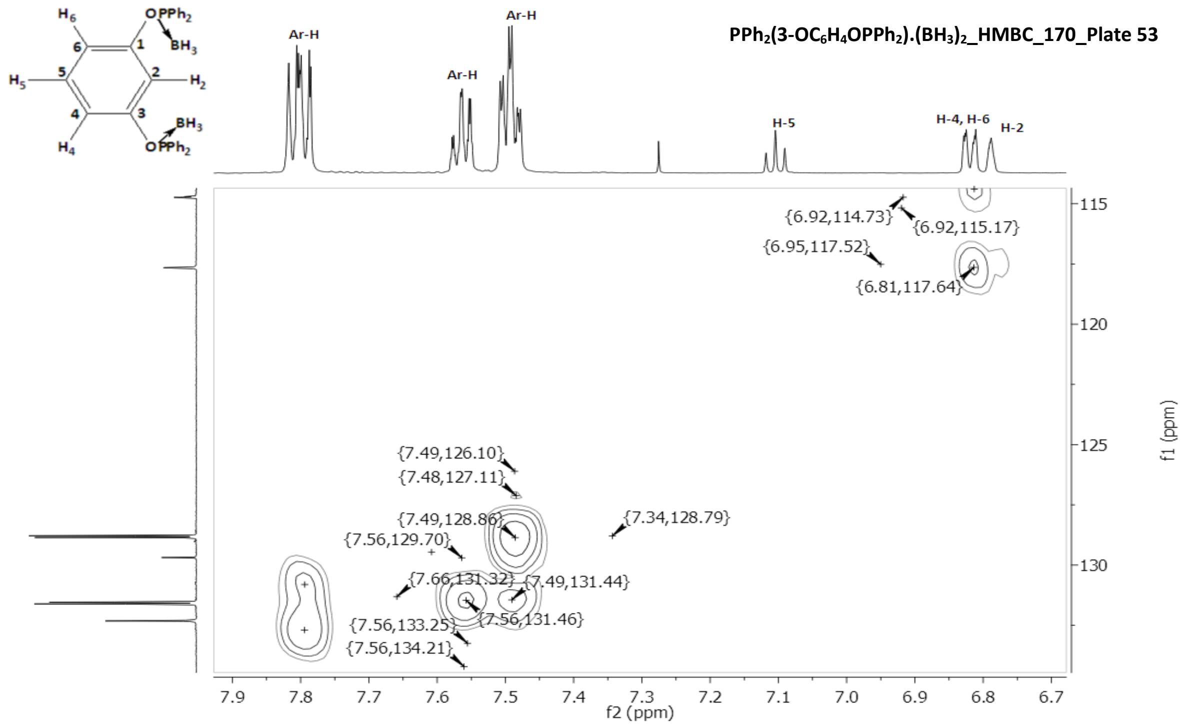
$PPh_2(3\text{-}OC_6H_4OPPh_2).(BH_3)_2$ _COSY_170_Plate 50



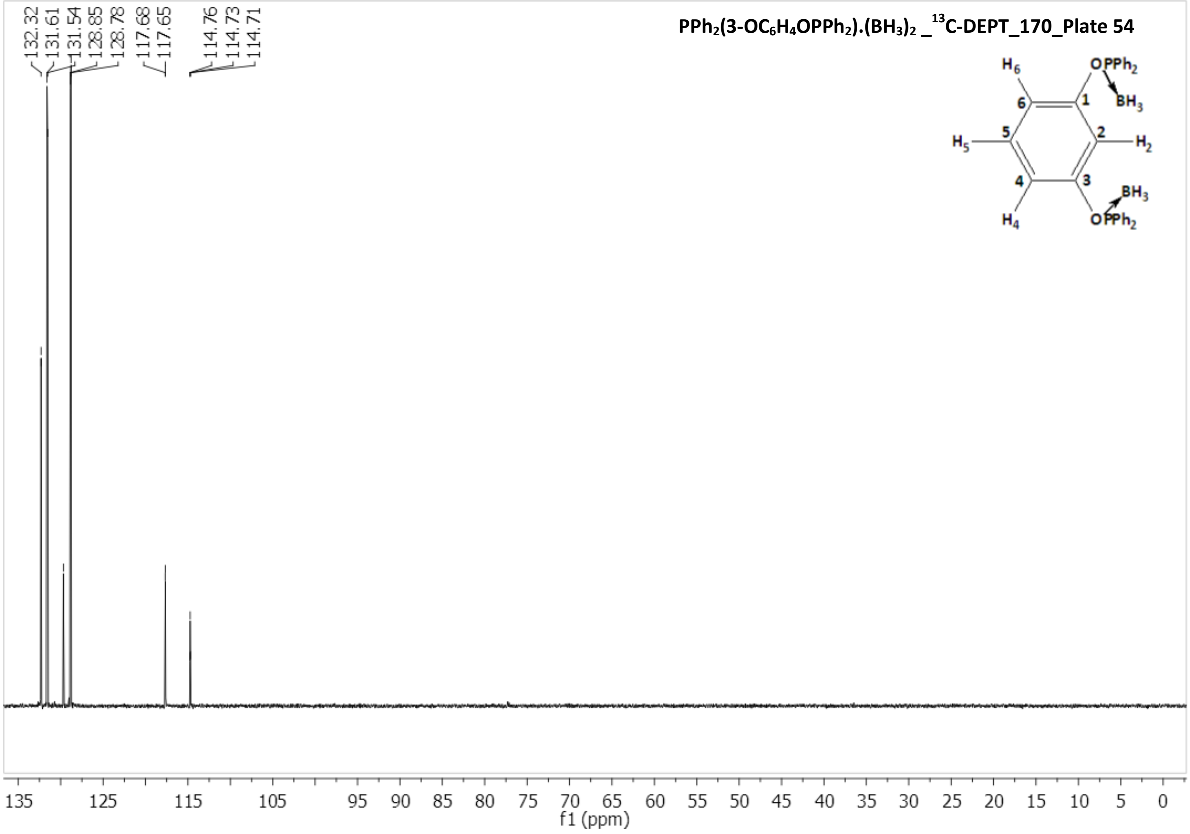
PPh$_2$(3-OC$_6$H$_4$OPPh$_2$).(BH$_3$)$_2$ _NOESY_170_Plate 51



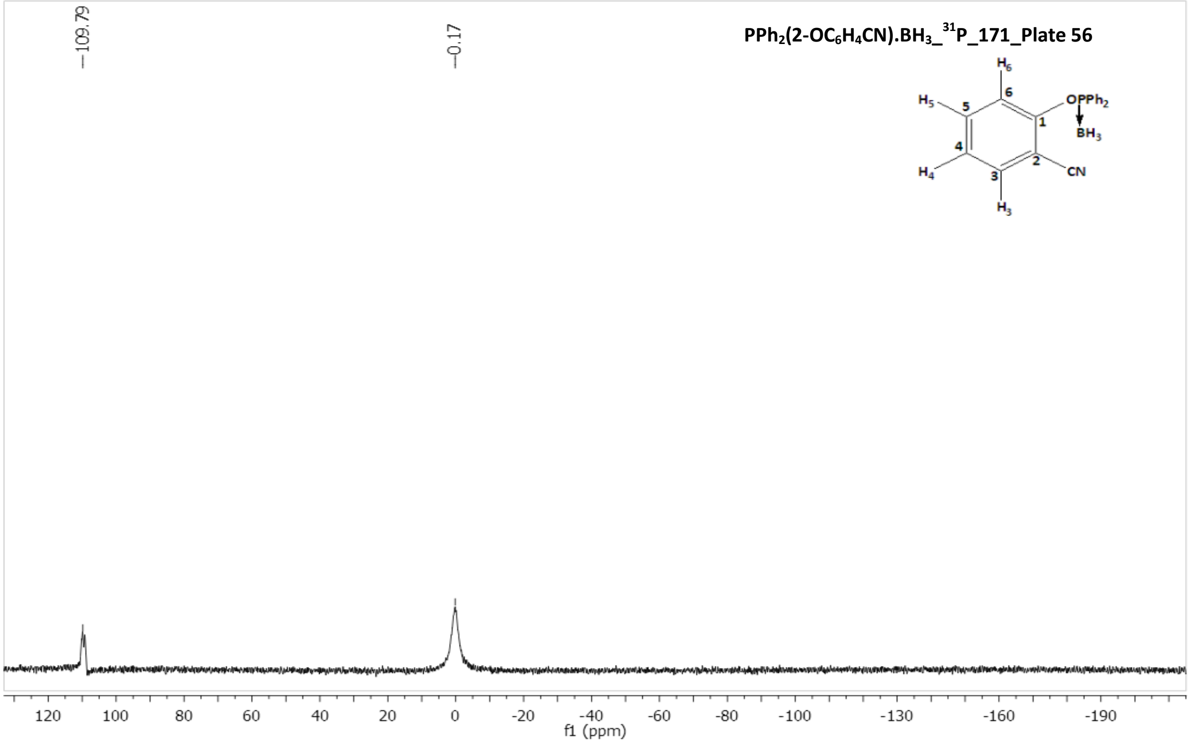
PPh$_2$(3-OC$_6$H$_4$OPPh$_2$).(BH$_3$)$_2$ _HMQC_170_Plate 52



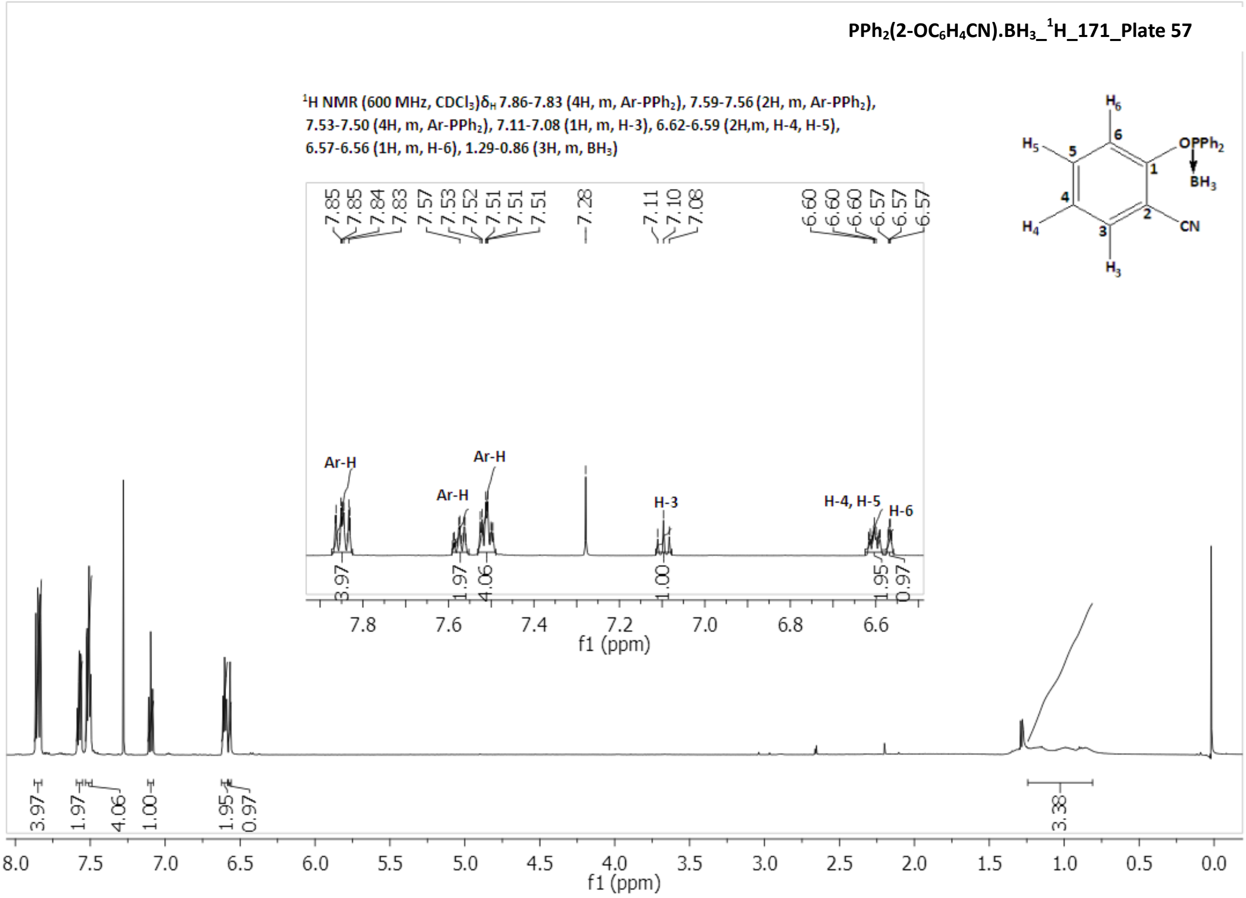
$PPh_2(3\text{-}OC_6H_4OPPh_2).(BH_3)_2$_HMBC_170_Plate 53



$PPh_2(3\text{-}OC_6H_4OPPh_2).(BH_3)_2$ _^{13}C-DEPT_170_Plate 54

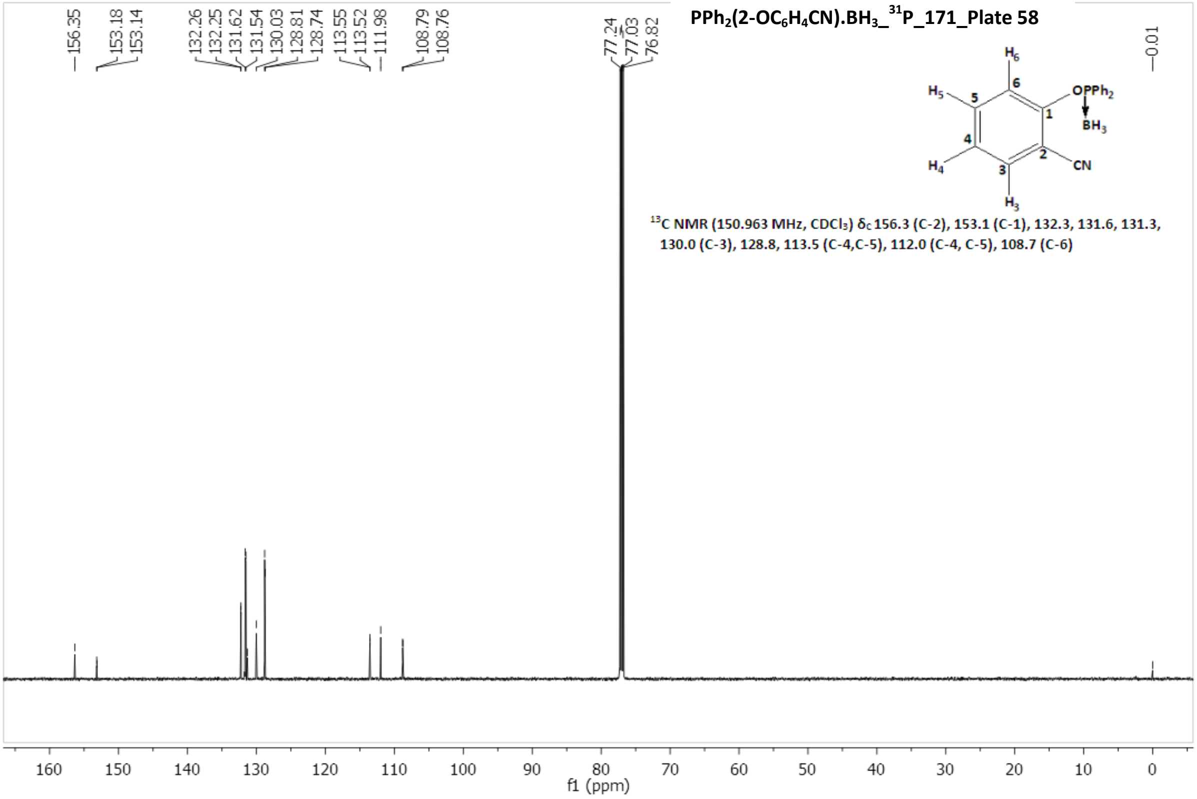


$PPh_2(2\text{-}OC_6H_4CN).BH_3$_^{31}P_171_Plate 56



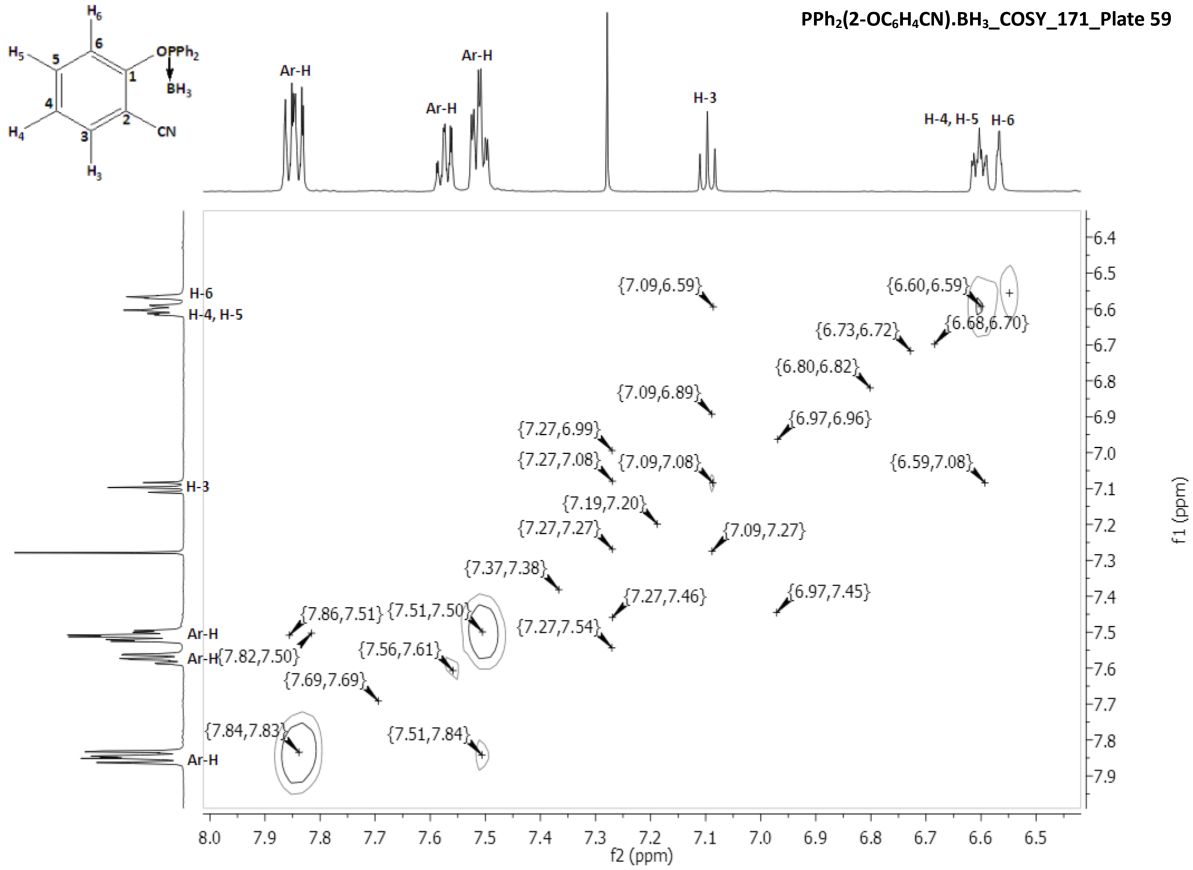
$PPh_2(2\text{-}OC_6H_4CN).BH_3$_^{1}H_171_Plate 57

^{1}H NMR (600 MHz, $CDCl_3$)δ_H 7.86-7.83 (4H, m, Ar-PPh_2), 7.59-7.56 (2H, m, Ar-PPh_2), 7.53-7.50 (4H, m, Ar-PPh_2), 7.11-7.08 (1H, m, H-3), 6.62-6.59 (2H,m, H-4, H-5), 6.57-6.56 (1H, m, H-6), 1.29-0.86 (3H, m, BH_3)

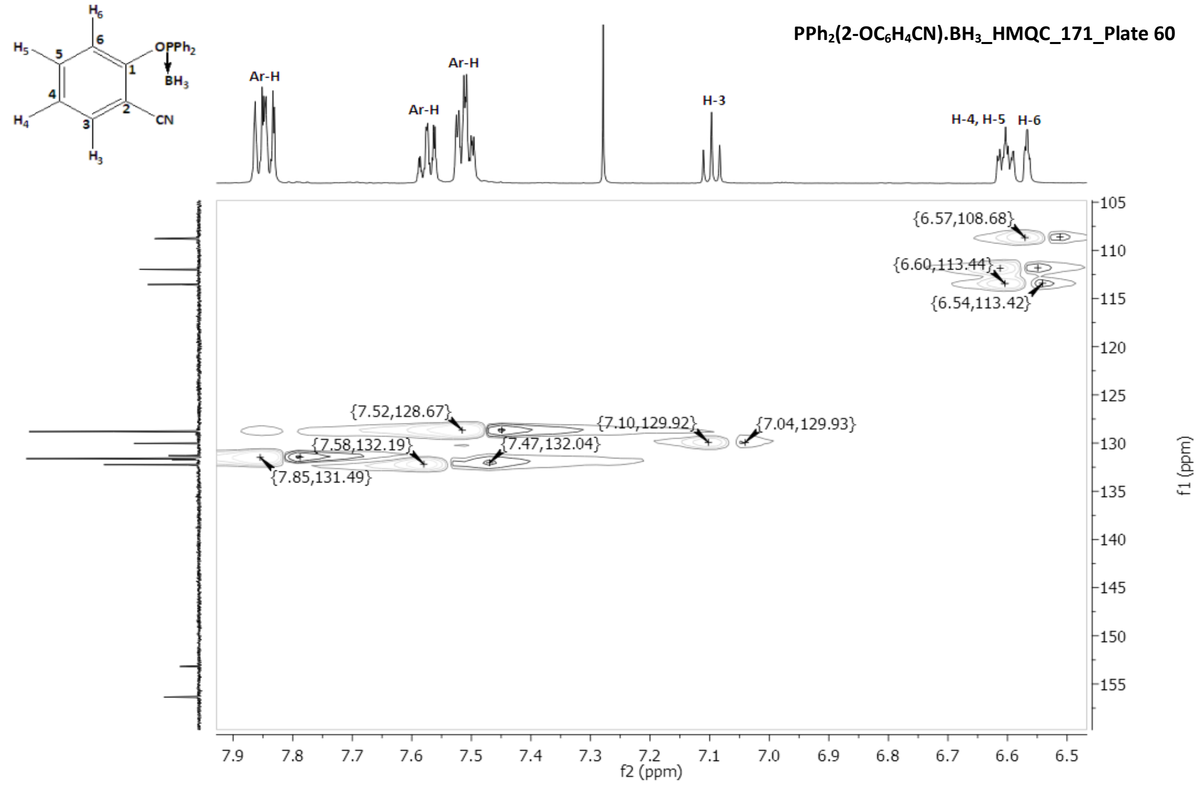


$PPh_2(2-OC_6H_4CN).BH_3$_^{31}P_171_Plate 58

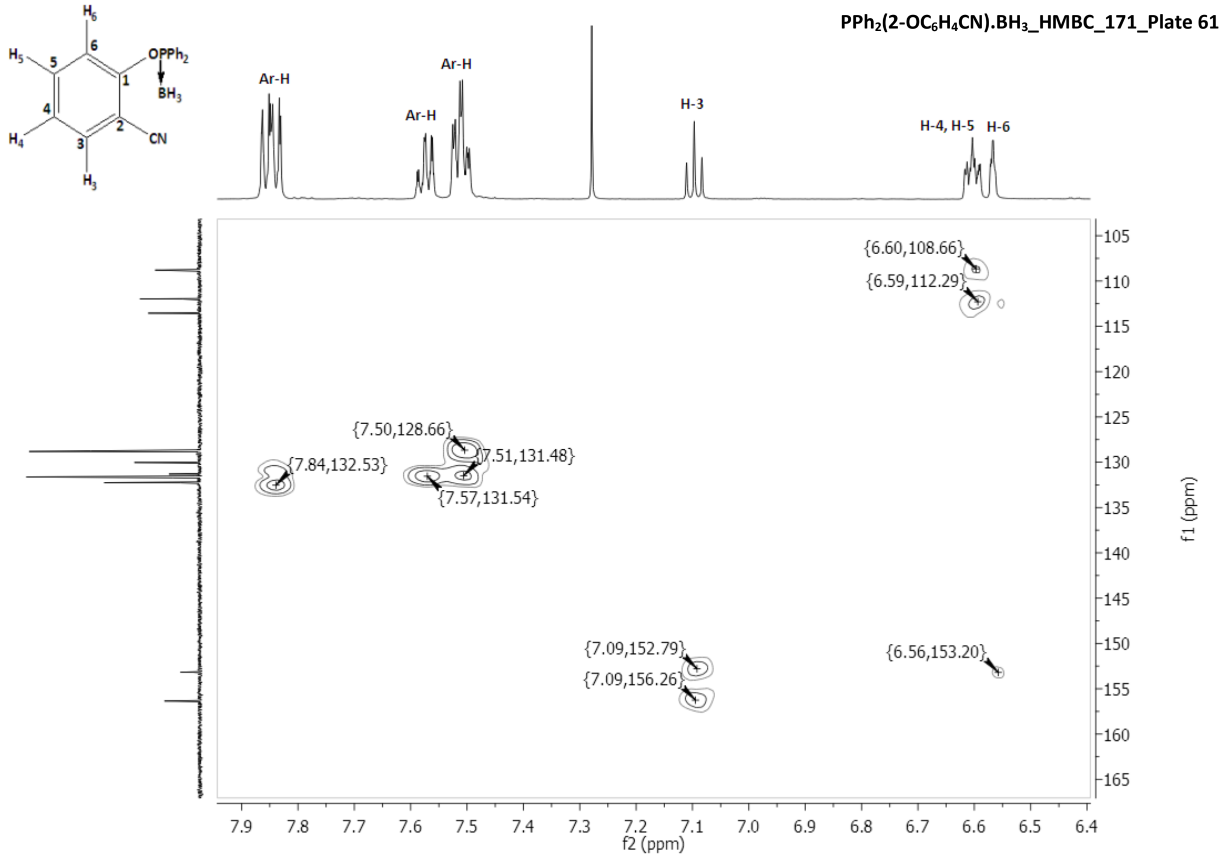
^{13}C NMR (150.963 MHz, CDCl$_3$) δ_C 156.3 (C-2), 153.1 (C-1), 132.3, 131.6, 131.3, 130.0 (C-3), 128.8, 113.5 (C-4,C-5), 112.0 (C-4, C-5), 108.7 (C-6)



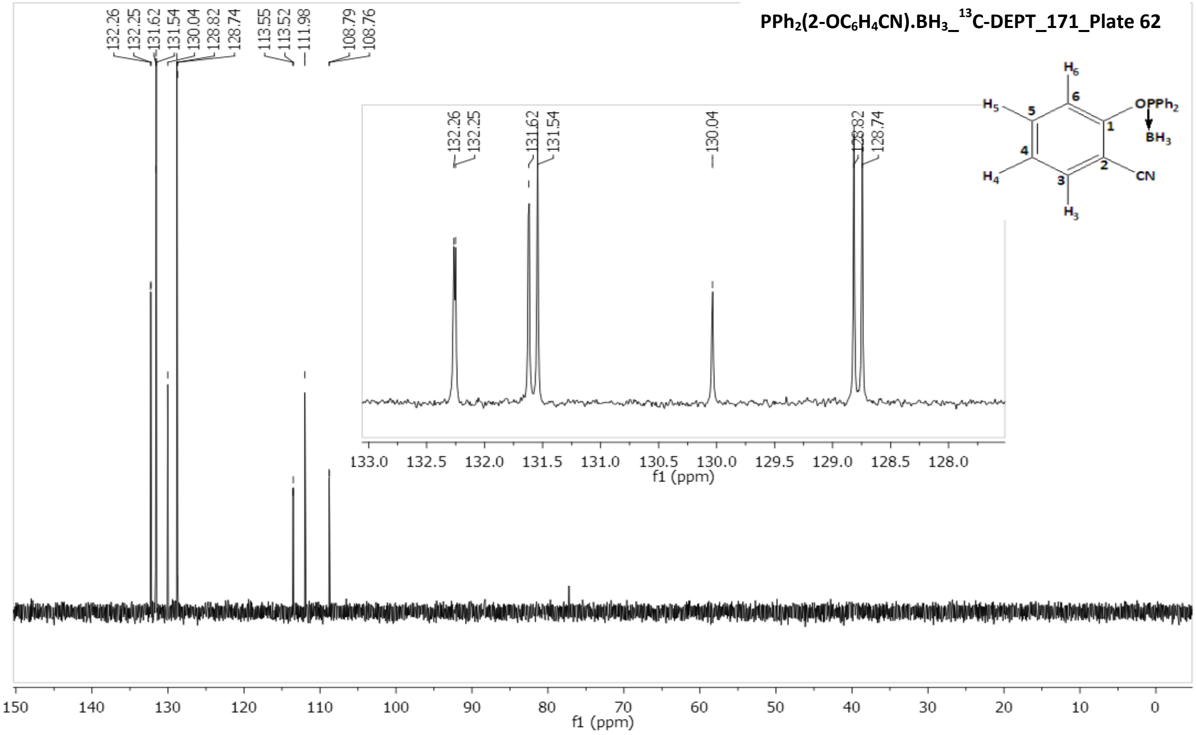
$PPh_2(2-OC_6H_4CN).BH_3$_COSY_171_Plate 59



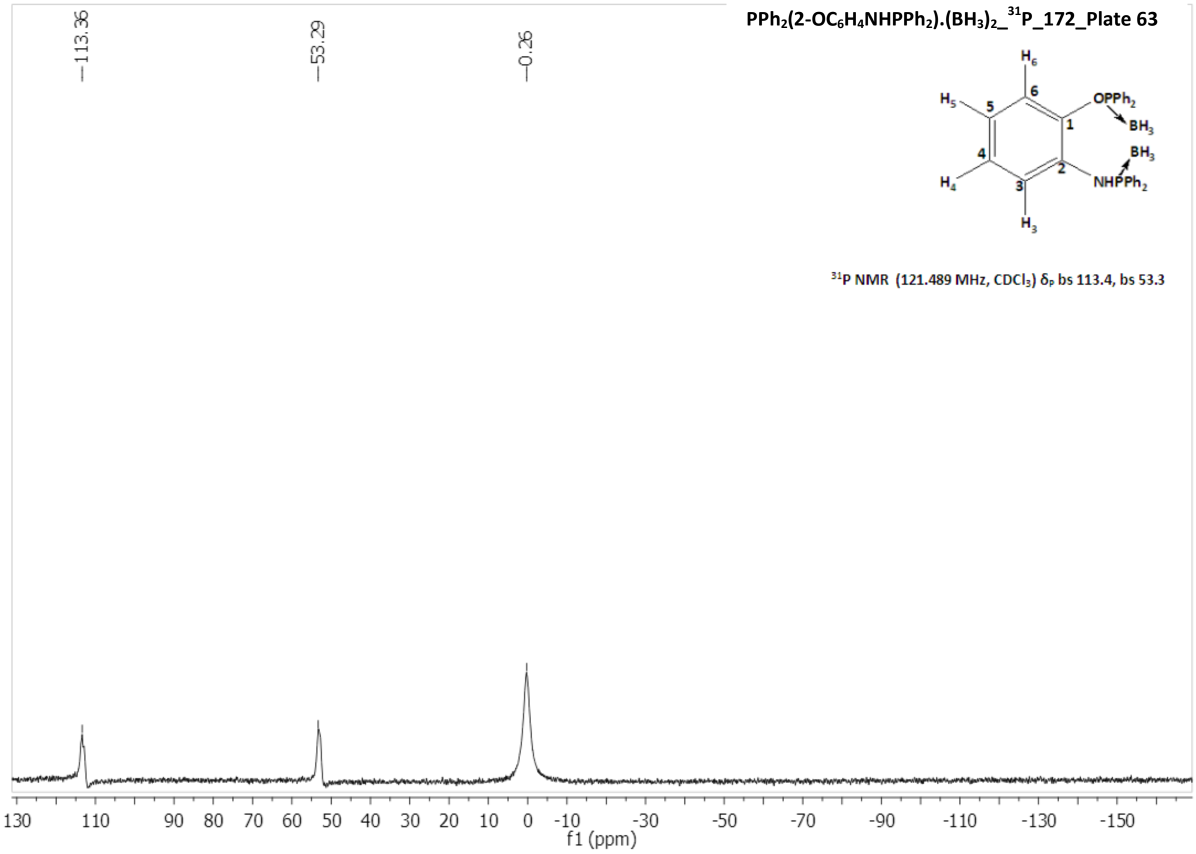
PPh$_2$(2-OC$_6$H$_4$CN).BH$_3$_HMQC_171_Plate 60



PPh$_2$(2-OC$_6$H$_4$CN).BH$_3$_HMBC_171_Plate 61



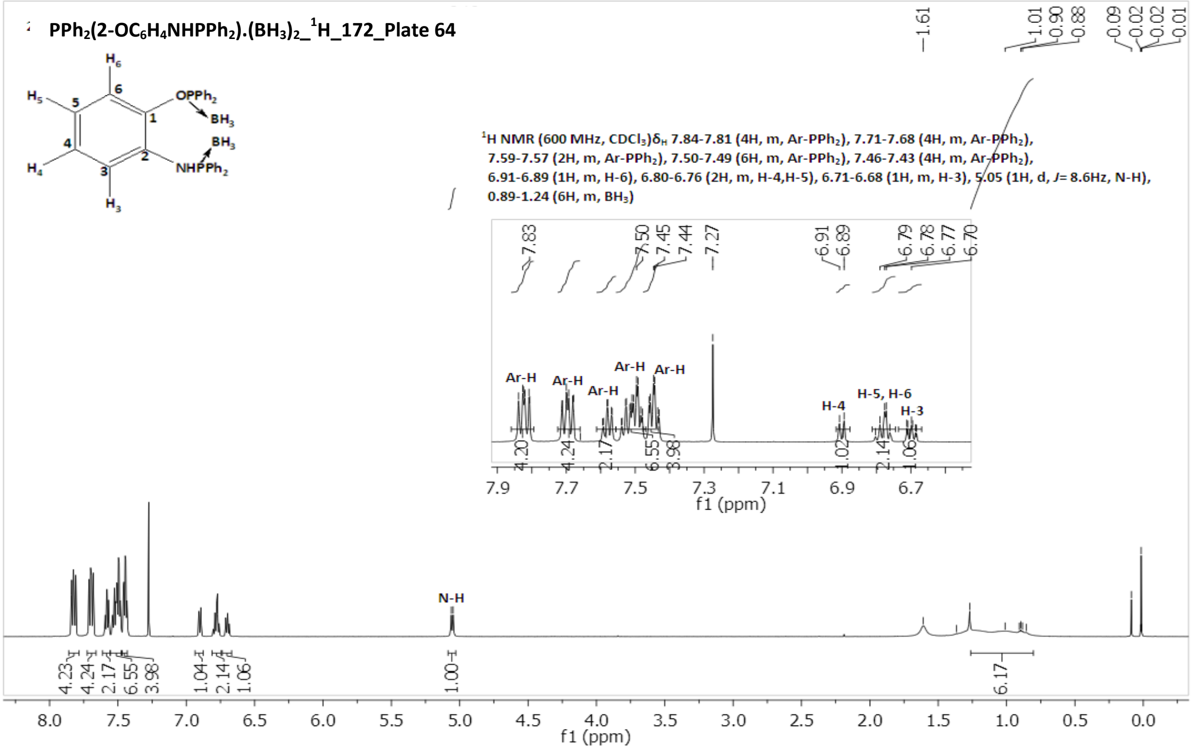
$PPh_2(2\text{-}OC_6H_4CN).BH_3$_^{13}C-DEPT_171_Plate 62



$PPh_2(2\text{-}OC_6H_4NHPPh_2).(BH_3)_2$_^{31}P_172_Plate 63

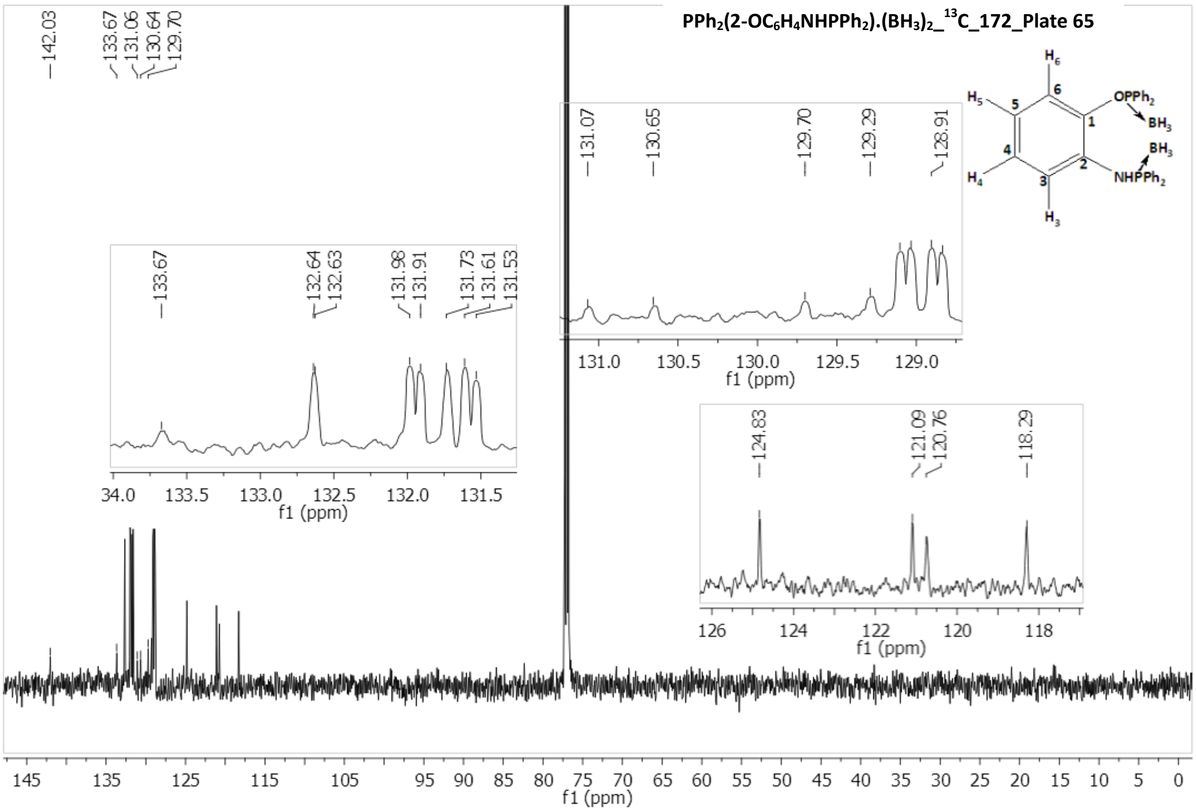
^{31}P NMR (121.489 MHz, $CDCl_3$) δ_P bs 113.4, bs 53.3

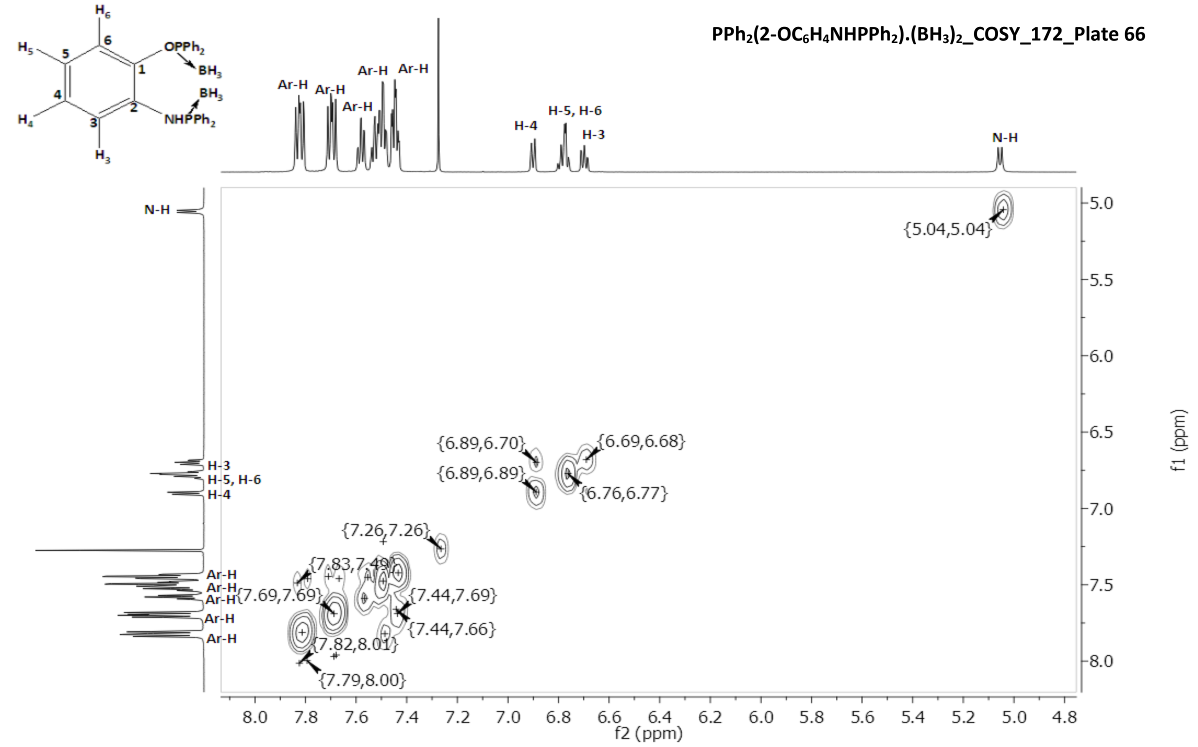
$PPh_2(2\text{-}OC_6H_4NHPPh_2).(BH_3)_2$_^{1}H_172_Plate 64



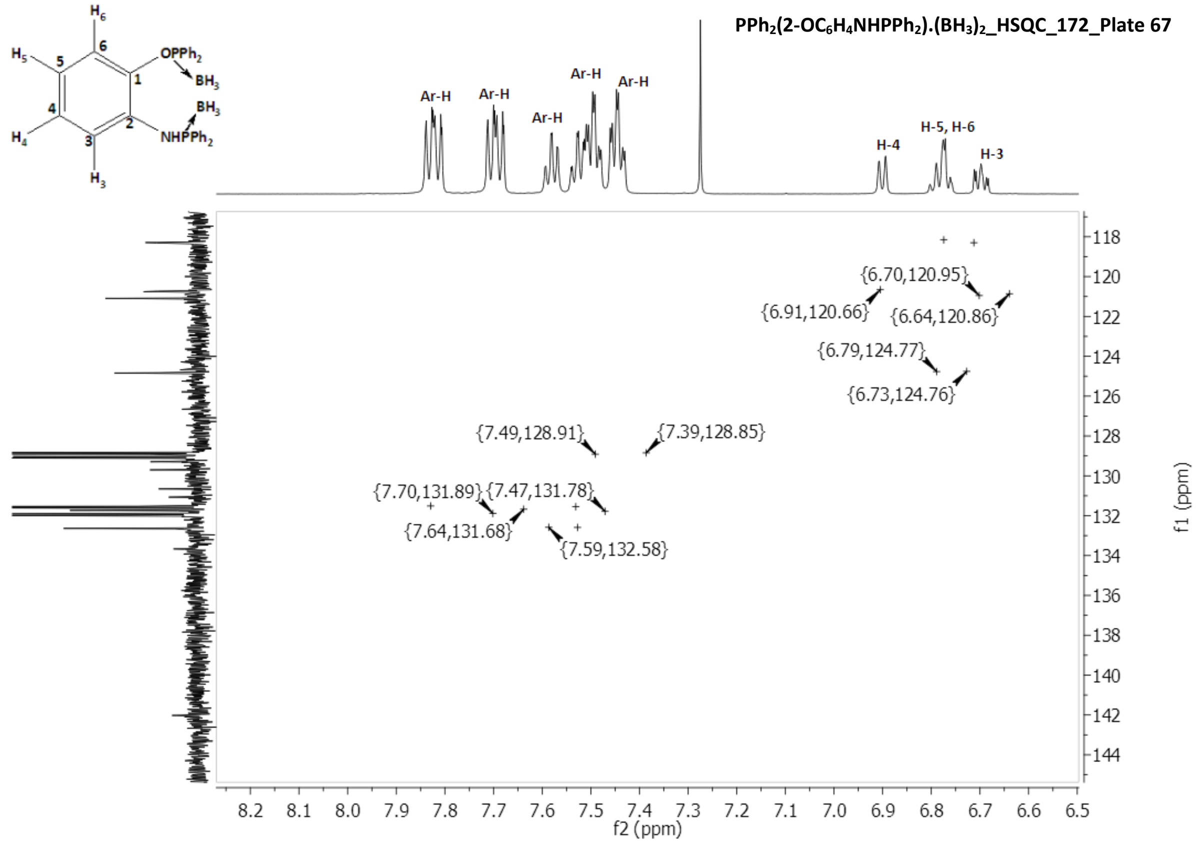
^{1}H NMR (600 MHz, $CDCl_3$)δ_H 7.84-7.81 (4H, m, Ar-PPh_2), 7.71-7.68 (4H, m, Ar-PPh_2), 7.59-7.57 (2H, m, Ar-PPh_2), 7.50-7.49 (6H, m, Ar-PPh_2), 7.46-7.43 (4H, m, Ar-PPh_2), 6.91-6.89 (1H, m, H-6), 6.80-6.76 (2H, m, H-4,H-5), 6.71-6.68 (1H, m, H-3), 5.05 (1H, d, J= 8.6Hz, N-H), 0.89-1.24 (6H, m, BH_3)

$PPh_2(2\text{-}OC_6H_4NHPPh_2).(BH_3)_2$_^{13}C_172_Plate 65

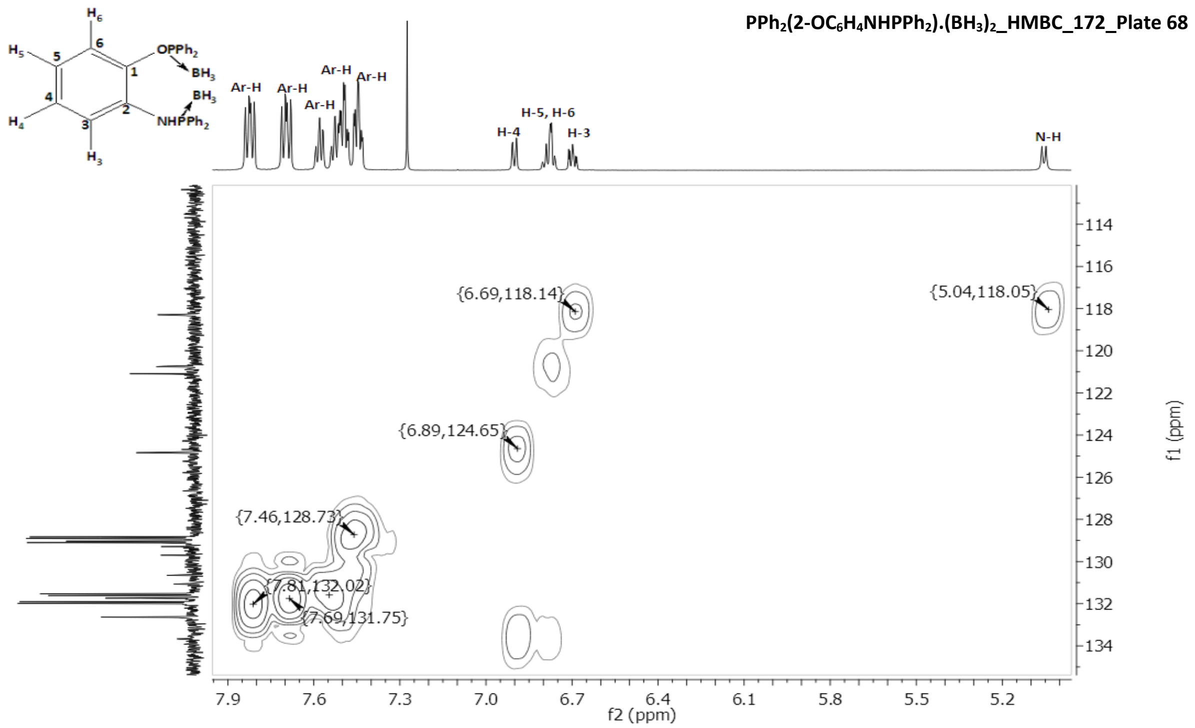


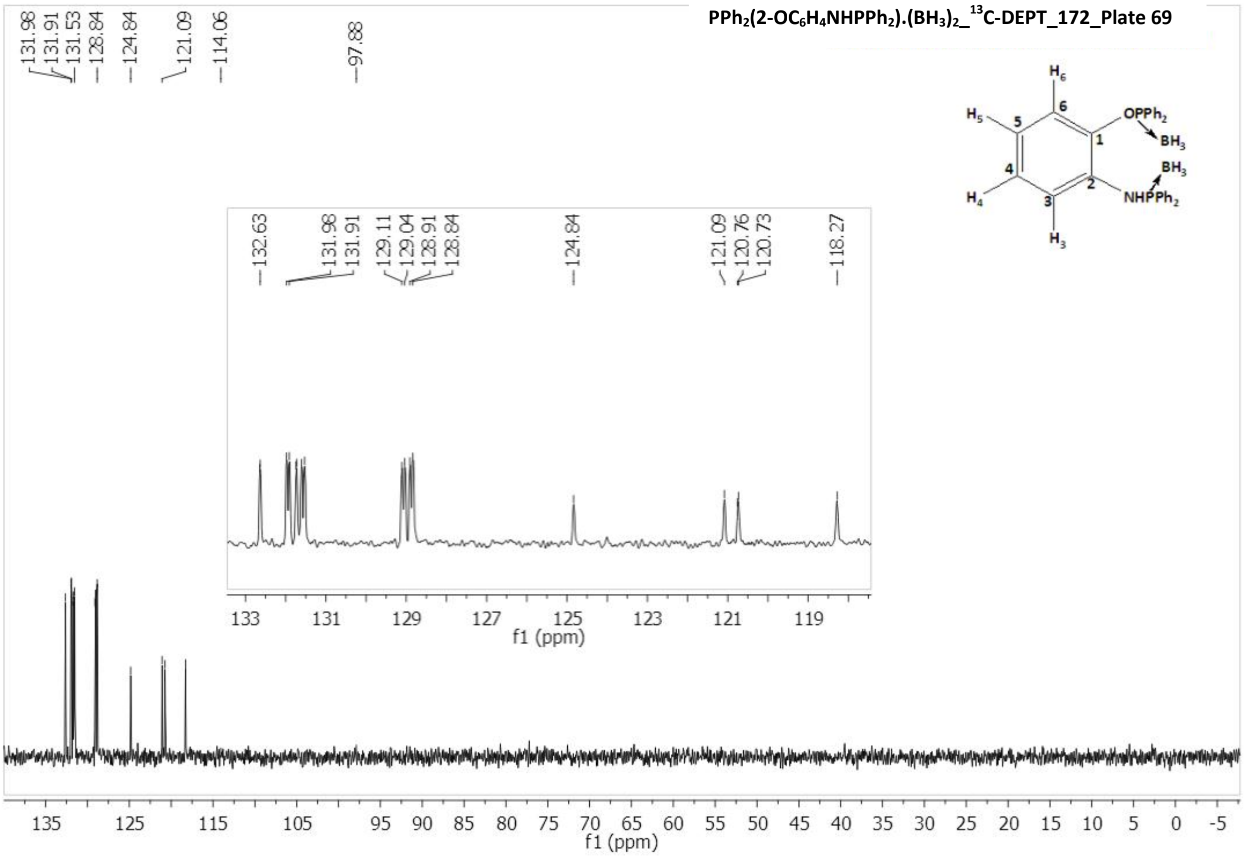


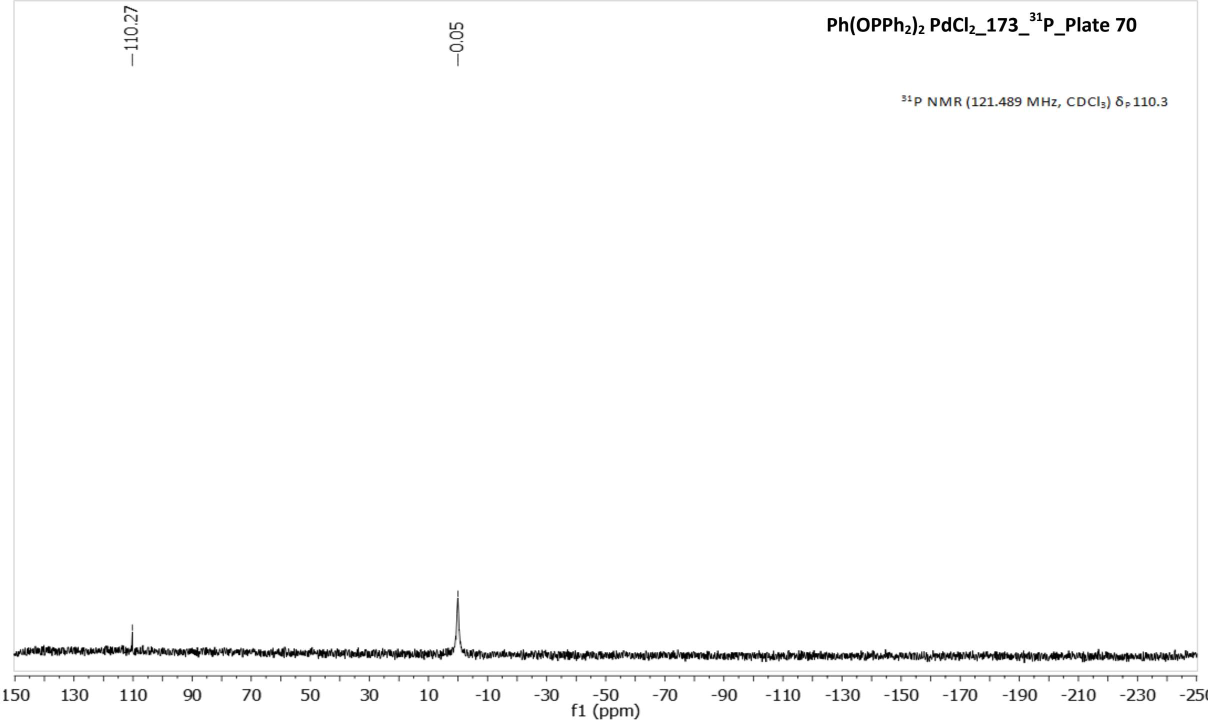
$PPh_2(2\text{-}OC_6H_4NHPPh_2).(BH_3)_2$_COSY_172_Plate 66



$PPh_2(2\text{-}OC_6H_4NHPPh_2).(BH_3)_2$_HSQC_172_Plate 67

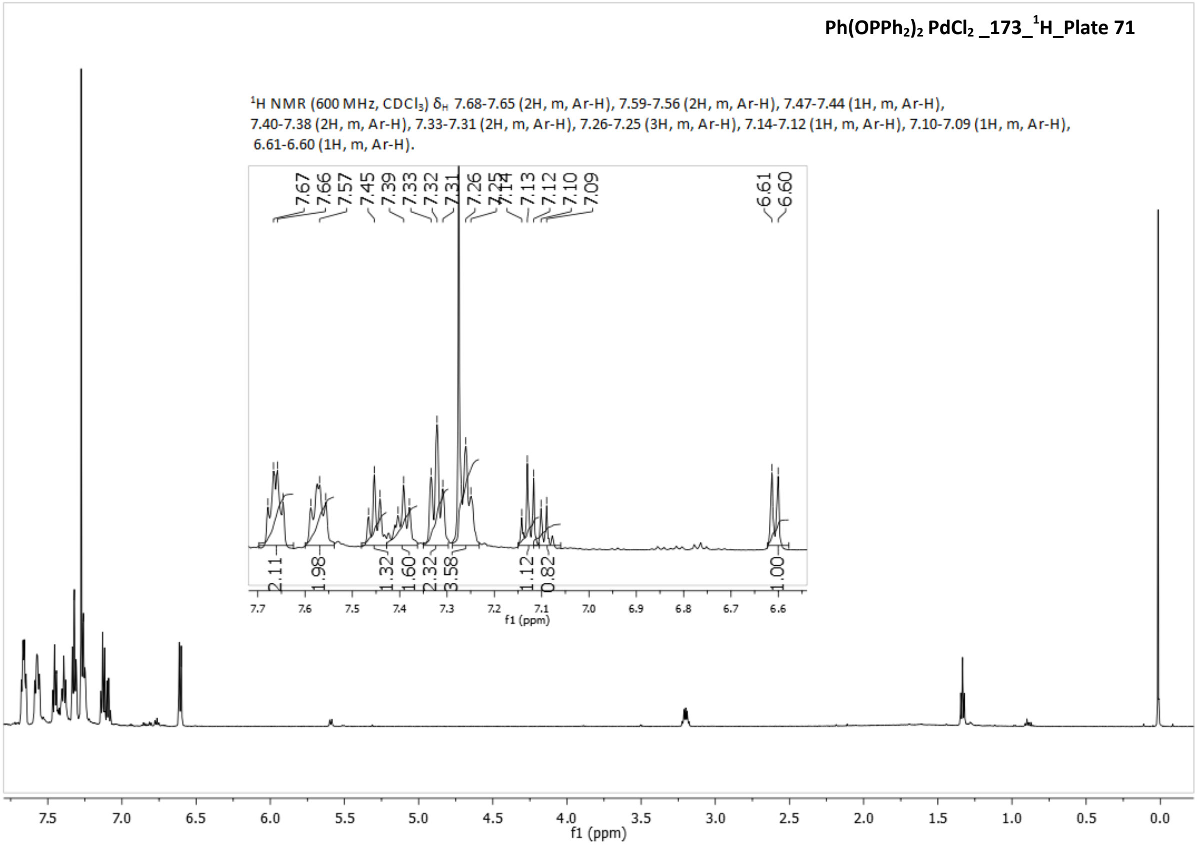

$PPh_2(2-OC_6H_4NHPPh_2).(BH_3)_2$_HMBC_172_Plate 68


$PPh_2(2-OC_6H_4NHPPh_2).(BH_3)_2$_^{13}C-DEPT_172_Plate 69



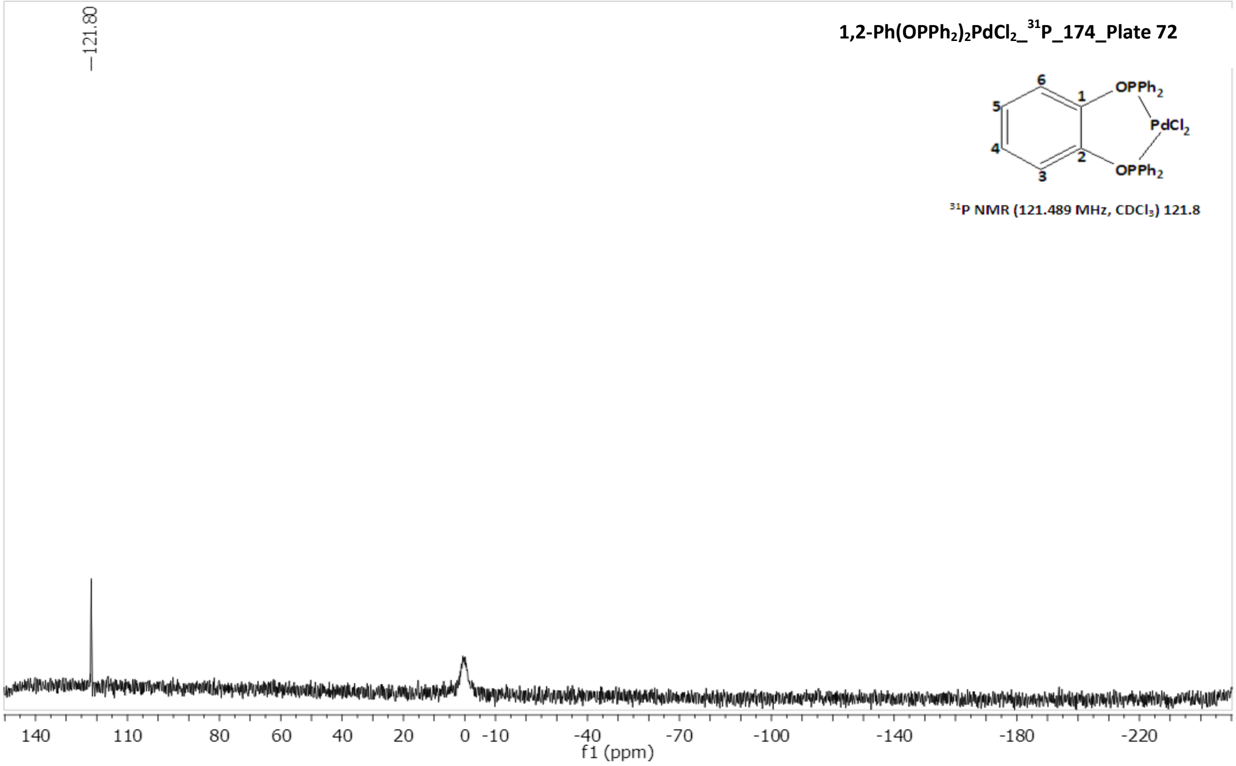
Ph(OPPh$_2$)$_2$ PdCl$_2$_173_^{31}P_Plate 70

^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 110.3



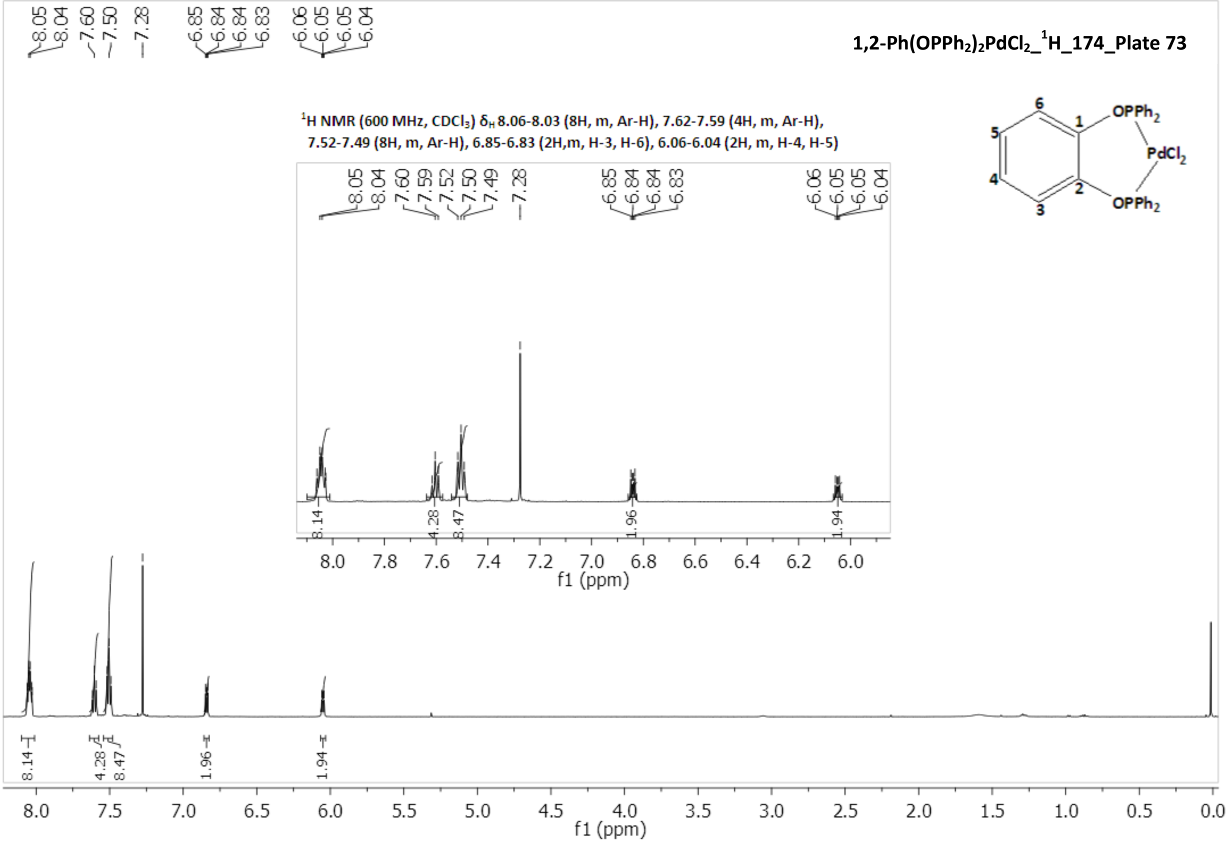
Ph(OPPh$_2$)$_2$ PdCl$_2$ _173_^{1}H_Plate 71

^{1}H NMR (600 MHz, CDCl$_3$) δ_H 7.68-7.65 (2H, m, Ar-H), 7.59-7.56 (2H, m, Ar-H), 7.47-7.44 (1H, m, Ar-H), 7.40-7.38 (2H, m, Ar-H), 7.33-7.31 (2H, m, Ar-H), 7.26-7.25 (3H, m, Ar-H), 7.14-7.12 (1H, m, Ar-H), 7.10-7.09 (1H, m, Ar-H), 6.61-6.60 (1H, m, Ar-H).



1,2-Ph(OPPh$_2$)$_2$PdCl$_2$_^{31}P_174_Plate 72

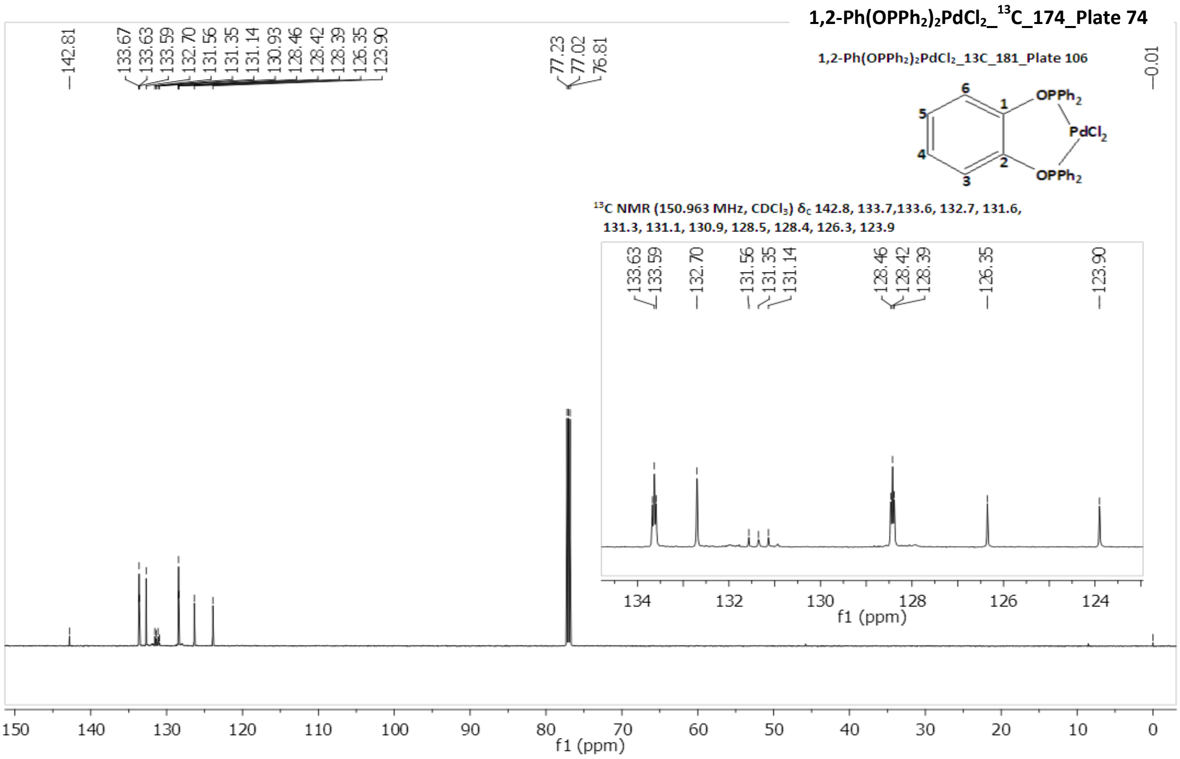
^{31}P NMR (121.489 MHz, CDCl$_3$) 121.8



1,2-Ph(OPPh$_2$)$_2$PdCl$_2$_^{1}H_174_Plate 73

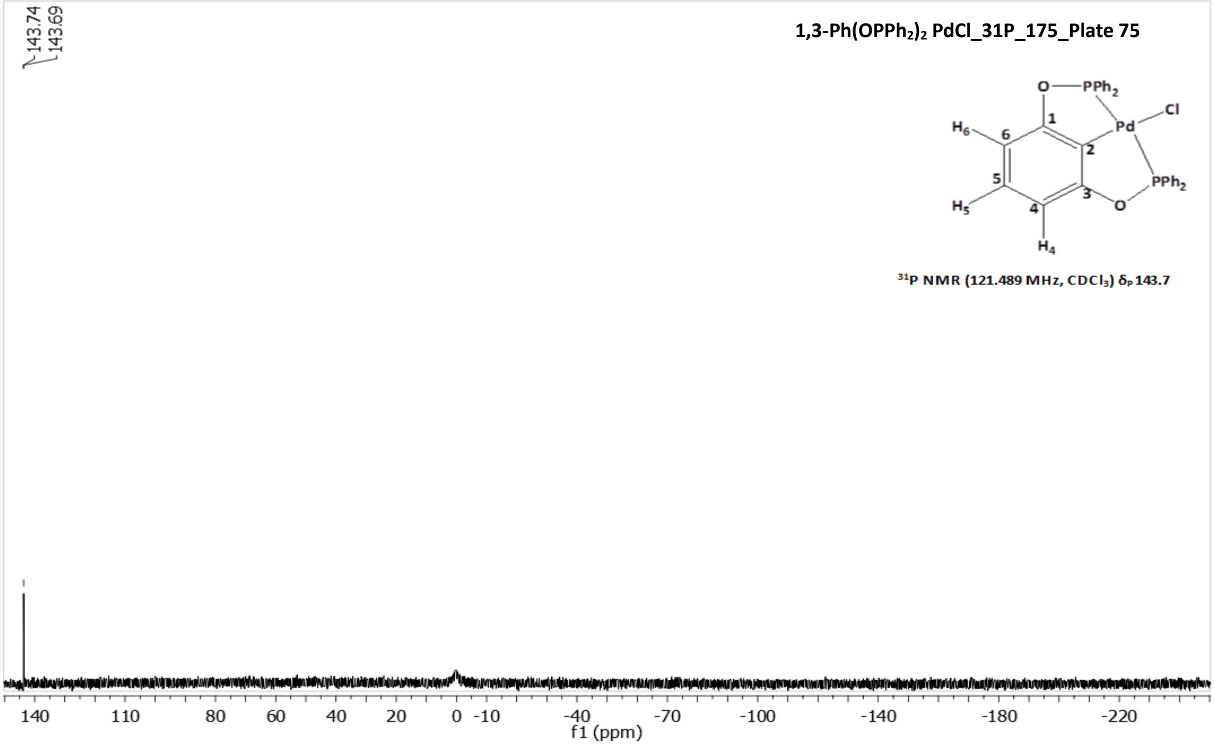
^{1}H NMR (600 MHz, CDCl$_3$) δ_H 8.06-8.03 (8H, m, Ar-H), 7.62-7.59 (4H, m, Ar-H), 7.52-7.49 (8H, m, Ar-H), 6.85-6.83 (2H,m, H-3, H-6), 6.06-6.04 (2H, m, H-4, H-5)

1,2-Ph(OPPh$_2$)$_2$PdCl$_2$_^{13}C_174_Plate 74

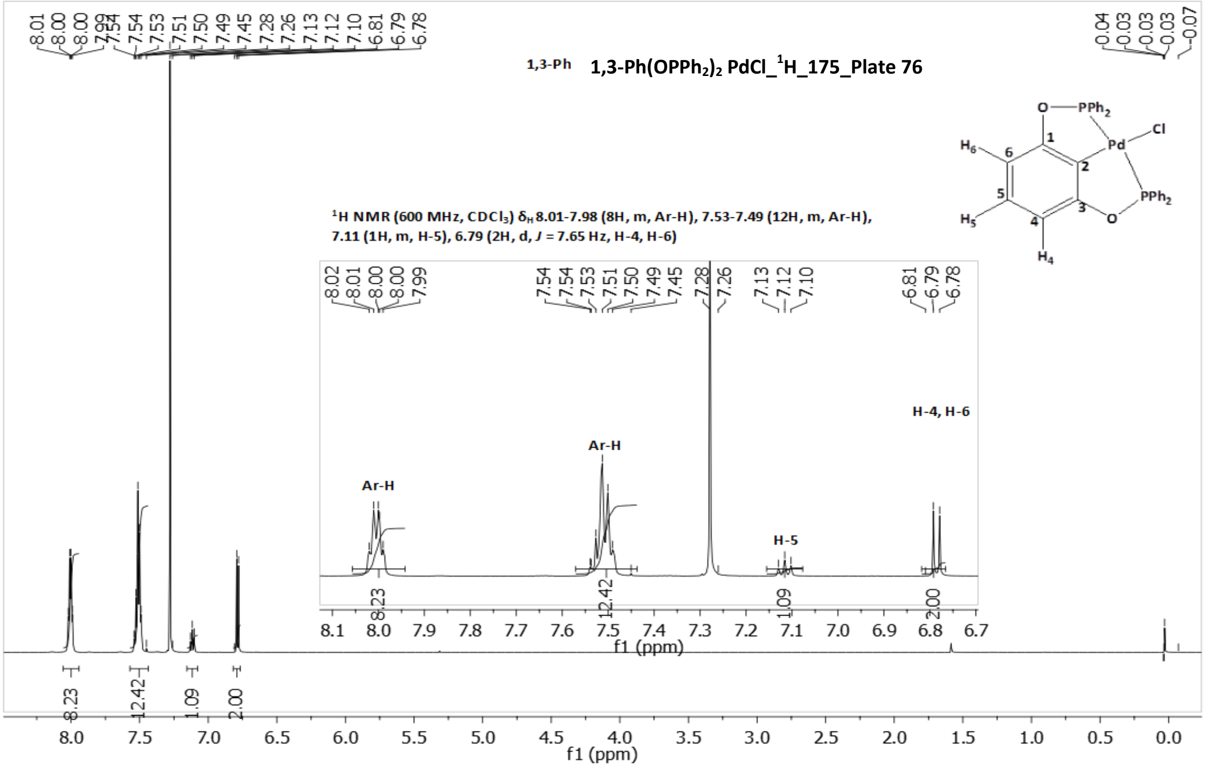


^{13}C NMR (150.963 MHz, CDCl$_3$) δ_C 142.8, 133.7,133.6, 132.7, 131.6, 131.3, 131.1, 130.9, 128.5, 128.4, 126.3, 123.9

1,3-Ph(OPPh$_2$)$_2$ PdCl_31P_175_Plate 75

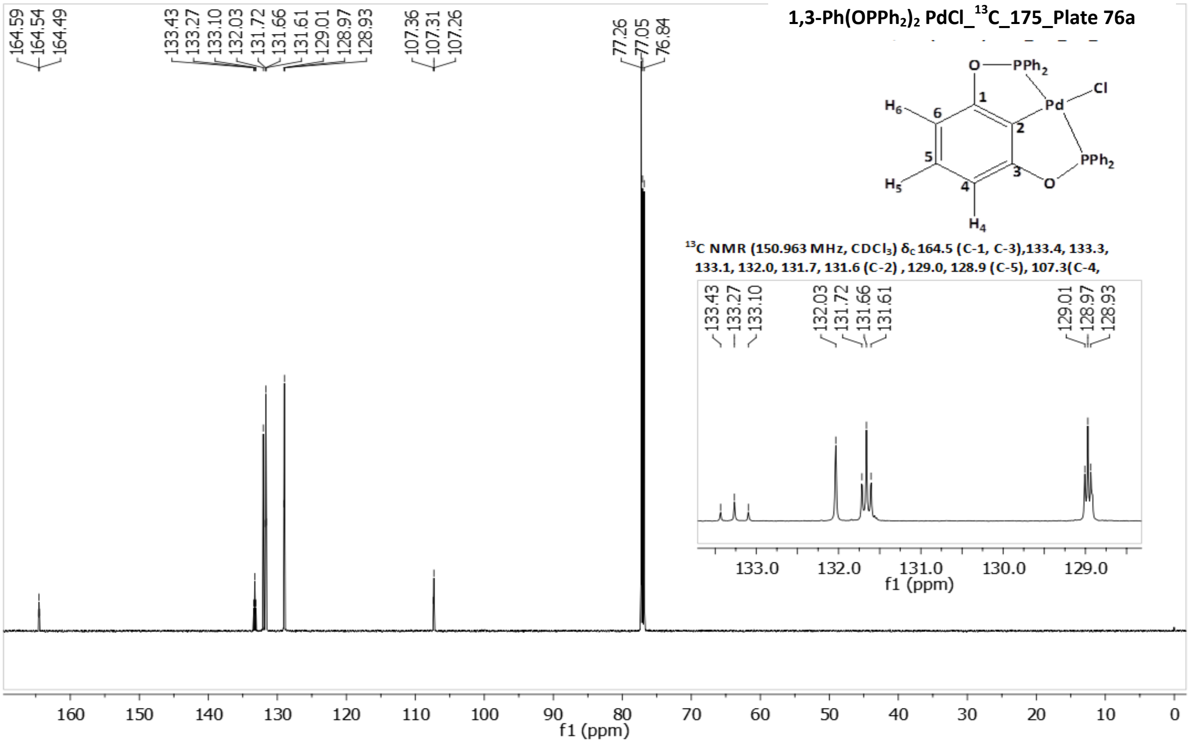


^{31}P NMR (121.489 MHz, CDCl$_3$) δ_P 143.7



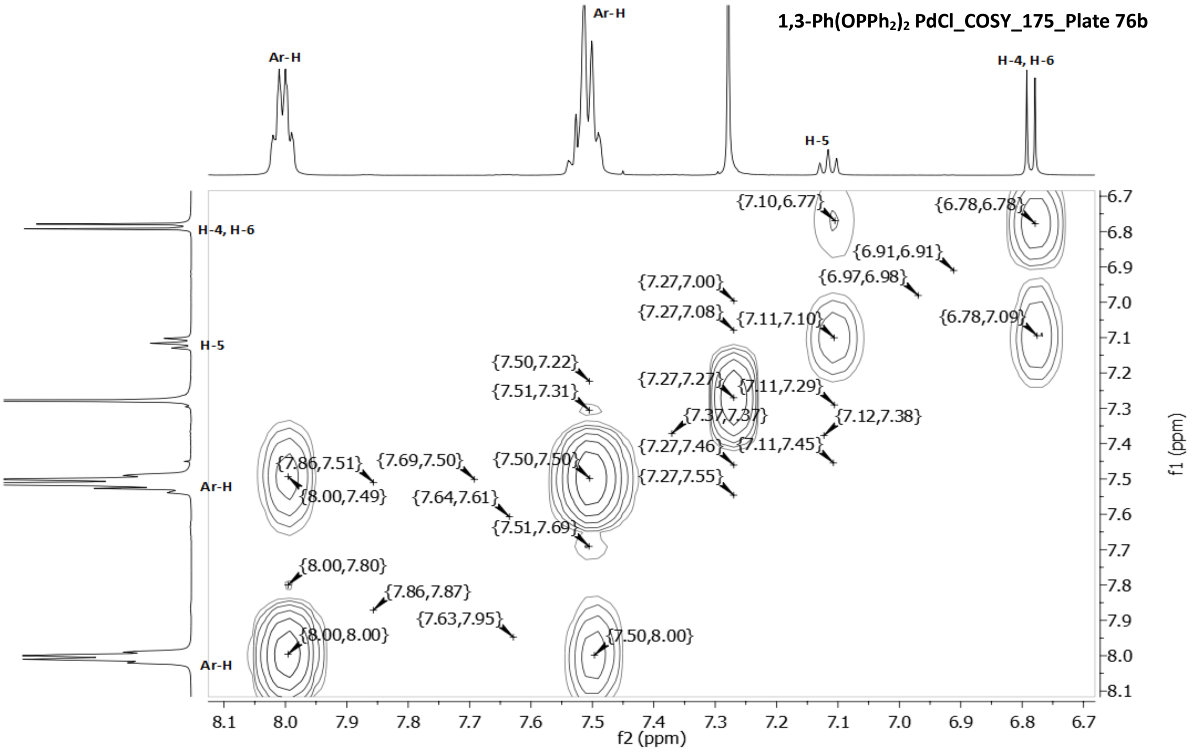
1,3-Ph(OPPh₂)₂ PdCl_^{1}H_175_Plate 76

^{1}H NMR (600 MHz, CDCl$_3$) δ_H 8.01-7.98 (8H, m, Ar-H), 7.53-7.49 (12H, m, Ar-H), 7.11 (1H, m, H-5), 6.79 (2H, d, *J* = 7.65 Hz, H-4, H-6)

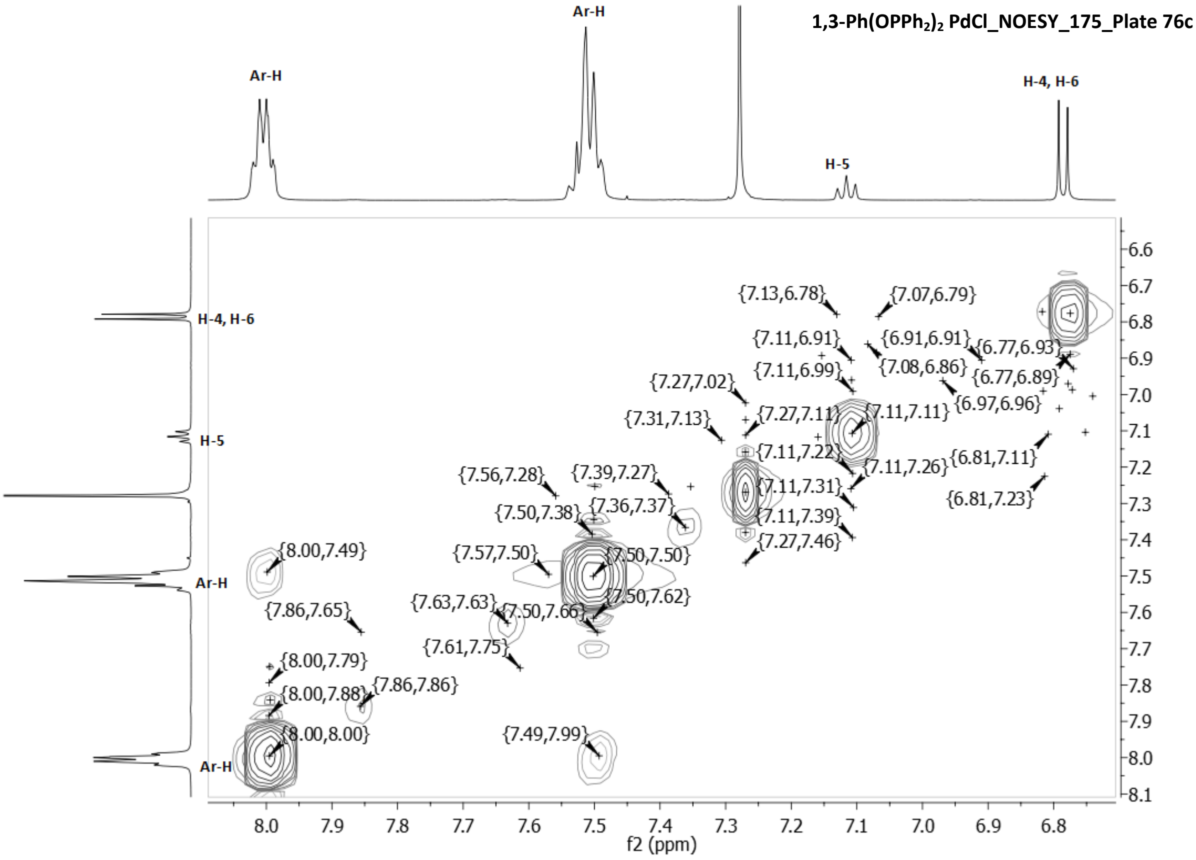


1,3-Ph(OPPh₂)₂ PdCl_^{13}C_175_Plate 76a

^{13}C NMR (150.963 MHz, CDCl$_3$) δ_C 164.5 (C-1, C-3),133.4, 133.3, 133.1, 132.0, 131.7, 131.6 (C-2) , 129.0, 128.9 (C-5), 107.3(C-4,

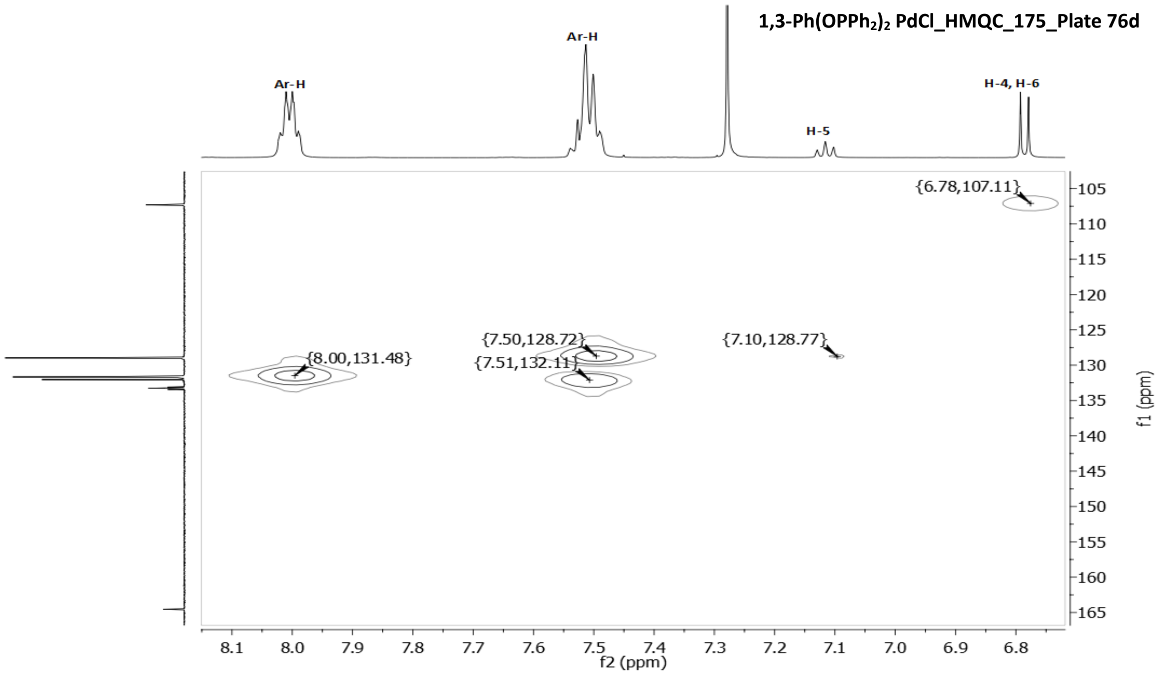


1,3-Ph(OPPh$_2$)$_2$ PdCl_COSY_175_Plate 76b

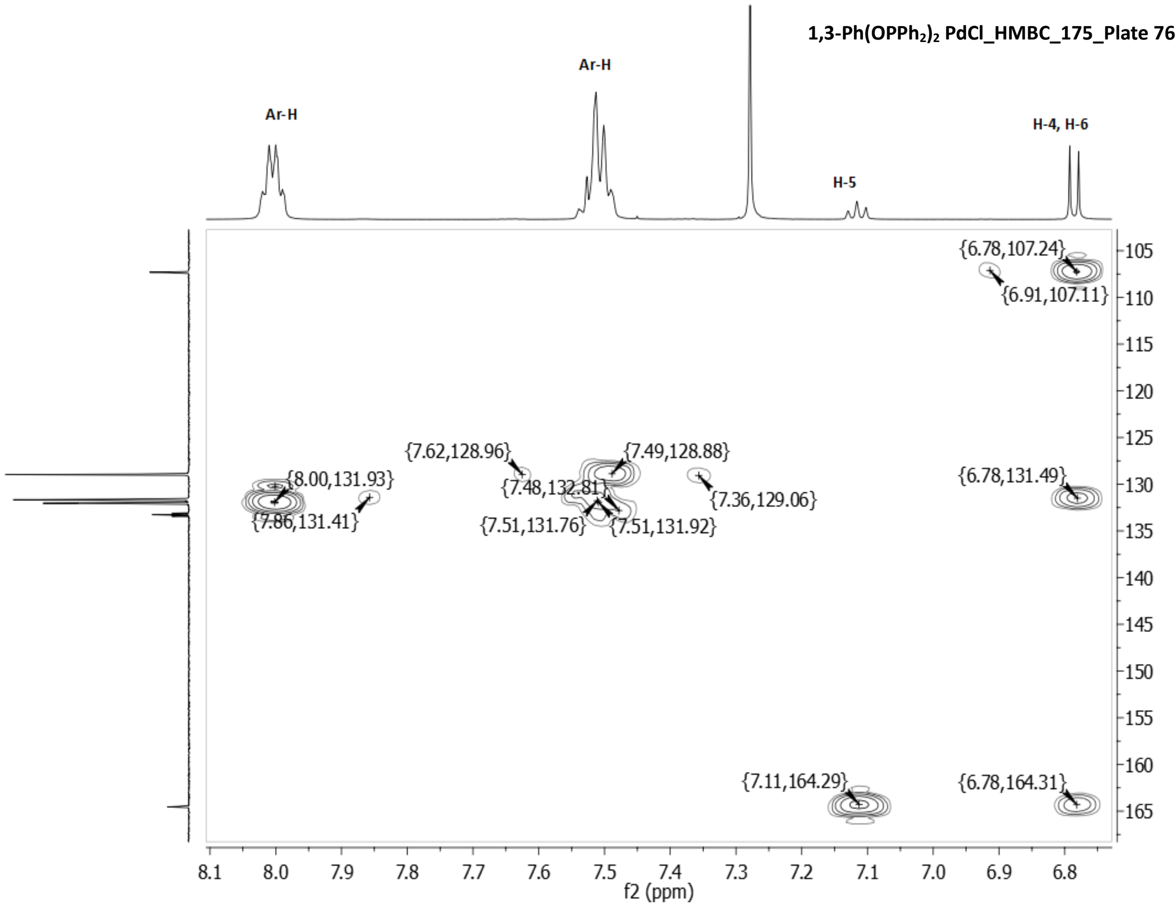


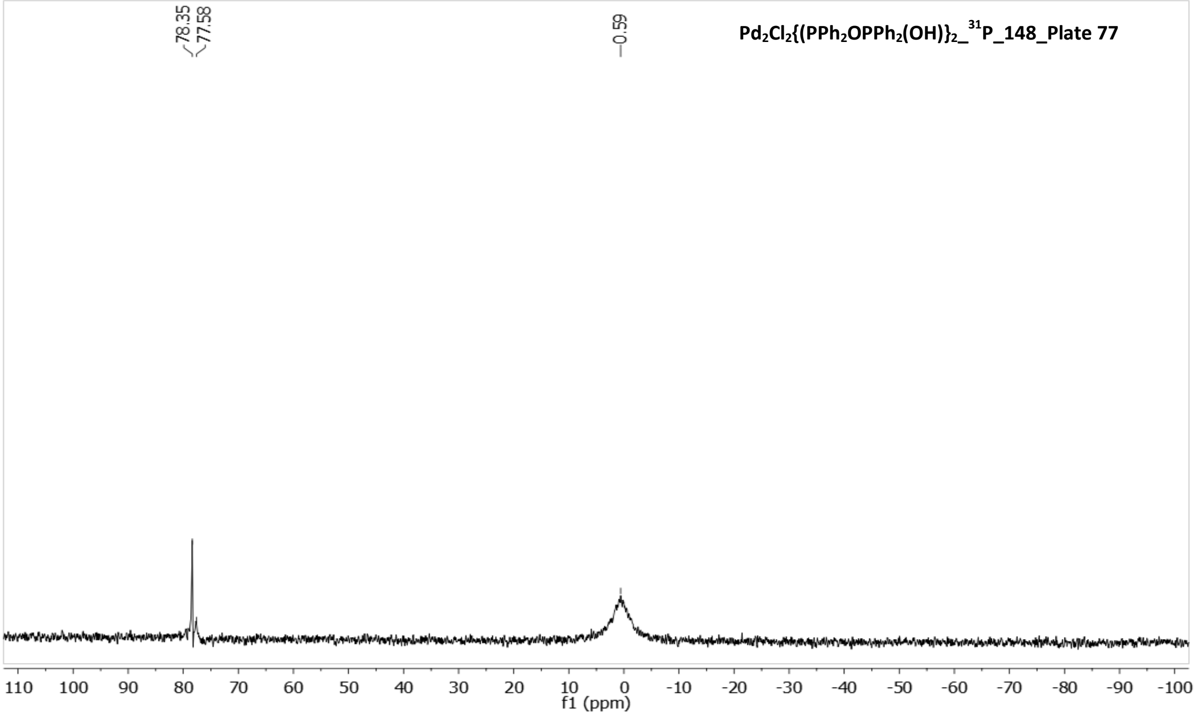
1,3-Ph(OPPh$_2$)$_2$ PdCl_NOESY_175_Plate 76c

1,3-Ph(OPPh$_2$)$_2$ PdCl_HMQC_175_Plate 76d

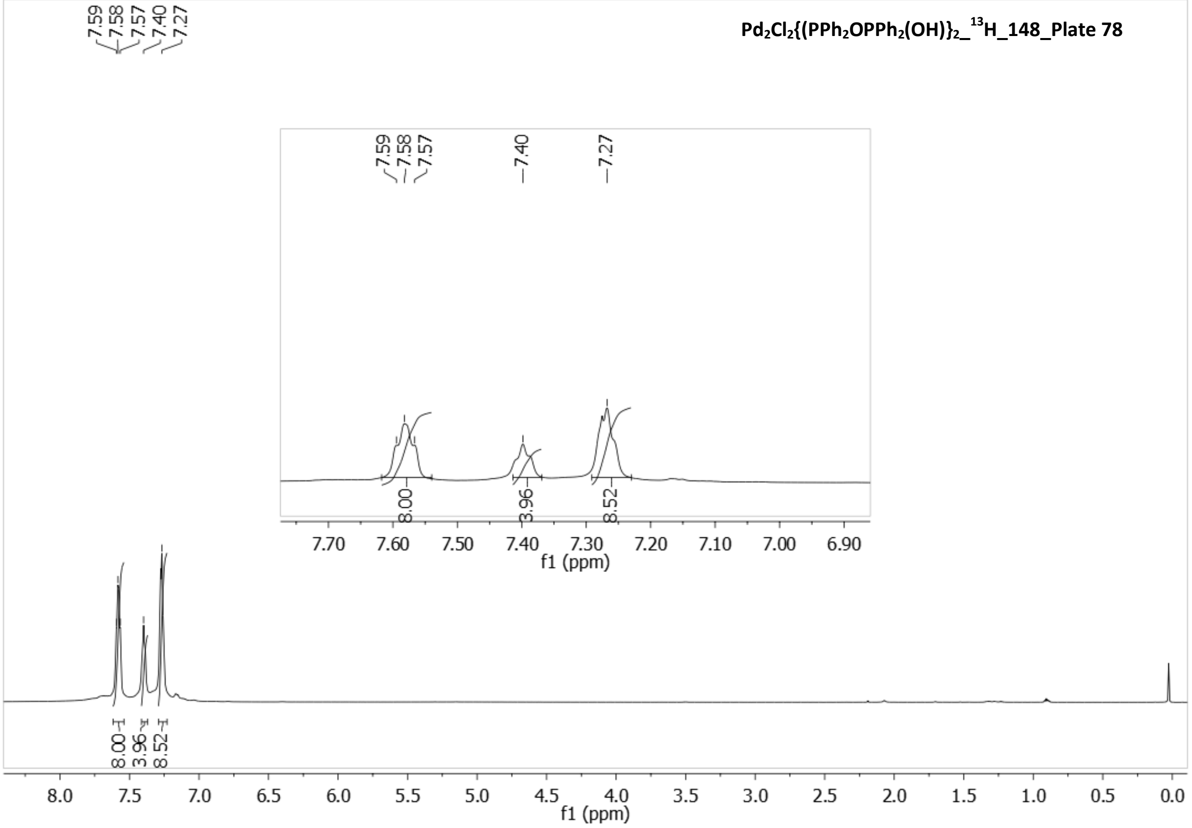


1,3-Ph(OPPh$_2$)$_2$ PdCl_HMBC_175_Plate 76e

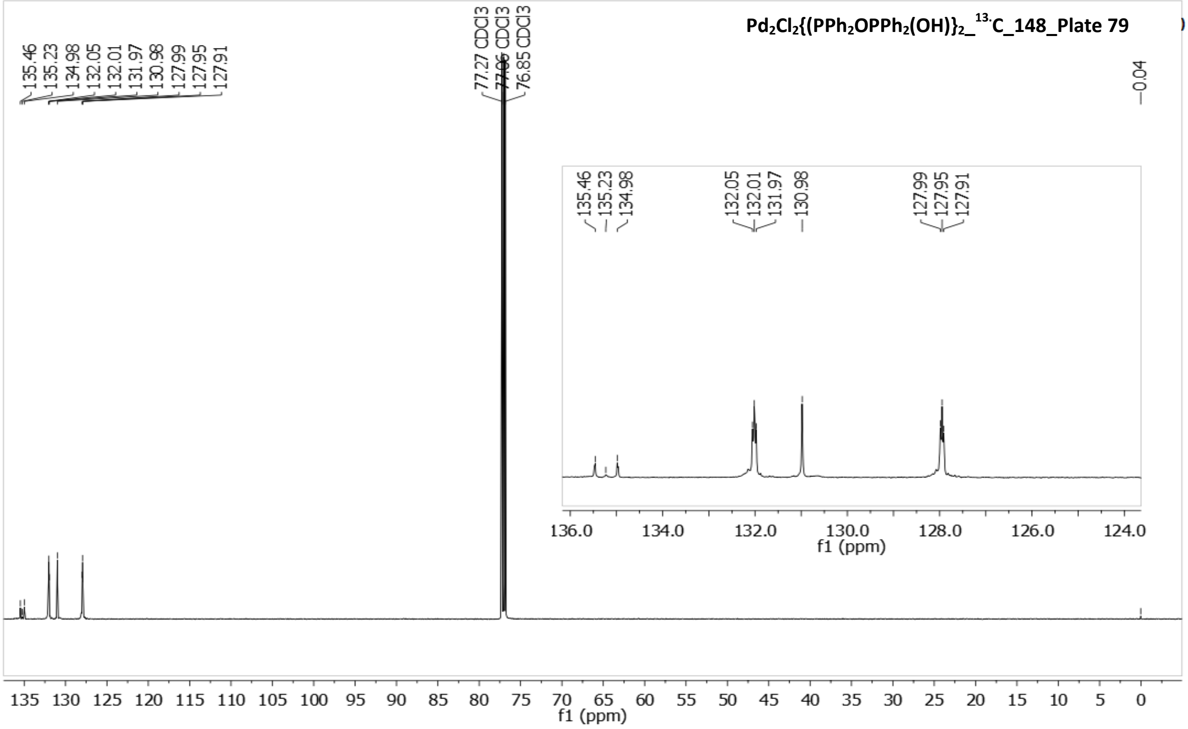


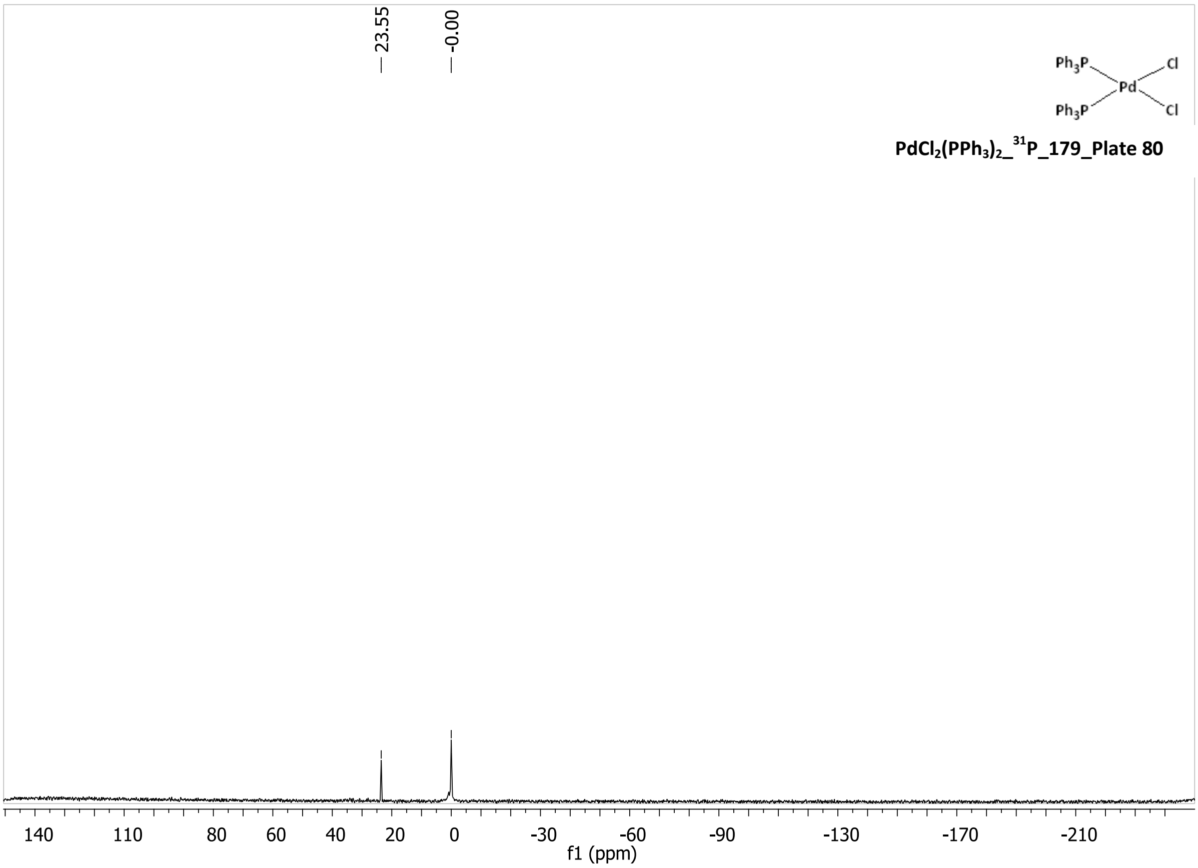


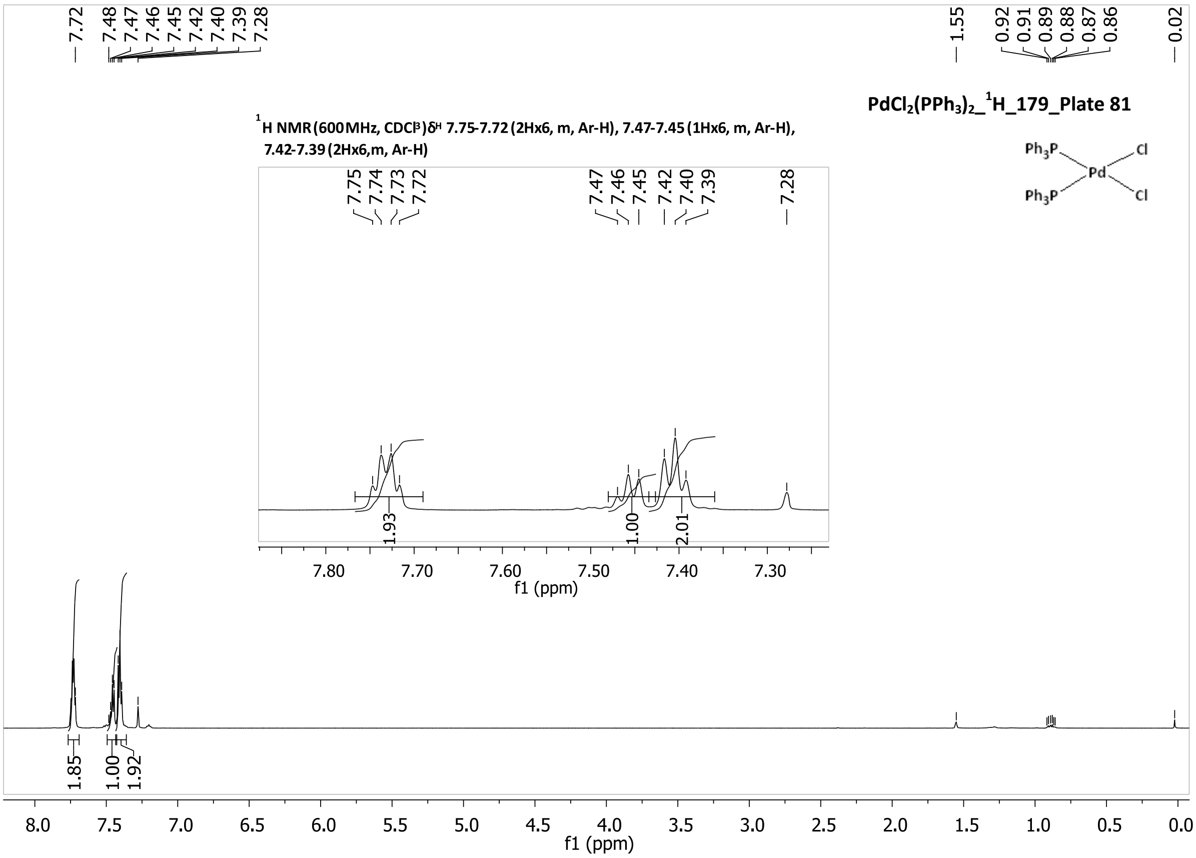
78.35
77.58
0.59
$Pd_2Cl_2\{(PPh_2OPPh_2(OH)\}_2$_^{31}P_148_Plate 77
110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100
f1 (ppm)

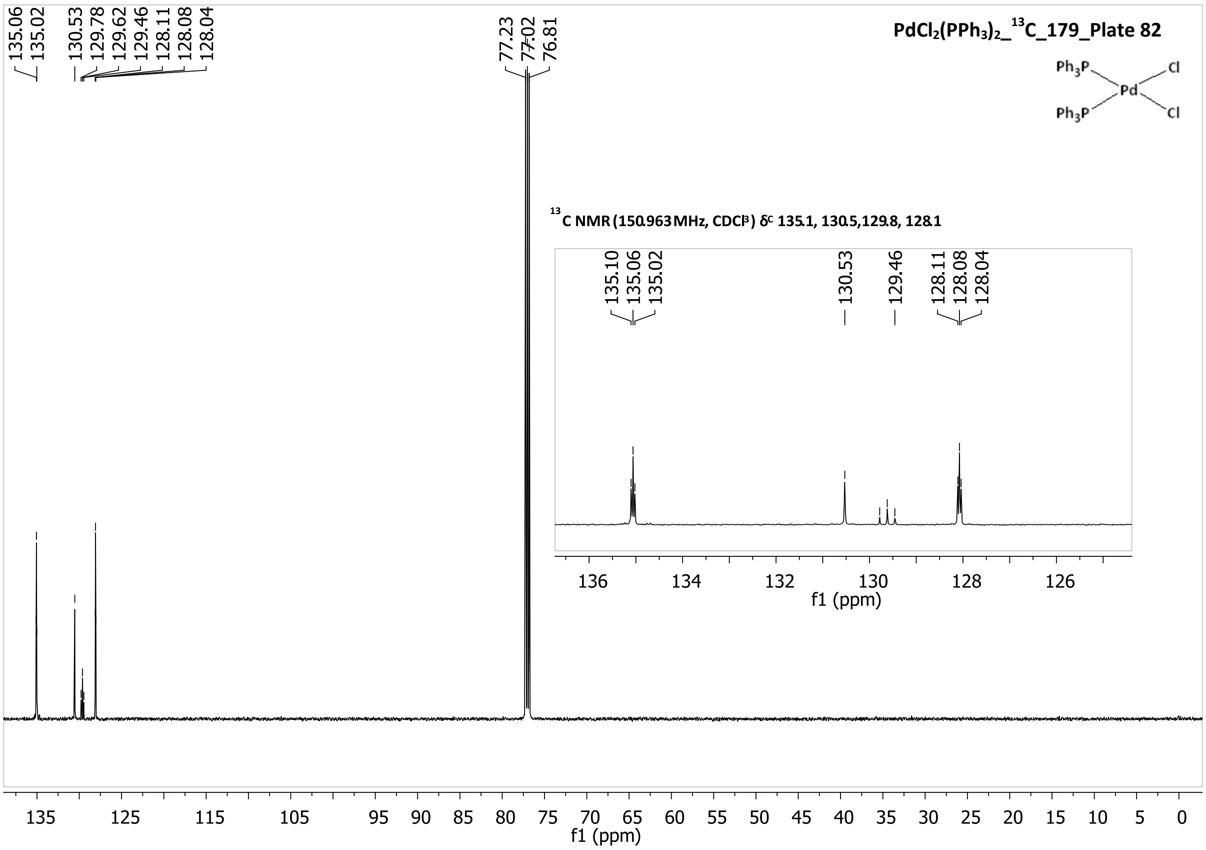


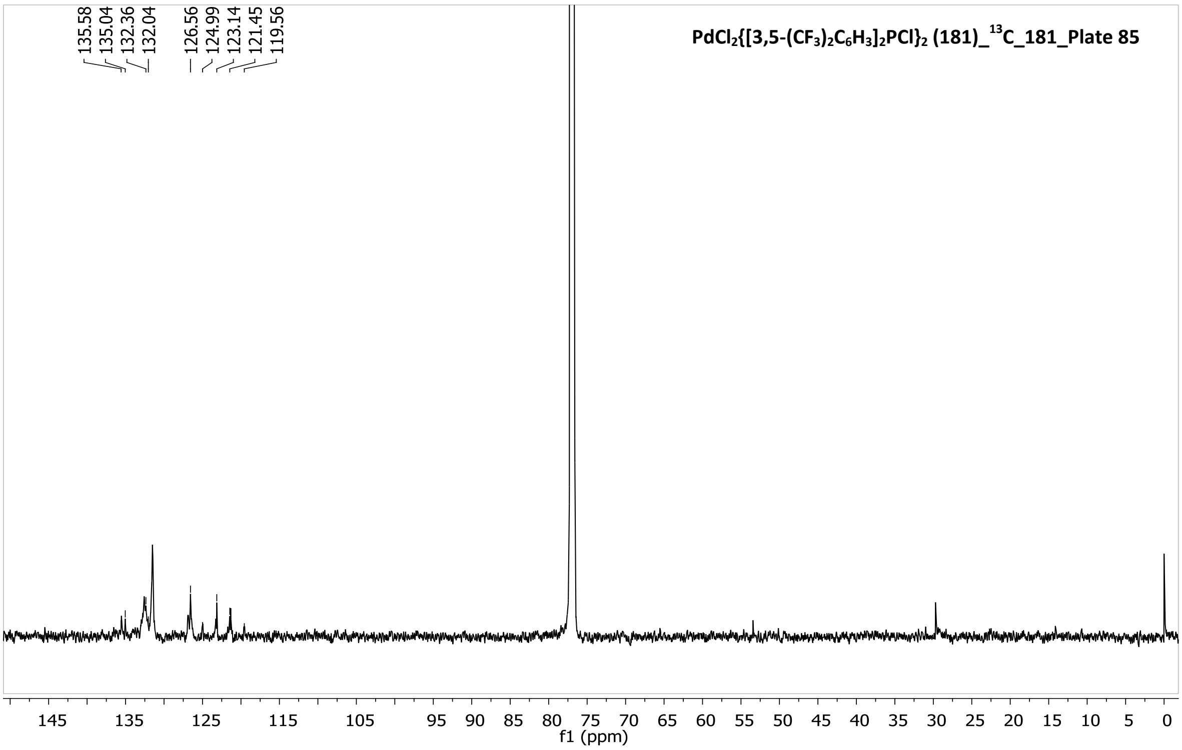
7.59
7.58
7.57
7.40
7.27
$Pd_2Cl_2\{(PPh_2OPPh_2(OH)\}_2$_^{13}H_148_Plate 78
7.59
7.58
7.57
7.40
7.27
8.00
3.96
8.52
7.70 7.60 7.50 7.40 7.30 7.20 7.10 7.00 6.90
f1 (ppm)
8.00
3.96
8.52
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Pd2Cl2{(PPh2OPPh2(OH)}2_13C_148_Plate 79
135.46
135.23
134.98
132.05
132.01
131.97
130.98
127.99
127.95
127.91
77.27 CDCl3
77.06 CDCl3
76.85 CDCl3
-0.04
136.0
134.0
132.0
130.0
128.0
126.0
124.0
f1 (ppm)
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)


23.55
-0.00
Ph3P
Pd
Cl
Ph3P
Cl
PdCl2(PPh3)2_31P_179_Plate 80
140 110 80 60 40 20 0 -30 -60 -90 -130 -170 -210
f1 (ppm)


7.72
7.48
7.47
7.46
7.45
7.42
7.40
7.39
7.28
1.55
0.92
0.91
0.89
0.88
0.87
0.86
0.02
PdCl$_2$(PPh$_3$)$_2$_^{1}H_179_Plate 81
Ph$_3$P
Pd
Cl
Cl
Ph$_3$P
^{1}H NMR (600 MHz, CDCl$_3$) δ_H 7.75-7.72 (2Hx6, m, Ar-H), 7.47-7.45 (1Hx6, m, Ar-H), 7.42-7.39 (2Hx6, m, Ar-H)
7.75
7.74
7.73
7.72
7.47
7.46
7.45
7.42
7.40
7.39
7.28
1.93
1.00
2.01
7.80
7.70
7.60
7.50
7.40
7.30
f1 (ppm)
1.85
1.00
1.92
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


135.06
135.02
130.53
129.78
129.62
129.46
128.11
128.08
128.04
77.23
77.02
76.81
PdCl$_2$(PPh$_3$)$_2$_^{13}C_179_Plate 82
Ph$_3$P
Pd
Cl
Cl
Ph$_3$P
^{13}C NMR (150.963 MHz, CDCl$_3$) δ_C 135.1, 130.5, 129.8, 128.1
135.10
135.06
135.02
130.53
129.46
128.11
128.08
128.04
136
134
132
130
128
126
f1 (ppm)
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)


135.58
135.04
132.36
132.04
126.56
124.99
123.14
121.45
119.56
$PdCl_2\{[3,5-(CF_3)_2C_6H_3]_2PCl\}_2$ (181)_^{13}C_181_Plate 85
145
135
125
115
105
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
f1 (ppm)