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# N-Heterocyclic Carbenes

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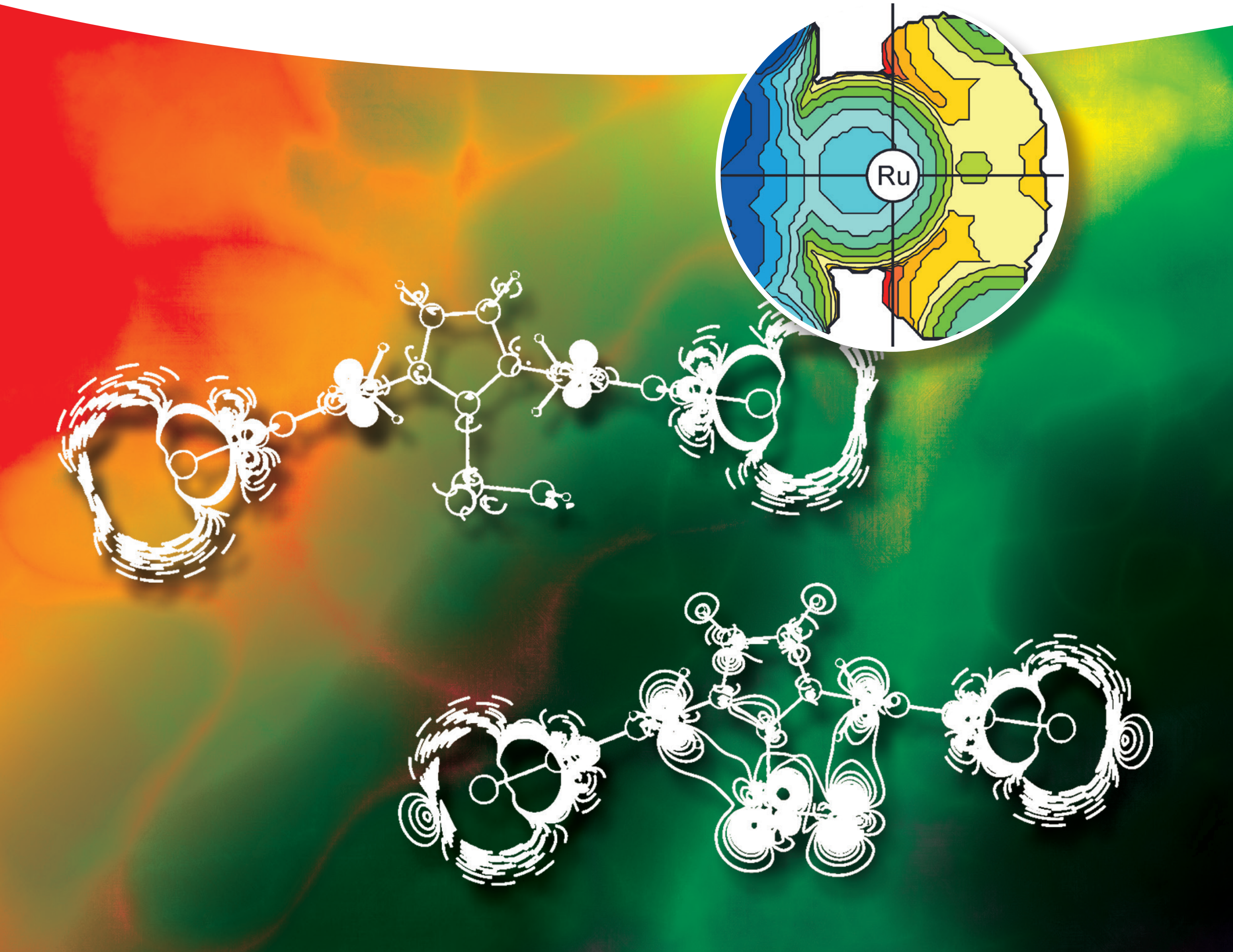

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# N-Heterocyclic Carbenes

## Effective Tools for Organometallic Synthesis

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*“To Carl: friend, mentor and not so old afterall…*
*And to Catherine, Maëlys and Kaelia, for always being there.”*

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# Preface

It has been eight years since the first monograph on *N*-heterocyclic carbenes (NHC) appeared [1]. In this rather short timespan the uses of NHCs in their many incarnations have contributed to advances in numerous areas of synthetic chemistry. These initial *curiosities* [2] have become workhorses in synthesis and homogeneous catalysis [3]. Catalytic studies nowadays almost always include the testing of a NHC or NHC precursor as part of a ligand/catalyst screening.

The thinking involving NHC in catalysis has also evolved considerably since the original *in situ* catalyst generation protocols and tertiary phosphine *mimic* analogies. The stabilizing effects of NHCs on organometallic complexes have permitted lower catalyst loading operations and unique mechanistic insights. The area has evolved in a very "green" direction and this trend I hope will continue as well-defined systems have been identified that belong within or sit off-cycle as catalyst reservoirs in important catalytic reactions. The use of these now almost ubiquitous ligands has helped the field better understand fundamental transformations, such as C—H activation and more interestingly C—H bond functionalization [4].

The present monograph presents important developments in metal-mediated transformations. I hope established and younger researchers alike will find here inspiration to take the past discoveries as a foundation to design novel scaffolds with original properties and deploy these in known and undiscovered catalysis and synthetic uses.

I will not use this preface to perform an exercise in *crystal-ball-gazing* and pontificate on what should or should not be explored as performing research in this area has made me a more humble and regularly amazed researcher. As many have, I came to this field by accident. Serendipity does and continues to play an important role in a number of developments in this now very fruitful (some may call it mature) area of research. I truly believe many more surprises are in store for us facing the pleasures and frustrations of exploring this fascinating area of Science.

I would like to thank Mrs. Carolyn Busby and Dr. David Nelson for their editorial assistance and I am grateful to the contributing authors who are true authorities in this still very rapidly evolving field.

St Andrews

*Steven P. Nolan*
February 2014

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# 1
# *N*-Heterocyclic Carbenes

*David J. Nelson and Steven P. Nolan*

## 1.1
## Introduction

Over the past few decades, stable carbenes have received a great deal of attention from a number of researchers [1]. In the singlet carbene compounds, a carbon center bears a lone pair of electrons in an $sp^2$ hybridized orbital while a $p$ orbital remains vacant (Figure 1.1a). Triplet carbenes are also known, where each of the two electrons occupy a degenerate p orbital (Figure 1.1b).

*N*-Heterocyclic carbenes (NHCs) are a specific form of this class of compound, where the carbene is located on an *N*-heterocyclic scaffold. While these species were initially not widely applied in chemistry, they have now been employed in a broad range of fields, including organocatalysis [2] and organometallic chemistry [3]. Hundreds of different NHCs are known in the literature, and much has been learned about their properties and reactivity. Various experimental and theoretical techniques have been applied toward this aim, including density functional theory (DFT) studies, which have allowed an insight into the bonding and orbital arrangements in NHCs. This chapter details the discovery and isolation of stable NHCs, the characterization of the electronic nature of this species, the factors that render them stable, and the nature of their bonding to metal centers. In addition, some of the ways in which the electronic and steric properties of these species can be explored and quantified will be discussed.

## 1.2
## Structure and Properties of NHCs

Prior to the isolation of stable NHCs, some information was known about the properties of these species. As early as the 1960s, researchers such as Wanzlick were active in probing the reactivity of NHCs generated *in situ* from, for example, the thermolysis of the corresponding dimers [4]. In this way, the nucleophilic reactivity of these species with a number of reagents was characterized

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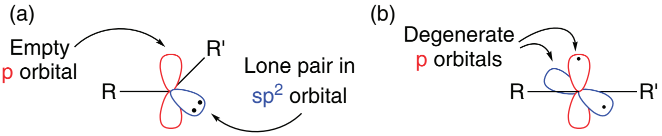
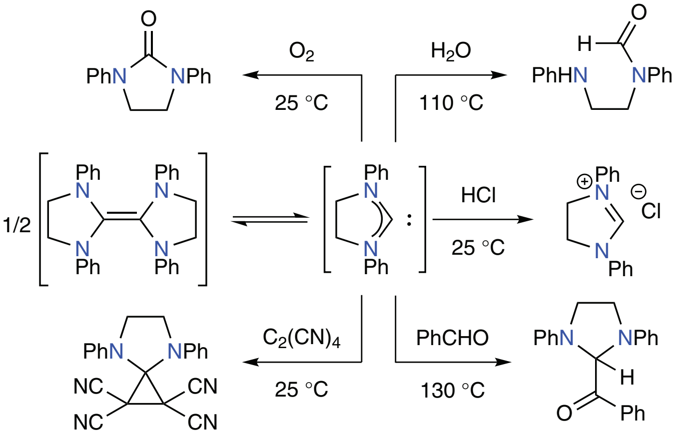
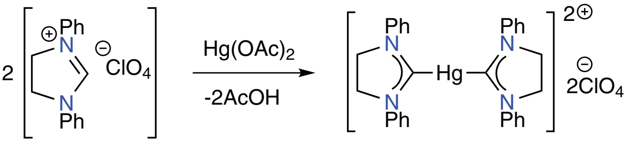


**Figure 1.1** (a) Singlet carbenes; (b) triplet carbenes.

(Scheme 1.1). In addition, reaction with HCl yielded the corresponding imidazolium chloride salts. Metal–carbene complexes were also prepared by Wanzlick and Schönherr, without isolation of the free carbene itself (Scheme 1.2) [5].



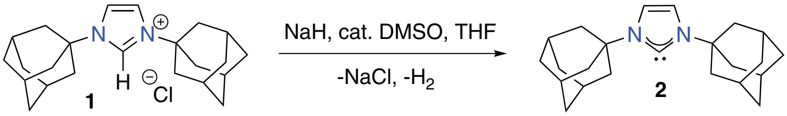
**Scheme 1.1** Early studies of the reactivity of N-heterocyclic carbenes. [4].



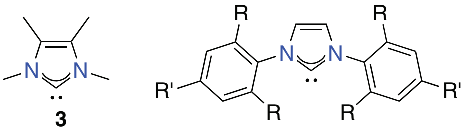
**Scheme 1.2** Synthesis of an NHC-mercury complex [5].

The isolation of stable NHCs was a key event in the chemistry of this valuable class of compound, as this allowed the preparation of material for detailed characterization. In addition, many modern syntheses of NHC–metal complexes rely on the use of isolated NHCs. In 1991, when Arduengo *et al.* exposed imidazolium chloride **1** to NaH and catalytic DMSO in THF, stable carbene **2** was isolated (Scheme 1.3) [6]. This species, also known as IAd, could be characterized by various methods, including X-ray crystallography and NMR spectroscopy.

Initially, it was unclear whether steric or electronic effects were the source of the stability of **2**. A subsequent publication from Arduengo *et al.* reported a further four stable carbenes **3**–**6** (**3** is typically referred to as ITME, and **4** as IMes) with various *N*-substituents, which were prepared in the same manner as **2**



**Scheme 1.3** Synthesis of IAd [6].

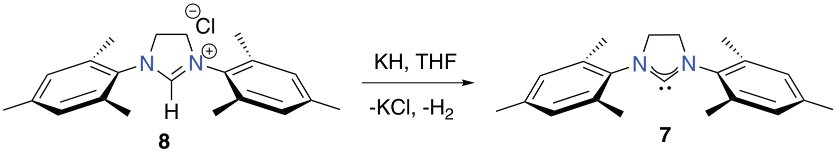


**4** R = Me, R' = Me
**5** R = H, R' = Me
**6** R = H, R' = Cl

**Figure 1.2** Stable NHCs isolated by Arduengo *et al.* [7].

(Figure 1.2) [7]. Notably, these were far less sterically hindered, suggesting that the origin of their stability was electronic, rather than steric, or was a combination of these factors.

The aromatic nature of the imidazolium ring was thought to be critical to the stability of NHCs. However, in 1995, NHC **7** (SIMes) bearing a saturated backbone and bulky mesityl *N*-substituents was obtained by deprotonation of the corresponding imidazolium chloride **8**, and was characterized by Arduengo *et al.* (Scheme 1.4) [8].



**Scheme 1.4** Synthesis of SIMes [8].

With a robust route to synthesize and isolate free carbenes in hand, several researchers applied a number of tools to investigate their properties and reactivity. A thorough understanding of these properties is essential to understand how these species can be applied in chemistry, and to inform the rational design of new NHCs. X-ray photoelectron spectroscopy (XPS) and DFT studies of a model carbene **9** (I$^t$Bu) confirmed the presence of a lone pair of electrons in the plane of the imidazolylidene ring, and an empty *p* orbital on the same carbon center [9]. However, there was initially some debate as to whether the carbene was best considered as a carbene or as an ylide (Figure 1.3); that is, whether a resonance contribution from the lone pair centered on nitrogen was a part of the bonding arrangement in NHCs. Understanding this aspect of the structure of NHCs was important in order to understand both how the structure of the

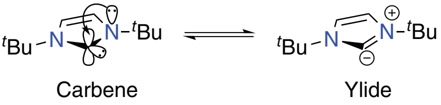


**Figure 1.3** Carbenic and ylidic resonance forms of *N*-heterocyclic carbenes (**9** (I$^t$Bu) is pictured).

NHC might affect reactivity, as well as allowing for the tuning of reactivity *via* structural modifications.

Initial studies by Dixon and Arduengo suggested that the ylidic form was not a major contributor to the structure of imidazolium-based NHCs [10]. Subsequent electron distribution mapping of a model carbene, **3**-$d_{12}$ (ITME-$d_{12}$) using X-ray and neutron radiation also suggested very little contribution from the ylidic form; these methods relied on mapping the electron distribution 0.7 Å above the plane of the NHC, which the authors proposed should indicate whether $p_\pi$–$p_\pi$ delocalization occurred. The lengthened C—N bonds in imidazolylidenes compared to the corresponding imidazolium salts were proposed to be further evidence of negligible interaction of the nitrogen lone pairs with the empty p orbital at the carbene. Visualization of the electron density using this method showed π electron density between C4 and C5 corresponding to the double bond, and the *p* electrons of the nitrogen; no evidence for an ylidic form was found. In addition, the $^{13}$C shielding tensor $\sigma_{11}$ was revealed to be negative, suggesting that the carbenic resonance form was dominant [11]. However, later work by Boehme and Frenking suggested that the method of electron density mapping that was employed was not appropriate, as it suggested negligible π-delocalization in pyridine and pyrrole, which are known to be aromatic [12]. *In silico* calculations by these authors, particularly those involving natural bond order (NBO) calculations, strongly suggested that $p_\pi$–$p_\pi$ delocalization was significant in both imidazol-2-ylidenes and imidazolidin-2-ylidenes, but more pronounced in the former.

A detailed study, published at the same time by Heinemann *et al.*, explored this $p_\pi$–$p_\pi$ delocalization in NHCs, and aimed to understand whether imidazol-2-ylidenes were aromatic species [13]. Three key characteristics of NHCs were explored: thermodynamic stability, geometric structure, and the charge distribution. Isodesmic calculations on acyclic carbenes and aminocarbenes showed that even when conjugation was not possible, the carbene was stabilized by adjacent amino groups due to their σ electron-withdrawing properties. Conjugation further increased stabilization; imidazolidin-2-ylidenes were more stable again, while imidazol-2-ylidenes were most stable (Figure 1.4). Similarly, structural data were consistent with π-delocalization. Calculated magnetic susceptibility anisotropies ($\Delta\chi$) were suggestive of cyclic π-delocalization, but to a lesser extent than in benzene. All of these results strongly suggest the involvement of $p_\pi$–$p_\pi$ delocalization from the nitrogen lone pair into the empty orbital at the carbene, and that imidazol-2-ylidenes show some aromatic character. In a later study by Bielawski and coworkers, it was shown that the electronic properties of acyclic

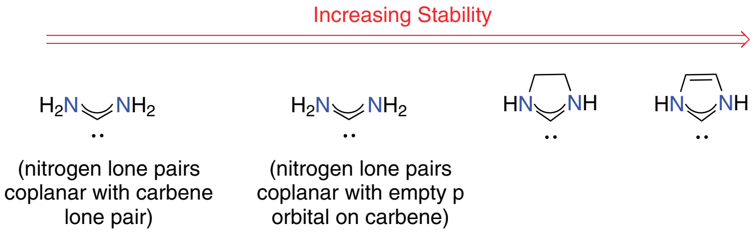


**Figure 1.4** Stability of some carbenes, as determined by isodesmic calculations for the reaction of each carbene with methane to generate NHC·$H_2$ and dihydrocarbene [13].

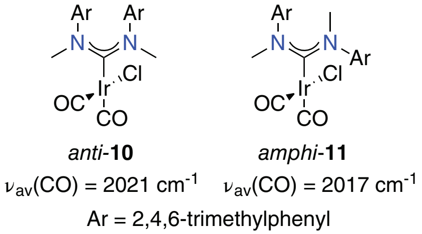


**Figure 1.5** [IrCl$(CO)_2$(L)] complexes in which the differing degrees of $p_\pi$–$p_\pi$ conjugation affects the electronic properties of the metal center [14].

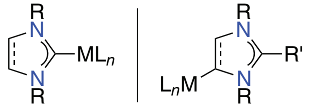
diaminocarbenes (as probed using the infrared spectra of [IrCl$(CO)_2$(L)] complexes **10** and **11**, shown later) were dependent on the ligand conformation, due to differing degrees of $p_\pi$–$p_\pi$ delocalization (Figure 1.5) [14].

Clearly, this delocalization is a key component of the bonding in NHCs, and for this reason NHCs are typically drawn with the inclusion of a curve between the nitrogen atoms in order to emphasize this aspect of their electronic structure.

## 1.3
## Abnormal Carbenes

While the majority of reports of imidazolylidenes bound to metal centers involve coordination *via* the C2 position (i.e., imidazol-2-ylidenes), there has been recent and growing interest in so-called abnormal carbenes, often referred to as aNHCs, where binding occurs *via* the C4 or C5 position (Figure 1.6) [15]. Often the substitution pattern is chosen to block the C2 position. The resulting imidazolylidenes are stabilized by only one nitrogen moiety, as the π-donating and σ-accepting properties of the second nitrogen atom are greatly reduced. Such species provide great scope for achieving different properties from so-called normal carbenes.

These species tend to show quite different electronic properties to their normally bound congeners. They are considerably more electron-donating due to



"normal" "abnormal"

**Figure 1.6** Normally versus abnormally bound imidazolylidenes.

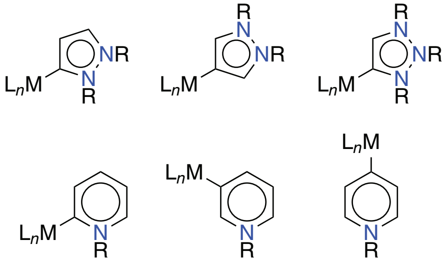


**Figure 1.7** NHC species with reduced heteroatom stabilization [15].

the reduced σ-withdrawal from the carbene center, as evidenced by calculated Tolman electronic parameter (TEP) [16] values (shown later) for a range of these species [17]. In addition, they have been shown to be more π-accepting (due to reduced $p_\pi$–$p_\pi$ delocalization), as determined by analysis of the $^{31}$P chemical shifts of the corresponding phosphinidene adducts [18]. The different properties of these ligands will naturally confer different properties and reactivity to the metal centers to which they are coordinated.

Other species with reduced heteroatom stabilization are also known; these include isomers of imidazolylidenes (e.g., 1,2-imidazol-3-ylidenes, 1,2-imidazol-4-ylidenes), 1,2,3-triazoly-4-lidenes, and pyrimidazolylidenes (Figure 1.7) [15].

## 1.4
## Why Are NHCs Stable?

Prior to the isolation of NHCs, various studies were carried out on species generated *in situ* [4]. However, once Arduengo succeeded in isolating a series of stable species, attention naturally turned to identifying *why* some species were stable and isolable, while others were not.

Heinemann and Thiel [19] and Carter and Goddard [20] both applied theoretical methods to investigate the singlet–triplet gap in prototypical carbene compounds, showing that this factor was key in the stability of NHCs. Triplet carbenes are known to be much less stable than singlet species [21]. Some of the factors affecting the singlet–triplet gap have been established for some time, such as the influence of the geometry of the carbene and the presence of