The chemistry of functionalised N-heterocyclic carbenes†

Olaf Kühl*

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This *tutorial review* presents the synthesis, chemistry and applications of functionalised N-heterocyclic carbenes NHC and their transition metal complexes. Functionalised NHC comprise those carrying a phosphino-, amino-, imino- or oxygen-containing functionality on the imidazole sidechain. Main applications have been the modification of catalysts and their immobilisation by fixation on a polymeric support using the functional group. Whereas the functionalisation of the NHC has not improved their performance in catalysis, new developments have occurred in the use of imidazole-containing biomolecules such as L-histidine or caffeine as precursors for NHC.

Introduction

For an Organic Chemist carbenes have traditionally been transient, highly reactive and short lived species that are useful to introduce a single carbon atom into a molecule.[1] Their reactivity comes mainly from their electronic unsaturation, *i.e.* carbon as group 14 element has four electrons, four valence orbitals and as carbene two valence bonds. It is therefore left with the choice to place either one electron into each of the two remaining orbitals (thus becoming a triplet carbene) or both electrons into one orbital and leaving the fourth orbital empty (singlet carbene) (see Fig. 1). Although a triplet carbene is more unstable than a singlet carbene, both are highly reactive and cannot be isolated. To the preparative chemist this situation presented itself as a challenge to synthesise a stable carbene that can be stored for a prolonged period of time. For over a century, all attempts to do so proved unsuccessful, although Fischer and Schrock were able to generate stable carbenes in the coordination sphere of transition metals.[2] The quest for stable uncoordinated carbenes, however, went on and led to the synthesis of a number of olefins that resulted from the dimerisation of usually cyclic carbenes (see Scheme 1). These dimers became known as Wanzlick-Carbenes, although Wanzlick never actually achieved his goal to synthesise a stable carbene, but came tragically close.[3]

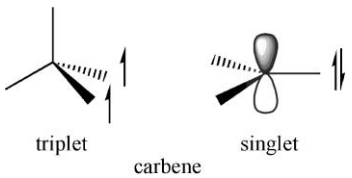
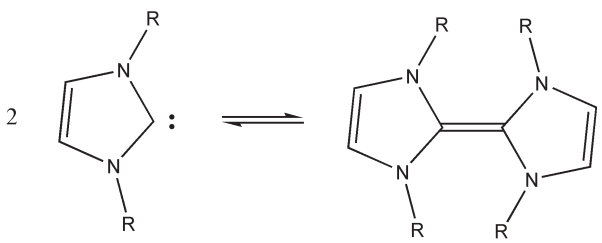


Fig. 1 Electronic structure of carbenes.

Naturally, the discovery of the first stable free carbene by Arduengo in 1991[3] and the realisation that these N-heterocyclic carbenes NHC can be used instead of phosphines in catalysis sparked a great interest in them.[2] They were found to be more electron-rich ligands than the phosphines they replaced[4] and more firmly bound to the metal catalyst.[2] Both are highly desirable properties and the main reasons for their success in catalytic applications. A stable carbene is a carbene that is persistent at ambient temperature (and often does not decompose even at temperatures higher

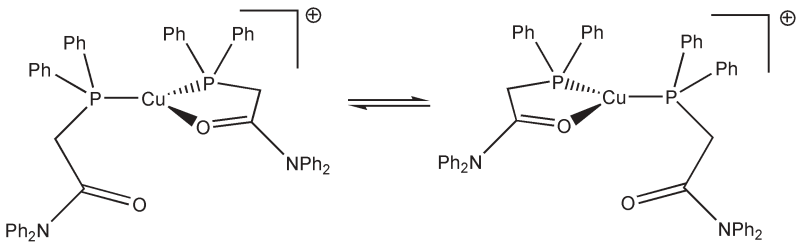


Scheme 1 Wanzlick carbenes.

The Department of Chemistry, The University of Alabama, Shelby Hall, Tuscaloosa, Al 35487-0336, USA. E-mail: okuhl@bama.ua.edu
† Dedicated to PD Peter Lobitz on the occasion of his 65th birthday, with my warmest congratulation and best wishes.

Olaf Kühl

Olaf Kühl is a Visiting Professor at the University of Alabama. His main research interests are in organometallic and coordination chemistry with an emphasis on ligand design, particularly in the areas of N-heterocylic germylenes, carbenes and phosphino ureas. After studying chemistry at Tübingen, he went to the University of British Columbia and the University of Adelaide for his Master Degree research project with Michael Bruce. He then joined the group of Evamarie Hey-Hawkins in Leipzig for his PhD. While working with Joachim Heinicke in Greifswald on N-heterocyclic germylenes, he started his own research programme in phosphino ureas, accepted a visiting professorship in Chemnitz and has recently moved to Tuscaloosa, where he collaborates with Anthony Arduengo III.

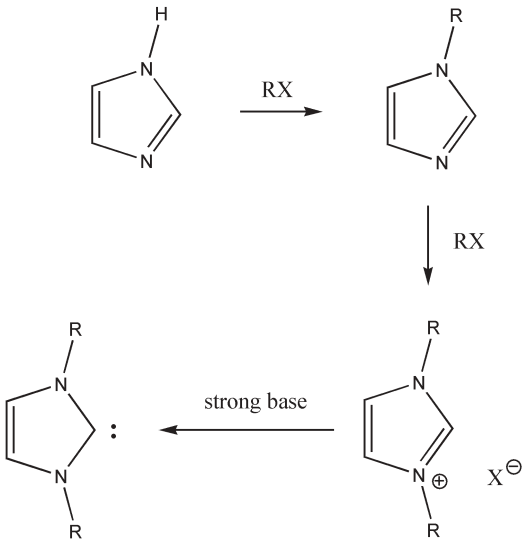


Scheme 2 Example of a complex with a hemilabile ligand.

than 200 °C), but requires an inert gas atmosphere and is extremely sensitive to moisture and chlorinated solvents.

In catalysis phosphines not only serve as simple ligands (monodentate or chelate), but can be designed to carry functional groups or other substituents that alter the properties of the catalyst. The substituents on phosphorus can be made to bind to a polymeric support to avoid loss of the catalyst (and the precious metal) in catalytic reactions, or the substituent on phosphorus can contain a second weakly ligating atom to provide a free coordination site for the substrate in catalysis. These ligands are known as hemilabile since only one ligating atom (usually phosphorus) binds strongly and the other only weakly (labile) to the metal (see Scheme 2). The labile group is most often an amino or ether functionality.[5] Another very important property introduced to the catalyst by the (phosphine) ligand is chirality. Most chiral phosphines are chiral in the carbon backbone and are bidentate, meaning that they bind with two phosphorus atoms to the same metal atom (see Fig. 2).[2]

N-Heterocyclic carbenes are synthesised from imidazole which can be functionalised on both nitrogen atoms (see Scheme 3). The simplest method to introduce chirality is to use a naturally occurring and commercially available chiral amine in the synthesis of the imidazole ring or to use a chiral alkyl halide to quaternise the second nitrogen in the synthesis of the imidazolium salt (see Fig. 3).[6,7] Functional groups can be introduced in the imidazole side chain by conventional synthetic methods. The potential of a hydroxyalkyl substituent on the imidazole ring was recognized very early.[2] The hydroxy group can be converted into an ester or an ether or substituted by a halogen[1] and subsequently converted into a phosphine (see Scheme 4).[8] Introduction of an amino sidegroup is equally facile.[9] The main limitation for the introduction of functional groups lies in the method of carbene formation. A free NHC is most often synthesised by abstraction of the hydrogen atom bonded to the carbon between the two nitrogen atoms. As this



Scheme 3 Synthesis of N-heterocyclic carbenes.

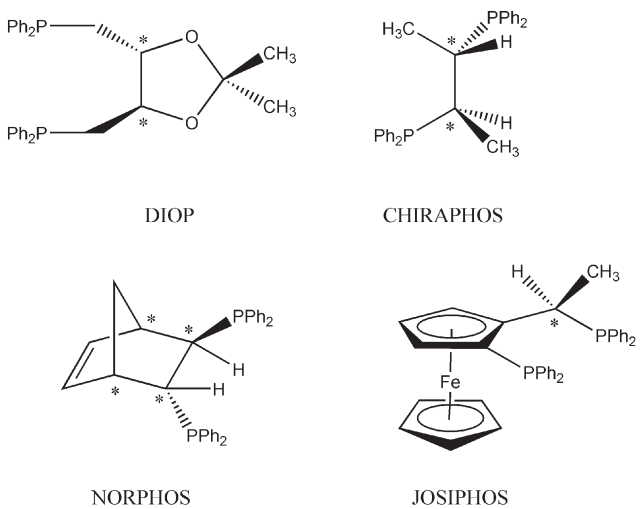


Fig. 2 Chiral phosphane ligands.

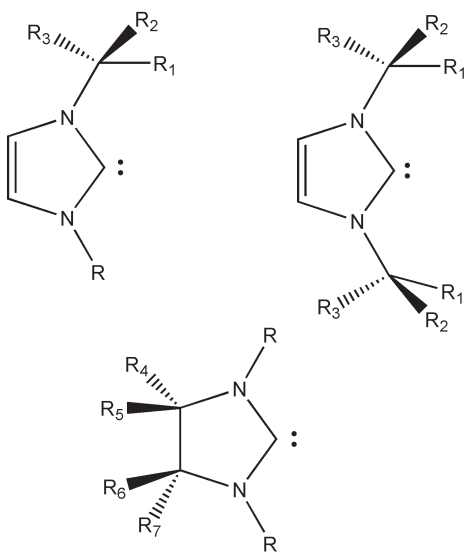
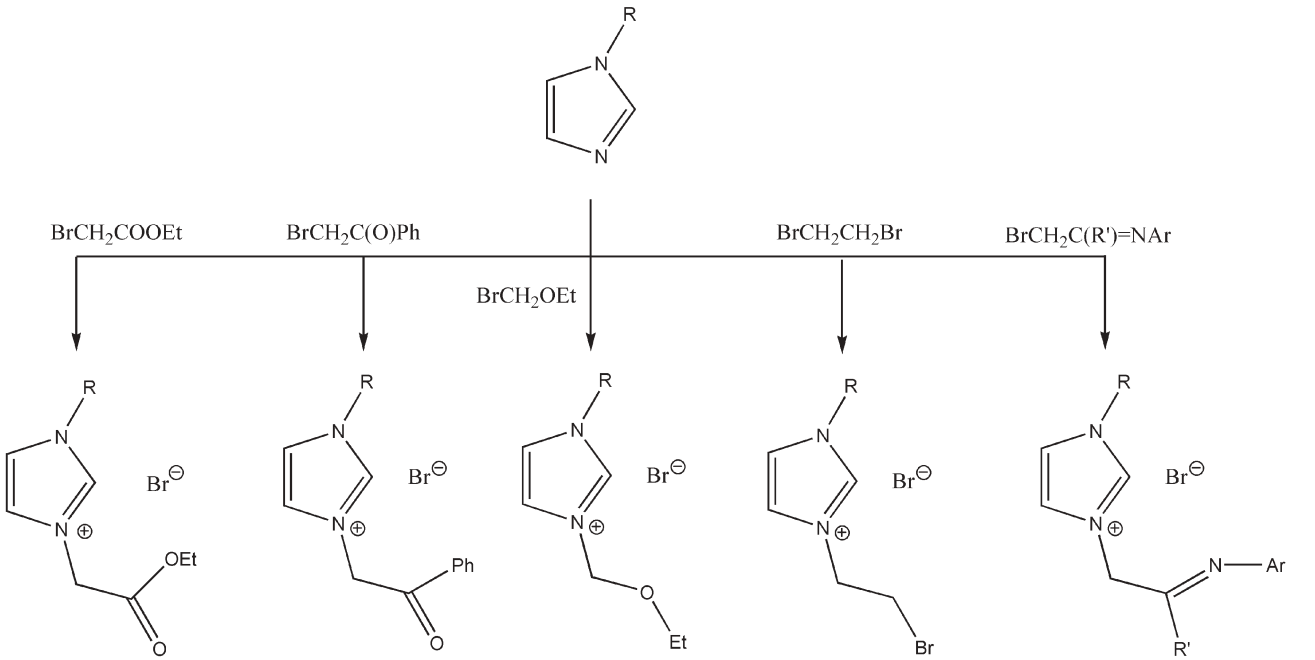


Fig. 3 Chiral N-heterocyclic carbenes.



Scheme 4 Functionalisation of imidazoles.

hydrogen atom is not very acidic, a strong base is needed. Functional groups on the imidazolium ring must therefore be inert to strongly basic conditions, preferably even at elevated temperatures. It comes as no surprise that the first functional groups introduced into NHC were tertiary amines, ethers, and phosphines, but other groups such as primary and secondary amides as well as alcoholates were soon to follow.

Introduction of the functional groups

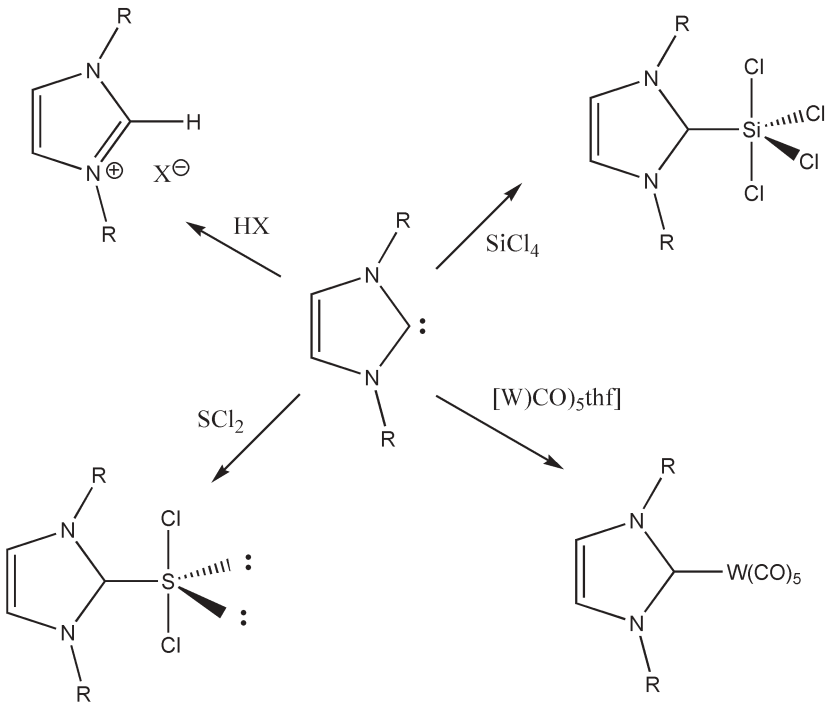
Although NHC are stable, they are still carbenes and highly reactive[10] and since a strong base was needed in their making, they themselves are easily protonated. In a wider context, a proton acceptor or Brønsted base can be seen as a nucleophile or Lewis base. As such it would react with an electrophile or Lewis acid. But, as a Lewis base is known in Organometallic Chemistry as a σ-donor, it is not difficult to predict that NHC make good σ-donor (electron rich) ligands, the property that has made NHC such a success story (see Scheme 5). However, their reactivity is of course not limited to Lewis acidic transition metals. NHC will react with any electrophile present and that limits the choice of possible functional groups that can be introduced.

A second consideration when contemplating the compatibility of functional groups with NHC is the very reason for their stability. It should be remembered that the stabilising factor is the interaction between the empty p-orbital of the carbene carbon (C2) and the electron lone pairs on the two adjacent nitrogen atoms. It can be envisaged that a strong nucleophile might bond to the carbene carbon utilising the empty p-orbital and thus creating a three-valent carbon species that can no longer be called a carbene (see Scheme 6). On second thoughts, however, that would be highly unlikely as the strong base used in excess in the generation of the NHC is itself a strong nucleophile and does not react with the carbene. Of course, there are other, more reactive and often transient carbenes (generated from diazomethane, diazo acetic ester or chloroform) that have long been used as reagents in organic chemistry, but they should not be confused with the stable and isolable N-heterocyclic carbenes.

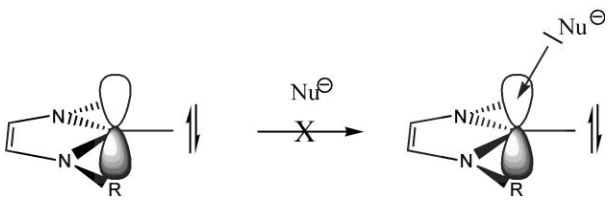
For these two reasons functionalisation of NHC was "historically" limited to phosphines,[8] tertiary amines like pyridine,[2] ester, keto and ether functionalities[11] and oxazolines.[6] Only recently, researchers have started to explore the suitability of stronger nucleophiles such as alcoholates[12] and secondary amides.[13] But, as in phosphine chemistry the "golden rule" of functionalised carbenes is to introduce the functional group first and generate the carbene (phosphine) last.[6]

Having introduced the "golden rule" of phosphine chemistry to its carbene analogues we will proceed to break it several times in the following brief summary of routes to synthesise phosphino functionalised carbenes. The best way to synthesise an imidazolium salt is to react an *N*-substituted imidazole with an alkyl- or arylhalide.[2] Thus, it is a good idea to utilise a functionalised alkylhalide. The functional group can then be used to introduce the phosphino group.

This approach was used by Nolan[8] and Lee[14] in their synthesis of *N*-aryl, *N*′-diphenylphosphinoethyl imidazolium salts (see Scheme 7). The first step is the reaction between the *N*-substituted imidazole with 1,2-dihaloethane (halogen = Br,[8] Cl[14]) followed by the introduction of the phosphino group utilising $HPPh_2$ and $KOBu^t$ in dmso (dimethyl sulfoxide) as polar solvent. The reaction can be carried out using imidazole itself and two equivalents of 1,2-dichloroethane.[15] The product is the *N*,*N*′-bis-chloroethyl imidazolium salt that can be converted into the *N*,*N*′-bis-diphenylphosphinoethyl imidazolium salt as above by reaction with $HPPh_2$ and $KOBu^t$ in dmso. Another interesting approach starts with the chiral



Scheme 5 N-Heterocyclic carbenes as σ-donor ligands.

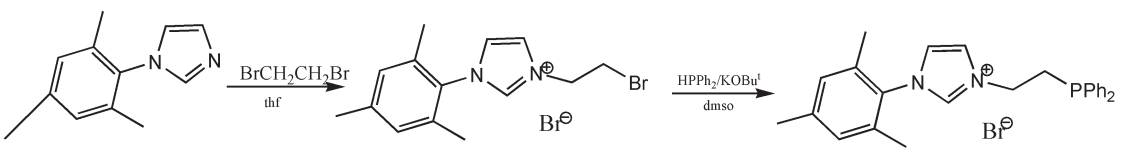


Scheme 6 Depiction of a conceivable nucleophilic attack on a N-heterocyclic carbene.

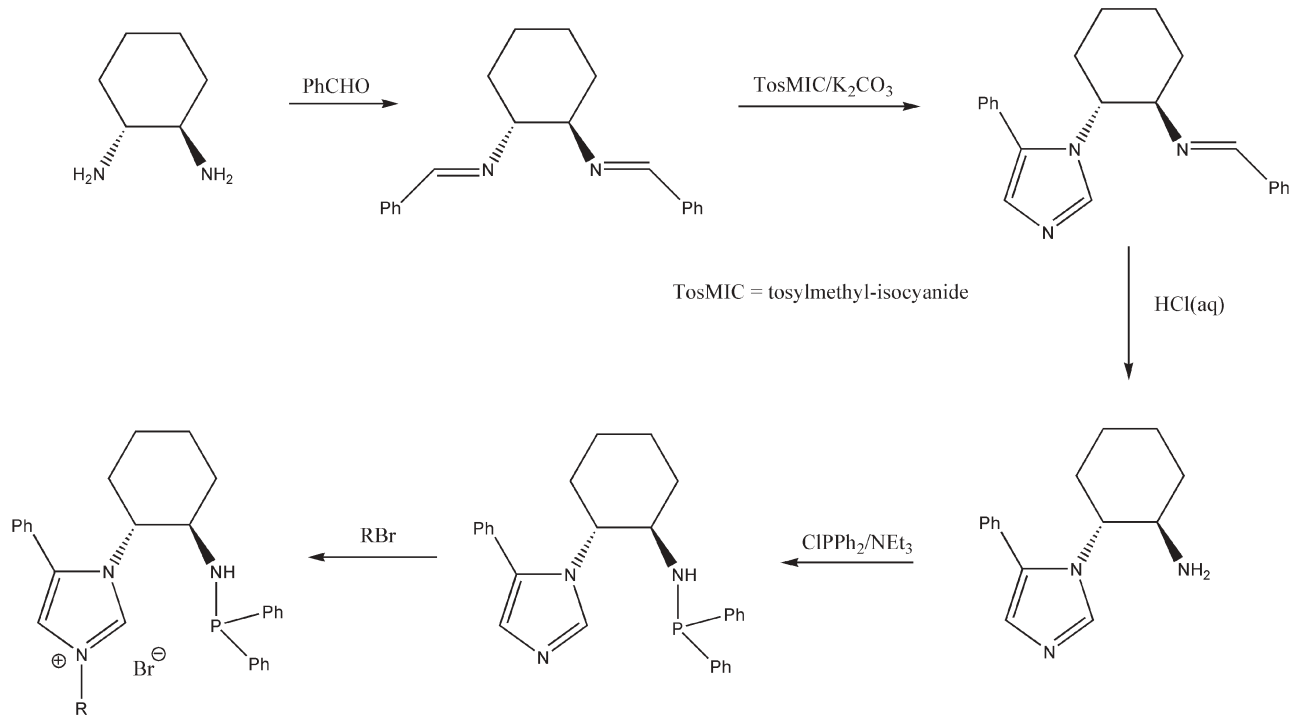
diamine 1,2-diaminocyclohexane (see Scheme 8).[16] One of the amino groups is used to synthesise the imidazole ring. During imidazole ring formation the other amino group needs to be protected (as imine). After the amino group is liberated by acid-catalysed hydrolysis, the phosphino group is introduced by reaction with $ClPPh_2$ in the presence of triethylamine as auxiliary base to bind the HCl that is formed during the reaction. We have now broken the ''golden rule'' since we still need to form the imidazolium salt by reaction with a suitable alkyl halide. This can be achieved by standard procedures. In this particular case, the initial attempt was indeed to introduce the phosphino group last, but reaction of the imidazolium salt with $ClPPh_2$ in the presence of triethylamine as auxiliary base gave a mixture of several phosphine-containing species and the alternative route was used with success. Obviously, the phosphino group can be introduced into the alkyl or aryl halide before it is reacted with the substituted imidazole breaking the ''golden rule'' yet again. This route was employed by Bolm[17] and Zhou.[18] Bolm introduced the planar chiral [2,2]-paracyclophane substituent onto the imidazole, but not before introducing a phosphino group onto the [2,2]-paracyclophane group (see Scheme 9). It should be noted that this interesting pathway calls for the enantiopure pseudo-ortho-dibromo-[2,2]-paracyclophane to be reacted with one equivalent of BuLi (butyllithium) and then $ClPPh_2$ to introduce one phosphino group only. A second equivalent of BuLi followed by reaction with CO_2 and reduction with $LiAlH_4$ introduces a hydroxymethyl group that can be converted into the respective halide and then used to form the imidazolium salt. The additional C1-unit introduced by CO_2 gives the substituent the required flexibility to act as an efficient chelate ligand.

A similar protocol was developed by Zhou *et al*. Starting from benzaldehyde, *N*,*N*-dimethylaminomethylbenzene was formed, lithiated in ortho-position and reacted with $ClPPh_2$ to introduce the phosphino group. Then the amino group is substituted with chloride and the molecule reacted with the respective imidazole to generate the mono- or bisphosphino imidazolium salt (see Scheme 10).

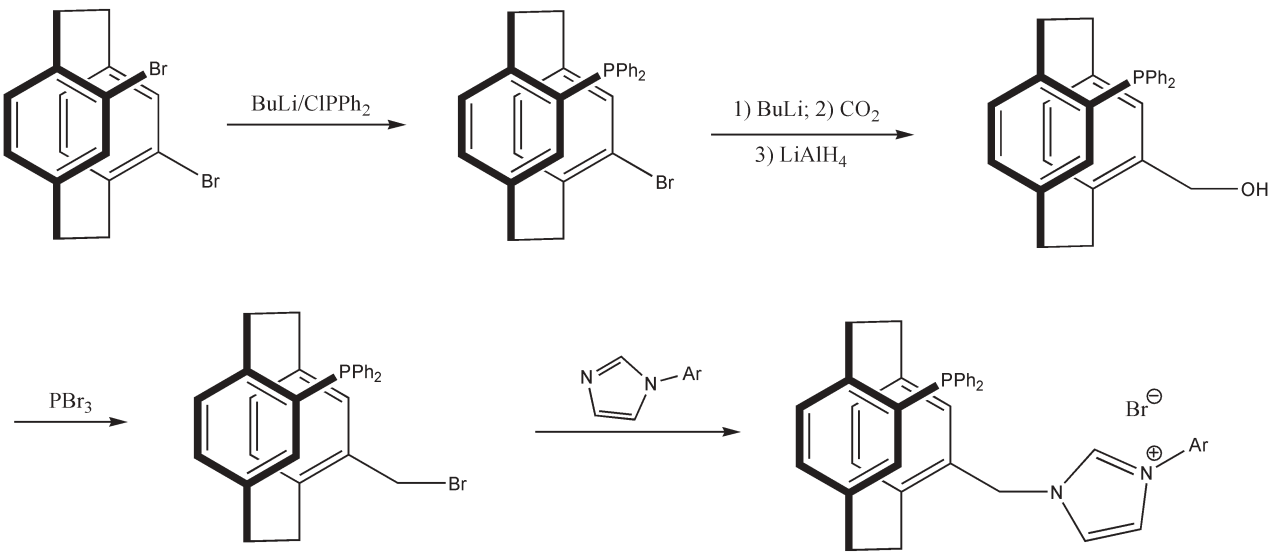
Introduction of an amino functionality is very similar with the added advantage that amino groups do not undergo as



Scheme 7 Introduction of a phosphino group onto the sidechain of an imidazolium salt.

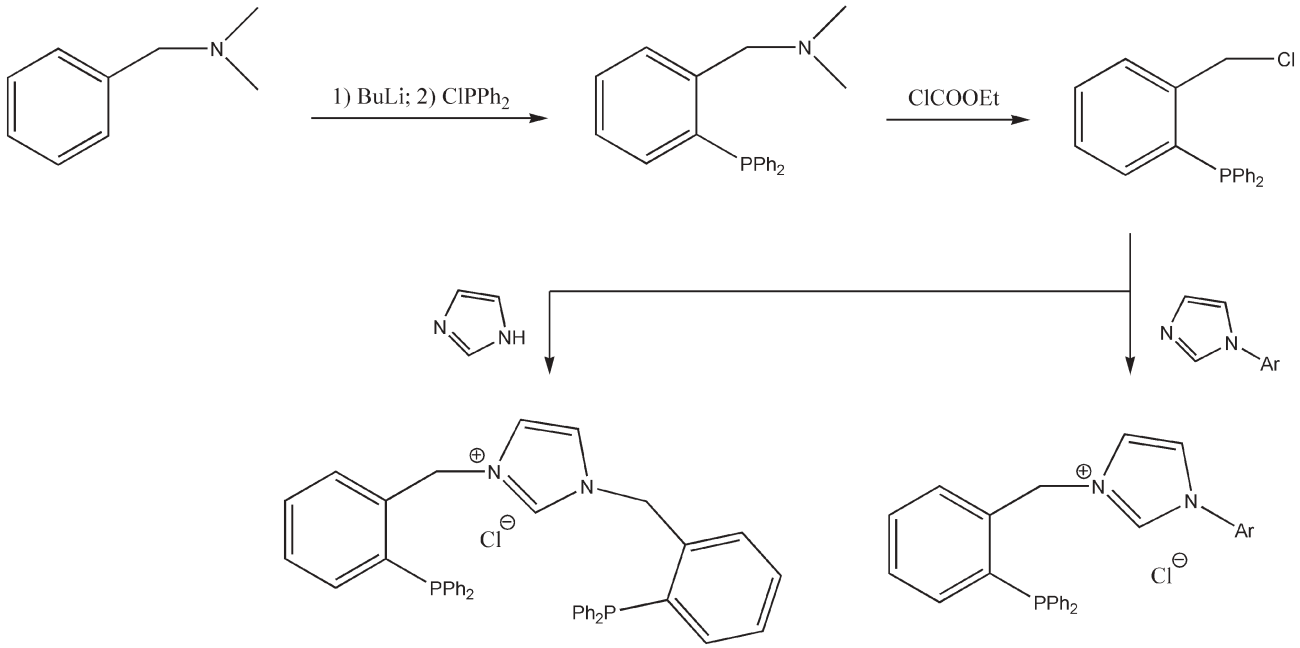


Scheme 8 Synthesis of a phosphino carbene with a chiral backbone.

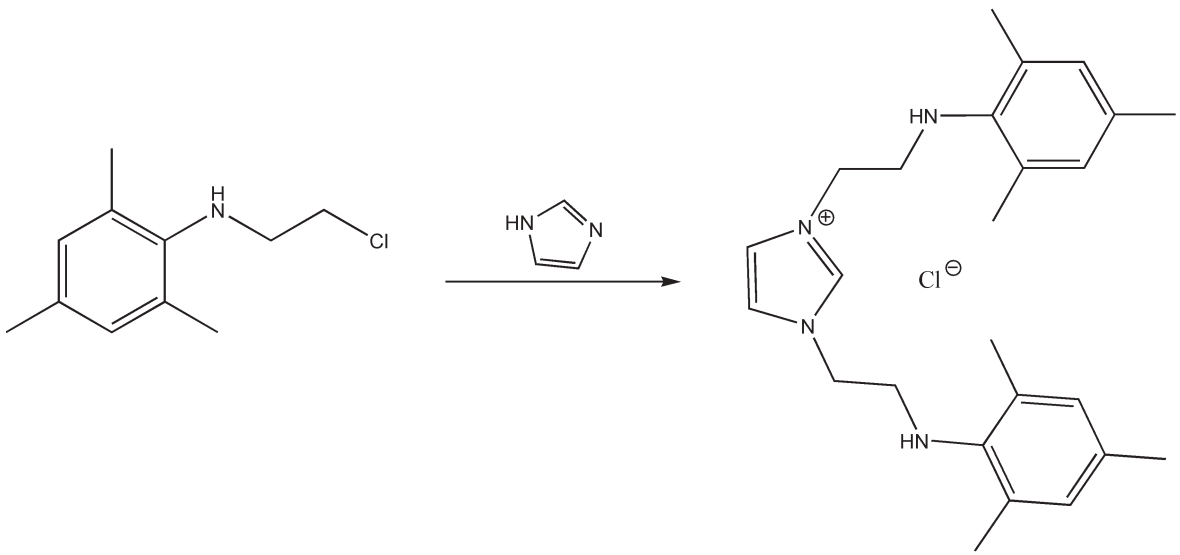


Scheme 9 Stepwise introduction of a phosphino group and an imidazolium salt on a chiral paracyclophane.

many side reactions as phosphines. Spencer and Fryzuk[13] have used a terminally chlorinated secondary amine to introduce the amino functinality (see Scheme 11). The same reaction was used by Arnold *et al.*[19] In both cases a secondary amine group was introduced into the sidechain and the question arises which proton will be abstracted first in the treatment of the imidazolium salt with a base to generate the carbene. Spencer and Fryzuk used the bulky base $KN(SiMe_3)_2$ whereas Arnold *et al.* used stepwise addition of butyllithium. Both research groups report the generation of the carbene with the proton situated on the nitrogen of the amino group in the sidechain. In each case the C2 carbon atom of the carbene was observeed in the ^{13}C-NMR spectrum and found to be in the range expected for the C2 of a NHC (211.0 and 215 ppm). Although that is conclusive evidence that the carbene was indeed formed, it has to be remembered that a carbene carbon is a hydrogen acceptor and thus capable to form hydrogen bonds with a hydrogen donor such as an amino group. It is therefore highly likely that the true structure in solution involves intramolecular hydrogen bonding between C2 and NH. Evidence for this is found in the structure for the carbene reported by Arnold *et al.*[19] The true composition is a LiBr adduct of the



Scheme 10 Stepwise introduction of phosphino groups onto the imidazole ring.



Scheme 11 Introduction of amino groups onto the imidazole ring.

carbene with lithium coordinated to C2 and NH (see Fig. 4). In the absence of LiBr, the position of the lithium atom can easily be assumed by the amino proton.

The question of acidic protons in the sidechain capable of binding to C2 also arises with imino groups that have a β-hydrogen atom. This enolisable imino group tautomerises to the enamine with the hydrogen bonded to nitrogen. It becomes possible that the enamide is formed prior to the carbene. Bildstein *et al.* describe such a system and report that no evidence for the carbene could be obtained (see Scheme 12)[20] indicating the tautomer as the likely product. In order to obtain the desired carbene, they substituted both β-hydrogen atoms with methyl groups[20] and obtained the carbene without further difficulties.

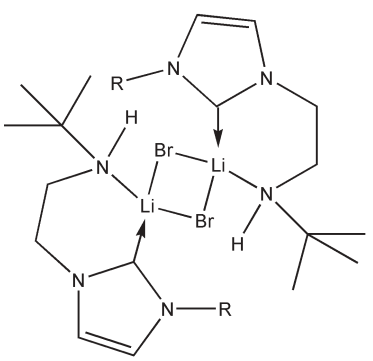
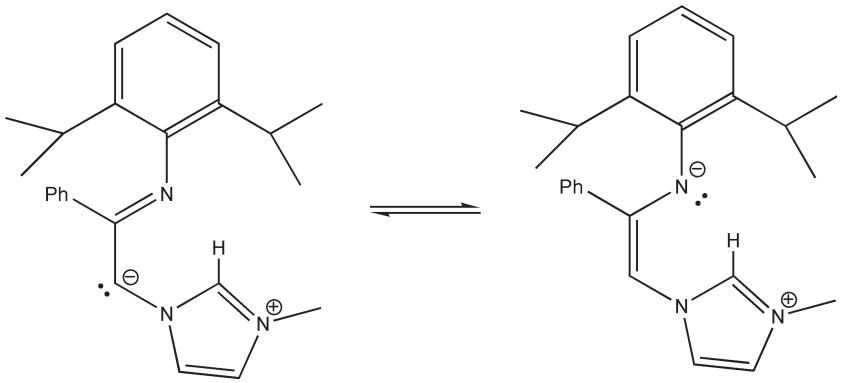


Fig. 4 The nucleophilicity of amino carbenes.



Scheme 12 Tautomerism of enolisable enamides in the sidechain of imidazolium salts.

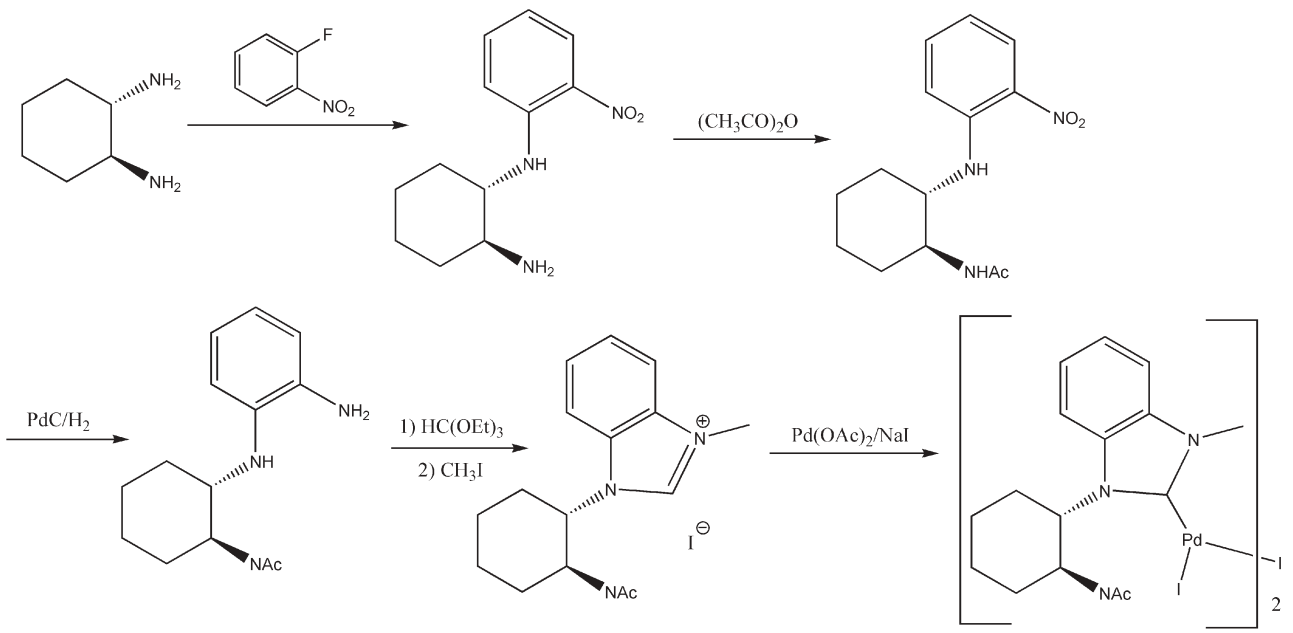
Enolisable imino-carbenes can be obtained by the silver salt method as was shown by Tilset *et al.*.[9] The driving force is formation of the silver–carbene bond. The silver carbene can act as a transmetallation agent to transfer the carbene to another transition metal where it can act as a chelate ligand.[9] Shi and Qian[21] have used a similar approach to carbene functionalisation as Hodgson and Douthwaite,[16] but instead of introducing a phosphino group they protected the primary amine by acetylation and reacted the imidazolium salt directly with a palladium species without prior formation of the carbene (see Scheme 13).

Obviously, phosphino and amino functionalities are not the only functional groups that can be introduced into NHC. It should also be possible to utilise oxygen in the form of ether, ester, keto or even alcoholato groups. The Arnold research group is among the pioneers in this field. Their method of introducing the alcoholate relies on the reaction of the imidazole with a suitable epoxide which renders an ethylene bridge between the hydroxy group and the imidazole (carbene) (see Scheme 14),[12,22] a method applied earlier by Herrmann *et al.*[11] Diéz-Barra *et al.*[23] developed a different and rather unusual method in reacting 1,2,4-triazole with acetylene carboxylic acid methyl ester. Two triazole units are bridged by a methylene group that also carries the ester (see Scheme 15). Reduction with $LiAlH_4$ yields the alcohol.

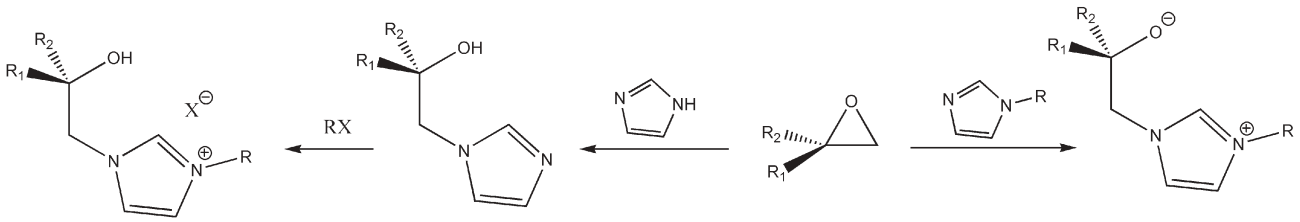
Kawaguchi *et al.* have used a more traditional approach already familiar to us by reacting imidazole with 2-bromomethylphenols.[24] It should be noted that Kawaguchi obtained the intended carbene from the imidazolium salt using $NaN(SiMe_3)_2$ only at low temperatures. Warming to ambient temperature initiated a 1,2-benzyl migration to the C2 carbon, probably by intramolecular nucleophilic attack on the carbene centre (see Scheme 16).

Introduction of a keto group was achieved by Waymouth *et al.* by reaction of a substituted imidazole with an α-bromomethyl ketone.[25] Subsequent carbene formation was effected as the silver adduct (see Scheme 17).

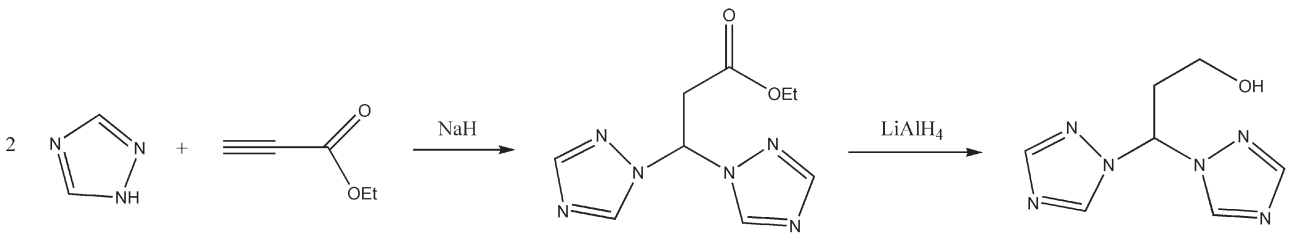
The introduction of esters,[26] ethers[11] and carboxylic acid amides[27] can be achieved using the same principal reactions as above, namely utilisation of an alkyl halide bearing the



Scheme 13 Synthesis of chiral N-heterocyclic carbenes carrying a carboxylic acid amide functionality.



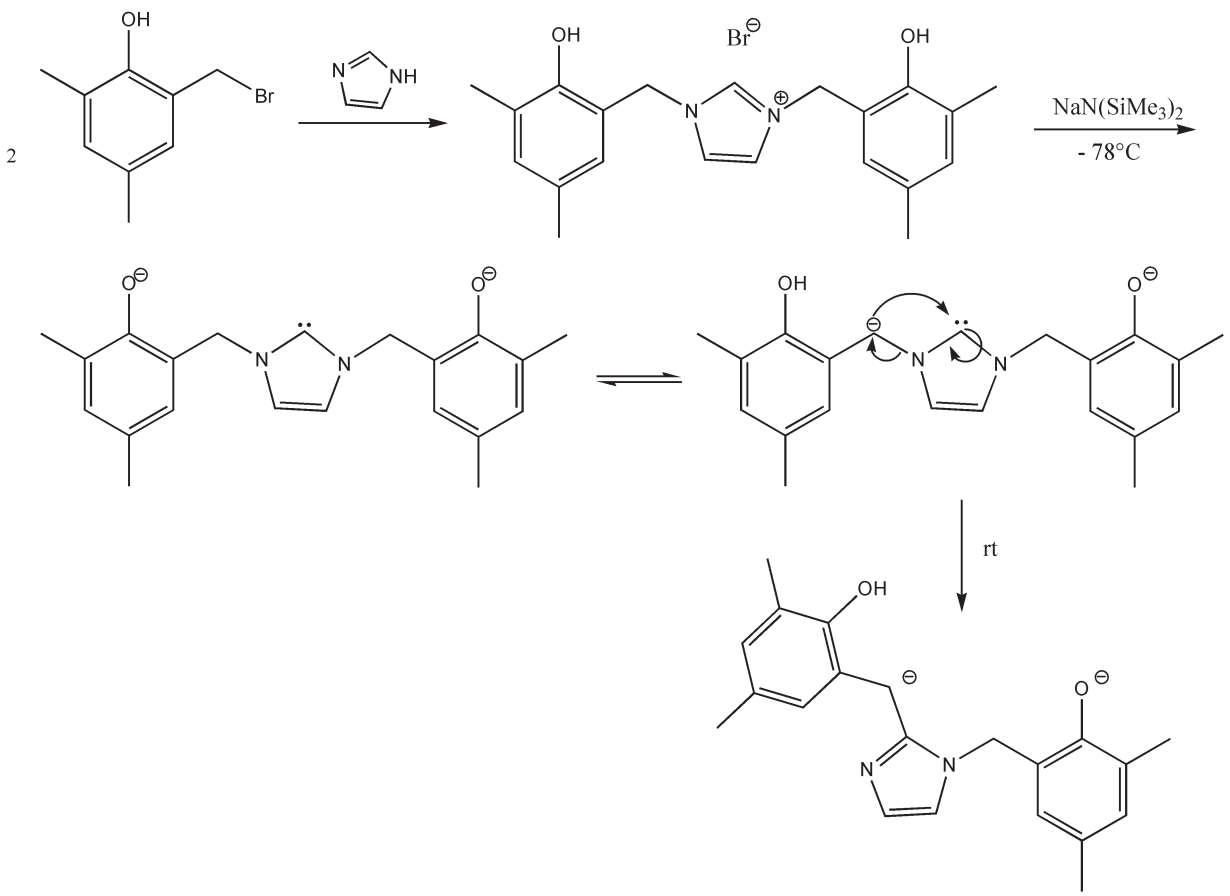
Scheme 14 Utilisation of an epoxide to introduce the hydroxy group into the imidazole sidechain.



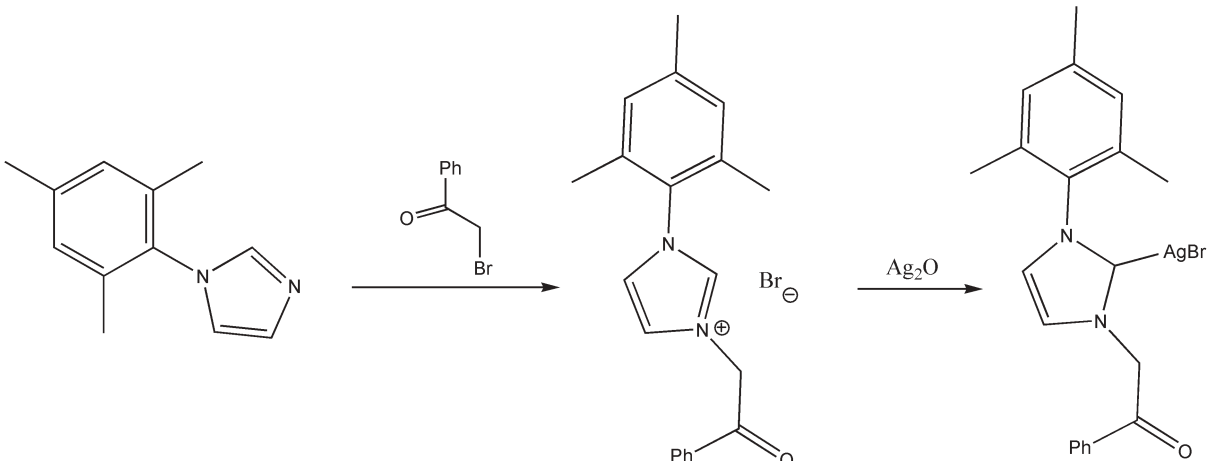
Scheme 15 Synthesis of a functionalised dicarbene *via* imidazole addition on an acetylene carboxylic acid ester.

functional group to be introduced. An interesting method to generate a polyether sidechain was published by Herrmann *et al.* as early as 1997.[11] Here, they reacted imidazole with an excess of ethylene oxide. Epoxide ring opening is effected by imidazole and chain growth by repetitive ring opening reactions by the alcohol formed.

A question we again have to ask ourselves is the compatibility of the oxo functionalities with carbene formation and carbene stability. Esters are known to be hydrolysed in the presence of acids or bases.[1] As NHC are usually generated by proton abstraction from C2 using a strong base[2,3] that may be a concern. It is hardly surprising that the presence of an ester



Scheme 16 Carbene decomposition pathway by intramolecular nucleophilic attack on the carbene carbon and subsequent 1,1-alkyl migration.



Scheme 17 Introduction of a keto group onto the imidazolium sidechain.

group has prompted researchers to use alternative ways of carbene formation. The silver salt method, where silver oxide or silver carbonate are used as the base, is a very elegant reaction. Neither silver oxide nor silver carbonate are appreciably soluble in most organic solvents. Thus, there is no significant concentration of the base in the organic phase and the functional group is in no danger of decomposition. At the same time, the silver atom coordinates to the newly formed carbene centre protecting it from reacting prematurely. Since transfer of the NHC to another transition metal is easily accomplished, the silver salt method has become a favourite with many research groups.

The other option is to react the functionalised imidazolium salt directly with the transition metal species of choice to form the carbene metal complex without prior carbene formation. This method is naturally limited to those transition metals that are able to activate C–H bonds. Some well known examples include palladium(II) acetate[23] or rhodium(I) compounds like $[Rh(COD)OC_2H_5]_2$ (COD = 1,5-cyclooctadiene).[11]

With amines and hydroxy groups such precautions are not necessary as can be discerned from the works of Arnold[19] and Fryzuk.[13] The reason can be found in the stability of the carbene centre towards highly nucleophilic groups like amides and alkoxides. The carbene itself is a very efficient nucleophile and thus coexists with other nucleophilic groups and competes with them for the electrophile.

Catalysis

The main driving force in the success story of NHC is their superior properties as ligands in catalytic processes. They replaced the phosphines in many processes where the ability of the ligand to transfer electron density to the metal centre gives the catalyst an advantage in the catalytic process.[2] As another main criterion is the ability of the ligand to form chelates, the introduction of a second ligating group into the carbene is a natural development for application in catalysis. A major motivation for the research groups to develop functionalised NHC was to improve catalytic processes requiring chelate ligands and development of ligands went hand in hand with testing for catalytic applications.

It is hardly surprising that most reported applications in catalysis utilising functionalised carbenes involve bis-carbenes, pyrido-carbenes and carbenes carrying chiral amines (for further reading see references 2, 6 and 7). From the functionalised carbenes covered in this review, examples of phosphino carbenes are by far the most numerous. The catalytic reactions explored are mainly C–C coupling reactions where traditionally phosphines are employed and examples include Heck, Suzuki, Sonogashira and Kumada–Corriu cross-coupling reactions. Unfortunately, an overview of these very important C–C bond forming reactions cannot be given within the scope of this review, but the interested reader is referred to references 2 and 21 for excellent summaries of the respective literature.

Some of the best studied catalytic reactions are hydrogenation and polymerisation reactions. A variety of excellent catalysts are known for either of them and there is thus no great need to develop more, except for chiral applications and the introduction of asymmetry. Examples for the development of non-chiral catalysts involving functionalised carbenes are correspondingly rare. Spencer and Fryzuk have developed their amido-carbenes as ligands for zirconium and hafnium complexes and tested their performance in the polymerisation of olefins.[13] They found them to be poor olefin polymerisation catalysts, but observed the ability to insert carbon monoxide and isocyanates into hafnium alkyl bonds.

Asymmetric hydrogenation is a typical application of chelating and chiral phosphines. Excellent reviews covering amino substituted NHC are available.[6,7] Here, it suffices to point to two examples where chiral phosphino carbenes were utilised. Bolm *et al* synthesised a planar chiral phosphinyl-imidazolylidene ligand and generated its iridium complex[17] (see Fig. 5). Planar chirality is not as common as "asymmetric carbon atoms" as the chiral element of an optically active molecule,[28] but has recently found increased application in asymmetric catalysis. Bolm *et al.* proved their concept on the hydrogenation of functionalised and simple alkenes of up to 89% enantiomeric excess ee (meaning that the two possible enantiomers were present in the product with 5 and 94%, respectively).

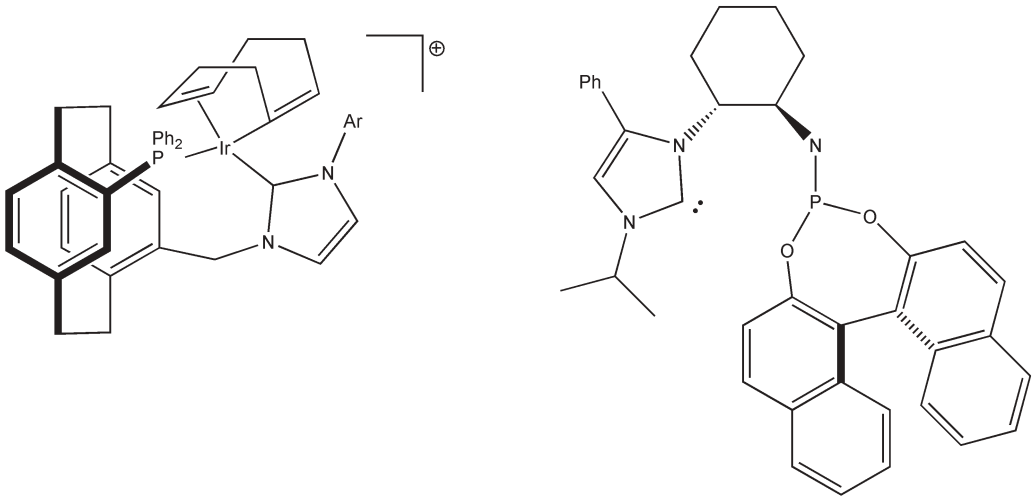


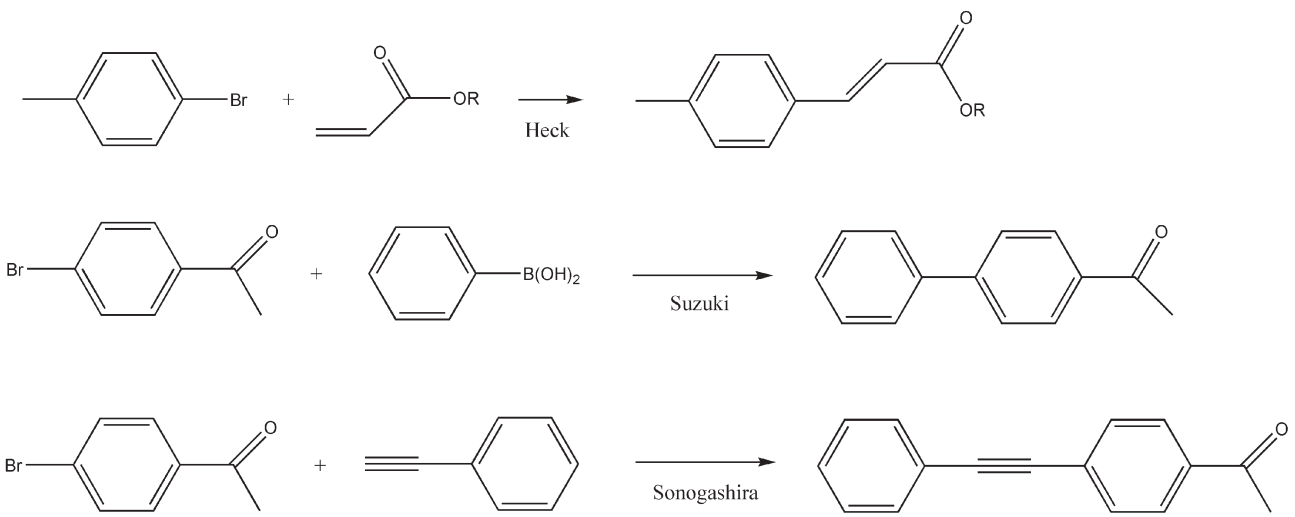
Fig. 5 Phosphino carbene chelate ligands displaying a chiral scaffold.

Hodgson and Douthwaite used (1*R*,2*R*)-*trans*-diaminocyclohexane as the chiral scaffold.[16] Their motivation to develop the ligand was in the slow reaction rates encountered for bis-carbenes and iminocarbenes in palladium catalysed allylic substitutions. They attributed this slow rate to charge build-up during the reductive elimination step and argued that the NHC and imino groups are not π-acidic enough to effectively counter this charge build-up. A diphenylphosphino group would be an obvious alternative. The concept works in as much as the phosphino carbenes improve the reaction rates for allylic substitution and transfer hydrogenation over the previously used bis-carbenes and iminocarbenes,[16] but the reaction rates are still far lower than those from more traditional ligands such as chelating bisphosphines. The reason is given by Hodgson and Douthwaite in their reasoning for introducing the phosphino group in the first place. If changing one NHC group back to a phosphine for the π-acidity improves performance, then changing both back to the bisphosphine will work even better.

For applications in Heck reactions and similar C–C coupling reactions the situation is fundamentally different. In these reactions the added σ-donor ability of the NHC gives them a distinct advantage over the phosphines.[2] The rationale for the introduction of NHC units is that they provide a greater catalyst stability and thus require a lower catalyst loading, *i.e.* less catalyst is needed and the reaction becomes less expensive. The downside is that chelate ligands show lower reaction rates and thus worse performance than monodentate ligands.[8]

The C–C coupling reactions mentioned in this section are named for the scientist who discovered them. They are mechanistically different and they have different reaction partners. The Heck reaction couples arylhalides with acrylates or styrenes, the Suzuki reaction utilises phenylboronic acid instead of the acrylates, and the Sonogashira reaction reported here is between 4-bromoacetophenone and phenylacetylene (see Scheme 18).

The first application of phosphino-carbenes for Heck reactions was reported by Nolan *et al.*[8] for the reaction between unactivated aryl bromides with n-butyl acrylate. They found that a low catalyst loading was indeed sufficient to perform the reaction with an acceptable reaction rate.



Scheme 18 Depiction of the Heck, Suzuki, and Sonogashira reactions.

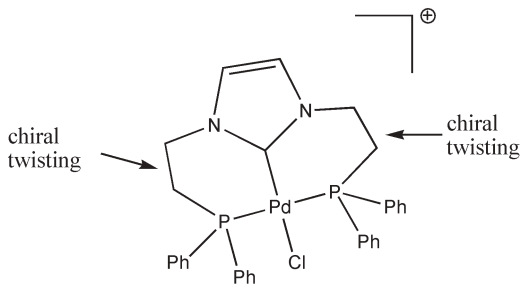


Fig. 6 A chiral catalyst displaying fast racemisation by twisting of the alkyl bridges in the two metallacycles.

Zhou *et al.* introduced an aryl bridge between the NHC unit and the phosphino functionality instead of the customary ethylene group in an attempt to improve the performance in the Heck reaction.[18] They again reacted unactivated aryl bromides and iodides with acrylates and styrenes and obtained the products in excellent yields. Their results are very interesting with respect to the steric requirements for the aryl substituent on the NHC unit. Nolan *et al.* used mesitylimidazole to synthesise the phosphino-carbene. Zhou *et al.* were not content with the standard NHC precursor mesitylimidazole. They varied the steric bulk on the aryl group by using phenyl- and 2,6-diisopropylphenylimidazole in addition to mesitylimidazole. They found that increasing bulk on the aryl substituent on the NHC unit is beneficial to ligand performance in the Heck reaction.

Lee *et al.* prepared a bisphosphino-carbene pincer ligand and tested its performance in Heck and Suzuki coupling reactions.[15] They found that the MPC2NC six-membered metallacycles formed by the metal, the NHC and the phosphino sidechain are twisted to create chirality. However, there is enough flexibility in the system to allow for rapid interconversion of the enantiomers (see Fig. 6). This would imply that these phosphino carbenes are not particularly suitable for asymmetric catalysis since a racemic catalyst would produce a racemic product. Heck coupling between aryl bromides or iodides with acrylates and styrenes were reported to proceed with excellent rates. It was found that dicationic catalysts were more effective than monocationic ones. However, aryl chlorides could not be used. The activation of unactivated aryl chlorides in Heck reactions is still a challenge and efforts to meet it are fuelled by the massive cost reduction achieved if the expensive aryl bromides could be substituted by low cost chlorides. The corresponding Suzuki reaction was only modestly successful.

Another report by Lee *et al.* describes the performance of monophosphino-carbenes in Suzuki cross-coupling reactions.[14] Again, the reactivity towards aryl bromides is good and unsymmetrical biaryls are formed readily. If aryl chlorides are used as substrates, however, the yields remain poor.

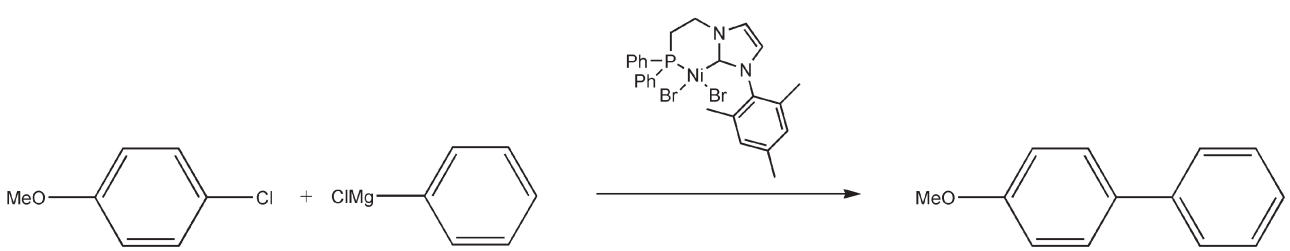
Labande *et al.* have used the phosphino-carbene ligand that we have already encountered in the work of Nolan *et al.*[8] for the Kumada–Corriu coupling reaction between phenylmagnesium chloride and 4-chloranisole (see Scheme 19).[29] The main advantage of this reaction is that it uses a Grignard reaction to activate the aryl chloride and thus makes aryl chlorides accessible for C–C coupling reactions. It also uses nickel as the catalyst metal which is much more cost effective than the palladium compounds of the other C–C coupling reactions. The disadvantage is that formation of the Grignard reagent from aryl chlorides has its limitations.[1]

No catalytic effect of the phosphino-carbene ligand could be observed in the reaction of phenyl magnesium chloride with iodobenzene, but with 4-chloroanisole the reaction was almost complete within one hour yielding the cross-coupling product in 80% yield making it marginally better than the established bis-carbene ligands. Not enough substrates were reported to establish a general trend as to substrate limitations.

The question arises whether phosphino-carbenes are indeed the best choice for these C–C coupling reactions or whether other functional groups instead of phosphines would not be more advantageous. McGuinness and Cavell explored the feasibility of keto and ester functionalised carbenes as ligands in Heck, Suzuki and Sonogashira coupling reactions with turnover numbers of up to 1 700 000 (Heck) and 127 500 (Suzuki) being obtained. The work illustrates the influence of the various functional groups on the performance of the catalyst. The best catalysts featured two NHC units bound to the metal with the functional groups pendent (see Fig. 7). Among the functional groups ester sidechains were less effective than pyridine substituents, presumably due to the lower thermal stability of the former. In any case, if the functional group is not used in the reaction, there is no reason for introducing it in the first place.

Shi and Qian have used the (1*R*,2*R*)-*trans*-diaminocyclohexane chiral scaffold to prepare a NHC functionalised with an acetylamide group on the second amino substituent.[21] Performance of this ligand system in Suzuki cross-coupling reactions was rather poor giving only mediocre yields as peak results.

A completely different approach to catalytic applications using functionalised NHC comes from the Arnold research group.[12] Arnold *et al.* used NHC carrying a chiral alcoholate sidechain in the alkylation of cyclohex-2-enone, a conjugated



Scheme 19 Depiction of Kumada–Corriu coupling utilising a functional carbene.

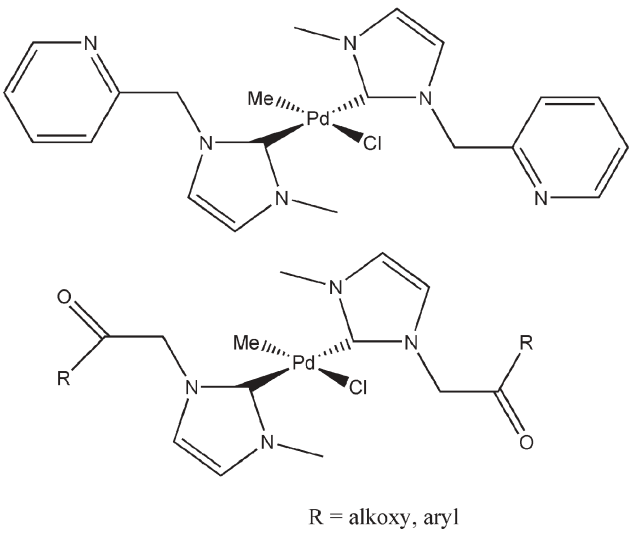


Fig. 7 Carbene catalysts with idle functional groups.

enon, with diethyl zinc as the alkylation agent (see Scheme 20). Enantiomeric selectivity was modest with 51% ee (or 3 : 1 ratio of the enantiomers), but represents one of the best performances of any catalytic system reported for this reaction.

From the perusal of the literature it can be seen that achiral functionalised NHC seem to have no performance advantage over established bis-carbene or bisphosphino chelates in most catalytic applications. In most cases their performance is considerably inferior. That changes when chiral applications are considered.[6,7] NHC that are chirally modified in substituents on the imidazole ring show low stereoselectivity and thus, the introduction of chirality with a chelating sidechain is a viable concept for asymmetric catalysis as it combines the electronic advantages of the NHC unit with a rigid chiral scaffold.

Immobilisation of the catalyst

However, the introduction of a functional group into the sidechain of a NHC ligand in catalytic applications can have other purposes than to improve the performance of the catalytic centre. Fürstner *et al.* have modified a ''second generation'' ruthenium carbene complex used in olefin metathesis with a terminal hydroxy group in the sidechain (see Fig. 8).[30] The hydroxy group was then used to attach the NHC unit, and with it the catalyst, on a silicon support. Normally, a ''second generation'' catalyst has two NHC ligands and one is lost in the activation process. In the present

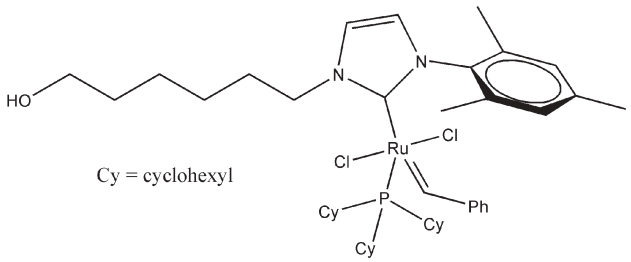


Fig. 8 Grubb's catalyst with functionalised sidechain on the carbene.

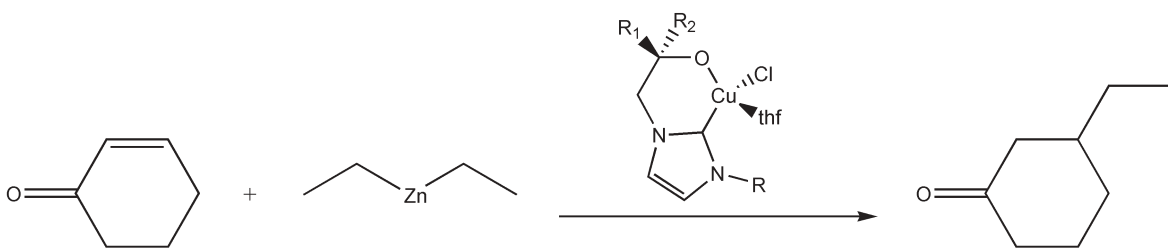
case it is necessary to have the tricyclohexyl phosphine unit instead of the second NHC to avoid loss of immobilisation with loss of ligand.

This facile solution for catalyst immobilisation follows a more complex approach reported by Buchmeiser *et al.*.[31] This research group attached the imidazolium salt to a norbornene unit that was then subjected to a ring opening metathesis polymerisation (ROMP) reaction to form the polymeric NHC precursor (see Scheme 21). The ROMP reaction had to be carried out with a molybdenum based Schrock catalyst because the ruthenium based Grubbs catalyst did not provide an endgroup that could be quantitatively capped with a suitable final endgroup.

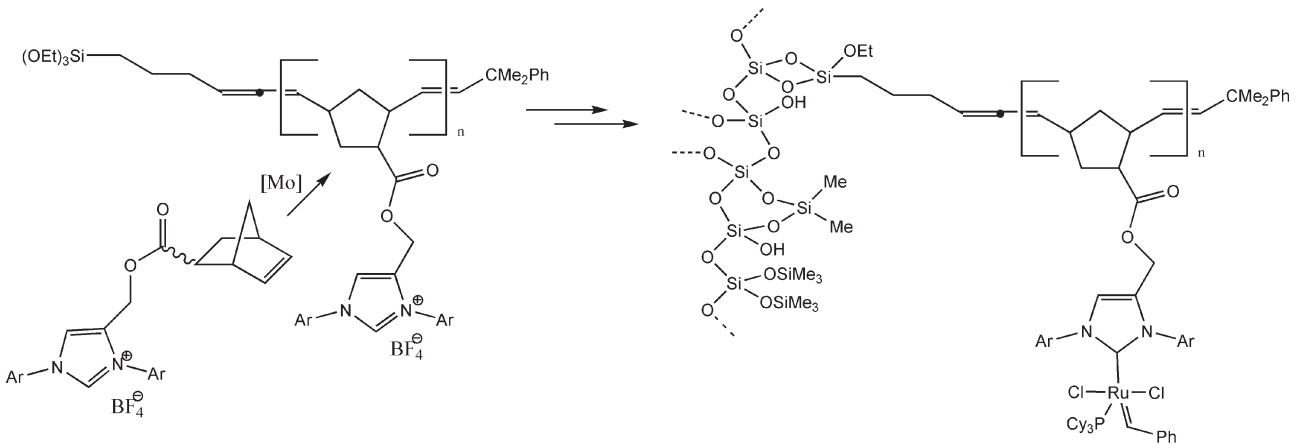
The triethoxysilane endgroup had to be introduced as the respective isocyanate and was then used to attach the polymer on the silicon support. In a final step, the NHC are formed and the ruthenium precursor loaded onto the polymer. Only 13% of the imidazolium sites are attached to ruthenium. The formation of this polymer supported Grubbs catalyst is doubtless a synthetic masterpiece, however, immobilisation of the Grubbs catalyst was achieved in a far less complicated manner only a few years later by a far simpler method by Fürstner *et al.*.[30]

Attachment of the catalyst by way of a hydroxy functionalised NHC was already envisaged by Herrmann *et al.*[11] They described model complexes suitable for attachment of the imidazolium salt and thus the catalyst to a polymeric support, but did not actually carry out the immobilisation step.

It should be mentioned that many imidazolium salts are liquids at room temperature and thus fall in the general category of ionic liquids. An excellent overview of the techniques to attach ionic liquids onto solid supports is available by Mehnert.[32] Here, the interested reader is directed to the concept that ionic liquids cannot only be attached covalently to the support, but also by simple deposition of the ionic liquid phase containing the catalyst onto the support surface.



Scheme 20 Copper(II) catalysts with functional carbene ligands employed in the asymmetric alkylation of an enone.



Scheme 21 Immobilisation of a Grubb's catalyst.

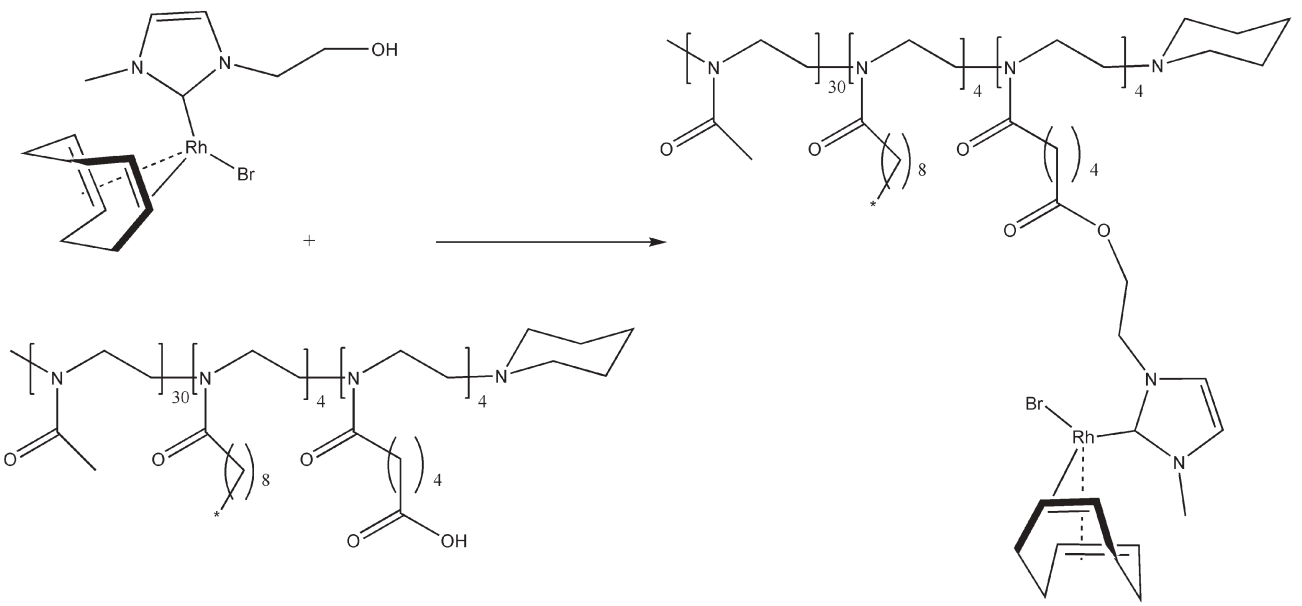
In a more conventional approach, Weberskirch *et al.* attached a rhodium carbene complex onto an amphiphilic block copolymer.[33] The concept is simple and involves the utilisation of a hydroxyalkyl substituted NHC as a ligand for the rhodium(I) catalyst used in hydroformylation of 1-octene. The catalyst is then loaded onto a water-soluble, amphiphilic block-copolymer by reacting the alcohol group of the catalyst with a carboxylic acid group of the block-copolymer (see Scheme 22).

Attachment of the catalyst to a polymeric support can also be facilitated using a bis-carbene as the ligand.[34] The bisimidazolium salt featuring a hydroxyalkyl sidechain on each of the two imidazolium units was reacted with palladium(II) acetate to form the neutral catalyst complex (see Scheme 23). Immobilisation was then achieved by reacting the functionalised catalyst with 4-(bromomethyl)phenoxymethyl polystyrene, known as Wang resin, as the polymeric support.

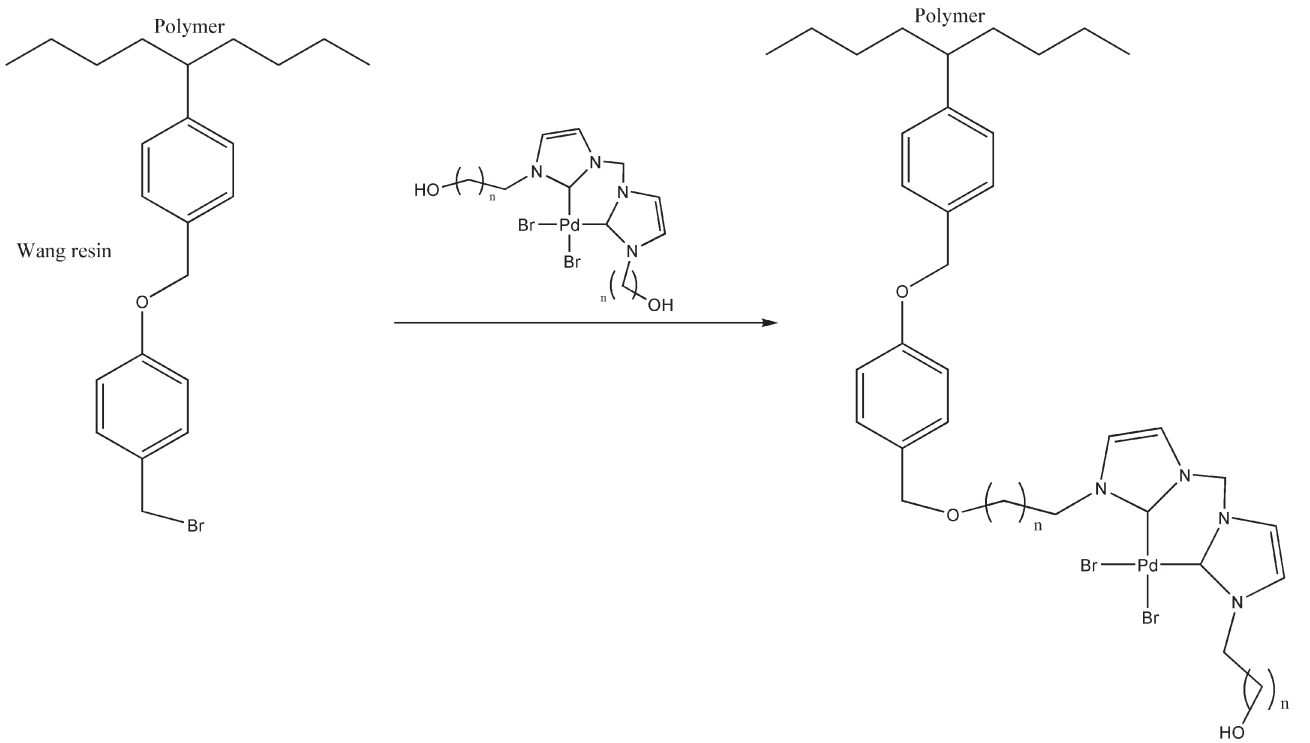
Immobilisation is a viable concept, when it does not appreciably lower the catalyst activity and when it can be facilitated by a simple method. A method is simple, when the synthesis of the functionalised catalyst is not significantly more complicated than that of the non-functionalised catalyst. Additionally, the support should be commercially available or be obtained readily from a commercially available precursor.

Outlook

Functionalised carbenes were initially intended to improve catalytic processes even further where functionalised phosphines were already very successful, in much the same way as NHC all but surplanted the phosphines in processes where hemilability, chirality or functionalisation is not a major concern.[2] However, no example could be found where the functionalised carbene performs better than the phosphine



Scheme 22 Immobilisation of an N-heterocyclic carbene on a block-copolymer.



Scheme 23 Immobilisation of a N-heterocyclic carbene using Wang resin.

it was meant to replace. The exceptions are chelating bis-carbenes and chiral NHC.[6,7] The reason is that the functionalisation dilutes the one great advantage of the NHC family of ligands, the exceptionally great σ-donor ability. It is therefore only viable, if the carbene obtains a necessary property (like chirality) that it cannot easily obtain any other way.

Realising that for the main part functionalised NHC will probably be confined to a few specialty applications, the field is already moving on. A few years ago, Herrmann pointed out that the coenzyme of vitamin B1 is a thiazolium cation (see Fig. 9) and fulfils its role in the deprotonated carbene form[2] concluding that the biochemistry of NHC is an open field ready to be explored. Preliminary reports targeting the amino acid histidine[35] and the purine-based xanthine derivative caffeine[36] have already been published.

Erker *et al.* have used the amino acid L-histidine as the carbene precursor.[35] The key step is the alkylation of the imidazole ring. Care has to be taken in protecting the amino and carboxylic acid functionalities and especially in choosing the right alkylation agent. The most potent alkylation agent Meerwein's salt, here in its ethyl form [Et_3O^+ BF_4^-], attacks the protected amine and racemises the histidine scaffold and so ethyl bromide and a base was used instead (see Scheme 24). Deprotonation is facilitated by the silver salt method and transmetallation renders the intended palladium complex.

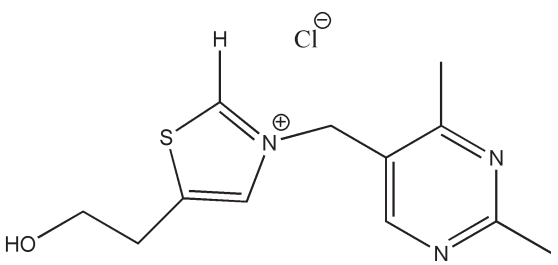
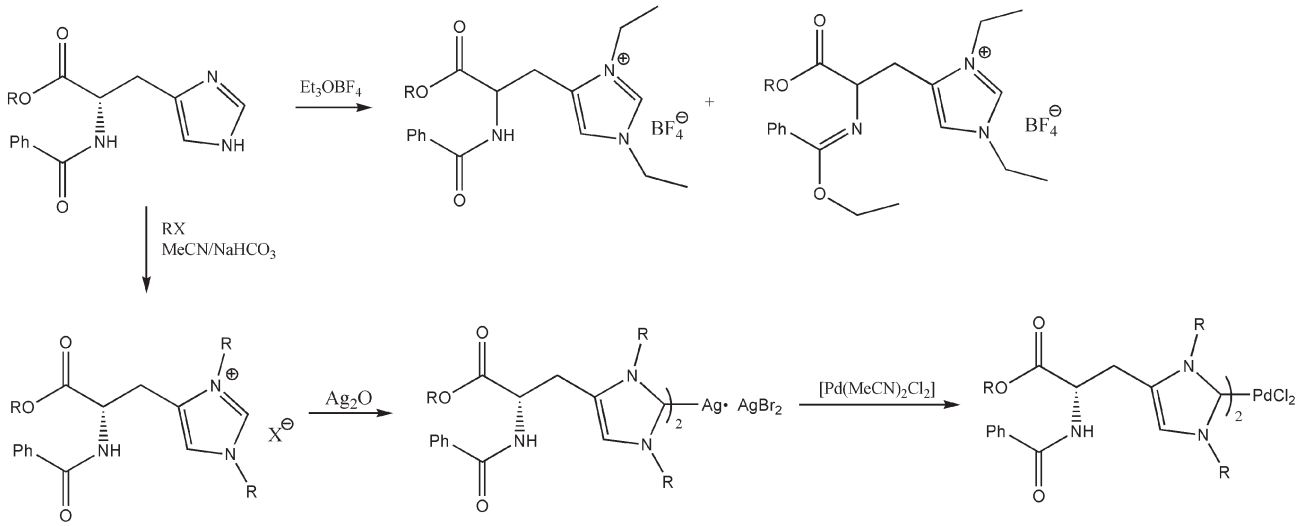


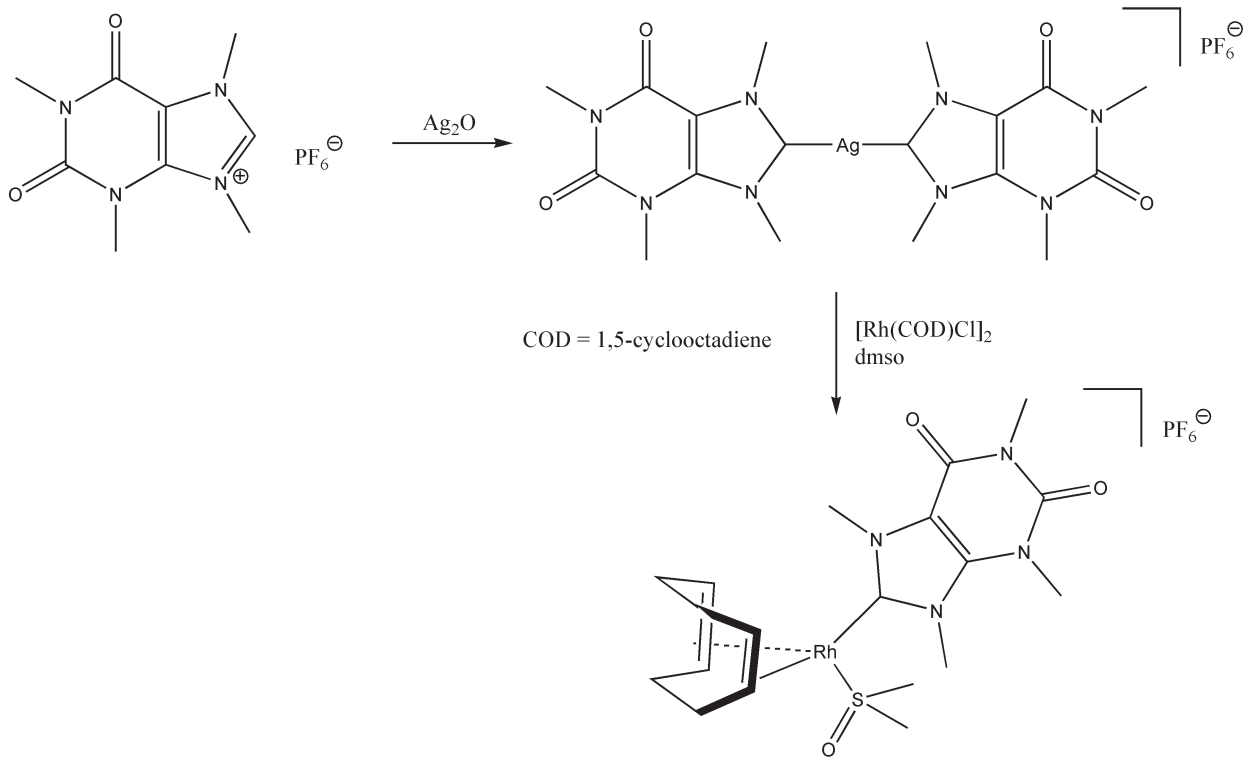
Fig. 9 The thiazolium cation of the vitamin B1 coenzyme.

Youngs *et al.* used caffeine, a natural occurring stimulant, in their synthesis of an NHC derived from biochemically active molecules.[36] Methylation can be achieved using Meerwein's salt, methyl iodide, methyl tosylate or indeed dimethyl sulfate. The latter was chosen by the authors presumably for cost effectiveness. However, dimethyl sulfate is extremely carcinogenic and lipophilic passing through the skin instantaneously upon contact with it. Normal disposable gloves do not give effective protection. After methylation, the imidazolium is obtained as the methyl sulfate salt. Since the anion is reactive under deprotonation conditions, it has to be exchanged for a more suitable anion like PF_6^- or indeed BF_4^-. It is strongly recommended to desist from using dimethyl sulfate as methylation agent in NHC chemistry. Deprotonation is facilitated by the silver salt method and transmetallation renders the intended rhodium complex (see Scheme 25).

We can expect to see more examples of carbenes derived from biomolecules such as amino acids, purines, nucleic acids and others to appear in the literature in the near future. And from there, it is only a small step towards metal carbene complexes supported by biopolymers.



Scheme 24 Ethylation of L-histidine.



Scheme 25 Using caffeine as a natural carbene precursor.

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