CHEMCOMM
Communication
www.rsc.org/chemcomm

Unexpected reactivity of two-coordinate palladium–carbene complexes; synthetic and catalytic implications†

Lisa R. Titcomb,[a] Stephen Caddick,*[a] F. Geoffrey N. Cloke,*[a] D. James Wilson[a] and Darren McKerrecher[b]

[a] *The Chemistry Laboratory, C.P.E.S., University of Sussex, Falmer, Brighton, UK BN1 9QJ.*
E-mail: f.g.cloke@sussex.ac.uk
[b] *AstraZeneca Pharmaceuticals, Mereside, Macclesfield, Cheshire, UK SK10 4TF*

Received (in Cambridge, UK) 16th May 2001, Accepted 21st June 2001
First published as an Advance Article on the web 11th July 2001

Ligand exchange reactions reveal unexpected lability of the carbene ligands in two coordinate palladium(0) *N*-heterocyclic carbene complexes; the latter are found to be very effective catalysts for amination of aryl chlorides.

In recent years it has become clear that *N*-heterocyclic carbenes can offer an interesting alternative class of ligand to the ubiquitous phosphines, especially for catalytic applications.[1] The extraordinary advantage that this class of ligand has afforded to metathesis catalysts is a testament to the potential of metal complexes derived from these ligands for organic synthesis.[2] Palladium catalysed protocols utilising imidazolium salts have also been shown to offer a significant advantage for a range of synthetically valuable coupling processes.[3] These salts can be precursors to heterocyclic carbenes and the *in situ* generation of metal–carbene complexes has been suggested as a key step in such reactions. However, although there are a number of reports describing structures of four-coordinate metal(II) carbene species[4] there is relatively little structural, mechanistic or theoretical work pertaining to the two-coordinate palladium(0) carbene species which might be expected to be generated under many of the reaction conditions.[5] It is important to establish whether such isolated complexes are indeed able to effectively mediate coupling reactions; this approach would also facilitate mechanistic studies essential for further developments. Herrmann and coworkers have recently reported the use of pre-formed two-coordinate palladium(0) carbene complexes for Suzuki reactions and noted significant differences in activity between the pre-formed complexes and those assumed to be generated *in situ*.[6] We have embarked upon a programme of work, which has been directed toward the synthesis and characterisation of a range of two-coordinate palladium(0) carbene complexes[7] and examination of their reactivity. Here we describe the synthesis and reactivity of two-coordinate palladium carbene complexes shown in Fig. 1.

We have previously prepared complex **1**, initially using metal vapour synthesis and more recently *via* a solution phase method, and we reported that **1** can be used to mediate a Sonogashira and an amination reaction.[8] However we found procedures using **1** to be less general than protocols already available and so from a preparative sense this was disappointing. Seminal work by Hartwig and coworkers suggested that a key aspect of pre-catalyst design would be the presence of a ligand which could dissociate to generate a mono(carbene)palladium species which, if consistent with other catalytic systems, could then undergo oxidative addition.[9,10] Moreover given the precedents in both palladium and ruthenium catalysis, we also decided to explore saturated *N*-heterocyclic carbenes as ligands since these would offer improved donor capabilities and render catalytic species more active.[11] For these reasons we have prepared the new, two-coordinate palladium complexes **2**, **3** and **4** and evaluated their ability to promote the amination of *p*-chlorotoluene under catalytic conditions.[12]

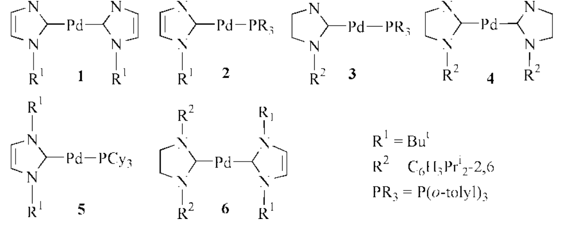
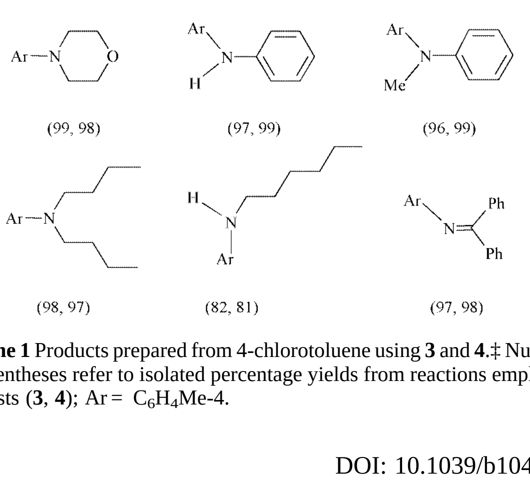


Fig. 1 Two-coordinate palladium carbene complexes.

Displacement of both phosphine ligands in [Pd{P(*o*-tolyl)$_3$}$_2$] by *N*-heterocyclic carbenes has been previously employed to prepare the corresponding [Pd(carbene)$_2$] complexes;[6] however, careful control of stoichiometry enabled the synthesis of the mixed carbene–phosphine complex **2** in good yield.

Contrary to our expectation we found that attempted amination of 4-chlorotoluene with morpholine using **2** led to a disappointing yield of 56% for the coupling which compared poorly to the yield obtained with the bis-carbene complex **1** (95%). We decided to examine two further pre-catalysts **3** and **4**, both of which incorporate the saturated heterocyclic carbene as ligand. The mixed catalyst **3** was prepared in very good yield, again by phosphine displacement from [Pd{P(*o*-tolyl)$_3$}$_2$]; however bis-carbene **4** could be more readily prepared using our alternative route employing sodium dimethyl malonate.[8]

We examined the ability of these complexes to promote amination reactions of 4-chlorotoluene and both catalysts gave excellent yields of isolated products shown in Scheme 1 for the amination of 4-chlorotoluene using primary, secondary and aryl-amines. Isolated yields were generally in excess of 95% using either catalyst and the reactions were generally complete within 1 h at 100 °C. Reactions utilising hexylamine required an

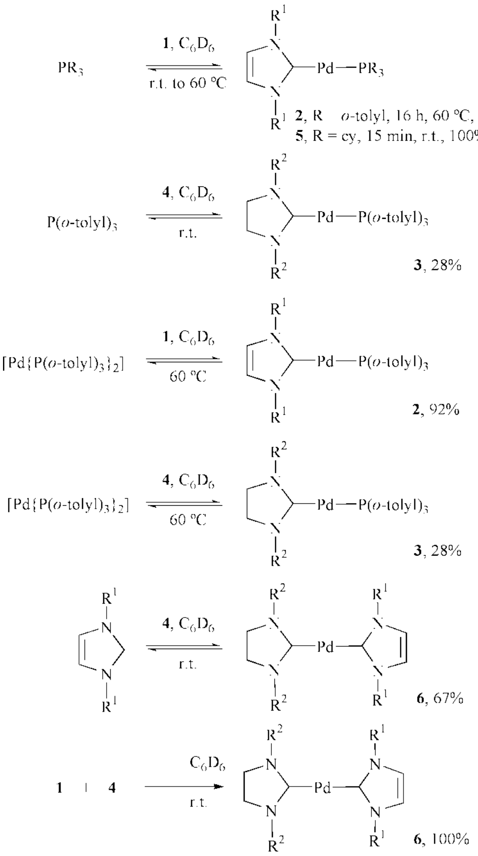


Scheme 1 Products prepared from 4-chlorotoluene using **3** and **4**.‡ Numbers in parentheses refer to isolated percentage yields from reactions employing catalysts (**3**, **4**); Ar = C_6H_4Me-4.

---

† Electronic supplementary information (ESI) available: details of experimental procedures and characterisation data for complexes **2**–**6**, ligand substitution reactions and general procedure for coupling reactions. See http://www.rsc.org/suppdata/cc/b1/b104297c/

DOI: 10.1039/b104297c



Scheme 2 $R^1 = Bu^t$; $R^2 = C_6H_3Pr^i{}_2$-2,6.

excess of amine (4 equivalents), and proceeded in slightly lower yield. In general the overall yields indicate that these are extremely good catalysts for amination, however in contrast to reported *in situ* methods, we were unable to promote these reactions at room temperature.[9]

The ability of the sterically encumbered catalysts **1** and **4** to undergo facile oxidative addition required for these amination reactions is surprising, as is the similarity in catalytic behaviour between **3** and **4**. Given the currently accepted view that metal *N*-heterocyclic carbene bonds are relatively strong compared to metal phosphine bonds,[1c] we had expected that the mixed species **3** would offer a superior class of pre-catalyst, as phosphine dissociation to generate a mono-carbene palladium species, followed by oxidative addition,[10,13] should be more facile than the required carbene dissociation in **4**. However the efficient behaviour of **4** as a pre-catalyst led us to conclude that carbene dissociation from palladium may be more facile than generally envisioned and this is borne out by further experimentation (Scheme 2).

Treatment of **1** with P(o-tolyl)$_3$ at 60 °C for 16 h resulted in a 33% conversion to the mixed carbene–phosphine **2**; prolonged heating had no effect on the product ratio. Similar behaviour was also observed in reaction of **1** with PCy_3, to give **5**, although in this case the reaction proceeded to 100% completion in < 15 min at room temperature, and in the reaction of **4** with P(o-tolyl)$_3$, which gave the mixed complex **3** (28%). Ligand redistribution reactions between **1** and [Pd{P(o-tolyl)$_3$}$_2$] and between **4** and [Pd{P(o-tolyl)$_3$}$_2$] were also found to occur to give **2** and **3** (92% and 28%, respectively). Finally we found that treatment of complex **4** with free unsaturated carbene gave the mixed bis-carbene complex **6** (67%); the latter could also be obtained quantitatively by ligand redistribution between **1** and **4** at room temperature. These experiments demonstrate that ligand substitution at palladium between phosphine and carbene is fairly general and that the metal carbene bond may be more labile than previously thought. This would explain the ability of complexes **1** and **4** to mediate amination and Sonagashira reactions and could be consistent with a mechanism requiring ligand dissociation prior to oxidative addition in the latter,[14] although associative pathways for the ligand exchange reactions in Scheme 2 cannot be ruled out at this stage.

In conclusion we have shown that two-coordinate palladium bis-carbene and mixed carbene–phosphine complexes will efficiently promote amination of aryl halides and demonstrated an unexpected lability of the palladium–carbene bond. These findings may be important in the design of new palladium–carbene catalysts for organic synthesis.

We are grateful to AstraZeneca and EPSRC for support of this project. We are grateful to Dr Abdul Sada for his contribution.

Notes and references

‡ *General procedure*: $KOBu^t$ (1.18 mmol) and complex **3** or **4** (0.016 mmol) were weighed into an ampoule (fitted with a Youngs tap) in a glove-box. Dioxane (10 ml) was added and then 4-chlorotoluene (0.79 mmol) and amine (0.95 mmol) added and the mixture heated at 100 °C. The reaction was allowed to cool to room temperature, the solvent removed and the resulting mixture loaded directly onto a silica-gel plug and eluted using ethyl acetate in hexane (20%). The solvent was evaporated and the product was determined to be > 95% pure by spectroscopic and analytical methods.

1 For reviews: (*a*) D. Bourissou, O. Guerret, P. Gabbai and G. Bertrand, *Chem. Rev.*, 2000, **100**, 39; (*b*) A. J. Arduengo, *Acc. Chem. Res.*, 1999, **32**, 913; (*c*) M. Regitz, *Angew. Chem.*, 1996, **35**, 725.
2 For reviews: L. Jafarpour and S. P. Nolan, *Adv. Org. Chem.*, 2001, **46**, 181; T. Weskamp, V. P. W. Bohm and W. A. Herrmann, *J. Organomet. Chem.*, 2000, **600**, 12; T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18.
3 For recent examples: A. Furstner and A. Leitner, *Synlett*, 2001, 290; G. A. Grasa and S. P. Nolan, *Org. Lett.*, 2001, **3**, 119; H. M. Lee and S. P. Nolan, *Org. Lett.*, 2000, **2**, 2053; J. Huang, G. Grasa and S. P. Nolan, *Org. Lett.*, 1999, **1**, 1307.
4 For recent examples: D. J. Nielsen, K. J. Cavell, B. W. Skelton and A. H. White, *Organometallics*, 2001, **20**, 995; D. S. McGuinness, K. J. Cavell and B. F. Yates, *Chem. Commun.*, 2001, 355; T. Weskamp, V. P. W. Bohm and W. A. Herrmann, *J. Organomet. Chem.*, 1999, **585**, 348; A. A. D. Tulloch, A. A. Danopoulos, R. P. Tooze, S. M. Cafferkey, S. Kleinhenz and M. B. Hursthouse, *Chem. Commun.*, 2000, 1247; E. Peris, J. A. Loch and R. H. Crabtree, *Chem. Commun.*, 2001, 201.
5 J. C. Green, J. G. Scurr, P. L. Arnold and F. G. N. Cloke, *Chem. Commun.*, 1997, 1963.
6 V. P. W. Bohm, C. W. K. Gstottmayr, T. Weskamp and W. A. Herrmann, *J. Organomet. Chem.*, 2000, **595**, 186.
7 P. L. Arnold, F. G. N. Cloke, T. Geldbach and P. B. Hitchcock, *Organometallics*, 1999, **18**, 3228.
8 S. Caddick, F. G. N. Cloke, G. K. B. Clentsmith, P. B. Hitchcock, D. McKerrecher, L. R. Titcomb and M. R. V. Williams, *J. Organomet. Chem.*, 2001, **617**, 635.
9 S. R. Stauffer, S. Lee, J. P. Stambuli, S. I. Hauck and J. F. Hartwig, *Org. Lett.*, 2000, **2**, 1423.
10 L. M. Alcaraz-Roman, J. F. Hartwig, A. L. Rheingold, L. M. Liable-Sands and I. A. Guzei, *J. Am. Chem. Soc.*, 2000, **122**, 4618.
11 J. Huang, E. D. Stevens and S. P. Nolan, *J. Am. Chem. Soc.*, 1999, **121**, 2674; J. Huang, H. J. Shanz, E. D. Stevens and S. P. Nolan, *Organometallics*, 1999, **18**, 2370.
12 For examples: J. F. Hartwig, in *Modern Amination Methods*, ed. A. Ricci, Wiley-VCH, Weinheim, 2000; B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125; J. F. Hartwig, *Angew. Chem., Int Ed.*, 1998, **37**, 2047.
13 For a discussion of oxidative addition see: C. Amatore and F. Pfluger, *Organometallics*, 1990, **9**, 2276; C. Amatore, A. Jutand and A. Suarez, *J. Am. Chem. Soc.*, 1993, **115**, 9531.
14 J. F. Hartwig and F. Paul, *J. Am. Chem. Soc.*, 1995, **117**, 5373; M. S. Sanford, M. Ulman and R. H. Grubbs, *J. Am. Chem. Soc.*, 2001, **123**, 749.