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Highly active catalysts for the Suzuki coupling of aryl chlorides

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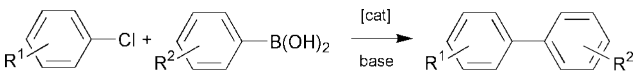
Simple tricyclohexylphosphine adducts of palladium complexes with orthometallated *N*-donor ligands show by far the highest activity yet reported in the Suzuki coupling of aryl chlorides, even under aerobic conditions.

The ability to use aryl chlorides as substrates in Suzuki biaryl coupling reactions (Scheme 1), rather than the far more commonly employed aryl bromides, is advantageous for two reasons. Firstly there are many more commercially available aryl chlorides than bromides and secondly they are much cheaper. These considerations are particularly important for industrial applications. Consequently the search for catalysts that can activate these substrates is a highly topical field of study. Recent notable advances in the use of aryl chlorides in Suzuki reactions have been made by the groups of Buchwald,[1] Guram[2] and Nolan.[3] Most of these catalyst systems rely on the use of complexes derived from di- or tri-alkyl substituted phosphine ligands which are either laborious to synthesise or are commercially available but comparatively expensive. The expense is compounded by the fact that the catalysts have to be used in relatively high loadings. These factors coupled with the current high cost of palladium detract from the appeal of using aryl chloride substrates when far cheaper ligands can be used in ultra-high dilutions for the activation of aryl bromides.[4]

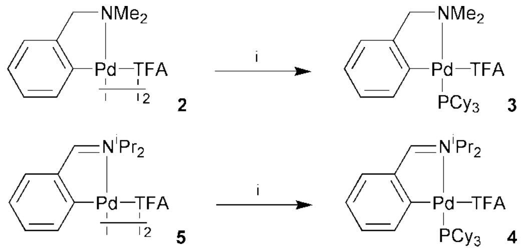


Scheme 1 The Suzuki biaryl coupling reaction.

By comparison with other phosphine ligands currently used in the activation of aryl chlorides, tricyclohexylphosphine is relatively cheap, readily available and easily handled. Littke and Fu have shown that palladium catalysts formed *in situ* with tricyclohexylphosphine show reasonable activity,[5] whilst Beller and coworkers have demonstrated that pre-formed Pd(0) complexes of the type [Pd(diene)(PCy$_3$)], **1**, are far more active.[6] Unfortunately, the synthesis and handling of the pre-formed complexes **1** are not particularly facile. It can be envisaged that an ideal catalyst for the Suzuki coupling of aryl chlorides would be one that: contains tricyclohexylphosphine; is easy to synthesise from cheap, commercially available materials; is easy to handle and shows good activity at low loadings.

We have previously obtained results that suggest that triphenylphosphine adducts of palladium complexes with orthometallated *N*-donor ligands act as precursors for low coordinate 'Pd–PPh$_3$' species in the Suzuki coupling of aryl bromides and that it is these low coordinate species that are the true active catalysts.[7] We were therefore interested to see whether analogous tricyclohexylphosphine adducts would show good activity in the Suzuki coupling of aryl chlorides. The preliminary findings of this study are reported below.[8]

The orthometallated amine complex **2** was used as a precursor as it is readily accessible from *N*,*N*-dimethylbenzylamine, which is commercially available and inexpensive and because we and later others have shown that the chloride-bridged analogue of **2** can be used in C–C bond forming processes.[9] Complex **2** readily reacts with tricyclohexylphosphine in dichloromethane to generate the adduct **3** in 60% yield after recrystallisation from dichloromethane–ethanol (Scheme 2). Complex **3** shows good air- and moisture-stability: ^{31}P NMR spectroscopy of a CDCl$_3$ solution shows only **3** and trace amounts of a second species after one month under aerobic conditions. For comparison purposes we also synthesised complex **4** by an analogous route from the metallated imine complex **5**. Complexes related to the precursor **5** have been found to give good activity in C–C coupling reactions with aryl bromides and iodides.[10]



Scheme 2 *Reagents and conditions*: i, PCy$_3$, CH$_2$Cl$_2$, r.t., 30 min.

4-Chloroanisole was chosen as the main test substrate for the optimisation studies as it is electronically deactivated and thus resistant to oxidative addition and consequently very reluctant to enter a catalytic manifold. Therefore any catalyst that can activate this challenging substrate would be expected to be active with a broad spectrum of aryl chlorides. The results of the coupling of 4-chloroanisole with phenylboronic acid are summarised in Table 1. A brief optimisation of solvents and bases (entries 1–8) showed that the activity of the catalyst was profoundly affected by reaction conditions and demonstrated that dioxane/Cs$_2$CO$_3$ mixtures gave the highest activity, although good activity was seen when K$_3$PO$_4$ was used as a base. We were delighted to see that complex **3** gave essentially complete conversion at 0.1 mol% catalyst loading and very high turnover numbers (TONs) of up to 8000 at 0.01 mol% loading. Astonishingly, no loss in activity was observed when coupling reactions were performed under air. The observed activity is over seven times higher than that of the catalysts **1** which give a maximum TON of 1120 for this reaction under similar conditions and an inert atmosphere.[6] To the best of our knowledge, the highest reported TON for any aryl chloride in the Suzuki reaction is 4600 for the comparatively easy to couple substrate 4-chloroacetophenone.[1b] Even at 60 °C catalyst **3** shows excellent conversion in the coupling of 4-chloroanisole at 1.0 mol% loading.

Whilst the parent dimer **2** shows virtually no activity in the coupling of 4-chloroanisole, catalysts prepared *in situ* from **2** and one equivalent of PCy$_3$ show essentially identical activity to **3**. However in this case the dilute solutions of the phosphine need to be made up under nitrogen whereas no special precautions are required with **3**. Increasing the amount of PCy$_3$ in *in situ* formed catalysts appears to have a deleterious effect on the activity. The complex **4** shows somewhat lower activity than **3**, in addition the need to pre-synthesise the imine ligand detracts from its appeal.

Encouraged by these results we investigated the use of **3** in the Suzuki coupling reactions of a range of aryl chlorides (entries 17–23). The reactions with the electron deficient substrates 4-chloroacetophenone, 4-chloronitrobenzene and

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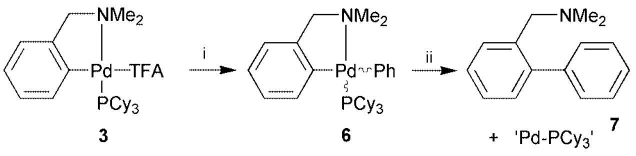
Table 1 Suzuki coupling of aryl chlorides with phenylboronic acid. *Reaction conditions*: aryl chloride (2.0 mmol), $PhB(OH)_2$ (3.0 mmol), base (6.0 mmol), solvent (20 ml), 17 h

Entry	Substrate	Catalyst ([Pd]/mol% Pd)	Base	Solvent	T/°C[a]	Conversion (%)[b]	TON/mol product (mol Pd)$^{-1}$
1	4-Chloroanisole	**3** (1.0)	K_2CO_3	Toluene	110	6	6
2	4-Chloroanisole	**3** (1.0)	KF	Toluene	110	18	18
3	4-Chloroanisole	**3** (1.0)	KF	NMP	130	1	1
4	4-Chloroanisole	**3** (1.0)	KF	DMA	130	8	8
5	4-Chloroanisole	**3** (1.0)	NaO_2CMe	Dioxane	100	25	25
6	4-Chloroanisole	**3** (1.0)	KF	Dioxane	100	22	22
7	4-Chloroanisole	**3** (1.0)	K_3PO_4	Dioxane	100	60	60
8	4-Chloroanisole	**3** (1.0)	Cs_2CO_3	Dioxane	100	100	100
9	4-Chloroanisole	**3** (0.1)	Cs_2CO_3	Dioxane	100	>99	>990
10	4-Chloroanisole	**3** (0.01)	Cs_2CO_3	Dioxane	100	74	7400
11	4-Chloroanisole	**3** (0.01)[c]	Cs_2CO_3	Dioxane	100	80	8000
12	4-Chloroanisole	**3** (1.0)	Cs_2CO_3	Dioxane	60	97	97
13	4-Chloroanisole	**2** (1.0)	Cs_2CO_3	Dioxane	100	<0.2	<0.2
14	4-Chloroanisole	**2** (0.01) + PCy_3	Cs_2CO_3	Dioxane	100	80	8000
15	4-Chloroanisole	**2** (0.01) + 2 PCy_3	Cs_2CO_3	Dioxane	100	24.5	2450
16	4-Chloroanisole	**4** (0.01)	Cs_2CO_3	Dioxane	100	26	2600
17	4-Chloroacetophenone	**3** (0.01)	Cs_2CO_3	Dioxane	100	100	10000
18	4-Chloronitrobenzene	**3** (0.01)	Cs_2CO_3	Dioxane	100	100	10000
19	4-Chlorobenzaldehyde	**3** (0.001)	Cs_2CO_3	Dioxane	100	99	99000
20	2-Chlorotoluene	**3** (0.1)	Cs_2CO_3	Dioxane	100	100	1000
21	2-Chloroanisole	**3** (0.1)	Cs_2CO_3	Dioxane	100	100	1000
22	2-Chlorotoluene	**3** (0.01)	Cs_2CO_3	Dioxane	100	100	10000
23	2-Chloroanisole	**3** (0.01)	Cs_2CO_3	Dioxane	100	96	9600

[a] Approximate internal temperature. [b] Determined by GC against hexadecane internal standard, based on aryl chloride. [c] Under air.

4-chlorobenzaldehyde all showed quantitative conversions at 0.01 mol% catalyst loading. Further reducing the catalyst loading gave a TON of at least 99 000 in the coupling of 4-chlorobenzaldehyde—over twenty times higher activity than observed previously in any aryl chloride coupling reaction.[1b] In order to evaluate the performance of **3** with more sterically demanding substrates, the reactions of 2-chlorotoluene and 2-chloroanisole were investigated. Both substrates were coupled with ease, the catalyst **3** again showing considerably higher activity than any other reported previously.

With respect to the mechanism, it seems highly unlikely that a Pd(II)/Pd(IV) catalytic cycle operates when complex **3** is used as a pre-catalyst, particularly when 4-chloroanisole, which is relatively resistant to oxidative addition reactions, is used as the substrate. It is far more likely that the active catalyst is a low-coordinate palladium(0) species. Such a species may conceivably be formed by a process involving nucleophilic attack of the phenylboronic acid at the metal centre followed by reductive elimination of the phenyl and metallated *N*,*N*-dimethylbenzylamine functions from the putative intermediate **6** (Scheme 3). Indeed GC and GC-MS analysis of the reaction mixture for the coupling of 4-chloroanisole at 60 °C showed the presence of substantial amounts of **7** ($\sim 63\%$) indicating that such a process almost certainly occurs under catalytic conditions. Mono-coordinate phosphine complexes have been implicated previously as catalysts in coupling reactions and it seems likely that they are the active species here.[6,11] This may help explain why doubling the concentration of PCy_3 in catalysts formed *in situ* drastically reduces the catalytic activity—effectively the Pd becomes over-ligated.



Scheme 3 *Reagents and conditions*: i, $PhB(OH)_2$, base; ii, reductive elimination.

Interestingly, regardless of the precise nature of the active catalyst species derived from **3** or from mixtures of **2** and PCy_3, they show far greater activity than preformed palladium(0) complexes of the type **1** or complexes formed *in situ* from PCy_3 and either $[Pd_2(dba)_3]$ or palladium acetate.[5,6] This demonstrates that the choice of palladium precursor can have a profound influence on the activity of the catalyst and that the orthopalladated *N*,*N*-dimethylbenzylamine moiety represents the most efficient source of active palladium species yet reported.

In summary we have found that the very easily synthesised, comparatively inexpensive complex **3** shows by far the highest activity yet reported in the Suzuki coupling of aryl chlorides, regardless of whether the substrates are electron rich or poor. Additionally this high activity is observed with catalysts formed *in situ* and when the reactions are performed under air.

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