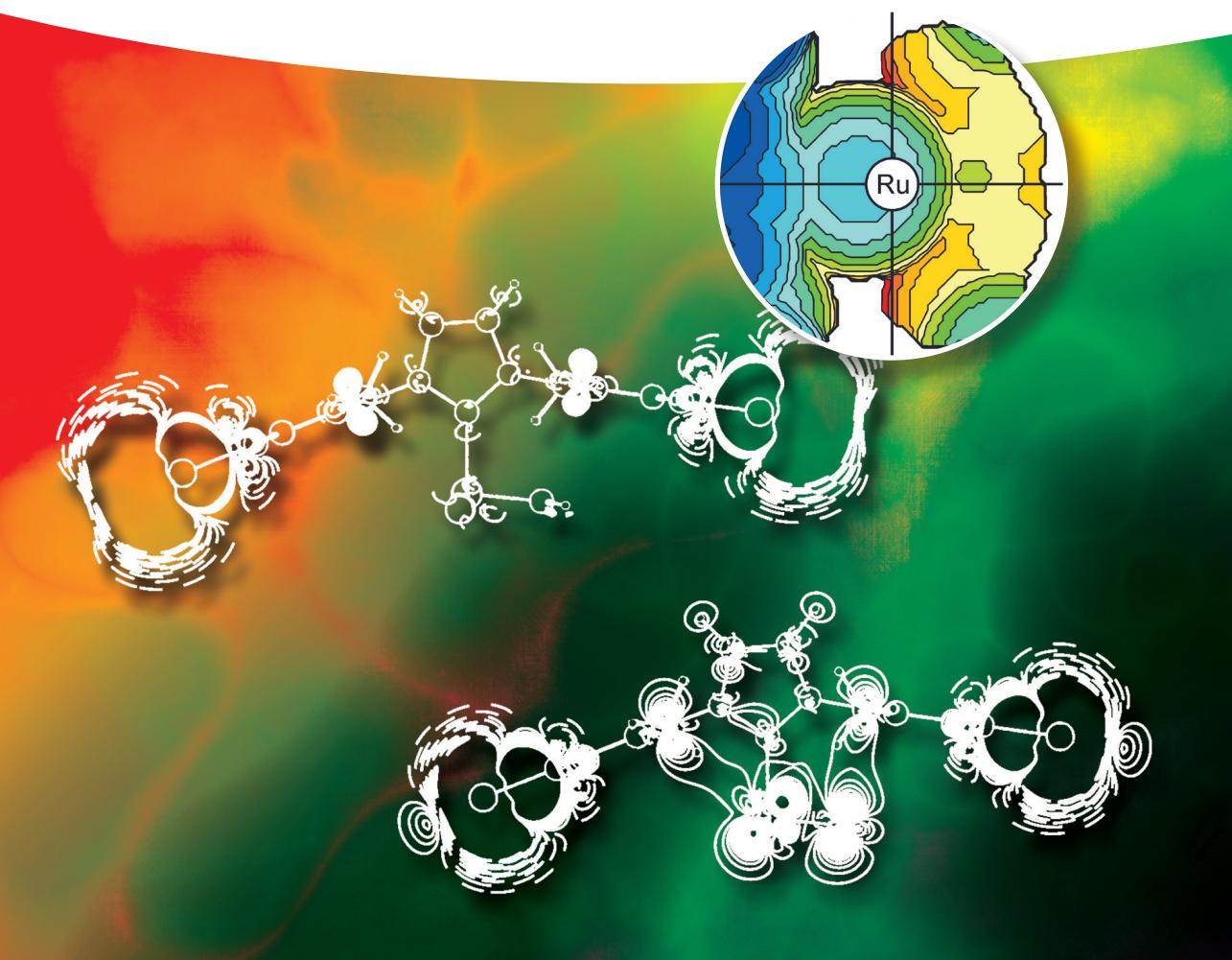


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N-Heterocyclic Carbenes

Effective Tools for Organometallic Synthesis



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WILEY-VCH
Verlag GmbH & Co. KGaA

Editor**Prof. Steven P. Nolan**

EaStCHEM School of Chemistry
University of St Andrews
St Andrews
KY16 9ST
United Kingdom

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Library of Congress Card No.: applied for**British Library Cataloguing-in-Publication Data**

A catalogue record for this book is available from the British Library.

**Bibliographic information published by the
Deutsche Nationalbibliothek**

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

© 2014 Wiley-VCH Verlag GmbH & Co. KGaA,
Boschstr. 12, 69469 Weinheim, Germany

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Print ISBN: 978-3-527-33490-2

ePDF ISBN: 978-3-527-67125-0

ePub ISBN: 978-3-527-67124-3

Mobi ISBN: 978-3-527-67123-6

oBook ISBN: 978-3-527-67122-9

Cover Design Bluesea Design, McLeese Lake, Canada

Typesetting Thomson Digital, Noida, India

Printing and Binding Markono Print Media Pte Ltd.,
Singapore

Printed on acid-free paper

Dedication:

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

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List of Contributors

Abdullah Mohamed Asiri

King Abdulaziz University
Center of Excellence for Advanced
Materials Research (CEAMR)
Jeddah 21589
P.O. Box 80203
Saudi Arabia

Stéphane Bellemín-Laponnaz

Université de Strasbourg-CNRS
Institut de Physique et Chimie des
Materiaux de Strasbourg
23 rue du Loess
67034 Strasbourg Cedex 2
France

and

Université de Strasbourg-CNRS
Institut de Chimie de Strasbourg
1 rue Blaise Pascal
67000 Strasbourg
France

Luigi Cavallo

King Abdullah University of Science
and Technology (KAUST)
Chemical and Life Sciences and
Engineering
Kaust Catalysis Center
Thuwal 23955-6900
Saudi Arabia

Catherine S.J. Cazin

University of St Andrews
EaStCHEM School of Chemistry
Purdie Building, North Haugh
St Andrews, Fife KY16 9ST
UK

Jason A.C. Clyburne

Saint Mary's University
Department of Chemistry
The Atlantic Centre for Green
Chemistry
Halifax
Nova Scotia B3H 3C3
Canada

Samuel Dagorne

Université de Strasbourg-CNRS
Institut de Physique et Chimie des
Materiaux de Strasbourg
23 rue du Loess
67034 Strasbourg Cedex 2
France

and

Université de Strasbourg-CNRS
Institut de Chimie de Strasbourg
1 rue Blaise Pascal
67000 Strasbourg
France

Steve Dierick

Université Catholique de Louvain
Laboratoire de Chimie Organique et
Médicinale
Place Louis Pasteur, 1, bte L4.01.02
B-1348 Louvain-la-Neuve
Belgium

Reto Dorta

University of Western Australia
School of Chemistry and
Biochemistry
35 Stirling Highway
6009 Crawley, WA
Australia

Laura Falivene

Università di Salerno
Dipartimento di Chimica e Biologia
Via Ponte don Melillo
84084 Fisciano
Italy

Daniel Guest

University of Sussex
Department of Chemistry
Brighton
BN1 9QJ
UK

Gregorio Guisado-Barrios

Universitat Jaume I
Departamento de Química
Inorgánica y Orgánica
Avda. Vicente Sos Baynat s/n
Castellón, E-12071
Spain

A. Stephen K. Hashmi

Ruprecht Karls University
Heidelberg
Institute of Organic Chemistry
Im Neuenheimer Feld 270
69120 Heidelberg
Germany

M. Taylor Haynes II

University of Michigan
Department of Chemistry
930 N. University
Ann Arbor, MI 48109-1055
USA

Mario Hoyos

CSIC
Instituto de Ciencia y Tecnología de
Polímeros
Juan de la Cierva, 3
28006 Madrid
Spain

Evan P. Jackson

University of Michigan
Department of Chemistry
930 N. University
Ann Arbor, MI 48109-1055
USA

Faima Lazreg

University of St Andrews
EaStCHEM School of Chemistry
Purdie Building, North Haugh
St Andrews, Fife KY16 9ST
UK

N. Gabriel Lemcoff

Ben-Gurion University
Department of Chemistry
P.O. Box 653
Beer-Sheva 84105
Israel

István E. Markó

Université Catholique de Louvain
Laboratoire de Chimie Organique et
Médicinale
Place Louis Pasteur, 1, bte L4.01.02
B-1348 Louvain-la-Neuve
Belgium

Jason D. Masuda

Saint Mary's University
 Department of Chemistry
 The Atlantic Centre for Green
 Chemistry
 Halifax
 Nova Scotia B3H 3C3
 Canada

Sudheendran Mavila

Ben-Gurion University
 Department of Chemistry
 P.O. Box 653
 Beer-Sheva 84105
 Israel

John Montgomery

University of Michigan
 Department of Chemistry
 930 N. University
 Ann Arbor, MI 48109-1055
 USA

Luke J. Murphy

Saint Mary's University
 Department of Chemistry
 The Atlantic Centre for Green
 Chemistry
 Halifax
 Nova Scotia B3H 3C3
 Canada

Oscar Navarro

University of Sussex
 Department of Chemistry
 Brighton
 BN1 9QJ
 UK

David J. Nelson

University of St Andrews
 EaStCHEM School of Chemistry
 North Haugh, St Andrews
 Fife KY16 9ST
 UK

Steven P. Nolan

University of St Andrews
 EaStCHEM School of Chemistry
 St Andrews
 KY16 9ST
 United Kingdom

Matthew J. Panzner

The University of Akron
 Department of Chemistry
 190 E Buchtel Commons
 Akron, OH 44325-3601
 USA

Eduardo Peris

Universitat Jaume I
 Departamento de Química
 Inorgánica y Orgánica
 Avda. Vicente Sos Baynat s/n
 Castellón, E-12071
 Spain

Albert Poater

Universitat de Girona
 Institut de Química Computacional
 i Catàlisi
 Departament de Química
 Campus de Montilivi
 E-17071 Girona
 Spain

Macarena Poyatos

Universitat Jaume I
 Departamento de Química
 Inorgánica y Orgánica
 Avda. Vicente Sos Baynat s/n
 Castellón, E-12071
 Spain

Katherine N. Robertson

Saint Mary's University
Department of Chemistry
The Atlantic Centre for Green
Chemistry
Halifax
Nova Scotia B3H 3C3
Canada

Alvaro Salvador

University of Western Australia
School of Chemistry and
Biochemistry
35 Stirling Highway
6009 Crawley, WA
Australia

Leonid Schwartsburg

University of Bath
Department of Chemistry
Claverton Down
Bath BA2 7AY
UK

Kerri L. Shelton

The University of Akron
Department of Chemistry
190 E Buchtel Commons
Akron, OH 44325-3601
USA

LeGrande M. Slaughter

University of North Texas
Department of Chemistry
1155 Union Circle # 305070
Denton, TX 76203-5070
USA

Claire A. Tessier

The University of Akron
Department of Chemistry
190 E Buchtel Commons
Akron, OH 44325-3601
USA

Patrick O. Wagers

The University of Akron
Department of Chemistry
190 E Buchtel Commons
Akron, OH 44325-3601
USA

Michael K. Whittlesey

University of Bath
Department of Chemistry
Claverton Down
Bath BA2 7AY
UK

Linglin Wu

University of Western Australia
School of Chemistry and
Biochemistry
35 Stirling Highway
6009 Crawley, WA
Australia

Thomas Wurm

Ruprecht Karls University
Heidelberg
Institute of Organic Chemistry
Im Neuenheimer Feld 270
69120 Heidelberg
Germany

Wiley J. Youngs

The University of Akron
Department of Chemistry
190 E Buchtel Commons
Akron, OH 44325-3601
USA

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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***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

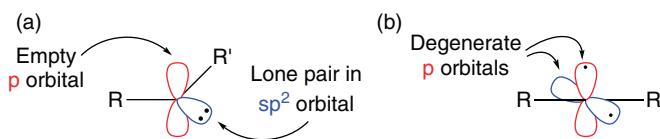
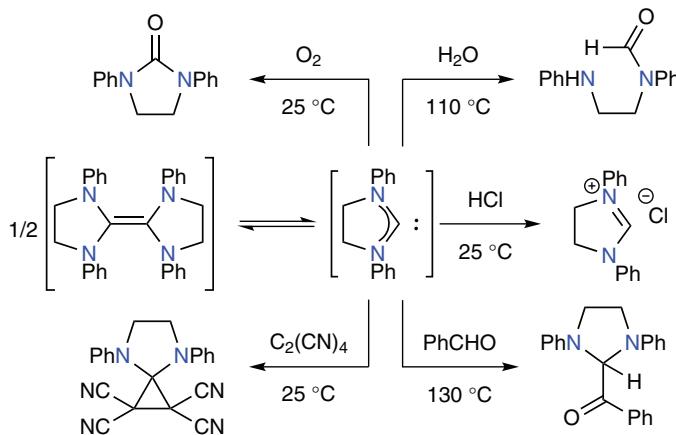
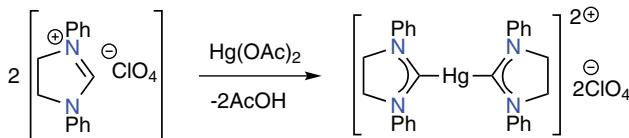


Figure 1.1 (a) Singlet carbenes; (b) triplet carbenes.

(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].



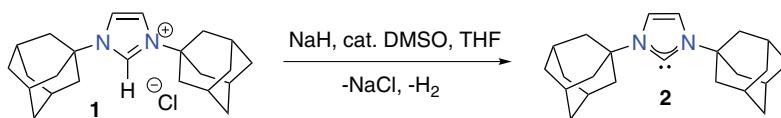
Scheme 1.1 Early studies of the reactivity of N-heterocyclic carbenes. [4].



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].

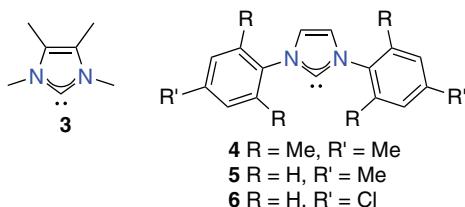
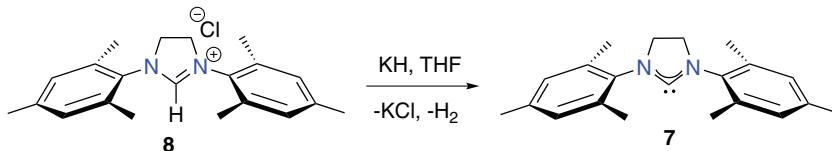


Figure 1.2 Stable NHCs isolated by Arduengo *et al.* [7].

(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 ($\text{I}^{\text{t}}\text{Bu}$) 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

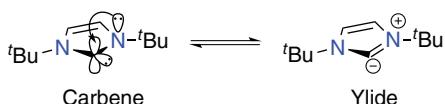


Figure 1.3 Carbenic and ylidic resonance forms of *N*-heterocyclic carbenes (**9** (*t*^tBu)) is pictured).

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*_π-*p*_π 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 ¹³C shielding tensor σ_{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*_π-*p*_π 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*_π-*p*_π 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*_π-*p*_π 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

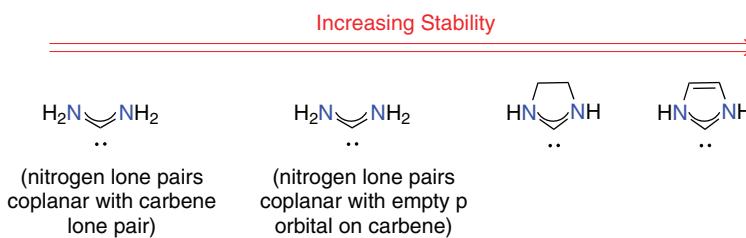


Figure 1.4 Stability of some carbenes, as determined by isodesmic calculations for the reaction of each carbene with methane to generate NHC-H₂ and dihydrocarbene [13].

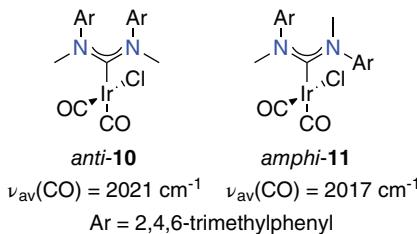


Figure 1.5 $[\text{IrCl}(\text{CO})_2(\text{L})]$ complexes in which the differing degrees of $p_{\pi}-p_{\pi}$ conjugation affects the electronic properties of the metal center [14].

diaminocarbenes (as probed using the infrared spectra of $[\text{IrCl}(\text{CO})_2(\text{L})]$ 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

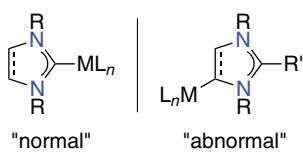


Figure 1.6 Normally versus abnormally bound imidazolylidenes.

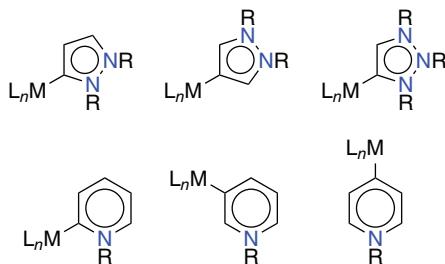


Figure 1.7 NHC species with reduced heteroatom stabilization [15].

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-triazol-4-ylidenes, 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