

Review

Non-Classical Anionic Naked *N*-Heterocyclic Carbenes: Fundamental Properties and Emerging Applications in Synthesis and Catalysis

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Abstract: Ongoing research exploring the chemistry of *N*-heterocyclic carbenes (NHCs) has led to the development and discovery of new NHC subclasses that deviate beyond Arduengo's prototypical *N,N'*-disubstituted imidazol-2-ylidene-based structures. These systems continue to enable and extend the fundamental role of NHC ligands in synthesis and catalysis. In this regard, the advent of protic NHCs has garnered particular interest. This derives in part from their applications to the selective preparation of unique molecular scaffolds and their unprecedented bifunctional reactivity, which can be exploited in transition metal-catalyzed processes. In comparison, the synthetic applications of closely related anionic naked NHCs remain rather underexplored. With this in mind, this review highlights the interesting fundamental properties of non-classical anionic naked NHCs, and focuses on their emerging applications in synthesis and catalysis.

Keywords: *N*-heterocyclic carbenes; non-classical NHCs; protic NHCs; naked NHCs; catalysis

1. Introduction

N-Heterocyclic carbenes (NHCs) have emerged as an integral component of contemporary coordination chemistry (Figure 1A). Since the isolation of the first stable free carbene species by Bertrand et al. in 1988 [1], and the first stable NHC by Arduengo et al. in 1991 [2], NHCs are now routinely utilized as versatile supporting ligands in metal complexes, and form the basis of many valuable catalyst systems that mediate an array of synthetic transformations [3–11]. The extent of research devoted to NHCs has led to the development and discovery of new NHC subclasses that have deviated from Arduengo's classical imidazol-2-ylidene based NHCs, thus expanding the structural and electronic diversity of this class of compounds and their associated applications. These modifications include forming carbenes on alternative carbon positions (i.e., abnormal or mesoionic carbenes) [12], featuring ring saturation [13], changing ring size [14–17], using fused ring systems [18–21], acyclic analogues [22], and even multidentate carbene ligands [23–30].

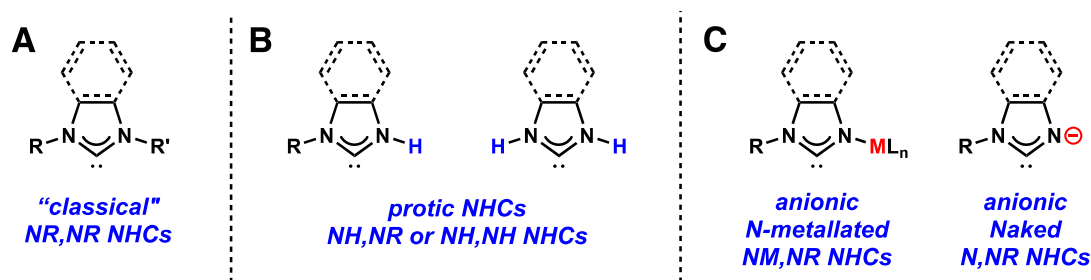


Figure 1. Substitution patterns of *N*-heterocyclic carbene (NHC) nitrogen atoms delineating: (A) "classical" NR,NR NHCs, (B) protic NH,NR or NH,NH NHCs, (C) and anionic NM,NR or naked N,NR NHCs.

A common feature of the aforementioned NHC subclasses is disubstitution of the NHC nitrogen atoms with alkyl or aryl substituents, which are collectively classified as "classical" NR,NR-NHC ligands (Figure 1A). Recent developments have led to the emergence of NHC ligands where one or both *N*-substituents are replaced with a hydrogen atom resulting in NH,NR or NH,NH-substitution patterns affording ligands known as protic NHCs (Figure 1B). These species have enjoyed significant interest owing to their unique ligand hydrogen bonding interactions and associated properties, which allow the corresponding NHC metal complexes to display valuable reactivity when applied in stereoselective macrocycle formation and catalytic processes, for example. Deprotonated NH,NR-NHCs represent another subclass of non-classical NHC ligands known as anionic naked N,NR NHCs, and are often isolated as their corresponding *N*-metallated complexes. These anionic NHCs differ from NHC ligands bearing anionic substituents and mixed abnormal/normal NHCs in that the unsubstituted nitrogen atom carries a formal negative charge (Figure 1C).

NHC chemistry has been the subject of many reviews highlighting their unique properties and applications in synthesis [3–11]. With this in mind, this review aims to provide an overview of recent advances in the preparation and synthetic applications of metal complexes bearing non-classical NHCs; in particular, anionic NM,NR-NHC and naked N,NR-NHC ligands. Progress in the preparation of the closely related protic NHCs and their applications in metal-mediated reactions will not be discussed in detail, as a recent review by Hahn and Kuwata covered this topic extensively [31]. To our knowledge, a review of anionic NM,NR-NHCs and naked N,NR-NHCs has not been published to date. Consequently, this review focuses on imidazole-based anionic NHCs with N,NR substitution patterns, thus excluding mixed normal/abnormal classical NR,NR NHCs which are anionic due to deprotonation of the azolium salt at two different sites (Figure 2) [32–36]. Specifically, the fundamental structural and electronic properties of these systems and their applications in synthesis are discussed. It should be noted that due to the emerging nature of this class of non-classical NHCs, only a handful of examples of the applications of these systems in catalysis have been reported to date. With this in mind, a primary aim of this review is to draw attention to the intrinsic and enabling fundamental properties of these anionic NM,NR-NHCs and naked N,NR-NHCs and highlight potential opportunities that may be explored to exploit the interesting and innate reactivity provided by this class of molecules in catalysis.

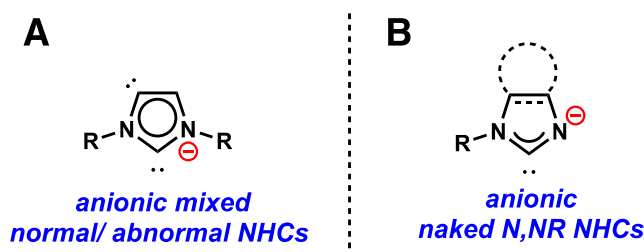
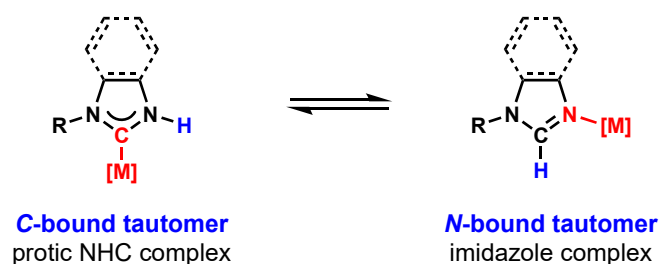


Figure 2. (A) Anionic Classical Mixed Normal/Abnormal *N*-Heterocyclic Carbenes (NHCs). (B) Anionic Naked N,NR NHCs.

2. Non-Classical NHCs and Their Metal Complexes

2.1. Protic NHC Metal Complexes

The most acidic proton in an NH,NR or NH,NH imidazolium salt is attached to the nitrogen atom, and not the C2 carbon. For this reason, the treatment of such a salt with base results in the regioselective deprotonation of the nitrogen atom and isomerization into the corresponding imidazole, rather than producing the free carbene. This has prevented the isolation of protic NHCs in their free form, and to date, these species have only been reported as their metal complexes. In principle, these protic NHC complexes could isomerize to the *N*-coordinated imidazole complex, but this is seldom observed in practice (Scheme 1) [37]. While imidazole is more thermodynamically stable than its protic free NHC tautomer, the high energy barrier that is calculated for the required 1,2-hydrogen shift suggests that the latter is kinetically favored [38,39]. Theoretical studies of the relative stabilities of the C-bound and *N*-bound tautomers suggest that strongly π -basic metal centers, hydrogen bonding at the N–H site(s), and the presence of ligands that cannot exert strong *trans* influences can stabilize the C-bound over the *N*-bound complex [40,41].



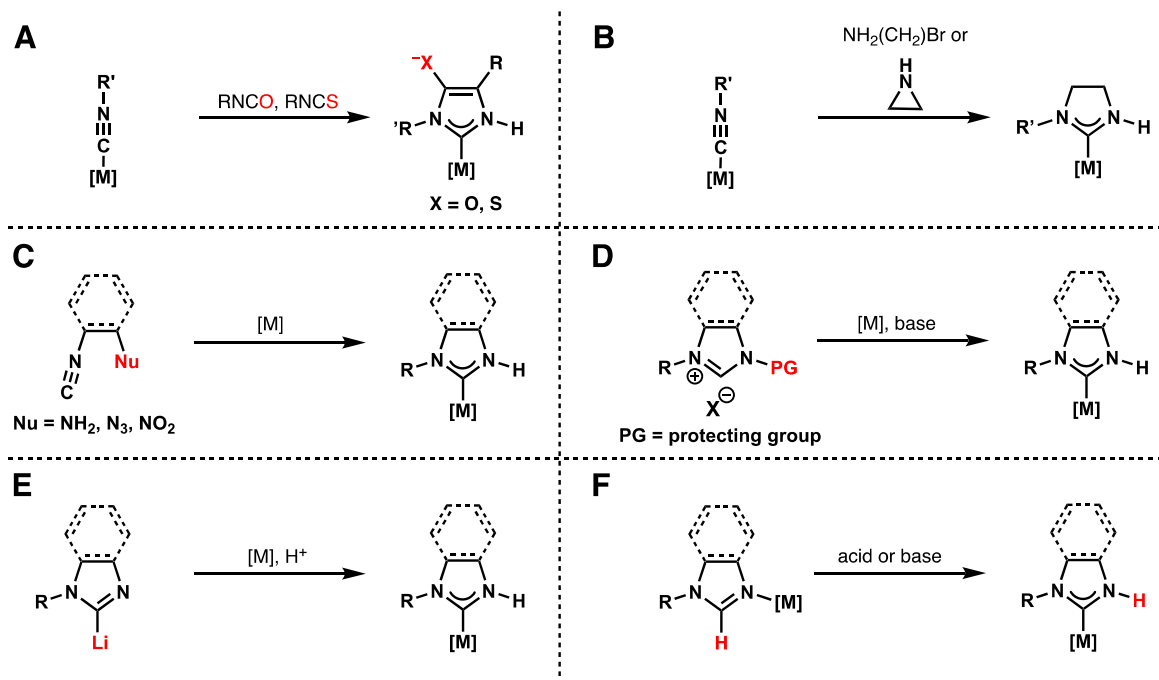
Scheme 1. Tautomeric forms of imidazole-based protic metal NHC complexes.

With the above-mentioned issues in mind, other strategies were developed to access protic NHC complexes, such as the metal-templated cyclisation of isocyanides and nitrogen-containing nucleophiles. Under basic conditions, a pre-coordinated metal isocyanide may be reacted with phenylisocyanate or phenylthioisocyanate to give protic NHC complexes bearing exocyclic oxy anions or thiolate functions, respectively (Scheme 2A) [42]. These versatile backbone substituents may undergo further alkylation or acylation, or act as monodentate donors. 2-bromoethylamine [43] and aziridine [44] may also be used as cyclization partners to form protic imidazolidin-2-ylidenes (Scheme 2B).

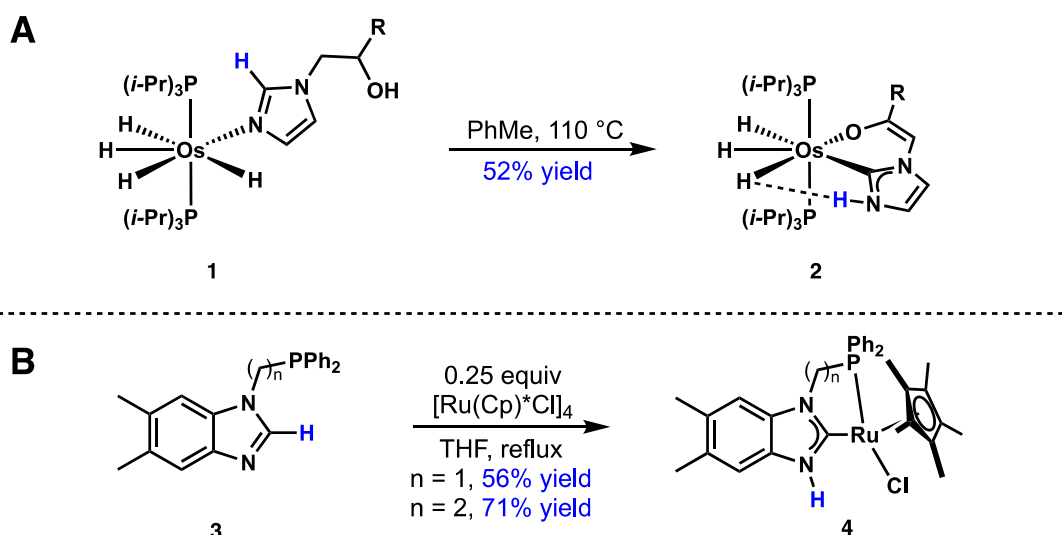
In cases where the isocyanide and nucleophile are contained within the same molecule, protic NHC complexes may be accessed via the intramolecular 1,2-addition across the C–N triple bond. This approach has been particularly successful in the preparation of backbone-saturated [45] and benzannulated protic NHCs (Scheme 2C) [46,47]. In a variation of this method, the isocyanide complex is generated in situ from an aminophosphinimine ligand [48]. Other methods involve the metalation of a preformed *N*-heterocycle bearing a labile *N*-protecting group that can later be cleaved to reveal the protic NHC complex (Scheme 2D) [49,50], C2 lithiation followed by transmetalation and *N*-protonation (Scheme 2E) [51–54], and finally the acid-induced or base-induced carbene/imidazole tautomerization from *N*-metalated imidazole metal complexes (Scheme 2F) [55,56].

In practice, the conversion of *N*-metalated imidazole complexes into their protic NHC tautomers is often the most convenient and versatile synthetic route, as post-metalation functionalization of the heterocycle can be difficult. The presence of chelating directors further encourages and stabilizes the resulting NHC metal complex, preventing tautomerization to the *N*-metalated form [57–65]. For example, Scheme 3A features an interesting transformation that converts osmium complex **1** to species **2**, and the transition metal center switches ligand donor atoms from nitrogen to the NHC carbon [58]. Presumably, the Lewis basicity of the chelating director influences *N*-metalation, as no *N*-metalated intermediate is observed in the presence of a pendant phosphine donor for the

transformation of complex **3** to species **4** (Scheme 3B) [57]. These types of transformations are thought to be operative in various proposed catalytic cycles involving protic NHC ligands displaying reversible deprotonation at the acidic N–H site.



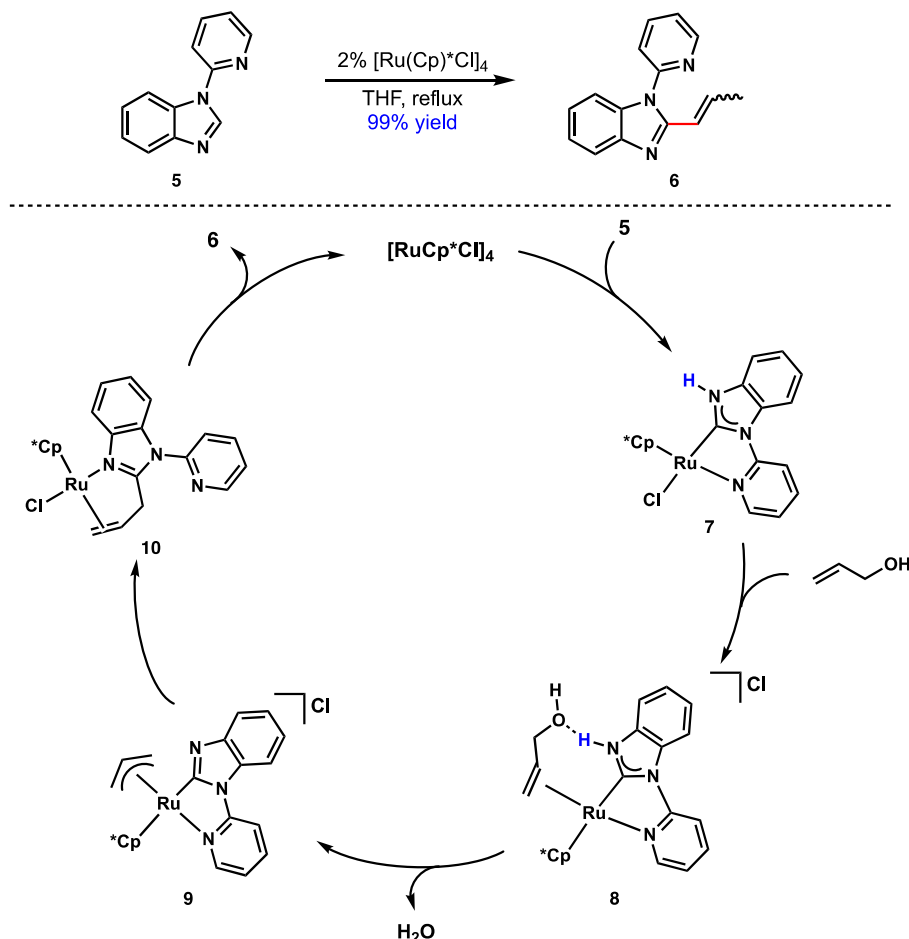
Scheme 2. Synthetic strategies for the preparation of protic NHC complexes: (A) metal-templated cyclization of isocyanides and nitrogen-containing nucleophiles; (B) metal-templated cyclisation of isocyanides with bromoethylamine or aziridine; (C) intramolecular metal isocyanide 1,2-addition; (D) metalation of pre-formed *N*-protected *N*-heterocycle followed by deprotection; (E) transmetalation of C2-lithiated *N*-heterocycle followed by *N*-protonation; (F) acid- or base-induced carbene/imidazole tautomerization from *N*-metalated imidazole metal complexes.



Scheme 3. Synthesis of a protic NHC complex by tautomerization of neutral imidazole-based ligands, facilitated by a pendant (A) oxygen donor [58] and (B) phosphine donor [57].

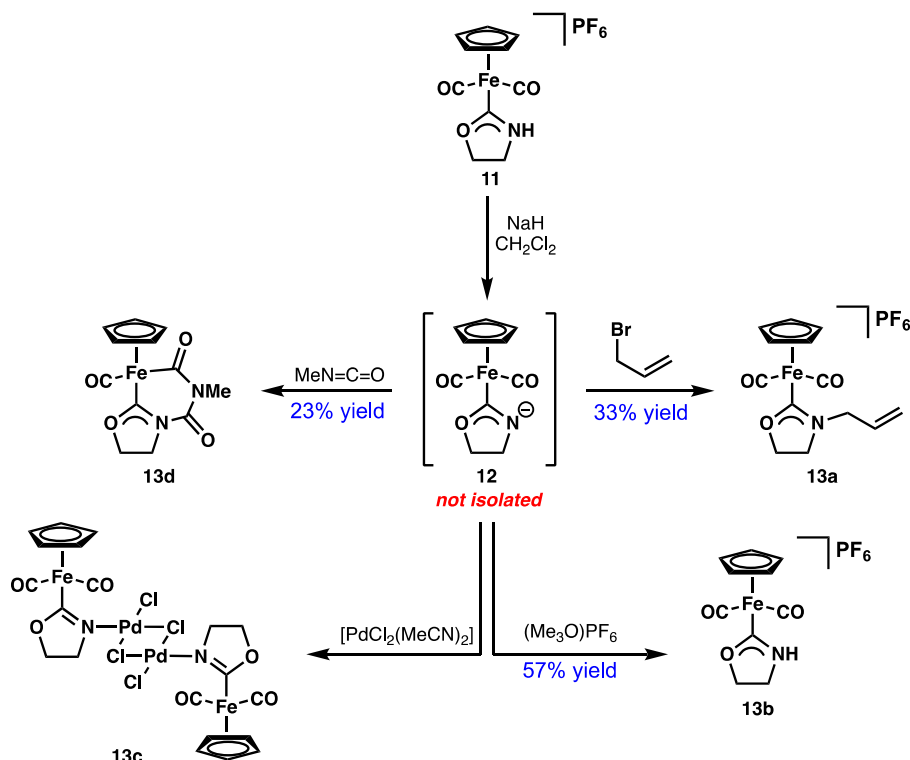
N-(2-Pyridyl)benzimidazole (**5**) can be allylated at the C2 position to give compound **6** in a Ru-catalyzed dehydrative C–C coupling reaction (Scheme 4) [59]. It is suggested that the process commences with the insertion of a ruthenium species into the C2–H bond of benzimidazole **5** to give

isolable intermediate **7**, which then coordinates to allyl alcohol. Next, the N–H proton and hydroxyl group in complex **8** are lost as water to give imidazol-2-yl allyl complex **9**. Facile elimination is expected due to the dual binding mode of the olefinic alcohol in species **8**. Reductive elimination of heterocycle **6** from intermediate **10** then occurs. Notably, compound **10** is also accessible via the stoichiometric reaction of species **7** and allyl alcohol. Similar processes are also proposed for the Rh-catalyzed intramolecular alkylation and the arylation of azoles, and analogous nitrogen/NHC carbon atom donor switching is invoked [59,66–68].



Scheme 4. Synthesis of a protic NHC complex by tautomerization of neutral imidazole ligands, facilitated by a pendant nitrogen donor: ruthenium-catalyzed dehydrative C–C coupling of a benzimidazole and allyl alcohol [59].

The above-mentioned examples reinforce suggestions that the deprotonation of the N–H site of a protic NHC generates an anionic nitrogen donor atom that may serve as a viable coordination site in the formation of naked N_2NR NHC metal complexes, NM_2NR -free NHC complexes, or even C/N bimetallic complexes. Indeed, deprotonation-induced reactions of protic NHC complexes have been developed to access a variety of transformations. This was first demonstrated by Angelici et al. in 1987 [69], in which the deprotonation of protic oxazolidin-2-ylidene iron complex **11** and the subsequent addition of electrophiles afforded a range of *N*-functionalized metal complexes **13** (Scheme 5). Hahn et al. have further exploited this reactivity for the template synthesis of organometallic macrocycles [70] and the stereoselective synthesis of facially coordinated tridentate mixed donor ligands [71–75]. Of particular interest is the intermediate **12**, which features a nitrogen atom bearing a formal negative charge, and its corresponding bimetallic complex **13c**. From the aforementioned examples, it is evident that studies involving protic NHCs have often uncovered interesting structures, which constitute so-called anionic NM_2NR and naked N_2NR NHCs (hereafter abbreviated collectively as N_2NR NHCs).



Scheme 5. Deprotonation-induced N-functionalization of an iron(II)-NHC complex.

2.2. Anionic NM,NR and Naked N,NR NHC Metal Complexes

N,NR NHCs were well-known before they became more widely recognized as anionic NHCs within the broader chemical community. In 1995, Boche et al. described a dimeric lithiated thiazol-2-yl compound **14** as a formyllithium equivalent (Figure 3) [76]. In contrast to common organolithium reagents such as methyllithium or butyllithium in which the alkyl component is typically regarded as a carbanion, these researchers argue that complex **14** exhibits a singlet carbene character in its crystal structure. A comparison with thiazole revealed that structure **14** experienced lengthening of the C2–N and C2–S bonds and shrinking of the N–C2–S angle from 115.1(8)° to 107.9(2)°, which mirrors the structural trends associated with moving from an imidazolium cation to an imidazol-2-ylidene. While the C2–N1 and C2–N3 bonds in imidazol-2-ylidenes are usually identical in length, a meaningful comparison cannot be made for species **14**, as the carbene carbon is flanked by two different heteroatoms.

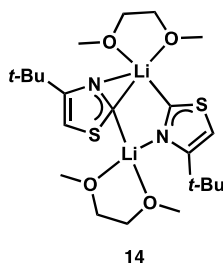
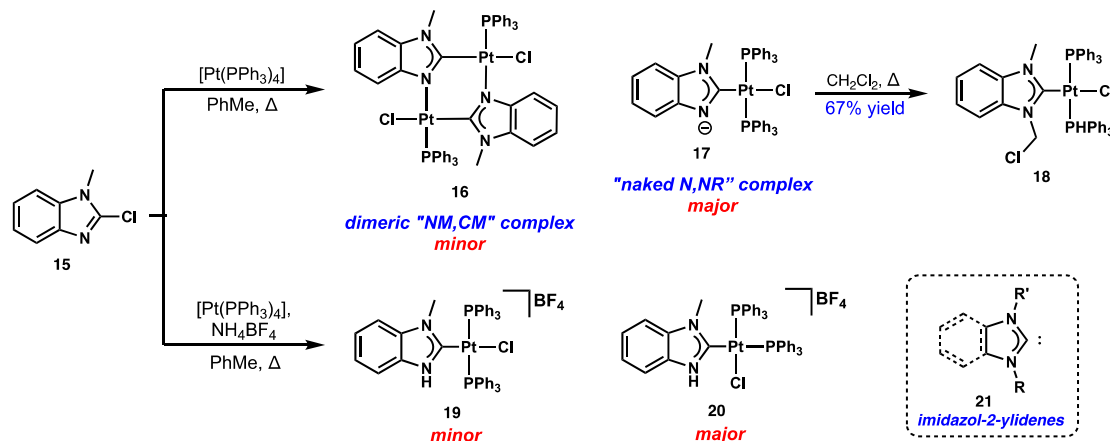


Figure 3. Lithiated 4-*tert*-butylthiazole **14** featuring C/N metalation.

Hahn et al. were the first to introduce the term “anionic NHC” when they reported complex **17**, which was one of the products isolated from the oxidative addition of zero-valent Group 10 metals to benzimidazole **15** (Scheme 6) [77]. These authors had previously alluded to the intermediacy of an anionic benzimidazole in the synthesis of protic NHC complexes via this oxidative addition route. It was determined that in the absence of a proton source, such as NH₄BF₄, an oxidative addition to

chloride **15** did not lead to protic NHC complexes **19** and **20**. Instead, N,NR complex **17** and its dimer **16** were obtained in a 4:1 ratio. The reaction of $[\text{Pt}(\text{PPh}_3)_4]$ and 2-chloro-*N*-picolylbenzimidazole also afforded a similar dimeric product, suggesting that the formation of $\text{N}(\text{M})_2\text{NR}$ complexes under aprotic conditions may be generalized to other 2-halobenzimidazoles [77].



Scheme 6. Reaction products obtained from the oxidative addition of $[\text{Pt}(\text{PPh}_3)_4]$ to 2-chloro-*N*-methylbenzimidazole (**15**) in the presence and absence of a proton source.

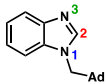
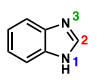
2.3. Carbene or Carbanion?

An important question that was posed when imidazol-2-ylidenes **21** were first discovered was whether deprotonation gives rise to a carbene or a carbanion. The Arduengo group endeavored to answer this question by using a combination of theoretical and experimental approaches. If the deprotonated azol-2-yl in question is indeed a carbanion, one should observe regions of high electron density or localized negative charge on a carbon atom that also participates in π -bonding interactions. However, Mulliken charge calculations for imidazol-2-ylidene estimate that most of the negative charge is borne by the nitrogen atoms, with only a small fraction residing on the carbene atom [78]. Electron density maps derived from the neutron diffraction data of 1,3,4,5-tetramethylimidazol-2-ylidene (IME) showed that most of the electron density within the ring was localized on the nitrogen atoms. This is perhaps a predictable result in light of the higher electronegativity of nitrogen relative to carbon [78]. The π electron densities surrounding the C2–N and exocyclic C–N bonds are similarly low, indicating that bonds connected to C2 have a minimal double-bond character. A minima for π electron density was found on C2. In addition, deformation density maps reveal a concentrated region of electron density at C2 in the plane of the molecule, which evolved into a pronounced deficit above the plane. This is consistent with C2 having an in-plane lone pair and a vacant π -orbital. In contrast, other endocyclic atoms exhibit little distortion in their nuclear positions. The electron density maps generated by density functional theory (DFT) studies were in excellent agreement with the empirically derived maps, suggesting that accurate models of electron distribution in NHCs can be made this way. When taken together, these data strongly support the interpretation of IMe as a carbene rather than a carbanion.

It is instructive to employ the same structural and electronic reasoning developed by Boche and Arduengo to establish whether or not the N,NR complex **17** is a carbene. From a structural point of view, species **17** is perhaps best described as having partial azole and partial NHC character. *N*-methyladamantylbenzimidazole and benzimidazole will be used as references for the parent azole, as structural data for 2-chloro-*N*-methylbenzimidazole (**15**) is not available. The key bond lengths and angles are summarized in Table 1. Compared to the neutral azoles, the N1–C2–N3 angles in compounds **20** and **18** are smaller, which is a feature that is associated with NHC formation. The same decrease in the N1–C2–N3 angle is observed for complex **16**, albeit to a lesser extent. The C2–Pt bond lengths in complex **17**, its protonated form species **20**, and the chloromethylated form **18** are relatively

similar to one another, signifying that all three heterocycles possess similar donor/acceptor properties. This could mean that, similar to the other two complexes, structure **17** is also a carbene.

Table 1. Comparisons of fundamental structural and spectroscopic data for NH,NR (**20**), N,NR, (**17**), and NR,NR NHC (**18**) complexes relative to reference benzimidazoles.

Parameter			20; N3 = Protonated [77]	17; N3 = Naked	18; N3 = Alkylated
N1–C2–N3 (°)	114.83(11) [79]	114.41(17)	107.1(4)	111.37(17)	106.7(2)
C2–N1 (Å); “A”	1.3629(14) [79]	1.345(2)	1.350(6)	1.389(2)	1.351(3)
C2–N3 (Å); “B”	1.3096(14) [79]	1.312(2)	1.349(6)	1.319(3)	1.364(3)
ΔA–B (Å)	0.053	0.033	0.001	0.070	0.013
C2–Pt (Å)	–	–	1.972(4)	1.987(2)	1.973(2)
¹³ C NMR δC ₂ (ppm)	144.3 (CDCl ₃) [80]	141.9 (d ₆ -DMSO)	157.8 (CD ₂ Cl ₂)	149.4 (CD ₂ Cl ₂)	163.3 (CD ₂ Cl ₂)

As noted earlier, another characteristic feature of NHC formation is the presence of C2–N1 and C2–N3 bonds of approximately equal lengths (but longer than the corresponding bonds in neutral azoles). This change is evident for the NHC complexes **20** and **18**, with a marked lengthening of the C2–N3 bond that ultimately results in a negligible difference between the C2–N1 and C2–N3 bond lengths. However, in species **17**, the C2–N1 bond becomes significantly longer than that in the neutral azoles and the NHC complexes, while the C2–N3 bond length is typical of neutral azoles. The disparity in C2–N1 and C2–N3 bond lengths for structure **17** exceeds the values observed for neutral azoles. This C2–N1 and C2–N3 bond length asymmetry appears to be characteristic of anionic azol-2-yl ligands in general [59,72].

Based largely on the stark difference in the C2–N1 and C2–N3 bond lengths, Hahn et al. initially assigned the structure-type **22b** to complex **17**, where the C2 atom and short C2–N1 bond are represented as an acyl-like anion and a double bond, respectively (Figure 4). However, this interpretation was contradicted by their natural bonding orbital (NBO) charge calculations for the N,NR ligand in species **17**. The calculated NBO charges suggest that the region with the highest electron density is found on N3 followed by N1, while C2 appears to be electron-deficient. DFT calculations support this, with these data indicating that the maximum negative electrostatic potential (of comparable value to Cl[−]) is located close to N2. Overall, the NBO and DFT models of species **17** are more consistent with a carbene flanked by an anionic nitrogen, as depicted in structure **22a**.

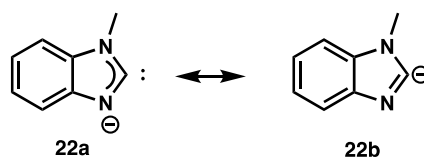


Figure 4. Possible carbenic (**22a**) and carbanionic (**22b**) resonance contributors for the N,NR ligand moiety in complex **17**.

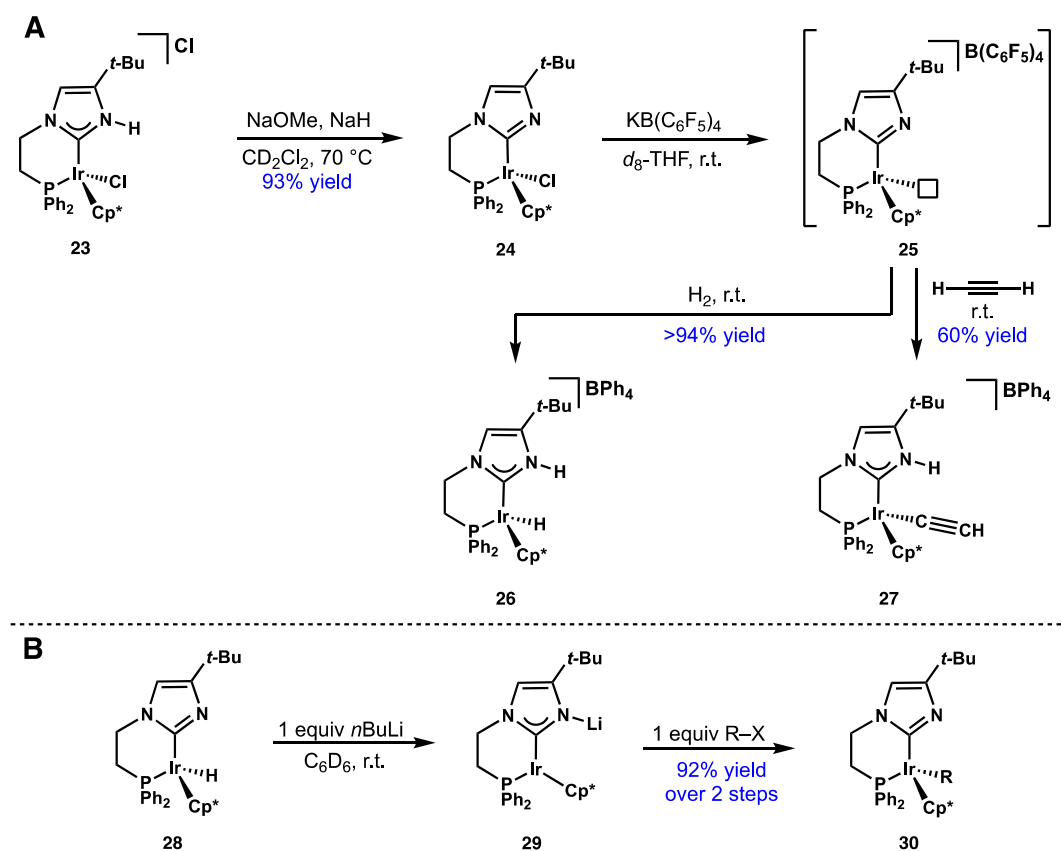
Hahn et al. note that the C2 resonance appears further upfield in the ¹³C NMR spectrum of complex **17** than for derivatives **19** and **18**. Although an extreme downfield shift is usually expected for a carbenic resonance, this may not necessarily suggest that the C2 within complex **17** is not a carbene. Rather, the upfield position of the resonance may be viewed as a consequence of the greater shielding experienced by C2, due to the higher electron density surrounding the adjacent anionic nitrogen. The upfield shift in the C2 resonance going from an NH/R,NR NHC complex to an N(M),NR NHC species has also been observed for other metals [65].

Finally, the reactivity of complex **17** further supports the assignment of the negative charge on N3 instead of C2. The dinuclear species **16** results from adduct formation between the Lewis basic unsubstituted nitrogen and the Lewis acidic metal center in a second molecule of species **17**.

The anionic nitrogen in complex **17** is strongly nucleophilic, and will attack electrophiles such as dichloromethane to produce the classical NHC complex **19**. On balance, the structural, electronic, and reactivity data provide sufficient justification that structure **17** can be considered an anionic NHC. However, the term has not been widely adopted, which is possibly due to the challenges involved in making the subtle distinction between a carbanion and an anionic carbene. Most of the $N(M),NR$ compounds in the literature are still named azol-2-yls, which is perhaps for this reason.

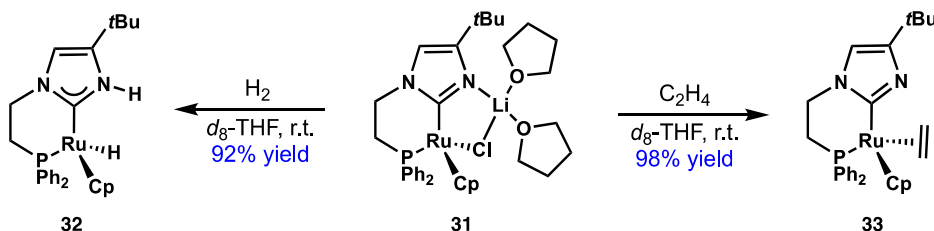
2.4. Preparation of $N(M),NR$ Complexes and Applications to Synthesis and Catalysis

N,NR complexes are probably most easily prepared by the deprotonation of an NH,NR complex with a suitable base [59,61,64]. Product **24** is generated from the treatment of the protic NHC complex **23** with NaOMe and NaH. Subsequent chloride abstraction results in the formation of derivative **25** featuring a vacant coordination site that can activate hydrogen and acetylene, affording products **26** and **27**, respectively (Scheme 7A). Similar to protic NHCs, species **24** can undergo N -methylation with methyl triflate to give a classical NR,NR NHC complex. The Ir–C2 bond length in complex **24** measures 2.059(3) Å, which is approximately 0.033 Å longer than the corresponding bond within structure **23**. This potentially suggests that in this example, the anionic NHC is a slightly weaker donor than its protic NHC congener. Related Ir(III) hydride complex **28** could be reduced to Ir(I) by hydride abstraction using *n*-butyllithium (Scheme 7B). Ensuing lithium adduct **29** is an NM,NR NHC complex, and its associated ^{13}C NMR spectrum features a signal that is consistent with a carbene resonance (δ 150 ppm). This is almost 20 ppm further downfield from the analogous ^{13}C NMR signal for complex **28**. Interestingly, the reaction of species **29** with methyl triflate or 1-iodobutane leads to alkylation at the metal instead of the nitrogen, and concomitant oxidation of the metal center to provide the corresponding Ir(III) compound **30**.



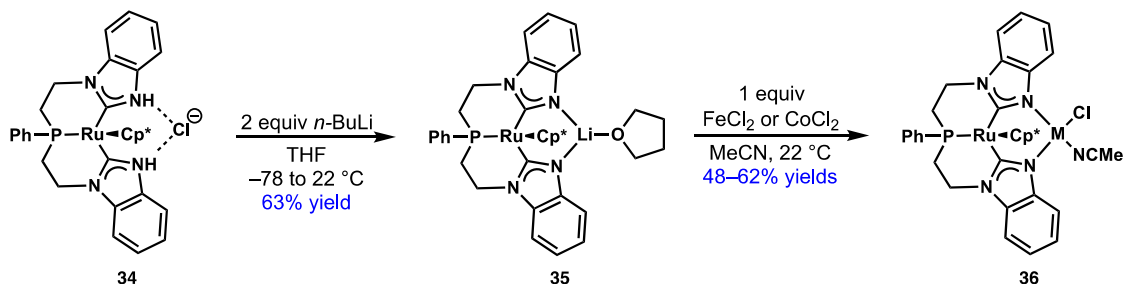
Scheme 7. (A) Anionic N,NR NHC complex formation from the deprotonation of a protic NHC complex. (B) Reduction of the iridium(III) center of a N,NR NHC complex to give a NM,NR complex, which can undergo alkylation on the metal.

The utility of heterobimetallic NM,NR complexes such as species **29** derives, in part, from their susceptibility to ligand exchange on the NHC-bound metal center, particularly when the exchange is driven by the precipitation of an insoluble lithium salt. Indeed, *N*-lithiated ruthenium complex **31** reacts with hydrogen, leading to the protic NHC/hydride complex **32**, and readily coordinates with ethylene to form **33** (Scheme 8) [61].



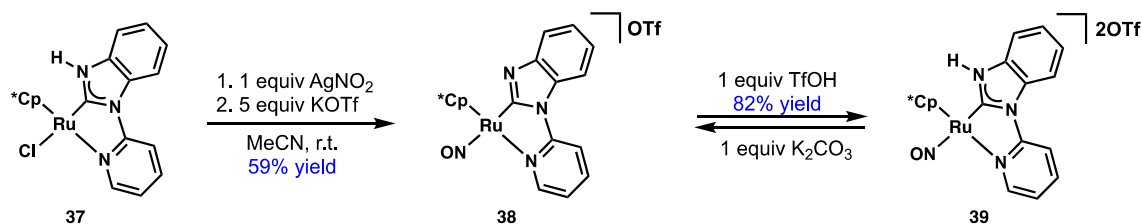
Scheme 8. Elimination of the *N*-coordinated metal in a heterobimetallic NM,NR NHC complex that facilitates ligand exchange at the metal center.

In some cases, metathesis occurs exclusively on N3, and the NHC-bound metal center is left unchanged when inorganic metal salts are used. Therefore, NM,NR NHC complexes may allow access to a variety of heterobimetallic complexes with bridging NHC ligands. For example, Cossairt and Flowers highlighted the potential of NM,NR NHC complexes as ligand transfer agents in their synthesis of a tridentate bis(carbene) complex **34** (Scheme 9) [63]. Lithiation affords heterobimetallic species **35**, and subsequent transmetalation provides access to new NM,NR NHC complexes, such as product **36**.



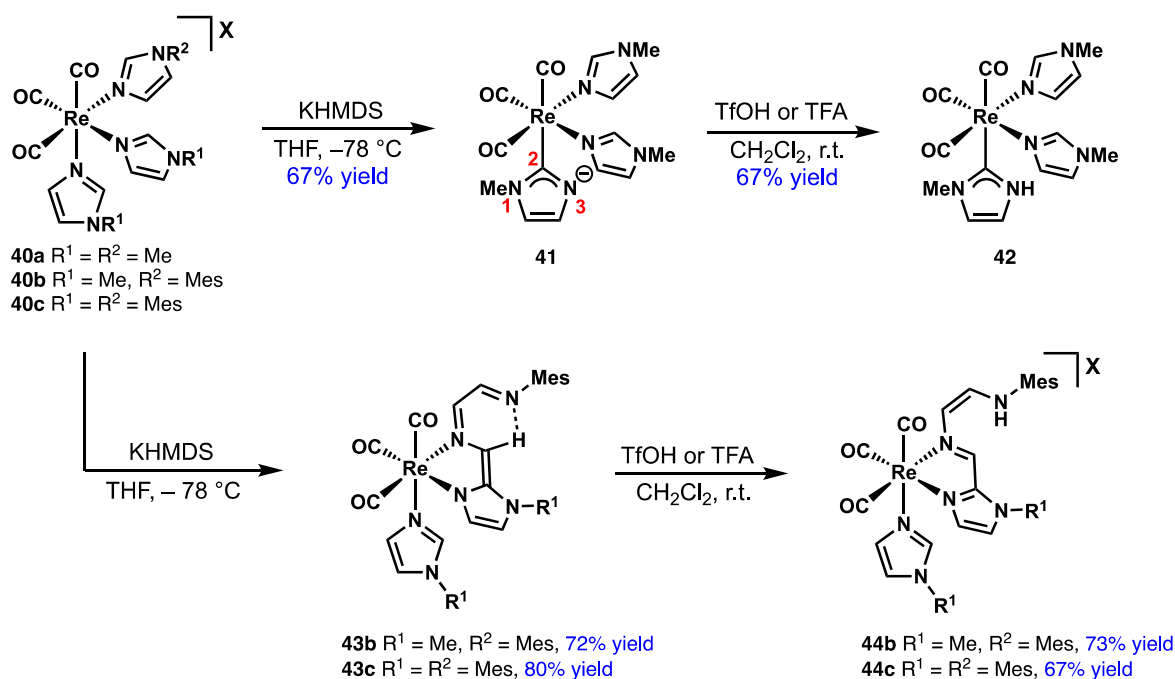
Scheme 9. Transmetalation at the anionic nitrogen site in NM,NR NHC complexes.

Anionic NHC complex **38** can be prepared from precursor **37** using the aforementioned base-assisted deprotonation method. However, the Brønsted acidity of the N–H moiety within a protic NHC complex can also be exploited under base-free conditions to deliver a N,NR NHC complex. For example, chloride abstraction from species **37** by AgNO₂ promotes an ensuing intramolecular proton migration. This generates a nitrosyl ligand from the nitrite ion via a dehydrative process, culminating in the formation of structure **38** after anion exchange with excess KOTf (Scheme 10) [59]. The authors also demonstrated that complexes **38** and **39** are interconvertible via acid/base-assisted protonation/deprotonation of the NHC nitrogen atom that enables switching between a protic and an anionic NHC motif. This property may find interesting applications in hydrogen transfer-type catalysis.



Scheme 10. Formation of a N,NR NHC complex **38** from protic NHC complexes **37** and **39** via the dehydrative conversion of a nitrite ion into a nitrosyl ligand under neutral conditions or base-assisted deprotonation.

Another method that has been used to access N,NR NHC complexes is the deprotonation and tautomerization of imidazole ligands. For example, the tris(*N*-methylimidazole)rhenium(I) complex **40a** can be deprotonated with KHMDS to give the N,NR NHC species **41**. Structure **41** was determined via NMR spectroscopy and single crystal X-ray diffraction (Scheme 11) [55]. A resonance at 182.4 ppm in the ¹³C NMR spectrum was assigned to C2 within complex **41**. This represents the furthest downfield signal associated with all of the N,NR NHC complexes that have been specifically discussed in this review thus far. Furthermore, protonation with strong acids such as triflic or trifluoroacetic acid afforded the NH,NR NHC product **42**, which was consistent with the presence of the naked nitrogen moiety within intermediate **41**.

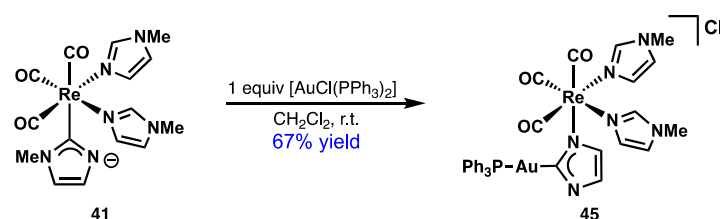


Scheme 11. Substituent-dependent formation of N(H),NR NHC complex **42** or ring-opening at N-alkylimidazole rhenium (I) complex **40**.

A topological analysis of the Laplacian of the electron density was performed for structures **41** and **42** using X-ray diffraction data. Complexes **41** and **42** both exhibited large non-bonded charge concentrations perpendicular to the plane at N3. Compound **41** also displayed an in-plane non-bonded charge concentration of similar magnitude at N3. However, the same was not true of product **42**, which instead showed a smaller bonded charge concentration. These observations are consistent with the presence of an in-plane lone pair on N3 for **41**, which is replaced by an N–H covalent interaction within structure **42**.

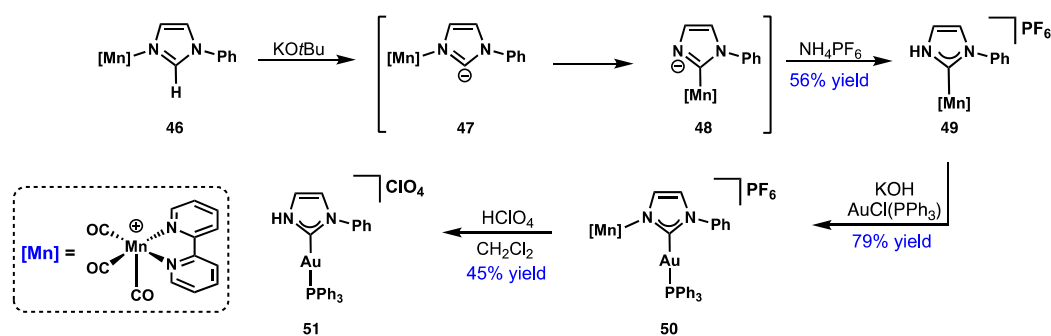
Interestingly, the *N*-substituents on the imidazole ligands have considerable bearing on the deprotonation outcome. If one or all of the methyl groups within complex **40a** are replaced with a

mesityl group, treatment with KHMDS results in the ring opening of an *N*-mesitylimidazole unit. It is thought that deprotonation takes place at the C2 position of one of the *N*-mesitylimidazole ligands, rapidly followed by the intramolecular attack of the NCHN moiety on an adjacent imidazole ligand by this nucleophilic C2 moiety. C–C coupling between the C2 atoms of two imidazole ligands and the ensuing ring-opening could furnish products **43b** and **43c**. DFT studies were employed to probe the reaction mechanism and suggest that the *N*-mesityl group enhances electron delocalization, and thus stabilizes, the transition state for the ring-opening step [81]. The amido-like nitrogen can be converted into the amine with the addition of acid to obtain species **44b** and **44c** in good yields. The N,NR NHC complex **41** can undergo a second metalation with $[\text{AuCl}(\text{PPh}_3)_2]$ to give the NM,NR NHC heterobimetallic complex **45** (Scheme 12) [81]. Notably, the imidazolyl fragment tautomerizes to the Re–N-bound form to accommodate the C-binding preference of the Au(I) center.



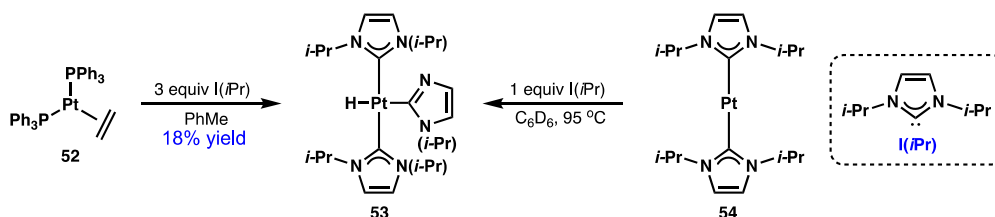
Scheme 12. Auration of N,NR rhenium(I) complex **41** involving tautomerization of the imidazolyl ligand.

A similar phenomenon has been observed in a manganese/gold system by Ruiz et al. (Scheme 13) [82]. In this case, manganese(I) imidazole complex **46** was transformed into the protic NHC complex **49**. The authors propose that the deprotonation of species **46** leads to an *N*-bound anionic species **47**, which isomerizes to C-bound analogue **48**. Although neither of these intermediates could be isolated, infrared spectroscopic analysis determined decreased $\nu(\text{CO})$ frequencies ($\sim 10\text{ cm}^{-1}$ on average) that were consistent with NHC formation. This is a reflection of the stronger donor capability of NHCs compared to their corresponding imidazole counterparts. Metalation of the NHC complex **49** was accomplished under basic conditions. Presumably, the soft gold(I) center initially coordinates to the hard anionic nitrogen on the NHC ligand, and subsequently undergoes a 1,2-migration in order to bind with the softer carbene donor to afford heterobimetallic product **50**. The Mn–N bond within species **50** can be cleaved with perchloric acid to give the gold(I) protic NHC complex **51**. This demonstrates that NM,NR NHC complexes of manganese(I) may serve as NH,NR carbene transfer agents for gold(I) species, which represents a complementary approach to the Ag_2O transfer method. The latter strategy is limited to preparing NR,NR NHCs. The route depicted in Scheme 13 for the formation of manganese(I) protic NHC complexes can be extended to benzannulated heterocycles such as benzimidazole and benzoxazole. However, their use as carbene transfer agents is currently prevented by the instability of the corresponding manganese(I)/gold(I) heterobimetallic complexes [83].



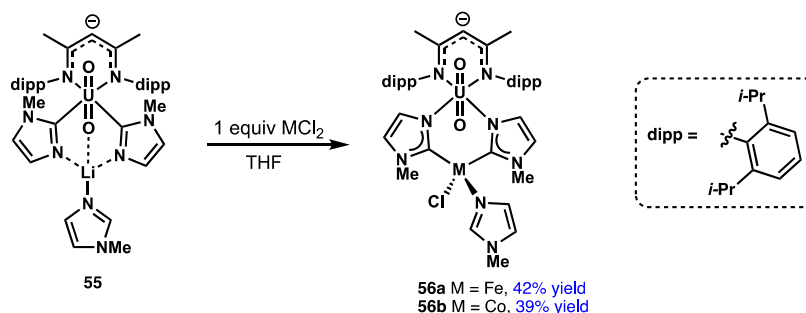
Scheme 13. Carbene transfer from a manganese(I) complex **49** to gold(I) complex **51** via heterobimetallic intermediate **50**.

Radius and Hering obtained N,NR platinum(II) complex **53** via the C–N bond cleavage of I(*i*Pr) (Scheme 14) [84]. When this reaction was conducted in nonpolar solvents, such as toluene or benzene, the reaction of $[\text{Pt}(\text{PPh}_3)_2(\eta^2\text{-C}_2\text{H}_4)]$ (**52**) with excess I(*i*Pr) generated species **53** as the major product, which occurred presumably via homoleptic bis-NHC platinum(II) complex **54**. The evolution of propylene was detected during this transformation, which is consistent with the C–N bond cleavage of I(*i*Pr) that was observed. When the analogous reaction was performed in hexanes, complex **54** precipitated from solution, which prevented subsequent reactions with free I(*i*Pr). Indeed, the authors showed that reacting compound **54** with equimolar quantities of I(*i*Pr) also affords product **53**. Radius and Hering did not consider the imidazolyl fragment within complex **53** to display carbene character, which was in part because of the elongated Pt–C_{imidazolyl} bond relative to the Pt–C_{NHC} bond. However, they acknowledged that this elongation may be due to the *trans* influence of the hydride ligand, and noted that a similar Pt–C_{NHC} bond length had been reported for an abnormal NHC complex [85].



Scheme 14. Platinum-mediated C–N bond cleavage affording N,NR complex **53**.

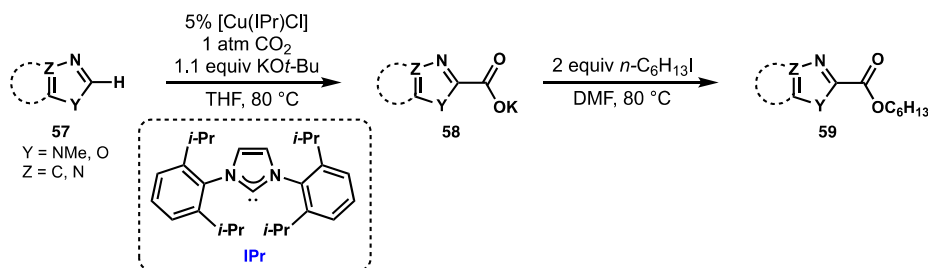
Since the carbene and carbanion represent resonance forms of each other, it is possible that these assignments are strongly dependent on the identity of the coordinated metal, and as such, these designations must be made on a case-by-case basis. For example, the uranyl complex **55** exhibits exceptionally short U–C bonds and an extreme downfield ^{13}C NMR signal that is most consistent with a carbanionic imidazolyl ligand (Scheme 15) [86]. In contrast, the M–C bond lengths in the isomerized iron(II) and cobalt(II) derivatives **56a,b** fall within the normal range expected for their respective NHC complexes. The new U–N bond is slightly shorter than those previously observed for U–N_{imidazole} complexes, which may be ascribed to the presence of a negative charge on the nitrogen atom. This suggests that the imidazolyl ligand may adopt the carbanionic resonance form when coordinated to the hard uranyl center, but undergoes electronic reconfiguration to become the carbene when bound to softer transition metal ions.



Scheme 15. Metalation and tautomerization of uranyl imidazolyl complex **55**.

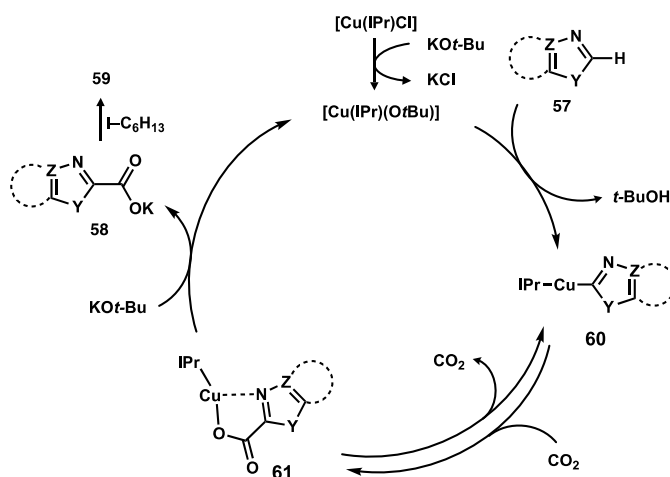
Evidence consistent with the existence of NM,NR-free NHCs have also been reported. Indeed, Ruiz et al. speculated that one such species (**47**, Scheme 13) may be an intermediate formed during the deprotonation of compound **46**, prior to N–C migration of the manganese(I) ion [82]. Furthermore, it is conceivable that deprotonation and rhenium(I) migration onto the C-center from complex **40a** proceeds via an NM,NR-free NHC species (Scheme 11). However, the isolation of such NM,NR-free NHCs have not been disclosed. Theoretical studies have invoked the formation of NM,NR-free NHC complexes in intriguing metal-catalyzed transformations. For example, DFT studies undertaken by Ariafard

et al. exploring the mechanisms of two independent experimental reports of copper(I)-catalyzed carboxylation from the Hou and Nolan groups provide evidence implicating NM,NR-type free NHC complexes [87]. Hou et al. performed the direct insertion of CO₂ into the C2–H bond of various N-heterocycles under relatively mild conditions (Scheme 16) [88].



Scheme 16. Direct copper(I)-catalyzed carboxylation of aromatic C–H bonds within heterocycles **57**.

Nolan and Cazin employed the closely related [Cu(IPr)(OH)] catalyst to install ester functionalities onto heteroarenes and polyfluorinated benzenes. These authors also applied the same chemistry to carboxylate N–H bonds of imidazoles, pyrazoles, and even oxygen-containing heterocycles such as 2-oxazolidinone [89]. Hou et al. proposed the catalytic cycle shown in Scheme 17; this cycle featured copper(I) intermediates **60** and **61**, which were both isolated from the stoichiometric carboxylation of benzoxazole [88]. The mechanism that was put forward comprised three main steps: (i) first, the activation of the heterocyclic C–H bond by copper(I); (ii) CO₂ insertion into the Cu–C bond, (iii) and finally, salt metathesis with KO^t-Bu to regenerate the active catalyst [Cu(IPr)(OtBu)] and produce carboxylate salt **58**, which ultimately provides ester product **59**.



Scheme 17. Proposed mechanism for the copper(I)-catalyzed direct carboxylation of aromatic N-heterocycles **57**.

Although carbon dioxide is inexpensive, abundant, and low in toxicity, this species is a notoriously inert molecule due to its high thermodynamic stability. Thus, the independent reports disclosed by the Hou and Nolan groups represent significant advances in the development of efficient and alternative methods for harnessing carbon dioxide in synthesis, which may have important implications for future approaches for carbon capture, storage, and reuse. Furthermore, the relatively mild reaction conditions employed suggest the capacity for high functional group tolerance in these processes. In order to better understand the carboxylation process, Ariaferd et al. conducted a detailed DFT investigation of the reaction mechanism proposed by Hou et al. [87].

Two possible pathways were identified for the first step of the catalytic cycle: namely, the protonolysis of [Cu(IPr)(OH)] by benzoxazole to form a copper(I) benzoxazole complex (Figure 5A).

Pathway I proceeds via a four-membered transition structure **TS-1a**, where proton transfer from benzoxazole to the OH ligand and benzoxazolyl migration to the copper species occur simultaneously. Alternatively, the reaction may occur via pathway II, which contains transition structure **TS-1b**, on which the copper complex interacts with the nitrogen instead of the carbon atom of benzoxazole during proton transfer to OH. The loss of water from **TS-1b** affords an NM,NR-free NHC, which then isomerizes into the C-metalated benzoxazolyl. Since **TS-1b** and **TS-1c** are lower in energy than **TS-1a**, the authors suggest that pathway II is more kinetically favorable than pathway I.

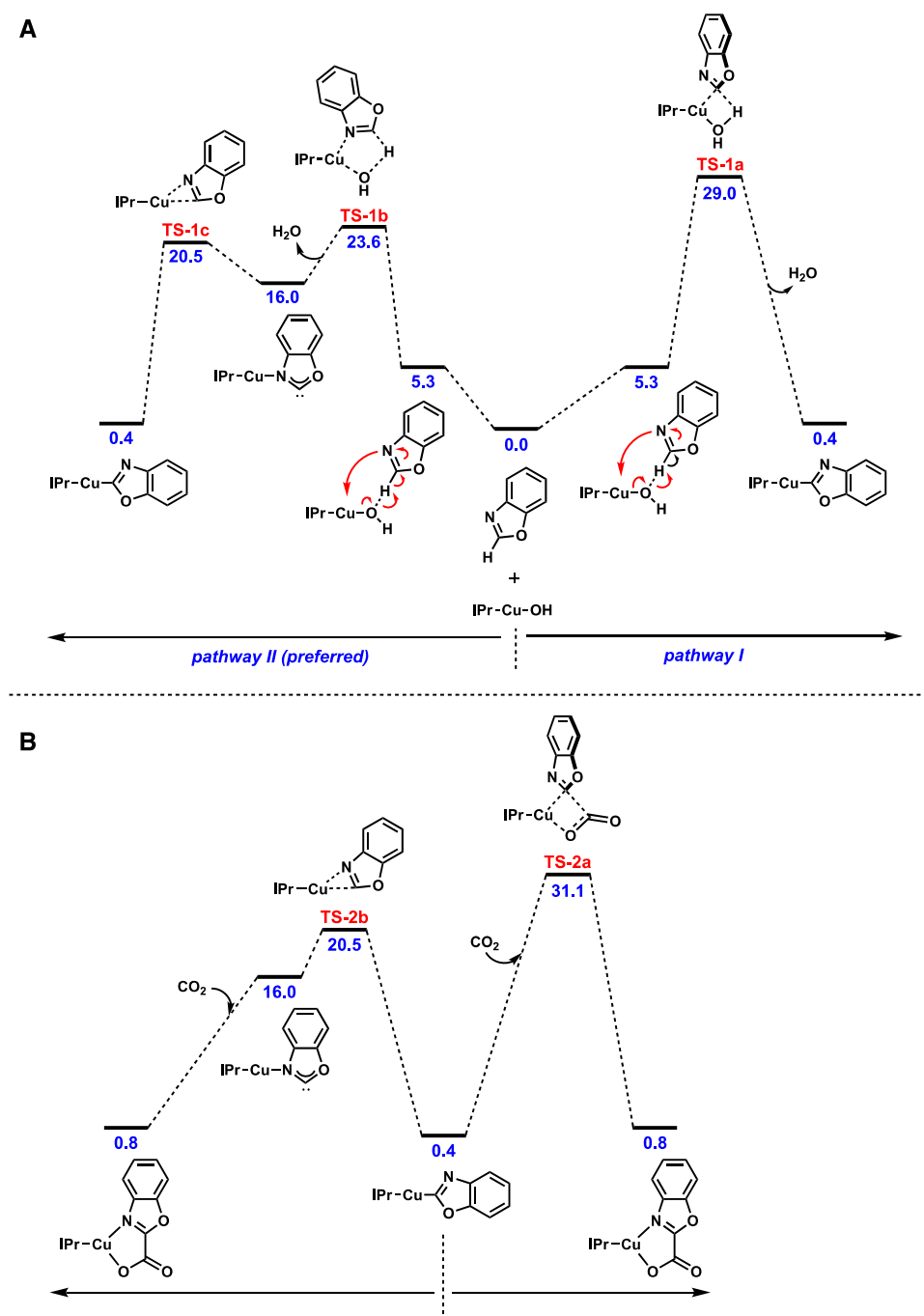


Figure 5. (A) Computed energy profiles for two possible pathways for the protonolysis of [Cu(IPr)(OH)] by benzoxazole determined via density functional theory (DFT). (B) Computed energy profiles for two possible CO₂ activation pathways from a copper benzoxazolyl complex determined via DFT. The relative free energies are given in kcal/mol.

The second step in the catalytic sequence concerns the insertion of carbon dioxide into the Cu–C bond of the copper(I) benzoxazolyl complex, resulting in a copper carboxylate complex (Figure 5B). The more conventional pathway III involves the nucleophilic attack of the Cu–C σ -bond on the electrophilic carbon atom within carbon dioxide, leading to four-membered transition structure **TS-2a**. The calculated energy barrier for this process is relatively high. However, Ariafard et al. were able to identify a second pathway with a lower energy barrier. This proposed mechanism, pathway IV, begins with the isomerization of the copper(I) benzoxazolyl complex into its *N*-metalated form. Remarkably, since the resulting NM,NR-free NHC is so much more nucleophilic than the Cu–C σ -bond, the functionalization of carbon dioxide is barrierless. The NM,NR-free NHC route also appeared to be the most energetically favorable for analogous CO₂ activation by a gold(I) species [90,91]. These findings highlight the dual functionality of NM,NR-free NHCs, which contain a Lewis acidic metal center and a Lewis basic free carbene, and suggest potential opportunities for these species to be exploited in cooperative catalysis.

Other instances of transformations that are cocatalyzed by an organometallic complex and a free NHC have been reported. For example, Yu and Zhang suggest that polyNHC dendrimer **62** can serve as both a ligand and a catalyst in the direct carboxylation into the C–H bond of terminal alkynes, enabling the synthesis of functionalized propiolic acids (Figure 6) [92]. These authors observed that the carboxylation of model substrate 4-nitro-1-ethynylbenzene proceeded most efficiently when only half a molar equivalent of CuCl (relative to the polyNHC) was employed. The yield of the propiolic acid product decreased markedly when a stoichiometric amount of CuCl was used, while no reaction occurred in the absence of CuCl. This prompted them to postulate that both the copper–NHC complex and the free NHC were required for optimal catalytic performance. Presumably, the [Cu(NHC)Cl] and free NHC fragments cooperatively activate both the terminal alkyne and carbon dioxide in the presence of a base. The NHC carboxylate coordinates to the proximal copper atom, facilitating the nucleophilic attack of the acetylide carbanion on the carboxylate carbon. This links the alkyne and carboxyl moieties within propiolic acid, which can be exchanged for another alkyne unit at the copper center.

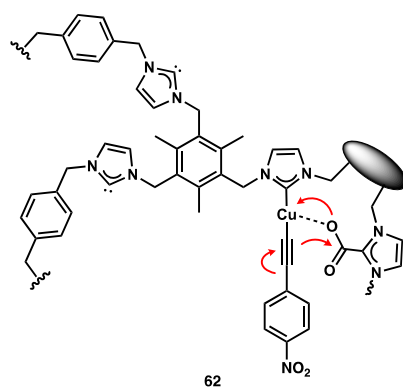


Figure 6. Cooperative CO₂ insertion into the C–H bond of terminal alkynes by copper(I) and a free carbene on a poly-NHC scaffold **62**.

In the dendrimer prepared by Yu and Zhang, the copper–NHC and free NHC are remote from each other. However, in Hou and Nolan's systems, the two functional sites in the putative NM,NR-free NHC intermediate are directly adjacent to each other. In fact, NM,NR-free NHCs could be viewed as the *N*-metalated tautomer **22a** (Figure 4). It has already been shown that complexes bearing structural motifs, such as **22a**, can activate hydrogen and acetylene gases, suggesting that it may be beneficial to ensure that the two complementary moieties are proximal. Given the general utility of the bifunctional ambident reactivity concept and encouraging evidence for the role of NM,NR-free NHCs in valuable carboxylation chemistry, further efforts directed toward the preparation and extensive study of these species is warranted. Certainly, this reactivity may extend beyond carbon dioxide to the activation of other inert small molecule feedstock chemicals.

To date, NM,NR-free NHCs have eluded isolation. Readers may have observed that there is little preventing the migration of the metal ion to the carbene, which forms the thermodynamically-favored complex in the preceding examples. DFT calculations estimate the energy separation between the copper–benzoxazolyl NM,NR-free NHC and its less energetic C-bound isomer at 15.4 kcal/mol (Figure 5). Perhaps with the appropriate structural modifications, this gap can be reduced to the point that the NM,NR-free NHC is stable enough to be isolated. Ideally, the barrier to tautomerization should be high so that the NM,NR-free NHC does not convert into the C-bound complex. The synthesis of protic NHC complexes encounter similar issues, so it is possible that strategies, such as using chelating pendant donors to direct the metal center onto a desired position, could be exploited in this domain.

3. Summary and Conclusions

Relative to the more established field of classical NHC chemistry, the fundamental understanding and applications of protic and naked NHCs is conspicuously lacking. The bonding nature of these non-classical carbenes remains a topic of debate and an area in which much remains to be discovered. As the knowledge and general understanding regarding the preparation and reactivity of protic and naked NHCs improves, their application in chemical synthesis will arguably become more widespread. It is possible that the synthetic applications of these systems may extend into chemical transformations that are traditionally performed by main group elements, such as a small molecule activation that is similar to the chemistry associated with frustrated Lewis pairs [93]. Furthermore, the aforementioned theoretical studies suggest the existence of *N*-metalated, NR-free NHC complexes in which the carbene moiety is available for cooperative reactivity [87].

Unlike classical NHCs, which tend to typically function solely as spectator ligands, the power of protic and naked NHC ligands relate to their non-innocent behavior, which is described by the bifunctional ambident reactivity concept. Their innate reactivity provides access to a rich variety of functionalized species, which lend themselves well to catalytic applications and processes that involve hydrogen bonding. The development of novel bifunctional catalysts may be enabled by utilizing this new subclass of NHCs. In addition, other applications may include exploiting these systems to facilitate the stereoselective synthesis of NHC-containing macrocycles and novel ligand scaffolds. Although protic and naked NHCs currently represent an emerging subclass of NHC molecules, their intrinsic properties and reactivity indicates that these systems have the capacity to contribute to broadening the power and scope of catalytic processes in the future.

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