Mixed Phosphite-Phosphine and Phosphinite-Phosphine Palladacyclic Complexes as Highly Active Catalysts for the Amination of Aryl Chlorides

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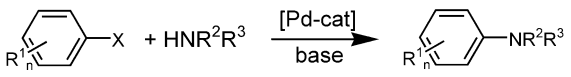
Abstract: Tri-*tert*-butylphosphine adducts of *ortho*-palladated phosphite and phosphinite complexes formed *in situ* are excellent catalysts for the Buchwald–Hartwig amination of aryl chloride substrates.

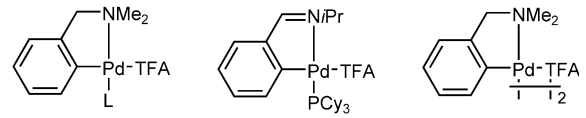
Keywords: amination; aryl chlorides; metallacycles; palladium

The Buchwald–Hartwig amination of aryl halides (Scheme 1) has emerged as a powerful technique for the formation of *N*-substituted anilines.[1] A major recent focus in coupling chemistry has been on the development of catalysts that are able to activate aryl chloride substrates since these tend to be cheaper and more readily available than their bromide and iodide counterparts, factors that make them particularly relevant to the industrial sector. Unfortunately the comparatively high C–Cl bond strength makes their activation by oxidative-addition comparatively difficult.[2] While there are now many reports on the use of aryl chlorides in amination reactions,[3] in most cases the catalysts employed need to be used in relatively high loadings (typically a few mol % Pd). Therefore the advantages associated with the use of aryl chlorides may be negated by the high cost of the catalyst systems and the need to remove palladium residues from the products down to the ppm level for use in fine chemicals and pharmaceutical applications. Consequently there is considerable interest in the development of catalysts that can activate aryl chlorides at low loadings.

Our interest has been in the development and use of palladacyclic catalysts in coupling reactions and recently we have been particularly interested in their application to the coupling of aryl chloride substrates. We have shown that complexes of the type **1** and **2**, either preformed or, more typically, produced *in situ* from appropriate phosphines and the complexes **3** make excellent catalysts for both the Suzuki coupling reaction and the Buchwald–Hartwig amination of aryl chlorides.[4] Even greater activity is seen in the Suzuki coupling of aryl chlorides with complexes of the type **4**, typically formed *in situ* from the complexes **5**, in which the *ortho*-metallated *N*-donor ligand is replaced by an *ortho*-metallated phosphite or phosphinite ligand.[5] The basis of this increase in activity has been discussed in terms of increased catalyst longevity rather than an increase in the rate of catalysis. The complex **4a** is also a useful catalyst for the Stille coupling of aryl chlorides.[6] We were interested to see whether the complexes of the type **4** would prove to be active catalysts for the



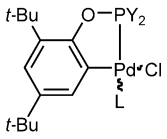
Scheme 1. The Buchwald–Hartwig amination of aryl halides.



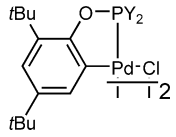
1a: L = PCy_3
b: L = $P(t\text{-}Bu)_3$
c: L = PCy_2(*o*-biphenyl)

2

3



4a: L = PCy_3; Y = OC_6H_3-2,4-(t-Bu)$_2$
b: L = $P(t\text{-}Bu)_3$; Y = OC_6H_3-2,4-(t-Bu)$_2$
c: L = PCy_2(*o*-biphenyl); Y = OC_6H_3-2,4-(t-Bu)$_2$
d: L = PCy_3; Y = Ph
e: L = PCy_3; Y = *i*-Pr
d: L = PCy_3; Y = *O*,*O*-OC_6H_4-2-CO_2



5a: Y = OC_6H_3-2,4-(t-Bu)$_2$
b: Y = Ph
c: Y = *i*-Pr
d: Y = *O*,*O*-OC_6H_4-2-CO_2

Figure 1.

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amination of aryl chlorides and the preliminary results from this investigation are presented below.

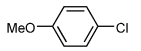
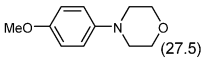
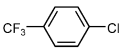
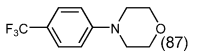
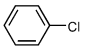
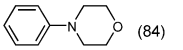
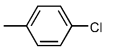
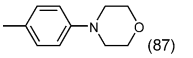
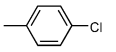
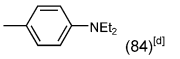
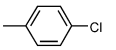
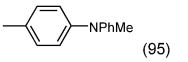
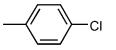
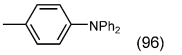
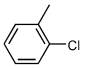
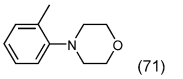
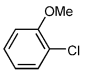
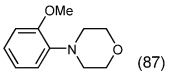
In the first instance we examined the coupling of the deactivated (electron-rich) aryl chloride substrate 4-chloroanisole with morpholine using a catalyst formed *in situ* from complex **5a** and 1 equivalent per palladium of tricyclohexylphosphine. This catalyst did not show a particularly high activity. Unlike in the Suzuki reaction, where PCy_3 is an excellent ligand for the coupling of aryl chlorides, provided the correct choice of palladium precursor is made,[4b,7] it seems, from both the data presented here and those obtained previously using complex **1a**, that PCy_3 is not a particularly useful ligand in the amination of deactivated aryl chlorides. However, when it is replaced by tri-*tert*-butylphosphine, then high levels of activity result. The excellent maximum turnover number (TON, mol product/mol palladium) of 960 (entry 4) is comparable with that obtained using the notionally related pre-catalyst system **1b**.[4b] By contrast, when this reaction is performed under identical conditions with a mixture of palladium acetate (0.1 mol % Pd) and two equivalents of P(*t*-Bu)$_3$ then a conversion of only 2% is obtained, corresponding to a TON of 20.[4b] As with the Suzuki coupling of aryl chlorides catalysed by PCy_3 or PCy_2(*o*-biphenyl) ligands,[4b] it can be seen that the precise nature of the palladium source is of enormous importance, with palladacycles acting as highly potent precursors.

Diarylamines, alkylarylamines and dialkylamines can all be used as substrates. As can be seen the isolated yields of most of the coupled products are good to excellent with a range of aryl chloride substrates, despite the fact that the work-up was not optimised. In all cases the ^{1}H NMR of the crude mixtures showed the conversions to be higher than the isolated yields of pure products, typically in the 90 – 100% range.

Changing from the ortho-palladated phosphite precursor **5a** to the less π-acidic phosphinite analogue **5b** leads to a reduction in activity (entries 5 and 6), in line with the results obtained in the Suzuki coupling of aryl chlorides with these catalysts.[5,12b]

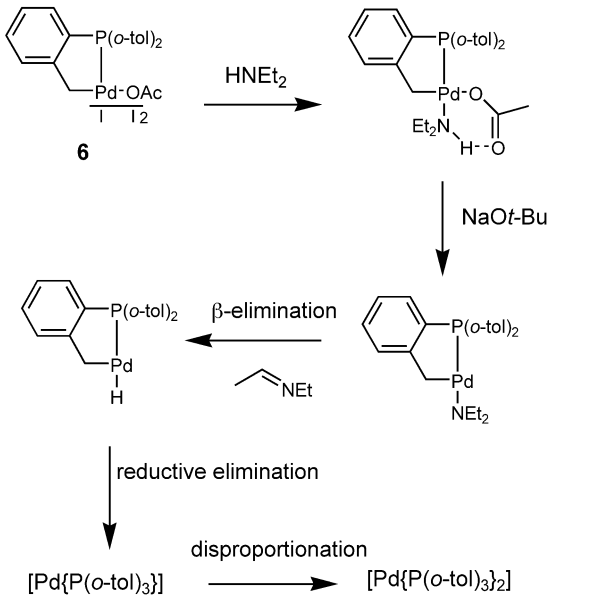
The active catalysts are likely to be palladium(0) species formed from the palladacyclic precursors either thermally or by a reductive process in which the *ortho*-metallated aryl group reacts with one of the coupling partners.[8,9] Hartwig has shown that the palladacyclic catalyst **6** undergoes activation by reductive elimination of the palladated methylene and a hydride introduced to the co-ordination sphere by β-elimination from a co-ordinated diethylamido ligand (Scheme 2).[10] The putative catalyst is a zerovalent mono- or bis-phosphine complex. While such a mechanism may be responsible for the formation of active catalysts when **5a**- and **5b**-P(*t*-Bu)$_3$ mixtures are used, it cannot be the only activation pathway. This is because we observe good activity with diphenylamine, which contains no available hydrogens for β-elimination from an intermediate diphenylamide ligand. For this reason complex **6** does not catalyse the coupling of this substrate.[10]

Table 1. Amination of aryl chlorides.

Entry	Aryl chloride	Amine	Catalyst (mol % Pd)	Product (Yield, %)[b] [Conversion, %][c]
1			**5a** + 2 PCy_3 (1.0)	 (27.5)
2	"	"	**5a** + 2 P(*t*-Bu)$_3$ (1.0)	" (97)
3	"	"	" (0.5)	" (93)
4	"	"	" (0.1)	" (96)
5	"	"	**5b** + 2 P(*t*-Bu)$_3$ (1.0)	" [38]
6	"	"	**5b** + 2 P(*t*-Bu)$_3$ (0.1)	" [47]
7		"	**5a** + 2 P(*t*-Bu)$_3$ (1.0)	 (87)
8		"	"	 (84)
9		"	"	 (87)
10		$HNEt_2$	"	 (84)[d]
11		HNPhMe	"	 (95)
12		$HNPh_2$	"	 (96)
13			"	 (71)
14		"	"	 (87)

[a] Aryl chloride (5.0 mmol), amine (6.25 mmol), NaO*t*-Bu (7.0 mmol), toluene (10 mL), 100 °C, 17 h.
[b] Isolated yield, not optimised.
[c] Conversion to coupled product, based on aryl chloride, determined by GC (hexadecane standard).
[d] 15 mmol of $HNEt_2$ used in a sealed tube.

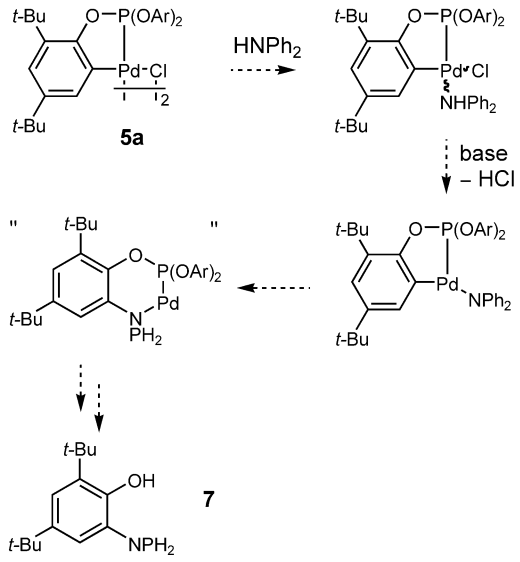
It is possible that the *ortho*-metallated ring in complexes of the type **5** can also be ring-opened by reductive elimination with an amido ligand (Scheme 3), a mechanism which effectively mimics the latter steps of an amination catalytic cycle. While stoichiometric reaction of complex **5a** with diphenylamine and NaO*t*-Bu in toluene at reflux temperature seems to generate palladium(0) as demonstrated by the development of a black colouration, spectroscopic characterisation of the reaction mixture gives, at present, equivocal results. However, a small peak in the GC/MS has a mass and fragmentation pattern consistent with the formation of the 2-aminated phenol **7**, suggesting that, to a limited extent, the speculative activation pathway shown in Scheme 3 *may* be operative. Further work to prove or



Scheme 2. The activation mechanism of a palladacyclic catalyst *via* β-elimination from a co-ordinated amine.[10]

refute this putative mechanism and determine whether any other activation processes are active is ongoing.

In conclusion, tri-*tert*-butylphosphine adducts of phosphinite- and, in particular, phosphite-based palladacycles show good activity as catalysts for the Buchwald–Hartwig amination of a range of aryl chloride and amine substrates even at loadings as low as 0.1 mol % Pd. The very low cost of the tris(2,4-di-*tert*-butyl)phosphite ligand[11] and the facile synthesis of its palladacyclic complex **5a**,[12] make this catalyst precursor particularly attractive for amination reactions.



Scheme 3. A putative activation pathway for complex **5a**.

Experimental Section

General Procedure for the Amination of Aryl Chlorides (Table 1, entries 1–4, 7–9, 11–14)

In a Schlenk tube a solution of the complex **5a** or **b** and the appropriate trialkylphosphine in toluene (5 mL) was stirred at room temperature for 5 min. The appropriate aryl chloride (5.0 mmol), amine (6.25 mmol), NaO*t*-Bu (0.675 g, 7.0 mmol) and more toluene (5 mL) were added and then the reaction mixture was heated at 100 °C for 17 hours. After cooling water (50 mL) was added, the product was extracted with CH_2Cl_2 (4×50 mL), the solution dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The product amines were purified by column chromatography. ^1H and ^{13}C NMR spectroscopic data for the product amines are consistent with reported data.[3f,13]

Method used for Entries 5 and 6

As above except rather than purifying the products by column chromatography, after quenching, extraction and drying ($MgSO_4$) the crude reaction mixture was concentrated to 5 mL on a rotary evaporator, hexadecane (0.068 M in toluene, 1.00 mL, internal standard) was added and the conversion to coupled product was determined by GC.

Coupling of 4-Chlorotoluene with Diethylamine (entry 10)

As for the general method, except that the reaction was performed in a thick-walled reaction tube (~40 mL) which was sealed with a Teflon stopcock and 15 mmol of $HNEt_2$ were used.

Acknowledgements

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References and Notes

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