■ HAN VINH HUYNH

THE ORGANOMETALLIC CHEMISTRY OF N-HETEROCYCLIC CARBENES

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of N-heterocyclic Carbenes

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The Organometallic Chemistry of N-heterocyclic Carbenes

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Foreword

Rarely over the last 50 years has a new type of ligand captured the imaginations of chemists as was the case with the N-heterocyclic carbenes (NHCs). The report by Arduengo *et al.* in 1991 on stable, "bottle-able" N-heterocyclic carbenes derived from imidazolium salts initiated an intensive stream of research on these compounds and their metal complexes which has now lasted unabated for 25 years. While NHC complexes have been known since the work of Öfele *et al.* and Wanzlick *et al.* in 1969, the parent free carbenes remained elusive up until the studies by Arduengo, validating earlier proposals by Wanzlick *et al.*

Meanwhile, a large number of cyclic diaminocarbenes derived from smaller or larger rings than the imidazolium salts used originally have been produced. In addition, the heteroatoms in the carbene ring have been varied to give P-heterocyclic carbenes or even the cyclic alkyl-amino carbenes (CAACs) featuring only one nitrogen atom in the heterocyclic carbene ring. From transient laboratory curiosities, NHCs have developed into an important class of carbon(II) donor ligands next to carbonyls and isocyanides. They have found multiple applications as sterically unique and demanding spectator ligands for the preparation of a various catalytically active metal complexes, culminating in the development of ruthenium-NHC complexes catalyzing various types of olefin metathesis. Other NHC complexes have found applications as organometallic metallodrugs, and poly-NHCs have even found use for the construction of discrete metallosupramolecular assemblies.

Knowing the very substantial current interest in NHCs and their metal complexes and the maturity of the research field in general, the usefulness of a text appealing to the novice in carbene chemistry and to serve as a reference for the advanced researcher becomes apparent. Good progress in this area has been achieved with this book by H. V. Huynh. Written by an experienced researcher in the field, the text discusses in nine chapters general aspects of NHC chemistry, as well as advanced topics such as mesoionic carbenes and expanded ring NHCs. Special emphasis is placed on NHC-metal complexes of groups 10 and 11, Ruthenium, Rhodium, and Iridium. The book illustrates clearly various methods for the preparation of NHCs and their complexes thereby demonstrating their vast potential in modern organometallic chemistry. In order not to discourage the reader by too voluminous a book, the author has placed emphasis on general concepts and methods rather than listing all known NHCs or their metal complexes.

Given the current state of research on NHCs, a general text on the subject is overdue. The author has found a middle way between a comprehensive, exhaustive description of the subject and mere conceptual highlighting of important topics. It is hoped that this text appeals to the diverse readership it was written for.

<div align="right">

F. Ekkehardt Hahn
Münster, September 2016

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Preface

Since its humble beginning, which started with curiosity-driven works of Wanzlick and Öfele in 1968, the chemistry of N-heterocyclic carbenes (NHCs) has matured considerably. The isolation of the first free NHC by Arduengo reported in 1991 has reignited interest in an almost forgotten area, and early catalytic applications of NHC complexes in C–C couplings reported by Herrmann further fueled the development of the field. Nowadays, NHCs are ubiquitous in mainstream and modern chemistry, where they are most commonly used as ligands and organocatalysts. Other areas for their application are just beginning to unfold. Given their prominent standing chemistry, it is surprising to note that there are currently no general textbooks dedicated to NHCs. The several books on NHCs available in the scientific literature are rather specific or mainly concentrate on their use in catalysis. These texts are suitable and valuable for experienced scientists. However, for university students at the undergraduate or graduate level and for any newcomer to the field, they may be too advanced, sometimes lacking basic, but crucial explanations for a better understanding of the subject.

This textbook attempts to bridge the gap between the novice and the expert. As such it is targeting the advanced undergraduate and graduate student and anyone wishing to explore NHC chemistry. It includes an historical account highlighting important milestones in the development of this chemistry from its early beginnings. Key properties of NHCs, their precursors and complexes are addressed, and a critical discussion on the nomenclature of NHCs is included. Moreover, common synthetic methods are explained in terms of outcome and driving force. Four out of nine chapters are dedicated to the NHC chemistry of the most common transition metals in this field, while the last two chapters provide an overview and outlook on developments "beyond" the field of classical NHCs.

Many examples given in this book were selected from works of early pioneers to pay tribute to their contributions. Others were chosen to highlight a specific property, reactivity, or behavior of NHCs or their complexes. The purpose of this textbook is not to provide a review on the extensive and most recent organometallic chemistry of NHCs in general. Therefore, I wish to apologize to all researchers in the field whose contributions could not be included, or have unknowingly been left out. A principal task of science is detecting mistakes and errors in a system for rectification and improvement. This textbook should certainly not be exempted from such scrutiny, and any constructive suggestions from colleagues all around the world will be greatly valued.

Being a sole author, it was a tremendous task of more than four years for me to complete this textbook in addition to my usual duties as a scientist and lecturer. I am grateful to all my current and former coworkers for their dedicated work in NHC chemistry, and wish to particularly mention Dr. Qiaoqiao Teng, Dr. Van Ha Nguyen, Mr Xiaoke Xie (Ph.D. cand.), Dr. Guo Shuai and Dr. Jan C. Bernhammer, who helped me in one way or another in the realization of this textbook. Moreover, I wish to thank my Wiley contacts Sarah Hall, Sarah Tilley Keegan, Nithya Sechin, Hari Sridharan, Chris Cartwright and Emma Strickland for

their input and patience. I am indebted to my friend, colleague, and former mentor Professor F. Ekkehardt Hahn for providing a Foreword to this book. The depictions in the textbook were created using site-licensed *ChemDraw Prime* and the freeware *Mercury 3.8* using CIF files from the CCDC websites.

Finally, I hope that students, lecturers, and active researchers in this field will find this textbook useful and stimulating. The chemistry of NHCs is fun, and indeed not that difficult at all.

Han Vinh Huynh
Singapore, September 2016

List of Abbreviations and Definitions

Abbreviation/term	Definition
$\%V_{Bur}$	Percentage of buried volume
γ	Gyromagnetic ratio
$+I$ effect	Positive inductive effect
$-I$ effect	Negative inductive effect
$+M$ effect	Positive mesomeric effect
$-M$ effect	Negative mesomeric effect
°C	Degree Celsius
5-NHC	Five-membered N-heterocyclic carbene
6-DAC	Six-membered diamidocarbene
6-NHC	Six-membered N-heterocyclic carbene
7-DAC	Seven-membered diamidocarbene
7-NHC	Seven-membered N-heterocyclic carbene
8-NHC	Eight-membered N-heterocyclic carbene
Å	Ångström
Ad	Adamantyl
aka	Also known as
All_2-bimy	1,3-diallylbenzimidazolin-2-ylidene
Ar	Aryl
BDE	Bond dissociation energy
Bh_2-bimy	1,3-dibenzhydrylbenzimidazolin-2-ylidene
bimy	Benzimidazolin-2-ylidene
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BMIM	1-butyl,3-methylimidazolin-2-ylidene
Bn_2-bimy	1,3-dibenzylbenzimidazolin-2-ylidene
Bn_2-tazy	1,4-dibenzyl-1,2,4-triazolin-5-ylidene
Bn-btzy	3-benzylbenzothiazolin-2-ylidene
BQ	p-benzoquinone
bzoxNHC	Benzoxazole-functionalized NHC
CAAC	Cyclic alkyl amino carbene
COD	1,5-cyclooctadiene
Cp	Cyclopentadienyl anion
Cp*	Pentamethylcyclopentadienyl anion
CuAAC	Copper-catalyzed azide-alkyne cycloaddition
Cy	Cyclohexyl
DAC	Diamidocarbene
DAE	Diallylether
dba	Dibenzylideneacetone
de	Diastereomeric excess
Dipp	2,6-diisopropylphenyl
ditz	1,2,4-triazolidine-3,5-diylidene
DMFU	Dimethylfumarate
DMSO	Dimethyl sulfoxide

dppd	1,3-diphenyl-1,3-propanedionate
DVDS	1,1,3,3-tetramethyl-1,3-divinyldisiloxane
EMIM	1-ethyl,3-methylimidazolin-2-ylidene
equiv	Equivalent(s)
ESI	Electrospray ionization
Et	Ethyl
eV	Electron volt
FPyr	1,2,3,4,6,7,8,9-octahydropridazino[1,2-*a*]-indazolin-11-ylidene
h	Hour
HB	Conjugate acid of general Brønsted base
HMBC	Heteronuclear multiple-bond correlation
HX	General Brønsted acid
Hz	Hertz
IAd	1,3-diadamantylimidazolin-2-ylidene
IBh	1,3-dibenzhydrylimidazolin-2-ylidene
^{i}Bu$_2$-bimy	1,3-diisobutylbenzimidazolin-2-ylidene
ICy	1,3-dicyclohexylimidazolin-2-ylidene
IFc	1,3-diferrocenylimidazolin-2-ylidene
I^{i}Pr$_{Me2}$	1,3-diisopropyl-4,5-dimethylimidazolin-2-ylidene
IMe	1,3-dimethylimidazolin-2-ylidene
IMe$_{Me2}$	1,3,4,5-tetramethylimidazolin-2-ylidene
IMes	1,3-dimesitylimidazolin-2-ylidene
imy	Imidazolin-2-ylidene
in situ	"In the reaction mixture", without isolation
INap	1,3-di(1-naphtyl)imidazolin-2-ylidene
Ind	Indenyl anion
Indy	Indazolin-3-ylidene
IPh	1,3-diphenylimidazolin-2-ylidene
IPr	1,3-(2,6-diisopropylphenyl)imidazolin-2-ylidene
^{i}Pr	Isopropyl
^{i}Pr,Bn-bimy	1-isopropyl,3-benzylbenzimidazolin-2-ylidene
^{i}Pr$_2$-bimy	1,3-diisopropylbenzimidazolin-2-ylidene
IPy	1,3-di(2-pyridyl)imidazolin-2-ylidene
IR	Infrared
I^{t}Bu	1,3-di(tert-butyl)imidazolin-2-ylidene
IUPAC	International Union of Pure and Applied Chemistry
kJ	Kilojoule
M	Molar
MAH	Maleic anhydride
Me	Methyl
Me$_2$-bimy	1,3-dimethylbenzimidazolin-2-ylidene
Mes	Mesityl
MHMDS	metal hexamethyldisilazide
MS	Molecular sieves
MVS	Metal vapor synthesis
NCA	Weakly or non-coordinating anion
NHC	N-heterocyclic carbene
NMR	Nuclear Magnetic Resonance
NOHC	N,O-heterocyclic carbene
Np	Neopentyl
Np$_2$-bimy	1,3-(2,2-dimethylpropyl)benzimidazolin-2-ylidene
NQ	1,4-naphthoquinone

NSHC	N,S-heterocyclic carbene
NuH	General nucleophile
p-cymene	1-Methyl-4-(1-methylethyl)benzene
PEPPSI	Pyridine-enhanced precatalyst preparation stabilization and initiation
Ph	Phenyl
Ph$_3$tria	1,3,4-triphenyl-1,2,4-triazolin-5-ylidene
ppm	Parts per million
Pr$_2$-bimy	1,3-di(*n*-propyl)benzimidazolin-2-ylidene
pta	1,3,5-triaza-7-phosphaadamantane
Pyry	Pyrazolin-3-ylidene
R	Usually alkyl group
RCM	Ring-closing metathesis
Ref	Reference
ROMP	Ring-opening metathesis polymerization
RT	Room temperature
SIBn	1,3-dibenzylimidazolidin2-ylidene
SIEt	1,3-diethylimidazolidin-2-ylidene
SIMe	1,3-dimethylimidazolidin-2-ylidene
SIMes	1,3-(2,4,6-trimethylphenyl)imidazolidin-2-ylidene
SIPh	1,3-diphenylimidazolidin-2-ylidene
SIPr	1,3-(2,6-diisopropylphenyl)imidazolidin-2-ylidene
SI^{t}Bu	1,3-di(tert-butyl)imidazolidin-2-ylidene
t	Time
T	Temperature
tazy	1,2,4-triazolin-5-ylidene
^{t}Bu	Tertiary butyl
TCNE	Tetracyanoethylene
TEP	Tolman's Electronic Parameter
THF	Tetrahydrofurane
THT	Tetrahydrothiophene
timy	1,3,4,5-tetramethylimidazolin-2-ylidene
tmeda	N,N,N′N′-tetramethylethylenediamine
TMSCl	Chlorotrimethylsilane
tol	Tolyl
tria	Triazolin-5-ylidene
UV-vis	Ultraviolet–visible
via	by using
*a*NHC	*Abnormal* N-heterocyclic carbene
MIC	*Mesoionic* carbene, here *mesoionic* 1,2,3-triazolin-5-ylidene
*r*NHC	*Remote* N-heterocyclic carbene
trz	*Normal* 1,2,3-triazolin-5-ylidene
Pyry	Pyrazolin-3/5-ylidene
D	Debye (unit for dipole moment)
Indy	Indazolin-3-ylidene

1 General Introduction

1.1 Definition of Carbenes

According to the International Union of Pure and Applied Chemistry (IUPAC) a carbene [1] is "*the electrically neutral species H_2C: and its derivatives, in which the carbon is covalently bonded to two univalent groups of any kind or a divalent group and bears two nonbonding electrons, which may be spin-paired (singlet state) or spin-non-paired (triplet state)*." In general terms, carbenes are therefore neutral compounds R_2C: derived from the parent methylene (H_2C:) that feature a divalent carbon atom with only six valence electrons, which result from four bonding electrons in the two R–C bonds and two non-bonding electrons remaining at the carbene center. The geometry at the carbene carbon can be either linear or bent, depending on the degree of hybridization [2]. The linear geometry is based on an *sp*-hybridized carbene center with two nonbonding, energetically degenerate *p* orbitals (p_x and p_y). On the other hand, the bent geometry is adopted when the carbene carbon atom is sp^2-hybridized. On transition from the *sp*- to sp^2-hybridization, the energy of one *p* orbital, usually called p_π, remains almost unchanged, while the newly formed sp^2-hybrid orbital, normally called σ, is energetically stabilized as it acquires partial *s* character (Figure 1.1). However, the linear geometry is rarely observed, and most carbenes contain a sp^2-hybridized carbene center and are therefore bent.

For the simple linear case and without considering π contributions of the R-substituents, only the $p_x^1 p_y^1$ electronic configuration is feasible according to Hund's first rule [3], due to the degeneracy of the p_x and p_y orbitals. The two unpaired electrons are both "spin up" ($m_s = \frac{1}{2}$) giving rise to a total spin of $S = 1$, which in turn results in a spin multiplicity of $M = 3$ (Equation 1.1). Therefore, linear carbenes are generally in a triplet state. On the other hand, two common electronic configurations are possible for the carbene carbon in bent species. The two nonbonding electrons can singly occupy the two different σ and p_π orbitals with parallel spins ($\sigma^1 p_\pi^1$), which also leads to a triplet ground state ($^3B_1$). Alternatively, the two nonbonding electrons can also be spin-paired in the energetically more favorable σ orbital ($\sigma^2 p_\pi^0$) leading to a singlet ground state ($^1A_1$).

In addition to the two ground states in bent carbenes, two less favorable electronic configurations are conceivable (not depicted) that give rise to singlet states. The first has two spin-paired electrons in the p_π orbital ($\sigma^0 p_\pi^2$, $^1A_1$), and the second has two electrons singly occupying the σ and p_π orbitals, but with opposite spins ($\sigma^1 p_\pi^1$), giving rise to an excited singlet state ($^1B_1$) [4]. The latter two electronic configurations and their states have little significance for the discussion in this work.

The properties and reactivities of bent carbenes are primarily determined by their ground state spin multiplicity [5]. The two singly occupied orbitals in triplet carbenes are unsaturated (open-shell) and can accommodate one more electrons of opposite spin each. Thus, it

Figure 1.1
Relationship between the carbene bond angle, the nature of the frontier orbitals and singlet–triplet separation.

is intuitive to assign an *electrophilic* or *diradical* character to the carbene carbon (Figure 1.1). Singlet carbenes, on the other hand, contain a fully occupied σ orbital (closed-shell, nucleophilic) and an empty p_π orbital (electrophilic). The presence of both electrophilic and nucleophilic sites makes singlet carbenes formally *ambiphilic*.

$$M = 2\,S + 1, where\ S = \Sigma m_s = \tfrac{1}{2} \times n\,(unpaired\ electrons)$$

Equation 1.1
Definition of spin multiplicity for the determination of singlet and triplet state.

Whether a bent carbene adopts the singlet or triplet ground state is determined by the relative energies of the σ and p_π orbitals, which in turn is influenced by the direct substituents R at the carbene carbon. A large energy gap of at least 2 eV (~193 kJ/mol) between the σ orbital and the p_π orbital is required to stabilize a singlet ground state, whereas an energy difference of less than 1.5 eV (~145 kJ/mol) leads to a triplet ground state [6].

The relative energies of σ and p_π orbitals can also be influenced by the steric and electronic effects of the substituents on the carbene carbon atom. For instance, electron-withdrawing substituents (–*I* effect) inductively stabilize the σ orbital by enriching its *s* character and leave the p_π orbital essentially unchanged, thereby increasing the energy gap between the σ and p_π orbitals. Thus the singlet state is favored. On the other hand, electron donating groups (+*I* effect) decrease the energy gap between σ and p_π orbitals, which stabilizes the triplet state.

Besides inductive effects, which govern the ground-state spin multiplicity in carbenes, mesomeric effects of the R-substituents also play a crucial role by influencing the degree of bending in singlet carbenes. If the carbene carbon is attached to at least one π-accepting group Z (–*M* effect), for example, Z = COR, CN, CF$_3$, BR$_2$, or SiR$_3$, a linear or quasi-linear geometry is predicted. In this case, the initial degeneracy of the p_x and p_y is broken through π interactions with the Z substituents, therefore allowing for an unusual linear singlet state.
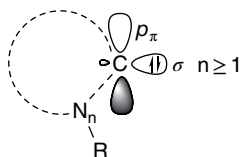
Figure 1.2
Minimum structural requirement for an N-heterocyclic carbene.

On the other hand, π-electron donating X substituents (+*M* effect), for example, X = N, O, P, S, and halogens, adjacent to the carbene center increase the energy of the p_π orbital of the carbene carbon atom. Since the σ orbital remains unchanged, the σ–p_π gap is increased, and hence a bent singlet state is favored.

N-heterocyclic carbenes (NHCs) are carbenes incorporated into heterocyclic rings that must contain at least one nitrogen atom. This minimum structural requirement for an NHC is highlighted in Figure 1.2. In addition to nitrogen, other heteroatoms may also be part of the ring system. Generally, they are bent singlet carbenes. Since they are a centerpiece of this book, the properties and electronic structures of NHCs will be discussed in more detail in Chapter 2.

1.2 Historical Overview of Carbenes, N-Heterocyclic Carbenes, and Their Complexes

The following section gives a brief overview on the milestones in the historical development of N-heterocyclic carbenes and their early use as ligands in organometallic chemistry. It is not the intention to provide a detailed account of short-lived carbene and carbenoid chemistry in general, which goes beyond the scope of this textbook, the focus of which is classical N-heterocyclic carbenes. The pioneering work of Jack Hine, William Doering, Philip Skell, Gerhard Closs, and later Robert A. Moss, Wolfgang Kirmse, Hideo Tomioka, and others on such highly reactive species are recounted elsewhere in detail [7], and will not be further mentioned here. Further, this section is divided into two parts. The first deals with the quest for free carbenes, while the second provides a brief summary dealing with the stabilization of carbenes, particularly of NHCs, by transition metals in an historical context. The milestones of these two separate quests are summarized in two timelines depicted in Figure 1.3 and Figure 1.4.

1.2.1 The Quest for Free Stable Carbenes

The quest for stable carbenes [8, 9], and in particular that for methylene (H_2C:) as the simplest possible representative began back in 1835 [10], when the French chemist Jean-Baptiste Dumas (1800–1884) tried to synthesize methylene by dehydration of methanol (CH_3OH) using phosphorus pentoxide or sulfuric acid. In those days, it was known that carbon can form compounds with oxygen and hydrogen in different oxidation states. In particular, these include carbon monoxide ($C^{II}O$), carbon dioxide ($C^{IV}O_2$) and methane ($C^{-IV}H_4$). Thus, the search for a carbon-hydrogen compound in which carbon adopts the missing intermediate –II oxidation state seemed a reasonable and doable task. In analogy

Quest for free carbenes
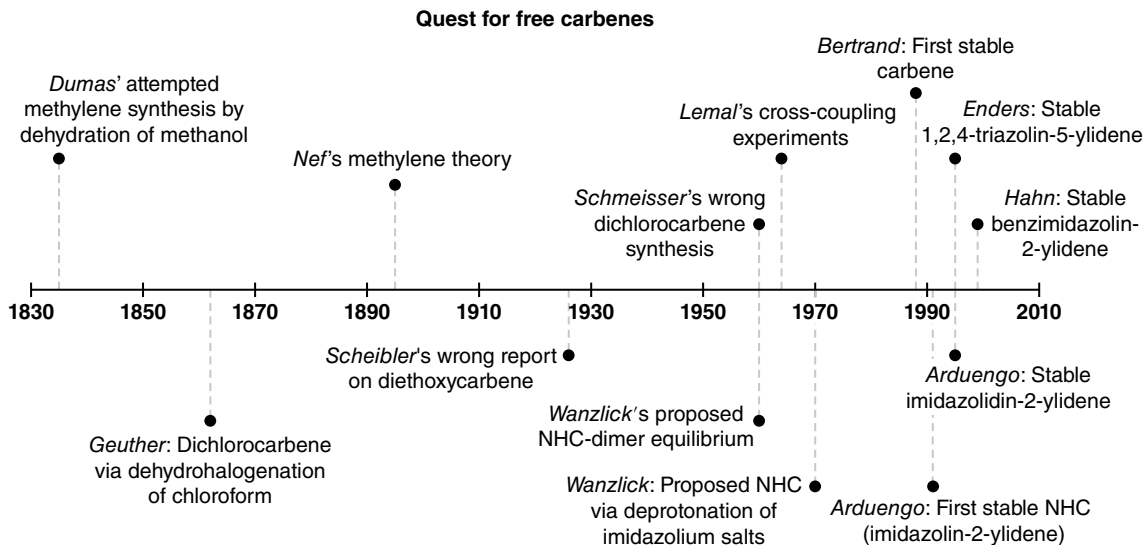
Figure 1.3
Milestones in the quest for free carbenes.

Quest for carbene complexes

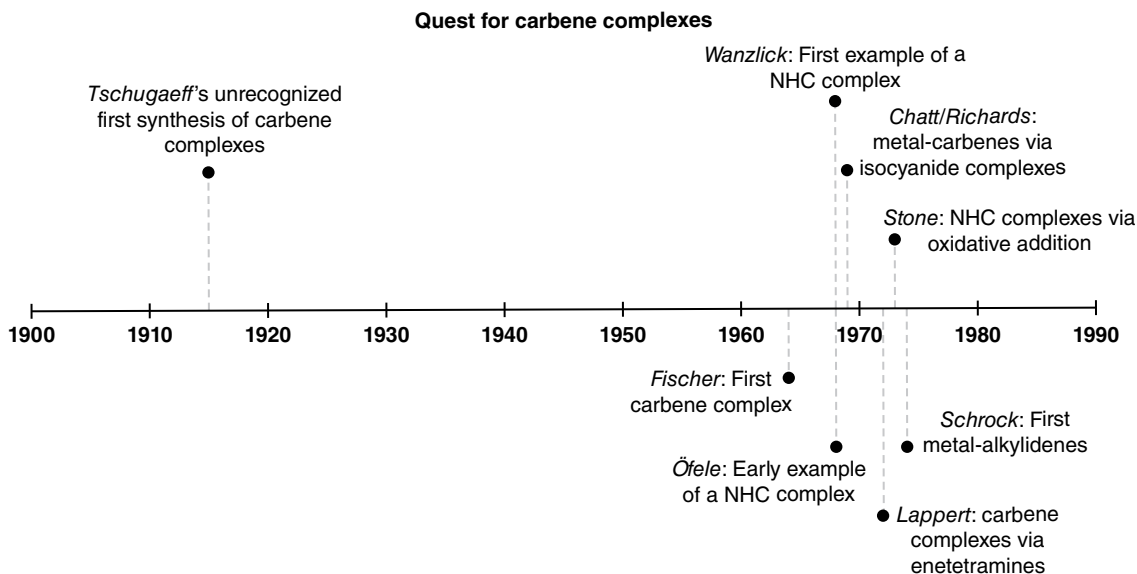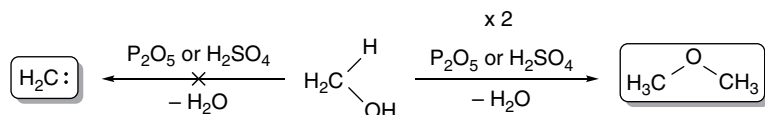**Figure 1.4**
Milestones in the quest for carbene complexes.

to the aforementioned gaseous carbon compounds, Dumas' reaction indeed afforded a gaseous compound. Nowadays, we know that he had prepared dimethyl ether (CH_3OCH_3), which indeed had formed by dehydration, but under condensation of two methanol molecules (Scheme 1.1) instead of from a single molecule.

Scheme 1.1
Dumas' attempt to prepare methylene afforded dimethyl ether.
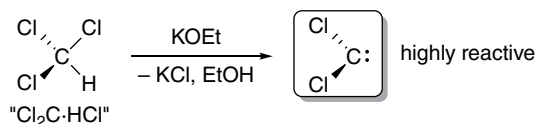
Scheme 1.2
Dehydrohalogenation of chloroform to give dichlorocarbene.
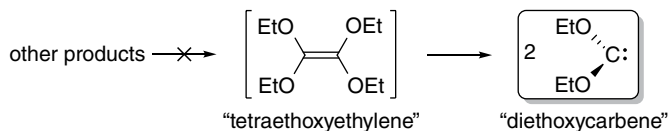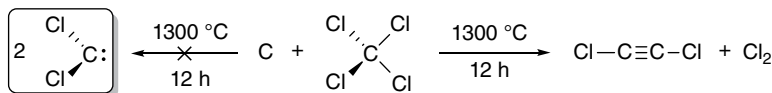

Scheme 1.3
Wrongly proposed formation of diethoxycarbene.

Pursuing a similar strategy, Anton Geuther (1833–1889) treated chloroform with potassium ethoxide solution in ethanol. He considered chloroform ($CHCl_3$ = "$Cl_2C \cdot HCl$") as a simple HCl adduct of dichlorocarbene (Cl_2C:), and in 1862, he proposed the formation of the latter according to Scheme 1.2 [11]. This dehydrohalogenation reaction indeed yielded the dichlorocarbene, which under the given reaction conditions was, however, too reactive to be isolated and quickly decomposed to other products.

In 1895 and 60 years after Dumas report, Johann Ulric Nef (1862–1915) announced that he would tackle the preparation of methylene and its nitrogen free derivatives based on his previous work on derivatives of hydrogen cyanide [12]. He subsequently proposed a theory, in which methylene can be regarded as a suitable building block in organic chemistry and predicted its large scale synthesis [13]. Nevertheless, methylene remained elusive.

The next proposed preparation of a carbene that attracted attention was reported in 1926 by Helmut Scheibler (1882–1966) [14]. According to this report, the reaction of sodium ethoxide with certain esters would—after a complicated and wrong reaction sequence—eventually give tetraethoxyethylene, which further decomposes to two molecules of diethoxycarbene (Scheme 1.3). Interestingly, Scheibler already proposed the formation of a carbene dimer, which dissociates into free monomeric carbenes. This proposal was heavily criticized by the chemical community at that time and finally revoked by later studies.

Another preparation of the highly reactive dichlorocarbene that attracted the attention of the scientific community was reported in 1960 by Martin Schmeisser (1912–1981), who suggested that treatment of tetrachloromethane with activated carbon at very high temperatures would give dichlorocarbene among a range of other products (Scheme 1.4). The claimed "carbene" could according to the authors be condensed as a yellow solid in a cold trap immersed in liquefied air. Furthermore, subsequent reactions such as phosgene formation in air and insertions into double bonds were used as indications of the successful

Scheme 1.4
Proposed dichlorocarbene synthesis by comproportionation of carbon with CCl_4.
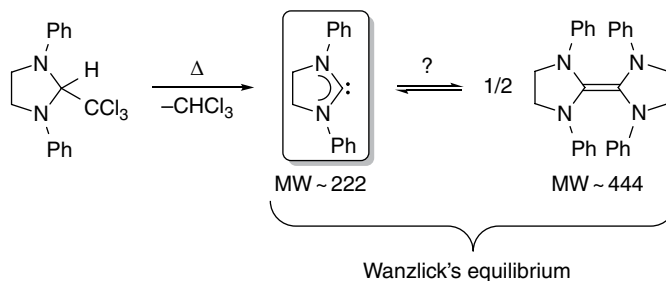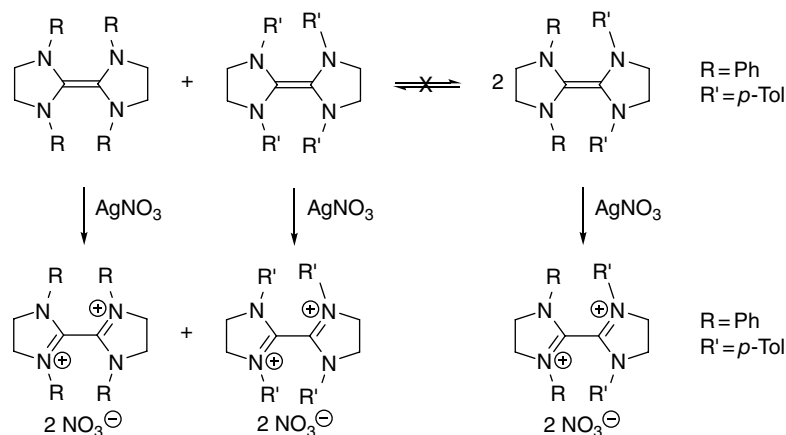

Scheme 1.5
Wanzlick's proposed synthesis of an NHC and its monomer–dimer equilibrium.

dichlorocarbene formation. Further studies by his own team revealed that the activated carbon did not react with CCl_4, but catalyzed its decomposition. The yellow product isolated was later correctly identified as a mixture of dichloroacetylene and chlorine.

These numerous failed attempts to isolate free carbenes led the chemical community to think of carbenes only as fleeting intermediates that are too reactive to be isolated [7]. Thus, any further report on their isolation was skeptically regarded. It was during such a time when Hans-Werner Wanzlick (1917–1988), a former student of H. Scheibler, reported in 1960 that thermolysis of 1,3-diphenyl-2-trichloromethylimidazolidine would lead to an α-elimination of chloroform and formation of a carbene, which could be isolated as a colorless crystalline material [15]. The molecular weight determined for this material was 300 Da, which is in between the theoretical value for the free carbene and its dimer, and therefore Wanzlick assumed a monomer–dimer equilibrium (Scheme 1.5).

For Wanzlick's search for a free carbene, it was unfortunate that he was working on the fully saturated imidazolidine-based system. Nowadays, we know that the dimeric entetramine form is more favorable for such systems. Although the elimination of chloroform was accepted, Wanzlick's proposed equilibrium, and therefore the existence of free carbenes in the reaction mixture, was heavily debated.

In 1964, David M. Lemal published results of cross-coupling experiments that provided evidence against the existence of Wanzlick's equilibrium and consequently ended Wanzlick's claim for the isolation of a free carbene [16]. Using NMR spectroscopy, Lemal and coworkers heated a mixture of two tetraaminoethylenes with very similar N-substituents in xylene under reflux for 2 h, and subsequently subjected the mixture to oxidation using $AgNO_3$ (Scheme 1.6). No oxidized derivatives of cross metathesis products were found, and instead, only symmetrical 2,2′-bis(imidazolinium) nitrates as oxidation products derived from the two starting materials were identified. Similar cross-coupling experiments and analysis by gas chromatography by Winberg and coworkers published in 1965 [17], confirmed Lemal's view that an equilibrium does not exist in the absence of any electrophiles.

Scheme 1.6
Cross-coupling experiments conducted by D. M. Lemal and coworkers.
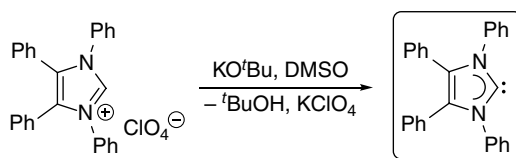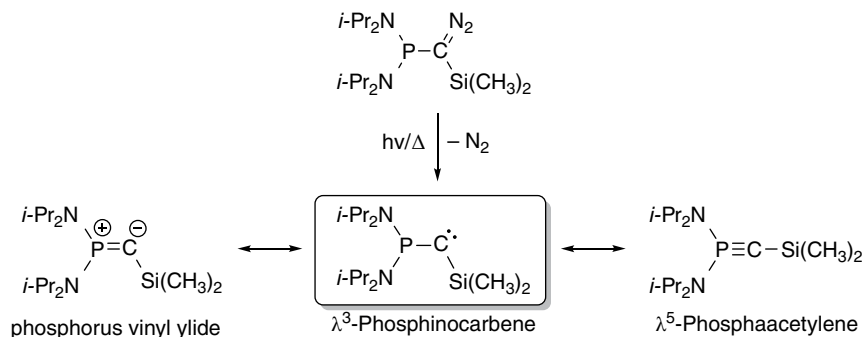

Scheme 1.7
Deprotonation of tetraphenylimidazolium salt to give a carbene.

In 1970, Wanzlick again proposed the formation of a free carbene that could be obtained by deprotonation of an imidazolium salt (Scheme 1.7) [18]. Although dimerization of this species was not observed, he unfortunately did not attempt to isolate the compound, which we nowadays know is indeed an N-heterocyclic carbene. Instead, subsequent reactions with transition metals and other electrophiles were studied with *in situ* generated carbenes.

Due to the many failures in isolating stable carbenes, this field of research remained relatively dormant during the next decade, until finally Guy Bertrand and his team in 1988 reported the isolation of the first free carbene that was stabilized by heavier main group elements. Thermolysis or photolysis of (trimethylsilyl)[bis(diisopropylamino)phosphino] diazomethane liberated dinitrogen and a new compound was obtained (Scheme 1.8), which showed properties and behavior similar to phosphaacetylenes, but peculiarly also that of carbenes [19]. The compound was reported to be stable for weeks at room temperature under an inert atmosphere. The ambiguity over whether the isolated compound was a carbene or phaspha-alkyne was finally addressed by a subsequent paper of the same group, where they provided further and convincing evidence for carbene-like reactivities of the species in question, such as insertion into double bonds and formation of oxirans with aldehydes [20]. These findings established [bis(diisopropylamino)phosphino]trimethyl-silylcarbene as the first stable nucleophilic carbene that has been isolated and fully characterized in substance.

Bertrand's work demonstrated that carbenes can be isolated in pure form. Nevertheless, handling of such carbenes is difficult and requires very elaborate synthetic skills. So, it

Scheme 1.8
Bertrand's [bis(diisopropylamino)phosphino]trimethylsilylcarbene and its relationship to the respective phospha-alkyne and ylide.
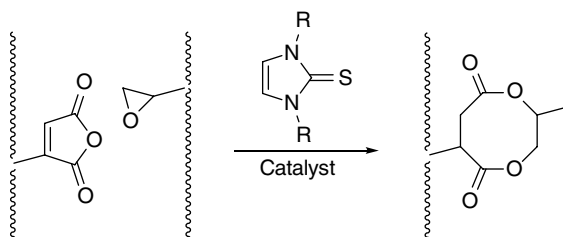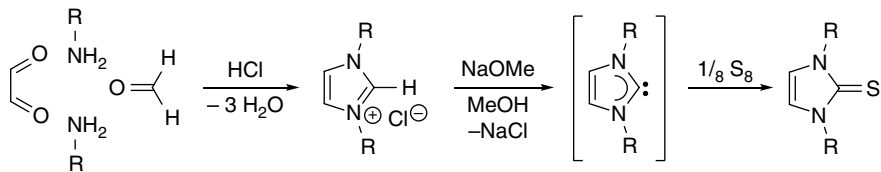

Scheme 1.9
Crosslinking of anhydride- and epoxide-functionalized low molecular weight polymers.

appears that the chemical community was just waiting for the next discovery, which would propel carbene chemistry from a niche area to mainstream research.

Around the same time as Bertrand's report on his first stable carbene, industrial chemists at DuPont had identified imidazolin-2-thiones as suitable organocatalysts for crosslinking of acid anhydride- and epoxide-functionalized low molecular weight polymers to higher molecular weight polymers for the production of watersoluble coatings for automotive use (Scheme 1.9).

Since imidazolin-2-thiones were not commercially available and older methodologies were too costly for preparation on an industrial scale, a newer cost efficient approach had to be developed. For this purpose, the old Wanzlick-type chemistry was re-investigated. The multi-component condensation reaction of one equivalent of gyoxal, two equivalents of primary amine and one equivalent of formaldehyde provided convenient access to imidazolium chloride salts after addition of hydrochloric acid. Deprotonation of such an imidazolium salt afforded an N-heterocyclic carbene *in situ*, which was trapped by addition of elemental sulfur to give the desired imidazolin-2-thiones (Scheme 1.10).

The reaction sequence was tested in the laboratory under an inert atmosphere to prevent decomposition of the *in situ* generated carbene prior to oxidation with sulfur. On an industrial scale using a 2000 L reactor, however, precautions to exclude moisture and air were impossible. Nevertheless, the product yields remained surprisingly high and comparable to those of lab scale experiments. It was therefore concluded that the supposedly reactive carbene intermediate must be relatively stable to survive such conditions.

Scheme 1.10
Preparation of imidazoline-2-thiones as crosslinking organocatalysts.
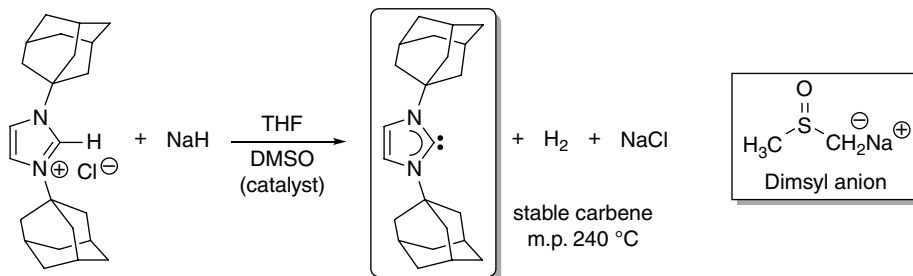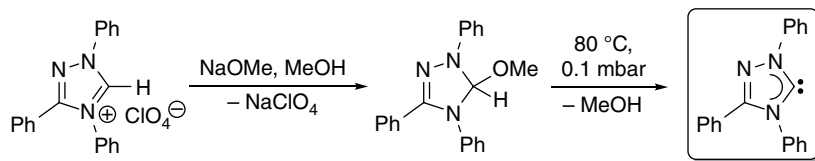

Scheme 1.11
Preparation of the stable 1,3-di-1-adamentylimidazolin-2-ylidene (IAd) as the first representative of free NHCs.

Subsequently, Anthony J. Arduengo III and his team made the first attempts to isolate free imidazolin-2-ylidenes bearing sterically bulky N-adamantyl wing tip groups, and reported their findings in 1991. The respective imidazolium chloride was treated with sodium hydride (NaH) in tetrahydrofurane (THF) with catalytic amounts of dimethyl sulfoxide (DMSO), which generated the dimsyl anion as an intermediate base (Scheme 1.11). Dihydrogen gas (H_2) and sodium chloride (NaCl) formed as easily removable byproducts. Concentration of the THF filtrate afforded large colorless single crystals, which were subjected to single crystal X-ray diffraction analysis to evaluate the solid state molecular structure of the isolated compound. The results obtained confirmed that deprotonation of 1,3-di-1-adamantylimidazolium chloride had yielded the first free N-heterocyclic carbene, which is indefinitely stable if kept under an inert atmosphere. Intriguingly, it is also thermally very stable and melts without decomposition at 240 °C [21].

Following Arduengo's successful and seminal isolation of the first free NHC, there have been numerous other reports detailing various methods through which free NHCs can be isolated [22].

In 1995, the groups of Dieter Enders and J. Henrique Teles together reported the isolation and solid state molecular structure of the first 1,2,4-triazolin-5-ylidene. This carbene was prepared by the addition of sodium methoxide to 1,3,4-triphenyl-1,2,4-triazolium perchlorate in methanol, which afforded the neutral 5-methoxy-1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazole. Upon heating to 80 °C under low pressure, the latter endothermically decomposes under α-elimination of methanol to form the stable 1,3,4-triphenyl-1,2,4-triazolin-5-ylidene (Scheme 1.12) [23]. Apparently, an additional heteroatom in the heterocyclic ring does not negatively affect the stability of the carbenes. Moreover, this carbene should become the first commercially available NHC. Notably, these researchers successfully applied, in principle, the same α-elimination approach that Wanzlick previously attempted in 1960.

Scheme 1.12
Enders α-elimination approach to the first stable 1,2,4-triazolin-5-ylidene.
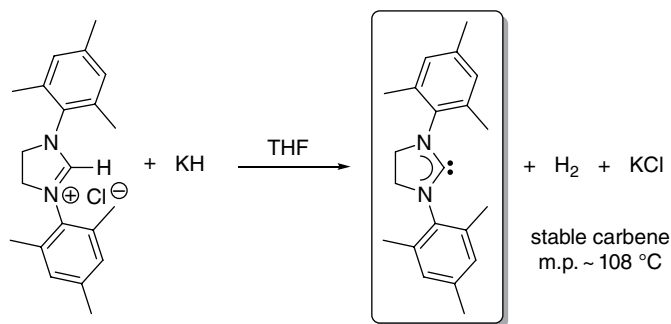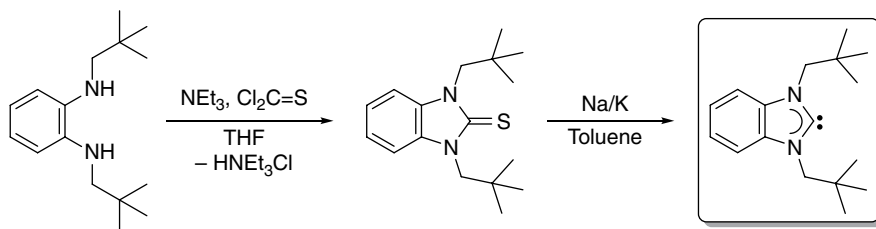

Scheme 1.13
Arduengo's isolation of the first imidazolidin-2-ylidene.

In the same year, Arduengo and coworkers also demonstrated that saturated imidazolidin-2-ylidenes can be isolated as monomeric species when sufficiently bulky N-substituents are applied to provide kinetic stability against dimerization to enetetramines.

Thus, by deprotonation of 1,3-dimesitylimidazolinium chloride with potassium hydride (KH) in dry THF, the researchers obtained the free and monomeric 1,3-dimesitylimidazolidin-2-ylidene (SIMes) as the first example of a saturated NHC (Scheme 1.13) [24]. This carbene was again structurally characterized by single crystal diffraction and showed a melting point of ~ 108 °C.

Finally, in 1999, F. Ekkehardt Hahn and coworkers reported the isolation and solid state structure of the first benzimidazolin-2-ylidene, completing the series of free NHCs for the four types of classical NHCs. The authors started with N,N′-dineopentyl-substituted *ortho*-phenylenediamines, which upon reaction with thiophosgene and triethylamine (NEt₃, to trap *in situ* generated hydrochloric acid) gave N,N′-dineopentylbenzimidazolin-2-thione. Reductive desulfurization using sodium/potassium alloy in toluene yielded the first free benzimidazolin-2-ylidene, which was also structurally characterized by single crystal X-ray diffraction (Scheme 1.14) [25]. Similar to saturated NHCs, the choice of sufficiently bulky wing tip groups is crucial to avoid dimerization to enetetramines.

It was now clear that stable NHCs of various backbones can be isolated in pure form. In retrospect, these later discoveries revealed that Wanzlick's hypothesis on stable NHCs was indeed correct, although he never isolated any by himself. Since the isolation of the first free NHCs 40 years after Wanzlick's proposal, the chemistry of NHCs has grown exponentially. Nowadays, free NHCs and many of their precursors are commercially available. They have become state-of-the-art organocatalysts and are routine ligands in organometallic chemistry and transition metal mediated catalysis. Applications of NHCs in other areas are beginning to surface, promising an even brighter future for these unique species.

Scheme 1.14
Hahn's approach for the isolation of the first benzimidazolin-2-ylidene.

red complex   yellow complex
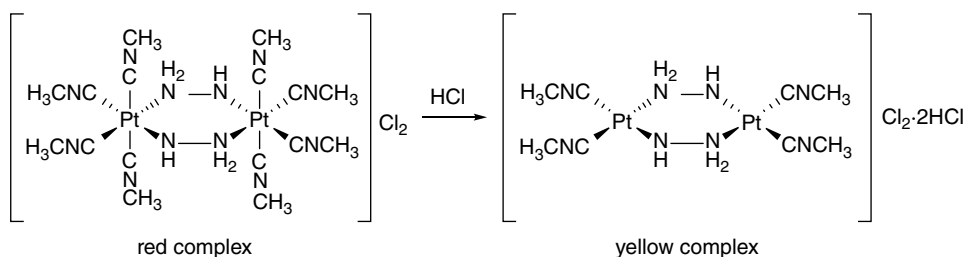
Scheme 1.15
Tschugajeff's wrongly proposed structures for his two colored complexes.

1.2.2 The Quest for Carbene Complexes

Compared to the quest for free carbenes, the historical events related to their stabilization by transition metals, and therefore attempts to isolate carbene complexes, were generally less debated. From today's point of view, the most obvious route to generate carbene complexes, and generally for all complexes, would be the reaction of a ligand with a chosen transition metal salt. However, such an approach for carbene complexes is historically insignificant, for the first free carbenes were only isolated in 1988 and 1991, respectively. Therefore, most successful pathways fall into the categories of metal-template-directed synthesis or *in situ* generation of free carbene in the presence of metal ions as carbene traps.

The first carbene complex was probably—but also unknowingly—prepared by Lew Alexandrowitsch Tschugajeff [26] (1873–1922) and coworkers in 1915 by the treatment of tetrakis(methylisocyanide)platinum(II) with hydrazine, which afforded a red crystalline complex. Protonation of this red complex with hydrochloric acid led to the release of methylisocyanide and the formation of yellow crystals. For both compounds, he wrongly proposed dimeric Pt^{II} species with bridging ligands, which were formally derived from the deprotonation of hydrazine (Scheme 1.15) [27].

Only a reinvestigation of Tschugajeff's complexes in 1970 by John E. Enemark and coworkers, that also included X-ray diffraction studies, revealed that these complexes were most likely the first carbene complexes to be synthesized [28]. The red and cationic acyclic monocarbene Pt(II) complex was formed by initial nucleophilic attack of hydrazine on coordinated carbon donors of two isocyanide ligands with concurrent proton shift. Protonation of the iminic nitrogen atom of the red complex with excess hydrochloric acid and isocyanide-chlorido ligand substitution led to reversible formation of the yellow and neutral dichlorido-dicarbene Pt^{II} complex (Scheme 1.16).
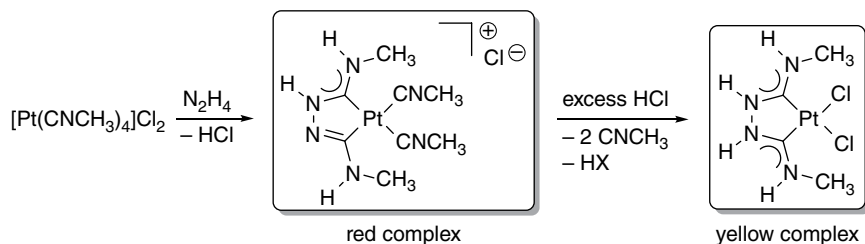
Scheme 1.16
Template-assisted approach to Tschugaeff's Pt^{II} carbene complexes.
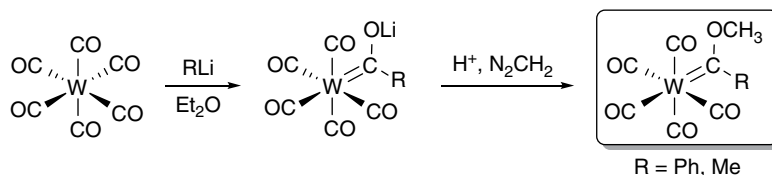
Scheme 1.17
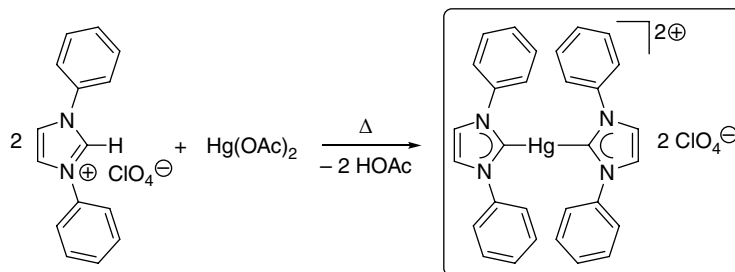Fischer's first carbene complex synthesis.

Notably, the attack of protic nucleophiles, such as alcohols or primary or secondary amines, on coordinated isocyanide ligands, has become a standard template-assisted approach to metal complexes, yielding acyclic and cyclic carbenes including NHCs.

However, the first person who knowingly prepared a metal-carbene complex was the German chemist and Nobel laureate Ernst Otto Fischer (1918–2007), working in Munich [29]. In 1964, he reported the attack of organolithium reagents on a coordinated carbonyl ligand in hexacarbonyltungsten(0). The resulting carbene complex anion could be precipitated as an ammonium salt or protonated with acids. Further reaction of the protonated complex with diazomethane gave stable complexes bearing either a methoxymethylcarbene or methoxyphenylcarbene ligand (Scheme 1.17) [30]. Such types of carbene complexes was named after their discoverer as *Fischer carbene complexes*. They typically contain metal centers in low to middle oxidation states, and the carbene donor is adjacent to at least one heteroatom-substituent. Furthermore, the co-ligands are usually good π-acceptors, and octahedral representatives generally fulfill the 18-electron rule. In terms of reactivity, Fischer carbene complexes typically undergo nucleophilic attack at the electrophilic carbene carbon.

In 1968 and four years after the publication of the first carbene complex by E. O. Fischer, the groups of Wanzlick in Berlin and Öfele in Munich almost simultaneously reported their work on the isolation of the first NHC complexes.

Wanzlick reacted 1,3-diphenylimidazolium perchlorate salt with mercury(II) acetate. Formally, the basic acetato ligands deprotonate the imidazolium salts to generate free carbenes, which immediately coordinate to the mercury center forming the cationic, linear 14-electron bis(1,3-diphenylimidazolin-2-ylidene)mercury(II) perchlorate complex (Scheme 1.18) [31].

In the same year, Karl Öfele reported a similar strategy for NHC complexes. In his case, *in situ* deprotonation occurred by heating the 1,3-dimethylimidazolium-pentacarbonylhydridochromate(0) complex salt, which under oxidative liberation of dihydrogen afforded the neutral pentacarbonyl(1,3-dimethylimidazolin-2-ylidene)chromium(0) complex (Scheme 1.19) [32].

Scheme 1.18
Wanzlick's route to the first NHC complex.
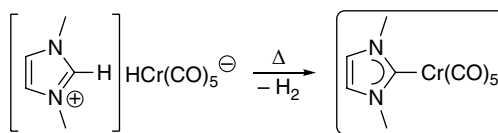
Scheme 1.19
Öfele's early NHC complex synthesis.
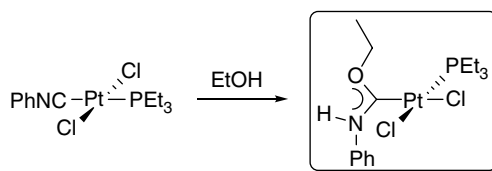
Scheme 1.20
Chatt and Richard's preparation of a carbene complex by nucleophilic attack on a coordinated isocyanide.

In 1969, more than 50 years after Tschugaeff's report on the reaction of protic nucleophiles with isocyanide complexes, Joseph Chatt (1914–1994) and Raymond L. Richards communicated a convenient route to carbene complexes by essentially the same approach. They reacted the complex *trans*-[PtCl$_2$(CNPh)(PEt$_3$)] with ethanol and obtained a white, sparingly soluble complex that turned out to be the mixed carbene/Phosphine complex *cis*-[PtCl$_2${C(OEt)NHPh}(PEt$_3$)] (Scheme 1.20) [33].

In 1971, Michael F. Lappert's (1928–2014) team demonstrated that carbene complexes can also be obtained by the reaction of carbene dimers with transition metal complexes. Since the existence of free carbenes was unknown at that time, this approach was the closest to an obvious reaction of the free ligand with a metal salt. The dimer of 1,3-diphenylimidazolidin-2-ylidene was chosen to react with a dimeric platinum(II)-phosphine complex in a 1:1 ratio to give two equivalents of the respective mixed phosphine-carbene Pt^{II} complex under chlorido-bridge-cleavage (Scheme 1.21) [34]. Later it was found that the use of bridged complex-dimers was not a necessity for the cleavage of electron-rich entetramines [35].

Shortly after in 1973, F. Gordon A. Stone (1925–2011) reported an elegant alternative route to carbene complexes via oxidative addition of simple 2-halo-azoles, for example,
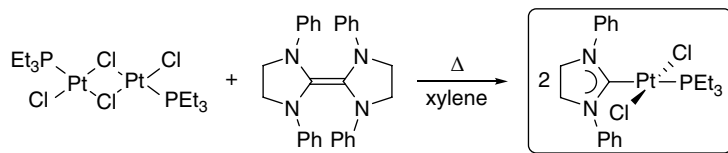
Scheme 1.21
Lappert's access to NHC complexes via cleavage of electron-rich entretramines with transition
metal complexes.
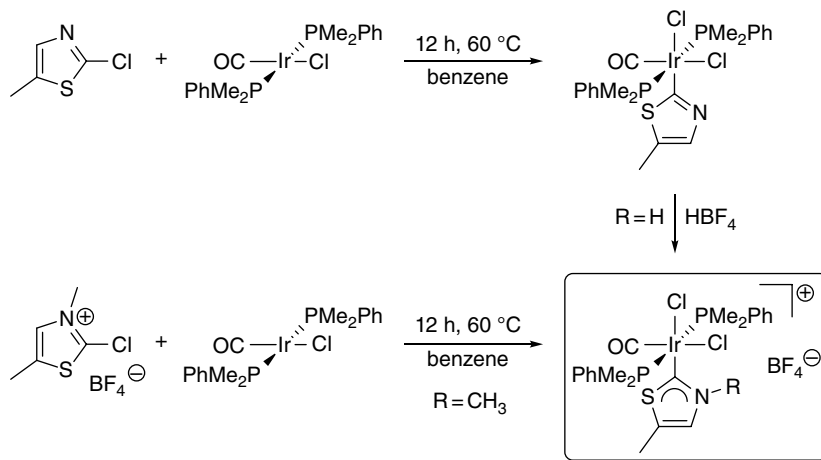
Scheme 1.22
Stone's pathway to NHC complexes via oxidative addition.

2-chloro-4-methylthiazole, 2-chlorobenzoxazole and 2-chlorobenzothiazole, to electron-
rich, low-valent metal precursors under carbon-halogen bond activation. Neutral *C*-bound
complexes were isolated as primary reaction products, which upon N-protonation with
perchloric or tetrafluoroboric acid gave rise to cationic NHC complexes (Scheme 1.22,
upper pathway) [36].

N-alkylation of the neutral *C*-bound complexes was unsuccessful, but complexes of
N-alkylated NHC ligands could be directly obtained by oxidative addition using the N-alkylated
azolium salts (Scheme 1.22, lower pathway) [37].

Up to this point in time, all carbene complexes reported contained singlet carbene ligands
that bear a heteroatom adjacent to the carbene carbon, and can thus be broadly classified as
Fischer carbene complexes. Complexes of carbenes with only hydrogen or alkyl substitu-
ents were unknown until Nobel laureate Richard R. Schrock reported the first example in
1974 [38]. Complexes of this type are referred to as *Schrock carbene (or alkylidene) com-
plexes* and are distinctively different from Fischer carbene complexes.

The first preparation involved the reaction of dichlorido-trineopentyltantalum(V) with
two equivalents of neopentyllithium in an attempt to investigate sterically bulky peralkyl
complexes (Scheme 1.23). Instead, the first Schrock alkylidene complex was obtained as
a very soluble orange crystalline material via α-hydrogen abstraction of a coordinated
neopentyl ligand.