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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 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,† and the subsequent extension of this work to N-heterocyclic carbenes (NHCs) by Arduengo‡ 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.‡ 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. To date a great diversity of NHCs has been developed, ranging from the normal imidazolylidenes to expanded-ring NHCs and to carbenes with reduced heteroatom-stabilisation like cyclic alkyl amino carbenes and abnormal NHCs.⁸

The absence of heteroatoms adjacent to the carbene carbon reduces the donor ability of the 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. Here we report on isoxazolylidines as a new family of abnormal remote NHCs, i.e., NHCs with no neutral carbene resonance structure and with no heteroatom adjacent to the carbene carbon.⁸ The precursor isoxazolium salts are readily accessible via versatile synthetic protocols including [2+3] cycloadditions, and they constitute—according to the evaluations shown here and in line with predictions—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, we have concentrated on an oxidative addition protocol, which avoids the manipulation of sensitive intermediates. Thus, quaternisation of commercially available 4-iodo-3,5-dimethylisoxazole with MeOTf or [Me2O]BF4 gave the isoxazolium salts in excellent yields (Scheme 1). Subsequent oxidative addition to Pd(PPh3)4 afforded the carbene complexes 2 as air-stable, off-white 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 (JPC = 3.9 Hz). The singlet in the 31P NMR spectrum (δ = 21.3) is in agreement with a mutual trans conformation of the two phosphate 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...
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 2 than structures B–E (Scheme 2).

![Scheme 2 Most relevant resonance structures contributing to 3,5-dimethylisoxazol-4-yldene.](image)

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)(PPh₃)₂]OTf 3–7 were synthesised (Fig. 2), all comprising NHCs with CH₂ 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 ³¹P 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 δₚ (Fig. 2). This behavior is independent of the solvent (DMSO-d₆ or CD₂Cl₂) and may be rationalised by considering the paramagnetic contribution δₛₑₑ to the isotropic shielding constant. Recent theoretical calculations predict that more basic carbene ligands induce a smaller HOMO-LUMO gap, which increases the population of the paramagnetic triplet state and hence δₛₑₑ. Consequently, more basic carbene ligands effect a shift of the δₚ values to lower field.

According to this ³¹P basicity scale, isoxazol-4-yldiene are stronger donors than the normal carbene, pyridine-2-ylidene, and even abnormal carbene (cf. δₚ of 4–7), but not as strong as the pyrazol-4-yldiene reported previously (cf. 3). This difference parallels the weaker donor properties of 2-oxazolylidenes as compared to normal imidazolylidenes and corroborates the higher inductive effect exerted by oxygen than by nitrogen. It is worth noting that the ³¹P NMR scale is consistent with recently computed Tolman electronic parameters for this class of ligands and also with a scale based on ¹³C NMR chemical shifts of a trans located NHC. While δₚ measurement may provide a more direct probe, perhaps with a somewhat better resolution, δₚ analysis is generally rapid and highly convenient due to the high natural abundance and sensitivity of the ³¹P nucleus. Due to these advantages, ³¹P 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 νCO method based on IR stretch vibrations of carbonyl ligands. Least square regression of the obtained data gives a good linear fit which allows for an estimate of the TEP based on ³¹P NMR chemical shifts according to the equation TEP = 2125 – 4.01 × δₚ.

The catalytic impact of the electronically different carbene ligands was tested in palladium-catalyzed 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 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. Bu₄NBr as additive. No clear correlation between the donor ability and the catalytic activity.

![Fig. 2 Measured ³¹P NMR chemical shifts for [Pd(NHC)(PPh₃)₂][CF₃SO₃] complexes (CD₂Cl₂) and calculated TEP values (from ref 12; slightly different substituents in remote positions were used in calculations for the pyrazol-4-yldene in 3 and for the imidazol-4-yldene in 5).](image)

| entry | catalyst | substrate | T (°C) | t (h) | conv’n |
|-------|----------|-----------|--------|------|-------|
| 1⁺ | 2a | 4-bromobenzaldehyde | 20 | 19 | 89% |
| 2⁺ | 3 | 4-bromobenzaldehyde | 20 | 19 | 80% |
| 3⁺ | 4 | 4-bromobenzaldehyde | 20 | 19 | 79% |
| 4⁺ | 5 | 4-bromobenzaldehyde | 20 | 19 | 84% |
| 5⁺ | 6 | 4-bromobenzaldehyde | 20 | 19 | 30% |
| 6⁺ | 7 | 4-bromobenzaldehyde | 20 | 19 | 1% |
| 7⁺ | 2a | 4-chloroacetophenone | 140 | 2 | 85% |
| 8⁺ | 3 | 4-chloroacetophenone | 140 | 2 | 90% |
| 9⁺ | 4 | 4-chloroacetophenone | 140 | 2 | 80% |
| 10⁺ | 5 | 4-chloroacetophenone | 140 | 2 | 67% |
| 11⁺ | 6 | 4-chloroacetophenone | 140 | 2 | 84% |
| 12⁺ | 7 | 4-chloroacetophenone | 140 | 2 | 79% |
| 13⁺ | 2a | 4-chlorotoluene | 140 | 2 | < 10% |

* General conditions: ArBr (1.0 mmol), PhB(OH)₂ (1.2 mmol), catalyst (1 mol%), Na₂CO₃ (1.5 mmol), H₂O (3 mL); † General conditions: ArCl (1.0 mmol), PhB(OH)₂ (1.2 mmol), catalyst (1 mol%), K₂CO₃ (1.5 mmol), Bu₄NCl (1.5 mmol) DMA (3 mL); ‡ All conversions determined by ¹H NMR spectroscopy, average of at least two runs.
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, 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 ³¹P NMR as a probe situates this NHCl 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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Notes and references

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‡ Electronic Supplementary Information (ESI) available: CCDC 757620.

For experimental and analytical details see DOI: 10.1039/b000000x.
‡ Typical procedure: Solid Pd(PPh₃)₄ (144 mg, 0.125 mmol) and 4-iodo-1,3,5-trimethylisoxazolium trflate 1a (50 mg, 0.125 mmol) were dissolved in dry CHCl₃ (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 re-dissolved into CHCl₃ (3 mL) and precipitated with Et₂O (3x), 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, H₃). ¹³C(¹H) NMR (100 MHz, CD₂Cl₂): δ 168.0 (¹JC = 3.9 Hz, C-Pd), 160.9 (¹JC = 1.9 Hz, C-Me), 134.7 (¹JC = 6.2 Hz, C₁₃), 131.3 (C₁₂), 130.8 (¹JC = 25.1, C₁), 128.5 (¹JC = 5.3, C₉), 120.5 (¹JC = 321.1 Hz, CF₃), 58.2 (N-CH₂), 14.3, 13.7 (2 × C–CH₂). ³¹P NMR (202 MHz, CD₂Cl₂): δ 21.3 (PPh₃). Anal. Calc. for CₙHₓP₂InO₆PdS: C, 50.73; H, 5.55; N, 2.42; S, 2.74; P, 19.27; In, 10.36; Pd, 8.19.

Crystal data for 3: yellow plate, CₙHₓP₂InO₆PdS, M = 989.81, triclinic, a = 13.39(7), b = 15.79(7), 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, λ = 4, 18577 measured reflections, 9996 unique (Rint = 0.0708), R1 = 0.1155, wR2 = 0.3298 for I > 2σ(I).

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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.