Smart N-Heterocyclic Carbene Ligands in Catalysis

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ABSTRACT: It is well-recognized that N-heterocyclic carbene (NHC) ligands have provided a new dimension to the design of homogeneous catalysts. Part of the success of this type of ligands resides in the limitless access to a variety of topologies with tuned electronic properties, but also in the ability of a family of NHCs that are able to adapt their properties to the specific requirements of individual catalytic transformations. The term "smart" is used here to refer to switchable, multifunctional, adaptable, or tunable ligands and, in general, to all those ligands that are able to modify their steric or electronic properties to fulfill the requirements of a defined catalytic reaction. The purpose of this review is to comprehensively describe all types of smart NHC ligands by focusing attention on the catalytically relevant ligand-based reactivity.

CONTENTS

1. INTRODUCTION

Noninnocent,[1,2] cooperative,[2−5] switchable,[6,7] and multifunctional[8,9] are different forms for referring to ligands that do more than providing an electronic environment and a sterically defined pocket to the metal fragment in a catalyst. Such ligands, are able to adapt their properties to the specific requirements for individual organic transformations and, therefore, the term "smart" may seem rather appropriate. In general, all ligands are important in the sense that they determine the reactivity of a complex in solution, stabilize specific oxidation states, or define the size and shape of the catalytic site. Once a ligand is chosen, the coordination environment of the catalyst is fixed, and this determines the rate and selectivity for a given reaction. "Smart" ligands are Switchable, Multifunctional, Adaptable, oR Tunable, and therefore they are able to directly interact with the substrate or modify their steric or electronic properties to fulfill the requirements of a defined catalytic transformation. In many cases the adaptability of a smart ligand is recognized postfactum, when the outcome of a specific catalytic reaction is shown to be different than the one that should have been expected if the role of the ligand was assumed to be only as spectator. However, once the cooperative effect has been identified, the new pattern of ligand-based reactivity can be used for the design of more effective multifunctional ligands.

Why smart N-heterocyclic carbene (NHC) ligands? It is well recognized that the impact of NHC ligands in homogeneous catalysis can only be compared with the impact that phosphines had during the 1970−1990 period. The success of NHC ligands is arguably attributed to their relatively easy preparation,[10]
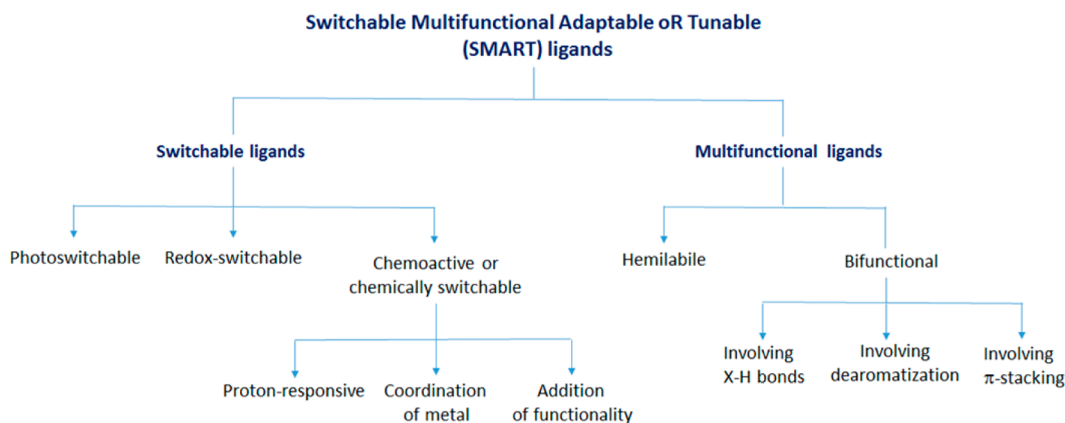
Figure 1. Presently known types of smart ligands.

which gives access to a large variety of structures with diverse topologies and electron-donating properties.[11−17] Also, NHCs may incorporate a limitless library of additional functions, and this gives this type of unique ligands clear advantages for the on-demand (or tailor-made) synthesis of homogeneous catalysts.

The purpose of this review is to describe all types of smart NHC ligands, by considering the classification given in Figure 1. We are aware that some other classifications may be equally valid, but we thought that this one gives a clear overview of what has been done in the field and allows a clear distinction of all types of different ligands. The review will place more emphasis on those examples for which the role of the ligand has a clear influence on the catalytic properties of the complex, but attention will also be given to those cases in which relevant studies on modification of the steric and electronic properties of NHC-based metal complexes is produced by external stimuli. Although several review articles have appeared regarding the properties of the different types of smart ligands as described here, this review is the first to globally consider all different types of smart NHCs.

As described here, smart ligands have been classified into switchable NHC ligands (section 2) and multifunctional NHC ligands (section 3). The term switchable catalysis is used to refer to all those catalysts that are able to switch their activities by virtue of a range of stimuli, such as light, pH, coordination events, redox processes, and changes of reaction conditions.[6] Although switchable catalysis is often understood as all the catalytic processes that can be *reversibly* switched on and off,[7] we will here consider also those examples in which the activity of the catalyst can be turned on or off by external stimuli, disregarding whether this change is reversible or not. Cases of reversible switchable catalysis are easily found for redox-,[18,19] pH-,[9] or light-driven[20−24] processes. Irreversible switchable catalysis is often found when the catalyst is turned on or off by virtue of an *irreversible* chemical modification involving the coordination sphere of the metal complex.

Multifunctional ligands are those that have been designed to do more than one thing.[8] This means that multifunctional ligands have additional functions that that can be useful in catalysis.[9] In our review, this group will include all existing examples regarding hemilabile ligands (section 3.1) and bifunctional ligands (section 3.2). Both hemilabile and bifunctional ligands refer to ligands whose reactivity depends on direct interaction with the substrates, and therefore, their presence has a direct influence on the catalytic properties of the catalyst.

2. SWITCHABLE N-HETEROCYCLIC CARBENE LIGANDS

The following subsections will be devoted to the photochemical (section 2.1), redox (section 2.2), and chemical (section 2.3) switching of NHC ligands and their applications in specific homogeneously catalyzed processes. Strategies aiming to append functional groups by modifying coordinated NHC ligands have been explored by a number of research groups for a handful of years. A review article regarding the post-modification of transition metal−NHC complexes as a toolbox for bioorganometallic chemistry was recently published by Cisnetti et al.[25] In that article, the authors wisely suggested that, in the near future, the postmodification of NHC ligands may help increase the number of biocompatible and bioconjugated NHC-based metal complexes. In the following subsections, existing examples of postfunctionalization of NHC ligands for homogeneous catalysis will be described.

2.1. Photoswitchable N-Heterocyclic Carbene Ligands

Photoswitchable systems allow for external (remote) modulation of chemical reactions by light.[22] A photoswitchable catalyst involves a catalytically active species that is susceptible to undergoing a reversible photochemical transformation and, as a result, modifying its intrinsic catalytic properties.[20,23] The first example of photoswitchable postmodification of a NHC ligand was described in 2009 by Yam et al.,[26] who obtained a series of di(thiophenyl)ethene-containing NHC complexes of Pd(II), Ag(I), and Au(I), whose steric and electronic properties could be modified by the photochemical reversible skeletal reorganization of the ligand, via a C−C bond activation (Scheme 1). Shortly after, the work was extended to the preparation of half-sandwich-type ruthenium(II) complexes, which showed photochromic properties upon UV irradiation to

Scheme 1. First Photoswitchable NHC-based Ligand[26]
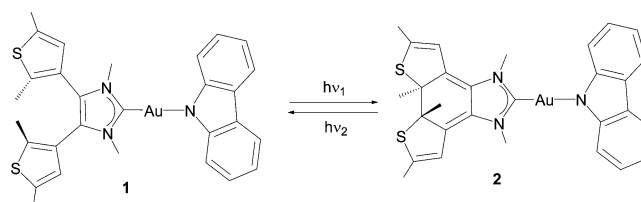
generate the annulated form of the dithienylethene moiety.[27] Interestingly, Bielawski and co-workers[21] studied the modification of the electron-donating character of the NHC ligand upon cyclization of the dithienylethene fragment, by estimating the shift in the Tolman electronic parameter (TEP), from evaluation of the CO stretching frequencies of the related $[IrCl(NHC)(CO)_2]$ complexes, and by using the well-accepted correlations.[12,28,29] From their studies, they concluded that the cyclization of the ligand produced a positive shift of 6 cm^{-1}, thus significantly reducing the electron-donating character of the NHC.[21]

The same type of ligand was later used by Neilson and Bielawski[30] to obtain a Rh(I) compound, whose catalytic properties in the hydroboration of alkynes and alkenes were studied. Upon photocyclization of the ligand, the activity of the rhodium complex was reduced by an order of magnitude, thus affording one of the first examples clearly showing modulation of the activity of a catalyst by phototuning its electronic properties (Scheme 2). The attenuated activity of the cycloannulated complex **4**, with respect to the open form **3**, was attributed to the decrease in electron-donor power of the ligand upon photoannulation, which in turn inhibits the rate-determining reductive elimination step of the hydroboration. Because the ring-closure reaction is reversible, the authors were able to perform an experiment in which activity of the catalyst was turned on and off by successively irradiating the reaction vessel with UV light ($\lambda = 313$ nm) and visible light ($\lambda > 500$ nm).

**Scheme 2. Photoswitchable Catalytic Hydroboration of Alkenes and Alkynes[30]**
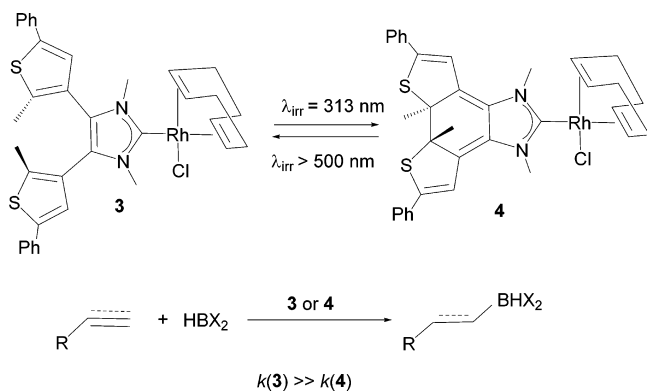
The catalytic photoswitchable properties of this dithienylimidazolylidene were observed to be associated with its role not only as a ligand (coordinated to a metal fragment) but also as an organocatalyst, where it showed interesting properties in transesterifications and transamidations[31] and in the ring-opening polymerization of ε-caprolactone and δ-valerolactone (Scheme 3).[32] In both cases, the activity of the NHC catalyst was significantly attenuated upon exposure to UV light, as a consequence of ring closure of the imidazolylidene. This was explained by the authors as a consequence of decreased electron density at the carbene of the ring-closed species (**6**), which forms an NHC–alcohol adduct.[32] The photoswitchable properties of the *isolated* free carbenes (**5** and **6**) were also studied.[33] Furthermore, the ring-closed isomer (**6**) was found to capture ammonia by N−H activation, which could then be released by the open isomer **5**, therefore affording an elegant example of a photoswitchable transformation.

Scheme 3. Photoswitchable Organocatalytic Reactions with Dithienylimidazolylidene
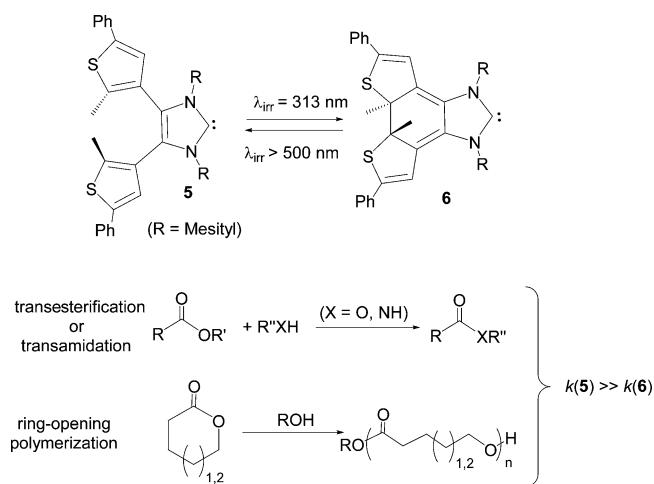
Another interesting example of a photoswitchable NHC ligand was described by Monkowius and co-workers in 2013.[34] This group obtained an azobenzene-functionalized NHC that was coordinated to silver and gold. Scheme 4 shows one example of this type of reaction for a selected compound. All gold complexes featured $E \rightarrow Z$ isomerization of the azobenzene tag upon irradiation with UV light. The thermal reverse reaction was relatively slow. Unfortunately, the catalytic properties of these complexes were not evaluated.

Scheme 4. Photoswitchable Behavior of Azobenzene-Tagged NHC Coordinated to Au(I)
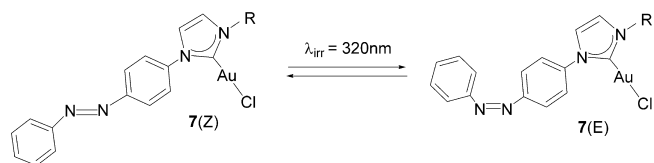
2.2. Redox-Switchable N-Heterocyclic Carbene Ligands

In a complex with a redox-active ligand, the ligand is considered to be the dominant source of electrons, with the metal retaining its original oxidation state.[18] In principle, the participation of a redox-active ligand in the catalytic cycle may be by accepting or donating electrons, or by actively cleaving or forming covalent bonds.[35] In general, redox-switchable catalysis seeks to regulate chemical reactions by simple reduction−oxidation manipulation. Redox-active ligands can be used as a reversible trigger to control catalytic reactivity. In the case of existing examples of redox-active NHC ligands for catalysis, most cases refer to situations in which oxidation/reduction of the ligand is used for tuning the electronic properties of the metal.[19] In this regard, redox-active NHCs are not ascribed to the classical concept of noninnocent redox ligands, for which the noninnocent behavior refers to the ambiguity or uncertainty of the oxidation state of the metal that is generated upon coordination to such a ligand.[2]

Rather than approaching this section in a chronological manner, we will first approach the studies dealing with electronic modification of redox-active NHC ligands upon introduction of a redox stimulus, and then we will describe the existing examples in which these ligands were used in redox-switchable catalysis.

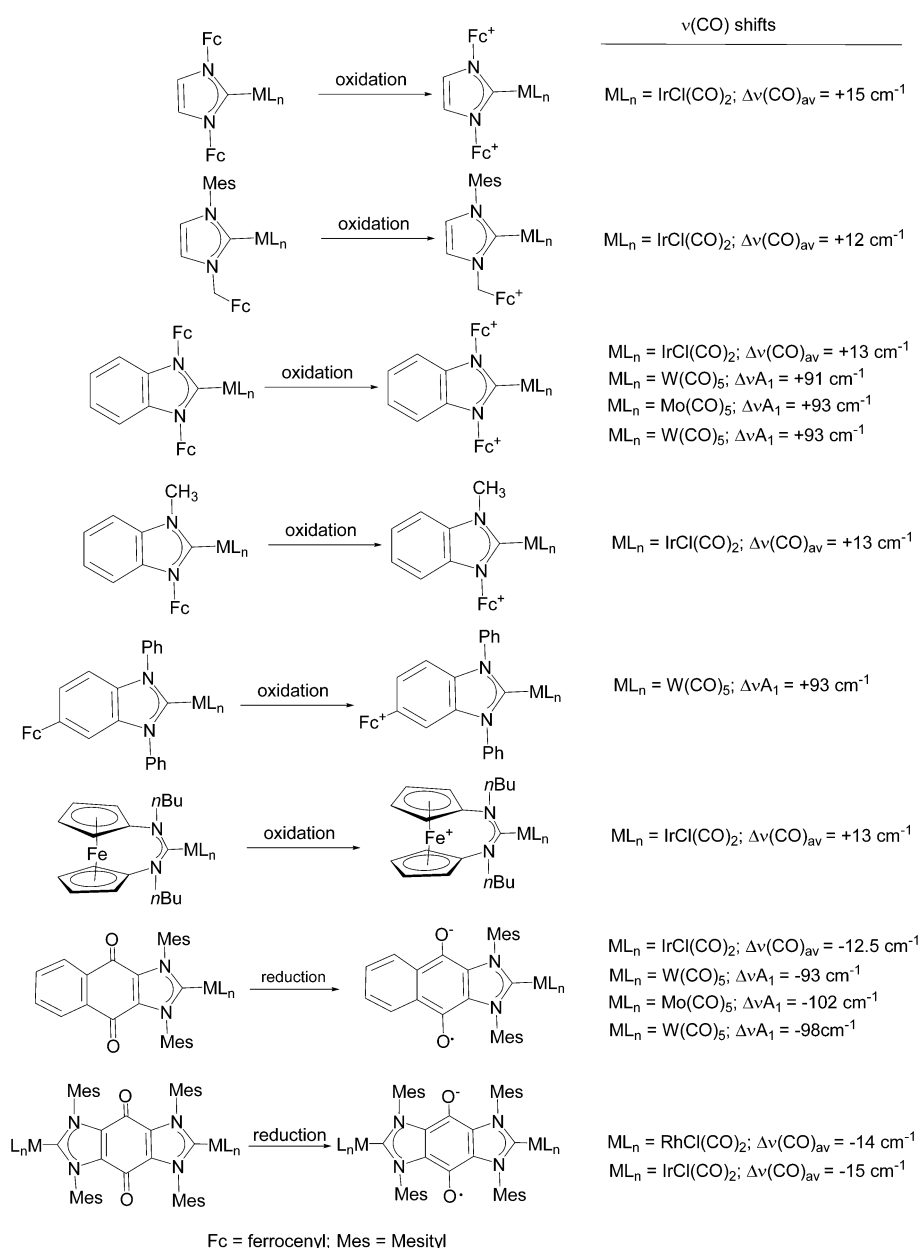In 2008, Bielawski and co-workers[36] described a series of six-membered N-heterocyclic carbenes with a 1,1′-ferrocenediyl backbone (diaminocarbene[3]ferrocenophanes), which were coordinated to Rh(I) to afford the related [RhCl(NH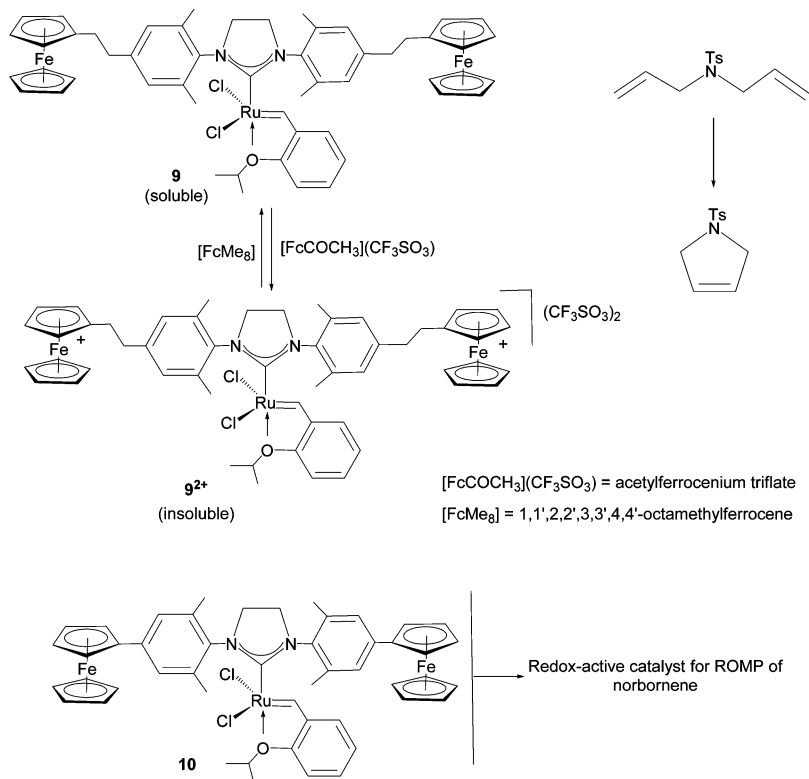C)-(COD)] and [RhCl(NHC)(CO)$_2$] complexes [Scheme 5 shows a selected Rh(I) complex]. The oxidation of the ferrocene moiety here is irreversible and leads to fast decomposition. Bulk electrolysis combined with time-resolved IR spectroscopy allowed examination of the carbonyl stretching frequency as a function of the oxidation state of the Fe center. The authors concluded that oxidation of the ferrocenyl fragment in **8** (Scheme 5) produced a positive shift of 20.5 cm^{-1}, which is consistent with an important reduction of electron density at the rhodium center, as a consequence of introducing a positive charge at the iron atom. Nevertheless, two later works by the same group reported lower shifts of $\nu_{av}(CO)$ for related [IrCl(NHC)(CO)$_2$] complexes (with the NHC ligands being the same as in **8** but with n-Bu and CH$_3$ groups instead of phenyl at the nitrogen atoms of the heterocycle) upon oxidation of the iron center. These shifts

Scheme 5. C−O Stretching Frequency Shift upon Oxidation of a Diaminocarbeneferrocenophane

$\nu(CO)_{av} = 2031$ cm^{-1} $\nu(CO)_{av} = 2051.5$ cm^{-1}

Scheme 6. Variations in $\nu(CO)$ Frequencies of a Series of Carbonyl−Metal Complexes with Redox-Active NHC Ligands[a]

$\nu(CO)$ shifts

ML$_n$ = IrCl(CO)$_2$; $\Delta\nu(CO)_{av}$ = +15 cm^{-1}

ML$_n$ = IrCl(CO)$_2$; $\Delta\nu(CO)_{av}$ = +12 cm^{-1}

ML$_n$ = IrCl(CO)$_2$; $\Delta\nu(CO)_{av}$ = +13 cm^{-1}
ML$_n$ = W(CO)$_5$; $\Delta\nu A_1$ = +91 cm^{-1}
ML$_n$ = Mo(CO)$_5$; $\Delta\nu A_1$ = +93 cm^{-1}
ML$_n$ = W(CO)$_5$; $\Delta\nu A_1$ = +93 cm^{-1}

ML$_n$ = IrCl(CO)$_2$; $\Delta\nu(CO)_{av}$ = +13 cm^{-1}

ML$_n$ = W(CO)$_5$; $\Delta\nu A_1$ = +93 cm^{-1}

ML$_n$ = IrCl(CO)$_2$; $\Delta\nu(CO)_{av}$ = +13 cm^{-1}

ML$_n$ = IrCl(CO)$_2$; $\Delta\nu(CO)_{av}$ = -12.5 cm^{-1}
ML$_n$ = W(CO)$_5$; $\Delta\nu A_1$ = -93 cm^{-1}
ML$_n$ = Mo(CO)$_5$; $\Delta\nu A_1$ = -102 cm^{-1}
ML$_n$ = W(CO)$_5$; $\Delta\nu A_1$ = -98cm^{-1}

ML$_n$ = RhCl(CO)$_2$; $\Delta\nu(CO)_{av}$ = -14 cm^{-1}
ML$_n$ = IrCl(CO)$_2$; $\Delta\nu(CO)_{av}$ = -15 cm^{-1}

Fc = ferrocenyl; Mes = Mesityl

[a]Data were taken from refs 37, 41, and 42.

Scheme 7. Soluble Switchable Catalysts Used for Ring-Closing Metathesis of *N*-Tosyldiallylamide and for Ring-Opening Metathesis−Polymerization of Norbornene

[FcCOCH$_3$](CF$_3$SO$_3$) = acetylferrocenium triflate

[FcMe$_8$] = 1,1',2,2',3,3',4,4'-octamethylferrocene

were 12 and 13 cm^{-1} for ligands containing *n*-Bu[37] or CH$_3$[38] groups, respectively, as will be described in more detail later in this section.

In 2009, Siemeling et al.[39,40] described a series of complexes of rhodium and molybdenum with the same type of diaminocarbene[3]ferrocenophanes. These authors showed that the carbenes could be easily oxidized to the corresponding radical cations. By computational calculations, it was established that the spin density of the radical oxidized diaminocarbene[3]-ferrocenophane is located at the iron atom and at the carbon of the carbene.[39]

Bielawski and co-workers[37] made a strong contribution to the study of variation of the donating abilities of a variety of ferrocenyl-functionalized NHCs upon oxidation of the ferrocenyl units. In order to perform a detailed analysis of the problem, a wide set of ferrocenyl-NHC ligands were tested (Scheme 6). These authors sought to evaluate how several structural characteristics influence the electronic consequences of incorporating redox-active fragments in the ligand. Such characteristics were (i) use of an imidazolylidene versus a benzoimidazolylidene, (ii) incorporation of one versus two ferrocenyl fragments, and (iii) the presence or absence of an aromatic ring fused to the backbone of the NHC. They also studied the influence of these characteristics on the electronic properties of the NHC ligand by introducing a reducible redox-active functionality, such as a naphthoquinone.

From the data obtained (shown in Scheme 6), it could be concluded that oxidation of the ferrocenyl-containing Ir(I) complexes resulted in nearly identical shifts in ν_{av}(CO) (typically between 13 and 15 cm^{-1}). An interesting example is the case of the iridium complex with a ferrocenyl group bound to the NHC nitrogen by a methylenic group, for which the electronic communication of the ferrocenyl fragment and

the iridium center is disrupted, yet the ν_{av}(CO) shift observed lies in a similar range.[42] For the reduction of the dimesitylnaphthoquinone-based NHC, the ν_{av}(CO) shift was −12.5 cm^{-1} (similar value but negative), in accordance with the enhancement of donor properties of the NHC ligand.[41] Shifts were also observed for the A$_1$ carbonyl frequencies of the carbonyl ligands in the [M(NHC)(CO)$_5$] complexes (M = Mo, W; frequency shifts ranged between 91 and 93 cm^{-1} for complexes with ferrocenyl-containing ligands, and between −93 and −102 cm^{-1} for complexes with dimesylnaphthoquinone-based ligand).[41] Analysis of these results indicated that the scaffold structure or the number of ferrocenyl units bound to the ligand does not produce an appreciable change in the tunability properties of the ligand upon oxidation, or in other words, that the redox tunability of the ligands does not strongly depend on the chemical identity of the redox-active functional group. Rather than that, it seems that the change in ligand-donating ability is due to the overall charge imparted to the molecule upon redox change.[37] This important work constituted the first detailed study on quantification of the electron-donating tunability of redox active-NHC ligands.

More recently, the same authors obtained a series of iridium cationic complexes bearing two bulky ferrocenylated NHC ligands. Oxidation of the ferrocenylated ligands on these [Ir(NHC)$_2$(CO)$_2$]$^+$ cations increased the measured ν_{av}(CO) by 10 cm^{-1}, and this value is independent of the number of redox-active groups at the compex,[43] in agreement with results published before.[37]

The first redox-switchable NHC-based complex was reported by Sussner and Plenio in 2005.[44] It was also the first example in which this type of redox-active ligand was used to pursue a catalytic application. The complex was a ruthenium-based Grubbs−Hoveyda-type olefin metathesis catalyst with two

**Scheme 8. Ferrocenyl-based NHC Complexes of Ru(II) Used in Ring-Closing Metathesis of Diethylmalonate**

Fc* = decamethylferrocene
[FcCOCH₃](BF₄) = acetylferrocenium tetrafluoroborate
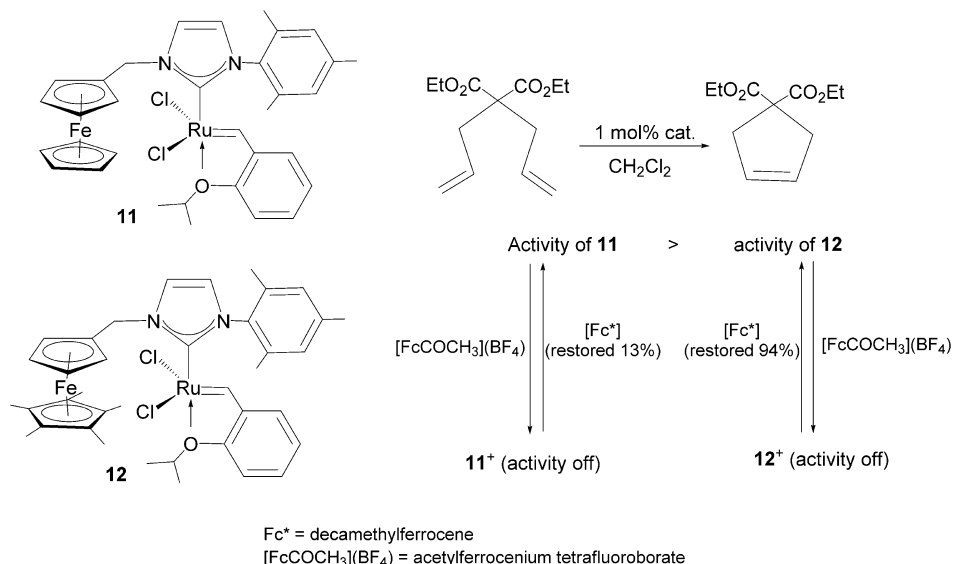
ferrocenyl fragments as redox-switchable tags (**9**, in Scheme 7). Oxidation of the ferrocenyl fragments with acetylferrocenium triflate produced a highly insoluble bisferrocenium complex, and this was elegantly used by the authors to control the solubility of the catalyst by reversibly oxidizing or reducing the complex. The catalyst was tested in the ring-closing metathesis (RCM) of *N*-tosyldiallylamide, and the authors showed that they were able to switch on and off the catalyst activity several times by adding acetylferrocenium triflate (off) or octamethyl-ferrocene (on). More interestingly, they were able to separate the catalyst from the products of the catalytic reaction at any time during the reaction and after its completion. In 2010, the same group studied the behavior of complex **10** as a redox-switchable catalyst for ring-opening metathesis−polymerization (ROMP) of norbornene.[45] Both neutral and dicationic complexes resulting from the oxidation of **10** showed similar activities in the reaction and rendered polymers with similar *E/Z* ratio. The authors rationalized these results on the basis of the small difference in electron donation of the NHC ligand in **10** and **10²⁺**, which in this case did not provide a significant change in the stereochemistry of the polymer obtained.

Ring-closing metathesis of diethylmalonate was tested with the ferrocene-containing NHC complex of Ru(II) **11** shown in Scheme 8.[42] The related compound with a 1′,2′,3′,4′,5′-pentamethylferrocenyl moiety, **12**, was also obtained, and the activities of these two complexes indicated a higher activity of **11** compared to that shown by **12**. When complex **11** was used in RCM of diethyl malonate, conversion reached 80% in 1 h. Addition of an oxidant reduced the activity of the catalyst, and the conversion decreased to 7% under the same conditions. Regeneration of neutral **11** by addition of a reductant did not restore the full activity of the catalyst (only 13% activity was restored). The same type of experiment was performed for catalyst **12**, for which the subsequent addition of an oxidant (acetylferrocenium tetrafluoroborate) and a reductant (deca-methylferrocene), produced deactivation of the catalyst and reactivation of its catalytic activity. For this complex, the activity could be restored to 94%.[42]

Bielawski and co-workers[38] also studied the ROMP of *cis,cis*-cyclooctadiene with **13** as catalyst (Scheme 9). They observed that addition of an oxidant (2,3-dichloro-5,6-dicyanoquinone)

**Scheme 9. Redox-Switchable Catalyst for ROMP of Cyclooctadiene**
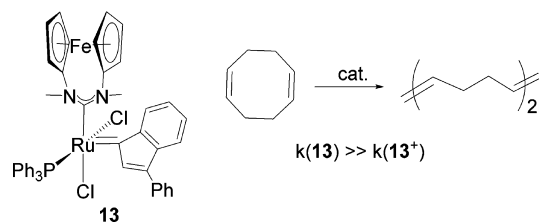
reduced the rate constant of the reaction by over an order of magnitude. Subsequent reduction of the oxidized catalyst (by addition of decamethylferrocene) restored the catalytic activity.

Sarkar and co-workers[46] were the first to use a mesoionic carbene (MIC) complex as a redox-switchable catalyst. They obtained a ferrocenyl-based mesoionic Au(I) complex (**14**, Scheme 10), which was used for cyclization of *N*-(2-propyn-1-yl)benzamide to 5-methylene-2-phenyl-4,5-dihydrooxazole. It was observed that the neutral complex was inactive in the reaction, but the oxidized cationic radical delivered 40% conversion after 5 h and 88% after 24 h.[46] The higher activity of the oxidized complex (obtained by in situ oxidation of **14** with acetylferrocenium) was attributed to its higher Lewis acidity, compared to the unoxidized form. These studies were carried out in more detail in a more recent work, where a larger set of redox-active MIC ligands was used, and in some cases the oxidized MIC-based gold complexes outperformed their neutral counterparts by almost a factor of 10.[47] With these contributions the authors illustrated how oxidized MIC-based catalysts may offer excellent performance when electron-poor ligands are needed. This is an interesting finding, because MIC ligands are mostly used when strong electron-donating ligands are needed.

Poyatos, Peris and co-workers[48] also contributed to the field by describing a benzo-fused ferrocenyl-imidazolylidene ligand, which was coordinated to iridium(I) and gold(I) (Scheme 11). After a detailed experimental and computational analysis, the authors concluded that oxidation of the metal complexes with acetylferrocenium tetrafluoroborate produced mixtures of the related oxidized complexes containing a ferrocenium-imidazo-
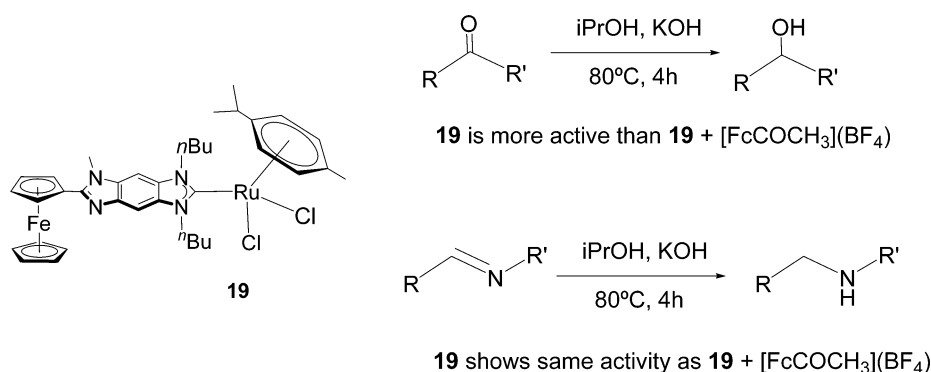
Scheme 10. First MIC-based Redox-Active Catalyst
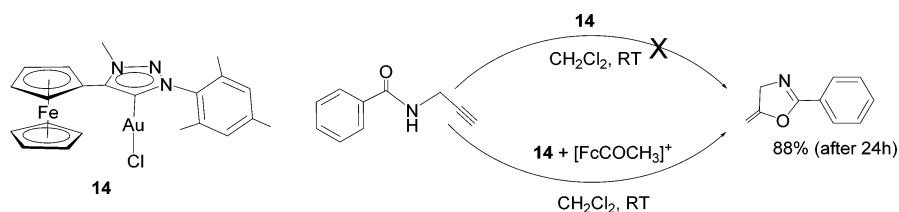
Scheme 11. Benzo-fused Ferrocenyl-imidazolylidene Complexes with Ir(I) and Au(I)
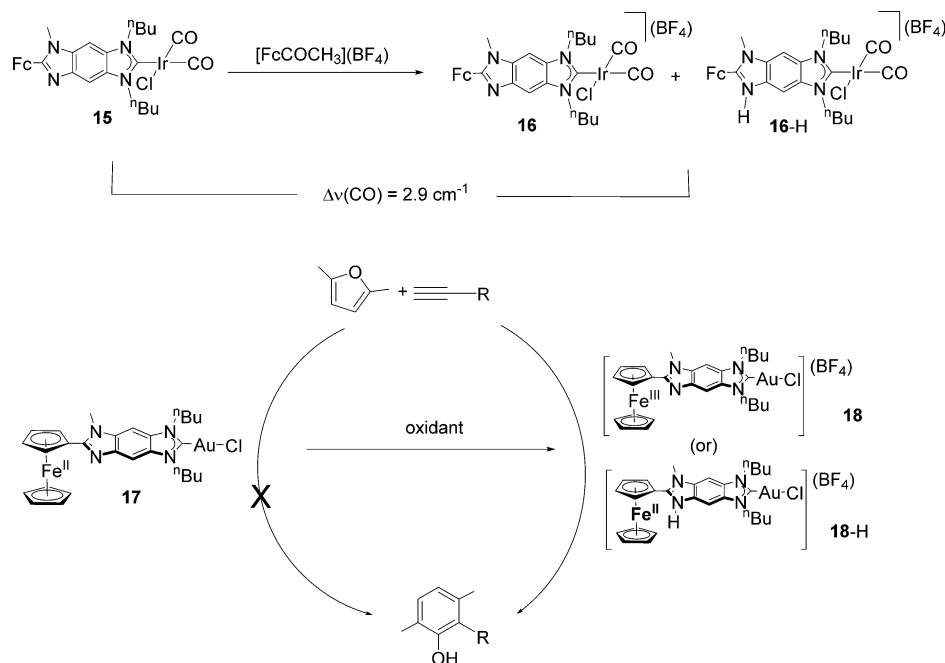
**Scheme 12. Redox-Switchable NHC−Ruthenium Catalyst in Transfer Hydrogenation**

lylidene ligand (Fe^{3+}), together with a protonated ferrocenyl-imidazolylidene (Fe^{2+}) compound. Protonation of the NHC ligand is produced at one unsubstituted nitrogen of the heterocycle closest to the ferrocenyl group and is presumably due to hydrogen abstraction from solvent by the cationic oxidized radical (redox-induced hydrogen abstraction). Oxidation of the ligand (regardless of whether it produced oxidation of the ferrocenyl fragment or protonation by hydrogen abstraction) produced a subtle increase in $\nu_{av}(CO)$ of the corresponding $[IrCl(NHC)(CO)_2]$ complex [see Scheme 11 for differences between **15** and **16**/**16**-H; $\nu_{av}(CO)$ shift =2.9 cm^{-1}], which is lower than the value expected, according to previously published results by other authors.[37] Coordination

of the ligand to gold(I) produced a redox-switchable catalyst (**17**) that was used in hydroamination of terminal alkynes and in cyclization of alkynes with furans.[48] For both reactions, it was assumed that the higher Lewis acidity of the gold complex upon oxidation (**18** or **18**-H) should provide a more active catalyst. This assumption was proven right for both reactions. In the hydroamination of terminal alkynes, the results indicated that oxidation of the ligand produced a moderate increase in activity of the gold catalyst. In the cyclization of alkynes with furans, the neutral complex was inactive, while the oxidized catalyst produced moderate to good yields of the final products.[48]

The same benzo-fused ferrocenyl-imidazolylidene ligand was later coordinated to ruthenium(II) (**19**, Scheme 12), and the

Scheme 13. Dimesitylnaphthoquinimidazolylidene−Ni(II) Complex in Redox-Switchable Kumada Coupling
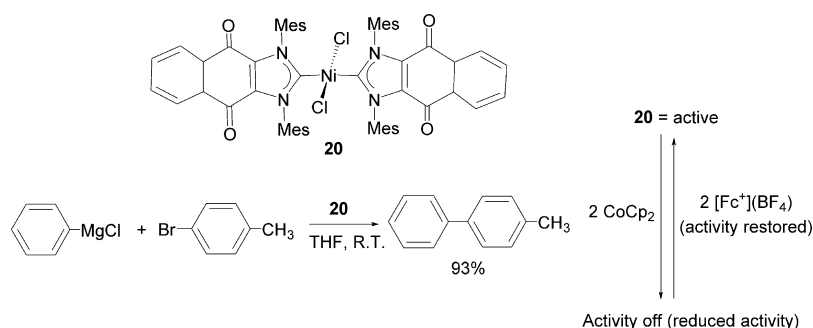
Scheme 14. Postfunctionalization of Imidazolylidene-olate
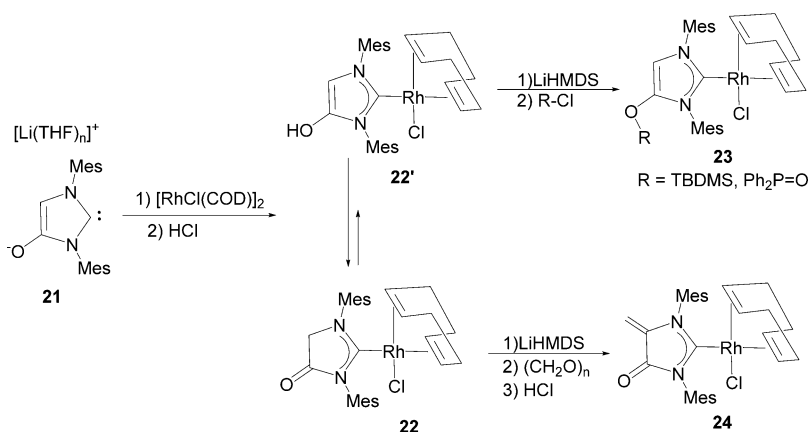
resulting complex was used as catalyst in the reduction of ketones and imines by transfer hydrogenation, with 2-propanol as the hydrogen source.[49] In this case, the neutral complex was far more active than the oxidized form in the reduction of ketones but afforded similar activity in the reduction of imines. This allowed modulation of the activity of the catalyst by successively adding acetylferrocenium tetrafluoroborate and cobaltocene, for the specific case of reduction of hexanophenone. Addition of acetylferrocenium tetrafluoroborate interrupted reduction of the substrate, while addition of cobaltocene restored the catalytic activity. These results indicated that the oxidized complex could potentially be used in the selective reduction of imines containing carbonyl groups.[49]

Some other ferrocenyl-containing NHC complexes showing redox-active properties were also reported,[50−57] but their properties were not exploited in homogeneous catalysis.

Ferrocenyl groups were not the only redox-active fragments introduced into NHC ligands in order to design redox-switchable NHC ligands. As already mentioned, some researchers introduced quinone groups, aiming that the reduction of quinone fragment should increase the electron-donating character of the NHC ligands. For example, Bielawski and co-workers[58] obtained a series of naphthoquinimidazolylidene complexes with Ni(II), Pd(II), and Pt(II) to study the redox-switchable Kumada cross-coupling reaction. They observed that the Ni(II) complex (20, Scheme 13) showed high activity in the process, and they studied the effect of controlling the activity of the complex by altering the redox state of the supporting NHC ligand. Addition of a reducing agent (2 equiv of cobaltocene) significantly reduced the catalytic activity of the complex, while subsequent addition of an oxidant (2 equiv of ferrocenium tetrafluoroborate) restored

the activity. The authors hypothesized that the diminished activity of the reduced catalyst reflected greater electron density at the nickel center, causing the transmetalation and reductive elimination steps of the catalytic cycle to occur at a much lower rate.[58]

### 2.3. Chemoactive N-Heterocyclic Carbene Ligands

In 2010, César and Lavigne and co-workers[59] used the term chemoactive NHC ligands to refer to N-heterocyclic carbenes with a functional group at the backbone susceptible to allowing further chemical modification once the ligand is bound to the metal fragment. This strategy allows real-time tuning of the electronic properties and therefore can be used to adapt the ligand to the requirements for a specific catalytic transformation. Therefore, chemoactive NHCs refer to all types of methods allowing the chemical postmodification of a NHC ligand, once this is already bound to a metal. This strategy to modulate the chemical properties of the NHC ligand differs from the premodification strategy, which implies that the functionality is added to the NHC in the multistep synthetic procedure of the carbene precursor, often an azolium salt. The types of chemical postmodification that will be treated in this section are addition of a functionality to the NHC backbone, coordination to a metal, and proton-responsive systems.

2.3.1. Postfunctionalization of N-Heterocyclic Carbenes with Reactive Backbones. In 2009, César and Lavigne and co-workers[60] obtained an imidazolylidene-olate, which can be considered as the first preprogrammed NHC for further derivatization. In fact, these authors were probably the first ones to study in detail the rich chemistry introduced by anionic NHC ligands.[61] Coordination of the in situ prepared anionic NHC (21) with [RhCl(COD)]₂ in the presence of hydrochloric acid afforded the keto-imidazolylidene rhodium(I)

Scheme 15. Gold Complexes with Chemoswitchable Carbenes

Mesomeric complexes observed in crystal structure
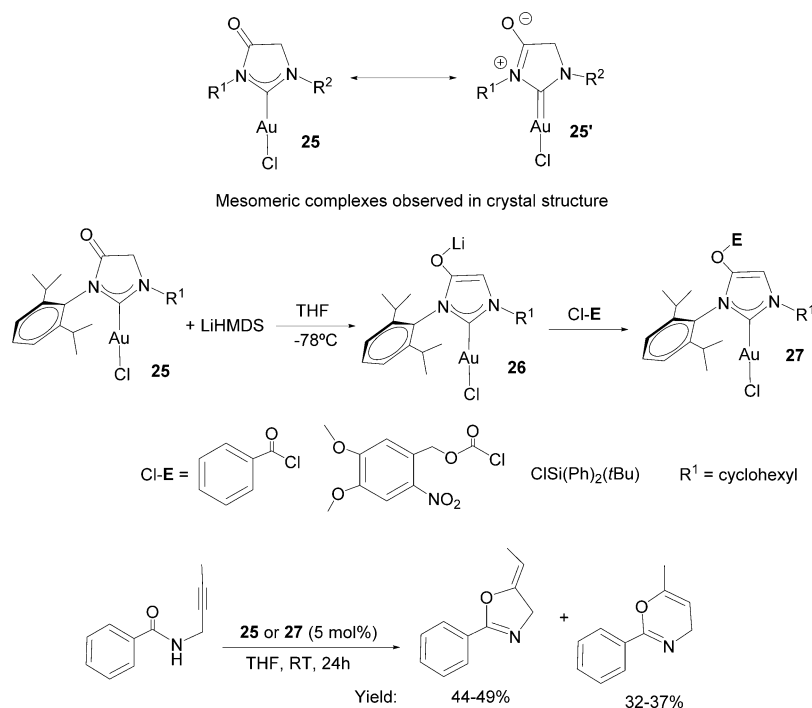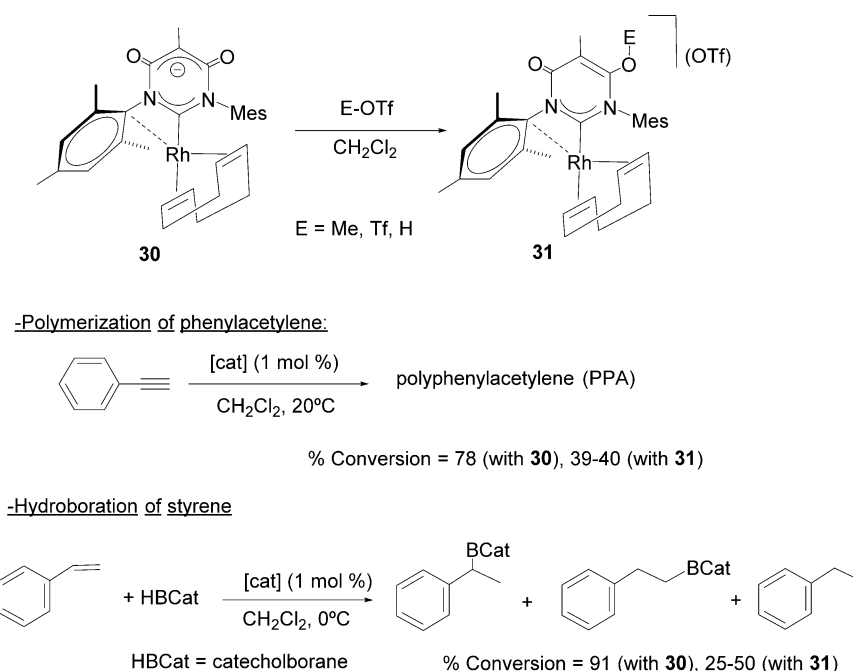

Scheme 16. Postfunctionalization of Amino-imidazolylidene
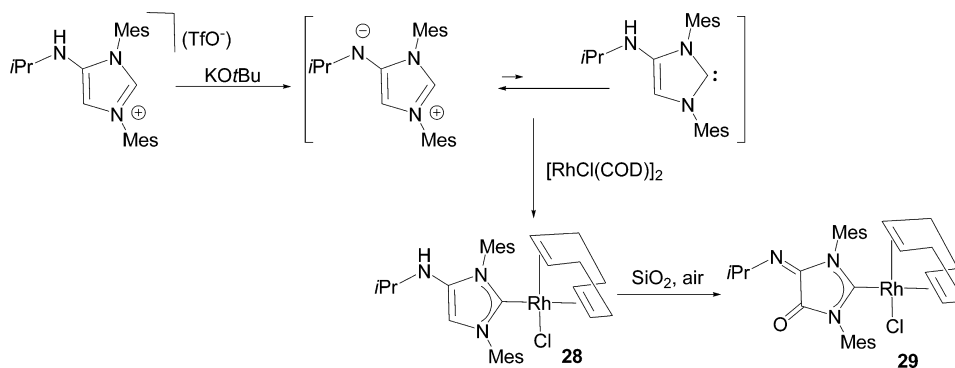
complex **22**.[60] This compound is assumed to show a tautomeric equilibrium with the enol-imidazolylidene, so reaction with $LiN(SiMe_3)_2$ followed by addition of an electrophile [terbutyldimethylsilyl chloride (TBDMSCl) or $Ph_2P(=O)Cl$] produced functionalization at the oxygen atom (complex **23**, Scheme 14). C-functionalization of the carbene ligand can be performed with paraformaldehyde as electrophile, via an aldolization−crotonization sequence, affording the olefinic carbene complex **24**.

Hashmi et al.[62] extended the coordination of this type of chemoswitchable imidazolylidene-olate ligands to gold, palladium, and platinum. The ligands contained a wide variety of aromatic and aliphatic wingtips (substituents at the nitrogen atoms of the N-heterocycle). Interestingly, the crystal structure of one of the gold complexes indicated the presence of two independent mesomeric molecules (**25** and **25′**). Switching of the electronic properties of the ligand was achieved by deprotonation of the carbonyl-imidazolylidene complex of gold, and subsequent addition of an electrophile (Scheme 15). The resulting complexes were active in the cycloisomerization of propargyl amides to alkylideneoxazolines and oxazines,

although the enolate-carbene complexes (**27**) did not show measurable different activities compared to their mother carbonyl-NHC gold complex **25**.[62] The same keto-imidazolylidene was recently used by Buchowicz and co-workers[63] for the preparation of the corresponding [NiCpCl(NHC)] complex. This complex, together with other half-sandwich nickel complexes with backbone-functionalized NHCs, were tested in the polymerization of styrene and methyl methacrylate and in the Suzuki−Miyaura cross-coupling.

Another interesting example of a chemoactive NHC ligand reported by César and Lavigne and co-workers[64] consisted of a imidazolylidene with a free NH function at the backbone. This carbene is in a tautomeric equilibrium with its mesoionic imidazolium isomer, although the carbene form is trapped by reaction with metal fragments (Scheme 16). Reaction of this species with $[RhCl(COD)]_2$ in the presence of potassium *tert*-butoxide produced a complex with the heterocyclic ligand in the form of the imidazolylidene (**28**), which does not show any tendency to tautomerize. This complex reacted in the presence of SiO_2 in air by incorporating an oxygen atom to the backbone, generating an amido-amidino-carbene complex (**29**).

Scheme 17. Effects of Chemical Modification of Anionic NHC Ligand on Catalyst Activity in Polymerization of Phenylacetylene and Hydroboration of Styrene

-Polymerization of phenylacetylene:

% Conversion = 78 (with **30**), 39-40 (with **31**)

-Hydroboration of styrene

HBCat = catecholborane

% Conversion = 91 (with **30**), 25-50 (with **31**)

Calculation of the Tolman electronic parameters (TEP) of the ligands (by obtaining the related $[RhCl(NHC)(CO)_2]$ complexes and comparing their IR C−O stretching frequencies) in **28** and **29** indicated that the four-electron oxidation of the carbene ligand was accompanied by an increase in the TEP value of 7.8 cm^{-1}, as a consequence of the lower electron-donating character of the ligand in **29**.[64]

The same researchers described a six-membered NHC with a remote anionic functional group within the heterocyclic backbone, which afforded zwitterionic metal complexes such as **30** (Scheme 17).[65] This complex underwent reaction with various electrophiles to afford cationic complexes **31**.[66] Addition of the electrophile produced an important decrease in the ligand donicity $(\Delta\nu_{av}(CO)$ in the range 13−16 cm^{-1}, according to variation of C−O stretching frequencies of the related $[RhCl(NHC)(CO)_2]$ complexes). The complexes were tested in the catalytic polymerization of phenylacetylene and in the hydroboration of styrene (Scheme 17), and for both cases, the zwitterionic complex was the best catalyst, thus revealing an apparent correlation between the donor character of the ligand and the activity of the complex.

Six-membered ring N-heterocyclic carbenes with malonate or imidate backbones were incorporated to the coordination sphere of cyclopentadienyl iron carbonyl complexes, affording a series of zwitterionic complexes (**32** and **33**, Scheme 18).[67] The donor properties of the ligands could be switched (reduced) by addition of methyl triflate, which reacts with one oxygen of the malonate group (**34**) or the nitrogen of the imidate backbone (**35**). The complexes were tested in hydrosilylation of benzaldehyde, where the zwitterionic complex with the malonate-NHC ligand was the one displaying higher activity. The authors rationalized these results as a consequence of the stronger electron-donating character of the malonate-NHC ligand in **32**. Complex **32** was further tested in the hydrosilylation of a variety of aldehydes, showing good efficiency and excellent chemoselectivity.[67] The same catalyst

Scheme 18. Malonate- and Imidate-NHC Complexes with FeCp(CO)₂

R = Me, nBu

Conversions: 98% (with **32**), <5% (with **33-35**)
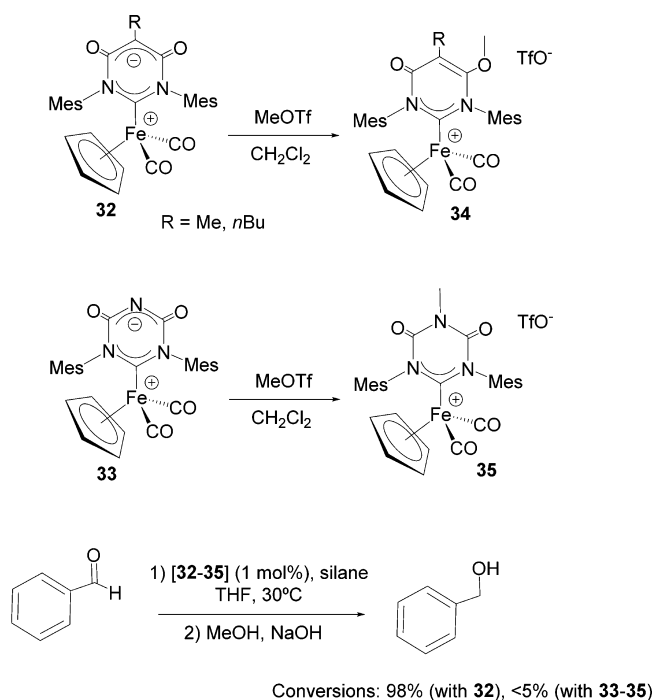
showed moderate activity in hydrosilylation of ketones and good activity in hydrosilylation of imines.

Several examples have been reported in which postfunctionalization of the NHC ligand is performed through an "autoclick" copper- or ruthenium-catalyzed alkyne−azide cycloaddition (CuAAC or RuAAC).[68−70] Although some examples have been described in which this type of strategy is used to modify the catalytic properties of NHC-based metal complexes, the method has not yet been used for the preparation of

switchable catalysts,[7] in the sense that modifications of the properties are not reversible, and also the "switching" is never produced in situ, during the course of the catalytic reaction. This type of postmodification strategy was first used by Elsevier and co-workers in 2010,[71] who described the modular approach to bidentate palladium complexes with triazolyl-NHC chelate ligands. The monodentate palladium alkenyl-imidazolylidene complex 36 underwent a copper-catalyzed click reaction with azidoadamantane to afford the C−N ligated complex 37, as described in Scheme 19. Complex 37, and other C−N similar chelate palladium complexes, were tested in the reduction of 1-phenyl-1-propyne by transfer hydrogenation with formic acid as hydrogen source.[71]

Scheme 19. CuAAC Click Reaction for Preparation of C−N Chelate Pd(II) Complex
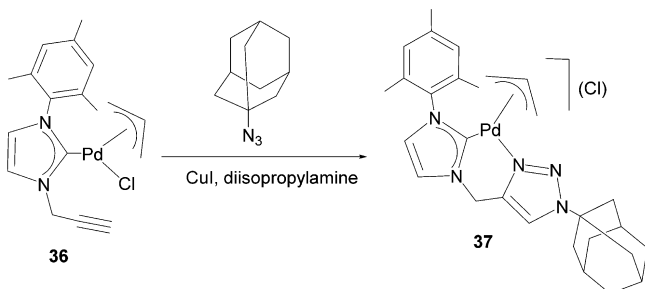
Only one year later, Guichard and Bellemin-Laponnaz and co-workers[72] used the RuAAC click process for functionalization of a series of NHC complexes of palladium and platinum. These authors used a wide set of azides and alkynes, aiming to generate an extensive library of NHC-based complexes with cytotoxic activity. An example of functionalization of a platinum complex with estrogen is shown in Scheme 20.

While these two previous examples were based on the introduction of alkyne functionalities onto the backbone of the NHC to facilitate the click process by reaction with a functionalized azide, Gautier and Cisnetti and co-workers[73] were the first ones to invert the process, by using azide-functionalized NHC complexes to facilitate postfunctionalization of the ligand. They first prepared a series of silver(I) and

gold(I) complexes functionalized with diverse 1,2,3-triazoles. Interestingly, the reaction with an activated alkyne could be produced by thermally-promoted and strain-promoted 1,3-dipolar cycloaddition without the need to add any copper catalyst.[73] By following a similar methodology, the same authors prepared a series of azido-NHC−Cu(I) complexes, which underwent a CuAAC reaction in the presence of alkynes, in a very interesting self-catalyzed (or autoclick) process without the need for any additional copper catalysts (Scheme 21).[74] The reaction worked well for saturated and unsaturated NHCs. More recently, by using this autoclick process, these authors were able to prepare a wide variety of functionalized gold and copper complexes, including a gold compound with a fluorescent biomarker.[75]

By using a bromopropyl-substituted benzoimidazolylidene−palladium complex (42, in Scheme 22), Huynh and Teng[76] were able to easily postmodify their complexes by adding a number of functionalities, including iodide, esters, azido, thiocyanato, and thioester groups (43−47). Although this strategy was not tested in homogeneous catalysis, the ease of postfunctionalization of these palladium complexes envisages a promising future in the field, also as a simple way for grafting the metal complexes onto solid materials for heterogenization of the catalysts. In a more recent work, using the same bromopropyl-substituted benzoimidazolylidene ligands, the authors prepared a bis(benzoimidazolylidene) complex, 48, which was postfunctionalized with a series of groups including hydroxyl, azido, thioether, thioester, amino, and thiocyanate.[77] Some of the resulting complexes were tested in the Mizoroki−Heck coupling reaction between aryl halides and *tert*-butyl acrylate (a selected example is shown in Scheme 22), where the presence of the ancillary ammonium group in 50 showed a significant positive effect on the activity of the catalyst, possibly due to the stabilization of the catalyst via formation of ion pairs.[77] Although the presence of the ancillary ammonium groups are clearly beneficial for the activity of 50, the catalyst performs better in the presence of an extra amount of ammonium salts.

The same strategy was used for the postmodification of indazolinylidene complexes of palladium(II). In this case a series of *trans*-[PdBr₂(amine)(indy)] (indy = indazolinylidene)
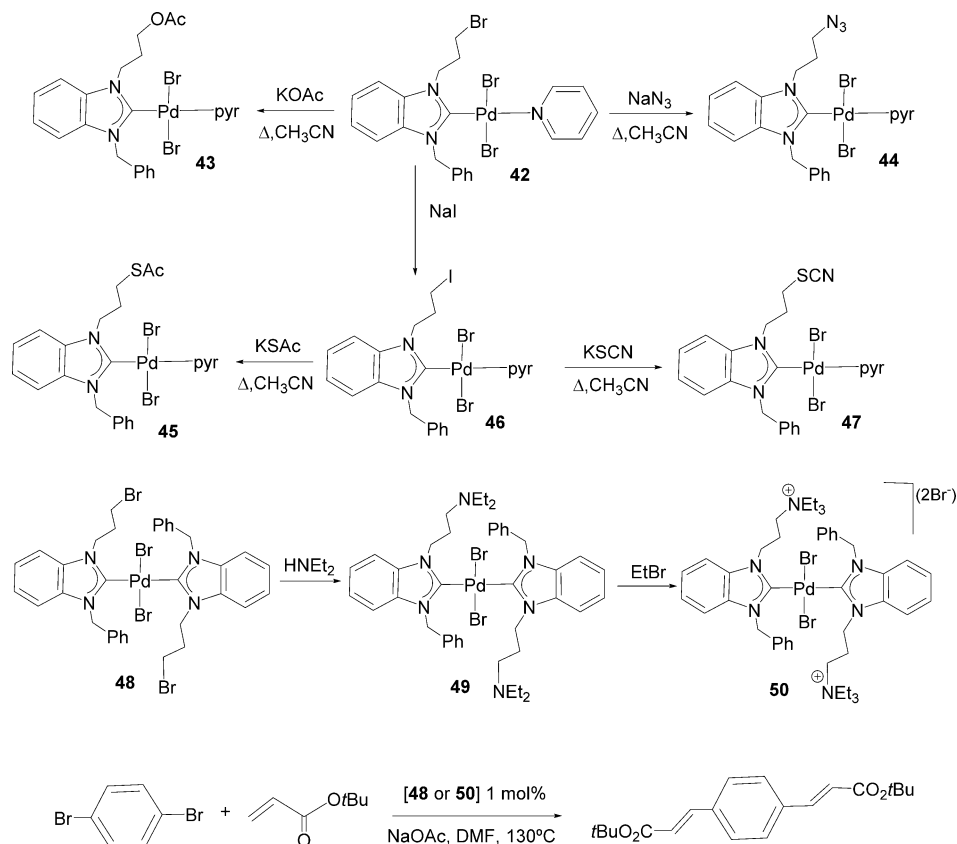
Scheme 20. Functionalization of Platinum(II) Complex with Estrogen
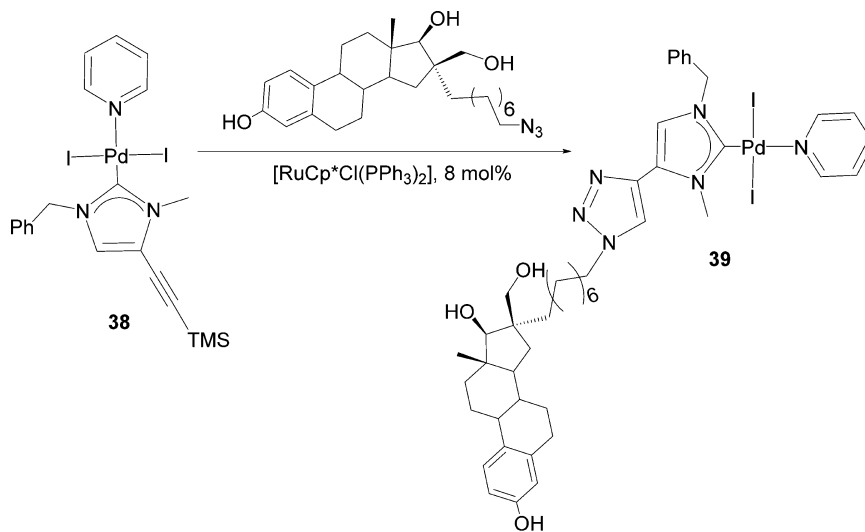
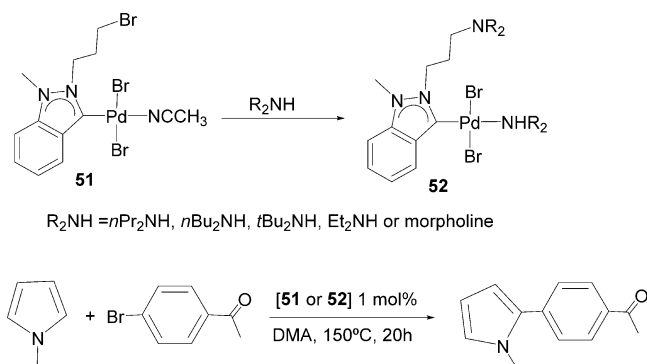**Scheme 21. CuAAC Click Reaction of Azide-Tagged Cu(I)−NHC Complex**
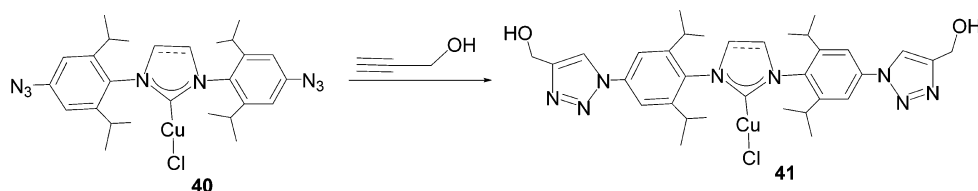
Scheme 22. Postfunctionalization of Palladium(II)−NHC Complexes by Nucleophilic Substitution

with pendant amines (**52** in Scheme 23) were obtained by reaction of a single precursor with an indazolinylidene ligand having a bromopropyl substituent at the nitrogen (**51**).[78] All these palladium complexes were tested in the arylation of 1-methylpyrrole with 4-bromoacetophenone, where the amine-functionalized catalysts showed a slightly higher activity

compared to **51**. The best activity was achieved for the reaction carried out with catalyst **52** bearing a diethylamino group.

Huynh and co-workers also developed an interesting example in which a series of thiolato-bridged dinuclear complexes of palladium (**53**) are oxidized by oxone to yield the related sulfonate-functionalized monometallic complexes (**54**).[79] These complexes are interesting because their solubility in water is very high, and for this reason they were used for the Mizoroki−Heck coupling of aryl halides with *tert*-butyl acrylate in aqueous medium (Scheme 24). The activity of complex **54** with a *o*-xylyl-sulfonate group, was very high for the coupling of bromobenzaldehyde, even at low catalyst loadings (0.05 mol %), but it failed to catalyze the coupling of aryl chlorides or unactivated aryl bromides.[79]

In a recent work, Bellemin-Laponnaz and co-workers[81] used the oxime ligation[80] as a click reaction methodology for postfunctionalization of a NHC−Pt(II) complex bearing a benzaldehyde moiety (**55** in Scheme 25). This process was combined with metal−ligand exchange, thus offering a very practical approach to the multifunctionalization of NHC−platinum complexes. The work constituted a new advance in

Scheme 23. Postmodification of Palladium(II) Complex with Indazolinylidene Ligand

R$_2$NH =*n*Pr$_2$NH, *n*Bu$_2$NH, *t*Bu$_2$NH, Et$_2$NH or morpholine

Scheme 24. Preparation of Sulfonate-Functionalized NHC−Pd(II) Complexes and Catalytic Activity in Mizoroki−Heck Coupling in Water

X = (CH₂)₂, (CH₃)₃, H₂C–⟨o-C₆H₄⟩–CH₂

arylhalide	yield (%)
4-bromobenzaldehyde	99
4-bromoacetophenone	97
4-bromotoluene	25
4-bromoanisole	6
4-chloroacetophenone	0
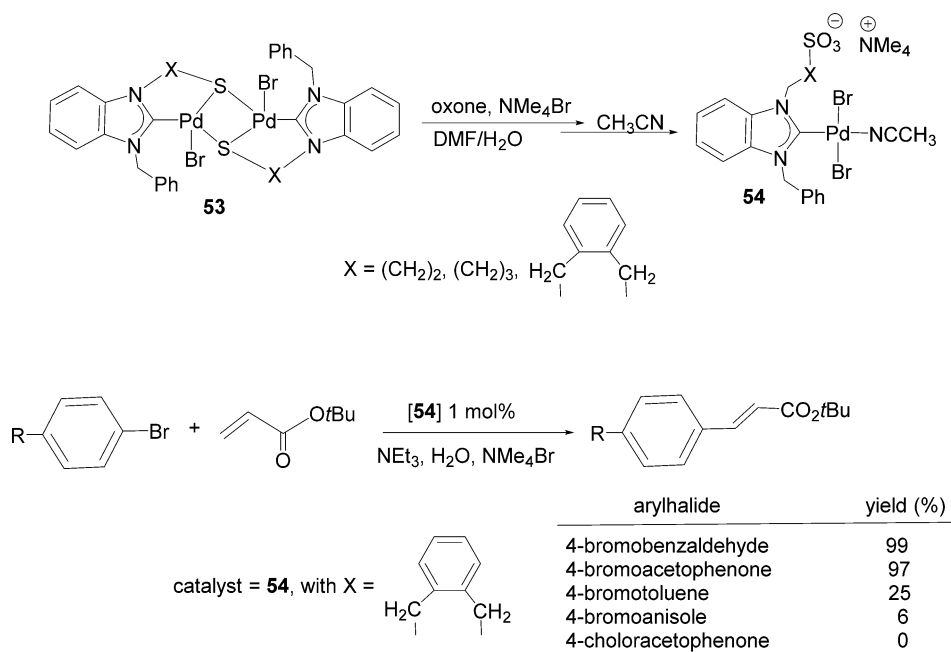
Scheme 25. NHC Functionalization by Oxime Ligation Followed by Ligand Exchange
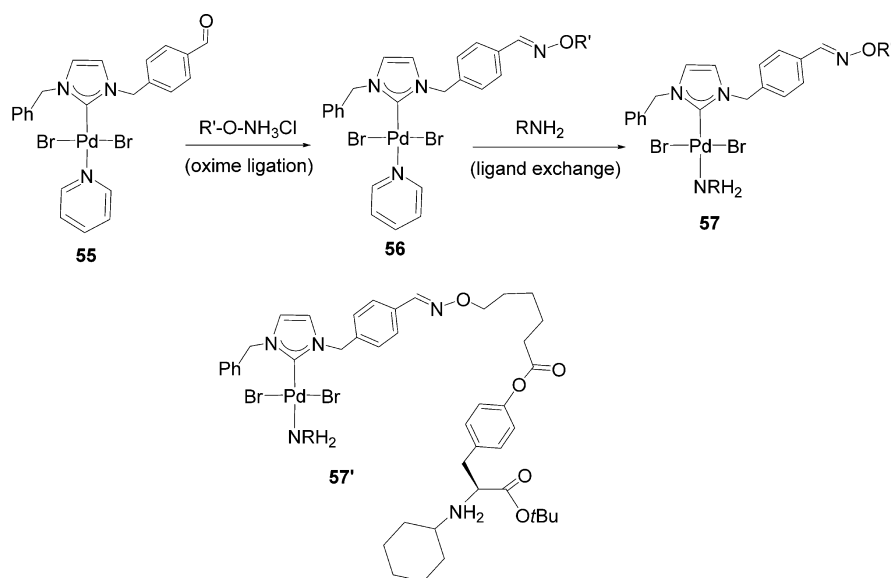
the search for simple methods to fine-tune NHC−metal complexes with biological activity.[81] Scheme 25 shows the general procedure, together with one example of the many possible multifunctionalized Pt(II) complexes described (**57′**).

An intriguing way of postfunctionalizing a chelate cyclometalated NHC ligand was described by Deng and co-workers in 2013.[82] The authors obtained a cobalt(II) bis(carbene) complex with cyclometalated mesityl groups (**58**, Scheme 26). The reaction of this complex with an arylhydrosilane afforded a silyl-donor-functionalized NHC complex (**59**), through a cobalt-mediated C−H activation and silylation protocol. The resulting complexes, with strong electron-donating ligands due to the presence of the silyl-metal-bound moieties, afforded very high activity in the hydrosilylation of 1-octene with PhSiH₃, also providing high selectivity toward the linear isomer product.

Scheme 26. Cobalt-Mediated Silylation of NHC Ligand

R = H, Me, Ph
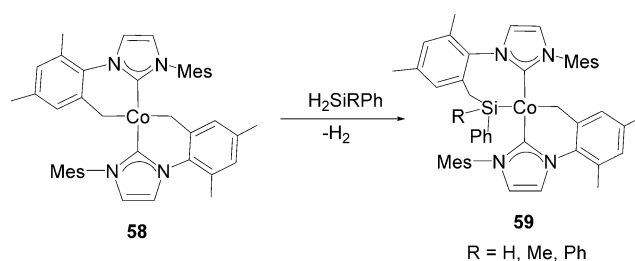
2.3.2. Postfunctionalization by Coordination of Metal Fragments. The coordination of a metal fragment to a distant coordination site attached to an NHC ligand may also be used for modification of the electronic and steric properties of the

NHC ligand. Some early examples of this strategy were used by Peris and co-workers,[83−90] who used a simple 1,2,4-triazoldiylidene ligand to prepare a series of homo- and heterodimetallic complexes, which were basically used for the design of tandem processes by the combination of orthogonal catalytic cycles facilitated by each of the metal fragments bound to the di-NHC ligand (Figure 2). These results were reviewed in a recent article,[91] and for this reason we will not go into deep details about this research.
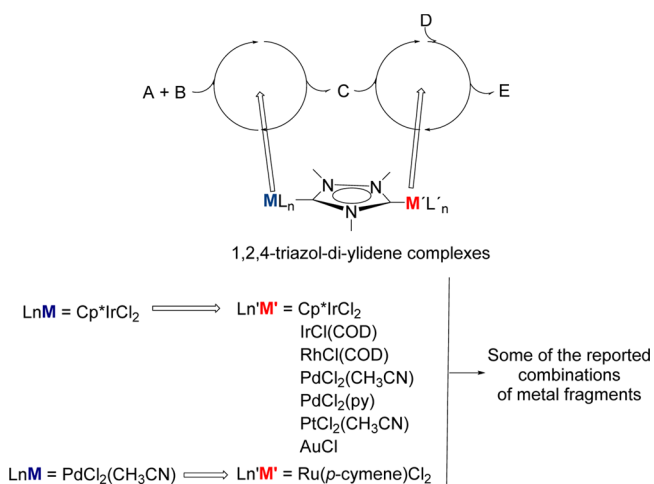
Figure 2. Triazoldiylidene complexes used for homogeneously catalyzed tandem processes.

An interesting finding derived from this research arose by computational study of variation of the Tolman electronic parameter (TEP) of the triazoldiylidene ligand as a consequence of the modification of the metal fragment bound to the other edge of the carbene ligand.[92] This variation is shown in Figure 3, which reflects how switching from the coordination of $[IrCp(CO)]$ to a $[RhCl(CO)_2]$ fragment is accompanied by a positive shift of the TEP value of 4.5 cm^{-1}, thus indicating an important decrease in electron-donating power of the ligand. By choosing other metal fragments, a fine-tuning of the electronic properties of the ligand can be obtained.[92]

César and Lavigne and co-workers[93] used another ambidentate Janus-type ligand, which combined an N-heterocyclic carbene and an anionic imidate (**60** in Chart 1). This bifunctional ligand could be bound to two different metal fragments and therefore, as for all the examples described in this section, the electronic structure is assumed not to be an

Chart 1. Selected Examples of Janus-type NHC Complexes Postfunctionalized by Coordination
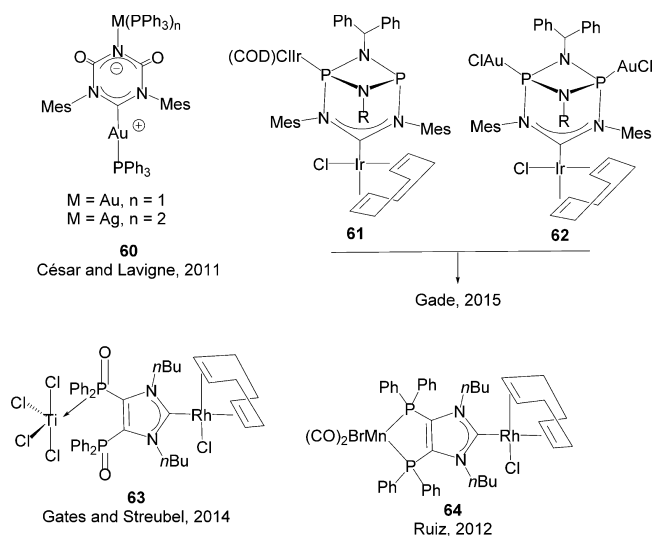
intrinsic property of the ligand. Other selected examples of polyfunctional carbene ligands that can be modified by coordination of metal fragments are the ones described by Wright and Gade and co-workers[94] (**61** and **62**), Gates and Streubel and co-workers[95] (**63**), Ruiz and Mesa[96] (**64**), Bertrand and co-workers,[97] and Bellemin-Lapponaz and Cesar and co-workers.[98] However, none of these species were tested in catalysis. Some other examples are known, but their chemistry and catalytic properties were described in a previous review article.[91]

Ganter and co-workers also contributed to the development of NHC-based metal complexes that could be modified by coordination of a second metal fragment, by attaching a cationic pentamethylcyclopentadienylruthenium fragment $([RuCp^*]^+)$ to a metal-coordinated benzoimidazolylidene ligand[99−101] and then to a dimethylperimidinylidene complex (Figure 4).[102] The TEP of the cationic species is shifted by approximately 5 cm^{-1} for both types of ligands, as a consequence of reduction of the electron-donating character of the carbene upon attachment of the cationic metal fragment. In line with these findings, Poyatos and co-workers[103] obtained a pyrene-imidazolylidene ligand, whose electronic properties were modified by 6 cm^{-1} (based on TEP units), by introduction of the same cationic ruthenium moiety.

A very interesting example in which the electronic properties of a NHC ligand can be switched by metal coordination was
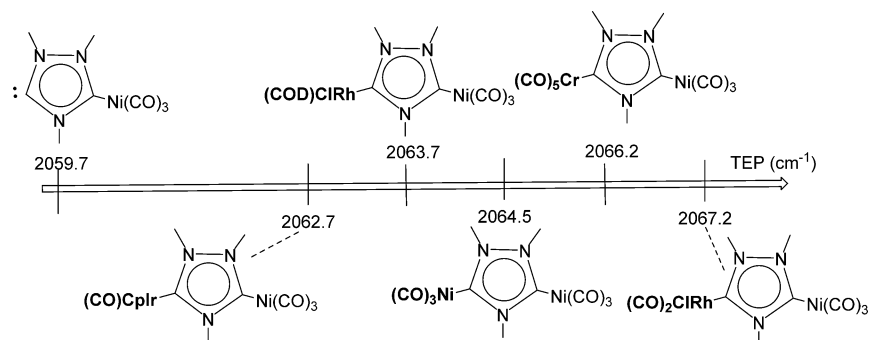
Figure 3. Modification of the TEP value of a triazoldiylidene ligand by coordination of different metal fragments.
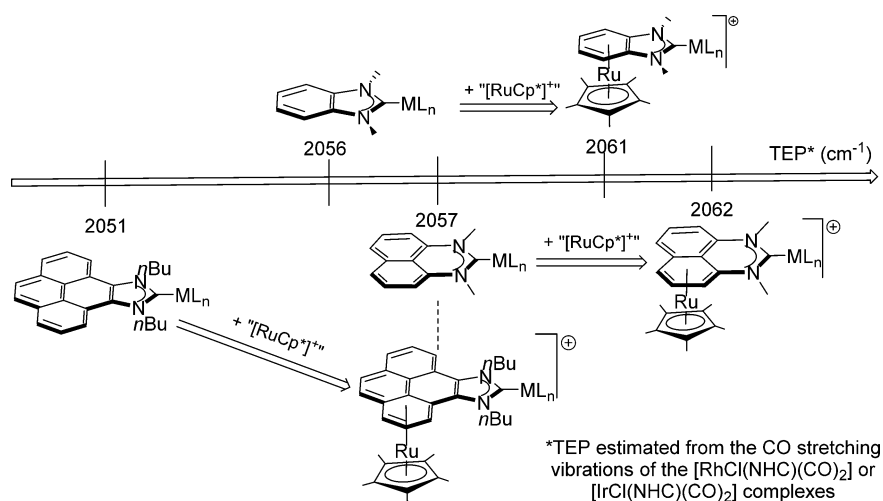
Figure 4. TEP variation by introduction of a [RuCp*]⁺ fragment on a series of arene-functionalized NHC−metal complexes.

reported by Choudhury and co-workers in 2014.[104] Their idea was to use a NHC-pyridyl ligand and use the labile coordination abilities of the pyridyl group for the reversible coordination of different metal fragments. They were successful in reversibly coordinating [IrCp*Cl₂] and [RuCl₂(*p*-cymene)] fragments to the pyridyl moiety, which could then be *decoordinated* by adding triphenylphosphine (Scheme 27).[104] The overall process constitutes a neat example of a pronounced on-demand reversible modulation of the electronic properties of the main (NHC-coordinated) metal center.
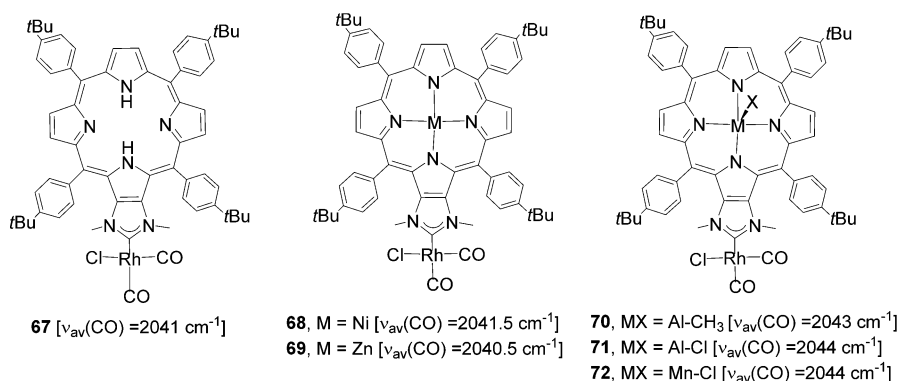
Scheme 27. Reversible Coordination (Coordination Switch) of Metal Fragment to NHC-Pyridyl−Ru(II) Complex
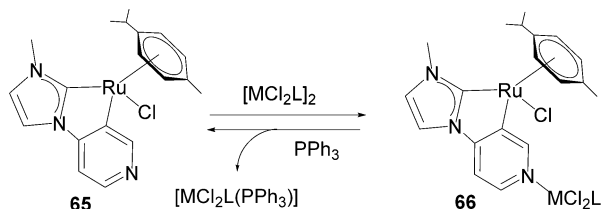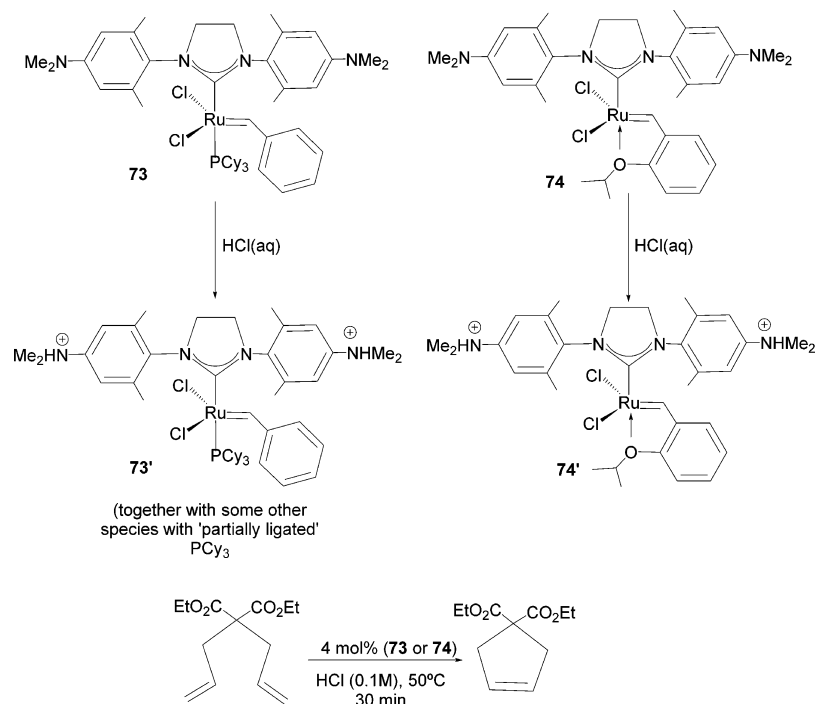

One of the very few examples in which the effects of remote coordination of a metal to a preformed NHC−metal complex were tested in catalysis was reported by Richeter and co-workers in 2013.[105] These authors prepared a NHC ligand fused to a porphyrin, so that the coordination abilities of the

porphyrin could be used for the incorporation of a second metal. Modification of the electronic properties of the carbene ligand was investigated by studying the modification of CO stretching frequencies of the related [RhCl(porphyrin-NHC)(CO)₂] complexes (Chart 2). It was established that porphyrin-NHC ligands with Mn(III) and Al(III) were weaker electron donors than the porphyrin-NHC ligand without any metal cation or with Ni(II) or Zn(II) (2−3 cm⁻¹ shift of average C−O stretching frequency of the related [RhCl(NHC)(CO)₂] complexes). The authors studied the organocatalyzed ring-opening polymerization of L-lactide with the porphyrin-NHC, and they observed that the properties of the catalyst were affected by the presence and nature of the metal cations bound to the porphyrin fragment.[105] It was assumed, that the differences were due to subtle modifications of the electronic properties of the NHC organocatalysts, although some other phenomena (such as aggregation of the porphyrin catalyst or coordination of ligands to the metal in the inner part of the porphyrin) could also be at play. By using the same porphyrin-NHC ligand, the same authors obtained mono-NHC and bis-NHC complexes of Au(I), with and without a nickel atom coordinated to the inner part of the porphyrin.[106] The monoporphyrin-NHC−Au(I)−Cl complex was tested in the photooxidation of cholesterol, where it showed higher activity than the free ligand without the Au−Cl fragment. This result was attributed to the "heavy atom" effect of Au(I), which promotes the intercrossing system $S_1 \rightarrow T_1$, allowing formation

Chart 2. Porphyrin-NHC−Rhodium Carbonyl Complexes and Average C−O Stretching Frequencies

67 [$\nu_{av}(CO)$ =2041 cm⁻¹]

68, M = Ni [$\nu_{av}(CO)$ =2041.5 cm⁻¹]
69, M = Zn [$\nu_{av}(CO)$ =2040.5 cm⁻¹]

70, MX = Al-CH₃ [$\nu_{av}(CO)$ =2043 cm⁻¹]
71, MX = Al-Cl [$\nu_{av}(CO)$ =2044 cm⁻¹]
72, MX = Mn-Cl [$\nu_{av}(CO)$ =2044 cm⁻¹]

Scheme 28. Proton-Responsive Ru—NHC Complexes Used in Olefin Metathesis

EtO₂C, CO₂Et → EtO₂C, CO₂Et

4 mol% (**73** or **74**)

HCl (0.1M), 50 °C
30 min

Scheme 29. A Grubbs—Hoveyda Metathesis Catalyst Combining Two Proton-Responsive Ligands and Its Activity in Two Standard Processes

75, 0.5 mol%

15 min, 20 °C

Equivalents of H₃PO₄	Conversion
0	93
2	97
4	<40

R = Ph, SPh

75

75, 0.5 mol%

30 min, 20 °C

Equivalents of H₃PO₄	Conversion
0	7.2
2	47
4	14
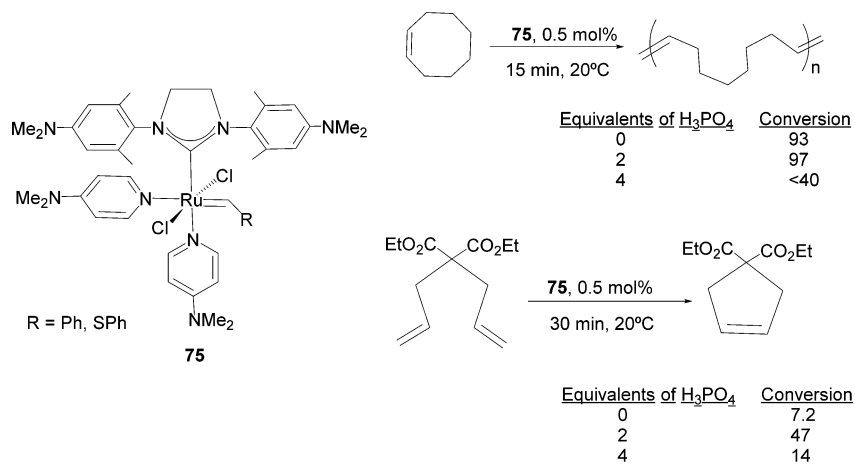
of $^1O_2$. Other porphyrin-functionalized NHCs were also reported by Furuta and co-workers,[107] Wang et al.,[108] and Ruppert and co-workers.[109,110]

2.3.3. Proton-Responsive N-Heterocyclic Carbene Ligands. Although natural chemical processes driven by pH-responsive systems are very common, the number of examples describing NHC-based catalysts using this type of strategy is very scarce, and they mostly refer to Ru(II)-catalyzed olefin metathesis processes. In this regard, the first pH-responsive Ru—NHC complexes used for olefin metathesis were described by Schanz and co-workers in 2008.[111] These researchers prepared two Ru(II) complexes (**73** and **74**), each bearing a mono-NHC ligand with two anchored NMe₂ groups. The initial idea is that these species may react with HCl to afford the mono- and diprotonated species (**73′** and **74′**), which show different reactivity patterns related to the mother unprotonated complexes and also are more soluble in aqueous media. The

two catalysts were tested in the ROMP reaction of exo-7-oxanorbornene, where they showed negligible activity. The same two catalysts were tested in the RCM of diallylmalonic acid, where they both produced moderate conversions (Scheme 28). These results were unexpected, as it was assumed that acidic conditions should have accelerated the initiation rates of the metathesis reaction. The authors interpreted the deactivation of catalytic activity as a consequence of the lower electron-donating character of the NHC ligand upon protonation.[111] The authors also performed a detailed study in which they proved that the activity in olefin metathesis can be externally controlled with acid addition, due to gradual protonation of NMe₂ groups of the NHC ligand and the concomitant reduction of electron-donating power of the NHC ligand, which was also verified by density functional theory (DFT) calculations.[112]

Plenio and co-workers[113] used a related Ru(II) Grubbs–Hoveyda catalyst with a NEt$_2$-substituted NHC and compared the activity of neutral and protonated catalysts in the ROMP of norbornene. Upon protonation, the double-bond geometry changed (from $E/Z = 0.78$ to $E/Z = 1.04$), and for this reason the authors concluded that addition of acid during the polymerization reaction allows for fine-tuning the E/Z ratio of the resulting norbornene.

More recently, Schanz and co-workers,[114] in line with their previous works, prepared two new pH-responsive Ru catalysts, each containing a dimethylaminopyridine ligand (**75**, with two different R groups, as shown in Scheme 29). In organic solvents these two catalysts gave good activities in the ROMP and RCM processes with standard substrates. The ROMP reaction in benzene was accelerated when 2 equiv (referred to the catalyst) of an acid (H$_3$PO$_4$) were added, but the activity decreased as soon as the amount of acid increased, probably as a consequence of significant reduction of the electron-donating character of the carbene ligand upon protonation of the amine moieties attached to the NHC. The RCM reaction in acidic aqueous medium did not work, probably due to catalyst degradation.[114]

Some other proton-responsive NHC-based complexes were described, although their catalytic properties were not evaluated. For example, in 2009, Glorius and co-workers[115] performed one of the very first studies on switching the electron-donor power of a NHC ligand by reversible protonation/deprotonation of an enolate-imidazolylidene ligand (Scheme 30), which was previously described by César

**Scheme 30. Deprotonation of Keto-imidazolylidene Ligand and TEP Change**
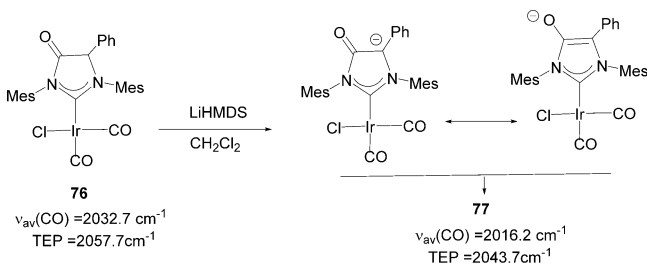
and Lavigne and co-workers.[60] Upon coordination, this ligand is known to stabilize the keto-imidazolylidene form, as mentioned in section 2.3.1. The coordination of this NHC to form the corresponding [IrCl(NHC)(CO)$_2$] complex (**76**) allowed for study of the variation of C–O stretching frequency and then to estimate the TEP shift produced by reversible deprotonation of the ligand.[115] This deprotonation was accompanied by a TEP decrease of 14 cm^{-1}, therefore indicating a very significant increase in electron-donating power of the NHC ligand. The reversibility of the process adds significance to the potential of this class of NHC ligands.

Richeter and co-workers[116] also estimated the change in electron-donating power of their porphyrin-NHC ligand upon protonation, by studying the shift in C–O stretching frequency of their related Rh(I) complex **67** (Chart 2). This protonation was produced by use of trifluoroacetic acid and afforded the related dicationic species, in which all four nitrogens of the porphyrin are bound to a proton. In this case, the protonation was accompanied by an increase in average C–O stretching frequency of 7 cm^{-1}, as a consequence of the lower σ-donating

character of the complex resulting from the diprotonation of **67**.[116]

Choudhury and co-workers[104] also used their ruthenium(II) complex with a NHC-pyridyl ligand (**65**) as a proton-responsive system, in which the electronic properties of the ligand were reversibly modulated by addition of an acid or a base (Scheme 31).

**Scheme 31. Reversible Protonation of Ruthenium Complex with Pyridyl-NHC Ligand**
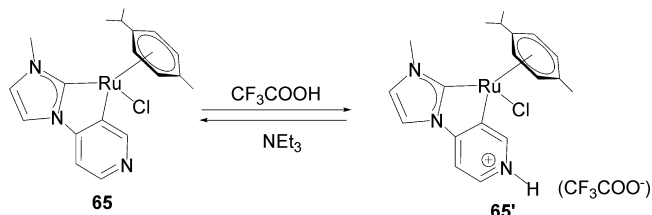
3. MULTIFUNCTIONAL N-HETEROCYCLIC CARBENE LIGANDS

As defined by Burrows in 2002,[8] "a multifunctional ligand is simply a ligand that has been designed to do more than one thing". Crabtree[9] made a more specific definition of these ligands, by suggesting that multifunctional ligands are those having additional functions that can be useful in catalysis. Although these two definitions would include all the NHC ligands described in section 2, we leave to this section only the examples regarding the use of hemilabile ligands (section 3.1) and ligands that have a relevant participation in the catalytic cycle, as the so-called bifunctional or cooperative ligands (section 3.2).[117] Related to hemilabile NHCs, ligands with flexible steric bulk (conformationally labile NHCs) will also be considered here. Therefore, while section 2 refers to ligands that adapt (or switch), by external stimuli, their steric or electronic properties to the requirements of the catalytic transformations, multifunctional ligands, as described in this section, will deal with all ligands whose reactivity depends on direct interaction with the substrates and therefore are directly involved in the catalytic cycle.

3.1. Hemilabile and Conformationally Labile N-Heterocyclic Carbene Ligands

The term hemilability in coordination ligands was introduced by Jeffrey and Rauchfuss in 1979.[118] A hemilabile ligand refers to a hybrid polydentate ligand where one of the coordinating groups can be displaced from the coordination sphere of the metal while at least one group remains firmly bound to the metal center.[119−121] This means that one of the donor groups needs to not be strongly bonded, so that it can reversibly dissociate in solution to open a coordination site. Therefore, hemilabile ligands yield the stability of a coordinative saturated metal complex while providing open coordination sites during the catalytic cycle. In NHC-based hemilabile ligands, the NHC part of the ligand is assumed to be the edge that is strongly bound to the metal, and therefore these types of ligands are often heteroleptic (or hybrid) ligands with a weakly bound functionality, which is often (but not exclusively) a N, O, or S donor group (Scheme 32). Although many different types of donor-functionalized NHC ligands have been described,[122−124] in this section we will only discuss those examples in which the study of hemilability of the ligand is explicitly described and

Scheme 32. NHC-based Hemilabile Ligands
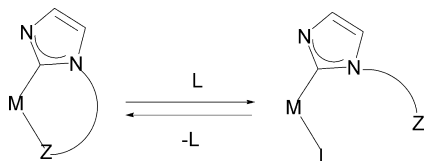
related to homogeneously catalyzed processes. These examples will mostly refer to NHC hybrid ligands with N and O, since P is often considered to bind strongly to the metal center and the chemistry of NHC-S ligands has been thoroughly reviewed recently.[125−127] A detailed review on anionic tethered NHC chemistry was also published by Arnold and co-workers in 2007,[128] and this included NHC-O hybrid ligands. An excellent review article regarding palladium complexes with NHC-based hemilabile ligands[129] has also been published.

Conformationally labile ligands may also be considered as multifunctional ligands in many ways, and they can also be considered related to hemilabile ligands. For this type of system, the steric hindrance imposed by the ligand can be tuned depending on the requirements of a specific catalytic reaction. Some key examples of this type of NHC ligand will be introduced in section 3.1.5.

3.1.1. N-Heterocyclic Carbenes with N-Donors. One of the first NHC-based hemilabile ligands used in catalysis was described by McGuinness and Cavell in 2000.[130] These authors prepared a series of NHC ligands containing pyridine and carbonyl donors, which were coordinated to palladium, affording neutral and cationic complexes. Depending on the metal precursors used and on the type of ligand, the resulting Pd−NHC complexes displayed chelating or dangling donors. While NHCs with carbonyl donors afforded the monodentate coordination of the ligands with dangling carbonyl functionalities, the NHC-pyridine ligands exhibited monodentate and chelating behavior, thus reflecting the hemilabile behavior of the NHC-pyridine ligand. The complexes were tested in the Heck and Suzuki−Miyaura couplings, where the two most active catalysts were 78 and 79 (Scheme 33). Complex 78

achieved 947 000 turnovers in the coupling of butyl acrylate with 4-bromoacetophenone (71% conversion), while in the same reaction conditions 79 gave a turnover number (TON) of 610 000. Both catalysts showed exceptional long-term stability. In the Suzuki coupling of 4-bromoacetophenone with phenylboronic acid, TONs over 100 000 were achieved.[130]

Chen and Lin[131] studied the hemilability of a series of palladium(II) complexes with a bis(pyridyl)-NHC ligand. Two ligands can bind to the metal in a bidentate chelating mode, yielding complex 80 (Scheme 34). This complex is susceptible to substitution by halides and phosphines, yielding complexes that contain both C,N-bidentate and monodentate NHC ligands. Complex 80 shows fluxional behavior in coordinating solvents as a consequence of solvent-assisted exchange involving unbound and coordinated pyridine. Complex 80 was active in the catalytic polymerization of CO/norbornene.[131]

Since the publication of these two early examples of pyridine-NHC hemilabile ligands in 2000,[130,131] the number of complexes containing NHC ligands with nitrogen donor groups has increased enormously,[132] and these include examples of coordination to palladium,[133−158] platinum,[154] rhodium,[122,150−152,159−169] iridium,[122,161−163,165,166,170−183] ruthenium,[179,181,182,184−193] nickel,[146,192,194−197] silver,[198−203] gold,[203] copper,[201,202,204] and iron.[152,205] A selected group of these complexes is shown in Chart 3.

Despite the large number of complexes with NHC ligands with nitrogen donors, the number of examples in which the hemilability of these complexes has been related to their catalytic properties is relatively scarce. An interesting study was described by Jiménez, Oro, and co-workers in 2008.[167] The authors obtained a series of [RhCl(NHC)(COD)] complexes, in which the NHCs contained aminoalkyl functionalities (99, Scheme 35). Upon chloride abstraction with silver salts, the aminopropyl-substituted NHC complex (n = 3, Scheme 35), undergoes C,N-chelation by binding the NMe₂ group to the metal. This chelate coordination could not be achieved for other aminoalkyl-NHC ligands (i.e., n = 2), thus suggesting that the chelate coordination is only possible for an appropriate

Scheme 33. Palladium(II) Complexes with NHC-Pyridyl Ligands in C−C Coupling Reactions
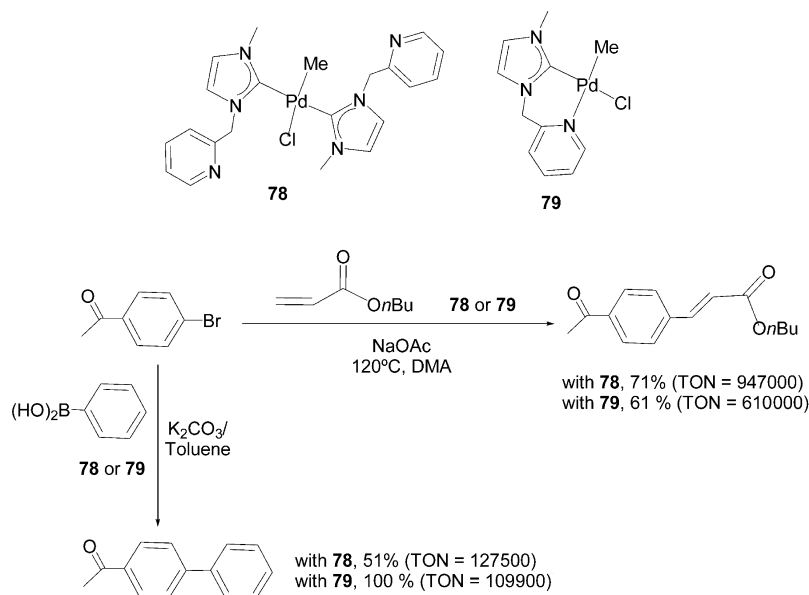
Scheme 34. Hemilability Shown by a Bis(pyridyl)-NHC Ligand
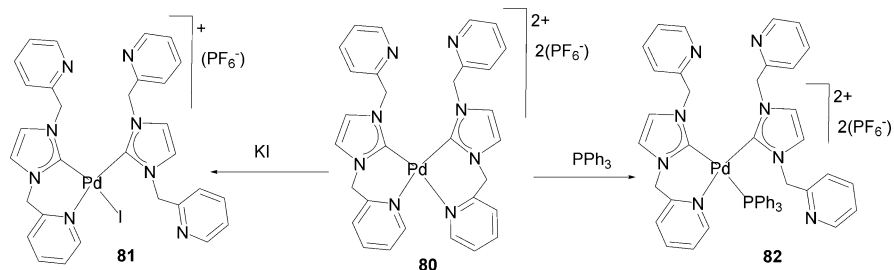
Chart 3. Some Examples of NHC Hemilabile Ligands with N-Donor Groups

83
Coleman, 2003

84
Pfaltz, 2006

85
Liu, 2006

86
Gade, 2006

87
Lee, 2007

88
Jiménez and Oro, 2008

89
Webster and Li, 2008

90 M = Rh, Ir
Douthwaite, 2009

91
Crabtree, 2009

92   **93**
Grotjahn, 2011

94
Jiménez and Pérez-Torrente, 2011

95
Valerga and Puerta, 2011

96
Cross, 2011

97
Morris, 2012

98
Pfaltz, 2013
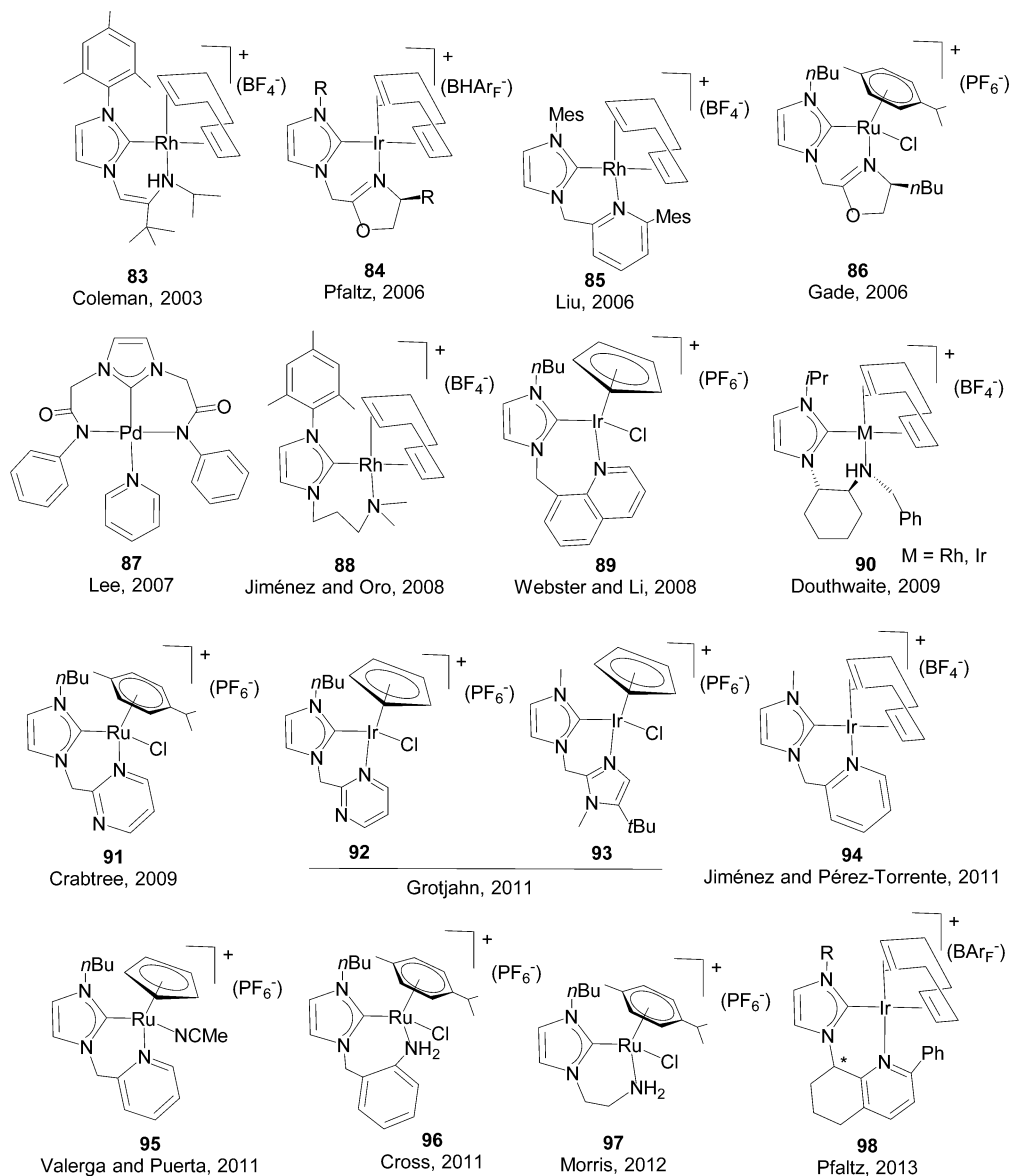
linker length (n = 3). The complexes were tested in hydrosilylation of terminal alkynes, where the neutral complexes were found to be the most active and selective catalysts.[167]

Also in 2008, a series of rhodium and iridium complexes with quinoline-tethered hemilabile NHCs were obtained by Webster and Li and co-workers.[163] Interestingly, the coordination to [IrCp*Cl$_2$]$_2$ rendered an equilibrium mixture of neutral and

cationic species (**100** and **101**, Scheme 36). The reaction of the ligand (or its azolium precursor) with [MCl(CO)$_2$]$_2$ (M = Rh or Ir), afforded a mixture of chelating and monodentate complexes for the case of rhodium, and only the chelating complex for the case of iridium (Scheme 36).[163]

In the case of complex **91** (Chart 3), described by Crabtree and co-workers,[179] the authors did not find evidence of hemilability of the chelate NHC-pyrimidine ligand, but the free

Scheme 35. Hemilabile NHC-Aminoalkyl Ligand
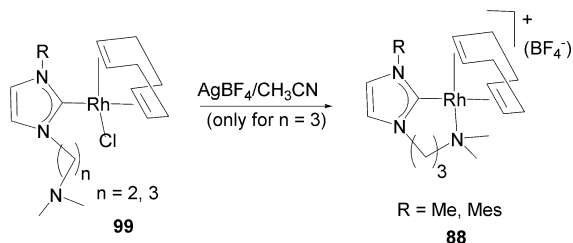
pyrimidyl group acted as an internal base in a series of borrowing-hydrogen processes (transfer hydrogenation, β-alkylation of secondary alcohols with primary alcohols, and N-alkylation of amines with primary alcohols), so that a mild base such as NaHCO$_3$ was sufficient to promote the process.[179]

Messerle and co-workers[206] also developed two NCN pincer ligands that displayed diverse coordination abilities with rhodium(I) and iridium(I) (Chart 4 shows examples of the rhodium complexes). It was found that increasing the length of the alkyl chain between the NHC and the pyrazole rings increased the lability of the pyrazole donors. For example, the coordination of the ethyl-connected ligand is tridentate in solution, but in the solid state it was found to be bidentate (106, Chart 4). The new complexes were tested in the intramolecular addition of NH and OH bonds, where the rhodium complex with the ethylene-connected ligand (106) was more active than the related one with a connecting methylene (105), therefore indicating that the hemilabile behavior of the ligand in 106 has a positive impact on its catalytic activity.[206]

In 2014, Pöthig and Kühn and co-workers[172] published a very detailed study on the hemilabile behavior of a series of iridium(I) complexes with N-functionalized NHC ligands of the type NCN (Scheme 37). The ligand shows a dynamic fluxional behavior between the κ^1C and κ^2C,N coordination, and this situation is not stopped even at temperatures as low as −90 °C. The authors related this behavior to the high catalytic activity of these complexes in the reduction of acetophenone by transfer hydrogenation. Further analysis of the reactivity of these types of complexes demonstrated that addition of a ligand like a phosphine produces substitution of the halide rather than displacement of the pyridine (109), which remains showing fluxionality. On the other hand, CO bubbling produces replacement of the COD ligand and stabilization of the species with the chelating κ^2C,N coordination (110 in Scheme 37).[172]

A very recent work was published by Bertrand and co-workers,[207] describing the preparation of a series of hemilabile cyclic alkyl(amino)carbenes (CAACs) featuring alkene, ether, amine, imine, and phosphine groups. These CAACs were coordinated to Cu(I) and Au(I). The authors showed how the carbene with a pendant imine could stabilize Au(III) and therefore facilitate the C−C oxidative addition of biphenylene to the Au(I) complex with an imine-functionalized carbene (Scheme 38). The same gold(I) complex showed high activity in the hydroarylation of α-methylstyrene with N,N-dimethylaniline. The authors reasoned that the presence of the imine group attached to the CAAC ligand should assist this catalytic reaction that involves a proton transfer, and for that reason the activity of complex 111 in the hydroarylation is higher than the activity shown by other related Au(I) complexes without the imine group.[207]

3.1.2. N-Heterocyclic Carbenes with S-Donors. Since the recent review published by Fliedel and Braunstein in 2014,[127] very few S-functionalized NHC ligands have been reported.[208,209] An interesting example was described by Liu and Chen and co-workers,[209] who prepared a series of palladium(II) complexes with bidentate sulfoxide-NHC ligands
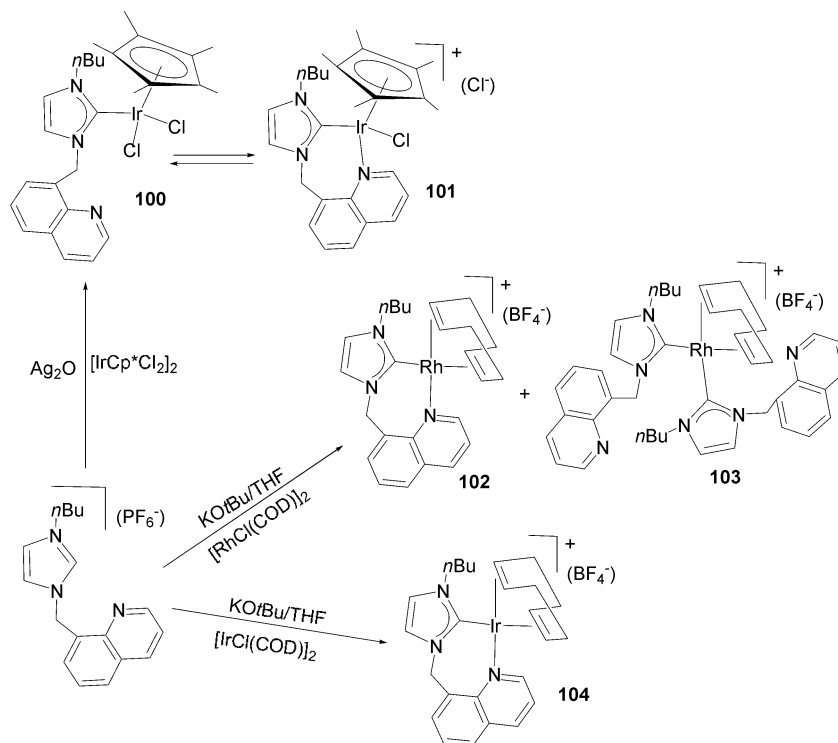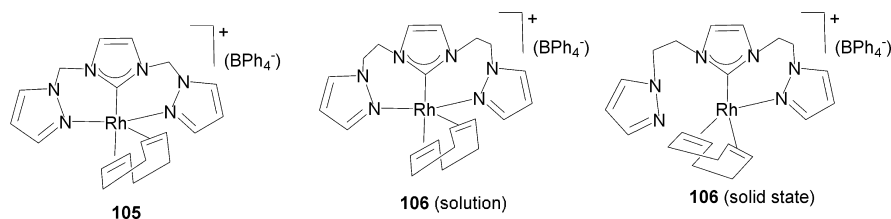
Scheme 36. Hemilabile Behavior of NHC-Quinoline Ligand

Chart 4. Rhodium(I) Complexes with Bis(pyrazolyl)imidadolylidenes

105   106 (solution)   106 (solid state)

Scheme 37. Hemilabile Behavior and Reactivity of Iridium(I) Complex with NHC-based NCN Ligands

107   108   109   110

E = CH, C-CH₃, N
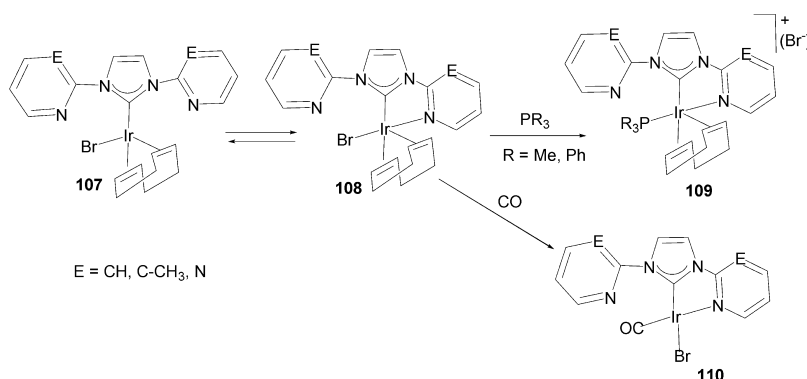
Scheme 38. Oxidative Addition of Phenylene to Au(I) Complex with Imine-CAAC Ligand

111   112
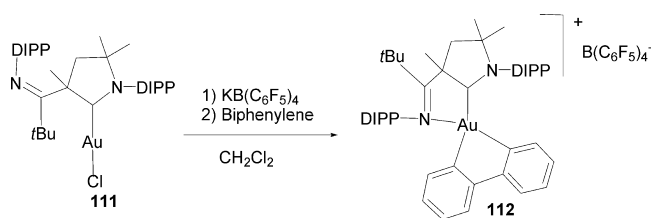
(113−118, Scheme 39). These authors also studied the behavior of an analogous thioether-functionalized NHC complex for comparison. Although both types of ligands showed hemilability, the sulfoxides were more labile than the thioethers. The sulfoxide-NHC ligands exhibited various coordination forms, including mono- and bidentate chelation, sulfur- and oxygen-bound sulfoxide coordination and also the presence of one or two ligands bound to the metal. The hemilability of the sulfoxide-NHC ligand is explained as a combination of intramolecular competition and intermolecular competition with solvent molecules, as illustrated by the example shown in Scheme 39.

3.1.3. N-Heterocyclic Carbenes with O-Donors. A large number of complexes with NHC ligands with oxygen donor groups have also been extensively studied. These may contain alcohol,[210−225] alkoxide,[193,222−227] phenoxide,[228−235] ether,[166,236−238] sulfonate,[239−243] or carboxylate[244] groups. Some selected recent examples of this type of complexes are depicted in Chart 5. With regard to their catalytic activity, most of the studies have provided evidence of the bifunctional (or cooperative) behavior of these complexes,[245] rather than their hemilabile behavior. Some selected examples related to the hemilabile behavior of these types of ligands are discussed below.

Scheme 39. Hemilability Shown by Palladium Complexes with Sulfoxide-NHC Ligands

113   114   115

116   117   118

Chart 5. Some Recent Examples of Complexes Bearing NHC Ligands with Oxygen Donor Groups

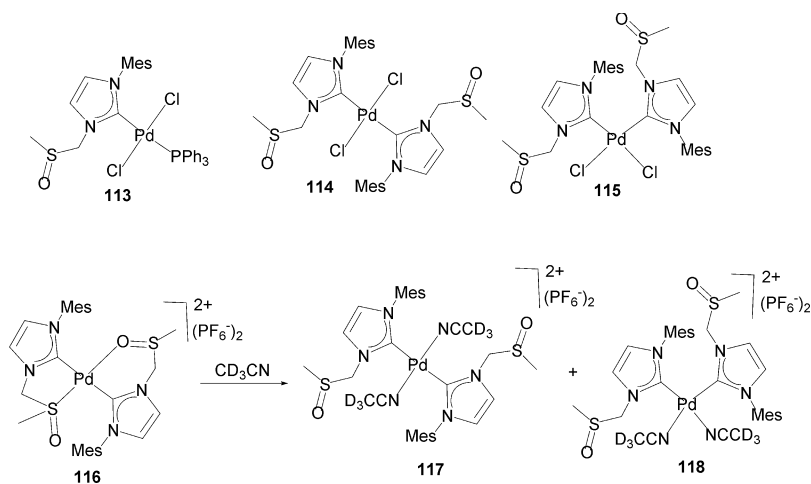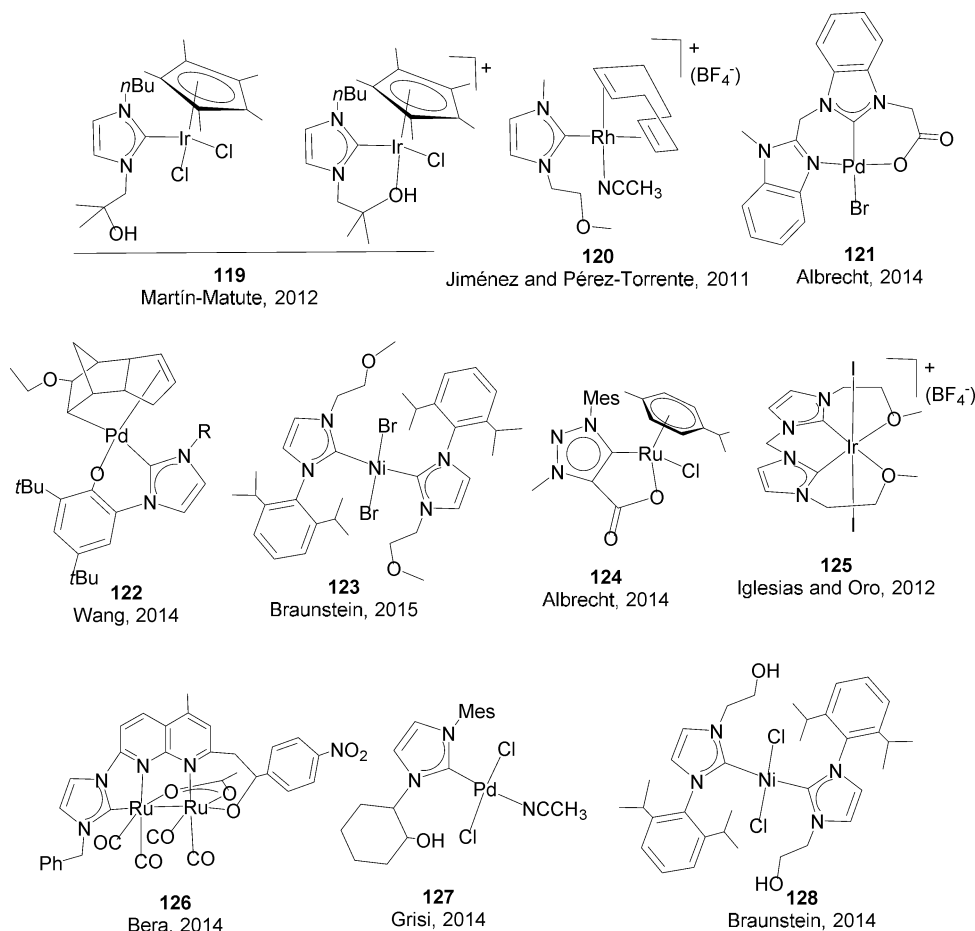Albrecht and co-workers[153] described in 2014 the preparation of the pincer type NHC-carboxylate complex **121**. The coordination and decoordination of the carboxylate arm of the ligand is triggered by addition of a base or acid, respectively. The bis-chelate or tris-chelate (pincer) palladium(II) complexes displayed distinct catalytic activities in Suzuki−Miyaura and Heck−Mizoroki cross-coupling reactions, for which the coordinating carboxylate in **121**, seemed to be beneficial, compared to the uncoordinated form.[153] Wang and co-workers[235] used palladium complex **122** for the polymerization of norbornene, with methylaluminoxane (MAO) as cocatalyst, achieving excellent catalytic activities. Braunstein and co-workers[246] obtained a series of nickel complexes with ether-functionalized NHC ligands, such as **123**, which were active in the polymerization of ethylene. The activity of the related Ni(II) complexes with unfunctionalized NHC ligands showed similar activity, therefore indicating a reduced role of the ether side arms.[246] Palladium complex **127**,[221] featuring an alcohol functional group, was tested in the arylation of furan and thiophene, where it showed moderate activity but excellent regioselectivity, although the authors did not find clear evidence of the benefits provided by the O-donor functionality.

Iglesias and Oro and co-workers[247] prepared the 14-electron Ir(III) complex **125** in 2012. The complex shows two latent coordination sites, which are accessible under catalytic conditions. The complex was tested in hydrosilylation of terminal alkynes, affording very good selectivity in the formation of the β-(Z)-vinylsilanes. This selectivity was first explained by a modified Chalk−Harrod mechanism taking

place,[248] in which a metal-assisted isomerization of the metal-alkenylsilane should be produced in the final steps of the catalytic cycle (see Scheme 40), and all this can be explained by the generation of a cavity by stepwise dissociation of the side arms of the ligand.[247] However, the possibility of this classical mechanism was discarded soon after, basically because DFT calculations suggested that oxidative addition of the Si−H bond to the rhodium or iridium center to afford a M(V) species was unfeasible, and also because alkynes did not react with **125** or with its rhodium analogue.[249] On this basis, an outer-sphere mechanism was proposed, where again the cavity generated by decoordination of the side arms favors formation of the β-(Z)-vinylsilanes. Further modification of these type of catalysts by the same authors provided a more detailed insight into the role of hemilabile ligands in this catalytic reaction.[250] The influence of these hemilabile ligands was also examined by the same authors by studying the behavior of catalysts in transfer hydrogenation of ketones and imines[251] and in hydrolysis and methanolysis of silanes.[252]

Braunstein and co-workers[225] described the hemilabile behavior of alkoxide-functionalized NHC ligands coordinated to nickel and palladium (Chart 6). The authors were able to selectively deprotonate and coordinate, or reprotonate and decoordinate, the alkoxide side arm. Dinickel complex **132** was tested in oligomerization of ethylene, where it showed higher activity than other Ni(II) complexes with unfunctionalized NHC ligands. The authors interpreted this result as a consequence of the increased lifetime of the catalyst, probably

Scheme 40. Proposed Mechanism for Hydrosilylation of Terminal Alkynes with Complex 125
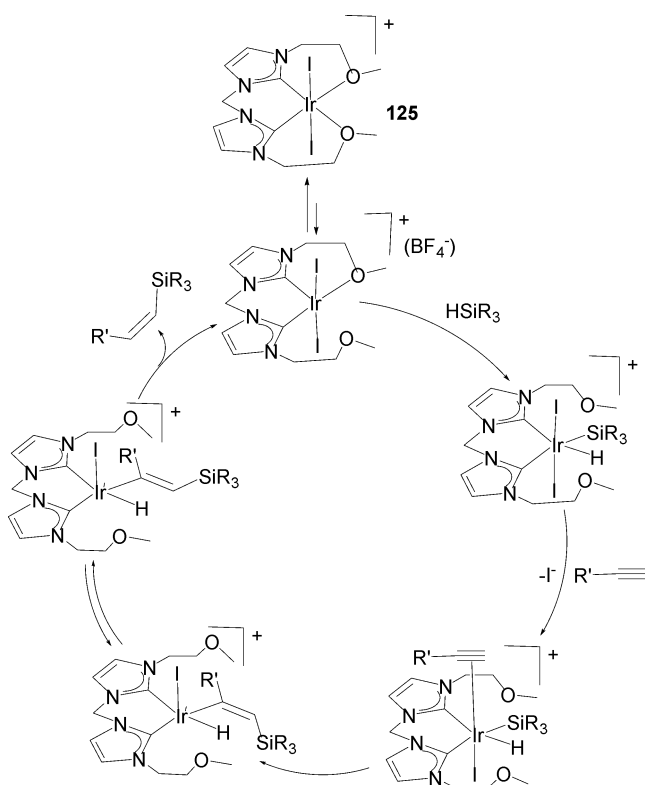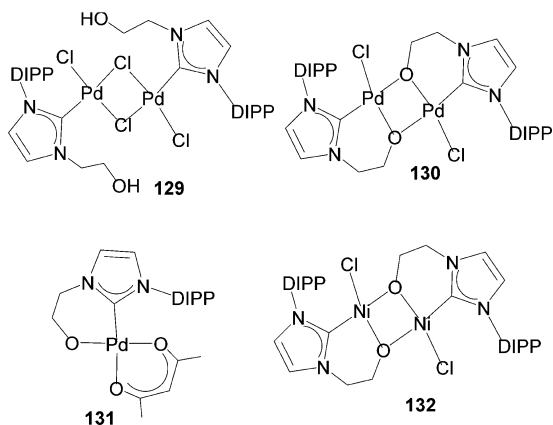

Chart 6. Complexes of Nickel and Palladium with Alkoxide-Functionalized NHCs

as a consequence of the presence of the C,O chelate or bridging ligand.

Zhou and Jordan[239] prepared a palladium complex with a sulfonate-NHC ligand, whose reactivity is dominated by the dissociation or displacement of the sulfonate functionality (Scheme 41). They studied the isomerization between complexes 133 and 134 and concluded that the reaction should proceed by dissociation of the sulfonate unit to form a three-coordinate intermediate (Scheme 40). The reaction is accelerated in solvents with hydrogen-bond donors (CD_3OD) and by the addition of Lewis acids $[B(C_6F_5)_3]$ that can labilize the sulfonate group.

In a very recent work, Ruddlesden and Ducket[253] described an iridium(I) complex bearing a phenolate-NHC ligand (135), which was a very effective precatalyst in the SABRE (signal

Scheme 41. Isomerization of Palladium Complex with Tethered Sulfonate-NHC Ligand
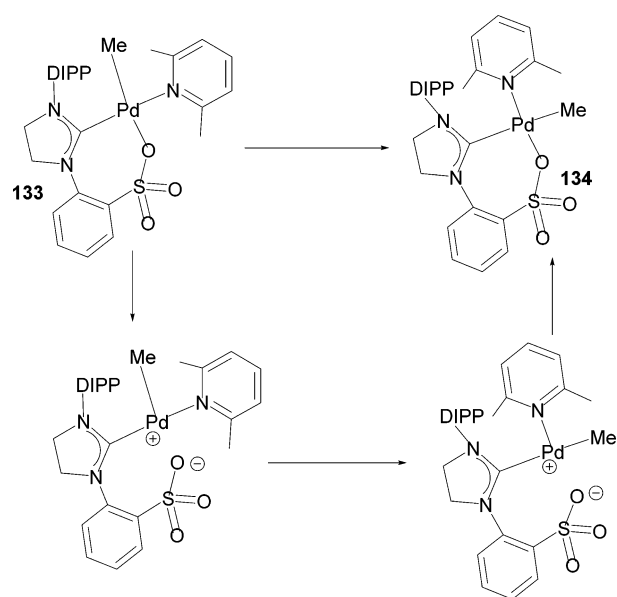
amplification by reversible exchange) process (Scheme 42). The complex contains an Ir−O bond, which is sensitive to the polarity of the solvent, and for this reason the catalytic activity of the complex is solvent-dependent. In nonprotic solvents, this bond is strong and reacts with pyridine and H_2 to form the Ir(III) complex 136. In protic solvents such as methanol, the Ir−O bond is labile, and the reaction with pyridine and molecular hydrogen yields complex 137. Both species have inequivalent hydrides (a requisite for acting as SABRE catalysts), and are active in the catalytic transfer of polarization from para-hydrogen to loosely bound ligands, such as pyridine, nicotinaldehyde, and nicotine.

Papish and co-workers[254] published a study aiming to determine which is the role of hemilability of the ether functionality in the transfer hydrogenation of ketones using (arene)Ru(II) complexes with an ether-functionalized NHC ligand. In their study, the authors did not find any evidence of O binding to the metal, and they concluded that for this type of complex, $[(\eta^6\text{-arene})Ru(II)]$, arene lability has a very important impact on the activity. This conclusion was supported by the fact that the trend of activity of the complexes was related to lability of the arene ligands, in the order benzene > p-cymene > hexamethylbenzene.[254]

3.1.4. N-Heterocyclic Carbenes with Alkenyl and Other C-Donors. Alkenyl-NHCs provide an interesting type of hemilabile ligand with potential applications in homogeneous catalysis. The first example of coordination of this type of ligand was described by Oro and Hahn and co-workers,[255,256] who described a series of iridium(I) complexes with N-allyl-substituted benzimidazolylidenes[256] and imidazolylidenes (Scheme 43).[255] By reaction of an alkenyl-imidazolium salt with $[Ir(\mu\text{-OMe})(COD)]_2$, the authors obtained the five-coordinate complex 138, in which one of the coordination sites is occupied by the alkenyl side arm. Halide abstraction with AgBF$_4$ yields the cationic complex 139, with the two alkenyl arms bound to the metal.[256] Reaction of 138 with NaOEt in ethanol affords the tetracoordinated complex 140, in which the two allyl fragments were hydrogenated to generate two n-propyl chains. The activity of 138 and 140 was tested in the

Scheme 42. Solvent-Dependent Behavior of Iridium Complex with NHC-Phenolate Ligand
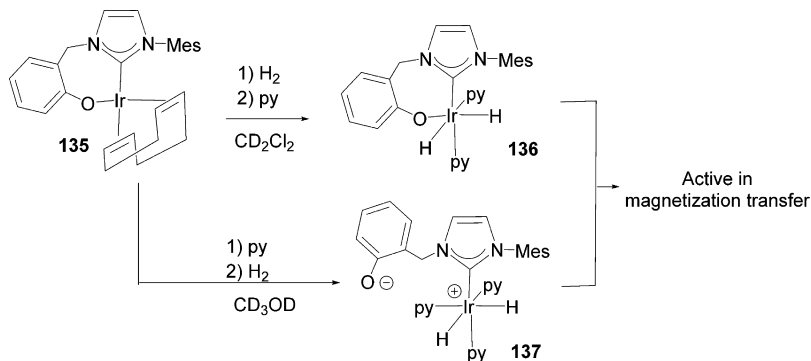
Scheme 43. Iridium Complexes with Allyl-Substituted Benzimidazolylidenes
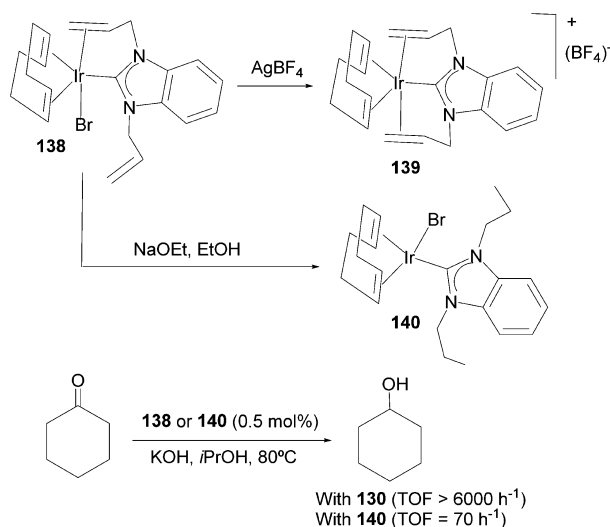
reduction of cyclohexanone by transfer hydrogenation in *i*PrOH (KOH was used as base), where **140** showed much higher activity. This was interpreted by the authors as a factor indicating that the allyl substituents remain unaffected along the catalytic reaction, and therefore the availability of the vacant coordination site is reduced in **138**, thus providing a less active catalyst.

Inspired by these results, Peris and co-workers[257] reported a series of Cp*Ir(III) with N-alkenyl-imidazolylidene ligands. Rather than aiming to obtain a hemilabile system, in which the olefin arm of the NHC ligand could reversibly decoordinate/coordinate to the metal, the authors aimed to irreversibly cleave

the olefin–metal bond under conditions used in a catalytic reaction (reduction of ketones and imines by transfer hydrogenation), and for that reason this type of ligand was referred to as hemicleavable. It was found that the chelating coordination of the alkenyl-imidazolylidene could only be achieved when short linkers between the NHC and the olefin were present (as in **141**, in Scheme 44), while longer linkers produced monocoordination of the ligand via the NHC part. The chelate carbene-alkenyl complexes showed very good activity in the reduction of ketones and imines by transfer hydrogenation. It was proposed that, under the reaction conditions used for the catalytic reaction (*i*PrOH, 80 °C and KOH), the catalyst was activated by irreversible hydrogenation of the coordinated alkene, generating a N-alkyl fragment (**142**).[257]

In 2008, Peris and co-workers[258] described a series of Ir(I) complexes with alkenyl-functionalized ligands. These complexes were similar to those previously reported by Hahn and Oro and co-workers[255] (in their case the complexes contained bromide ligands instead of chlorides). Complexes **143** (Scheme 45) showed fluxional behavior, due to the coordination/decoordination of the alkene with the iridium center.[258] By studying this fluxional behavior by variable-temperature (VT) NMR spectroscopy, the authors were able to experimentally estimate that the Ir–olefin bond energy was ΔH = 20.9 kcal/mol for **143** with X = H. Complexes **143** were active in the hydrosilylation of terminal alkynes, where they proved to be very selective in the production of Z-vinylsilanes.[258]

Alkenyl-imidazolylidene ligands were also coordinated in the chelate fashion to CpNi(II) complexes,[259] but the catalytic activities of the resulting complexes were not reported. Horn and Albrecht[260] described a (p-cymene)Ru(II) complex with a hemilabile alkenyl-NHC ligand (**145**), which showed high

Scheme 44. Hemicleavable NHC-Alkenyl Ligands bound to Cp*Ir(III)

Active in the reduction of ketones and imines by transfer hydrogenation
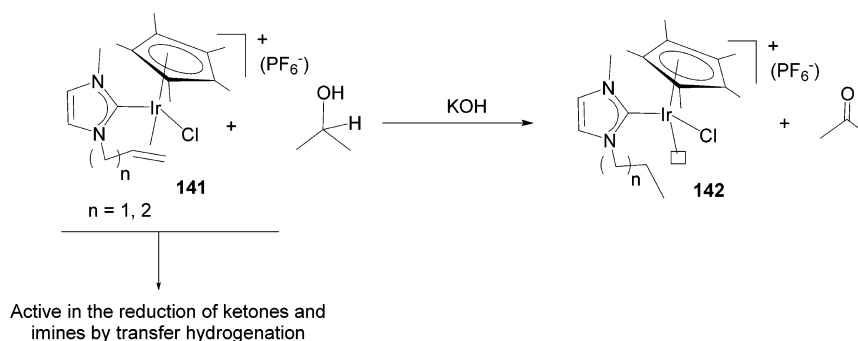
Scheme 45. Alkenyl-NHC Complexes of Ir(I) in Hydrosilylation of Terminal Alkynes

Scheme 46. (*p*-Cymene)Ru(II) Complexes with Hemilabile NHC-based Ligands Used in Reduction of Dodecene

CD$_3$OD afforded deuteration at the ortho position of the metalated phenyl ring in 24 h, thus strongly suggesting that a dynamic equilibrium with the "demetalated" complex **150** occurs (Scheme 47).

Scheme 47. Hemilability Shown by Cyclometalated NHC-Phenyl Ligand Coordinated to Cp*Ir(III)
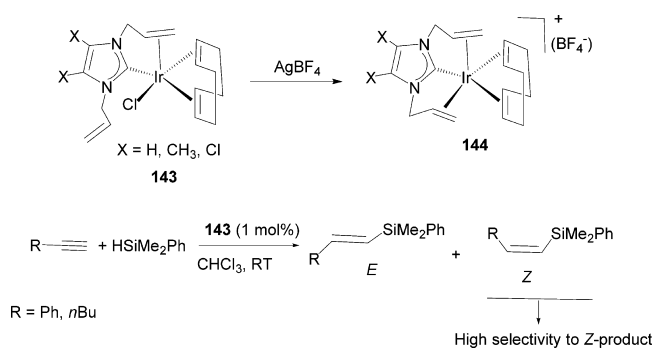
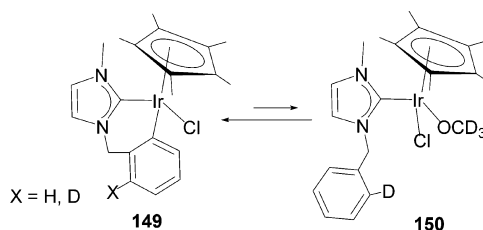activity in reduction of unfunctionalized olefins by transfer hydrogenation. In their work, the authors compared the activity of several catalyst precursors displaying NHC-based hemilabile ligands. The catalysts showed strongly diverging behavior in the hydrogenation of dodecene to dodecane, with **146** being completely inactive and **145** being the most active one (Scheme 46). Catalyst **145** was tested in the hydrogenation of a wide set of olefins, where it also showed activity in the olefin isomerization as a competitive process.[260] In a subsequent study, the same set of complexes shown in Scheme 46 were tested in the transfer hydrogenation of ketones and activated olefins.[261] Again, the complex with the tethered olefin was the most active among the four different catalysts. Depending on reaction conditions, **145** was also able to convert nitriles and α,β-unsaturated ketones.

A very interesting example of hemilability was described by Bullock and co-workers in 2007,[262] who obtained hydrides of the type [CpM(CO)$_2$(IMes)H] [M = W, Mo; IMes =1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]. Hydride abstraction from these complexes leads to [CpM(CO)$_2$(IMes)]$^+$, in which one of the C=C double bonds of one of the mesityl groups binds the metal. Ketones and alcohols can displace this weak coordinated C=C group. The tungsten complex showed moderate activity in hydrogenation of acetone with H$_2$.[262]

N-Arylated NHCs have also shown hemilabile behavior in Cp*Ir(NHC) complexes, as in the example reported by Peris and co-workers in 2006.[263] The reaction of **149** in refluxing

3.1.5. Conformationally Labile N-Heterocyclic Carbenes. Conformationally labile NHCs are ligands with flexible steric bulk, so that the steric hindrance imposed by the ligand can be tuned depending on the requirements of a specific catalytic reaction. These types of ligands may be considered as multifunctional, as they may look somehow related to hemilabile ligands. The firsts to apply this concept in catalysis were Glorius and co-workers,[264] who developed an imidazo-lylidene with flexible cyclohexyl groups, which is expected to exist in the form of three different conformers (Chart 7). Upon coordination to Pd, conformation **a** is expected to favor oxidative additions on Pd(0), while the more sterically demanding conformers (**b** and **c**) should enhance reductive elimination and facilitate the formation of Pd monocarbene species. These ligands were used for the preparation of palladium catalysts [in situ from Pd(OAc)$_2$], which were shown to be efficient for room-temperature Suzuki−Miyaura coupling of hindered and unhindered, activated and deactivated aryl chlorides and arylboronic acids. Soon after, the same group developed a series of NHCs derived from bioxazolines with larger flexible cycloalkyl groups (structure **d**), which were also applied for the preparation of effective palladium catalysts for the Suzuki−Miyaura coupling. Remarkably, the catalysts derived from these ligands were able to catalyze the production of tetra-ortho-substituted biaryls from aryl chlorides.[265]

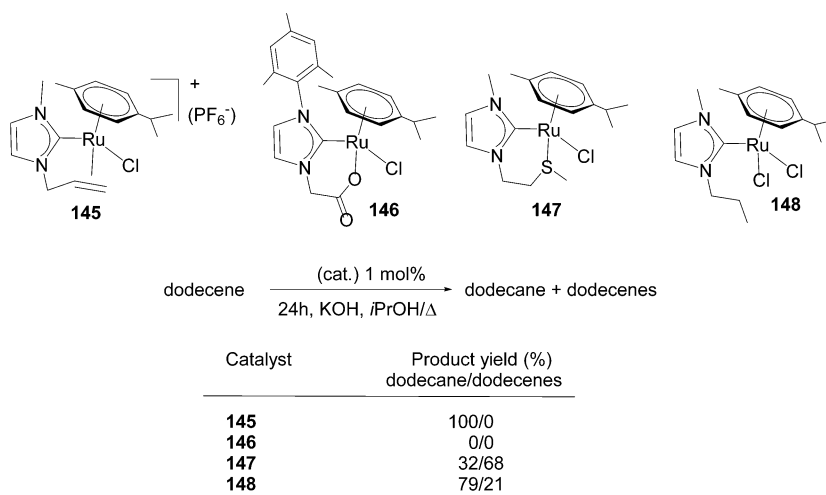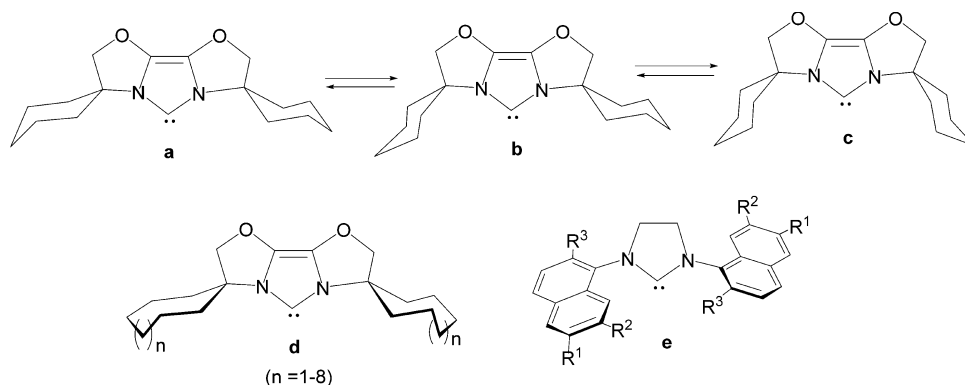| Catalyst	Product yield (%) dodecane/dodecenes
145	100/0
146	0/0
147	32/68
148	79/21

Chart 7

In the same line, Dorta and co-workers[266] described a family of imidazolin-2-ylidenes functionalized with naphthyl units (structure **e**, Chart 7). Interconversion of the two possible atropisomers [C_2-symmetric (anti) and C_s-symmetric (syn)] was studied in detail by ^{1}H NMR. The palladium-derived complexes showed superior activity compared to other analogous palladium complexes without the bulky substituents.

Some other recent relevant examples of large yet flexible NHC ligands were reported by Nolan and co-workers[267,268] (Pd, for Suzuki−Miyaura and Buchwald−Hartwig reactions; Au, for alkyne hydration, nitrile hydration, and synthesis of homoallylic ketones) and Mauduit and co-workers[269] (Ru, for olefin metathesis).

3.2. Bifunctional N-Heterocyclic Carbene Ligands

Bifunctional catalysts operate by establishing control of a catalytic process through multiple weak catalyst−substrate interactions[117,270−272] and by enabling a cooperative effect that is translated into a superior ability for substrate activation and selectivity.[273,274] These weak interactions are of the non-covalent type (mostly due to hydrogen bonding or π-stacking); thus, bifunctional catalysis can also be regarded within the field of supramolecular catalysis.[275,276] A recent review was fully devoted to bifunctional catalysis with transition metal-based NHC complexes.[245] More specific review articles were published dealing with the bifunctional behavior of protic NHC complexes[277] and NHC complexes bearing NH units,[278] so the field has been covered in detail until 2016. With these taken into account, the present review will cover only selected examples. Section 3.2.1 deals with bifunctional processes involving the participation of NH, OH, or CH bonds of the ligand, and section 3.2.2 deals with bifunctional processes through aromatization/dearomatization. Finally, Section 3.2.3 will describe the most recent advances on the use of NHC ligands with rigid polyaromatic fragments, and how π-stacking interactions influence the catalytic properties of the related catalysts.

3.2.1. Bifunctional Processes Involving the Participation of C−H, O−H, or N−H Bonds of the Ligand.
3.2.1.1. Ligand C−H Bonds. A recent example of metal−ligand cooperativity was described by Mashima and co-workers,[279] who showed how the hemilability of a N-xylyl-N′-methylperimidine carbene bound to an iridium catalyst was crucial in the dehydrogenative silylation of arylpyridines with triethylsilane (Scheme 48). The precatalyst used was the Ir(I) complex **151**. The authors observed that intramolecular C−H activation of the N-xylyl group of the perimidine-based NHC efficiently improved the catalytic reaction. On the basis of their

Scheme 48. Proposed Mechanism for Iridium-Catalyzed Silylation of Arylpyridines
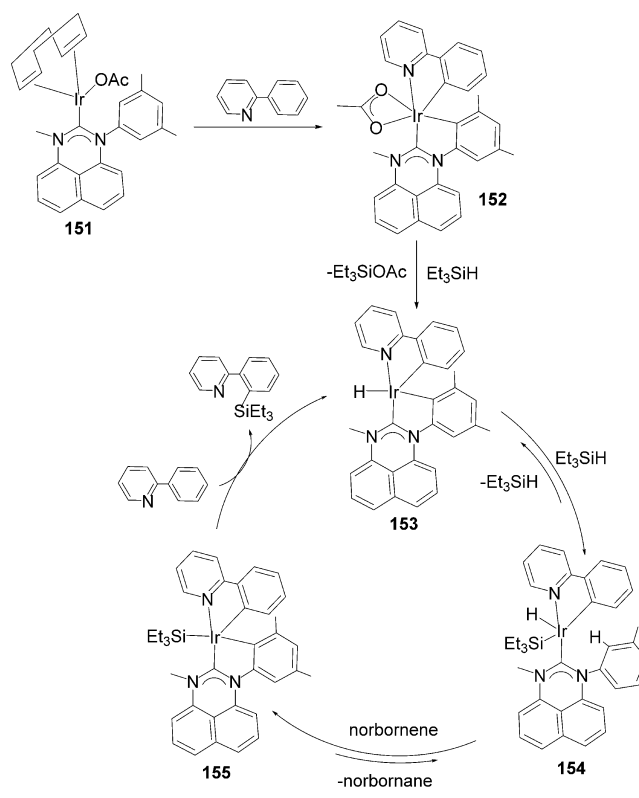
experimental findings, the authors suggested that, during the catalytic cycle, the carbene ligand changed its steric and electronic properties. The cyclometalated NHC acted as hydride acceptor, returning to the monodentate NHC, thus showing the utility of the metalated xylyl group as a labile coordination site of hemilabile ligation (see the equilibrium between **153** and **154**). In their work, Mashima and co-workers[279] proposed a catalytic cycle, from which they were able to isolate and characterize a number of intermediates. Scheme 48 shows the proposed catalytic cycle, displaying only some selected reaction intermediates.

3.2.1.2. Ligand O−H Bonds. Iridium complexes with tethered O-donor functionalities have been used as bifunctional catalysts for the condensation of amines with alcohols, with very relevant works published by Martín-Matute and co-workers.[222−224] In their most recent work, these authors performed a detailed study on mechanistic aspects of the

reaction by combining experimental and computational methods.[222] From their study, the authors concluded that the alcohol-functionalized ligand participates in almost all steps of the catalytic cycle, by accepting or releasing protons to substrates and intermediates, as shown in Scheme 49. The

Scheme 49. Proposed Mechanism for Coupling of Amines and Alcohols with Iridium Catalyst Containing NHC-Alcohol Ligand
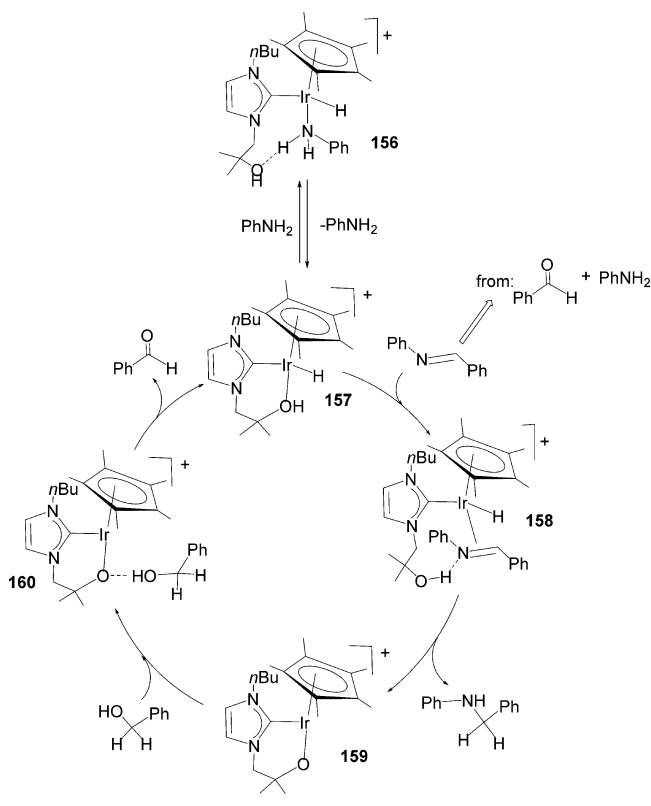
alcohol functionality also facilitates the reaction by hydrogen-bonding to substrates. The bifunctional behavior of this iridium catalyst allows the reaction to be performed under base-free conditions, with a 1:1 ratio of the substrates (no excess of any substrate is needed), and under very mild reaction conditions

($T = 50$ °C). By starting from the catalyst precursor **119** (Chart 5), the catalyst resting state was formed (**156**, Scheme 49), and characterized in situ.

An interesting example of the acceptorless dehydrogenation of alcohols to aldehydes, and dehydrogenative coupling of alcohols with amines, was described by Bera and co-workers in 2014,[227] using the diruthenium complex **126** (Chart 5) as catalyst. The authors performed a detailed study by using experimental and computational methods, concluding that metal−metal and metal−ligand cooperation are crucial in the dehydrogenative coupling of amines and alcohols to afford the corresponding imines. They also found that the presence of the acetate bridging ligand plays an important role by facilitating the occurrence of β-elimination.[227] Scheme 50 shows the proposed mechanism for the process.

3.2.1.3. Ligand N−H Bonds. Morris and co-workers[189−192,280−282] have been very active in the research of NHC-based bifunctional catalysts. They prepared series of ruthenium and iridium complexes with NHC ligands tethered with amine donors. The activity of the cationic [Ru(p-cymene)(NHC-NH$_2$)] complexes **97** (Chart 3) and **162** was studied in transfer hydrogenation of ketones to afford the corresponding alcohols.[190,191] Both experimental and theoretical (DFT) studies concluded that reduction of acetophenone occurred through an inner-sphere mechanism involving decoordination of the amine group of the NHC-NH$_2$ ligand; therefore this ligand would only be behaving as hemilabile, not exchanging the hydrogen of the amine with either of the substrates.[282] This mechanism was proved to be more feasible than the outer-sphere bifunctional mechanism, which should involve the transfer of a H$^+$/H$^-$ couple to acetophenone from the hydride amine complex. The authors explained that the cationic hydride-amine complex **163** (Scheme 51) reacted very slowly with acetophenone in the absence of base, due to the decreased hydricity of the hydride ligand, thus making the outer-sphere mechanism unfavored.[190,191]

The results are different when the [RuCp*(NHC-NH$_2$)-(pyr)](PF$_6$) complex **164** is used. This complex can be activated in the presence of an alkoxide base, to form a neutral hydride-amine complex (**165**). In this case, the hydridic character of the neutral metal hydride is expected to favor the outer-sphere bifunctional mechanism for reduction of ketones. On the basis of experimental and theoretical (DFT)

Scheme 50. Proposed Mechanism for Dehydrogenative Coupling of Alcohols and Amines by Diruthenium Complex 126
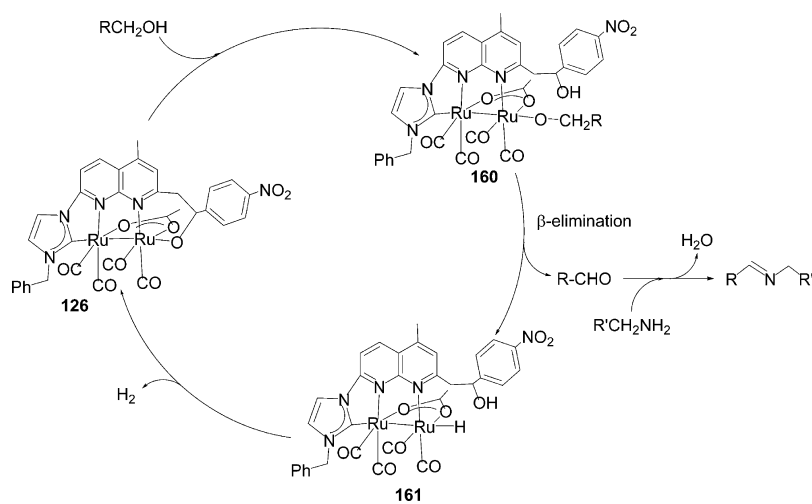
Scheme 51. Inner-Sphere versus Outer-Sphere Mechanisms for Ru(II) Precatalysts with NHC-Amine Ligands
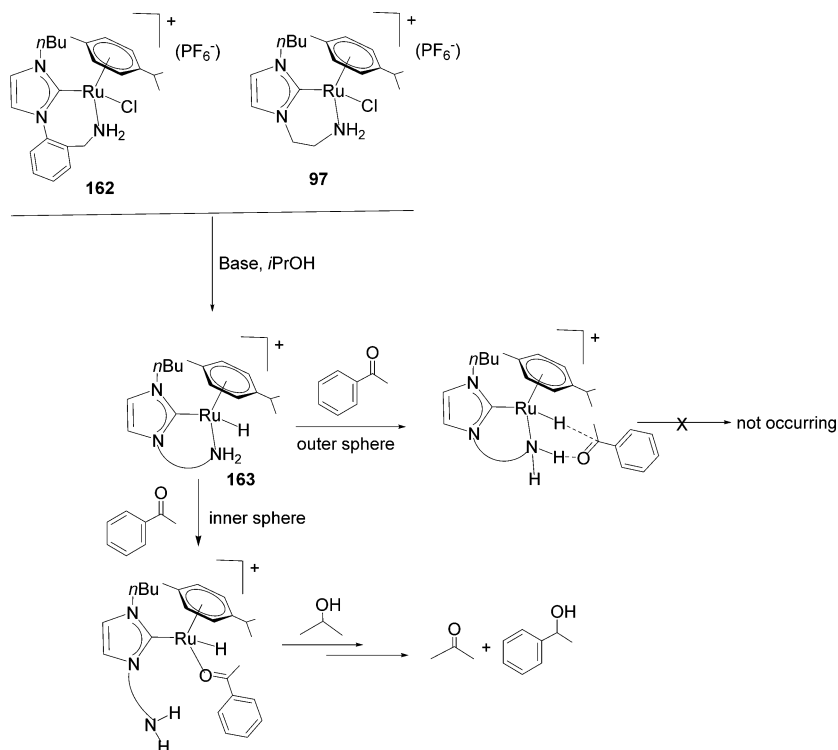
studies, Morris and co-workers[189] proposed the mechanism shown in Scheme 52 for the reduction of ketones with H_2. On the other hand, theoretical calculations predicted that the outer-sphere mechanism is not favored when the related cationic iridium(III) hydride amine complex $[IrCp*(NHC-NH_2)H]^+$ is used, due to the poor nucleophilicity of this cationic hydride.[189] Nevertheless, the authors showed evidence that this complex, in the presence of excess alkoxide base, hydrogenates ketones via an outer-sphere mechanism involving a neutral hydride intermediate $[Ir(\eta^4-Cp*H)(NHC-NH_2)H]$, which was formed by migration of a hydride ligand to the Cp* ligand, a process that seems to be favored by the presence of the N-heterocyclic carbene ligand.[190]

In a more recent report, the $[RuCp*(NHC-NH_2)(pyr)]$-(PF_6) complex **164** was used for hydrogenation of esters with H_2.[281] The authors proved that the reaction occurred through a concerted bifunctional outer-sphere mechanism, via formation of a six-membered ring transition state involving hydrogen-bonding interaction of the carbonyl oxygen of the ester and the N—H group of the NHC-NH$_2$ ligand. The same NHC-NH$_2$ ligand was used to prepare the iridium(I) complex $[Ir(NHC-NH_2)(COD)](PF_6)$ (**166**) (Scheme 53). Upon oxidative addition with HCl, the iridium(III) hydride **167** was formed. This complex proved to be very active in the H_2 hydrogenation of molecules with unsaturated bonds (TOF > 800 h^{-1} for hydrogenation of acetophenone), although in this case, the authors did not perform mechanistic studies in order to elucidate if the process proceeded via a bifunctional outer-sphere mechanism.[280]

Hahn and co-workers[283−285] developed a series of metal complexes with protic NHC ligands (*p*NHCs). It was proposed that the NH function of the *p*NHC ligands may act as a directing group for formation of hydrogen bonds to selected substrates.[286,287] The NH group of *p*NHC ligands is known to directly participate in some catalytic events. For example,

Scheme 52. Alcohol-Assisted Outer-Sphere Bifunctional Mechanism with $[RuCp*(NHC-NH_2)H]$ Catalyst
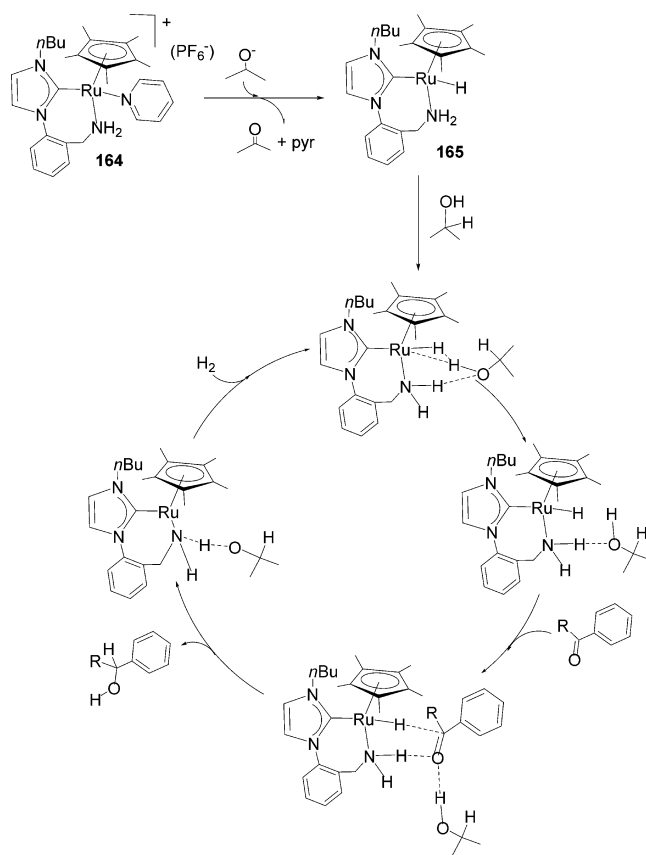
Grotjahn and co-workers[288] showed that the Ru(II) complex **168**, displaying a *p*NHC-PPh$_2$ ligand, was able to quantitatively

Scheme 53. Hydrogenation of Acetophenone with [IrCl(H)(NHC-NH₂)(COD)](PF₆)
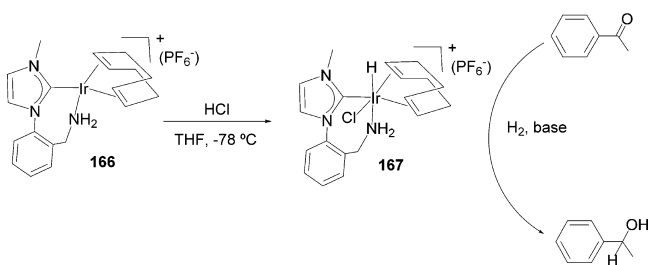
hydrogenate acetophenone in the presence of *i*PrOH under base-free conditions (Scheme 54). By carefully studying the chemical reactivity of the *p*NHC ligand, the authors concluded that the complex may reduce ketones via a bifunctional outer-sphere mechanism involving the participation of the NH group.

Scheme 54. Base-Free Hydrogenation of Acetophenone with Ru(II) Complex with *p*NHC-PPh₂ Ligand
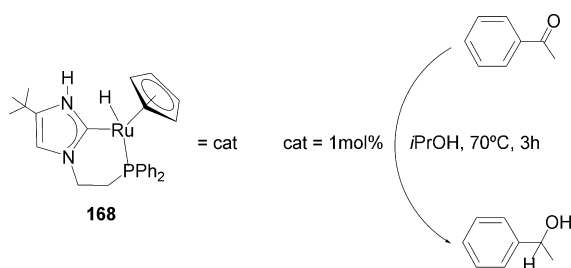
Grotjahn and co-workers[289] described **169** (Chart 8), a Cp*Ir(III) hydride with a *p*NHC-PPh₂ chelate ligand. The authors carefully studied the reactivity of the NH bond and suggested that secondary interactions involving this group should provide benefits in homogeneously catalyzed processes by means of the bifunctional character of the ligand. Similar studies were also performed by Hahn and co-workers[290] with complex **170**, bearing a protic benzimidazolylidene ligand.

Chart 8. Two Cp*Ir(III) Complexes with *p*NHC-PPh₂ Chelate Ligands
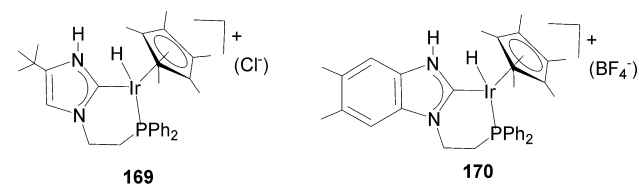
Ghosh and co-workers[210,291−293] developed a series of Ni(II) complexes bearing amido-functionalized NHCs (**171**) for base-free Michael addition of β-dicarbonyls, β-keto esters, and α-cyano esters with activated ethylenes. The fact that the authors were able to perform the reaction in the absence of base is remarkable. Supported by DFT calculations, it was proposed that the rate-limiting-step of the reaction was the nucleophilic attack of a metal-bound enolate of a 1,3-dicarbonyl adduct to the approaching activated ethylene.[291] The reaction pathway involves first the protonation and decoordination of the basic amide function of the NHC-amido l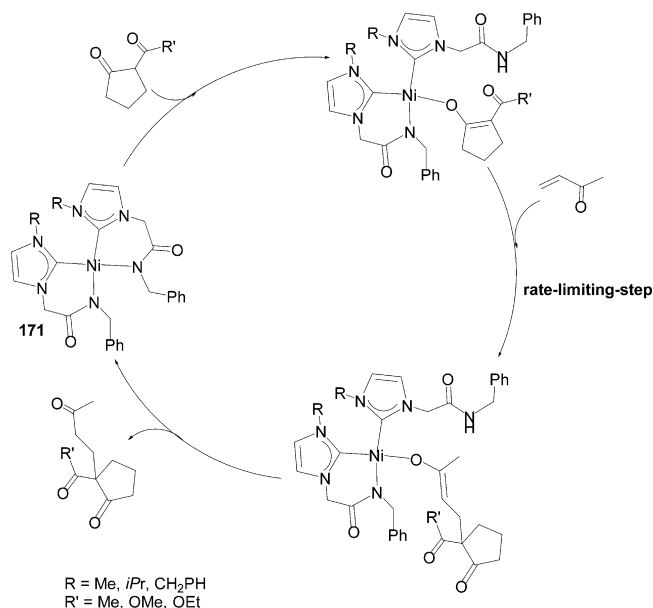igand by the substrate (2-acetylcyclopentanone in Scheme 55), thus indicating a bifunctional process with active participation of the amido

Scheme 55. Bifunctional Pathway Proposed for Michael Addition Facilitated by Ni(II) Complex with NHC-Amido Ligand

group in the process. Then nucleophilic attack of the bound enolate on activated olefin and release of the final product would complete the cycle. The authors were also able to study the asymmetric version of the reaction, by using NHC-amido ligands with chiral ancillary substituents. With these catalysts, chiral inductions ranging between 2% and 75% enantiomeric excess (ee) values were obtained.[294]

By using a N-heterocyclic carbene functionalized with a naphthyridyl group, Bera and co-workers[295] prepared a Rh(I) complex (**172**) that showed excellent catalytic activity in the hydration of a wide variety of organonitriles to form the corresponding organoamides at room temperature. A maximum turnover frequency of 20 000 h⁻¹ was achieved for hydration of acrylonitrile. The presence of the 1,8-naphthyridyl group is crucial for the process, because an analogous Rh(I) complex without the naphthyridyl group {[RhBr(COD)(Me₂-NHC)]; Me₂-NHC = 1,3-dimethylimidazol-2-ylidene} turned out to be inactive. The proposed mechanism of the catalytic reaction (Scheme 56) involves the participation of the pendant naphthyridine by forming a double hydrogen bond with a molecule of H₂O, which provides significant entropic advantage to the hydration process. By DFT calculations, the authors calculated the transition state of the process (**173**, TS), revealing proton movement from water to the naphthyridine nitrogen, with a complementary interaction between the oxygen and the nitrile carbon.[295] The work constitutes a clear example of bifunctional water activation and cooperative proton migration as the key steps of the catalytic cycle.

In a very recent work, Hahn and co-workers[296] described iridium(III) complexes bearing a chelating bis(NHC) composed of a classic NHC and an anionic imidazolylidato donor, which were moderately active in reduction of various imines with hydrogen. The authors hypothesized that the complexes should act as bifunctional catalysts by initially forming a chelate C_{NHC}−C_{pNHC} ligand.

3.2.2. Bifunctional Processes through Aromatization/Dearomatization. Several pincer-type complexes based on pyridine are known to display a mode of metal−ligand

Scheme 56. Bifunctional Mechanism for Hydration of Organonitriles by Rhodium(I) Complex with NHC-Naphthyridyl Ligand
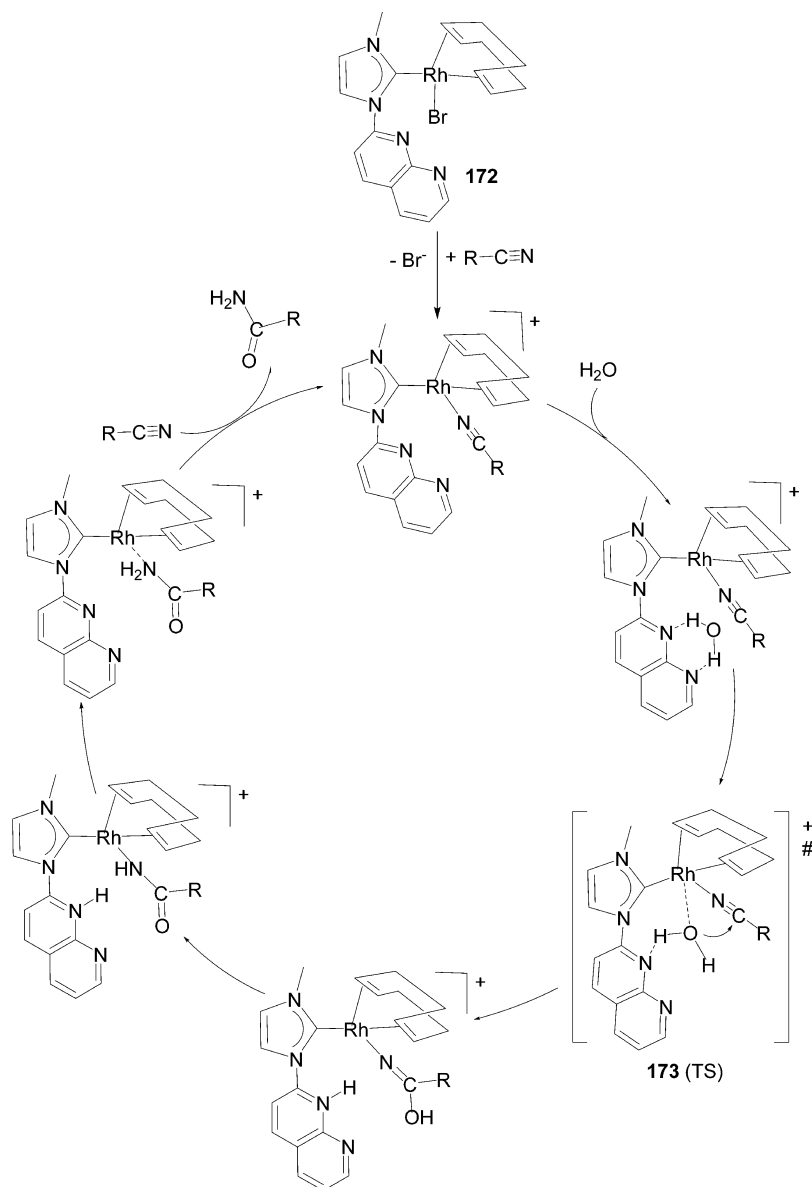
Scheme 57. Activation of Nitriles by Lutidine-Derived Bis(NHC) Ruthenium(II) CNC Pincer Complexes

R = Mesityl
R' = CH₃, Ph
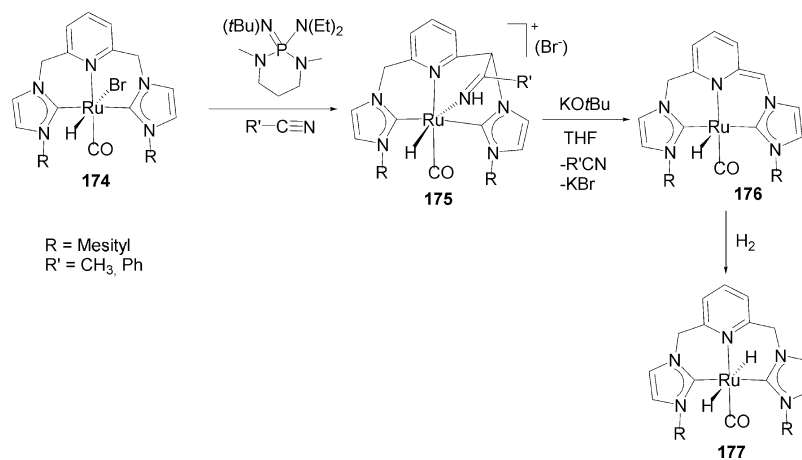
cooperation involving aromatization/dearomatization of the central pyridine ring. The concept was pioneered and developed by Milstein and co-workers.[297−299] This bifunctional behavior occurs without formal change of the metal oxidation

state and has been widely used for reactions involving transformations of amines and alcohols.

In a recent contribution, Pidko and co-workers[300] described the preparation of several lutidine-derived bis(NHC) ruthenium(II) CNC pincer complexes (**174**). In the presence of phosphazene base, these complexes are capable of activating nitriles to give ketimino compounds (**175**, Scheme 57). Compound **175** reacts with strong bases to yield a dearomatized complex (**176**), which reacts with H_2 to form the dihydride **177**.[300]

Complex **176** was found to be very reactive in the activation of CO_2 and H_2, although it leads to a stable compound (**178**) that is not catalytically competent (Scheme 58).[301] On the

Scheme 58. Activation of CO_2 by Lutidine-Derived Bis(NHC) Ruthenium(II) CNC Pincer Complex
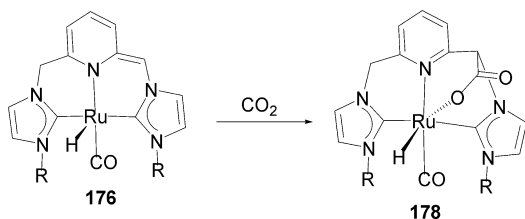
other hand, the bis(hydrido) complex **177** is very active in hydrogenation of CO_2 to formate, although DFT calculations suggest that the mechanism does not involve metal–ligand cooperative transformations (Scheme 59).[301] The reaction needs to use H_2/CO_2 ratio of 39/1 to avoid deactivation of the process by formation of **178**.

The bipyridine-NHC–Ru(II) complex **179** was described by Milstein and co-workers in 2011.[302] In the presence of potassium bis(trimethylsilyl)amide (KHMDS), this complex forms the dearomatized complex **180** (Scheme 60). The in situ prepared **180** was tested in the hydrogenation of nonactivated esters under mild reaction conditions, where it proved to be

Scheme 59. Reduction of CO_2 to Formate by Lutidine-Derived Bis(NHC) Ruthenium(II) CNC Pincer Complex
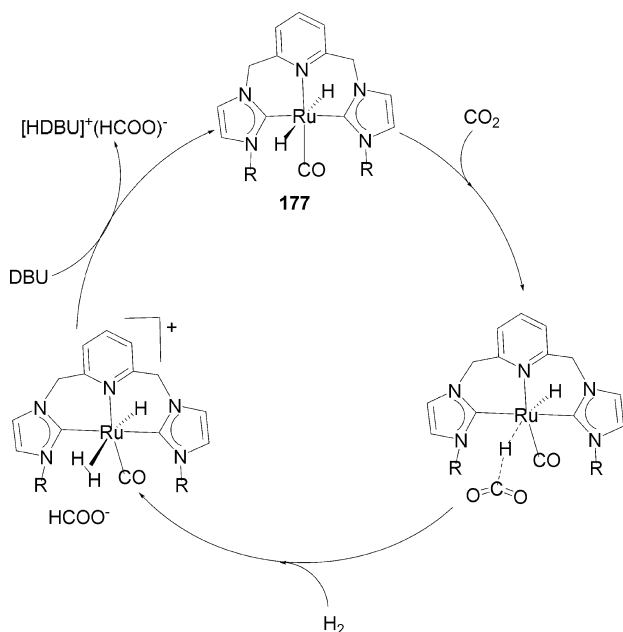
Scheme 60. Dearomatization of Bipyridine-NHC–Ru(II) Complex and Activity in Hydrogenation of Esters
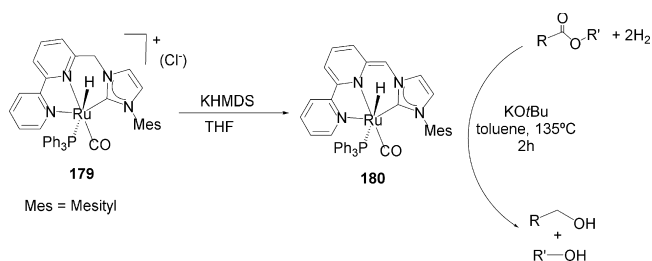
one of the most active catalysts reported to date.[302] For example, under 50 atm pressure of H_2, hydrogenation of ethyl benzoate resulted in a high TON of 2840, with almost quantitative formation of benzyl alcohol and ethanol.

A similar dearomatization process was observed by Song and co-workers,[303] when they reacted their Ru-CNN pincer complex **181** with KHMDS. The resulting dearomatized product, **182**, reacts with H_2 to form the ruthenium(II) dihydride **183**. Interestingly, the experiments carried out with D_2 demonstrated that both pincer arms participate in the H_2 activation, thus producing the incorporation of six deuterium atoms into the molecule, as shown in Scheme 61. Complex **181** catalyzes the hydrogenation of unactivated esters under mild reaction conditions.[303]

3.2.3. Bifunctional N-Heterocyclic Carbene Ligands with Rigid Polyaromatic Functionalities: Homogeneous Catalysis and π-Stacking.
Noncovalent interactions such as π-stacking may play an important role in homogeneously catalyzed reactions. This type of effect, which may have been unrecognized for other systems, was systematically studied for the case of NHC-based metal catalysts.

Clear evidence of the influences of π-stacking and catalysis was observed by Grela and co-workers back in 2008[304] (Scheme 62). These authors observed that the use of fluorinated aromatic solvents was beneficial in olefin metathesis reactions catalyzed by Ru Grubbs-type catalysts with a SIMes ligand [SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]. On the basis of their studies, they hypothesized that π−π stacking interactions between the fluoroaromatic solvent and the N-aromatic substituent of the NHC ligand may enhance the stability of the 14e ruthenium active species, as shown by DFT calculations.[305] Several authors had previously suggested that π−π stacking interactions should play a role in Ru-catalyzed metathesis reactions.[306−309]

The π-stacking interaction between aromatic substrates and the ligand of a catalyst may be boosted if the ligand is functionalized with a rigid polyaromatic functionality. The important catalytic consequences of using NHC ligands decorated with rigid polyaromatic fragments in homogeneous catalysis were recently pointed out by Peris,[310] according to research mostly developed in his group. The first clear evidence of the participation of π-stacking interactions between aromatic substrates and a polyaromatic-based NHC ligand were observed for the triphenylene-tris(imidazolylidene)-based palladium and gold catalysts **184** and **185** (Scheme 63).[311] The studies were performed by comparing the catalytic efficiency of these catalysts in three different reactions (palladium-catalyzed α-arylation of propiophenone with aryl bromides, Suzuki−Miyaura coupling between aryl bromides and arylboronic acids, and gold-catalyzed hydroamination of phenylacetylene). For all three reactions tested, the catalytic

Scheme 61. Dearomatization and Reactivity of Ru(II) CNN Pincer Complex
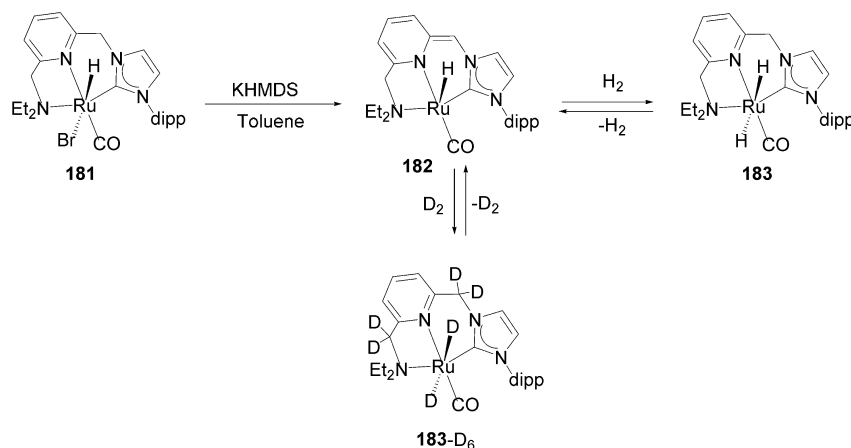
Scheme 62. Beneficial Effect of Fluorinated Solvents in Activity of Catalysts in Olefin Metathesis
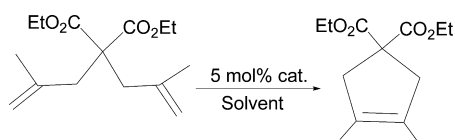
The activity of the catalyst is solvent dependent:

$C_6F_5CF_3 >> C_6H_5CH_3 > ClCH_2CH_2Cl$

cat. =

functionalities. The higher activity shown by these two complexes was hypothesized to be a consequence of the π-stacking interaction between the triphenylene core of the catalysts and the aromatic substrates, which should have an effect on the catalytic performance of the catalysts. The fact that addition of catalytic amounts of π-stacking additives, such as pyrene or hexafluorobenzene, produced partial inhibition of the activity of **184** and **185** was one of the main supports of this hypothesis.

In line with these findings, several other complexes displaying polyaromatic NHC-based complexes were obtained and their catalytic activities were evaluated.[312,313] An interesting study resulted from comparing the activity of a series of dipalladium complexes bridged by bis(imidazolylidenes) with phenylene or biphenylene spacers (**186−188**, Scheme 64).[313] The N-substituents were methyl or methylpyrene groups. The results in Suzuki−Miyaura coupling between aryl halides and arylboronic acids revealed that all complexes with pyrene tags displayed higher activity than those with methyl groups. The addition of a catalytic amount of pyrene (or anthracene) to the reactions resulted in partial inhibition of the activities of the

activity of **184** and **185** was higher than the activity shown by model trimetallic and monometallic complexes formally having the same stereoelectronic properties but without polyaromatic

Scheme 63. Triphenylene-based NHC Complexes of Palladium and Gold and Catalytic Reactions Tested

Scheme 64. Comparison of Activity of Dimetallic and Monometallic Complexes of Palladium with and without Pyrene Tags

n=1, R = CH₂-pyrene, **186**
n=2, R = CH₂-pyrene, **187**
n=2, R = Me, **188**

R = CH₂-pyrene, **189**
R = Me, **190**
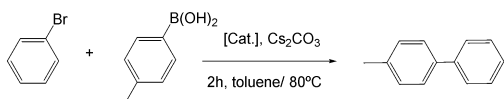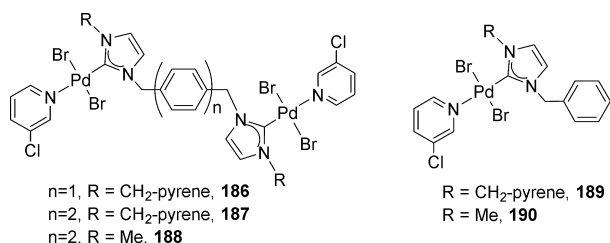
pyrene-containing complexes, while the activity of the complex with the N-methyl groups was unaffected. The same effect was observed when the activities of monometallic complexes **189** and **190** were studied. Again, the addition of pyrene produced a partial inhibition of activity of the pyrene-containing complex (**189**) while not affecting the activity of the methyl-substituted catalyst (**190**).[313]

Preparation of a series of mono-NHC ligands decorated with polyaromatic functionalities allowed the study of the influence of π-stacking additives on electronic properties of NHC ligands. The electrochemical studies on a series of [NiClCp(NHC)] complexes (NHC = imidazolylidene, benzimidazolylidene, and pyrene-imidazolylidene for **191−193**, respectively) revealed interesting results when the three complexes were titrated with a π-stacking additive such as pyrene.[314] While the imidazolylidene and benzimidazolylidene nickel complexes were relatively insensitive to the addition of pyrene (maximum positive shift of the half-wave potential observed, $\Delta E_{1/2} = 20-30$ mV), the addition of pyrene to the pyrene-imidazolylidene complex of nickel (**193**) produced a maximum positive shift in potential of 75 mV (Scheme 65). This finding demonstrated

Scheme 65. Effect of Pyrene Addition on Redox Potential of Three NHC Complexes of Nickel(II)

191
$\Delta E_{1/2} = 0.659$ V
Addition of 2 eq. of pyrene
$\Delta E_{1/2} = 0.683$ V

192
$\Delta E_{1/2} = 0.684$ V
Addition of 2 eq. of pyrene
$\Delta E_{1/2} = 0.719$ V

193
$\Delta E_{1/2} = 0.659$ V
Addition of 2 eq. of pyrene
$\Delta E_{1/2} = 0.734$ V

that while all three complexes were sensitive to the addition of pyrene, the complex with the pyrene-imidazolylidene ligand was the one to show a more pronounced effect, most likely due to π-stacking between added pyrene and the pyrene fragment of the ligand.[314]

In order to experimentally quantify the modification of electron-donating character of NHC ligands with extended polyaromatic fragments, a series of [IrCl(NHC)(CO)₂] complexes were obtained (Scheme 66).[315] The study was carried out by evaluating the variation of C−O stretching

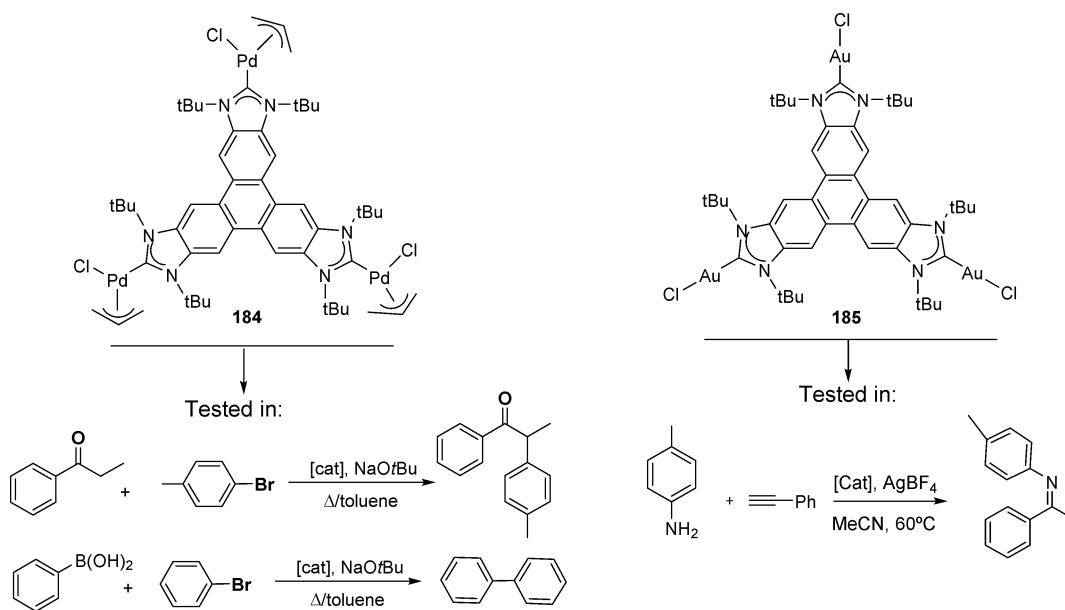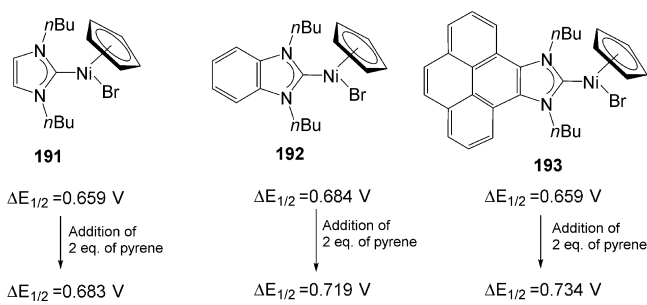frequencies in IR spectra of the complexes upon addition of pyrene or hexafluorobenzene. While the variations were negligible for the imidazolylidene and benzimidazolylidene complexes (**194** and **195**, respectively), the rest of the compounds with extended polyaromatic fragments revealed significant variations of the C−O stretching frequencies. In all cases, the addition of hexafluorobenzene produced a decrease in frequency, while the addition of pyrene produced the opposite effect. The maximum variation was 2.9 cm⁻¹ for the case of the iridium complex with the pyrene-imidazolylidene (**198**). These results revealed that the electronic character of the ligand may be postmodified by adding a suitable π-stacking additive.[315]

The iridium complexes displayed in Scheme 67 were tested in the reduction of ketones by transfer hydrogenation and in the β-alkylation of secondary alcohols with primary alcohols. The study of the reactions revealed the important role of pyrene tags in the catalysts.[316] In the reduction of ketones, when pyrene-tagged catalysts (**199** or **200**) and aromatic substrates were used, the catalytic activity is inhibited by addition of an external catalytic amount of pyrene. Other combinations of catalysts and substrates do not produce any variation in the catalytic outcome of the reaction. Detailed study of the coupling of secondary alcohols with primary alcohols revealed important findings about the mechanism of the reaction. When pyrene-tagged catalysts and aromatic substrates were used, the reaction followed a zeroth-order dependence relative to concentration of the substrates. All other combinations afforded a second-order rate. Study of the reaction orders with respect to concentration of the catalysts revealed that the catalysts with a pyrene tag (**199** and **200**) showed a fractional (<1) reaction order with respect to the catalyst, while the catalyst without the pyrene functionality (**201**) showed a reaction order of 1. This result is a clear consequence of the self-association of pyrene-containing catalysts. All these observations clearly revealed that pyrene-containing catalysts are able to engage in noncovalent interactions with aromatic molecules, which can either be substrates in a homogeneous catalyzed reaction or the same molecule of catalyst, to afford self-assembled systems.[316]

4. CONCLUSIONS AND OUTLOOK

This review article exemplifies how the role of NHC ligands goes far beyond the traditional role of a common spectator ligand. The variety of structures awaiting design is limitless, and this places NHC ligands in an advantageous position compared to other traditional ligands used in homogeneous catalysis. Now a number of examples of photoswitchable, redox-switchable, chemoswitchable, hemilabile, and bifunctional NHC ligands are known. Most of the examples described here refer to types of ligand adaptability that have been previously described for other types of ligands. For these cases, NHCs have provided new perspectives and new reactivity patterns that allowed discovery of novel catalytic singularities. Interestingly, NHCs have also provided new types of adaptability in the case of bifunctional ligands with poly-aromatic functionalities. It is probably the special topological features of NHCs (mostly their fan-shaped structure), and also the easy access to structures with rigid polyaromatic systems, that have allowed the discovery that π-stacking interactions may have important consequences in future catalyst design. This effect may also operate for other types of ligands, although the lack of a systematic approach, probably due to synthetic limitations, has left it unrecognized.

Scheme 66. Qualitative Variation of IR C–O Stretching Frequencies of a Series of [IrCl(NHC)(CO)$_2$] upon Addition of Pyrene or Hexafluorobenzene

negligible variation of
IR C-O stretching frequency
upon addition of
pyrene or hexafluorobenzene

significant variation of
IR C-O stretching frequency
upon addition of
pyrene or hexafluorobenzene
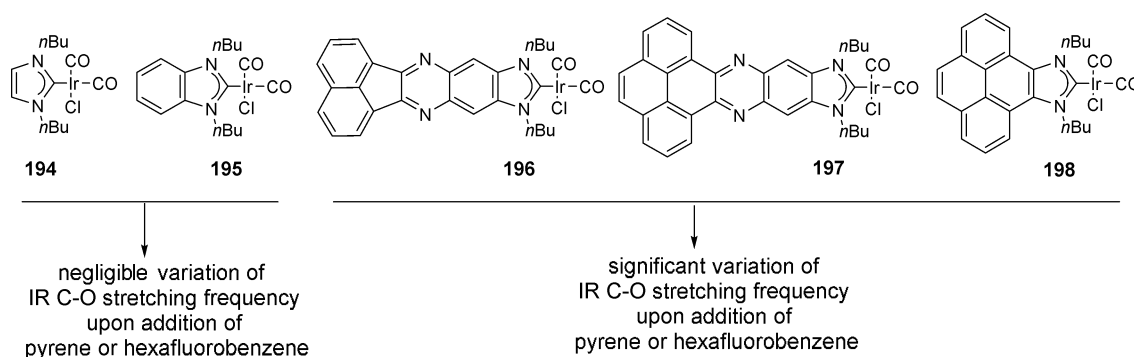
Scheme 67. Comparison of Activity of Iridium–NHC-based Catalysts with and without Pyrene Tags

Effects of addition of pyrene (10 mol%)

Catalyst	R'^O^R	Effect
199	cyclohexanone	not affected
200	cyclohexanone	not affected
201	cyclohexanone	not affected
199	acetophenone	inhibition
200	acetophenone	inhibition
201	acetophenone	not affected
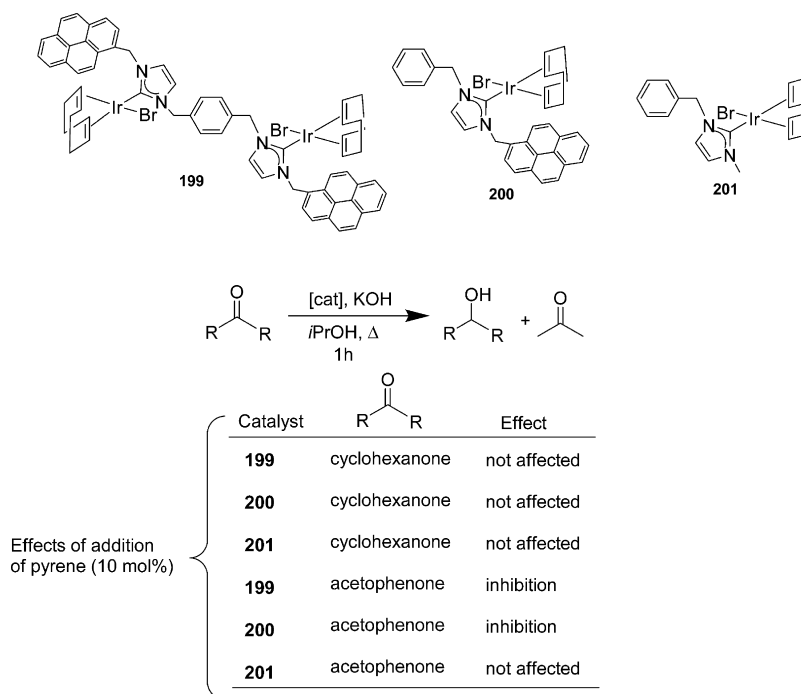
If we wanted to schematically illustrate the maturity of the field of smart NHCs, it could be useful to use the known hype cycle, which was developed by Gartner Inc. in 1995.[317,318] The hype cycle is a time-dependent graphic that represents a conceptual presentation of the maturity of a technology through five different phases (Figure 5) and gives a view of how a technology will evolve over time. It is considered as the graphic representation of Amara's law,[319] which states that "we tend to overestimate the effect of a technology in the short run and underestimate the effect in the long run". It can also be applied to specific areas of research. On average, we can consider that smart NHCs are at their early adolescence, at an age where the first generation of compounds is being developed and enthusiastic expectations are on the rise. The individual location of each smart NHC type may need a more personal analysis, since the position of each researcher may well differ according to their research interests. The author's personal opinion was triggered by the suggestion of one of the reviewers, who wisely suggested that a review of this type should clearly specify where the field is headed and what areas need attention and hold opportunity. On this basis, the positions of each type
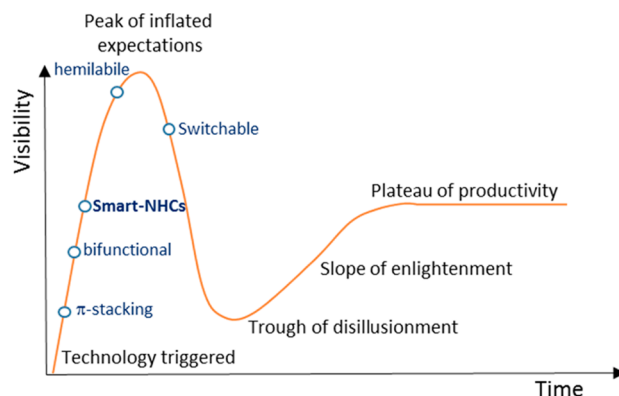

Figure 5. Hype cycle with the location of each type of smart NHC (author's personal estimation).

of smart NHC depicted in Figure 5 may be rationalized as follows: (1) Switchable NHC-based ligands are located in the place where the peak of expectations has been surpassed. The high expectations created by the potential of this type of ligand

is now facing the reality that these ligands may have limited applicability due to the relative low number of photoswitchable systems available (more research is needed here), and to the fact that redox-switchable NHCs seem to be sensitive to the charge generated on the complex rather than to the type of redox moiety used. (2) The number of NHC-based hybrid ligands continues to grow as their potential use as hemilabile ligands increases. However, the number of hybrid NHC ligands that showed clear hemilability in homogeneous catalysis is not so high, and the relatively low number of examples proving clear catalytic benefits may indicate that this family of NHCs is close to reaching the peak of expectations. (3) Despite the large number of examples regarding bifunctional NHCs, we now seem to be facing a period where limitless applications of this family of NHCs are continuously appearing. Within this group of ligands, NHCs with π-stacking abilities are still in their infancy, and probably some time needs to pass before the number of potential practical applications can be envisaged. Hopefully, this classification is useful for encouraging future research in the field.

In summary, smart NHC ligands are capable of adapting the reactivity of a metal catalyst to the specific requirements of a defined catalytic transformation. NHCs themselves are smart, in the sense that NHC chemistry has rapidly adapted to new times and needs for novel reactivities. These advances and the continuing development of new applications will certainly help to ensure an important place for NHC-based catalysts for many years to come.

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Notes

The author declares no competing financial interest.

Biography

Eduardo Peris graduated in chemistry in 1988 and received his Ph.D. in chemistry (1991) from the Universidad de Valencia, under the supervision of Professor Pascual Lahuerta. In 1994 he joined Professor Robert Crabtree's group at Yale University, where he stayed for two years, working on a research project regarding the determination of hydrogen bonding to metal hydrides (dihydrogen bond). In October 1995 he moved to the Universitat Jaume I (Castellón, Spain) as assistant professor (1995−1997), then associate professor (1997−2007), and finally full professor of inorganic chemistry. At the Universitat Jaume I, he started a research project related to the use of organometallic push−pull compounds with nonlinear optical properties. During the past decade, he has developed an intense research activity on the chemistry and catalytic applications of N-heterocyclic carbene-based organotransition metal catalysts. Most of his activity was devoted to the preparation of new catalysts for the activation of small molecules, with special attention to processes implying the activation of C−H bonds, carbon dioxide, and reactions involving borrowing-hydrogen methodologies. During the last five years, the group also devoted great attention to the design of catalysts for tandem catalytic reactions. The use of heterodimetallic complexes of Ir/Rh and Ir/Pd allowed for studying their activity in catalytic tandem processes in which each metal mediated a mechanistically distinct reaction. The current interest of his group is the design of new polytopic rigid N-

heterocyclic carbene ligands (NHCs) for the preparation of improved catalysts and the design of supramolecular organometallic structures for molecular recognition. He has authored or coauthored about 170 articles in international chemistry journals and more than 10 book chapters or monographs. In 2012 he was awarded the Spanish Royal Society of Chemistry award in the field of inorganic chemistry research. In the period 2007−2010, he was a member of the Advisory Board of Organometallics, and he is currently the president of the Spanish Organometallic Chemistry Group (GEQO) of the Spanish Royal Society of Chemistry (RSEQ).

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