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Dossier
Special Issue in Honour of Yves Chauvin
Numéro spécial en l'honneur de Yves Chauvin

Carbenes in Synthesis and Homogeneous Catalysis

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Résumé — Les carbènes en synthèse et en catalyse homogène — Les carbènes N-hétérocycliques sont d'excellents ligands pour le rhodium ou l'iridium et les complexes qui en résultent peuvent agir comme catalyseurs de la réaction de transfert d'hydrogène et de la réaction de Heck. Les derniers résultats obtenus par notre équipe sont exposés : synthèse des ligands et applications en catalyse ; élaboration des sels d'imidazolium pour faciliter la chélation ; liaison anormale des carbènes.

Abstract* — *Carbenes in Synthesis and Homogeneous Catalysis — *N-heterocyclic carbenes are excellent supporting ligands for Rh and Ir complexes that can act as catalysts for hydrogen transfer and Heck reactions. Recent developments on synthesis of ligands and complexes and on catalytic applications from our group are reviewed. Design of imidazolium salts to facilitate chelation is discussed as well as abnormal binding of NHCs.*

DEDICATION

Dedicated to Yves Chauvin, my 'godfather' (*parrain*) when I was an Attaché de Recherche in the CNRS lab at Gif-sur-Yvette, in admiration of his great personal and scientific qualities.

INTRODUCTION

Homogeneous catalysis by transition metal complexes has transformed both industrial and organic synthetic chemistry in many ways. In some cases entirely new reactions are permitted, such as alkene metathesis or methanol carbonylation to acetic acid. metallocene polymerization catalysts also exquisite control of the microstructure and properties of the polypropylene polymer produced. Catalysts can also speed up known reactions such as hydrogen transfer. Asymmetric catalysts can form enantioenriched products, often with very high enantiomeric excess.

Catalyst properties are tuned by choice of metal and ligand. Moving from one metal to another is a very large discontinuity, so delicate control of properties requires a ligand set that can readily be altered in small steps such that its electronic and steric properties can be independently tuned. The traditional ligand class of P-donor ligands, PR_3, not only has excellent tunability by alteration of R, but the Tolman 'map' provides a quantitative account of the variation in electronic and steric properties with change of R.

1 N-HETEROCYCLIC CARBENES

In the last ten years, N-heterocyclic carbenes (NHCs) have emerged as a new ligand set that rivals PR_3 in tunability, as

NHC = N-heterocyclic carbene; cod = 1,5-cyclooctadiene; iPr = isopropyl; R = generalized substituent; MLn = metal and generalized ligands.

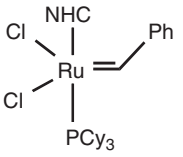


Figure 1

'Second generation' Grubbs Catalyst modified by an NHC ligand.

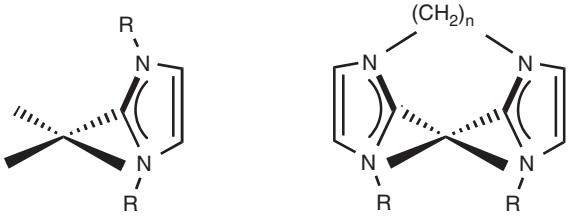
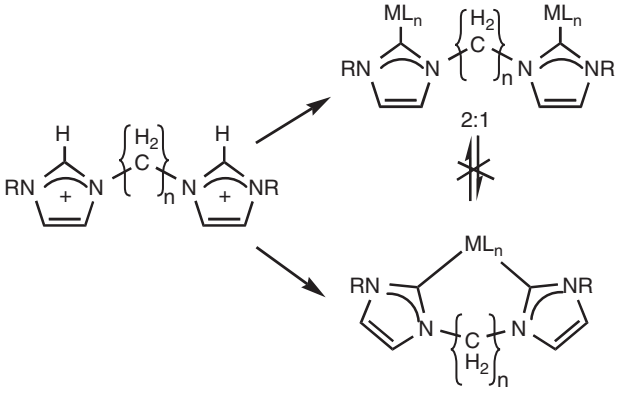


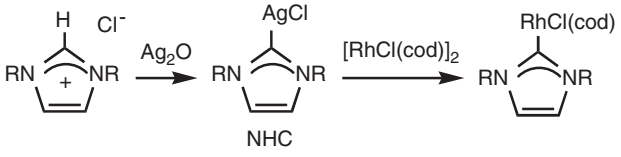
Figure 2

The preferred NHC conformation in a square planar complex, shown on the left, is only achievable in a chelate with a long linker (right), with n = 3 or 4.

Equation 1



Equation 2



Equation 3

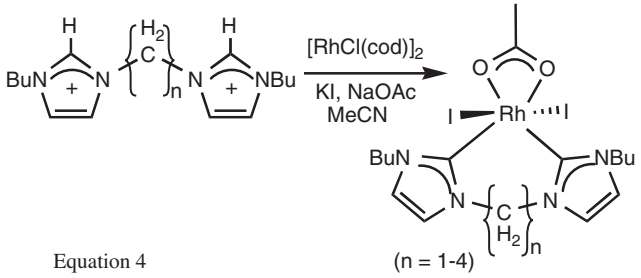
well as having a good performance as a spectator ligand in catalysis. This latter property arises from the ability of the NHC to stabilize the intermediates and transition states for the catalytic reaction such that the potential energy surface is relatively flat, while itself remaining firmly bound to the metal and not participating directly in the reaction.

Phosphines, particularly chelating ones, have helped develop the catalytic chemistry of rhodium and iridium, but N-heterocyclic carbenes (NHCs), normally derived from deprotonation of imidazolium salts *(Equation 1)* and coordination of the resulting carbon centered lone pair, have been greatly valued as spectator ligands in catalysis [1]. The best example *(Fig. 1)* is the NHC-modified Grubbs metathesis catalyst obtained by replacing a phosphine in the standard catalyst by an NHC ligand with mesityl wingtip substituents [2]. Monodentate NHCs tend to be used, in part because chelating NHCs are hard to install on a metal. Attempts using the usual synthetic routes often give 2:1 M:L complexes, each NHC binding to a separate metal. Unlike phosphines, NHCs bind irreversibly, so the kinetic 2:1 M:L products do not rearrange to the desired 1:1 chelates *(Equation 2)*.

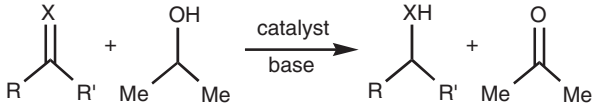
2 LINKER EFFECTS IN N-HETEROCYCLIC CARBENE COMPLEXES

A recent study [3] provided an insight into how to design chelating NHCs to give 1:1 or 2:1 complexes, as desired. Reaction of the bis-imidazolium salt with strong base, as in Equation 1, is not reliable because the linker CH bonds can also be deprotonated. Treatment of the imidazolium salt with Ag_2O has proved [4] most useful for preparation of monodentate NHC Rh(I) complexes. This involves the Ag NHC complex as intermediate, followed by transmetallation from silver to rhodium, as shown in *Equation 3*.

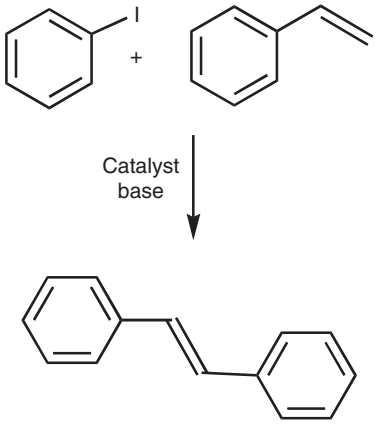
Applying this strategy to precursor imidazolium salts that could give chelating NHCs proved more complicated than expected [3]. With the wingtip nitrogen substituent being *n*-butyl, the reaction outcome depended on the linker length, n. For short linkers (n = 1 or 2) the product was the 2:1 complex, but for longer linkers (n = 3 or 4) the product was the chelating 1:1 complex. A steric origin was suggested for the selectivity. The NHC ligands have a sterically bulky axis containing the linkers and the wingtip *n*-Bu groups and a sterically slim axis normal to the bulky axis. An NHC in a square planar Rh(I) complexes prefers to orient itself out of the square plane of the Rh(I) so that the bulky N-substituents occupy the empty sites above and below the Rh(I) square plane. Only when the linker is long *(Fig. 2)* can this be achieved in a chelate complex. In a short linker case, the preferred conformation can only be achieved by formation of a 2:1 complex with each NHC in an out of plane conformation. Other factors governing the reactivity have since



Equation 4



Equation 5



Equation 6

emerged beyond the linker length, but this study is in progress.

In a direct metallation procedure *(Equation 4)*, a 1:1 Rh(III) chelate complex was formed for all values of linker length, showing that chelation is in principle possible even for the short linkers in the octahedral environment of the Rh(III) complex. In this case the smaller ligand, the acetate, is located opposite the bis-NHC, and neither acetate nor iodide is very bulky so that chelation is possible. The configuration adopted is therefore a delicate function of the exact complex and synthetic route. H_2 is probably evolved to maintain redox balance in the oxidation of the metal in Equation 4 because the reaction does not seem to depend on the presence of air.

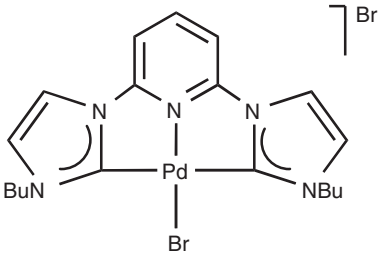


Figure 3

This CNC pincer catalyst is extremely robust both thermally and to air oxidation.

3 CATALYTIC ACTIVITY OF N-HETEROCYCLIC CARBENE COMPLEXES

These Rh(III) complexes and their iridium analogues are excellent catalysts (up to 6000 turnovers·h^{-1}) for hydrogen transfer reduction of ketones by isopropanol *(Equation 5)* [5]. In what is sometimes considered a 'green' reduction procedure [6], these catalysts proved equally applicable to aldehydes and imines, substrates that are less often encountered in prior reports. There was a surprisingly strong dependence of the activity on the nature of the wingtip substituent. Neopentyl, lacking a beta-hydrogen, proved to be the best, perhaps because the presence of a beta-hydrogen leads to Hofmann degradative cleavage of the substituent group.

Phosphine complexes tend to thermally decompose at 100-150°C, so catalytic activity cannot be increased by heating above that range; many are also air-unstable. The majority of the NHC catalysts we have investigated prove to be air and thermally stable to an unusual degree. This is beneficial in ease of handling. An extreme case was a CNC 'pincer' complex *(Fig. 3)* synthesized by treatment of the precursor imidazolium salt with $Pd(OAc)_2$ at 160°C, that shows similar catalytic activity under either argon or air for a standard Heck reaction between PhI and styrene in refluxing diethylacetamide (DEA, bp 184°C) in the presence of NaOAc as base. Turnovers as high as 16 000 were found with low catalyst loadings. Thermal decomposition to give nanoparticulate palladium which acts as a heterogeneous catalyst is always a risk at high temperatures but addition of mercury caused no change in catalytic activity. This mercury test is consistent with homogeneous catalysis rather than heterogeneous because Hg(0) poisons heterogeneous catalysts [7]. The same catalyst also brings about related Suzuki and Sonogashira carbon-carbon coupling reactions [8].

Replacement of the nitrogen of the central pyridine motif by a carbon and of the direct linker by a methylene bridge *(Fig. 4)* gave a related CCC pincer with a chiral conformation but this was relatively inactive as a catalyst probably because pyridine dissociation is required to create needed

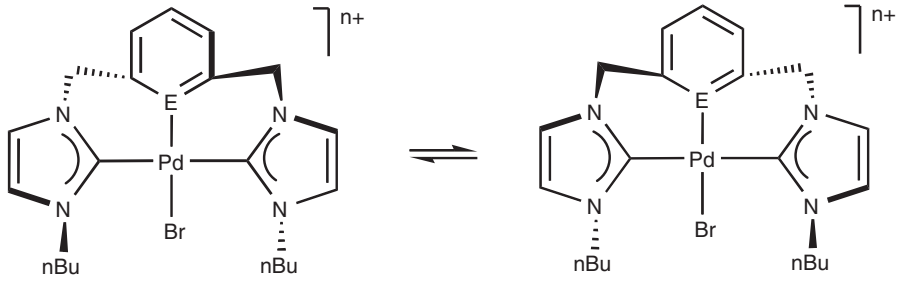
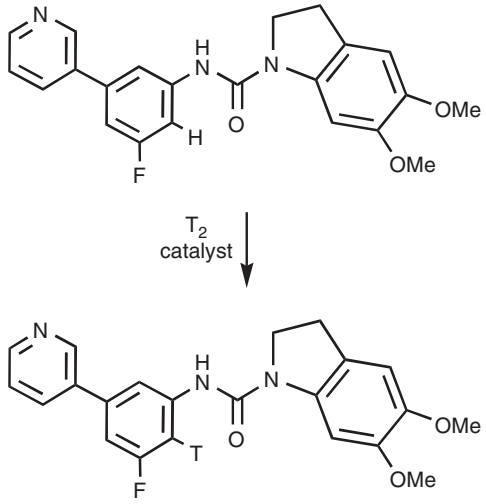


Figure 4

These CCC (E = C, n = 0) and CNC (E = N, n = 1) pincer complexes have a pair of enantiomeric conformations. The CNC version has much faster fluxional exchange between the two forms because the N can dissociate.



Equation 7

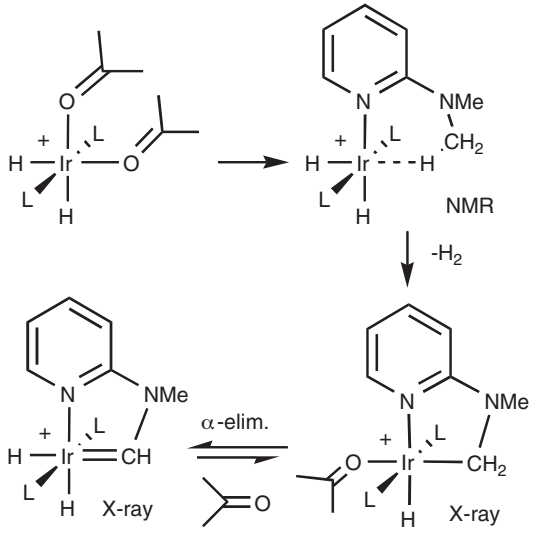


Figure 5

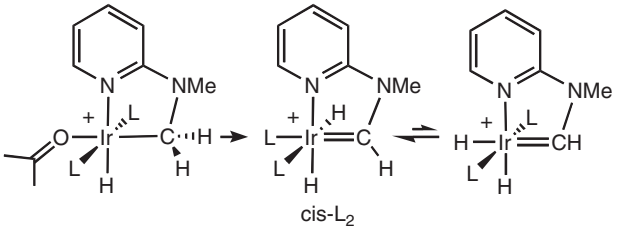
The cyclometalation assisted isotope exchange pathway for this substrate involves a double geminal CH activation with formation of a carbene.

empty sites at Pd in the CNC case. The corresponding CNC pincer was more active and also gave faster fluxional exchange between the two forms because the N can dissociate (fluxional exchange barriers: CNC, 52 kJ/mol; CCC, 75 kJ/mol) [9]. A review covers this and other recent homogeneous catalytic applications of chelate and pincer N-heterocyclic carbene complexes [10].

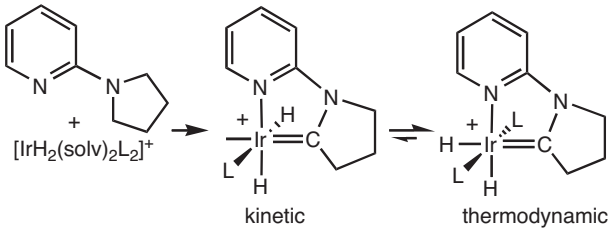
4 CYCLOMETALATION AND ABNORMAL BINDING OF N-HETEROCYCLIC CARBENES

Cyclometalation, chelate controlled C-H activation, has been intensively developed recently as a means of functionalizing organic compounds [11]. In one application, our iridium catalysts, originally examined for deuterium exchange [12] have now been used for the selective commercial tritiation of pharmaceuticals *(Equation 7)* [13]. We have looked at the mechanism in some detail and found an unexpected problem when a CH_2 group to be exchanged is also α to a nitrogen atom *(Fig. 5)*. In such a case, double geminal CH activation tends to occur to give a carbene that is stabilized by the α nitrogen atom and isotope exchange is relatively slow. The agostic intermediate of Figure 5 was observed by ^{1}H NMR spectroscopy at low temperature and the alkyl and carbene complexes were stable enough to fully characterize, including by X-ray diffraction. Computational work in collaboration with Eisenstein and Clot identified the factors that flatten the PE surface for the fast reacting substrates, notably the alternation of high and low trans effect ligands in mutually trans sites during the cycle. A cis-phosphine intermediate, predicted by the computational work *(Equation 8)* but initially undected experimentally, was finally identified by using a conformationally more rigid substrate *(Equation 9)* [14].

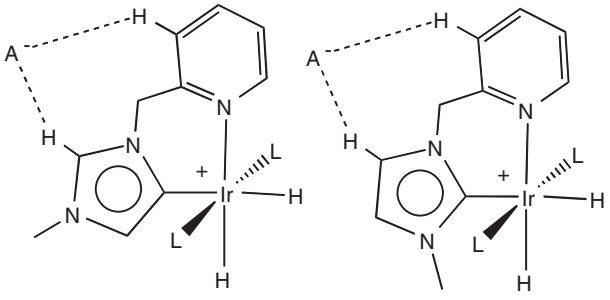
In another development of cyclometalation, this time as a means to access NHC complexes, we found that imidazolium salts with pyridine wingtip substituents do not always cyclometallate with $IrH_5(PPh_3)_2$ to give normal



Equation 8



Equation 9



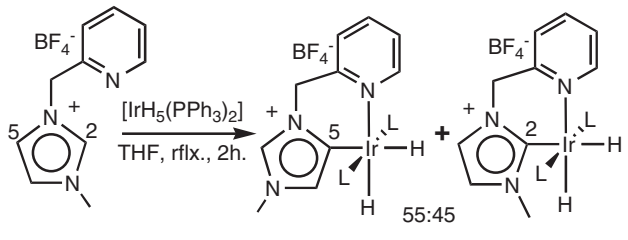
Free carbene	0	-14.9
$IrH_2L_2^+$, no A^-	0	-10.1
$A^- = BF_4$	0	-3.0
$A^- = Br$	0	-1.6

Figure 6

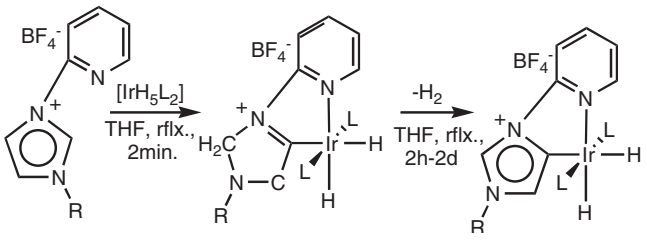
The calculated energy differences between normal and abnormal NHC isomers in kcal/mol.

(C2-bound) NHC complexes. In one case both normal and abnormal (C5-bound) NHCs were formed on metallation [15]. More often, with larger wingtip substituents, the abnormal complex was the only product. In the case where the NHC and pyridine were directly linked, a hydrogenated intermediate was observed and in one case (R = mesityl) fully characterized, including by X-ray diffraction. In ONIOM (B3PW91/UFF) calculations, Eisenstein and Clot showed that the abnormal NHC has exceptionally strong ion pairing with the counterion. The calculated consequences for the normal/abnormal energy difference are large. The free normal NHC is fully *ca*. 15 kcal/mol more stable than the abnormal; when the metal and ligands are present this value drops to 10 kcal/mol; finally, when the counterion is included, the two isomers become almost isoenergetic *(Fig. 6)*. bromide and BF_4 are not significantly different — although the latter is intrinsically a weaker hydrogen bonder it is also chelating and can make contacts with up to three CH bonds of the ligand.

Changing the counteranion along the series Br, BF_4, PF_6, SbF_6 in their ion-paired 2-pyridylmethyl imidazolium salts causes the kinetic cyclometallation products with $IrH_5(PPh_3)_2$ to switch from the normal C2 path to the abnormal C5 path [16]. Computational work (DFT) suggests that the abnormal path involves C-H oxidative addition to Ir(III) to give Ir(V), followed by loss of H_2 with little anion dependence. The normal path, in contrast, goes by heterolytic C-H activation with proton transfer to the adjacent hydride. The proton that is transferred is accompanied by the counteranion in what we term an anion-coupled proton transfer, leading to an anion dependence of the N path, and therefore of the normal/abnormal selectivity. The normal path goes via Ir(III), not Ir(V), because the normal NHC is a much less strong donor ligand than the abnormal NHC. PGSE NMR experiments in collaboration with Alceo Macchioni (Perugia) support the formation of ion-pair in both the reactants and the products. ^{19}F, ^{1}H-HOESY NMR experiments indicate an ion-pair structure for the products that is consistent with the computational prediction of the ion pair structure.



Equation 10



Equation 11

CONCLUSION

Carbenes and particularly NHCs are having an increasing impact on organometallic synthesis and catalysis. The present review provides a few examples from our own group showing how careful ligand design is needed to facilitate chelation in NHCs and how the resulting complexes can be useful in catalysis. Abnormal NHCs are discussed including an unexpected anion effect on the CH activation pathway leading to these complexes.

ACKNOWLEDGEMENTS

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