Dearomatization of transition metal-coordinated N-heterocyclic ligands and related chemistry

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Abstract

This review focuses on chemistry published by the authors during the last decade, and relevant chemistry from other areas is included to provide an appropriate context. 2,2'-bipyridine (bipy) and 1,10-phenanthroline (phen), employed for a long time in all areas of coordination chemistry, are archetypical auxiliary ligands that stabilize metal fragments but are not themselves the site of the reactivity. Several examples of dearomatization of one of the pyridine rings of coordinated bipy and phen are discussed, including one example of ring opening. The highly reactive species resulting from deprotonation of coordinated N-alkylimidazoles can result, besides of the mentioned dearomatization, in other intramolecular C-C coupling reactions involving monodentate pyridines, other N-alkylimidazoles, imine, nitrile, isonitrile and carbonyl ligands. In some examples, the products of these couplings, and of those between two pyridines, can be oxidatively rearomatized, affording pyridylimidazoles and bipyridines. Similar deprotonations leading to C-C couplings have been demonstrated for deprotonation of dimethylsulfide and methylphosphane ligands. In some instances, the deprotonation of coordinated N-alkylimidazoles produces complexes with rare N-alkylimidazol-2-yl ligands. The protonation or alkylation of the non-substituted nitrogen of the later affords coordinated N-heterocyclic carbenes.
1. Introduction.

This article aims to review the recent work by our group in new aspects of transition metal-based reactivity of pyridine and imidazole ligands, many of which involve dearomatization of those heteroaromatic rings. Six member pyridines (1, Figure 1) and five member imidazoles (2, Figure 1) are some of the most important N-heterocycles.\textsuperscript{1} There are several reasons for this relevance. One is the prevalence of pyridine and imidazole rings in natural systems and in non-natural molecules with physiological activity. Imidazole groups of histidine residues are some of the main donor groups toward metals in metalloproteins, including enzymes. This has been perhaps the main reason why imidazoles or imidazole-containing ligands have been the subject of many studies in coordination chemistry.\textsuperscript{2} Despite this wealth of work, few studies dealt with the reactivity of coordinated imidazoles beyond substitution reactions and proton transfer reaction (including hydrogen bond formation) to and from a non-coordinated imidazole nitrogen atom. N-alkylimidazolium salts (3, Figure 1) have been thoroughly studied materials; for instance, as ionic liquids.\textsuperscript{3} One of the ways to access such salts is by alkylation of free N-alkylimidazoles. The deprotonation at C2 of N-alkylimidazolium cations is one of the most general ways to prepare N-heterocyclic carbenes (NHC, 4 in Figure 1), a type of ligands that are having a huge impact in contemporary chemistry.\textsuperscript{4} In particular, NHCs are employed as ligands in many catalytic processes, where their strong donor character, high steric profile, strong affinity for metal centers, leading to the high thermal stability of their complexes, and tunability, make them useful auxiliaries. Applications of NHC metal complexes outside the realm of catalysis are currently being found as a result of intense research in this area.\textsuperscript{5} Despite the close relationship between N-alkylimidazoles and NHC ligands, few transformations linking the two types of compounds were known. Recent contributions by our group are discussed in this paper, along with appropriate mentions of previous and subsequent work by others.

Pyridines, being both good $\sigma$-donor and $\pi$-acceptor, are excellent ligands for all kinds of metal fragments. The ability of pyridines to accept electron density in their low-lying $\pi$-symmetric empty orbitals make them redox-active ligands, and is also the basis of the rich photophysic behavior of many metal complexes containing pyridine-based ligands, in particular rhenium carbonyl
complexes. These properties have been particularly exploited for metal complexes of the strongly chelating 2,2-bipyridine (bipy, 5 in Figure 1) and 1,10-phenanthroline (phen, 6 in Figure 1) and their derivatives, which have been employed as ligands for a long time. The complexes of monodentate pyridines are often rather labile, a fact that considerably restricts their applications and the study of the reactivity of the coordinated pyridines beyond their substitution. In contrast, several types of pyridine-based polydentate ligands, including the relatively simple bipy and phen, form robust metal complexes that are very stable against substitution. Pyridyl-based ligands are typically resistant toward oxidation and very rarely have been found to undergo chemical modification of the pyridyl ring. However, it must be noted that this is not the result of an inert nature of pyridines. Pyridines are electron-poor aromatic heterocycles in which one of the CH groups of benzene has been replaced by the more electronegative nitrogen atom. Therefore, pyridines react with nucleophiles, which attack mainly the ortho and para positions, those with a higher positive charge. The product of such nucleophilic additions is a non-aromatic amide with a high tendency to recover aromaticity, typically by a subsequent elimination step, so that the overall addition-elimination reaction is formally a substitution. Indeed, the tendency to give substitution, as opposed to addition, products, is typical of aromatic substrates. If the pyridine does not contain a good leaving group, such as a halide, the second step involves a formal elimination of hydride, and the overall transformation is called an aromatic hydrogen substitution. Alternatively, aromaticity can be regained by oxidation, formally a hydride abstraction, often in fact a combination of electron transfer and proton abstraction steps. While those reactions are well known of free pyridines, including bipy and phen, there was virtually no precedent of nucleophilic attack to transition metal coordinated pyridines. For monodentate pyridines, this can be attributed to their lability; however, this cannot explain the lack of examples of nucleophilic attack on coordinated bipy or phen ligands, especially given the vast number of their transition metal complexes and how extensively they have been employed in every phase of coordination chemistry. Neither can it be attributed to lack of interest; in fact, there has been a considerable interest in demonstrating nucleophilic attacks to transition metal-coordinated bipy and phen ligands following Gillard’s controversial suggestions that such attacks take place to
the bipy and phen ligands of some cationic metal complexes in basic aqueous solution, as it will be discussed below.

\[
\begin{array}{ccc}
1 & 2 & 3 \\
\text{N} & \text{N} & \text{R}
\end{array}
\begin{array}{ccc}
4 & 5 & 6 \\
\text{N} & \text{N} & \text{R}
\end{array}
\]

Figure 1. Main types of N-heterocyclic species dealt with in this work.

Metal-mediated transformations of pyridines are thus mainly the realm of main group highly electron-rich compounds such as alkyl derivatives of lithium, magnesium and zinc, aluminum hydrides, etc. This chemistry will be very succinctly covered with an emphasis on recent developments, as it will the related alkyl migration to pyridines which have been found in a number of f-block derivatives, a topic which has been recently reviewed. In particular, rollover cyclometalations, which are important processes that can be operative in bipy complexes, will not be mentioned, and the interested reader is referred to a recent account of this chemistry.\(^\text{11}\)

Most of this article will focus on our own chemistry, including several examples of dearomatization of pyridyl rings of coordinated bipy and phen. Common features of all these reactions are the very mild conditions under which they have been carried out, and their intramolecular nature. In one instance, the reaction is initiated by the nucleophilic attack of a terminal phosphanido ligand on electron-poor alkenes and alkynes. In all the other examples, it is the result of the deprotonation of one of the CH groups of a ligand. Metal-coordinated N-alkylimidazoles, dimethylsulfide, trimethylphosphone and monodentate pyridines have been demonstrated to generate, on deprotonation, internal nucleophiles, which then carry out the C-C coupling with proximal metal-coordinated heteroaromatic rings. Deprotonated N-alkylimidazoles have been coupled also with nonaromatic ligands such as imines, nitriles,
isonitriles and CO. Deprotonated monodentate pyridines have been coupled with other pyridine ligands, affording 2,2'-bipyridine chelates within the metal template. A key feature in designing such coupling reactions is that the deprotonated ligand must be cis to the electrophilic ligand to which the attack is planned to occur, so that the nucleophile resulting from the deprotonation and its electrophilic counterpart are close in the space and can couple without leaving the metal coordination sphere. Many dearomatized products have been characterized in solution; in several examples, in addition, they have been isolated as crystalline solids and structurally characterized by single-crystal X-ray diffraction. A noteworthy feature of the C-C coupling events mentioned above is that they occur between partners that do not require functionalization other than coordination to the metal, therefore constituting a modular, metal-templated approach to the direct synthesis of metal complexes containing elaborate polydentate ligands from complexes of the monodentate ligands that serve as building blocks.

2. Addition of main group organometallic reagents to pyridines and related heteroaromatics.

The addition of main group-based organometallic or hydride reagents to pyridines and similar systems takes place through coordination of the heterocyclic molecule to the Lewis acid metal center followed by formation of dearomatized species, for which there is a small but growing body of structural information.

The addition of nucleophiles to pyridines, pyridinium cations and other electron-poor heteroaromatic substrates has been known for a long time.\textsuperscript{12-14} An example is the Chichibabin amination, in which typically sodium amide adds to the 2 position of a pyridine.\textsuperscript{15-17} Reactions of this kind are thought to proceed through an initial step in which the pyridine coordinates the main group metal cationic center, followed by the addition of the nucleophile (an alkyl or hydride) to the 2-position of the pyridine to afford a nonaromatic intermediate, the Meisenheimer adduct. From this species, rearomatization to the 2-substituted pyridine takes place through formal hydride elimination, as showed in Scheme 1. This kind of mechanism is generally operative in the chemistry of electron-poor arenes.\textsuperscript{18} Note however, that the Chichibabin reaction has been
carried out in a variety of conditions, including homogeneous and heterogeneous media, so
different mechanisms can reasonably be expected. An elegant and synthetically useful
fluorination of pyridines and diazines, inspired by the Chichibabin reaction, has been recently
reported by Fier and Hartwig. Interestingly, in the (to our knowledge) only theoretical study of
the mechanism of the Chichibabin reaction, Dransfield and co-workers found that the most
favorable mechanism involves the elimination of dihydrogen, rather than sodium hydride as it is
usually assumed.

![Scheme 1. Proposed mechanism of the Chichibabin reaction.](image)

Alternative mechanisms involve heteroarynes or ring opening-ring closure sequences. Main
group alkyl and, in some cases, hydride reagents, add to pyridines (the reaction is sometimes
called carbometalation, or pyridine insertion into the M-C bond) affording either the dearomatized
N-metallo-1,2-dihydropyridines or their 1,4-isomers. Usually the 1,2-isomers are produced under
kinetic control and the 1,4-isomers, under thermodynamic control. Often mixtures of both
isomers are obtained, although regioselectivity has been achieved under certain conditions.
These main group complexes of dihydropyridines have been found to be the intermediates in
the reactions between pyridines and organometallic reagents to afford alkylpyridines. In some
instances, di- and tri-alkylpyridines have been prepared employing an excess of the
organometallic reagent.

Note that the classical syntheses of dihydropyridines (e.g. Hantzsch synthesis) employ de novo
construction of the rings by multicomponent reactions rather than starting from pyridines, and
that some of the pyridine reduction processes are actually reductions of pyridinium cations (e.
g. Fowler’s sodium borohydride reduction of the N-acylpyridinium salts produced in situ by the
reaction of pyridines with chloroformate esters).
Neutral N-H or N-R dihydropyridines are employed both by nature (the NADH and NADPH dinucleotide coenzymes) and by synthetic chemists as selective reducing agents in transformations driven in large part by the tendency of dihydropyridines to achieve rearomatization. In the field of transition metal organometallic chemistry, dihydropyridines have been either formed on the coordination sphere of a metal to which they are bound through the C=C double bonds, or used as substrates. Ishitani studied the formation of intermediate complexes containing 1,4-dihydropyridines $\eta^2$-coordinated to ruthenium fragments in the reaction of pyridinium cations with ruthenium hydride complexes; Myers employed complexes of a strongly $\pi$-basic metal fragment with $\eta^2$-coordinated pyridinium cations to access metal-complexed dihydropyridines; Rudler found dihydropyridines to be useful reagents in the chemistry of Fischer carbenes, and Liebeskind employed dihydropyridine $\pi$-complexes as intermediated in the synthesis of more reduced heterocycles, such as piperidines.

The reaction of pyridines with organolithium reagents afforded mainly 2-substituted pyridines through alkyl addition to generate a dearomatized lithium complex of dihydropyridine. From this species, it has been thought that elimination of highly insoluble lithium hydride would yield the final 2-alkylpyridine product. Reaction mixtures usually contain some amount of the 4-alkylated isomer. Snaith and coworkers found that rather than undergoing an actual elimination of lithium hydride, N-lithium dihydropyridines hydrolize (e. g., with traces of moisture) to N-H dihydropyridines, which subsequently oxidize (e. g. on atmospheric exposure) to 2-alkylpyridines.

Mulvey and co-workers reported evidence pointing to intramolecular hydride transfer from a dihydropyridide ligand to a pyridine ligand within a lithium complex (Scheme 2), and the crucial role of the stoichiometry in the reactions between pyridines and organolithium reagents. These results indicate the necessity of considering the entire coordination compound and to gain as much knowledge as possible of its structure both to understand and to synthetically exploit the reactivity of main group organometallics. Mulvey, Robertson and co-workers recently isolated and structurally characterized several N-lithio-2-alkyl-dihydropyridines.
Methods consisting of nucleophilic addition followed by oxidative rearomatization are some of the simpler and more expedient methods for pyridine functionalization. However, preactivation of the pyridine by its transformation to a pyridine N-oxide or an N-alkyl- or N-acyl pyridinium cation is often required. In 2013 and 2014 Knochel and co-workers reported nucleophilic additions to pyridines mediated by BF$_3$.\textsuperscript{31,32} They found that the formation of pyridine-BF$_3$ adducts has a dramatic effect on the reaction course. Indeed, some reactions do not occur without the presence of BF$_3$ and, in other instances, the regioselectivity towards the product of addition to the 4-position is attributed to BF$_3$ complexation. A similar effect of pyridine activation by its complexation has been found by Urabe and co-workers in the additions of benzyl Grignard reagents.\textsuperscript{33}

In the reactions between pyridines, in particular bipy and phen, and other electron-poor N-heterocycles, and main group organometallic or hydride reagents, the formation of strongly colored solutions have been noted a long time ago, and bipy and phen have been used as visual indicators in the titrations of organolithium and Grignard reagents.\textsuperscript{34} However, attempts to isolate stable metal complexes from these reactions failed. Kaim and others showed that, instead of the previously assumed polar mechanism (carbanion transfer from the metal to the heterocycle), many reactions between the metal reagent (alkyllithium, organomagnesium, organozinc, aluminum hydride, etc.) and the heterocyclic substrate take place through a radical mechanism.\textsuperscript{35-37} Thus the initially formed adduct between the metal reagent and the heterocycle (a charge transfer adduct) undergoes an intramolecular single electron transfer to form a radical anion of the heterocyclic substrate and the radical cation of the metal reagent. One of the possible pathways from that system leads to the diamagnetic product of alkyl or hydride transfer.

**Scheme 2.** Proposed hydride transfer between ligands in a lithium complex.
to the heterocycle. Trapping of radicals and ESR spectroscopy provided evidence in support of such a radical pathway. Note, however, that most studies of the reactivity of main group alkyl or hydride reagents with electron-poor heteroaromatics do not include the probing of the possible intermediacy of radicals. Radical-based reactions of electron-poor heteroarenes can be synthetically useful.\textsuperscript{38} Note also that radicals can display a considerable nucleophilic character so that, for instance, radical addition to pyridines can be mainly directed to the 2 and 4 positions.

Maron, Okuda and co-workers reported in 2010 that bis(\(\eta^3\)-allyl)calcium reacts with pyridine to regioselectively afford a species with two anionic, dearomatized 1,4-dihydropyridide ligands, each resulting from the addition of an allyl group to a coordinated pyridine.\textsuperscript{39} In excess pyridine, an octahedral complex could be isolated and structurally characterized by X-ray diffraction, which contains four intact pyridine ligands, and the two anionic ligands in trans positions. Its reaction with E-Cl electrophiles generates the neutral N-protected 1,4-dihydropyridines and calcium chloride.

The mechanism of the dearomatization was studied by NMR and by computational methods. An adduct between the diallylcalcium moiety and pyridine initially forms, followed by allyl migration from calcium to the ortho position of two of the coordinated pyridines to afford the product of double 1,2-insertion. Next, the final double 1,4-insertion product is formed by a rate determining Cope rearrangement step.

The Lansbury reagent, formed as the product of the reaction between pyridines with lithium tetrahydroaluminate (lithium alanate), has been employed as a useful reducing agent in organic chemistry for a long time. Hensen and co-workers demonstrated that Lansbury reagent has the [Li(pyridine)\(_4\)]\([\text{Al(1,4-dihydropyridide)}_4]\) composition and structurally determined its structure and those of similar derivatives.\textsuperscript{40}

Budzelaar et al. studied the reactions of a pyridylbis(imine) pincer ligand with aluminum alkyls. Along with other species, they found products of alkyl addition to the pyridine ring. Radical and ionic mechanisms were considered. Regarding the later, the authors found the best results in their computational modeling for the alkyl transfer from an anionic R\(_3\)AlCl\(^+\) species to the pyridine ring of the pincer ligand coordinated to the cationic RAICl\(^+\) fragment.\textsuperscript{41}
In 2011 Okuda and coworkers reported a study of the reactivity of tris(η\(^1\)-allyl)aluminum complexes toward pyridines. In some cases, they found formation of dearomatized products of the allyl addition to the ortho position of pyridine.\(^{42}\) Previous studies by other groups found either no reaction or just formation of stable pyridine adducts in the reaction between pyridines and other trialkylaluminum reagents. Okuda proposed a Claisen rearrangement in the case of allyl addition to explain the especial behavior of this alkyl group. They encountered a dramatic solvent effect in the reaction. Thus [Al(η\(^1\)-allyl)\(_3\)(py)], quantitatively formed as the product of the reaction between [Al(η\(^1\)-allyl)\(_3\)(THF)] and pyridine, was found to be stable in pentane for weeks; in contrast, in THF solvent, the dearomatized product of allyl attack to the pyridine ortho position was formed. Allyl attack is prevented by the presence of methyl groups not only at the ortho (steric blocking), but also on the meta or para positions of the pyridine ring, indicating that electron-rich pyridines are not electrophilic enough for undergoing the nucleophilic attack of the allyl group. Accordingly, 4-dimethylaminopyridine does not react, whereas 4-trifluoromethylpyridine affords mainly the product of ortho-allyl addition.

Addition of diorganozinc reagents, which are relatively mild nucleophiles, to pyridines have been typically carried out employing transition metal catalysis. In 2015 Hevia and co-workers reported the regioselective addition of lithium arylzincate reagents [LiZnPh\(_3\)] and [Li\(_2\)ZnPh\(_4\)] (prepared by co-complexation of the appropriate amounts of to LiPh and ZnPh\(_2\)) to the 9-position of acridine under microwave irradiation.\(^{43}\) They found a much better performance of the heterometallic reagents compared to simple diarylzinc reagents, which has been attributed to a combination of the anionic activation of the organozinc reagent (by forming ZnPh\(_3\)^– or ZnPh\(_4\)^2– species) and an enhancement of the electrophilicity of the heterocycle by its coordination to the lithium centers. Note the relation with the Budzelaar’s aluminum system mentioned above. Indeed, the authors structurally characterized the dearomatized product of the addition to the 9-position, in which the nitrogen atom is coordinated to Li(THF)\(_3\)^+, as shown in Scheme 3.
3. Reaction of pyridines with early transition metal complexes.

Early transition metal chemistry, including that of the f-block elements, shares some features with that of the main group metals due to a high polarity of the element-metal bonds. Early transition metal hydride and alkyl complexes, endowed with strongly electrophilic metal centers, often react with the CH groups in the $\alpha$ position of N-heterocyclic ligands. For pyridines, such reaction produces $\kappa^2$-(C,N)-pyridyl complex, depicted in Figure 2 (structure 7). Note that the pyridyl ring of this type of complex maintains the aromaticity. These pyridyl complexes display a rich reactivity such as insertions of unsaturated organic molecules (e.g., olefins) in the M-C bond, eventually initiating catalytic cycles. Alternatively, if a second molecule of an N-heterocycle binds the same metal center, interligand C-C coupling can take place. For instance, the reaction of an unsaturated alkyl complex with two equivalents of pyridine can generate a bipy ligand on the metal coordination sphere. This chemistry has been excellently reviewed.$^{44,45}$ Some early transition metal fragments are capable of binding pyridines in the very rare $\kappa^2$-(C,N) mode. In contrast with the $\kappa^2$-(C,N)-pyridyl complexes mentioned above, pyridine (as opposed to pyridyl) ligands coordinated in the $\kappa^2$-(C,N) mode are dearomatized, and are considered to possess metaloaziridine character (see structure 8 in Figure 2).

**Figure 2.** $\kappa^2$-(C,N)-pyridyl (7) and $\kappa^2$-(C,N) pyridine (8) ligands.
Pyridine and its analogs are some of the main contaminants present in petroleum crudes, and they should be removed to avoid the emission to the atmosphere of nitrogen oxides from fuel combustion. To this end, large-scale hydrodenitrogenation (HDN) of petroleum crudes is carried out along with hydrodesulfurization (HDS) and hydrodeoxygenation (HDO) processes. These hydrotreating processes employ sulfidized transition metal oxides as heterogeneous catalysts. Since the sulfur-containing organic pollutants would poison the catalysts of subsequent processes to which the petroleum will be subjected, these processes operate under conditions that have been optimized for HDS. Under these conditions, the HDN process, which is of obvious economic and environmental relevance, is not very efficient. The mechanism of HDN is incompletely understood and it has been hoped that homogeneous models could shed some light on its nature and eventually lead to improvements in the efficiency of the process. Hence, particular attention has been devoted to those few transition metal-based homogeneous systems that have been found to be able to mediate the ring opening of pyridines.\textsuperscript{46,47}

In 1988, Wolczanski and co-workers reported the first example of a metal complex containing a pyridine ligand bonded in the $\kappa^2$-$(C,N)$ mode.\textsuperscript{48} The key to obtain this previously unknown coordination mode was the employment of the extremely reactive Ta(silox)$_3$ (silox= OSiBu$_3$) complex, which was prepared by reduction of the previously known, stable complex TaCl$_2$(silox)$_3$ with excess sodium amalgam. Ta(silox)$_3$ is a tricoordinated, highly reducing complex in which the axial coordination of normal two electron donors is discouraged by the presence of a metal-centered, two-electron filled molecular orbital perpendicular to the molecular plane. This feature is of particular relevance for the reaction with pyridine, which is a potential two-electron $\sigma$-donor when coordinated in the most common $\kappa^1$-$(N)$ mode. The extraordinary reactivity of Ta(silox)$_3$ is illustrated by the result of its reaction with the equimolar amount of CO, reported in 1986 by the same group: one could expect simply binding of carbon monoxide to afford a carbonyl complex, since many carbonyl complexes effectively stabilize low oxidation state metal fragments as a result of a significant back bonding. Instead, the reaction, an extreme form of an oxidative addition, breaks down the very strong carbon-oxygen bond of carbon monoxide, affording a mixture of O=Ta(silox)$_3$ and (silox)$_3$Ta=C=C=Ta(silox)$_3$, both Ta(V) species with
pseudotetrahedral geometries around the metal atoms. The presence of strong metal-carbon or metal-nitrogen double bonds in the products must be a significant contribution to the driving force of the reaction. The product of the reaction of Ta(silox)$_3$ with pyridine is a metallaaaziridine complex in which the metal-bonded C and N atoms display geometries consistent with sp$_3$ hybridizations. The bond between these C and N atoms is a single bond; therefore, the pyridine has been potentially activated towards the subsequent C-N bond breaking. In 1997, Wolczanski and co-workers reported that the thermolysis of a niobium complex analogous to the tantalum species discussed above resulted in the ring-opening of the $\kappa^2$-(C,N)-coordinated pyridine, affording products containing Nb-nitrene and Nb-alkylidene bonds, as shown in Scheme 4.

\begin{equation}
\text{Scheme 4. Pyridine ring-opening mediated by a niobium complex reported by Wolczanski et al.}
\end{equation}

In 1987, one year before the first $\kappa^2$-(C,N)-coordinated pyridine was reported, Cordone and Taube reported the first example of an $\eta^2$-(C,C)-coordinated arene: 2,6-lutidine. In this case, the metal fragment was Os(NH$_3$)$_5$, with which Taube, Harman and co-workers conducted an extensive dearomatization chemistry. The pentaammineosmium fragment is strongly reducing; however, $\eta^2$-coordination of pyridines through a carbon-carbon double bond is only observed when the nitrogen is sterically blocked, as in 2,6-lutidine, or quaternized (pyridinium cations). In general, when the aromatic substrate possesses functions capable of acting as two-electron donors, these are the ones that coordinate osmium, a fact attributed to the avoidance of the (destabilizing) disruption of the aromatic system. Wigley and co-workers reported the preparation of a $\kappa^2$-(C,N)-coordinated pyridine complex and its subsequent ring-opening by nucleophilic attack (Scheme 5). The complex does not result from the reaction of a metal precursor with a free pyridine, but from the reaction of a nitrile with a tantallacyclopentadiene, which in turn is formed as the product of the reduction of a Ta(V) precursor with sodium amalgam.
in the presence of two equivalents of a terminal acetylene. It must be noted, however, that the same authors obtained related complexes featuring $\kappa^2$-(C,N)-coordinated quinoline and 6-methylquinoline ligands. The compound containing the $\kappa^2$-(C,N)-coordinated pyridine reacts with nucleophiles such as hydride (its source being superhydride, LiBHET$_3$), Grignard, or organolithium reagents. The attack of these nucleophiles occurs initially at the metal, where they replace a chloride ligand, but subsequently, the hydride or alkyl group migrates to the metal-bonded carbon atom of the $\kappa^2$-(C,N)-coordinated pyridine, affording a metallacyclic product in which the ring opening of the ligated pyridine has taken place. In this product the pyridine nitrogen has been incorporated into a metal-bonded nitrene group (see Scheme 5); as in the pyridine ring-opening reported by Wolczanski (see above) surely the formation of the strong Ta=N bond is a significant contribution to the driving force of the reaction.

Scheme 5. Synthesis of a $\kappa^2$-(C,N)-coordinated pyridine complex and its ring-opening by nucleophilic attack (Wigley et al.).

Mindiola and co-workers, on the other hand, reported a completely different type of pyridine ring-opening reaction.$^{57,58}$ The reaction of an unsaturated titanium alkylidene intermediate, generated by alkane elimination from an (alkyl)alkylidene complex, with pyridines results in ring-opening...
metathesis of one of the pyridine C=N bonds across the Ti-C triple bond, yielding the metallaaazabicyclic products depicted in Scheme 6.

![Scheme 6. Titanium-mediated pyridine ring-opening developed by Mindiola et al.](image)

The above discussed examples have been taken as a suggestion that the metal-mediated ring opening of pyridines under homogeneous mild conditions would require a complex with a $\kappa^2$-(C,N)-coordinated pyridine as precursor and, therefore, a very particular type of metal fragments. The vast majority of metal complexes feature pyridines coordinated in the $\kappa^1$-(N) mode, in which the pyridine ligand remains aromatic; it was though that such species would not be able to mediate pyridine ring opening.\(^6\)

4. The elusive nucleophilic attack on transition metal-coordinated 2,2'-bipyridine and 1,10-phenanthroline.

Bipy and phen are some of the most prominent ligands in all areas of coordination chemistry. Because of their combination of good $\sigma$-donor and $\pi$-acceptor properties, and their tendency to form robust five-member chelate rings, these aromatic diimines form stable complexes with all metals in every oxidation state. In them, with very few exceptions, bipy and phen act as spectator ligands, stabilizing the complex without being themselves the center of the reactivity. Some forty years ago, while investigating the behavior of cationic bipy and phen transition metal complexes in basic aqueous solution, Gillard and Lyons interpreted certain spectral features as due to species (termed covalent hydrates) formed by hydroxide anion (or water) addition to the diimine ligands.\(^5\) Gillard proposed that coordination to positively charged, Lewis-acidic metal centers activated the pyridine groups towards nucleophilic attack, and likened these complexes to the pyridinium cations produced by nitrogen quaternization.\(^6\)\(^6\) This proposal sparked a long-
standing controversy, and work by other groups satisfactorily explained the evidence presented by Gillard in terms of hydroxide attack on the metal rather than on the bipy or phen ligands, thus discrediting Gillard's hypothesis.\textsuperscript{62-66}

In particular, Lay pointed out that, unlike alkyl cations, a transition metal fragment such as the ones Gillard was considering (which were from mid to late transition metals with relatively high electron counts) would be able to, besides withdrawing electron density via $\sigma$, release electron density into the empty $\pi$ orbitals of the heterocycle,\textsuperscript{67} and Blackman and co-workers showed that formation of pentacoordinated complexes by hydroxide attack to $[\text{Pt(bipy)}_2]^{2+}$ complexes explained the early observations that prompted Gillard to propose attack to bipy.\textsuperscript{68} In 2002, Zhang et al. demonstrated the hydroxide attack on bipy and phen in the presence of cupric ions, suggesting that chemistry like that proposed by Gillard can be operative in certain systems.\textsuperscript{69} However, the fact that these reactions have needed to be carried out under hydrothermal conditions can be taken as an indication of the difficulty of functionalizing the metal-bonded pyridine rings, a transformation that involves their dearomatization. The subsequent isolation of an intermediate in these hydrothermal reactions containing both phen and OH ligands coordinated to the same metal atom, led Latham \textit{et al.} to suggest initial attack by $\text{OH}^-$ to the metal, followed by a metal to phen migration.\textsuperscript{70} A perusal of the literature indicated that not only the attack of the hydroxide anion, the one of the original Gillard’s proposal, to transition metal-bonded pyridines, but in fact any nucleophilic attack to these ligands, is extremely rare. A review of the chemistry carried out by Gillard and co-workers as well as by others following Gillard’s seminal suggestions have been recently published by one of the major players in the field.\textsuperscript{71}

5. Reactivity of carbonyl rhenium and molybdenum complexes.

5.1. \textit{Reactions of the phosphido complex $[\text{Re(PPh}_2]\text{(CO)}_3\text{(phen)}]$ with activated acetylenes and olefins.}

In the past, our group has been concerned with the study of the reactivity towards electrophiles of complexes containing basic ligands such as alkoxo,\textsuperscript{72,73} hydroxo,\textsuperscript{74-76} amido,\textsuperscript{77-81} alkylidenamido,\textsuperscript{82,83} etc. Alkoxo complexes $[\text{Re(OR)(CO)}_3\text{(bipy)}]$ reacted with
dimethylacetylenedicarboxylate (DMAD) to afford the product of formal insertion of DMAD into the Re-O bond, presumably through nucleophilic attack of the coordinated alkoxo to one of the acetylenic carbons.\textsuperscript{72} This would develop a negative charge at the other acetylenic carbon, which then would attack the metal, from which the oxygen would be displaced, as shown in Scheme 7a. This displacement would be aided by the positive charge developed on the metal-bonded oxygen, which would make it a good leaving group. For the reactions of DMAD with hydroxo or arylamido complexes, the target of the intramolecular nucleophilic attack is not the metal, but one of the proximal CO ligands.\textsuperscript{76,80} H migration from the hydroxo or arylamido group to the oxygen of the same carbonyl group helps to preserve the Re-O or Re-N bonds and to transform the CO into a hydroxycarbene group, which is incorporated into a five-member metallacycle, as shown in Scheme 7b.

\textbf{Scheme 7.} Reactions of DMAD with alkoxo (a) or hydroxo (b) complexes.

We have synthesized the phosphido (phosphanido) complex [\(\text{Re}(\text{PPh}_2)(\text{CO})_3(\text{phen})\)] and carried out preliminary studies of its reactivity.\textsuperscript{77} In contrast with the reactions of alkoxo, hydroxo or arylamido complexes discussed above, the reactions of the phosphido complex with either methyl propiolate or methyl acrylate afford products consistent with conjugated addition of the phosphido ligand to the acetylene or olefin to afford a zwitterionic adduct\textsuperscript{84} (reminiscent of those involved in several types of phosphe-catalyzed coupling reactions),\textsuperscript{85} followed by
intramolecular attack of the other carbon to one of the ortho carbons of the phen ligand (Scheme 8).

Evidence of attack to the phen ligand is found both in solution, where the NMR indicates a non-symmetric phen, and in the solid state. The structure of the product, determined by X-ray diffraction, confirms the formation of a carbon-carbon bond and the non-planarity of the phen moiety. The comparison of the bonding distances N(1)-C(11) = 1.452(11), C(11)-C(12) = 1.540(14) and C(12)-C(13) = 1.307(10) Å in the product with those in the phosphido precursor (1.329(11), 1.387(15) and 1.354(17) Å respectively) indicates the dearomatization of the pyridine ring as a result of the intramolecular nucleophilic attack.

The reaction of the phosphido complex with DMAD proceeds similarly, affording complex 9. However, whereas the product of the reaction with methyl propiolate has been found to be indefinitely stable in solution, the product of the analogous reaction with DMAD slowly evolves to its tautomer 10 as shown in Scheme 9. Compounds 9 and 10 have been characterized by IR, NMR and X-ray diffraction. The transformation of 9 into 10 is at least partly driven by an increase in the conjugation. The reaction of 9 with nBuLi (which, monitored by IR, showed the formation of a species with low νCO bands, consistent with deprotonation to form an anionic complex) followed by treatment with HOTf, instantaneously affords 10, suggesting that the hydrogen migrates as a proton, rather than as a hydrogen atom or as a hydride.

The most striking feature of the reactions of the phosphido complex with the activated olefin and acetylenes is the rapid dearomatization of the phen ligand under very mild conditions. It seems likely that the reaction is somewhat facilitated by its intramolecular nature. Also noteworthy is the stability of the dearomatized products, which have made possible to discover the tautomerization discussed above and to crystallize the products by solvent slow diffusion. Compared with the alkaline salts resulting from the addition of, for instance, RLi reagents to pyridines, the dearomatized products of the reactions of the phosphido complex discussed above are neutral complexes, without the possibility of eliminating an alkaline hydride (which, having a large lattice energy, must contribute considerably to the driving force of the reaction). Additionally, the presence of the metallacycle hampers the regaining of planarity that would be required for rearomatization. It must be noted that the product of the attack to phen is the only product of the reaction, and no product of attack to one of the two proximal CO ligands was detected. This stands in contrast with the previously reported reactions of terminal phosphido complexes with DMAD, where formation of five-member metallacycles resulted from the coupling of the phosphido ligand, DMAD and one CO ligand.\textsuperscript{87-89} Note that our results in the reactions of the hydroxo and amido complexes with DMAD discussed above indicate that the proximal carbonyl ligands are susceptible to similar coupling reactions to form five-member metallacycles in pseudooctahedral rhenium tricarbonyl bipy complexes. Therefore, the unprecedented observed coupling involving the coordinated phenanthroline is not only viable under very mild conditions, but also preferred over the coupling involving one of the CO ligands.
5.2. Dearomatization by deprotonation of complexes with N-alkylimidazole ligands.

In 2008 we reported that the reaction of \([\text{Re(N-MesIm)(CO)}_3\text{(bipy)}]\text{OTf} (11)\) (N-MesIm= N-mesitylimidazole; mesityl= 2,4,6-trimethylphenyl) with the strong base \(\text{KN(SiMe}_3\text{)}_2\) affords a product consistent with deprotonation of the imidazole C2-H group, followed by attack of that carbon to the ortho (C6) carbon of the bipyridine ligand (complex 12, Scheme 10a). This reaction stands in contrast with the transformation of an N-alkylimidazole (N-RIm) into an anionic, C-bonded imidazolyl ligand (trapped by protonation to afford a stable cationic NH,NHC complex) by deprotonation of a \([\text{Mn(N-RIm)(CO)}_3\text{(bipy)}]\text{]+}\) complex reported by Ruiz and Perandones in 2007 (Scheme 10b). Note that imidazoles have been widely employed as ligands in transition metal chemistry, and that metallation of free N-alkylimidazoles at C2 was a known reaction. However, the deprotonation of metal-coordinated N-alkylimidazoles has been virtually unexplored before.

Scheme 10. Imidazole-bipy C-C coupling (a) or transformation of N-RIm to NH-NHC complexes (b).

As in the reactions of the phosphido complex discussed above, the C-C coupling reaction resulting from the deprotonation of \([\text{Re(N-MesIm)(CO)}_3\text{(bipy)}]\text{OTf}\) affords a product in which one
of the pyridine rings of the bipyridine ligands is dearomatized, and it takes place under very mild conditions.

Reactions similar to the deprotonation of [Re(N-MesIm)(CO)₃(bipy)]OTf were carried out with its N-methylimidazole (N-Melm) analog as well as with the two similar compounds containing phen instead of bipy. The stability of the products varied greatly. The neutral product of [Re(N-MesIm)(CO)₃(bipy)]OTf deprotonation was sufficiently stable to permit isolation and full characterization, including X-ray crystallography. In solution the dearomatization of the attacked ring is indicated by the upfield shift of several of the signals corresponding to its CH groups. The solid-state structure of this species confirms the formation of the new C-C bond between the central carbon (C2) of the imidazole ring and the C6 carbon atom of the bipyridine ligand, and the dearomatization of the attacked pyridine ring, geometrically shown by its loss of planarity (see Figure 3). Unlike in the C-C coupling reactions of the phosphido complex discussed above, where six-member metalacycles were formed, now the product of the imidazole-bipy coupling features a five-member ring. As a result of the C-C forming reaction, the aromatic imine functionality in the reactant is transformed into an amido group in the product.

![Molecular structure of complex 12.](image)

The combination of amido ligands, with a high tendency to act as π-donors, with high oxidation state metal fragments possessing empty orbitals of appropriate symmetry, usually leads to very
stable complexes.\textsuperscript{94} Although in principle, for an octahedral d\textsuperscript{6} complex, with the \(\pi\)-symmetric t\textsubscript{2g} orbitals completely filled, \(\pi\)-donation from the amido ligand should not be possible, the electron density from the amido lone pair can be donated to the strongly \(\pi\)-acceptor CO ligands via the \(\pi\)-symmetric metal orbitals.\textsuperscript{95} Such donation, which would stabilize the complex, would lead to a planar amido group. A planar at nitrogen geometry, characterized by a sum of the angles about the nitrogen atom being 360°, has been encountered in most structurally characterized amido complexes, including in arylamido rhenium tricarbonyl complexes, in which structural evidence supports the delocalization of the amido lone pair through the aryl substituents.\textsuperscript{77} In contrast, complex 12, the product of the deprotonation of [Re(N-MesIm)(CO)\textsubscript{3}(bipy)]OTf, which is a rare example of a stable amido complex of a low valent metal without aryl substituents at the amido nitrogen, features a pyramidal amido group, the sum of the angles around the amido nitrogen being 335°. This feature can be attributed to the constrained geometry resulting from the amido group being part of a rigid tridentate ligand.

Besides of the structural evidence -the geometries about both the carbon and the nitrogen are consistent with sp\textsuperscript{3} hybridization in the product-, this amido character is reflected in the reactivity. Thus, the neutral products resulting from the deprotonation of the [Re(N-RIm)(CO)\textsubscript{3}(N-N)]OTf (R= Me, Mes; N-N= bipy, phen) compounds react with MeOTf. For three of the compounds, the reactions afford stable, cationic complexes featuring amino groups resulting from methylation at nitrogen (Scheme 11). One of these derivatives (N-MesIm, phen) was fully characterized, including X-ray diffraction. Comparing the two series of compounds, namely, the neutral amido products with the cationic complexes that result from the methylation of the amido compounds, the later have been found to be significantly more stable. This is attributed to the high nucleophilic character of the amido ligand, a fact that has been previously noted in monodentate amido rhenium tricarbonyl complexes.\textsuperscript{77,78,80}
Scheme 11. Methylation of the amido group of the dearomatized, C-C coupled products, affording stable amino complexes or a ring-opening product (13).

In the cationic amino complexes resulting from at-nitrogen methylation of the amido complexes, both NMR and X-ray data indicate the presence of a dearomatized pyridyl ring as in the amido precursor. The neutral species formed in the deprotonation of [Re(N-Melm)(CO)_3(bipy)]OTf reacts with excess methyl triflate under very mild conditions (15 minutes stirring at room temperature) affording compound 13 (see Scheme 11 and Figure 4), which was characterized spectroscopically and by X-ray diffraction. The most interesting feature in the structure of 13 is that it reveals, besides the double methylation of its nitrogen atom, that nitrogen extrusion occurred in the pyridine ring to which the nucleophile attack took place. The product features a tridentate ligand with pyridine, imidazole and dimethylamino donor groups, and a cyclopentadienyl bridgehead group formed as the product of the mentioned nitrogen extrusion from the attacked pyridine ring. The treatment of the neutral product of the initial deprotonation with the stoichiometric amount of MeOTf failed to yield a monomethylated product akin to the one resulting from methylation of 12; however, taken collectively, the results outlined above...
suggest that ring opening occurs via a second methylation of such a product. The fact that the monomethylated phen complex does not react with excess MeOTf suggest that the additional aromatic ring in the phen ligand somewhat hinders the rearrangement leading to nitrogen extrusion.

**Figure 4.** Molecular structure of the cation of compound 13.

The overall transformation that starts with the deprotonation of the cationic N-methylimidazole bipyridine complex and ends in the pyridine ring opening shows that pyridine ring opening under mild conditions can be achieved starting from a very stable metal complex in which the bipy ligand, usually very inert, is coordinated in its normal mode, i.e., both pyridyl rings bind the metal only through their nitrogen atoms, in contrast with previous examples of homogeneous metal-mediated pyridine ring-opening, which necessitated highly reactive early transition metal fragments capable of binding pyridines in the $\kappa^2_{2}$(C,N) mode.

**5.3. Couplings and dearomatization initiated by deprotonation of C(sp$^3$)-H bonds.**

The C-C coupling reactions discussed above have been initiated by the deprotonation of the C(sp$^3$)-H bond of an N-alkylimidazole ligand. We have found that similar C-C couplings can be carried out through the deprotonation of aliphatic CH groups such as those of coordinated
dimethylsulfide\textsuperscript{96} or trimethylphosphane,\textsuperscript{97} which triggers the C-C coupling between the resulting methylene group and one of the pyridyl groups of bipy and phen co-ligands.

The product of the reaction of [Re(CO)\textsubscript{3}(bipy)(S(CH\textsubscript{3})\textsubscript{2})]OTf with a slight excess of KN(SiMe\textsubscript{3})\textsubscript{2} showed insufficient thermal stability to allow crystallization and thus was fully characterized only in solution by means of NMR. To aid in this characterization the labeled analog [Re(CO)\textsubscript{3}(bipy)(S(\textsuperscript{13}CH\textsubscript{3})\textsubscript{2})]OTf was similarly synthesized and deprotonated. The results of the NMR studies indicated that the methylene group resulting from the deprotonation of one of the methyl groups of S(CH\textsubscript{3})\textsubscript{2} attacked the C2 position of bipy, in contrast with the attack at C6 found in the C-C coupling resulting from N-alkylimidazole deprotonation.\textsuperscript{90} The product has been found to be the mixture of the diasteromers showed in Scheme 12. The reaction of the mixture of diasteromers with the equimolar amount of trimethylphosphane afforded a single compound, resulting from the displacement (from the rhenium coordination sphere) of the sulfide donor group by the phosphane (Scheme 12). In an analogous fashion, the diasteromeric mixtures reacted with bis(dimethylphosphino)methane (dmpm), affording a single product in which the sulfide group has been replaced by a monodentate dmpm. No product containing a bidentate dmpm ligand could be detected, despite the high nucleophilicity of this diphosphane, showing that the low stability of the diasteromeric mixture resulting from the deprotonation and C-C coupling does not arise from lability of the ligands (e.g., decarbonylation).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=\textwidth]{scheme12.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 12.} C-C coupling and pyridine dearomatization initiated by the deprotonation of a dimethylsulfide ligand.
This low stability was thus attributed to the dearomatization of one of the pyridyl rings, and thus a similar C-C coupling was sought which would involve a nonaromatic diimine in the hope that it would afford a more stable product. Thus compound [Re(CO)₃(2,6-iPr-BIAN)(S(CH₃)₂)]BAr₄ (2,6-iPr-BIAN= 1,2-bis[(2,6-diisopropylphenyl)imino]acenaphthene) was prepared and characterized both spectroscopically and by X-ray diffraction, and it was allowed to react with KN(SiMe₃)₂. Indeed, the stable, single product of the reaction was found to be the neutral complex resulting from the coupling between the methylene group of an H₃CSCH₂ fragment, produced in the deprotonation of the coordinated dimethylsulfide, and one of the imine carbons of the diimine chelate. A factor that can make the BIAN-derived amido complexes more stable compared with their bipy counterparts is the steric protection lent by the bulky aryl group in the former.

The deprotonation of [Re(CO)₃(bipy)(P(CH₃)₃)]OTf with KN(SiMe₃)₂ afforded a mixture of two products (Scheme 13). One of them was the neutral cyano complex [Re(CO)₂(CN)(bipy)(P(CH₃)₃)], formed from attack of the amide on one of the CO ligands, a known reaction that involves the elimination of hexamethyldisiloxane, O(SiMe₃)₂.⁹⁸ The second, minor product, was the expected result of the deprotonation of one of the phosphane methyl groups and subsequent intramolecular attack on the bipy C6 position. Note the difference with the similar reaction of the dimethylsulfide complex discussed above, in which the attack was to the bipy C2 position instead.⁹⁶

![Scheme 13. Formation of cyano and dearomatized C-C coupled products initiated by deprotonation of a trimethylphosphane ligand.](image-url)
As in the reaction of the sulfide complex just described, the product of C-C coupling was found to be too unstable for isolation, but could be characterized by NMR at low temperature. Stable 2,6-Pr-BIAN analogs were isolated and characterized, including by X-ray diffraction, for P(CH₃)₃, P(CH₃)₂Ph and P(CH₃)Ph₂ complexes (see Figure 5 for the P(CH₃)₃ derivative). The deprotonation has been found to take place exclusively at the methyl -not at the phenyl-substituents. The amido groups in the C-C coupling products were found to be planar at nitrogen, pointing to amido lone pair delocalization. At first sight such delocalization could be expected to occur onto the aryl amido substituents. However, coplanarity would be the optimal orientation of the aryl group with respect to the amido ligand in order to maximize the overlap between π orbitals and allow the electronic delocalization onto the aryl group, and actually the amido group was found to be very far from coplanar with the aryl substituent (the dihedral angle between amido and aryl planes has been found to be 79° for the trimethylphosphane derivative). Presumably this large deviation from coplanarity is due to the steric hindrance imposed by the bulky isopropyl groups, as it is typical of BIAN complexes. Therefore, the planarity at the amido nitrogen in the sulfide and phosphane derivatives results at least in part from π-donation from the amido group to the strongly π-acceptors CO ligands via the metal π orbitals.⁹⁵

![Figure 5](image.png)

**Figure 5.** Molecular structure of the BIAN C-C coupled product obtained by deprotonation of a trimethylphosphane ligand.
5.4. Coupling between two monodentate heterocyclic ligands.

Most small molecules, and certainly most metal-complexing ligands, are constituted by a few building blocks; therefore, a modular synthesis employing cross-coupling reactions between appropriate precursors could serve as a general synthetic approach. However, those appropriate precursors must be reactive enough, so conventional cross coupling procedures require first the preparation of functionalized versions of the individual building blocks. For instance, in Pd-catalyzed C-C coupling schemes, one of the partners must be an electron rich compound, such as a main group organometallic, organoborane, etc., while the other must be an electrophile possessing a good leaving group, such as a triflate or iodide (Scheme 14).

\[
\text{HetAr}^1 - M + X - \text{HetAr}^2 \rightarrow \text{HetAr}^1 - \text{HetAr}^2
\]

Scheme 14. General scheme of most late-metal catalyzed C-C coupling reactions.

That adds further complication to the whole synthesis and generates unwanted byproducts. Some subunits, notably the 2-pyridyl group, are particularly problematic. Pyridyl groups are prevalent motifs in several types on natural and unnatural products, and in particular in polydentate ligands. Several families of coordination compounds, and in particular rhenium tricarbonyl complexes, which have been the focus of most of our work, are potentially useful due to their catalytic, luminescent or anticancer properties. The several examples of inter-ligand C-C coupling within the metal coordination sphere discussed above suggested to us the possibility of employing similar schemes to assemble monodentate ligands, including pyridines, without the need of any previous functionalization other than metal coordination. The synthesis of polydentate ligands, especially non-symmetric ones, is often a challenging task. In currently employed methodologies, the free ligand is first synthesized and purified employing conventional organic synthesis procedures, which are frequently tedious, multistep methodologies affording a low overall yield and require separation of byproducts. Then, the ligand is reacted with an appropriate metal source to afford the targeted metal complex. We envisaged an alternative scheme in which small, non-functionalized building blocks, like pyridines, imidazoles, etc., are first coordinated to a metal center by simple substitution reactions. Preassembly of those
subunits would be taken care of by the geometric preferences of the metal fragment. For instance, the strong preference for a fac disposition of the three CO ligands in octahedral metal complexes ensures that any two of the remaining coordination sites are mutually cis and thus optimally placed for a C-C coupling. Additional advantages of the metal coordination are an enhanced acidity of the CH groups to be deprotonated and an enhanced reactivity of the electrophilic counterpart, both leading to more reactive systems and thus to milder conditions, which in turn would provide more selective reactions.

Rhenium tricarbonyl complexes containing two N-alkylimidazole ligands and one pyridine were synthesized by the reaction of [Re(CO)₃(N-RIm)₂(OTf)] (which in turn is easily prepared from the reaction of [Re(CO)₅(OTf)] and N-alkylimidazoles) with either pyridine or 4-picoline and the equimolar amount of NaBAR'₄. The new precursors [Re(CO)₃(N-RIm)₂(py)]BAR'₄ (R= Me, Mes) are readily prepared in a half-gram scale, are relatively stable and can be kept for several weeks in Schlenk flasks under a nitrogen atmosphere. A key for the success of the reactions discussed below is that in solution, [Re(CO)₃(N-RIm)₂(py)]⁺ complexes -and, in general, rhenium(I) tricarbonyl octahedral complexes- do not undergo ligand scrambling. Their reactions with KN(SiMe₃)₂ in THF at -78°C immediately afford solutions with νCO bands at lower wavenumber values, consistent with deprotonation. The addition of silver triflate afforded cationic products (Scheme 15).

![Scheme 15. Imidazole-pyridine cross-coupling at a rhenium center.](image)

The solid state structures of two of these products were crystallographically determined, confirming the presence of a fac-Re(CO)₃ fragment bonded to an intact N-alkylimidazole ligand.
and to a bidentate ligand formed by the coupling between the C2 positions of an N-alkylimidazole ligand and the C2 carbon of pyridine (Figure 6). This is consistent with the deprotonation of the C2-H group of the N-alkylimidazole, followed by the intramolecular nucleophilic attack of the deprotonated group on the C2 carbon (the most electrophilic position) of the monodentate pyridine. The resulting bidentate ligand initially formed as the product of the C-C coupling would feature a dearomatized pyridyl ring, like those formed in the nucleophilic attacks to the pyridine rings of the bidentate bipy or phen ligands discussed above. Subsequently, that ring would be rearomatized by reaction with the one electron oxidant silver triflate. Such rearomatizations could not be carried out with the products of coupling between a deprotonated N-alkylimidazole and a bidentate bipy or phen ligand discussed above, the likely reason being that the rigid fac-tridentate ligand formed as the product of the C-C coupling cannot become planar, as it would be required for rearomatization.

Figure 6. Molecular structure of a pyridylimidazole complex obtained by C-C coupling of imidazole and pyridine ligands.

The fact that two equivalents of silver triflate are needed suggest the participation of two one-electron oxidation events, in agreement with formal hydride removal. In the absence of mechanistic studies, it is proposed that the neutral, dearomatized product of C-C coupling is oxidized by one equivalent of silver triflate to afford a radical cation, a species that would be deprotonated to afford a neutral radical; this would then be oxidized by the second equivalent of
AgOTf yielding the observed cationic complex. Since only one equivalent of KN(SiMe$_3)_2$ was employed, the putative radical cation would be deprotonated by hexamethyldisilazane, HN(SiMe$_3)_2$, which would have been formed as the product of the initial deprotonation by KN(SiMe$_3)_2$.

The course of the reaction has been found to be the same for the N-methylimidazole and N-mesitylimidazole ligands. No other organometallic compounds could be detected as reaction products. Note that free pyridylimidazoles, which are often employed as ligands, are usually prepared by de novo construction of the pyrazole ring. Compounds containing [Re(CO)$_3$(N-RIm)(dmap)$_2$]BAR$_4$ (R= Me, Mes, dmap= 4-dimethylaminopyridine) cationic complexes were subjected to the same deprotonation/oxidation sequence, affording single products from coupling between the C2 positions of the N-alkylimidazole and the pyridine (Figure 7). These reactions selectively afford the products of cross-coupling between one imidazole and one pyridine, without homocoupling (complexes containing biimidazole or bipyridine ligands) products, regardless of the particular composition of the cationic precursors: two imidazoles and one pyridine, or two pyridines and one imidazole. This is attributed to the higher acidity of the C2-H group of the N-alkylimidazole ligand and the higher electrophilic character of the pyridine ligand. Note that even the relatively electron-rich dmap ligand is electrophilic enough to undergo the C-C coupling reaction.

Figure 7. Solid-state structure of the complex obtained by the cross coupling of dmap and N-MesIm starting from [Re(CO)$_3$(N-MesIm)(dmap)$_2$]BAR$_4$.  

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The presence of an intact N-alkylimidazole ligand in the cationic complexes formed in the reactions of pyridine-imidazole coupling and rearomatization suggested to us the possibility of its deprotonation. The internal nucleophile presumably resulting from deprotonation of the C2 position of the monodentate N-RIm ligand could attack either the pyridine or the imidazole ring of the non-symmetric bidentate ligand. Thus, the reaction of tricarbonyl rhenium (imidazole)(pyridylimidazole) compounds with KN(SiMe₃)₂ afforded neutral (IR) products too unstable for isolation and even for NMR characterization. These species were in situ protonated with HOTf, affording stable products, which could be fully characterized (Scheme 16).

![Scheme 16](image)

**Scheme 16.** C-C coupling between a monodentate N-RIm ligand and the pyridine ring of a pyridylimidazole chelate.

The determination of its solid-state structure by X-ray diffraction established the protonation at the nitrogen of the dearomatized ring, and the presence of a fac-capping tridentate ligand resulting from the coupling between the C2 position of the N-RIm ligand and the ortho position of the pyridyl ring of the bidentate ligand. The metrical data of the pyridyl ring indicate its dearomatization, in agreement with the NMR solution data. When an analogous reaction was conducted starting with the precursor containing an N-MesIm monodentate ligand, the product of its deprotonation was not stable enough for isolation, but could be characterized in solution, and its spectroscopic data suggested deprotonation of the monodentate N-RIm ligand and attack to the 2-pyridyl ring, leading to its dearomatization. The reaction of this neutral species with triflic acid afforded a stable product (which was also crystallized and fully characterized) resulting from protonation at nitrogen similar to the one previously discussed. These results indicate that the
intramolecular attack by the deprotonated N-alkylimidazole takes place selectively on the pyridine ring, as no product of attack to the imidazole ring could be detected. Note that the full sequence of reactions leading to these products with a tridentate ligand from the starting complexes containing three monodentate N-heteroaromatic ligands (two N-alkylimidazoles and one pyridine) involve two consecutive C-C coupling events between the C2 carbons of the two N-alkylimidazoles and the two ortho positions of the pyridine ring.

The C-C coupling methodology outlined above was extended (in spite of the lower acidity of pyridines compared with N-alkylimidazoles) to the coupling between two pyridine ligands to afford complexes containing a 2,2'-bipyridine ligand. Thus, when \([\text{Re(CO)}_3(\text{dmap})_3]\text{OTf}\) (which was readily prepared from \([\text{Re(OTf)(CO)}_5]\) and dmap) was treated with \(\text{KN(SiMe}_3)_2\) and then with \(\text{AgOTf}\), the single organometallic product was found to be \([\text{Re(CO)}_3(2,2'-\text{bipy}-4,4'\text{-NMe}_2)(\text{dmap})]\text{OTf}\), which was fully characterized, including X-ray diffraction. Compounds \([\text{Re(CO)}_3(\text{py-R})_3]\text{OTf}\) (py-R= pyridine or 4-methoxypyridine), prepared by the reaction of the appropriate pyridine with the labile \([\text{Re(CO)}_3(\text{DMSO})_3]\text{OTf}\) compound, afforded \([\text{Re(CO)}_3(\text{bipy-R})(\text{OTf})]\) products resulting from the coupling of two of the coordinated pyridines to afford a bipy ligand when treated first with \(\text{KN(SiMe}_3)_2\) and then with \(\text{HOTf}\) (which has been found to be a cleaner oxidant in this case than \(\text{AgOTf}\)). The product containing the parent 2,2'-bipyridine ligand, a known complex, was identified by comparison (IR and NMR) with a authentic sample, and the product of C-C coupling between two 4-methoxypyridine ligands was fully characterized, including X-ray diffraction.

These results demonstrated that deprotonation of a pyridine ligand coordinated in the by far most commonly encountered \(\kappa^1(N)\) mode is feasible. This methodology for inter-pyridine coupling could be successfully extended to two different pyridine ligands, affording complexes with non-symmetric bipy ligands. Thus \([\text{Re(CO)}_3(\text{dmap})_2(\text{py})]\text{BAR}'_4\) and \([\text{Re(CO)}_3(\text{dmap})_2(\text{py-4-OMe})]\text{BAR}'_4\) were prepared from addition of either pyridine or 4-methoxypyridine to \([\text{Re(CO)}_3(\text{dmap})_2(\text{OTf})]\) in the presence of the equimolar amount of \(\text{NaBAR}'_4\). The deprotonation of these mixed pyridine compounds with \(\text{KN(SiMe}_3)_2\) followed by oxidation with \(\text{AgOTf}\) afforded \([\text{Re(CO)}_3(\text{dmap})(N-N')\text{BAR}'_4\) compound featuring non-symmetric 2,2'-bipyridines resulting from
cross-coupling between different pyridine ligands (Scheme 17). As in the formation of compounds with pyridylimidazole complexes (see above), no formation of symmetric, homocoupled (from coupling of two equal pyridines) could be spectroscopically detected.

**Scheme 17.** Synthesis of a non-symmetric bipy ligand by C-C coupling followed by oxidation.

The formation of bipyridines by C-C coupling between two pyridyl groups on the coordination sphere of group III complexes has been reported by Diaconescu et al. A difference with our system is that whereas Diaonescu starts with the metallation of one pyridine to afford a $\kappa^2(C,N)$ pyridyl ligand (see Scheme 18), we coordinated two neutral pyridine ligands in the $\kappa^1(N)$ normal coordination mode and then reacted the resulting stable cationic complex with an external base.

**Scheme 18.** Coupling between two pyridine ligands on a scandium complex by Diaconescu et al.

**5.5. Ring-opening of imidazole rings.**

The study of the deprotonation of coordinated N-alkylimidazoles was extended to cationic fac-Re(CO)$_3$ complexes containing three such ligands. This reaction produces neutral
imidazolyl complexes as it will be discussed in Section 6.2 for [Re(CO)$_3$(N-Melm)$_3$]OTf. In contrast, if at least one of the imidazole ligands is an N-arylimidazole, neutral complexes resulting from intramolecular attack of the deprotonated N-RIm ligand to the C2 carbon of one of the other N-RIm ligands, which as a consequence undergoes ring opening, are produced (see Scheme 19). In the products, the 1,3-diaza fragment resulting from imidazole ring opening display a cisoid geometry as a result of an intramolecular hydrogen bond, shown in dashed line in Scheme 19. Protonation or methylation of these products occurs at the non coordinated nitrogen of the ring opened moiety, affording transoid products.

Scheme 19. Imidazole C-C coupling and ring-opening at Re(I) complexes.

Carver and Diaconescu have reported the ring opening of N-methylimidazole upon reaction of scandium or yttrium benzyl complexes with three equivalents of Melm for 5 hours at 70° C (Scheme 20). The authors propose that the reaction occurs via C-H activation of one of the imidazoles (to afford an imidazole-imidazolyl intermediate which could be characterized for an yttrium analogue).
Scheme 20. Proposed mechanism for scandium-mediated imidazole coupling and ring-opening by Diaconescu et al.

Electrophilic addition at the imine-type nitrogen to generate an imidazolium cation, followed by the attack of a nucleophile (usually hydroxide anion) at C2 has been proposed as the mechanism for a number of imidazole cleavage processes, from the venerable Bamberger reaction\textsuperscript{109} to the recent tandem ring opening of imidazoles with electron-deficient acetylenes and water.\textsuperscript{110} Of these reactions, particularly mild conditions (45-60° C) have been reported for the later. N-alkylimidazoles metalated (e.g., lithiated) at C2 have been found to display considerable stability towards ring opening in comparison with other metalated N-heterocycles, allowing their employment in reactions with organic electrophiles.\textsuperscript{93} Is somewhat surprising that, although N-
alkylimidazoles have been widely employed as ligands, deprotonation of metal-coordinated N-alkylimidazoles and the reaction of metalated N-alkylimidazoles with transition metal complexes remain very little explored.\textsuperscript{111}

5.6. **Couplings between N-alkylimidazoles and imine ligands.**

In contrast with the reactivity displayed by the rhenium complexes discussed above, the deprotonation of \([\text{Mo}(\eta^3\text{-methallyl})(\text{CO})_2(\text{bipy})(\text{N-RIm})]^+\) complexes yielded the neutral imidazolyl complexes, discussed on Section 6.2, and no product of C-C coupling could be detected. DFT calculations, however, indicated that the energy differences between the pathway leading to the observed imidazolyl product and that leading to attack on bipy is only 3.5 kcal/mol.\textsuperscript{112} That led us to synthesize several compounds of the type \([\text{Mo}(\eta^3\text{-methallyl})(\text{CO})_2(\text{pyridylimino})(\text{MeIm})]\text{OTf}\) and study their deprotonation with \(\text{KN(SiMe}_3\text{)}_2\), expecting that the nonaromatic imine function would be more reactive than bipy and hence could be the target of the deprotonated imidazole.\textsuperscript{113} Indeed, attack by the deprotonated imidazole C2 carbon to the nonaromatic imine carbon, as shown in Scheme 21 has been found to be the sole product.

\begin{center}
\includegraphics[width=\textwidth]{scheme21.png}
\end{center}

\textbf{Scheme 21.} Imidazole-imine C-C coupling and protonation of the resulting amido group to afford cationic amino complexes.

DFT calculations showed that the products of C-C coupling were the favored ones both kinetically (they were formed in a process without computable barrier) and thermodynamically.
Some of the neutral C-C products were found to be stable enough to permit isolations; for those too unstable, protonation at the nitrogen originating from the nonaromatic imine with HOTf yielded stable cationic complexes that were isolated as triflate salts and could be fully characterized. Since allylmolbdenum dicarbonyl complexes are not as substitutionally inert as the Re(I) complexes discussed above, possible intermolecular pathways involving the transfer of the monodentate imidazole (or deprotonated imidazole) ligands between metal centers were considered as a possibility (note that imidazolate bridges have been found by Braunstein, Danopoulos and co-workers).\textsuperscript{111} They, however, were ruled out by a crossover experiment in which a mixture of two compounds having different pyridylimine and N-alkylimidazole ligands was treated with KN(SiMe\textsubscript{3})\textsubscript{2} afforded only the products of intramolecular C-C coupling (Scheme 22).

\begin{equation}
\text{Scheme 22. Crossover experiment showing the intramolecular nature of the N-RIm-imine coupling reactions.}
\end{equation}

5.7. Coupling between N-alkylimidazoles and nitriles or isonitriles.

Nucleophilic attacks on the sp-hybridized carbon atom of nitrile and isonitrile ligands are well known, so in principle the coupling between these unsaturated ligands and C2-deprotonated N-alkylimidazole co-ligands could offer a potential pathway to access new anisobidentate chelates
within the coordination sphere of a metal.\textsuperscript{114} Two possible difficulties were considered, one for each type of monodentate unsaturated ligand: nitriles are labile; therefore, attack to the metal by either the base or the deprotonated N-RIm ligand could compete with attack at the coordinated nitrile; as for isonitriles, the planned attack at the metal-bonded carbon atom would afford a four member ring, perhaps of limited stability; note that such a product would be comparable (carbonyl and isonitrile ligands are isoelectronic) to the computationally encountered (but not stable enough for spectroscopic detection) intermediate in the reaction leading to imidazolyl complexes, which is formed via C-C coupling between a CO and the C2-deprotonated N-RIm ligand.

Nitrile and isonitrile compounds were prepared by the reaction of complexes \([\text{Re(CO)}_3(\text{N-RIm})_2(\text{OTf})]\) with pivalonitrile or tert-butylisocyanide and the salt NaBAR'\textsubscript{4} in dichloromethane.\textsuperscript{115} Employing the later as a triflate abstractor is based on the low solubility of sodium triflate in dichloromethane, and is needed to achieve the displacement of triflate from the cationic complex by the poor donor nitrile, or by the low-nucleophilic isonitrile.

The \([\text{Re(CO)}_3(\text{N-RIm})_2(\text{tBuCN})]\)BAR'\textsubscript{4} and \([\text{Re(CO)}_3(\text{N-RIm})_2(\text{BuNC})]\)BAR'\textsubscript{4} compounds, which could be isolated and characterized, instantaneously reacted with KN(SiMe\textsubscript{3})\textsubscript{2} in THF at low temperature to afford, as indicated by the change in the color and the IR spectrum of the solution. For the nitrile complexes, the limited stability of the neutral (as judged by their \(\nu_{\text{CO}}\) IR bands) products precluded their isolation and even \textit{in situ} NMR characterization. Reaction of these neutral species with MeOTf or H\textsubscript{OTf} afforded cationic complexes, which were isolated and fully characterized (see Scheme 23). Their NMR data are in agreement with the initial deprotonation of the N-alkylimidazole ligand at its C2-H position and subsequent attack of the “internal nucleophile” to the \(\alpha\) carbon of the nitrile. The result of the C-C coupling reaction would be the formation a five-member chelate ring featuring an alkylideneamido (N-metaloimine,\textsuperscript{82} ketimide\textsuperscript{116}) donor group. A rhenium tricarbonyl complex has been found to be one of the very few highly reactive -yet isolable- alkylideneamido complexes,\textsuperscript{82} in contrast with the chemical inertness displayed by these ligands when coordinated to most other fragments.\textsuperscript{116} A similar high reactivity may be the origin of the instability of the products of the deprotonation of \([\text{Re(CO)}_3(\text{N-}
R(Im)₂[(BuCN)]BAr₄ (Scheme 23). Methylation of the alkylideneamido nitrogen would produce stable, cationic imino complexes. Treatment of the solutions containing the neutral unstable intermediate with triflic acid afforded similar products, resulting from protonation at nitrogen. The structure of one these protonated derivatives, solved by X-ray diffraction (see Figure 8), helped to establish the reactivity pattern sketched above.

Scheme 23. Rhenium-mediated couplings between imidazole and nitrile (top) or isonitrile (bottom) ligands.
The products of the deprotonation of the isonitrile complexes were found to be stable both in solution and in the solid state and could be completely characterized, including the X-ray structural determination of one of the derivatives (Figure 9). They result from the coupling between C2(imidazole) and the isonitrile carbon, resulting in the formation of four member chelates, consisting of an imidazole and a κ¹(N)-iminoacyl donor groups (Scheme 23). Note that complexes with κ¹(N)-iminoacyl ligands are relatively rare, as most iminoacyls are κ²(N,C)-coordinated to early transition metals. Reaction of these complexes occurred at the iminoacyl nitrogen, resulting in the formation of cationic aminocarbenes (see Scheme 23). It is interesting to note that the conceptually simple synthesis of non-heterocyclic carbenes by successive additions of a nucleophile and an electrophile to isonitriles remains little explored. The discussed results show that the intramolecular C-C coupling initiated by C2-deprotonation of N-alkylimidazole ligands can lead to the formation of four member rings and to the attack on usually labile nitriles. In addition, the reactions are selective, affording the described products, and not the foreseeable products of attack on CO ligands or N-alkylimidazole co-ligands.
Figure 9. Molecular structure of the C-C coupling product resulting of the deprotonation of the isocyanide compound [Re(CO)$_3$(N-MesIm)$_2$(tBuNC)]BAr$^+$.

5.8. Deprotonation of N-alkylimidazole ligands in phosphane-carbonyl complexes

In view of the previously discussed results, which show that even notoriously inert co-ligands such as bipy and phen can be the target of deprotonated N-alkylimidazole ligands, we set out to explore the deprotonation of N-alkylimidazole ligands in carbonyl complexes containing only phosphane co-ligands. Since the later cannot be the site of nucleophilic attack, we anticipated the possibility of obtaining products of attack on the CO ligands. As mentioned above, such an attack has been computationally found to yield intermediates in the formation of imidazolyl complexes, but stable products of the intramolecular attack of deprotonated N-RIm ligands on carbonyl co-ligands were not observed previously.

The deprotonation of a coordinated N-methylimidazole ligand in cationic Re(I) tricarbonyl phosphane complexes [Re(CO)$_3$(MeIm)$_2$(PR$_3$)]BAr$^+$ employing the amide KN(SiMe$_3$)$_2$ showed a dramatic dependence on the nature of the phosphane. Thus, whereas for trimethylphosphane complexes, imidazolyl products were obtained, when the phosphane is either triphenylphosphane or methylidiphenylphosphane, the deprotonation followed by methylation with excess MeOTf reaction afforded the mixture of products shown in Scheme 24.
Scheme 24. Reactivity of [Re(CO)₃(Melm)₂(PR₃)]BAr'₄ with the strong base KN(SiMe₃)₂.

Compound 15, which is the major product of the reaction, contains a binuclear cationic complex resulting from a double activation of a N-methylimidazole ligand. Its structure (Figure 10 shows the X-ray structure of the cation of the triphenylphosphane derivative) suggests that the C₂ carbon of the deprotonated imidazole attacks one of the cis CO ligands, forming a four-member metallacycle. Methylation of the oxygen of the involved carbonyl generates a methoxycarbene moiety. The same imidazolate ring binds the second rhenium fragment as an abnormal nitrogen-heterocyclic carbene through its C₅ position, indicating a double imidazole deprotonation. This second rhenium center completes its coordination sphere with one phosphane, two carbonyls and an N, N'-bidentate ligand that results from the formal coupling of a molecule of CO (from the carbonyl ligand missing at this rhenium center), one imidazole and one imidazolyl ligand. The oxygen atom of the CO molecule involved in this coupling has been methylated, so the carbon atom originating from CO is now sp³-hybridized. The minor product (16 in Scheme 24) contains a cationic complex with two cis carbonyls, two trans phosphanes and a chelate bis(C-imidazolyl)ketone ligand similar to the one just described for the binuclear complex, but without methylation at oxygen.
When compound 14 was deprotonated using n-butyllithium instead of KN(SiMe\textsubscript{3})\textsubscript{2}, the product was a neutral imidazolyl complex which turned out to be too unstable for isolation. Its reaction with triflic acid afforded a stable, cationic complex featuring an NH-NHC ligand (Scheme 25), which could be crystallized as its triflate salt and characterized in the solid state by single-crystal X-ray diffraction, and in solution by IR and NMR. This difference in reaction outcome as a function of the base employed suggests a relative stabilization of the deprotonated N-methylimidazole as a result of the interaction of its C2 carbon atom with lithium, a smaller, more polarizing cation than potassium.

**Scheme 25.** Transformation of a N-MeIm ligand in a NH-NHC by a deprotonation/protonation sequence.
The formation of the products 15 and 16 obviously involved complex, multistep reactions, and proposing a meaningful mechanistic sequence would require additional work. Nevertheless, the outlined results demonstrate several points, including the deprotonation of N-alkylimidazole at C5 and subsequent formation of “abnormal” nitrogen-heterocyclic carbenes, the formation of alkoxycarbenes via intramolecular attack of a C2-deprotonated N-alkylimidazole ligand to a CO co-ligand, the CO activation by the attack of two C2-deprotonated N-alkylimidazole ligands, and the dramatic effect of the employed strong base on the nature of the products.

6. Metal-mediated tautomerization of N-heterocycles to NHC complexes.

As we have mentioned above, the coordination of organic molecules to transition metals can be used as a pathway to activate them. In certain instances, a dramatic modification of its nature is found to be the consequence of such coordination. A well established example of this concept is the metal-induced acetylene to vinylidene tautomerization (Figure 11). This process has been studied, both theoretically and experimentally, and an activation barrier of 76 kcal·mol⁻¹ has been found, the vinylidene species being 44 kcal·mol⁻¹ less stable than the acetylene isomer. In the presence of a number of metal fragments the process becomes thermodynamically favored and kinetically available, affording the corresponding vinylidene metal complexes, the relative energy of the two tautomers being inverted.

![Figure 11](image-url)
6.1. Tautomerization of pyridines.

The possible isomerization of pyridine to its 2-carbene tautomer was first proposed by Hammick as early as in 1937, but it took over 60 years to prove its existence. This type of tautomerization is frequently the key step in important biological processes, where the energetically less stable tautomer is often responsible for the biological activity. The extremely unstable pyridyl-2-yldene was generated in the gas phase by Schwarz et al, and characterized by means of mass spectroscopy. Pyridin-2-yldines are more than 40 kcal·mol⁻¹ less stable than pyridines, but coordination to transition metal fragments can strongly stabilize them. In 1987 Taube published the first pyridine carbene complex synthesized in solution, a 2,6-lutidinium ylide coordinated to Os(II) through the para carbon (Figure 12). In the last 10 years the number of pyridylene complexes has increased considerably, probably due to the use of different strategies to provide an additional stability to the carbenic species.

![Figure 12. First metal-pyridylene complex synthesized by Taube et al.](image)

In 2006 Carmona, Poveda et al. achieved the tautomerization of 2-substituted pyridines into the carbene tautomers mediated by the \([\text{Tp}^\text{Me}^2\text{Ir}](\text{C}_6\text{H}_5)_2\text{N}_2)(\text{Tp}^\text{Me}^2= \text{hydrotris}(3,5\text{-dimethylpyrazolyl})\text{borate})\) fragment (Scheme 26). The steric hindrance provided by the substituents at the 2-position precluded the formation of the \((\kappa^1,\text{N})\)-coordinated pyridine complexes while the formation of the N-heterocyclic carbenes was not affected by this issue, as the substituent in the 2-position is away from the coordinated carbon atom.

![Scheme 26. Formation of Ir(III) pyridylene complexes from 2-substituted pyridines.](image)
Concurrently, in the research group of Esteruelas stable carbene tautomers of quinoline and 8-methylquinoline were synthesized by coordination to osmium- and ruthenium-chloro complexes.\textsuperscript{125} It is interesting to note that an increased stability of the resulting NHC complexes is provided by an intramolecular NH···Cl interaction between the NH group and a chloride ligand coordinated to the same metal atom (see Figure 13a). The bulkiness of the substituent and the co-ligands, along with an intramolecular hydrogen bond are also crucial in the formation of a carbene tautomer of 2-ethylpyridine bonded to a hydride osmium(II) complex (Figure 13b).\textsuperscript{126}

\begin{center}
\textbf{Figure 13.} Stabilization of N-heterocyclic carbene complexes by intramolecular hydrogen bonds.
\end{center}

There is just one example of a non-substituted pyridylidene complex obtained as a 1:1 mixture together with the N-adduct (Scheme 27).\textsuperscript{127} This outstanding transformation was mediated by an iridium complex featuring two Ir-CH\textsubscript{2} bonds that resulted from the metallation of two methyl groups of mesityl substituents of the trispyrazolylborate ligand (Tp\textsuperscript{Me}= hydrotris(5-mesitylpyrazolyl)borate). The presence of an Ir-CH\textsubscript{2} bond within a chelate is essential for the tautomerization process.
Scheme 27. Tautomerization of non-substituted pyridine achieved by Carmona et al.

In contrast, there are some examples in which parent pyridylidenes have been implicated in the functionalization of pyridines.\textsuperscript{128-132} In this context Bergman, Ellman and coworkers found that the formation of the Rh-NHC complex 18 via C-H bond activation of the heterocycle 17 (see Scheme 28) was the key step in the Rh-catalyzed coupling of N-heterocycles and olefins.\textsuperscript{129} The 1,2-hydrogen shift involved in this process was studied in detail, using experimental and computational methods, and an intramolecular hydrogen transfer pathway through Rh-H intermediates was found to be the more plausible mechanism.

Scheme 28. C-H activation of N-heterocycle 17 by a Rh(I) complex.

Tautomerization of 2-substituted pyridines to NH-N-heterocyclic carbenes induced by Tp\textsuperscript{Me2}Ir(III) fragments (mentioned above) has been extended to the broadly used 2,2'-bipyridine and 1,10-phenanthroline ligands.\textsuperscript{133} A new and unexpected coordination mode was found as monohapto N-heterocyclic carbenes, in which an intramolecular hydrogen bonding between the NH unit of the coordinated ring and the imine-type N atom of the other ring adds stability to these species (Figure 14, complexes 19 and 20). A similar thermal activation was published for terpyridine which is able to act as a mono- or bidentante NHC towards one or two metal atoms.\textsuperscript{134} A couple of examples have been published where chelation is the driving force to successfully achieve the tautomerization of a pyridine moiety.\textsuperscript{135,136} An example of this strategy is shown in
Figure 14 (complex 21) in which an Ir(I) fragment allows the formation of a stable metalacycle upon $\alpha$-CH activation of 1,9-phenanthroline.

Figure 14. Pyridylene tautomers of 2,2'-bipyridine (complexes 19 and 20). Tautomerization of 1,9-phenanthroline aided by the chelation effect (structure 21).

6.2. Tautomerization of imidazoles.

In spite of the higher stability of imidazole-2-ylidenes and their metal complexes, tautomerization of imidazoles to the corresponding NHCs are also scarce processes. The relative stability of imidazole N- or C-metal bound isomers was computationally studied by Crabtree and Einsentein, who found a strong dependence on the nature of the metal fragment. Sundberg et al. published in 1974 the first example of N- to C- tautomerization of an imidazole ligand mediated by a Ru(II) complex (Scheme 29), but an acidic media was needed and very low yields were obtained.

Scheme 29. First example of a metal-mediated imidazole to NH-NHC tautomerization.

The only other example of tautomerization of a non-chelated imidazole ligand to its NHC form was proposed by Bergman and Ellman in their studies of Rh(I) catalyzed C-C coupling between alkenes and benzimidazole. The NHC is formed in situ via C-H activation of the heterocycle.
(Scheme 30) being one of the first examples in which a NHC plays a non ancillary role in a catalytic transformation.

\[
\begin{align*}
\text{Scheme 30. Isomerization of a benzimidazole derivative to its NHC isomer promoted by Rh(I).}
\end{align*}
\]

The additional stability gained because of the formation of a bidentate chelate ligand has been used to achieve imidazole to NHC tautomerization for a N-phosphane-functionalised imidazole in the presence of iridium\(^{140}\) and ruthenium\(^{141}\) metal fragments (structure 22 in Figure 15). An analogous activation occurred when 2-pyridylbenzimidazole is refluxed in THF with [RuCp*Cl]\(_4\) to afford the 5-membered chelate complex 23 depicted in Figure 15\(^{142}\) or in the reaction of an N-arylimine-functionalized imidazole with [Ir(cod)(µ-Cl)]\(_2\) aided by a halogen abstractor to afford complex 24 (Figure 15).\(^{143}\) The reverse tautomerization, i. e. from NH-NHC to imidazole ligands mediated by these two metals (Ir and Ru) have also been reported by Whittlesey\(^{144}\) and Li\(^{145}\).

\[
\begin{align*}
\text{Figure 15. Examples of tautomerization of N-alkylimidazol derivatives to NH-NHCs assisted by chelation.}
\end{align*}
\]

The groups of Siebert\(^{146}\) and Erker\(^{147}\) studied the reactivity towards a strong base of imidazole-borane adducts, showing that for the BH\(_3\) moiety the anionic 3-boraneimidazol-2-ylidene could be isolated (structure 25 in Scheme 31), whereas migration of BR\(_3\) (R=Et, C\(_6\)F\(_5\)) groups to the
carbene carbon atom was observed for trialkyl- or triarylborane reagents (complex 26 in Scheme 31).

Scheme 31. Reactivity of imidazole-borane adducts studied by Siebert and Erker.

As we have mentioned above, in the last years our research interest has been focused on the deprotonation of N-alkylimidazole ligands coordinated to organometallic fragments. A cationic metal complex bearing a N-RIm ligand can be regarded as a N-metallated imidazolium salt (Figure 16), and therefore the deprotonation of the central imidazole CH group would afford a NHC in an analogous manner to the most general method used to prepare imidazol-2-ylidenes from imidazolium salts. Our results show that the species resulting from such deprotonation reaction are very reactive, mainly because of their high nucleophilic behavior, and their evolution strongly depends on the nature of the metal fragment and its coligands, as well as on the substituent of the imidazole.

Figure 16. Analogy between an imidazolium salt (A) and a cationic imidazole metal complex (B).

The reaction of [Re(CO)₃(N-Melm)₂]OTf (27) with the equimolar amount of KN(SiMe₃) afforded a neutral imidazol-2-yl product, 28 (Scheme 32). The formation of 28 implies, once the deprotonation has occurred, the isomerization of the heterocyclic ligand from the N- to the C-rhenium bonded species. Examples of this type of complexes, which feature a C-bonded
imidazol-2-yl ligand with a non-substituted nitrogen, are very rare.\textsuperscript{116,140-142,146-148} In addition, these species tend to be elusive and have been previously proposed for the tautomerization of N-alkylimidazole to NHC ligands.\textsuperscript{91} Compound 28 reacts smoothly with electrophiles, such as HOTf, to afford the product of protonation on the non-coordinated nitrogen, compound 29 (Scheme 32). The overall transformation from compound 27 to 29 can be seen as a tautomerization of an imidazole to a NH-NHC ligand promoted by a strong base, complex 28 being a stable intermediate. This reaction sequence is reminiscent of the mechanism proposed by Ruiz for the transformation of an imidazole into an NHC ligand at a Mn(I) center,\textsuperscript{91} although in that case the authors could not isolate the neutral complex (analog to 28), probably due to its lower stability.

\textbf{Scheme 32.} Tautomerization of a N-methylimidazole ligand promoted by a deprotonation/protonation sequence.

In compound 28 the heterocyclic ligand is an imidazol-2-yl, but its structural and spectroscopic properties are very close to those of the rhenium N-heterocyclic carbene compound 29 (see Figure 17). Thus the Re-C1 distances are undistinguishable (2.190(7) Å in 28, and 2.191(5) Å in 29) and the \(^{13}\)C NMR chemical shifts for the Re-bonded carbon are 182.4 (28) and 178.7 ppm (29). The rest of the metrical data for the N-heterocyclic ligand show a high electronic delocalization for both complexes. Also noteworthy is the similarly high trans influence, reflecting the high donor ability of both C-bonded N-heterocyclic ligands as judged from the Re-C11 bond distances (1.958(7) Å for 28 and 1.945(6) Å for 29), compared with the other Re-C\textsubscript{carbonyl} bond distances (1.901(5) Å for 28, and 1.916(6) Å for 29). The presence of a hydrogen atom on N2 in 28 is the only difference between the metallic complexes present in 28 and 29, and it was
confirmed by a topological analysis of the Laplacian of the electron density ($\nabla^2 \rho$). This study indicated the presence of an in-plane lone pair at N2 in complex 28 and of an N-H bond in 29, as well as the electron delocalization mentioned above.

![Figure 17. NMR and structural similarities between imidazole-2-yl and NH-NHC ligands coordinated to \{Re(CO)$_3$(N-Melm)$_2$\} fragment.](image)

In contrast, complexes [Re(CO)$_3$(N-Melm)$_x$(N-Meslm)$_{3-x}$]$^+$ ($x=1,2$), with at least one N-arylimidazole ligand, led, after deprotonation reaction, to the C-C coupling and ring-opening products,$^{106}$ as it has been mentioned in Section 1.3.

On the other hand, the related neutral complex [Re(OTf)(CO)$_3$(N-Melm)$_2$] (30) reacted instantaneously with KN(SiMe$_3$)$_2$ to yield compound 31 (see Scheme 33).$^{149}$

![Scheme 33. Tautomerization of two N-Melm ligands promoted by a single equivalent of base.](image)

The new complex contained a fac-{Re(CO)$_3$} fragment bonded to one N-Melm ligand, one imidazol-2-yl-ligand and one NH-NHC ligand, the last two resulting from N- to C-coordination change of two N-Melm ligands. The N-H group of the NH-NHC ligand acts as hydrogen bond
donor towards the non-coordinated nitrogen of the imidazol-2-yl ligand, contributing to the coplanarity of the two heterocyclic ligands (as shown in Figure 18 for the analogous mesityl derivative). A molecular mirror plane is evident from the NMR spectra of 31, indicating the fast (even at low temperature) H⁺ transfer between the two nitrogens, i.e., the complex can be described as featuring two imidazol-2-yl ligands that share a proton. The Re-bonded carbon of these ligands occurs at 180.7 ppm in the ¹³C NMR spectrum, and the two Re-C bond distances are undistinguishable (Re-C2 2.214(10) and Re-C22 2.207(9) Å), showing the close similarity between imidazol-2-yl and NH-NHC ligands. The yield of 31 notably increased when its preparation was conducted in the presence of the equimolar amount of N-methylimidazole (N-Melm), as expected since, in its absence, part of the bis(imidazole) precursor 30 must have acted as a sacrificial source of N-Melm.

\[ \text{Figure 18. Molecular structure of the mesityl derivative analogous to compound 31.} \]

Density functional theory (DFT) calculations about the reaction mechanism showed that the most favorable one is that shown in Scheme 34. The Gibbs free energy in THF solution (in parentheses) is referred to that of the deprotonated species \([\text{Re(OTf)(CO)}_3(N\text{-Melm})_2]^−\) (structure I, Scheme 34) and N-Melm. The reaction starts with loss of triflate from I to give intermediate IIa in which the Re atom is simultaneously interacting with the non-coordinated N atom and the C-2 atom of the imidazolyl ligand. Intermediate IIa undergoes a rotation of the imidazole ring
around the N-Re bond through TS-IIa/IIIa to give the intermediate IIIa. TS-IIIa/IVa connects IIIa with intermediate IVa wherein the two heterocyclic ligands are C-bound to the Re atom. Finally, addition of N-Melm to IVa leads to the formation of a rhenium imidazol-2-yl(carbene) complex Va without any transition state. The formation of the rhenium imidazolyl-carbene complex would imply a Gibbs energy barrier in solution of 21.5 kcal/mol, consistent with the fast formation of the product experimentally observed. A key feature of the proposed mechanism is the intermediacy of η²-N,C-imidazolyl complexes, which make possible ligand dissociation without going through high-energy five-coordinate species. Stable η²-N,C-imidazolyl complexes have been disclosed by Diaconescu et al. in scandium and uranium chemistry.¹⁵⁰

Scheme 34. Proposed (based on DFT computations) mechanism for the formation of imidazolyl-NHC complex 32 from the neutral bis(imidazole) derivative 30.

The reaction of 31 with trifluoromethanesulfonic acid (HOTf) afforded 32, the triflate salt of the bis(NH-NHC) complex resulting from protonation at nitrogen (Scheme 33). The overall formation of 32 from 30 involves, besides the substitution of OTf by the entering imidazole, the formation of two new Re-C bonds at the expense of the two Re-N bonds. As we have discussed above, deprotonation of a coordinated N-Melm ligand in [Re(CO)₃(N-Melm)₃]OTf followed by protonation of the resulting imidazol-2-yl ligand affords a NHC complex (see Scheme 32).
formation of the bis(carbene) complex from the bis(imidazole) precursor is not just twice that process, because the addition of only one equivalent of base triggers the Re-N to Re-C rearrangement of two imidazole ligands. It is also noteworthy that in the deprotonation reactions of a) the tris(N-MesIm) compound, or b) the triflato complex 30 in the presence of free N-MesIm, the components of the reactant mixture are the same, whereas different isomers are obtained as products. The formation of the ring-opening product in the former case or the imidazolyl-carbene in the later shows again the extreme sensitivity of the reaction course to the exact nature and number of the ligands.

The wide variety of products obtained from the reactivity of the rhenium compounds prompted us to extend our studies of deprotonation of N-alkylimidazole ligands to molybdenum organometallic species. The chosen cationic compounds of formula $[\text{Mo}(\eta^3\text{-C}_4\text{H}_7)(\text{bipy})(\text{CO})_2(N-R\text{Im})]^{+}$ feature, like those of rhenium, pseudo-octahedral structures in which the imidazole and each ring of the bipy ligand are in cis positions. The addition of a strong base to $[\text{Mo}(\eta^3\text{-C}_4\text{H}_7)(\text{bipy})(\text{CO})_2(N-R\text{Im})]^+$ complexes, followed by protonation or alkylation of the resulting neutral product, leads to the formation of Mo-NHC-compounds (Scheme 35). This reactivity constitutes another example in which the addition of a strong base, followed by an acid promotes the tautomerization of an N-alkylimidazole ligand to NH-NHC.

![Scheme 35](image_url)

**Scheme 35.** Synthesis of imidazol-2-yl and NHC complexes from N-alkylimidazole ligands coordinated to $\{\text{Mo}(\eta^3\text{-C}_4\text{H}_7)(\text{bipy})(\text{CO})_2\}$ fragment.

In agreement with the experimental results, a DFT study showed that the most favorable reaction mechanism for the Mo(II) complexes consisted in an initial attack of the imidazole deprotonated
carbon atom onto a cis-CO ligand, to afford in a second step imidazol-2-yl species (Figure 19). This mechanism is reminiscent of the one found for [Mn(bipy)(CO)]_3(N-RIm)]OTf compounds, suggesting that this new and unexpected 'carbonyl mechanism' can be quite general for related transformations. As it is shown in Figure 19, pathway A, that led to the C-C coupling product, is favored over pathway B, which affords formation of the imidazole-2-yl complex, by only 3.5 kcal mol\(^{-1}\). In addition to this, the formation of Mo-IIb (-7.0 kcal mol\(^{-1}\)) implies a Gibbs energy barrier of only 4.8 kcal mol\(^{-1}\), which is clearly lower than the one required for obtaining Mo-IIa (8.3 kcal mol\(^{-1}\)). The better kinetic accessibility of Mo-IIb in conjunction with the fact that its evolution to Mo-IIIb shows a Gibbs energy barrier in solution (11.8 kcal mol\(^{-1}\)) clearly lower than that for the reversion to Mo-IIa (15.3 kcal mol\(^{-1}\)) via Mo-I, and that the Mo-IIIb product is considerably stable (13.4 kcal mol\(^{-1}\)), make B the most favorable pathway, affording the formation of imidazol-2-yl products instead of the C-C coupling species, as it is encountered experimentally.

**Figure 19.** Schematic view of the reaction mechanisms found for the deprotonation reaction of [Mo(η^3-C$_5$H$_7$)(bipy)(CO)]_2(N-MesIm)]^+ at the B3LYP/6-31G(d) (LANL2DZ for Mo) level of theory.
In 2013 Darensbourg evidenced the occurrence of a base-promoted conversion of a N-alkylimidazole ligand to the corresponding NH-NHC mediated by a dinitrosyl iron complex.\(^{152}\)

6.3. Tautomerization of other azoles.

Compared with imidazol-2-ylidenes less attention has been paid to N,X-heterocyclic carbenes (X= O, S), mainly due to the instability of the free ligands which easily undergo dimerization processes.\(^{153}\) A probably better alternative would be to force the tautomerization of the coordinated azole ligand upon a deprotonation/protonation (or alkylation) sequence as that described above for N-alkylimidazole ligands. This method is illustrated in Scheme 36 for \{Mn(azole)(CO)\(_3\)(bipy)\}\(^+\) (azole= oxazole, thiazole) complexes to afford the corresponding heterocyclic carbenes.\(^{154}\) Prior to this work, deprotonation of 4-methylthiazole\(^{155}\) or benzothiazole\(^{156}\) ligands coordinated to \{Cr(CO)\(_3\)\} followed by methylation had led to the formation of the carbene complexes, but lack of selectivity had been observed as the dimethylated azole complexes were also obtained.

\[
\begin{align*}
\text{[Mn]} & \quad \text{[Mn]} \\
\text{[Mn]}=\text{(Mn(CO)}_3\text{(bipy)}\text{)} & \quad \text{NH}_4\text{PF}_6 \\
\end{align*}
\]

Scheme 36. Tautomerization of oxazole and thiazole to the corresponding carbene derivatives at a Mn(I) fragment.

7. Metal-ligand cooperation based on aromatization/dearomatization processes.

The chemical behavior of transition metal complexes is dramatically dependent on the steric and electronic properties of the ligands coordinated to the metal center. Modification of the ligands properties has been used as a tool to improve the desired properties of metal complexes depending on the particular processes, i. e. increasing its electrophilic/nucleophilic, basic/acid
character, etc. A particular area in which this concept has been broadly used is in homogeneous catalysis. In the vast majority of reactions catalyzed by metal complexes, the catalytic activity is primarily based on the metal while the ligands are considered as spectators, as they do not participate in the chemical transformations directly. In the last decade the development of bifunctional catalysts has gained interest showing that the metal center and its coordinated ligands can jointly cooperate in the catalytic cycle.\textsuperscript{157} A particular case of this type of metal-ligand cooperation (MLC), studied by Milstein et al., is based on dearomatization/aromatization processes on the ligand. These studies have been comprehensively covered in several recent reviews,\textsuperscript{158-160} but due to their relevance and fundamental importance they have been, although briefly, also included herein. These authors found that pyridine-based PNP and PNN (structures 33 and 34, Figure 20), and bipyridine-based (structure 35, Figure 20) pincer ligands can stabilize coordinatively unsaturated complexes.

![Figure 20. PNP and PNN pincer ligands studied by Milstein et al.](image)

The facile deprotonation of the pincer backbone at one of the methylene spacer groups affords the dearomatization of the pyridine ring, which must be stabilized by being part of the pincer ligand. The dearomatized complexes can activate various chemical bonds including H-H, C-H, O-H and N-H bonds. These activations are carried out by cooperation between the metal and the ligand, regaining aromatization of the ligand by protonation of the benzylic carbon atom (Scheme 37).
Scheme 37. Activation of H-Y chemical bonds by cooperation of the metal and the ligand through a dearomatization/rearomatization process.

Several pincer complexes of this type, mainly based on Ru\textsuperscript{158} and Fe\textsuperscript{159} which are able of participate in MLC processes, have been described showing their ability as versatile catalysts for hydrogenation, dehydrogenation and related reactions. It has to be highlighted that the first application of dearomatization-reprotonation was the employment of complex 36 for the dehydrogenation of alcohols, wherein the combined metal and dearomatized ligand act in cooperative manner to convert, for example, primary alcohols to esters or secondary alcohols to ketones, with concomitant extrusion of H\textsubscript{2} (Scheme 38).\textsuperscript{161}

Scheme 38. Dehydrogenation of alcohols to esters or ketones with a dearomatized pincer complex.
Milstein and co-workers reported that, in a similar manner to aliphatic alcohols, water could also be activated using complex 36 with the dearomatized PNN backbone (Scheme 39). Upon reaction with water at room temperature, aromatization takes place to quantitatively form the trans-hydrido-hydroxo complex 37. Thermal activation of a second molecule of water releases molecular hydrogen and leads to the formation of cis-hydroxo complex 38. DFT studies indicate that this process involves H₂ liberation from 37 by coupling of the hydride ligand with a proton from the side arm, followed by addition of H₂O to the generated dearomatized intermediate. Significantly, irradiation of complex 38 led to the regeneration of compound 37 concomitant with evolution of O₂. This sequence would involve a photochemically induced reductive elimination of H₂O₂ from dihydroxo complex 38, thereby generating a Ru(0) intermediate (39, not observed) that undergoes intramolecular proton transfer to regenerate the starting compound. Therefore, this is a new approach toward a complete cycle for the generation of dihydrogen and dioxygen from water promoted by a soluble metal complex.

Scheme 39. Proposed reaction mechanism for the generation of O₂ and H₂ from H₂O mediated by a Ru(PNN) complex.
8. Conclusions and outlook.

Pyridines react with several types of main group organometallic compounds to give metal-pyridine adducts, proposed on the basis of computational studies or by extrapolation of the behavior encountered in non-reactive systems. They evolve to metal complexes of anionic dihydropyridines, which have been isolated only in a few cases, and which finally yield substituted pyridines. Only in the last few years some groups have started to employ N-coordination of the pyridine to an external Lewis acid (e.g., BF$_3$) combined with nucleophilic addition of an organometallic reagent, or the reaction of the pyridine with a bimetallic reagent containing different Lewis acid and nucleophilic metal sites (e.g., lithium aryl zincates), obtaining selective, synthetically useful methodologies. In contrast, the pyridine rings in transition metal complexes containing pyridyl-based ligands -which are among the most useful and widely studied within coordination chemistry- are typically very inert. In the seventies this notion was challenged by Gillard, who proposed that apparent anomalies in the behavior of cationic bipy and phen transition metal complexes in basic aqueous media could be the result of hydroxide attack to one of the pyridine carbon atoms. However, subsequent studies casted doubt on this proposal. Our group demonstrated several instances of C-C coupling via intramolecular nucleophilic attack to the pyridyl rings on Re-coordinated bipy and phen ligands under very mild conditions, most of them initiated by deprotonation of C-H groups of several types of commonly employed monodentate ligands. The products of such reactions feature metal-bonded, dearomatized dihydropyridyl groups. The products of coupling between two monodentate N-alkylimidazole or pyridine ligands could be rearomatized by oxidation to afford pyridylimidazole or bipyridine ligands, including non-symmetric chelates. The reaction of one of the dearomatized products of the bipy-N-alkylimidazole coupling with excess MeOTf led to pyridine ring opening, a transformation previously limited to three examples of very reactive early transition metals. C-C coupling schemes were extended to ligands other than pyridines, allowing the modular construction of non-symmetric polydentate ligands on the metal coordination sphere.

In some cases the deprotonation of coordinated N-alkylimidazoles afforded very rare imidazole-2-yl ligands. Their reaction with electrophiles afford NHC ligands; in particular, their reaction with
acids yield NH,NHC ligands. This kind of reaction can serve to directly access metal complexes of NHC ligands directly from stable, easily accessible N-alkylimidazole complexes. Computational studies proved to be very useful in shedding light on the kinetics and thermodynamics of the competing pathways that lead in some systems to C-C coupling and in others to imidazolyl formation. Most of these reactions have been carried out employing highly stable, easily available rhenium tricarbonyl complexes, whose chemistry has been previously almost exclusively dominated by substitution reactions.

A growing number of types of transition metal compounds are finding applications as catalysts, materials, and drugs. Therefore, the synthesis of transition metal complexes is becoming a proper goal beyond their classical employment as auxiliaries towards the synthesis of metal-free organic molecules. The traditional synthetic approach is based on the separate synthesis of the ligands employing conventional organic procedures, which in the case of non-symmetric, polydentate ligands can be far from straightforward, followed by their binding to the metal through substitution reactions. In some cases, this scheme could be advantageously replaced by the modular synthesis of the polydentate ligands from easily available monodentate ligands, which would be first coordinated to the metal and then coupled, taking advantage of the ligand activation and geometric preorganization by their metal coordination.

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