Expanding the family of mesoionic complexes: donor properties and catalytic impact of palladated isoxazolylidenes†

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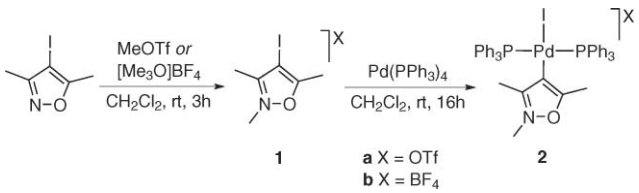
Abnormal isoxazolylidene complexes, a new subclass of mesoionic complexes containing an isoxazolium-derived carbene type ligand, have been synthesised *via* oxidative addition and compared to structurally related mesoionic complexes by using ^{31}P NMR spectroscopy as a convenient probe for their donor ability and in catalytic cross-coupling reactions.

The discovery and isolation of the first stable carbene by Bertrand two decades ago,[1] and the subsequent extension of this work to *N*-heterocyclic carbenes (NHCs) by Arduengo[2] triggered the exploitation of these species as versatile ligands for transition metal complexes. Pioneering work by Herrmann, Grubbs, and Nolan illustrate the outstanding impact of NHCs on many homogeneous catalysts, often outperforming more ubiquitous phosphine ligands.[3] Improved catalyst stability and reactivity is generally assigned to the more covalent and hence stronger bonding of NHCs to metal centres, and to the higher donor ability of carbenes.[4] To date a great diversity of NHCs has been developed, ranging from the normal imidazolylidenes[5] to expanded-ring NHCs[6] and to carbenes with reduced heteroatom-stabilisation like cyclic alkyl amino carbenes[7] and abnormal NHCs.[8]

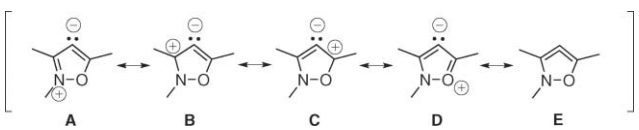
The absence of heteroatoms adjacent to the carbene carbon reduces the stability of the free ligand. Simultaneously, the inductive effects of the heteroatoms are less pronounced, which enhances the donor ability of the ligand considerably. As a consequence, carbenes with low heteroatom stabilisation increase the electron density at the coordinated metal centre substantially, thus evoking new reactivity patterns.[9] Here we report on isoxazolylidenes as a new member of the family of abnormal remote NHCs,[8] *i.e.*, NHCs with no neutral carbene resonance structure and with no heteroatom adjacent to the carbene carbon.[10] The precursor isoxazolium salts are readily accessible *via* versatile synthetic protocols including [2 + 3] cycloadditions,[11] and they constitute—according to the evaluations shown here and in line with predictions[12] based on computational analysis—a class of ligands that are among the strongest neutral donors known to date.

Even though the free carbene route has been successfully applied for the synthesis of specific abnormal and remote carbene complexes,[13] we have concentrated on an oxidative addition protocol,[14] which avoids the manipulation of sensitive intermediates. Thus, quaternisation of commercially available 4-iodo-3,5-dimethylisoxazole with MeOTf or $[Me_3O]BF_4$ gave the isoxazolium salts **1** in excellent yields (Scheme 1). Subsequent oxidative addition to $Pd(PPh_3)_4$ afforded the carbene complexes **2** as air-stable, off-white solids.‡ Successful metallation was indicated by the pertinent $^{13}C\{^1H\}$ NMR signal of the palladium(II)-bound carbon atom, which appeared as a triplet at 168.0 ppm ($^2J_{PC}$ = 3.9 Hz). The singlet in the ^{31}P NMR spectrum (δ_P 21.3) is in agreement with a mutual *trans* conformation of the two phosphine ligands in **2**.



Scheme 1 Synthetic pathway for the preparation of palladium(II) isoxazolylidene complexes **2**.

A single crystal X-ray diffraction analysis of **2a** confirmed the global connectivity pattern. However, pronounced disorder in the OTf^- anion precluded the refinement to converge. Better structural data were obtained upon exchanging the counteranion to BF_4^-. Suitable crystals of **2b** were grown by slow diffusion of hexanes into a saturated CH_2Cl_2solution. The molecular structure (Fig. 1) reveals the expected square planar geometry of the complex, with the two phosphines situated in mutual *trans* position. Interestingly, the geometry around nitrogen is indicative for sp^2 hybridisation, as no pyramidalisation was observed. This fact combined with the short C–N bond length (C3–N1 1.27(3) Å) suggests that the resonance structure **A** contributes more significantly to the ground state of the remote isoxazolylidene in complex **2** than structures **B–E** (Scheme 2).



Scheme 2 Most relevant resonance structures contributing to 3,5-dimethylisoxazol-4-ylidene.

The donor strength of the isoxazolylidene in **2** and its impact on palladium mediated-catalysis was compared to different types of isostructural NHC ligands. In an attempt to minimise stereoelectronic effects, complexes $[Pd(NHC)(PPh_3)_2I]OTf$ **3–7** were synthesised (Fig. 2), all comprising NHCs with CH_3 groups *ortho* to the metal-bound carbon. As a consequence, the steric

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† Electronic supplementary information (ESI) available: Experimental and analytical details. CCDC reference number 757620. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0dt00027b

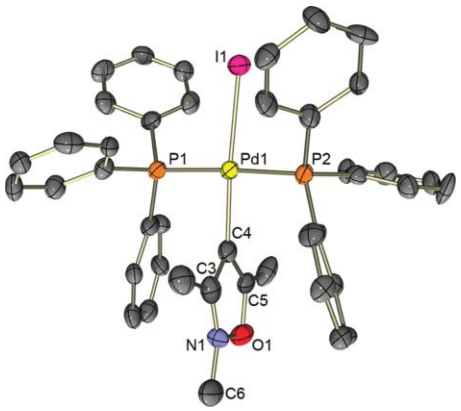


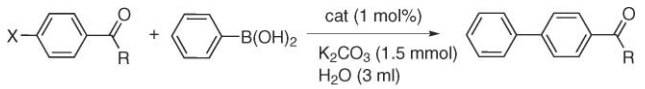
Fig. 1 Solid state molecular structure of **2b** (30% probability, hydrogen atoms, BF_4^- counterion and second independent molecule omitted for clarity). Selected bond lengths (Å) and angles (°): I1–Pd1 2.6466(18), Pd1–C4 2.037(19), Pd1–P1 2.330(5), Pd1–P2 2.339(5), O1–C5 1.34(2), O1–N1 1.40(2), N1–C3 1.27(3), C3–C4 1.41(3), C4–C5 1.37(3); I1–Pd1–P1 89.50(13), I1–Pd1–P2 93.25(13), I1–Pd1–C4 176.1(6), P1–Pd1–P2 176.63(19), P1–Pd1–C4 88.1(5), P2–Pd1–C4 89.3(5), O1–N1–C6 113.7(19), C3–N1–C6 136(2), O1–N1–C3 109.6(16), C3–C4–C5 101.8(18).

impact about the carbene core should be essentially identical in all complexes **2–7** and differences may therefore be attributed predominantly to electronic modulations.

Remarkably, the ^{31}P NMR shifts of complexes **2–7** show a clear trend that reflects the expected ligand basicity: stronger electron donors result in a lower frequency of δ_P (Fig. 2). This behavior is independent of the solvent (DMSO-d_6 or CD_2Cl_2) and may be rationalised by considering the paramagnetic contribution σ_{para} to the isotropic shielding constant. Recent theoretical calculations predict that more basic carbene ligands induce a smaller HOMO–LUMO gap,[15] which increases the population of the paramagnetic triplet state and hence σ_{para}. Consequently, more basic carbene ligands effect a shift of the δ_P values to lower field.

According to this ^{31}P basicity scale, isoxazol-4-ylidene are stronger donors than the normal carbene, pyridin-2-ylidene, and even abnormal carbene (*cf.* δ_P of **4–7**), but not as strong as the pyrazol-4-ylidene reported previously (*cf.* **3**).[14b] This difference parallels the weaker donor properties of 2-oxazolylidenes as compared to normal imidazolylidenes[16] and corroborates the higher inductive effect exerted by oxygen than by nitrogen. It is worth noting that the ^{31}P NMR scale is consistent with recently computed Tolman electronic parameters for this class of ligands,[12] and also with a scale based on ^{13}C NMR chemical shifts of a *trans* located NHC.[17] While δ_C measurement may provide a more direct probe, perhaps with a somewhat better resolution, δ_P analysis is generally rapid and highly convenient due to the high natural abundance and sensitivity of the ^{31}P nucleus. Due to these advantages, ^{31}P NMR probing may provide a general method for determining the relative donor strength of a variety of carbene subclasses, provided the metal–carbon core is sterically comparable. In addition, this method is complementary to the frequently used ν_{CO} method based on IR stretch vibrations of carbonyl ligands.[18] Least square regression of the obtained data gives a good linear fit which allows for an estimate of the TEP based on ^{31}P NMR chemical shifts according to the equation TEP = 2125–4.01 × δ_P.

Table 1 Palladium-catalyzed Suzuki–Miyaura cross-coupling



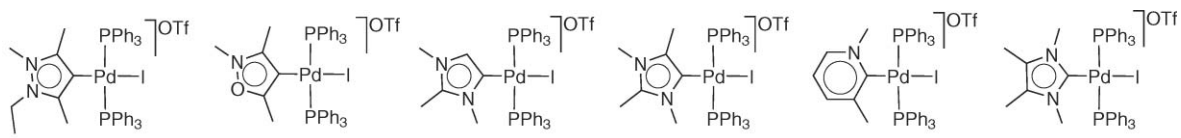
1.0 mmol 1.2 mmol

X = Cl, Br
R = CHO, C(O)CH$_3$

Entry	Catalyst	Substrate	T/°C	t/h	Conv.
1[a]	**2a**	4-Bromobenzaldehyde	20	19	89%
2[a]	**3**	4-Bromobenzaldehyde	20	19	80%
3[a]	**4**	4-Bromobenzaldehyde	20	19	79%
4[a]	**5**	4-Bromobenzaldehyde	20	19	84%
5[a]	**6**	4-Bromobenzaldehyde	20	19	30%
6[a]	**7**	4-Bromobenzaldehyde	20	19	1%
7[b]	**2a**	4-Chloroacetophenone	140	2	85%
8[b]	**3**	4-Chloroacetophenone	140	2	90%
9[b]	**4**	4-Chloroacetophenone	140	2	80%
10[b]	**5**	4-Chloroacetophenone	140	2	67%
11[b]	**6**	4-Chloroacetophenone	140	2	84%
12[b]	**7**	4-Chloroacetophenone	140	2	79%
13[b]	**2a**	4-Chlorotoluene	140	2	< 10%

[a] General conditions: ArBr (1.0 mmol), $PhB(OH)_2$ (1.2 mmol), catalyst (1 mol%), K_2CO_3 (1.5 mmol), H_2O (3 mL). [b] General conditions: ArCl (1.0 mmol), $PhB(OH)_2$ (1.2 mmol), catalyst (1 mol%), K_2CO_3 (1.5 mmol), Bu_4NCl (1.5 mmol) DMA (3 mL); all conversions determined by ^{1}H NMR spectroscopy, average of at least two runs.

The catalytic impact of the electronically different carbene ligands was tested in palladium-catalysed Suzuki–Miyaura coupling reactions using aryl bromides (Table 1). Under moderate conditions, the abnormal carbene complexes (**2a–5**) show higher activity than the (abnormal) pyridylidene complex **6** or the classical carbene complex **7** (entries 1–6). This enhanced catalytic performance may originate from the enhanced basicity of the ligand, which is expected to facilitate the rate-limiting oxidative addition of the aryl halide to the palladium centre.



	3	**2a**	**4**	**5**	**6**	**7**
δ_P	22.56	21.28	20.66	20.48	18.96	18.76
TEP (calcd)	2034.6	2041.9	2043.3	2039.9	2048.2	2065.3

Fig. 2 Measured ^{31}P NMR chemical shifts for $[Pd(NHC)(PPh_3)_2I][CF_3SO_3]$ complexes (CD_2Cl_2) and calculated TEP values (from ref. 12; slightly different substituents in remote positions were used in calculations for the pyrazol-4-ylidene in **3** and for the imidazol-4-ylidne in **5**).

Activated aryl chlorides were converted only with limited success under similar conditions using 4-chloroacetophenone as substrate, yet moderate 22–37% yields were obtained at 80 °C and in the presence 1.5 eq. Bu_4NBr as additive. No clear correlation between the donor ability and the catalytic activity was evident, though palladium black was formed in these runs and the catalytic activity ceased after 2 h. Substantial improvements were achieved upon changing the solvent system from H_2O to *N*,*N*-dimethylacetamide (DMA). In the presence of Bu_4NCl as additive and at elevated temperatures, activated chlorides were arylated within three hours. In order to establish the impact of the carbene, reactions were stopped before reaching full conversion (Table 1, entries 7–12). Interestingly, the most basic carbene-type ligands show the best performance (entries 7, 8), though the correlation between ligand basicity and catalytic activity is only modest. Non-activated aryl chlorides such as chlorotoluene were not fully converted even after prolonged reaction times (entry 13). Further ligand optimization, especially addressing the steric demand of NHCs for efficiently promoting oxidative addition reactions,[12,19] constitutes an obvious strategy for further enhancing the catalytic activity of the complexes and for transforming also more challenging substrates such as deactivated aryl chlorides.

In summary, we have developed a straightforward approach to palladium(II) complexes comprising novel mesoionic carbene-type ligands that are derived from isoxazolium salts. Evaluation of the donor ability of the 4-isoxazolylidene ligand using ^{31}P NMR as a probe situates this NHC at the more basic edge, thus enlarging the toolbox for the synthesis of new, highly electron-rich metal centres. As a first application, a protocol for the arylation of aryl chlorides has been developed, which is remarkably efficient, especially when considering the optimisation potential, for example through steric modification of the ligand scaffold. Besides introducing a convenient ligand basicity scale for a variety of NHC subclasses, these results may pave the way for the synthesis of more efficient homogeneous catalysts.

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Notes and references

‡ *Typical procedure*: solid $Pd(PPh_3)_4$ (144 mg, 0.125 mmol) and 4-iodo-1,3,5-trimethylisoxazolium triflate **1a** (50 mg, 0.125 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and stirred for 16 h at ambient temperature. After concentrating the pale orange solution to 3 mL, the product precipitated by addition of Et_2O (10 mL). The precipitate was redissolved into CH_2Cl_2 (3 mL) and precipitated with Et_2O (3×), and subsequently washed with Et_2O until the solution remained colourless. The residue was dried under vacuum, affording **2a** as an off-white solid (102 mg, 80%). ^1H NMR (360 MHz, CD_2Cl_2): δ 7.65–7.45 (m, 30H, H_{ar}), 3.60 (s, 3H, N–CH_3), 1.90, 1.86 (2 × s, 3H, C–CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2): δ 168.0 ($^2J_{PC}$ = 3.9 Hz, C–Pd), 160.9 ($^3J_{PC}$ = 1.9 Hz, C–Me), 134.7 ($^2J_{PC}$ = 6.2 Hz, C_{ar}), 131.3 (C_{ar}), 130.8 ($^1J_{PC}$ = 25.1, C_{ar}), 128.5 ($^3J_{PC}$ = 5.3, C_{ar}), 120.5 ($^1J_{FC}$ = 321.1 Hz, CF_3), 38.2 (N–CH_3), 14.3, 13.7 (2 × C–CH_3). ^{31}P NMR (202 MHz, CD_2Cl_2): δ 21.3 (PPh_3). Anal. Calcd for $C_{43}H_{39}F_3INO_4P_2PdS$ (1018.12): C, 50.73; H, 3.86; N, 1.38. Found: C, 50.91; H, 4.03; N, 1.48. *Crystal data for* **2b**: yellow plate, $C_{42}H_{41}BF_4INO_3P_2Pd$, M = 989.81, triclinic, a = 13.3917(9), b = 15.7897(10), c = 20.5894(15) Å, α = 92.386(6), β = 99.693(6), γ = 90.623(5)°, U = 4287.1(5) Å^3, T = 173(2) K, space group $P\bar{1}$, Z = 4, 18 577 measured reflections, 9996 unique (R_{int} = 0.0708), R_1 = 0.1155, wR_2 = 0.3298 for $I > 2\sigma(I)$.

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