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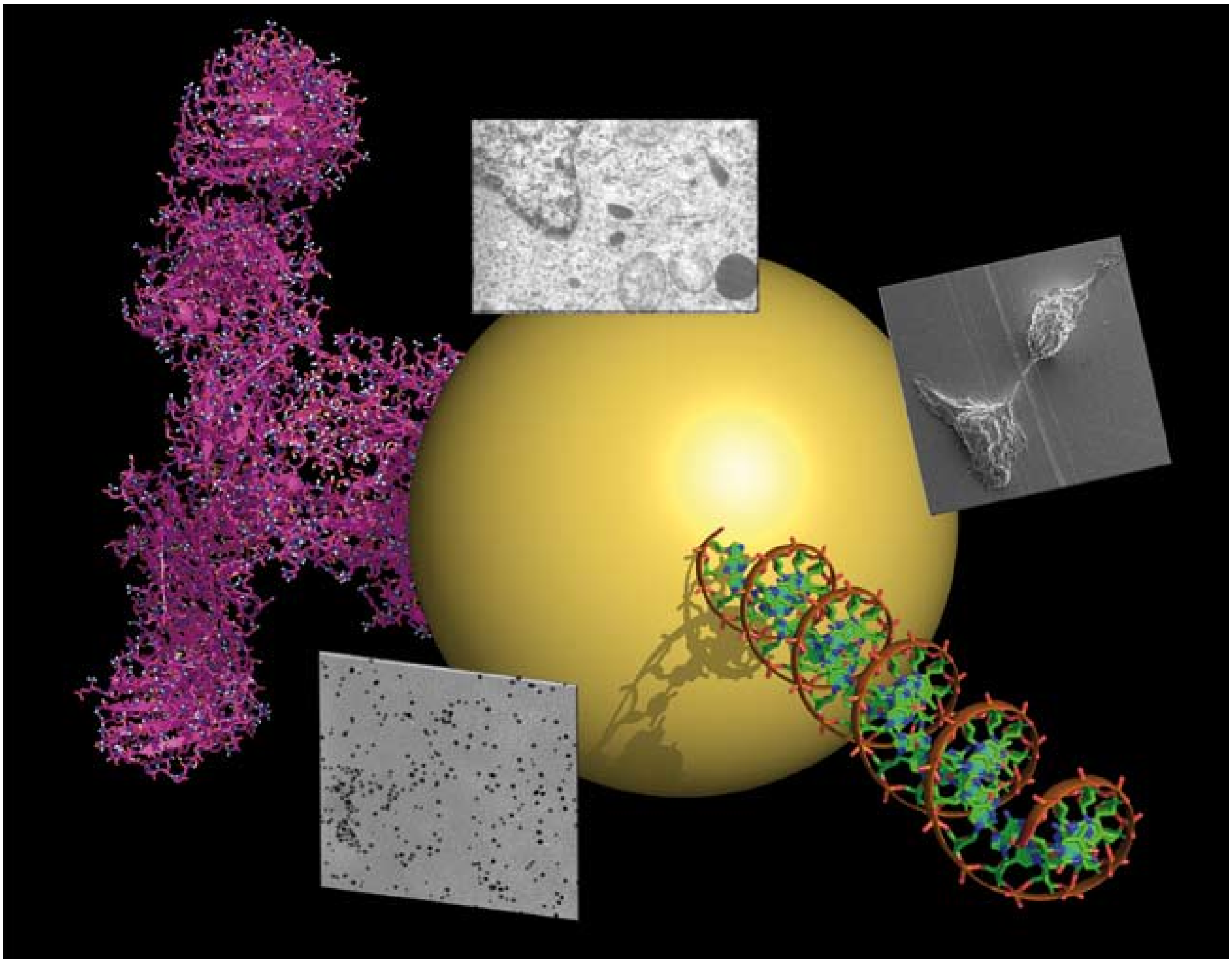
2008 Gold: Chemistry, Materials and Catalysis Issue



Carbene complexes of gold: preparation, medical application and bonding†

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New preparative methods for gold carbene complexes have been developed and older ones modified to prepare compounds with specific inherent properties for targeted applications. One of the important areas of application that has grown rapidly and wherein carbene complexes are increasingly significant falls within the field of medicine. Sophisticated theoretical calculations have accompanied many synthetic studies. These aspects are covered in this *critical review* (65 references).

Introduction

In his Nobel lecture presented in 1973,[1] E. O. Fischer discussed the then newly-discovered carbene complexes while highlighting their future opportunities. More than thirty years later, Chauvin[2] Schrock[3] and Grubbs[4] spoke from the same podium about the then already utilised opportunities of metal–carbene interactions in alkene metathesis: carbene complexes of transition metals became part and parcel of mainstream synthetic chemistry.[5] Furthermore, such complexes found application in areas as diverse as supramolecular[6] and medicinal chemistry.[7] The past decade saw the blooming of so called N-heterocyclic carbene (NHC) compounds, first as free carbenes[8] and then as stabilising ligands in a large variety of metal complexes that in certain instances act as active precatalysts.[9]

Initially, carbene complexes of gold received scant attention but steady developments did occur[10] and in the past five to ten years their value came to be recognised, not only as individual and selective precatalysts, but as dynamic intermediates that play an important role in directed organic synthetic strategies. In many instances, theoretical studies accompanied the practical investigations. Gold carbene complexes are now also slowly but surely joining mainstream chemistry. In addition, such NHC complexes in particular, have found application not only as catalysts but in various other endeavours, as will be shown here. However, the extension of existing synthetic procedures and the complete characterisation of new compounds still remain the most important activities in the carbene chemistry of gold and therefore also deserve proper attention as in the past.

This critical review concentrates mainly on the work that has been carried out since 1999 (when Schmidbaur's comprehensive book on gold chemistry,[11] as well as a volume in the Chemistry of Functional Groups series dealing explicitly with organic compounds of gold and silver,[12] were published). The increasing importance of gold complexes in organic synthesis is not discussed in detail but the topic is extensively dealt with in another review by Nolan in this issue. In the period under discussion, in particular the syntheses of NHC complexes of gold have been described in one review article,[13] whereas such compounds also receive attention in chapters devoted to gold chemistry in the Comprehensive Organometallic Chemistry series, edition III.[14]

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In the first section of this review, the synthetic approaches followed in the past 6–7 years to make carbene complexes of gold are discussed. Brief mention is made of carbene complex intermediates in organic synthesis and this is followed by a discussion of applications that carbene complexes have found in medicine-related work. In conclusion, theoretical approaches come under the spotlight.

Synthetic approaches

The known carbene complexes of gold have been prepared according to five different approaches or small variations in these. Most of the methods have been described previously in the two books and reviews mentioned above but further extensions now provide initiatives for future work. The major protocols involve (i) nucleophilic addition to co-ordinated isocyanides, (ii) homolytic double bond cleavage of selected olefins, (iii) transmetallation of the carbene ligand, (iv) carbeniate transmetallation and (v) substitutive addition or trapping of free carbenes.

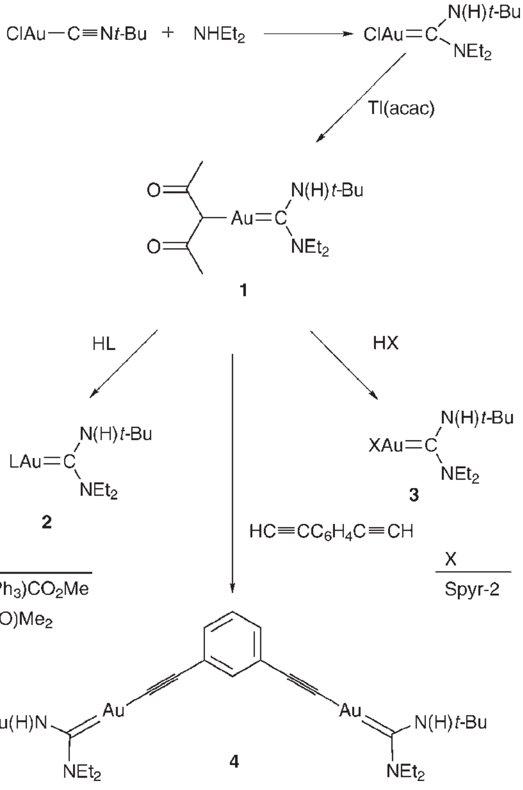
(i) Nucleophilic addition

The pioneering work of Bonati and Minghetti[15] in which a nucleophilic heteroatom, N or O, in amines or alcohols attaches itself to the carbon atom of the isocyanide while the proton migrates to the nitrogen represents an important milestone in the carbene chemistry of gold. Their compounds are also the only ones that could be included in Puddephatt's book on gold chemistry in 1978.[16] As this review also attests, many other complexes were made later and already in '*Gold*: *Progress in Chemistry*, *Biochemistry and Technology*' (1999) more than 40 references to articles on gold carbene compounds appear.[17]

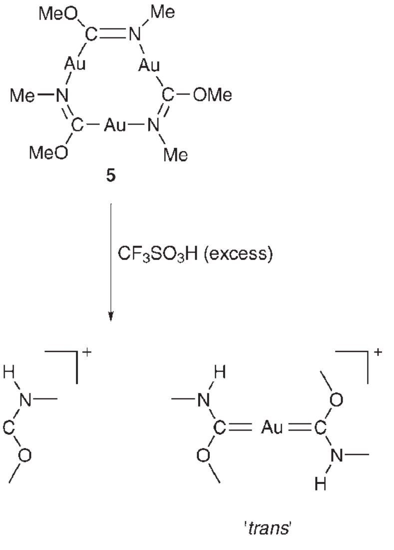
Recently, the Vicente group has employed this classical method to prepare a series of new gold carbene complexes.[18] C-coordinated acetylacetonate appears *trans* to the carbene ligand and functions as a proton acceptor (the 'acac method') towards terminal alkynes, onium salts, as well as 2-pyridinethiol, to afford the corresponding mononuclear, ylide, amino or pyridinethiolate complexes (**2** and **3**, Scheme 1) as well as one dinuclear compound, **4**.

It has long been known that protonation of cyclic iminomethylgold complexes such as **5** (Scheme 2; prepared from a gold isocyanide and alkoxide—not alcohol as in the Bonati method) presents an alternative synthetic route to similar carbene complexes. Recently, structural isomers of such homoleptic carbene complexes have been isolated by Balch and co-workers (Scheme 2) and later also the solid and frozen liquid luminescence of related complex salts (prepared by the standard nucleophilic addition method) were measured and rationalised in terms of the presence of extended chains of Au(I) centers connected by aurophilic interactions.[19]

Howell *et al.*[20] studied the well-known solubilising effect of poly(oxyethylene) chains to impart water solubility by forming gold(I) carbene complexes *via* the addition of $MeNH(CH_2CH_2O)_nMe$ (n = 1–11) to Au(CNPh)Cl. The resultant carbene complexes served as substrates for the laser decoration of gold onto ceramic surfaces.



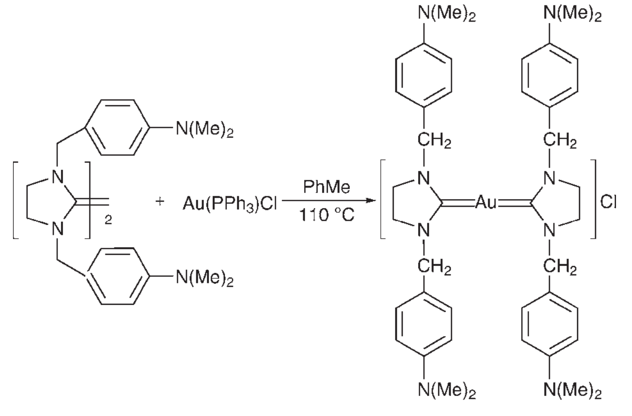
Scheme 1



Scheme 2

(ii) Double bond cleavage

Although Lappert and co-workers's homolytic cleavage of electron rich olefins[21] has largely been superseded by other approaches, Çetinkaya and his co-workers[22] have prepared an imidazolinylidene gold complex **7** according to this method (Scheme 3) and then polymerized the product almost quantitatively to polyimides (**8**) with various dianhydrides in a one-step procedure (Scheme 4).

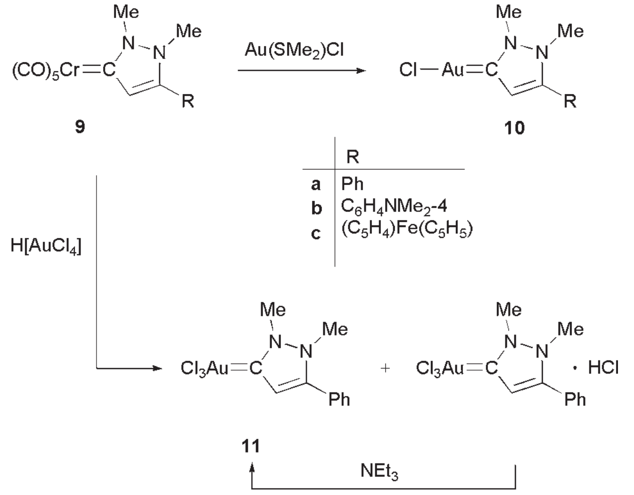


6 **7**

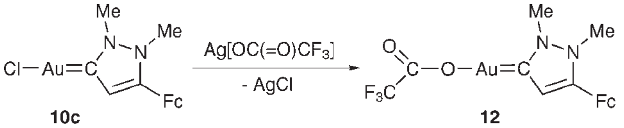
Scheme 3

(iii) Transmetallation

In an important study, Aumann and Fischer[23] were the first to apply a transmetallation protocol in gold carbene synthesis. Their carbene ligands were of the Fischer-type and initially attached to group 6 metals. Although gold(III) centra were provided, both gold(I) and gold(III) carbene complexes could be isolated. Later, Liu and co-workers[24] transferred the saturated carbene ligand, $:\overline{\mathrm{CN(R)CH_2CH_2N}}\mathrm{R}$ (L; R = Et or $CH_2CH{=}CH_2$), from $(CO)_5WL$ to gold by substituting both ligands in $Au(Me_2S)Cl$ to effect formation of a biscarbene complex with Cl^- acting as a counterion. Very recently, pyrazolin-3-ylidene was shown to exchange its initial group 6 metal partner in **9** (Scheme 5) for both gold(I), **10**, and gold(III), **11**.[25] The Cl^- ligands in products such as **10a–c** could readily be displaced by trifluoroacetate to afford a relatively stable complex carrying carbene- and oxygen–carbon-donor ligands (**12**, Scheme 6). Other examples in which halide substitutions occur are mentioned later.



Scheme 5



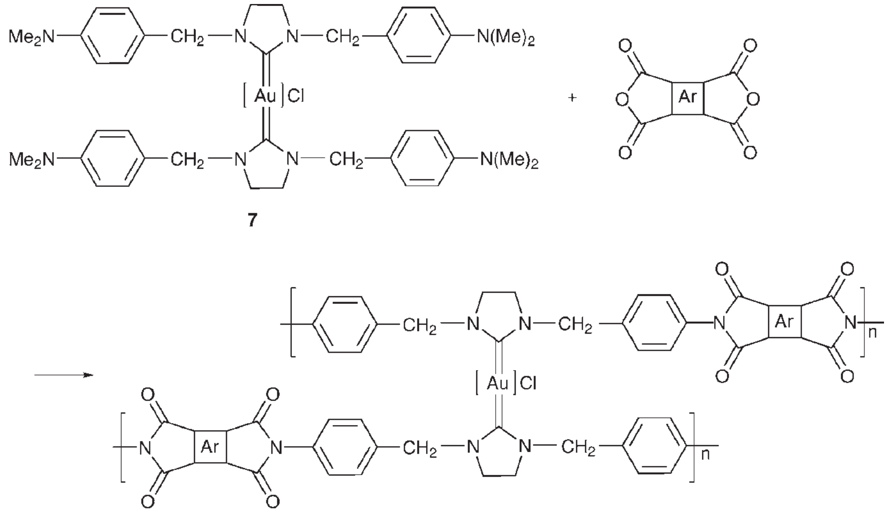
10c **12**

Fc = $(C_5H_4)Fe(C_5H_5)$

Scheme 6

As an extension of much earlier work by Fischer and Beck, certainly the most successful and useful transmetallation procedure and one that found wide application, was developed by Lin and his co-worker, Wang.[26] In their most direct method, Ag_2O was used to deprotonate an azolium salt to furnish a biscarbene silver complex, (**13**, Scheme 7). Transfer to gold occurs readily. The AgCl that is produced in the process can be reused to generate more of the silver carbene complex source. Various modifications under phase transfer conditions (PTC) are now available (*vide infra*).

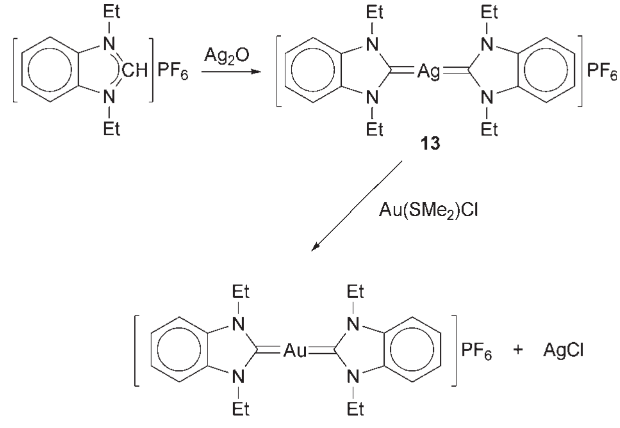
In their attempts to maintain Au···Au interactions in solution, Catalano and his co-workers[27] employed pyridyl units attached to an NHC framework. A particular advantage of the



7

8

Scheme 4



Scheme 7

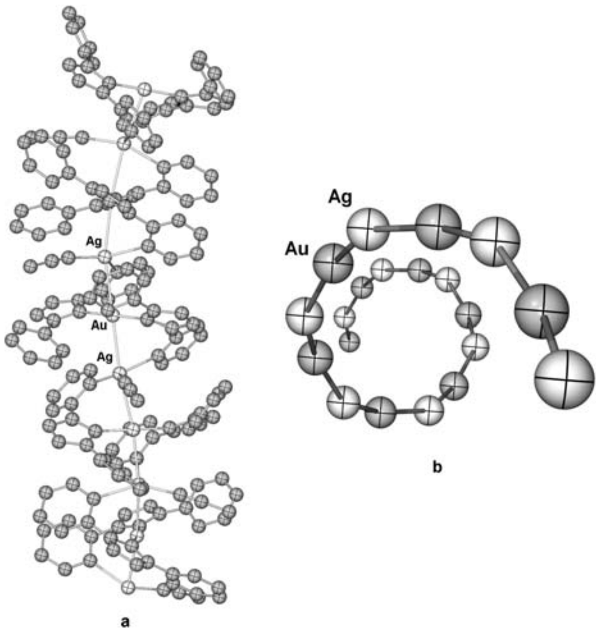
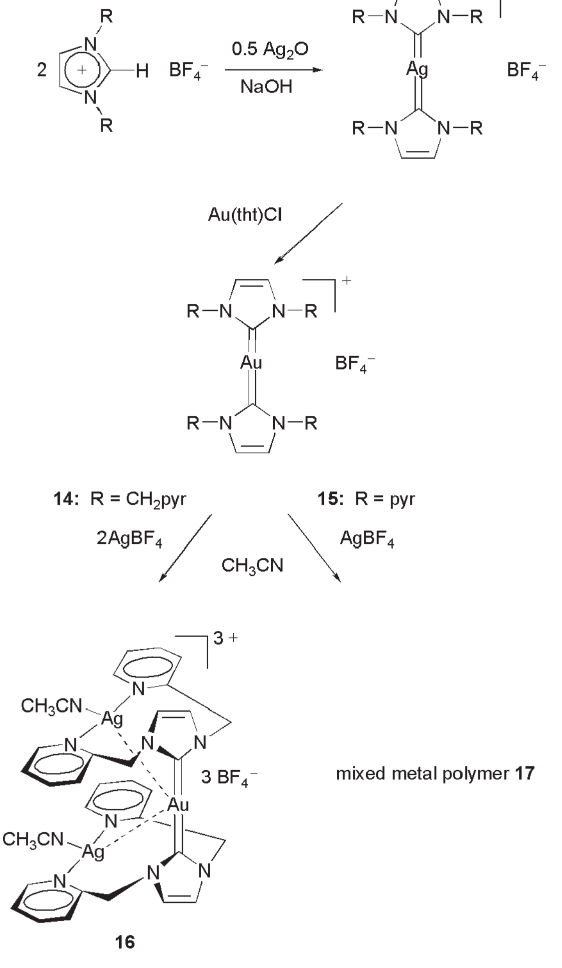


Fig. 1 Crystal structure representations showing (a) the extended structure of **17** and (b) the helical metal core with alternating Au–Ag separations of 2.8359(4) and 2.9042(4) Å. The linear two coordination of gold and trigonal three coordination of Ag is clearly reflected in (a).

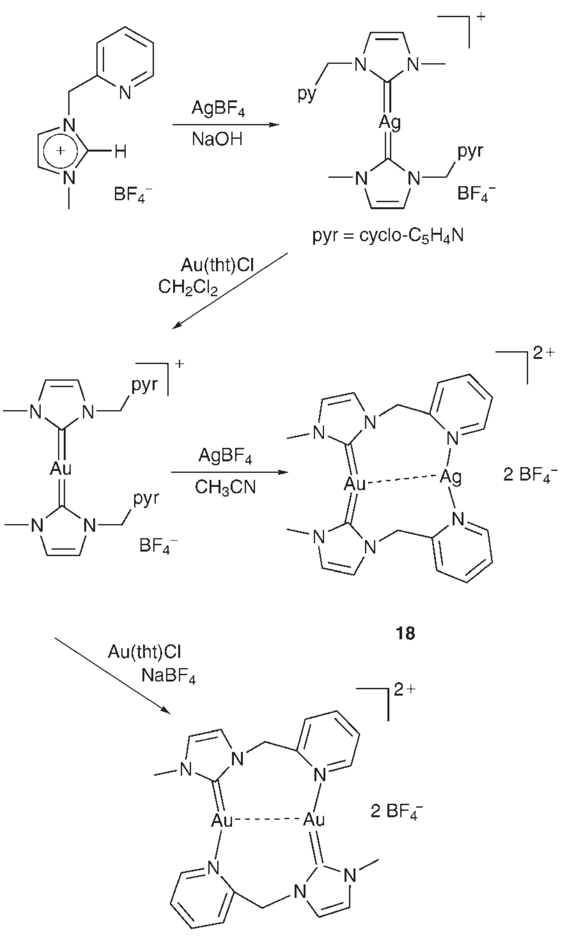
Ag_2O deprotonation method used by them is that a variety of silver compounds as well as their related gold products could be studied in the same investigation. Reactions wherein gold is involved are shown in Scheme 8. The mononuclear products **14** and **15** exhibit no significant Au$\cdots$Au interactions in the crystalline state. Further treatment of the two homoleptic complexes with an excess of $AgBF_4$ afforded completely different products (**16** and **17**) both now containing silver and gold. Compound **16**, a trimetallic species $[AuAg_2(pyrCH_2\text{–}imidazolylidene)_2(NCCH_3)_2][BF_4]_3$, contains silver ions coordinated to the pyridyl moieties. These ions also interact weakly with a gold atom at a distance of approximately 3.2 Å. By reducing the flexibility of the pyridyl-containing side chain, it was possible to isolate a coordination polymer, **17**, in which alternating Ag–Au–Ag and Au–Ag–Au angles of 171.8° and 166.2° gave the extended metal chain a helical form as is shown in Fig. 1. Only one of the pyridyl rings on an azolylidene ring participates in co-ordination to silver.

Changes within the auxiliary ligands greatly influence the connections between the metal units. With the uncoordinated pyridyl ring in the last carbene replaced by a methyl group, four different polymers were produced. Each contained similar homoleptic gold(I) centers connected to trigonally coordinated silver(I) that is surrounded by either a nitrile molecule or a nitrate ligand and two pyridyl groups. All these polymers were found to be arranged in unrelated zigzag patterns. When a CH_2 spacer was inserted between the imidazolylidene and the pyridyl unit, only the dimetallic gold–silver compound, **18**, or the gold–gold complex $[Au_2\{CH_3im(CH_2pyr)\}_2](BF_4)_2$, **19**, were obtained (Scheme 9).[28]

In Australia, Baker and co-workers[29] had prepared compound **20** (Scheme 10) by the Lin method and then, in an ensuing reaction, proceeded to substitute the Cl^- ligand with other halides, **21**, pseudo-halides, **22**, or a methyl group, **23**, while using three different methods. On the basis of the ratio of N- *versus* S-bonded thiocyanate present as indicated by IR spectroscopy for **21c**, they concluded that the carbene exerts a

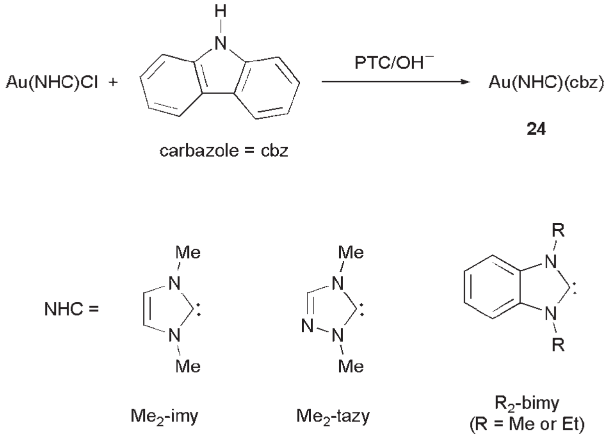


Scheme 8



Scheme 9

trans influence comparable to that of P(OPh)$_3$. The dominating importance of the NHC–Au σ-interaction was accentuated by correlating variation in C(carbene) ^{13}C chemical shifts and Au–C(carbene) bond distances with the σ-donor ability of the ligand that appeared *trans* to the carbene ligand.

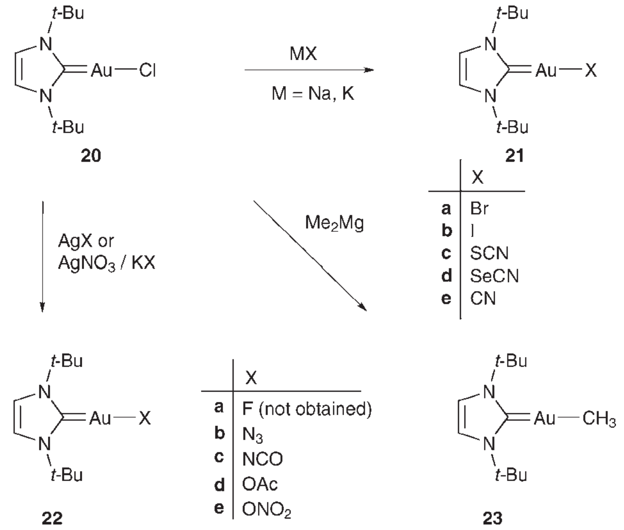


Me$_2$-imy : 1,3-dimethylimidazol-2-ylidene
Me$_2$-tazy : 1,3-dimethyltriazol-2-ylidene
R$_2$-bimy : 1,3-dimethyl or 1,3-diethylbenzimidazol-2-ylidene

Scheme 11

Chang, Lin and other co-workers,[30] very similarly but using phase transfer during the halide replacement, have prepared NHC–carbazolate complexes, **24**, of Au(I) (Scheme 11). Somewhat in contrast to the previous authors, they interpret the consistently increased N–C(carbene) bond lengths in the complexes compared to those in free azolium salts as evidence for non-negligible π-back bonding to the carbene. As a word of caution pertaining to the assignment of low-energy emission bonds, it is notable that such transitions here are of the intraligand type and occur without the presence of any significant Au···Au interaction.

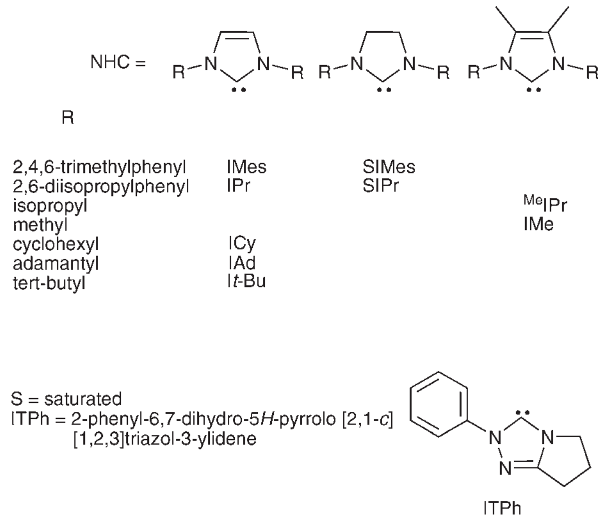
In the laboratory of Nolan, a certain preference for the *in situ* transmetallation method compared to a ligand exchange has been expressed.[31] The latter procedure had initially been applied by Arduengo and others for the preparation of carbene complexes of other group 11 metals excluding gold.



	X
a	Br
b	I
c	SCN
d	SeCN
e	CN

	X
a	F (not obtained)
b	N$_3$
c	NCO
d	OAc
e	ONO$_2$

Scheme 10



R			
2,4,6-trimethylphenyl	IMes	SIMes	
2,6-diisopropylphenyl	IPr	SIPr	
isopropyl			$^{\mathrm{Me}}$IPr
methyl			IMe
cyclohexyl	ICy		
adamantyl	IAd		
tert-butyl	I*t*-Bu		

S = saturated
ITPh = 2-phenyl-6,7-dihydro-5*H*-pyrrolo [2,1-*c*] [1,2,3]triazol-3-ylidene

Scheme 12

By comparing ^{13}C chemical shifts of free (Scheme 12) and gold-coordinated carbenes, (eqn (1) and (2)), Nolan concluded that very little difference in donor ability to a gold(I) centre is apparent between the chosen ligands.

$$\text{NHC} + \text{Au(SMe}_2\text{)Cl} \longrightarrow \underset{\textbf{25}}{\text{Au(NHC)Cl}} \qquad (1)$$

NHC = IPr, SIPr, ^{Me}IPr, IMe, ICy, IAd, I*t*-Bu (compare Scheme 12)

$$\text{NHC}\cdot\text{HCl} \xrightarrow{\text{Ag}_2\text{O}} \text{Ag(NHC)Cl} \xrightarrow[\textbf{26}]{\text{Au(SMe}_2\text{)Cl}} \text{Au(NHC)Cl} \qquad (2)$$

NHC = IMes, SIMes, ITPh (compare Scheme 12)

Later, members of the same group[32] have shown how one of these complexes may be converted into a catalyst precursor carrying a labile acetonitrile ligand (Scheme 13) that can effectively transfer the carbene present in ethyl diazoacetate on to various organic substrates.

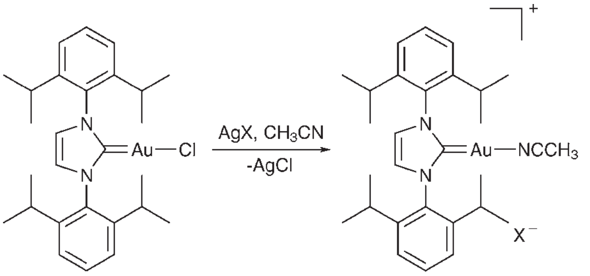
In a related protocol, Ricard and Gagosz[33] very recently used a metathesis reaction between a number of Au(NHC)Cl complexes that were first prepared in Nolan's laboratory and bis(trifluoromethanesulfonyl)imidatesilver(I) to prepare air-stable, crystalline NHC gold complexes that contain imidate (Tf_2N^-) as a weakly coordinating counterion (eqn (3)).

$$\text{Au(NHC)Cl} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{AgNTf}_2} \underset{\textbf{28}}{\text{Au(NHC)NTf}_2} + \text{AgCl} \qquad (3)$$

NHC = *i*-Pr, IMes, IAd, SIPr, SIMes (compare Scheme 12)

These compounds were tested as precatalysts in a range of known reactions catalysed by gold complexes (*vide infra*) including enyne cyclizations and carbene transfer, and were found to be, in most cases, at least as active as the complexes that had previously been employed in such reactions.

Using one of the bulky Nolan complexes (Au(NHC)Cl, NHC = SIPr, eqn (1) and Scheme 12), Gray, Sadighi and others[34] startlingly managed to isolate and fully characterize the only example of a gold(I) fluoride complex, **30**, stabilised by the presence of the NHC ligand (Scheme 14). The intermediate alkoxide, **29**, was also the first of its kind to be prepared (compare ref. 25). DFT calculations indicated significant pπ–dπ interactions between the fluoride and the gold and allocated a large partial negative charge to the fluorine atom. The interactions predicted between the carbene ligand and gold resemble those that had been reported even earlier by other authors (compare a later section).



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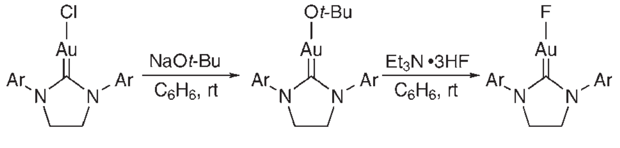
X = PF_6, BF_4

Scheme 13



Ar = 2,6-(*i*-Pr)$_2$C$_6$H$_3$ **29** **30**

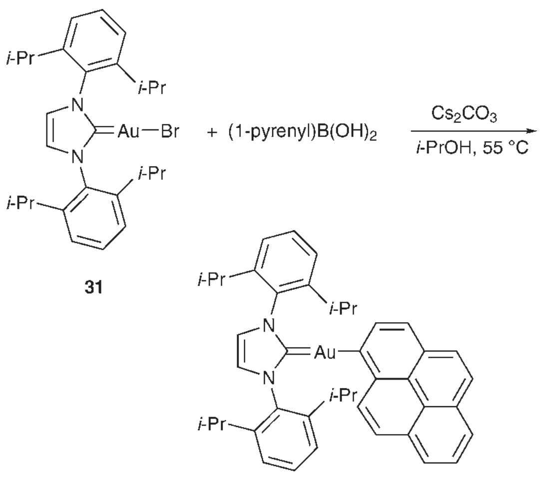
Scheme 14

Gray and his co-workers,[35] pursuing the design and isolation of photoactive compounds, developed a new method to attach aromatic groups to a chosen gold carbene fragment. Commercial 1-pyreneboronic acid reacts with a compound from Nolan's laboratory, the Au(NHC)Br complex **31**, in the presence of Cs_2CO_3 to afford the product **32** in 75% yield (Scheme 15). Ongoing efforts endeavour to enhance intersystem crossings in the charge transfer spectra of such complexes by varying both ligands attached to gold(I).

The Lin method has successfully been utilised to prepare cationic, gold-containing, macrocyclic complexes (**33**, Scheme 16) with two linear gold linkages adopting a cross arrangement in the solid state when the smaller of the two chosen substituents is placed on the imidazolylidenes. The same researchers, Li, Zhang, Wang and others[36] have similarly used their 'flexible bridge' idea to prepare mononuclear NHC-containing metallacrown complexes, of silver and gold, (classes **34** and **35**, Scheme 17).

Going one step further than the Catalano group, (*vide supra*) Chen *et al.*[37] placed pyridylmethyl substituents on two imidazolium units and linked them by (amongst others) a $(CH_2)_2O(CH_2)_2$ chain. Consecutive treatment with Ag_2O and $Au(SEt_2)Cl$ in CH_3CN afforded, after carbene transfer, a cationic dinuclear gold complex (**36**, Scheme 18) which is related to another recently reported product, **19** wherein gold is also coordinated by an NHC ligand and a pyridyl functionality.

In a clever attempt to prepare an unprecedented gold cluster stabilised by NHCs, Zhou and Chen[38] have prepared a pyrazole-linked bis(NHC) diazolium salt and then used the



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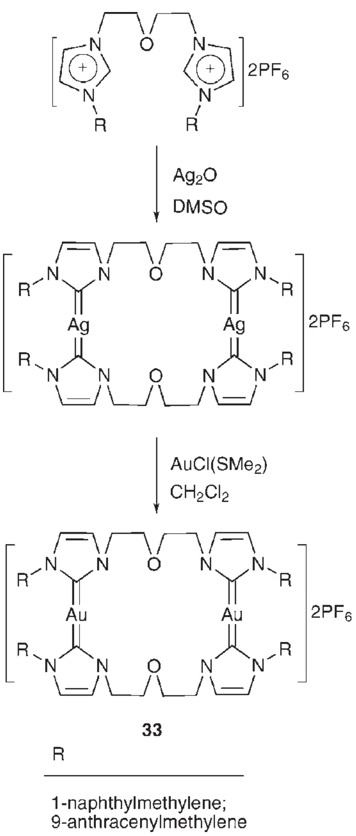
32

Scheme 15



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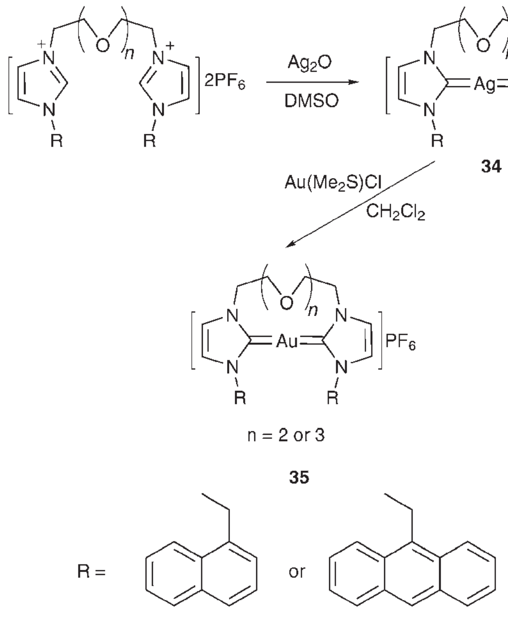
Scheme 16

Lin method to prepare isostructural tetranuclear structural isomers of silver and gold (**37**, Scheme 19) in which the square planar metal atoms are each bonded to one NHC donor group and to one of the nitrogen donors on a pyrazolate linker. The gold atoms are separated by an average distance of 3.284 Å.



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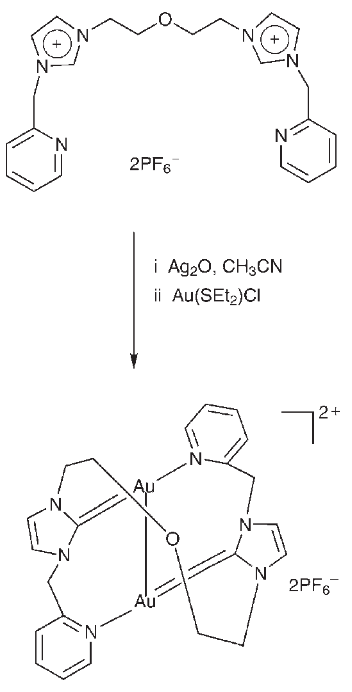
35

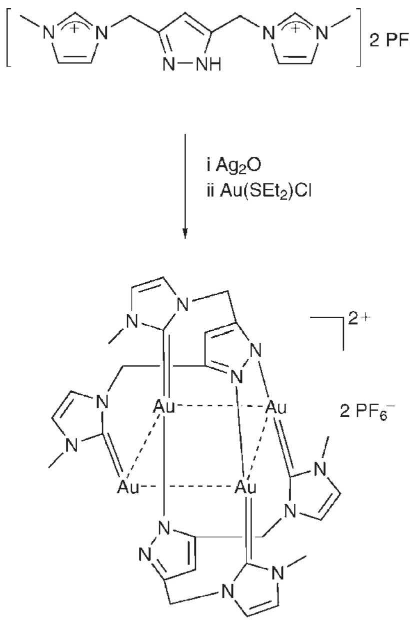
Scheme 17



36

Scheme 18

An intriguing intramolecular metal fragment exchange (**38** → **39** → **40**) that involves the isolobal cationic fragments Ph_3PAu^+ and $(CO)_3MnL^\wedge L^+$ ($L^\wedge L$ = bipy) both attached to deprotonated substituted phenylimidazole has been discovered by Ruiz and Perandones[39] (Scheme 20). Thereafter the manganese fragment is selectively removed by protonation to produce the gold carbene complex. The scheme in the article again indicates how complicated a discussion of changes in chemical bonding to explain dynamic processes becomes when the metal carbene bond is represented by a single line.



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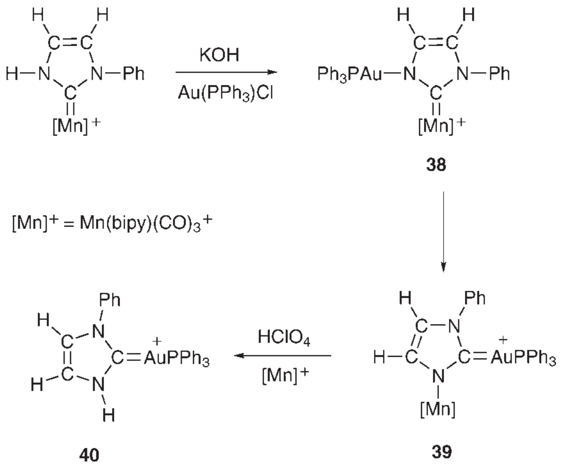
Scheme 19



Scheme 20

(iv) Carbeniate transmetallation

The results obtained using a carbeniate transmetallation route from lithium azolyls have been summarized in a Mini Review by Raubenheimer and Cronje[10] and also recently by Lin and Vasam.[13] Particular advantages of this method are first that, in certain instances, the precursor azolyl complex may be isolated and studied if required and second that, in addition to alkylation, protonation is also an option to form carbene complexes therefrom. Certain attempts to use the method proved unsuccessful.[40] Two approaches that have been followed in the preparation of rare gold pyridylidene complexes (Scheme 21) illustrate the method.[41] Related complexes of palladium have found recent application in homogeneously catalysed C–C coupling and those investigations also address the issue of zwitterionic representation against carbenoid character (*e.g.* **41a** *versus* **41b**)[42]—presently also a burning question in gold(I) catalysed nucleophilic additions to acetylenes (*vide infra*).

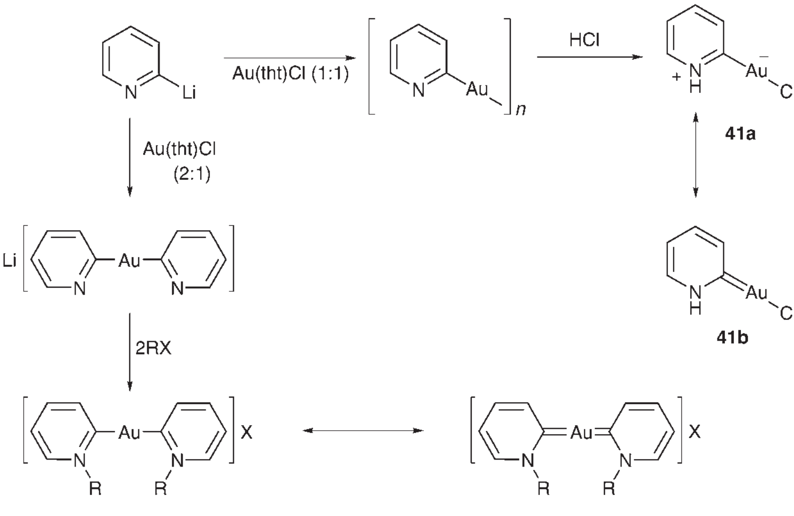
(v) Addition or trapping of carbenes

Free Arduengo carbenes have not generally been isolated in pure form before coordination to gold centra. Nevertheless, as mentioned before (compare eqn (1)), this method has been used in Nolan's group. Even before that, Fehlhammer and his co-workers[43] used monoanionic dicarbene ligands, bis(imidazol-2-ylidene-1-yl)borates **43**, (Scheme 22; BIS,^{R} R = Me, Et, *i*-Pr), to replace both existing ligands on Au(PPh$_3$)Cl and to effect formation of 12-membered dimetallocycles, **44**. The transannular Au···Au separation in one of the products represents a weak interaction. More recently, Roesky *et al.*[44] utilised free NHC carbenes to substitute CO in Au(CO)Cl and then proceeded to substitute chloride and to add ethynyl by using ClMgC≡CH, while Grützmacher *et al.*[45] deprotonated a bistropimidazolium salt, **45**, with the strong base KO*t*-Bu and trapped the resulting unstable carbene with Au(PPh$_3$)Cl to form a monocarbene(phosphine)gold(I) complex (**46**, Scheme 23).

Also circumventing the tedious isolation of the free carbenes or even transmetallation from silver complexes, and encouraged by their positive experience with palladium complexes, Baker, Berners-Price and co-workers[46] deprotonated azolium-linked cyclophanes in the presence of Au(SMe$_2$)Cl with weak carboxylate bases (albeit at 100 °C) and employed solubility differences or precipitation to isolate a series of carbene complexes of the [Au$_2$(dicarbene)$_2$]$^{2+}$ type (Scheme 24). Crystal structure determinations indicated that aurophilic interactions in the products could be manipulated by tailoring of the cyclophane and cyclophane-like building blocks and in this manner regulate the luminescent properties of the products.

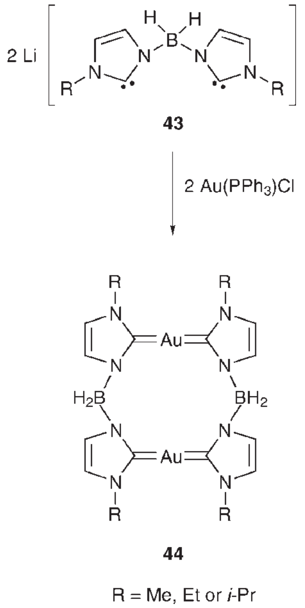
Homogenous catalysis—a brief commentary

The use of various gold compounds in organic synthesis mostly catalysed by non-carbene gold complexes has increased

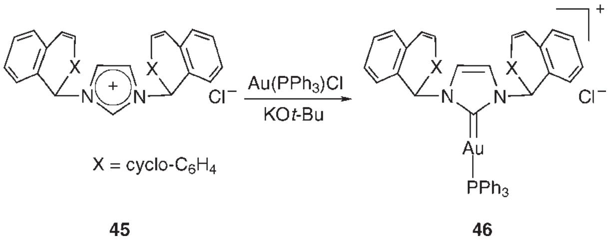


R	X
H	Cl
Me	CF$_3$SO$_3$

Scheme 21



Scheme 22

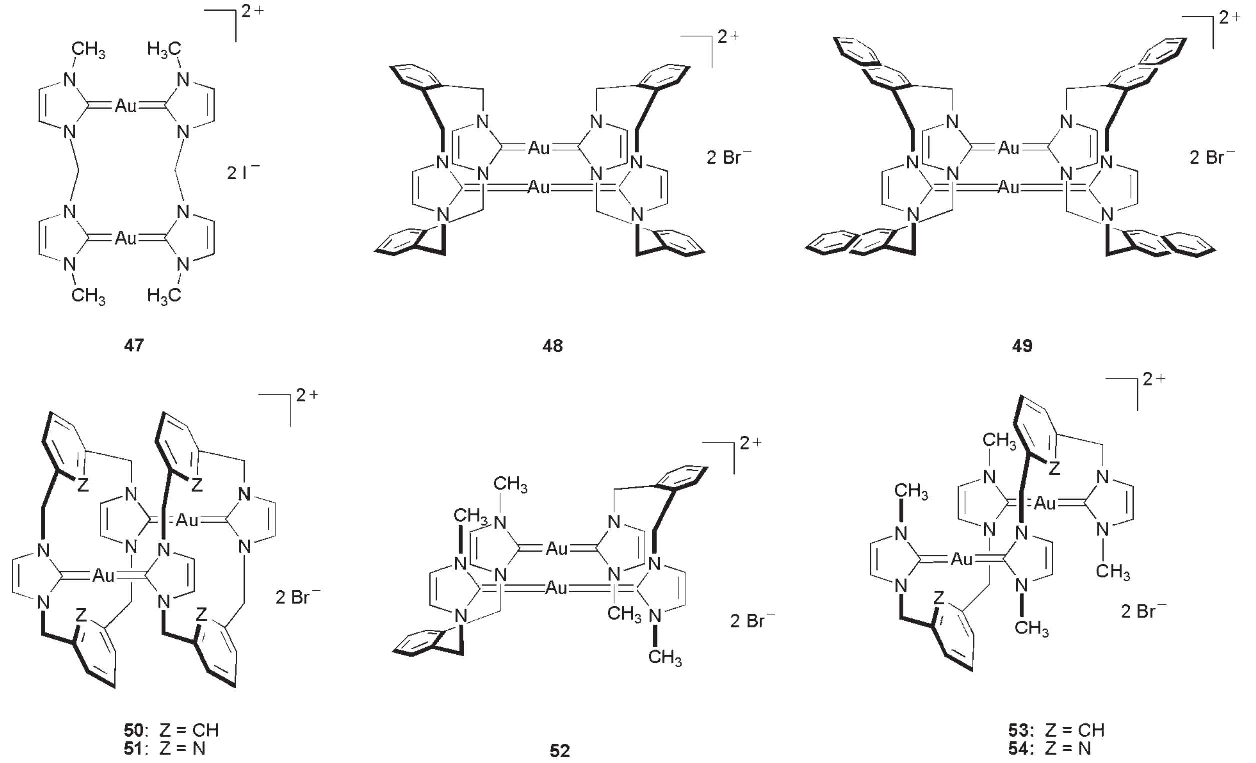


Scheme 23

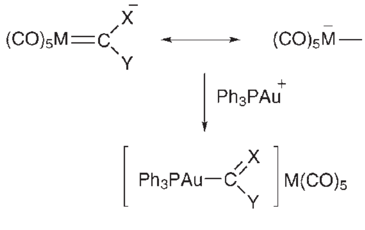
with rapid strides over the past five years. This critical review is not the ideal place to deal with such advancements in detail but one particular general aspect is of concern here: transiently formed gold carbene complexes could play an important role in the activation process of terminal acetylenes. Probably the most far-reaching reactions involve the already mentioned enynes where skeletal rearrangements, attached group migrations and subsequent additional nucleophilic addition may occur.[33] Complex reaction mechanisms have been proposed and cyclization routes have been summarised recently by Echavarren and co-workers for 1,6-enynes.[47]

The activating property of the cationic gold fragment has been described by Gorin and Toste[48] as one of 'mediating the bond formation by delocalising the cationic charge onto the metal and thus stabilising the transition state(s)'. A suitable mechanism would involve formal carbene formation by metal to carbon π back-donation, but it still remains important (a) to establish whether, for certain, gold complexes really participate in π-interaction with carbon donors and (b) to characterise intermediates in some of the postulated processes. Such mechanisms that involve diorganocarbene complexes are not unique to gold and have commonly been invoked for other soft, platinum group metals.

When the Ph_3Au^+ fragment reacts with anionic Fischer-type carbene complexes (Scheme 25), the acyl, imidoyl or substituted vinyl products formed have all been represented by Raubenheimer and co-workers[49] as mesomeric carbene complexes but particularly in situation **c** strong physical, theoretical and indirect structural evidence have been presented that relate to the issue mentioned in (a) above: the



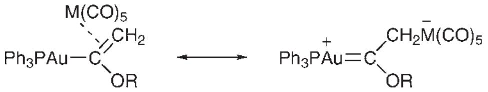
Scheme 24



55

	M	X	Y
a	W	O	Ph
b	Cr or W	NH, NMe	Me, Ph
c	Cr or W	CH_2	OMe, OEt
d	Cr or W	CH_2	NMe_2, NR_2
e	Cr	CH_2	SPh

Scheme 25



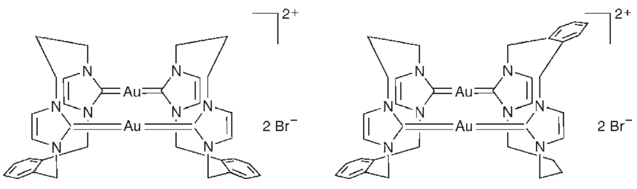
55c **55c′**

M	R
Cr, W	Me
Cr, W	Et

Scheme 26

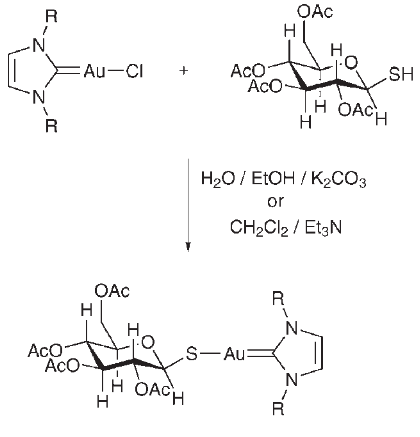
classical gold carbene representation **55c**′ (Scheme 26) should indeed be considered the most important contributing canonical form.

It needs to be emphasized that the importance of the Au–C(carbene) double bond character remains ambiguous and it is well known that the role of metal–carbon back bonding even in other transition metal–NHC complexes has not been resolved convincingly. In recently prepared 'remote' six-membered NHC complexes of Pd, carbene character has mainly been assigned on the basis of NMR evidence because bond distance variation is generally an insensitive indicator of bond type.[42] Owing to weak correlations between bond distances and other physical data, one might ask whether the arrow concept, so useful in describing electronic redistributions in organic molecules, is really directly applicable where metal interactions are involved. On the other hand, quantum mechanical calculations are often far more explicit and indicate significant metal–ligand π-interactions (*vide infra*). Certainly, more experimental work seems necessary. Until such time, one should probably conclude that even a little bit of carbene character could go a long way in stabilising the gold intermediates under discussion.



cis-**56** *trans*-**56**

Scheme 27



57

R = Me, *i*-Pr, *n*-Bu, *t*-Bu, Cy

Scheme 28

Medical applications of gold carbene compounds

For earlier developments in the medicinal chemistry of gold, we refer to comprehensive independent treatments by Shaw[50] and Fricker.[51]

Baker, Berners-Price and co-workers using the complexes in Scheme 24 investigated for the first time the ability of carbene complexes, acting as lipophilic compounds, to induce mitochondrial membrane permealisation in rat liver mitochondria. They proposed that mitochondrial swelling and activity do not necessarily correlate. It seemed that a different mechanism was operative than with other lipophilic complexes such as $Au(dppe)_2^+$ and pyridylphosphine analogues. Later, since the luminescence profile of complex **48** (Scheme 24) was unsuitable for determining the intracellular distribution thereof by using fluorescence microscopy, a new dinuclear complex was designed to support a shorter Au···Au separation than in **48**.[52] The new imidazolium salt, again upon deprotonation with a mild base (sodium acetate), afforded, with $Au(SMe_2)Cl$, two rigid geometric isomers of complex **56** (Scheme 27) that could be separated by fractional crystallisation. Complex *cis*-**56** remained stable in a chosen mouse macrophage cancer cell line and indicated the potential to investigate the cellular processing of such gold complexes using confocal fluorescence microscopy.

Using initially both the Arduengo and Lin transmetallation methods with Au(NHC)Cl complexes, the same corresponding authors made a series of Auranofin analogues, **57**, by halide

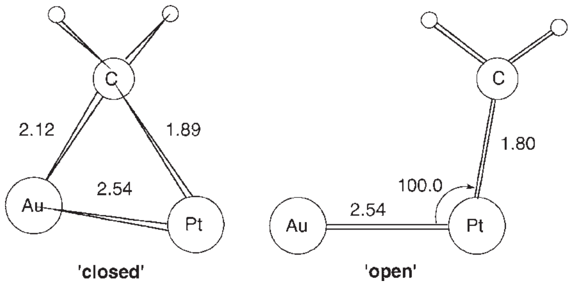
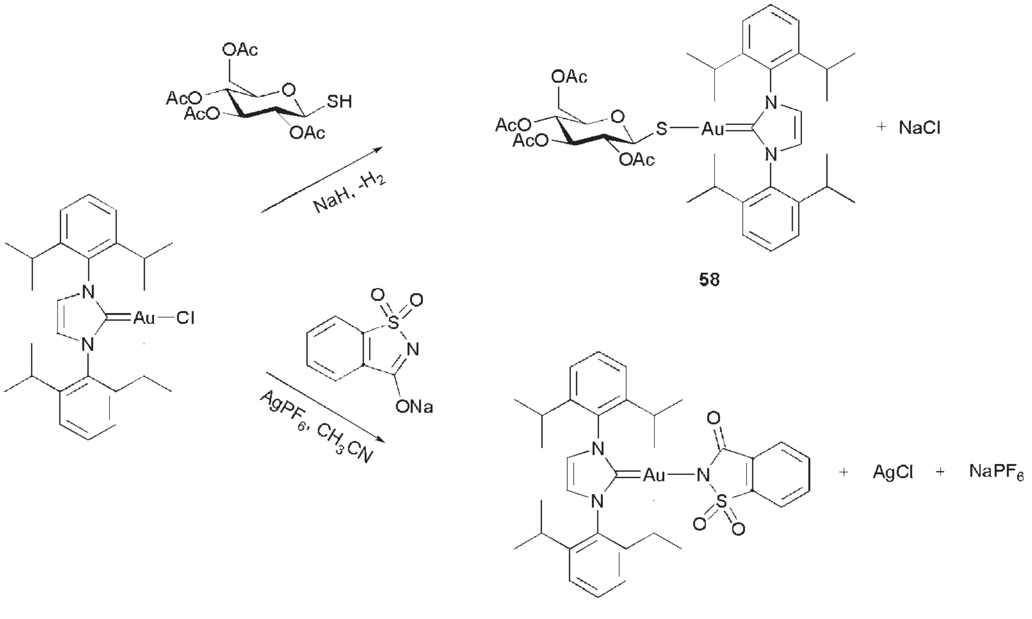


Fig. 2 Optimised low-energy structures of $PtAuCH_2^+$ according to B3LYP level calculations (bond lengths in Å, angles in degrees).



Scheme 29

substitution (Scheme 28).[53] Finally, with cationic $Au(NHC)_2^+$ complexes prepared by *in situ* substitution of both ligands in $Au(SMe_2)Cl$, mitrochondrial swelling was shown to increase parallel with the lipophilicity of the complex.[54] No support for π-back bonding in any of the complexes from the solid state structures or low temperature NMR measurements was forthcoming.

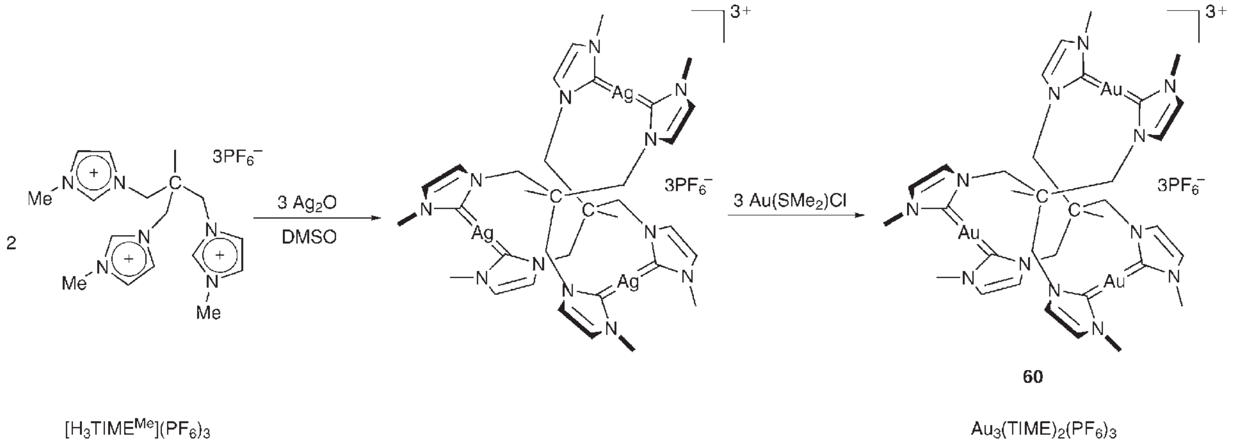
The cationic $Au(NHC)_2^+$ gold complexes prepared by Çetinkaya's group,[55] using free carbenes or Lappert's method to generate the carbene ligands and $Au(PPh_3)Cl$ as source of gold(I), are particularly active antibacterial agents and the nature of the substitution on the nitrogen atoms has a pronounced effect on their activities and selectivities.

Extending earlier work from Baker and co-workers, Nolan *et al.*[56] also reported an NHC Auranofin mimic (**58**, Scheme 29) and used *in situ* generated $Au(IPr)NCCH_3^+$ (compare Scheme 13) to produce a desired saccharin complex, **59**. Notable is the N attachment of the ligand in the latter product owing to the low affinity of gold for oxygen.

Raubenheimer and co-workers,[57] using the Lin method, have reported a heterobimetallic gold(I) NHC complex that contains a conjugatively attached ferrocenyl moiety. This phosphine-free 'complex of a complex' is tumour specific against two chosen cancer cell lines but the question regarding possible anti-tumour activity enhancement by the presence of the ferrocenyl group remains unresolved and needs to be addressed further.

Gas-phase reactions and theoretical investigations

As mentioned before, in various publications quantum mechanical calculations are reported that serve to rationalise the experimental results and mostly to clarify the bonding within the carbene complexes. Generally they are of the DFT-type



Scheme 30

and the results are pretty consistent in describing gold–carbene interactions. Only a brief summary is given here since theoretical approaches to gold chemistry are treated in depth in another review by Pyykkö in this issue.

In his review article on relativistic effects in gas-phase ion chemistry, Schwarz[58] has shown that $Au(CH_2)^+$ exclusively and with high efficiency yields $CH_2NH_2^+$ and neutral AuH in its reaction with NH_3. This reaction, driven by weak $Au^+–CH_2$ and strong Au–H bonds, differs remarkably from those of other transition metal carbene complexes. Later, Schwarz and co-workers[59] studied reactions of $Pt_nAu_nCH_2^+$ with NH_3; the platinum–gold carbene clusters are formed within the mass spectrometer by reaction of the base metal clusters with CH_4 or CH_3X (X = Cl, Br). Significantly only the dinuclear carbene complex $PtAuCH_2^+$ mediates C–N bond formation with NH_3 to presumably form an aminocarbene complex, $PtAuC(H)NH_2^+$ (eqn 4) while $Au_2CH_2^+$ or $PtAu_2CH_2^+$ are unreactive towards NH_3.

$$[(PtAu)CH_2]^+ + NH_3 \longrightarrow [(PtAu){=}C(NH_2)H]^+ + H_2 \qquad (4)$$

This result points to the presence of particular electronic or structural influences present in the dinuclear Pt–Au carbene complex. Motivated by these interesting experimental results from Schwarz's group, Cao and co-workers[60] calculated energy profiles for bimetallic carbene complexes $PtAuCH_2^+$ in connection with NH_3 activation. The co-existence of very similar closed and open low-energy triangular precursor structures (Fig. 2) was sufficient reason for the reactivity of the bimetallic species.

In Meyer's laboratory,[61] tris(carbene) ligand systems, of which unstable 1,1,1-tris[(3-methylimidazol-2-ylidene)methyl]-ethane (TIME^{Me}; Scheme 30) is a prime example, have been developed for possible activation of small molecules, and the sequent gold complex **60** is then prepared by the Lin method. The bonding within the complex has been studied by DFT calculations using a 'fragment approach'. Energy decomposition analysis indicates that π-bonding in such gold carbene complexes contributes *ca.* 15% of the total orbital interaction.

Continuing their work on the nature of the gold–carbene bond, Frenking and co-workers[62] investigated mixed carbene–halogen and bis(carbene) complexes at the BP86 level with the simple imidazol-1-ylidene as model carbene ligand. Using EDA, these authors independently also came to the conclusion that, although the metal–ligand π-interaction is certainly not 'negligible' compared to the σ-interaction, it constitutes usually less than 20% of the total orbital interaction energy which in turn, however, accounts for only 22–25% of the total attractive interaction between the metal and this ligand.

Gradient corrected (BP86) density-functional calculations incorporating relativistic effects were used by Jacobsen[63] to study and compare N- and P-heterocyclic carbenes and their gold complexes. In support of Frenking's results, it was found that cationic complexes of gold form stronger bonds than neutral ones. Also, methyl substituents on the nitrogens of NHCs increase the metal–carbene bond strength by 25–35 kJ mol^{-1} and, although PHCs (P-heterocyclic carbenes) form bonds comparable in strength to NHCs, they are better π-acceptors and the π-bonding makes up a larger percentage of the total orbital contribution ('intrinsic bond strength')—up to 45% compared to ≤20% when considering NHCs.

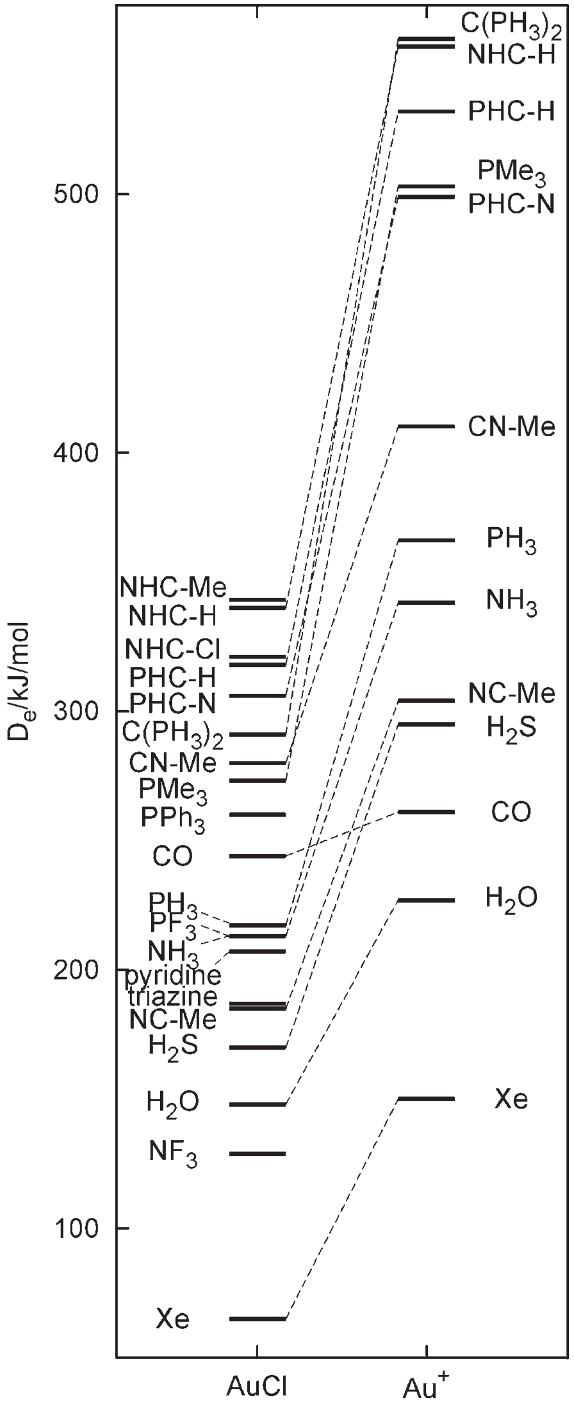


Fig. 3 Calculated dissociation energies of various ligands to AuCl and naked Au^+. (Reproduced with permission of *Chem. Asian J.* 2006, **1**, 623–628).[65]

Dipole and second-order polarizabilities of Au(I*t*-Bu)X (X = halogen) were calculated using time-dependent DFT combined with the sum-over-states method.[64] Remarkably, large static polarizabilities that play a major role in optical response were found to increase from F to I for charge transfer from the halogen to the carbene with the gold acting as a bridge and being simultaneously acceptor and donor. Related compounds hold promise for application as non-linear optical materials.

Pyykkö and Runeberg,[65] working at the BP86 level of theory, have compared the bonding dissociation energy of Au^+–L and ClAu–L for a chosen series of ligands, L (Fig. 3). The two sets of calculations indicate virtually the same trend with the NHC ligands top of the scale and the cyclic diphosphinocarbenes (PHCs) filling the second position.

Conclusions

Gold carbene chemistry is still growing at an ever-increasing pace. The bulk of the work reported over the past 5–7 years has concentrated on the preparation and characterization of new compounds and has mainly been driven by the now ready availability of a variety of N-heterocyclic carbene ligands which have already made a tremendous impact on the chemistries of other transition metals. Exceptional efforts were put into the development of the transmetallation methods for the preparation of complexes, particularly from silver complexes that form readily, have sufficient thermodynamic stability but nevertheless allow the carbene ligand to be transferred on to the chosen gold centre. Deprotonation of the generally preferred imidazolium salt precursors were achieved by a variety of bases, from weak to strong. It is now also clear that NHC ligands are suitable to stabilise gold complexes that contain hard O-donor ligands or fluoride.

Many investigations have been strengthened by theoretical investigations describing the metal–carbene interaction. One could probably conclude that on the basis of the DFT models employed, consensus has been achieved amongst theoreticians that the gold carbene bond should be described as one having a low but significant amount of π-character despite the fact that experimental verification of this result is not necessarily unambiguous. Particularly illuminating are the theoretical results that explain the reactivity of simple gold–platinum carbenes towards NH_3 in the gas phase compared to the inactive gold-only analogues, in terms of the close similarity of closed and open precursor structures in the former situation.

Applications in homogeneous catalysis have also developed in tandem with the isolation of new carbene complexes. For these reviewers, however, one of the most important developments concerns the incorporation of gold carbene complexes as intermediates in catalytic cycles for gold-catalysed intramolecular enyne interactions in solution. Whether these results will stimulate the isolation and/or characterisation of new classes of diorganocarbene complexes of gold, is being awaited with anticipation.

Carbene complexes of gold have now also found meaningful application in the medicinal and biochemical fields and it is probably a question of time before the correct activity-enhancing and bio-acceptable co-ligands are found that would lead to further breakthroughs in this interdisciplinary field. Very obvious gaps in the chemistry of gold carbene complexes are shown by the almost complete absence of any kinetic and thermodynamic investigations. Furthermore, only a very limited number of gold(III) carbene complexes have been made and their properties researched and chronicled.

Acknowledgements

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