Synthesis and reactivity of alkylpalladium *N*-heterocyclic carbene complexes†

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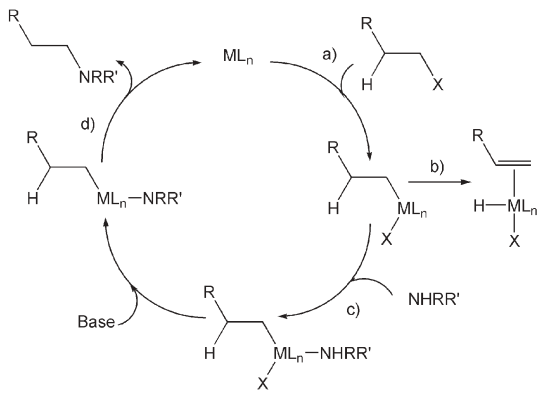
The transamination of alkylpalladium halide *N*-heterocyclic carbene complexes has enabled the isolation of products that reveal interesting insights into the factors which might be barriers to the development of a palladium-catalysed alkyl–amination reaction.

In recent years palladium-catalysed cross-coupling reactions have become an indispensable tool to the organic chemist.[1] Advances in electron rich ligands (alkyl phosphines and *N*-heterocyclic carbenes (NHCs)) have extended the scope of aryl halide cross-coupling reactions, to include aryl chlorides (previously unreactive).[2] Whilst Suzuki,[3] Negishi,[4] Heck,[5] Kumada,[6] and Buchwald–Hartwig amination[7] reactions have been successfully employed using aryl halides, alkyl halides have proved much more challenging. In fact, Pd-catalysed alkyl–amination cross-couplings (Scheme 1) have not been previously explored to any great extent, and to date only theoretical studies have been reported.[8]

Whilst displacement of halides by amines can occur without the requirement of Pd, these reactions can often be troublesome *e.g.* the formation of *N*-neopentyl morpholine from neopentyl chloride and morpholine requires heating to 200 °C and a reaction time of 3 days in a sealed bomb.[9] Thus, a palladium-catalysed version of such a class of reaction might offer considerable advantages. However, as with all palladium-catalysed transformations involving alkyl halides, one of the largest barriers to be overcome is competitive β-hydride elimination (Scheme 1).[10,11]



Scheme 1 Proposed mechanism for alkyl–amine cross-coupling reactions. (a) Oxidative addition (b) β-hydride elimination (c) transamination (d) reductive elimination.

In order to start to develop a palladium-catalysed amination of alkyl halides, it is important to understand the mechanism of the processes that would be involved. We believe that combined structural and mechanistic studies can generate useful information for the development of new organometallic protocols for organic synthesis. Herein, we report our efforts towards the isolation of alkyl halide oxidative addition (OA) and transamination products of Pd–NHC complexes. Although these preliminary studies have not yet allowed us to identify a palladium-catalysed amination of alkyl halides, a number of important new patterns of organometallic reactivity have been identified.

Studies were undertaken using alkyl halides containing no β-hydrogens, such that oxidative addition could be thoroughly examined. Therefore, the oxidative addition of neopentyl halide (halide = I/Br/Cl) to Pd(I^{t}Bu)$_2$ in d_6-benzene was followed by ^{1}H NMR spectroscopy at room temperature. In the case of neopentyl iodide, the formation of 2,5-dimethylhexane was observed after 10 minutes, with concomitant formation of PdI$_2$(I^{t}Bu)$_2$, presumably the result of intermolecular exchange, as previously described by Cavell and McGuinness.[12] Addition of neopentyl bromide to Pd(I^{t}Bu)$_2$ at room temperature led to no observable reaction. However, at 75 °C the unexpected activation of one C–H bond of ^{t}Bu in I^{t}Bu occurred, followed by reductive elimination to yield neopentane.[13] This indicates that oxidative addition occurred but that the resulting four-coordinate complex is thermally unstable. On the other hand, when neopentyl chloride was reacted with Pd(I^{t}Bu)$_2$ at 75 °C only degradation of the starting palladium complex was observed (no reaction occurs at room temperature).

As a consequence of these initial findings, an alternative route, illustrated in Scheme 2 (reaction A), was developed to form an alkylpalladium halide NHC complex, for use in further elaboration of the alkyl–amination cross-coupling catalytic cycle. To this end, the novel [(neopentyl)Pd(Cl)(1,5-COD)] **1** was synthesised and used in the formation of Pd–NHC complexes (Scheme 2). Addition of one equivalent of I^{t}Bu to **1** formed exclusively the dimeric complex *trans*-[(neopentyl)Pd(Cl)(I^{t}Bu)]$_2$, **2** (Scheme 2 reaction A). Crystals of **2**, suitable for single X-ray crystallographic analysis, were grown from Et$_2$O at −20 °C. The structure is shown in Fig. 1, together with selected bond lengths and angles, and

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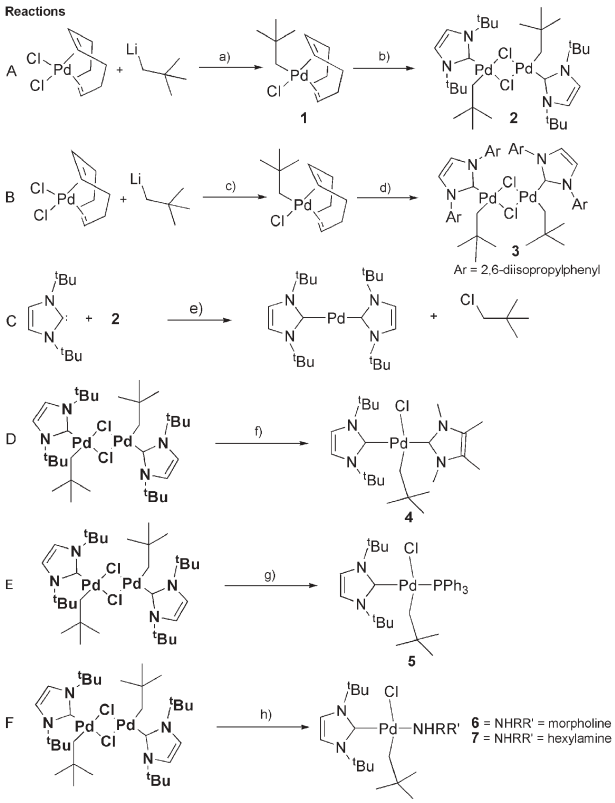
† Electronic supplementary information (ESI) available: Complete crystallographic details for **2**, **3** and **6**, experimental procedures and full characterising data for all new compounds. See DOI: 10.1039/b700671c



Scheme 2 Synthesis and reactivity of dimers **1** and **2** (a) Et_2O; −75 °C (b) I^{t}Bu; rt; Et_2O (c) Et_2O; −75 °C (d) IPr; toluene; rt (e) C_6D_6; rt (f) ITMe; toluene; rt (g) PPh_3; toluene; rt (h) morpholine or hexylamine; toluene; rt.

confirms the expected square planar geometry around the metal centres.

Intriguingly, in the 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) analogue of **2** (*cis*-[(neopentyl)Pd(Cl)(IPr)]$_2$, **3** (Scheme 2, reaction B), the neopentyl substituents no longer adopt the *trans* geometry in the solid state but prefer the *cis* orientation as confirmed by X-ray crystallography (Fig. 2). ^{1}H

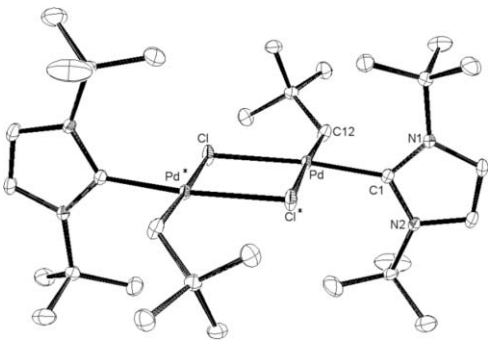


Fig. 1 Molecular structure of **2** (thermal ellipsoids at 30%). * indicates atoms at an equivalent position (1 − *x*, 1 − *y*, 1 − *z*), and that the compound lies about an inversion centre. Selected bond distances (Å) and angles (°): Pd–Cl 2.3975(7), Pd–Cl* 2.5252(7); Pd–C(12) 2.075(3), Pd–C(1) 1.980(3), C(1)–N(1) 1.364(4), C(1)–N(2) 1.371(3). C(1)–Pd–C(12) 86.14(11), C(1)–Pd–Cl 172.76(8), C(12)–Pd–Cl 100.36(8), C(1)–Pd–Cl* 89.64(8), C(12)–Pd–Cl 175.28(9), Cl–Pd–Cl* 83.98(2), Pd–Cl–Pd* 96.02(2), N(1)–C(1)–N(2) 105.0(2).‡[1]

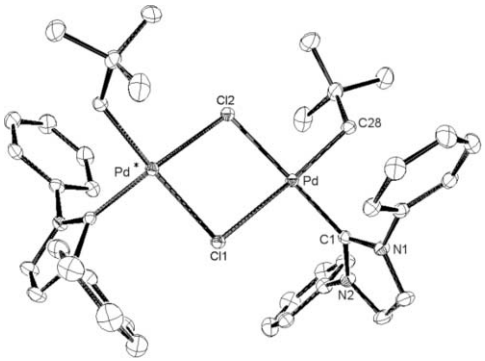


Fig. 2 Molecular structure of **3**. (thermal ellipsoids at 30%). * indicates that these atoms are at an equivalent position (−*x*, *y*, ½ − *z*). The compound has crystallographically imposed twofold symmetry, with the two chlorine atoms on the twofold axis. Selected bond distances (Å) and angles (°) (^{i}Pr groups and H omitted for clarity): Pd–C(1) 1.977(4), Pd–C(28) 2.053(4), Pd–Cl(2) 2.3932(9), Pd–Cl(1) 2.4887(9), N(1)–C(1) 1.369(4), N(1)–C(2) 1.383(5), N(2)–C(1) 1.373(5). C(1)–Pd–C(28) 89.81(14), C(1)–Pd–Cl(2) 168.82(10), C(28)–Pd–Cl(2) 94.03(11), C(1)–Pd–Cl(1) 93.65(10), C(28)–Pd–Cl(1) 176.49(10), Cl(2)–Pd–Cl(1) 82.46(3), Pd–Cl(1)–Pd* 94.71(4), Pd–Cl(2)–Pd* 100.37(5), N(1)–C(1)–N(2) 103.2(3).§[1]

NMR studies at 85 °C revealed that **3**, in solution, undergoes a fast *cis–trans* isomerisation process, which does not occur with **2**. Furthermore, at low temperature (−10 °C) the C–H of the isopropyl groups in **3** separate into two distinct multiplets, while the CH_3 split into four doublets, indicative of either a retardation of the *cis–trans* isomerisation or the cessation of the carbene rotation around the Pd–$C_{carbene}$ bond. Overall, this implies that IPr imposes less steric constraints than I^{t}Bu, which is in contrast to the widely accepted belief that IPr is bulkier than I^{t}Bu. However, a DFT study by Cavallo *et al.* gives credence to these findings.[14] In fact, Cavallo *et al.* quantified the steric factors of the NHC ligands by examining the volume of a sphere centred on the metal, covered by overlap with atoms to various NHC ligands, measured as $\%V_{Bur}$ (buried volume). The volume of this sphere represents the space around the metal atom that must be shared by the different ligands upon coordination. The bulkier the ligand, the larger the amount of that sphere will be occupied, and the greater the $\%V_{Bur}$. In Cavallo *et al.*'s study the $\%V_{Bur}$ occupied by [(IPr)Pd(allyl)Cl] was found to be smaller than [(I^{t}Bu)Pd(allyl)Cl].[14]

Further addition of 1,3-bis(*tert*-butyl)imidazol-2-ylidene (I^{t}Bu) to **2**, surprisingly led to reductive elimination of neopentyl chloride and formation of Pd(I^{t}Bu)$_2$ (Scheme 2, reaction C), and similarly reaction of **3** with IPr affords Pd(IPr)$_2$. However, through judicious choice of ligand, the monomeric heteroleptic compounds [(neopentyl)Pd(I^{t}Bu)(ITMe)(Cl)], **4**, and [(neopentyl)Pd(I^{t}Bu)(PPh_3)(Cl)], **5** were successfully obtained by addition of two equivalents of 1,3,4,5-tetramethylimidazol-2-ylidene (ITMe) or two equivalents of PPh_3 to **3**, respectively (Scheme 2, reactions D and E). The formation of **4** and **5** further demonstrates that the dimer **2** is readily cleaved, yielding monomeric species in the presence of ligands with smaller cone angles/$\%V_{Bur}$, *e.g.* PPh_3 ($\%V_{Bur}$ = 22%) than either I^{t}Bu ($\%V_{Bur}$ = 37%) or IPr ($\%V_{Bur}$ = 29%).[14] With this in mind, it appeared reasonable that the transamination products could form stable intermediates and thus be isolated.

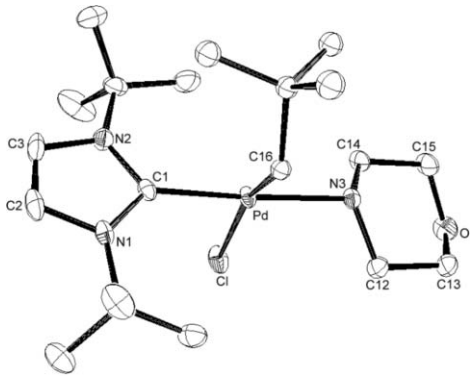


Fig. 3 Molecular structure of **6** (thermal ellipsoids at 30%). The neopentyl group is unequally disordered over two sites (0.757/0.243) and only the major one is shown. Selected bond distances (Å) and angles (°): Pd–C(1) 1.988(5), Pd–C(16) 2.072(16), Pd–C(16) 2.109(18), Pd–N(3) 2.126(4), Pd–Cl 2.4821(13), N(1)–C(1) 1.373(6), N(1)–C(2) 1.393(7). C(1)–Pd–C(16) 90.0(5), C(1)–Pd–N(3) 176.70(18), C(16)–Pd–N(3) 87.6(9), C(1)–Pd–Cl 90.03(14), C(16)–Pd–Cl 162.41(18), N(3)–Pd–Cl 91.45(11), C(1)–N(1)–C(2) 109.8(4), C(3)–N(2)–C(1) 110.0(5), N(1)–C(1)–N(2) 104.2(4), N(1)–C(1)–Pd 128.7(4), C(3)–C(2)–N(1) 107.6(5), C(2)–C(3)–N(2) 108.3(5).¶

The transamination products, [(neopentyl)Pd(I^{t}Bu)(morpholine)Cl], **6**, and [(neopentyl)Pd(I^{t}Bu)(hexylamine)Cl], **7**, were successfully isolated by addition of hexylamine or morpholine to **2**, in toluene, at room temperature (Scheme 2, reaction F). These are the first examples of transamination Pd–NHC complexes derived from an alkylpalladium NHC complex. Crystals of **6**, suitable for X-ray analysis were grown from toluene at ambient temperature revealing *cis* geometry between the neopentyl and morpholine groups (Fig. 3), ideal for reductive elimination. Rather surprisingly, subsequent attempted deprotonation of the coordinated amines in either **6** or **7** by a variety of bases (KO^{t}Bu, NaOCEt$_3$, LHMDS, and NaH) failed to yield either the palladium amide complex or any alkylamine product (in the absence of Pd the previously described bases are not capable of deprotonating the free amine). Instead morpholine is liberated, with concurrent formation of neopentane, the CH-activated complex (*vide supra*) and Pd(I^{t}Bu)$_2$. These findings raise interesting questions as to why reductive elimination does not occur in the presence of base. One possibility is that the electron donating effect of the alkyl substituent, combined with the strong σ-donation of I^{t}Bu, must increase the electron density on the metal centre sufficiently to require only a weak interaction with the amine lone pair. It may therefore be that the pK_a of the –NH is not significantly lowered to allow for deprotonation by the standard bases used in aryl–amination cross-coupling reactions.

In summary, a range of novel alkyl–Pd–NHC complexes have been described, including the surprisingly stable transamination products **6** and **7**. These studies have revealed significant steric sensitivity surrounding the Pd–NHC centre. It has become apparent that relatively minor variations in steric bulk lead to either success or failure of the synthesis of the desired complex, an important consideration when attempting to translate these mechanistic and structural studies to catalytic applications. These results further suggest that alkyl–amine cross-coupling reactions may not only be complicated by β-hydride elimination, but also by the formation of a surprisingly stable transamination product.

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Notes and references

‡ Selected crystal data for **2**: empirical formula = $C_{32}H_{62}Cl_2N_4Pd_2$, M_r = 786.56, T = 173(2) K, crystal system = monoclinic, space group = $P2_1/c$ (No. 14), unit cell dimensions a = 11.1540(3), b = 9.7982(2), c = 17.5999(4) Å, V = 1833.85(7) Å^3, Z = 2, μ = 1.15 mm^{-1}, reflections collected = 26967, independent reflections = 3596 [R_{int} = 0.066], final R indices [$I > 2\sigma(I)$] R_1 = 0.031, wR_2 = 0.061, R indices (all data) R_1 = 0.041, wR_2 = 0.064. CCDC 633696. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b700671c

§ Selected crystal data for **3**·2(Et$_2$O), empirical formula = $C_{64}H_{94}Cl_2N_4Pd_2{\cdot}2(C_4H_{10}O)$, M_r = 1351.37, crystal system = monoclinic, space group = $C2/c$ (No. 15), unit cell dimensions a = 22.4708(6), b = 17.9840(7), c = 19.0590(5) Å, V = 7392.9(4) Å^3, Z = 4, μ = 0.60 mm^{-1}, reflections collected = 24839, independent reflections = 7207 [R_{int} = 0.070], final R indices [$I > 2\sigma(I)$] R_1 = 0.043, wR_2 = 0.104, R indices (all data) R_1 = 0.068, wR_2 = 0.124. CCDC 633697.

¶ Selected crystal data for **6**: empirical formula = $C_{20}H_{40}ClN_3OPd$, M_r = 480.40, T = 173(2) K, crystal system = monoclinic, space group = $P2_1/n$ (No. 14), unit cell dimensions a = 9.6642(3), b = 23.1895(5), c = 10.4673(3) Å, V = 2335.69(11) Å^3, Z = 4, μ = 0.92 mm^{-1}, reflections collected = 21525, independent reflections = 4570 [R_{int} = 0.073], final R indices [$I > 2\sigma(I)$] R_1 = 0.046, wR_2 = 0.108, R indices (all data) R_1 = 0.077, wR_2 = 0.129. CCDC 633698.

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