



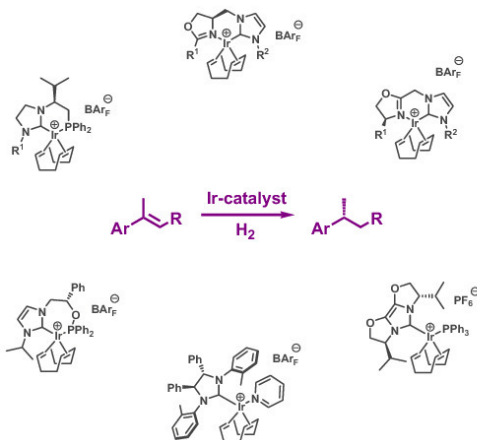
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N-Heterocyclic Carbene Ligands for Iridium-Catalysed Asymmetric Hydrogenation



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1.1 *N*-Heterocyclic carbene (NHC)

1.1.1 Historical perspective

Since the pioneering work of Doering in 1954, carbenes have been recognised as a unique type of intermediate with characteristics distinct from radicals already known in the organic chemistry community.¹ Since then, research on carbenes has rapidly expanded, but almost no attempts were made to stabilise carbenes until the 1980s when Tomioka started to study persistent triplet diarylcarbenes.²

The first isolable carbenes were reported in 1988 by Bertrand³ (**1**) and 1991 by Arduengo⁴ (**2**). Phosphinocarbene **1** can be distilled at 80-85°C/10⁻² Torr and *N*-heterocyclic carbene (NHC) **2** is a crystalline solid that melts at above 240-241°C (Figure 1.1).

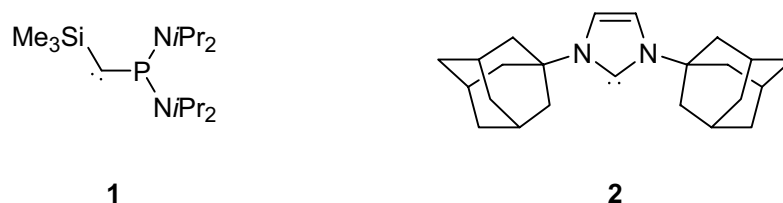


Figure 1.1 The first isolated carbenes.

Although NHCs have been known since the pioneering work of Wanzlick, who observed their dimerisation⁵ and was able to trap them to form mercury-salt carbene complexes,⁶ thirty years went by before the first NHC was isolated. The particular stability of the NHCs made them very popular and during the following years further analogues were synthesised (Figure 1.2). In 1995, Arduengo proved⁷ using NHC **3** that aromaticity was not needed for stabilisation, and in 1996 Alder isolated acyclic NHC **4**.⁸ This research area has been continually expanded with the isolation of four-membered carbene⁹ **5** by Grubbs and alkyl carbene¹⁰ **6** by Bertrand in 2004.

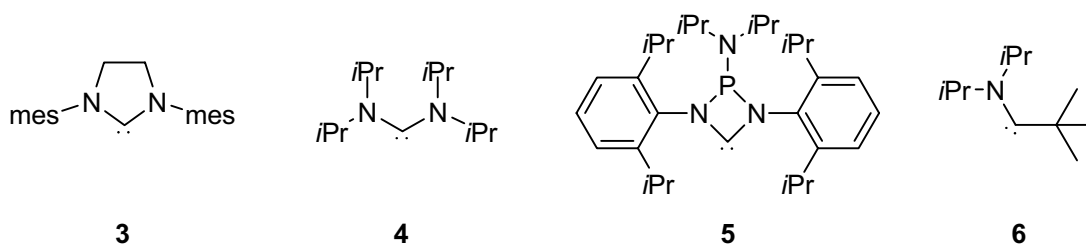


Figure 1.2 Stable NHCs and their derivatives.

1.1.2 Nomenclature

For the sake of homogeneity, the following nomenclature will be used throughout this work.¹¹ NHCs **7** which are related to an imidazoline structure will be called *1,3-di-R-imidazolin-2-ylidenes* and NHCs **8** with a saturated C-C double bond will be described as *1,3-di-R-imidazolidin-2-ylidenes* (Figure 1.3).



Figure 1.3 Nomenclature of the various NHCs.

1.1.3 General characteristics

Carbenes are neutral divalent carbon with only six electrons in its valence shell. With two nitrogen substituents next to the C_{carbene} atom, the NHCs are predicted to stabilise their singlet state (two paired electrons in the σ orbital) by a push-pull effect (Figure 1.4).¹² Firstly, the σ -electronwithdrawing nitrogen inductively stabilises the σ -nonbonding orbital by increasing its s-character. Secondly, the energy of the vacant p_{π} -orbital is increased by interaction with the symmetric combination of the nitrogen lone pairs. Combination of the two effects increases the σ - p_{π} gap and favours therefore the singlet state. Moreover, the pseudo sp^2 hybridisation adopted by the C_{carbene} atom in its singlet state matches the bent geometry of the NHC five-membered ring.



Figure 1.4 Electronic stabilisation of NHCs.

The interaction of the nitrogen lone pair with the p_{π} -orbital of the carbene is reflected by a N- C_{carbene} bond length of 1.365 Å, which is consistent with double bond character. An accurate assessment of the π backbonding was found by analysing dynamic $^1\text{H-NMR}$ behaviour of bis(diisopropylamine)carbene **4**.⁸ As the major part of this process involves

rotation about the N-C_{carbene} bonds, the measured barrier to rotation of 53 kJ/mol was mostly attributed to the substantial π -component of these bonds.

Dimerisation of NHCs has been known since the first attempts to isolate them.⁵ Alder recently showed that dimerisation is thermodynamically unfavorable for imidazolin-2-ylidenes **7** (singlet/triplet gap of 354 kJ/mol), but very likely to happen for imidazolidin-2-ylidenes **8** due to lack of aromaticity and acyclic NHCs due to loss of conjugation through twisting around the N-C_{carbene} bond.¹³ The reaction is likely to be proton catalysed.

The ¹³C-NMR chemical shifts¹⁴ range from 210-220 ppm downfield from TMS for aromatic imidazolin-2-ylidenes **7**, to 235-245 ppm for imidazolidin-2-ylidenes **8** and acyclic NHCs.

1.1.4 Generation of diaminocarbene / pKa

Three principal methods were successfully used for the generation of diaminocarbenes: i) deprotonation of imidazolium salts **9** or formamidinium salts **10**, ii) desulfurisation of thioureas **11** and iii) thermolysis of methanol adducts of type **12** (Figure 1.5).

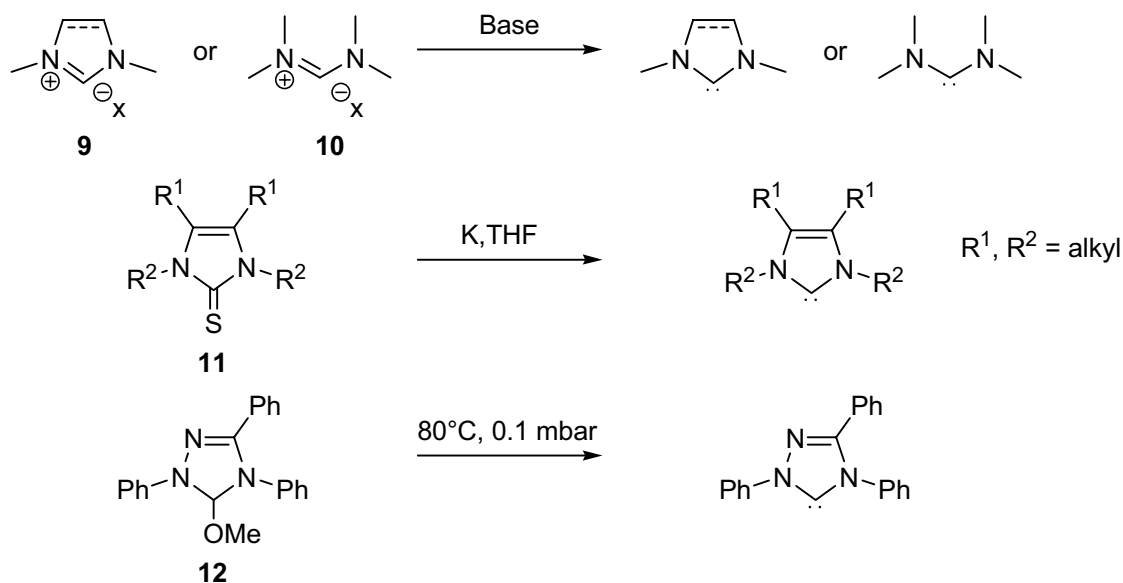


Figure 1.5 Three principal methods for the generation of NHCs.

The pKa value was measured for diisopropyl-imidazolin-2-ylidene on the DMSO scale and found to be 24 by Alder.^{15,16} For di-*tert*-butyl-imidazolin-2-ylidene Streitwieser found a pKa of 20 on the THF scale.¹⁷ Therefore, it is not surprising that the principal method used to synthesise NHCs is deprotonation of the corresponding imidazolium or formamidinium salts. For the isolation of the first NHC, Arduengo's group used NaH/KH in THF in the presence of KO*t*Bu and DMSO (to generate the dimsyl ion).⁴ Herrmann showed that milder conditions

such as sodium amide in liquid ammonia and THF at -40°C , were also efficient.¹⁸ With a pK_a increased by 2 to 6 units, formamidine salts underwent nucleophilic addition of the base rather than deprotonation.¹⁶ This problem was solved by the use of hindered alkali amide bases such as lithium diispropylamide or potassium hexamethyldisilazide.

In 1993, Kuhn and Kratz reported another pathway to imidazolin-2-ylidene by reduction of the corresponding thiourea using metallic potassium.¹⁹ This heterogeneous reaction, which has proved difficult to reproduce,¹⁶ is attractive because the only other product is potassium sulfide which is insoluble in THF.

Finally, another successful method was established by Enders who synthesised in a good yield a triazol-2-ylidene by thermolysis of its methanol adduct.²⁰ One drawback of this methodology is the extreme sensitivity of the methanol adduct.

1.2 N-Heterocyclic carbene metal complexes

1.2.1 Historical perspective

Carbenes were introduced to inorganic chemistry by Fisher and Maasböl who reported that reaction of phenyl lithium with $\text{W}(\text{CO})_6$, followed by addition of acid and then diazomethane, gave complex **13** (Figure 1.6).²¹ A few years later Wanzlick and Öfele's first syntheses of NHC metal complexes respectively **14** and **15**, extended the Fischer type carbene family.^{22,23} In 1974, Schrock developed²⁴ a new type of carbene, the so-called Schrock carbene, with a totally different reactivity (**16**).

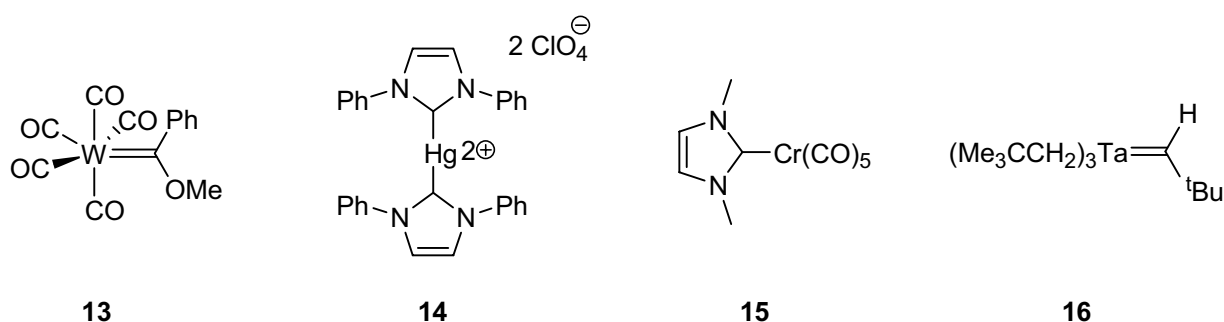


Figure 1.6 Fischer, Wanzlick, Öfele and Schrock carbenes.

1.2.2 NHC ligand properties

Although the metal carbene bond in Schrock and Fischer carbene complexes are both described as double bond, they differ by the polarity of the electron density. This difference

arises from the difference in energy between the d_{π} orbital of the metal and the p_{π} orbital of the carbene (Figure 1.7). If the d_{π} orbital is lower in energy than the p_{π} orbital, the metal carbon bond is polarised δ^- on the metal and δ^+ on the carbene and it is a Fischer carbene complex. Contrary, if the d_{π} orbital is higher in energy than the p_{π} orbital, the metal carbon bond is polarised δ^+ on the metal and δ^- on the carbene and it is a Schrock carbene complex. A particular example of Fischer carbenes are NHCs which have a p_{π} orbital of very high energy since their multiple bonding between the carbene atom and the two nitrogen atoms. As a result, the p_{π} orbital does not interact well with the d_{π} , thus preventing almost any π -backbonding from the metal to the carbene. In the NHC complexes, the metal carbon bond is therefore best represented by a single bond.

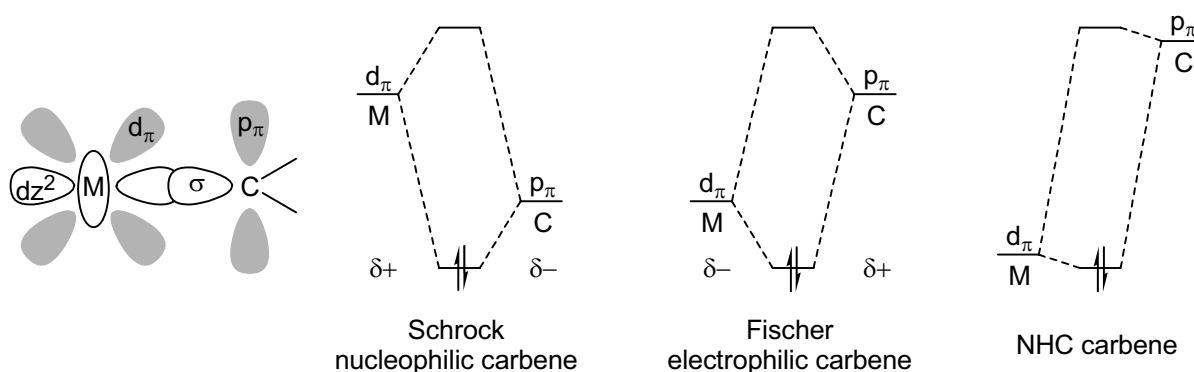


Figure 1.7 Partial molecular diagram for Schrock, Fischer and NHC carbene complexes.

The fundamental difference between a typical Schrock alkylidene moiety and an NHC as a ligand is underlined in the crystal structure of $[\text{RuCl}_2(\text{NHC})_2(=\text{CHC}_6\text{H}_4\text{Cl})]$ (NHC = 1,3-diisopropylimidazol-2-ylidene) where the two types of carbenes are linked to the same metal centre.²⁵ The ruthenium-carbon bond of the Schrock carbene, generally written as a double bond, has a bond length of 1.821(3) Å, whereas the Ru-C bond length to the NHC (2.107(3) Å and 2.115(3) Å) justifies its representation as a single bond (σ -donor and virtually no π -acceptor).

Measurement of IR carbonyl absorption frequencies of NHC carbonyl metal (Fe, Cr, Rh, Mo and Ir) and their phosphine analogues showed the significantly increased donor capacity of NHC relative to phosphines, even to trialkylphosphines.²⁶⁻²⁸ Experimental investigations,²⁹ calorimetric studies^{30,31} and experimental calculations³² agree that the ligand dissociation energy of NHCs from Ru complexes is higher than for phosphines. Further calculations with other metals such as Au, Cu, Ag, Pd and Pt led to similar conclusions.^{33,34}

By analogy to the cone angle defined for phosphines by Tolman,³⁵ a method to quantify the steric parameters of NHCs has been proposed by Nolan³¹ who described NHCs as "fences" with "length" and "height".

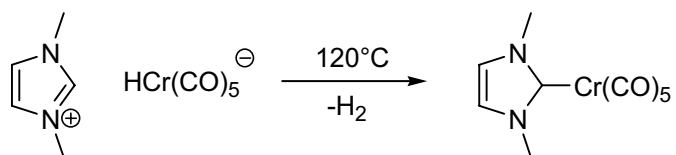
The structural differences for free NHCs and metal complexed NHCs are very small. In ¹³C-NMR spectra, the signals for the free carbene carbon are usually shifted upfield by about 20-30 ppm upon complexation of the free NHC to a transition metal.

1.2.3 Complexation

Four synthetic methodologies have been most commonly applied in the literature for the preparation of NHC metal complexes: i) proton abstraction with bases prior to metalation, ii) *in situ* deprotonation of the imidazolium by basic metalates or basic counter-ions, iii) use of an external base in a one pot reaction with the metal, and iv) transmetallation via silver complexes.

NHCs are very strong σ donors and show dissociation energies higher than phosphines for a large range of metals (*vide supra*). Therefore, when their free form can be isolated, their complexation is achieved in high yield. It has been shown that free NHCs are able to cleave dimeric metallic species such as $[(\eta^4\text{-cod})\text{RhCl}]_2$ ³⁶ and exchange phosphine²⁵ or pyridine³⁷ ligands.

In his original work,²³ Öfele formed NHCs by *in situ* deprotonation of the corresponding imidazolium salts using the metal itself (Scheme 1.1). The basic metalate ion $[\text{HCr}(\text{CO})_5]^-$ serves as base and ligand acceptors at the same time. One drawback of this method is the limited availability of the metal precursor.



Scheme 1.1 *In situ* deprotonation by a basic metalate ion

Basic counter-ions of the metal precursors can also act as deprotonating agents. For example, a convenient method to synthesise NHC-Pd(II) complexes is by mixing $\text{Pd}(\text{OAc})_2$ with the corresponding imidazolium salt. In a similar way, μ -alkoxo complexes of $(\eta^4\text{-cod})$ rhodium(I) and iridium(I), formed *in situ* by adding μ -chloro bridged analogues to a solution of sodium alkoxide in the corresponding alcohol, will deprotonate an imidazolium salt and deliver the corresponding NHC complex.²⁶

The use of an external base to generate NHCs in the presence of a metal precursor is also an efficient method. Potassium *tert*-butoxylate and sodium hydride in THF at room temperature can be used to co-ordinate NHCs to Cr(CO)₆ and to W(CO)₆ *in situ*.³⁸ A large variety of bases ranging from triethylamine,³⁹ lithium diisopropylamide⁴⁰ to phosphazene bases⁴¹ have been successfully used over the past years.

Recently, a method for preparing NHC metal complex via silver complex has been developed by Wang.⁴² Silver NHC complexes are readily prepared upon mixing the corresponding imidazolium salt with Ag₂O in CH₂Cl₂ at room temperature. Subsequent reaction with a chloro-metal precursor gives the desired NHC metal complex that can be easily separated from AgCl, the latter being insoluble in THF.

1.2.4 Abnormal binding modes for NHC ligands

In 2001, Crabtree discovered an unexpected binding mode of NHCs. Instead of having coordination at the C(2) position of the NHC, the metal was linked at C(4) or C(5) (Figure 1.8).⁴³ Since this publication, there have been an increasing number of reports of NHC with abnormal binding mode.⁴⁴⁻⁴⁶



Figure 1.8 C(2) and C(4) or C(5) binding mode of the NHCs.

Non-classical carbene formation was initially observed by mixing pyridine-substituted imidazolium salts with [IrH₅(PPh₃)₂] in refluxing C₆H₆. Since theoretical calculation predicts⁴⁷ that binding at the C(4) or C(5) position is less favoured, it was reasoned that steric effects of the bidentate pyridine-NHC around the metal centre controlled the reaction. However, the isolation of monodentate NHC complexes with a C(4) or C(5) binding mode proved that the chemistry involved is more complicated than previously thought. Abnormal co-ordination of NHCs is still intensively studied.

1.3 Catalysis involving NHCs

1.3.1 Ruthenium metathesis

Due to their σ -donor ability and their strong metal-carbon bond, NHC ligands have been applied as directing ligands in various catalytic transformations.⁴⁸ It is however in ruthenium-catalysed olefin metathesis type reactions that NHC ligands have proved their efficiency, giving access to unprecedented successful catalytic systems.

A breakthrough in catalytic metathesis reactions was achieved when NHC ligands were used to replace one of the phosphines of complex **17** (Figure 1.9). Herrmann showed that having one imidazolin-2-ylidene in place of a phosphine (**18**) favours the dissociative substitution of the phosphine ligand with an olefinic substrate, giving rise to a more active species.^{29,49} Catalysts **18** showed excellent activities in the ring opening metathesis of 1,5-cyclooctadiene. In the same year, Grubbs introduced⁵⁰ a new generation of ring closing metathesis catalysts containing an even more basic NHC. Catalyst **19**, which contains an imidazolidin-2-ylidene ligand, showed outstanding activities combined with a large functional group tolerance. Moreover, the use of imidazolidin-2-ylidene allowed access to more chiral catalysts, by introduction of chirality at the C(4) and C(5) positions of the NHC. The application of complexes **20** in the desymmetrisation of triolefins yielded the ring closing metathesis products in high enantioselectivities.⁵¹

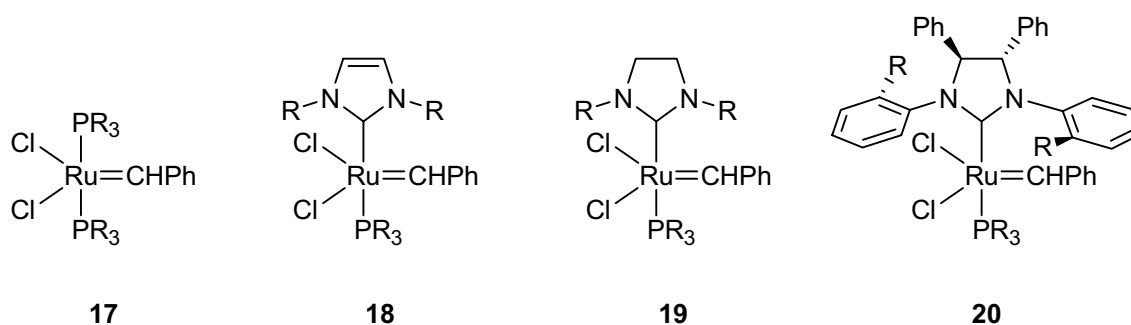


Figure 1.9 NHCs in ruthenium metathesis.

1.3.2 Asymmetric catalysis

The first example of chiral carbenes used in asymmetric catalysis appeared in 1996/1997 with the pioneering work of Enders⁵² and Herrmann.⁵³ Since then, the field has largely expanded and now there are many reports on the use of NHCs for asymmetric homogeneous catalysis.⁵⁴ Enders successfully applied the NHC and their derivatives in carbene catalysed asymmetric