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Account / Revue

New routes to carbene complexes for thermally and oxidatively robust homogeneous catalysts

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Abstract

Two synthetic methods allow synthesis of catalytically active metal carbene complexes from imidazolium salts without passing through the free carbene. Abnormal carbene binding via C-4(5) is possible, influenced by ion pairing. Imidazolium-based ionic liquids may be non-innocent solvents in homogeneous catalysis. ***To cite this article: E. Peris, R.H. Crabtree, C. R. Chimie 6 (2003) 33–37.***

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Résumé

Des complexes carbéniques issus de sels d'imidazolium sont synthétisés par deux voies, sans passer par le carbène libre, et peuvent être utiles en catalyse homogène. De tels carbènes peuvent également se lier anormalement en C-4(5), selon le contre-ion. On avance l'hypothèse que des liquides ioniques peuvent potentiellement jouer le rôle de ligands en catalyse homogène. ***Pour citer cet article: E. Peris, R.H. Crabtree, C. R. Chimie 6 (2003) 33–37.***

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Keywords: metal carbene complexes; imidazolium salts; free carbene; ion pairing; ionic liquids; homogeneous catalysis

Mots clés : complexes carbéniques ; sels d'imidazolium ; carbène libre ; paires d'ions ; liquides ioniques ; catalyse homogène

1. Introduction

The concept of forming N-heterocyclic carbene (NHC) complexes by replacing the acidic 2-H of the imidazole ring by a metal fragment dates back to the work of Öfele and of Lappert [1] (Fig. 1). The area remained quiescent for decades until Arduengo [2] showed that the free carbene could be obtained as a species stable enough for crystallographic characterization if sufficiently bulky alkyl or aryl groups were present at the 1 and 3 positions. Herrmann [3] took the story a step further by showing that such carbenes are excellent stabilizing ligands for a variety of homogeneous catalysts. Tens of research groups [4a] have added carbenes to their armory and have provided further examples of catalysts for a wide variety of reactions. Among organometallic catalysts, only phos-

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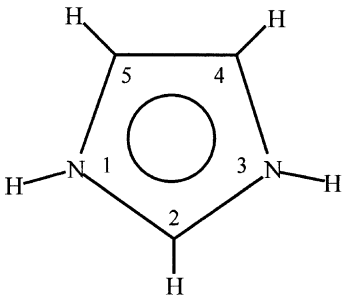
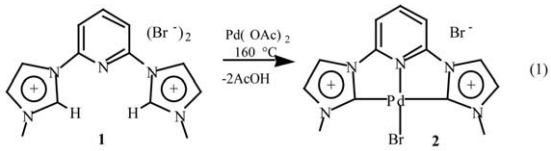
phines are currently more versatile than carbenes and since the carbene field is much less developed, we can expect rapid advance in the next few years. We have also recently reviewed related aspects of our work in the field [4b].



2. Base-assisted metallations

Our efforts have been directed towards incorporating NHCs into chelate [5] and pincer [6] ligand systems such as have proved invaluable in phosphine-based catalysis. This requires us to avoid the standard synthetic route [4] via deprotonation at the imidazole 2-position because this requires strong bases and nucleophiles. These are likely to prove incompatible with the types of poly-imidazolium salts that are needed to gain access to chelate and pincer NHCs because these can contain a variety of acidic and electrophilic centers that would lead to mixtures of products. In addition, we wanted to be able to use smaller wingtip groups at 1 and 3 positions than are required to stabilize the free carbenes.

Agostic C–H binding to metals [7] is known to acidify the proton that is bound, leading to the idea that a metal acetate might be able to give direct metallation via the reaction of equation (1). In this scheme, the oxidation state of the final product is expected to be the same as that of the starting acetate. As a test of this procedure for a CNC pincer carbene complex, we looked at the reaction of equation (1), in which the readily prepared bis-imidazolium salt, **1**, reacts with $Pd(OAc)_2$ at 165 °C to give the square planar Pd(II) complex, **2** [8]. The complex is unaffected by heating for many days at 165 °C in DMSO and air, in contrast with phosphine derivatives which tend to decompose at this temperature even in the absence of air. Note the use of the pyridine unit to act as the initial binding site for the ligand, bringing the imidazolium rings into the vicinity of the metal.

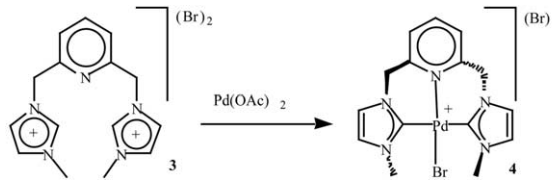


(1)

The robustness of **2** is demonstrated by its ability to catalyze the Heck reaction at 165 °C, even in air. We checked that the system retained activity in the presence of Hg(0), suggesting that metallic Pd(0) is not the catalytically active species. The related Sonogashira and Suzuki coupling reactions are also catalyzed by **2** [8].

The high stability of **2** prompted a study of its immobilization in a clay to look at the catalytic activity of the heterogeneized system [9]. Indeed, **2** and related compounds with different wingtip alkyl groups (*n*-Bu, CH_2Ph, etc.) can readily be immobilized by impregnation on montmorillonite K-10, affording effective supported catalysts for the standard Heck coupling. The supported catalysts so obtained show catalytic activity similar to that of their homogeneous counterparts. The determination of Pd content on the supported catalysts by XPS and elemental analysis, before and after each catalytic reaction, shows that leaching is negligible. The XPS analysis of the catalysts after its use in the catalytic reactions showed that no Pd(0) is produced. Once the reaction conditions were optimized, we were able to recycle the catalyst at least ten times, without significant loss of activity, even in the cases where the reactions were performed at 180 °C.

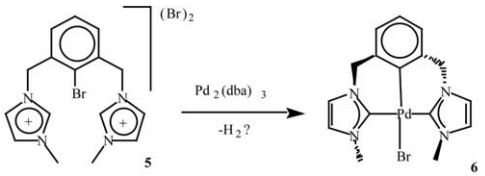
The methylene-linked CNC pincer, **3** [10], is also readily metallated in a similar manner to give a twisted pincer complex, **4**, with a chiral conformation (equation (2)). Ready conversion between the two chiral atropisomers is possible on the NMR timescale, so the complexes cannot be used for the asymmetric version of the Heck reaction. It should be possible to block the interconversion by replacing a linker proton with an alkyl or aryl group, however, in which case the wingtip R groups would project in a chiral manner into the substrate binding pocket.



(2)

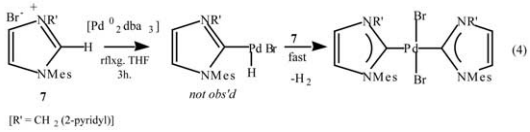
3. Metallation via CH activation

Such a CH activation has been demonstrated for Pt(0) [11] and is suspected for Pd(0) [12]. Another indication of the viability of CH activation as a synthetic route, came from our synthesis of the CCC pincer analogue, **6**, from precursor **5**. In this case, a C–Br oxidative addition was chosen to install the phenylene group in analogy with the pyridine group of the CNC pincer. As the oxidative addition was expected to require a low-oxidation-state starting material, we turned to the common Pd(0) complex, Pd_2dba_3. The final product contained a bis-carbene product with no indication of the monocarbene intermediate (equation (3)). This route was efficient under air or argon, so H_2 may be released in the reaction.



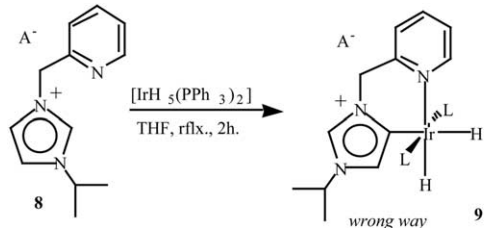
(3)

This proposal of H_2 release was followed up by looking at the reaction of the mono-imidazolium salts, **7**, with Pd_2dba_3 [13]. Instead of the formation of a carbene Pd(II) hydride, only the bis carbene was isolated or observed even with restricted amounts of imidazolium salt and under mild conditions (equation (4)). This makes it seem that the second step of the reaction, between a metal hydride and an imidazolium salt, can be very fast, even though intermolecular. This suggested that a general route to carbene complexes might be possible by reaction of a metal hydride with an imidazolium salt.



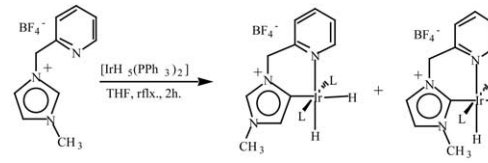
(4)

We were therefore encouraged to look for other examples of the proposed pathway of equation (4) [14]. Since IrH_5L_2 (L = PPh_3) is known to react with pyridine in THF at reflux to give $[Ir(py)H_3L_2]$, we looked at the pyridine–carbene chelate precursor, **8**. This indeed reacts with IrH_5L_2, but to give the abnormal 'wrong way' product **9**, in which the metal is attached, not to the activated C-2 position, but to C-5 (equation (5)). This was obvious both from the X-ray structure and from the spectroscopic data.



(5)

On moving to the smaller wingtip Me group, we were able to obtain a 55:45 ratio of the wrong and right carbenes (equation (6)). Later work described below yielded the pure right (C-2) and wrong (C-5) carbenes for study. One well-marked spectroscopic difference between the two was the chemical shift difference between the two imidazolium protons in the two isomers. In the normal carbene, these are little different and, accordingly, are little apart from one another in the NMR spectrum. In the abnormal form, in contrast, the two Hs differ substantially, one being the active 2-H and the other being the C-5 H endo to the metal. These differ by a full 2–4 ppm in chemical shift. The mechanism of the formation of the C-4(5) bound NHC is still uncertain and needs further study.



(6)

This work established the existence of 4(5)-bound carbene complexes, where the electronic situation is presumably closer to that in the more normal Fischer carbenes of type $L_nMCR(NR_2)$. It also implies that catalysts that are formed in situ by incubation of a metal salt with an imidazolium ion may not have the expected structure. Abnormal binding may be generally expected for hydride precursors but we find it can be suppressed by blocking the 4,5 sites, for example using the benzimidazolium analogues.

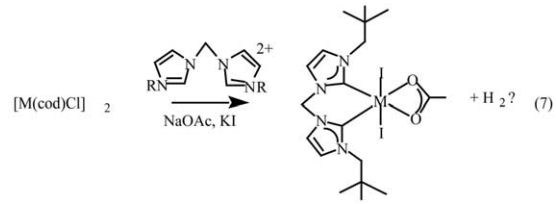
A remarkably strong anion effect was seen in this system: the BF_4^- imidazolium salt gave the 55:45 mixture of isomers mentioned above, but Br^- as counterion gave essentially only the C-2 product and SbF_6^- gave essentially only the C-4(5) form. Such a large shift from one product to another is unexpected and probably related to the existence of tight ion pairs for

organometallic ions in solution in solvents such as CH_2Cl_2 or THF. Theoretical work by Clot and Eisenstein [15] on the system showed that while the free carbene and the Ir complex favor binding at C-2, inclusion of the counter-ion in the calculation (DFT) led to an essentially isoenergetic situation. Attempts to interconvert the isomers completely failed, so these are kinetic not thermodynamic products, but the same ion-pairing effects presumably operate at the relevant transition states.

The ion-pair structure was directly observed in a prior case in NMR using NOE effects and the experimentally favored ion-pair structure was predicted from DFT calculations of the electric field around the cation [16]. In the present case, ion pairing was readily apparent because the C-2 proton of the C-4(5) carbene, pointing to the exterior of the molecule, shifts by about 2 ppm on addition of Br-ion to the SbF_6 salt but no other resonance is much affected. Together with the C-H··anion hydrogen bonding seen in the X-ray structure, this illustrates the special affinity of the C-4(5) carbene for the anion, stabilizing this form relative to the C-2 one.

This result illustrates the potential importance of the counter-ion, often ignored in organometallic work to the extent of omitting it from the diagram of the complex reported in the paper. This attitude commonly leads to work being carried out with only one counter-ion in which case counter-ion effects would be missed. Ion pairing has been implicated in metallocene polymerization, however [17]. A change of anion has sometimes proved beneficial in improving the ee of asymmetric catalytic reactions with late transition metals [18].

Our initial work in catalytic rhodium [19] and iridium chemistry is illustrated in equation (7) where the bidentate carbene precursor salt has no initial binding site such as the pyridine of the CNC pincer. In spite of this, the synthesis of the product occurs in good or acceptable yield. The Rh(III) product has rather poor catalytic activity but the Ir(III) species can be very active for transfer hydrogenation from *i*PrOH as solvent to Ph_2CO, with up to 50 000 turnovers per hour at 80° C (M = Ir; Ph_2CO/cata/base: 1000/1/5) in the presence or absence of air. By far the best wingtip group in this chemistry is neopentyl. This could be preferred because it lacks β-hydrogens, which exempts it from Hoffmann degradation of the wingtip alkyls, but benzyl that also lacks β-Hs is poor.



Neopentyl groups seem to improve the synthetic yields as well as giving highly active catalysts, so we have continued to use them. The weak link in the bis-carbene is probably the central CH_2 group that we hope to replace by a more inert linker in future work. Again the catalyst system is entirely unaffected by air and is very robust compared to comparable phosphine systems. The tolerance of what are usually catalyst poisons such as air and water could make these catalysts more generally useful than phosphine analogues and hold hope for future developments. Such catalysts could also be regarded as at least somewhat 'green' in avoiding the presence of phosphorus and in not needing inert atmosphere or dry conditions, provision of which imply energy input.

4. Non-innocence of imidazolium derived ionic liquids as solvents

The ready metallation of the imidazolium salts under a variety of conditions raises another point relevant to green chemistry. Ionic liquids commonly used in that field as solvents for TM catalysts are very often imidazolium salts [20]. It is therefore obvious that carbene complexes could well be formed in situ under reaction conditions in which case the ionic liquid could play more than a purely solvent role; an example of such a situation has indeed just been reported [21].

5. C-Bound histidine in metalloenzymes

Since metals are often bound via histidine (His) in metalloenzymes, but X-ray structural studies of the protein cannot distinguish between C and N, it is possible that His may be capable of binding in a non-classical C-form [22]. If so, organometallic species could be far more common in biology than currently recognized. In collaboration with Sini and Eisenstein [23], we looked at this problem by calculating the

energy difference expected between C and N bound forms of imidazole. The results showed that for many metal fragments the C-bound form was predicted to be thermodynamically more stable. The better hydrogen bonding possible by the NH bonds at positions 1 and 3 in the C-bound form, versus a single such bond in the N-bound form may help stabilize the C-His form. A metalloenzyme could readilyarrange the presence of suitable hydrogen bond bases to favor the C-form. The N to C rearrangement might be expected to have a significant barrier, but in a single case Taube [24] experimentally observed such a rearrangement at room temperature, so the barrier need not be excessive. No cases are yet known in enzymes, however, but it is hard to tell C from N binding. A recent review has reiterated this proposal [3b].

6. Outlook

The strong binding, thermal stability and air stability of carbene complexes mean that they have substantial advantages over other ligand types. The easy incorporation of imidazolium and related heterocycles such as triazoliums into complex architectures suggests that they may prove useful in a variety of materials and sensor applications or in situations where a molecular recognition element or cooperative reactive function is appended to a catalytic site. Their oxidative robustness should allow catalysis of oxidation reactions, previously difficult in view of the oxidation of PR_3 complexes.

7. Conclusions

Synthetic routes that avoid strong bases allow N-heterocyclic carbenes to be incorporated into pincer and chelate ligands that can give catalysts that are very thermally robust and are catalytically active even in air. Binding at C-5 is observed in some cases depending on the nature of the counter-ion. Neopentyl wingtip groups prove to be particularly useful. The possibilityof C-bound histidine in metalloenzymes is discussed.

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References

[1] (a) J. Muller, K. Ofele, G. Krebs, J. Organometal. Chem. 82 (1974) 383; (b) D.J. Cardin, B. Cetinkaya, M.J. Doyle, M.F. Lappert, Chem. Soc. Rev. 2 (1973) 99; (c) B. Cetinkaya, P. Dixneuf, M.F. Lappert, J. Chem. Soc. Dalton Trans. (1974) 1827–1833.

[2] A.J. Arduengo, R.L. Harlow, M. Kline, J. Am. Chem. Soc. 113 (1991) 361.

[3] (a) K. Ofele, W.A. Herrmann, D. Mihalios, M. Elison, E. Herdtweck, W. Scherer, J. Mink, J. Organomet. Chem. 459 (1993) 177; (b) W.A. Herrmann, Angew. Chem. Int. Ed. Engl. 41 (2002) 1291.

[4] (a) D. Bourissou, O. Guerret, F.P. Gabbai, G. Bertrand, Chem. Rev. 100 (2000) 39.

[5] P.C.J. Kamer, P.W.N. van Leeuwen, J.N.H. Reek, Acc. Chem. Res. 34 (2001) 895.

[6] R.A. Gossage, L.A. Van De Kuil, G. Van Koten, Acc. Chem. Res. 31 (1998) 423.

[7] R.H. Crabtree, Angew. Chem. Int. Ed. Engl. 32 (1993) 789.

[8] (a) E. Peris, J.A. Loch, J. Mata, R.H. Crabtree, Chem. Commun. (2001) 201; (b) J.A. Loch, M. Albrecht, E. Peris, J. Mata, J.W. Faller, R.H. Crabtree, Organometallics 21 (2002) 700.

[9] M. Poyatos, F. Marquez, E. Peris, C. Claver, E. Fernandez, New. J. Chem. (2003).

[10] S. Grundemann, M. Albrecht, J.A. Loch, J.W. Faller, R.H. Crabtree, Organometallics 20 (2001) 5485.

[11] D.S. McGuinness, K.J. Cavell, B.F. Yates, B.W. Skelton, A.H. White, J. Am. Chem. Soc. 123 (2001) 8317.

[12] M.S. Viciu, G.A. Grasa, S.P. Nolan, Organometallics 20 (2001) 3607.

[13] S. Grundemann, M. Albrecht, A. Kovacevic, J.W. Faller, R.H. Crabtree, J. Chem. Soc. Dalton Trans. (2002) 2163.

[14] S. Grundemann, A. Kovacevic, M. Albrecht, J.W. Faller, R.H. Crabtree, Chem. Commun. (2001) 2274.

[15] E. Clot, O. Eisenstein, unpublished data.

[16] A. Macchioni, C. Zuccaccia, E. Clot, K. Gruet, R.H. Crabtree, Organometallics 20 (2001) 2367.

[17] G. Lanza, I.L. Fragala, T.J. Marks, J. Am. Chem. Soc. 122 (2000) 12764.

[18] D.G. Blackmond, A. Lightfoot, A. Pfaltz, T. Rosner, P. Schnider, N. Zimmerman, Chirality 12 (2000) 442.

[19] M. Albrecht, R.H. Crabtree, J. Mata, E. Peris, Chem. Commun. 32 (2002).

[20] P.J. Dyson, D.J. Ellis, T. Welton, Can. J. Chem. 79 (2001) 705.

[21] L.J. Xu, W.P. Chen, J.L. Xiao, Organometallics 19 (2000) 1123.

[22] R.H. Crabtree, Lecture I.234, ICCC34, Edinburgh, Scotland, 2000.

[23] G. Sini, O. Eisenstein, R.H. Crabtree, Inorg. Chem. 41 (2002) 602.

[24] R.J. Sundberg, R.F. Bryan, I.F. Taylor, H. Taube, J. Am. Chem. Soc. 96 (1974) 381.