

Relativistic effects in homogeneous gold catalysis

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Transition-metal catalysts containing gold present new opportunities for chemical synthesis, and it is therefore not surprising that these complexes are beginning to capture the attention of the chemical community. Cationic phosphine–gold(I) complexes are especially versatile and selective catalysts for a growing number of synthetic transformations. The reactivity of these species can be understood in the context of theoretical studies on gold; relativistic effects are especially helpful in rationalizing the reaction manifolds available to gold catalysts. This Review draws on experimental and computational data to present our current understanding of homogeneous gold catalysis, focusing on previously unexplored reactivity and its application to the development of new methodology.

Interest in the catalytic chemistry of Au(I) complexes has undergone a marked increase. Although traditionally undeveloped as homogeneous catalysts, such species have recently been employed in a plethora of organic transformations. The strong Lewis acidity of cationic Au(I), coupled with its potential to stabilize cationic reaction intermediates, imparts unique reactivity to such catalysts, which has been exploited in the development of new synthetic methods. As the reactivity of Au(I) complexes continues to be uncovered experimentally, the theoretical underpinnings of these new observations warrant consideration. Relativistic effects provide a theoretical framework for rationalizing the observed reactivity—the contracted 6s orbital and expanded 5d orbitals account for the attributes of Au(I) catalysts. Thus, integrating theoretical and synthetic studies of Au(I) provides a deeper understanding of the fundamental properties of Au and illuminates further avenues for study.

Theoretical chemistry of gold: practical considerations

The relation between structure and function has become a model for chemistry and biochemistry, and thus theoretical studies of the electronic structure of Au provide insight a priori into how it might function as a catalyst and what reactive pathways might be accessible. The theoretical chemistry of Au has recently been well reviewed, and only a few salient points are highlighted here^{1,2}. The most prominent characteristics of the electronic structure of Au are the consequence of strong relativistic effects (see Box 1)^{3,4}. In Au, the relativistic contraction of the 6s orbital results in greatly strengthened Au–L bonds, where L is the ligand (Fig. 1)⁵. Beyond the observed large Au–L bond strengths, further experimental corroboration of this distortion from the otherwise expected electronic structure lies in the phenomenon of ‘aurophilicity’⁶, the tendency for Au–Au interactions to be stabilizing on the order of hydrogen bonds, and also in the large first ionization potential observed for Au (9.22 eV versus 7.57 eV for Ag).

In contrast with the prevalence of tricoordinate and tetracoordinate Cu(I) and Ag(I) complexes, Au(I) predominantly adopts a linear, bicoordinate geometry^{7,8}. The practical consequence of the limited coordination motifs typically observed in Au(I) chemistry is the general need to abstract a ligand from neutral bicoordinate Au(I) species so as to induce catalytic reactivity. Additionally, organoaurate(I) species are not particularly nucleophilic relative to the corresponding copper complexes. Theoretical studies indicate

that the Au 5d electrons are held with greater energy than the Cu 3d electrons due to decreased electron/electron repulsion in the diffuse 5d orbitals, resulting in less nucleophilic metal species that do not tend to undergo oxidative addition⁹. Computational and experimental studies on reductive elimination from LR₃Au(III) complexes show such a process to be relatively disfavoured as well^{10,11}. These observations are consistent with the broadly observed reactivity of Au(I) and Au(III) complexes, which do not readily cycle between oxidation states, although such reactivity is accessible¹². Au(I) species are therefore generally tolerant of oxygen, indicating that reactions catalysed by Au might be run without precautions to exclude air. Beyond this practical benefit, the apparent redox stability of Au(I) complexes under ambient conditions allows the development of new modes of reactivity by precluding the traditional oxidative addition/reductive elimination cycles so prevalent in late transition-metal catalysis.

An alkynophilic Lewis acid?

Many of the investigations into the catalytic reactivity of Au exploit the propensity of both Au(III) and cationic Au(I) complexes to activate alkynes towards nucleophilic addition. Research in this area has been extensively reviewed^{13,14}, and only selected highlights will be presented here. Early investigations into the potential of Au to catalyse synthetic transformations used primarily Au(III) halides and it was found that a wide array of nucleophiles could be added to alkynes in an intramolecular^{15–18} or intermolecular¹⁹ fashion. These initial studies aroused the interest of researchers pursuing green chemistry, who have since exploited the apparent insensitivity of Au to aqueous conditions to develop a series of reactions using water or alcohols as solvent^{20,21}.

In 1998, a seminal contribution by Teles *et al.* demonstrated the utility of cationic phosphineAu(I) species in catalysing the hydration of alkynes²². Subsequently, and especially since 2003, Au(I) species have featured more prominently in Au catalysis. R₃PAuX (X = trifluoromethanesulphonate (OTf) or other weakly coordinating counterions), formed *in situ* by the abstraction of Cl[−] from R₃PAuCl by AgX or by the protonolysis of R₃PAuCH₃ with acid, were shown to be superb catalysts for a series of C–C bond-forming reactions, including Conia-ene^{23,24} and hydroarylation^{25–27} reactions, as well as several carbon–heteroatom bond-forming reactions^{28–30}

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Box 1 | Relativistic effects

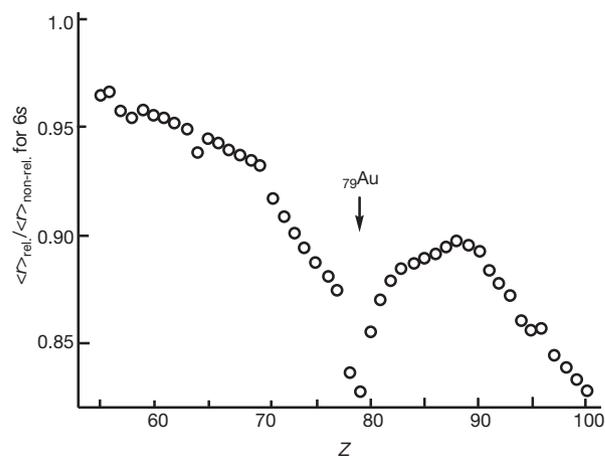
The theoretical underpinning for relativistic effects arises from the confluence of quantum mechanics and special relativity^{3,96}. Schrödinger's equation, unveiled in 1926, correctly predicts the atomic orbital energy levels for hydrogen but is unable to account for the fine structure of the hydrogen atomic spectrum, in which the bands are split. Although accounting for spin as a perturbation of the Schrödinger equation corrects for this, in systems in which electrons move at speeds approaching the speed of light (c) a more general relativistic consideration is required. In 1928 Dirac developed a new equation taking special relativity into account, thereby permitting solutions to systems in which electrons move at significant velocities. The term 'relativistic effects' therefore refers to any phenomenon resulting from the need to consider velocity as significant relative to the speed of light.

One basic consequence of the special theory of relativity is that mass increases towards infinity as a body's velocity approaches c , which can be expressed mathematically as $m = m_0/\sqrt{1 - (v/c)^2}$, where m is the corrected mass, m_0 is non-relativistic (rest) mass, and v is velocity. For a given atom, the average radial velocity of the $1s$ electrons is $V_r = Z$, where Z is the atomic number. The expression v/c can therefore be calculated as $Z/137$ (137 atomic units (a.u.) = c). For example, in Hg, $Z = 80$ and v/c for the $1s$ electrons is $80/137 = 0.58$; that is, the $1s$ electrons have a radial velocity that is 58% of c .

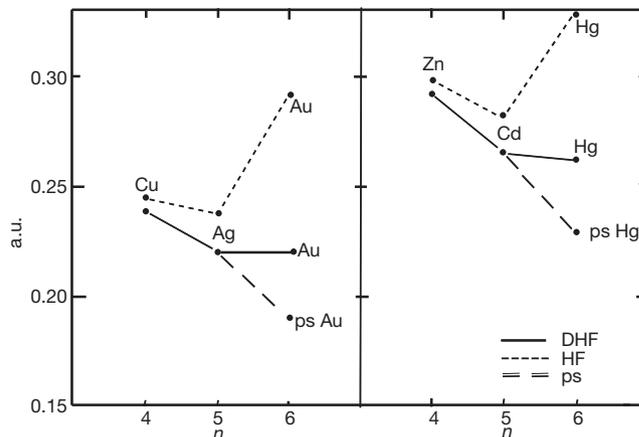
There are three major phenomena that result from relativistic effects^{4,97}: the first can easily be rationalized by considering the equations above. In non-relativistic calculations, $c = \infty$ and v/c therefore approaches 0, so no mass correction need be applied to the particles under consideration. In situations in which c is considered to be 137 a.u., the mass of an electron will increase considerably. Because the Bohr radius of an electron orbiting a nucleus is inversely proportional to the mass of the electron, this increase in mass corresponds to a decrease in radius. This relativistic contraction of the $1s$ orbital also applies to all other s and p orbitals. Thus, the electrons are closer to the nucleus and have greater ionization energies. Practically, this contraction is only significant for elements in which the $4f$ and $5d$ orbitals are filled (Box 1 Figure 1).

The second manifestation of relativistic effects is indirect; electrons occupying the d and f orbitals are better shielded by the electrons in the contracted s and p orbitals and therefore see a weaker nuclear attraction. The third effect of a relativistic treatment is spin-orbit coupling, which accounts for the fine splitting in the hydrogen atomic spectrum noted above.

Relativistic effects are crucial to understanding the electronic structure of heavy elements; consideration of other phenomena, such as the lanthanide contraction, are insufficient (Box 1 Figure 2)^{98,99}. Among the experimental observations conventionally explained by relativistic effects is the colour of Au. The golden colour is due to excitation of the $5d$ electrons to the Fermi level, which occurs with a bandgap of 2.38 eV; blue visible light is therefore absorbed. In silver, by contrast, the bandgap is much larger and no visible light is absorbed. The smaller bandgap in Au is due to the relativistic contraction of the $6s$ and $6p$ orbitals and the expansion of the $5d$ orbitals.



Box 1 Figure 1 | Calculated relativistic contraction of the $6s$ orbital. The relativistic and non-relativistic $6s$ orbital radii were determined computationally¹⁰⁰. Notably, Pt, Au and Hg are markedly influenced. (Reprinted from ref. 4, with permission from the American Chemical Society.)



Box 1 Figure 2 | Calculated ionization potentials for the Group 11 and Group 12 transition metals. Three different methods are compared: Dirac–Hartree–Fock (DHF) (relativistic), Hartree–Fock (HF) (non-relativistic), and pseudopotential (ps) (without regard for f electrons). The difference between the HF and ps calculations results from accounting for the lanthanide contraction; the difference between DHF and HF results from accounting for relativistic effects. The experimental ionization potentials closely match those given by DHF. (Reprinted from ref. 99, with permission from Elsevier.)

(Fig. 2). Gold has also been used with some success in additions of nucleophiles to allenes^{31–33}, alkenes^{34,35} and dienes^{36,37}, although whether these reactions proceed by means of activation of the π -system by Au remains an area of active investigation, especially for additions to unactivated alkenes^{38,39}.

Cationic Au(I) species are superior Lewis acids compared with other Group 11 metals for many transformations, and intuitively it seems that relativistic contraction of the valence s or p orbitals of Au should be responsible, because they should correspond to a relatively low-lying lowest unoccupied molecular orbital (LUMO) and therefore strong Lewis acidity. This conclusion can also be derived from considering the high electronegativity of Au (2.4, compared with 1.9 for Ag): strong Lewis acidity generally correlates with electronegativity (provided that a coordination site is available for accepting an electron pair). It is crucial to realize that the electronegativity of Au is a result of the relativistic contraction of the valence $6s$ and $6p$ orbitals;

thus, consideration of relativistic effects does not merely corroborate an analysis based on electronegativity but actually provides a theoretical underpinning to understand it.

From a computational standpoint, natural bond orbital (NBO) population analyses of the Au atomic orbital occupancies for cationic Au(I)–phosphine complexes indicated that for AuPH_3^+ the $6s$ occupancy was 0.438 electrons, whereas for the corresponding complex AgPH_3^+ the $5s$ occupancy was only 0.156 (refs 8, 40). This suggested that the Au–phosphine bond was far more covalent than the Ag–phosphine bond, an unsurprising notion considering the comparison of AuH and AgH presented in Fig. 1, and complemented by the decreased charge density calculated on Au in comparison with that on Ag (0.66 versus 0.86).

As models for complexation of a second Lewis basic ligand, $\text{Au}(\text{PH}_3)_2^+$ and $\text{Ag}(\text{PH}_3)_2^+$ were considered. The Au $6s$ occupancy increased twofold, to 0.796, whereas the Ag $5s$ occupancy was 0.449

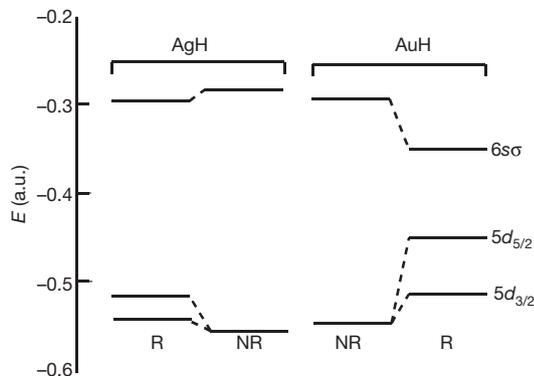


Figure 1 | Comparison of AuH and AgH bond energies. Calculated (Hartree-Fock) molecular orbital energies for AgH and AuH are shown with (R) and without (NR) consideration of relativistic effects⁵. In the non-relativistic calculation, the two molecules had similar bond energies. In the relativistic calculation, the $6s$ contraction resulted in a far stronger AuH σ -bond. (Reprinted from ref. 4, with permission from the American Chemical Society.)

(refs 8, 40). This suggests rehybridization of the phosphineAu(I) molecular orbitals to resemble a three-centre four-electron bond that greatly increases the occupancy of the s orbital. The other orbitals that might accept electrons, the $6p$, remained largely unoccupied (0.011 electrons). Although simplistic, this consideration, if generalized, can rationalize the superior Lewis acidity of Au, because the low-lying s orbital should be responsible for binding in phosphineAuL⁺. Additionally, because Au(I)⁺ is a large, diffuse cation that shares positive charge with the phosphine ligand, one might expect orbital rather than charge interactions to dominate in binding a second ligand. Thus, phosphineAu(I)⁺ may be considered a 'soft' Lewis acid, preferentially activating 'soft' electrophiles, such as π -systems.

Although the 'soft' Lewis acidity of Au(I) can be rationalized, further consideration is needed to understand the superior reactivity of Au-alkyne complexes towards nucleophilic addition. Studies on Au⁺-ethylene and Au⁺-ethyne bonding indicate ~ 10 kcal mol⁻¹ greater stabilization for the ethylene complex over the ethyne complex^{41,42}. Because Au(I) apparently does not selectively complex alkynes over other π -systems, the observed reactivity may be due to

discrimination by the nucleophile in selecting between Au(I)-activated electrophiles. Such selectivity can be understood by considering the relative energy levels of ethyne and ethylene LUMOs: alkynes have intrinsically lower highest occupied molecular orbitals and LUMOs than the corresponding alkenes (by ~ 0.5 eV), and are therefore less nucleophilic and more electrophilic⁴³. It can therefore be expected that an Au-alkyne complex should have a lower LUMO for the addition of a nucleophile than an analogous Au-alkene complex; this is potentially the source of the 'alkynophilicity' observed in Au(I)⁺-catalysed reactions.

The mechanism of Au(I)-mediated activation of an alkyne towards addition by methanol was originally investigated by the Teles group in calculations that predicted a *cis*-oxyauration of the alkyne^{22,44}. In contrast, labelling experiments by the Toste group in the Conia-ene carbocyclization²³ and Hashmi *et al.* in the cycloisomerization of propargyl amides⁴⁵ are consistent with *anti*-addition of Au and a nucleophile across an alkyne.

Initial explorations demonstrated some effect of oxidation state on Au catalysis: the regioselectivity was reversed for the intermolecular hydroarylation of alkynes with arenes in the presence of Au(I) as opposed to Au(III)⁴⁶. More telling work by Gevorgyan on the Au(I)- and Au(III)-catalysed cyclization of halogenated allenones to form halofurans offers insight into the mechanistic pathways available in reactions catalysed by Au (Fig. 3)⁴⁷. In this case, catalysts in each oxidation state led to divergent products. With Au(I) a product consistent with activation of the allene was observed, whereas with Au(III) the product formed was consistent with activation of the ketone moiety. Unrelated calculations by Straub support this notion of functional group discrimination, indicating that AuCl₃ exhibits a thermodynamic preference for aldehyde coordination over alkyne coordination by 21.3 kJ mol⁻¹, while also being capable of catalysing reactions through alkyne-activation pathways⁴⁸.

Especially for Au(I), ligand effects can influence reaction outcome; Au(I)-phosphine species are well studied^{18,40}, offering a tunable ligand set for optimizing catalyst reactivity. In the Au(I)-catalysed ring expansion of propargylcyclopropanols, [(4-CF₃-C₆H₄)₃P]AuCl was shown to be superior to other Au-phosphines⁴⁹. Buchwald-type ligands were most effective in the intramolecular hydroamination of allenenes⁵⁰, whereas N-heterocyclic carbene (NHC) ligands were optimal for an indene synthesis⁵¹. Additionally, the trimeric Au

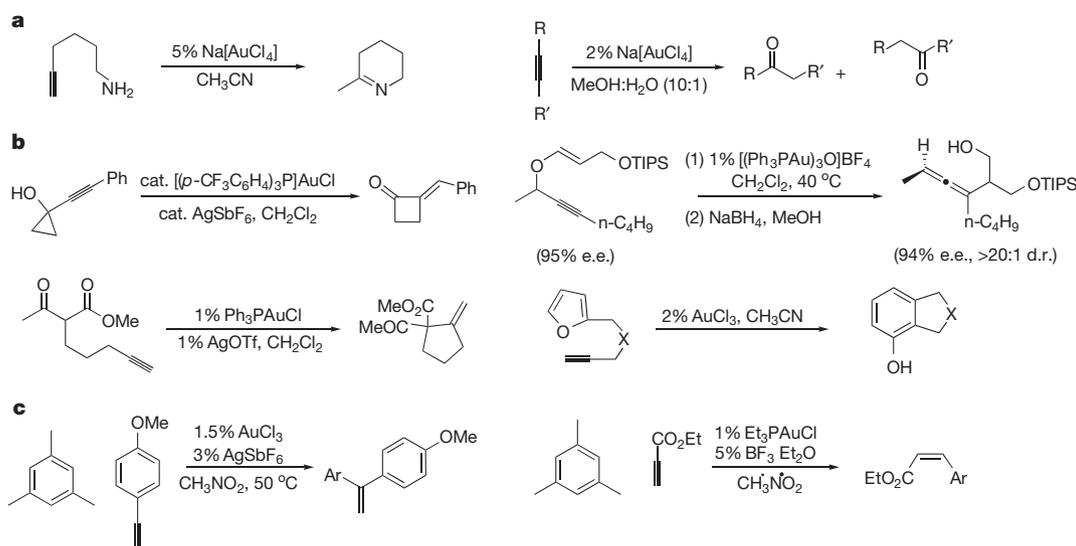
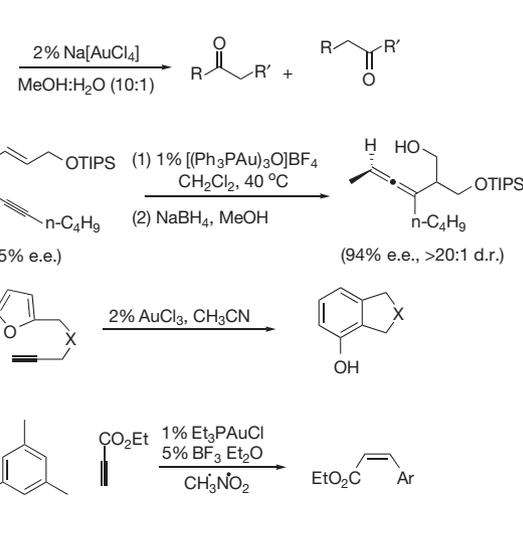


Figure 2 | Catalytic activation of alkynes. Au(III) and Au(I)⁺ are excellent Lewis acids capable of catalysing the addition of a wide variety of nucleophiles to alkynes. **a**, Representative examples featuring heteroatom-carbon bond formation include hydroamination¹⁵ and hydration¹⁹ reactions. **b**, Activated carbon nucleophiles have been extensively investigated: the illustrated ring expansion⁴⁹, Conia-ene²³,



propargyl Claisen⁵² and cycloaddition/fragmentation¹⁷ carbon-carbon bond-forming reactions are among those reported. d.r., diastereomeric ratio; e.e., enantiomeric excess; TIPS, tri-(isopropyl)silyl). **c**, Hydroarylation has been studied with Au(I) and Au(III): different reactivity is observed depending on the oxidation state of Au (ref. 25).

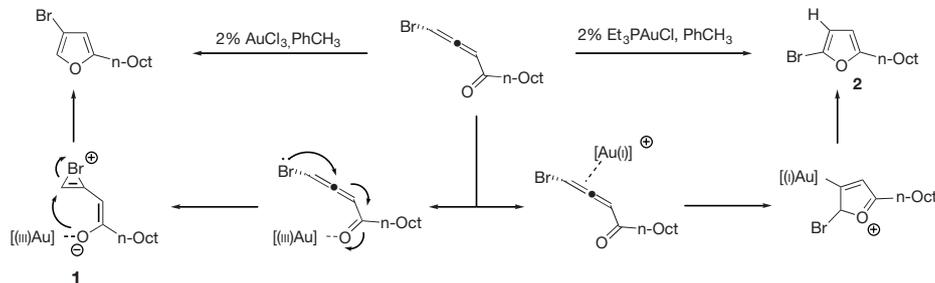


Figure 3 | Oxidation state determines product. Choice of Au source dictated the product distribution obtained from the cyclization of halogenated allenones⁴⁷. The observed results are consistent with mechanisms in which Au(III) activated the ketone, leading to isomerization

through the bromonium intermediate **1**, whereas Au(I) coordinated the allenone, leading to product **2** in which no halogen migration occurred. Oct, (CH₂)₇CH₃.

complex (PPh₃Au)₃OBF₄ was superior to monomeric Au phosphines as a catalyst for the propargyl Claisen rearrangement⁵². Although some initial studies to improve the stability of Au(III) catalysts through the use of ligands have been reported^{53,54}, most efforts have focused on Au(I).

Relativistic effects and backbonding

Although Au(I) is a versatile catalyst for activating alkynes towards nucleophilic addition, a question arose: are Au complexes only capable of mediating reactions by functioning as Lewis acids? After all, innumerable possible Lewis and Brønsted acids might similarly activate alkynes. One particularly intriguing calculation suggesting a coordination mode other than simple Lewis acid–base interaction was performed by Irikura & Goddard, who determined that the AuCH₂⁺ fragment **3** should feature multiple bond character, through σ -complexation of singlet CH₂ and backbonding from Au to methylene (Fig. 4)⁵⁵. Schwarz undertook similar calculations in evaluating the extent of relativistic effects on cationic late-metal carbene complexes; it was found that although AuCH₂⁺ possessed the lowest bond-dissociation energy among the metal carbenes examined, more than 70% of the total bond energy for Au was a contribution from relativistic effects⁵⁶. More recently, Barysz & Pyykkö proposed that AuC⁺ **4** should have some triple-bond character⁵⁷, and mass spectroscopic evidence for such a species has been accumulated⁵⁸.

These calculations indicating significant backbonding from Au(I) into vacant *p* orbitals contrast the absence of backbonding observed in Au–carbonyl and Au–alkyne complexes. Both [Au(CO)]⁺ and

[Au(CO)₂]⁺ have been characterized spectroscopically⁵⁹. The ν_{CO} (2,194 and 2,208 cm⁻¹) are actually greater than that of free CO, suggesting σ -only complexation of CO to Au⁺ without backbonding from Au into the ligand π^* orbital. Calculations on Au(I)–ethylene and Au(I)–ethyne complexes indicate that backbonding accounts for a far smaller fraction of the bonding energy than in the analogous Cu complexes^{41,42}. Thus, Au(I)⁺ cannot be considered to participate significantly in Chatt–Dewar–Duncanson-type bonding^{60,61} because antibonding orbitals are apparently too high in energy for meaningful backbonding to occur, whereas lower-energy non-bonding *p* orbitals may be more suitable for overlap with the filled Au *5d* orbitals. This may be relevant to the Lewis acidity of Au(I); the lack of backbonding from Au(I) into π -ligands could render the ligands more electron deficient, contributing to the ease of nucleophilic addition.

Synthetically, limited progress has been made in isolating Au complexes with carbenoid character. Gold–NHC complexes are known, although there is no structural evidence for multiple-bond character in the metal–ligand bond⁶². Transmetalation of Fischer carbenes from Group VI metals to Au has been accomplished, and the resulting metal-complexed vinyl Au species **5** was proposed to have significant Au carbene character on the basis of nuclear magnetic resonance spectroscopy, X-ray crystallography, and calculations⁶³. This experiment corroborates the theoretical studies of Au(I)-carbenoid species mentioned earlier and suggests the potential of Au to engage in backbonding into the LUMO of σ -bonded organic cations.

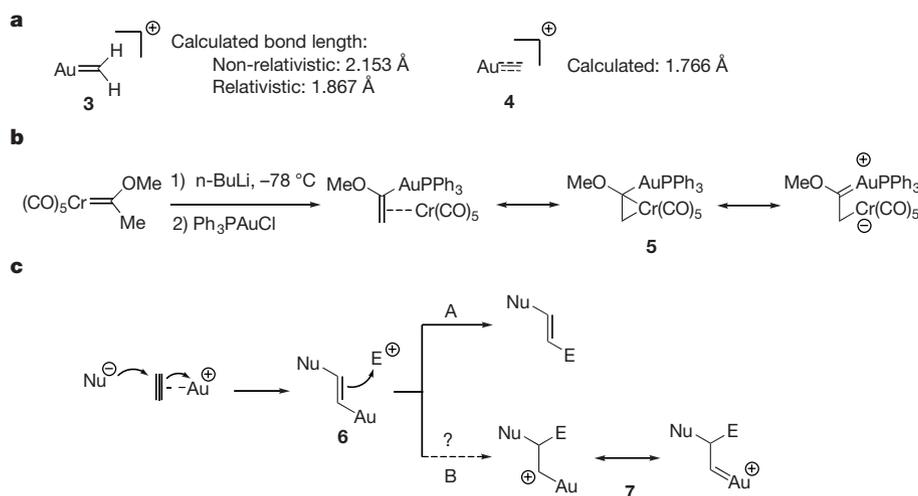


Figure 4 | Proposed multiply-bonded Au–C structures. **a**, Au-alkylidene (**3**) and Au-alkylidyne (**4**) structures have been calculated^{56,57}, and relativistic effects are posited to be largely responsible for the predicted multiple-bond character. **b**, Experimental data consistent with carbene character in Au species **5** was accumulated in the transmetalation of a

chromium Fischer carbene to Au(I)⁶³. **c**, Practically, these studies imply that the Au *5d* electrons backbond into conjugated empty carbon *p* orbitals, and thus Au complexes may be viable for stabilizing cationic intermediates, such as **7**, in catalytic reactions. Nu, nucleophile.

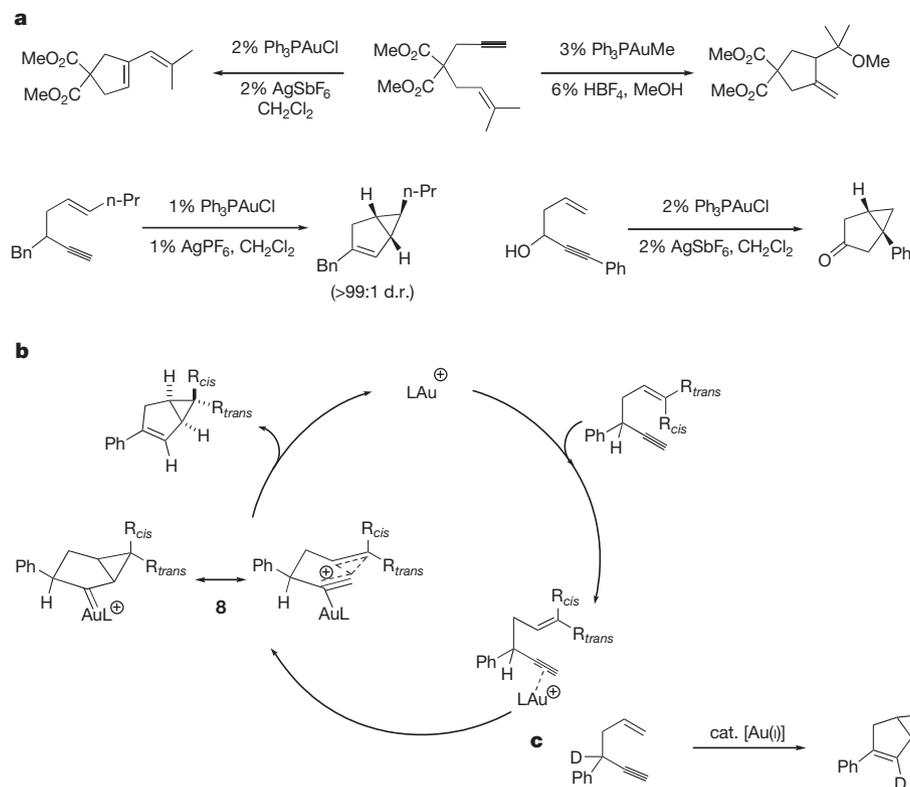


Figure 5 | Enyne cycloisomerization. **a**, Au(I)-catalysed cycloisomerizations of 1,5- and 1,6-enynes are proposed to proceed through carbocationic intermediates stabilized by Au^{66–69}. **b**, The proposed catalytic cycle for the cycloisomerization of 1,5-enynes posits resonance-stabilized intermediate

8. **c**, Although deuterium labelling provides evidence for the presence of intermediate **8**, the extent of carbene as opposed to carbocationic character is difficult to judge.

In all of the synthetic applications of Au(I) catalysts discussed so far, the proposed vinyl–Au intermediate **6** formed from the initial addition of a nucleophile to an alkyne breaks down by means of protodemetalation (Fig. 4, path A); recently, such intermediates have also been trapped by other electrophiles in an intramolecular fashion^{31,64,65}. On the basis of the theoretical data presented above, an alternative manifold may be envisaged (Fig. 4, path B): Au(I)⁺ would first activate an alkyne towards nucleophilic addition as before; Au could then facilitate trapping of an electrophile by backbonding from the relativistically expanded 5*d* orbitals into the developing conjugated cation **7**.

The first experimental evidence that such a hypothesis might accurately reflect the reactivity of Au came nearly simultaneously in reports by the Echavarren group^{66,67}, the Fürstner group⁶⁸ and the Toste group⁶⁹, all dealing with the Au(I)-catalysed cycloisomerization of enynes (Fig. 5). These cycloisomerizations proceed through cationic intermediates, and it was proposed that Au might lower the barrier to accessing these by backbonding to delocalize the positive charge by the formation of carbenoid species. Enynol cyclisomerizations were subsequently performed with Au(III) sources, and analogous intermediates were proposed⁷⁰.

The mechanistic hypotheses put forth for the Au-catalysed cycloisomerization reactions are preceded by those posited for similar enyne isomerizations with Pt(II) salts: Fürstner *et al.* have previously

discussed a carbene–cation continuum in describing reaction intermediates⁷¹. The extent of carbenoid as opposed to simple cationic character at the carbon adjacent to the metal is unclear and depends on the catalyst⁷². Divergent product formation in the InCl₃- and AuCl-catalysed syntheses of halophenanthrenes suggests that Au(I) species may have significant carbene character whereas other catalysts for alkyne activation, such as In(III)⁷³ and Ga(III)⁷⁴, show more traditional Lewis acidic reactivity (Fig. 6)⁷⁵.

Pt(II) shows similar reactivity to Au(I) in many cases^{72,76,77}, an unsurprising observation given that relativistic effects also heavily influence Pt, and so similarly stabilized cationic intermediates may be accessed. The crucial advantage of Au(I) catalysis is that electrophilic activation of alkynes with cationic Au(I) proceeds even in the presence of strongly donating ligands, such as phosphines, whereas the activation of alkynes by Pt(II) generally proceeds with simple salts or in the presence of CO (ref. 78). Although phosphinePt(II) pre-catalysts have recently been reported to activate alkynes, the role of the ligand remains unclarified^{79,80}. The use of phosphineAu(I) complexes, in contrast, demonstrably permits the tuning of reactivity and, as initially demonstrated in a pioneering study by Hayashi and Ito, stereoselectivity⁸¹.

Although the report by Hayashi and Ito on isocyanate aldol chemistry provided a proof of principle for enantioselective Au

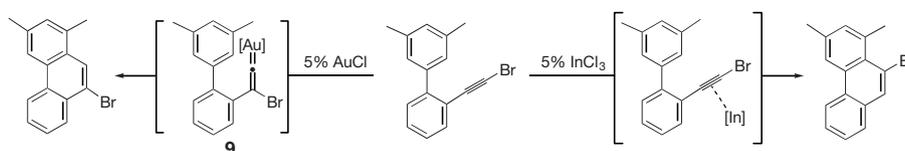


Figure 6 | Comparison of reactivities of Au(I) and In(III). Evidence for Au-carbene character was accumulated in the metal-catalysed synthesis of halophenanthrenes: halogen migration in the reaction with AuCl is

consistent with the formation of alkyldiene intermediate **9**, whereas catalysis with InCl₃ resulted in the product arising from Lewis acidic activation of the alkyne by π-complexation⁷⁵.

catalysis, only recently has this been extended to reactions proceeding by means of Au-catalysed activation of alkynes. A recent report from the Echavarren group achieved this, as the isomerization–alkoxylation of 1,6-enynes was investigated in the presence of Au(I)-complexes featuring chiral phosphine ligands⁸². Although only moderate enantiomeric excess (e.e.) could be obtained (most examples had less than 50% e.e., but one had 94% e.e.), these results were crucial in demonstrating that the ligand on Au could create a chiral environment, which was perhaps surprising in view of the preferred linear coordination geometry of Au(I), which necessitates that the source of chirality be far from the centre of induced stereochemistry.

Further illumination in discriminating between carbenoid and cationic intermediates came in the course of studies on the Au(I)-catalysed Rautenstrauch rearrangement of 3-acetoxy-1,4-enynes (Fig. 7)⁸³. A carbenoid intermediate in the reaction mechanism seemed reasonable, analogous both to the posited mechanism for the Au-catalysed cycloisomerization of enynes and that proposed for the Pd-catalysed version of the Rautenstrauch⁸⁴. Surprisingly, chirality transfer in the course of the cycloisomerization indicated that formation of a Au carbene did not precede the cyclization, because that would presumably necessitate C–O bond cleavage and concurrent loss of stereochemical information. Therefore, a Nazarov cyclization-like transition state **10** was proposed, in which C–C bond formation occurs in concert with C–O bond cleavage. Subsequent calculations predicted an asynchronous mechanism, in which the C–O bond breaks immediately before bond formation, albeit on a timescale on which stereochemical information is retained in the helical intermediate **11** (ref. 85). Similar reactivity has been

observed in the Au(III)-catalysed intramolecular cyclopropanation of 5-acetoxy-1,6-enynes: chirality transfer is again inconsistent with carbene formation^{86–88}.

Carbenoid reactivity

In light of the chirality transfer observed in the Rautenstrauch reaction, it may be suggested that slowing the rate of trapping of the intermediate generated from propargyl esters in the presence of cationic Au(I) might allow access to intermediates of highly carbenoid character (Fig. 8). One simple way to accomplish this is to render the reaction intermolecular; presumably intramolecular C–O bond cleavage is rapid relative to intermolecular trapping. An Au(I)-catalysed intermolecular cyclopropanation reaction⁸⁹, by analogy with the Ru chemistry reported by Ohe and Uemura⁹⁰, was therefore developed. In contrast with the Au(I)-catalysed Rautenstrauch rearrangement, stereochemical information from enantioenriched propargyl esters was not conserved. Notably, the cyclopropanation reaction occurred stereospecifically with *cis* and *trans* β -methyl styrene, widely regarded as a benchmark test for a concerted cyclopropanation mechanism and consistent with formation of the carbene intermediate **12**. The intermolecular cyclopropanation is also catalysed by AuCl₃, albeit with lower selectivity⁹⁰. Crucially, the use of (AuCl)₂(R-DTBM-Segphos) (where DTBM-Segphos is (4,4'-bi-1,3-benzodioxole)-5,5'-diylbis(di(4-*tert*-butyl-3,5-dimethoxyphenyl)phosphine)) **13** resulted in an enantiomeric excess of up to 94% for the cyclopropanation of a variety of styrene derivatives.

Further methods of probing the backbonding potential of Au are of interest; an intramolecular alternative to the electrophilic trapping

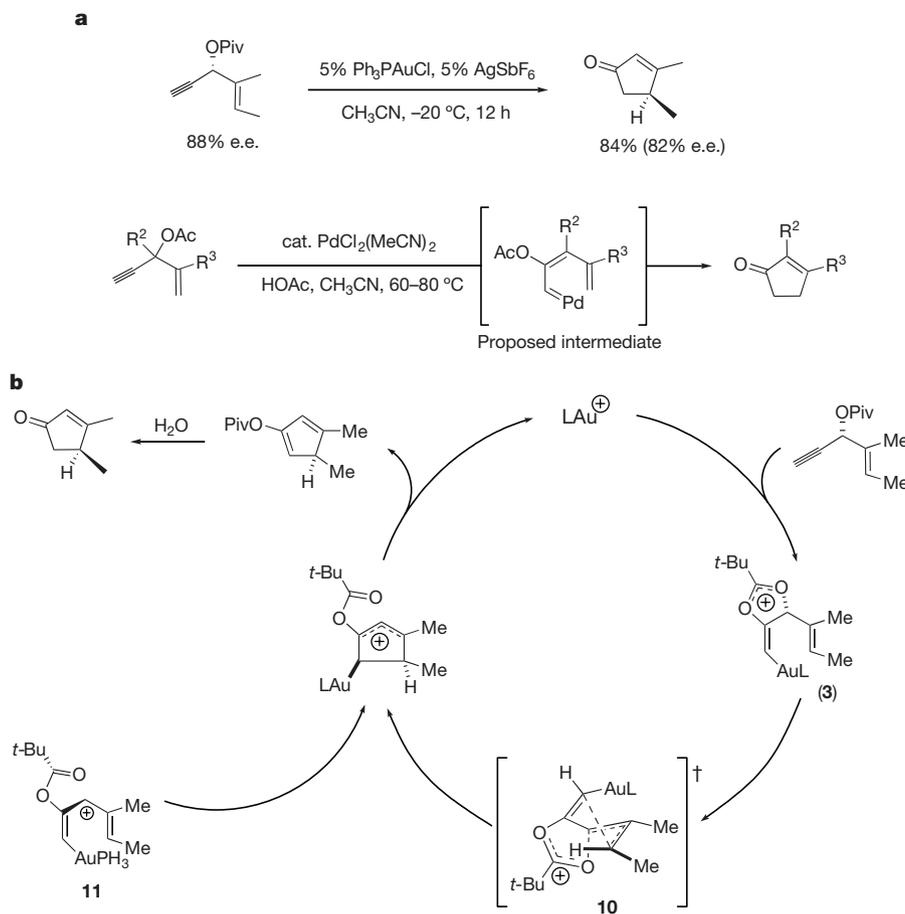


Figure 7 | Mechanism of the Rautenstrauch reaction. **a**, The Au(I)-catalysed Rautenstrauch rearrangement proceeded with chirality transfer from enantioenriched propargyl vinyl esters⁸³, suggesting a mechanism different from that posited in the Pd-catalysed case because the formation of a carbenoid intermediate should result in racemization⁸⁴. **b**, Two possible

mechanisms leading to the conservation of stereochemical information have been proposed: both transition state **10**, indicating a concerted cyclization mechanism, and helically chiral intermediate **11** could account for the observed stereochemistry⁸⁵. Piv, pivalate.

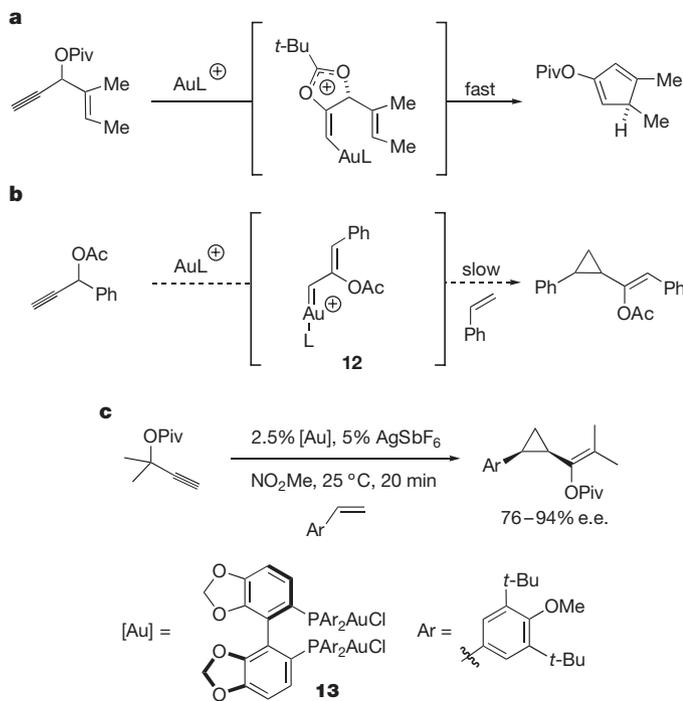


Figure 8 | A proposed carbenoid intermediate. **a**, The rate of intramolecular trapping of the intermediate generated from propargyl esters and Au(I)^+ was fast in the Rautenstrauch rearrangement⁸³. **b**, It was proposed that intermolecular trapping would be sufficiently slow to permit the formation of carbenoid intermediate **12**. **c**, Thus, an intermolecular cyclopropanation of alkenes with propargyl esters was developed⁸⁹. The result of a chirality transfer experiment contrasted with observations made in the Rautenstrauch cyclization: stereochemical information was not conserved, which is consistent with the proposed intermediacy of **12**. The asymmetric cyclopropanation of styrenes was accomplished with $(\text{AuCl})_2(\text{R-DTBM-Segphos})$ **13**. Piv, pivaloate; DTBM, 4-tert-butyl-3,5-dimethoxyphenyl.

presented in Fig. 4 was envisioned. Hypothetically, Au(I) could activate an alkyne towards nucleophilic addition, and then assist in displacing a pendant leaving group (Fig. 9). From this proposal an Au(I) -catalysed intramolecular acetylenic Schmidt reaction was developed⁹¹. The proposed intermediate **14** in the acetylenic Schmidt reaction could be trapped through ring expansion of carbocycles and intramolecular migration of a siloxy substituent. Judicious choice of ligand was necessary in developing optimal reaction conditions, and $(\text{AuCl})_2(\text{Ph}_2\text{PCH}_2\text{PPh}_2)$ treated with AgSbF_6 proved ideal. It is possible that auriphilic interactions between the two Au atoms ligated to the phosphine have a function in stabilizing the catalyst, although the precise benefit derived from the bis-phosphine ligand remains unknown⁹².

The reactivity of cationic Au(I) species observed so far is strongly consistent with the stabilization of conjugated cationic intermediates by means of backbonding from Au. Au(III) and Pt(II) catalysts show similar reactivity in many circumstances, although so far phosphine Au(I) complexes are the catalysts of choice for controlling stereo-selectivity. The quest for isolated Au complexes with unambiguous carbenoid character continues. Isolation and characterization of catalytic reaction intermediates may be helpful in this regard, alongside efforts to effect carbene transfer to $\text{Au}^{63,93}$. More rigorous studies to determine precisely the active catalysts and operative mechanisms in reactions catalysed by Au are clearly needed. In addition, theoretical work directly addressing the superior π -acidity of Au in the presence of alkynes and explaining the electronic structure of proposed intermediates in catalytic cycles will be invaluable in designing new generations of catalysts and reactions.

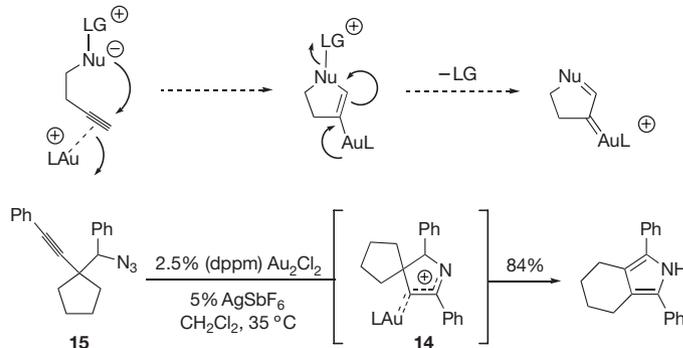


Figure 9 | Intramolecular acetylenic Schmidt reaction. An intramolecular variant on the hypothesis depicted in Fig. 4 was examined by means of the development of a pyrrole synthesis from homopropargyl azides⁹¹. The cyclization reaction was proposed to proceed through delocalized cation **14**, in which the positive charge is partly delocalized onto Au. Evidence for this organogold intermediate was provided by intramolecular trapping experiments, including ring expansion of carbocycle **15**. dppm, $\text{Ph}_2\text{PCH}_2\text{PPh}_2$; LG, leaving group.

As the upsurge in reviews and reports on the subject testifies, homogeneous Au catalysis invites increasing attention and excitement^{94,95}. Gold complexes are superb Lewis acids for the activation of alkynes, a phenomenon best understood in the light of the relativistically contracted 6s orbital of Au. Gold carbenoid species are proposed to exist transiently in the course of several catalytic cycles, and this reactivity may be attributed to the relativistically expanded 5d orbitals of Au; the 5d electrons remain too low in energy to engage in meaningful backbonding to anti-bonding orbitals but are able to delocalize into lower-energy, empty, non-bonding orbitals. The exploitation of Au catalysts in developing new reactivity benefits greatly from a fundamental understanding of the electronic structure of the metal and serves as a model for integrating theoretical and synthetic chemistry in the development of new methodology.

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