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An improved synthesis of bis(1,3-di-*N*-*tert*-butylimidazol-2-ylidene)palladium(0) and its use in C–C and C–N coupling reactions

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Abstract

A new, improved synthesis of [Pd{$\overline{CN(^tBu)(CH)_2N}(^tBu)$}$_2$] (**1**) and its use as a catalyst in coupling reactions, including aminations, is presented. An interesting side product formed in the synthesis of **1**, [Pd(η^3-C_4H_7){($\overline{CN(^tBu)(CH)_2N}(^tBu)$}Cl] (**2**), is also discussed. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: *N*-heterocyclic carbenes; Aminations; Coupling reactions; Palladium complexes

1. Introduction

Palladium mediated transformations have found widespread applications in organic synthesis and in particular zerovalent Pd catalysts have enjoyed remarkable popularity as reagents for a diverse range of coupling reactions [1]. Perhaps the most commonly employed catalyst for C–C coupling reactions is [Pd(PPh_3)$_4$] which can be readily prepared from $PdCl_2$ and PPh_3 in the presence of hydrazine hydrate and is also commercially available [2]. Whilst this (or indeed a Pd(II) pre-catalyst) can be used as an effective reagent for coupling reactions, the labile nature of the Pd-P bonds in this system means that a variety of species may be present in the reaction mixture [3,4]. Moreover this may have an impact on the catalyst turnover and thus efficiency. With these factors in mind it would seem that alternative ligand environments may offer opportunities to devise new classes of Pd catalysts with improved efficiency.

In recent years it has become apparent that the ligating properties of *N*-heterocyclic carbenes exhibit some similarity to phosphines. Recent theoretical and experimental work on the complex [Pd{$\overline{CN(^tBu)(CH)_2N}(^tBu)$}$_2$] (**1**) and its platinum analogue showed that the metal-ligand bonding occurs predominantly through σ donation from the carbene lone pairs to the metal centre [5]. A number of reports have successfully demonstrated that a range of such carbene ligands can be incorporated into Pd(II) complexes and offer an alternative class of pre-catalysts, with improved stability (and potential turnover capacity), for C–C coupling reactions [6]. Until recently there had been no report of a two-coordinate Pd(0) carbene species, presumed to be the active catalyst in the latter [7,8]. We present results of a study which describes a simple one-pot procedure for the preparation of such a species and some preliminary work which shows, for the first time, that an isolated Pd(0) carbene complex can catalyse an amination coupling reaction.

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2. Synthesis

Recent results from our laboratories showed that two coordinate palladium (0) carbene species could be readily prepared *via* metal vapour synthesis (MVS) [7]. Herrmann et al. have also shown that such species can be prepared from bis(tri-*ortho*-tolylphosphine)-palladium(0) and the free carbene by displacement of the phosphine ligands [8]. This procedure requires the synthesis of tri-*ortho*-tolylphosphine and [Pd(η^3-C_3H_5)(η^5-C_5H_5)] as precursors to the bis-phosphine palladium complex; the synthesis of the latter from tri-*ortho*-tolylphosphine and [Pd(dba)$_2$] has also been reported [9]. Given the potential interest in new catalysts of this type, we sought to devise a more simple preparative route to these complexes. A classic synthesis of zerovalent palladium phosphine complexes involves addition of a nucleophile to the bound allyl unit of a Pd(II) complex, typically [{Pd(η^3-C_3H_5)Cl}$_2$] or [{Pd(η^3-C_4H_7)Cl}$_2$], in the presence of stoichiometric phosphine ligand to trap the Pd(0) centre which results from attack at the allyl ligand [10]. Thus our initial attempts to prepare 1 involved treatment of [{Pd(η^3-C_4H_7)Cl}$_2$] with either one equivalent per Pd of either sodium methoxide or potassium *tert*-butoxide in the presence of [CN(^{t}Bu)(CH)$_2$N(^{t}Bu)] at 0°C, which led to the isolation of a 1:2 mixture of **1** and [Pd(η^3-C_4H_7){(CN(^{t}Bu)(CH)$_2$N(^{t}Bu)}Cl] (**2**); carrying out these reactions at elevated temperature (90°C) resulted in reduction of the starting material to palladium metal. Reaction of [(Pd(η^3-C_4H_7)Cl)$_2$] with two equivalents of [CN(^{t}Bu)(CH)$_2$N(^{t}Bu)] yielded **2** in quantitative yield. Crystals of **2** suitable for X-ray diffraction studies were obtained from a toluene solution at ambient temperature. Fig. 1 shows the molecular structure of **2**, with selected bond lengths and angles collated in Table 1. From consideration of bond angles, the gross geometry around the Pd(II) centre is best regarded as pseudo-square planar; the palladium–carbon bond trans to the chlorine atom is significantly shorter than the bond *trans* to the carbene ligand (Pd–C(12) = 2.121(4) Å cf. Pd–C14 = 2.158(4) Å). This is consistent with the previously reported triphenylphosphine analogue [Pd(η^3-C_4H_7)(PPh_3)Cl] [11,12]. The palladium–carbene bond length in **2** is 2.061(3) Å which is comparable with those in previously reported carbene palladium(II) complexes, which range from 1.95 to 2.07 Å; the bond distances and angles within the carbene ligand in **2** are also comparable to those found in related compounds [13]. The geometry and bond lengths in the η^3-C_4H_7 group in **2** are essentially identical (within estimated S.D.s) to those found in [Pd(η^3-C_4H_7)(PPh_3)Cl] [11,12]. Variable temperature nuclear Overhauser effect (nOe) experiments on the terminal allyl protons showed no evidence for fluxional behaviour in the allyl group up to a temperature of 70°C, in contrast to the previously reported phosphine analogue [14,15]: irradiation of each of the terminal allyl protons did not lead to any enhancement effects in the other terminal allyl protons. However, irradiation of one set of ^{t}Bu protons showed an enhancement of 2.5% in the other ^{t}Bu group at 25°C increasing to 33% at 55°C, indicating slow rotation about the palladium–carbene bond on the NMR timescale.

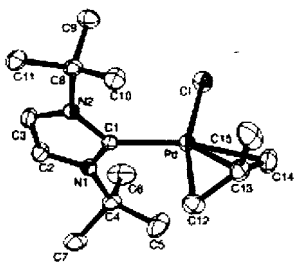


Fig. 1. Molecular structure of [Pd(η^3-C_4H_7)-{(CN(^{t}Bu)(CH)$_2$N(^{t}Bu)}Cl] (**2**). Thermal ellipsoids are shown at the 50% probability level.

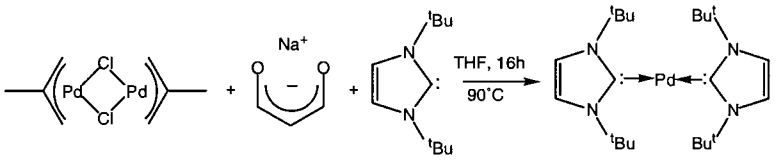
Table 1
Selected bond lengths and angles in [Pd(η^3-C_4H_7)-{(CN(^{t}Bu)(CH)$_2$N(^{t}Bu)}Cl] (**2**)

Bond	Distance (Å)	Group	Angle (°)
Pd–C(1)	2.061(3)	C(1)–Pd–C(12)	102.90(15)
Pd–C(12)	2.121(4)	C(12)–Pd–C(14)	68.03(18)
Pd–C(13)	2.163(4)	C(12)–Pd–C(13)	38.76(15)
Pd–C(14)	2.158(4)	C(13)–Pd–C(14)	37.38(17)
Pd–Cl	2.378(1)	C(14)–Pd–Cl	97.33(14)
C(1)–N(2)	1.362(4)	C(1)–Pd–Cl	91.53(10)
N(2)–C(3)	1.381(5)	N(1)–C(1)–N(2)	104.7(3)
C(3)–C(2)	1.348(5)	C(1)–N(2)–C(3)	110.3(3)
C(2)–N(1)	1.389(5)	N(2)–C(3)–C(2)	107.9(3)
N(1)–C(1)	1.370(4)	C(3)–C(2)–N(1)	106.3(3)
		C(2)–N(1)–C(1)	110.7(3)

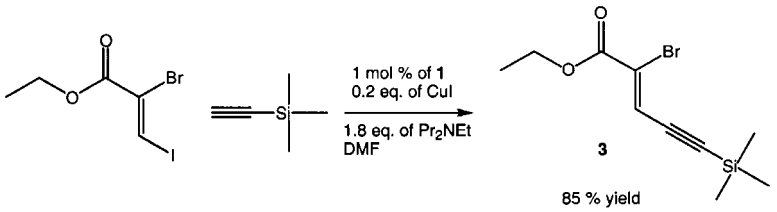
However, addition of sodium dimethylmalonate to [{Pd(η^3-C_4H_7)Cl}$_2$] in the presence of two equivalents of [CN(^{t}Bu)(CH)$_2$N(^{t}Bu)] leads to formation of the desired bis-carbene palladium(0) complex in a one-pot procedure. Complex **1** is obtained in 60% yield after filtration of the reaction mixture followed by recrystallisation from THF at −50°C (Scheme 1).

3. Catalysis

Complex **1** has very recently been shown to act as single component catalyst in the Suzuki cross-coupling reaction [8] and here we are able to report that **1** is also able to catalyse a Sonogashira type cross-coupling reaction with an efficiency comparable to that of [Pd(PPh_3)$_4$] (Scheme 2).



Scheme 1. Synthesis of [Pd{$\overline{CN(^tBu)(CH)_2N(^tBu)}$}$_2$] (**1**).



Scheme 2. Sonogashira type coupling using **1**.

The bromoeneyne, **3**, shown in Scheme 2 is a common building block for our investigations into the synthesis of enediyne natural products and their analogues [16,17]. Ethyl-2-iodo-3-bromopropenoate was found to couple to trimethylsilylacetylene using **1** to afford **3** in 85% isolated yield. Particularly encouraging is the good conversion observed using only 1 mol% of **1** which is comparable with the use of [Pd(PPh$_3$)$_4$] [16,17].

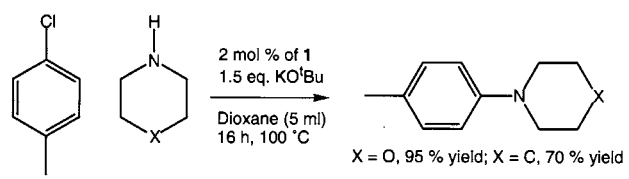
Catalytic amination of chloroarenes has been effected by palladium-phospine systems, e.g. [Pd(dba)$_2$]/P^{t}Bu$_3$ for *p*-chlorotoluene with di(^{n}butyl)amine (1 mol% Pd, 70°C, 12 h, 88% yield) [18]. Recent work by Nolan et al. and Hartwig et al. has shown that imidazolium and imidazolinium salts with bulky substituents can also be used as additives in palladium catalysed reactions to effect the coupling of an otherwise inert aryl chloride to an amine [19,20]. We have also commenced preliminary investigations into the use of **1** as a catalyst for such couplings. These investigations have shown for the first time that such two coordinate palladium(0) complexes can act as useful catalysts for these reactions (Scheme 3): *p*-chlorotoluene can be coupled to morpholine and piperidine in 95% and 70% yields, respectively, which compare favourably with reported yields (82% and 96%, respectively) using the imidazolium salt route to generate the catalyst in situ [19].

4. Conclusions

An improved one-pot synthesis of [Pd{$\overline{CN(^tBu)(CH)_2N(^tBu)}$}$_2$] (**1**) has been developed and an intermediate, [Pd(η^3-C$_4$H$_7$)-{($\overline{CN(^tBu)(CH)_2N(^tBu)}$}Cl] (**2**), in the formation of **1** has been isolated and fully characterised. No evidence for fluxionality of the allyl group in **2** is observed at 70°C in contrast to the triphenylphosphine analogue. The complex **1** has been used in a Sonogashira type coupling and, for the first time, in amination reactions of *p*-chlorotoluene. Further investigations into the use of **1** in couplings with other aryl halides and amines are ongoing.

5. Experimental

Unless otherwise stated, all experimental procedures were carried out using standard high vacuum and Schlenk techniques, under an atmosphere of dry argon, or under dinitrogen in an MBraun or a Miller–Howe glove box. Glassware was dried in an oven at 150°C prior to use. THF was distilled from potassium metal and toluene from sodium metal under dinitrogen prior to use; d_6-benzene was dried over molten potassium then vacuum transferred to an ampoule under argon prior to use. NMR spectra were recorded at 295 K on a Bruker DPX 300 MHz spectrometer, with chemical shifts (δ) reported in ppm, relative to the residual proton chemical shifts of the internal deuterated solvent (^{1}H and ^{13}C) set relative to external TMS, and relative to external LiCl (^{7}Li). Coupling constants are quoted in Hz. Electron impact mass spectra were recorded on a VG Autospec mass spectrometer. Elemental analyses were carried out by Medac Ltd., Brunel Science Centre, Surrey, UK. Morpholine, piperidine and *p*-chlorotoluene were purchased from Aldrich and passed



Scheme 3. Amination of *p*-chlorotoluene with morpholine and piperidine.

through a column of basic alumina prior to use. Potassium *tert*-butoxide was purchased from Aldrich and sublimed twice at 157°C, 1×10^{-5} mbar. Anhydrous dioxane was purchased from Aldrich and stored in an ampoule under argon over 4 Å molecular sieves. [CN(ᵗBu)(CH)$_2$N(ᵗBu)] [7] and [(Pd(η^3-C$_4$H$_7$)Cl)$_2$] [21] were synthesised according to literature procedures.

5.1. Synthesis of bis(1,3-di-tert-butylimidazol-2-ylidene)palladium(0) [Pd{CN(ᵗBu)(CH)$_2$N(ᵗBu)}$_2$] (1)

[CN(ᵗBu)(CH)$_2$N(ᵗBu)] (183 mg, 1.02 mmol), [(Pd(η^3-C$_4$H$_7$)Cl)$_2$] (100 mg, 0.254 mmol) and sodium dimethylmalonate (78 mg, 0.506 mmol) were placed in an ampoule equipped with a Rotaflo stopcock and THF added (30 ml). The mixture was heated at 90°C for 16 h with stirring after which the solution was brown. After cooling to room temperature, the mixture was filtered from some free palladium metal and the solution concentrated. Crystallisation at −50°C yielded the product as a yellow solid in 60% yield (143 mg).

Elemental analysis. Anal. Found: C, 56.67; H, 8.54; N, 12.22. Calc. for [C$_{22}$H$_{40}$N$_4$Pd]: C, 56.58; H, 8.63; N, 12.00%.

^{1}H-NMR (C$_6$D$_6$): δ 2.12 (18H, s, NC(CH$_3$)$_3$), 6.74 (2H, s, NCHCHN). ^{13}C{^{1}H}-NMR (C$_6$D$_6$): δ 31.96 (s, NC(CH$_3$)$_3$), 57.35 (s, NC(CH$_3$)$_3$), 113.95 (s, NCC).

5.2. Synthesis of chloro(1,3-di-tert-butylimidazol-2-ylidene)(methylallyl)palladium(II) [Pd(η^3-C$_4$H$_7$)-{(CN(ᵗBu)(CH)$_2$N(ᵗBu)}Cl] (2)

To a Schlenk tube containing [(Pd(η^3-C$_4$H$_7$)Cl)$_2$] (260 mg, 0.66 mmol) and [CN(ᵗBu)(CH)$_2$N(ᵗBu)] (237 mg, 1.32 mmol) toluene (20 ml) was added. The solids dissolved to give an orange solution. The solution was concentrated and the product crystallised at ambient temperature in 90% yield.

^{1}H-NMR (C$_6$D$_6$): δ 1.55 (s, 9H, NC(CH$_3$)$_3$), 1.69 (s, 9H, NC(CH$_3$)$_3$), 1.71 (s, 3H, CH$_2$CCH$_3$CH$_2$), 2.15 (s, 1H, broad), 3.05 (m, 1H), 3.24 (s, 1H, broad), 4.07 (m, 1H) (CH$_2$CCH$_3$CH$_2$), 6.69 (m, 2H, NCCH). ^{13}C{^{1}H}-NMR (C$_6$D$_6$): δ 22.73 (s, CH$_2$CCH$_3$CH$_2$) 31.73 (s, NC(CH$_3$)$_3$), 31.99 (s, NC(CH$_3$)$_3$), 52.04 (s, CH$_2$CCH$_3$CH$_2$), 57.96 (s, NC(CH$_3$)$_3$), 58.53 (s, NC(CH$_3$)$_3$), 67.91 (s, CH$_2$CCH$_3$CH$_2$), 118.06 (s, NCCH), 118.12 (s, NCCH), 127.29 (s, CH$_2$CCH$_3$CH$_2$), 178 (s, NCN). EI MS: m/z 378 (33%, M$^+$), 341 (7%, M$^+$ −Cl), 286 (100%, M$^+$−C$_4$H$_7$ and Cl), 229 (93%, M$^+$-C$_4$H$_7$, Cl and ᵗBu). C$_{15}$H$_{27}$ClN$_2$Pd (378): Calc.: C, 47.87, H, 7.18, N, 7.45. Anal. Found: C, 47.72, H, 6.95, N, 7.52. Crystal data: C$_{15}$H$_{27}$ClN$_2$Pd, monoclinic, FW 377.24, space group $P2_1/c$ (no. 14); $a = 10.951(4)$, $b = 9.987(4)$, $c = 15.400(6)$ Å, $\beta = 98.8°$, $U = 1664(1)$ Å^3, λ(Mo–K$_\alpha$) = 0.71073 Å, $Z = 4$, $D_{calc} = 1.51$ Mg m^{-3}, μ(Mo–K$_\alpha$) = 1.27 mm^{-1}, $T = 173$ K. Data was collected on an Enraf-Nonius CAD4 diffractometer using a crystal of dimensions $0.3 \times 0.3 \times 0.2$ mm. A total of 4832 unique reflections were measured of which 4067 had $|F^2| > 2\sigma(F^2)$. The final residuals were $R_1 = 0.045$ (for $I > 2\sigma(I)$) and $wR_2 = 0.121$ for all data.

For a procedure for the synthesis of (*Z*)-ethyl-2-bromo-3-iodopropenoate, its coupling with trimethylsilylacteylene and for characterisation data for (*Z*)-ethyl-2-bromo-3-iodopropenoate and (*Z*)-ethyl-2-bromo-3-ethynyl-(trimethylsilyl)propenoate (**3**) see Refs. [16,17].

5.3. Coupling of p-chlorotoluene with morpholine and piperidine

5.3.1. General procedure

The catalyst (7.4 mg, 0.16 mmol) and KOᵗBu (133 mg, 1.19 mmol) were weighed into a tube in a glovebox and capped with a septum. Dioxane (5 ml) was added. Chlorotoluene (100 mg, 0.79 mmol) followed by the amine (0.95 mmol) were injected into the tube. The mixture was heated at 100°C for 16 h. The product was purified by absorption of the crude reaction mixture onto silica followed by flash chromatography eluting with a solvent gradient starting with hexane and finishing with 5% EtOAc–hexane.

The respective coupling products were found to be identical by ^{1}H-NMR with literature data for 1-(4-methylphenyl)piperidine [22] and 1-(4-methylphenyl)-morpholine [23].

6. Supplementary material

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 148362 for complex **2**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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