Chapter 10

Pincer and Chelate N-Heterocyclic Carbene Complexes of Rh, Ir and Pd

Synthetic Routes, Dynamics, Catalysis, Abnormal Binding and Counterion Effects

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Mild synthetic routes to the title complexes have been developed, including activation of imidazolium C-H bonds, metallation assisted by a weak base, and transmetallation from metastable silver complexes. Abnormal binding via imidazole C5 rather than the usual C2 is found as a kinetic product in Ir(III) chelate complexes; the C2/C5 product ratio is strongly dependent on the counterion. Counterion dependence is also found for a fluxional process in a CNC pincer complex and explained on the basis of anion coordination. Electronic and steric properties of N-heterocyclic carbenes (NHCs) are documented for Rh(I) and Ir(I) complexes. C versus N binding is proposed as a possible binding mode for histidine. Computational work in collaboration with Eisenstein and Clot is a key element in understanding many of these effects. Hydrogen transfer catalysis is observed for Ir(III) complexes of bidentate NHCs, and the Heck reaction is catalyzed by CNC pincer complexes of Pd(II). The systems are surprisingly robust thermally and with respect to air.
Introduction

The first metal complexes of N-heterocyclic carbenes (NHCs) (1, 2), shown in Figure 1, were reported concurrently in 1968 by Öfele (1) (3), and by Wanzlick and Schönher (2) (4). Both compounds were prepared directly from imidazolium salts. Lappert made major contributions in the 1970s (5), preparing a wide variety of transition metal-NHC compounds from electron-rich olefins, e.g. 3 and 4. Nile showed that rhodium-NHC compounds, including 3, were active catalysts for hydrosilylation (6). The isolation of the first stable, crystalline NHC 5 in 1991 by Arduengo et al. (7) spurred a recent revival of this chemistry, since metal compounds could be made by adding the neutral free carbene to appropriate metal precursors. NHCs have been found to be exceptionally strongly-binding ligands, and are increasingly used in organometallic catalysis thanks to Herrmann's early work, notably the 1995 report of Heck coupling by palladium-biscarbene compounds (8). Excellent results have been obtained using NHCs as spectator ligands for aryl amination (9), olefin metathesis (10, 11), and other reactions (12). The ligand precursors, disubstituted azolium salts, are relatively easy to synthesize, allowing for ligands with diverse structural and electronic properties to be designed. A strong base such as potassium tert-butoxide or potassium hydride is usually used to prepare the free carbene, by deprotonating the azolium salt at carbon. This limits the

![Figure 1. Early examples of metal complexes of N-heterocyclic carbenes 1-4 and the first crystalline free carbene 5.](image-url)
possible range of ligand design, because acidic protons or electrophilic sites may be attacked by the base. We have recently focused on the use of multidentate NHCs as spectator ligands for late metal catalysis, and this has required the development of less harsh procedures for synthesizing metal-NHC compounds.

**Activation of the Imidazolium C-H Bond**

One potentially very mild way to make transition metal-NHC complexes is by oxidative addition of the azolium C-H bond to an appropriate low-valent metal center. Theoretical and experimental work by McGuinness et al. (13) has shown that this is a viable synthetic route. In interesting recent work, Heinekey and coworkers (14) found that one C-H bond of tris(1-pyrazolyl)borate was activated by iridium to produce an NHC-like metal-carbon bond, indicating that prior metal coordination by N-donor ligands may facilitate the desired C-H activation by electron-rich metal centers. We were able to synthesize the Fischer-type iridium-carbene 9 via the double C-H activation route shown in Figure 2 (15), and we observed the agostic intermediate 7 by low-temperature NMR spectroscopy. The α-elimination could be reversed easily to give 8, a proposed intermediate in the forward reaction, by addition of acetone. This unusual result demonstrates both the heteroatom stabilization of metal-carbene species and the aid of a pendant donor group in C-H activation.

Using this strategy with a related starting material, IrH₄(PPh₃)₂ (10), we sought to prepare chelating NHC compounds by C-H activation of the imidazolium salt, as shown in Figure 3 (16). Much to our surprise, when the potentially bidentate ligand 11b was reacted with 10, the "wrong" C-H bond was apparently activated to give the C-5 metallated compound 12b. This compound may be considered to be an abnormally bound heterocyclic carbene, in which the Fischer carbene character is probably reduced from that in the normal carbenes. The compound may also be considered as a metallated imidazolium salt. Fortunately, NHCs metallated at C-5 are easily distinguished from the normal, C-2 metallated carbenes by NMR spectroscopy, although we verified the binding mode by X-ray diffraction in several cases.

Previously, only metallation of the imidazole C-2 position had been observed, and free carbenes formed by deprotonation of imidazolium salts are always deprotonated at this position. One factor favoring the formation of the abnormal carbene in this case is steric crowding at the metal center (17). When
Figure 2. Fischer carbene complex prepared via double C-H activation.

Figure 3. Abnormal carbene formed by metallation at imidazole C4.

R is bulky, the abnormal carbenes 12a-c are formed, but for small R such as methyl, a mixture of the abnormal carbene 12d and the standard C-2 carbene 13d is formed (Figure 4). If the Ir ring size is decreased from 6 to 5, by omitting the methylene linker, only the abnormal carbenes (12e-h) are formed. The normal carbene 13i could still be formed if the C-4 and C-5 positions were...
blocked by using a benzimidazolium salt. These reactions may be performed without the necessity of excluding air or water.

The modest steric size of the i-Pr group does not seem to be a sufficient reason to prevent normal carbene formation because many normal carbenes are formed, even in our system, with much bulkier R groups, such as mesityl. The mechanism of the apparent metallation is under study and it may turn out that the reaction in fact goes by a much more complex pathway.

Recently, we observed (18) that by modifying the counterion of the imidazolium salt, and hence also for the cationic Ir-carbene product as well, we could control the ratio of normal to abnormal carbene formed for R = isopropyl and methyl. By using increasingly strongly interacting anions in the series [SbF$_6$] < [PF$_6$] < [BF$_4$] < [Br$^-$], the normal C-2 carbenes are formed to a greater extent. While the origin of this effect is not yet understood, theoretical studies (QM/MM) have indicated that the anion tends to pair specifically by hydrogen bonding with a non-coordinated imidazolium C-H bond in the products. If this is true in the transition state, which seems likely, the product distribution may be controlled by differential stabilization of the transition states by ion pairing. Work is still in progress to better determine the origin of this effect.

Very recently, in work not yet published, we have observed the acid-catalyzed isomerization from abnormal to normal carbenes. If HBF$_4$ is added to solutions of 12b-d, complete conversion to the normally bound carbenes occurs. This indicates that the C-5 metallated products are kinetic, with the possible reason to prevent normal carbene formation because many normal carbenes are formed, even in our system, with much bulkier R groups, such as mesityl. The mechanism of the apparent metallation is under study and it may turn out that the reaction in fact goes by a much more complex pathway.

Figure 4. Normal carbene formed by metallation at imidazole C2.
exception of R = mesityl (12a), which does not convert to the C-2 form in the presence of acid.

The formation of abnormal NHCs should serve as a caution when using imidazolium salts as NHC precursors in organometallic catalysis or when proposing mechanisms in the field. It is no longer safe to assume that the imidazolium salt can only bind to the metal at C-2, especially if very bulky N-substituents are used.

We have also used C-H activation as a route to prepare palladium-NHC complexes (19). The reaction of the potentially chelating imidazolium salts 14a-c with Pd2(dibenzylideneacetone)3 gives the bis-carbene complexes 15a and 16b,c, presumably the result of two C-H oxidative additions with loss of H2 (Figure 5). The mesityl N-substituent may prevent both ligands from chelating.

Figure 5. Palladium bis-NHC complexes by C-H activation.
and the trans geometry of 15a, though expected to be electronically disfavored for two such high trans effect ligands, is strongly favored on steric grounds. Regardless of the ratio of imidazolium salt added to palladium, only bis-carbene complexes have ever been observed. This implies that the Pd-monocarbene intermediate is much more reactive toward C-H oxidative addition than the starting material. We have proposed a mechanism involving initial C-H oxidative addition of 14 to Pd(0), probably with prior N-donor coordination (17) (Figure 6). The resulting palladium hydride species 18 could then reductively eliminate HBr and the resulting Pd(0) intermediate 19 could oxidatively add

![Figure 6. Proposed mechanism for formation of 15 and 16.](image-url)
another imidazolium C-H bond, followed by protonation and H\textsubscript{2} elimination to give 15,16. Alternatively, the second C-H addition could occur directly to 18, generating a palladium(IV) dihydride intermediate that would rapidly eliminate H\textsubscript{2} to give 15,16.

For low-valent metal precursors, C-H activation is therefore a viable route to metal-NHC synthesis. In cases where the free carbene cannot be formed, this may provide a route to otherwise inaccessible complexes.

**Metallation Assisted by a Weak Base**

Although bases such as acetate are far too weak to deprotonate imidazolium salts directly, they may assist in metallation, as shown by Herrmann and coworkers in the reaction of Pd(OAc)\textsubscript{2} and an imidazolium salt to give a palladium bis-carbene species (8). This reaction may proceed through a concerted mechanism where the proton is transferred directly to metal-bound acetate. This pathway may rely on the fact that agostic C-H bonding (20) increases the acidity of the agostic proton. Using this method, we prepared a series (21-23) of palladium CNC pincer (tridentate meridional) complexes (Figure 7). These complexes, very stable to air and heat, were found to be highly active catalysts for the Heck reaction at high temperatures even in air. Compound 21b was also shown to catalyze the related Suzuki and Sonogashira reactions.

A related compound, 23, the first example of a CCC pincer NHC complex

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\text{Figure 7. Synthesis of CNC-pincer complexes of palladium.}
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(22), is formed via initial C-Br oxidative addition to Pd(0) (Figure 8). When used in situ, Na₂CO₃ is sufficiently basic to promote NHC binding via deprotonation of the imidazolium groups.

![Synthesis of CCC-pincer complex of palladium.](image)

Figure 8. Synthesis of CCC-pincer complex of palladium.

While 21a,b are flat and hence are symmetric across the Pd coordination plane, compound 21c and 23 are puckered; the methylene protons resonate as an AB pattern in low-temperature NMR spectroscopy. At higher temperatures, the signals coalesce into a singlet. The dynamic process proposed is a double ring-flip inversion between two chiral C₂-symmetric atropisomers (Figure 9). We have explored the mechanism of this process in detail (24), by modifying the inner and outer sphere anions for the cationic 21c. Experimental and theoretical studies indicate that two mechanisms of inversion can operate. If a coordinating anion is used, the anion displaces the pyridine functionality prior to inversion. This is an apparently unique example of organometallic fluxionality where the rate-limiting step is substitution by the outer sphere anion. If a noncoordinating anion is used, pyridine cannot be displaced. This forces an intramolecular inversion, which results in a higher energy barrier. A similarly high barrier is seen in compound 23, where no anion is present and the aryl group is tightly bound. Compounds of this type could have applications in asymmetric catalysis if the inversion barrier were large enough to allow separation of enantiomers and to withstand the temperatures required for catalysis. Recently, Tulloch et al. (25) have reported complexes analogous to 21c, with R = mesityl or 2,6-diisopropylphenyl. These complexes show no inversion up to 80°C.

Chelating carbene ligands had rarely been successfully installed on rhodium (26, 27), and we are unaware of any previous cases for iridium. Thanks to a
collaboration with Peris and coworkers (Castellón, Spain), we were able to synthesize a series of Rh(III) (28) and Ir(III) (29) compounds with bidentate NHC ligands (Figure 10). It is unclear how M(I) is oxidized to M(III) in these reactions, which proceed similarly whether air is excluded or not. The compounds were found to be catalytically active for the transfer hydrogenation of ketones to alcohols in basic solution, via hydrogen donation from solvent isopropanol. Iridium was significantly more active than rhodium, with the most active N-substituent being neopentyl, perhaps because this group lacks a beta hydrogen and is inert to Hofmann degradation. Compound 25f, loaded at 0.1 mol%, gave an impressive 50,000 turnovers per hour for the reduction of

![Figure 9. "Ring-flip" atropisomerism process observed by NMR spectroscopy.](image)

![Figure 10. Syntheses of Rh(III) and Ir(III) bis-NHC complexes.](image)
benzophenone at 80°C. Labeling experiments (29) on 25f support a monohydride mechanism for transfer hydrogenation.

Compounds 25 are air and water stable, and even the catalytic reactions are unaffected by the presence of air or water in the system. This stands in contrast to phosphine-based systems, where catalysis often must be performed under inert and/or dry conditions.

In an effort to compare the effects of chelating triazole-based NHCs with the more commonly used imidazole-based ligands, we found a very interesting result. The reaction (Figure 11) of ligand precursors 26a,b with [Rh(norbornadiene)Cl]2 gave some of the expected biscarbene products 27a,b, along with a majority of the unexpected products 28a,b (30). The diene ligand has rearranged to a nortricyclyl group, bound in a fac geometry with respect to

![Figure 11](image)

*Figure 11. Metallation of bis-NHCs to give Rh-nortricyclyl complex.*

the bis-NHC. Mechanistic investigations are not yet complete, but a plausible mechanism involves oxidative coupling followed by C-H reductive elimination (Figure 12). Such a mechanism could plausibly be responsible for the dissociation of cyclooctadiene in the formation of 25a-g, and would account for the oxidation of M(I) to M(III), if initial C-H oxidative addition of an azolium salt produced the required metal hydride species.
Transmetallation from Ag-carbene Complexes

The important work of Wang and Lin (31) demonstrated that silver(I) complexes of NHCs could be synthesized directly from imidazolium salts and Ag₂O or Ag₂CO₃. These complexes are capable of transferring the carbene ligand to other metals, as has been demonstrated for Pd (25, 31-33) and Au (31). We have extended this methodology to rhodium and iridium (34) in the syntheses of the monocarbene compounds 31a,b (Figure 13). Because the benzylic protons are diastereotopic by NMR spectroscopy, these compounds demonstrate hindered rotation about the M-carbene bond. We displaced the rather bulky cyclooctadiene ligand with 2 CO molecules to form 32a,b. The benzylic protons now exchange on the NMR timescale, and we were able to calculate the activation free energies for M-C bond rotation. Our observations confirmed that for NHCs, the M-C bond is essentially single (1), although M-C rotation may be hindered sterically. IR spectroscopy of 32a,b allowed the estimation of the donor power of the NHC ligand, which supported theoretical calculations (35) and previous experimental work (36), indicating that NHCs are more strongly donating than even alkyl phosphines.

Implications for Metalloproteins

Given the known strength of the M-C bond in imidazole-based NHCs, the question arises of whether histidine residues in proteins could bind through carbon instead of nitrogen. This has never been reported, but the hypothetical C-bound tautomer is essentially indistinguishable by X-ray diffraction from the conventional N-bound form (Figure 14). The situation here is notably different from known NHCs, because the N-substituents can both donate electron density to the ring, and more importantly, block N-M binding from occurring. In one case, Taube and coworkers (37) directly observed the tautomerism for a ruthenium compound, demonstrating that C-binding can be thermodynamically preferred even when N-binding is possible.
In collaboration with Sini and Eisenstein, the relative stability of species 33 and 34 have been calculated for a series of metal fragments (38). For several of these fragments, the C-bound form was found to be more stable. Moving down a group tends to increase the relative stability of the C-bound form. The presence of the potentially H-bonding ligands M-Cl cis to imidazole also stabilized the C-bound tautomer via N-H···Cl hydrogen bonds. It is plausible that an appropriately arranged metal-binding site in a metalloprotein could cause a similar effect.

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Figure 13. Synthesis of Rh(I) and Ir(I) complexes of NHCs via transmetallation.

Figure 14. C-M versus N-M binding in histidine.
Conclusions

N-heterocyclic carbenes are proving to be very useful ligands for a wide variety of catalytic applications, owing to their strong binding, and the stability of many NHC complexes to heat and air. The new synthetic routes now available for substituted azoles permit the rapid construction of complex ligand architectures, often a relatively arduous task for phosphines. The development of these more gentle metallation protocols should allow incorporation of more elaborate functionalities, such as molecular recognition elements or pendant reactive groups.

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Literature Cited