

Mild and rational synthesis of palladium complexes comprising C(4)-bound *N*-heterocyclic carbenes

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Oxidative addition of pyridyl-functionalised 4-iodoimidazolium salts to palladium(0) gives catalytically active complexes in which the *N*-heterocyclic carbene is bound to the palladium(II) centre in a non-classical bonding mode *via* C(4).

Very rapidly, *N*-heterocyclic carbenes (NHCs) have evolved as a powerful class of ligands for the development of new and highly efficient catalytic systems.¹ Transition metal complexes of carbenes have been prepared by various methods, including transmetallation, typically from silver carbenes,² and oxidative addition to low-valent metal precursors.³ Probably the most widely applied method consists of base-mediated metallation of imidazolium salts, assuming that proton abstraction and subsequent metallation occurs at the most acidic position, *i.e.* at C(2) (see Chart 1 below).

Recently, it has been shown that under specific conditions, metallation takes place at the imidazolium C(4) or C(5) position rather than at C(2), thus providing complexes containing so-called abnormally or non-classically bound carbenes.^{4–6} The relevance of this bonding mode is probably best appreciated by the fact that non-classical carbenes are exceptionally basic ligands with a higher donor power than most of the known neutral ligands including basic PrBu_3 and classically bound NHCs.⁵ For example, palladium complexes comprising a non-classical carbene ligand showed a catalytic activity in Suzuki cross-coupling reactions that surpasses that of classical analogs.⁶ Despite these promising initial results, reports on non-classical carbene complexes have remained remarkably scarce.⁷ Perhaps the largest constraint arises from the restricted synthetic accessibility of such complexes, since the acidity of H(4) is considerably lower than that of H(2). Moreover, the free carbene is relatively unstable and hence a route involving sequential deprotonation and metallation appears less attractive. Thus far, synthetic strategies that promote C(4)-bonding of imidazolium-derived heterocyclic carbenes have concentrated almost exclusively⁴ on the deactivation of the imidazolium C(2) carbon through substitution of the acidic proton by an inert CH_3

or aryl group. Generally, this efficiently suppresses metal coordination *via* C(2) and allows a concerted deprotonation–metallation protocol to be applied to activate the C(4) position. However, several drawbacks limit the use of this approach. For example, transmetallation *via* Ag-carbenes is restricted since Ag_2O induces C–C(2) bond activation of certain 2-alkylimidazolium salts and yields, after transmetallation, classically bound carbene complexes.⁸

Here, we report on an oxidative addition protocol as a rational route to non-classically bound carbene complexes. Thus, metallation is directed to the C(4) position by an activating iodide substituent rather than a deactivating alkyl or aryl group at C(2). At the same time, chelating donors are incorporated in the ligand framework in order to support the metal–carbon bond once formed.⁹ While oxidative addition of zero-valent Pd and Pt precursors to imidazolium C(4)–H bonds has been described for specific cases,¹⁰ the C–I oxidative addition applied here is expected to provide a more general access to non-classical carbene bonding to a variety of low-valent transition metals. In particular, this method does not require protection of the C(2) position prior to metallation.

The potentially *C,N*-bidentate coordinating ligand precursor **1** comprising an imidazolium C(4)–I bond has been prepared by iodination and subsequent *N*-alkylation of imidazol following established procedures.¹¹ Oxidative addition of $[\text{Pd}(\text{dba})_2]$ as the zero-valent metal precursor in CH_2Cl_2 occurs smoothly at room temperature, yielding palladium(II) complex **2** comprising a C(4)-bound heterocyclic carbene (Scheme 1).[†] This compound is soluble in polar solvents such as MeCN, MeNO_2 , and MeOH, and sparingly in CH_2Cl_2 . Palladation at C(4) induces a downfield shift of the imidazolium H(5) NMR signal from 8.20 to 8.97 ppm. The low-field singlet at δ_{H} 9.25, attributed to the proton attached to the imidazolium C(2), indicates that this position remained unaffected. Furthermore, the displacements observed for the pyridine proton signals upon metallation suggest coordination of the pyridine nitrogen and chelate formation. No metal complexes have been detected that may originate from C(2)–H bond oxidative addition.¹²

Unambiguous structural evidence for carbene bonding *via* C(4) has been obtained through X-ray diffraction analysis on single

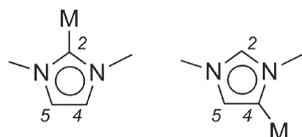
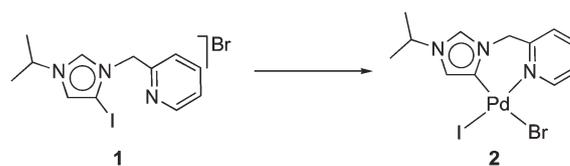


Chart 1



Scheme 1 Oxidative addition of 4-iodoimidazolium salt **1**. Reagents and conditions: $[\text{Pd}(\text{dba})_2]$, CH_2Cl_2 , 0 °C to RT, 12 h.

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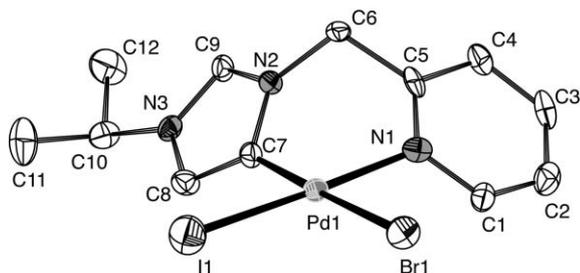
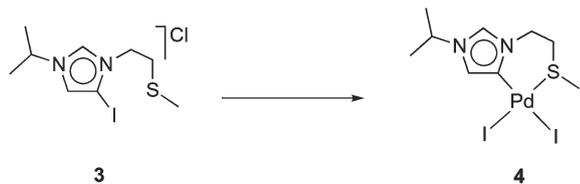


Fig. 1 ORTEP representation of **2** (30% probability level, hydrogen atoms and co-crystallised solvent omitted for clarity). Pertinent bond lengths (Å) and angles (°): Pd1–C7 1.961(7), Pd1–N1 2.098(6), Pd1–I1 2.5179(9), Pd1–Br1 2.5143(10), C7–C8 1.393(10), C7–N2 1.396(9); C7–Pd1–N1 86.7(3), C7–Pd1–I1 89.2(2), C7–Pd1–Br1 177.9(2), N1–Pd1–I1 175.9(2), N1–Pd1–Br1 91.2(2), I1–Pd1–Br1 92.93(3).

crystals of **2**.[‡] The molecular structure (Fig. 1) shows a palladium centre in a distorted square-planar environment (C–Pd–N 86.7(3)°), defined by the C,N-bidentate coordinating picolylcarbene and two halides. The Pd–C bond length is 1.961(7) Å and thus identical within standard deviation to related complexes featuring classically bound picolylcarbene ligands.¹³ This is remarkable since C(4)-bound NHC ligands are considered as better σ donors than their C(2)-bound analogs⁵ and hence, a shorter Pd–C bond distance may be expected. This is not evidenced by the data provided, perhaps due to the fact that the Pd–C bond length is also affected by the chelate bite angle.¹⁴ The heterocyclic C7–C8 bond (1.393(10) Å) is markedly longer than in classically C(2)-bound carbenes (typically 1.33 Å) and indicates a fully π -conjugated carbene ligand. A stronger *trans* influence of non-classical carbenes may be deduced from the Pd–Br bond of 2.5143(10) Å, which is some 0.03 Å longer than in the corresponding C(2)-bound counterparts. The imidazolylidene and pyridine heterocycles are twisted out of the metal coordination plane by roughly 40° each. Notably, the *cis* product represents both the kinetic and the thermodynamic product of the oxidative addition, since the two ligands exerting the highest *trans* influence, *viz.* carbene and iodide, are in a mutual *cis* arrangement.¹⁵

Other iodinated imidazolium salts react similarly to give C(4)-bound carbene complexes. For example, the thioether-functionalised imidazolium salt **3** yields the palladium(II) complex **4** according to a protocol related to that used for the preparation of **2** (Scheme 2). While this suggests that different halide-functionalised imidazolium salts can be metallated at C(4), it is interesting to note that the most widely applied C(2) protection strategy has not been successful thus far for the preparation of related non-classically bound carbene complexes. The reaction of [Pd(OAc)₂] with either **5** or **6** (see Chart 2), both comprising a



Scheme 2 Formation of C,S-bidentate chelating C(4)-bound carbene complexes. Reagents and conditions: [Pd(dba)₂], DMSO, RT, 12 h, then excess NaI, acetone.

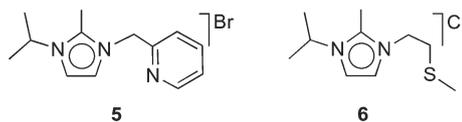


Chart 2

CH₃-substituent to inhibit C(2) metallation, failed to give the anticipated palladium complexes. Irrespective of the applied reaction conditions, the unreacted ligand precursor was consistently recovered as the main fraction. These results may illustrate that oxidative addition represents a method that is complementary to base-mediated metallation of C(2)-protected imidazolium salts. Such an approach may be particularly useful for base-sensitive ligand precursors which do not allow for carbene formation with strong bases.⁷

The catalytic activity of the non-classical carbene palladium complex **2** and **7** was probed in the Heck olefination of aryl bromides with styrene (Table 1).[§] At low temperature, conversion of activated aryl bromides is very low and temperatures as high as 140 °C are required to achieve full conversion (entries 1–3). Less active aryl bromides such as bromotoluene or -anisole were converted at considerably lower rates (entries 4,5). This catalyst performance compares well with the catalytic activity typically observed for classically bound carbene complexes,¹⁶ and does not indicate a significant influence of the stronger donor properties of C(4)-bound carbene ligands. Due to the forcing reaction conditions needed for catalyst activation, we could not exclude *a priori* the formation of colloidal Pd⁰ as the catalytically active species.¹⁷ A set of experiments were therefore carried out aiming at elucidating the nature and stability of the catalyst. A first run (entry 6) has been performed in the presence of metallic mercury, which is known to effectively suppress heterogeneous but not homogeneous catalysis.¹⁸ When a preheated solution containing catalyst **2**, a large excess of mercury (*ca.* 1500×) and the aryl bromide was treated after 1 h with styrene, a substantial drop of conversion was noted (entries 2, 6). The successful inhibition of catalyst turnovers suggests that the metal–carbene bond—albeit considered to be strong⁵—is cleaved under the applied reaction conditions and that the observed catalytic activity originates predominantly from colloidal Pd nanoparticles.¹⁹ Alternative deactivation mechanisms such as the base-promoted formation of catalytically silent bis-chelate complexes²⁰ should not be affected by mercury and seem to play a minor role. Furthermore, the catalyst system is insensitive to small quantities of tetrahydrothiophene (THT, entry 7) and the conversion remains high. Only at

Table 1 Heck olefination of arylbromides catalysed by **2**

Entry	R	Conditions	Conversion	TON
1	NO ₂	80 °C	9%	18
2	NO ₂	140 °C	94%	188
3	CHO	140 °C	95%	190
4	CH ₃	140 °C	9%	18
5	OCH ₃	140 °C	5%	10
6	NO ₂	140 °C, excess Hg	34%	68
7	NO ₂	140 °C, 0.1 mol% THT	94%	188

very high THT concentrations (100 × excess vs Pd) substrate conversion decreases to 68%. This indicates that the catalyst system is not significantly poisoned by sulfur-containing impurities.

In conclusion, oxidative addition of iodo-functionalised imidazolium salts to zero-valent palladium precursors provides a mild and rational access to N-heterocyclic carbene complexes that are non-classically bound *via* C(4). In some cases, this methodology is complementary to direct metallation and may be useful for ligand systems that are thermally unstable. The applied synthetic protocol allows the installation of various chelating donor groups *via* regioselective *N*-functionalisation in order to tune the properties of the coordinated metal centre. The catalytic activity of the corresponding C(4)-bound carbene palladium complex **2** is comparable to classical C(2)-bound carbene complexes and presumably originates from Pd–carbene bond breaking and colloidal Pd⁰ formation. Currently, we are exploiting the scope and limitations of this oxidative addition protocol for the synthesis of various non-classical carbene complexes with other late transition metals.

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Notes and references

† Synthesis of **2**: Solid [Pd(dba)₂] (141 mg, 0.25 mmol) was added to a suspension of imidazolium salt **1** (100 mg, 0.25 mmol) in dry CH₂Cl₂ at 0 °C. The mixture was allowed to warm to room temperature and was filtered after 24 h through celite. The filter residue was extracted with copious amounts of MeNO₂ (8 mL total) and precipitated with Et₂O. This gave **2** (72 mg, 54%) as a yellow powder. Crystals suitable for X-ray diffraction were grown by slow DMSO–Et₂O liquid–liquid diffusion.

Anal. found (calcd) for C₁₂H₁₅BrIN₃Pd (514.50): C 28.12 (28.01), H 2.43 (2.94), N 8.11 (8.17); ¹H NMR (500 MHz, DMSO-*d*₆, 298 K): δ 9.25 (br s, 1H, H²_{imi}), 8.97 (s, 1H, H⁵_{imi}), 8.14 (br s, 1H, H⁶_{py}), 7.79 (m, 1H, H_{py}), 7.61 (m, 1H, H_{py}), 7.15 (m, 1H, H_{py}), 5.58 (s, 2H, NCH₂), 4.51 (sept, ³J_{HH} = 6.4 Hz, 1H, CHMe₂), 1.39 (d, ³J_{HH} = 6.4 Hz, 6H, CCH₃); ¹³C{¹H} NMR (125 MHz, DMSO-*d*₆, 298 K): δ 154 (br, C_{py}), 151.86 (C_{py}), 139.96 (C_{py}), 132.16 (C²_{imi}), 124.98 (C_{py}), 124.69 (C_{py}), 124 (br, C_{imi}), 54.30 (NCH₂), 51.16 (CHMe₂), 22.24 (CCH₃), C–Pd not observed.

‡ Crystal data for **2**: Empirical formula [C₁₂H₁₅BrIN₃Pd × C₂H₆OS], *M* 592.61, orange block, monoclinic, space group *P*2₁/*n* (no. 14), *a* = 10.6134(9), *b* = 14.8459(16), *c* = 12.0432(10) Å, β = 91.267(10)°, *V* = 1897.1(3) Å³, *Z* = 4, *D*_c = 2.075 g cm⁻³, MoKα radiation, λ = 0.71073 Å, *T* = 173(2) K, 11103 reflections measured, 3656 unique (*R*_{int} = 0.0573). Final *GoF* = 0.912, *R*₁ = 0.0418, *wR*₂ = 0.1133, *R* indices based on 2369 reflections with *I* > 2σ(*I*) (refinement on *F*²), 204 parameters, 0 restraints. *Lp* and absorption corrections applied, μ = 4.826 mm⁻¹. CCDC 615954. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b611212a.

§ General Heck Procedure: Unless stated otherwise, aryl halide (1 mmol), NaOAc (1.1 mmol), styrene (1.5 mmol), diethylene glycol dibutyl ether (0.25 mmol, ¹H NMR standard) and eventual additives were suspended in dimethylacetamide (DMA, 4.5 mL). The mixture was preheated to 140 °C for 10 min, then the catalyst solution (10 mM in DMA, 0.5 mL, 5 μmol corresponding to 0.5 mol%) was added. At the times indicated, a sample was withdrawn and extracted with hexane and H₂O. The organic layer was

dried (Na₂SO₄), evaporated to dryness, and analysed by ¹H NMR spectroscopy.

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