

Molecule Matters

N-Heterocyclic Carbenes – The Stable Form of $R_2C:$

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Divalent carbon compounds which were once considered as highly reactive organic intermediates have been tamed by the modern day synthetic chemist in the form of *N*-heterocyclic carbenes. The land marks in the history of development of these compounds and their applications as ligands in the Nobel Prize winning work on olefin metathesis catalysts are described.

Introduction

Can we have stable carbon compounds in the divalent state? This was a question uppermost on the minds of many creative synthetic chemists for a long time. Such species, which have been named carbenes, are generally highly reactive organic intermediates with six valence electrons and the general formula: $R^1R^2C:$ (two substituents and two free electrons on the carbon). The first attempt to prepare carbenes dates back to the times of the French chemists Henri Victor Regnault (1810–1878) and Jean Baptiste André Dumas (1800–1884), when they tried to prepare methylene by dehydrating methanol using phosphorus pentoxide or concentrated sulfuric acid. The development of organic chemistry witnessed the use of carbenes as highly unstable intermediates in many reaction mechanisms and also as reactive species generated in many photolytic reactions such as that of diazoalkanes, diazirines and epoxides.

Depending on the spin state of the lone pair of electrons on the carbon, one can have two types of carbenes; singlet or triplet. Singlet carbenes have the electrons paired ($\uparrow\downarrow$) and have an sp^2 hybrid structure. Triplet carbenes have two unpaired electrons ($\uparrow\uparrow$). They may be either sp^2 or sp hybridised. They are paramagnetic and may be observed by spectral methods if they can exist

Keywords

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long enough without decomposition. They are also generally stable in gaseous state while singlet carbenes are often found in aqueous medium. For simple hydrocarbons, triplet carbenes usually have energies $\sim 8 \text{ kcal mol}^{-1}$ (33 kJ mol^{-1}) lower than the singlet carbenes. In general, triplet is the ground state and singlet, the excited state species [1].

Fischer and Schrock Carbenes

One of the relatively early breakthroughs in stabilizing carbenes was as organometallic complexes. The work of Emil Otto Fischer (1973 Nobel Prize) and Richard R Schrock (2005 Nobel Prize)¹ led to the discovery of two classes of carbene complexes of transition metals commonly known as the Fischer carbenes and the Schrock carbenes [2] (*Figure 1*).

The first examples of such compounds with a metal-carbon double bond was discovered in 1964 by Fischer. These compounds are of the type $(\text{CO})_5\text{M}=\text{C}(\text{R})(\text{OR}')$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$), and as they are formally derived from the coordination of a carbene $\text{R}_2\text{C}:$ to a metal center, they have been named as carbene complexes or more precisely as Fischer carbene complexes. The metal is in a low oxidation state and the bonding of the carbene is reminiscent of metal-carbon monoxide complexes. A second type of $\text{M}=\text{C}$ bond with metal center in high oxidation state was subsequently prepared by Richard Schrock. These were called Schrock carbene complexes or metal alkylidene complexes [e.g., $\text{Cp}_2\text{Ta}(\text{CH}_3)(\text{CH}_2)$].

The properties and chemical behavior of Schrock and Fischer carbenes are significantly different, reflecting the role of metal-

¹ K Sivapriya and S Chandrasekaran, Metathesis: A "Change-your-partners" dance, Chemistry Nobel Prize 2005, Vol.11, No.4, Resonance, 2006.

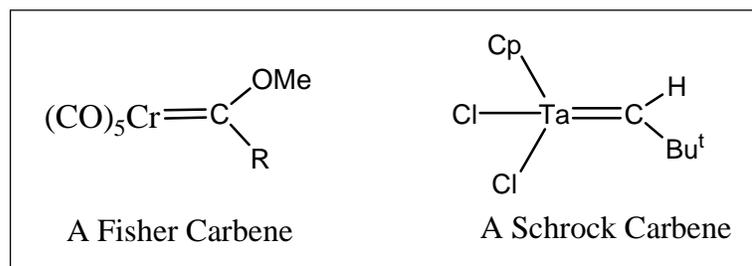


Figure 1. Examples of Fischer and Schrock carbenes.

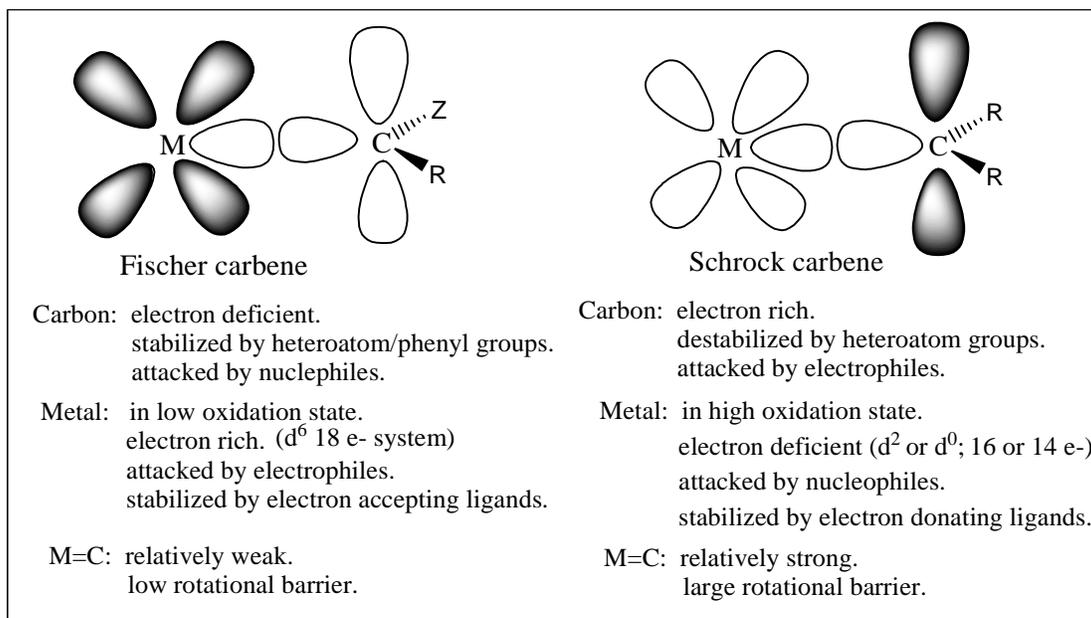
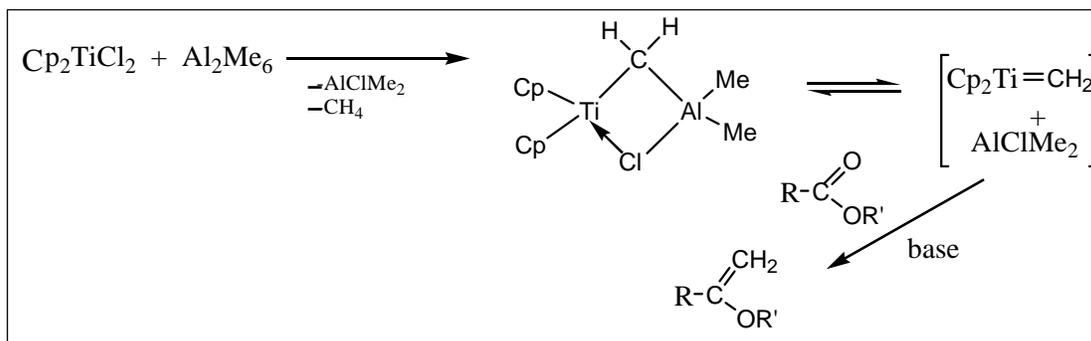


Figure 2. Comparison of electronic properties and reactivity of Fischer and Schrock carbenes.

carbene bonding (Figure 2). The metal in a Schrock alkylidene is electrophilic, and is stabilized by electron-donating ligands as well as back-bonding from an occupied p-orbital of the carbon atom. This results in a strong metal-to-carbon double bond. The overall bonding in the complex leaves the carbon atom of the Schrock carbene nucleophilic. Fischer carbenes have nearly opposite properties. The metal is electron rich, in part because of coordinate donation of an electron pair from the carbene carbon atom and CO ligands. Competition for the d-electrons of the metal takes place between π bonding ligands such as CO, and the empty p-orbital on carbon. This in turn, is stabilized by overlap with electron pairs on the heteroatom substituents ($Z = \text{NR}_2$, SR, OR, or Ph). The resulting C=M multiple bond is weakened, and has a low barrier to rotation. Many of the chemical properties of Fischer carbenes are ester-like. Also, α -hydrogen atoms of these carbene complexes have enhanced acidity. For example $(\text{CO})_5\text{Cr}=\text{C}(\text{OCH}_3)\text{CH}_3$ has a pK_a of 12.3.

Tebbe's reagent, a mixture of Cp_2TiCl_2 and Al_2Me_6 can be considered as the protected form of the unstable carbene $\text{Cp}_2\text{Ti}=\text{CH}_2$ (Figure 3). Many of its reactions are complimentary





to the Wittig reagent used in organic reactions for conversion of a C=O group to a CH₂ group. More interestingly, conversion of esters into vinyl ethers is also possible with Tebbe's reagent which is not feasible with Wittig reagent.

Figure 3. Synthesis and reactivity of Tebbe's reagent.

Grubbs and Schrock Olefin Metathesis Catalysts

The most important and spectacular application of metal carbenes is in olefin metathesis reactions for which Robert Grubbs and Richard Schrock received the Nobel Prize in 2005 [3-8]. Olefin metathesis is the reaction of two olefinic bonds, i.e., carbon-to-carbon double bonds, which in the presence of a metathesis catalyst form two new olefins, one of which is likely to be ethylene gas, and therefore is easily removed. When the original two double bonds are at the opposite ends of a chain of carbons, their reaction might be expected to form polymers, which is what often happens, or they might also interact with each other to produce a ring compound. The type of reactions promoted by olefin metathesis catalysts are given in *Figure 4*.

Robert Grubbs and colleagues discovered ruthenium-based olefin metathesis catalysts. What is noteworthy about these catalysts is that they are stable in air, tolerate water, and can operate at elevated temperatures. On the other hand, the molybdenum-based catalysts prepared by Richard Schrock and coworkers are highly air and moisture sensitive but are more active than the catalyst initially prepared by Grubbs. The properties of one of the famous Grubbs metathesis catalysts (known as Grubbs first generation catalyst) and the well-known Schrock

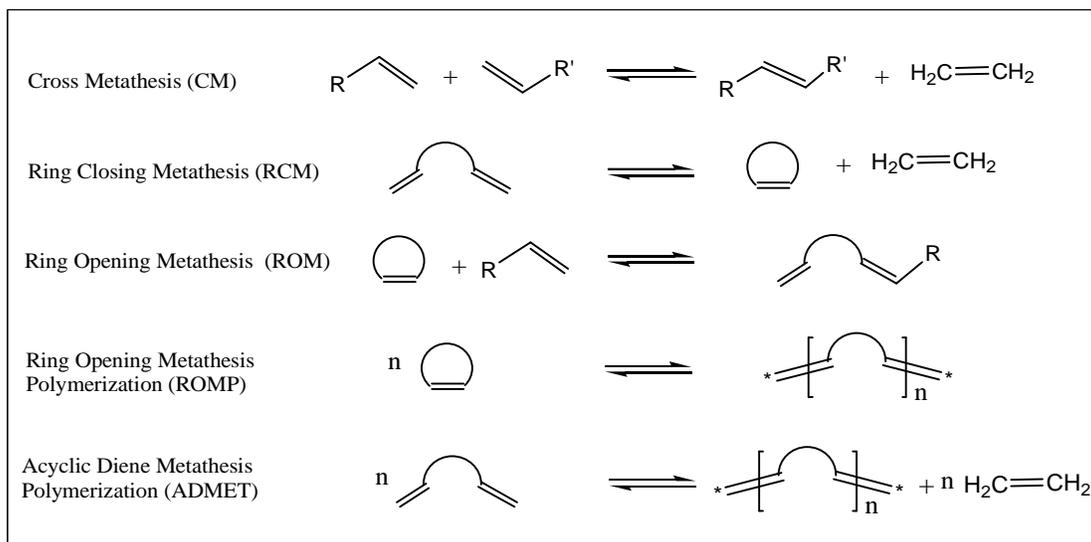
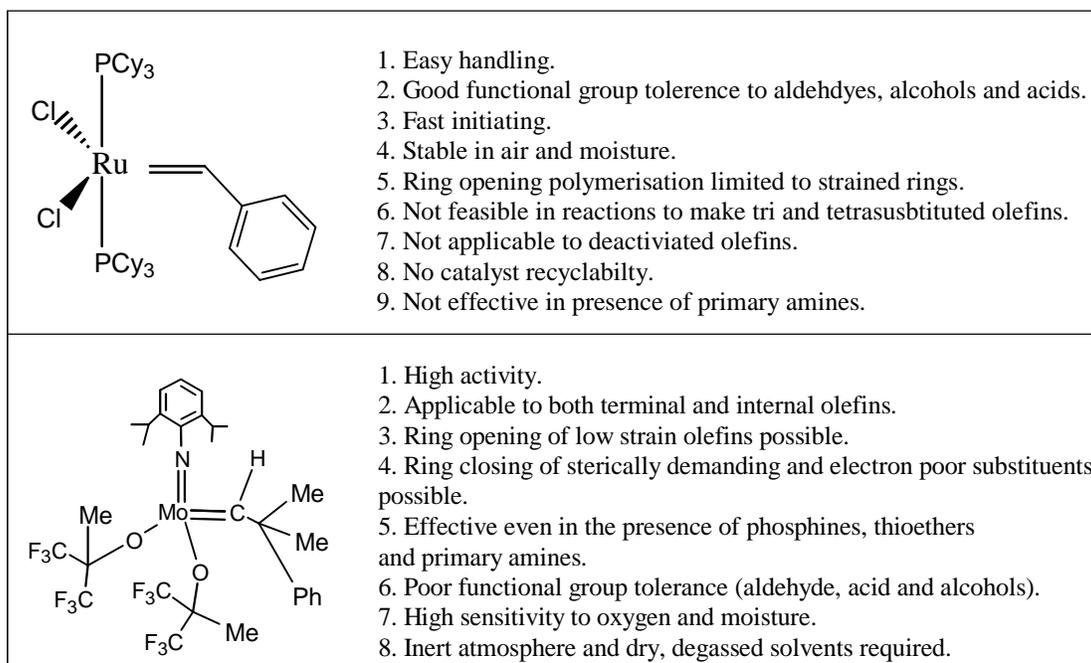


Figure 4. Various types of olefin metathesis reactions. metathesis catalyst are listed in *Figures 5 and 6*, respectively.

Synthesis of these catalysts is carried out using carbene precursors. It is also interesting to note that the well-known Grubbs

Figure 5 (top). Properties of Grubbs first generation catalyst.

Figure 6 (bottom). Properties of Schrock's molybdenum-based catalyst.



catalysts have properties intermediate between that of the classical Fischer and of Schrock types. Grubbs himself has mentioned that his catalysts cannot be strictly classified under the Fischer/Schrock categories (see *Box 1*).

One of the questions often asked about these catalysts is: between Schrock's and Grubbs catalysts, which is better? Amir H Hoveyda, another well-known scientist involved in olefin metathesis says that the ruthenium catalysts are used more often than the molybdenum catalysts because they are easier to handle. He says "When we need high reactivity, we go with molybdenum. When we can run reactions under mild conditions, we use ruthenium. They are the two wings of the same angel. The angel can't fly if you clip either one."

N-Heterocyclic Carbenes, The Stable Carbenes

Phosphine ligands are a very important class of molecules widely used in the synthesis of coordination and organometallic compounds. This is illustrated in the numerous examples of highly efficient catalysts applied to traditional homogeneous catalytic processes such as hydrogenation [RhCl(PPh₃)₃], hydroformylation [RhCl(CO)(PPh₃)₂] or palladium catalyzed coupling reactions [Pd(PPh₃)₄]. However, the disadvantages of phosphines are the high cost of producing tertiary (especially chiral) phosphines and their sensitivity towards conversion to the more stable phosphine oxides. Except PPh₃ and a few aryl phosphines the rest are quite sensitive to oxidation and some are even pyrophoric in nature. The emergence of the stable *N*-heterocyclic carbenes was a welcome replacement for phosphines in the development of homogeneous catalysts. *N*-heterocyclic carbenes (normally represented as NHCs) themselves are organic catalysts.

Stable carbene research was initiated in 1991 with the discovery of *N, N'*-diadamantyl-imidazol-2-ylidene by the research group of Anthony J Arduengo, III, who managed to isolate and obtain an X-ray structure of this stable carbene [9]. It was found that the kinetic stability of NHCs is mostly due to the bulkiness of the

Box 1.

Grubbs wrote about his first generation ruthenium catalyst [*J. Am. Chem. Soc.*, 114, 3974 (1992)]: "Typically, high oxidation state metallaolefins are called alkylidene complexes while low oxidation state analogues are referred to as carbene complexes. The new complex described here does not show all of the characteristics of either of these two classes of complexes." The distinction between high- and low-oxidation-state carbenes is misleading, Grubbs says, "I've tried to contend that there is a continuum of reactivity. The Fischer systems tend to be electron poor at the carbon center while the Schrock systems tend to be electron poor at the metal center, and they give different chemistries. I don't know where the ruthenium catalysts fit in between, but they work. If we had stuck with those oxidation-state classifications, we would have been out of luck."



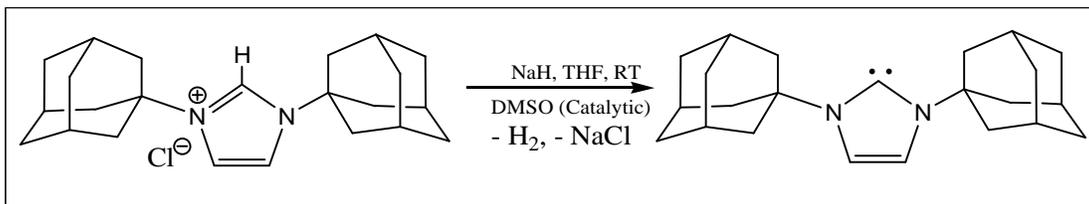


Figure 7. Synthesis of the Arduengo's *N*-heterocyclic carbene.

alkyl/aryl groups bound to the nitrogen atoms which shields the carbene carbon to some extent and reduces the reactivity.

Such carbenes were first proposed by Breslow in 1957, isolated for the first time as highly sensitive compounds by Guy Bertrand in 1989, and finally isolated as stable crystalline solids by Arduengo (Figure 7). Arduengo's carbene was found to be indefinitely stable at room temperature (in the absence of oxygen and moisture), and melted at 240–241 °C without decomposition. Another interesting feature of this molecule was a characteristic resonance in the ^{13}C NMR spectrum at 21.1 ppm for the carbenic carbon. The X-ray structure revealed longer N–C bond lengths in the ring of the carbene than in the parent imidazolium compound, indicating that there was very little double bond character to these bonds [10].

Following the discovery by Arduengo, many new stable NHCs were prepared. In many cases, such carbenes are stable in the absence of moisture and oxygen, and can be isolated and stored indefinitely. Some NHCs dimerise slowly over days, whilst the least stable triplet state carbenes have half-lives of a few seconds. The main advantage observed in several reactions is their electron donating capability which is greater than that of most basic phosphines.

A wide range of NHC ligands which are available now commercially, exhibit high activities in various important organic transformations when combined with metal pre-catalysts. NHC ligands with sterically demanding groups such as mesityl, isopropyl, and adamantyl have been used in many reactions. The most commonly used NHCs are listed in Table 1. Some of the advantages of *N*-heterocyclic carbenes as ligands are:

Arduengo's carbene was found to be indefinitely stable at room temperature (in the absence of oxygen and moisture), and melted at 240–241 °C without decomposition.



| | NHC (symbol)* | NHC-Structure | Complex | ν_{CO} in cm^{-1} (in CH_2Cl_2) |
|----|-------------------|---------------------------|--|---|
| 1 | IMes | | $\text{Ni}(\text{CO})_3(\text{IMes})$ | 2050.7 |
| 2 | SIMes | | $\text{Ni}(\text{CO})_3(\text{SIMes})$ | 2051.5 |
| 3 | IPr | | $\text{Ni}(\text{CO})_3(\text{IPr})$ | 2051.5 |
| 4 | SIPr | | $\text{Ni}(\text{CO})_3(\text{SIPr})$ | 2052.2 |
| 5 | ICy | | $\text{Ni}(\text{CO})_3(\text{ICy})$ | 2049.6 |
| 6 | IAd | | $\text{Ni}(\text{CO})_2(\text{IAd})$ (tricoordinate) | 2007.2 |
| 7 | I ^t Bu | | $\text{Ni}(\text{CO})_2(\text{I}^t\text{Bu})$ (tricoordinate) | 2009.7 |
| 8 | | $\text{P}(\text{Bu}^t)_3$ | $\text{Ni}(\text{CO})_3(\text{P}(\text{Bu}^t)_3)$ | 2056.1 |
| 9 | | PCy_3 | $\text{Ni}(\text{CO})_3(\text{PCy}_3)$ | 2056.4 |
| 10 | | PPh_3 | $\text{Ni}(\text{CO})_3(\text{PPh}_3)$ | 2068.9 |

* The symbols are in use from 1999 for referring to NHCs with varying substituents on the imidazolyl nitrogen atoms. I and SI indicates imidazolyl and saturated imidazolyl respectively.

- 1) They are stronger donors than phosphines and can displace readily, other ligands *trans* to them, the well-known *trans* effect.
- 2) The strong metal-carbenic bond of the NHC complex favors reaction kinetics which involves less of NHC dissociation from the metal complex.

Table 1. The CO stretching frequencies of important Ni(CO)NHC complexes.

Tolman (1977) used ν_{CO} of $\text{Ni}(\text{CO})_3$ phosphine complex as a measure of electron donor ability of the phosphine.

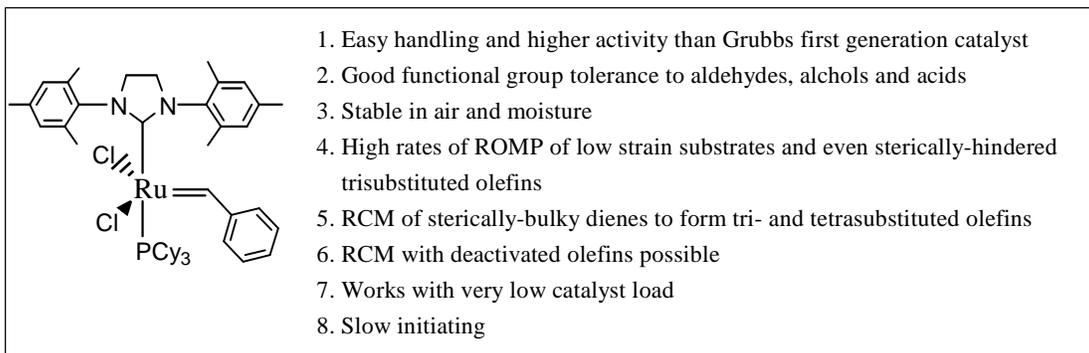
3) The presence of sterically hindered groups bound to the *N*-atoms facilitating the reductive elimination of the product from the metal during catalysis.

Tolman in 1977 had devised a method for comparing the electron-donating ability of phosphine ligands [11]. This was determined by reacting one equivalent of the phosphine (monodentate) with $\text{Ni}(\text{CO})_4$ to make a $\text{Ni}(\text{CO})_3(\text{phosphine})$ complex. The IR stretching frequency of the carbonyl group (ν_{CO}) of the $\text{Ni}(\text{CO})_3(\text{phosphine})$ complex was then measured. Larger the electron density donated by the phosphine ligand to the metal center, stronger the π -back bonding to the carbonyl ligands, and consequently weaker the CO bond, and lower the ν_{CO} . Tolman was able to arrange tertiary phosphines based on their electron donor capability and the most basic phosphine was found to be $(\text{Bu}^t)_3\text{P}$.

Steven Nolan in 2005 reported the first systematic study comparing the electronic properties of widely used NHCs to tertiary phosphines [12]. He carried out reactions of seven well-known NHCs with $\text{Ni}(\text{CO})_4$ and prepared complexes where carbonyl groups were replaced by NHCs in a study similar to that of Tolman. The ν_{CO} stretching frequencies of the complexes formed were measured for a one-to-one comparison with phosphines. The data clearly demonstrated that the *N*-heterocyclic carbenes are better electron donors than the most basic alkyl phosphine $(\text{Bu}^t)_3\text{P}$ (see *Table 1*). The saturated NHCs are slightly less electron donating than their unsaturated analogues.

Several beneficial uses of NHC-substituted organometallic complexes over the conventional phosphine complexes have been reported. The most visible among these are in the olefin metathesis catalysts starting with Grubbs second generation catalyst and a series of later generation olefin metathesis catalysts. In fact the dramatic changes in catalytic properties brought about by incorporating an NHC in place of a phosphine ligand has been so useful that almost all the later generations of olefin metathesis catalysts do have NHCs bound to the metal atom. NHCs have shown improved performance over phosphines also in iridium catalyzed





hydrogenation, platinum catalyzed hydrosilylation and palladium catalyzed cross-coupling reactions. A comparison of the properties of Grubbs second generation catalyst (Figure 8) to his first generation catalyst clearly indicates the significance of NHCs as ligands.

Initially, Grubbs had prepared carbene complexes with two PPh_3 units which were modified to create the Grubbs first generation catalyst having two PCy_3 ligands in *trans* orientation. This complex was stable but its activity was much lower compared to Schrock's molybdenum-based catalysts. Later on, Grubbs came up with his second generation catalyst having one NHC group *trans* to PCy_3 . Since NHC ligands are more basic than phosphines, the reactivity of the catalyst is increased making it easier to push the *trans* PCy_3 ligand off the metal (*trans* effect). It is important to note that the increased reactivity of the second generation catalyst can now help to bring about metathesis on tri- and tetra-substituted double bonds, which used to be possible only by molybdenum-based catalysts. The introduction of the NHC ligand makes the ruthenium catalysts as reactive as the molybdenum catalysts. Also it is important to note that the second generation catalysts are still tolerant to acidic functional groups. A more important variation came with Amir Hoveyda's discovery of a recyclable, reusable and even immobilizable catalyst again based on NHCs which came to be known as Grubbs-Hoveyda catalyst [13]. This catalyst was also superior to Grubbs second generation catalyst in reactions with electron deficient olefins.

Figure 8. Properties of Grubbs second generation catalyst.

The introduction of the NHC ligand makes the ruthenium catalysts as reactive as the molybdenum catalysts.

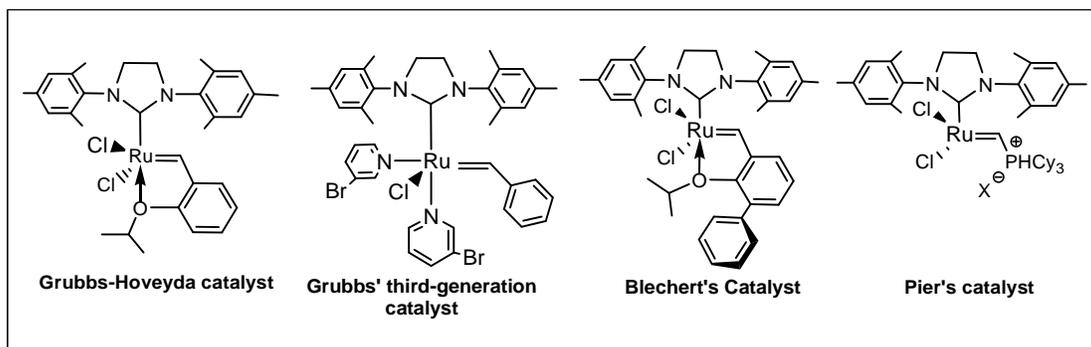


Figure 9. Recent examples of NHC based olefin metathesis catalysts.

More and more examples of NHC-based new catalysts for olefin metathesis were discovered in the last 4-5 years (Figure 9). A major obstacle identified and addressed in recent years is the relatively slow initiation of the metathesis reaction of ruthenium catalysts partly as a result of the presence of the NHC group. The slow initiation affects the efficiency of the catalyst. This issue was addressed by Blechert by using steric effects to destabilize the five-membered ruthenacycle of the Hoveyda catalyst. Grubbs third generation catalyst has two weakly bound 4-bromopyridyl groups whose easy removal during reaction provides for this complex, initiation rates around six orders of magnitude higher than the Grubbs second generation catalyst. In 2004, Warren Piers reported a rapid initiating catalyst which itself was a 14 electron species and did not require any ligand loss for activation [14].

Metathesis of hindered olefins, especially ring closing metathesis forming tetra-substituted cycloalkenes also remained a difficult task with poor yields even with Grubbs second generation and Grubbs–Hoveyda catalysts [15]. In 2007, Grubbs and coworkers were able to modify the mesityl substituted NHC and get a very high yielding (>95%) route for the ring closing metathesis of hindered olefins. The basic change brought out in the catalyst was changing the mesityl group on the NHC to a mono-ortho-alkyl-substituted aryl group [16]. Grubbs also came out with a highly water soluble and stable catalyst by modifying the *N*-heterocyclic carbene (Figure 10).

Hoveyda discovered a recyclable, reusable and even immobilizable catalyst based on NHC_3 .

In conclusion, carbenes which were known as only highly reactive intermediates were tamed by synthetic chemists, structurally characterized and utilized for a host of applications. It has also been shown that they are valuable compounds with properties surpassing the best phosphines available today, for many homogeneous catalysis reactions.

Synthetic chemists continue to unravel interesting and useful surprises centered around the chemistry of stable *N*-heterocyclic carbenes which are of great value in organic chemistry.

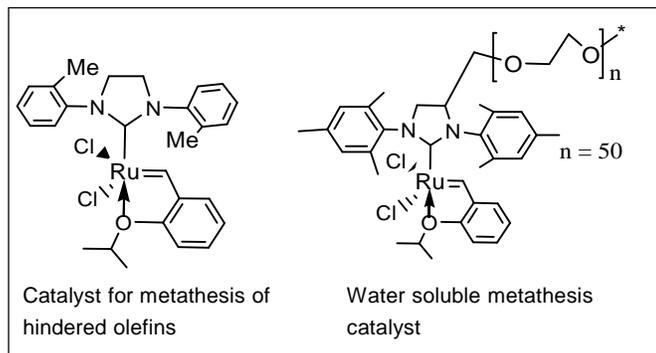


Figure 10. Metathesis catalyst with modified NHCs.

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