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Preface

Catalysis enables the efficient use of natural resources and will therefore become an increasingly important key technology. Many decades of intense research have resulted in many applications of a tremendously useful class of phosphine ligands in catalysis; however, cost, sensitivity and oxidative degradation of phosphine ligands are a major hassle. Therefore the pioneering report by Herrmann et al. on the first application of N-heterocyclic carbene (NHC) palladium complexes as catalysts in 1995 piqued the attention of many chemists. In the following decade numerous applications of NHC complexes as phosphine mimics and beyond have been found in all areas of transition metal catalysis. Many attractive features can be associated with NHC complexes, such as being electron-rich and sterically demanding ligands that form stable metal complexes. NHC complexes are no longer curiosities but have truly conquered research areas like cross-coupling and metathesis reactions. However, despite this level of maturity, many important and even fundamental questions remain open. What exactly is the nature of the metal–carbene bond and (when) does π-backbonding play a significant role? How can the shape of NHC complexes be adequately described and measured so that ligands can be systematically compared with each other?

This volume provides the reader with the most important and exiting results pertaining the use of NHC complexes in transition-metal catalysis. Following an introductory chapter, which deals with the properties of NHC compounds and discusses some insightful examples, routes to NHC complexes will be described, a prerequisite for doing catalysis. Chapters on NHC complexes in oxidation chemistry and in metathesis reactions are accompanied by a chapter on palladium-catalyzed reactions and another on catalysis by other metals. Finally, this book would be incomplete without treating applications in asymmetric catalysis, which rounds out this volume.

We hope that the quality of these contributions as well as our excitement for this topic will guarantee joyful and insightful reading!

Marburg, August 2006 Frank Glorius

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The series *Topics in Heterocyclic Chemistry* presents critical reviews on "Heterocyclic Compounds" within topic-related volumes dealing with all aspects such as synthesis, reaction mechanisms, structure complexity, properties, reactivity, stability, fundamental and theoretical studies, biology, biomedical studies, pharmacological aspects, applications in material sciences, etc. Metabolism will be also included which will provide information useful in designing pharmacologically active agents. Pathways involving destruction of heterocyclic rings will also be dealt with so that synthesis of specifically functionalized non-heterocyclic molecules can be designed.
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N-Heterocyclic Carbenes in Catalysis—An Introduction

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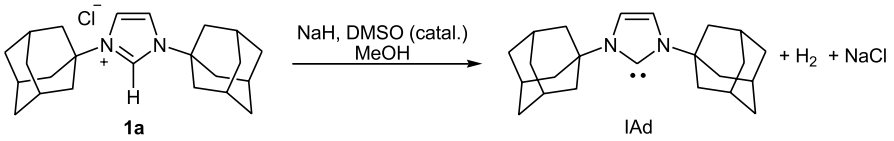
Abstract N-Heterocyclic carbene (NHC) has become a major ligand class and has proven to be more than just a "phosphine mimic". Some important features like electronic and steric properties are discussed and typical examples of NHC are given herein.

Keywords Catalysis · Cross-coupling reaction · Electronic properties · Metathesis · N-heterocyclic carbene · Topology

1 Introduction

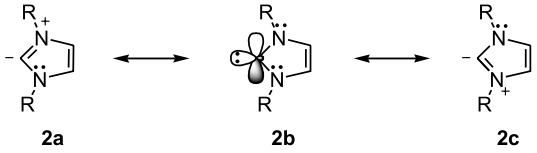
For a long time, carbenes, neutral carbon species with a divalent carbon atom bearing six valence electrons, were considered to be too reactive to be isolated [1]. As a consequence, many chemists hesitated to make use of these compounds, especially as spectator ligands for transition metal chemistry. However, whereas the majority of carbenes are short-lived reactive intermediates, this picture does not hold for N-heterocyclic carbenes [2].

N-heterocyclic carbenes, singlet carbenes with the carbene being incorporated in a nitrogen-containing heterocycle, were first investigated by Wanzlick in the early 1960s [3]. Shortly thereafter, the first application of NHC as a ligand for metal complexes was independently described by Wanzlick [4] and Öfele [5] in 1968. Nevertheless, the field of N-heterocyclic carbenes as ligands in transition metal chemistry remained dormant until 1991 when a report on the extraordinary stability, isolation and storability of crystalline NHC IAd by Arduengo et al. ignited a rapidly growing research field (Scheme 1) [6, 7]. Alerted by a number of false reports on the isolation of stable carbenes in the decades prior to their own finding, Arduengo et al. were very careful in analyzing their reaction. Measurement of the amount of NaCl and H_2 formed as well as the spectroscopic and X-ray structural analysis of IAd unequivocally proved the identity of the first stable and storable carbene.

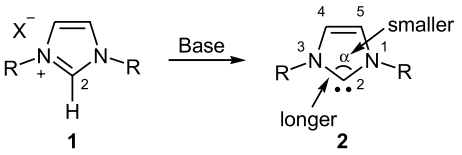


Scheme 1 Formation of the first stable NHC

These N-heterocyclic carbenes are electronically and sterically stabilized. First of all, steric shielding of the carbene carbon by means of the sterically demanding adamantyl groups is an important factor. More generally, it can be said that steric shielding of the carbene carbons increases the carbene's lifetime. Consequently, the *N*,*N*-dimethyl-substituted imidazolium-derived carbene IMe is significantly less stable than IAd, however, can still be isolated. Second and most importantly, the singlet carbene is stabilized by the orbital interaction of its empty p-orbital with the electron lonepairs of the two neighboring nitrogen atoms. Whereas "traditional" carbenes are generally considered to be electron-deficient, N-heterocyclic carbenes are electron-rich, nucleophilic compounds, which is indicated by the resonance forms **2a** and **2c** (Scheme 2). How significant is resonance structure **2b** and is it legitimate to call these compounds carbenes, since **2b** does violate the octet rule? The significance of the carbene resonance structure **2b** is supported by a structural comparison of imidazolin-2-ylidenes **2** with their corresponding



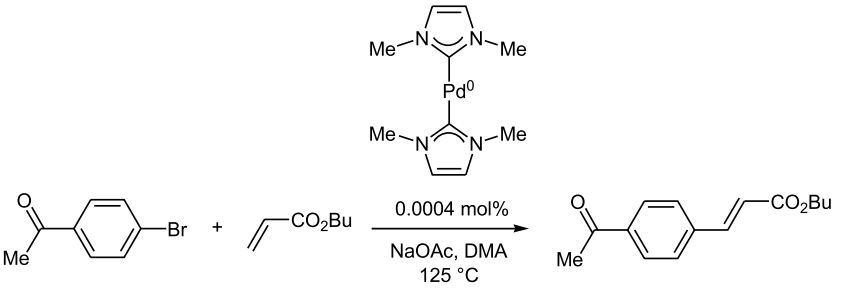
Scheme 2 1,3-disubstituted imidazolin-2-ylidene



Scheme 3 Structural comparison of imidazolium salt and NHC

imidazolium salts **1** (Scheme 3): the C2 – N bonds are longer in the carbene than in the imidazolium salt and the N – C – N angle is smaller in the carbene state, both findings indicating an increased σ-bond character in **2** and thus the importance of **2b** [8].

In the following years a wealth of reports on exciting N-heterocyclic carbenes and other stable carbenes like acyclic ones have appeared [8–10]. This development was fueled by the pioneering work of Herrmann et al. who were the first to demonstrate the catalytic activity of NHC transition metal complexes [11]. In this initial report it was shown that palladium NHC complexes are excellent catalysts for a number of Heck reactions, exemplifying high catalyst activity and a remarkably long catalyst lifetime (Scheme 4). This finding piqued the attention of many chemists and numerous applications of N-heterocyclic carbenes as phosphine mimics and beyond have been found in all areas of transition metal catalysis [12].



Scheme 4 First application of N-heterocyclic carbenes in transition metal catalysis

2 Outline of this Volume— Application of N-Heterocyclic Carbenes in Transition Metal Catalysis

Following the introduction to this volume provided herein, the following authors will continue the discussion of N-heterocyclic carbenes in this volume. Peris will discuss routes to NHC complexes, a prerequisite for doing catalysis. First and foremost, *palladium* catalysis has benefited from the use of NHC. The unique properties of NHC allow their use in oxidation catal-

ysis, mainly in conjunction with palladium, as will be discussed by Rogers and Stahl. Moreover, palladium NHC complexes have played an eminent role in the area of cross-coupling reactions and this will be highlighted by Díez-González and Nolan. Besides, a rich chemistry of other metals with N-heterocyclic carbenes has also been developed and this will be the focus of the chapter by Tekavec and Louie. Especially ruthenium-catalyzed metathesis reactions have profited from the exchange of a tricyclohexylphosphine by an NHC ligand, resulting in ruthenium complexes with increased activity and this will be analyzed by Despagnet-Ayoub and Ritter.

In addition, many reports on applications of N-heterocyclic carbenes in organocatalysis have appeared [13–17], however, this is not the focus of this volume. This volume will be rounded out by a discussion of applications of N-heterocyclic carbenes in asymmetric catalysis by Gade and Bellemin-Laponnaz, a fascinating area of increasing importance.

3
Attractive Features of NHC

The attractivity of N-heterocyclic carbenes as ligands for transition metal catalysis is a result of the following features.

3.1
Electronic Character

N-Heterocyclic carbenes are very electron-rich, neutral σ-donor ligands. The degree of π-acceptor power of N-heterocyclic carbenes is still disputed and unclear. Experimental and theoretical results range from no π-back-bonding at all to up to 30% of the complexes' overall orbital interaction energies being a result of π-back-bonding. Clear-cut conclusions are hampered by the dependency on the metal, the co-ligands, the substituents on the NHC and the orientation of the NHC ligand relative to the metal [18–21].

The electron-donating property can be quantified by comparison of the stretching frequencies of CO ligands of complexes like $LRh(CO)_2Cl$ [22], $LIr(CO)_2Cl$ [22] or $LNi(CO)_3$ [23] with L = NHC or PR_3. From these studies it is clear that N-heterocyclic carbenes are more electron-rich ligands than even the most basic trialkyl phosphines (Table 1). Furthermore, it is evident that N-heterocyclic carbenes have very similar levels of electron-donating ability, whereas phosphines span a much wider electronic range going from alkyl to aryl phosphines. The reason for this marked difference is that for N-heterocyclic carbenes only substituents on the periphery of the ligand are exchanged, whereas for phosphines the different substituents are directly attached to the donor atom itself. The best way to change the electronics of an NHC seems to be to alter the nature of the azole ring. In this respect, it is

Table 1 IR values for the carbonyl stretching frequencies in $LNi(CO)_3$ measured in CH_2Cl_2 [23, 26]

Ligand	υ_{CO} (A_1) [cm^{-1}]	υ_{CO} (E) [cm^{-1}]
IMes	2050.7	1969.8
SIMes	2051.5	1970.6
IPr	2051.5	1970.0
SIPr	2052.2	1971.3
ICy	2049.6	1964.6
PPh_3	2068.9	1990
PCy_3	2056.4	1973
$PtBu_3$	2056.1	1971

reasonable to assume that the order of the electron-donating power increases in the order benzimidazole < imidazole < imidazoline, which is in line with some computational data [24, 25].

It is unclear how well the electronic nature of carbene is represented in the ^{13}C NMR signal of the carbene. This signal is normally found at 235–245 ppm for imidazolidin-2-ylidenes, at 235 ppm for benzimidazolin-2-ylidenes and between 210 and 220 ppm for imidazolin-2-ylidenes [27]. Kunz et al. reported an interesting relationship between the X–$C_{carbene}$–X angles of 5-membered ring carbenes and the chemical shift of their carbene ^{13}C NMR signal: the smaller the angle the smaller the chemical shift. It is important to note that other structural parameters, for example, $C_{carbene}$ – N bond lengths, do not follow such a trend.

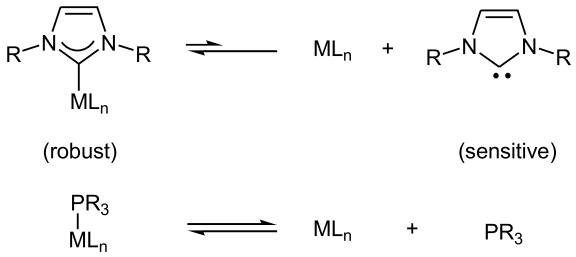
This electron-richness of N-heterocyclic carbenes has an impact on many elementary steps of catalytic cycles, for example, facilitating the oxidative addition step. Therefore, NHC metal complexes are well suited for cross-coupling reactions of non-activated aryl chlorides—substrates that challenge the catalyst with a difficult oxidative addition step [28]. Furthermore, as a consequence of their strong electron-donor property, N-heterocyclic carbenes are considered to be higher field as well as higher *trans* effect ligands than phosphines.

3.2 Complex Stability

N-Heterocyclic carbenes form intriguingly stable bonds with the majority of metals [12, 21, 29]. Whereas for saturated and unsaturated N-heterocyclic carbenes of comparable steric demand very similar bond dissociation energies have been observed, phosphines generally form much weaker bonds (Table 2) [21]. As a result, the equilibrium between the free carbene and the carbene metal complex lies far more on the side of the complex than

Table 2 Steric demand and bond strength of some important ligands [21, 40]

Ligand	$\%V_{Bur}$ for M-L (2.00 Å)	BDE [kcal/mol] (theoretical) for L in $Ni(CO)_3L$
IMes	26	41.1
SIMes	27	40.2
IAd	37	20.4
I*t*Bu	37	24.0
PPh_3	27	26.7



Scheme 5 Equilibrium of complexation

is the case for phosphines (Scheme 5). This minimizes the amount of free NHC in solution and thus increases the life time of the complex as well as its robustness against heat, air and moisture. It has to be kept in mind that N-heterocyclic carbenes, while they can be isolated and stored, are still very sensitive and reactive towards many electrophilic compounds.

The resulting extraordinary stability of NHC-metal complexes has been utilized in many challenging applications. However, an increasing number of publications report that the metal-carbene bond is not inert [30–38]. For example, the migratory insertion of an NHC into a ruthenium-carbon double bond [30], the reductive elimination of alkylimidazolium salts from NHC alkyl complexes [37] or the ligand substitution of NHC ligands by phosphines [36, 38] was described. In addition, the formation of palladium black is frequently observed in applications of palladium NHC complexes, also pointing at decomposition pathways.

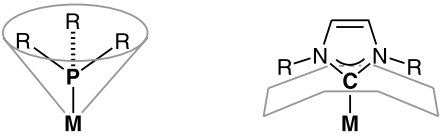


Fig. 1 Shape of phosphines and NHC

3.3 Sterics

Despite the fact that N-heterocyclic carbenes have often been used as phosphine mimics, their shape is very different (Fig. 1). For phosphine complexes, the substituents R on the phosphorus point away from the metal, resulting in the formation of a cone. Therefore, the steric demand of these ligands can easily be described using Tolman's ingenious cone angle descriptors [26]. The topology of N-heterocyclic carbene is different from this and it is more complicated to define parameters measuring the steric demand of these ligands. The R substituents on the nitrogen atoms have a strong impact on the ligand's shape. N-heterocyclic carbenes have been described as fence- or fan-like [39], the substituents pointing toward the metal, thereby "wrapping" it to some extent and forming a pocket (Fig. 1). In addition, the NHC ligands are anisotropic and a rotation around the metal-carbene bond can substantially change the steric and electronic interactions.

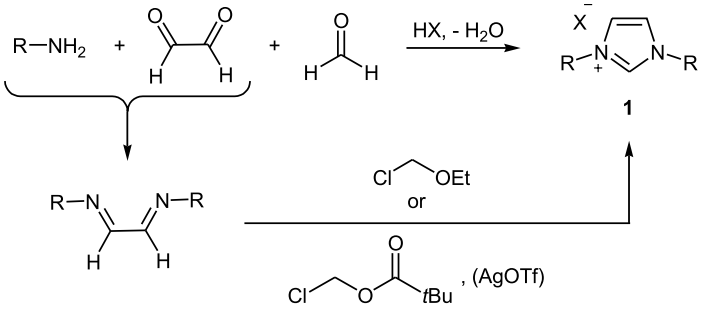
In an attempt to quantify the steric demand of NHC ligands Nolan et al. have introduced the $\%V_{bur}$, the volume buried by overlap between a sphere with a radius of 3 Å centered around the metal with the atoms of the ligand within this sphere [40]. The bond length of the M – L bond is set to the same value for all ligands bound to the same metal (Table 2; M – L = 2 Å). The bulkier a specific ligand, the larger the amount of the sphere ($\%V_{Bur}$) that will be occupied by the ligand. However, this $\%V_{Bur}$ can only be one steric parameter, since it does not take into account the ligands' anisotropy.

4 Imidazolium Salt Synthesis

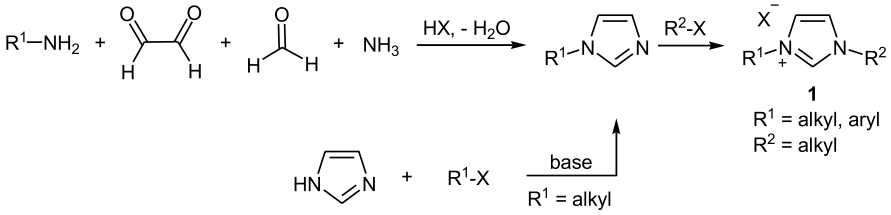
The most common way to prepare N-heterocyclic carbenes is the deprotonation of the corresponding azolium salts, like imidazolium, triazolium, tetrazolium, pyrazolium, benzimidazolium, oxazolium or thiazolium salts or their partly saturated pendants, with the help of suitable bases. The pK_a value of imidazolium and benzimidazolium salts was determined to be between 21 and 24, which puts them right in between the neutral carbonyl carbon acids acetone and ethyl acetate [41, 42]. Arguably, *imidazolium*-based carbenes have proven to be especially versatile and useful and their synthesis should be discussed in more detail. The synthesis of imidazolium salts has been developed over many decades and numerous powerful methods exist [43].

For the synthesis of imidazolium salts **1** two different routes can be distinguished. On one hand, existing imidazoles can be alkylated using suitable electrophiles, resulting in the formation of *N*-alkyl-substituted imidazolium salts. Alternatively, the imidazolium ring can be built up, for example by con-

densation reactions (Schemes 6, 7). This latter route has become the method of choice for many sterically demanding imidazolium salts. Because of the increased interest in N-heterocyclic carbenes and imidazolium salts, many synthetic methods have been improved recently. For example, glyoxal is reacted with formaldehyde and a primary amine in the presence of a strong acid, resulting in the formation of imidazolium salts. Alternatively, the bisimine intermediate can be isolated and treated with electrophilic C_1-fragments like chloromethylethyl ether or chloromethyl pivalate [44–47]. In some critical cases, the addition of stoichiometric amounts of silver triflate was proven to be beneficial [47]. Unsymmetrically *N*,*N*′-disubstituted imidazolium salts can be formed by alkylation of monosubstituted imidazoles (Scheme 7) [48–55]. Finally, careful choice of the counter anion is advisable since it greatly influences the solubility of the imidazolium salt, non-coordinating counterions like OTf^- or BF_4^- increasing the salts solubility.

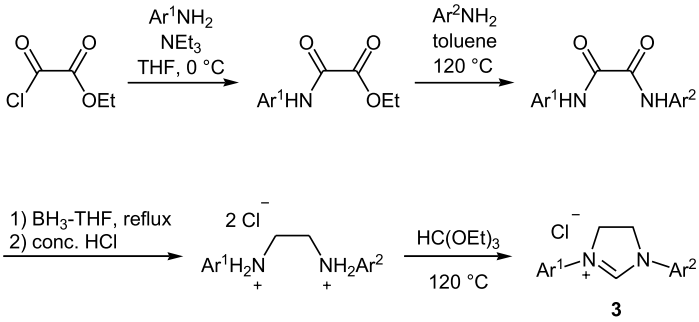


Scheme 6 Synthesis of symmetrical imidazolium salts



Scheme 7 Synthesis of unsymmetrical imidazolium salts

Nevertheless, there are certainly a number of painful limitations. There is no simple and efficient method for the synthesis of unsymmetrical *N*,*N*′-diaryl-substituted imidazolium salts, very desirable compounds. Furthermore, the Buchwald–Hartwig-like cross-coupling reaction of *N*-monosubstituted imidazoles with arylhalides, which would result in the formation of imidazolium salts, has not been reported yet. However, unsymmetrical *N*,*N*′-



Scheme 8 Synthesis of imidazolidinium salts

diaryl-substituted 4,5-*dihydro*imidazolium salts **3** can be prepared, allowing the independent variation of the substituents (Scheme 8) [56, 57].

5
Different Monodentate NHC Ligand Classes

The following section briefly highlights some of the most important achiral ligand classes. Four-, five-, six- and seven-membered N-heterocyclic carbenes have been reported as ligands for transition metals, the majority being 5-membered carbene ligands.

5.1
4-Membered NHC

Grubbs et al. developed the first 4-membered NHC ligand **4** (Fig. 2). Steric shielding of the carbene carbon was found to be crucial for success and even mesityl groups were not sufficiently sterically demanding to prevent carbene dimerization. Only the 2,6-diisopropyl-substituted substituents shown in **4** allowed for the isolation of the free NHC [58]. The ν(CO) values of the corresponding rhodium dicarbonyl complex (ν(CO) in toluene: 2080 and 1988 cm^{-1}) indicate that **4** is a slightly less strong σ-donor than the dihydroimidazol-2-ylidene analogue [59]. In addition, the activity of a ruthe-

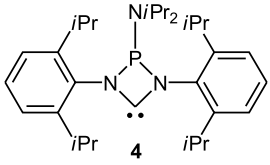


Fig. 2 A 4-membered NHC

nium complex of **4** was lower than that of the standard catalysts in several metathesis reactions.

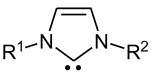
5.2 5-Membered NHC

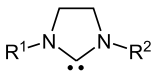
The vast majority of N-heterocyclic carbenes are based on 5-membered ring systems. It was found that sterically demanding substituents on the NHC are not only beneficial for the stability of the NHC, but also for its catalytic properties. Arguably, the most important and most often employed N-heterocyclic carbenes are imidazol-2-ylidenes IMes and IPr and the imidazolidin-2-ylidenes SIMes and SIPr (Fig. 3). The reactivity of the corresponding transition metal complexes is described in detail in the following sections.

The advent of NHC ligands has sparked the design of new ligand architectures. Especially intriguing is the possibility to strongly influence the metals coordination sphere, since in contrast to phosphines, the R substituents point towards the metal. Along these lines a number of catalysts were developed longing for maximal impact on the metal's coordination sphere [60–66].

In this respect, the IBiox family of ligands is of interest, being readily derived from bioxazolines (Fig. 4) [47, 60, 61, 67]. First, the unique 4,5-dioxygen substitution influences the ligands' electronic properties and creates a donor power comparable to very electron-rich phosphines like P*t*Bu$_3$, but slightly less electron-rich than other imidazolium-based N-heterocyclic carbenes. Interestingly, all IBiox ligands virtually have the same electronic character. Second, these ligands bear a characteristic rigid tricyclic backbone. The substituents R^1 and R^2 on the peripheral rings surround the carbene carbon, thereby creating a unique opportunity to influence the metal's coordination sphere (Fig. 5).

Additionally, and as a consequence of the cycloalkyl substitution on the rigid tricyclic backbone, the IBiox ligands are sterically demanding, while being flexible, with restricted degrees of freedom (*flexible steric bulk*) [60, 61]. While shielding the metal the IBiox ligands are adaptable, allowing the coordination sphere of the metal to expand and contract. This renders these ligands valuable for catalytic transformations of sterically demanding substrates.





R^1, R^2	**5**	**6**
2,4,6-$(Me)_3C_6H_2$	IMes	SIMes
2,6-$(iPr)_2C_6H_3$	IPr	SIPr
cyclohexyl	ICy	
tert-butyl	I*t*Bu	
1-adamantyl	IAd	

Fig. 3 Most important imidazol-2-ylidenes and imidazolidin-2-ylidenes

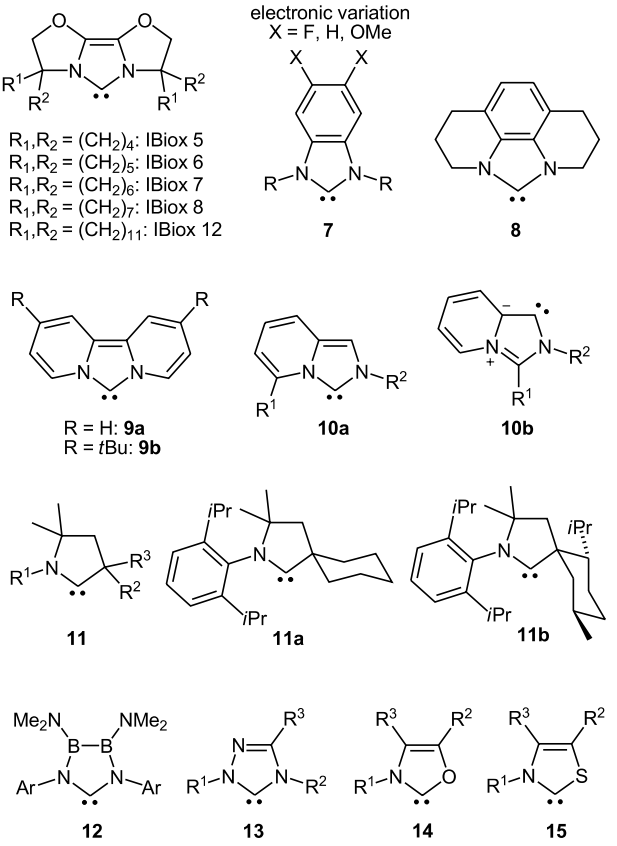


Fig. 4 Some 5-membered NHC

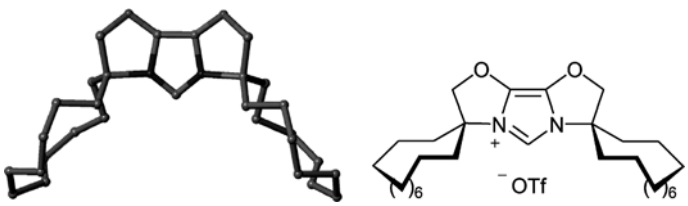


Fig. 5 X-ray structure of IBiox12-HOTf (anion omitted for clarity)

Finally, another advantage of these ligands becomes obvious when looking at the whole IBiox family of ligands. The steric bulk of the ligands can be varied virtually without affecting the electronic character (vide supra)—an ideal scenario for a systematic screening of ligands (Fig. 6). It is important to note that this is a rare property for monodentate ligands. For example, increasing the size of monodentate phosphines at the same time changes both electronic and steric properties.

These attractive features enable the IBiox ligands to successfully act in challenging cross-coupling reactions, like the formation of tetra-ortho-substituted biaryls by Suzuki–Miyaura coupling [61] or in the Sonogashira coupling of secondary alkyl halides [67]. In these reactions, dramatically different results were obtained for different IBiox ligands, thus demonstrating the role of optimization of the ligands' steric demand.

Benzimidazolium-based N-heterocyclic carbenes **7** [68–72] and **8** [73] are an interesting, though less commonly investigated class of NHC. Organ et al. tried to push forward this concept of inability by the preparation of a series of independently sterically *and* electronically tunable benzimidazolium-derived N-heterocyclic carbenes [74, 75].

Unfortunately, however, this endeavor was hampered by synthetic difficulties and only a series of three electronically different ligands **7** resulted (Fig. 4, X = F, H or OMe; R = adamantyl). The investigation of these ligands in the palladium-catalyzed Suzuki–Miyaura coupling revealed only slight reactivity differences. It seems that the electronic variations possible within a given NHC ligand platform are rather small, suggesting that the variation of the sterics of N-heterocyclic carbenes is a more promising approach to optimization.

Bipyridocarbene **9a** was first synthesized by Weiss et al. and is a very electron-rich NHC (Fig. 4) [76, 77]. This can be seen from the very strong high-field shift of its carbene signal in the ^{13}C NMR spectrum at 196 ppm [78]. However, the lability of this compound hinders its application in catalysis. Kunz et al. recognized that *tert*-butyl substitution results in the formation of more stable NHC **9b**, which has very recently allowed the first X-ray structural analysis of these types of carbenes [27].

Lassaletta et al. [63] and Glorius et al. [62] independently developed imidazo[1,5-a]pyridine-3-ylidenes **10a**, which can be seen as benzannulated imidazolin-2-ylidenes **5** or, alternatively, as hybrids between the bipyridocarbene **9** and the standard imidazocarbenes **5** (Fig. 4). Again, these ligands are very electron-rich carbenes, indicated by the ν(CO) for *cis*-(CO)$_2$RhCl(**10**) with R^1,R^2 = Me: 2079 and 2000 cm^{-1}. First applications of these ligands in catalysis are promising, especially since the R^1 substituent of **10a** is in close proximity to the catalytically active metal and can be varied over a wide range [62].

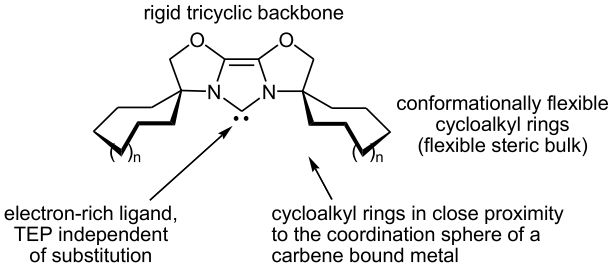
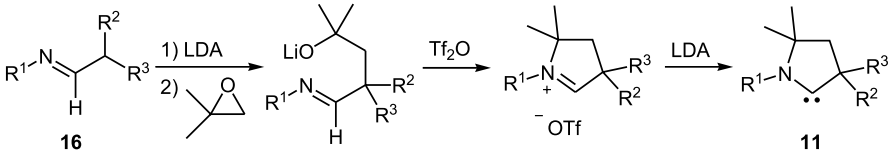


Fig. 6 Features of the IBiox ligands

For imidazolium salts **1**, an alternative pathway with deprotonation and carbene generation at the C4/C5-position was observed previously; the carbenes thus generated are called *abnormal* carbenes [79–81]. Likewise, suitably substituted imidazo[1,5-a]pyridinium salts can be deprotonated to mesoionic carbenes **10b** and the corresponding silver, iridium and rhodium complexes were formed.

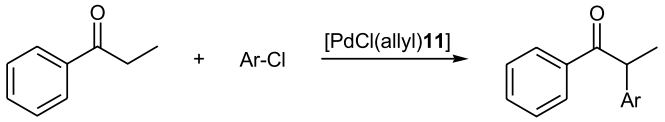
Stable cyclic (alkyl)(amino)carbenes (CAAC) have been developed by Bertrand et al. and can be readily prepared in a few steps starting from simple imines **16** (Fig. 4, Scheme 9) [64, 65, 82–84]. A special feature of these 5-membered ring carbenes is their stabilization by the help of a quarternary carbon next to the carbene.

Using this ligand backbone **11**, the interesting ligands **11a** and **11b** were successfully prepared (Fig. 4). These ligands showed pronounced reactivity differences in the palladium-catalyzed α-arylation of propiophenone (Table 3). Rigid ligand **11b** generally was the ligand of choice in these transformations, however, it failed completely for the sterically very demanding 2,6-dimethylchlorobenzene (entries 2 and 4). Ligand **11a**, on the other hand, is sterically demanding but flexible, it exhibits *flexible steric bulk* (vide supra). This ligand gave only low yields of the desired product with sterically less



Scheme 9 Facile synthesis of CAACs

Table 3 α-Arylation of propiophenone



Entry	Ar – Cl	Catalyst ([mol%])	*T* [°C]	*t* [h]	Yield [%]
1	2-MeC_6H_4Cl	**11a** (0.5)	23	36	10
2	2-MeC_6H_4Cl	**11b** (0.5)	23	36	82
3	2,6-$Me_2C_6H_3Cl$	**11a** (1)	50	20	81
4	2,6-$Me_2C_6H_3Cl$	**11b** (0.5)	50	20	0

Conditions: THF (1 mL), NaO*t*Bu (1.1 mmol), propiophenone (1.0 mmol), aryl chloride (1.0 mmol). Yields as determined by NMR spectroscopy

Fig. 7 Low-coordinate complexes stabilized by complexation to ligand **11b**

demanding substrates, but it was found to be the optimal ligand for 2,6-dimethylchlorobenzene (entries 1 and 3) [64].

In another very insightful application, Bertrand et al. employed ligand **11b** for the isolation of low-coordinate transition metal complexes. In these compounds **16** and **17** (Fig. 7), the cyclohexyl ring shields one coordination site of the metal and stabilizes it by means of agostic interactions [65].

Other structurally interesting 5-membered carbenes like **12** [85], **13** [13, 86], **14** [87–89] or **15** [90, 91] are probably less important for organometallic applications.

5.3 6- and 7-Membered NHC

Larger ring size N-heterocyclic carbenes like 1,3-disubstituted pyrimidin-2-ylidenes **18** [92–95], perimidine-based carbene **19** [96], **20** [97] or chiral 7-membered NHC **21** [98] have only rarely been reported (Fig. 8). Ligands **18** were tested in ruthenium-catalyzed metathesis reactions [99] and in palladium-catalyzed cross-coupling reactions [100] and were found to be less reactive than standard carbene catalysts. Still, these ligands open new possibilities for catalyst design. Of special interest are electronic variations resulting from different backbone structures and a change of the topology of the substituents on the NHC. This was demonstrated nicely by Richeson et al [96]. Incorporating a naphthyl ring system in ligand **19** led to pronounced changes in the shape of the NHC. Specifically, going from 5- to 6-membered N-heterocyclic carbenes increases the size of the N–$C_{carbene}$–N angle from 100–110° in **5** and **6** to 115.3° in **19**. Furthermore, the $C_{carbene}$–N–R angle α is reduced from 122–123° in **5** and **6** to 115.5° in **19**, causing an increased steric impact of the *N*-substituents on the carbene carbon. On the basis of the ν(CO) values of the corresponding *cis*-$(CO)_2$RhCl(**19**) complex, ligand **19** is an even stronger electron donor than the dihydroimidazol-2-ylidenes **6**, but weaker than the acyclic carbene C(N*i*$Pr_2)_2$.

At first, N-heterocyclic carbenes **20** look bizarre to the organic chemist, since they are organic/inorganic hybrid compounds. However, borazines, sometimes called “inorganic benzene”, are isoelectronic with benzene and are therefore extraordinarily stable heterocycles. “Exchange” of a borane

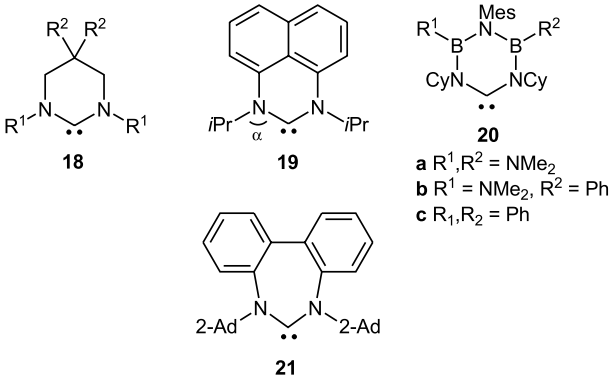


Fig. 8 Six- and seven-membered NHC

moiety against an isoelectronic carbene moiety provides NHC **20**. The substituents of **20** can be varied independently and the electronic properties of the ligand can therefore readily be tuned [97]. Stable complexes of these ligands have been formed, but so far, no reports on the catalytic activity of transition metal complexes of **20** have appeared.

Very recently, Stahl et al. reported the first synthesis of a 7-membered NHC ligand [98]. Despite substantial effort, the isolation of the free carbene **21** was not successful. However, palladium complexes of **21** could be formed and structurally characterized. Ligand **21** is C_2 symmetric as a result of a torsional twist which is thought to attenuate the antiaromatic character of the 8π-electron carbene heterocycle [101, 102]. It will be interesting to see, if the synthesis of conformationally stable analogues and their application in asymmetric catalysis will be feasible.

Using a monodentate ligand does not necessarily mean that only one ligand coordinates to the metal. Since these monoligated metal species are very important for catalytic activity, their synthesis is highly desirable. More details on the development of well-defined and highly active monoligated palladium NHC catalysts will be provided in later parts of this volume [103–109].

6 Bi- and Multidentate NHC

Besides these monodentate ligands, many multidentate ones have been prepared and used in different fields of chemistry and only a few should be mentioned here. Rigid bidentate benzimidazole-based N-heterocyclic carbenes were successfully used to synthesize main-chain conjugated organometallic polymers **23**, an interesting class of materials with desirable electronic and mechanical properties (Fig. 9) [110].

Other bidentate N-heterocyclic carbenes were used to form stable chelate complexes. A fine example is the use of palladium NHC complex **24** in the catalytic conversion of methane to methanol (Fig. 10) [111]. In this case the stability of the complexes is a requirement, since the reaction takes place in an acidic medium (trifluoroacetic acid) at elevated temperatures (80 °C) mediated by strong oxidizing agents (potassium peroxodisulfate).

Exciting metal complexes can also be obtained with chelating tri- and tetradentate ligands. Iron(III) and chromium(III) complexes of the tripodal tricarbene ligand **25** in the form $[M(\mathbf{25})_2]^+$ have been described (Fig. 11) [112, 113].

The efficient formation of macrocyclic ligands can be very challenging. An efficient template-controlled synthesis for tetracarbene ligands with crown ether topology was developed by Hahn et al. [114–116]. First, a transition metal complex **26** with four unsubstituted benzimidazol-derived NHC **7** (R,X = H) was formed. Finally, a template-controlled cyclization of alkyl or aryl isocyanides resulted in the subsequent linking of the carbene ligands and formation of the desired product **27**. Intriguingly, the carbene ligands are not stable when removed from the transition metal.

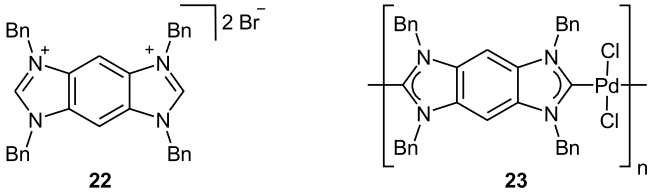


Fig. 9 Metal-organic polymers made by N-heterocyclic carbenes

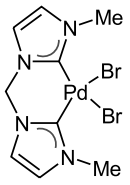


Fig. 10 Palladium NHC complex for challenging CH activations

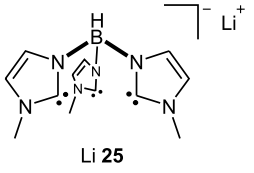
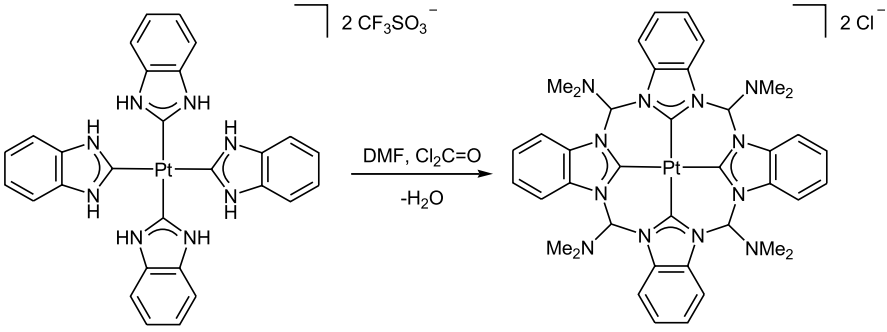


Fig. 11 A tridentate NHC ligand



26 27

Scheme 10 A tetradentate NHC ligand build up by template-controlled synthesis

7 Conclusion

N-heterocyclic carbenes have become a new tool in organometallic chemistry and the field of the application of NHC in catalysis has reached a certain level of maturity. Yet, it is astonishing that so many fundamental questions are still not completely solved. What exactly is the nature of the metal-carbene bond and (when) does π-backbonding play a significant role? How can the shape of the NHC adequately be described and measured, so that ligands can systematically be compared with each other? And (when) will we be able to predict a carbene's properties before we prepare it in the lab? Research with NHC is still vibrant and it doesn't need an augur to predict that many exiting and unexpected results will be unveiled.

Note Added in Proof

Very recently, a powerful method for the synthesis of unsymmetrical imidazolium salts was reported: Fürstner A, Alcarazo M, Cesar V, Lehmann CW (2006) Chem Commun, 2176

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N-Heterocyclic Carbenes as Ligands for High-Oxidation-State Metal Complexes and Oxidation Catalysis

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Abstract N-Heterocyclic carbenes (NHCs) possess properties that are ideally suited for their use as ligands in transition-metal oxidation chemistry and catalysis. Their strong sigma-donating ability stabilizes metals in high oxidation states, and their high M–L bond dissociation energies reduce their tendency to dissociate and undergo oxidative decomposition of the free carbene. In this chapter, we summarize these unique properties and survey the use of NHCs as ligands to stabilize high-valent transition-metal chemistry and their role in metal-catalyzed oxidation reactions. Catalytic applications of NHC-metal complexes include alcohol oxidation and alkene and alkane functionalization.

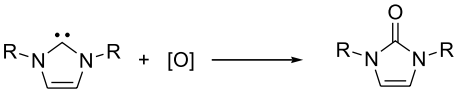
Keywords N-Heterocyclic Carbenes · Oxidation · Catalysis · Dioxygen

Abbreviations

COD	1,5-cyclooctadiene
Cp*	Pentamethylcyclopentadienyl
IAd	1,3-diadamantyl-2,3-dihydro-1*H*-imidazol-2-ylidene
I^{t}Bu	1,3-di-*tert*-butyl-2,3-dihydro-1*H*-imidazol-2-ylidene
IBu	1,3-dibutyl-2,3-dihydro-1*H*-imidazol-2-ylidene
ICy	1,3-dicyclohexyl-2,3-dihydro-1*H*-imidazol-2-ylidene
IMe	1,3-dimethylimidazolin-3-ylidene
IMes	1,3-bis(2,4,6-trimethylphenyl)-2,3-dihydro-1*H*-imidazol-2-ylidene
I^{i}Pr	1,3-bis(2,6-diisopropylphenyl)-2,3-dihydro-1*H*-imidazol-2-ylidene
IPh	1,3-Diphenyl-2,3-dihydro-1*H*-imidazole
ITmt	1,3-bis-(2,6,2″,6″-tetramethyl-[1,1′;3′.1″] terphenyl-5′-yl)-2,3-dihydro-1*H*-imidazol-2-ylidene
ITol	1,3-Di-*p*-tolyl-2,3-dihydro-1*H*-imidazole
^{Me}IPr	1,3-diisopropyl-4,5-dimethyl-2,3-dihydro-1*H*-imidazol-2-ylidene
NHC	N-Heterocyclic Carbene
OPiv	2,2-dimethylpropionate (pivalate)
^{Ph}IPr	1,3-Diisopropyl-4,5-diphenyl-2,3-dihydro-1*H*-imidazole
SI^{t}Bu	1,3-di-*tert*-butyl-4,5-dihydroimidazol-2-ylidene
SIMes	1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
SI^{i}Pr	1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene
TIMY	1,3,4,5-tetramethyl-2,3-dihydro-1*H*-imidazol-2-ylidene
Triazol	4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene
Tp′	Hydridotris(3-*tert*-butyl-5-methylpyrazolyl)borate

1 Introduction

N-Heterocyclic carbenes (NHCs) continue to emerge as effective ligands in transition-metal chemistry and homogeneous catalysis. Since the isolation of the first stable free carbene in 1991 [1], interest in these compounds as ligands for transition-metal complexes has grown dramatically [2–7]. This interest can be attributed, in part, to both their similarities to and differences from ubiquitous phosphine ligands. Phosphines are seldom used as ancillary ligands in oxidation chemistry because of their intrinsic oxidative instability. Free NHCs are also susceptible to oxidative decomposition (e.g., Eq. 1), but when coordinated to a metal center, NHCs are remarkably robust and hold significant promise for use in oxidation chemistry. NHCs possess key properties that enhance their potential utility: their strong



Equation 1

σ-donating ability stabilizes metals in high oxidation states and their high M – L bond dissociation energies render them less susceptible to oxidative decomposition. A discussion of these properties, a survey of the applications of NHCs to the stabilization of high-oxidation-state metal complexes, and the use of NHC's as ancillary ligands in metal-catalyzed oxidation reactions are provided below.

2
Overview of NHC Ligand Properties

Thorough analysis of the chemical properties of NHCs as ligands is provided elsewhere in this volume. The following brief survey highlights those properties of NHCs that make them well suited for application to oxidation chemistry.

2.1
Electronic Properties

Several systematic experimental and computational studies have compared the sigma-donating abilities of NHCs and tertiary phosphines for a variety of transition-metal complexes [8–17]. As illustrative examples, analyses of the nickel-carbonyl complex **1** and iridium carbonyl complex **2** (Fig. 1) re-

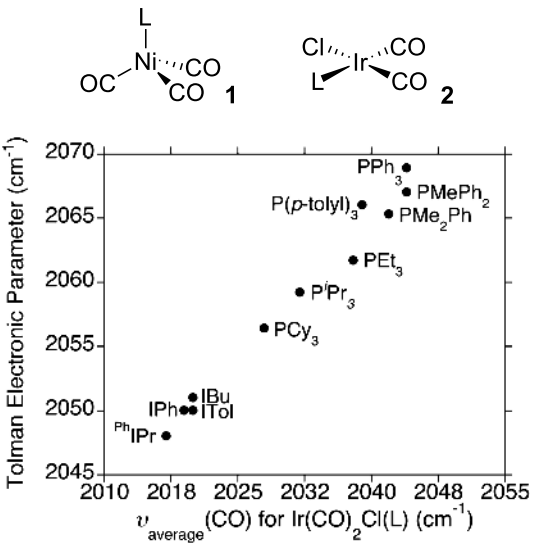


Fig. 1 Relationship between the Tolman electronic parameters and IR stretching frequencies for complex **2** (data compiled from [12, 16])

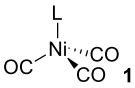
veal that NHC complexes have lower C – O stretching frequencies than their phosphine counterparts [7, 12, 16, 17]. These data, which conform to those of other studies, suggest that the NHCs are stronger σ-donors than even the most basic tertiary phosphines. Computational studies suggest that the M – C bond of NHC-metal complexes is primarily σ-bonding in character, with little contribution from π-back-bonding [4]. The strong σ-donating ability of NHCs revealed by these studies underlies the ability of NHCs to stabilize high-oxidation-state metal complexes.

2.2 NHC–Metal Bond Strengths

Phosphines and NHCs undergo facile conversion to the corresponding phosphine oxides and ureas under oxidizing reaction conditions (cf. Eq. 1). This decomposition pathway can be slowed or eliminated by protonation of the ligand or coordination to a metal center. For example, the air sensitivity of P^tBu_3 and related trialkylphosphines may be minimized by employing the phosphonium salt, $[HPR_3]BF_4$, as a ligand precursor in catalytic reactions [18]. Despite this partial solution, phosphine ligands are seldom compatible with metal-catalyzed oxidation reactions. Dissociation of the ligand at any point during the catalytic reaction results in rapid ligand oxidation. Recent studies indicate that NHCs possess significantly higher M – L bond strengths than phosphines [9, 12–16]. This property appears to foster significantly higher ligand stability under oxidizing reaction conditions and allows NHCs to be employed in metal-catalyzed oxidation reactions.

Both steric and electronic factors contribute to M – L bond strengths. The Tolman-cone-angle measurement, used to assess the size of tertiary phosphines [19], is an inappropriate indicator of the size of NHCs because of their planar spatial orientation. Therefore, a "buried volume" parameter, $\%V_{Bur}$, has been used to compare the relative sizes of phosphine and NHC ligands [13, 17]. This calculated parameter estimates the percentage of spherical space around the metal that is consumed by a given ligand. Because it does not assume a conical ligand shape, $\%V_{Bur}$ is a more general measure of a ligand's steric influence. Based on this parameter, the largest NHCs, I^tBu, SI^tBu and IAd, are significantly larger than even the largest tertiary phosphine, P^tBu_3, whereas other commonly used NHCs have steric properties similar to bulky phosphines (Table 1). For ligands of comparable size, NHCs have significantly higher DFT-calculated bond dissociation energies (BDEs) than phosphines (Table 2). Only the very bulky NHCs, IAd, I^tBu and SI^tBu, exhibit BDEs lower than that of the phosphines in the four-coordinate Ni complex, **1** (Table 1) [17]. Calculations of a less hindered, three-coordinate, trigonal planar complex, $Ni(NHC)(CO)_2$, reveal that all of the NHCs possess a higher M – L bond strength than phosphines. This trend in M – L bond strengths has been attributed to the enhanced basicity (i.e., donor ability) of NHCs relative

Table 1 DFT-calculated M – NHC bond dissociation energies (kcal mol^{-1}) and $\%V_{Bur}$ for the carbene ligands in nickel-carbonyl complexes



1

Ligand	BDE of L in **1** kcal mol^{-1}	$\%V_{bur}$
I^{t}Bu	24.0	37
SI^{t}Bu	21.8	38
IAd	20.4	37
IMes	41.1	26
SIMes	40.2	27
I^{i}Pr	38.5	29
SI^{i}Pr	38.0	30
ICy	39.6	23
PH_3	22.7	17
PPh_3	26.7	22
P^tBu_3	28.0	30

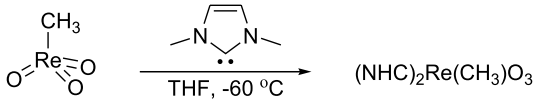
to phosphines [20]. That NHCs undergo less facile ligand dissociation relative to phosphines provides a compelling justification for the enhanced utility of NHCs relative to phosphines in metal-catalyzed oxidation reactions.

3 N-Heterocyclic Carbenes as Ligands in Fundamental Transition-Metal Oxidation Chemistry

As phosphine analogs, N-heterocyclic carbenes are frequently employed as ligands for low-valent transition-metal complexes [2, 4, 6]. Significantly less is known about NHCs as ligands for high-oxidation-state metal complexes and for metals bearing oxidizing ligands such as oxides and peroxides. The following sections summarize the early developments in this area.

3.1 N-Heterocyclic Carbenes for the Stabilization of High-Oxidation-State Metals

Transition-metal oxides are useful oxidizing reagents for organic molecules and often participate in oxygen-atom transfer reactions [21]. A prototypical example is CH_3ReO_3 (MTO), which serves as a versatile reagent for stoi-



Equation 2

chiometric and catalytic oxidation reactions [22]. The sterically unhindered NHC, 1,3-dimethylimidazolin-3-ylidene, reacts with MTO to yield a bis-NHC adduct, $(NHC)_2Re(CH_3)(O)_3$, at – 60 °C (Eq. 2) in THF [23]. This complex was characterized by comparison of spectroscopic features to those of related $L_2Re(CH_3)(O)_3$ complexes; however, it is unstable and decomposes when the solution is warmed above – 20 °C. Nevertheless, it is significant that the complex can be prepared without immediate NHC oxidation to the cyclic urea derivative. The analogous reaction of the NHC with Re_2O_7 led to immediate reduction of the Re(VII) center, presumably via NHC oxidation, although the organic reaction products were not identified. By comparison, phosphines react rapidly with MTO to yield the corresponding phosphine oxides [24, 25].

Since this initial report, NHCs have been used to stabilize a number of additional high-valent metal complexes bearing oxo and nitrido ligands (Chart 1) [26–32]. In contrast to the MTO example, these complexes and the high-valent metal precursors employed in their synthesis are not especially strong oxidants. Consequently, the preparation of these complexes often can be achieved by simple addition of the NHC to an unsaturated metal center or via displacement of a weakly coordinated solvent molecule such as THF.

Several interesting features have been noted in the studies of complexes **3–10**. Cationic Mo(VI) complexes of the type $[MoO_2ClL_3]Cl$ were not known until the synthesis of **6** [26]. With other ligands, including DMF,

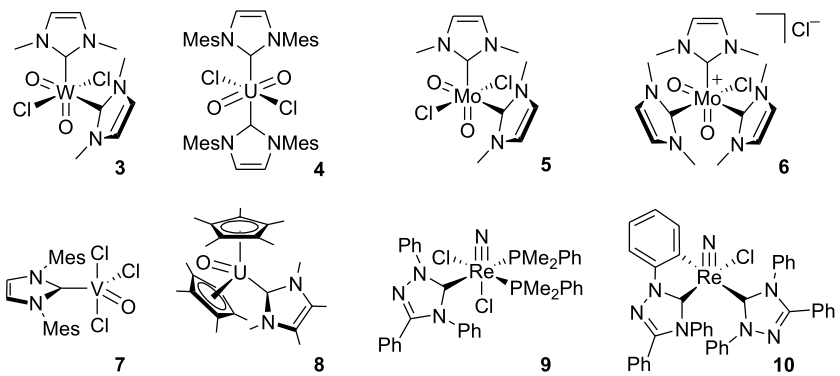


Chart 1 NHC-coordinated high-valent metal complexes

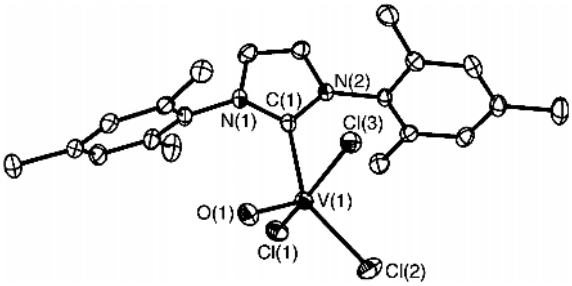


Fig. 2 X-ray structure of $IMesVCl_3O$, **7**

$OPPh_3$ and pyridine, the Mo complexes prefer the neutral formulation, $MoO_2Cl_2L_2$ [33–35]. This contrast probably arises from the strong donating ability of NHCs, which can stabilize the cationic metal center more effectively than other neutral ligands. The vanadium and uranium complexes, **7** and **8**, respectively (Chart 1), were the first examples of NHC-coordinated metal-oxo complexes characterized by X-ray crystallography [29, 32]. The NHC-vanadium adduct exhibits significantly greater hydrolytic stability relative to other trichloro-oxo-vanadium(V) species. Two of the V – Cl ligands orient approximately perpendicular to the plane of the heterocyclic ring (Fig. 2). Crystallographic and computational analysis supports the presence of a $Cl - C_{carbene}$ interaction in which electrons from a chloride lone pair donate into the formally vacant p-orbital of the $C_{carbene}$ atom. The uranium(IV) oxo **8** represents the first example of an organometallic uranium mono-oxo complex [32]. The unique nature and stability of the terminal oxo ligand has been attributed to the steric bulk of the NHC, which influences the spatial orientation of the Cp* ligands.

In addition to the metal-oxo complexes, several examples of NHC-stabilized rhenium(V)-nitrido complexes exist, e.g., **9** and **10** (Chart 1) [28]. These adducts, which feature triazole-based ligands, were prepared via displacement of phosphine ligands. The stability of both phosphine and triazole-based carbenes in these reactions suggest the nitrido ligand is relatively unreactive.

3.2 Reactions of NHC-coordinated Metal Complexes with Molecular Oxygen

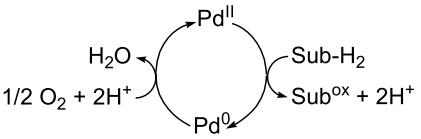
Reactions between molecular oxygen and well-defined transition-metal complexes have been the subject of extensive study for decades [21]. Recent studies demonstrate the suitability of NHCs as ancillary ligands in this chemistry, and in several cases, the enhanced stability of NHCs over phosphines is noted. Certain limitations associated with NHC-ligand instability have also been identified, particulary in the study of first-row transition metals.

3.2.1 Palladium

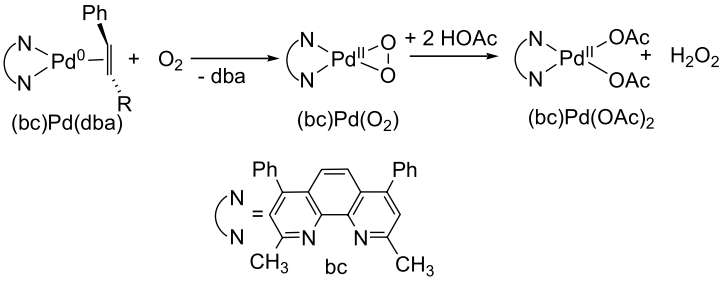
The development of palladium-catalyzed oxidation reactions has grown rapidly in recent years, and particular attention has been directed toward reactions that undergo direct dioxygen-coupled turnover (Scheme 1) [36–38]. The latter reactions are distinct from the well known Wacker process because no cocatalyst is needed to facilitate reoxidation of the reduced Pd catalyst. Recent aerobic oxidation reactions commonly feature the use of oxidatively stable ligands such as pyridine, phenanthroline and related derivatives [37]. NHC ligands are also effective (see Sect. 4.2 below) [39]. Several studies probing fundamental Pd(0)-dioxygen reactivity have been reported in recent years, including those with NHC-coordinated Pd complexes.

The first examples of well-defined reactions between dioxygen and Pd(0) complexes were reported in the late 1960s [40, 41]. η^2-Peroxopalladium(II) complexes were prepared via direct oxygenation of Pd(0) precursors bearing phosphines and isocyanides as ancillary ligands. Both of these ligand classes are susceptible to oxidation. Indeed, homogeneous Pd is a highly efficient catalyst for the aerobic oxidation of triphenylphosphine to triphenylphosphine oxide [42].

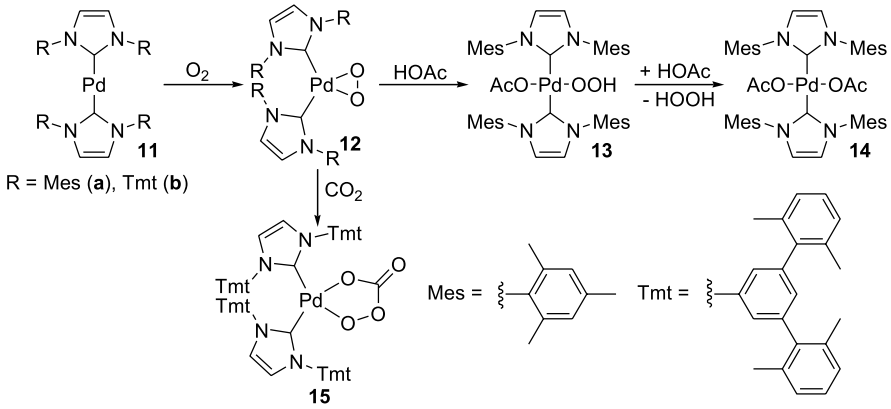
Oxygenation reactions of Pd(0) have been revisited recently in order to gain fundamental insights into this catalytically important reaction, and these studies have employed both phenanthroline and NHC ligands [43–45]. The use of bathocuproine (bc), a phenanthroline derivative, enabled isolation and crystallographic characterization of (bc)Pd(η^2-O_2) [43] (Scheme 2). Addition



Scheme 1 General mechanism for Pd-catalyzed aerobic oxidation reaction



Scheme 2 Synthesis and isolation of bathocuproine palladium complexes



Scheme 3 Reaction of Bis-NHC palladium(0) complexes with molecular oxygen

of acetic acid to this complex results in formation of hydrogen peroxide and (bc)Pd(OAc)$_2$ via rapid protonolysis of both Pd – O bonds.

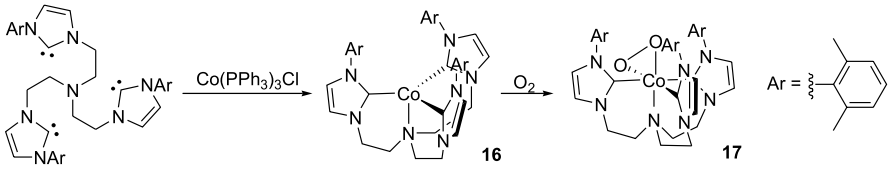
A somewhat different result is obtained from analogous reactions with the NHC-coordinated complex, (IMes)$_2$Pd^0 (**11a**). This complex is extremely air-sensitive and reacts with dioxygen, even in the solid state, to produce the peroxo-complex, (IMes)$_2$Pd(η^2-O$_2$) (**12a**). Addition of acetic acid to this complex yields the hydroperoxide complex, *trans*-(IMes)$_2$Pd(OAc)(OOH) (**13**). Prolonged reactions times are necessary before the second equivalent of acetic acid reacts to produce hydrogen peroxide and (IMes)$_2$Pd(OAc)$_2$ (**14**) [44] (Scheme 2). The Pd(0) complex **11b**, bearing the more-sterically-hindered NHC ligand ITmt, also reacts with molecular oxygen to produce the η^2-peroxo complex [45]. If crystalline **11b** is exposed to ambient air at room temperature, the sample reacts directly to form a peroxocarbonate adduct **15** (Scheme 3). The complex results from CO_2 insertion into a Pd – O bond of **12b**. The IMes complex **12a** does not exhibit solid-state reactivity with CO_2. The difference in the reactivity of these two complexes probably arises from the different steric constraints present in the crystalline forms of **12a** and **12b**. Specifically, the ITmt ligand does not possess substituents in the ortho position of the N-aryl groups [45].

The significantly greater stability of metal-complexed NHCs relative to phosphines will permit further analysis of these fundamental reactions. Ongoing studies promise to provide significant insight into the aerobic oxidation of Pd(0) in Pd-catalyzed oxidation reactions.

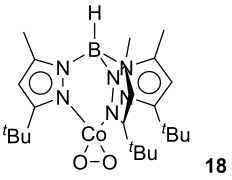
3.2.2
First-Row Transition Metals: Co, Ni and Cu

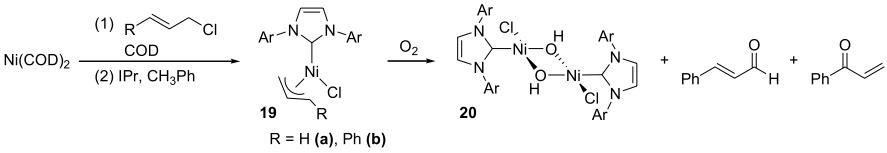
Several recent studies have probed the reactivity of dioxygen with first-row transition metals coordinated by NHC ligands. Cobalt complexes with a variety of different ligands bind dioxygen and have been investigated for use as oxygen carriers and oxidation catalysis [46, 47]. A cobalt(I) complex with a unique tripodal NHC ligand, **16**, was synthesized recently (Scheme 4). Upon reaction with molecular oxygen, it yields a pseudo-octahedral cobalt(III) η^2-peroxo product, **17** [48]. The O – O vibrational frequency (890 cm^{-1}) and bond length [1.429(3) Å] differ significantly from the values observed for the closely related tris(pyrazolyl)borate complex $Tp'Co^{III}(\eta^2\text{-}O_2)$, **18** [961 cm^{-1} and 1.355(3) Å] [49, 50]. These data, which indicate the O_2 ligand in **17** is more reduced than in **18**, suggest that the neutral NHC ligand is more electron rich than the anionic Tp′ ligand. The increased electron-donating ability undoubtedly reflects the tetradentate character of the NHC ligand (one tertiary amine + three NHCs) relative to the tridentate Tp′ ligand; however, the strong donor character of the NHCs probably contributes as well. The η^2-peroxo complex **17** exhibits nucleophilic character, and reacts with electrophilic substrates such as tetracyanoethylene and benzoyl chloride.

Selective reactions of molecular oxygen with NHC-coordinated nickel(I) and nickel(II) complexes have been reported [51, 52]. π-Allyl Ni(II) complexes **19a** and **19b** were prepared via a one-pot procedure from $Ni(COD)_2$ (Scheme 5). Upon exposure to an atmosphere of dioxygen, these complexes react to yield the binuclear hydroxide-bridged Ni complex **20**. Use of the phenyl-substituted allyl complex **19b** permits characterization of the organic products, which consist of a 5 : 3 ratio of cinnamaldehyde and phenyl vinyl ketone. Control experiments and ^{18}O-labeling studies demonstrated that the oxygen atoms in the Ni dimer and the organic products arise from dioxygen,

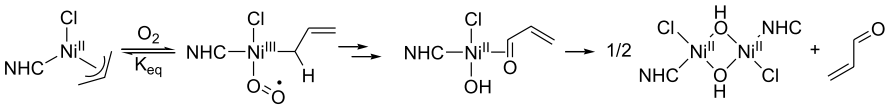


Scheme 4 Synthesis and oxygenation of Tris-carbene cobalt complex





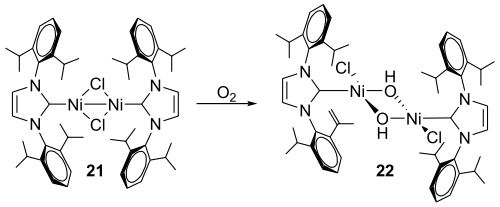
Scheme 5 Preparation and oxygenation of π-allylnickel NHC complexes



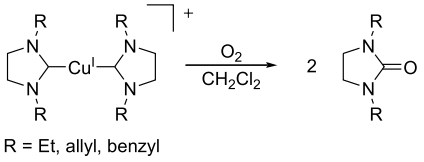
Scheme 6 Proposed mechanism for allylic ligand oxidation

not adventitious water. A simplified mechanistic proposal for this reaction is shown in Scheme 6. Separately, a chloride-bridged, dimeric Ni(I) complex, **21**, was prepared. This complex also undergoes reaction with molecular oxygen to yield a binuclear hydroxide-bridged Ni complex, **22** (Eq. 3). In this case, the four-electron reduction of dioxygen occurs with concomitant dehydrogenation of one isopropyl group of a single I^{i}Pr ligand in the dimer.

The reactivity of dioxygen with nitrogen-coordinated copper(I) complexes has received extensive attention over the past two decades [53, 54]. To date, analogous reactivity has not been realized for NHC-coordinated Cu(I). Sterically unhindered bis-carbene complexes of Cu(I) undergo rapid conversion to the corresponding ureas upon exposure to air in CH_2Cl_2 solution (Eq. 4) [55]. This result suggests NHCs may not be universally applicable to metal-mediated oxidation chemistry.



Equation 3



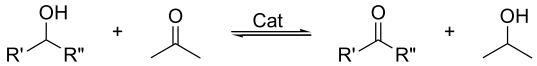
Equation 4

4
Oxidation Reactions Catalyzed by NHC-Coordinated Metal Complexes

The previous section highlighted the utility of NHC ligands in stoichiometric reactions of transition metals. NHCs have also been employed in metal-catalyzed oxidation reactions. Applications include selective alcohol, alkene and alkane oxidation reactions.

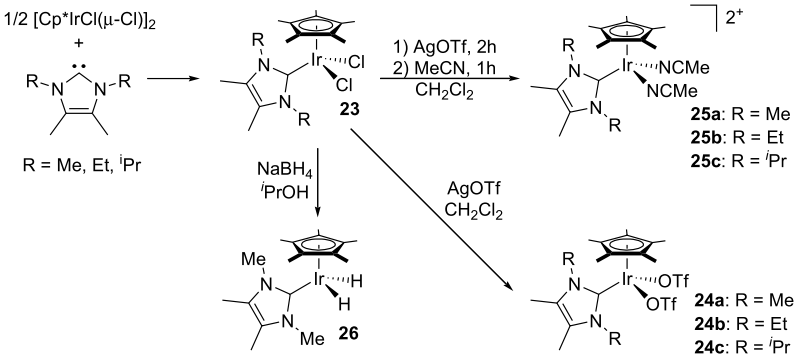
4.1
Oppenauer-Type Alcohol Oxidation

Metal-catalyzed oxidation of alcohols to aldehydes and ketones is a subject that has received significant recent attention [21, 56, 57]. One such method that utilizes NHC ligands is an Oppenauer-type oxidation with an Ir or Ru catalyst [58–62]. These alcohol oxidation reactions consist of an equilibrium process involving hydrogen transfer from the alcohol substrate to a ketone, such as acetone (Eq. 5), or an alkene. Because these reactions avoid the use of a strong oxidant, the potential oxidative instability of NHC ligands is less problematic. Consequently, these reactions represent an important target for future research into the utility of NHCs.

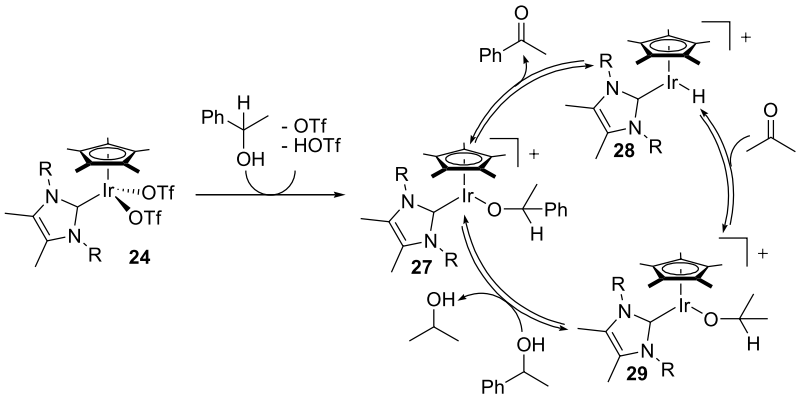


Equation 5

The Ir^{III} complex $[Cp^*IrCl(\mu - Cl)]_2$ serves as a catalyst for the oxidation of primary and secondary alcohols oxidation in acetone as the solvent [63]. The moderate effectiveness of this catalyst, however, prompted the preparation of several Ir^{III} analogs bearing an NHC ligand [58–60] (Scheme 7). It



Scheme 7 Synthesis of Cp*Ir NHC complexes



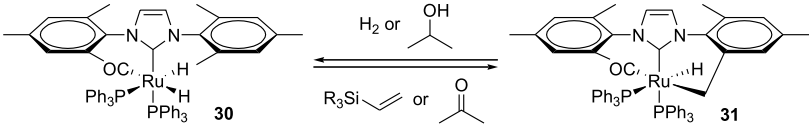
Scheme 8 Proposed mechanism for Oppenauer-type alcohol oxidation

was reasoned that NHC ligands might increase electron density at the metal center and increase the reactivity of an intermediate iridium-hydride with acetone (see intermediate **28**, Scheme 8).

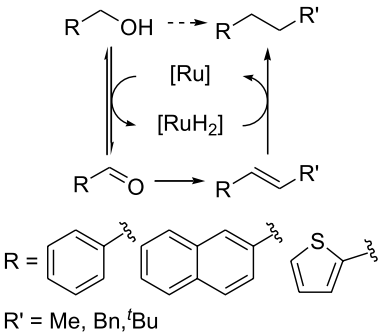
These complexes were screened in the oxidation of *sec*-phenethyl alcohol with acetone as the solvent and K_2CO_3 as a base [59]. It was found that the presence of smaller substituents on the nitrogen atoms of the NHC ligand promote catalytic activity, and the dicationic complex, **25a**, is the most active catalyst. Accordingly, use of complex **25a** enabled the catalyst loading to be lowered to 0.025 mol %, and 3200 turnovers were achieved. The utility of this catalyst was demonstrated for both primary and secondary benzylic alcohols and several aliphatic alcohols.

Analogs of **25**, wherein the NHC ligands are replaced with PPh_3 or P^nBu_3, are almost completely inactive under comparable conditions [59]. Although a number of mechanistic details remain to be established, it is clear that including an NHC ligand in the Ir^{III} coordination sphere exerts a beneficial effect on the catalytic activity.

Ruthenium catalysts with NHC ligands, **30** and **31**, have also been employed in transfer dehydrogenation reactions [61, 62]. Both acetone and alkenes have been used as the hydrogen acceptor in these reactions. When $(IMes)Ru(H)_2(PPh_3)_2(CO)$ (**30**) reacts with acetone or an alkene, it transfers an equivalent of H_2 and undergoes C – H activation of an *ortho*-methyl group of the IMes ligand to yield a new complex $(IMes')RuH(PPh_3)_2(CO)$ (**31**) (Eq. 6) [61].



Equation 6



Scheme 9 Proposed mechanism and substrate scope for tandem alcohol oxidation/Wittig reaction/alkene hydrogenation sequence

This C – H activation event is reversible, and is required to achieve catalytic turnover [62]. A series of alcohols, mostly secondary benzylic examples, have been oxidized using this catalyst. The catalytic activity does not match that of the Ir examples described above, but it has been used in several tandem reactions that feature both dehydrogenation and hydrogenation steps to achieve interesting transformations. One example is a tandem alcohol oxidation/Wittig reaction/alkene hydrogenation sequence (Scheme 9) [61, 62].

4.2 Palladium-Catalyzed Aerobic Alcohol Oxidation

Palladium-catalyzed aerobic oxidation of alcohols to aldehydes and ketones have been studied extensively in recent years, and a number of effective catalysts have been developed (Chart 2). This work has been the subject of several recent reviews [21, 36–38, 56, 64–67] and will not be summarized in depth

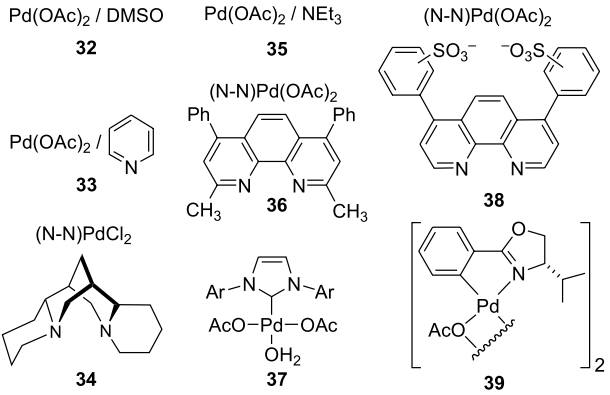
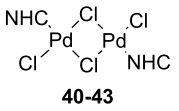


Chart 2 Palladium complexes employed in aerobic alcohol oxidation

here; however, this field highlights prospects for the use of NHC ligands in homogeneous metal-catalyzed oxidation reactions.

In 2001, two groups independently reported a $PdCl_2$/(–)-sparteine catalyst system **34** for the oxidative kinetic resolution of secondary alcohols [68, 69]. The reactions proceed with high selectivity for large number of substrates. Mechanistic studies revealed that (–)-sparteine serves both as a ligand for Pd and as a Brønsted base in the alcohol oxidation reaction [70, 71]. Recognition of this dual role for (–)-sparteine raised the possibility that kinetic resolution could be achieved with achiral Pd complexes, if (–)-sparteine is available as a chiral base in the reaction. This hypothesis was successfully demonstrated with NHC-coordinated Pd complexes, **40–43** (Table 2) [72]. The results obtained with enantiomeric chiral NHCs (*S*,*S*)-**43** and (*R*,*R*)-**43** reveal the presence of "matched" and "mismatched" diastereomeric interactions between the chiral NHC and (–)-sparteine during the reaction (Table 2, Entries 6 and 7). These results represent the first use of NHC ligands in aerobic oxidation catalysis. The presence of a strong Pd – NHC bond undoubtedly enhances the NHC oxidative stability and contributes to the success of these reactions.



40-43

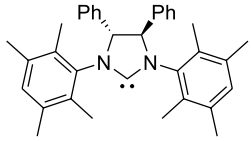
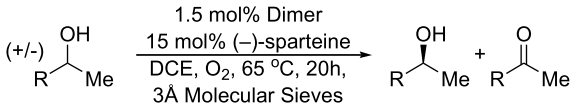
Dimer	NHC
40	I^iPr
41	IMes
42	SIMes
43	

Table 2 Use of Pd(II) dimers in oxidative kinetic resolution of secondary alcohols

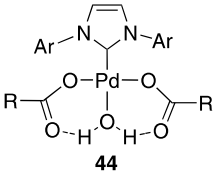


Entry	Dimer	R	% Conversion (% ee)	k_{rel}[a]
1	**40**	C_6H_5	64.5 (96.0)	11.6
2	**40**	2-naphthyl	52.7 (65.9)	7.8
3	**40**	*p*-$OMeC_6H_4$	42.8 (58.2)	14.3
4[b]	**41**	C_6H_5	36.2 (34.9)	6.1
5[b]	**42**	C_6H_5	45.0 (54.1)	6.4
6[c]	(R,R)-**43**	C_6H_5	39.7 (36.4)	4.5
7[c]	(S,S)-**43**	C_6H_5	34.6 (42.0)	11.8

[a] Average of multiple experiments. [b] (–)-Sparteine (20 mol%).
[c] Dimer (2.5 mol%), (–)-sparteine (20 mol%).

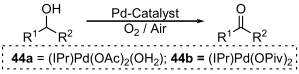
The alcohol-oxidation catalyst systems consisting of $Pd(OAc)_2$/pyridine [73, 74] and $Pd(OAc)_2/NEt_3$ [75] are perhaps the most "user-friendly" examples developed to date. Detailed mechanistic investigation of these catalyst systems revealed a common feature: key intermediates in the catalytic cycle consist of Pd complexes that possess only one neutral donor ligand (pyridine or triethylamine) [76–78]. Furthermore, excess pyridine and NEt_3 inhibit catalytic turnover by competing with the substrate for coordination sites on Pd. If the pyridine and NEt_3 concentrations are too low, however, the catalyst decomposes because facile ligand dissociation enables the aggregation of Pd metal. These observations prompted the development of a new class of NHC – Pd catalysts for alcohol oxidation, $(NHC)Pd(O_2CR)_2(OH_2)$ (**44**) [72, 79–82]. The NHC provides a single, strongly coordinating, neutral donor ligand to stabilize the Pd center, the carboxylate ligands are available to serve as a base in the reaction, and the water ligand can readily dissociate to provide access to the substrate.

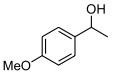
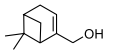
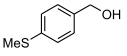
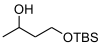
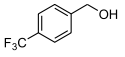
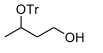
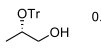
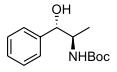
With $(I^iPr)Pd(OAc)_2(OH_2)$ (**44a**) as the catalyst, a variety of benzylic, allylic and aliphatic alcohols are oxidized efficiently (Table 3) [81]. Co-catalytic quantities of acetic acid (or, in some cases, NBu_4OAc) play a critical role in the reaction and permit the catalyst loading to be lowered to 0.5 mol %. The related catalyst $(I^iPr)Pd(OPiv)_2$ (**44b**) is effective under remarkably mild con-



44

Table 3 Aerobic alcohol oxidation employing $(I^iPr)Pd(OAc)_2$ and $(I^iPr)Pd(OPiv)_2$ complexes



Entry	Alcohol	Catalyst	Conversion (%)	Entry	Alcohol	Catalyst	Conversion (%)
1		0.5 mol% **44a**, Air, 60 °C, 14h 4 mol% AcOH	99	6		1 mol% **44b**, Air, rt, 14h 0.5 mol% PivOH	99
2		1 mol% **44b**, Air, rt, 14h 0.5 mol% PivOH	92	7		1 mol% **44a**, O_2, 60 °C, 14h 1 mol% AcOH	93
3		1 mol% **44b**, Air, rt, 14h 0.5 mol% PivOH	47	8		1 mol% **44a**, O_2, 60 °C, 13h 5 mol% NBu_4OAc	94
4		1 mol% **44b**, Air, rt, 14h 0.5 mol% PivOH	97	9		0.5 mol% **44a**, O_2, 60 °C, 15h 5 mol% NBu_4OAc	92
5		0.5 mol% **44a**, O_2, 60 °C, 10h 5 mol% NBu_4OAc	85	10		1 mol% **44b**, Air, rt, 14h 0.5 mol% PivOH	89

ditions (1 mol % **44b**, 0.5 mol % PivOH, ambient air as the O_2 source, room temperature), although its substrate scope is more limited than **44a** [81].

The significant influence of carboxylic acid on these reactions prompted a fundamental investigation into its role in the aerobic oxidation of 1-phenylethanol catalyzed by **44a** (0.5 mol %) [80]. At low concentrations ($\leq$ 0.62 mol %), acetic acid has a beneficial effect on the reaction rate (Fig. 3a). Beyond this concentration, acetic acid exhibits an inhibitory effect. Acetic acid also influences the catalyst stability (Fig. 3b). In the absence of acetic acid, the reaction proceeds only to low levels of conversion. At 0.75 mol % acetic acid, the reaction begins with a high initial rate, but the time-course deviates from the expected first-order dependence on [alcohol] (Fig. 3b). The first-order dependence observed when [AcOH] is $\geq$ 2 mol % suggests that the catalyst is more stable (albeit somewhat less active) under these conditions.

These data have been rationalized by recognizing that acetic acid plays several roles in the catalytic mechanism (Scheme 10) [80]. In the absence of acetic acid, the Pd(0) intermediate, **49**, undergoes competitive decomposition and oxygenation. Low concentrations of acetic acid enhance the rate and minimize catalyst decomposition by trapping the reversibly formed peroxopalladium(II) intermediate, **50**. Acetic acid also can stabilize the catalyst by reversible formation of a Pd-hydride species, **48**. At high [AcOH], the reaction rate is slowed because acetic acid inhibits formation of the alkoxide intermediate **47**.

Among the significant outcomes of these studies was the demonstration that a single NHC ligand could withstand the aerobic oxidation conditions in these reactions. This ligand stability suggests that the NHC does not dissociate from the Pd center, despite numerous cycling between Pd^{II} and Pd^0 oxidation states.

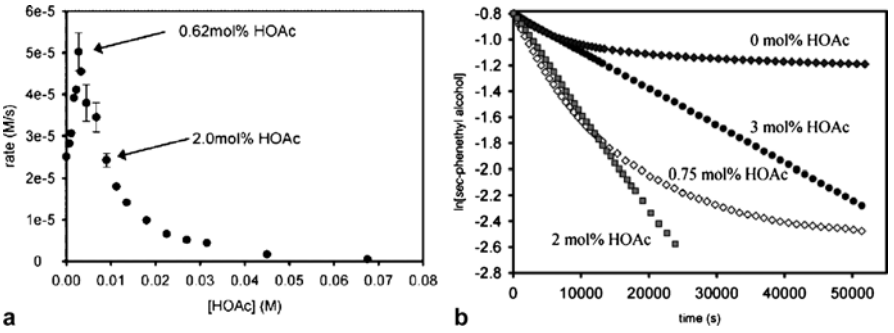
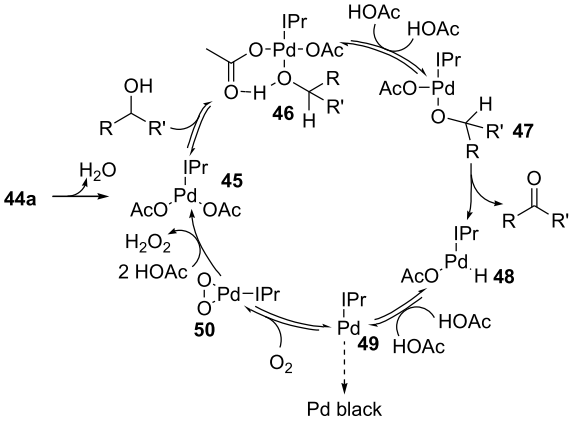


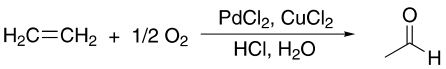
Fig. 3 **a** Rate dependence of *sec*-phenethyl alcohol oxidation using various acetic acid concentrations. **b** Natural logarithm of *sec*-phenethyl alcohol concentrations versus time at various acetic acid concentrations. Reprinted with permission from Mueller JA, Goller CP, Sigman MS (2004) J Am Chem Soc 126:9724, Copyright 2004, American Chemical Society



Scheme 10 Proposed mechanism for aerobic alcohol oxidation using $IPrPd(OAc)_2OH_2$

4.3
Palladium-Catalyzed Oxidation of Alkenes

The field of homogeneous palladium catalysis traces its origin to the development of the Wacker process in the late 1950s (Eq. 7) [83]. Since this discovery, palladium-catalyzed reactions have evolved into some of the most versatile reactions for the synthesis of organic molecules [84, 85]. Palladium-catalyzed Wacker-type oxidation of alkenes continues to be an active field of research [86–88], and several recent applications of NHC-coordinated Pd catalysts have been reported for such reactions.



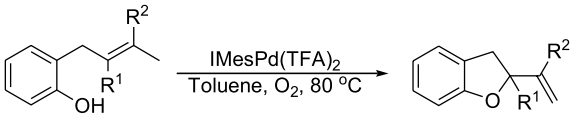
Equation 7

4.3.1
Intramolecular Oxidative Heterocyclization Reactions

Palladium(II)-promoted oxidative cyclization of alkenes bearing tethered nucleophiles represents an intramolecular variant of the Wacker reaction. These reactions, which typically generate five- and six-membered heterocycles, have been the subject of considerable interest in organic chemistry [89–96]. Contemporary interest centers on the development of enantioselective examples [95, 97] and reactions that employ dioxygen as the sole oxidant for the Pd catalyst [92–96].

Both oxygen and nitrogen heterocycles have been prepared with mono-NHC-coordinated Pd^{II} complexes of the general structure **44**. *o*-Allylphenol

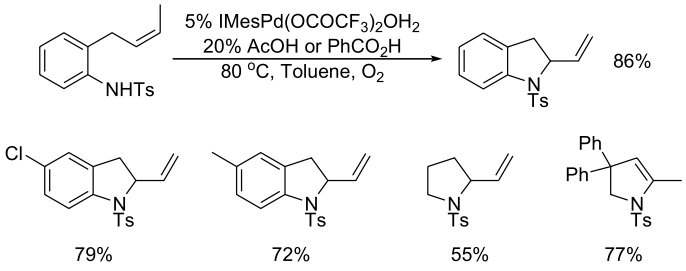
Table 4 Oxidative heterocyclization of oxygen nucleophiles



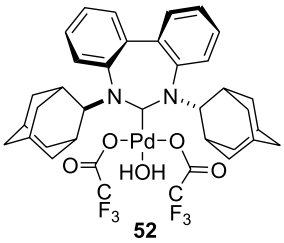
Entry	R^1	R^2	Yield (%)
1	H	H	89
2	H	CH_3	91
3	CH_3	H	92
4	CH_2	CH_3	96

derivatives undergo efficient oxidative cyclization to yield dihydrobenzofuran derivatives under 1 atm of molecular oxygen (Table 4) [96]. The catalyst is prepared in situ by mixing 1.2 equivalents of the ligand imidazolium salt with palladium(II) trifluoroacetate. Use of the trifluoroacetate counterion is important; with acetate and chloride ions, the reaction was less efficient and produces mixtures of five- and six-membered heterocycles. The presence of base (20 mol % DMAP and 2 eq Na_2CO_3 with respect to the substrate) was reported to be necessary to avoid side reactions and maintain catalyst activity. Similarly good results were also obtained with I^iPr and SI^iPr as the NHC ligand.

Nitrogen-containing heterocycles have been prepared in a similar manner [98]. In this case, both aliphatic and aromatic Ts-protected amines cyclize to yield 5-membered heterocycles with 5 mol % $(IMes)Pd(O_2CCF_3)_2(OH_2)$ (**51**) as the catalyst (Scheme 11). The corresponding $PdCl_2$ catalyst, **41**, is completely inactive, whereas the $(IMes)Pd(OAc)_2(OH_2)$ complex is comparable to **51**. The reaction proceeds most effectively when cocatalytic quantities (10–20 mol %) of acetic acid are present. Under these conditions, the reaction is even successful with ambient air as the source of dioxygen.



Scheme 11 Intramolecular oxidative amination



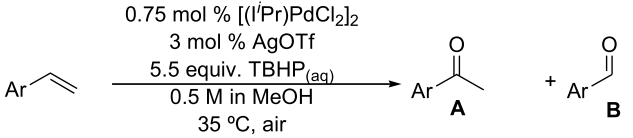
52

Recently, palladium(II) complexes bearing a new class of seven-membered NHC ligands was reported [99, 100]. The trifluoroacetate analog **52** catalyzes the nitrogen heterocyclization reaction with yields similar to those obtained with the IMes complex **51**, although the reactions times are somewhat longer [98]. These C_2 symmetric ligands may find future application in asymmetric catalysis once enantiomerically resolved analogs become available.

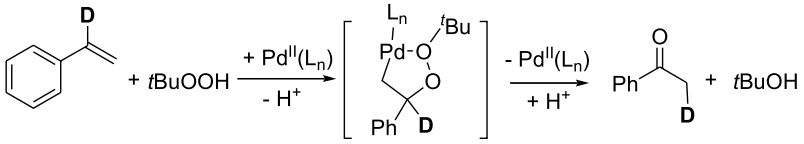
4.3.2 Intermolecular Oxidation of Alkenes

The Pd-catalyzed conversion of terminal alkenes to methyl ketones is a reaction that has found widespread use in organic chemistry [87, 88]. These reactions, as well as the industrial Wacker process, typically employ $CuCl_2$ as a co-catalyst or a stoichiometric oxidant. Recently Cu-free reaction conditions were identified for the Wacker-type oxidation of styrenes using *t*BuOOH as the oxidant. An NHC-coordinated Pd complex, in-situ-generated (I^iPr)Pd(OTf)$_2$, served as the catalyst (Table 5) [101]. These conditions min-

Table 5 Wacker-type oxidation of alkenes employing (I^iPr)Pd(OTf)$_2$



Entry	Ar	Time (h)	Yield (%)	**A**:**B**
1	Ph	24	75	> 130:1
2	2-methylphenyl	48	79	36:1
3	3-methylphenyl	32	83	22:1
4	4-methylphenyl	16	86	22:1
5	2,4,6-trimethylphenyl	24	71	> 150:1
6	3-chlorophenyl	48	80	> 150:1



Scheme 12 Proposed hydride-shift mechanism for the Wacker oxidation of styrene catalyzed by $(I^iPr)Pd(OTf)_2$

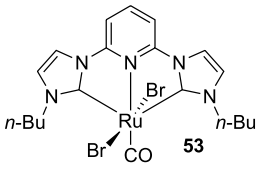
imize polymerization and oxidative cleavage of the alkene, which represent common side reactions in the Wacker oxidation of styrene.

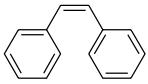
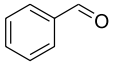
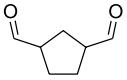
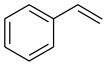
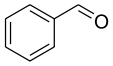
Attempts to use molecular oxygen as the oxidant failed except in solvents that undergo efficient autoxidation to the corresponding hydroperoxide (e.g., THF). Mechanistic studies, including isotopic labeling studies, indicate that *t*BuOOH is the source of the oxygen atom incorporated into the product, and the reaction proceeds via a hydride-shift pathway that avoids formation of an enol intermediate (Scheme 12).

4.4 Oxidative Cleavage of Alkenes

The oxidative cleavage of alkenes to aldehydes and ketones is commonly achieved via ozonolysis. Transition-metal catalysts, including $RuCl_3$, RuO_4, and OsO_4, together with stoichiometric oxidants also may be used for this

Table 6 Oxidative cleavage of alkenes to aldehydes



Entry	Olefin	Product	Yield (%)
1			99
2			58
3			99
4			72
5			99

Conditions: 1 mL $CDCl_3$ / 0.1 mL H_2O, 1.25 equiv $NaIO_4$, 1 mol% **52**. Product yields were determined by NMR.

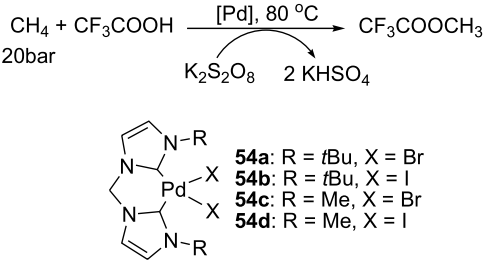
transformation [102, 103]. An NHC-coordinated Ru complex, **53**, has been reported to catalyze the oxidative cleavage of alkenes by $NaIO_4$ (Table 6) [104]. A relatively small reaction scope was explored, but electron-deficient alkenes were found to react more slowly than electron-rich alkenes. Preliminary studies suggest the NHC – Ru complex remains intact during the reaction, but further studies will be necessary to confirm this result.

4.5 Selective Oxidation of Methane

The selective oxidation of alkanes represents one of the most important and difficult challenges in the chemical industry, and significant recent attention has focused on the use of electrophilic late-transition-metal catalysts to achieve this goal [105–109]. These reactions are often performed in strong-acid solvents that enhance the electrophilicity of the metal center. The use of these solvents also results in formation of alkyl ester products that are deactivated toward further C – H oxidation.

Chelating bis-NHC Pd-complexes **54a–d** exhibit remarkable stability in trifluoroacetic acid solvent and catalyze the oxidation of methane to methyl trifluoroacetate with potassium peroxodisulfate as the oxidant (Table 7) [110, 111]. Palladium complexes bearing chelating nitrogen ligands, including bipyrimidine and phenanthroline derivatives, were inactive under comparable conditions. The yield of methyl ester is 2–3-fold higher with the NHC – Pd complex **54c** relative to $Pd(OAc)_2$ in the absence of ligands (Table 7, entries 3 and 5). This ligand effect is rather modest but does suggest that NHC ligands exhibit a beneficial effect on the reaction. The anionic palladium ligand also influences the catalytic activity. Whereas the bromide complexes **54a** and **54c** promote catalytic turnover, the iodide complexes **54b** and **54d** are inactive. Improved yields were reported at higher temperature and pressure with **54c** as the catalyst.

Table 7 Oxidation of methane catalyzed by Pd-NHC cComplex



Entry	[Pd]	Turnovers[a]
1	**54a**	5.1
2	**54b**	0
3	**54c**	9.8
4	**54d**	0
5	$Pd(OAc)_2$	3.8
6	**54c**	30[b]

[a] By GC analysis, relative to Pd.
[b] T = 90 °C, *t* = 14h, $p(CH_4)$ = 30 bar.

5 Conclusions

The results outlined above highlight significant prospects for use of N-heterocyclic carbenes as ligands in oxidation chemistry. Nevertheless, this field remains in the early stages of development. With strong sigma-donor properties, NHCs are well suited to stabilize high-oxidation-state metal complexes; however, the number of complexes that have been prepared to date is quite small and very little has been described concerning the oxidizing properties of these complexes. Significant opportunities exist to expand the use of NHCs as ancillary ligands in metal-catalyzed oxidation reactions. The relatively high NHC – metal bond strength slows ligand dissociation and helps to prevent oxidative decomposition of the NHC ligand. Further studies are needed to probe the scope (and limitations) of metal complexes, catalysts, oxidizing agents, and reaction conditions that are compatible with the use of NHCs as ancillary ligands.

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Palladium-catalyzed Reactions Using NHC Ligands

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Abstract N-heterocyclic carbenes (NHCs) have attracted increasing attention since their discovery. Notably, they have allowed for major advances in palladium-catalyzed reactions. Mainly known for their application in cross-coupling reactions, this review intends to provide a broader overview of (NHC)-palladium systems in organic transformations.

Keywords Palladium · N-heterocyclic carbene · Cross-coupling reaction · Catalysis

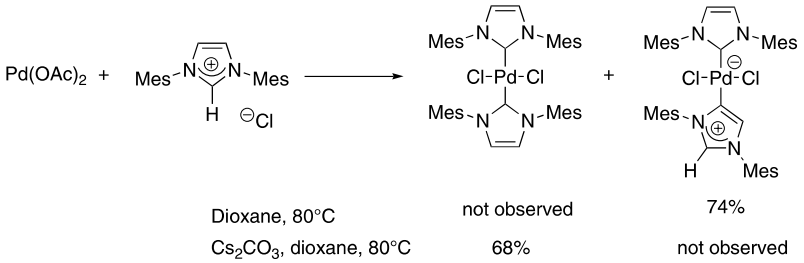
Abbreviations

Am	amyl, methylbutyl
Cyp	cyclopentyl
dba	dibenzylideneacetonate
DMAc	*N*,*N*-dimethylacetamide
dmmdiy	1,1′-dimethyl-3,3′-methylene-4-diimidazolin-2,2′-diylidene
dvds	1,3-dimethylvinylsiloxane
IAd	*N*,*N*′-bis(adamantyl)imidazol-2-ylidene
IMes	*N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	*N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
ItBu	*N*,*N*′-bis(*tert*-butyl)imidazol-2-ylidene
ma	maleic anhydride
M_n	molecular weight (in number)
MW	microwave
NMP	*N*-methylpyrolidinone
SIPr	*N*,*N*′-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene
SIMes	*N*,*N*′-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
TBAB	tetrabutylammonium bromide
TBHP	*tert*-butylhydroperoxide
TFA	trifluoroacetate

1 Introduction

Since the introduction of Grignard reagents in the beginning of the twentieth century, main group and transition metals have been used extensively in organic synthesis [1]. Among these metals, palladium is one of the most versatile and widely used on both industrial and laboratory scales [2, 3]. Tertiary phosphine ligands have been largely used to control reactivity and selectivity in organometallic chemistry and homogeneous catalysis [4]. However, these ligands are often air-sensitive and significant phosphorus–carbon bond degradation occurs when these are subjected to high temperatures, which leads to catalyst deactivation.

N-heterocyclic carbenes (NHC) were first reported by Wanzlick [5, 6] in the 1960s and (NHC)–transition metal complexes have been known since 1968 [7–10]. But it was not until the early 1990s that Arduengo and co-



Scheme 1 Synthesis of (NHC)–palladium complexes

workers provided the access to free isolable carbenes from imidazolium salts prepared in a one-step synthesis [11]. Since then, NHCs have been shown to be excellent phosphine mimics [12]. Not only do they possess comparable or better donating properties, but also they generally show higher thermal stability and better stabilizing effects than most of the commonly utilized phosphines [13].

In this report we highlight the latest advances in the use of NHC/palladium systems in organic transformations. Both in situ-generated catalyst or well-defined systems will be presented. Nevertheless, the reader should keep in mind that special care must be taken when postulating the nature of active species for in situ-generated NHC–Pd systems. Lebel and co-workers [14] recently showed that specific reaction conditions could lead to the formation of unusual complexes when an imidazolium salt was reacted with $Pd(OAc)_2$ (Scheme 1). While metal binding at the C(2) position is usually expected, formation of a complex with one of the imidazolium rings bound by the C(5) position was observed when no additional base was employed. Comparison of reactivity of both complexes with in situ formed catalyst in Heck reactions showed that, unlike what would have been expected, the "unusual" complex was a more suitable precursor for this coupling reaction.

This work illustrates perfectly the importance of the design of well-defined catalytic systems. For the readers' convenience, the structures of the most commonly employed carbene ligands are presented in Fig. 1.

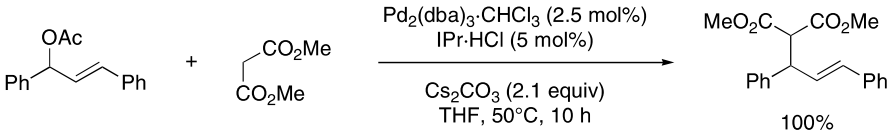
R		
2,6-diisopropylphenyl	IPr	SIPr
2,4,6-trimethylphenyl	IMes	SIMes
tert-butyl	I^{t}Bu	

Fig. 1 Structure of N-heterocyclic carbene ligands

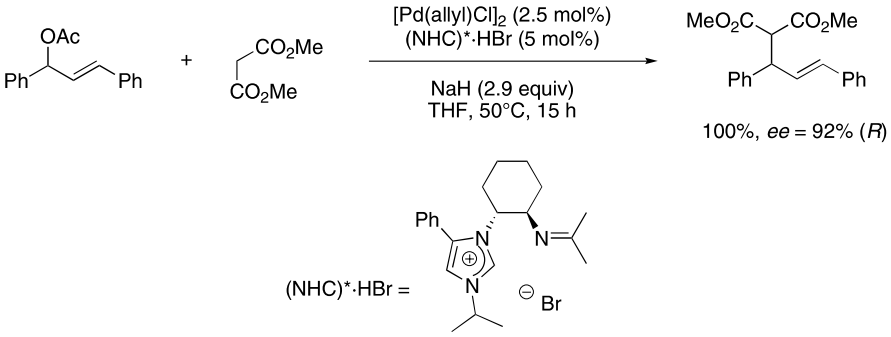
2
Allylic Alkylation

Since its discovery by Tsuji [15, 16] and catalytic expansion by Hata [17] and Atkins [18], allylic substitution has become the most popular palladium-catalyzed method for carbon–carbon bond formation along with cross-coupling reactions. However, the first report using NHC in this transformation only appeared recently [19]. An imidazolium salt with a bulky substituent on the nitrogen atoms, IPr · HCl, was found to be a suitable ligand for allylic substitution with soft nucleophiles (Scheme 2). $Pd_2(dba)_3$ as palladium source and Cs_2CO_3 as base completed the catalyst system.

It is important to note that no reaction was observed in the absence of the carbene salt and that as for the phosphine-based systems, the reaction proceeded with overall retention of stereochemistry. The use of NHC-imine ligands in asymmetric allylic alkylation reaction has also been reported [20]. Excellent yields but low ee were obtained. The best example is shown in Scheme 3.



Scheme 2 NHC/Pd-catalyzed allylic substitution with dimethyl malonate



Scheme 3 NHC/Pd-catalyzed asymmetric allylic substitution with dimethyl malonate

3
Copolymerization Reactions

The virtually unlimited availability of CO renders it extremely appealing as a monomer in copolymerization reactions. Herrmann and co-workers [21] reported the copolymerization of CO and ethene using dicationic chelating carbene complexes of palladium(II) (Fig. 2). Given the large molecular weight of the obtained copolymer and the relatively modest TONs they observed, the authors postulated that only a small percentage of palladium pre-catalyst actually participates in the production of copolymer.

Cavell and co-workers later demonstrated the feasibility of the CO insertion in a (NHC)methylpalladium complex [22]. The resulting acyl-palladium complex is prone to decomposition to yield acylimidazolium salts and Pd(0) (Scheme 4), which might explain the deactivation of the catalyst during the copolymerization reaction.

Better catalytic behavior was observed in the copolymerization of CO and norbornadiene with palladium complexes containing a hemilabile pyridyl-carbene ligand [23]. The choice of a pyridine-functionalized carbene can be explained by the fact that the hemilabile arm in such a ligand is capable of reversible dissociation from the metal center, leading to vacant coordination sites for the complexation of the substrates while the strong donor moiety remains bound to the metal.

A related system permitted the synthesis of aromatic polycarbonates (PCs) via oxidative carbonylation [24] of a biphenol [25]. High yields (~ 80%) with close to industrially useful molecular weight (M_n = 94 000) were obtained in this case (Scheme 5).

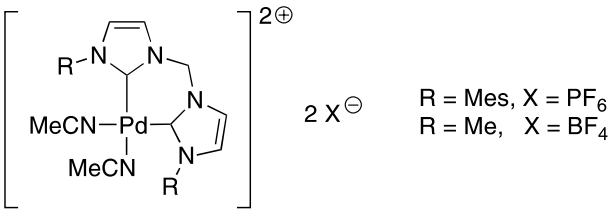
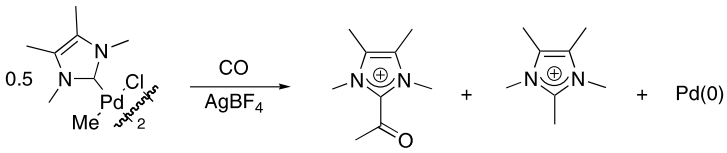
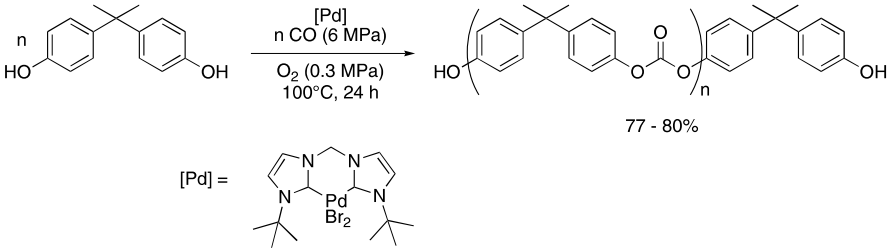


Fig. 2 Pd(II) carbene complexes for copolymerization reactions



Scheme 4 Reaction of a methylpalladium complex with CO

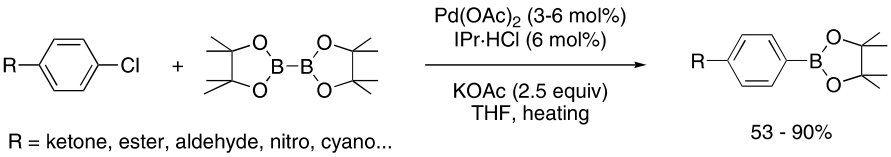


Scheme 5 Oxidative carbonylation of a biphenol

4
Cross-Coupling Reactions

4.1
Carbon–Boron Bond Formation

Since aryl boronic acids and aryl boronates are widely used in a number of metal-catalyzed C – C bond-forming reactions, there is an increasing demand for these versatile nucleophiles [26]. Fürstner and co-workers first reported a general NHC/palladium-catalyzed coupling of aryl chlorides with pinacolborane [27]. Good to excellent yields were obtained from electron-withdrawing-bearing aryl chlorides using KOAc as the base in hot THF (refluxing or heated at 110 °C in a sealed tube) (Scheme 6).



Scheme 6 Borylation of aryl chlorides

Milder reaction conditions can be used for this transformation when aryldiazonium salts are used as coupling partners [28]. In this case, the reactions can be carried out at room temperature to yield the expected borylated products in excellent yields. Furthermore, the addition of a base is no longer necessary, notably since it increases the formation of undesired byaryl product.

4.2
Carbon–Carbon Bond Formation

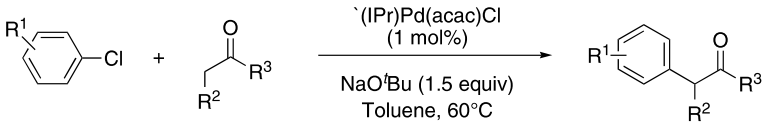
4.2.1
α-Arylation of Carbonyl Compounds and Related Transformations

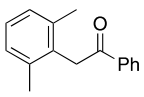
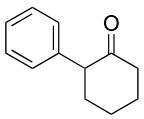
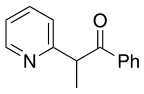
4.2.1.1
α-Arylation of Carbonyl Compounds

The cross-coupling of aryl halides and enolates is a powerful method to prepare α-arylated carbonyl compounds that are difficult to access through classic organic chemistry [29]. (NHC)Pd(allyl)Cl species [30] were the first NHC-bearing complexes used as pre-catalysts for the α-arylation of ketones [31, 32]. More recently, novel (IPr)Pd(acac)Cl complexes have shown remarkable catalytic activity in this transformation [33]. From aryl chlorides, excellent yields were obtained after short reaction times at 60 °C, the lowest temperature reported to date with a carbene-based system (Table 1).

Carbonyl compounds other than ketones have been even less studied. Only Hartwig and co-workers have shown the effectiveness of the combination Pd(II)/SIPr for the α-arylation of esters [34] and amides [35] at room tem-

Table 1 (NHC)Pd(acac)Cl-catalyzed α-ketone arylation

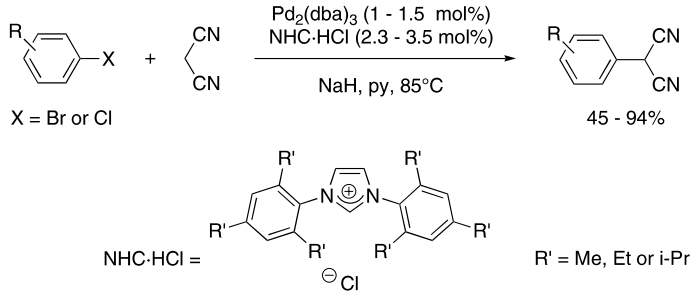


Product	Time (h)	Yield (%)
	1	95
	2	86
	2	89

perature. Furthermore, in the latter work, the authors showed that in the intramolecular α-arylation of amides, carbene ligands could induce better enantioselectivity than phosphines.

4.2.1.2 α-Arylation of Malonitrile

The coupling of aryl halides with active methylene compounds, such as malonitriles and cyanoacetates, is of increasing interest due to its inherent difficulty and the interest of the resulting products as synthetic intermediates in the preparation of bioactive [36, 37], heterocyclic [38, 39] or conducting compounds [40]. Bulky NHCs have been found to be excellent ligands in the coupling of aryl halides with malonitrile [41] in hot pyridine using NaH as base (Scheme 7).



Scheme 7 Cross-coupling of aryl halides and malonitrile mediated by in-situ-generated Pd/NHC systems

The activity of this catalytic system was somewhat lower with aryl chlorides (yields were between 51 and 94%) but still it was better performing that previously reported systems [42–47]. Of note, this coupling could be carried out in THF instead of pyridine on the condition of using aryl iodides as starting materials [48].

4.2.2 The Heck Reaction

The Heck reaction was the first catalytic application reported with palladium-NHC complexes [49, 50] and since then it has been considered a standard reaction for testing new palladium systems. Not only for their reactivity, but also stability as in most of the cases long reaction times under harsh conditions are required to obtain good yields [51–66].

A number of mixed-carbene phosphine chelates have been reported following an early theoretical study suggesting the suitability of these ligands

for the Heck reaction [67]. Three representative examples from Nolan [68], Herrmann [69] and Zhou [70] are shown in Fig. 3. These catalytic systems could enable the coupling of aryl iodides and bromides with acrylates and/or styrene.

Palladium/"regular" imidazolium salt systems have also been successfully used in the coupling of aryl bromides and acrylates [71]. With $Pd(OAc)_2$/IMes · HCl as catalyst system, nearly quantitative yields were obtained after short reaction times (Scheme 8).

Ionic liquids have been pointed out as better solvents for this type of Heck reaction than classic organic solvents [72]. In fact, the coupling of aryl chlorides was first achieved in tetraalkylamonium bromides at 140–150 °C using monocarbene-Pd(0) complexes as catalyst.

To date, milder reaction conditions have only been reported with diazonium salts as coupling partners. These salts are typically more reactive than aryl iodides and have the extra advantage that no addition of base is generally required [73]. Different diazonium salts could be coupled with styrene derivatives and acrylates at room temperature (Table 2), even with catalyst loadings as low as 0.1 mol %.

The efficiency of the carbene-based systems has led to their application in total synthesis. For example, Andrus and co-workers [74] recently reported a new synthetic approach to resveratol, the probable causative agent of the "French paradox" [75]. A decarbonylative Heck reaction was the key step of this concise and cost-effective synthesis [76–78].

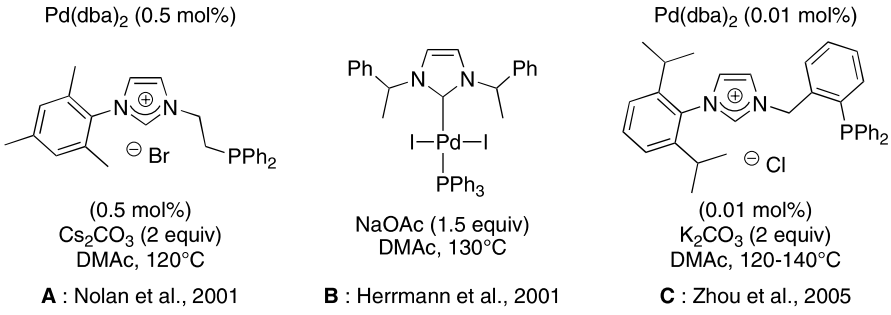
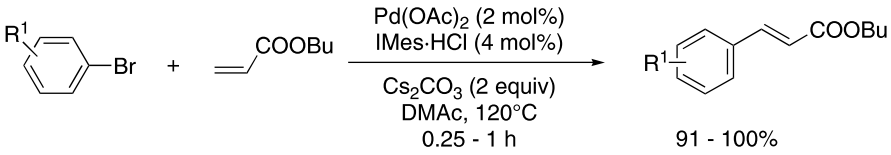
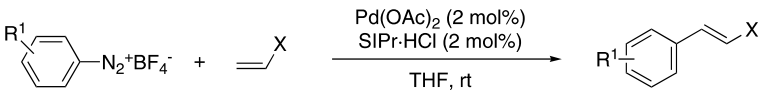


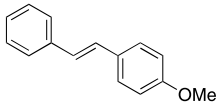
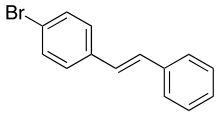
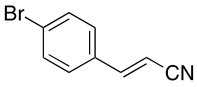
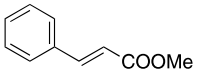
Fig. 3 Catalytic systems based on mixed carbene-phosphine chelates



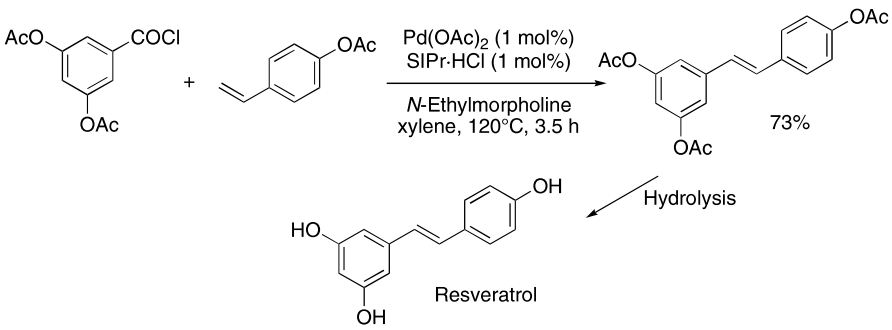
Scheme 8 Pd/NHC-catalyzed cross-coupling of aryl bromides and acrylates

Table 2 Pd/SIPr-catalyzed Heck coupling with styrene and acrylates

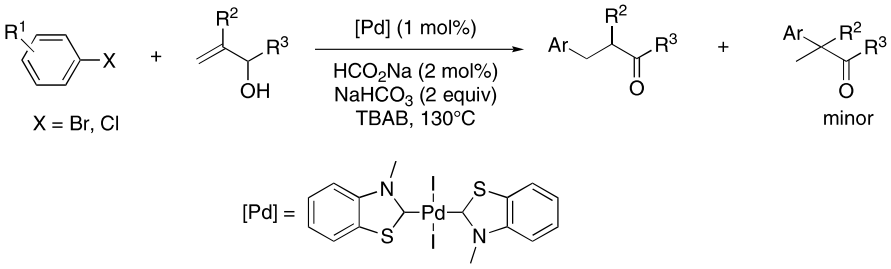


Product	Time (h)	Yield (%)
	4.5	78
	4	91
	3.5	61
	3	68

In a related transformation, a palladium-benzothiazole carbene complex has been reported to efficiently catalyze the arylation of allylic alcohols [79]. Carrying the reaction in an ionic liquid, the authors could couple aryl bromides and activated aryl chlorides with terminal allylic alcohols with remarkable regioselectivity (Scheme 10). The interest of this methodology was also highlighted by its application to the synthesis of three intermediates in the synthesis of medicinal products [80–82].



Scheme 9 Decarbonylative Heck reaction in the synthesis of resveratrol



Scheme 10 Arylation of terminal allylic alcohols

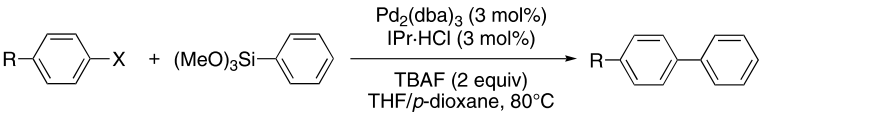
This benzothiazole-palladium complex has also been successfully used for the synthesis of β-aryl-substituted cinnamates in TBAB from the corresponding 1,2-disubstituted acrylates [83, 84].

4.2.3 The Hiyama Reaction

Silicon is considered an environmentally benign element, since organosilicon compounds are oxidized ultimately to biologically inactive silica. High stability, low cost and wide availability are additional characteristics that render silicon-based compounds interesting transmetalating agents [85–88]. In addition, the configuration of a silyl-substituted carbon is stable and thus optically active organosilicon compounds are available via asymmetric reactions [89].

The combination $Pd(OAc)_2$/IPr · HCl in a dioxane/THF mixture has been reported to be efficient for the coupling of aryl bromides and activated aryl chlorides with phenyltrimethoxysilane (Table 3) [90].

Table 3 Pd/IPr-catalyzed coupling of aryl halides with phenyltrimethoxysilane



R	X	Time (h)	Yield [a] (%)
H	Br	3	100
COMe	Br	1	100
Me	Cl	4	29
CN	Cl	2	100

[a] GC yields

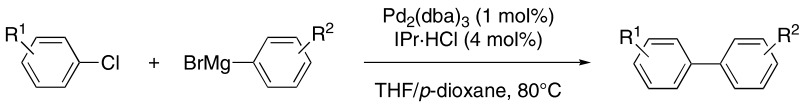
The formation of the undesired homocoupling product could be decreased using a larger excess of silane and reducing the reaction temperature to 60 °C. This catalytic system could also mediate the coupling of aryl halides with vinyltrimethoxysilane to form substituted styrenes in good yields.

4.2.4 The Kumada–Tamao–Corriu Reaction

As arylboronic acids and other organometallic reagents used in C – C coupling reactions are often synthesized from the corresponding Grignard or organolithium reagents [91], a general method employing these reagents directly in cross-coupling would be valuable. On the other hand, the direct coupling of Grignard or lithium reagents with aryl halides is rarely successful, with the exception of certain aryl fluorides [92–94]. In 1972, Kumada and Tamao [95] and Corriu [96] showed independently that the reaction of Grignards with alkenyl or aryl halides could be catalyzed by Ni(II) complexes. A few years later, the first example of a Pd-catalyzed Kumada reaction was reported by Murahashi [97]. The use of unactivated aryl chlorides in the coupling with an arylmagnesium bromide was first achieved with IPr as the ancillary ligand [98]. As shown in Table 4, excellent yields in biaryl products were obtained with this catalytic system. Remarkably, *ortho* substituents and various functional groups such as ether, alcohol and ester, were well tolerated and formation of homocoupling products was only observed as a minor product.

NHCs are also efficient ligands for the palladium-catalyzed coupling of primary alkyl chlorides with aryl Grignard reagents [99]. Functionalization on both coupling partners is also tolerated in this case. This was due to the mild reaction conditions and fast reaction rates (1 hour of reaction at room temperature).

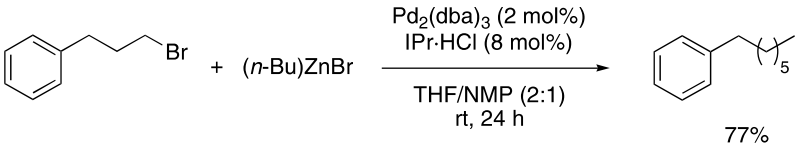
Table 4 Palladium/imidazolium salt-catalyzed cross-coupling of aryl halides with aryl Grignard reagents



R^1	R^2	Time (h)	Yield (%)
p-Me	–	3	99
o,*o*-diMe	–	5	87
p-OH	–	3	95
p-OMe	*o*-F	3	99

4.2.5
The Negishi Reaction

While palladium-catalyzed cross-coupling reactions of unsaturated electrophiles are well established, the use of coupling partners possessing β-hydrogen atoms is still a challenge. A nickel-catalyzed alkyl/alkyl Negishi reaction was first reported by Knochel [100–103] and later Fu demonstrated the effectiveness of $Pd(PCyp_3)_2$ for Negishi couplings of primary alkyl halides and tosylates at 80 °C [104]. Recently, Organ and co-workers [105] showed that the coupling of unactivated bromides with alkylzinc reagents could be carried out at room temperature when IPr · HCl was used as the ligand precursor (Scheme 11). Under the optimal conditions, good to excellent yields were obtained with high tolerance towards a variety of functional groups: esters, nitriles, amides, alkynes and acetals.



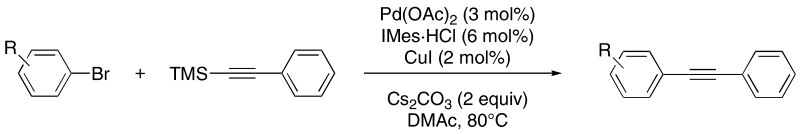
Scheme 11 Optimized conditions for the coupling of an unactivated alkyl bromide with *n*-butylzinc bromide

4.2.6
The Sonogashira Reaction

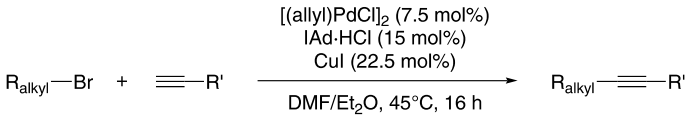
The coupling of terminal alkynes with aryl or alkenyl halides, also named the Sonogashira reaction, provides a straightforward methodology in the synthesis of arylalkynes and conjugated enynes which play an important role in the assembly of bioactive natural molecules and new materials [106–108]. The first examples of Sonogashira coupling using NHC ligands were limited to activated aryl bromides [109–111]. The combination $Pd(OAc)_2$/IMes · HCl/Cs_2CO_3 was found to be efficient in the coupling of aryl bromides with alkynylsilanes (Table 5) [112]. The use of 1-phenyl-2-(trimethylsilane)acetylene instead of phenylacetylene as the coupling partner allowed the authors to suppress the undesirable dimerization of the alkynyl moiety.

It is important to note that even if the addition of CuI as co-catalyst was desirable with deactivated aryl halides, a high yield in coupling product could be obtained under copper-free conditions. Furthermore, the reaction could be smoothly carried out with an aliphatic alkyne in short reaction times but with this catalyst system only 51% of the coupling product was formed from chlorobenzene.

Table 5 $Pd(OAc)_2$/IMes · HCl-catalyzed Sonogashira reaction



R	Time (h)	Yield (%)
p-Me	0.5	86
o-Me	0.5	93
p-OMe	0.5	88
p-OMe	0.5	93



Scheme 12 Sonogashira coupling of unactivated alkyl bromides

The coupling of a phenylacetylene without the trimethylsilyl group was possible when a bulkier ligand such as phenantrylimidazol-2-ylidene was used as the ligand [113]. Even if high yields were obtained from aryl bromides, this system was ineffective for the conversion of aryl chlorides.

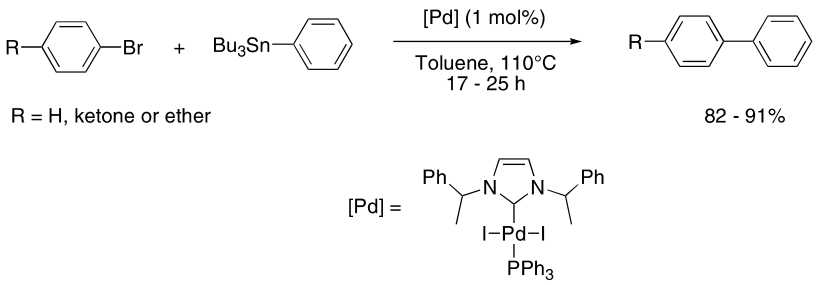
Tridentate pincer bis-carbene [114] and *N*-carbamoyl-substituted heterocyclic carbene complexes of Pd(II) [115] have also been used to couple aryl bromides and iodides with aromatic or aliphatic alkynes. Surprisingly, the latter catalytic system requires the use of 1 mol % of PPh_3. Its role in the catalytic cycle is still unclear but it might facilitate the initial generation of Pd(0) species.

To date, no efficient application of carbene ligands to the coupling of aryl chlorides is known. However, the first cross-coupling of unactivated, β-hydrogen-containing alkyl electrophiles has been achieved with a Pd/NHC-based system [116]. Optimized conditions allowed the coupling of alkyl bromides and iodides in good yields under mild conditions (Scheme 12). Ligand optimization showed that the bulkiest NHC ligands afforded the best yields in coupling product and that a number of phosphines (PPh_3, trialkylphosphines and alkyldiaminophosphines) were ineffective.

4.2.7 The Stille Reaction

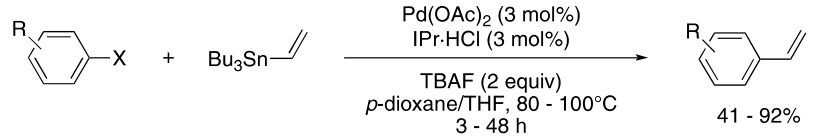
Despite the many phosphine/palladium systems developed for the coupling of organohalides with organotin compounds [117–119], this reaction re-

mains largely unexplored with NHC ligands. Herrmann and co-workers [120] showed that mixed palladium(II) complexes bearing both a NHC and a phosphine ligand could successfully catalyze the coupling of aryl bromides with organotin reagents (Scheme 13).



Scheme 13 Stille reaction catalyzed by a mixed Pd(II) complex

Another system, a mixture of $Pd(OAc)_2$ and IPr · HCl, can mediate this reaction in the presence of a fluorine source [121]. The use of TBAF is essential for this reaction as it can act as a base, deprotonating the imidazolium salt, as a fluorous medium for tin extraction and as a fluorinating agent. In fact, the in situ formation of a hypervalent organnostannate speeds up the transmetallation step and therefore eases the coupling reaction. Unfortunately, the reaction is limited to aryl bromides and activated aryl chlorides, on the other hand vinylstannates can also be used as coupling partners (Scheme 14).

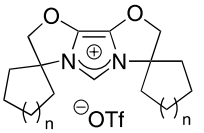


Scheme 14 Pd/IPr-catalyzed coupling of aryl halides and a vinylstannane

4.2.8 The Suzuki–Miyaura Reaction

Since the first reports of Suzuki–Miyaura cross-coupling with carbenes as ancillary ligands [122, 123], increasing attention and efforts have been devoted to this transformation [124–140].

Glorius and co-workers [141] recently reported the preparation of a novel family of N-heterocyclic carbenes derived from bioxazolines (IBiox). These tricyclic ligands (Fig. 4), which are electron rich, sterically demanding and have restricted flexibility, have been shown to be extremely efficient in cross-coupling reactions [142].



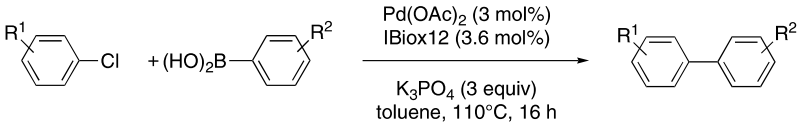
IBiox5·HOTf, n = 1
IBiox6·HOTf, n = 2
IBiox7·HOTf, n = 3
IBiox5·HOTf, n = 4
IBiox12·HOTf, n = 8

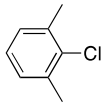
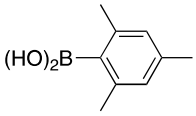
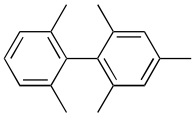
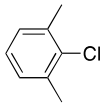
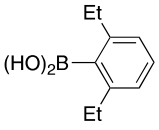
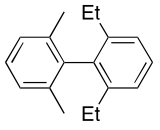
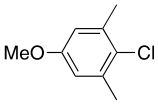
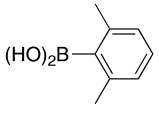
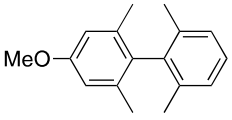
Fig. 4 Structure of the IBiox salts

When IBiox12 · HOTf was employed as the ligand precursor for the Suzuki–Miyaura coupling of sterically hindered aryl chlorides and aryl boronic acids, excellent to good yields were obtained in refluxing toluene for a variety of starting materials (Table 6). Notably, this work represents the first report of tetra-*ortho*-substituted biaryl compounds achieved from aryl chlorides [143].

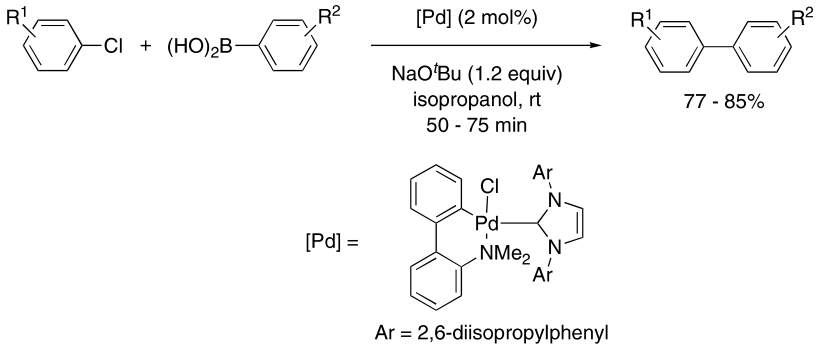
To date, the most efficient catalyst system for the synthesis of di- and tri-substituted biaryls is based on a NHC-bearing palladacycle, NaO^{t}Bu and technical grade isopropanol [144]. This combination allows the coupling of

Table 6 Synthesis of tetra-*ortho*-substituted biaryl compounds by Suzuki–Miyaura cross-coupling



Aryl chloride	Boronic acid	Product	Yield (%)
			96 87 [a]
			75
			83

[a] [(IBiox12)PdCl$_2$]$_2$ (3 mol %)



Scheme 15 Room temperature Suzuki coupling of aryl chlorides

a number of hindered aryl chlorides and boronic acids at room temperature in minutes (Scheme 15).

4.3 Carbon–Nitrogen Bond Formation

4.3.1 Amination of Aryl Halides

N-Aryl amination, or the Buchwald–Hartwig reaction, has proven to be a useful and versatile method to obtain aryl amines, which are of great synthetical and industrial interest [145]. The first examples of carbene/palladium-catalyzed amination of aryl halides showed that in situ-generated catalyst could efficiently mediate the coupling of aryl halides with primary and secondary amines, imines and indoles [146–148]. Even if most of these reactions could be carried out at room temperature with aryl iodides and bromides, elevated temperatures were required in order to couple aryl chlorides.

The design of well-defined complexes has led to better yields in coupling products from aryl chlorides under, sometimes, smoother reaction conditions. (NHC)-palladium(0) complexes [149–151] or NHC-palladium dichloride dimers [152] have been reported to catalyze the coupling of aryl chlorides and amines in high yields (Fig. 5). The latter system even allowed the reaction to be carried out under aerobic reaction with technical grade solvent without significant loss of activity.

The lowest temperature reported to date for the coupling of aryl chlorides has been achieved with an NHC-palladacycle (Scheme 16) [153]. Preliminary results also showed that with this catalytic system, the coupling of 4-chlorotoluene and morpholine could be achieved at room temperature in only two hours.

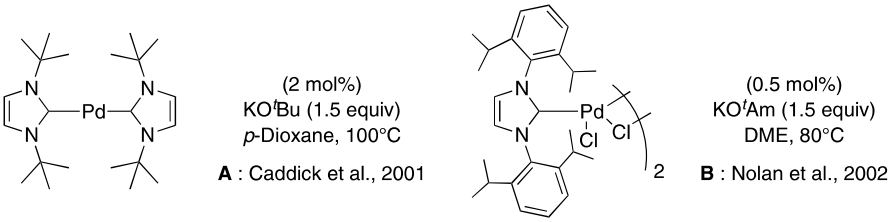
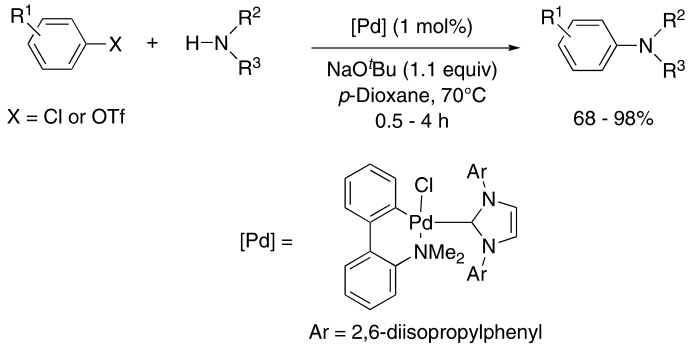


Fig. 5 NHC-based catalytic systems for aryl amination



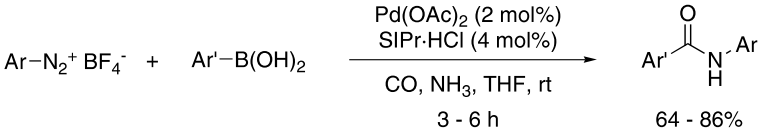
Scheme 16 A palladacycle-mediated Buchwald–Hartwig reaction

Further attempts to optimize this transformation with carbene-based systems involve microwave-assisted heating [154] or the use of ionic liquids as the solvent [155].

4.3.2 Carbonylative Amidation Reaction

This four-component reaction represents a straightforward method for the preparation of unsaturated esters and amides [156–159]. The system $Pd(OAc)_2$/SIPr · HCl has been reported to efficiently catalyze the coupling of diazonium salts with boronic acids in the presence of CO and ammonia [160] to yield the corresponding amides in good yields (Scheme 17).

Optimization studies showed that CO pressure had to be maintained at 5 atm in order to minimize the formation of by-products such as anilines or



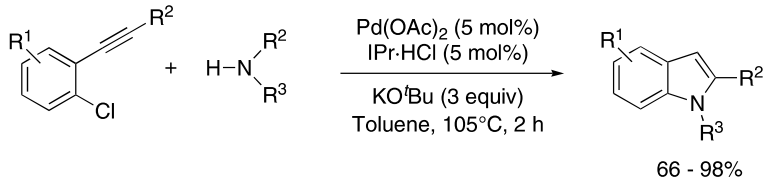
Scheme 17 $Pd(OAc)_2$/SIPr · HCl-catalyzed carbonylative amide formation

biaryl compounds. Not only boronic acids, but also boranes and borate salts can be used as coupling partners with this catalytic system. Of note, this system was first optimized in the absence of ammonia for the preparation of aromatic ketones [161, 162].

4.4 Miscellaneous Cross-coupling Reactions

The versatility and stability of (NHC)-palladium-based systems in cross-coupling reaction has allowed their utilization in elegant multistep one-pot processes.

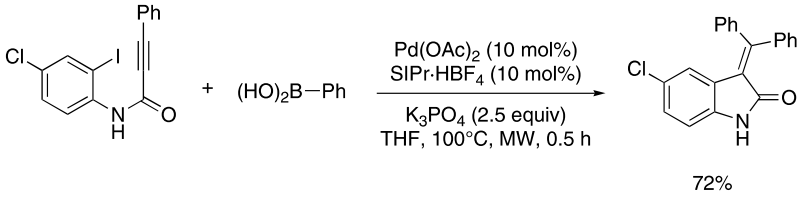
The abundance of indole derivatives in natural products results in continuous efforts in the development of flexible and especially regioselective approaches for this architecture [163]. A general approach to the synthesis of indoles from *o*-alkynylhaloarenes relying on the combination $Pd(OAc)_2$/IPr · HCl has recently been reported [164]. High yields after short reaction times were obtained in refluxing toluene (Scheme 18).



Scheme 18 NHC/palladium-catalyzed indole synthesis

Furthermore, a one-pot indole synthesis starting from *o*-chloroiodobenzenze was also achieved using a single catalyst system consisting of $Pd(OAc)_2$, CuI, IPr · HCl and Cs_2CO_3.

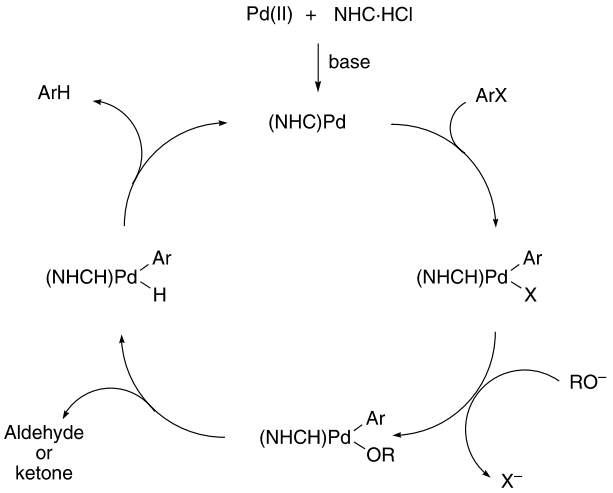
(Methylene)indolinones have also been prepared by a tandem Heck-carbonylation/Suzuki-coupling [165]. Even though this methodology was further developed with $Pd(PPh_3)_4$, the combination $Pd(OAc)_2$/SIPr · HBF_4 showed comparable activity (Scheme 19).



Scheme 19 NHC/palladium-catalyzed synthesis of indolinone

5
Dehalogenation Reactions

Dehalogenation of aryl halides is usually considered a side-reaction in cross-coupling, even though it is an important reaction in organic chemistry as well as in industry due to the high toxicity of these types of compounds [166]. A palladium/imidazolium salt (SIMes · HCl) has been proven efficient for the dehalogenation of aryl bromides and chlorides at relatively high temperature [167]. The use of a base containing β-hydrogen atoms appeared to be essential for the feasibility of the reaction which led to the authors proposing the formation of a palladium hydride as a key intermediate (Scheme 20).



Scheme 20 Proposed mechanism for dehalogenation of aryl halides

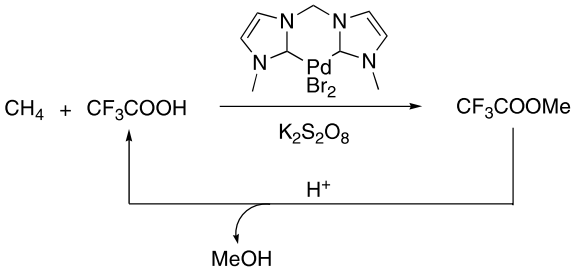
A well-defined complex, (IPr)Pd(allyl)Cl, provided an improved method for this transformation [168]. With very low catalyst loading (0.5–0.025 mol %), the dehalogenation of aryl chlorides could be carried out at 60 °C in less than 2 hours or in 2 minutes when micro-wave heating was used.

6
Transformations Through C–H Activation

6.1
Oxidation of Methane to Methanol

The well known thermal stability of (NHC)–Pd complexes combined with their surprising resistance in strong acids and under oxidative conditions

has allowed for a broadening of their application field to C – H activation. Whereas the catalytic conversion of methane into methanol is still one of the major challenges for chemists, it has been efficiently achieved using a NHC-bearing complex as catalyst in trifluoroacetic acid [169]. This system has the advantage that it can be run as a closed loop: the formed ester can be distilled from the reaction mixture, hydrolyzed and the acid along with the remaining methane can be transferred back to the reactor (Scheme 21).

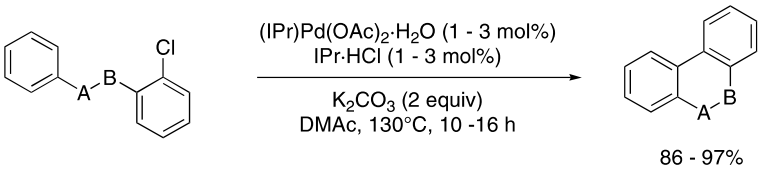


Scheme 21 Methane oxidation mediated by (NHC)–Pd(II) complexes

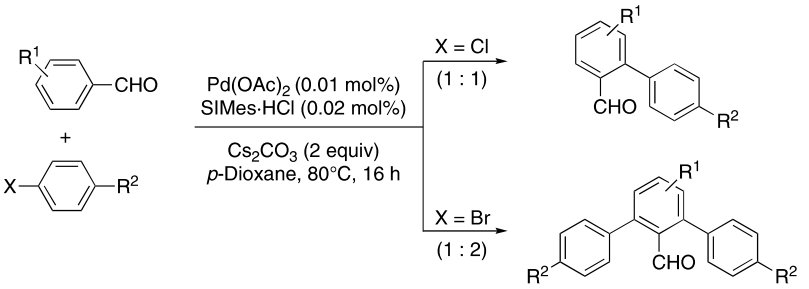
Interestingly, analogous platinum complexes decomposed under these acidic conditions. Even if the optimized yield is still below industrial expectations, tuning of the carbene, counterion nature and reaction conditions should lead to major improvement [170].

6.2 Direct Arylation Reactions

The possibility of coupling an aryl halide with an unreactive C – H bond opens a plethora of possibilities in the synthesis of biaryl compounds [171, 172]. A (NHC)Pd(II) complex has recently been used to promote the intramolecular direct arylation of aryl chlorides [173]. Whereas a number of complexes with different NHC were screened, (IPr)Pd(OAc)$_2$ was found to be the pre-catalyst of choice (Scheme 22). The use of IPr · HCl as additive led to an enhancement of reactivity, probably due to the preventive effect on the catalyst decomposition at the high reaction temperature. These conditions



Scheme 22 (IPr)Pd(OAc)$_2$-catalyzed intramolecular direct arylation



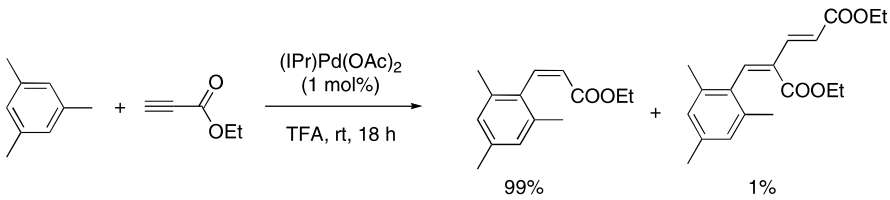
Scheme 23 Pd/NHC-catalyzed *ortho*-arylation of benzaldehydes

allowed for the formation of five and six-membered rings bearing an ether, amine, amide or alkyl tether.

The *ortho*-arylation of aromatic aldehydes in the presence of a combination of Pd(II)/saturated imidazolium salt has also been reported [174]. Remarkably, the formation of the mono- or bi-*ortho*-substituted product could be easily controlled depending on the nature of the aromatic halide employed (Scheme 23). Both electron-donating and electron-withdrawing substituents were well tolerated by the catalytic system and heteroaromatic aldehydes could also be coupled.

6.3 Hydroarylation of Alkynes

Catalytic activation of aromatic C – H bonds leading to useful organic C – C bond formation is of considerable interest for the chemical and pharmaceutical industries, and remains a challenge to organic chemists [175–178]. It would provide simple, clean, and economic methods for producing aryl-substituted compounds directly from simple arenes since no prefunctionalization such as halogenation would be required. Fujiyama has described the palladium-catalyzed synthesis of stilbenes from simple arenes in TFA [179–181]. Remarkably, a well-defined complex, $(IPr)Pd(OAc)_2$, has been reported to efficiently catalyze the hydroarylation of ethyl propiolate in TFA at room temperature (Scheme 24) [182]. Arenes bearing alkoxy



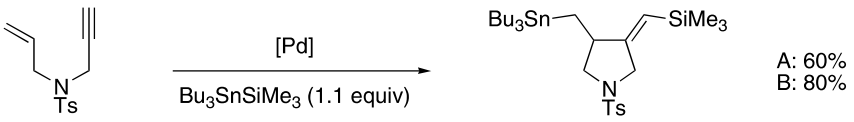
Scheme 24 Pd/NHC-catalyzed hydroarylation of ethyl propiolate

and halide substituents or internal alkynes could also be used in this reaction.

It is important to note that under the same conditions, ligandless $Pd(OAc)_2$ led to only 57% conversion after 24 h of stirring. To date, the catalytic cycle of this transformation is poorly understood, but it is thought to be based on Pd(II) exclusively [179–181].

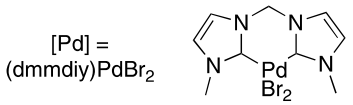
7
Cyclization of Enynes

The transition metal-catalyzed cycloisomerization of enyne systems is a powerful synthetic tool for the construction of a variety of architectures [183, 184]. The bismetallative cyclization of enynes has the advantage of introducing new metal–carbon bonds in the reaction products that can be used for further functionalization [185, 186]. Two different systems with N-heterocyclic carbenes as ligands have been reported to be efficient in the Pd-catalyzed bismetallative cyclization of enynes in the presence of $Bu_3SnSiMe_3$. The combination $Pd_2(dba)_3$/imidazolium salt/Cs_2CO_3 [187] or (dmmdiy)$PdBr_2$/Na[3,5-$(CF_3)_2C_6H_4]_4B$ [188] could convert nitrogen-containing enynes into cyclized products containing a vinylsilane moiety and a homoallylstannane (Scheme 25).



A: $Pd_2(dba)_3$-$CHCl_3$ (3 mol%)/ NHC·HCl (6 mol%), Cs_2CO_3 (12 mol%), DME, 40°C, 11 h

B: (dmmdiy)$PdBr_2$ (1 mol%), Na[3,5-$(CF_3)C_6H_4]_4B$ (1 mol%), THF, rfx, 24 h



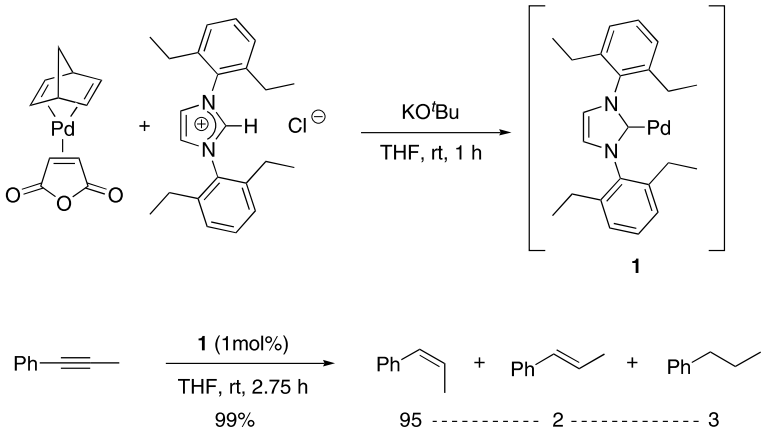
Scheme 25 NHC/Pd-catalyzed bismetallative cyclization of enyne with $Bu_3SnSiMe_3$

The synthetic utility of this strategy, which is not limited to one family of substrates, has been proven by the transformation of the cyclized products into cyclopropanol derivatives [189].

8
Hydrogenation Reactions

In spite of the successful use of NHCs in a number of palladium-catalyzed reactions, no system for hydrogenation was reported until 2005. This can be easily explained as it had been observed that hydridopalladium-carbene species decompose due to attack of the hydride on the carbene, which results in its reductive elimination to yield the corresponding imidazolium salt [190]. However, Cavell and co-workers recently showed that the oxidative addition of imidazolium salts to bis-carbenic palladium complexes leads to isolable NHC-hydridopalladium complexes [191]. This elegant work evidenced the remarkable stabilizing effect of NHC ligands in otherwise reactive species and led to the development of the first NHC-palladium catalyst for hydrogenation.

Not only have NHC – Pd(0) catalysts been shown to be stable under hydrogenation conditions, but they were able to hydrogenate 1-phenyl-1-propyne with remarkable efficiency and selectivity [192]. The best results were obtained with [Pd{*N*,*N*′-bis(2,6-diethylphenyl)imidazol-2-ylidene}] as catalyst. This complex can be efficiently formed in situ starting from [Pd(ma)(nbd)] and selectively semihydrogenated aryl-substituted alkynes to *Z* alkenes (Scheme 26).



Scheme 26 Hydrogenation of 1p-henyl-1-propyne to 1-phenyl-1-propene and *n*-propylbenzene

To date, only one other palladium-based system has shown good selectivity in the hydrogenation of alkynes to *Z*-alkenes, however, only poor selectivity was obtained in the case of arylalkynes [193, 194].

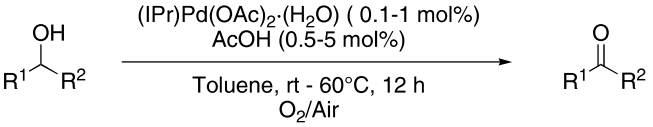
9
Oxidation Reactions

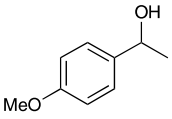
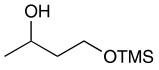
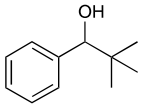
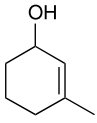
9.1
Oxidation of Alcohols

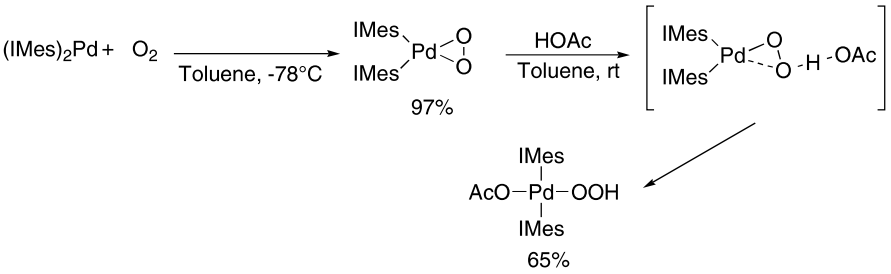
Catalytic oxidation of alcohols with molecular oxygen has attracted much attention as an alternative to "traditional" oxidation methods such as Dess–Martin [195], Jones [196] or Swern [197] oxidations, which require the use of stoichiometric toxic reagents and/or low temperatures. Significant advances have been made in Pd-catalyzed aerobic alcohol oxidations in the last few years [198–200]; Sigman and co-workers have shown the broad scope of two IPr – Pd(II) complexes with low catalyst loadings and mild temperatures [201, 202]. Some representative examples are summarized in Table 7.

Efforts aimed at fully understanding the mechanism of these oxidation reactions are still needed but new insights regularly appear in the literature [203–205]. The isolation and characterization of a dioxygen-derived palladium(II)–hydroperoxide complex—species generally postulated as intermediates in this reaction—has been achieved for the first time by Stahl et al. [206] (Scheme 27). The capability of IMes ligands to undergo *cis–trans* isomerization has been pointed out as essential for the formation of this complex.

Table 7 Aerobic oxidation of alcohols



Alcohol	Conversion (%)	Alcohol	Conversion (%)
	> 99		93
	91		92



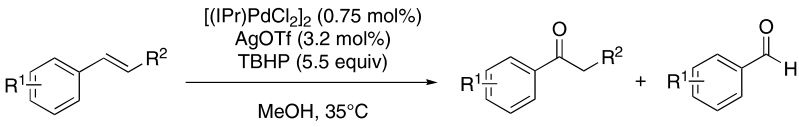
Scheme 27 Peroxo and hydroperoxo intermediates in aerobic oxidation

9.2 Wacker Oxidation and Related Transformations

The palladium-catalyzed oxidation of terminal olefins to methyl ketones, or Wacker oxidation, is a common transformation even at the industrial scale [207–209]. However, the classic use of $CuCl_2$ as a cocatalyst largely limits the choice of ligands for the palladium center and leads to the formation of chlorinated by-products [207]. A promising NHC–palladium catalyst system has been developed by Sigman and co-workers [210]. A number of styrene derivatives could be oxidized to the corresponding acetophenones under mild conditions (Table 8). It is important to note that significant formation of benzaldehyde was observed only in the case of internal olefins with this system (Table 8, entry 4), while ligandless palladium systems are known to lead to important amounts of oxidative cleavage [211, 212].

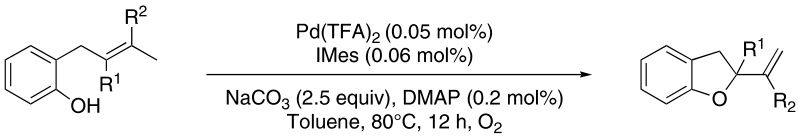
The authors proposed that $(IPr)Pd(OH_2)_3 \cdot (OTf)_2 \cdot (H_2O)_2$ is the actual catalyst as similar catalytic results were obtained directly from this complex. Moreover, mechanistic studies showed that TBHP rather than water acts as the oxygen source in the addition to the olefin.

Table 8 Wacker oxidation of styrene derivatives



R^1	R^2	Time (h)	Yield (%)	Ketone : Aldehyde
Ph	H	24	75	> 130 : 1
m-Cl	H	48	80	> 150 : 1
m-NO_2	H	24	79	> 150 : 1
Ph	Ph	48	42	42 : 35

Table 9 Intramolecular Wacker-type cyclization



R^1	R^2	Yield (%)
H	Me	91
Me	H	92
Me	Me	96
H	H	96

On the other hand, Wacker-type oxidative cyclization is a versatile approach for the construction of oxygenated stereocenters [213, 214]. The synthesis of a number of dihydrobenzofurans catalyzed by an in situ-formed carbene–palladium complex has been reported by Muñiz [215]. When $Pd(TFA)_2$ in combination with IMes were employed, high yields in pure cyclized products were obtained after simple work-up (Table 9). However, palladium salts containing chlorine or acetate groups led to the formation of mixtures containing the desired product and its six-membered ring isomer.

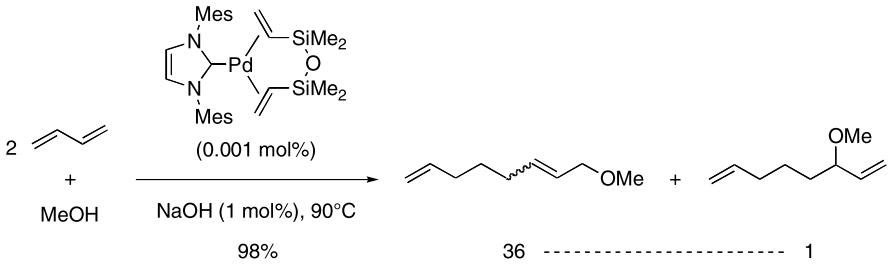
10
Telomerization Reactions

In general, the telomerization reaction is defined as the dimerization of two molecules of a 1,3-diene in the presence of an appropriate nucleophile HX to yield substituted octadienes [216, 217]. This reaction allows us to assemble simple starting materials in a 100% atom efficiency [218] and to easily prepare useful intermediates in the total synthesis of natural products [219, 220] and industrial precursors [221]. In light of numerous studies, the mechanism of the palladium-catalyzed telomerization reaction is well understood [222, 223]. It is accepted that one strongly bound and sterically hindered ligand on the metal center is desirable to generate highly active species, characteristics fulfilled by (NHC)–Pd(0) complexes.

10.1
Telomerization of Dienes with Alcohols

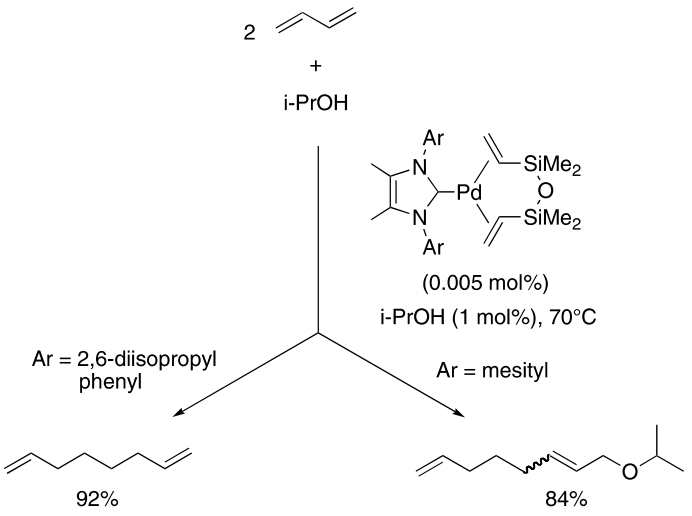
Monocarbene–palladium(0) complexes bearing a dvds group [224] are the best well-defined catalysts to date for the telomerization of butadiene with

alcohols. Unprecedented reaction rates in the reaction of butadiene and methanol have been reported by Beller and co-workers [225]. Furthermore, when compared to phosphine-based systems, higher chemoselectivity and a better linear to branched product ratio were observed [226, 227] (Scheme 28).



Scheme 28 Telomerization of 1,3-butadiene with methanol

The preparation of different (NHC) – Pd^0(dvds) complexes allowed the authors to make a systematic comparison of structure/activity for the telomerization reaction [228]. This study showed that electron-withdrawing substituents on the carbene backbone destabilizes the catalyst and therefore enhance its reactivity. These catalysts are applicable to primary and secondary alcohol as well as phenols and represent the first industrially viable catalyst system for palladium-catalyzed telomerization of butadiene with alcohol.



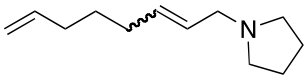
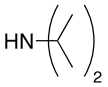
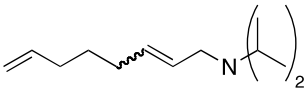
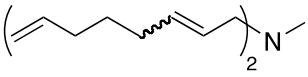
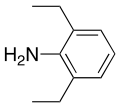
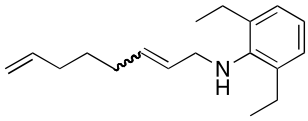
Scheme 29 Selectivity in telomerization or dimerization product by modification of the palladium carbene catalyst

The reactivity of the palladium complexes can be finely tuned depending on the chosen carbene. As shown on Scheme 29, from butadiene and isopropanol and under the same reaction conditions, different groups on the nitrogen atoms of the carbene lead to different major products [229]. When Ar = mesityl, the linear methoxyoctadiene was isolated in high yield, but the presence of diisopropylphenyl groups on the ligand led to the major formation of the corresponding octadiene. Even though this kind of compound is normally considered as a by-product of the telomerization reaction, they can be interesting intermediates in the preparation of oligomers [230], polymers [231] and bicyclic alcohols [232].

10.2 Telomerization of Dienes with Amines

Less attention has been paid to the use of amines as nucleophiles in the telomerization reaction. A single report from Nolan and co-workers [233] has shown that well-defined cationic palladium complexes are efficient catalysts in the telomerization of butadiene with amines under mild conditions (Table 10). In the case of primary amines, the concentration of the reactants and their steric hinderance dictates the formation of a mono- or double-alkylated product.

Table 10 Telomerization of butadiene with various amines [a]

Amine	Product	Time (h)	Yield (%)
		0.5	98
		6	95
H_2NMe		3	92
		1	70

[a] Conditions: $[(IPr)Pd(allyl)]PF_6$ (0.2 mol %), THF, 60 °C

11 Perspectives

Ten years have passed since the first report of a NHC/palladium-catalyzed reaction. In only 10 years, these ligands have brought a real revolution to metal-catalyzed organic reactions, even if their exploration remains at its early stages when compared to phosphorus-based systems. Their future is bright and we feel that new and exciting applications for these ligands are just waiting to be discovered.

Acknowledgements SDG thanks the Education, Research and Universities Department of the Basque Government (Spain) for a postdoctoral fellowship. The National Science Foundation is greatly acknowledged for support of this work.

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Routes to N-Heterocyclic Carbene Complexes

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Abstract The manuscript describes the methods that are most often used in the preparation of N-heterocyclic carbene (NHC) complexes. These methods include: (1) insertion of a metal into the C = C bond of bis(imidazolidin-2-ylidene) olefins; (2) use of carbene adducts or "protected" forms of free NHC carbenes; (3) use of preformed, isolated free carbenes; (4) deprotonation of an azolium salt with a base; (5) transmetallation from an Ag – NHC complex prepared from direct reaction of an imidazolium precursor and Ag_2O; and (6) oxidative addition via activation of the C2 – X (X = Me, halogen, H) of an imidazolium cation.

Keywords C – H activation · Imidazolium · N-heterocyclic carbene · Synthetic procedures · Transition metal

1 Introduction

Due to their topological and electronical versatility, N-heterocyclic carbenes (NHCs) are an increasingly useful type of ligand in transition metal compounds. The first NHC complexes were described by Öfele and Wanzlick in

1968 [1, 2]. With the exception of the studies by Lappert on the coordination of NHC to late transition metal complexes [3–7], the area remained quiescent for more than 20 years, until Arduengo showed that sterically protected carbenes could be obtained as free species stable enough for crystallographic characterization [8]. The first catalytic applications of NHC complexes described by Herrmann in 1995, together with the recognition that NHCs are excellent stabilizing ligands for a variety of homogeneous catalysts [9], prompted many research groups to provide a large number of NHC-based catalysts for a wide variety of reactions.

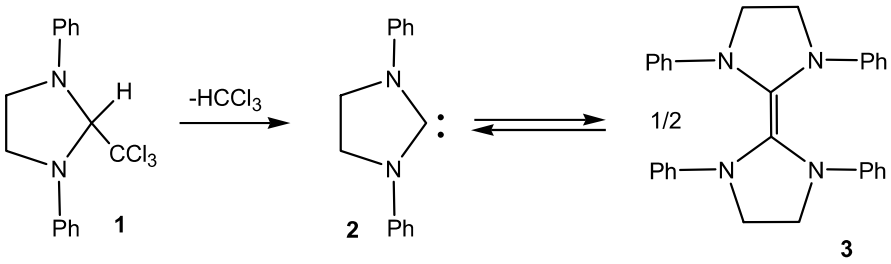
Unlike phosphines, the coordination of NHCs to metal centers usually requires the activation of a precursor, which makes NHC-based complexes relatively less accessible than the analogous phosphine compounds. There is a variety of methods for forming carbenes, most of them from the corresponding azolium salts, and these have been reviewed [10–14]. The methods for preparing NHC–metal complexes can be classified according to the nature of the NHC precursor and to the activation method employed. In this sense, the most widely used strategies are:

1. Insertion of a metal into the C = C bond of bis(imidazolidin-2-ylidene) olefins
2. Use of carbene adducts or "protected" forms of free NHC carbenes
3. Use of preformed, isolated free carbenes
4. Deprotonation of an azolium salt with a base
5. Transmetallation from a Ag – NHC complex prepared from direct reaction of an imidazolium precursor and Ag_2O
6. Oxidative addition via activation of the C2 – X (X = Me, halogen, H) of an imidazolium cation

2 Insertion of a Metal into the C = C Bond of Bis(imidazolidin-2-ylidene) Olefins

During the early attempts to synthesize free NHC, Wanzlick and colleagues tried to prepare 1,3-diphenylimidazolidin-2-ylidene (**2**) by thermal elimination of chloroform from **1**, but they rather obtained the dimeric electron-rich olefin **3** (Scheme 1) [15–17]. Wanzlick postulated that the carbene **2** could be formed as an intermediate during the formation of **3**, and proposed the existence of an equilibrium between **2** and **3**. Evidence supporting this equilibrium came later with the works performed by the research groups of Denk, Hahn, Lemal, and Cavell [18–21].

The equilibrium described in Scheme 1 sets the basis for the preparation of NHC complexes from electron-rich olefins. In fact, one of the methods more often used for the preparation of enetetramines is the dimerization of

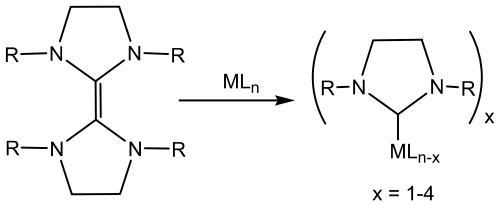


Scheme 1

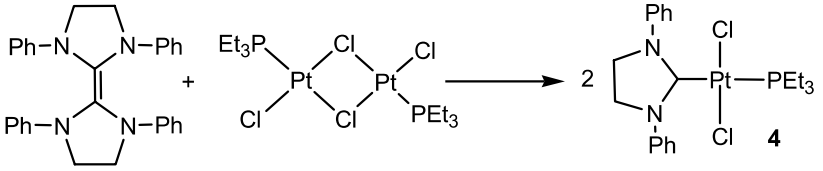
non-stable NHCs. With the pioneering works of Lappert and coworkers [3–6], electron-rich olefins (enetetramines) of the type **3** were soon used as NHC precursors (carbenoids) in the synthesis of new carbene–transition metal adducts. Reaction of the electron-rich olefins with the corresponding metal complexes can provide mono-, bis-, tris-, and even tetrakiscarbene complexes (Scheme 2). All the NHC complexes obtained by this method contain saturated NHCs. An extensive review on this type of reaction was published by Lappert in 1988 [22].

The first carbene complex, **4**, prepared by this method is shown in Scheme 3 [23].

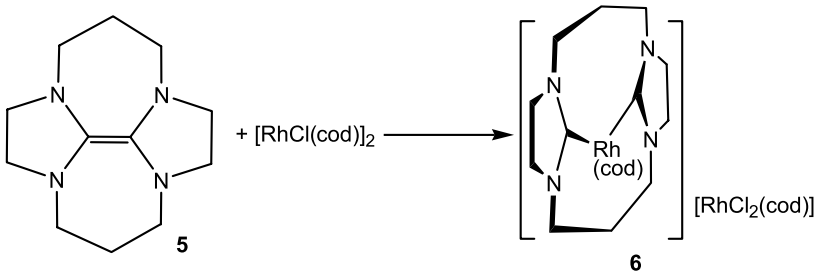
Heating of enetetramines in refluxing toluene in the presence of metal precursors such as manganese, iron, ruthenium, chromium cobalt, and nickel carbonyls provides the corresponding NHC complexes [4, 22, 24, 25]. Other ligands such as PPh_3, *py*, and $P(OMe)_3$ can also be replaced by a NHC using this method [22]. The transannularly bonded electron-rich olefin **5**



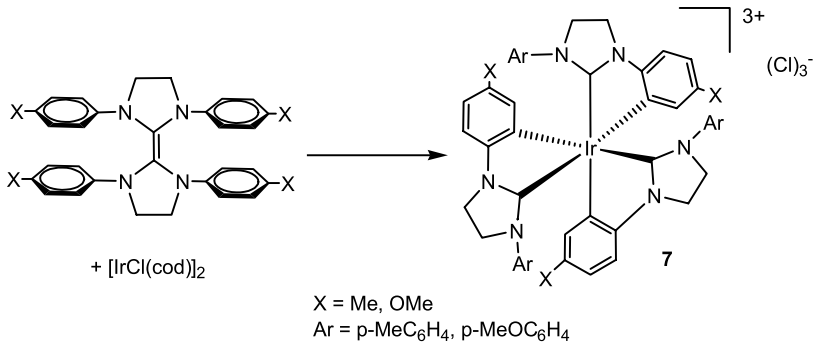
Scheme 2



Scheme 3



Scheme 4

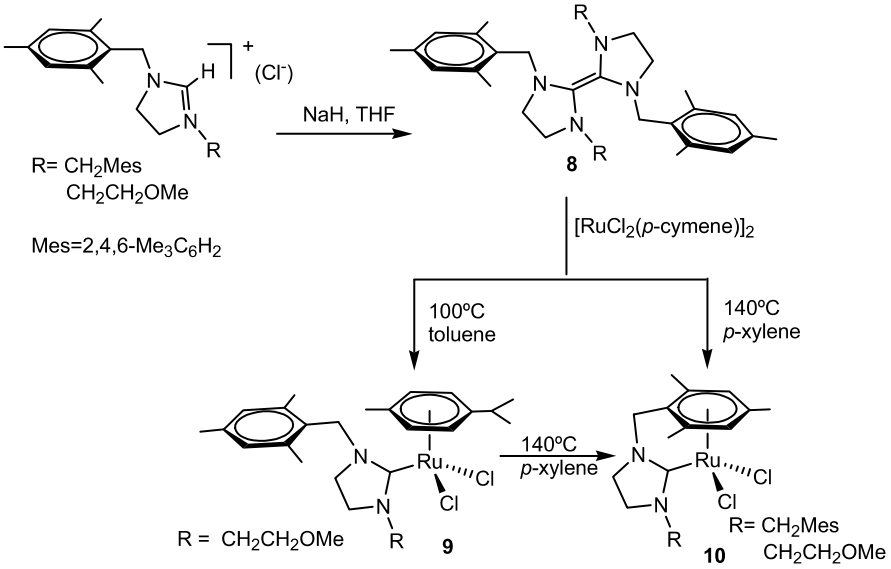


Scheme 5

reacts with dimeric Rh(I) complexes such as $[RhCl(cod)]_2$ (cod = 1,5-cyclooctadiene) giving rise to the dicarbene–metal chelate complex **6** by insertion of the metal atom into the C = C bond (Scheme 4) [5]. Other monocarbenes of rhodium and ruthenium were also obtained by reaction of the corresponding metal precursor dimers ($[RhCl(cod)]_2$, $[RuCl_2(p\text{-cymene})]_2$) with the corresponding enetetramines [26].

In a similar way, triscarbene-chelate Ir(III) complexes can be obtained by the reaction of an aryl-enetetramine with $[IrCl(cod)]_2$. In the formation of **7** (Scheme 5) the reaction proceeds by the insertion of the metal into the C = C bond of the olefin followed by spontaneous orthometallation of the N-aryl substituent [6].

More recently, two types of Ru complexes were obtained by the reaction of mesityl-substituted electron-rich olefins with $[RuCl_2(p\text{-cymene})]_2$ [27]. Cleavage of the chlorine bridges occurs first to yield the expected (NHC)(*p*-cymene)Ru(II) complex **9**. Under harsher reaction conditions (140 °C in *p*-xylene) further arene displacement takes place to yield the chelated η^6-mesityl-NHC – Ru complex **10** (Scheme 6). The olefin **8** was easily obtained by deprotonation of the corresponding dihydroimidazolium salt.

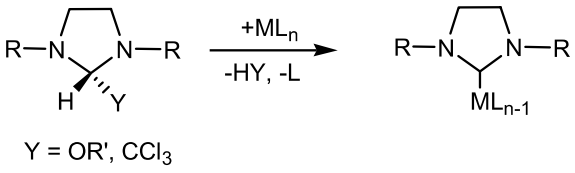


Scheme 6

Other NHC – Ru(II) complexes were also obtained by the same procedure [28].

3
Use of Carbene Adducts or "Protected" Forms of Free NHC Carbenes

Isolation of novel free carbenes is not always trivial, mainly due to difficulties with decomposition and the need to handle free NHCs under inert atmosphere conditions. In this context, the use of protected forms of free NHC carbenes has appeared as a useful alternative to the preparation of NHC complexes. N-Heterocyclic rings containing alkoxide or trichloromethyl groups, such as shown in Scheme 7, can be considered as NHC-adducts in the sense that they can readily eliminate alcohol or chloroform to unmask the carbene, which would then coordinate to the metal.



Scheme 7

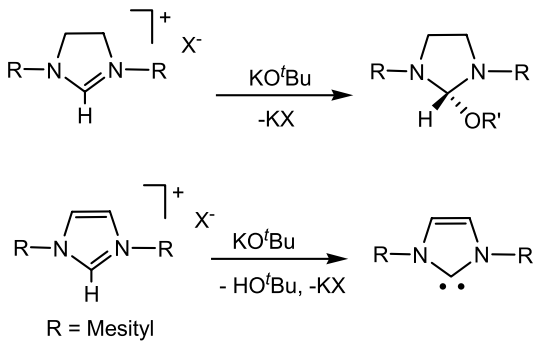
For these reactions it is not clear whether the released NHC reacts with the metal or the adduct first dimerizes to form the corresponding enetetramine (Scheme 1), which would then insert the metal as in the reactions shown in Sect. 2. In fact, it is long known that the trichloromethyl and alkoxy derivatives afford the olefins in hot xylene [29], and this could explain why these complexes are effective in place of electron-rich olefins in the preparation of Pt–carbene complexes, as shown in Scheme 3.

The reaction of triazolium and benzimidazolium salts with sodium methoxide yields the corresponding methoxy-triazoles and benzimidazoles [30, 31], which can be also used as triazolilydene and benzimidazolilydene precursors. Notably, adduct formation does not occur for certain unsaturated imidazolium salts with a C = C backbone. For the latter, reaction with $KOBu^t$ results in direct deprotonation to the free NHC (Scheme 8, also shows the reaction of a dihydroimidazolium salt with $KOBu^t$) [32].

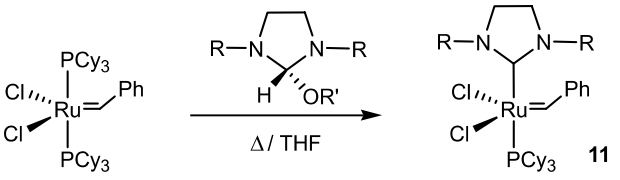
Grubbs and coworkers have obtained a series of imidazolidin-2-ylidene complexes of Ru, **11**, from NHC–alcohol adducts, by exchange of a phosphine ligand (Scheme 9) [33].

By a similar method, the same group obtained triazolilydene Ru(II) complexes, **12**, in high yield (Scheme 10) [32], improving the previously reported preparation method using the isolated free carbenes [34].

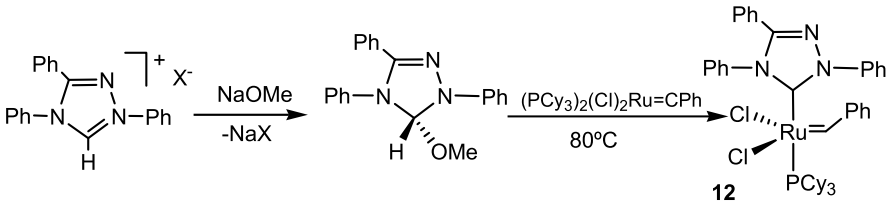
More recently, Yamaguchi and coworkers have described the preparation of a series of NHC–borane adducts, **13**, by addition of $LiBEt_3H$ to the cor-



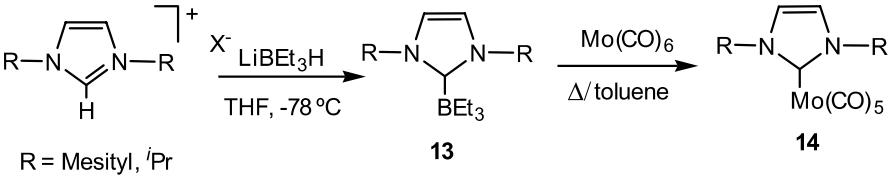
Scheme 8



Scheme 9



Scheme 10



Scheme 11

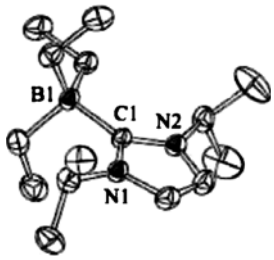


Fig. 1 Molecular structure of **13** (R = ^{i}Pr)

responding imidazolium salts [35]. These adducts are stable (two crystal structures have been reported, one shown in Fig. 1) and can be used as versatile synthons for the preparation of NHC complexes (Scheme 11). Bidentate NHC adducts of group 13 trihydrides and trihalides have also been described and fully characterized [36].

4
Preformed, Isolated Free Carbene

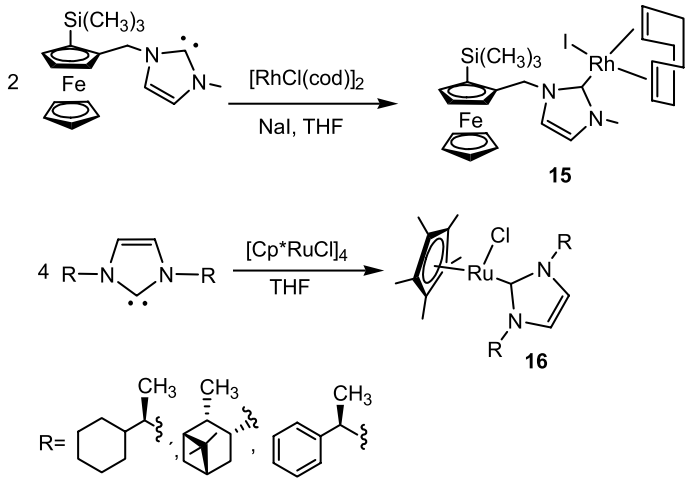
The preparation of the first free stable NHCs by Arduengo [8] broke with the idea that these compounds were too unstable to be used as ligands in the preparation of transition metal complexes. Although in the beginning it was thought that the stability of free NHCs is mainly due to steric effects, it is now assumed that electronic effects play a more important role [37]. Arduengo was the first to propose that both the nitrogen lone pairs and the C = C (in

unsaturated NHCs) provide enough kinetic stability to allow the isolation of this type of carbenes [38–40], and this, in fact, may justify why most of the NHCs obtained from the "free NHC route" are of the unsaturated form. The use of preformed NHCs has the advantage that they can be directly used to replace labile ligands on a suitable complex precursor.

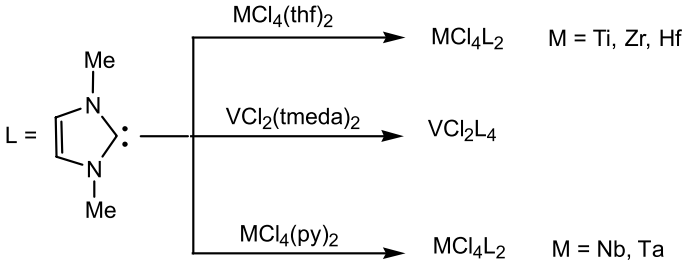
The most widely used method for the preparation of free NHCs is the deprotonation of an azolium salt with NaH or $KOBu^t$ [10, 14, 37]. In the case of *N*,*N*′-methylene-bridged bisimidazolium salts, the preparation of the free dicarbenes is only possible by the use of potassium hexamethyldisilazide (KHMDS) in toluene [14, 41]. Other strong bases deprotonate the methylene bridge breaking the bisazol unit [42].

Imidazol-2-ylidenes and triazol-2-ylidenes react with a large variety of metal complexes to afford the replacement of ligands such as tetrahydrofuran, carbonyl, phosphines, and pyridine. In the case of the reaction with homoleptic metal carbonyls $M(CO)_n$ (M = Cr, Mo, W, Fe, Ni), one or two carbonyl ligands can be readily replaced [43]. The reaction of free NHCs with dimeric complexes with bridging ligands such as halides, carbon monoxide, or acetonitrile can result in the cleavage of the dimetallic structure. This has been observed for reactions with $[MCl(cod)]_2$, $[Cp^*MCl_2]_2$ (M = Rh, Ir) [44–49], $[(p\text{-cymene})RuCl_2]_2$ [44, 45, 50], $[Os(CO)_3Cl_2]_2$ [45], and even higher nuclear clusters such as $[Cp^*RuCl]_4$ [51]. The introduction of chiral carbenes for the preparation of asymmetric catalysts is also possible by this method [52], as in the reactions shown in Scheme 12 for the preparation of **15** [49] and **16** [53].

Preformed NHCs can also be used for the preparation of complexes with metals unable to π-backdonate, like high oxidation state species of early transition metal complexes. Carbenes for these metals were only possible for the



Scheme 12

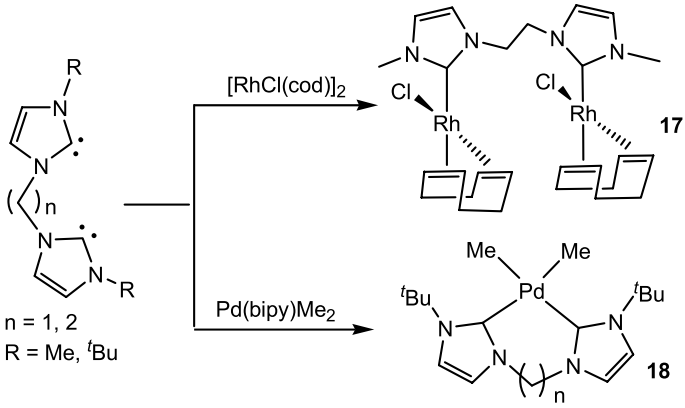


Scheme 13

Schrock type, but the high stability of NHCs has broken this rule affording new series of early transition metal complexes. For example, the NHC complexes shown in Scheme 13 were obtained from the reaction of the free NHCs and the corresponding TMEDA–, THF–, and *py*–metal adducts [54]. Direct reaction of the NHC with $TiCl_4$ also provides the coordination of one carbene affording $(NHC)TiCl_4$ [55].

Free bis- and tris-NHCs have also been prepared and used in coordination chemistry. Herrmann and coworkers prepared bis-NHC – Rh complexes by reaction of the corresponding free bis-carbenes with $[RhCl(cod)]_2$, in which the ligand is bridging two Rh(I) units (Scheme 14) [44, 45]. The same type of ligand can react with $Pd(bipy)Me_2$ [56] and $NiCl_2(PMe_3)_2$ [41] to provide the corresponding Pd(II) and Ni(II) complexes in which the ligand is chelating. Scheme 14 shows the reactions leading to the Rh [44, 45] and Pd [56] species.

Some biscarbenes have been crystallographically characterized, such as the one reported by Danopoulos and coworkers (Fig. 2) [57], which was soon coordinated to a series of metals such as Pd [58], Co [59], Ru [57], Fe [59, 60], Cr [59, 61], Ti, and V [59], some of them shown in Scheme 15.



Scheme 14

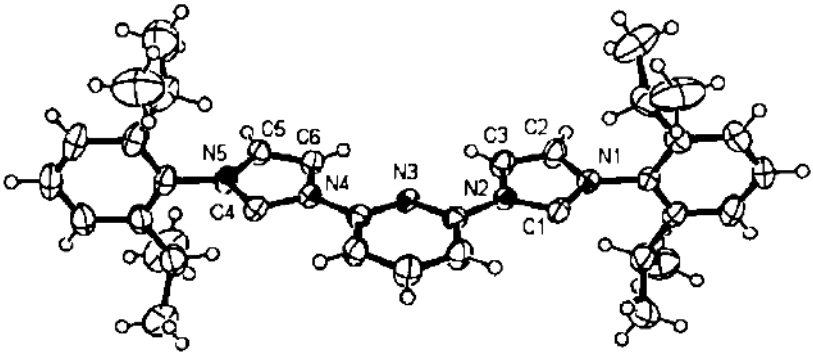
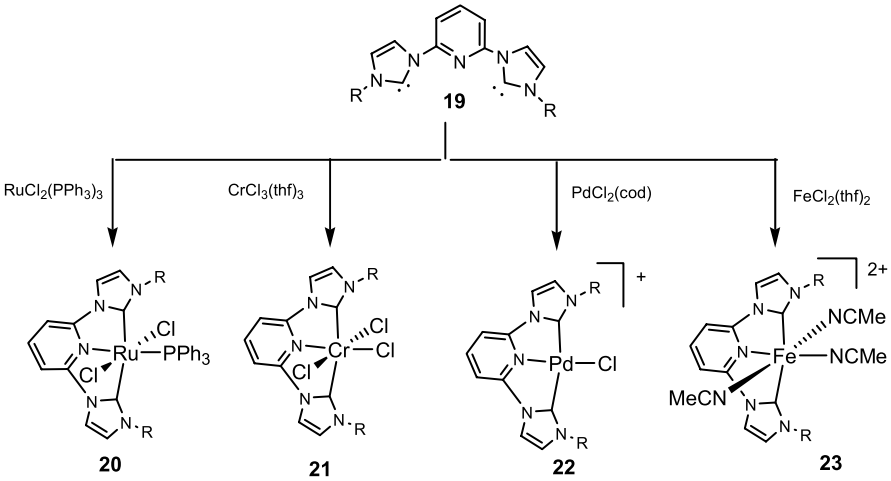
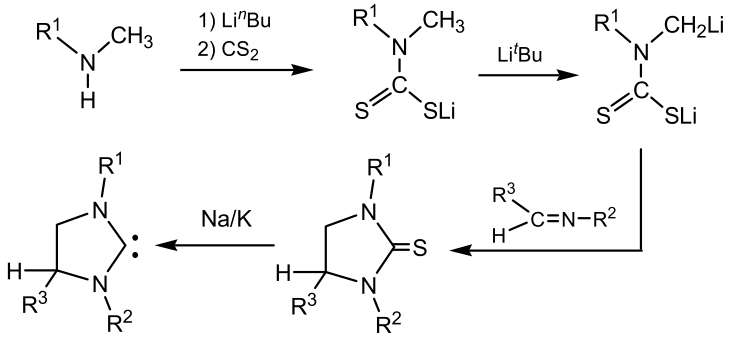


Fig. 2 Molecular structure of **19** (R = 2,6-$^{i}Pr_2C_6H_3$)



Scheme 15



Scheme 16

In 1993, Kuhn reported that cyclic thiourea derivatives like 1,3,4,5-tetramethyl-2(3H)-thione can be used as NHC precursors [62]. In most cases the thione affords an easy access to the free carbenes by treatment with sodium or potassium [62–71]. This method provides an efficient way to prepare unsymmetrically substituted saturated NHCs (Scheme 16) [35, 72].

5
In Situ Deprotonation of Azolium Salt with a Base

The in situ deprotonation of an azolium salt to produce the desired NHC has the advantage that the carbene does not have to be isolated, thus simplifying the reaction workups when the aim is preparation of the metal complex. This avoids the handling of the free NHCs, which most of the times are air- and moisture-sensitive. Two types of azolium in situ deprotonation reactions can be found in the literature, depending on the deprotonation process employed: (i) addition of an external base and (ii) use of metal complexes with basic ligands.

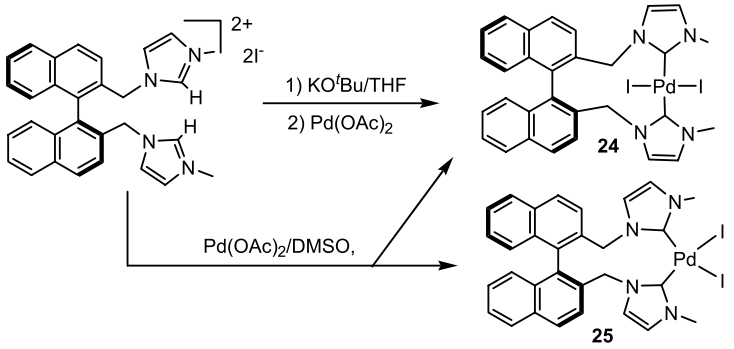
5.1
Deprotonation with an External Base

Several strong bases have been used in the deprotonation of azolium salts prior to the addition of the metal precursor to provide the desired NHC complex. The election of the base is sometimes crucial in order to achieve the desired results. Changes in basicity and nucleophility can produce variations in the reaction products, or undesired activations of the ligand and metal complex. In this sense, bases such as NaH [73, 74], Li^{n}Bu [75, 76], Li^{t}Bu [77], LiO^{t}Bu or KO^{t}Bu [43, 78–81], NaOEt [82, 83], and KN(SiMe$_3$)$_2$ [57, 84] are among the most widely used, and can be applied to imidazolium, triazolium, and benzimidazolium salts for their complexation to a large variety of metals. The use of strong bases requires that dry solvents must be used for the reaction, and in many occasions low temperatures are needed during the deprotonation process, in order to avoid undesired activations of the ligand precursor. The method is useful for the preparation of simple monocarbene complexes, but it can also be used in the preparation of chelate bis- [56, 75], and even one tris-carbene [76]. For example, chiral imidazolium and triazolium salts can be deprotonated with KO^{t}Bu, and react in the presence of Pd(II) diacetate to afford the corresponding dimeric mono-NHC complexes [80]. Following the same reaction procedures and using similar phenylazolium salts, the reaction with [(*p*-cymene)RuCl$_2$]$_2$ and [Cp*RhCl$_2$]$_2$ produces the cleavage of the chloro bridges producing mononuclear NHC – M species. Abstraction of one hydrogen of the phenyl group and elimination of HCl lead to ortho-metallated pseudo-tetrahedral ruthenium and rhodium complexes,

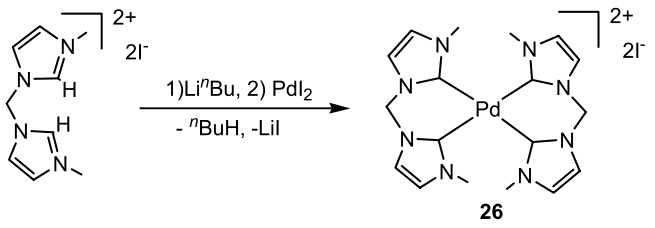
with a stereogenic center at the metal [85]. The combined use of KO^{t}Bu and NaH in THF has also been used to deprotonate imidazolium salts and generate NHCs, which can be used in situ and coordinate, e.g., to $Cr(CO)_6$ and $W(CO)_6$ [43].

Sometimes the reaction products depend on the deprotonation method used. For example, RajanBabu and coworkers have obtained chiral N-heterocyclic biscarbenes of Pd and Ni from a binaphtyl bisimidazolium salt. The in situ deprotonation of the bisimidazolium salt with KO^{t}Bu prior to the addition of $Pd(OAc)_2$ gives exclusively the *trans* isomer, **24**, while direct reaction of the salt with the metal complex in hot DMSO (see next section) gives a mixture of the *cis*-(25) and *trans*-isomers (Scheme 17) [81].

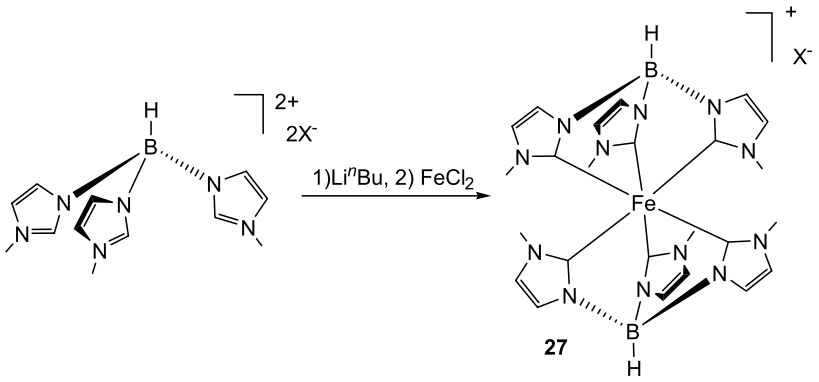
Methylene-bridged bisimidazolium salts can also be deprotonated by Li^{n}Bu at low temperatures (– 70 °C) generating a biscarbene that can coordinate to a metal complex. In the case of reaction with PdI_2, an homoleptic complex containing bidentate biscarbenes can be obtained, **26** in Scheme 18 [75]. By a similar procedure, Fehlhammer and coworkers obtained the first chelating tris-NHC complex, **27** in Scheme 19, with a triscarbene ligand similar to Trofimenko's trispyrazolyl borate [76]. Interestingly, the same imidazolium precursor coordinates to lithium after reaction with *n*BuLi, providing a dimetallic complex with two triscarbene ligands, whose molecular structure was determined by X-ray diffraction [86].



Scheme 17

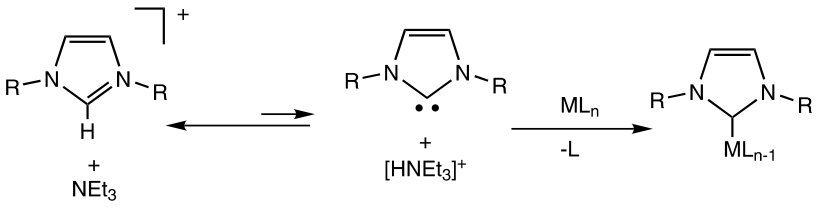


Scheme 18



Scheme 19

The use of a strong base is very convenient in the sense that it warranties complete deprotonation of the azolium precursor, and can be used for a wide variety of azolium salts and metal precursors. However, for those metal or carbene precursors with acidic or electrophilic centers other than the C2 – H position in the azolium ring, undesired activations can be produced leading to decomposition products. For example, the bisimidazolium salt depicted in Scheme 18 is very sensitive to the base used, and deprotonation of the methylene bridge is often observed. For these cases weak bases can be used, this allowing the reaction to proceed under less basic/nucleophilic conditions. For the election of the weak base, a clear knowledge of the acidity/basicity of the azolium/NHC has to be accounted. The basicity of NHCs has been studied from the experimental [87, 88] and theoretical points of view [89]. The most basic carbene shows pK_a values (in MeCN) of 39.1, while the least basic one is 25.6 (pK_a values refer to the acidity values of the azolium salts) [89]. This in turn means that the least basic NHC is more basic than the most basic phosphine [P(^{t}Bu)$_3$, pK_a $\sim$ 10], thus implying a high proton affinity. From this point of view it is not easy to justify why weak bases such as NEt_3, NaOAc, and Cs_2CO_3 provide very good results in the preparation of NHC – M complexes starting from azolium salts. Although detailed studies have not been made, it is difficult to believe that high concentrations of free carbenes are generated from mixtures of azolium salts and weak bases. A possible explanation for the



Scheme 20

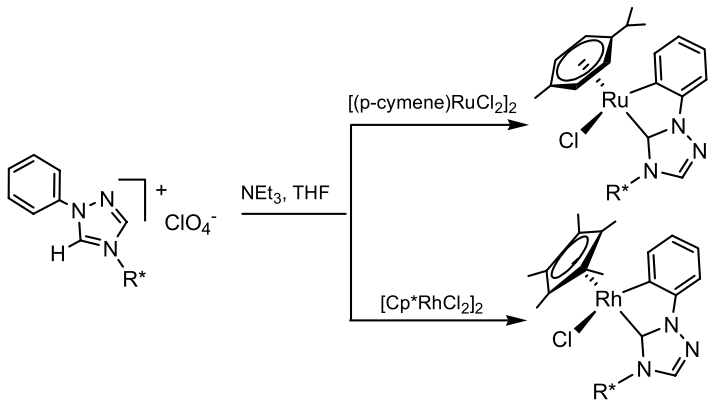
high yields in the preparation of NHC compounds by this method may come from the stabilization provided by the NHC complex, thus making the overall reaction favorable [90] (Scheme 20).

Triethylamine has been used in THF to deprotonate triazolium salts, which in the presence of $[(p\text{-cymene})RuCl_2]_2$, $[Cp^*RhCl_2]_2$, and $[RhCl(cod)]_2$ provides the corresponding mono-NHC complexes [85, 91]. In the case of chiral triazolium salts, the reaction with $[RhCl(cod)]_2$ and $[RhCl(nbd)]_2$ provides square planar complexes with axial chirality and enantiomeric excesses of up to 97%, depending on the size of the chiral substituent on the triazolylidene ligand [91]. Similar phenyltriazolium salts were coordinated to Ru and Rh complexes in the presence of NEt_3 providing orthometalated complexes with a pseudo-tetrahedral arrangement of the ligands. Hence a stereogenic center is created leading to the existence of two diastereomers where chiral carbene ligands are used. Diastereoselectivities of up to 95% were achieved (Scheme 21) [13].

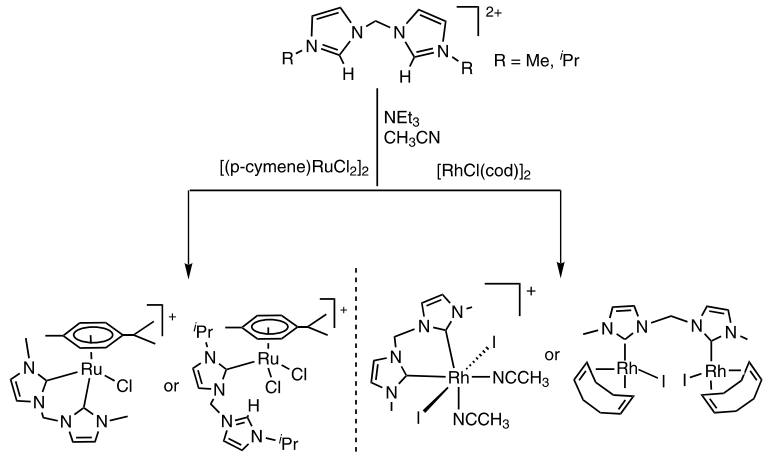
Triethylamine has also been used to obtain chelate bis-NHC complexes of Rh, Ru, and Ir [90, 92–97]. For example, the reaction of bisimidazolium salts with $[RhCl(cod)]_2$ [90] and $[(p\text{-cymene})RuCl_2]_2$ [97] afforded mono- and bis-NHC complexes, depending on the steric hindrance provided by the N-alkyl group, as shown in Scheme 22.

Pincer (tridentate-*mer*) coordination from a pyridine-bisimidazolium (**28**) salt can be achieved using NEt_3 and the addition of $[RhCl(cod)]_2$ [92] or $[RuCl_2(cod)]_2$ [93] as metal complexes, affording compounds **29** and **30**, respectively (Scheme 23).

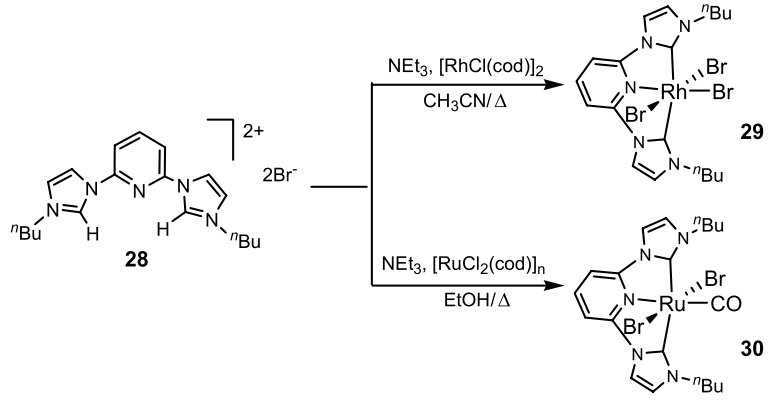
In the presence of Cs_2CO_3, imidazolium and bezimidazolium salts can react with $[(p\text{-cymene})RuCl_2]_2$ to afford the corresponding $(p\text{-cymene})RuCl_2$ (NHC) complexes [98]. Following the same procedure, benzimidazolium salts with a mesityl substituent can react with $[(p\text{-cymene})RuCl_2]_2$ to yield the benzimidazolylidene–Ru complex with the mesityl group η^6-coordinated to



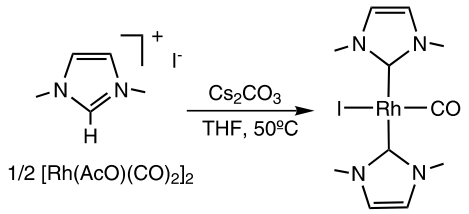
Scheme 21



Scheme 22

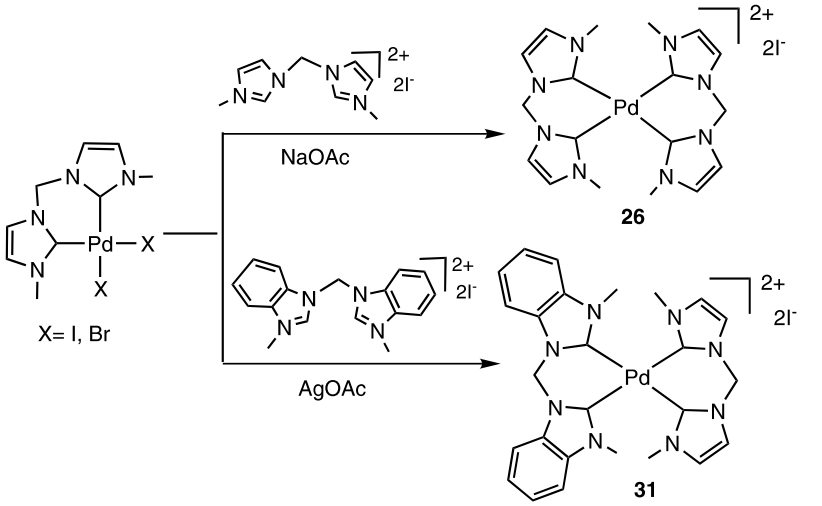


Scheme 23



Scheme 24

the Ru atom [27], in a similar form to that shown for complex **10** in Scheme 6 for a related 3,4-dihydroimidazolylidene complex. The preparation of a series of Vaska-type NHC – Rh(I) complexes, $RhCl(CO)(NHC)_2$, was performed by Haynes and coworkers from the reaction of $[Rh(AcO)(CO)_2]_2$ and the cor-



Scheme 25

responding imidazolium salt in the presence of Cs_2CO_3 (Scheme 24). Cesium carbonate proved to be significantly more effective than sodium carbonate in this role, possibly due to its higher solubility in the reaction medium (THF) [99].

Sodium acetate has also proved to be a convenient base for deprotonation of imidazolium salts. For example, in the coordination of a phosphine-functionalized NHC ligand, Lee and coworkers start from the corresponding imidazolium salt which is deprotonated with NaOAc in the presence of $PdCl_2$, affording a chelate phosphino–NHC complex of Pd(II) [100]. Sodium acetate was also used in the deprotonation of methylene-bridged bisimidazolium salts, to afford homoleptic chelating NHC complexes of Pd and Ni (Scheme 25). The starting Pd and Ni biscarbene complexes were previously obtained by deprotonation of the same bisimidazolium salts with a basic ligand of the metal precursors (see next section) [101]. A mixed bisbenzimidazolylidene/bisimidazolylidene Pd complex, **31**, was also obtained by using AgOAc, which had a twofold role in the reaction: deprotonation of the bisbenzimidazolium salt and removal of the bromine ligands by precipitation as AgBr (Scheme 25). The same base can be used in the deprotonation of bisimidazolium salts used in the preparation of bis-NHC complexes of Rh [102, 103] and Ir [104, 105]. In these latter cases the acetate coordinates to the metal in the final bis-NHC – M–acetate complexes.

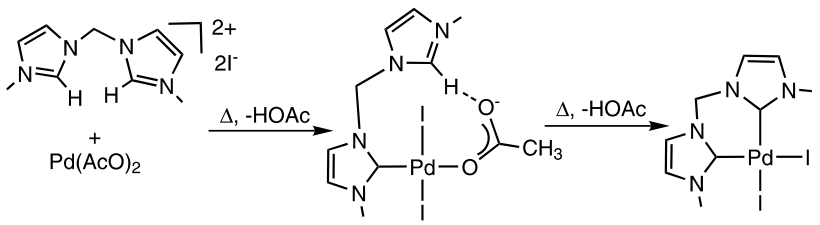
Basic solvents such as liquid ammonia can be used to deprotonate azolium salts and generate the corresponding NHCs. Herrmann was the first to use this method [44, 45] to obtain a series of complexes of Ru, Rh, and W. The reaction proceeds under mild reaction conditions, but needs to be carried out at temperatures lower than – 30 °C. The acidity of the C-2 protons seems to

be enhanced by hydrogen bonding, and novel ylidenes that were not readily accessible by known procedures were obtained by this method.

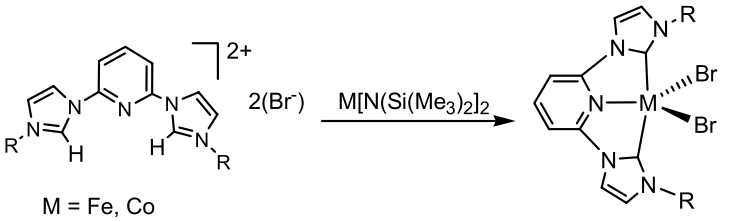
5.2
Deprotonation with Metal Complex with a Basic Ligand

In situ deprotonation of the NHC precursors can be achieved by basic ligands on the metal complexes. Commercially available or easy-to-prepare metal complexes with acetate, alkoxide, hydride, or acetylacetonate ligands are frequently used. Wanzlick [2] and Öfele [1] used this method to synthesize the first imidazolylidene complexes starting from $Hg(OAc)_2$ and $[CrH(CO)_5]^-$, respectively. More than 25 years later the use of metal(II) diacetates became a method which was often used to prepare imidazolylidene, triazolylidene, and benzimidazlylidene complexes of Pd and Ni, providing monodentate [9, 45, 101, 106] bidentate [101, 107–112], and tridentate [113, 114] NHC complexes. As in the example shown in Scheme 17, chiral bidentate-NHC – Pd(II) complexes have also been obtained following this route [81]. In these reactions the acetate is eliminated as acetic acid. In the case of the methylene-bridged bisimidazolylidene complexes of Pd and Ni, these could be obtained only by this route until the corresponding free biscarbenes could be obtained in 1999 [41]. Scheme 26 shows the preparation of a bis-NHC complex of Pd(II) by this method [14].

Similar biscarbene ligands have been coordinated to Rh starting from $Rh_2(OAc)_4$, providing mononuclear species of Rh(III) of the type $RhI_2(OAc)$(bis-NHC) [103]. The same bis-NHC precursor reacts with $[Rh(OEt)(cod)]_2$ affording complexes of the type $[Rh(bis\text{-}NHC)(cod)]^+$ and $[Rh(bis\text{-}NHC)(CO)_2]^+$ in which the metal remains in the (I) oxidation state [82]. Other Rh(I) and Ir(I) complexes were obtained from the corresponding μ-alkoxo complexes of (cod)Rh(I) and (cod)Ir(I) and the azolium salts at room temperature [45, 83]. The method can be used with benzimidazolium and triazolium salts [83]. The Ru complex $[Cp^*Ru(OCH_3)]_2$ reacts with imidazolium salts yielding the 16-electron species $Cp^*RuCl(NHC)$ [115]. Other μ-alkoxo and μ-hydroxo bridged complexes of chromium, molybdenum, tungsten, rhenium, and palladium lead to the formation of the corresponding NHC – M species by direct reaction with the corresponding azolium salts [116–119].



Scheme 26

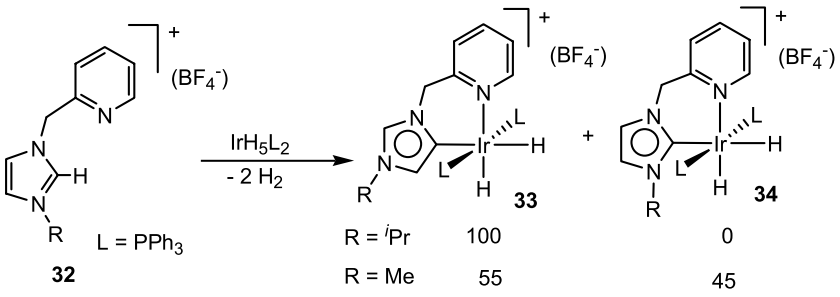


Scheme 27

$Ni(acac)_2$ has also proved to be an efficient metal precursor by losing the acetylacetonate ligand in the form of acetylacetone. RajanBabu has used this metal precursor to coordinate the binaphtyl-chelate-chiral ligand shown in Scheme 17 [81].

Danopoulos and coworkers have obtained N-heterocyclic pincer biscarbene complexes of Fe(II) [60] and Co(II) [120] by aminolysis of $M[N(SiMe_3)_2]_2$ (M = Fe, Co), as shown in Scheme 27.

Hydrides can also be used to generate NHC complexes from the corresponding imidazolium salts. Using this methodology, Crabtree and coworkers found an interesting example where the metallation of the NHC occurred via a "wrong way", i.e., the metal is bound not to the activated C-2 position, but to the C-5 position [121, 122]. This interesting way of NHC binding (now generally called "abnormal" NHC binding) was first observed for the reaction of an N-isopropyl substituted methylene-linked pyridin-imidazolium salt **32** and $IrH_5(PPh_3)_2$ (Scheme 28). The formation of the abnormal NHC is favored by the lower steric strain at the metal center. On moving to the smaller wingtip Me group, a mixture of the normal and abnormal carbenes is obtained (Scheme 28). In any case, theoretical calculations suggested that the normal binding is thermodynamically favored when the anion-free complexes $\mathbf{33}^+$ are considered, but ion-pairing has a significant effect in lowering the energy of the abnormally binding species, presumably due to the energy differences in the C-2/C-5 C – H hydrogen bonding to the anions. In this



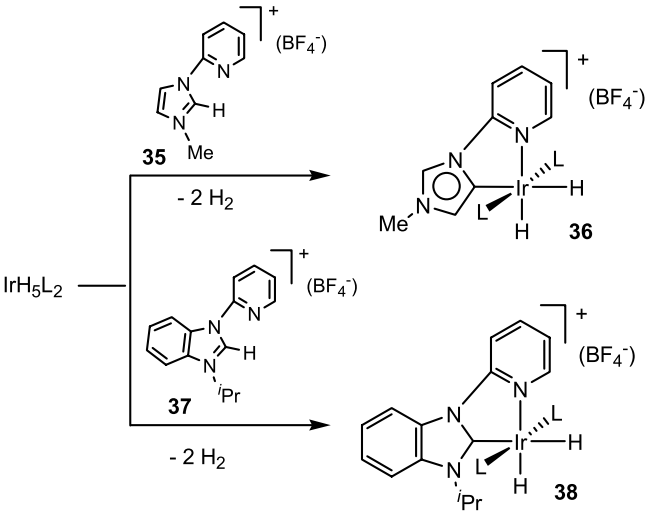
Scheme 28

sense, the counter-anions BF_4, PF_6 and SbF_6 seem to have a preference on the abnormal binding, whereas Br favors the normal C-2 bond [123, 124].

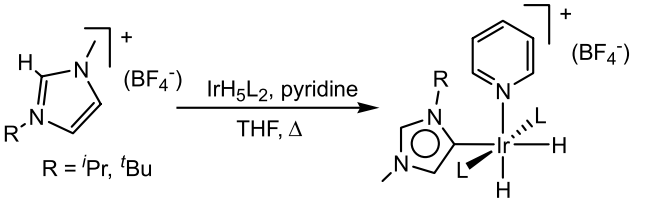
The "abnormal" metallation is also favored when the carbon-truncated pyridine-imidazolylidene precursor **35** (with a smaller bite angle) is used. For these precursors the abnormal binding is produced even when small wingtip groups are used, as shown in Scheme 29. Under the same conditions, the pyridin-benzimidazolium analog (37) afforded the C-2 carbene complex, **38** (Scheme 29) [122].

Chelation is not necessary to promote the abnormal metallation. When imidazolium salts with one bulky substituent (^{i}Pr, ^{t}Bu) are refluxed with pyridine and $IrH_5(PPh_3)_2$ in THF, C-5-bound complexes are obtained in good yield, with the least sterically hindered of the three imidazole carbons selectively bound to Ir (Scheme 30) [125]. Infrared spectroscopy on carbonyl derivatives indicated that abnormally bound NHCs are much stronger electron donors than their ubiquitous C-2 counterparts [125].

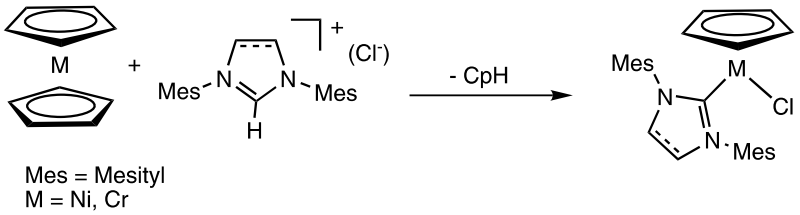
Abnormal binding is not restricted to Ir. Other polydentate NHCs have been reported to form abnormal bonds to transition metal complexes, such as



Scheme 29



Scheme 30



Mes = Mesityl
M = Ni, Cr

Scheme 31

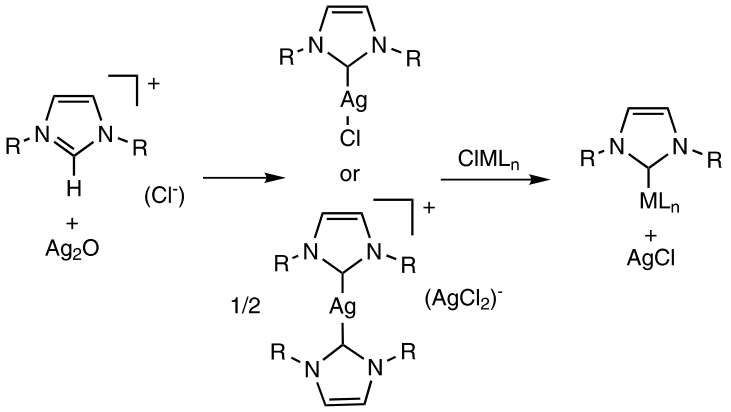
the Cu compound reported by Meyer [126], and the Fe compound described by Danopoulos [60].

Under certain conditions cyclopentadienyl ligands deprotonate imidazolium salts and can be removed from the metal center allowing the introduction of the NHC. This has been observed for some metallocene complexes such as chromocene [127] and nickelocene [128, 129]. Scheme 31 shows these reactions.

6
Transmetallation from a Silver–NHC Complex

In 1998, Wang and Lin reported that the lability of the Ag – NHC bond could make Ag – NHC complexes useful as carbene transfer agents. In their work, two benzimidazolylidene complexes of Ag(I) were used as carbene sources to provide NHC complexes of Pd and Au, by reaction with $PdCl_2(MeCN)_2$ and $AuCl(SMe_2)$, respectively [130]. Since then, the number of papers on Ag – NHC complexes has significantly increased [131, 132], as they have become a valuable way of obtaining carbene complexes of a wide variety of metals with interesting catalytic applications. The use of Ag – NHC complexes as carbene transfer reagents provides in many cases a convenient way to overcome the difficulties arising from using strong bases, inert atmospheres, and complicated workups. In most cases transmetallation reactions can be carried out under aerobic conditions, and the process has been shown successful with a variety of metals such as Au, Cu, Ni, Pd, Pt, Rh, Ir, and Ru. In a typical reaction, an imidazolium salt would react with Ag_2O to provide a mono- or bis-NHC complex of Ag(I). This compound can be used in situ if a convenient amount of a metal complex (usually with halide ligands) is added, hence providing the corresponding M – NHC complex (Scheme 32). The lability of the Ag – NHC bond and the low solubility of the silver halide can be considered the driving forces of the reaction.

Saturated NHCs are relatively inactive towards transmetallation compared to unsaturated carbenes. This has been rationalized in terms of the stronger donation of the saturated NHC to the silver center, thus inhibiting the lability

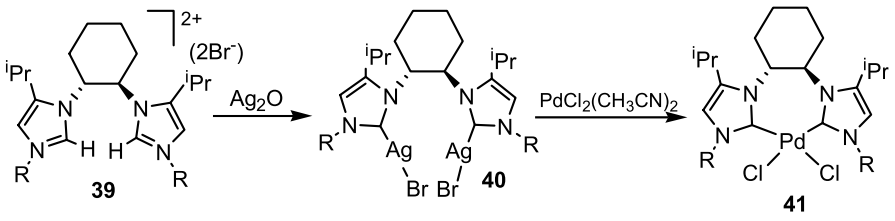


Scheme 32

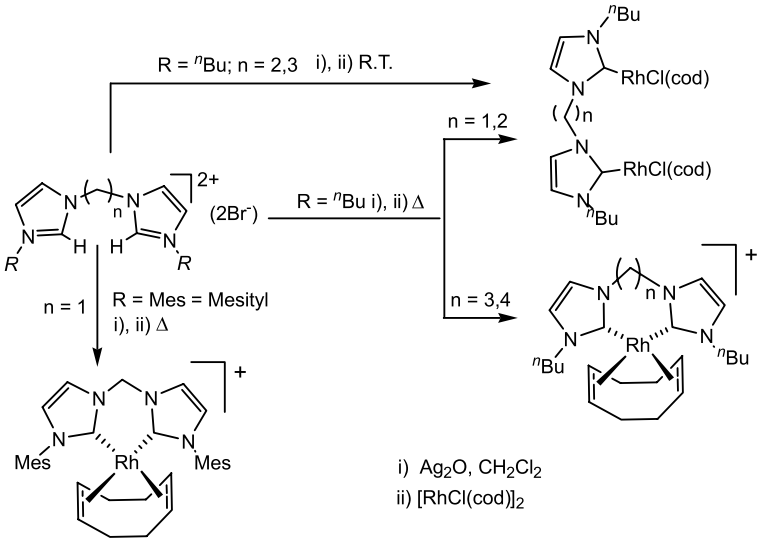
of the Ag – NHC bond [131]. The metal to which transmetallation has been most widely used is, by far, Pd. Several Pd complexes have been used as precursors, such as $PdCl_2(cod)$, $PdBr_2(cod)$, $PdBr(CH_3)(cod)$, $PdCl(CH_3)(cod)$, $PdCl_2$, $[Pd(allyl)Cl]_2$, $PdCl_2(CH_3CN)_2$, and $PdCl_2(PhCN)_2$ [131, 132]. For example, the reaction of the chiral bisimidazolium salt **39** affords the binuclear Ag – NHC complex **40**, which reacts with $PdCl_2(CH_3CN)_2$ to provide the chiral Pd complex **41** (Scheme 33) [133].

The reaction conditions used for the transmetallation can afford different types of compounds. For example, the reaction of bisimidazolylidene complexes of silver with $[RhCl(cod)]_2$, yield dimetallic complexes of Rh(I) with a bridging bisimidazolylidene or monometallic Rh(I) complexes with a chelate bis-NHC ligand, depending on the length of the linker between the azole rings and the temperature of the reaction [102]. The size of the N-substituents also contribute to the final geometry of the complex, as shown by the introduction of bulky mesityl groups that force the chelating coordination [134]. These reactions are shown in Scheme 34.

Tridentate triscarbene ligands such as [1,1,1-tris(3-alkylimidazol-2-ylidene)methyl]ethane (TIME) react with Ag_2O to afford complexes with three Ag(I) centers bridged by two tripodal NHC fragments via each of the

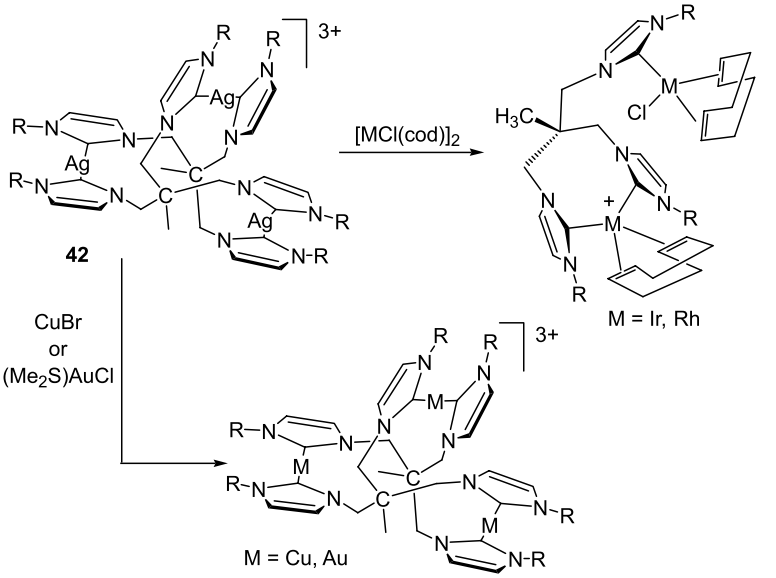


Scheme 33



Scheme 34

pendant arms, **42** (Scheme 35) [135]. This complex can react with a variety of metal complexes, such as Cu(I), Au(I) [136], Rh(I), and Ir(I) [137] yielding complexes with different topologies, as shown in Scheme 35. The introduction of a nitrogen atom in the tripodal ligand provided a N-anchored



42

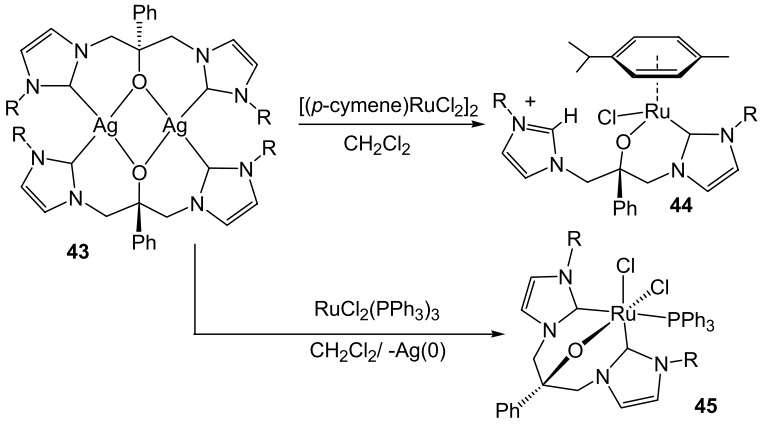
Scheme 35

tetradentate-tris-NHC, also used to prepare Cu(I) [138], Rh(I), and Ir(I) complexes [139].

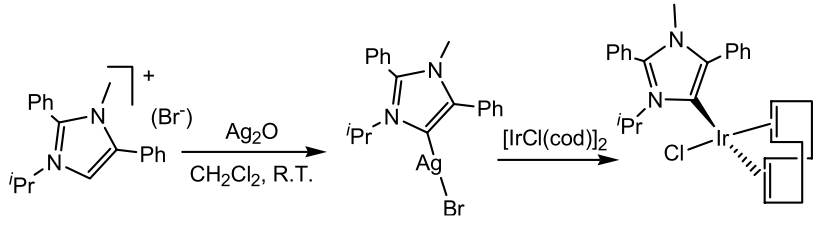
Sometimes the Ag – NHC reagent has a twofold effect: (i) transmetallation of the carbene and (ii) oxidation of the metal. The reaction of the dimetallic Ag biscarbene **43** with $[(p\text{-cymene})RuCl_2]_2$ yields the Ru(II) complex **44** (Scheme 36). However, when the same complex **43** reacts with $RuCl_2(PPh_3)_3$, a Ru(III) complex is obtained (**45**) with a CCO tripod coordination of the ligand [140]. In this latter case, the reduction of Ag(I) to Ag(0) is confirmed by the formation of a silver mirror in the reaction vessel. Compound **43** can also react with CuI to afford a square planar NHC – Cu(I) complex [141].

Interestingly, Crabtree and coworkers found that abnormal binding of NHCs is also possible in Ag – NHC complexes when the C-2 position of the initial imidazolium salt is blocked by a phenyl group. Transmetallation to $[IrCl(cod)]_2$ affords stable abnormal Ir – NHC complexes when bulky substituents are introduced in the C-4 position, also protecting the Ir(I) complex from decomposition through protonolysis (Scheme 37) [125].

NHCs can also be transferred from NHC complexes of Cr, Mo, and W. Complexes of the type NHC – $M(CO)_5$ (M = Cr, Mo and W) have been suc-



Scheme 36



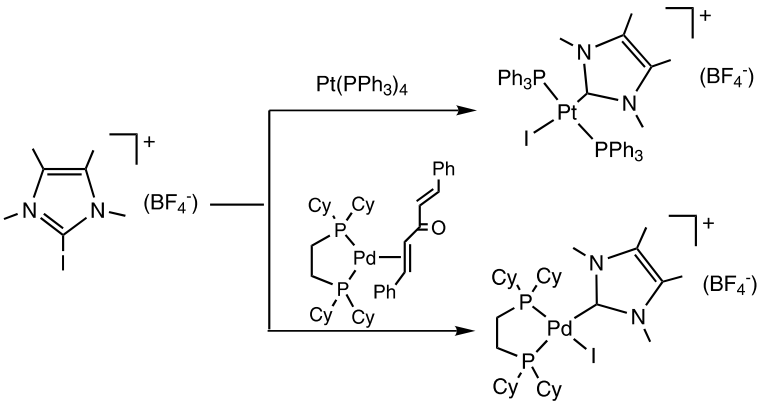
Scheme 37

cessfully used in the transfer of the NHC ligand to Rh(I), Pd(II), Pt(II), Cu(I), Ag(I), and Au(I) [142, 143].

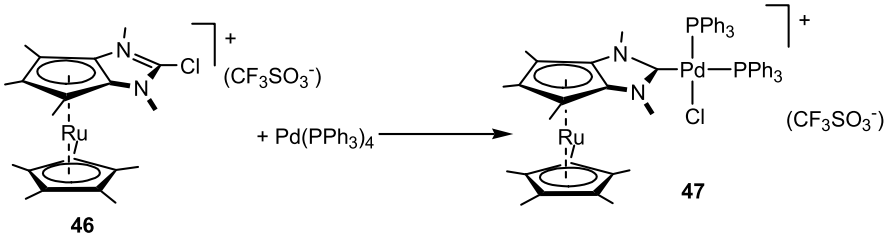
7
Oxidative Addition Via Activation of the C2 – X Bond (X = Me, Halogen, H) of an Imidazolium Cation

Direct oxidative addition of C2 – X bonds (X = Me, halogen, H) of imidazolium cations to low-valent transition metal compounds constitute a facile access to NHC – M complexes under certain circumstances. The oxidative addition of C – Cl bonds in azolium salts to generate carbene complexes has been known since 1974 [144, 145]. In that case, 2-chloro-methylthiazolium salts were used as carbene precursors. In 2001, Cavell and coworkers extended the method to 2-iodo-imidazolium salts, and studied the oxidative addition process to group 10 M(0) complexes, both from an experimental and theoretical point of view (Scheme 38) [146–148]. In the same work, C2 – H (experimentally and theoretically) and C2 – Me (theoretically) oxidative additions were also studied, thus indicating that the method could also be extended to bonds other than C-halogen [146]. The theoretical calculations predicted that addition of imidazoliums to Pt(0) and Ni(0) is more exothermic than to Pd(0). Further, Ni(0) was predicted to have a lower barrier than Pt(0) and Pd(0). The oxidative addition barriers would be in the order C – Me > C – H > C-halogen, the haloimidazoliums providing the more exothermic processes.

The oxidative addition of 2-chloroimidazolium salts to Pd(0) was also used by Fürstner and coworkers, providing a series of imidazolylidene complexes of Pd(II). The use of a chiral chloroimidazolium salt provided a enantiopure Pd – NHC complex [149]. A more recent example of C – Cl oxidative add-



Scheme 38



Scheme 39

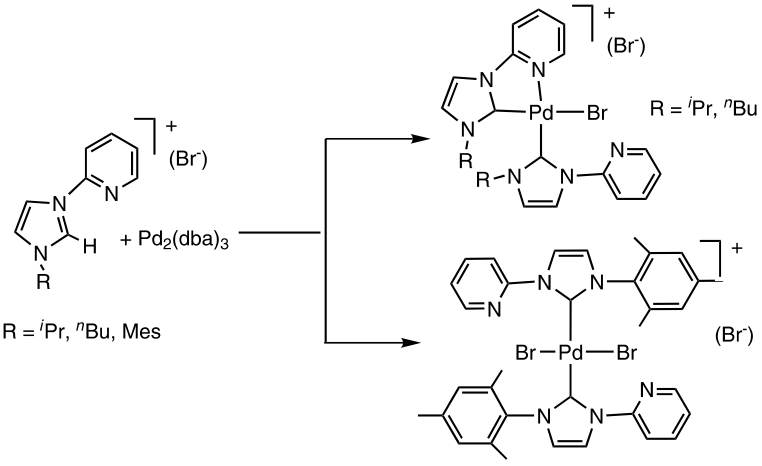
ition of imidazolium salts was described by Arduengo and coworkers, who obtained the cyclopentadienyl-annulated imidazolylidene–Pd(II) complex **47** by C – Cl oxidative addition of the imidazolium salt **46** (Scheme 39) [150].

The oxidative addition of 2-methylimidazolium salts has been studied from the theoretical point of view [146, 147]. In fact, the reaction is the reverse of the ubiquitous reductive elimination reaction observed for hydrocarbonyl-Pd – NHC complexes [151, 152]. The DFT studies predict that the reaction of the 2-methylimidazolium salt with the model complex $Pt(PH_3)_2$ is exothermic. The reductive elimination hydrocarbonyl-Pd – NHC complexes has also been studied in detail by DFT calculations [153].

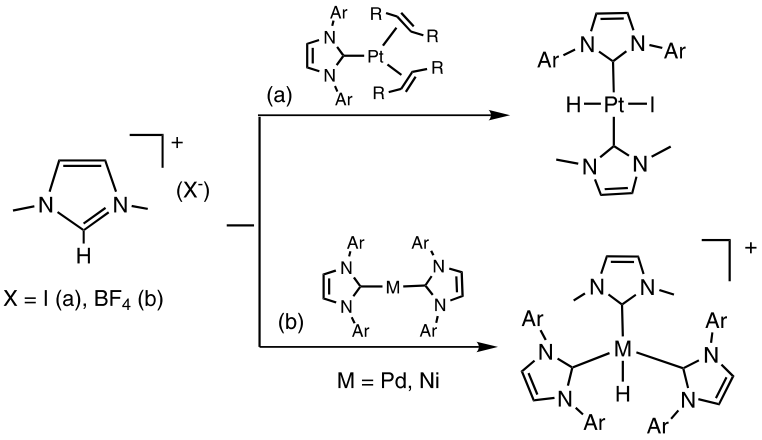
Oxidative addition of C2 – H bonds of imidazolium salts to low valent metals was first observed by Nolan and coworkers in 2001, who proposed a NHC – Pd – H intermediate in the catalytic cycle of the dehalogenation of aryl halides with $Pd(dba)_2$ in the presence of imidazolium salts [154]. More direct evidence of this process was described by Crabtree and coworkers two years later [155]. The reaction between a pyridine-imidazolium salt and $Pd_2(dba)_3$ afforded the preparation of bis-NHC – Pd(II) complexes by C2 – H oxidative addition (Scheme 40). The presumed Pd – H intermediates were not detected. The authors proposed a mechanism via two successive C – H oxidative additions followed by reductive elimination of H_2 [155].

The isolation of the first NHC – M – H complexes obtained by oxidative addition of an imidazolium salt to a low valent group 10 metal was achieved by Cavell and coworkers in 2003 [156]. A NHC – Pt(0) complex with two monoalkene ligands reacted with an imidazolium salt to provide an isolable NHC–PtH complex (Scheme 41). Carbene metal hydrides of Ni and Pd were obtained one year later by C – H oxidative addition of the corresponding imidazolium salts to bis-NHC Ni(0) and Pd(0) complexes (Scheme 41) [157].

Blocking the C2 position with alkyl groups may afford C – H oxidative additions of the imidazolium salts yielding abnormal carbenes. This strategy was followed in the reaction a Pt(0) complex with C2-methylated imidazolium salts, which provided the oxidative addition of the C4,5 – H bond, as shown in Scheme 42 [158]. This behavior provides evidence that the substitution of imidazolium-based ionic liquids at the C2 may not be enough to prevent their involvement in reactions for which they are solvents.

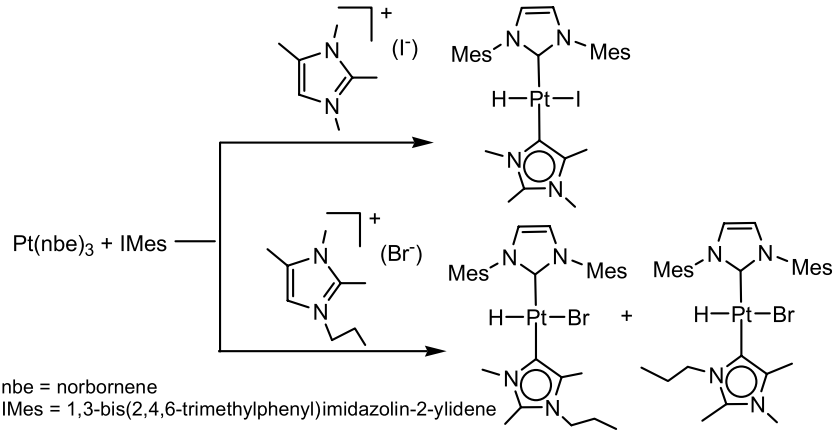


Scheme 40

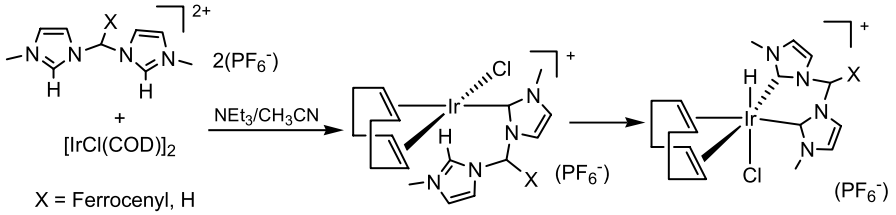


Scheme 41

The C2 – H oxidative addition of imidazolium salts to metal complexes was recently proved for metals other than low valent group 10. The reaction of a ferrocenyl-bisimidazolium salt to $[IrCl(cod)]_2$ in the presence of NEt_3 provided the first evidence of the preparation of a stable NHC–Ir(III)–H complex by direct oxidative addition of the imidazolium salt [96]. It was proposed that the ferrocenyl fragment may be sterically protecting the M – H from further reductive elimination, but later it was shown that this fragment was not necessary in order to obtain the desired NHC–Ir(III)–H complexes (Scheme 43) [159]. The role of the weak base (NEt_3 in this case) had to be reconsidered in order to explain the overall metallation process, and it was proposed that a mechanism as that shown in Scheme 44 may better explain the process. The oxidative addition of the C2 – H bond of the imida-

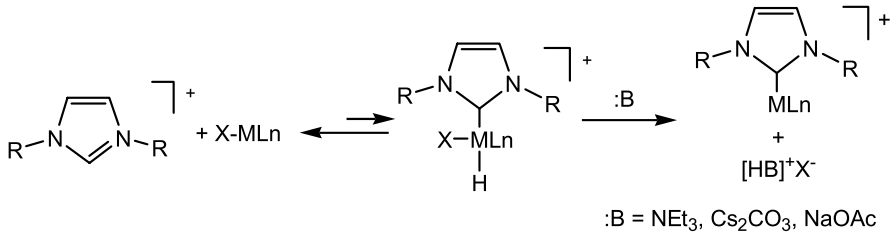


Scheme 42

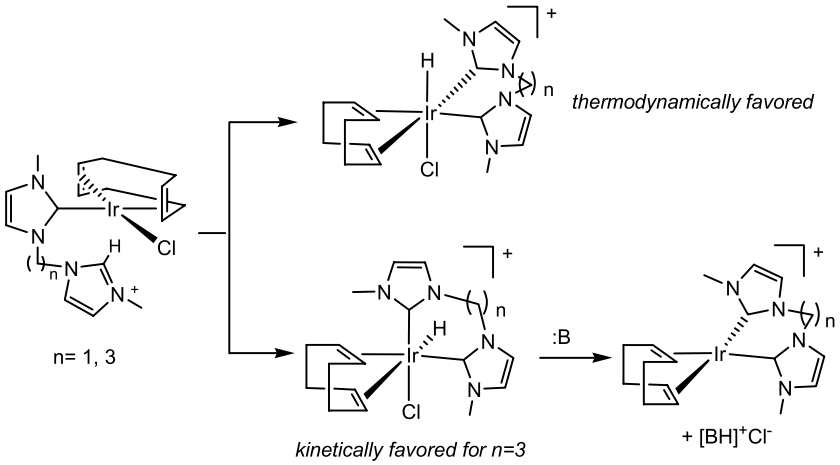


Scheme 43

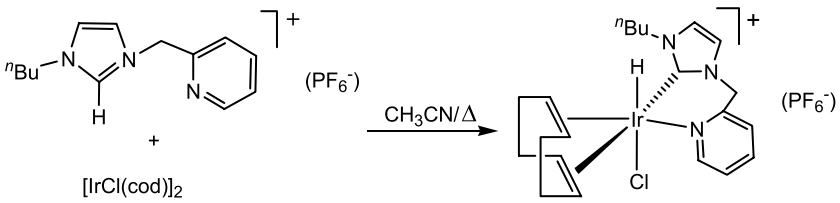
zolium salt may be followed by the reductive elimination of HX supported by the weak base, and this would explain why NHC – M – H complexes are so scarce. A combined experimental and theoretical approach was recently described in order to find an unified mechanism for the metallation of a series of bisimidazolium salts with different lengths of the linkers between the azolium rings [159]. From the theoretical results, it is concluded that the metallation of the second imidazolium ring proceeds by C2 – H oxidative addition. The final formation of the bis-NHC–Ir(III)–H (short linker) or bis-



Scheme 44



Scheme 45



Scheme 46

NHC – Ir(I) (long linker), depends on whether the oxidative addition product yields the *trans* (short linker) or *cis* (long linker) products, since only the latter would be ready to undergo the reductive elimination of HCl (Scheme 45). The *trans* products are the thermodynamically favored complexes, but in the case of the ligands with long linker lengths, the *cis* complexes are kinetically favored, thus providing the bis-NHC – Ir(I) reductive elimination products [159].

The chelate effect also favors the oxidative addition of the C2 – H bonds of imidazolium salts because it provides stabilized complexes. The reaction of a pyridine-imidazolium salt with $[IrCl(cod)]_2$ yields the oxidative addition product, even in the absence of a base (Scheme 46) [160].

8 Other Methods

The sections above described the more frequently used methods for the preparation of NHC complexes from imidazolium salts. Several other methods

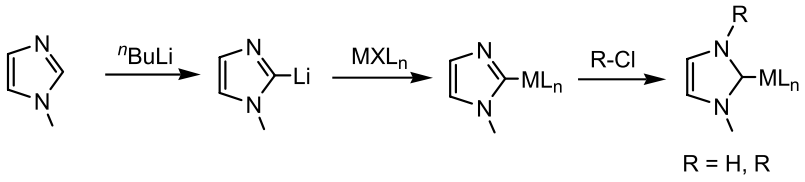
have also been described but they have been used in a more reduced number of examples.

The transmetallation of lithiated heterocycles has been described as a method to provide NHC complexes, and other Fischer-type carbene complexes [161]. The method proceeds via the alkylation of an alkylimidazole with BuLi to generate the lithiated azole, which can transmetallate to the metal complex. Further reaction with an acid or an alkylating agent would provide the desired NHC – M complex (Scheme 47).

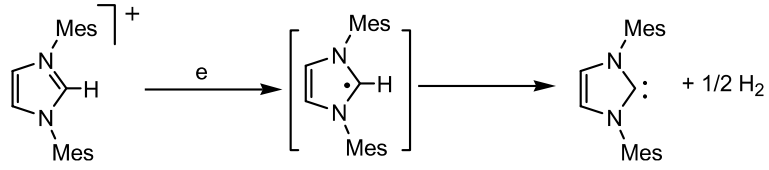
The method can be used for certain transition metal complexes containing halides or other labile ligands. For example, this method has been used for the preparation of a bis-NHC – Au(I) complex, starting from $AuCl(SMe_2)$, AuCN [162], AuCl(THT) [163], (THT = tetrahydrothiophene) [162], $AuCl(PPh_3)$ [162], and $[MCl(CO)_5]^-$ (M = Cr, W) [164].

The electrochemical reduction of an imidazolium cation has recently been described as a convenient method for the preparation of imidazol-2-ylidenes (Scheme 48) [165]. The reduction of the imidazolium cation can also be performed by using a strong reductant such as potassium [165]. The procedure has not been used in a preparation of NHC – M complexes, but a clear synthetic application can be envisaged.

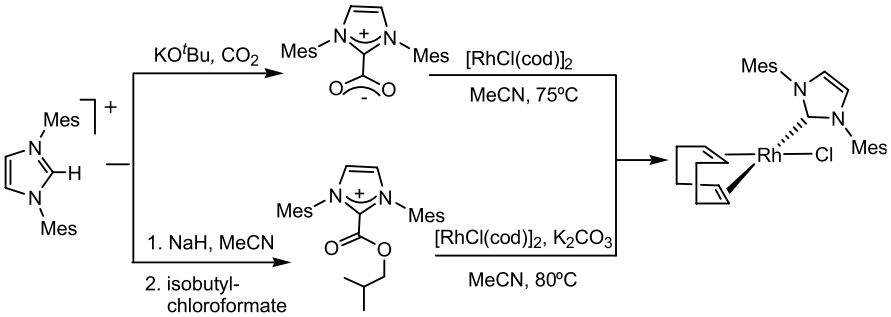
Crabtree and coworkers have recently proved that imidazolium-2-carboxylates can be used as efficient precursors to NHC – M complexes of Rh, Ir, Ru, and Pd, which are obtained under mild conditions, short reaction times, and very high yields [166]. The imidazolium-carboxilates can be obtained by reaction of an imidazolium salt with CO_2 in the presence of $KOBu^t$ (Scheme 49). Alternatively, an imidazolium esther (prepared from reaction of an imidazolium salt with NaH and isobutyl chloroformate) can be used in the NHC transfer reaction. This method provides some of the mildest reaction condi-



Scheme 47



Scheme 48



Scheme 49

tions reported in the literature for the preparation of NHC – M complexes, and may offer access to a new range of compounds [166].

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Chiral N-Heterocyclic Carbenes as Stereodirecting Ligands in Asymmetric Catalysis

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Abstract After the first attempts to use chiral NHC ligands in asymmetric catalysis in the late 1990s, which initially met with only limited success, several novel structural concepts have emerged since the beginning of this decade that have led, literally, to an explosion in the field. With a significant number of highly selective chiral catalysts based on chiral NHCs having been reported very recently, several general trends in the design of new NHC-containing molecular catalysts for stereo-selective transformations in organic synthesis have emerged. This development is the focus of this review.

Keywords N-heterocyclic carbenes · Enantioselective catalysis · Transition metal complexes

1 Introduction

Ligand design in asymmetric catalysis is guided by several simple concepts and principles. Since the detailed mechanisms of catalytic transformations are rarely fully established, the "search pathway" is frequently guided by considerations related to the molecular shape of the active catalyst.

For example, the development of chiral catalysts is frequently based on symmetry considerations in order to reduce the number of diastereomeric intermediates and transition states that play a role in the catalytic cycle [1]. This approach has been vindicated by the successful development of several large families of ("privileged") chiral ligands, which nowadays belong to the basic "tool kit" of asymmetric catalysis, such as chiral diphosphines, salen derivatives and bisoxazolines [2]. These privileged families of ligands possess characteristic properties that lead to the induction of high stereoselectivities in their catalytic reactions. The identification of the key structural elements, which induce high enantioselectivities, will thus lie at the root of a successful design of novel stereoselecting ligands based on NHC units [3].

NHC ligands have certain similarities to phosphines with regard to their electronic properties, which is why they are frequently regarded as their functional analogues. On the other hand, their stereochemical "topography" is distinctly different from that of diarylphosphine units they aim to replace. Whereas phosphines, possessing three substituents at the ligating atom, are generally more or less cone-shaped, the flat heterocyclic structure of the NHC-ligand may be more appropriately viewed as a structural "wedge" that has to be functionalized and thus molded into a chiral ligand system.

The introduction of chirality into NHCs will therefore follow different strategies than those that have proved to be successful in phosphine-based asymmetric catalysis. For example, N-heterocyclic carbene units will not create an "edge-to-face" arrangement of their aryl substituents, a structural feature common to many chiral diphosphines, such as the derivatives of Diop, Binap, Josiphos, Chiraphos and others. Results obtained in asymmetric catalysis, using chiral phosphine ligands, are therefore not directly transferable to the respective NHC-analogues.

The development chiral carbene ligands for asymmetric catalysis began in 1995 with the pioneering work of Enders and Herrmann. However, it was not until 2001 that the first truly efficient chiral catalyst containing an NHC unit was published by Burgess et al. Currently, the field of stereoselective catalysis based on N-heterocyclic carbenes is in the process of rapid expansion and a deeper understanding of the key factors for successful ligand design is only slowly emerging. A first overview of the field of chiral NHC ligands in catalysis by Burgess et al. covered the literature until the end of 2002 [4]. This was followed up by our review of the rapidly expanding field 2 years later [5]. Since then the field has again grown dramatically, with reports of many more successful applications of chiral NHCs in stereoselective catalytic transformations. As put forward previously, we define a number of distinct classes of such ligands that are characterized by the position of the chiral structural motif in relation to the donor unit. At present, five large families of chiral N-heterocyclic carbene ligands appear to dominate the ligand design in this field:

1. NHC ligands with N-substituents containing centers of chirality;
2. NHC ligands containing chiral elements within the N-heterocycle;
3. NHC ligands containing an element of axial chirality;
4. Carbenes containing an element of planar chirality;
5. Carbenes incorporating oxazoline units.

These five families of NHC derivatives will be highlighted separately in the following sections although there are frequent combinations between them that will be specifically addressed.

2 *N*HC Ligands with N-Substituents Containing Centers of Chirality

The strategy that was pursued at first in the design of chiral NHCs was based on the introduction of N-substituents containing a chiral center located on the C-atoms adjacent to the nitrogen atoms in 1 and 3 position within the ring. Their general formula and structure are as represented in Fig. 1:

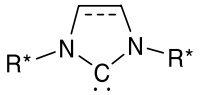
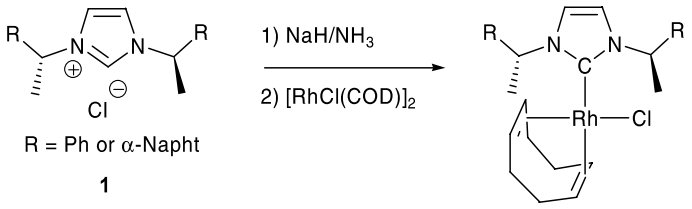


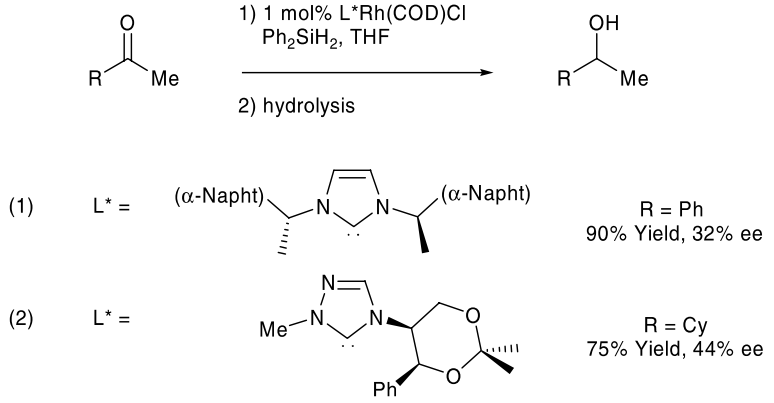
Fig. 1 Basic structural unit of *N*-heterocyclic carbene ligands bearing chiral *N*-substituents

The first chiral NHCs of this type were developed by Herrmann and Enders in 1996. Herrmann's group [6] synthesized a symmetric imidazolium salt **1** (as carbene precursor), starting from an enantiopure chiral amine which was readily converted to the heterocycle using a multi-component reaction previously developed by Arduengo [7]. After coordination to a rhodium(I) complex precursor (Scheme 1), this ligand was tested in the hydrosilylation of acetophenone.

The new catalysts displayed good activity but low stereoselectivity for this transformation (32% ee) (Scheme 2, Eq. 1).



Scheme 1 Synthesis of a rhodium(I) complex from chiral imidazolium **1**



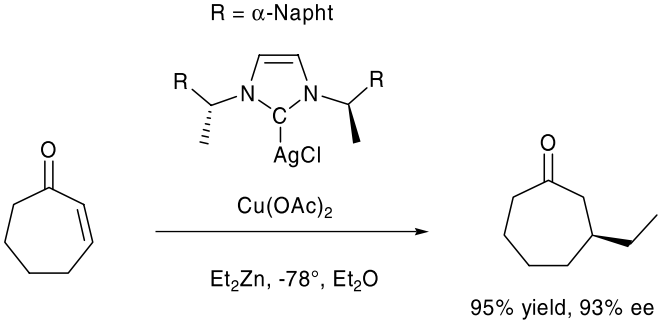
Scheme 2 Asymmetric hydrosilylation using the first chiral *N*HCs

Enders and coworkers developed a non-symmetrical triazolylidene ligand containing a single chiral N-substituent, its triazolium precursor being depicted in Scheme 2 (Eq. 2) [8]. The synthesis of the corresponding rhodium(I) complex led to the generation of a mixture of diastereomers. This is a consequence of the non-symmetrical carbene ligand that is disposed orthogonally to the square coordination plane of the rhodium complex. This mixture of complexes has also been tested in the hydrosilylation of methyl ketones giving low to moderate enantioselectivities (ee up to 44%) (Scheme 2, Eq. 2) [9].

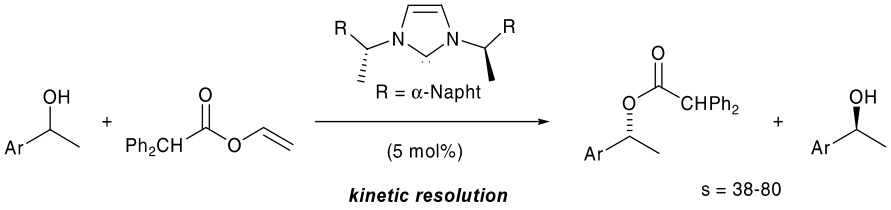
In general, the chiral induction of these ligands has remained low, which is probably due to the rapid internal rotation of the chiral substituents around the C – N axis and the flexibility of the substituents. This may leave the active chiral space at the metal center relatively ill-defined.

However, an encouraging result was obtained very recently for the 1,4-conjugate addition of dialkyl zinc to a variety of Michael acceptors catalyzed by copper. Alexakis, Roland and coworkers have investigated the addition of diethyl zinc to cycloheptenone and observed an enantiomeric excess of 93% (95% yield) in the presence of $Cu(OAc)_2$ and the silver carbene derivative of imidazolium **1** (Scheme 3) [10]. Silver carbene complexes are efficient transfer agents to copper(II) and therefore the potentially harmful use of a base to generate the catalytic species is avoided.

In a interesting example of organocatalysis, Suzuki et al. studied the enantioselective acylation of secondary alcohols using chiral NHCs [11, 12]. The approach was partly based on the work of Nolan and Hedrick who had independently reported NHC-catalyzed transesterifications [13, 14]. The enantioselective acylation was subsequently improved by using more sterically hindered acylating agents such as diphenylacetate derivatives (Scheme 4), leading to selectivity factors ($s = k_{rel}$) of up to 80 [15, 16].



Scheme 3 Enantioselective copper-catalyzed 1,4-conjugate addition



Scheme 4 Enantioselective acylation of secondary alcohols catalyzed by chiral *N*-heterocyclic carbenes

The triazolium salt **2** has also been used as a purely organic catalyst [17]. It is an active catalyst for asymmetric benzoin-type condensation reactions yielding the reaction products with enantiomeric excesses of 20–80%, which at the time marked a major advance with respect to the previously established catalysts (Scheme 5, Eq. 1) [18]. It was also found to catalyze the asymmetric intramolecular Stetter reaction with moderate to good enantioselectivities (41–74% ee) (Scheme 5, Eq. 2) [19].

These enantiomeric excesses were improved with a new type of triazolinylidene with a bicyclic molecular structure that was developed in Leeper's group (Fig. 3) [20]. The internal rotation around the N – C(substituent) axis is blocked in this bicyclic molecule with a sterically demanding substituent having the same orientation as the ligating atom, thus poten-

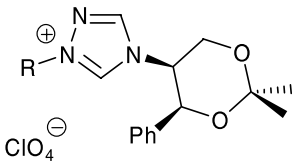


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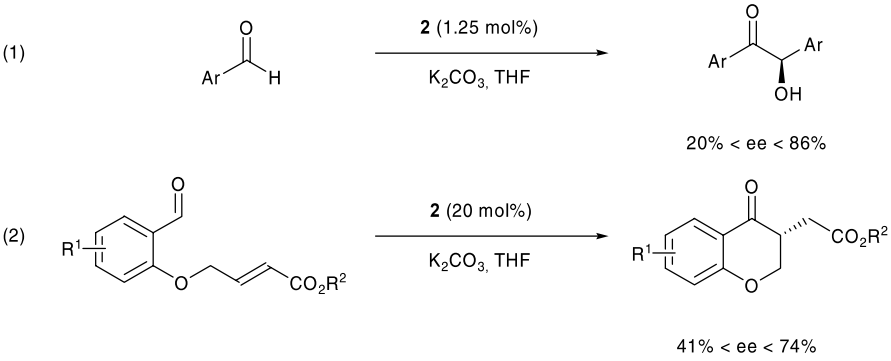
Fig. 2 The chiral triazolium perchlorate salt **2** synthesized in Enders' group



Scheme 5 Application of **2** in asymmetric organocatalysis

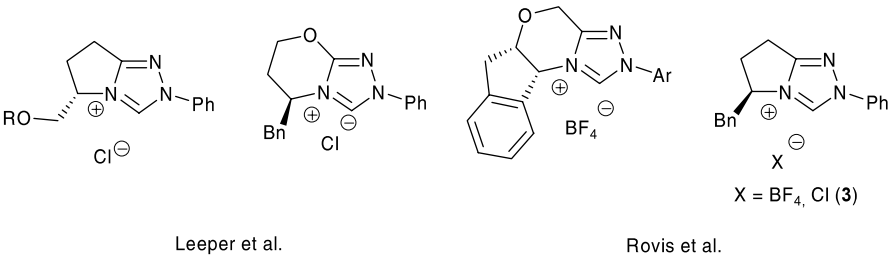
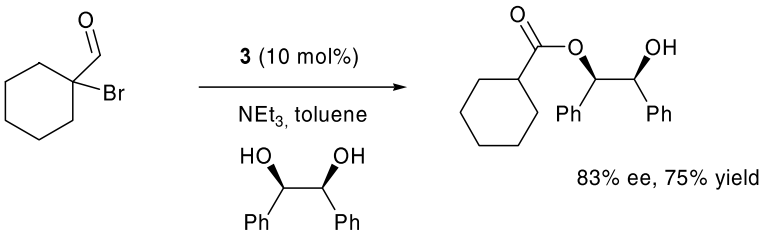


Fig. 3 Triazolium salts developed by Leeper and Rovis

tially favoring a high asymmetric induction. These carbenes were tested in the benzoin condensation reaction mentioned above (Scheme 5, Eq. 1) pushing the ee's of the products to values of up to 82%. Very recently, related ligand systems have been employed by Rovis et al. (Fig. 3) for the Stetter reaction, giving the coupling products in very high enantioselectivity [21, 22]. They subsequently demonstrated the efficiency of these catalysts in the formation of quaternary stereocenters [23, 24] and in a novel internal redox reaction, which gave good enantiodiscrimination in the desymmetrization of a *meso*-diol (Scheme 6) [25].

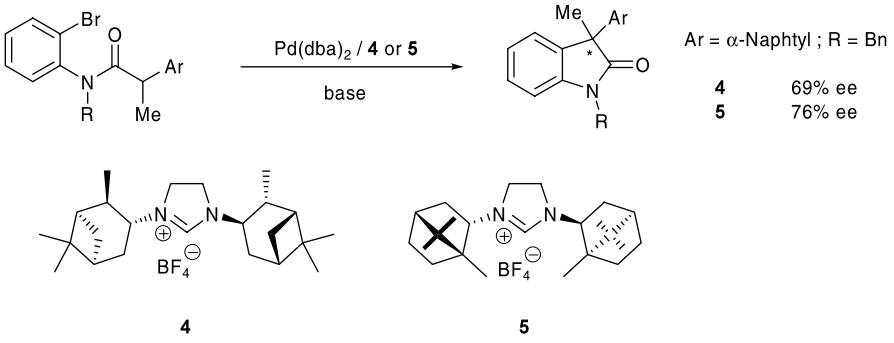


Scheme 6 Desymmetrization of a *meso*-diol

An important contribution to the design of NHC ligands with N-substituents containing centers of chirality was made by Hartwig's group in 2001. The imidazolinium salts **4** and **5** were synthesized from (–)-isopinocamphenylamine and (+)-bornylamine, respectively, and were tested as stereodirecting ligands in the palladium-catalyzed asymmetric oxindole reaction [26]. The key step in this reaction is an intramolecular α-arylation of a ketone catalyzed by palladium, which the same group have previously reported [27]. These ligands gave superior results to those obtained with the established chiral phosphines, such as Binap, Duphos, Phox and Josiphos, even though there remains potential for improvement of the stereoselectivity of this catalytic reaction (ee's of up to 76% were obtained with **4** and **5**) (Scheme 7).

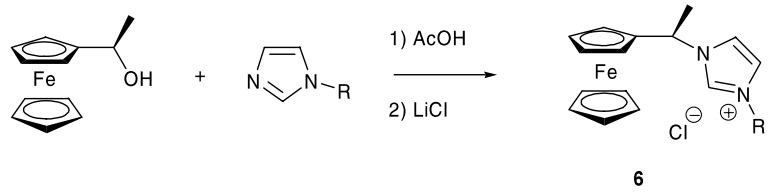
Chung et al. reported the enantioselective synthesis of chiral NHCs, such as **6**, using a chiral ferrocene derivative (Scheme 8) [28]. The nucleophilic substitution of the hydroxy function by an imidazole in an acidic medium gives the imidazolium salt with retention of the configuration at the chiral C-atom.

The type **6** carbenes have been used as ligands in the rhodium(I) and iridium(I)-catalyzed transfer hydrogenation of ketones displaying low to moderate stereoselectivities in the conversion of most substrates. Somewhat higher enantioselectivities were obtained with complex **8b** containing the chiral C_2-symmetric carbene derived from **7** (Scheme 9).



4 **5**

Scheme 7 Asymmetric catalytic oxindole synthesis



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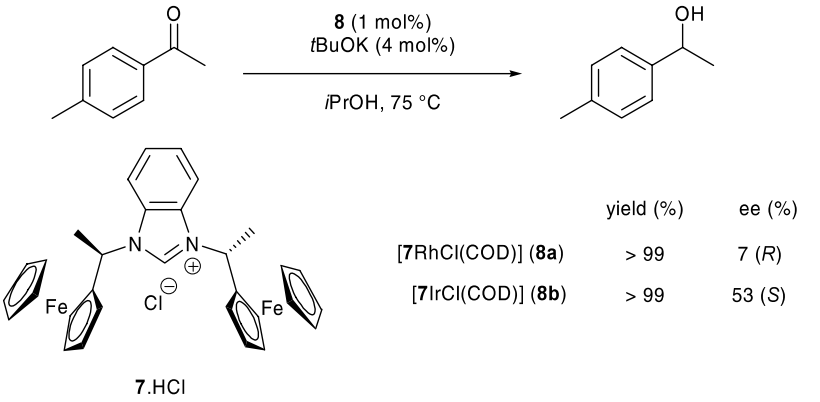
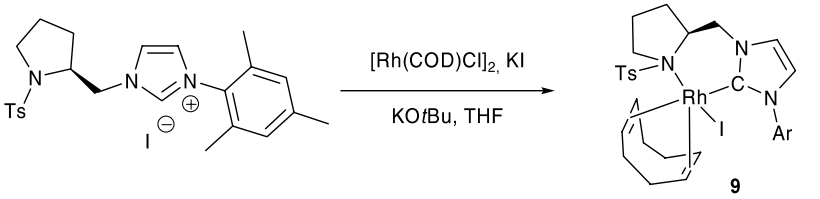
Scheme 8 Synthesis of carbene ligands with 1-(ferrocenyl)ethyl *N*-substituents



Scheme 9 Transfer hydrogenation of aryl(alkyl)ketones catalyzed by **7**

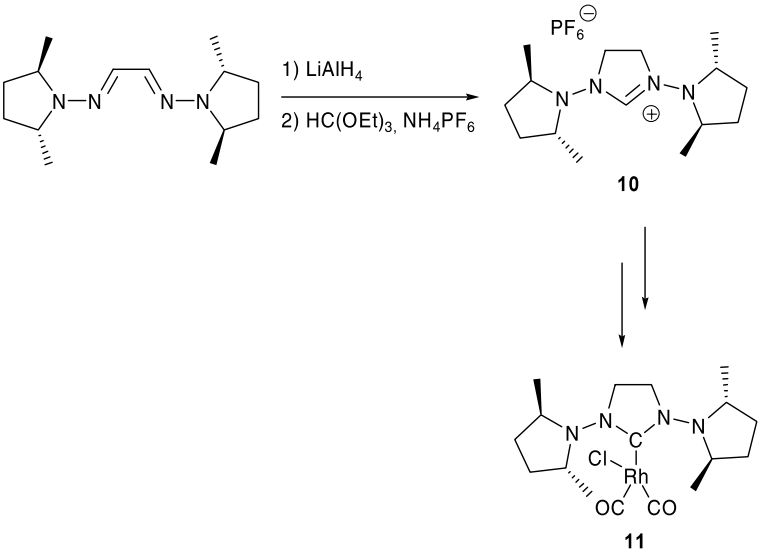


Scheme 10 Synthesis of rhodium carbene **9**

An N-heterocyclic carbene rhodium complex derived from L-proline has been reported (Scheme 10). The rhodium complex **9** is active catalyst for the addition reaction of arylboronic acids to aldehydes, albeit with low ee's (21% at best) [29].

An interesting family of chiral N-heterocyclic carbenes, 1,3-bis(*N*,*N*-dialkylamino)imidazolinylidenes, has been reported by Lassaletta et al. [30]. The synthesis of this family of ligands employs the bis-hydrazone derivative as a readily accessible starting material (Scheme 11). Reduction and subsequent condensation with $HC(OEt)_3$ afforded the imidazolinium salt precursor of the carbene. Treatment of **10** with $[Rh(COD)Cl]_2/KN(SiMe_3)_2$ gave a rhodium(I) complex which in turn was reacted with CO to give the isolable rhodium complex **11**. The values of the two CO stretching vibrations ν_{CO} could be used to gauge the donor ability of the ligand, and it appears that the donor capacity of this carbene is higher than for other imidazolinylidenes.

Among the NHC ligands with N-substituents containing centers of chirality, polydentate ligands that combine the NHC unit with an anionic functional group have been developed recently. They thus combine two complementary ligating "anchor" units, which avoids the rotation of the chiral substituents around the C – N axis. Arnold and coworkers reported the synthesis of the



Scheme 11 Synthesis of imidazolinylidene **10** and the rhodium complex **11**

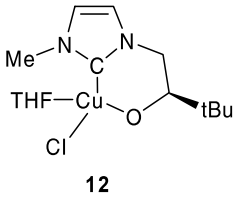
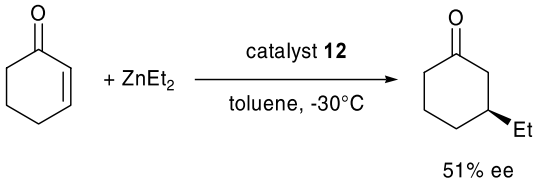


Fig. 4 A chiral alkoxycarbene copper complex



Scheme 12 Copper-catalyzed conjugate addition of diethylzinc to cyclohexanone

chiral copper complex **12** (Fig. 4) [31]. This alkoxy-functionalized NHC is readily synthesized from a chiral epoxide. The catalytic conjugate addition of diethyl zinc to cyclohexanone has been studied and a 51% enantiomeric excess was obtained with catalyst **12.**

Mauduit et al. reported the synthesis of the related, potentially bidentate carbene precursor **13** [32, 33]. The synthesis of the imidazolinium salt is straightforward and achieved by reaction of β-aminoalcohols and ethyl-

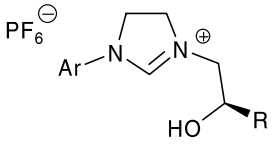


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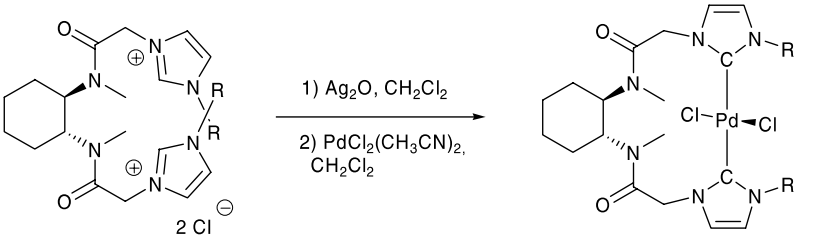
Fig. 5 Alkoxy-imidazolinium salt developed by Mauduit et al.

oxalylchloride giving the ligand precursors on a multigram scale. As for the system referred to above, the enantioselective copper-catalyzed conjugate alkylation of cyclic enones was investigated. Good enantioselectivities were obtained at room temperature (up to 90% ee with cyclohexanone as substrate). The crucial role of the hydroxy group in the ligand was demonstrated by carrying out the catalysis with the siloxy protected ligand, which gave lower enantioselectivities.

Enantiomerically pure *trans*-1,2-diaminocyclohexane has been used as a fundamental building block in the design of chiral ligands, the most prominent example being the chiral salen ligand in Jacobsen's epoxidation catalyst [34]. Such ligands based on chiral diamines have been widely employed in enantioselective catalytic transformations [35–37]. These results have inspired several research groups in their synthesis of NHCs containing a *trans*-cyclohexanediamine backbone.

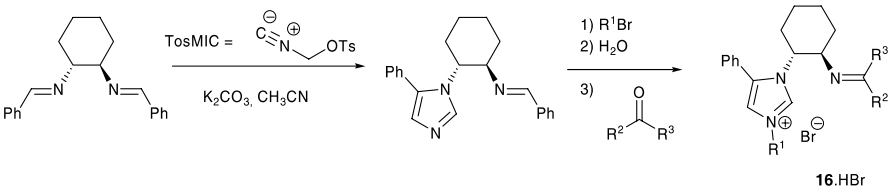
The first such ligand system (**14**) was developed in Burgess's group and was used in the synthesis of the palladium(II) complex **15**, in which the biscarbene acts as a trans-chelating ligand (Scheme 13) [38]. However, there are no reports of the use of **15** in Pd-catalyzed reactions.

Douthwaite et al. have published two types of chiral bidentate NHC ligands [39]. The first of these contains an imidazolylidene and an imine linked by a *trans*-cyclohexanediamine core according to the synthetic strategy outlined in Scheme 14. The facile modular variation of the peripheral substituents in this class of ligands principally allows for the rapid screening of large ligand libraries.

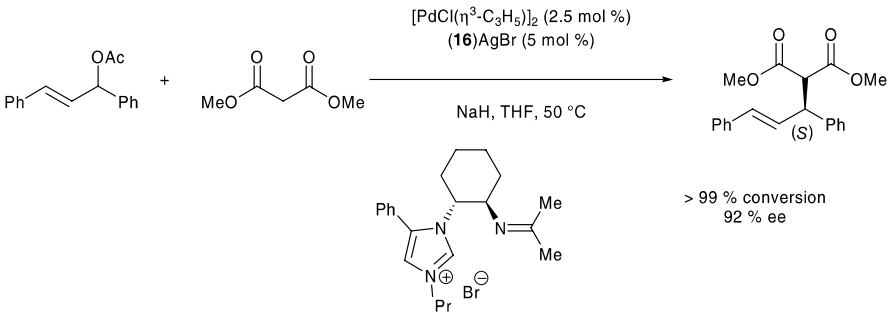


14 15

Scheme 13 Coordination of **14** to palladium(II)



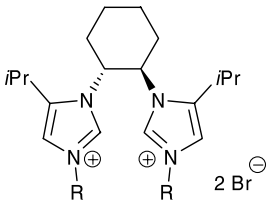
Scheme 14 Synthesis of Douthwaite's imidazolium-imine salts



Scheme 15 Allylic alkylation catalyzed by a palladium complex bearing the carbene-imine ligand **16**

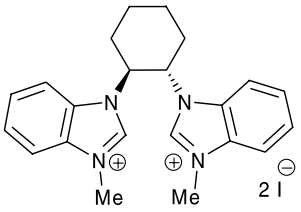
The carbene-imines derived from **16** have been tested in palladium catalyzed allylic alkylations, one example of these being depicted in Scheme 15. As previously observed, NHC ligands do not seem to give rise to very active allylic alkylation catalysts [40] and relatively high catalyst loadings (5 mol %) and elevated temperatures (50 °C) are required for this transformation. In general, the increase of the steric demand of the carbene unit in these ligands and its decrease in the imine moiety lead to the highest enantioselectivities, the best result being that with the ligand shown in Scheme 15.

The same group also synthesized the C_2-symmetric di-imidazolium salt **17**.$(HBr)_2$ shown in Fig. 6 [41]. Its palladium(II) complex [**17** $PdCl_2$] has been tested and only showed poor selectivity (11% ee) in the enantioselective



17.$(HBr)_2$

Fig. 6 A chiral bis(imidazolium) salt with a cyclohexane-1,2-diamine backbone



18

Fig. 7 A chiral bis(benzimidazolium) salt

α-arylation of amides previously described by Hartwig for the formation of oxindoles (Scheme 7).

Finally, Shi and Qian reported the synthesis of the racemic di-benzimidazolium **18** obtained in 4 steps from the (+/–) *trans*-cyclohexanediamine (Fig. 7) [42]. The reaction with $Pd(OAc)_2$ gave a dimeric bidentate NHC-Pd complex which was found to be moderately active in Suzuki and Heck reactions.

In conclusion, the NHC ligands possessing chiral N-substituents, which have been studied to date, may be efficient as stereodirecting ligands if the N-substituents are either sterically very demanding or locked in fixed conformations. Chiral induction is greater the closer the element of chirality is located with respect to the N-substituent. Whilst this type of chiral N-heterocyclic carbenes generally gives moderate results in asymmetric catalysis the introduction of a functional group in the chiral N-substituent (e.g. N or OH) may generate a potentially bidentate ligand that can be more effective in stereoselective catalytic transformations.

3
*N*HC Ligands Containing Chiral Elements within the N-Heterocycle

Imidazolinylidenes contain sp^3-carbon atoms in the 4- and 5-position of the heterocycle and thus provide the possibility of a second strategy for the generation of chiral NHCs. By an appropriate choice of substituent (R) at the 4- and 5-position two (homo)chiral centers may be obtained and the chiral information then transmitted to the active space at the metal center of a catalyst by means of the two N-substituents R′ (Fig. 8).

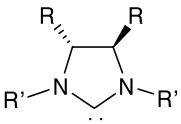


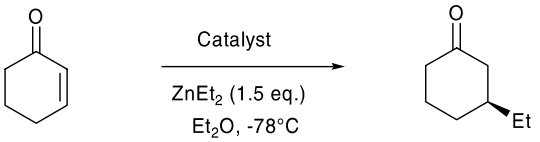
Fig. 8 Schematic representation of an imidazolinylidene ligand

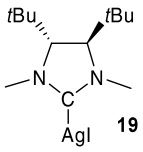
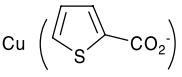
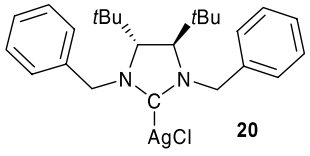
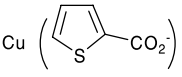
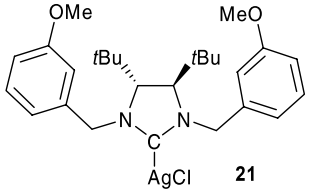
The imidazolinium salts, which are being used as ligand precursors, are generally prepared from C_2-symmetric chiral vicinal diamines [43, 44].

The coordination of NHC ligands greatly enhances the copper-catalyzed asymmetric addition of diethylzinc to cyclohexenone [45]. Employing imidazolinylidene ligands with chiral centers in the heterocycle, the alkylation of α-enones [46, 47] was systematically studied by the groups of Mangeney and Alexakis [10, 48–50]. A summary of the results obtained is presented in Table 1.

The generation and coordination of the imidazolinylidenes to the Cu^I centers was preferentially achieved by transmetallation using silver(I) carbene complexes as ligand transfer reagents [51]. This method has the advantage of involving reagents that are air and moisture stable and thus lend themselves to catalyst screening.

Table 1 1,4-addition of diethylzinc to cyclohexanone catalyzed by imidazolinylidene-copper complexes



Entry	Copper source	Ligand transfer reagent	Ee (%)
1	$Cu(OTf)_2$	 **19**	30
2		 **20**	58
3		 **21**	69

Whereas two methyl N-substituents are inefficient in transmitting the chiral information encoded at the rear side of the heterocyclic ligand (Entry 1 in Table 1), the stereoselectivity is improved by the introduction of N-benzyl substituents (Entry 2). The steric repulsion between the *tert*-butyl and benzyl groups leads to a C_2 symmetric arrangement of the latter with respect to the carbene donor function as is apparent in the molecular structure determined by X-ray diffraction for the silver(I) complex **20** [51]. In this way the chirality in the heterocycle is transmitted towards the reaction center. Introduction of methoxy groups in the meta-position of the phenyl rings of the benzyl substituents slightly increases the selectivity of the catalyst (Entry 3).

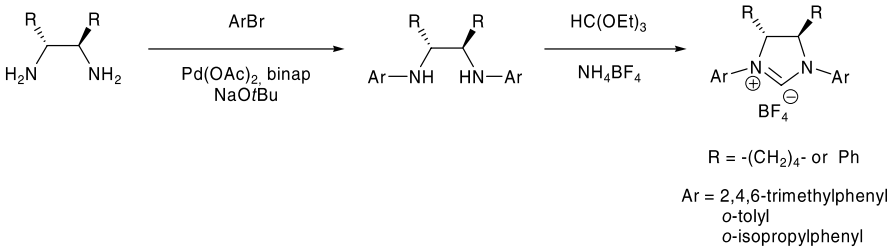
Chiral imidazolinylidenes with N-aryl substituents have been employed by Grubbs and coworkers in the stereoselective ring closing metathesis of olefins [52]. The introduction of the aryl groups as N-substituents was achieved by a palladium catalyzed Buchwald–Hartwig coupling (Scheme 16) [53].

Olefin metathesis does not generate stereogenic centers, however, the reaction may be employed in the desymmetrization of prochiral (poly)olefins of the kinetic resolution of racemates. In the example depicted in Scheme 17, a trialkene is desymmetrized, and the preference for the cyclization reaction with one of the two symmetry-equivalent C = C double bonds leads to the enantioselective formation of the reaction product, a chiral dihydrofuran.

The following principal conclusions can be drawn from this study:

1. The stereodirecting ligands containing the 1,2-diphenylethylenediamine backbone gives higher enantioselectivities than the ones with the 1,2-diaminocyclohexane skeleton.
2. *Ortho*-monosubstituted N-aryl substituents in the carbene ligands lead to greater selectivity than, for instance, the more symmetrical mesityl-substituted derivative.

The rationale offered for these observations is based on the hypothesis that steric repulsion between the backbone phenyl groups and the *ortho*-aryl substituents stabilizes their mutual anti-conformation, which in turn permits



Scheme 16 Synthesis of *N*-arylated chiral imidazolinium salts

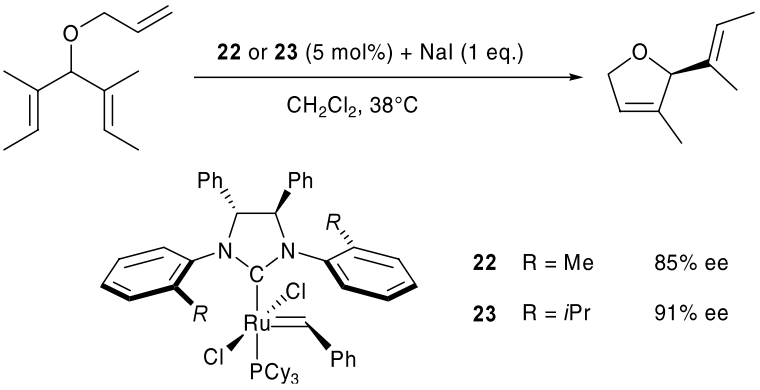
a more efficient transmission of the chiral information to the active site of the catalyst.

The application of complexes **22** and **23** in the desymmetrization of triolefins has yielded the ring closing metathesis products in high enantioselectivity, and upon replacement of the *ortho*-methyl groups by the bulkier isopropyl substituents in **23** the selectivity was even further increased (Scheme 17). The origin of enantioselectivity of the reaction has been investigated in a detailed theoretical study [54].

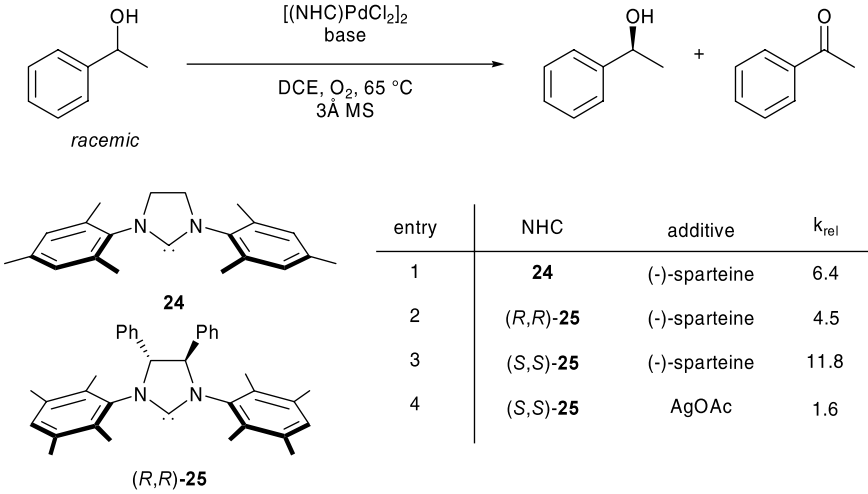
Chiral N-arylated imidazolinylidene ligands have been employed in the palladium(II) catalyzed aerobic oxidation of secondary alcohols to the corresponding ketones [55]. The chiral variant of this reaction, which does not generate a new element of chirality, is again based on the kinetic resolution of racemic mixtures. The active catalyst is formed in situ by a combination of two precursors, a dinuclear NHC-palladium(II) complex and an achiral (acetate) or chiral base ((–)-sparteine) (Scheme 18).

It has previously been shown that the (–)-sparteine may play a dual role in this catalytic process, that of a chiral ligand and a chiral base [56]. However, in the presence of the NHC ligand the ligated (–)-sparteine is substituted and thus only acts as chiral base. Comparison of the results obtained with ligand **25** with those observed with **24** suggest that the association of the two enantiomers with the chiral base leads to a synergic chiral induction for the (*S*,*S*) enantiomer (Scheme 18, Entry 3) whereas the combination with the (*R*,*R*) enantiomer is unfavorable (Entry 2). This nicely illustrates the concept of match and mismatch for stereodirecting elements in chiral catalysts [28]. The fact that a non-chiral base such as acetate gives rise to a very low selectivity factor in the kinetic resolution indicates the importance of the chiral base (–)-sparteine for the efficiency of the catalytic transformation.

A novel chiral bidentate imidazolinylidene ligand (**26**) has recently been developed in Helmchen's group [57]. It is related to Grubbs' imidazolinyli-



Scheme 17 Desymmetrization of trialkenes by asymmetric ring-closing metathesis



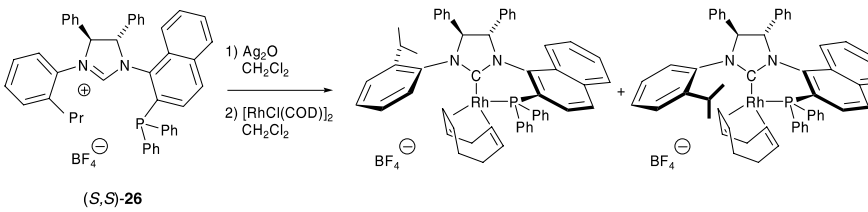
entry	NHC	additive	k_{rel}
1	**24**	(-)-sparteine	6.4
2	(*R*,*R*)-**25**	(-)-sparteine	4.5
3	(*S*,*S*)-**25**	(-)-sparteine	11.8
4	(*S*,*S*)-**25**	AgOAc	1.6

Scheme 18 Kinetic resolution of secondary alcohols by aerobic oxidation

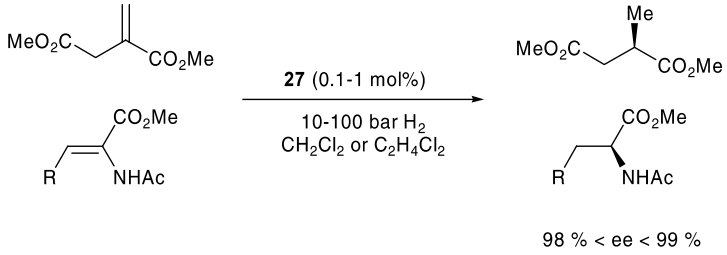
denes by replacement of one of the two N-aryl groups by a 2-diphenylphosphinonaphth-1-yl unit (Scheme 19). Complexation to rhodium(I) was achieved by transmetallation with the silver(I) complex [58] and yields two diastereomeric atropisomers (**27**) with respect to the *i*Pr – C_6H_4 – N bond in a ratio of 1 : 2.

This mixture of diastereomers of **27** was tested in the catalytic hydrogenation of dimethylitaconate and methyl Z-acetamidoacrylate (Scheme 18). The catalytic activity of these complexes is relatively high although lower than that of some of the previously studied purely phosphine based systems, while the enantioselectivity proved to be excellent (ee's between 98 and 99% under optimized conditions).

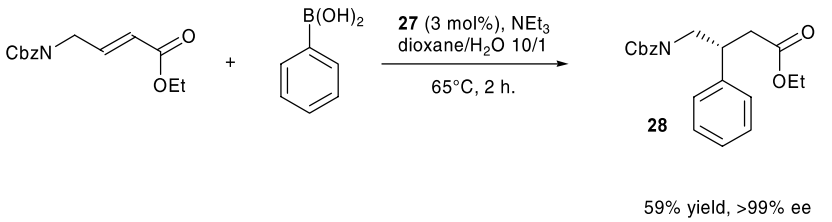
Rhodium complex **27** has also been successfully applied in the enantioselective conjugate addition of arylboronic acids [59]. In the synthesis of the 4-amino-3-aryl-butyric acid derivative **28**, Helmchen et al. found that the addition product was obtained in > 99% ee (59% yield) within 2 h at 65 °C, whereas previous attempts with (S)-BINAP and [Rh(acac)$(C_2H_4)_2$]



Scheme 19 Formation of diastereomeric complexes **27**



Scheme 20 Asymmetric hydrogenation with the mixture of diastereomers of **27**

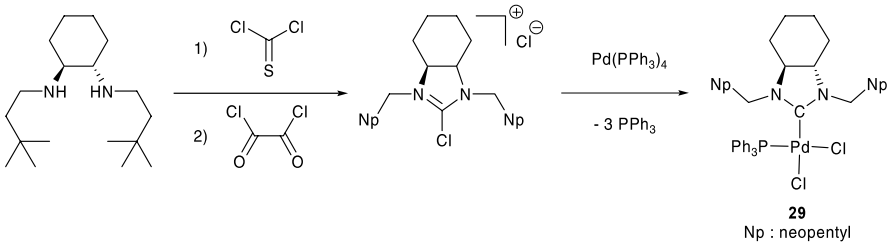


Scheme 21 Enantioselective conjugate addition of arylboronic acid with catalyst **27**

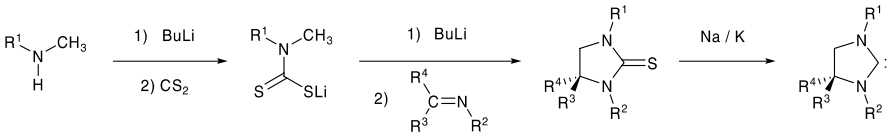
as the catalytic system gave 86% ee after 24–48 h reaction time at 100 °C (Scheme 21).

Finally, Fürstner et al. published the synthesis of the enantiopure chiral palladium(II) complex **29**, in which the NHC, contains a *trans*-1,2-cyclohexanediamine backbone (Scheme 22), although no application of this system in catalysis has been reported to date [60, 61]. The N-heterocyclic carbene palladium complex is obtained by oxidative addition of $Pd(PPh_3)_4$ to 2-chloro-1,3-disubstituted imidazolium salts that are easily accessible.

In conclusion, while the first chiral imidazolinylidenes tested in asymmetric catalysis only gave a moderate chiral induction, more recent results have clearly indicated that the encoding of chiral information in the backbone of the heterocycle may give rise to highly efficient stereodirecting ligands. The potential versatility of this approach is apparent in a recent contribution



Scheme 22 Synthesis of complex **29** by oxidative addition



Scheme 23 Synthesis of non-symmetrical imidazolinylidenes reported by Hahn et al.

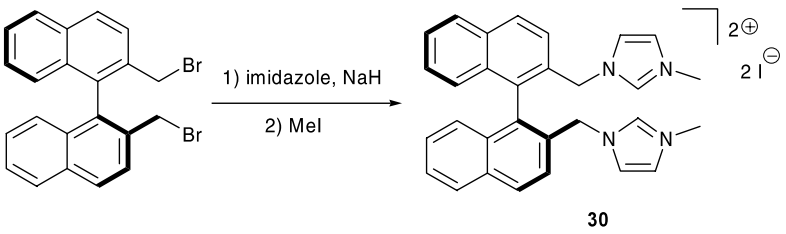
reporting the synthesis of nonsymmetrical imidazolinylidenes by the reaction sequence displayed in Scheme 23 [62]. While the products have only been isolated as racemic mixtures, this concept may lead to novel chiral NHC ligands.

We also note that another possibility of introducing chirality within the heterocycle is the use of a seven-membered N-heterocyclic carbene. Most of the structures with four, five or six-membered rings possess a nearly planar heterocycle with the exception of seven-membered ring NHCs [63].

4
*N*HC Ligands Containing an Element of Axial Chirality

The 1,1′-binaphthyl unit is one of the most widely used structural motifs in ligand design for asymmetric catalysis. First introduced by Noyori, enantiomerically pure ligands derived from it give rise to some of the most selective catalysts developed to date [64]. The most widely used examples of this family of ligands are BINAP [65, 66] and BINOL [67]. Their chirality is based on the blocked rotation around the C – C axis linking the two naphthyl units giving configurationally stable atropoisomers [68].

In 2000, Rajanbabu et al. published the synthesis and coordination chemistry of the first chiral NHC containing a 1,1′-binaphthyl unit as the chiral element (Scheme 24) [69]. It contains two imidazolium rings linked to the 1,1′-binaphthyl backbone in the 2 and 2′ position through methylene bridges. This linkage was achieved by nucleophilic substitution and the imidazolium salts subsequently generated in an N-quaternization step with methyl iodide.



30

Scheme 24 Synthesis of the bis(imidazolium) salt **30**

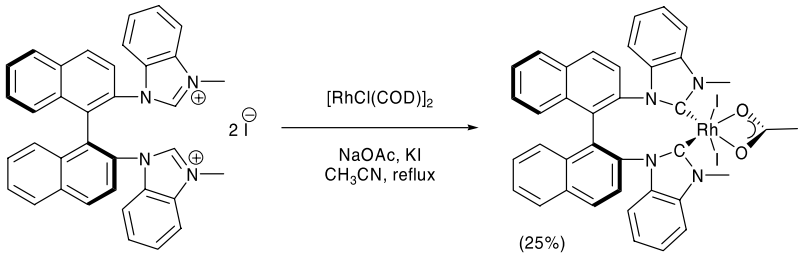
The coordination chemistry of this ligand depends on the metal involved and the method of the in situ carbene formation. Whereas **30** is exclusively *trans*-coordinating with nickel, regardless of the manner in which the carbene is generated, the same configuration is observed for the corresponding palladium(II) system, provided that the free bis-carbene has been generated prior to the complexation. Direct metallation of the imidazolium salt by stirring it with a palladium salt in dmso at reflux results in the formation of a *cis*/*trans* mixture of complexes. The formation of *cis*-*trans* mixtures of the palladium complexes of **30** is due to the flexibility of the ligand and the 11-membered metallacycles. It is thus not surprising that there are no reports of stereoselective catalysis employing this ligand.

A related bis-carbene ligand **31** (Scheme 25) with greater structural rigidity has been recently reported by the group of Min Shi [70]. In that ligand system the N-heterocycles are directly linked to the 1,1′-binaphthyl backbone in a four-step synthesis starting with enantiomerically pure BINAM. Complexation to rhodium was achieved according to a procedure developed by Crabtree and Peris, directly generating the hexacoordinate rhodium(III) complex in modest yield [71]. The binaphthyl backbone imposes C_2 symmetry upon the bis-carbene ligand and a mutual *anti* orientation of the N-methyl substituents with respect to the plane into which chelate ring is inscribed [72].

Complex **32** has been employed in the asymmetric hydrosilylation of ketones, displaying good activity and excellent enantioselectivities (92% < ee < 98%) for aryl–alkyl ketones, while the selectivity observed in the transformation of the more demanding dialkyl ketones is somewhat lower (67% < ee < 96%).

This is the first example of a chiral *bis*-carbene ligand acting as an efficient stereodirecting element in an enantioselective catalytic transformation and is encouraging for future developments in the field. The only disadvantage is the divergent synthetic strategy for the ligand, making its systematic variation cumbersome.

In 2002, Hoveyda et al. reported the synthesis of a novel chiral anionic bidentate carbene ligand combining an NHC unit with a phenolato donor and its use in asymmetric olefin metathesis [73]. The five-step synthesis of the

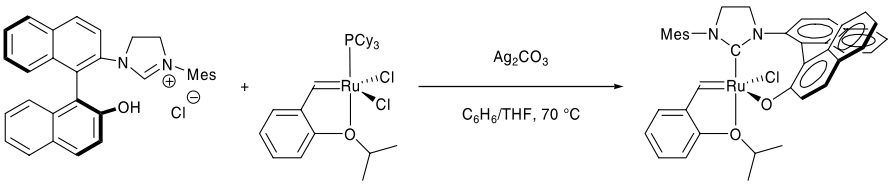


Scheme 25 Synthesis of the rhodium(III) complex **32**

imidazolinium salt **33** requires (*S*)-2-amino-2′-hydroxy-1,1′-binaphthalene (NOBIN) and mesitylamine as starting materials. Its complexation to ruthenium(II) was achieved by reaction of Hoveyda's metathesis catalyst with the in situ generated silver(I) carbene complex derived from **33.** In this synthesis the silver carbonate acts as a base both for the imidazolinium ring and the phenol-OH function (Scheme 26) and plays the role of carbene ligand transfer reagent already mentioned above for various other cases.

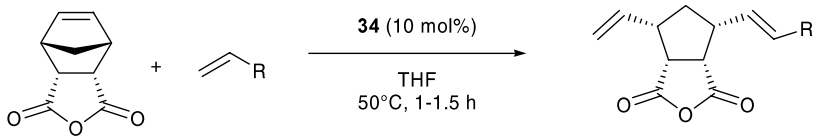
Compound **34** was tested both in ring-closing reactions and ring-opening cross-metatheses. While no stereoselectivity was reported for the ring closures, the asymmetric ring opening cross-metathesis (AROM/CM) gave interesting results. As displayed in Scheme 27, the latter involves the reaction of a strained bicyclic norbornene-related substrate with a terminal alkene.

The newly formed C = C bonds have almost exclusively *trans*-configuration (> 98/2), and the excellent enantioselectivity, with which the reaction product is obtained (ee up to 98%), illustrates the considerable potential of complex **34** in asymmetric catalysis. Furthermore, this compound is air stable, may be purified by chromatography on silica, does not require dried solvents and may be reused after catalysis without significant loss in enantioselectivity. Since **34** was found to be slightly less active in olefin metathesis



33 **34**

Scheme 26 Synthesis of the olefin metathesis catalyst **34**



E isomer

R	E/Z	ee (%)
Ph	> 98/2	80
nC_5H_{11}	> 98/2	>98
Cy	> 98/2	> 98

Scheme 27 AROM/CM reaction catalyzed by **34**

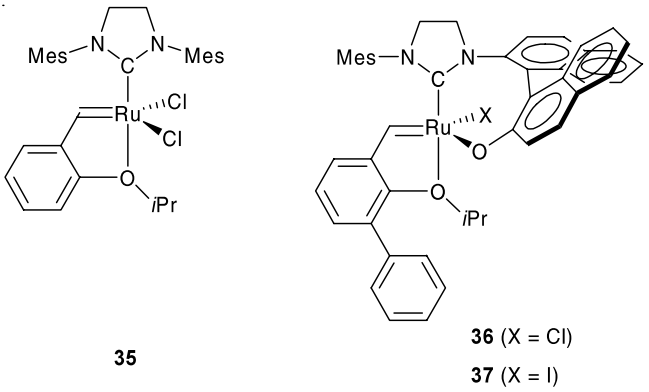
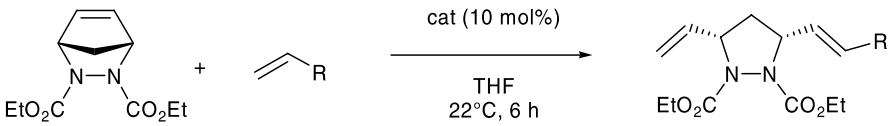


Fig. 9 Hoveyda type olefin metathesis catalysts

than the previously studied "second generation" Hoveyda catalysts, such as **35** (Fig. 9) [74], several modifications of **34** have been tested [75]. Among these, **36** displayed in Figure 9 is 130 times more active than **34** for the reaction shown in Scheme 27 (relatives rates were calculated from the time for the reaction to reach full conversion).

The introduction of a phenyl substituent in the *ortho* position of the aryl-ether unit in **36** supports the formation of the catalytically active four-coordinate species derived from **34** leading to the increase in activity by two orders of magnitude, an effect which has previously been observed for derivatives of the achiral catalyst [76, 77].

The enhanced AROM/CM activity of catalyst **36** in comparison to **34** has greatly increased the scope of this reaction as illustrated by the transformation shown in Scheme 28 for which **34** only gave low conversion. In



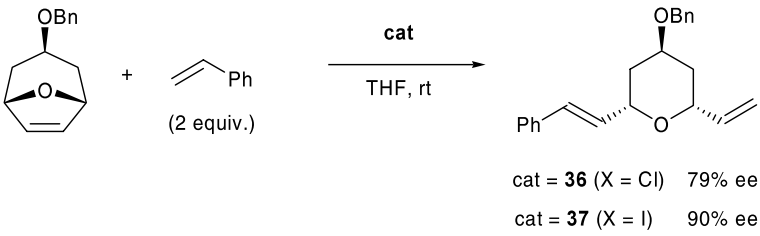
cat = **34**	cat = **36**	
< 10 % conversion	R = Ph	92 % ee, 65 %
	R = *n*-C_6H_{13}	68 % ee, 55 %
	R = Cy	87 % ee, 53 %

Scheme 28 Ru-catalyzed AROM/CM of an *N*-heterobicyclic alkene

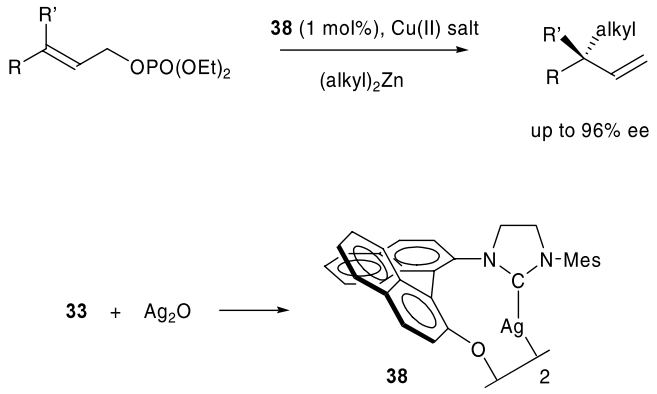
contrast **36** gave the reaction products in good yield and high enantioselectivity. The *N*-*N*-unit in the enantiomerically enriched reaction product in principle allows a multitude of subsequent functionalization steps.

Catalyst **36** was also used for the enantioselective synthesis of functionalized tetrahydropyrans, important building blocks in several biologically active molecules (Scheme 29) [78]. The enantioselectivity of such a reaction was significantly improved by using a ruthenium *iodide* complex **37**. This halogen effect has been previously observed in the ring-closing metathesis (*vide supra*) [52].

This family of chiral anionic bidentate carbene ligands, which combine an NHC unit with a phenolato donor, may also be successfully applied in the copper-catalyzed enantioselective formation of tertiary or quaternary carbon centers. The enantioselective Cu-catalyzed allylic alkylation of phosphate derivatives with alkylzinc reagents was investigated and precursor **33** was found to give the best results among the various bidentate carbenes which were studied from that family of ligands [79]. The efficiency and selectivity was enhanced by preparing the silver(I) complex of **33**. Complex **38** is air stable and is the more effective ligand transfer reagent than the parent imidazolinium salt **33** (Scheme 30).



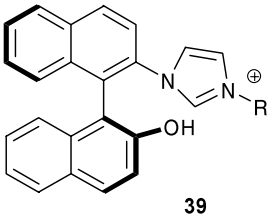
Scheme 29 Ru-catalyzed AROM/CM of an oxabicyclic olefin



Scheme 30 Application of **33** in the Cu-catalyzed enantioselective allylic alkylation

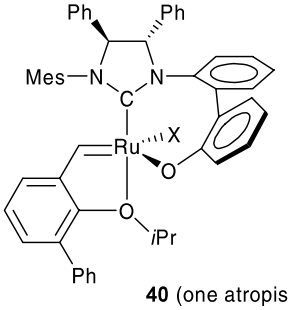
Crabtree and Chianese have extended the scope of Hoveyda's ligand by making the imidazolium salt **39** in two steps from 1,1′-diamino-2,2′-binaphthyl (Fig. 10) [80]. They prepared neutral rhodium and iridium complexes with that ligand precursor and applied these complexes in the asymmetric hydrosilylation of acetophenone. Moderate enantioselectivities were obtained with the iridium derivative (up to 60% ee) whilst the rhodium catalysts only gave low enantioselectivities.

In their search for ligand precursors related to imidazolinium salt **33**, which may be prepared with less synthetic effort, Hoveyda and collaborators designed a new family of chiral bidentate NHCs [81]. Instead of using an optically pure binaphthyl amino alcohol, an achiral biphenyl derivative was used. The chirality was then induced by the stereogenic centers of the diamine backbone favoring only one atropisomer upon the coordination of the ligand to the respective metal center (silver, copper or ruthenium **40**) (Fig. 11) [82]. Both Ru-catalyzed asymmetric olefin metathesis and Cu-catalyzed allylic alkylation were carried out with high yields and optical purity, using catalyst systems that were generated in situ by reaction of the respective metal salts with the silver complex of **40** as ligand transfer reagent.



39

Fig. 10 A chiral imidazolium-binaphthol studied by Crabtree and Chianese



40 (one atropisomer)

Fig. 11 An example of a new generation of chiral Ru-based olefin metathesis catalysts

5
Carbenes Containing an Element of Planar Chirality

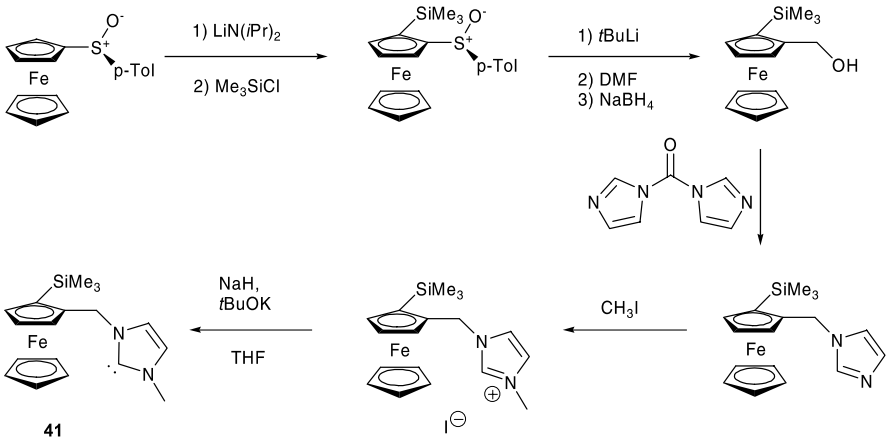
Ligands containing an element of planar chirality, in particular ferrocene derivatives, have proved to be excellent stereodirecting ligands in asymmetric catalysis [83]. Typical examples of this family of ligands are Togni's JOSIPHOS, which is being used industrially [84], as well as the chiral derivatives of DMAP (4-dimethylaminopyridine) developed by Fu's group which have been successfully used both in organocatalysis and transition metal catalysis [85, 86].

Bolm et al. reported the first planar chiral NHC at the beginning of 2002 [87]. The synthetic strategy is based on an oriented *ortho*-metallation starting from a chiral sulfoxide, followed by the conversion of the sulfoxy group to a hydroxymethyl unit. The imidazole ring is then linked to this intermediate with the aid of *N*,*N*-carbonyl diimidazole and subsequently quarternized with methyl iodide to give the imidazolium ligand precursor of the carbene **41** (Scheme 31).

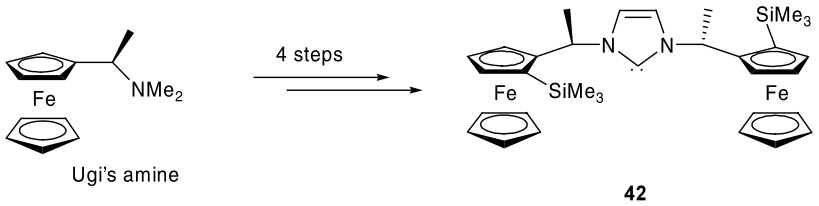
First tests of the ligand in the hydrosilylation of ketones catalyzed by [(**41**)RhI(COD)] only yielded racemic mixtures of the secondary alcohols, and no further application in asymmetric catalysis of **41** has been reported to date.

Following this first publication by Bolm's group, Togni et al. reported the synthesis of the C_2-symmetric chiral carbene ligand **42** using Ugi's chiral 1-ferrocenylethylamine as starting material (Scheme 32) [88].

The chiral carbene **42** contains two types of chiral elements, planar chirality in the ferrocenyl units and chiral centers at the carbon atoms linking the ferrocene with the N-heterocycles. This combination is frequently found



Scheme 31 Synthesis of the planar-chiral *N*HC **41**



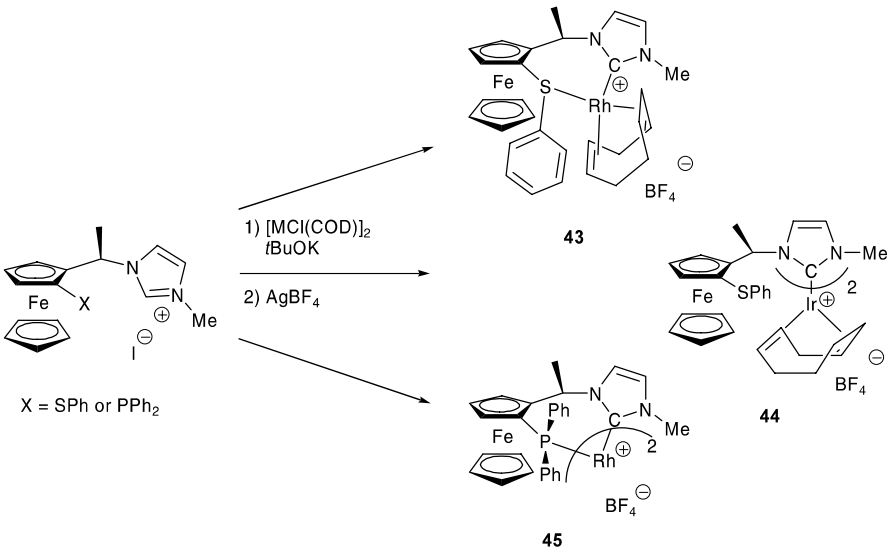
Scheme 32 Chiral imidazolylidene synthesized by Togni et al.

in ferrocene-derived chiral ligands, however, its interplay determining the selectivity of a stereoselective transformation seems to depend crucially on the type of the reaction and no general conclusions seem to be possible at this stage. So far there are no reports of the use of **42** in asymmetric catalysis.

Ugi's ferrocenylamine has also been used in the synthesis of chiral bidentate NHC heterodonor ligands in which the second ligating unit is either a diphenylphosphino or phenylsulfid group [89]. Several rhodium(I) and iridium(I) complexes have been prepared which are depicted in Scheme 33.

Complexes **44** and **45**, which contain two NHC ligands coordinated to the metal center were found to be inactive in the attempted asymmetric hydrogenation of dimethylitaconate, while **43** catalyzed the reaction with low enantioselectivity (44%, 18% ee).

Very recently, Togni reported a chiral C_2-symmetric tridentate PCP ligand (**47**) [90] related to the previously developed triphosphine Pigiphos (**46**)



Scheme 33 Coordination chemistry of chiral ferrocenyl phosphine/sulfide-imidazolium salts

(Fig. 12) [91]. This phosphine-carbene ligand has been used in the nickel catalyzed hydroamination of acrylonitrile derivatives [92].

The coordination of **47** to palladium(II) is achieved by direct metallation of the imidazolium salt with $Pd(OAc)_2$ giving the cationic square planar complex **48** (Scheme 34). The coordination to ruthenium(II) gave the cationic complex **49** in which the PCP-ligand **47** is meridionally coordinated and both of the chloro ligands in the Ru-precursor have been displaced. The reaction of **47** with a copper(I) source gave a dinuclear complex **50** with an unusual binding mode of the NHC ligand which bridges the two copper centers [93].

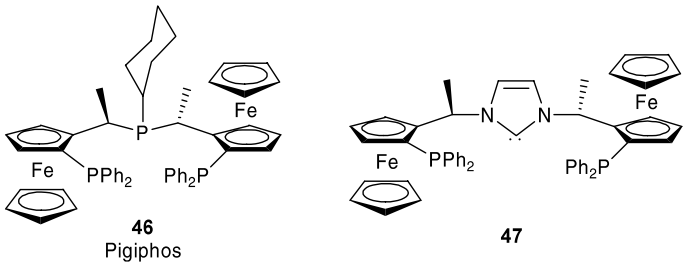
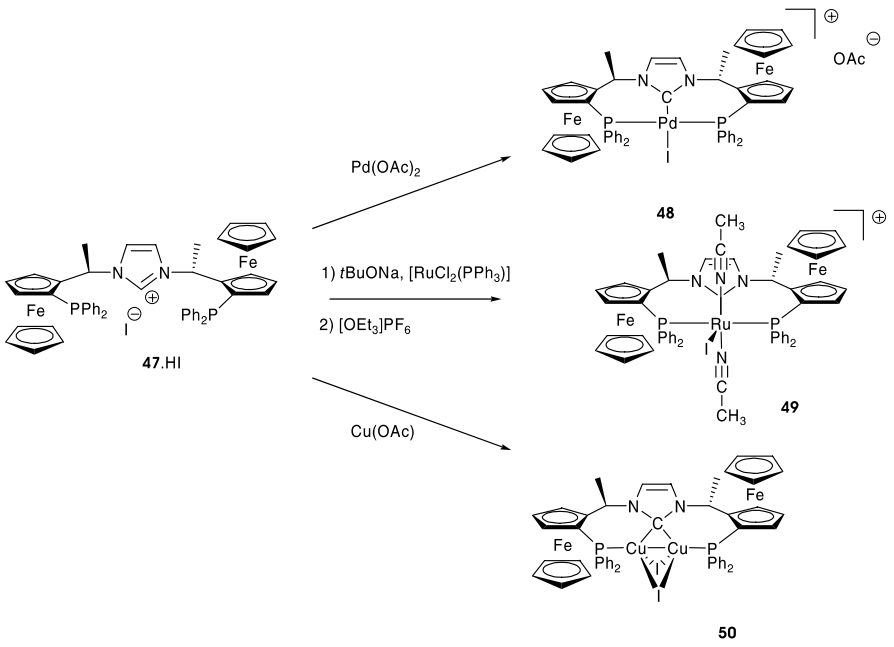


Fig. 12 Togni's chiral bis(ferrocenylphosphino)carbene



Scheme 34 Coordination chemistry of the tridentate PCP ligand derived from the imidazolium salt **47**

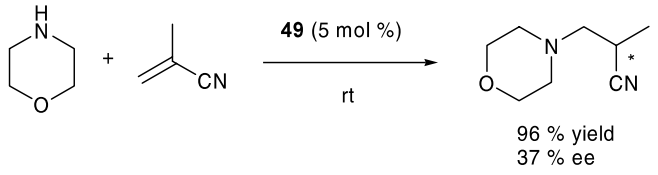
Complex **49** catalyzes, among other reactions, the addition of morpholine to methylacrylonitrile giving the amination product with modest selectivity (37% ee) (Scheme 35). In order to obtain catalytically active species with palladium, complex **48** was converted into dicationic derivatives of the general type $[Pd(NCCH_3)(PCP)](PF_6)_2$. Using this catalyst, the addition of morpholine to methylacrylonitrile could be achieved with 47% ee. Further improvement in selectivity was obtained by the introduction of methyl substituents at the 3- and 5-positions of the phenyl groups in diphenylphosphanyl derivative leading to ee's of over 70% [94].

The chiral amine **51** has been used to develop the synthesis of imidazolium **52** which was attached to palladium(II) (Scheme 36). Preliminarily studies in the asymmetric amide cyclization (Scheme 7) showed a good catalytic activity (70% yield) albeit with with low ee (9%) for that particular reaction [95].

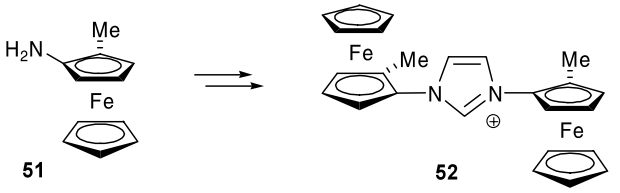
The synthesis and application in catalysis of a novel monodentate NHC ligand, in which the N-substituents are chiral paracyclophanes was reported at the end of 2003 [96]. A Pd-catalyzed Suzuki–Miyaura reaction allows the facile coupling of S_p-pseudo-*ortho*-bromoamino[2,2]paracyclophane **53** depicted in Scheme 37 with aryl or cyclohexyl groups [97], and a subsequent one-pot procedure gives the corresponding imidazolinium dicyclophanes **54a–d.**

These monodentate ligands, containing very bulky chiral N-substituents, have been applied in the asymmetric rhodium(I)-catalyzed conjugate addition of arylboronic acids to α-enones (Scheme 38) originally developed by Miyaura, Hayashi and coworkers [98].

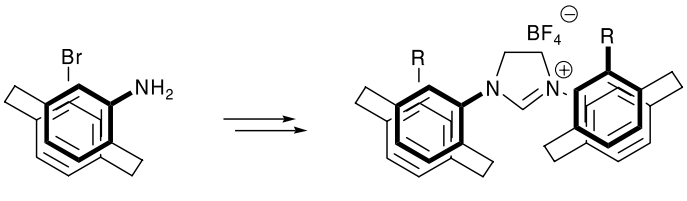
Using the chiral imidazolinylidenes derived from **54** this reaction could be carried out at lower temperatures than those required with the previously employed catalyst $[Rh(acac)(C_2H_4)_2]$/BINAP (100 °C). This increase in activ-



Scheme 35 Hydroamination of methacrylonitrile catalyzed by **49**



Scheme 36 Design of a chiral bis(ferrocenyl)imidazolium salt



53

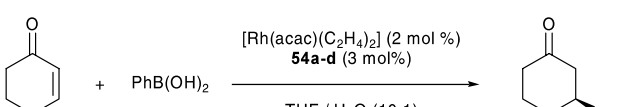
54a R = H

54b R = Ph

54c R = Cy

54d R = *o*-anisyl

Scheme 37 Synthesis of the chiral paracyclophane imidazolinium salts **54a–54d**

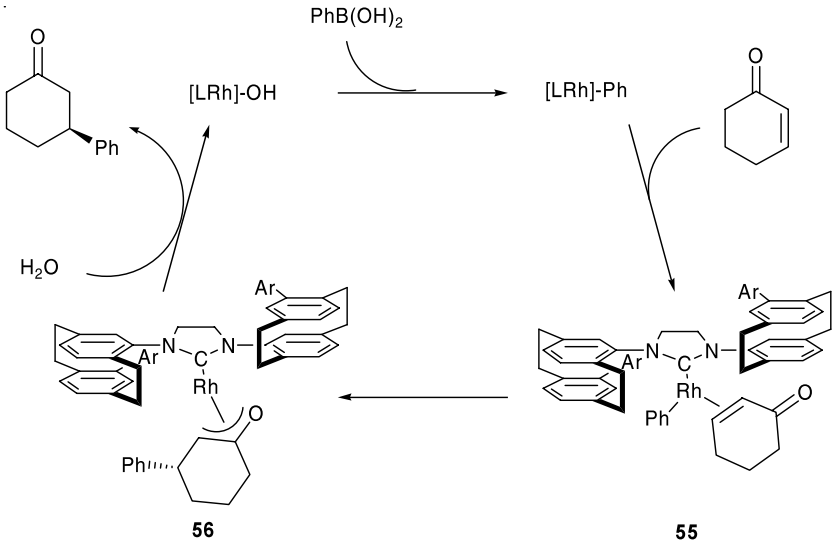


Ligand	Yield (%)	ee (%)
54a	69	61
54b	86	91
54c	89	97
54d	96	98

Scheme 38 Rhodium(I)-catalyzed conjugate addition of phenylboronic acid to α-enones

ity has to be seen in connection with the same observation made previously for the addition of arylboronic acids to aldehydes [99] and is found, in general, upon going from diphosphines to monophosphines (such as PBu_3) [100] and further to bulky NHCs (such as IMes and IPr) [101]. The enantiomeric excesses of the reaction in Scheme 37, obtained with the optimized catalyst derived from **54**, are good to excellent (ee's ranging 61–98%) and, in particular, with ligand **54d** high selectivities were obtained with a wide range of arylboronic acids and cyclic enones while acyclic enones led to slightly decreased selectivity.

A mechanistic explanation for the chiral induction in this process has been proposed and is depicted in Scheme 39. It is based on the results obtained in a previous investigation of the BINAP derived catalyst [102, 103]. As discussed for C_2-chiral diphosphines, the active space at the metal center, the geometry of which is defined by the ancillary ligand, may be viewed as being composed of four quadrants. Two of these quadrants (top-right and bottom-left) are blocked by the cyclophane moieties. Upon phenyl transfer from $PhB(OH)_2$ and coordination of the enone, the intermediate **55** is generated (Scheme 39). The cyclohexenone will preferentially π coordinate, occupying one of the free quadrants to minimize the steric interligand repulsion with **54**. The transfer of the Rh – Ph group to the C = C bond occurs by migratory insertion with attack upon the *Si* face of the olefin to give the oxallylrhodium intermedi-

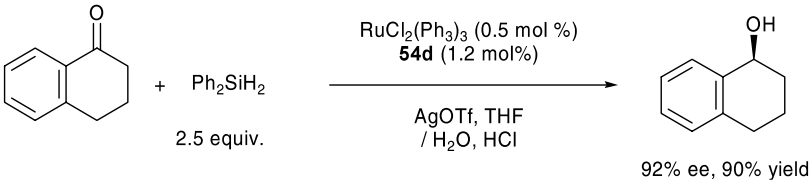


Scheme 39 Proposed catalytic cycle explaining the chiral induction in the rhodium(I)-catalyzed conjugate addition of phenylboronic acid to α-enones

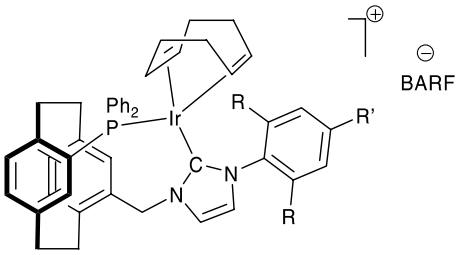
ate **56** which hydrolyzes to re-form the active hydroxy-rhodium complex and (S)-3-phenylcyclohexanone. Ligands such as **54** have also been tested in the asymmetric hydrosilylation of ketones with high yield and selectivity [104]. With a catalyst, which was generated in situ by reaction of imidazolinium salt **54d** with ruthenium dichloride tris(triphenylphosphine) and silver triflate, acetophenone was reduced with Ph_2SiH_2 to give the corresponding alcohol in 97% ee and 98% yield. The catalytic system **54d**-ruthenium also gave excellent yields and enantioselectivities with more hindered aryl ketone substrates or cyclic aryl ketones (Scheme 40).

Bolm and coworkers very recently tested the iridium(I) complex derivatives **57a–57c** in asymmetric hydrogenation [105]. These complexes contain a bidentate carbene-phosphine ligand with a chiral *pseudo-ortho*-[2,2]paracyclophane unit built into its backbone (Fig. 13).

Catalyst **57a** was found to be the most selective for the transformation of non-functionalized alkenes (ee's of up to 82% for E-1,2-diphenylpropene)



Scheme 40 An example of application of **54d** in the hydrosilylation of ketone



(*R*p)-**57a** : R = R' = H
(*R*p)-**57b** : R = R' = Me
(*R*p)-**57c** : R = *i*Pr ; R' = H

Fig. 13 Iridium complexes containing a chiral phosphine-carbene ligand

and the increase in the steric bulk on going to **57c** leads to lower enantioselectivities. For functionalized olefines, the hydrogen pressure sensitively influences the selectivity, the best results being obtained with **57c** under an H_2 pressure of 1 bar (ee's of up to 89% for dimethylitaconate). Bidendate carbene-phosphine oxide ligands derived from **57** have also been investigated in the asymmetric rhodium-catalyzed 1,2-addition of aryl boronic acids to aromatic aldehydes giving low enantioselectivities (up to 38% ee) [106].

In conclusion, even though ferrocenyl-substituted chiral carbenes have so far not given rise to highly efficient enantioselective catalysts, the strategy of using planar chiral structural elements in carbene ligand design is promising in view of the recent results obtained with chiral paracyclophane derivatives. Furthermore, the latter example supports the conclusion at the end of Sect. 1, that increase in the steric bulk of chiral N-substituents leads to greater chiral induction in the enantioselective catalysis with these species.

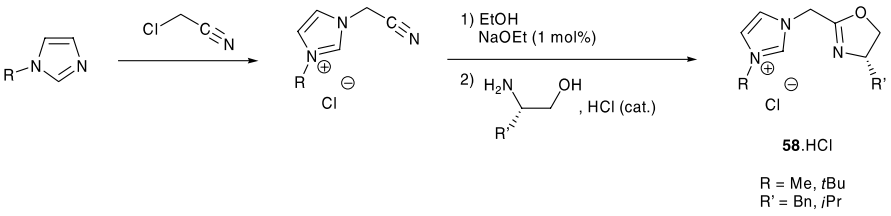
6
Carbenes Incorporating Oxazoline Units

During the past 15 years the oxazoline ring has been established as a "privileged" structural motif in ligand design for asymmetric catalysis [107, 108]. The key features are its rigidity and quasi-planarity as well as its facile accessibility by condensation of an amino-alcohol with a carboxylic acid derivative [109, 110]. In spite of their sensitivity to mineral and Lewis acids, they are remarkably stable towards nucleophiles, bases and radicals. Upon coordination of the oxazoline ring through the N-atom, the stereodirecting substituent will be situated in close proximity to the metal center and will thus directly control the active space available for the substrate(s). It was therefore of interest to combine this structural element of chiral ligand design with a N-heterocyclic carbene unit. In 1998, Herrmann et al. reported the synthe-

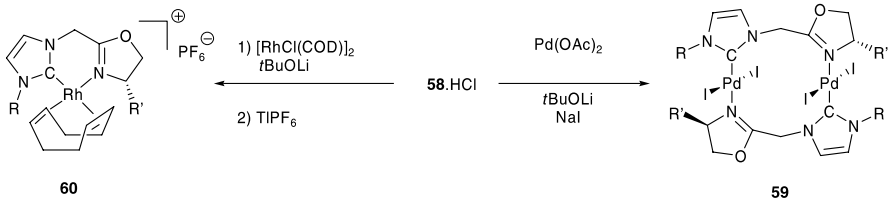
sis of the first chiral carbene containing an oxazoline unit. In this bidentate ligand the oxazoline ring is linked in its 2-position to the imidazole ring *via* a methylene bridge [111]. The key step in the synthesis of the imidazolium precursor is the acid-catalyzed cyclization of the oxazoline by reaction of a iminoester, formed in situ from a nitrile function, and the amino alcohol (Scheme 41).

Compound **58** was subsequently coordinated as a carbene-oxazoline ligand to rhodium(I) and palladium(II) (Scheme 42). Carbene **58** acts as a bidentate chelating ligand in the rhodium(I) complex and the six-membered metallacycle thus formed adopts a boat conformation. On the other hand, the palladium complex **59** is dinuclear with two oxazoline-carbenes acting as bridging ligands. The rhodium complex **60** was employed in the hydrosilylation of ketones giving the secondary alcohols in moderate enantioselectivity (ee's up to 70%) [112].

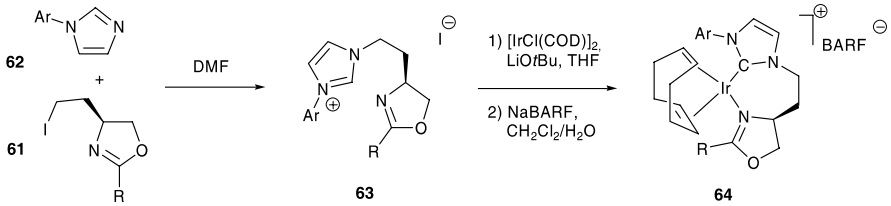
A major step forward in the development of asymmetric catalysis with chiral N-heterocyclic carbene complexes has been the work of Burgess et al. on the asymmetric hydrogenation of alkenes using iridium(I) catalysts containing NHC-oxazolines such as **63** [113, 114]. Their design was inspired by the chiral bidentate phosphine-oxazoline ligands (*Phox*) developed by Helmchen and Pfaltz, which had proved to be highly selective in the enantioselective hydrogenation of non-functionalized trisubstituted alkenes [115, 116]. Furthermore, Burgess and coworkers had previously studied a novel family of P,N-ligands, dubbed *JM-Phos* [117, 118], and were guided by the analogy between phosphanes and NHCs in the design of the new class of oxazoline-carbenes represented by **63** (Scheme 43).



Scheme 41 Synthesis of the imidazolium precursor of Herrmann's oxazolinyl-carbene ligand



Scheme 42 Coordination of the carbene **58** to rhodium(I) and palladium(II)

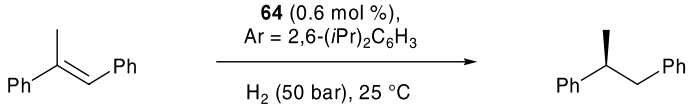


Scheme 43 Synthesis of an iridium(I) complex bearing Burgess's chiral oxazoline-imidazolylidene ligand

In the imidazolium salts **63**, obtained by nucleophilic substitution of the iodo-derivative **61** by an imidazole **62**, the oxazoline is linked by the carbon atom in the 4-position. Coordination of the bidentate ligand to the $\{Ir(COD)\}^+$ complex fragment is then achieved by in situ deprotonation (Scheme 43). This modular design allows facile and rapid access to a large ligand library by variation of the substituents in the 2-position of the oxazoline and at the "terminal" N-atom of the heterocyclic carbene.

Complexes **64** have been tested in the asymmetric hydrogenation of *E*-1,2-diphenylpropene, and derivative **64d** proved to be the most active and selective for this reaction. Some results of the catalyst screening are summarized in Scheme 44, illustrating the importance of the modular ligand design.

The authors have put forward an explanation for the high selectivity of catalyst **64d** and pointed out the key structural features leading to an efficient chiral induction with this class of complexes. The ligand in **64d**, in particular, displays high efficiency since the bulky 2,6-(iPr)$_2$-C_6H_3 group effectively blocks one of the quadrants of the active space in the catalyst, allowing good control of the geometry of the coordination sphere around the metal.



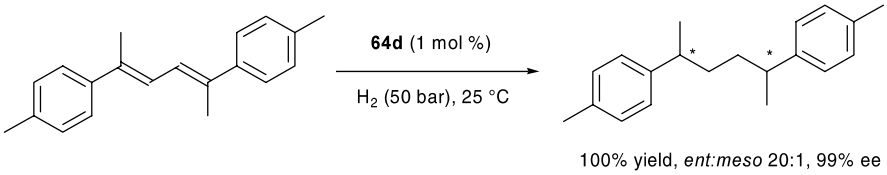
	R	ee (%)	Yield (%)
64a	Ph	13	25
64b	$CHPh_2$	25	12
64c	tBu	50	81
64d	1-Ad	98	99

Scheme 44 Catalytic hydrogenation of E-1,2-diphenylpropene with complexes **64a–d**

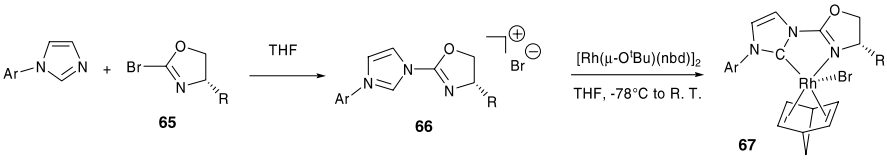
Remarkably, complex **64d** has also been successfully employed in the stereoselective hydrogenation of dienes yielding the reduced products with up to 20 : 1 diastereoselectivity and 99% ee (Scheme 45) [119, 120]. These results mark a real progress in that field since 1,3-dienes are difficult to hydrogenate with high catalyst activity and enantioselectivity. It should be noted that Crabtree's (achiral) catalyst $Ir(py)(PCy_3)(COD)PF_6$, which is the most important homogeneous catalyst for the hydrogenation of unfunctionalized hindered alkenes, generally displayed low activity for such substrates [121].

Gade and co-workers reported the synthesis of an oxazolinyl-carbene which is obtained by direct linkage of the two heterocycles. The new ligand system was obtained by reacting the 2-bromooxazoline **65** [122] with an imidazolium precursor in THF (Scheme 46) [123]. N-heterocyclic carbene rhodium complexes could be obtained by reaction of the imidazolium salt **66** with $[\{Rh(\mu\text{-O}t\text{Bu})(nbd)\}_2]$ generated in situ [124].

This direct condensation of an oxazoline and an imidazole to give the respective imidazolium salts provides a straightforward and modular route to the development of a new family of stereodirecting ligands. Based on this strategy, a highly stereoselective Rh^I catalyst for the asymmetric hydrosilylation of ketones was developed [125]. Whereas, for example, the asymmetric hydrosilylation of 2-naphthyl methyl ketone with complex **68** was carried out with 99% yield and 91% ee (Table 2, Entry 1), the enantioselectivities for most aryl alkyl ketones were found to be slightly below those of the most efficient phosphane-based systems. However, catalyst **68** was found to be more efficient in the hydrosilylation of unsymmetrical dialkyl ketones (Table 2, e.g., Entries 2–4), which are difficult substrates [126]. The selectivity for the reduction of prochiral dialkyl ketones is comparable or even superior to the best previously reported for prochiral nonaromatic ketones: Whereas cyclopropyl methyl ketone was hydrosilylated with an enantioselectivity of 81% ee, the in-

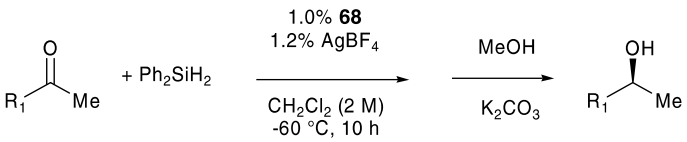


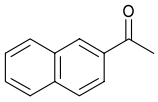
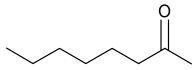
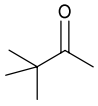
Scheme 45 Catalytic hydrogenation of a diene with complex **64d**

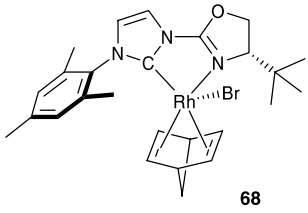


Scheme 46 Synthesis of ligand precursor **66** and complexation with rhodium(I) **67**

Table 2 Asymmetric hydrosilylation of ketones with catalyst **68**



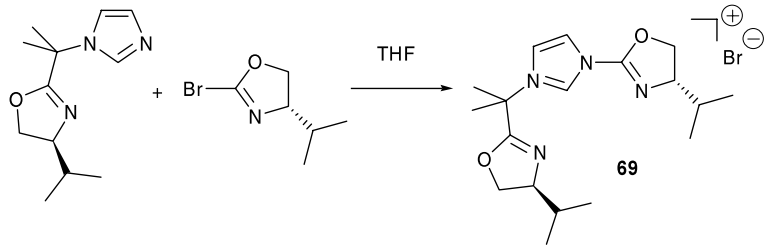
Entry	Ketone	Ee (%)	Yield (%)
1		91	99
2		79	95
3		95	70
4		65	n.d.



68

crease of the steric demand of one of the alkyl groups led to improved ee's, reaching 95% ee in the case of *tert*-butyl methyl ketone. Linear chain *n*-alkyl methyl ketones, which are particularly challenging substrates, were reduced with good asymmetric induction, such as in the case of 2-octanone (79% ee) and even 2-butanone (65% ee).

The combination of the Herrmann's carbene ligand **58** and the Gade's NHC family **66** resulted in a new chiral N-heterocyclic carbene **69** (Scheme 47) [127]. The coupling strategy allows the free combination of oxazoline substituents in



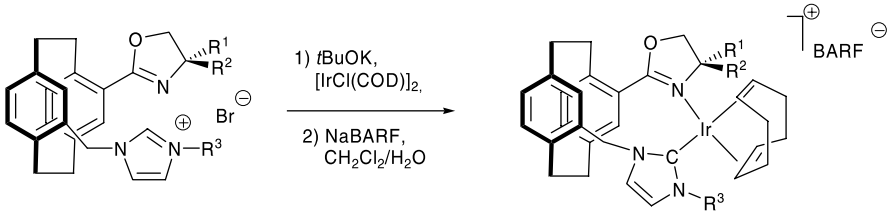
69

Scheme 47 Synthesis of the bis(oxazoline)carbene ligand **69**

a highly modular way. The tridentate ligand has been coordinated to Pd(II) and Rh(III) and established that this ligand is topologically related to the bis(oxazoline)pyridine *pybox*, with an overall reduced symmetry (loss of the C_2-axis) [128].

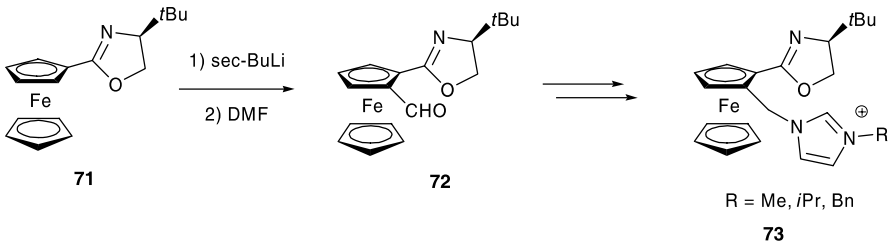
Bidentate oxazoline-imidazolylidene ligands, in which both units are linked by a chiral paracyclophane, have been studied in Bolm's group [129]. In this case, the planar chirality of the *pseudo-ortho*-paracyclophane is combined with the central chirality of an oxazoline (Scheme 48). Compounds **70** were tested in the asymmetric hydrogenation of olefins displaying moderate selectivity (ee's of up to 46% for dimethylitaconate in the presence of **70b**).

Yet another combination of a molecular fragment possessing planar chirality (ferrocene) and an oxazoline ring has also been investigated in a similar context (Scheme 49) [130]. The use of a chiral oxazolinylferrocene **71** allows an ortho-functionalization with sec-butyl lithium. Trapping with DMF afforded the aldehyde **72,** which was converted into imidazolium **73** in three reaction steps. Complexation with rhodium(I) was investigated and application of the complexes thus obtained in hydrosilylation of acetophenone was investigated. All complexes were active giving the secondary alcohol in high



	R^1	R^2	R^3
(*Sp*)-**70a**	Me	Me	Me
(*Sp*)-**70b**	Me	Me	Mes
(*S*,*Sp*)-**70c**	*t*Bu	H	Me

Scheme 48 Oxazoline-*N*HC ligands, bridge by a paracyclophane unit and their iridium complexes



71 **72** **73**

Scheme 49 Oxazoline-*N*HC ligand bridge by a planar chiral ferrocene

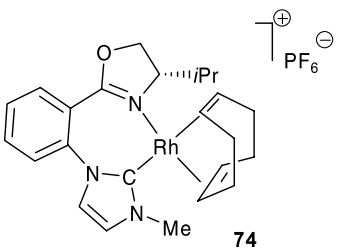
yield but with very low enantioselectivity (< 6% ee). This is one of many examples in the literature in which the combination of several elements of chirality does not necessarily lead to improved selectivity.

Inspired by the chiral phosphine/oxazoline ligands developed by Helmchen and Pfaltz [131], Crudden and coworkers, have prepared a chiral NHC-oxazoline possessing a rigid backbone (Fig. 14) [132]. The rhodium complex **74** has been used in the catalytic hydroboration of olefins and the hydrosilylation of prochiral ketones with enantiomeric excesses that did not exceed 10%.

Finally, two chiral monodentate N-heterocyclic carbene ligands that contain an oxazoline unit have been reported. Glorius et al. reported the synthesis of the imidazolium salts **76** by cyclizing the corresponding bisoxazolines **75** (Scheme 50) [133].

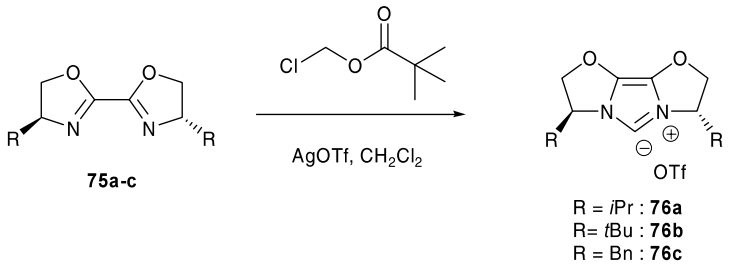
The key step is the introduction of a C_1 synthon to link the two oxazoline-N atoms. The combination of chloromethyl pivalate and silver triflate generates a highly electrophilic reagent undergoing double nucleophilic substitution at its central carbon atom and thus giving the desired imidazolium salt. A major advantage of this strategy is the facile accessibility of the bisoxazolines along with the modularity of their synthesis. The imidazolium salts **76** have been employed in Pd-catalyzed asymmetric α-arylations (such as represented in Scheme 7) albeit with only moderate results (ee's < 43%).

Enders and Kallfass reported the synthesis of unsymmetrical triazolium salt **78** [134]. This compound is obtained by a three-step procedure from the corresponding oxazolidinone **77**.



74

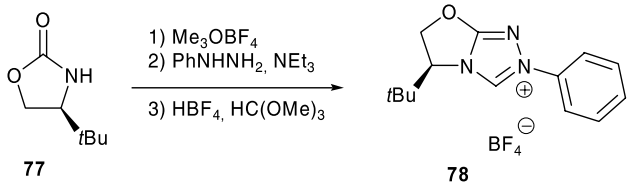
Fig. 14 Oxazoline-carbene-based rhodium hydrosilylation catalyst developed by Crudden et al.



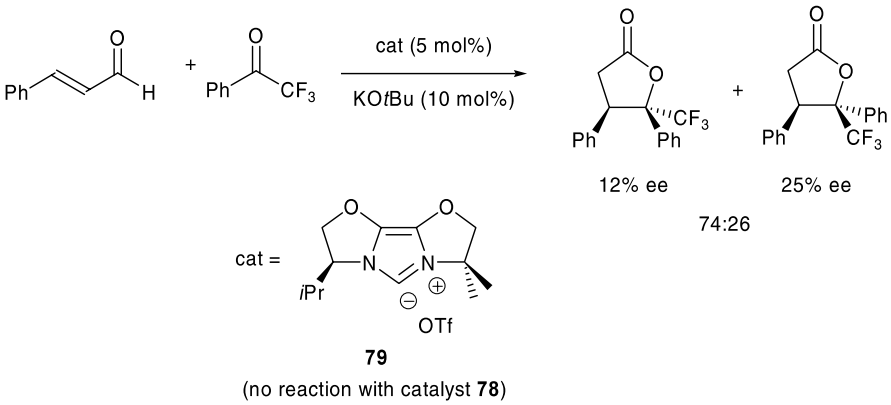
75a-c

R = *i*Pr : **76a**
R= *t*Bu : **76b**
R = Bn : **76c**

Scheme 50 Synthesis of imidazolium salts from the corresponding bisoxazolines



Scheme 51 Synthesis of oxazoline-based triazolium salt



Scheme 52 Synthesis of γ-butyrolactone catalyzed by **79**

This ligand, which has a bicyclic structure strongly related to Leeper's and Rovis' ligands (*vide supra*) [20–25], was found to be a very efficient organocatalyst in the asymmetric benzoin condensation (ee's up to 99%, see Scheme 5, Eq. 1).

In a remarkable example of asymmetric organocatalysis, Glorius and Burstein have investigated the formation of γ-butyrolactone from α,β-unsaturated aldehydes with aromatic aldehydes or ketones using NHCs (Scheme 52) [135]. This reaction is a conjugate umpolung of α,β-unsaturated aldehydes [135, 136]. In the search of a catalytic enantioselective formation of γ-butyrolactone, they found that the imidazolium derived from bisoxazoline **79** was effective whereas triazolium salt **78** did not give any product. Although enantiomeric excesses are still low, this result clearly illustrates the potential of ligand family **76.**

7 Conclusions

In a field that is growing as rapidly as that of stereoselective catalysis with chiral NHCs, it is difficult to lay out general guidelines for successful research

strategies. However, several basic structural motifs have recently emerged in the design of chiral N-heterocyclic carbene ligands and have been categorized and summarized in this overview. While all of them may be considered in the solution of a particular catalyst design problem, there seems to be a general trend that emerges for the most efficient new ligand systems. For instance, for monodentate carbene ligands, a well-defined chiral molecular shape – aided by rigid (cross-linked) structural units – appears to be the prerequisite for high stereoselectivity, as has been previously observed for other ligands used in asymmetric catalysis.

Since the coordination of NHC ligands to late transition metals is generally robust, they may be considered as "anchor" functions in a multifunctional stereodirecting ancillary ligand. Such an anchor unit may then readily be combined with the established "privileged" chiral ligating units. In order to facilitate the optimization of a given catalyst, it is of importance that the coupling of the "anchor" (NHC) with the stereodirecting element occurs in a simple (preferably the final) reaction step of the ligand synthesis. Some of the expertise gained in the development of functionalized phosphine ligands appears to be applicable to NHC-heterodonor ligands while the fundamental stereochemical difference between the tricoordinate phosphorus and the essentially planar direct environment of the carbene function has to be taken into account. Finally, an important advantage of NHC derivatives over phosphines has already made them strong competitors for the role of the dominating structural units in ligand design: their ease of preparation, the chemical and thermal stability of their precursors and their facile integration into more complex multifunctional ligand systems.

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Transition Metal-Catalyzed Reactions Using N-Heterocyclic Carbene Ligands (Besides Pd- and Ru-Catalyzed Reactions)

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Abstract Major advances in transition-metal catalyzed reactions have taken place since the discovery of N-heterocyclic carbenes (NHCs). This review provides a summery of recent M-NHC catalyzed reactions including cycloadditions, rearrangements, coupling reactions, polymerizations, and the additions of H-X.

Abbreviations

COD	Cycloocta-1,5-diene
Cy	Cyclohexyl
IAd	*N*,*N*′-Bis(adamantyl)imidazol-2-ylidene
IMes	*N*,*N*′-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	*N*,*N*′-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
I*i*Prim	*N*,*N*′-Bis(isopropyl)-4,5-dimethylimidazol-2-ylidene
I*i*Pr	*N*,*N*′-Bis(isopropyl)imidazol-2-ylidene
I*t*Bu	*N*,*N*′-Bis(*tert*-butyl)imidazol-2-ylidene
SIPr	*N*,*N*′-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene
SIMes	*N*,*N*′-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
TMS	Trimethylsilyl

1 Introduction

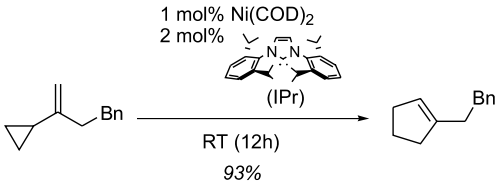
With the application of N-heterocyclic carbene (NHC) ligands, the number of transition metal-catalyzed reactions has grown considerably in the past decade. The replacement of traditional amine or phosphine ligands with electron-rich NHC ligands has led to a substantial enhancement in catalytic activity. This chapter summarizes the recent impact that the use of NHC ligands has had in furthering the field of transition metal-mediated catalysis.

2 Rearrangement Reactions

2.1 Rearrangement Reactions of Vinyl Cyclopropanes

The use of Ni as a catalyst for the rearrangement of vinylcyclopropanes (VCPs) to cyclopentenes was first reported in 1979 [1, 2]. In combination with a phosphine ligand, activated VCPs could be converted to the corres-

ponding cyclopentenes at elevated temperatures. Recently, it was shown that replacement of the phosphine ligand with an NHC ligand led to a dramatic increase in catalytic activity [3]. Sterically hindered N-aryl-substituted NHCs, such as IPr or SIPr, gave greater yields of isomerized products at faster reaction rates than less bulky NHCs (such as ICy and I*i*Prim). VCPs possessing an electron-withdrawing group, heteroatom, or phenyl group on the cyclopropane ring underwent rapid isomerization and afforded high yields of the corresponding cyclopentene. Furthermore, VCP substrates lacking any functionality that could promote rearrangement readily isomerized at ambient conditions (Eq. 1). In contrast, no conversion was observed when phosphine ligands were employed, even after prolonged periods at elevated temperatures. Overall, a variety of cyclopentenes were prepared in excellent yield through this procedure.

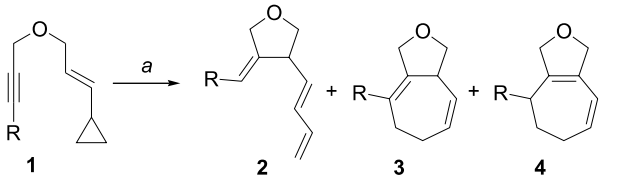


Equation 1

2.2 Rearrangement Reactions of Cyclopropylen-ynes

Ni/NHC-based systems also catalyze the rearrangement reaction of cyclopropylen-ynes to afford three different structures, two of which are distinct from those obtained employing Rh- and Ru-based catalysts (Eq. 2) [4–7]. Although the combination of $Ni(COD)_2$ and SIPr displayed the fastest rate of reaction, the size of the substituent on the alkyne (R) had a significant effect on the nature of the heterocyclic product that formed (Table 1). When R was small (e.g., R = Me (**1a**), entry 1), product **2a** formed exclusively. However, a mixture of rearrangement products was obtained from substrates **1b** and **1c** (entries 2 and 3), which included the expected skipped triene (**2b** and **2c**) in addition to a bicyclic seven-membered ring (**3b** and **3c**). Furthermore, when R was large (e.g., R = *t*-Bu (**1d**) or TMS (**1e**), entries 4 and 5), isomerized seven-membered rings (**4d** and **4e**) were formed exclusively in good yields.

A plausible mechanism that diverges at a common intermediate and may account for the product distributions is shown in Scheme 1. Reaction between the Ni catalyst and cyclopropylen-yne **1** would ultimately afford eight-membered metallacycle **6**, which could result from either initial oxidative coupling between an alkene and alkyne (**5a**) [8–10] or initial isomerization of the VCP (**5b**). Ultimately, β-hydride elimination from **6** and reductive elimi-



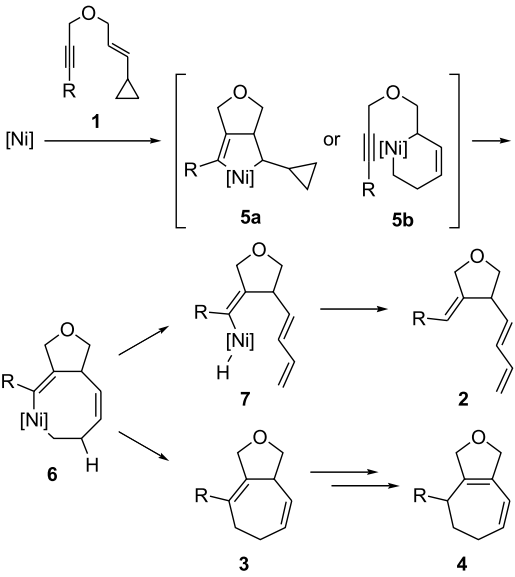
(a) 5 mol% $Ni(COD)_2$, 5 mol% SIPr, toluene, room temperature

Equation 2

Table 1 Product distribution in the Ni-catalyzed rearrangement of **1**[a]

Entry	Substrate	**2** : **3** : **4**[b]	% Yield[c]
1	R = Me (**1a**)	1 : 0 : 0	54 (**2a**)
2	R = Et (**1b**)	3 : 2 : 0	34 (**2b**)
			27 (**3b**)
3	R = *i*Pr (**1c**)	1 : 2 : 0	28 (**2c**)
			38 (**3c**)
4	R = *t*Bu (**1d**)	0 : 0 : 1	82 (**4d**)
5	R= TMS (**1e**)	0 : 0 : 1	88 (**4e**)

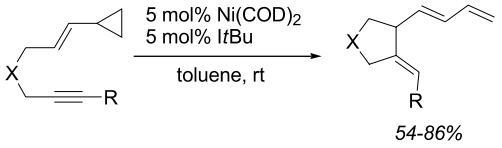
[a] Reaction conditions: 5 mol % $Ni(COD)_2$, 5 mol % SIPr, toluene, ambient temperature
[b] Determined by GC using naphthalene as an internal standard
[c] Isolated yield (average of two runs)



Scheme 1 Proposed mechanism for the rearrangement of **1**

nation would afford product **2**. In contrast, if both the ligand and R are large, β-hydride would be inhibited and direct reductive elimination would yield seven-membered ring **3**. Product **4** would arise from further isomerization of **3**.

By substituting SIPr for an N-alkyl-substituted NHC ligand (I*t*Bu), the skipped-triene product (**2**) could be prepared selectively from cyclopropylenyne substrates, regardless of substituent size (e.g., R) (Eq. 3) [11]. Thus, skipped-triene products were formed exclusively under mild conditions (room temperature, 2 h).



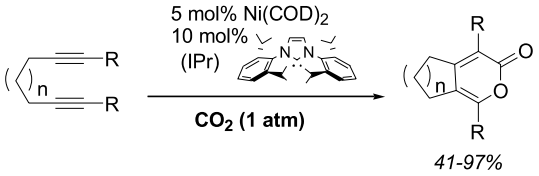
Equation 3

3 Cycloaddition Reactions

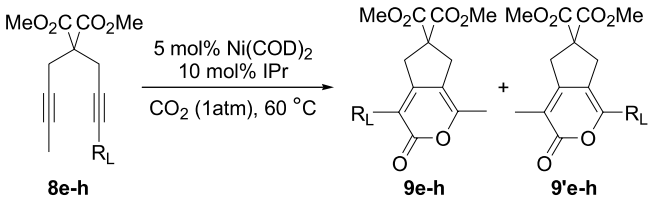
An attractive method for the rapid construction of the heterocyclic core of numerous biologically active pharmacophores is the cycloaddition or rearrangement of unsaturated substrates. Considerable effort has been focused on developing transition metal catalysts that mediate such transformations. Ultimately, reactions which require prohibitively harsh conditions (high temperature, high pressure) may become practical (room temperature, atmospheric pressure) when a transition metal catalyst is employed. Of the transition metal-based catalysts, Ni/NHC systems are some of the most versatile and have been used in the synthesis of both oxygen- and nitrogen-containing heterocycles.

3.1 Cycloaddition of Diynes and Carbon Dioxide

The Ni/phosphine-catalyzed coupling of two alkynes with CO_2 to afford pyrones was first discovered by Inoue and further developed by Tsuda [12–20]. These reactions generally involve high pressures of CO_2 and elevated temperatures. In addition, only a limited number of diynes could be successfully converted to the corresponding pyrone. As with many cycloaddition reactions, oligomerization of the diyne was a major side reaction that competed with pyrone formation. These obstacles were overcome when IPr was used as the ligand in lieu of phosphines [21]. The steric bulk of this ligand helped to suppress oligomerization of the diyne. As a result, a variety of bicyclic py-



Equation 4



Equation 5

Table 2 Nickel-catalyzed cycloaddition of CO_2 and asymmetrical diynes [a]

Entry	Substrate	R_L	Product	**9 : 9** [b]	% Yield [c]
1	**8e**	Ethyl	**9e**	62 : 38	75
2	**8f**	*i*-Pr	**9f**	80 : 20	64
3	**8g**	*t*-Butyl	**9g**	100 : 0	64
4	**8h**	TMS	**9h**	100 : 0	83

[a] Reaction conditions: 5 mol % $Ni(COD)_2$, 10 mol %, IPr, 0.10 M substrate in toluene at 60 °C, 30 min
[b] Determined by GC and ^1H NMR analysis
[c] Isolated yields (average of two runs)

rones were obtained in generally high yields (Eq. 4). Notably, all pyrones were obtained using ambient pressure and relatively low reaction temperatures.

Ni/IPr serves as a general catalyst system for the coupling of diynes and CO_2. To date, this catalyst does not provide pyrones from either terminal diynes or sterically hindered diynes. Terminal diynes oligomerized at a faster rate than CO_2 incorporation. In contrast, sterically hindered diynes (R = *t*-Bu or TMS) did not react under any reaction conditions (elevated temperature and pressure).

Asymmetrical diynes, including diynes possessing one sterically demanding substituent, did undergo clean conversion to pyrones [22]. As shown in Table 2, when the steric difference between the two terminal substituents on the diyne is small (e.g., Me vs. Et), a nearly equal mixture of two py-

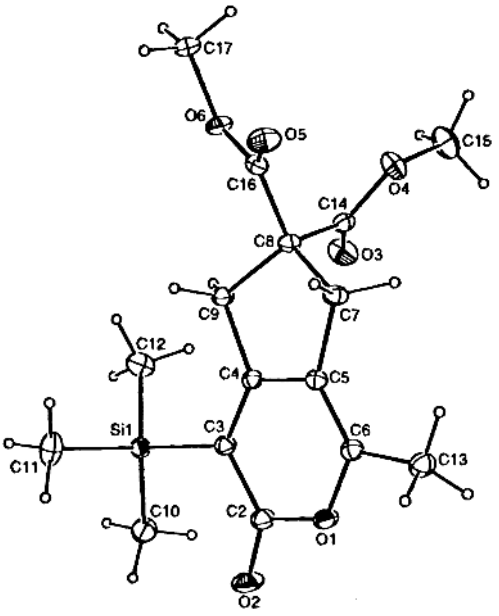
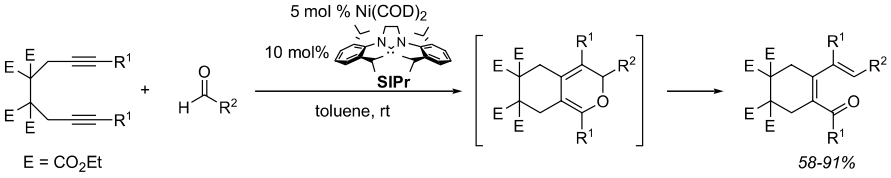


Fig. 1 X-ray structure of **9h**

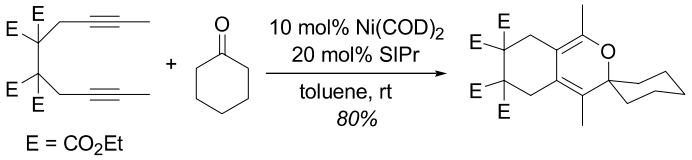
rone regioisomers was obtained (entry 1). However, as the relative difference between the two terminal groups was increased, the regioselectivity of the reaction improved and one isomer was preferentially formed over the other. Furthermore, the use of a diyne which contained a methyl group and a very bulky group (such as *t*-Bu or TMS) afforded only one regioisomer (entries 3 and 4), as determined by single crystal X-ray analysis (Fig. 1).

3.2
Cycloaddition of Unsaturated Hydrocarbons and Carbonyl Substrates

Pyrans constitute another class of oxygen-containing heterocycles that have been prepared from Ni-catalyzed cycloaddition reactions. The coupling of diynes and aldehydes could be mediated by the combination of a Ni(0)



Equation 6



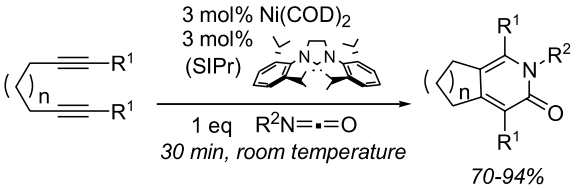
Equation 7

catalyst and a phosphine ligand; however, reaction temperatures exceeded 130 °C [23]. By replacing the phosphine ligand with SIPr, a striking increase in catalytic activity was observed and cycloadducts were obtained at room temperature (Eq. 6) [24]. Both aryl and aliphatic aldehydes were successfully incorporated into the dienones. Furthermore, despite the depressed reactivity of unactivated ketones [25], the cyclization of cyclohexanone proceeded smoothly and afforded pyran in good yield (Eq. 7). It is likely that the increase in the overall catalytic activity stems from the ability of the NHC ligand to enhance carbon–oxygen bond-forming reductive elimination.

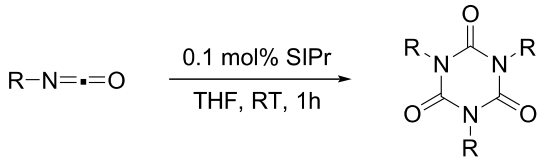
3.3
Cycloaddition of Diynes and Isocyanates

Nitrogen-based heterocycles can also be prepared through Ni/NHC-catalyzed cycloaddition reactions. For example, Ni/SIPr catalyzed the cycloaddition of diynes with isocyanates under the mildest conditions to date [26]. In particular, excellent yields of pyridones are obtained from diynes and isocyanates at room temperature using only 3 mol % catalyst. As shown in Eq. 8, a variety of diynes were subjected to these optimized conditions. Both aryl and alkyl isocyanates were readily converted to the respective 2-pyridone. Sterically hindered substrates appeared to have very little effect on the reaction, as excellent yields of product were obtained with bulky isocyanates and bulky diynes.

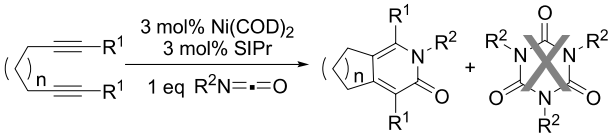
The increased reactivity of isocyanates, relative to carbon dioxide, was reflected in the wider range of cycloaddition partners. For example, terminal diynes as well as nontethered alkynes (e.g., 3-hexyne) were also successfully converted to 2-pyridones rather than undergoing rapid telomerization to aromatic by-products. Importantly, the cycloaddition of an asymmetrical



Equation 8



Equation 9



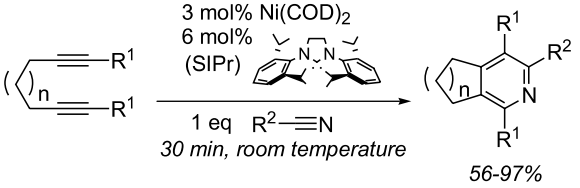
Equation 10

diyne afforded a pyridone with the larger substituent in the 3-position. Thus, the same regioselectivity with pyrone products was observed, indicating that a similar cycloaddition mechanism is most likely involved.

The NHCs were found to react with isocyanates to afford isocyanurates (Eq. 9) [27, 28]. Although SIPr was found to be an effective catalyst for isocyanurate formation (for a wide variety of isocyanates), no isocyanurate was observed in most Ni-catalyzed cycloaddition reactions of diynes and isocyanates (Eq. 10). Furthermore, isocyanurates were not formed reversibly during the course of the reaction since no pyridones were obtained when isocyanurates were used as the sole source of isocyanate. These data further highlight the efficacy of the Ni/NHC catalyst system.

3.4 Cycloaddition of Diynes and Nitriles

The combination of Ni(0) and a phosphine ligand had been used to catalyze the cycloaddition of diynes with CO_2 [15–20], aldehydes [23], and isocyanates [29–31]. The corresponding cycloaddition with nitriles, however, had not been demonstrated. The absence of this cycloaddition reaction may be due to the inability of Ni/PR_3 systems to facilitate the hetero-oxidative coupling of an alkyne and a nitrile [32]. By employing an NHC ligand, the nucleophilicity of the Ni catalyst was enhanced, which led to a greater interaction with the nitriles. Thus, diynes and nitriles could be converted to pyridines under ambient conditions (Eq. 11) [33]. In general, both aryl and alkyl nitriles were readily converted to the respective pyridine, although alkyl nitriles gave slightly diminished yields. Notably, sterically hindered nitriles (such as *o*-tolunitrile, *tert*-butyl nitrile, and naphthalene-1-carbonitrile) delivered the desired pyridines. In addition, heteroaryl nitriles were readily converted to pyridines in high yields. In accordance with previous cycloadditions of diynes and C = X-containing substrates, the coupling of an unsymmetri-



Equation 11

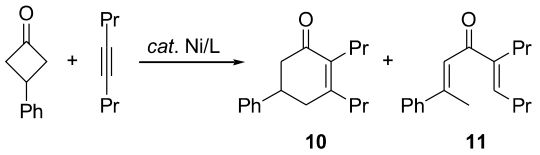
cal diyne and acetonitrile afforded a single regioisomer in 58% yield. Initial hetero-oxidative coupling of the TMS-terminated alkyne and nitrile followed by insertion of the methyl-terminated alkyne explains the observed regioselectivity.

4
Reductive Coupling Reactions

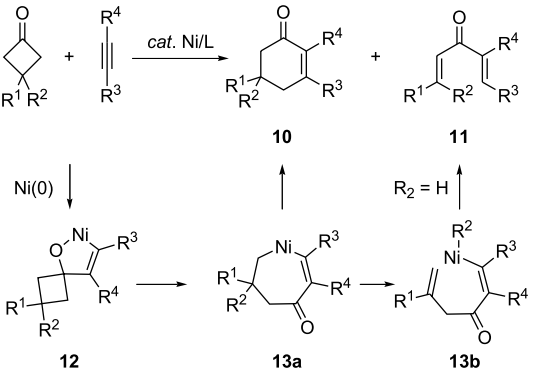
4.1
Reductive Coupling Reactions: No Added Reductant

Murakami and coworkers recently reported that cyclobutanones can be coupled with alkynes to afford ring-expanded cyclohexenones (such as **10**, Eq. 12) [34]. While phosphine ligands were generally employed to facilitate the reaction, the authors also demonstrated that IPr was an effective ligand. In reactions involving asymmetrically substituted alkynes, such as 1-phenyl-1-propyne (R^3 = Ph, R^4 = Me), the methyl group was located α to the carbonyl group in the major product. The observed regioselectivity can be explained in terms of a favorable electronic interaction when the aryl substituent (R^3) is located on the α carbon in nickelacycle **12** (Scheme 2). A similar phenomenon has been observed in other nickel-promoted coupling reactions involving alkynes [35, 36].

Analogous to the cycloadditions described above, the first step of these ring expansion reactions is believed to involve the initial oxidative coupling between the carbonyl and the alkyne to afford a nickelapentenacycle (**12**, Scheme 2) [37, 38]. Subsequent β-carbon elimination relieves ring strain and affords a seven-membered nickelacycle **13a** that reductively eliminates the



Equation 12



Scheme 2 Formation of ring-expanded cyclohexenones

Table 3 Ligand effects

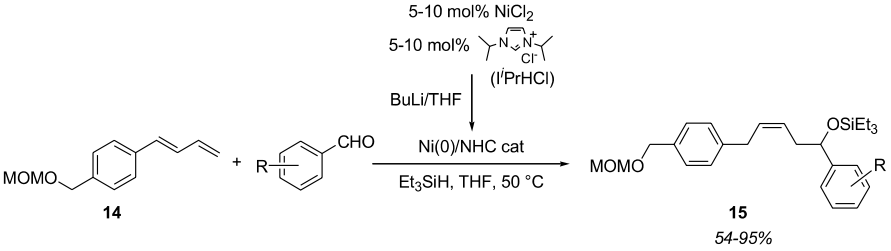
Entry	mol % $Ni(COD)_2$	L (mol %)	**10** (%)	**11** (%)
1	10	P(*c*-Hex)$_3$ (20)	41	54
2	10	PPh_3 (20)	37	26
3	10	IPr (10)	61	–
4	20	IPr (20)	79	–

cyclohexenone product and regenerates the catalyst. When a β-hydrogen is available (i.e., R^2 = H), β-H elimination becomes competitive with reductive elimination and acyclic products (**11**) are seen in appreciable amounts. However, replacement of the phosphine ligand with an NHC ligand such as IPr appeared to suppress this side reaction and afforded good yields of the desired cyclohexenone product (Table 3).

4.2 Reductive Coupling Reactions in the Presence of a Reductant

Nickel-catalyzed cyclizations, couplings, and cycloadditions involving three reactive components have been an active area of research for the past decade [39, 40]. Central to these reactions is the involvement of a low-valent nickel capable of facilitating oxidative coupling of an unsaturated hydrocarbon (such as an alkyne, allene, or alkene) and a carbonyl substrate (such as an aldehyde or ketone). The use of NHCs as ligands has been evaluated for couplings of aldehydes. Such reactions typically afford *O*-protected allylic alcohols in good yields.

In 2001, Mori and coworkers showed that the use of NHC ligands can dramatically influence the olefinic geometry in the Ni-catalyzed coupling re-

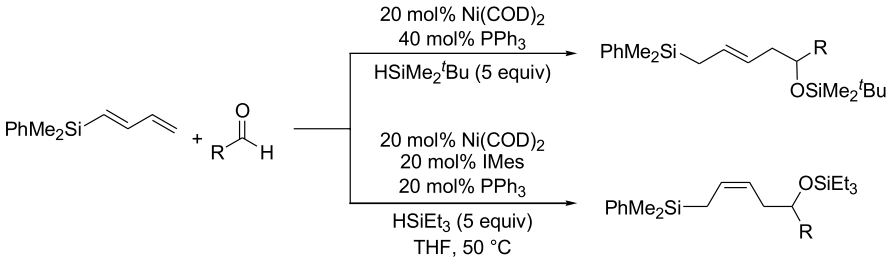


Equation 13

action of 1,3-dienes and aldehydes [41]. Specifically, when Ni/PPh_3 is used as the catalyst, homoallylic silyl alcohol products were obtained in the *E* configuration. However, when PPh_3 was replaced with IPr, homoallylic alcohol products were obtained in the *Z* configuration. The reaction of diene **14** with a handful of aryl aldehydes was investigated. Electron-withdrawing substituents on the aldehydes seemed to somewhat impede the reaction. Yields were generally good and ranged from 54 to 95% (Eq. 13).

This paper was one of the first to demonstrate the generation of a Ni(0)/NHC catalyst in situ from air-stable Ni(II) precursors and an NHC – HCl salt. It was known that the addition of base to NHC – HCl generates the free NHC ligand. In addition, it was also known that Ni(II) can be reduced by organolithium reagents. Mori combined these protocols by using BuLi to reduce the Ni(II) starting material and to deprotonate IPr – HCl. Although Grignard reagents were also evaluated, no Ni(0)/NHC species were observed by ^{13}C NMR.

Mori later found that a silyl diene could serve as a substrate in Ni-catalyzed coupling reactions with aryl aldehydes (Scheme 3) [42]. No comment on the ability to use more substituted diene partners was mentioned. IMes proved to be a superior ligand to I*i*Pr, in contrast to reactions of aryl dienes described above. However, similar to the reactions of aryl dienes, reactions run with PPh_3 and reactions run with IMes displayed differences in product distribution. That is, reactions run with PPh_3 gave *E* products whereas reactions run with IMes gave *Z* products (Scheme 3). Interestingly, higher yields were



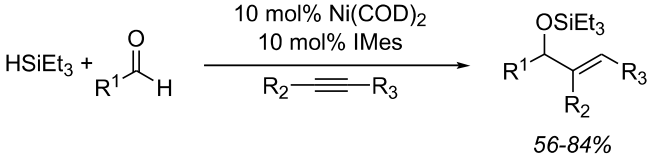
Scheme 3 Silyl diene as substrate in Ni-catalyzed coupling reactions with aryl aldehydes

obtained when an equivalent of PPh_3 was added to the reactions. It is possible that the added PPh_3 serves to stabilize the coordinatively unsaturated Ni – NHC complex, thereby increasing the lifetime of the catalyst. In all cases, reaction times were consistently longer in reactions run with IMes than with PPh_3.

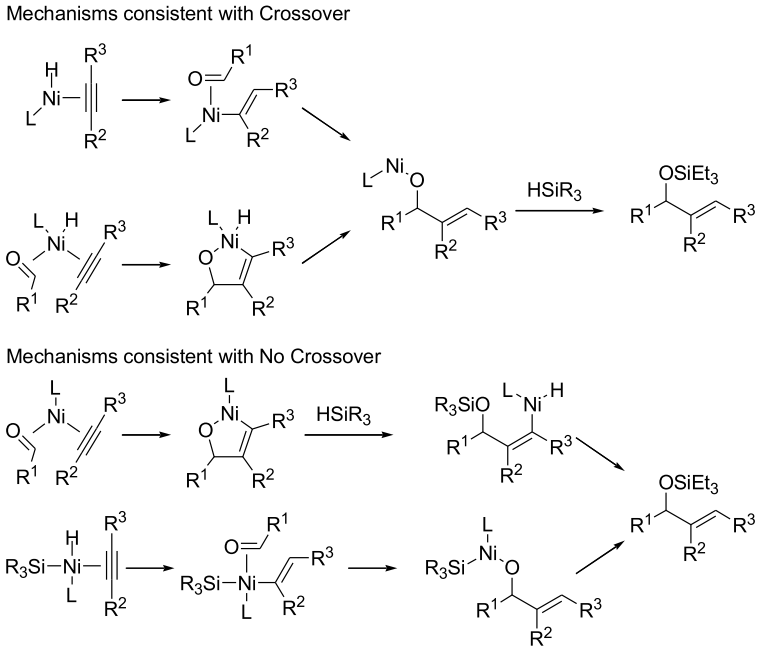
Montgomery and coworkers have focused much attention on the development of Ni-catalyzed reductive couplings [39, 40]. More recently, they have employed NHCs as ligands in the reductive coupling of alkynes and aldehydes with silanes as the reductant (Eq. 14). For example, it was found that the combination of Ni and IMes provides an excellent catalyst system to afford allylic silyl ethers from both aromatic and aliphatic aldehydes in good to excellent yields (56–84%). Both aromatic and aliphatic aldehydes, including electron-rich aromatic aldehydes and sterically demanding aliphatic aldehydes, were used as coupling partners. The alkyne may be internal or terminal, with aromatic or aliphatic substitution patterns being tolerated in both cases. In almost all cases, good regioselectivity was observed (generally 98 : 2) except with an internal aliphatic alkyne (1.3 : 1).

Interestingly, the reactions run with the NHC ligand displayed different reactivity than their original $Ni(COD)_2/PBu_3$ system. It appears that the two catalyst systems may proceed through different mechanisms (Scheme 4). Crossover experiments revealed that significant crossover occurred in reactions run with PBu_3, whereas negligible crossover was observed in reactions run with IMes. Although the actual mechanism and reason for the difference in crossover between the two reactions is still not clearly understood, it is clear that two distinct mechanisms are involved. In reactions run with PBu_3, the authors suggest that either a nickel hydride or nickel silyl species, but not both, is involved. In contrast, the lack of crossover seen with IMes suggests that oxidative coupling of the aldehyde and alkyne and subsequent reaction of the silane may be operative. Alternatively, the Ni/IMes catalyst may oxidatively add the silane, undergo successive alkyne and aldehyde insertions, and ultimately reductively eliminate the product.

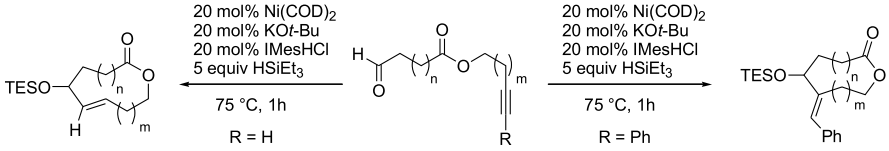
This procedure was later used for the macrocyclization of ynals (Scheme 5) [43]. Macrocyclic rings ranging in size (e.g., 14- to 22-membered rings) and all possessing endocyclic *E*-olefins were obtained from terminal ynals in good yields (62–70%) using a catalyst derived from $Ni(COD)_2$, KO^tBu, and IMes – HCl. Internal alkynes were also examined. Phenyl-substituted alkynes



Equation 14



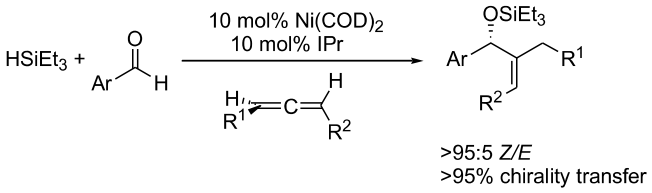
Scheme 4 Possible mechanisms



Scheme 5 Macrocyclization of ynals

afforded macrocycles possessing an exocyclic olefin selectively, regardless of ligand employed (phosphine or NHC). However, the selectivity for exocyclic versus endocyclic olefins diminished with methyl-substituted alkynes.

Jamison and coworkers have used a similar approach for the coupling of allenes, aldehydes, and silanes (Eq. 15) [44]. They first explored the use of



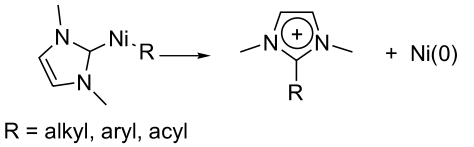
Equation 15

phosphines such as $P(Cy)_3$. The ration of allylic and homoallylic products was excellent (> 95 : 5) but significant erosion of enantiomeric purity (95 to 62%) occurred. The use of IPr solved this problem and a range of internal allenes and aryl aldehydes were converted to the corresponding allylic silyl ethers in yields ranging from 40 to 80%. In all cases, the *Z* geometry corresponded to attachment of the aldehyde to the more hindered face of the allene.

5
Oligomerization and Polymerization

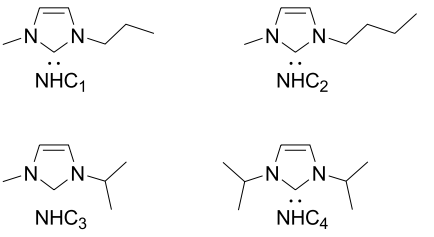
5.1
Olefin Dimerization

When Ni(II) – NHC complexes contain an alkyl, aryl, or acyl group, reductive elimination can occur, affording Ni(0) compounds and 2-mediated organoimidazolium salts (Eq. 16). This pathway results in catalyst decomposition for reactions by Ni – NHC systems [45]. In Ni – NHC-catalyzed olefin dimerization, Cavell and Wasserscheid showed that this decomposition is inhibited when reactions are run in ionic liquids rather than more classical solvents such as toluene [46].

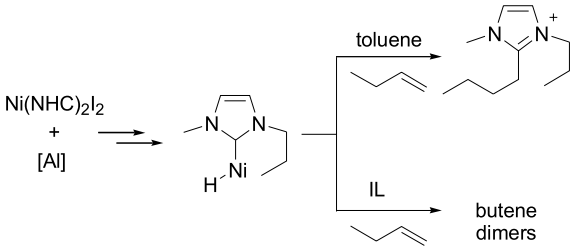


Equation 16

A series of $Ni(NHC)_2I_2$ complexes were prepared and evaluated as catalysts in both toluene and ionic liquids (ILs). In toluene, no butene oligomers were formed at 20 °C. Instead, butene was incorporated into the imidazolylidene cation in the 2-position (Scheme 6). These results suggest that although Ni hydrides and alkyls were being formed, these species reductively elimi-



Structure 1



Scheme 6 $Ni(NHC)_2I_2$ complexes as catalysts in toluene and ionic liquids

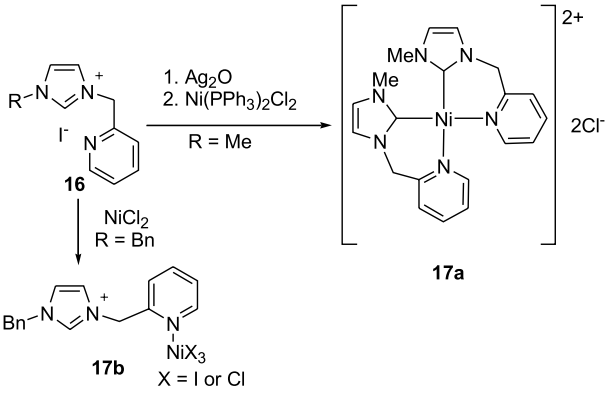
Table 4 1-Butene dimerization in ILs

Entry	Catalyst	Yield (%)	TON	TOF (h^{-1})
1	$NiI_2(NHC_1)_2$	56.3	2815	5630
2	$NiI_2(NHC_2)_2$	70.2	3510	7020
3	$NiI_2(NHC_3)_2$	38.2	1910	3820
4	$NiI_2(NHC_4)_2$	50.7	2535	5070
5	$NiCl_2(PCy_3)_2$	29.5	1475	2950

nated too rapidly for chain growth to occur. In contrast, all reactions run in a buffered melt (composed of a mixture of 1-butyl-3-methylimidazolium chloride, $AlCl_3$, and N-methylpyrrole) showed complete conversion to butene dimers. Interestingly, greater turnover numbers (TONs) and turnover frequencies (TOFs) were observed in reactions catalyzed by Ni – NHC complexes versus $NiCl_2(PCy_3)_2$ (Table 4). In addition, $Ni(NHC_1)_2I_2$ displayed different selectivity from that of $NiCl_2(PCy_3)_2$ toward different isomers in the dimerization of propene. Desirable highly branched propene dimers were obtained in higher ratios with $NiCl_2(PCy_3)_2$. Changes in the organic side chain of the carbene did not lead to an increase in branching, which may suggest the formation of a common active species resulting from incorporation of the imidazolium cation onto the Ni complex. Also, in ionic liquids, phosphine dissociation may not play a significant role.

5.2 Insertion Polymerization

By changing the NHC ligands to NHCs possessing a hemilabile pyridine linkage, Jin and coworkers were able to use Ni(II) – NHC complexes as catalysts for the polymerization of norbornene and ethylene in the presence of methylaluminoxane (MAO) as a cocatalyst [47]. The Ni complexes were prepared via Scheme 7. Although the free carbenes of **16** could not be generated successfully, the desired Ni compounds (**17**) could be prepared via the



Scheme 7 Preparation of Ni complexes **17a** and **17b**

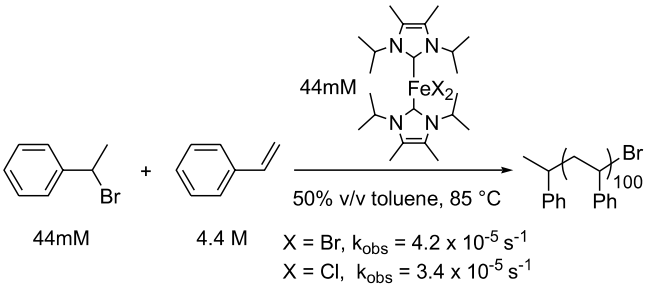
preparation of Ag – NHCs and subsequent reaction with $Ni(PPh_3)_2Cl_2$. X-ray analysis revealed that both compounds possess essentially square planar geometries and the two chelates adopt a *cis* arrangement around the nickel atom.

The catalytic activity for olefin polymerization was evaluated for complex **17a**. High molecular weight addition-type polynorbornene (PNB) with a moderate molecular weight distribution ($M_w = 10^6$, $M_w/M_n = 2.3–3.5$) was obtained when **17a** was activated with MAO. The activity was highest at 80 °C (10^7 g of PNB/(mol of Ni) h^{-1}) resulting from an increase in the concentration of active catalyst centers at that temperature. However, further increases in temperature led to catalyst decomposition rather than higher turnover numbers.

Complex **17a** displayed moderate catalytic activity toward the polymerization of ethylene (3.3×10^5 g/mol h^{-1}). In addition, higher molecular weight distributions were observed ($M_w/M_n = 12.8$). The ^{13}C NMR analysis of the polyethylene showed that methyl branches predominate (with ca. 3.4 methyl branches per 1000 carbon atoms), suggesting that chain walking does not affect polymerization to a high degree. When only the pyridine moiety (and not the imidazolium salt) is ligated (**17b**) [48], ethylene polymerization occurs twice as effectively (6×10^5 g PE/(mol of Ni) h^{-1}) under similar conditions (only 30 min rather than 60 min).

5.3
Atom Transfer Radical Polymerization

Louie and Grubbs prepared an iron-based catalyst for atom transfer radical polymerization (ATRP) [49]. By heating a solution of I*i*Prim and FeX_2 (X = Br, Cl), crystals of $Fe(I\mathit{i}Prim)_2X_2$ were obtained. These complexes mediated the homogeneous ATRP of styrene and methyl methacrylate with

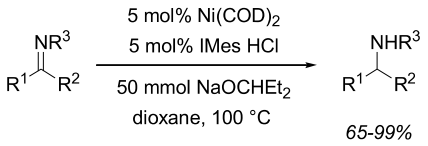


Equation 17

excellent efficiency (Eq. 17). In addition, polymerizations could be run by using FeX_2 and I*i*Prim directly to generate the active catalyst in situ, although observed rates were slightly lower which may be due to an induction period involving catalyst formation. Importantly, polymerization rates were high and polydispersities were low (ca. 1.1). The molecular weight of both the polystyrene and poly(methyl methacrylate) increased linearly over time and agreed with theoretical weights, demonstrating good control. In both cases, the bromo complex had a higher observed rate constant than the chloro complex, which may be related to the difference in the iron halide bond dissociation energies.

6
Transfer Hydrogenation

Fort and Schneider showed recently that the combination of Ni(0) and IMes catalyzed the transfer hydrogenation of imines to the corresponding amines in the presence of $NaOCHEt_2$ (Eq. 18) [50]. A variety of aldimines and ketimines were reduced in good to excellent yields under mild conditions. A range of NHC ligands were explored, including those possessing pendant, hemilabile pyridines. However, only IMes was effective and gave high yields of the expected product. Surprisingly, reactions run under identical conditions except with IPr afforded only trace amounts of product. Clearly no correlation between catalyst activity and NHC ligand could be rationalized.



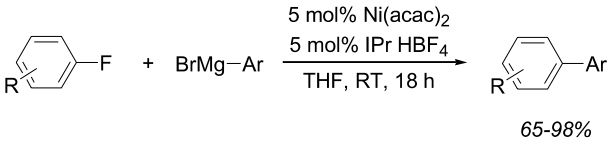
Equation 18

Thus, using Ni(0) and IMes, amines possessing a wide range of functionalities were obtained in yields ranging from 65 to 99%. No hydrogenation was observed with cyano- and pyridine-substituted imines and is likely due to ligand displacement and subsequent catalyst deactivation.

7
Nickel-Catalyzed Cross-Coupling

7.1
The Kumada–Corriu Reaction

The use of metals other than Pd for cross-coupling reactions has received much attention due to the high cost of Pd precursors. Toward this end, Böhm and Herrmann have shown that 5 mol % of the $Ni(IPr)_2$ complex efficiently catalyzes the coupling of aryl Grignards and aryl fluorides to yield the biaryls in high GC yields [51]. Further investigation led to the discovery that a better catalyst could be generated in situ from a 1 : 1 mixture of $Ni(acac)_2$ and the IPr – HBF_4 salt, thus eliminating the need to synthesize the air-sensitive $Ni(IPr)_2$ complex (Eq. 19). It is believed that this mixture generates a highly reactive 12-electron Ni complex bearing a single carbene. Using this system, both electron-rich and electron-poor aryl fluorides were successfully coupled with a variety of aryl Grignards generating the biaryls in good to excellent yields. While four different pathways can be considered for the C – F bond transformation [(1) nucleophilic aromatic substitution, (2) elimination–addition via aryne intermediates, (3) radical pathways, and (4) polar pathways via oxidative addition], experimental data strongly support a polar pathway.

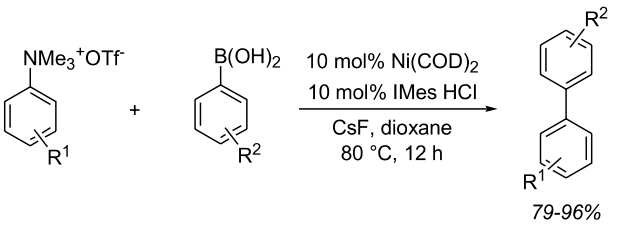


Equation 19

7.2
The Suzuki–Miyaura Reaction

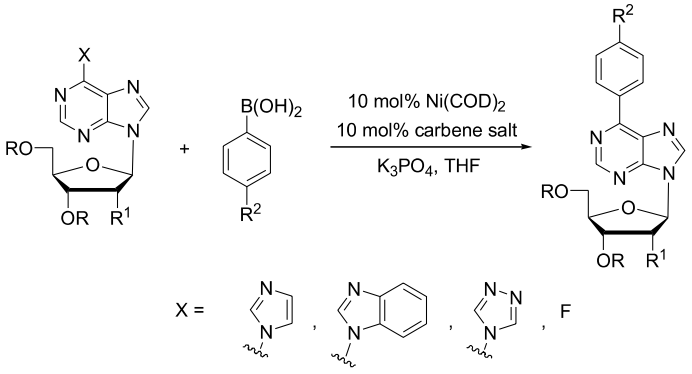
Nickel/carbene complexes have also been successfully employed in the Suzuki–Miyaura cross-coupling reaction. One of the first successful applications of this was demonstrated by Blakey and MacMillan, wherein boronic acids were coupled with aryltrimethylammonium salts [52]. It was found that the transformation could be accomplished using 10 mol % $Ni(COD)_2$,

10 mol % IMes – HCl, and 3 equivalents of CsF in dioxane (Eq. 20). A wide range of aryltrimethylammonium triflates and aryl boronic acids were successfully coupled using this protocol.



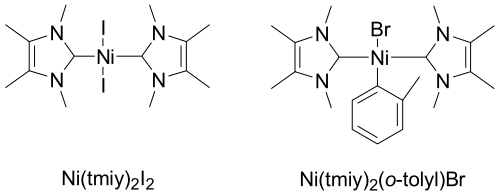
Equation 20

A system similar to that of Blakey and MacMillan was later developed by Liu and Robins, in which purine derivatives containing imidazol-1-yl, 1,2,4-triazol-4-yl, and fluoro leaving groups at the 6-position could be coupled with both electron-rich and -poor aryl boronic acids (Eq. 21) [53, 54]. While the Blakey–MacMillan system used the IMes – HCl carbene, it was found that the purine derivatives required the use of the larger SIPr – HCl (or IPr – HCl, in the case of triazole leaving groups). It is also interesting to note that the choice of base is highly substrate dependent. In the purine reaction, K_3PO_4 was found to generally be the best base while in the trimethylammonium triflate reaction, CsF was far superior to K_3PO_4.



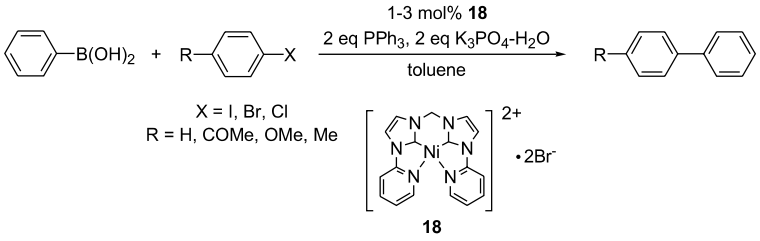
Equation 21

Examples of well-defined, highly active Ni/carbene complexes catalyzing the Suzuki reaction have also been reported. McGuinness and coworkers have shown that using as little as 0.03 mol % of $Ni(tmiy)_2I_2$ or $Ni(tmiy)_2$(*o*-tolyl)Br (tmiy = 1,3,4,5-tetramethylimidazol-2-ylidene) in the coupling of 4-bromoacetophenone with phenylboronic acid led to 19% (TON = 630) and 58% (TON = 1930) conversion of the aryl halide, respectively [55].



Structure 2

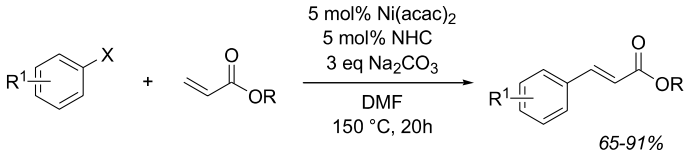
More recently, Chiu and coworkers have developed a Ni complex containing a tetradentate pyridine/NHC ligand (complex **18**, Eq. 22) which catalyzes the Suzuki reaction at catalyst loadings between 1 and 3 mol % [56]. Aryl iodides, bromides, and chlorides with both electron-rich and -poor aryl rings were compatible. However, electronically poor or electronically neutral aryl bromides performed much better than did electron-rich aryl bromides. It was also found that the use of 2 equivalents of PPh_3 was crucial to achieving high yields with aryl chlorides.



Equation 22

7.3 The Heck Reaction

Nickel/NHC complexes have been examined as catalysts for the Heck coupling as well. Inamoto and coworkers have discovered that a variety of aryl bromides and iodides could be coupled with acrylates using 5 mol % $Ni(acac)_2$ and 5 mol % of the appropriate NHC salt in the presence of Na_2CO_3 (Eq. 23) [57]. While the majority of aryl halides could be coupled using the

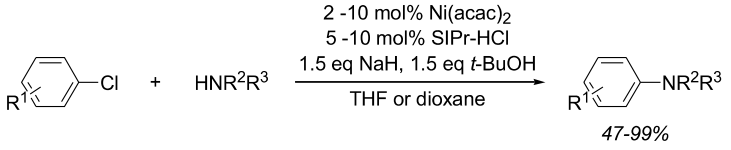


Equation 23

IMes – HCl salt, this was substrate dependent. For instance, aryl iodides possessing OMe groups at the *para* or *meta* position required the use of the IPr – HCl salt as ligand while 4-bromobenzaldehyde required the use of the SIPr – HBF_4 salt.

7.4 Amination Reactions

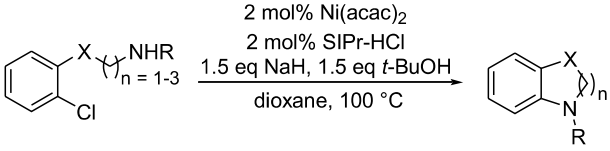
The use of Ni/NHC catalysts has been extended to carbon–nitrogen bond-forming reactions. Fort and coworkers have found that in situ generation of the Ni(0) and SIPr carbene efficiently catalyzes the coupling of aryl chlorides with various amines (Eq. 24) [58, 59]. During the course of the study, it was discovered that Ni(0) could be generated from $Ni(acac)_2$ in the presence of NaH and *t*-BuOH. It is believed that the in situ generated NaO^tBu serves three purposes in the reaction: (1) it activates the NaH used to reduce the Ni(II) to Ni(0), (2) it deprotonates the imidazolium salt to generate the free carbene, and (3) it serves to deprotonate the amine. While several imidazolium salts were tested for the reaction, SIPr – HCl was found to be the most effective, even surpassing the originally disclosed bipy. Using the protocol developed, both electron-rich and -poor aryl chlorides were successfully coupled with secondary cyclic and acyclic amines, primary and secondary anilines, and primary alkyl amines all in good yields.



Equation 24

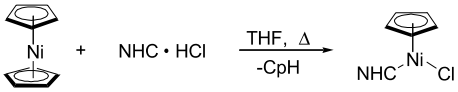
An intramolecular variant of this reaction was also developed to synthesize five-, six-, and seven-membered rings (Eq. 25) [60]. Again, the use of the SIPr ligand was found to be the most effective catalyst, but in a 1 : 1 Ni/SIPr ratio. It is interesting to note that the use of the SIPr ligand is complementary to the use of the bipy ligand. Specifically, the SIPr ligand can catalyze the coupling of primary amines with aryl chlorides where the bipy ligand cannot. However, when X = O, only bipy was found to be able to synthesize the seven-membered ring.

Nolan and coworkers have also recently developed an amination of aryl bromides and chlorides with morpholine using 5 mol % of the well-defined CpNi(NHC)Cl catalyst [61]. The catalyst can be easily prepared by refluxing the NHC – HCl in a THF solution of nickelocene (Eq. 26). The well-defined catalyst has the advantage of not having to generate the free carbene, which can sometimes be problematic depending on the stability of the carbene.



Equation 25

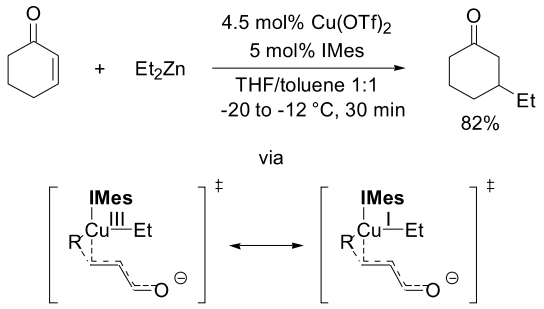
While the IMes, SIMes, IPr, and SIPr complexes were all tested for catalytic activity, the SIPr complex was found to be the most effective. It should be noted that while the reaction conditions are very similar to those developed by Fort, Nolan found that KO^{t}Bu rather than NaO^{t}Bu was necessary to achieve good results.



Equation 26

8 Copper-Catalyzed Conjugate Additions

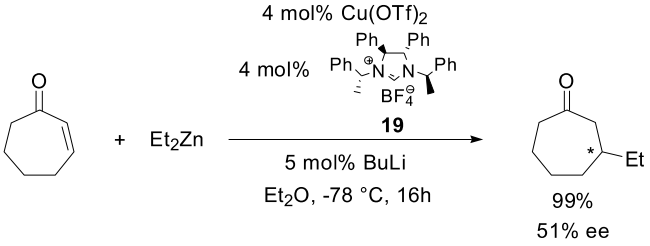
The use of NHC ligands has also found application in copper-catalyzed conjugate additions. This was initially disclosed by Woodward and coworkers who found that IMes provided a large rate increase in the copper-catalyzed $ZnEt_2$ addition into cyclohexanone (Eq. 27) [62]. It is believed that the increase in rate arises from the strong σ donation of the carbene, which in turn provides stabilization of the copper(III) transition state. This avoids the need for the metal center to attain a high-energy Cu^{3+} $3d^8$ configuration with the developing enolate. While the use of the carbene was found to greatly enhance the



Equation 27

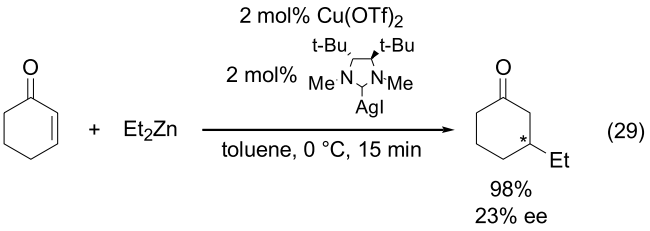
rate of addition, the substrate scope was limited and was sensitive to the steric requirements of the enone.

Building on the success of Woodward's use of an achiral NHC to catalyze the conjugate addition of dialkyl zincs, Alexakis and Roland simultaneously reported the use of chiral NHCs to achieve the asymmetric addition into enones. In Alexakis's system, the catalyst was generated in situ by addition of BuLi to a suspension of imidazolium salt **19**, $Cu(OTf)_2$, and enone in toluene followed by addition of Et_2Zn (Eq. 28) [63]. While conversions and yields were found to be nearly quantitative, ee values were moderate with 51% being the highest reported.



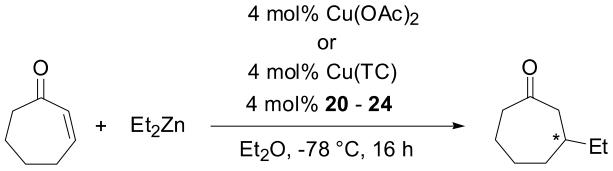
Equation 28

In the Roland system, the chiral silver(I) diaminocarbene complex (generated from Ag_2O and the imidazolium salt) was used to transfer the carbene to the copper (Eq. 29) [64]. The silver(I) complexes have the distinct advantage of being compatible with acidic protons in chains of azolium salts, as a strong base is not necessary for their use. They are also stable and not hygroscopic, increasing the ease of handling. As with Alexakis's system, conversions and yields were high, but ee values were low with the best being 23%.

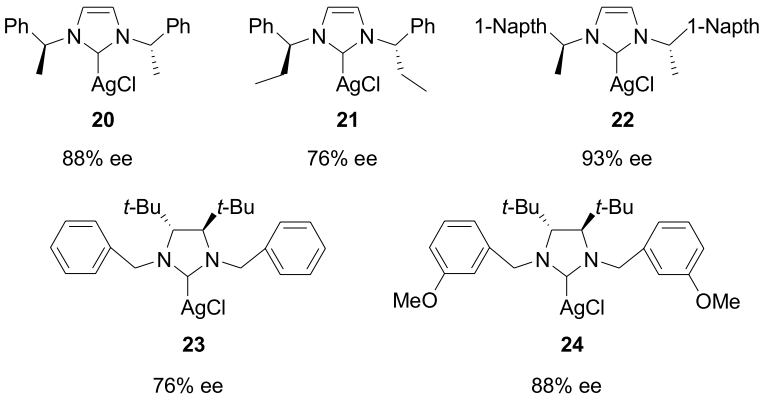


Equation 29

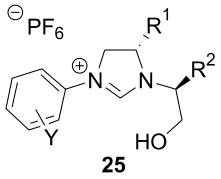
Later, in a collaborative work between Roland and Alexakis, it was found that the use of copper carboxylates as the copper source and Et_2O as the solvent was critical to achieving high ee values (Eq. 30) [65]. In this study, several Ag/carbene complexes (**20**–**24**) were tested and found to produce significantly higher ee values than those in previous studies. Other Michael acceptors such



Equation 30



Structure 3



Structure 4

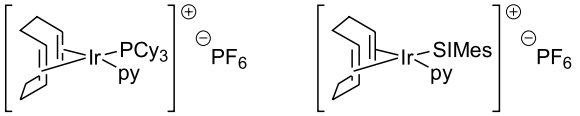
as benzalacetone and nitrostyrene also gave good conversions and yields, but with lower ee values.

More recently, an in-depth study of various alkoxy-NHC ligands of the general structure shown in ligand **25** has been completed [66]. The optimal conditions were determined to be $Cu(OTf)_2$ as the copper source, ambient temperature, BuLi or DBU as the base, and Et_2O as solvent. It was determined that the best ligands possessed the bulky mesityl group, which blocked the approach of the substrate from that side of the ligand. Furthermore, it was determined that the alkoxy moiety was crucial for achieving high enantioselectivity. It was also necessary to have the chiral center at the C-2 position of the alkoxymethylene side chain near the NHC backbone.

9
Rhodium- and Iridium-Catalyzed Hydrogenation

9.1
H_2 Hydrogenation

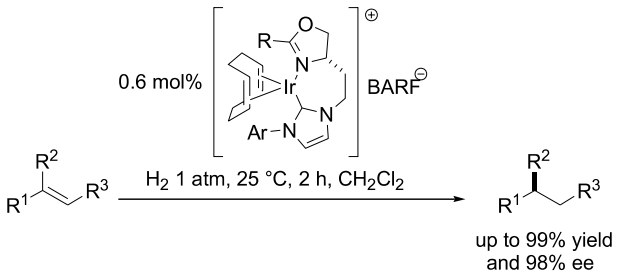
The use of NHCs has also found application in the catalytic hydrogenation of olefins. By the simple ligand exchange reaction of $[Ir(COD)_2(py)_2]PF_6$ with SIMes in toluene, Nolan and coworkers have prepared the SIMes analog (**27**) of Crabtree's catalyst (**26**) [67]. The reactivity of this complex was tested for catalytic activity in the hydrogenation of several olefins. While the complex did show activity, it was less efficient than Crabtree's catalyst at ambient temperature and atmospheric H_2 pressure. However, the SIMes complex did display greater activity at 60 psi of H_2 pressure and 50 °C.



26 **27**

Structure 5

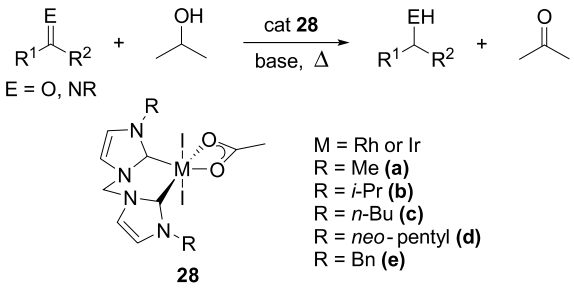
Soon after Nolan's disclosure, Burgess and coworkers reported the use of optically active Ir NHC/oxazoline complexes to enantioselectively hydrogenate olefins bearing no coordinating functionality (Eq. 31) [68, 69]. The hydrogenations were found to proceed with excellent yield and enantioselectivity under extremely mild conditions (room temperature, 1 atm of H_2 pressure, and catalyst loading of 0.6 mol %). In fact, increasing the H_2 pressure led to a *decrease* in enantioselectivity for certain substrates. While several ligands were evaluated for the reaction, a ligand possessing R = adamantyl and Ar = 2,6-^{i}Pr$_2$C$_6$H$_3$ was found to give excellent ee values. The range of substrates was not excessively broad, but simple *E* and *Z* trisubstituted olefins were compatible as well as 1,1-disubstituted olefins.



Equation 31

9.2
Transfer Hydrogenation

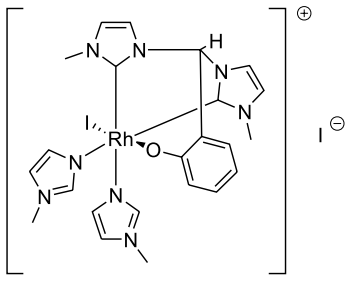
Carbene complexes of Ir and Rh have been used in transfer hydrogenation reactions. Crabtree and coworkers found that complexes of the type **28** catalyze the reduction of ketones to the corresponding alcohols (E = O, Eq. 32) [70–72]. Both of the air-stable Rh and Ir complexes **28b** efficiently catalyzed the reduction of ketones using 0.1 mol % catalyst in the presence of 0.5 mol % KOH. However, while the Rh complex was effective for the reduction of both ketones and imines [70], the Ir catalyst was unable to effectively reduce imines or amine-containing substrates. The inability of the Ir catalyst to reduce imines is most likely due to the substrate inhibition of the catalyst [71]. However, upon changing the base to an alkali-metal carbonate and changing the linker on the carbene ligand to a neopentyl group, the Ir catalyst was successful in reducing aldehydes to the corresponding alcohols [72].



28

Equation 32

Nolan and coworkers have described the use of their cationic Ir complex **27** as an effective catalyst for transfer hydrogenations [73]. While complex **27** was found to be effective, the analog bearing the NHC ICy was found to be su-



29

Structure 6

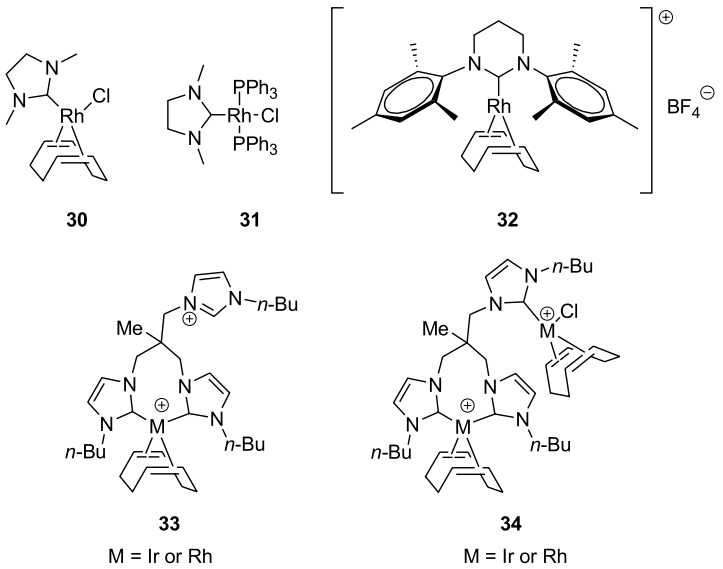
perior. Using this catalyst, ketones, olefins, enones, and nitro functionalities were reduced using 0.025 mol % catalyst and 0.05 mol % KOH. It should be noted that this catalyst was able to reduce unactivated olefins where Crabtree's complex **26** proved ineffective.

The use of the Rh complex **29** bearing a tridentate carbene ligand has also been described for the transfer hydrogenation of ketones and imines [74]. The catalyst was found to be highly active, needing only 0.001 mol % (up to 68 000 TON) to completely reduce to substrates.

10
Rhodium- and Iridium-Catalyzed Hydrosilylation

10.1
Hydrosilylation

Metal/carbene complexes (**30**–**34**) have also proved fruitful in the hydrosilylation of alkynes, olefins, enones, and ketones. Lappert and Maskell showed that ketones and alkynes could be reduced to silyl ethers and vinylsilanes, respectively, using complexes **30** and **31** (Eqs. 33 and 35) [75]. The yields tended to be high (92 and 98%, respectively), but the reactions needed to be run neat. Poor selectivity was observed in the hydrosilylation of alkynes producing a mixture of the β-*trans*, β-*cis*, and α products.

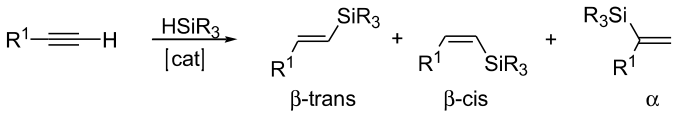


30 **31** **32**

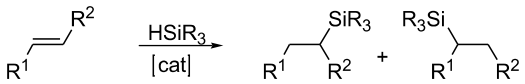
33 **34**

M = Ir or Rh M = Ir or Rh

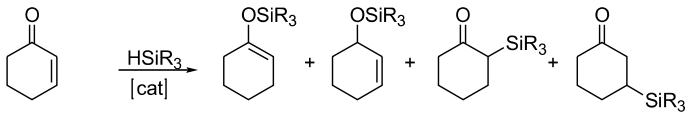
Structure 7



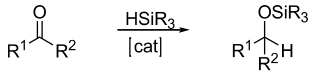
Equation 33



Equation 34



Equation 35



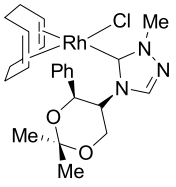
Equation 36

Buchmeiser and coworkers found that complex **32** is also capable of catalyzing the various hydrosilylations (Eqs. 33–36) with 0.05 mol % of the complex [76]. In the hydrosilylation of alkynes, poor selectivity was again observed yielding mixtures of the β-*trans*, β-*cis*, and α products in combined yields of 9–69%. Only the hydrosilylation of 1-hexyne with dichloromethylsilane gave good selectivity, generating only the β-*trans* vinylsilane in 36% yield. Better selectivity was observed for the hydrosilylation of terminal olefins and cyclohexenone, yielding only the β-addition alkylsilane and the silylenol ether, respectively. Aryl aldehydes were also successfully reduced to the silyl ethers in 17–37% yield. For all of the hydrosilylations, $HSiEt_3$ produced the highest yields.

Peris and coworkers have also disclosed Ir and Rh complexes **33** and **34** which can catalyze the hydrosilylation of alkynes [77]. Again, poor selectivity was observed as mixtures of the β-*trans*, β-*cis*, and α addition products were obtained. Generally speaking, it was found that Rh catalysts were more reactive than the Ir catalyst and the dimetallic complexes were much more active than their monometallic counterparts. It is believed that the difference in reactivity between the dimetallic and monometallic complexes arises from the dimetallic species' ability to oxidize to the corresponding M(III) species, thus preventing oxidative addition of the silane.

10.2
Asymmetric Hydrosilylation of Ketones

The asymmetric hydrosilylation of ketones is an attractive approach to generate chiral secondary alcohols. The use of NHCs as ligands in this process has been slow to emerge as the planarity of the imidazole ring limits enantioselectivity. Early work by the Enders group showed that using chiral Rh catalysts such as **35**, methyl ketones could undergo hydrosilylation to give moderate enantioselectivities up to 44% [78, 79].

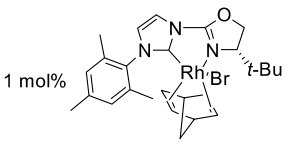


35

Structure 8

Gade and coworkers had much better success with the application of an oxazoline/carbene-derived ligand [80]. Catalyst **36** (Eq. 37), when paired with $AgBF_4$, was found to impart high enantioselectivities in the hydrosilylation of aryl ketones (88–91% ee) in excellent yields. High enantioselectivities were also observed for dialkyl ketones including ketones lacking α branching, which tend to be more challenging.

The Shi and Crabtree groups have found that iridium and rhodium complexes derived from BINAM (1,1'-binaphthyl-2,2'-diamine) are also capable of the transformation. While Shi's Rh catalyst **37** [81] gave similar results to those reported by Gade, Crabtree's Ir catalyst **38** [82] was less effective, providing optical induction of only 60%.



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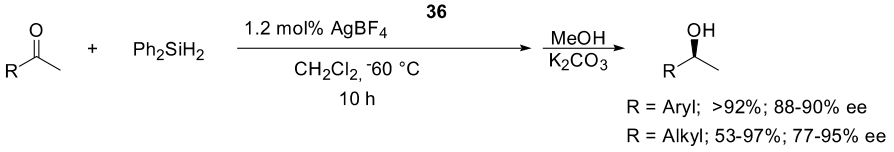
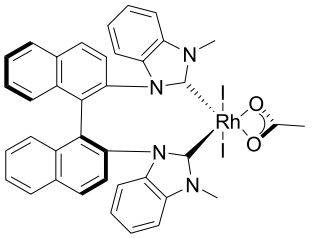


Equation 37



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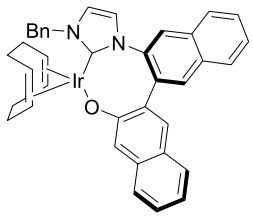
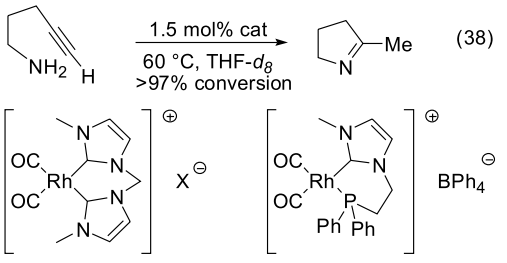


38

Structure 9

11 Hydroaminations

The hydroamination of alkynes has received a great deal of attention. Recently, NHC/Rh complexes have been reported to catalyze this transformation. Turner and coworkers have found that Rh catalysts derived from the NHC chelating ligands are capable of catalyzing intramolecular hydroaminations (Eq. 38) [83, 84]. Using 1.5 mol % of complex **39**, 76 and 85% conversions were obtained after 16 h for the BPh_4 and PF_6 analogs, respectively [83]. It was later discovered that the mixed donor phosphine–NHC complex **40** was much more reactive, giving almost complete conversion in 14 h [84]. It is believed that the increased reactivity of the mixed donor complex arises from the greater lability of the phosphine as compared with the carbene.



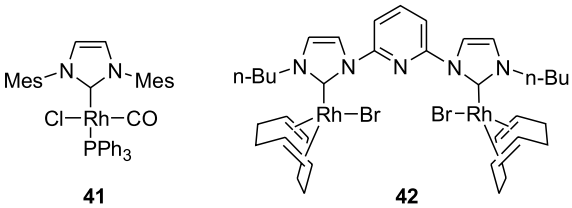
X = PF_6 or BPh_4

39 40

Equation 38

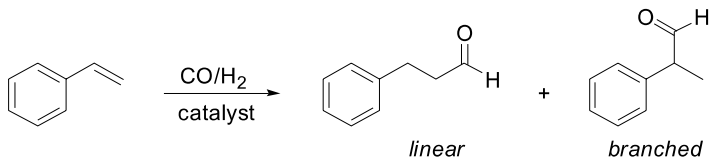
12 Hydroformylations

The hydroformylation of alkenes is a synthetically and industrially useful reaction (Eq. 39). Recently, Rh/NHC complexes have been applied toward this



41 42

Structure 10



Equation 39

reaction. Crudden and coworkers disclosed that the Rh catalyst **41** is able to efficiently hydroformylate various styrenes in both high yields (85–95%) and high selectivity of the branched product (> 95 : 5) [85]. The addition of 2 mol % of PPh_3 was found to be crucial for high activity. Peris and coworkers have also reported that dimetallic Rh complex **42** is a competent catalyst for the transformation [86]. While high selectivities for the branched product were obtained for styrene derivatives (> 95 : 5), 1-octene and 2,5-furan gave poor selectivity.

13 Conclusions

The number of synthetic methods catalyzed by transition metal complexes (such as Ni, Cu, Rh, Ir, Ru, and Pd) has risen since the discovery that NHCs can serve as ligands for transition metals. By coordinating an NHC ligand, the stability of the transition metal typically increases. In addition, the increased donacity of the NHC ligand helps to enhance the catalytic activity. Clearly, the arrival of these NHCs has opened new vistas in the ever-growing field of transition metal-mediated catalysis.

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N-Heterocyclic Carbenes as Ligands for Olefin Metathesis Catalysts

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Abstract Olefin metathesis is a powerful tool to form carbon–carbon double bonds in organic and polymer chemistry. The introduction of N-heterocyclic carbenes as ligands for ruthenium catalysts led to an impressive evolution in olefin metathesis. Indeed, the NHC–ruthenium complexes (second generation) display higher activity and reactivity compared to the parent phosphine-based complexes (first generation). In this chapter the improvements of the second generation catalysts will be illustrated. We will further present a brief discussion of the mechanism and the synthesis of NHC-containing olefin metathesis catalysts. In the final part, a survey of currently available second generation

catalysts will be discussed with a particular emphasis on structural modifications of the NHC ligand.

Keywords Homogeneous catalysis · N-heterocyclic carbenes · Olefin metathesis · Osmium · Ruthenium

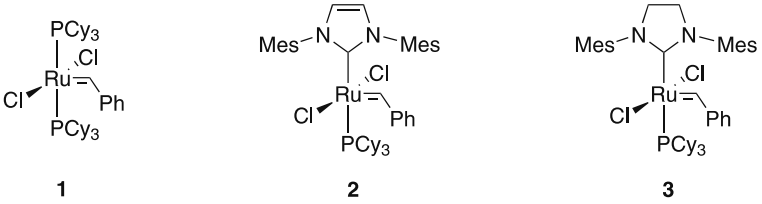
Abbreviations

CM	Cross metathesis
COD	*cis*,*cis*-Cycloocta-1,5-diene
conv.	Conversion
NHC	N-Heterocyclic carbene
RCM	Ring-closing metathesis
ROMP	Ring-opening metathesis polymerization

1 Introduction

Olefin metathesis has become a widely used method for the construction of carbon–carbon double bonds in organic and polymer chemistry [1]. The preparation of well-defined, functional group tolerant, and reactive transition metal complexes for olefin metathesis has initiated a vast evolution in this field, which culminated in the award of the Nobel Prize 2005 *for the development of the metathesis method in organic synthesis* to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock. The introduction of NHCs as ligands can be considered a major breakthrough for the development of more efficient olefin metathesis catalysts. Indeed, second generation ruthenium catalysts such as **2** [2–5] and **3** [6] display the high activity of molybdenum complexes and the high tolerance toward functional groups exhibited by first generation ruthenium catalysts such as **1** (Fig. 1) [7, 9] (for lead references of molybdenum-based catalysts, see [8]).

This chapter will give an outline of how the application of NHCs has influenced the field of olefin metathesis. The improvements in activity and reactivity observed with second generation catalysts compared to first generation catalysts will be the major focus. We will not provide a comprehensive



1 **2** **3**

Fig. 1 First and second generation ruthenium catalysts

review of the rapidly growing field of olefin metathesis, but instead will highlight specific examples to showcase the main achievements of ruthenium catalysts bearing NHCs. Subsequently, we will present a brief discussion of the synthesis and the mechanism of complexes such as **2** and **3** followed by a survey of currently available catalysts containing NHC ligands.

2
Improvements in Metathesis with NHC–Ruthenium Catalysts

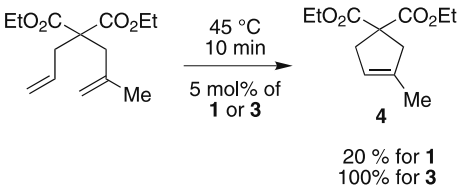
The major advantages of ruthenium catalysts bearing NHCs such as **2** and **3** are their superior stability compared to the first generation catalysts such as **1** and their increased activity for olefin metathesis. The bench stability of second generation catalysts is increased which facilitates handling but, more importantly, the thermal stability and tolerance of oxygen and moisture in solution exceed those of the first generation catalysts [6, 10–12]. This beneficial feature is presumably, at least in part, due to a decreased rate of phosphine dissociation to generate a coordinatively unsaturated 14-electron (14e) species (see discussion of the mechanism). In general, NHC-based ruthenium catalysts have higher reactivity in ring-closing metathesis, cross metathesis, and polymerizations. Commonly, faster reaction rates are observed and thus reaction temperatures can be lowered, which results in slower rates of catalyst decomposition. The accessible substrate scope for a given reaction class with second generation catalysts is greater than with first generation catalysts. Importantly, the increased activity of the NHC-containing catalysts also allows for catalysis of new, different transformations, which could not be accessed by the earlier catalysts [13–33] (Ritter et al., unpublished results).

Despite the various advantages of second generation catalysts, which will be the major focus of this chapter, it has to be pointed out that the first generation catalysts have not been superseded but retain their utility in organic and polymer synthesis and sometimes afford even superior results [34].

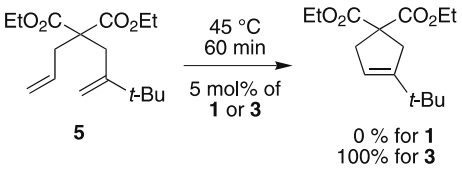
2.1
Ring-Closing Metathesis

In ring-closing metathesis reactions, catalyst **3** shows increased activity compared to **1** in forming substituted cyclopentenes such as **4** (Eq. 1) [6]. The improved reactivity of **3** is also exemplified in the metathesis reaction of the sterically more crowded and thus more challenging substrate **5** which, under the given reaction conditions, can be reacted in high yield with **3** but not with **1** (Eq. 2) [13]. It is a general trend that bulky substituents, especially in the allylic position or directly at the double bond, significantly slow the metathesis reactions and that **3** affords higher yields for such substrates than **1**. For other demanding substrates such as macrocycles catalyst **3** has

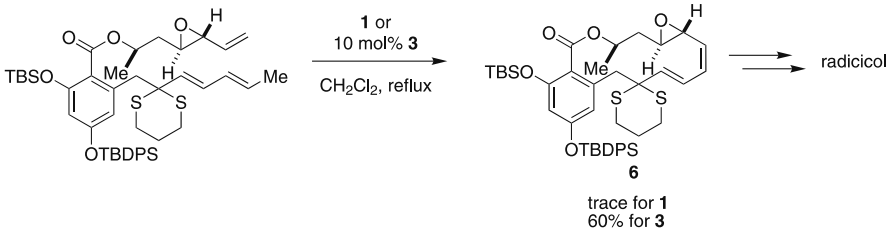
broadened the utility of olefin metathesis [14, 15]. This is nicely exemplified in the syntheses of radicicol by Danishefsky et al. [16, 17] and aspercyclide C by Fürstner et al. [18]. While **1** furnished macrocycle **6** in trace amounts, utilization of catalyst **3** afforded **6** in 60% yield (Eq. 3). A yield of 69% was obtained for the macrocyclization reaction of **7** using **2**, whereas **1** was not a competent catalyst for this reaction since the reaction remained incomplete even when using 50 mol % of **1** (Eq. 4).



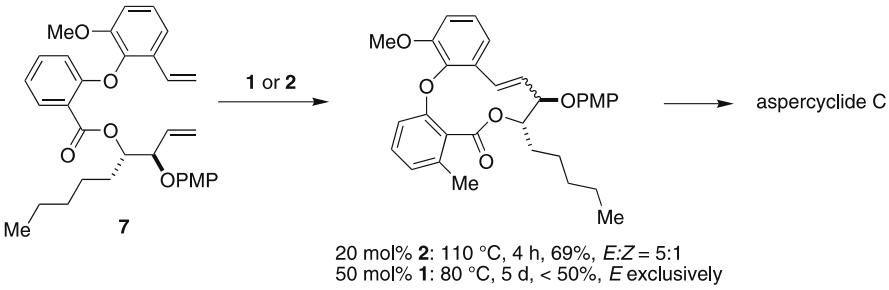
Equation 1



Equation 2



Equation 3

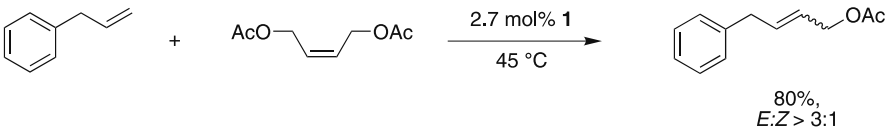


Equation 4

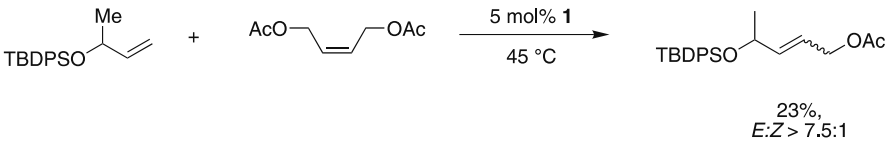
2.2 Cross Metathesis

Cross metathesis is an intermolecular variant of olefin metathesis. Arguably, cross metathesis has benefited the most from the introduction of more active catalysts due to their ability to significantly expand the scope of substrates which now can participate in cross metathesis [19]. Only reactive olefins (unhindered, not electron poor) could be employed for cross metathesis reactions catalyzed by **1** (Eq. 5) [20]. Introduction of steric bulk dramatically decreases reaction yields (Eq. 6) and electron-deficient olefins fail to participate in cross metatheses when using **1**. Grubbs et al. showed that by using second generation catalysts a great variety of functionalized and substituted olefins can be used for cross metathesis. α,β-Unsaturated carbonyl compounds [21], vinyl phosphonates [22], and vinyl sulfones [23] can undergo cross metathesis in high yield to form homodimers (Eq. 7) [24], or chemoselective cross metathesis (Eqs. 8, 9) [22, 25]. Highly substituted olefins such as trisubstituted double bonds can be formed in high yield. The introduction of prenyl groups, common groups in natural products, can be efficiently achieved through cross metathesis by using isobutylene or 2-methyl-2-butene as cross metathesis partners (Eq. 10) [26, 27]. This method was employed in complex syntheses such as those toward the natural product garsubellin A (Eq. 11) [28] or the synthesis of the natural product flustramine B (Eq. 12) [29].

Cross metathesis catalyzed by **1** has found only limited use not only due to a fairly narrow substrate scope as outlined above, but also because of the



Equation 5



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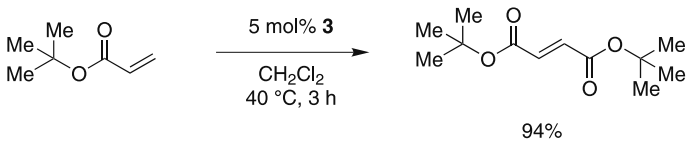
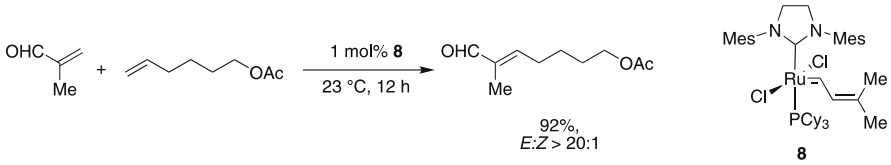
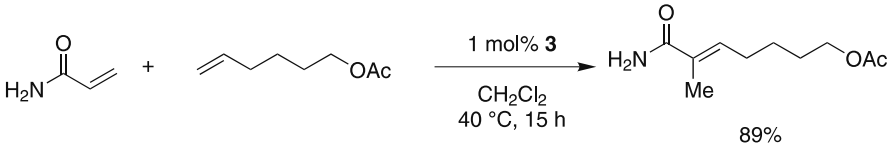


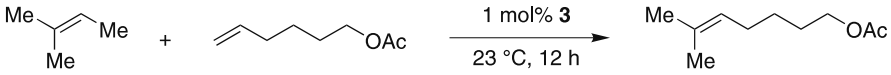
Equation 7



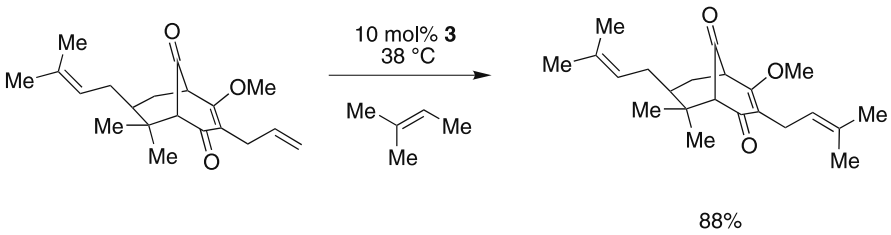
Equation 8



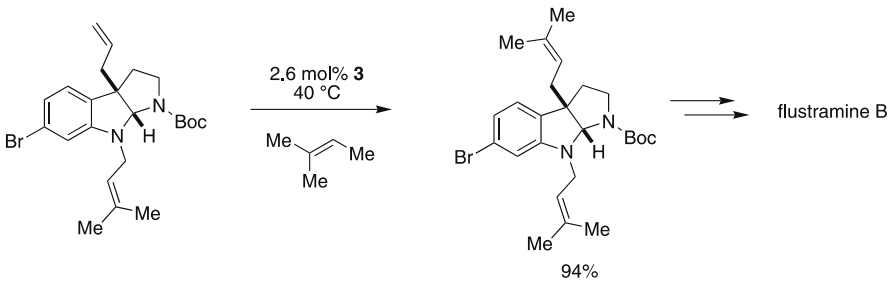
Equation 9



Equation 10



Equation 11



Equation 12

statistical yield of this reaction. With simple olefins the product yields are limited to 50% if the reaction partners are used in a 1 : 1 ratio. To overcome this handicap, Grubbs et al. have developed empirical guidelines for the prediction of the outcome of cross metathesis reactions based on the different reactivity of various olefins with a given olefin metathesis catalyst [19]. This categorization of olefins is based on the different rate at which functionalized

Table 1 Olefin categories for selective metathesis

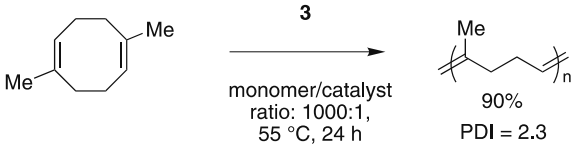
Olefin type	Catalyst **1**	Catalyst **3**
Class 1 (fast homodimerization)	Terminal olefins, allyl silanes, 1° allylic alcohols	Terminal olefins, allyl silanes, 1° allylic alcohols, styrenes
Class 2 (slow homodimerization)	Styrene, 2° allylic alcohols	Styrenes (large *ortho* substituents), acrylates, acrylamides, vinyl ketones
Class 3 (no homodimerization)	Vinyl siloxanes	1,1-Disubstituted olefins, trisubstituted olefins, 3° allylic alcohols
Class 4 (spectators to CM)	1,1-Disubstituted olefins, disubstituted α,β-unsaturated carbonyls	Vinyl nitro olefins

olefins undergo self-metathesis. Olefins have been classified into four categories from rapid homodimerization (class 1), over slow homodimerization (class 2) and no homodimerization (class 3), to spectators to cross metathesis (class 4). The most important factors for olefin type classification are steric bulk, especially in the allylic position or directly on the double bond, and electronic factors with the least substituted and most electron-rich double bonds being the most reactive. Hence, terminal olefins or unhindered allylic alcohols are classified as type 1 olefins for catalyst **3**, whereas acrylates and vinyl ketones are part of class 2 olefins and 1,1-disubstituted and trisubstituted olefins are class 3 olefins [19]. This classification now allows for the prediction of chemoselective cross metathesis reactions when the reaction partners are part of different classes, affording the products in high yields as demonstrated in Eqs. 8–12. Table 1 gives a brief summary of the olefin categorization for catalysts **1** and **3**. It is important to note that catalyst **3** covers a greater olefin variety in classes 1–3 than **1**, and hence a larger set of selective cross metathesis reactions can be accessed. The spectator olefins for cross metathesis (class 4) are more numerous for **1** than for **3**.

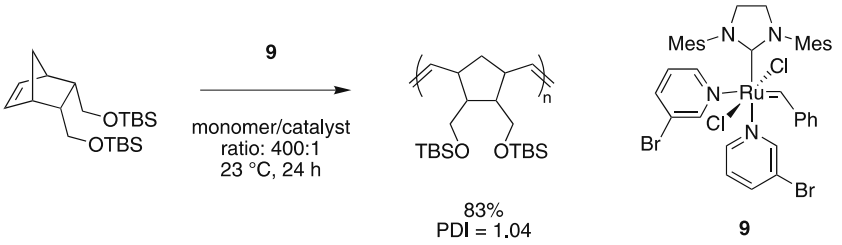
2.3 Ring-Opening Metathesis Polymerization

In ROMP cyclic olefins are polymerized to polyalkenamers. Both **1** and **3** can be used for this reaction, but catalyst **3** was found to be significantly more efficient for the polymerization of cyclooctene derivatives (Eq. 13) [30]. Polymerization commences with initiation of the catalyst through dissociation of a neutral ligand such as a tricyclohexylphosphine for **1** and **3** (see

Mechanism, Sect. 4). Since propagation (productive polymerization) is fast compared to catalyst initiation when using **3**, the polydispersities of the obtained polymers are generally broad. The polydispersity index (PDI) is a ratio that represents the broadness of a molecular weight distribution; the control of polydispersity is associated with the rate of catalyst initiation. The introduction of 3-bromopyridine as ligand in second generation catalysts significantly increases the rate of initiation. Therefore, catalyst **9** is capable of polymerizing strained olefins with polydispersity indices close to 1 in high yield (Eq. 14) [31]. The success of this catalyst is based on high activity in propagation due to the NHC ligand and fast initiation due to the labile 3-bromopyridine ligands.

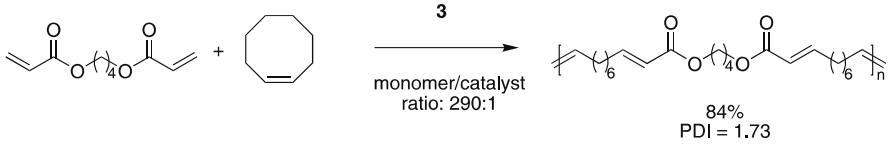


Equation 13



Equation 14

Alternating polymers can be produced by taking advantage of the functional group tolerance, high activity, and chemoselectivity of **3**. Copolymerization of cycloalkenes such as cyclooctene or cyclopentene with diacrylates affords regular alternating polymers (Eq. 15) [32]. Based on the different reactivity of the two monomers (class 1 and class 2, respectively) the more



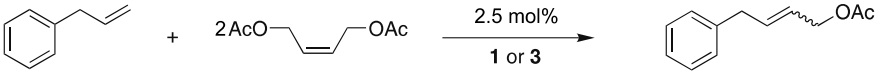
Equation 15

reactive cycloalkene reacts first to form a polyalkenamer. Upon consumption of all cycloalkene, secondary metathesis commences to insert one diacrylate unit into each double bond of the polyalkenamer to afford a regular copolymer. The terms ROIMP (ring-opening insertion metathesis polymerization) [32] and ALTMET (alternating diene metathesis polycondensation) [33] have been introduced to describe this process.

2.4 *E/Z* Selectivity

The control of olefin geometry is an important task when building double bonds. When using olefin metathesis, the products are often obtained as mixtures. Ring-closing metathesis of small or medium-sized rings generally yields *Z* olefins as an obvious consequence of avoiding ring strain, but ring-closing metathesis for the formation of macrocycles or cross metathesis reactions lack this high degree of selectivity. When a high degree of control in olefin geometry is obtained, the product distribution is primarily governed by the thermodynamic preference of the product alkene rather than the nature of the catalyst. Thus, a general catalyst system for olefin metathesis that affords double bonds with stereochemical purity is highly desirable for both *E* and *Z* olefins, but still remains elusive [1].

A difference in *E*/*Z* selectivity between first and second generation catalysts can, however, be noticed, with the more active catalysts generally affording a greater fraction of the thermodynamically favored product. When comparing the different product ratios obtained with catalysts **1** and **3**, the difference in product selectivity is most likely not inherent to the catalyst but due to the inefficiency of **1** in catalyzing secondary metathesis. Secondary metathesis is the reaction of product alkenes with the catalyst; thus, equilibration to the thermodynamically favored product is possible. If the catalyst is not active enough to react with the double bond initially formed, such an equilibrating process cannot take place and the reaction is kinetically controlled. Cross metathesis of allylbenzene with diacetoxy-2-butene catalyzed by **1** affords the product olefin as a 3 : 1 *E*/*Z* mixture [20], whereas a 10 : 1 mixture is observed using **3** (Eq. 16) (Ritter T, Heil A, Wenzel AG, Funk TW, Grubbs RH (2006) manuscript accepted for publication). This tendency can also be observed in the ring-closing metathesis of **7** (Eq. 4). Although an almost equal mixture of products could be expected for thermodynamic rea-



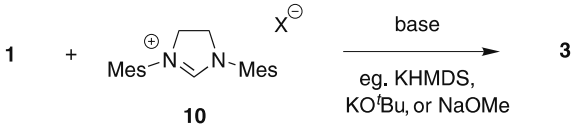
80%, *E*:*Z* = 3:1 for **1**
80%, E/Z = 10:1 for **3**

Equation 16

sons [18], **1** affords the macrocycle as a single isomer whereas the more active **3** affords a 5 : 1 *Z*/*E* mixture.

3
Synthesis of NHC–Ruthenium Complexes

Three general methods for the formation of NHC–ruthenium bonds of second generation olefin metathesis catalysts are available: (a) deprotonation of a formamidinium salt will afford an NHC in situ which will in turn displace a phosphine from a suitable ruthenium precursor; (b) the NHC is generated through decomposition of hemilabile adduct; and (c) silver carbenes can be used as NHC transfer agents. The generally applied method is the in situ formation of an NHC from the corresponding imidazolium or dihydroimidazolium salts upon treatment with base. Although the NHCs are generally stable [35–39], their isolation is normally not required and better results can be obtained when they are prepared in situ [40]. KHMDS (potassium hexamethyldisilazide) is a common base to deprotonate salts such as **10** and **11** and form the NHC, which can displace a phosphine to generate the NHC–ruthenium catalysts (Eqs. 17, 18).



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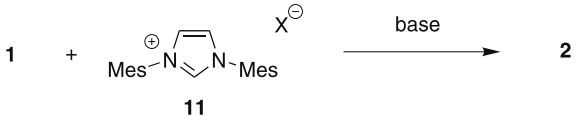
Equation 17



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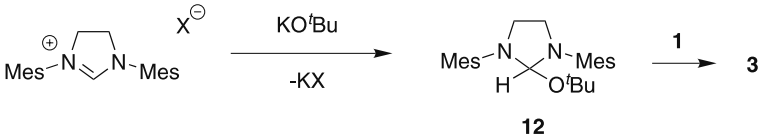
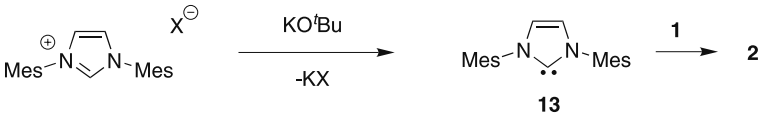
Equation 18

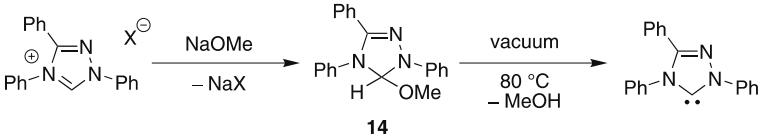
Bases such as methoxide or *tert*-butoxide give adducts such as **12** which can be isolated and characterized [40] but generally afford the corresponding carbene at room temperature upon loss of methanol or *tert*-butanol, respectively (Eq. 19). Thus, the NHC is formed in situ and can produce the desired complexes with a ruthenium precursor. In contrast to the saturated *tert*-butanol adducts of the NHC (**12**), the corresponding adducts from unsaturated NHCs have not been isolated and afford the carbene directly, presumably due to the higher stability of the aromatic carbene **13** (Eq. 20). The methanol adducts of the triazolium-based NHCs such as **14** [41] are more stable and



Equation 19



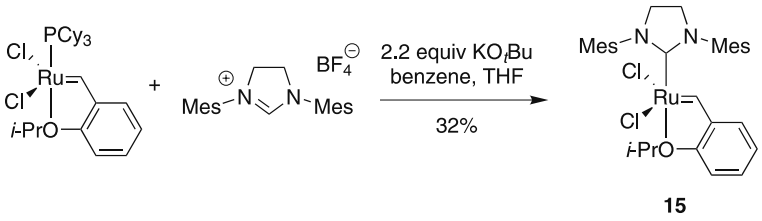
Equation 20



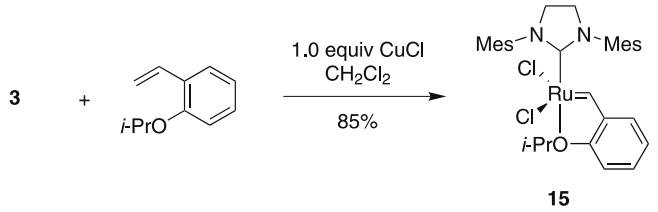
Equation 21

can be used as a convenient, air-stable source of carbene, because they lose methanol upon heating (Eq. 21). During the synthesis of NHC–ruthenium complexes, substitution of chloride ligands by *tert*-butoxide has been observed at prolonged reaction times and elevated temperatures [42, 43]. This commonly undesired side reaction can be avoided by utilization of the less nucleophilic, weaker base hexafluoro-*tert*-butoxide [6].

Complexes bearing a chelating benzylidene ligand such as **15** can be easily synthesized using similar procedures as described above by employing different ruthenium precursors in which the chelating ligand is already present (Eq. 22) [44]. Alternatively, stoichiometric metathesis of **3** and isopropoxystyrene can afford the product in higher yield (Eq. 23). The addition of CuCl can be beneficial in both procedures. The copper serves as a phosphine scavenger to prevent recoordination of the phosphine to ruthenium.



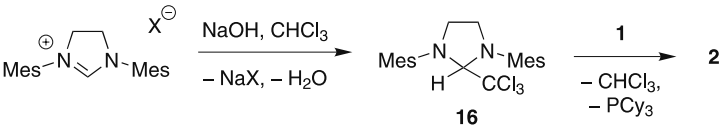
Equation 22



15

Equation 23

The chloroform adducts such as **16** are thermally significantly more stable than the corresponding *tert*-butanol adducts (Eq. 24). The synthesis of the chloroform adducts was originally described by Arduengo and Schmutzler through the reaction of NHC with chloroform [45]. An improved and easier synthesis of the chloroform adducts has been described by Grubbs et al., in which dihydroimidazolium salts are converted directly through reaction with NaOH in chloroform [40]. This reaction can be conducted on a large scale and does not suffer from air or moisture sensitivity. The chloroform adducts can be decomposed upon heating to form chloroform and the NHC, which can in turn react with a suitable ruthenium precursor. An additional benefit of the chloroform adducts is that they can be used for catalyst syntheses under base-free conditions. This can be essential for the preparation of catalysts bearing acidic protons such as **17**, since deprotonation of **17** by KO^{t}Bu presumably affords the vinylvinyl species **18** which is unstable and leads to catalyst decomposition (Eq. 25) [40].



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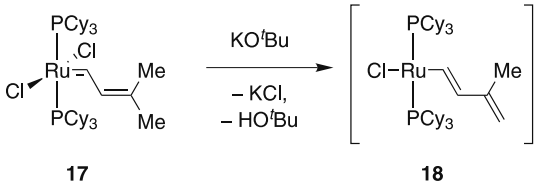
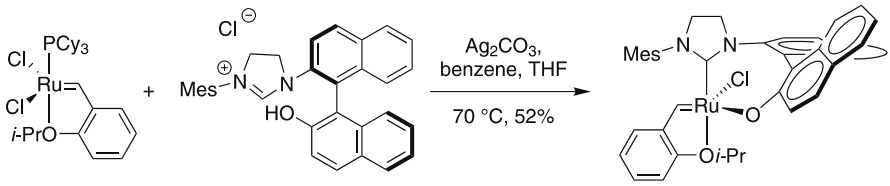
Equation 24



17 18

Equation 25

An alternative for carbene–ruthenium bond formation is the use of a carbene transfer agent. Silver carbenes have demonstrated their utility in serving as valuable carbene sources for the preparation of various transition metal



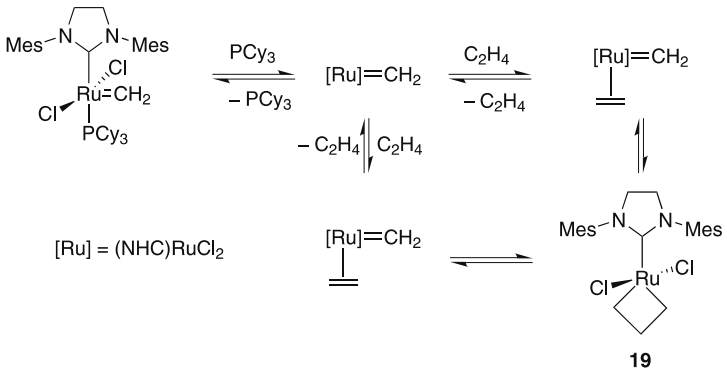
Equation 26

carbene complexes [46]. Hoveyda et al. have exploited this method for the preparation of chiral complexes (Eq. 26). The stable silver carbene can be isolated prior to reaction with a ruthenium precursor [47] or be prepared in situ [48, 49]. Silver carbonate or oxide are used as silver sources and operate as a base as well.

It is worth mentioning that most of the catalysts described in this chapter can be easily purified by column chromatography and are air-stable solids.

4 Mechanism

Mechanistic investigations of ruthenium-catalyzed olefin metathesis by **1** and **3** have shown that the catalytic cycle commences with dissociation of a phosphine ligand to presumably generate a coordinatively unsaturated 14e ruthenium complex (Scheme 1) [50, 51]. This step is commonly referred to as catalyst initiation, which most likely provides the catalytically active species. Originally, the increased activity of **3** over **1** was attributed to the strong σ-donor ability of the NHC ligand resulting in a strong *trans* effect. It was believed that as a consequence an increased rate of phosphine dissociation



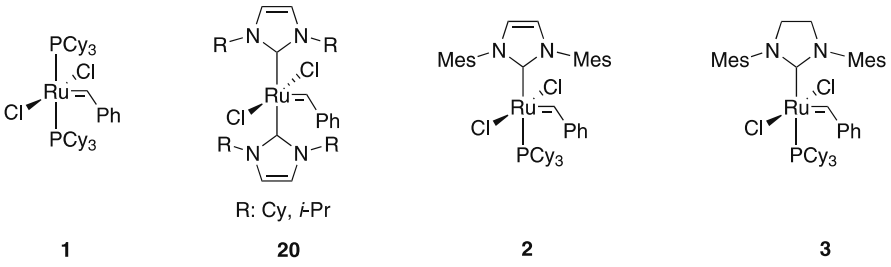
Scheme 1 Mechanism of olefin metathesis

was responsible for the overall rate enhancement. However, detailed analysis by Grubbs et al. demonstrated that the rate of phosphine dissociation from **3** is two orders of magnitude slower than that from **1** [50, 51]. The generated 14e species can either rebind phosphine to remove the complex from the catalytic cycle or bind olefin for productive metathesis. The affinity of the NHC-derived complexes to bind olefins in preference to phosphines is responsible for the significant rate enhancements. The increased activity was shown to be four orders of magnitude greater with **3** than with **1**.

The accepted mechanism for olefin metathesis proceeds through formation of a metallacyclobutane after olefin coordination to the 14e species. Piers et al. have collected the first evidence for the metallacyclobutane intermediate **19** in the condensed phase [52]. The proposed C_{2v} symmetry of this key structure has been predicted by calculations [53] (for related theoretical investigations on olefin metathesis, see [54–57]). Metallacyclobutane formation is likely to determine the regio- and stereochemical outcome of the metathesis reaction, and insight into its geometry is therefore critical in the development of new, selective catalysts. Cycloreversion and olefin dissociation complete the catalytic cycle to re-form the catalytically active species ([Ru] = CH_2) which can bind phosphine to re-form the precatalyst or olefin for a subsequent metathesis transformation.

5
Structural Diversity of NHC–Ruthenium Catalysts

The first introduction of NHC ligands to ruthenium complexes for olefin metathesis catalysts was reported by Hermann et al. in 1998 [58]. These derivatives exhibit two unsaturated NHC ligands (**20**) and show little improvement in activity when compared to the parent bis(phosphine) complex **1** (Fig. 2). Due to the stronger σ-donor ability of NHCs compared to phosphines, catalyst initiation by dissociation of one NHC is disfavored. Subsequently, the synthesis of phosphine–NHC complex **2** that contains a bulkier NHC ligand was reported by different research groups [2–5]. This complex



1 **20** **2** **3**

Fig. 2 Chronological order of ruthenium olefin metathesis catalysts

exhibits a high ring-closing metathesis activity while retaining the remarkable air and water stability of the parent ruthenium complex **1**. Grubbs et al. later showed that utilization of a more basic saturated NHC ligand, the 4,5-dihydroimidazol-2-ylidene, yields the more efficient metathesis catalyst **3** [6].

Since the discovery of catalysts **2** and **3** containing one NHC ligand, the attractive family of NHC–ruthenium complexes has been rapidly expanded. In the following section, the different structural modifications of complexes **2** and **3** reported in the literature will be presented (phosphine and halide ligands, benzylidene ligand, NHC ligand).

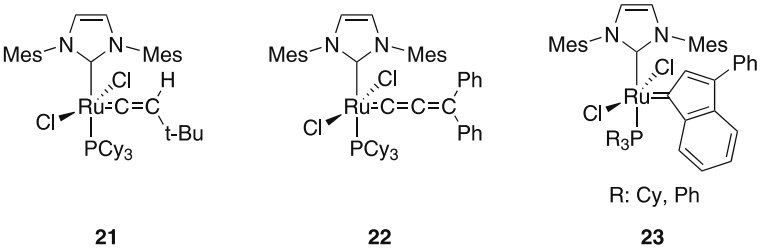
5.1 Phosphine and Halide Ligands

Studies of complexes with different phosphine and halide ligands led to the observation that there is no linear correlation between the basicity of the phosphine and catalyst initiation (dissociation of the phosphine), since the steric properties of the phosphine also affect the activity of the catalyst. Higher activity was reported for chloride complexes than the corresponding bromide or iodide complexes [50].

5.2 Alkylidene Ligand

Ruthenium vinylidene **21** [59, 60], allenylidene **22** [61], and indenylidene **23** [62, 63] derivatives are stable and show catalytic activity in olefin metathesis reactions (Fig. 3).

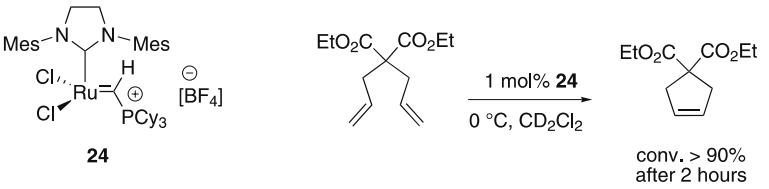
In 2005, Piers et al. prepared the 14-electron (14e) phosphonium alkylidene ruthenium complex **24**. This catalyst displays higher activity in the RCM of diethyl diallylmalonate at 0 °C when compared to the second generation catalyst **3** (> 90% conversion after 2 h for **24** versus 25% conversion after 4 h for **3** and > 90% after 5 h for the Schrock molybdenum-based catalyst) (Eq. 27). RCM reactions of trisubstituted, six-membered ring, or seven-membered ring substrates are catalyzed at room temperature affording good



21 **22** **23**

Fig. 3 Metathesis-active vinylidene, allenylidene, and indenylidene ruthenium catalysts

yields in short reaction times. The high activity of catalyst **24** at low temperature may be explained by the elimination of the phosphine dissociation step in the catalytic cycle. The ruthenium complex is already in its catalytically active form [64].



Equation 27

A new family of ruthenium olefin metathesis catalysts bearing a chelating benzylidene ligand was introduced by Hoveyda et al. [44]. The phosphine-free ruthenium complex **15** (Fig. 4) is a prominent member of this class and displays a higher reactivity level toward electron-deficient olefins such as acrylonitrile [65, 66], fluorinated olefins [67], and others [68] when compared to catalyst **3**. Different substitutions on the isopropoxybenzylidene ligand can fine-tune the catalytic properties [69, 70]. Blechert et al. showed that the introduction of a sterically demanding substituent adjacent to the chelating isopropoxy moiety (see complex **25**) dramatically improves the activity of the catalyst due to a faster dissociation of the bulky ligand to generate the active 14e species [71, 72]. Electronic effects of the isopropoxybenzylidene ligand were studied with the result that an electron-withdrawing group (nitro group in *para* position) can also afford a more active catalyst (**26**). The decreased electron density of the oxygen atom on the isopropoxy fragment reduces the chelating ability and facilitates the formation of the catalytically active 14e ruthenium species [73, 74]. It is also worth mentioning that latent ruthenium olefin metathesis catalysts with a benzylidene ligand chelating through a nitrogen atom have been synthesized, such as the 2-pyridylethanyl car-

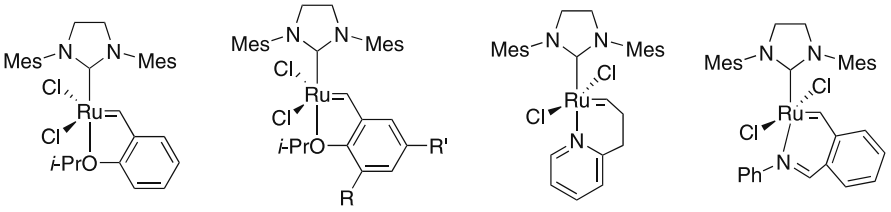


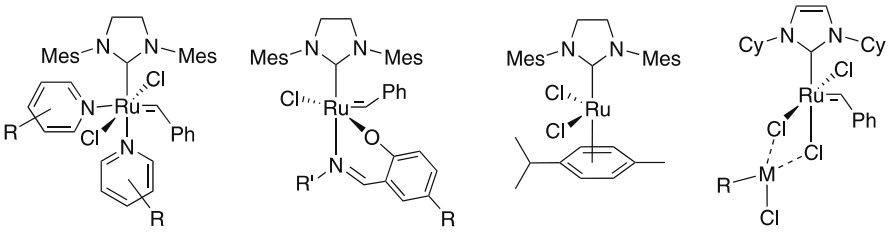
Fig. 4 NHC–ruthenium catalysts with chelating benzylidene ligand

bene ruthenium complex **27a** [75] and the phenyl(2-vinylbenzylidene)amine carbene ruthenium complex **27b** [76]. These catalysts initiate slowly while maintaining high activity.

5.3 Other Ligands

Ruthenium catalysts containing one NHC ligand with different architectures have been reported. For example, the bispyridine complexes **9**, **9a**, and **9b** are exceptionally fast initiators in olefin metathesis reactions (Fig. 5). The poorly coordinating pyridine ligands allow for the generation of a highly efficient ruthenium catalyst (**9**) which can perform the challenging acrylonitrile CM (poor results are obtained with catalyst **3**). Complex **9a** is a preferable starting material for the generation of a variety of ruthenium-based catalysts because pyridine ligands can be readily substituted with other donors such as phosphines [42, 66].

A variety of NHC–ruthenium catalysts exhibiting different coordination spheres were synthesized, for example Schiff base (see complex **28**) [77], arene (see complex **29**) [78], and metallic moieties (see complexes **30**) [7, 79, 80] (Fig. 5) and show activity in RCM and ROMP.



9a R: H
9 R: 3-Br
9b R:4-Ph

28 **29** **30**

Fig. 5 Metathesis-active catalysts with conceptually different coordination spheres

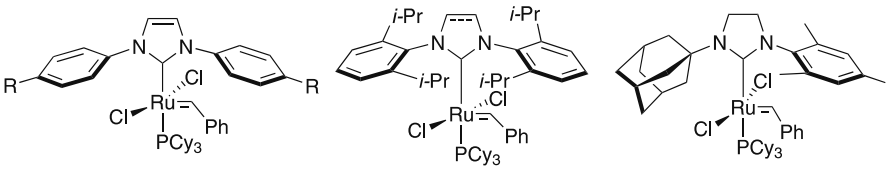
5.4 NHC Ligand

A number of studies have been carried out on various frameworks of the NHC ligand. The effects of the substituents on the heterocycle (on the nitrogen atoms or on the C – C backbone) as well as the ring size of the NHC (six- and four-membered ring NHC) have been investigated.

5.4.1
Substituents on the Nitrogen Atoms

Substitution of the mesityl group on the nitrogen atoms with sterically less demanding aryl substituents such as the 4-methylphenyl (see complex **31a**) or the 4-chlorophenyl (see complex **31b**) group led to significantly less active catalysts for the RCM of diethyl diallylmalonate [81] (Fig. 6). The decrease in activity can be attributed to a slower initiation due to the alleviated steric repulsion between the substituents in the *ortho* positions of the nitrogen atom and the dissociating phosphine, or a higher rate of decomposition of the active species. Indeed, the reduced steric protection of the ruthenium center may favor a bimolecular decomposition [12]. Complex **32** with the bulkier aryl group 2,6-diisopropylphenyl displays higher activity in the CM of terminal olefins than its mesityl analogs (**2** or **3**). However, for internal olefins (such as methyl oleate and *trans*-4-decene) lower activity is observed. The increased steric demand of the isopropyl groups in close proximity to the ruthenium center allowed for faster dissociation of the phosphine, but in the case of crowded olefins the large 1,3-bis(2,6-diisopropylphenyl)-NHC ligand might hinder the approach of olefin molecules to the ruthenium center [82–84]. At elevated temperatures, the decomposition of catalyst **32** is fast, probably due to a more likely C – H or C – C bond activation of the isopropyl substituents [84]. Highly crowded NHCs were tested as ligands for olefin metathesis catalysts. Initially, Mol et al. tried to synthesize the bis(adamantyl) NHC–ruthenium complex but were unsuccessful. However, the adamantyl-mesityl NHC complex **33** could be isolated but showed no activity for CM of 1-octene at 100 °C. The increased steric hindrance provided by the adamantyl substituents may explain the dramatic decrease in metathesis activity [85].

Unsymmetrically substituted unsaturated NHC catalysts (silyl ether-mesityl **34** [86, 87], perfluoroalkyl-mesityl **35** [86], ester-mesityl **36** [88]) can catalyze the RCM of dienes, however, with lower yields than those obtained with the parent catalyst **2** (Fig. 7). Subsequently, Blechert et al. reported the synthesis of alkyl-mesityl saturated NHC complexes **37** and **38**. These catalysts show a generally lower reactivity than the corresponding symmetric catalysts **3** and **15** in RCM and CM [89].



31a R: Me
31b R: Cl

32

33

Fig. 6 Ruthenium catalysts with different sterically demanding aryl groups on the NHC

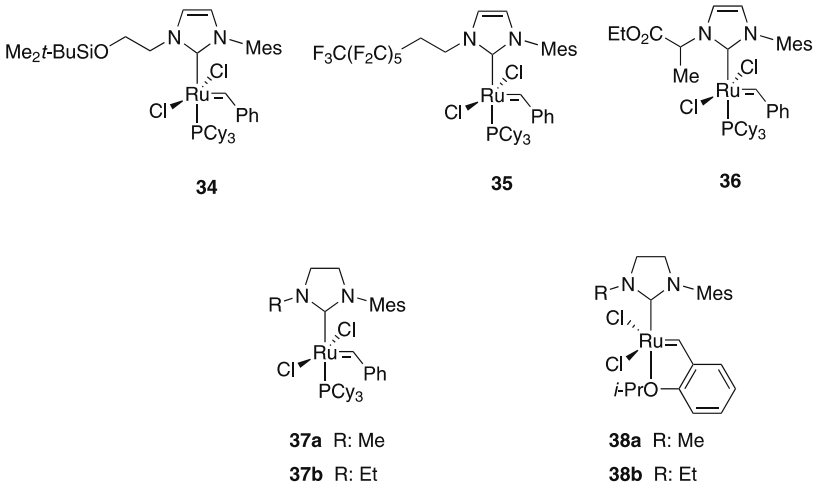
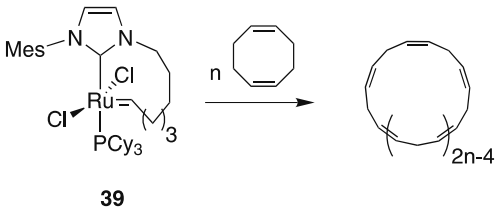


Fig. 7 Unsymmetrically substituted NHC–ruthenium catalysts

The metallacycle ruthenium complex **39**, bearing a tethered NHC–alkylidene unit, catalyzes the formation of cyclic polymers by ROMP of COD (Eq. 28). Polymer formation is believed to proceed through a transient macrocyclic complex in which both ends of the growing polymer chain remain attached to the ruthenium center. Subsequent intramolecular chain transfer releases cyclic polymer [90, 91].

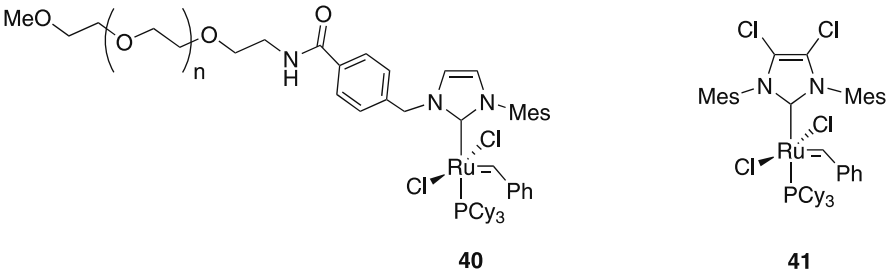


39

Equation 28

Water-soluble catalysts containing one NHC ligand were investigated by incorporating a poly(ethylene glycol) derivative on the NHC group (Fig. 8). Excellent activity (~ 95% yield) is observed with catalyst **40** for the ROMP of ammonium norbornenes in water in the presence of 1 equivalent of HCl with respect to catalyst. The equilibrium of the initiation step (phosphine dissociation) is shifted toward the 14e species by protonation of free phosphine, thus preventing its recoordination. Catalyst **40** is also active for the RCM of dienes in protic organic solvents such as methanol [92].

The strong complexing ability of carbene ligands also allowed for the synthesis of second generation catalyst immobilized on a solid support through



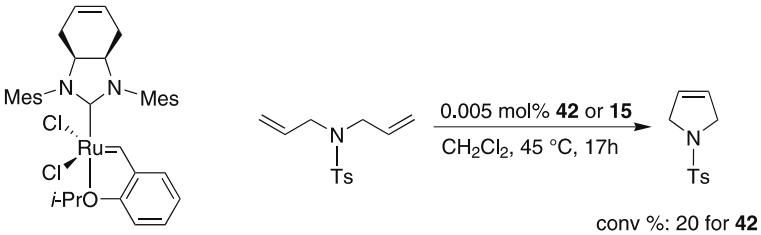
40 **41**

Fig. 8 Water-soluble and dichloroimidazole-derived NHC–ruthenium catalysts

the NHC moiety. These systems display a high activity in both RCM and ROMP [93–95].

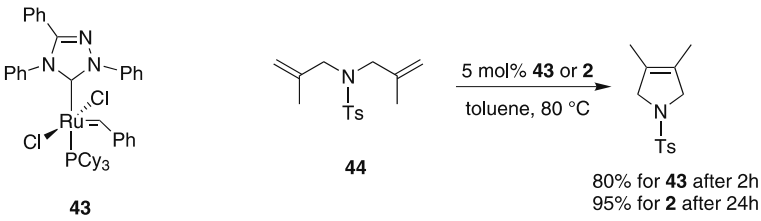
5.4.2 NHC Backbone

The introduction of two chloride atoms on the NHC backbone has little effect on the reactivity of the resulting complex **41** (Fig. 8) in the RCM of dienes [86]. Catalyst **42**, exhibiting a cyclohexene group as part of the NHC heterocycle, displays a decrease in productivity in the RCM reaction of *N*,*N*-diallyltoluene-4-sulfonamide compared to the parent catalyst **15** [96] (Eq. 29). The triazol-5-ylidene catalyst **43** allows for the cyclization of disubstituted di-



42

Equation 29



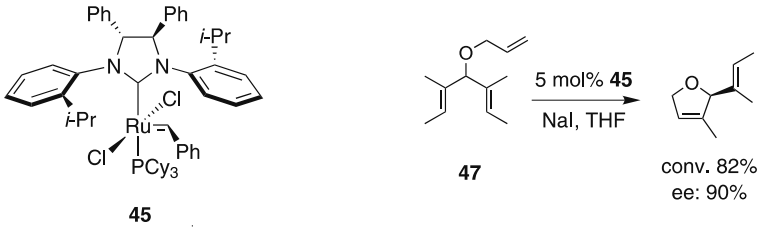
43 **44**

Equation 30

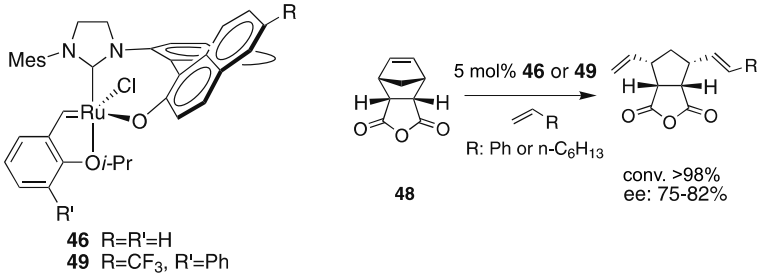
enes **44** with a yield of 80% in 2 h. Prolonged reaction times, however, do not lead to further conversion, most likely because of the limited lifetime of complex **43** in solution (Eq. 30) [86].

5.4.3 Chiral NHCs

There is no inherent reason why first generation-based complexes should not find applications in asymmetric transformations. However, the strong complexing ability and the architecture of NHCs allowed for easy introduction of chirality to olefin metathesis catalysts. Two types of enantioselective catalyst, for example complexes **45** [97] (for related Mo catalysts [98]) and **46** [49], have been reported in the literature. Catalyst **45**, derived from a chiral diamine, achieves the RCM of (*E*)-olefin **47** in 82% conversion and 90% ee (Eq. 31). Catalyst **46** bearing an anionic bidentate carbene naphtholato ligand induces high enantioselectivity in the asymmetric ring-opening metathesis/cross metathesis (AROM/CM) of tricyclic norbornene **48** (Eq. 32). However, complex **46** is less active than the achiral parent system **15**, since longer reaction times and elevated temperatures are required to achieve complete conversion. Structural modifications of complex **46** to increase its activity have been explored. The introduction of a bulky substituent (phenyl) in the *ortho* position of the aryl ether unit facilitates the dissociation of the



Equation 31

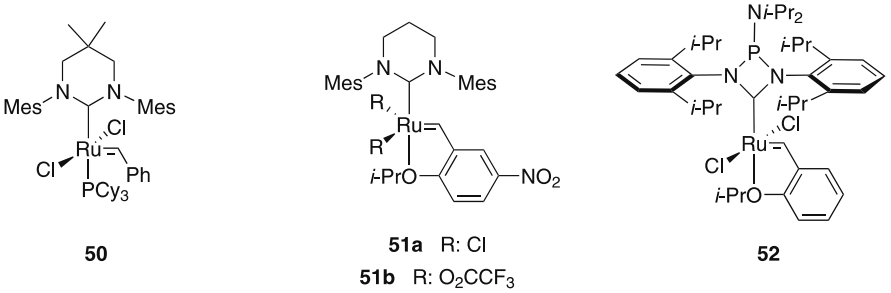


Equation 32

isopropoxy ligand, and the substitution on the binaphthyl group with a trifluoromethyl moiety diminishes the electron-donating capacity of the naphtholate. Indeed, catalyst **49** promotes AROM/CM of **48** 140 times faster than **46** [48].

5.4.4 Ring Size of the NHC

Modifications of the NHC ring size affect the electronic and steric properties of the NHC ligand. Grubbs et al. reported the synthesis of the six-membered ring NHC–ruthenium catalyst **50** (Fig. 9). According to the X-ray structure of the complex, the mesityl groups bend more toward the chloride–benzylidene plane than in the parent complex **3**, resulting in a higher steric shielding in proximity to the ruthenium center. Catalyst **50** shows lower activity in the RCM of diethyl diallylmalonate and in the ROMP of COD when compared to complex **3** [99]. Similar behavior was observed for catalysts **51a** and **51b** [100]. This behavior is probably due to the more congested environment around the metal center that disfavors olefin coordination. Further modifications on ring size were investigated by preparing the four-membered ring NHC complex **52**. This catalyst displays a lower reactivity than the parent complex **15** in the CM of allylbenzene with *cis*-1,4-diacetoxy-2-butene as well as in the ROMP of COD [101].



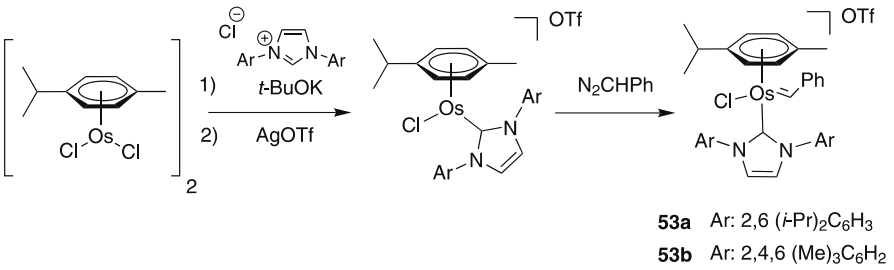
50 **51a** R: Cl **51b** R: O_2CCF_3 **52**

Fig. 9 Ruthenium catalysts with six- and four-membered ring NHCs

6 Other Metals for Olefin Metathesis

Only one example of an NHC-containing olefin metathesis catalyst containing a transition metal other than ruthenium has been reported in the literature. The NHC–osmium complexes **53a** and **53b** (Scheme 2) are synthesized from the dichloro(η^6-*p*-cymene)osmium dimer by addition of the NHC prepared in situ and abstraction of the chloride, followed by introduction of the benzylidene moiety with phenyl diazomethane.

Complexes **53** are efficient catalysts for the homodimerization of 1-octene and styrene. Complex **53a** bearing the sterically more demanding 1,3-bis(2,6-diisopropylphenyl)-NHC ligand shows a higher reactivity than the mesityl-substituted **53b**. These complexes also catalyze the CM of 1-octene or styrene with methyl acrylate (~ 80% yield), the RCM of diethyl diallylmalonate at 40 °C (~ 95% yield), and the ROMP of cyclooctene at 60 °C (~ 90% yield). By GC-MS analysis the presence of free *p*-cymene was detected in the beginning of the reactions. From these results it may be concluded that the first step of the catalytic cycle is arene decoordination to generate a 12-electron $[OsCl(=CHPh)(NHC)]^+$ derivative as the catalytically active species [102].



Scheme 2 Synthesis of NHC–osmium catalysts

7 Conclusion

The introduction of catalysts containing NHC ligands has revolutionized the field of olefin metathesis. The enhanced activity allowed for new transformations which were inaccessible with first generation catalysts and the substrate scope could be significantly expanded in different applications of ring-closing metathesis, cross metathesis, and polymerization. The architecture of NHC ligands has permitted the development of a variety of structural modifications and can deliver new complexes for applications such as chiral metathesis. The invention of new NHC ligands will strongly influence the future evolution of more active and selective catalysts for olefin metathesis. These will find important implementations in small molecule synthesis, pharmaceutical research, and materials science.

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