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Expanding the family of mesoionic complexes: Donor properties and catalytic impact of palladated isoxazolyldenes †

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Abnormal isoxazolyldene 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 ³¹P 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 Arduengo² 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 imidazolyldenes⁵ to expanded-ring NHCs⁶ and to carbenes with reduced heteroatom-stabilisation like cyclic alkyl amino carbenes⁷ 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 isoxazolyldenes 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 predictions¹² 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 [Me₃O]BF₄ gave the isoxazolium salts **1** in excellent yields (Scheme 1). Subsequent oxidative addition to Pd(PPh₃)₄ afforded the carbene complexes **2** as air-stable, off-white

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

Fig. 1 Solid state molecular structure of **2b** (30% probability, hydrogen atoms, BF₄ 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).

solids. Successful metallation was indicated by the pertinent ¹³C{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 ³¹P NMR spectrum (δ_p 21.3) is in agreement with a mutual *trans* conformation of the two phosphine ligands in **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 BF₄⁻. Suitable crystals of **2b** were grown by slow diffusion of hexanes into a saturated CH₂Cl₂ solution. 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 sp² hybridisation, as no

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 $[\text{Pd}(\text{NHC})(\text{PPh}_3)_2][\text{CF}_3\text{SO}_3]$ 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-ylidene in **5**).

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 isoxazolydene 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 isoxazolydene 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 $[\text{Pd}(\text{NHC})(\text{PPh}_3)_2]\text{OTf}$ **3–7** were synthesised (Fig 2), all comprising NHCs with CH_3 groups *ortho* to the metal-bound carbon. As a consequence, the steric 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 ($\text{DMSO}-d_6$ 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, pyridine-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-oxazolyldenes as compared to normal imidazolyldenes¹⁶ 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

Table 1 Palladium-catalyzed Suzuki-Miyaura cross-coupling.

entry	catalyst	substrate	$T/^\circ\text{C}$	t/h	conv'n
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), $\text{PhB}(\text{OH})_2$ (1.2 mmol), catalyst (1 mol%), K_2CO_3 (1.5 mmol), H_2O (3 mL); ^b General conditions: ArCl (1.0 mmol), $\text{PhB}(\text{OH})_2$ (1.2 mmol), catalyst (1 mol%), K_2CO_3 (1.5 mmol), Bu_4NCl (1.5 mmol) DMA (3 mL); all conversions determined by ^1H NMR spectroscopy, average of at least two runs.

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 $\text{TEP} = 2125 - 4.01 \times \delta_p$.

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 (**2b–5**) show higher activity than the 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.

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 H₂O to *N,N*-dimethylacetamide (DMA). In the presence of Bu₄NCl 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-isoxazolyliene ligand using ³¹P 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, an efficient 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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‡ Typical procedure: Solid Pd(PPh₃)₄ (144 mg, 0.125 mmol) and 4-iodo-1,3,5-trimethylisoxazolium triflate **1a** (50 mg, 0.125 mmol) were dissolved in dry CH₂Cl₂ (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 Et₂O (10 mL). The precipitate was redissolved into CH₂Cl₂ (3 mL) and precipitated with Et₂O (3×), and subsequently washed with Et₂O 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, CD₂Cl₂): δ 7.65–7.45 (m, 30H, H_{ar}), 3.60 (s, 3H, N–CH₃), 1.90, 1.86 (2 × s, 3H, C–CH₃). ¹³C {¹H} NMR (100 MHz, CD₂Cl₂): 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, CF₃), 38.2 (N–CH₃), 14.3, 13.7 (2 × C–CH₃). ³¹P NMR (202 MHz, CD₂Cl₂): δ 21.3 (PPh₃). Anal. Calcd for C₄₃H₃₉F₃INO₄P₂PdS (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, C₄₂H₄₁BF₄INO₃P₂Pd, *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) Å, *U* = 4287.1(5) Å³, *T* = 173(2) K, space group P-1, *Z* = 4, 18577 measured reflections, 9996 unique (*R*_{int} = 0.0708), *R*₁ = 0.1155, *wR*₂ = 0.3298 for *I* > 2σ(*I*).

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Expanding the family of mesoionic complexes: Donor properties and catalytic impact of palladated isoxazolyldenes

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¹⁰ Isoxazol-4-ylidene is introduced as a new subclass of strongly donating NHC ligands with donor properties that are among the strongest known to date, an aspect that has been exploited by developing an efficient process for the palladium-catalysed arylation of aryl chlorides.