<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Expanding the family of mesoionic complexes: donor properties and catalytic impact of palladated isoxazolylenes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors(s)</strong></td>
<td>Iglesias, Manuel; Albrecht, Martin</td>
</tr>
<tr>
<td><strong>Publication date</strong></td>
<td>2010</td>
</tr>
<tr>
<td><strong>Publication information</strong></td>
<td>Dalton Transactions, 39 (22): 5213-5215</td>
</tr>
<tr>
<td><strong>Publisher</strong></td>
<td>RSC Publishing</td>
</tr>
<tr>
<td><strong>Item record/more information</strong></td>
<td><a href="http://hdl.handle.net/10197/3709">http://hdl.handle.net/10197/3709</a></td>
</tr>
<tr>
<td><strong>Publisher's version (DOI)</strong></td>
<td>10.1039/C0DT00027B</td>
</tr>
</tbody>
</table>
Expanding the family of mesoionic complexes: Donor properties and catalytic impact of palladated isoxazolylidenes †

Manuel Iglesias* and Martin Albrecht*‡

Received (in XXX, XXX) Xth XXXXXXXXXX 200X, Accepted Xth XXXXXXXXXX 200X
First published on the web Xth XXXXXXXXXX 200X
DOI: 10.1039/b000000x

Donor properties and catalytic impact of palladated isoxazolylidenes †

This journal is © The Royal Society of Chemistry [year]

afforded the carbene complexes available 4 sensitive intermediates. Thus, quaternisat
addition protocol, carbene complexes, applied for the synthesis of specific abnormal and remote
computational analysis evaluations shown here and in line with predictions cycloadditions,
carbene carbon. report on isoxazolyli
substantially, thus evoking new reactivity patterns.
As a consequence, carbenes with low heteroatom stabilisation
which enhan
inductive effects of the heteroatoms are less pronounced,
reduces the stability of the free ligand. Simultaneously, the
alkyl amino carbenes carbenes with reduced heteroatom
great diversity of NHCs has been developed, ranging from the
centres, and to the higher donor ability of carbenes.

The discovery and isolatio
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 imidazolylidenes5 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 isoxazolylidenes as a new family of the normal of
abnormal remote NHCs, i.e., NHCs with no neutral carbene
resonance structure and with no heteroatom adjacent to the
carbone 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
carbone complexes13 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
solids. Successful metallation was indicated by the pertinent
13C1H 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 (δh 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

---

**Scheme 1** Synthetic pathway for the preparation of palladium(II)
isoxazolylidine 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 (º): II-Pd1 2.6466(18), Pd1-C4 2.037(19), Pd1-P1 2.330(5), Pd1-P2 2.330(5), C1-C5 1.342(2), O1-N1 1.40(2), N1-C3 1.27(2), C3-C4 1.31(2), C4-C5 1.37(3), C1-Pd1-C4 89.50(13), II-Pd1-P2 93.25(13), II-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).

---

**Table 1** Selected bond lengths (Å) and angles (º).
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 isoaxazolylidene in complex 2 than structures B–E (Scheme 2).

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

The donor strength of the isoaxazolylidene in 2 and its impact on palladium-mediated-catalysis was compared to different types of isostructural NHC ligands. In an attempt to minimise stereoelectron effects, complexes [Pd(NHC)(PPh3)2]OTf 3–7 were synthesised (Fig. 2), all comprising NHCs with CH3 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 CdCl2) and may be rationalised by considering the paramagnetic contribution σpara 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 σpara. Consequently, more basic carbene ligands effect a shift of the δP values to lower field.

According to this 31P basicity scale, isoaxazol-4-ylidene 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-ylidene reported previously (cf. 3).14b This difference parallels the weaker donor properties of 2-oxazolylidenes as compared to normal imidazolylidenes16 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,12 and also with a scale based on 13C NMR chemical shifts of a trans located NHC.17 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 δC0 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 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-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. Bu3NBr as additive. No clear correlation between the donor ability and the catalytic activity

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

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>T / °C</th>
<th>t / h</th>
<th>conv’n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ª</td>
<td>2a</td>
<td>20</td>
<td>19</td>
<td>89%</td>
</tr>
<tr>
<td>2ª</td>
<td>3</td>
<td>20</td>
<td>19</td>
<td>80%</td>
</tr>
<tr>
<td>3ª</td>
<td>4</td>
<td>20</td>
<td>19</td>
<td>79%</td>
</tr>
<tr>
<td>4ª</td>
<td>5</td>
<td>20</td>
<td>19</td>
<td>84%</td>
</tr>
<tr>
<td>5ª</td>
<td>6</td>
<td>20</td>
<td>19</td>
<td>30%</td>
</tr>
<tr>
<td>6ª</td>
<td>7</td>
<td>20</td>
<td>19</td>
<td>1%</td>
</tr>
<tr>
<td>7ª</td>
<td>2a</td>
<td>140</td>
<td>2</td>
<td>85%</td>
</tr>
<tr>
<td>8ª</td>
<td>3</td>
<td>140</td>
<td>2</td>
<td>90%</td>
</tr>
<tr>
<td>9ª</td>
<td>4</td>
<td>140</td>
<td>2</td>
<td>80%</td>
</tr>
<tr>
<td>10ª</td>
<td>5</td>
<td>140</td>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>11ª</td>
<td>6</td>
<td>140</td>
<td>2</td>
<td>84%</td>
</tr>
<tr>
<td>12ª</td>
<td>7</td>
<td>140</td>
<td>2</td>
<td>79%</td>
</tr>
<tr>
<td>13ª</td>
<td>2a</td>
<td>140</td>
<td>2</td>
<td>&lt; 10%</td>
</tr>
</tbody>
</table>

ª General conditions: ArBr (1.0 mmol), PhBr(OH), (1.2 mmol), catalyst (1 mol%), K2CO3 (1.5 mmol), H2O (3 mL); ‡ General conditions: ArCl (1.0 mmol), PhBr(OH), (1.2 mmol), catalyst (1 mol%), K2CO3 (1.5 mmol), Bu3NCl (1.5 mmol) DMA (3 mL); all conversions determined by 31P NMR spectroscopy, average of at least two runs.

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-ylidene in 3 and for the imidazol-4-ylidene in 5).
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 aryalted 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 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.

The authors thank Dr. A. Neels and Ms. O. Sereda for X-ray diffraction measurements. This work was financially supported by the Swiss National Science Foundation, COST D40, and the European Research Council through a Starting Grant. M.A. also acknowledges the Alfred Werner Foundation for an Assistant Professorship.

**Notes and references**

1. School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland. E-mail: martin.albrecht@ucd.ie; Fax: (+353-1)-7162501.
2. Electronic Supplementary Information (ESI) available: CCDC 757620.
3. For experimental and analytical details see DOI: 10.1039/b000000a.
4. Typical procedure: Solid Pd(PPh₃)₄ (144 mg, 0.125 mmol) and 4-iodoxy-1,3,5-trimethylisoxazolium triflate 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 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, CDCl₃): δ 7.65-7.45 (m, 30H, H₂), 3.60 (s, 3H, N–CH₃), 1.90, 1.86 (2 × s, 3H, C–CH₃). ¹³C(¹H) NMR (100 MHz, CDCl₃): δ 168.0 (J_C=3.9 Hz, C–Pd), 160.9 (J_C=1.9 Hz, C–Me), 134.7 (J_C=6.2 Hz, C₁), 131.3 (C₂), 130.8 (J_C=25.1, C₃), 128.5 (J_C=5.3, C₄), 120.5 (J_C=321.1 Hz, CF₃), 58.2 (N–CH₃), 14.3, 13.7 (2 × C–CH₃). ³¹P NMR (202 MHz, CDCl₃): δ 21.3 (PPh₃). Anal. Calc. for C₉H₈F₄INO₃P: C, 50.48; H, 3.60; F, 19.05; N, 3.60; P, 7.92. Found: C, 50.05; H, 3.60; F, 19.02; N, 3.56; P, 7.88.
5. K, space group P-1, Z = 4, 18577 measured reflections, 9996 unique (Rint = 0.0708), R1 = 0.1155, wR2 = 0.3298 for I > 2σ(I).

10. According to IUPAC nomenclature, abnormal carbones belong to the class of mesoionic compounds, and the complexes should hence be termed mesoionic complexes rather than carbene complexes. The term mesoionic is formally more appropriate than abnormal or remote carbene, yet it omits the genealogically relationship to normal NHCS and Fischer carbones. Based on the data currently available, all these classes of carbene complexes should be described as mesoionic complexes.
17. H. V. Huyhn, Y. Han, R. Jostibasu and J. A. Yang, Organometallics, 2009, 28, 5395.
Expanding the family of mesoionic complexes: Donor properties and catalytic impact of palladated isoxazolylidenes

Manuel Iglesias and Martin Albrecht

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.