

Functionalised [(NHC)Pd(allyl)Cl] Complexes: Synthesis, Immobilisation and Application in Cross-Coupling and Dehalogenation Reactions

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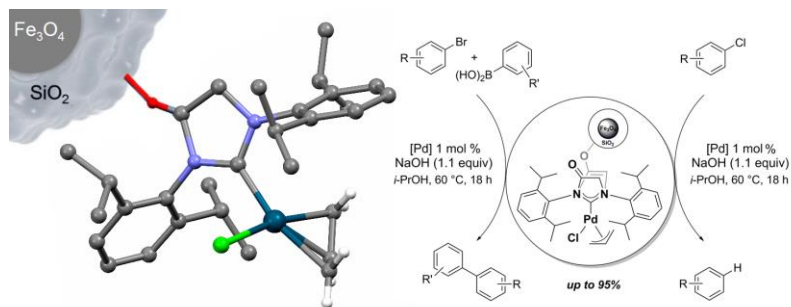
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Abstract: A novel NHC–palladium(II) (NHC = N-heterocyclic carbene) complex and its immobilised version have been prepared and fully characterised. Optimisation studies led to good catalytic activities in Suzuki-Miyaura cross coupling and chloroarene dehalogenation reactions. Furthermore, the unexpected palladium-mediated transfer hydrogenation of a carbonyl compound is reported.

Keywords: Cross-Coupling * Dehalogenation * N-Heterocyclic Carbene * Palladium Complexes * Transfer hydrogenation.

Graphical Abstract

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1. Introduction

Cross-coupling reactions represent one of the major success stories of transition metal catalysis, and have unarguably changed the way chemists envision retrosynthetic analysis of their targets, particularly in the case of biaryl compounds. Despite the interest in alternative metals, palladium derivatives remain the catalyst of choice for most applications [1]. Ligandless, or PPh_3 -based systems are well established in the literature, however, sterically demanding, strongly σ -donating ligands have been crucial for the development of extremely performing catalysts. Hence, it is not surprising that, together with alkene metathesis, cross-coupling reactions are the most popular application of N-heterocyclic carbenes as ligands. Following pioneering work by Herrmann in 1995 [2], a variety of $[(\text{NHC})\text{Pd}]$ architectures have been reported in the literature [3,4]. Among these, palladium(II) allyl complexes attracted our attention since they are easily accessible, moisture- and oxygen-stable and have shown excellent catalytic activities in different cross-coupling reactions [5]. It was hypothesised that the immobilisation of such species on magnetic nanoparticles would combine the high activity of palladium–NHC catalysts with the facile separation and recyclability of a heterogeneous catalyst [6]. Indeed, our recent research led to the development of a highly performing supported copper(I) catalyst for the azide-alkyne cycloaddition reaction [7]. It was therefore anticipated that a modified NHC bearing a hydroxyl substituent on the backbone would allow the immobilisation of a palladium complex on silica-coated nanoparticles. This strategy minimises changes around the metal centre during the catalytic reactions, often linked to the loss in performance observed for complexes attached to surfaces through the N-substituents of the NHC [8].

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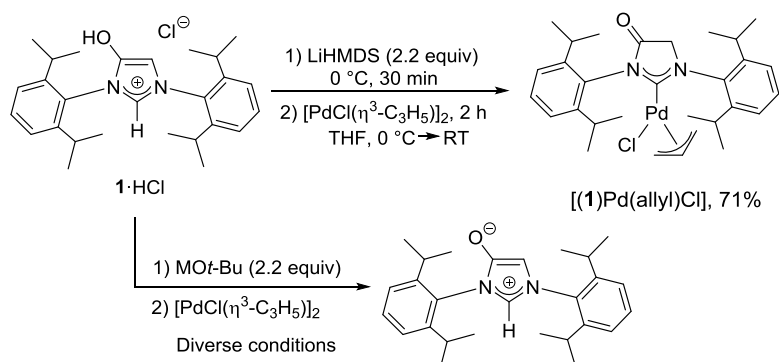
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2. Results and Discussion

2.1 Preparation of the catalysts

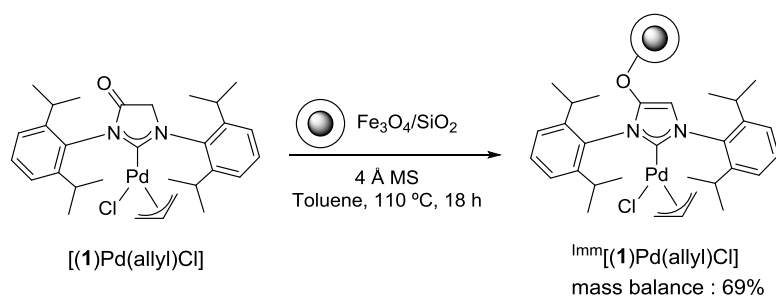
The 4-hydroxyimidazolium salt **1**·HCl used in this work was synthesised [9] and the corresponding $[(\text{NHC})\text{Pd}(\text{allyl})]$ complex was prepared by treating **1**·HCl with an slight excess of LiHMDS at 0 °C, followed by addition of $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$. $[(\textbf{1})\text{Pd}(\text{allyl})\text{Cl}]$ was then isolated as a light green solid in good yield (Scheme 1). This complex was stable in air and could be stored for months at room temperature. When other bases were used (*i.e.* KOt-Bu or NaOt-Bu), no NHC complexation was observed even at high temperatures. Instead, a zwitterionic derivative was isolated as the only reaction product (Scheme 1).

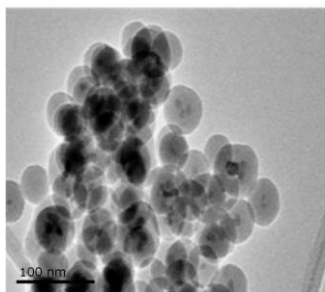


Scheme 1. Synthesis of [(1)Pd(allyl)Cl].

In contrast to 1·HCl, the ¹H NMR spectrum of [(1)Pd(allyl)Cl] notably displayed two distinctive roofed doublets at 4.52 and 4.38 ppm, attributed to the CH₂ protons on the backbone and indicating that this complex was isolated in its keto form. The signals due to the allyl ligand appeared between 4.84 and 1.52 ppm, in accordance with the spectra of other reported [(NHC)Pd(allyl)Cl] complexes [10]. [(1)Pd(allyl)Cl] was further characterised using ¹³C{¹H} NMR, IR spectroscopies and HRMS. Unfortunately, all attempts to grow crystals suitable for X-ray crystallography failed.

In order to develop an immobilised catalyst, magnetic nanoparticles (Fe₃O₄) were prepared following established literature procedures [11, 12, 13, 14]. The immobilisation of [(1)Pd(allyl)Cl] on these was carried out with 4 Å MS in refluxing toluene. It was anticipated that the resident silanol groups on the silica coating magnetic particles would bind to the backbone of the NHC complex in its enol tautomer, due to the (mildly) acidic nature of the silica coating. The resulting material was centrifuged and washed with dichloromethane to remove any remaining unattached species and then dried overnight under vacuum to give ^{Imm}[(1)Pd(allyl)Cl].





Scheme 2. Immobilisation of [(1)Pd(allyl)Cl] and resulting TEM image.

The immobilised complex was first characterised by inductively coupled plasma analysis (ICP) that indicated a metal loading of $0.57 \mu\text{mol}^{\text{Pd}}/\text{mg}$. This is lower than the theoretical maximum loading ($0.83 \mu\text{mol}^{\text{Pd}}/\text{mg}$), but in accordance with the reaction mass balance (Scheme 2) [14]. Transmission electron microscopy (TEM) images showed nanoparticles of $45.5 (\pm 2.2)$ nm in diameter with a magnetic core (Scheme 2). TEM also confirmed the absence of palladium nanoparticles in the prepared material with palladium only detected on the surface of the nanoparticles. Furthermore, energy dispersive X-ray spectroscopy (EDS) analysis of $^{\text{Imm}}[(1)\text{Pd}(\text{allyl})\text{Cl}]$ detected Pd and Cl from the original palladium complex, as well as the Fe and Si from the nanoparticles [14].

2.2. Suzuki-Miyaura Cross-Coupling Reactions

The prepared systems were then tested in Suzuki-Miyaura cross-couplings, using 4-bromotoluene and phenylboronic acid (1.05 equiv) as model substrates. This reaction was first carried out using conditions reported previously for the parent [(NHC)Pd(allyl)Cl] complexes: 3 equiv NaOt-Bu in dioxane at 60°C [15]. With 1 mol % of $^{\text{Imm}}[(1)\text{Pd}(\text{allyl})\text{Cl}]$, a conversion of 84%, similar to the reported 91% with [(IPr)Pd(allyl)Cl], was observed after 18 h (non-optimised reaction time, Table 1, entry 1). Since milder reaction conditions are likely to facilitate the recovery and recycling of any supported catalyst, the base loading was then reduced to 1.1 equiv. Even though a loss in conversion was observed, using KOt-Bu instead of its sodium analogue, led again to a good conversion of 78% (Table 1, entries 2 and 3). No significant changes were observed using isopropanol, a significantly greener solvent than dioxane. While complete conversion was obtained under these conditions at a higher temperature of 80°C , only 22% of **2a** formed at room temperature. Using the relatively mild conditions of entry 4, $^{\text{Imm}}[(1)\text{Pd}(\text{allyl})\text{Cl}]$ was compared to its untethered analogue [(1)Pd(allyl)Cl], as well as [(IPr)Pd(allyl)Cl] (Table 1, entries 7 and 8). In both cases, higher conversions were

obtained of around 90%. Most importantly, novel [(1)Pd(allyl)Cl] displayed a catalytic activity comparable to previously reported [(IPr)Pd(allyl)Cl].

Table 1. Optimisation studies.

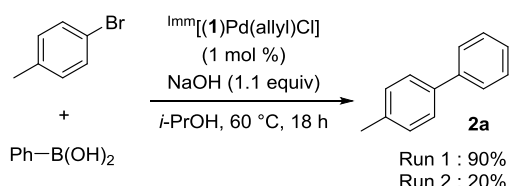
Entry	Base	Solvent	T (°C)	Conv (%) ^[a]
1	NaOt-Bu	1,4-Dioxane	60	84 ^[b]
2	NaOt-Bu	1,4-Dioxane	60	60
3	KOt-Bu	1,4-Dioxane	60	78
4	KOt-Bu	<i>i</i> -PrOH	60	76
5	KOt-Bu	<i>i</i> -PrOH	80	>95
6	KOt-Bu	<i>i</i> -PrOH	RT	22
7	KOt-Bu	<i>i</i> -PrOH	60	91 ^[c]
8	KOt-Bu	<i>i</i> -PrOH	60	93 ^[d]
9	KOH	<i>i</i> -PrOH	60	87
10	NaOH	<i>i</i> -PrOH	60	90

^[a] ¹H NMR conversions are the average of at least two independent experiments. ^[b] Reaction carried out with 3 equiv of base. ^[c] Reaction carried out in the presence of 1 mol % of [(1)Pd(allyl)Cl]. ^[d] Reaction carried out in the presence of 1 mol % of [(IPr)Pd(allyl)Cl].

In an attempt to further increase the yield while keeping the temperature at 60 °C, alternative bases were tested. Gratifyingly, KOH and NaOH led to high conversions under otherwise identical conditions (Table 1, entries 9 and 10), demonstrating that simple, inexpensive bases could be used. Overall, NaOH and *i*-PrOH were selected as optimal pairing for these cross-coupling reactions at 60 °C. When the model reaction was carried out under optimised conditions using 4-chlorotoluene instead of the bromo derivative, an average conversion of 40% was obtained either at 60 or 80 °C. Importantly, all these reactions were carried out in technical grade solvents and without any precautions to exclude oxygen or moisture from the reaction mixtures.

Next, after a first run of the model reaction, the catalyst was separated using a magnet and dried. Its metal content was determined by ICP in order to carry out the second run with the same 1 mol %

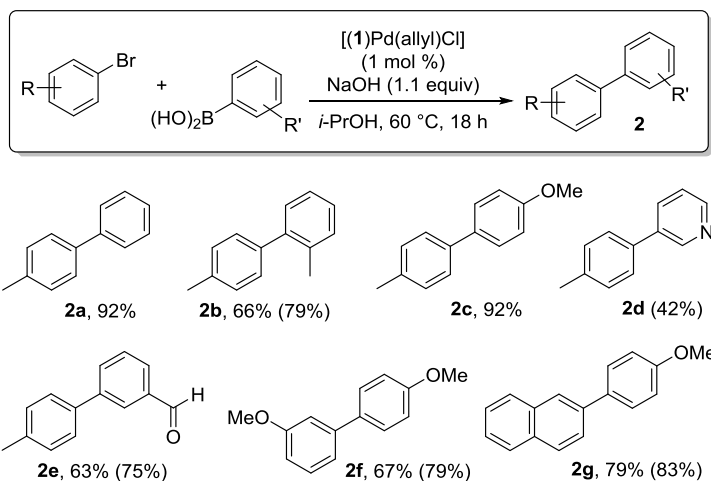
palladium loading (Scheme 3). However, the reaction conversion dropped to 20% after only recycling once.



Scheme 3. Recycling experiments with $\text{Imm}[(\mathbf{1})\text{Pd(allyl)Cl}]$. Conversions determined by ^1H NMR spectroscopy are the average of at least two independent experiments.

Unsurprisingly, the TEM analysis of the recycled material clearly showed that palladium nanoparticles (≈ 10 nm in diameter) had formed during the first catalytic run [14], and no iron oxide/silica core shell nanoparticles could be detected. These observations show that, in contrast to our earlier work on cycloaddition reactions [7], this catalyst reported is not robust enough under the reaction conditions to resist the loss of its structural integrity and forms palladium nanoparticles. Nevertheless, this result also supports ligated Pd–NHC species as the active species in these Suzuki-Miyaura couplings, instead of the palladium nanoparticles formed during the reaction. The generation of palladium nanoparticles is indeed a recurring issue in catalytic applications. Depending on the system, such nanoparticles can either be the actual active species [16, 17], or mainly inactive degradation products, as in this case.

In the light of these results, the scope of the reaction was next explored using $[(\mathbf{1})\text{Pd(allyl)Cl}]$ only, since it had displayed a slightly higher activity during the optimisation. A range of biaryl derivatives was successfully isolated in analytically pure form after column chromatography (Scheme 4). *Ortho*-substituents and functional groups such as ethers and aldehydes were successfully tolerated by this catalytic system. Only in the case of a 2-pyridyl substrate was low conversion into cross-coupled product observed.



Scheme 4. [(1)Pd(allyl)Cl]-mediated Suzuki-Miyaura cross coupling reactions. Isolated yields are the average of at least two independent experiments. ¹H NMR conversions are shown in brackets for reactions that did not reach completion.

Biaryl **2b** was analysed by ICP to determine metal contamination both before and after column chromatography. While the crude product obtained after work-up contained 87.6% of the palladium used in the reaction, after column chromatography no palladium could be detected. As a comparison, the same product **2b** obtained using ^{imm}[(1)Pd(allyl)Cl] contained only 8.9% of the original palladium, which could again be entirely removed during the purification step.

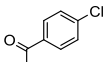
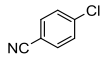
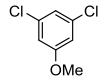
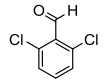
2.3 Dehalogenation Reactions

[(NHC)Pd(allyl)Cl] complexes have also been applied dehalogenation reactions [15]. Often regarded as undesired side-reactions, the metal-catalysed reduction of halogenated organic compounds, particularly arenes, is of substantial importance due to their high toxicity to the environment [18].

Dehalogenation reactions were explored under the same reaction conditions optimised for the cross-coupling experiments, and the crude reaction product(s) were analysed by GC-MS. Even if they were not suitable for cross-coupling reactions, it was interesting to note that chloroarenes readily reacted in the presence of [(1)Pd(allyl)Cl]. All reactions depicted in Table 2 proceeded very cleanly and no by-product formation was observed in any of them. An *ortho*-substituent did not prove problematic in the case of 2-chloronaphthalene, however a much lower conversion was observed in the case of 2-chloroanisole (Table 2, entries 2 and 3). Quite surprisingly a similar conversion was obtained with *para*-chlorobenzonitrile (16% at 60 °C or 35% at 80 °C, Table 2, entry 4). In contrast, 2-

chlorothiophene was dehalogenated with an excellent conversion under identical conditions (Table 2, entry 5).

Table 2. [(1)Pd(allyl)Cl]-mediated dehalogenation reactions of chloroarenes.

$ \begin{array}{c} \text{R}-\text{C}_6\text{H}_4\text{Cl} \xrightarrow[\substack{\text{NaOH (1.1 equiv)} \\ i\text{-PrOH, 60 } ^\circ\text{C, 18 h}}]{\substack{[(1)\text{Pd(allyl)Cl}] \\ (1 \text{ mol } \%)}} \text{R}-\text{C}_6\text{H}_4\text{H} \end{array} $			
Entry	Chloroarene	Product(s)	Conv (%) ^[a]
1			>95
2			94
3			19
4			35 ^[b]
5			94
6		 + 	16 + 12
7		 + 	71 + 29

^[a] ¹H NMR conversions are the average of at least two independent experiments. ^[b] Reaction carried out at 80 °C.

From 3,5-dichloroanisole, a mixture of mono- and bis-dehalogenated products was obtained (Table 2, entry 6). More surprising was the outcome of the reaction of 2,6-dichlorobenzaldehyde, where two reaction products were identified, both being benzylic alcohols formed by a transfer hydrogenation reaction (Table 2, entry 7) [19]. This was unexpected since this reactivity is well-established with other metals such as ruthenium or iridium, while the palladium-mediated transfer hydrogenation of carbonyl derivatives remains largely unexplored [20, 21].

Importantly, when boronic acids are present dehalogenated products formed only as traces, if at all. Also, no reduction of the formyl group in **2e** was observed, which indicates that the boronic acid

readily reacts with the base, inhibiting the significant formation of any other reaction product. These results also support the hypothesis that [(1)Pd(allyl)Cl] is not a suitable cross-coupling pre-catalyst for chloroarenes, unlike parent [(IPr)Pd(allyl)Cl] [15] due to an adverse electronic effect of the functionalised backbone on either the transmetallation, or reductive elimination steps.

3. Conclusions

A novel [(NHC)Pd(allyl)Cl] complex, bearing an NHC with a modified backbone was prepared and fully characterised. This complex displayed very similar reactivity to commercially available [(IPr)Pd(allyl)Cl] in Suzuki and dehalogenation reactions under relatively milder and greener reaction conditions (1 mol % [Pd], 1.1 equiv NaOH, *i*-PrOH, 60 °C). An immobilised version of [(1)Pd(allyl)Cl] on silica-coated magnetic nanoparticles also performed well in initial runs, but could not be reused under such reaction conditions. This might be due to the pernicious effect of the base on the silica linker, or to the generation of H₂ under catalytic conditions. Indeed, the transfer hydrogenation of a benzaldehyde derivative was observed. Such reactivity is largely underdeveloped for palladium and it is currently under investigation.

Acknowledgements

This work was supported by Imperial College London and EPSRC. We thank GlaxoSmithKline (GSK) for supplying the boronic acids used for products **2b**, **2d** and **2e**.

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