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Synthetic Methods

Catalytic Carbophilic Activation: Catalysis by Platinum and Gold π Acids

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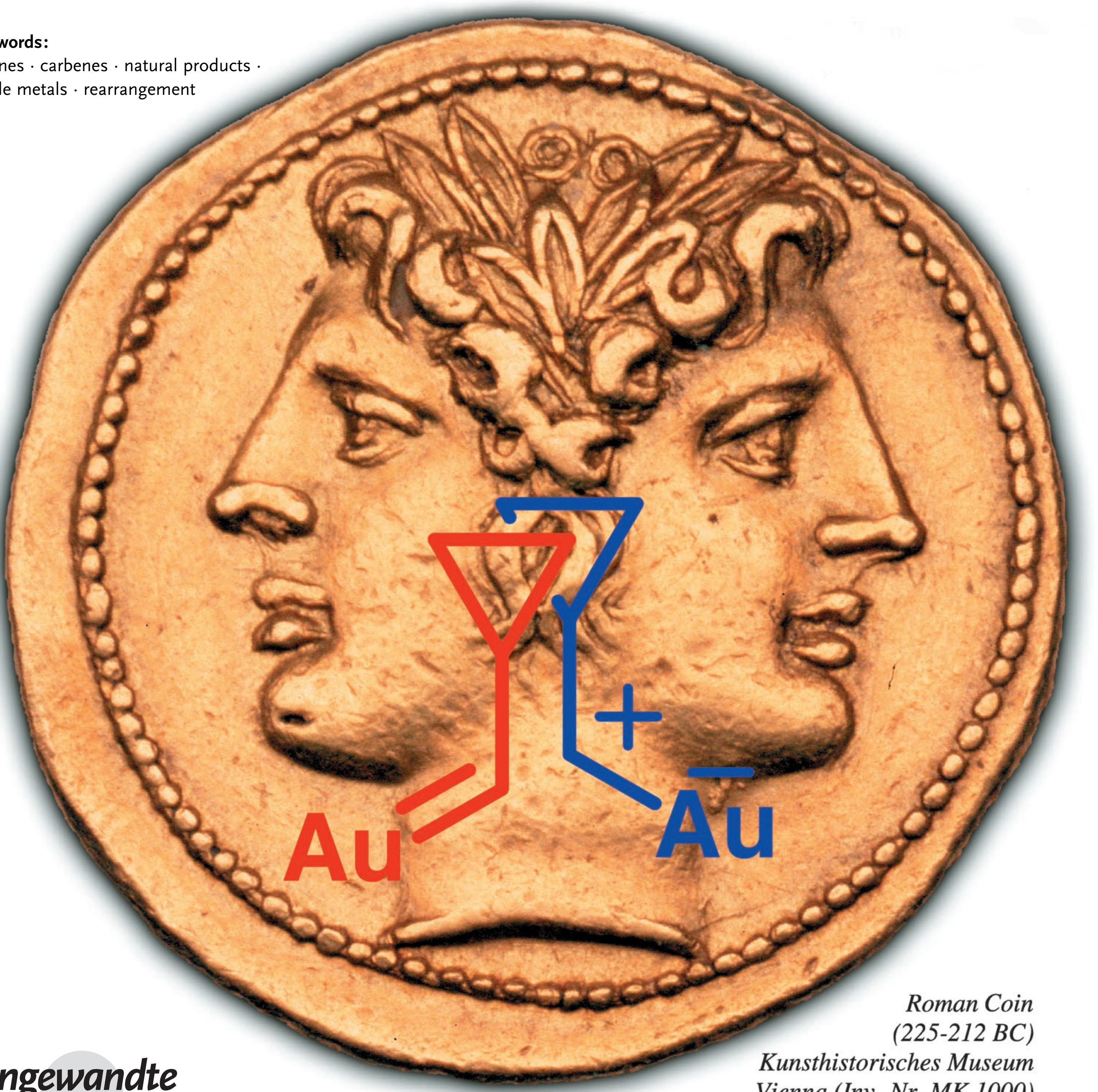

*Roman Coin
(225-212 BC)
Kunsthistorisches Museum
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The ability of platinum and gold catalysts to effect powerful atom-economic transformations has led to a marked increase in their utilization. The quite remarkable correlation of their catalytic behavior with the available structural data, coordination chemistry, and organometallic reactivity patterns, including relativistic effects, allows the underlying principles of catalytic carbophilic activation by π acids to be formulated. The spectrum of reactivity extends beyond their utility as catalytic and benign alternatives to conventional stoichiometric π acids. The resulting reactivity profile allows this entire field of catalysis to be rationalized, and brings together the apparently disparate electrophilic metal carbene and nonclassical carbocation explanations. The advances in coupling, cycloisomerization, and structural reorganization—from the design of new transformations to the improvement to known reactions—are highlighted in this Review. The application of platinum- and gold-catalyzed transformations in natural product synthesis is also discussed.

From the Contents

> “*Is it one living thing*
> *That has become divided within itself?*
> *Are these two who have chosen each other,*
> *So that we know them as one?*”
> Ginkgo biloba
> West-Östlicher Divan, J. W. von Goethe [**]

1. Introduction

One of the most successful chemical concepts ever formulated is the interpretation of acid/base behavior by Gilbert N. Lewis (1875–1946).[1,2] Since any species with a reactive vacant orbital or available lowest unoccupied molecular orbital is classified as a “Lewis acid”, all entities carrying net positive charge, and thus every metal cation and cationic metal complex, fall into this category. While the generality and marvelous simplicity of this concept allows a multitude of experimental data to be rationalized, many attempts have been made over the last few decades to further categorize the numerous “acids” that fall under this definition.[3]

In this context, an important qualitative scheme was introduced by Pearson.[4] According to the principle of “hard” and “soft” acids and bases (HSAB), the “polarizability” of the reactive entity represents the key parameter for analysis of empirical reactivity trends and affinities.[5] This rational was rapidly embraced because it assists in the navigation of the tremendous encyclopedia of reactivity modes, even though several possible pitfalls of the HSAB theory exist and should be carefully considered.[5] However, it was the recognition of the importance of frontier orbital control which resulted in the greatest leap forward. Coupled with the power of computational chemistry and the advances in the structure determination of reactive intermediates, this set a sound basis for a more quantitative understanding of acid/base behavior. Most of the experimental and theoretical work was devoted to the design, use, and understanding of Lewis acids based on main-group elements or transition metals of the fourth period of the Periodic Table.[2]

This situation is now rapidly changing. The advantages associated with the use of lanthanides were recognized in recent years and are now widely used.[6] Surprisingly, it was the peculiar Lewis acid properties of the late, heavy,[7] and noble metals, most notably those of the sixth period, which were the last to receive broad attention. However, this field is currently gaining considerable momentum and belongs to the most rapidly growing subdisciplines of contemporary catalysis research.[8] It is the purpose of this Review to provide an overview of these developments, with particular emphasis placed on the rather unique Lewis acid properties of platinum and gold species (as well as their close relatives). To this end, structural information and representative computational data are analyzed to provide guidance through the seemingly diverse, yet actually very coherent, preparative results, which are summarized in the later chapters of this Review. Finally, selected applications to target oriented synthesis are meant to illustrate the growing confidence of the practitioners to subject elaborate and highly valuable materials to platinum- or gold-catalyzed reactions. Although several important issues still remain to be solved, most notably the extension

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[**] Ist es ein lebendig Wesen,
Das sich in sich selbst getrennt?
Sind es zwei, die sich erlesen,
Dass man sie als eines kennt?

of carbophilic activation to asymmetric synthesis, it is hoped that this Review will help to sustain and even expedite further advances in this fascinating field.

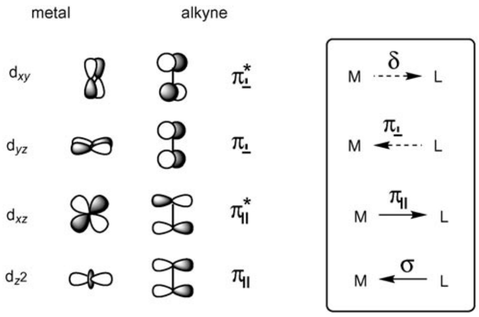
2. Basic Concepts of Carbophilic Activation

2.1. Structural Aspects of "π Acidity" and "Alkynophilicity"

The bonding situation in transition-metal complexes with alkenes or alkynes as π ligands is usually discussed within the framework of the Dewar–Chatt–Duncanson (DCD) model,[9,10] which considers the bond as a donor–acceptor interaction between two closed-shell fragments.[11,12] Although an in-depth theoretical description is beyond the scope of this Review, we intend to correlate the results of representative computational and structural investigations with empirical concepts to provide guidance for discussion of the preparative results outlined in Sections 4 and 5.

In general the DCD model assumes that a σ bond is formed by overlap of the π system of the ligand with an empty metal orbital of suitable symmetry. A π interaction then results through back-donation of electron density from a filled metal d orbital into an antibonding π* orbital of the alkene or alkyne. This interpretation was rapidly accepted by the scientific community after its introduction in the early 1950s,[9,10] and most of the subsequent debate has been devoted to appraising the relative magnitudes of the synergistic σ and π interactions, as well as the choice of metal orbitals employed in bonding. In such a discussion, however, one must not overlook the electrostatic interactions that also come into play between a ligand and metal template. In fact, computational analyses for $[M^+(C_2H_4)]$ and $[M^+(C_2H_2)]$ (M = Cu, Ag, Au) at very advanced levels of theory indicate that approximately half of the total bonding force is actually electrostatic in nature.[13,14]

There are four principle components that can contribute to the bonding of alkynes as ligands (Scheme 1). The in-plane $\pi_{\parallel}$ orbitals are responsible for a σ-symmetric $M \leftarrow L$ donation as well as for the π-symmetric $M \rightarrow L$ back-donation referred to above. The orthogonal, out-of-plane $\pi_{\perp}$ orbitals can engage in $M \leftarrow L$ π donation (an interaction of importance in alkyne complexes in which the ligand serves as a four-electron donor), while mixing of an occupied d orbital of the metal and the empty $\pi^*_{\perp}$ orbital of the alkyne can result in an additional component of $M \rightarrow L$ back-donation. This latter interaction, however, has δ symmetry, which results in only a weak overlap, and therefore leads to a minute contribution to the bonding.



Scheme 1. Qualitative orbital diagram showing the interaction between a transition metal and an alkyne ligand.

This qualitative picture applies well to the d^8-platinum and d^{10}-gold complexes which constitute the focal point of this Review.[12] The contributions of the individual terms have been analyzed in a more quantitative fashion by using high-level computational methods. For the parent Au^+–acetylene complex ($[Au^+(C_2H_2)]$), the σ interaction accounts for the largest contribution to the orbital term (ca. 65%), followed by the in-plane $\pi_{\parallel}$ back-donation (ca. 27%), whereas the effect of the orthogonal $\pi_{\perp}$ term is small (ca. 7%) and that of the δ bond can be ignored (ca. 1%). Thus, one may conclude that alkynes (as well as alkenes) are strong two-electron σ donors but fairly weak π acceptors toward Au^I (as well as Pt^{II}), although some back-donation does occur and cannot be neglected.[13a,14,15]

Complex formation necessarily alters the structures of the metal fragment and the ligand. The Dewar–Chatt–Duncanson model predicts an elongation of the double or triple bond as a consequence of the net shift of electron density from the bonding π orbital into the antibonding π* orbital. A partial pyramidalization (of alkenes) or bending (of alkynes) then occurs as a consequence of the ensuing rehybridization. Hence, the degree of distortion from the geometry of the unbound ligand may be taken as an observable indication for the degree of back-bonding. Therefore a closer look at the structure of representative metal–alkyne as well as metal–alkene complexes is appropriate.

Alois Fürstner received his PhD in 1987 (Prof. H. Weidmann) at the Technical University Graz, Austria. After postdoctoral studies with Prof. W. Oppolzer in Geneva, Switzerland, he completed his Habilitation in Graz (1992) before joining the Max-Planck-Institut für Kohlenforschung, Mülheim (Germany) in 1993 as a group leader. Since 1998, he has been Director at this Institute and is also affiliated with the University of Dortmund. He has received several awards for his research on organometallic chemistry, homogeneous catalysis, metathesis, and natural product synthesis.

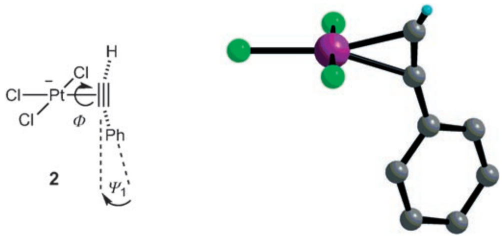
Paul Davies studied Chemistry at the University of Sheffield, and received an MChem in 1999. He was awarded his PhD in 2003 from the University of Bristol, where he worked with Prof. Varinder K. Aggarwal. He then moved to the Max-Planck-Institut für Kohlenforschung (Mülheim, Germany) as a postdoctoral research associate with Prof. Fürstner. In 2006 he became Lecturer at the University of Birmingham. His current research focus concerns the use of catalysis for synthetic purposes, and involves the development of novel strategies and the design of new catalyst systems.

Zeise's salt K[$PtCl_3(C_2H_4)$] (**1**) was the first well-defined organometallic compound prepared (even though its true nature was unraveled much later) and represents a prototypical example of a π complex.[16] Several independent analyses[17] have shown that the bound ethylene molecule is oriented perpendicular to the Cl_3Pt^+ plane ($\Phi = 90.0°$), the C=C bond is elongated to a minor extent (137 pm in **1** compared to 135 pm in ethylene), and the alkene deviates only slightly from planarity (Figure 1). These structural characteristics advocate the notion that ethylene acts as a strong σ donor but very weak π acceptor, a conclusion that is in line with the theoretical predictions and the analysis of spectroscopic data of this famous complex.[18] The overall depletion of electron density renders the ligand susceptible to nucleophilic attack. It is reasonable to assume that the corresponding ethylene complex of $PdCl_2$ will have similar characteristics. The induced electrophilicity constitutes the basis for the Wacker–Hoechst oxidation and a host of related transformations that were developed over the last few decades.[19] The ability of Pd^{II} to serve as a π acid is thus responsible for one of the biggest industrial applications of homogenous catalysis to date (ethene→acetaldehyde, ca. 3×10^6 tonnes per year).[19e]

1

Figure 1. Crystal structure of the complex anion of Zeise's salt (**1**) together with a schematic representation.

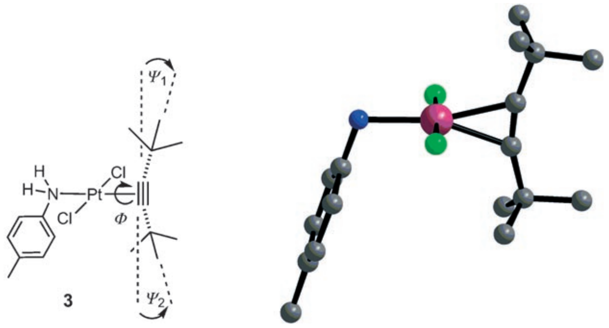
Only very minor structural changes occur upon formal replacement of the olefin in **1** by either a terminal or internal alkyne.[20,21] Again, the almost perpendicular orientation of the π ligand to the Cl_3Pt^+ plane is evident from the representative example depicted in Figure 2.[22] Only a slight distortion of the bound alkyne and a small change in the stretching frequency of the C≡C bond ($\tilde{\nu} = 1908\ cm^{-1}$ for complex **2**, $\Delta\tilde{\nu} < 10\%$) are observed. Mulliken population analyses confirm the dominance of σ donation over π back-bonding, thus indicating induction of partial positive charge on the ligand.[20] In fact, it was proposed early on in the literature that an alkyne in the coordination sphere of an electron-withdrawing Pt^{II} fragment should be regarded as a metal-bound carbocation.[23,24] Even though such a view certainly oversimplifies the actual bonding situation, it nevertheless provides valuable guidance for the understanding of the chemical behavior of such entities; the legitimacy of this concept will be elaborated later (see Section 4.3). Yet another aspect of immediate relevance for an understanding of the catalytic properties of such systems is the finding that the alkyne moieties in complexes of type **2** undergo facile ligand exchange with other alkynes and are easily replaced by ethene. This property ensures ready displacement of the product by new substrate and therefore enables "turnover" of a catalytically active metal template.



2

Figure 2. Crystal structure of the anion [$PtCl_3(PhC{\equiv}CH)$]$^-$ (**2**) together with a schematic representation; $\Phi = 82.5°$, $\psi_1 = 15.2(9)°$, $r_{C\equiv C} = 1.23(1)$ Å (as compared to 1.208(1) Å in free phenylacetylene).[20b]

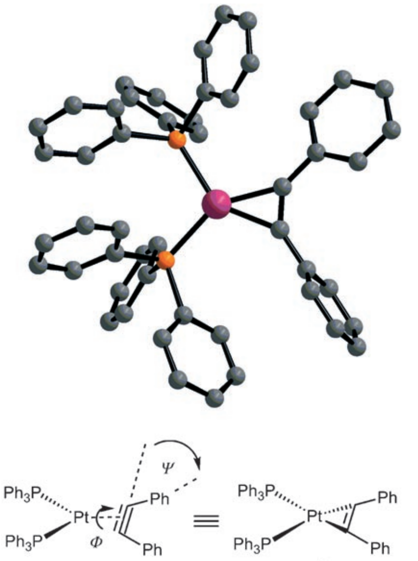
These distinctive structural features are by no means limited to the chloroplatinate complexes discussed above, but are also found in their neutral counterparts. Even the bulky *tert*-butyl groups in **3** are bent only slightly away from the metal atom ($\psi \approx 15°$; Figure 3).[25]



3

Figure 3. Crystal structure of [$PtCl_2(tBuC{\equiv}CtBu)(MeC_6H_4NH_2)$] (**3**) together with a schematic representation; $\Phi = 90.1°$, $\psi_1 = 14.7°$, $\psi_2 = 18.4°$, $r_{C\equiv C} = 1.24$ Å.

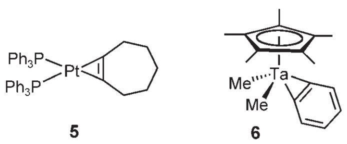
The structural characteristics of these Pt^{II} complexes can be fully appreciated when compared with the structure of the representative Pt^0 complex **4** depicted in Figure 4. The much more electron-rich metal fragment engages in significant back-donation of electron density from the metal into the



4

Figure 4. Crystal structure of [$Pt(PhC{\equiv}CPh)(PPh_3)_2$] (**4**) together with a schematic representation of its platinacyclopropene-like structure; $\Phi = 3.99°$, $\psi = 60.0°$, $r_{C\equiv C} = 1.32$ Å.

$\pi^*_{\parallel}$ orbital of the alkyne, as evidenced by the considerable "*Z*-olefin character" of the bound ligand, which deviates from linearity by 60°. Moreover, the ligand is forced into a coplanar arrangement with the P-Pt-P plane, the bond length is considerably elongated, and the stretching frequency of the "alkyne" is significantly decreased ($\tilde{\nu} = 1750\ \text{cm}^{-1}$). In fact, compound **4** is best described as a metallacyclopropene rather than as a simple π complex. The significant barrier to rotation around the axis between the metal and the centroid of the C≡C bond is in line with such a description.[11] This particular bonding situation is characteristic for alkyne (and alkene) complexes of electron-rich low-valent late-transition metals and is even more pronounced for many complexes of early transition metals in various oxidation states.[11,26] The considerable "olefin character" imparted on the alkyne ligand through back-donation of electron density into the antibonding π* orbitals even results in such strained and highly reactive entities as cycloheptyne or benzyne being stabilized effectively (Figure 5).[27,28] All complexes falling into the metallacyclopropene (or metallacyclopropane) category are expected to be nucleophilic at the carbon atom.



5 **6**

Figure 5. Stabilization of cycloheptyne and benzyne in the form of the metallacyclopropene complexes **5** and **6**, respectively, of a strongly back-donating metal template.

The dichotomy of the bonding situation in the platinum complexes outlined above is statistically significant.[29,30] First and foremost, the increase in the C≡C bond length correlates well with the observed deviation of the alkyne ligand from linearity (Figure 6). Furthermore, the Pt···C distances in Pt^0–alkyne complexes (average: 2.03(2) Å) are significantly shorter than those in Pt^{II}–alkyne complexes (average: 2.19(6) Å),[31] thus indicating considerable "metallacyclopropene" character in the former case. This bonding situation is also reflected in the dihedral angles Φ between the plane of the Pt–alkyne entity and the PtL$_n$ plane (L = any spectator ligand). For all the tetracoordinate platinum complexes incorporating a single "side-on" alkyne ligand available from the Cambridge Crystallographic Data Center (CCDC), the dihedral angle Φ ranges between 0 and 10° if the formal oxidation state of Pt is zero, and greater than 75° if the platinum atom is in the formal oxidation state +II (Figure 7).[32]

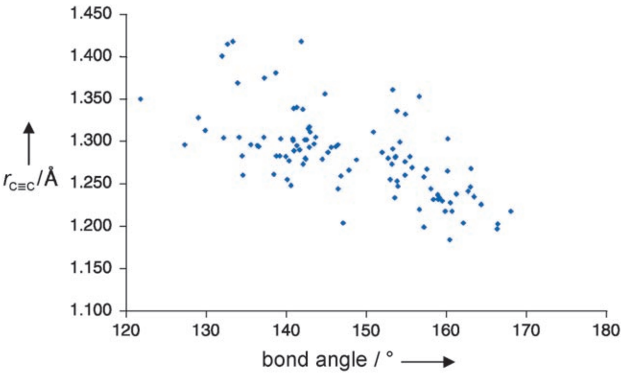


Figure 6. Correlation between the C≡C bond length and the deviation from linearity of alkyne ligands within the coordination sphere of mononuclear platinum complexes.

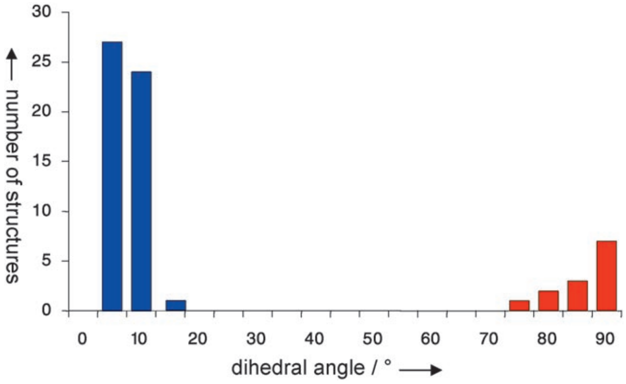


Figure 7. Dihedral angles between the platinum–alkyne plane and the PtL$_n$ fragment for all the mononuclear, tetracoordinate platinum complexes containing a single alkyne ligand. The histogram correlates the number of structures available from the CCDC database with the observed dihedral angles. Blue: Pt^0 complexes; red: Pt^{II} complexes.

High-level computational studies of the bonding situation in Au$^+$–alkyne complexes showed that ethylene is a slightly better σ donor than acetylene.[14,30] Hence it is unlikely that this cation will distinguish between the different π systems of polyunsaturated substrates, such as enynes, to any appreciable extent, and even if it does, will rather disfavor the alkyne unit. The high selectivity observed in many of the Au^I- and Pt^{II}-catalyzed processes, which are usually triggered at the alkyne site, is therefore supposedly kinetic in origin. In other words, the pronounced "alkynophilicity" of the late-transition-metal catalysts likely reflects the preference of the incoming nucleophile for attack at the coordinated triple bond.[33]

At this point it is important to emphasize that only ground-state arguments have been considered so far; it remains to be discussed to which extent they are relevant for assessing the reactivity of a π-bonded ligand. For various model complex–ligand systems, computational studies indicate that the transition state for nucleophilic addition reactions are not near the equilibrium η^2 structure.[34] It is now widely accepted that slippage of the ML$_n$ fragment along the axis of the bound alkyne or alkene accompanies ligand activation.[35,36] The electrophilicity is enhanced upon $\eta^2 \rightarrow \eta^1$ deformation, as relaxation of the symmetry allows mixing of previously orthogonal orbitals and facilitates charge transfer from the nucleophile to the π ligand and finally to the metal center, especially in cationic complexes (Scheme 2).[37,38] This conclusion is

Scheme 2. Schematic representation of the redistribution of electrons upon nucleophilic attack onto an alkene bound to a π-acidic metal template.[37c,45].

rather intuitive, as a deformation resembling slippage inevitably occurs along the reaction coordinate.

The very same computational investigations also showed that each of the favorable factors that result in an activated olefin or alkyne, once the slipped transition state is reached, are already preexistent in the η^2 ground-state structure.[35a] Under this premise, the information gathered from crystallographic and vibrational data (as discussed above for some representative cases) allows the reactivity of different metal complexes to be anticipated to an appreciable extent.

The prototypical bonding situations of a purely "donor–acceptor type" on the one hand and a "metallacyclopropane (-propene)" entity on the other hand clearly constitute no more but the extreme cases of a continuum.[39] However, we believe that it is useful and appropriate to define any metal fragment that binds to a carbon–carbon multiple bond, and thereby deprives it of part of its electron density, as a "π acid".[40] Coordination to such electron sinks induces partial positive charge on the ligand, just as complexation of classical Lewis acids such as $TiCl_4$ or $ZnCl_2$ does to a carbonyl group,[41] and therefore renders the π system electrophilic in character. It is the partial slippage away from the symmetrical η^2 coordination in the transition state which engenders productive overlap of the orbitals of the nucleophile with the distorted π system. Overall, π-acidic metal fragments can be regarded as the "soft" counterparts to the conventional Lewis acids which have affinity for the "hard" heteroelements.[40,41] Interactions between alkynes or alkenes with "π-acidic" metal fragments result in a larger loss of π-electron density than is gained through back-donation; furthermore, electrostatic contributions to bonding are significant or even essential. Defining structural characteristics of the resulting electrophilic complexes are seen in:

- the minor changes in the C–C bond length between the coordinated and the free ligand,
- near linear or near trigonal coordination geometries for alkyne and alkene ligands, respectively,
- low degrees of rehybridization of the C atoms in question (as evident, for example, from pertinent ${}^1J_{CH}$ coupling constants or crystal-structure analyses),
- low inherent barriers for the rotation of the ligand around the metal–ligand centroid axis.[42]

Vibrational data, most notably the C–C stretching frequencies, may also provide valuable hints, although it should be noted that Raman and IR data are not unambiguous in this regard.[43] Furthermore, numerous experimental and theoretical investigations support the intuitive view that a positive charge on the metal center results in enhanced electrophilicity of the bound π ligand relative to the neutral analogues.[44,45]

2.2. Reactivity of π-Acidic Systems

Numerous electrophiles other than Pt^{II} and Au^{I} fall under the definition of "π acids" given above. However, complexation and activation of a multiple bond constitutes just the very first step of a (catalytic) chemical transformation. What remains to be discussed are the reasons why certain π acids are particularly useful in the realm of catalysis.

Important differences become immediately apparent upon comparison of the behavior of a proton (H^+) with the isolobal fragments LAu^+ and Hg^{2+}.[46] It is common knowledge that addition reactions to olefins or alkynes catalyzed by a Brønsted acid usually require harsh conditions and are plagued by numerous side reactions of the carbocation intermediate formed.[47] Replacement of the proton by isolobal Hg^{2+} constitutes a classical solution to this problem.[48] The "soft" character of this large and polarizable cation ensures a much greater affinity to the substrate, which ultimately translates into mild reaction conditions and high yields of the desired addition products. Spectroscopic data provide clear evidence that the ligand in the incipient π complex is electron deficient and hence susceptible to attack by the nucleophile in the usual *trans* manner.[49,50] Although many addition reactions to alkynes occur with catalytic quantities of Hg^{II},[48,51] the resulting $C(sp^3)$–Hg bond in the analogous reactions of alkenes is usually kinetically stable and requires an extra step to release the organic ligand. Thus, the overall transformation is rendered stoichiometric in toxic mercury salts.

Such problems can be conveniently solved in many cases by the use of LAu^+ (or Pt^{II}, see below). This carbophilic fragment is considered as essentially nontoxic; it combines high affinity to the π system of the substrate with the advantages of a kinetically labile carbon–metal bond that can be readily cleaved under the reaction conditions, thus ensuring efficient turnover. In fact, the addition of MeOH to alkynes was one of the first practical applications of gold catalysis in organic synthesis. Notebly, this transformation was investigated in an industrial laboratory.[52] Although an early computational study had suggested a *syn*-addition mechanism,[146b] it is now generally accepted that reactions of this type follow the regular *trans*-addition pathway (see below).[53] This concept is by no means limited to the use of alcohols as the nucleophilic partners but has been successfully extended to a host of other inter- as well as intramolecular addition processes involving various oxygen, nitrogen, and carbon nucleophiles. Many examples falling into this category are summarized in Section 4, together with more detailed mechanistic analyses.

At first sight, the isolobal relationship between H^+ and LAu^+ as well as a certain analogy in their chemical behavior may suggest that noble metal templates should be viewed merely as expensive equivalents of a proton with increased carbophilic character. This simplistic view, however, misses some of the most intriguing properties of these catalysts that are evident from high-level computational studies together with clear-cut structural data.

Ab initio calculations of a large set of bare $[M{=}CH_2]^+$ entities have shown that carbenes of the 5d transition metals are distinguished by particularly high bond energies, which peak at Pt.[54,55] Thereby, the bonding situation for platinum and gold is close to a purely dative case.[54] If seen within the framework of the Dewar–Chatt–Duncanson model, the overlap between a lone pair of electrons on a singlet methylene entity with an empty (hybrid) orbital on the metal has σ symmetry. This dative bond is counterbalanced by overlap of a metal d_{xz} orbital with the empty p_x orbital of the ligand to form the π bond (Figure 8). In other words, Au as well as Pt can engage in electron back-donation from the metal atom to a carbene ligand. It is important to recognize that this effect contrasts the reluctance of the very same metal templates to back-donate into the π* orbital of an alkyne or alkene ligand (see above). Hence, gold and platinum fragments activate a C–C triple (double) bond toward nucleophilic attack yet are able to stabilize incipient "carbene intermediates"; other late 5d elements may also display similar behavior.[55] This pronounced stabilization of the methylene fragment is responsible for the capacity of Pt^+ and neighboring elements to spontaneously dehydrogenate even methane.[54,55] The substantial shortening and strengthening of the metal–carbene bond are largely due to relativistic effects, most notably in the case of gold (see Section 2.3).[55–57]

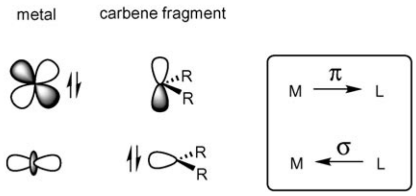


Figure 8. Dominant orbital interactions in a Fischer-type carbene complex.

It is appropriate to consider the available structural information for carbene complexes of platinum and gold in more detail because of their likely intervention in many of the reactions summarized below. Firstly, it is notable that prototypical Fischer-carbene complexes of chromium, molybdenum, and tungsten readily undergo carbene transfer on reaction with gold salts, thus indicating that the gold–carbene complexes are thermodynamically highly stable.[58] Both Au^I– as well as Au^{III}–carbene complexes are known, and in the former case show the expected linear coordination geometry (Figure 9).[59] However, it has been deduced from the molecular structures in the solid state that the C–Au "carbene" bond in such species shows very little, if any,[60] double-bond character. In fact, it is the C–N distance which is relatively short,[61] thus indicating that the stabilization of the "carbene" center actually derives mainly from the p_π–p_π interaction with the heteroelement.

The structure of complex **8** is even more relevant for the following discussion of the reactivity of gold-activated alkynes (Figure 10).[62] At first sight, **8** may be regarded as a vinylgold species coordinated to a $(CO)_5W$ template; the analysis of the bond length and orders, however, shows beyond doubt that the mesomeric forms of a carbene complex and, even more so, of a gold-stabilized carbocation dominate. This overall picture is highly reminiscent of the computed transition-state structure depicted in Scheme 2, where slippage of the π-acidic metal fragment (LAu^+ in this case) activates the coordinated π ligand for attack by an external nucleophile (the $(CO)_5W^-$ template in this case) and stabilizes the incipient "carbene" by some degree of back-donation. Similar to the case of **7**, however, it has been pointed out that the formulation of a "Au=C" bond in **8** is purely illustrative; in fact, the bond length (2.067(4) Å) even exceeds that of some prototypical $C(sp^2)$–Au single bonds;[60] hence, considerable partial positive charge will reside on the "carbenoid" C atom.[62] Whether this molecular entity is interpreted as a "gold carbene" or as a "gold-stabilized carbocation" is therefore largely a matter of semantics, and the use of the expression "carbenoid" seems appropriate to express this ambiguity.[63] The expression "carbenoid" is more generally applied to reagents such as the Simmons–Smith species, which may act as either carbenes or C-centered nucleophiles. Despite this common practice, however, the duality in the behavior of the reactive species under consideration in this Review suggests that this term would also be appropriate in the present context.

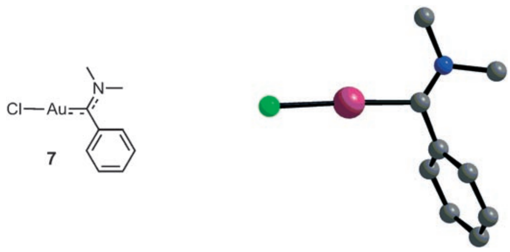


Figure 9. Crystal structure of a Fischer-type gold "carbene" together with a schematic representation; $r_{Au\text{-}C} = 2.02(3)$ Å.[59]

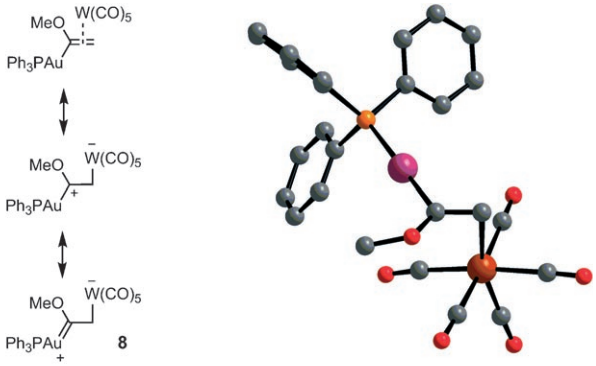


Figure 10. Crystal structure of the gold "carbene" complex **8** along with a schematic representation of the extreme mesomeric forms that depict the actual bonding situation; $r_{Au\text{-}C} = 2.067(4)$ Å.

The overall bonding situation in the known platinum carbenes is similar to that in the gold series.[64,65] Likewise, Fischer-type palladium carbenes are distinguished by a considerable single-bond character of the $C(sp^2)$–metal bond,[66] even if electron-donating ligands complement the coordination sphere. Two representative cases are depicted in Figures 11 and 12. Once again, the structural parameters are fully consistent with the view that the "carbene" ligand actually closely resembles a metal-stabilized carbocation.[24,63,67]

As will be discussed in more detail in Section 4, "carbene" complexes have been invoked in many catalytic transformations effected by gold and platinum templates that were discovered during the last decade. If an alkyne unit activated by such a π acid is attacked, for example, by an alkene as the nucleophile, it formally evolves into a "carbene" substituted

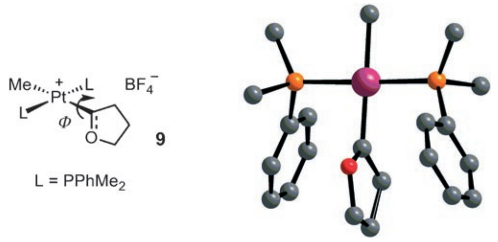


Figure 11. Crystal structure of the cationic unit of complex **9** together with a schematic representation; $\Phi = 87.3(6)^\circ$, $r_{\text{Pt-C}} = 2.00(2)$ Å.

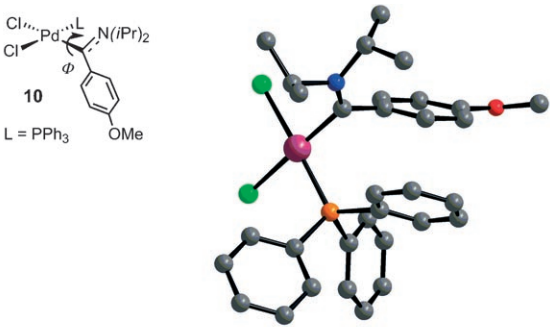
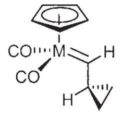


Figure 12. Crystal structure of $[(Ph_3P)Cl_2Pd{=}C(C_6H_4OMe)N\mathit{i}Pr_2]$ (**10**) together with a schematic representation; $\Phi = 74.3^\circ$, $r_{\text{Pd-C}} = 1.9937(12)$ Å.

by a cyclopropyl group (Scheme 3). Bearing the preceding discussion in mind, it will come as no surprise that two seemingly conflicting views have been used in the literature to interpret the behavior of these putative intermediates, depending on whether one prefers the "carbene" nomenclature or interprets reactive intermediates of this type as metal-stabilized cations.[68] In the latter case, the link to the "nonclassical" carbocation problem is immediately apparent, because the mesomeric extremes of a "cyclopropylmethyl", "homoallyl", or "cyclobutyl cation" form will apply.[69]

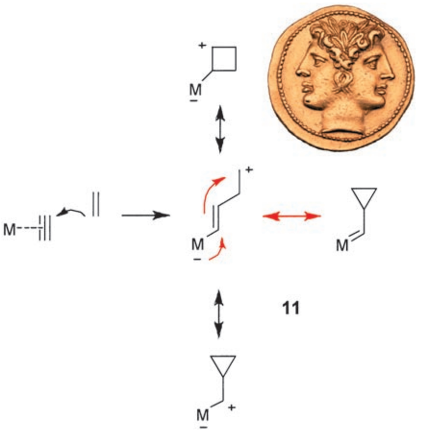
To the best of our knowledge, no such reactive species has been isolated and structurally characterized for M = Au or Pt, although analogous complexes are known for other metal fragments and have been thoroughly investigated.[70–72] It is of prime importance for the following discussion that the spectroscopic data of the related "nonstabilized" complexes **12** (M = Fe, Ru) clearly indicate very significant delocalization of positive charge into the cyclopropyl ring, with the observed effects closely paralleling those of free cyclopropylmethyl cations in solution (Figure 13).[70]



12, M = Fe, Ru

Figure 13. "Cyclopropylcarbenes" of iron and ruthenium demonstrating considerable cationic character.

All the available data for the platinum and gold series suggest that a dogmatic approach to the question of whether reactive intermediates of type **11** are "metal carbenes" or "metal-bound carbocations" is inappropriate. Even high-level computational studies do not provide an unambiguous answer, thereby leaving ample room for interpretation.[73] Therefore, it is reasonable to assume that the purely cationic and the strict carbenoid descriptions are again nothing but the mesomeric extremes of a generic picture.[68] At the present level of understanding, one cannot help but conclude that such entities are "Janus-like" in character, and neither face can go without the other. For the practitioner, however, it is important to note that the chemical behavior can be understood in carbenoid as well as in cationic terms, provided that either view is consistently applied. We have previously talked about a "congruence of mechanism" and still firmly believe in the validity of this view.[8a]



Scheme 3. The attack of an alkene onto an alkyne activated with a π-acidic metal template results in the formation of a metal–cyclopropyl carbenoid endowed with considerable "nonclassical" carbocation character.

2.3. Relativistic Effects and Coordination Chemistry

Before going into a more detailed discussion of the use of Au^{n+} ($n = 1, 3$) and Pt^{n+} ($n = 2, 4$) as catalysts in advanced organic synthesis (Sections 4 and 5), a short summary of the relativistic effects dominating the coordination behavior of these late-transition metals is mandatory. Since several succinct and authoritative treatises on the important consequences of relativity in transition-metal chemistry are available and will not be duplicated herein,[56,57,74] we limit this section to implications of immediate relevance for the understanding of catalytic reactivity.

Relativity causes the contraction of the atomic s orbitals, as a result of a non-zero probability of finding electrons with $l = 0$ at the nucleus, and an expansion of the atomic d and f orbitals, because of an increased shielding effect by the contracted core. In most cases, the interplay between these opposing effects leads to a net contraction of the bond length, which is at a maximum for gold but is also operative for its immediate neighbors in the sixth period.[56,57,74] Such bond contractions, however, are sensitive to the nature and electronegativity of the ligand: For example, they are much more pronounced for a bound phosphane than for a chloride ligand,[75] a fact with potential implications for catalysis. The formal "pulling in" of a ligand results in more effective orbital overlap and increased bond strength, as has already been discussed for "carbene" entities in the coordination sphere of gold and platinum. Furthermore, the altered intrinsic energies and diffuse character of the d orbitals qualitatively explain the chemically "soft" character of Au^I and related late-transition-metal cations.

Another highly relevant aspect of the coordination chemistry of Au^I is its strong preference for the coordination number two, most notably in phosphane complexes.[76–79] Although higher coordinate gold–phosphane complexes are known, gold is the least predisposed amongst the Group 11 elements to increase its coordination number any further.[75] A comparison of the crystal structures of the three representative complexes depicted in Figures 14–16 is particularly informative. [AuCl(PPh$_3$)] (**13**) is essentially linear (α = 179.6°), with the Au–P bond being shorter than the corresponding Au–Cl bond.[80] Particularly striking is the structure of the corresponding three-coordinate homologue [AuCl(PPh$_3$)$_2$] (**14**).[81] The large difference in the Au–P bond lengths shows that the second Ph$_3$P moiety is only very weakly bound. The apparent aversion of Au^I against a third ligand is even more visible in the computed structure of the parent complex of this type, that is [AuCl(PH$_3$)$_2$] (**15**), which consists of an almost linear entity (α = 178.2°) that associates with the second phosphane only very loosely.[75] Interestingly enough, the latter actually directs its lone pair toward the H atoms of the first PH$_3$ unit rather than to the gold atom (Figure 15). Another noteworthy detail of the structure of **14** in the solid state is the long Au–Cl bond, which indicates a substantial weakening of this bond relative to that in **13**. In fact, formal replacement of PPh$_3$ in **14** by more electron donating phosphanes such as PCy$_3$ results in the expulsion of the halide from the first coordination sphere of the metal, thus giving rise to a perfectly linear, two-coordinate cationic unit [Cy$_3$P-Au-PCy$_3$]$^+$ (**16**) with a chloride counterion (Figure 16).[82,83]

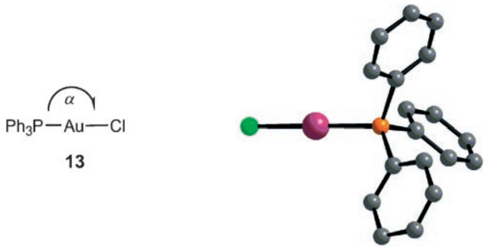


Figure 14. Structure of [AuCl(PPh$_3$)] (**13**) in the solid state together with a schematic representation; α = 179.6°, $r_{\text{Au-P}}$ = 2.235 Å, $r_{\text{Au-Cl}}$ = 2.279 Å.[80]

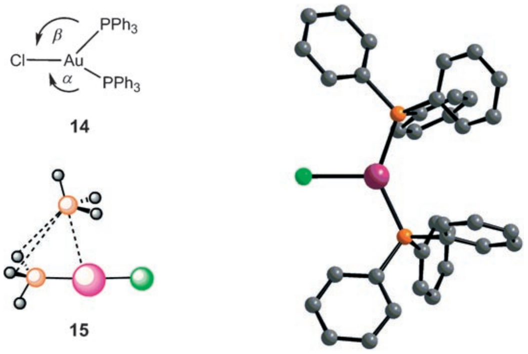


Figure 15. Structure of [AuCl(PPh$_3$)$_2$] (**14**) in the solid state together with a schematic representation (α = 115.1°, β = 108.1°, $r_{\text{Au-P1}}$ = 2.230 Å, $r_{\text{Au-P2}}$ = 2.313 Å, $r_{\text{Au-Cl}}$ = 2.526 Å)[81] and comparison with the computed structure of [AuCl(PH$_3$)$_2$] (**15**).[75]

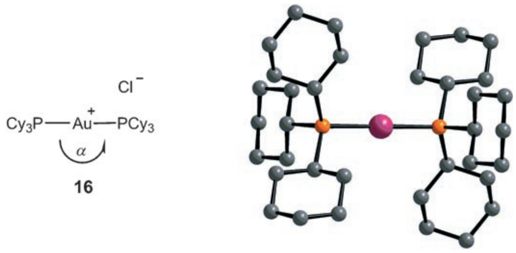


Figure 16. Structure of [AuCl(PCy$_3$)$_2$] (**16**) in the solid state together with a schematic representation; α = 180°.[82]

This very pronounced preference of Au^I to form two-coordinate linear complexes has important implications for the emerging field of gold-catalyzed organic transformations. One practical consequence is the need to abstract one ligand from neutral gold species of the type LAuX to induce sufficient reactivity in many cases. Furthermore, it is inherently difficult to chelate bidentate (phosphane) ligands to a single gold atom; usually the formation of various sorts of di- or polynuclear complexes prevails. A characteristic example is the now commercially available complex [(AuCl)$_2$(dppm)] (**17**; dppm = bis(diphenylphosphanyl)methane), which exists in two different crystalline forms in the solid state. These structures (Figure 17) show significantly different Au···Au distances (5.617 versus 3.341 Å), which are clearly beyond or at the limit of an attractive aurophilic contact.[84] As the use of chelating bidentate ligands, however, arguably constitutes the most successful design principle in asymmetric catalysis to date,[85] it is by no means straightforward to translate this

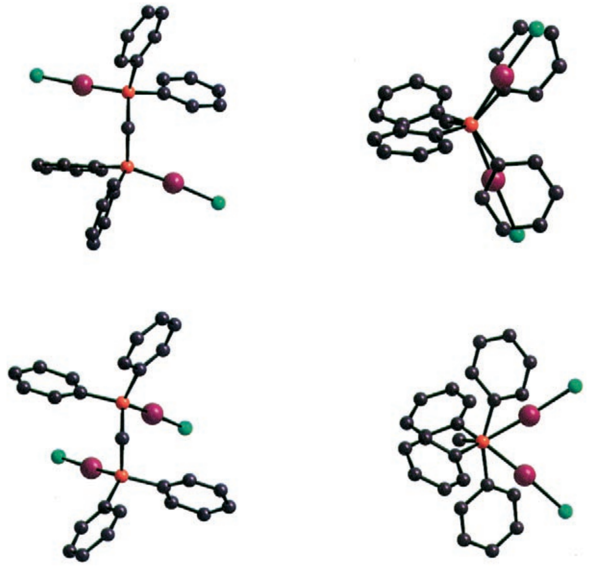


Figure 17. Comparison of the two different crystal structures of [(AuCl)$_2$(dppm)] (**17**), showing significantly different Au···Au distances (top: 5.617 Å, bottom: 3.341 Å).[84]

concept directly into gold catalysis. This may be one of the major reasons why effective chiral gold catalysts are so far very scarce (see Section 4.3).[86,87] Many important lessons in ligand design remain to be learned before broadly applicable, highly effective, modular and practical chiral gold catalysts may become available.

To this end, it might be necessary to exploit yet another peculiarity of the coordination chemistry of gold, namely the propensity of this metal to engage in Au···Au interactions.[88] These contacts generally occur perpendicular to the principle axis of the linearly arranged two-coordinate Au^I centers, with typical values ranging from 2.75 to 3.4 Å.[89] The binding energies of such metallophilic contacts are comparable to that of a prototypical hydrogen bond, despite the fact that both metal centers carry charges of the same sign and have no valence electrons available to make covalent bonds. Dispersive (van der Waals) forces and (virtual) charge transfer, again enhanced by relativistic effects, were invoked to explain this seeming contradiction.[56] The pronounced "aurophilicity" of gold directs the formation of a large number of gold clusters and diverse supramolecular aggregates with fascinating coordination numbers and geometries.[56,74–76,88,90,91] It remains to be seen whether this peculiarity can be translated into the creative design of catalysts for organic synthesis; there is no doubt, however, that gold chemistry holds promise for true "cluster catalysis".

3. Catalytic and Modifiable Carbophilic Activators

The reluctance of platinum and gold species to participate in standard catalytic cycles based on redox principles such as oxidative addition and reductive eliminations has resulted in them being overlooked.[92] However, it is this exact property that has opened up new perspectives within catalysis.[8,93]

Part of the popularity of this field is due to the practicality associated with using platinum- and gold-based catalysts. The initial work in this area utilized simple metal salts, such as $PtCl_2$ and $AuCl_3$. These types of catalysts have remained successful even as the field has progressed, a consequence of their effectiveness and, in the case of $PtCl_2$, its air-stable, non-hygroscopic nature. With the activation process invoking electrophilicity, a move toward cationic metal templates, which may be stabilized by a suitable spectator ligand such as a phosphane, N-heterocyclic carbene, or pyridine derivative, has resulted in increased activity. The ionization of either LAuX with soluble silver salts, or protonolysis of LAuMe with release of methane are the most widely practiced methods for the generation of LAu^+ species. The latter technique may be advantageous in cases where traces of residual silver might not be innocent. Although cationic entities of this type are generally prepared in situ, they have been isolated and structurally characterized in certain cases.[94] No firm guidelines are yet available as to the optimum choice of counterion used in the ionization process, and so a certain degree of screening may be necessary. Recent work suggests that the triflimide complex $[Au(NTf_2)(PPh_3)]$ demonstrates a good compromise, thus allowing high activity to be obtained from a remarkably air-stable catalyst.[95] Likewise, the gold–oxo species $[\{(PPh_3)Au\}_3O]BF_4$ has been employed successfully and deserve further scrutiny.[96]

The use of Au^{III} complexes with pyridinecarboxylic acid ligands has allowed the catalyst loading to be reduced to a significant extent.[97] Similarly, the choice of the spectator ligand has been shown to have an effect on the efficiency of the catalytic processes.[98] Moving to cationic species and higher oxidation states also increases the affinity to hard donor sites, and it therefore comes as no surprise that many of the transformations exploiting heteroelement activation make use of such species. Although not completely general, many of the processes are favored when the reactions are carried out in media that are only weakly donating. The linear coordination pattern displayed by Au^I results in bisphosphane ligands, which are widely employed as chelating species on other transition metals, typically picking up two (or more) gold atoms.[84] The corresponding dinuclear segphos complex is the most effective asymmetric catalyst so far reported, although there is ample room for further optimization.[99,100] In general, there is a great need for new catalyst design to encompass a wider range of asymmetric reactions. In view of the rich coordination chemistry of gold and its propensity to form larger clusters through aurophilic interactions, the role of such aggregates need to be more systematically addressed (see Section 2.3).

The number of ligands successfully employed in platinum catalysis for the carbophilic activation of alkynes is even more limited. Only electron withdrawing and kinetically labile moieties such as cod,[161] β-pinene,[164] and most notably CO[151,166] have generally led to a significant improvement. Although chiral cationic platinum species are well known,[101] the literature is suspiciously void of successful applications for the activation of alkynes.[308] However, recent advances in the asymmetric activation of olefins holds promise that this gap may be addressed in the near future.[102,103]

4. From Concept to Synthetic Applications: Platinum and Gold Catalysis in Organic Synthesis

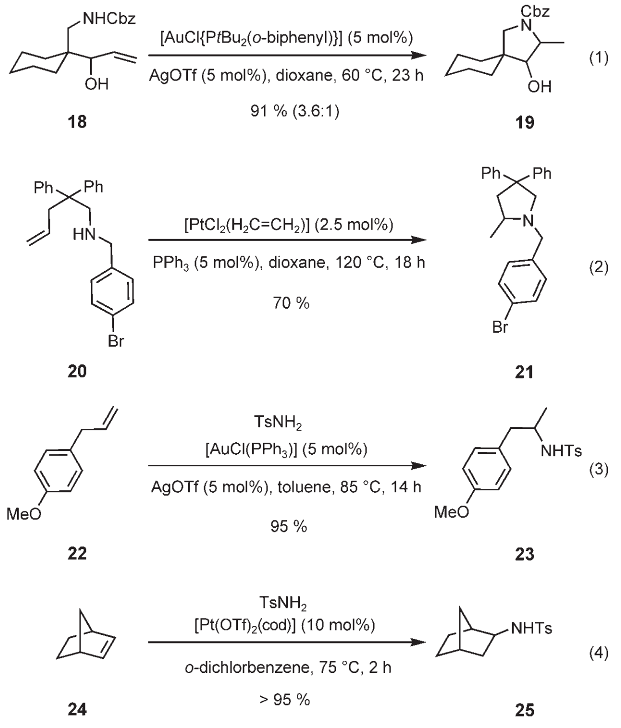
The recent acceleration in research activity in the field of platinum and gold catalysis demonstrates the relevance of the concepts outlined above to synthetic chemistry. Whilst platinum and gold are considered expensive, they are in fact comparable in cost to the palladium, rhodium, and iridium complexes that are commonly used for standard manipulations, including large-scale industrial applications. Therefore, it is clear that a wider use of these noble metals should not be automatically precluded on the grounds of their price. Furthermore, as there is no conventional redox chemistry involved within any of the reactions outlined below, these species can be returned in their original active form, thus minimizing or even avoiding the requirement for reprocessing.[138]

These platinum- and gold-catalyzed reactions have many advantageous qualities: they are operationally safe, simple, and practical to perform, and also do not generally require rigorously inert reaction conditions. From a chemical perspective they are distinguished by a superb reaction profile, with simple starting materials being converted through an array of transformations into products of significantly increased complexity. They are notably atom-economical[104] and exhibit excellent chemoselectivity towards C–C π systems, thus leaving a diverse range of other functional groups untouched. The ability to transform simple and robust units obviates the handling of highly reactive groups and therefore simplifies the wider synthetic routes that can employ this approach. These beneficial properties impart step-economy in the context of target-oriented synthesis.[105]

4.1. Activation of Alkenes and Allenes

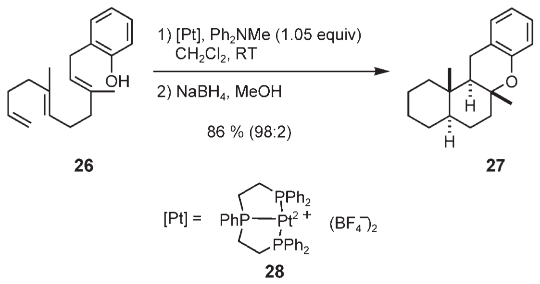
In principle, platinum and gold salts are capable of activating all C–C-π systems (alkenes, dienes, alkynes, allenes, arenes). Whilst nucleophilic addition to a metal-activated alkyne offers a diverse range of reaction outcomes, the analogous transformation with alkenes is less varied, with 1,2-addition predominating.[103] However, these reactions by themselves represent powerful tools in the synthetic arsenal, with progress in hydroamination technology being particularly noteworthy (Scheme 4). Appreciable levels of enantioselectivity have been reached and mild conditions are now commonplace for this important reaction.[106–116]

A recent example combined gold-catalyzed hydroamination with the in situ generation of the required homoallylic amine precursor by a ring-opening coupling of an amine and a methylenecyclopropane.[117]



Scheme 4. Inter- and intramolecular platinum- and gold-catalyzed hydroamination of olefins. cod = cyclo-1,5-octadiene, OTf = trifluoromethansulfonate, Ts = *para*-toluenesulfonyl, Cbz = benzyloxycarbonyl.

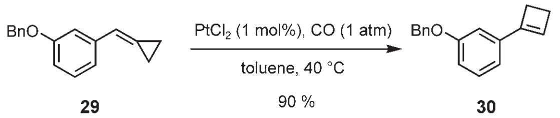
Another way to garner the reactivity induced by the π acid has been demonstrated in the cyclization cascades of polyenes (Scheme 5).[118,119] The transfer of the cation through the molecule is reminiscent of the well-established biogenetic pathways that were previously mimicked synthetically by the activation of polar triggers, most notably epoxides, mediated by oxophilic Lewis acids.[120,121]



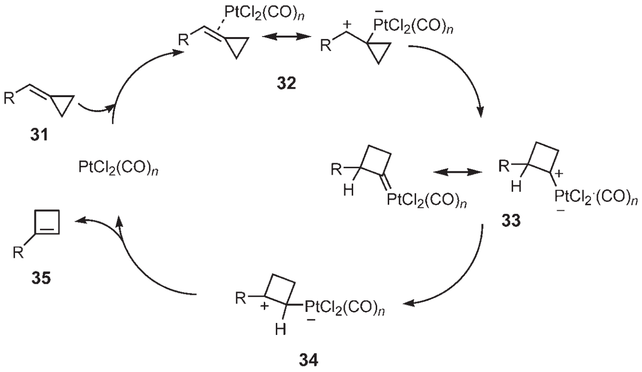
Scheme 5. Platinum-catalyzed cascade cyclization of polyenes.

The positive charge induced on an olefinic ligand is also responsible for the platinum-catalyzed rearrangement of vinylcylopropanes to cyclobutenes (Scheme 6). In this particular case the system was proposed to evolve via a metal carbene in a manner that is more commonplace in the alkyne series (Scheme 7).[122,123]

The higher reactivity profile of allenes means they readily participate in analogous reactions catalyzed by a variety of π acids. In addition to gold and platinum species, silver salts are highly effective.[124,125] Of particular value is the cyclization of allenes bearing pendant hydroxy or amine units to dihydropyrans and dihydropyrroles, respectively, with chiral information transfered from the allene axis to the product.[126]



Scheme 6. Platinum-catalyzed rearrangement of a methylenecyclopropane.



Scheme 7. Proposed mechanism for the ring expansion of methylenecyclopropanes to cyclobutenes.

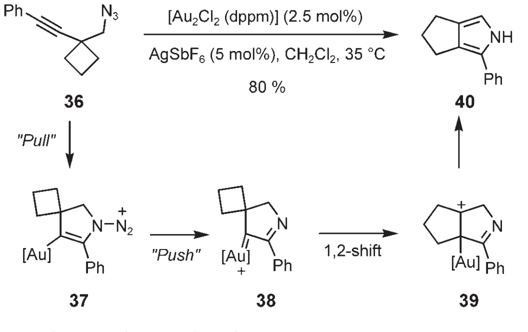
4.2. *Activation of Alkynes*

The elementary steps that follow initial complexation of the substrate to the π acid are discussed below. It is important to note however, that in most of the catalytic processes discussed later there is no direct physical evidence for the putative intermediates, and therefore the mechanisms are largely proposed on the basis of reaction outcomes and theoretical calculations. It goes without saying that a better understanding of the actual nature of the reactive species is highly desirable as it would strongly increase the predictive power and lead to more rational catalyst design.

As outlined in more detail in Section 2, the electrophilic activation of an alkyne introduces a new level of complexity beyond the alkene situation. Specifically, slippage of the metal along the C≡C axis polarizes the substrate in the direction of a vinylic cation, with the regiochemistry being determined by the substituents. Nucleophilic attack on such a reactive entity results in a polarized intermediate which can be formulated as a “carbenoid” in its mesomeric forms, as a result of the potential of gold and platinum to back-donate electron density. The bonding mode of the known structures pertinent to this discussion show the same ambiguity as to whether they are best formulated as metal carbenes or metal-bound carbocations (see Section 2.2). Although high-level theoretical calculations may give deeper insight into the exact description, which most likely differs from case to case, it is unhelpful to make a strong distinction between the forms. They are best viewed as the two sides of the same coin for the purposes of interpreting reactivity data and predicting possible product structures.

4.2.1. *Pull-Push Reactivity*

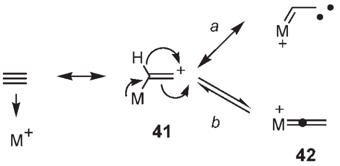
Depletion of electron density (“pull”) by coordination to the π acid in concert with the capacity of the gold or platinum center to back-donate electron density (“push”) imparts consecutive electrophilic and nucleophilic character to the vicinal carbon atoms of the alkyne substrate. This pull-push nature is apparent throughout many examples, but is illustrated particularly beautifully in the acetylenic Schmidt reaction (Scheme 8).[127,128] Initial electron-withdrawal leads to 5-*endo*-dig cyclization of the azide onto the alkyne, followed by extrusion of molecular nitrogen upon back-donation of electron density. In this example, the resulting gold “carbene” is ultimately stabilized through a 1,2-alkyl shift followed by release of the catalyst and aromatization of the newly formed heterocycle.



Scheme 8. The acetylenic Schmidt reaction.

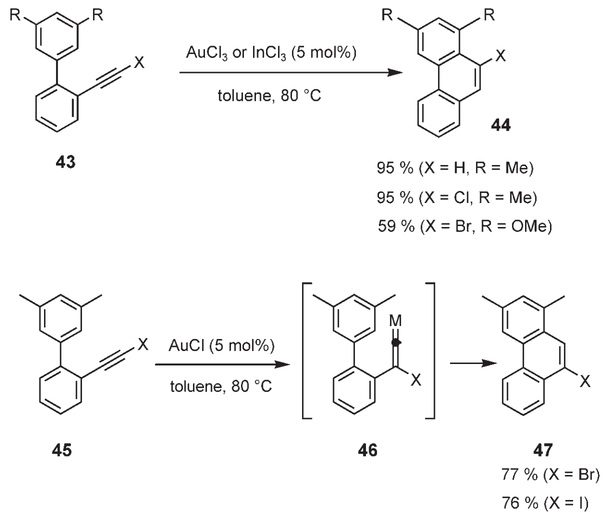
4.2.2. *Vinylidene Intermediates*

The system may also evolve through back-donation down an alternative pathway, in which a 1,2-shift (hydride, halide, etc.) results in the formation of a metal–vinylidene complex **42** (Scheme 9, route b).[129] At this stage the carbon atom bound to the metal center, rather than that at the vicinal position, would suffer initial nucleophilic attack. The generation of vinylidenes from alkynes is better known for other metals,[130–134] but has recently been evidenced to play a role in the platinum and gold series.



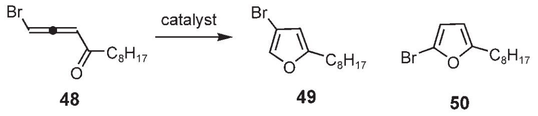
Scheme 9. Fundamental processes in the noble-metal activation of an alkyne.

An example of phenanthrene synthesis demonstrates the dichotomy seen using catalysts in different oxidation states.[135] As $AuCl_3$ (as well as $InCl_3$) is less able to back-donate, the reactive intermediate undergoes a Friedel–Crafts-type hydroarylation of the triple bond (Scheme 10). In contrast, the more electron-rich AuCl back-donates to a degree sufficient to enable a vinylidene pathway to become active, thereby resulting in the formation of the regioisomeric phenanthrene **47**.[135] Subsequent theoretical studies corroborate this proposed explanation.[136]



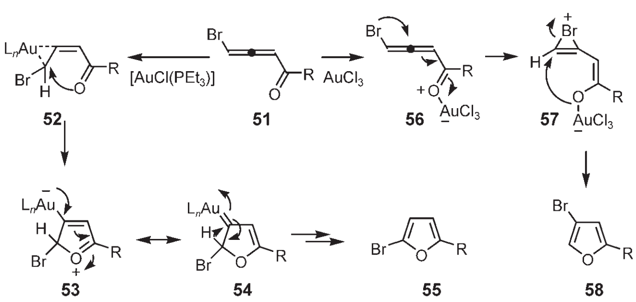
Scheme 10. An illustration of the dichotomy in the catalytic behavior of Au^I and Au^{III}.

Another example that demonstrates that the catalytic properties of gold might differ depending on the oxidation state comes from a recent synthesis of halofurans by the cyclization of bromoallenylketones (Schemes 11 and 12).[137] However, in processes where such a discrepancy in reactivity is not apparent, some ambiguity can remain as to the actual nature of the active species.[138]



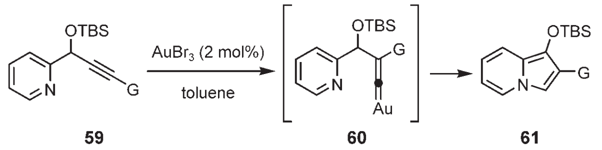
	49		50	
$AuCl_3$	95	:	5	86 %
$[AuCl(PEt_3)]$	< 1	:	99	(no yield given)

Scheme 11. Gold-catalyzed regiodivergent synthesis of halofurans.



Scheme 12. Proposed mechanistic explanation for the observed divergence in the reactions with Au^I and Au^{III}.

The gold–vinylidene pathway has also been invoked in a heterocycle synthesis based on the 1,2-migration of silicon, germanium, or tin from the terminal position of the starting alkyne to the adjacent carbon atom in the resulting annulated pyrroles (Scheme 13).[139] Similarly, a platinum-catalyzed indene formation was explained by a C–H insertion of a metal–vinylidene intermediate (Scheme 14).[140]

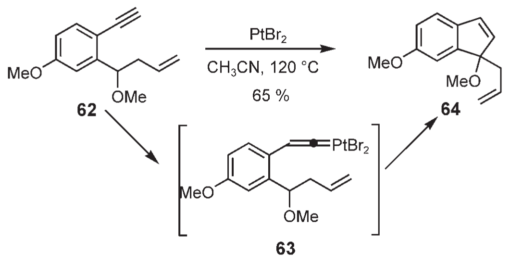


G =	61
$SiMe_3$	63 %
$SnBu_3$	64 %
$GeMe_3$	92 %

Scheme 13. Au^{III}-catalyzed pyrrole synthesis featuring a 1,2-shift of main-group units. TBS = *tert*-butyldimethylsilyl.

4.3. Nucleophilic Attack on Activated Alkynes

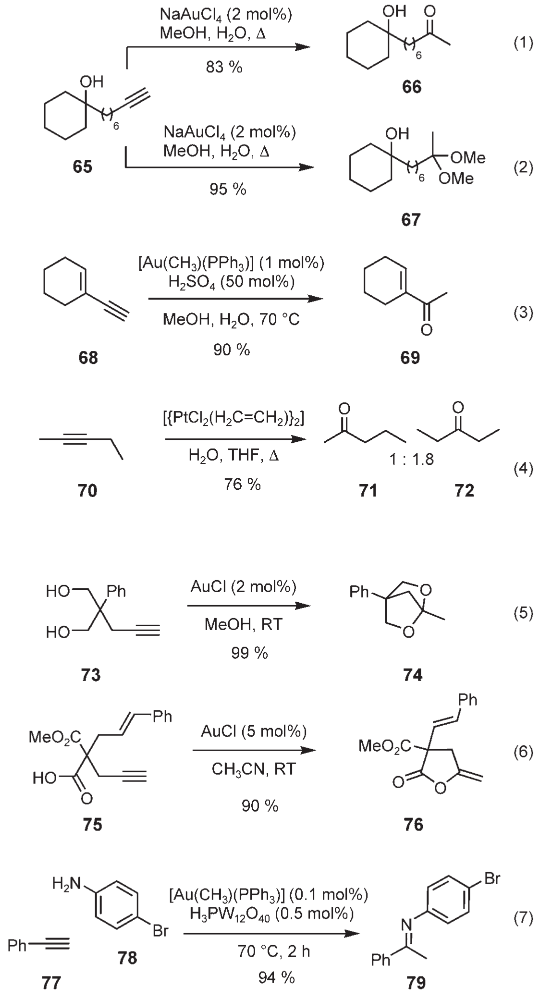
The diverse range of transformations that have resulted from the π-acid activation of alkynes are discussed in the following sections. Based on the considerations and processes discussed above, subsequent transformations are best considered by grouping them according to the nucleophilic component of the reaction.



Scheme 14. Platinum-catalyzed indene formation via a putative vinylidene intermediate.

4.3.1. Heteroatom Nucleophiles

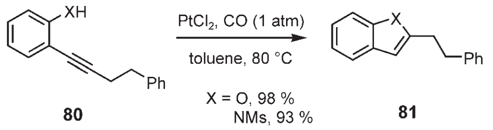
Much as the addition of a heteroatom across an olefin is catalyzed effectively by platinum and gold species, the analogous reactions of alkynes are also widely used. As the π system is only partially transformed during these reactions, valuable functional groups including ketones,[141–145] acetals,[146] enol ethers[147,148] or enol esters,[149] imines,[150] enamines, and enamides can be accessed (Scheme 15). The mild



Scheme 15. Inter- and intramolecular addition of heteroatoms to alkynes.

conditions involved make these reactions attractive alternatives to the use of organolanthanides, alkali metals, or inherently less tolerant transition metals.

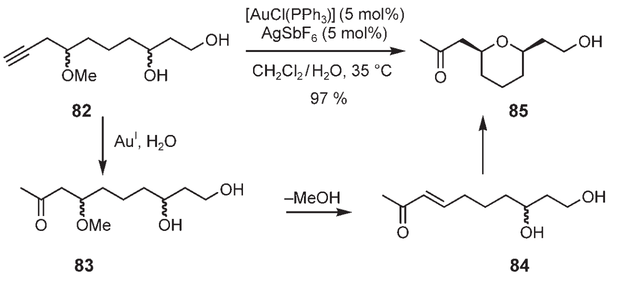
Intramolecular hydroaminations and hydroalkoxylations are readily amenable to the formation of heteroaromatic rings such as indoles and benzofurans, respectively (Scheme 16).



Scheme 16. Platinum-catalyzed hydroamination of hydroxylation of alkynes. Ms = methanesulfonyl.

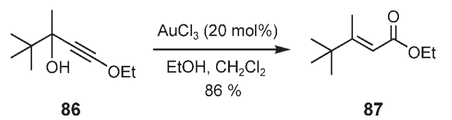
The reactions proceed at ambient temperature, although they are significantly faster when performed at 80 °C. Low catalyst loadings (0.5–1 mol %) usually suffice to obtain near quantitative yields in numerous examples. In contrast to most other catalysts used for similar purposes, no external base is necessary to promote the reaction.[151–153]

Such transformations can also be used as components of more involved processes: an example is the Au^I-catalyzed hydration of the homopropargylic ether **82** which affords the β-alkoxyketone product **83** (Scheme 17). On in situ elimination of methanol, a 1,4-addition by a pendant nucleophile onto the resulting enone **84** yields the 2,6-disubstituted tetrahydropyran **85** (or related heterocycles) in good yield and high diastereoselectivity. In this case the gold catalyst performs two roles: activating the alkyne and subsequently the enone by π complexation.[154]



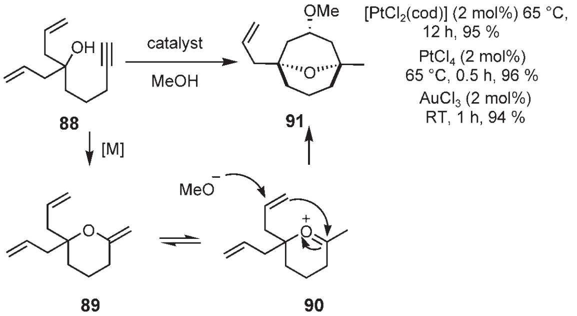
Scheme 17. Gold-initiated cascade leading to the preparation of heterocycles.

The Au^{III}-catalyzed Meyer–Schuster rearrangement may proceed by a similar hydration/elimination process (Scheme 18). However an alternative mechanism featuring Au^{III}-promoted elimination of the hydroxy group followed by hydrolysis of the oxonium intermediate can not be discounted, particularly because of the increased oxophilicity of the chosen catalyst.[155]



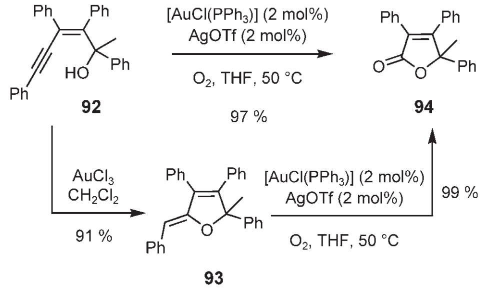
Scheme 18. Gold-catalyzed Meyer–Schuster rearrangement.

A gold-catalyzed intramolecular hydroalkoxylation with a homoallylic alcohol leads to a significant gain in molecular complexity on subsequent Prins-type cyclization during an operationally simple, one-pot process (Scheme 19).[156]



Scheme 19. Platinum- or gold-catalyzed tandem hydroalkoxylation/Prins-type cyclization.

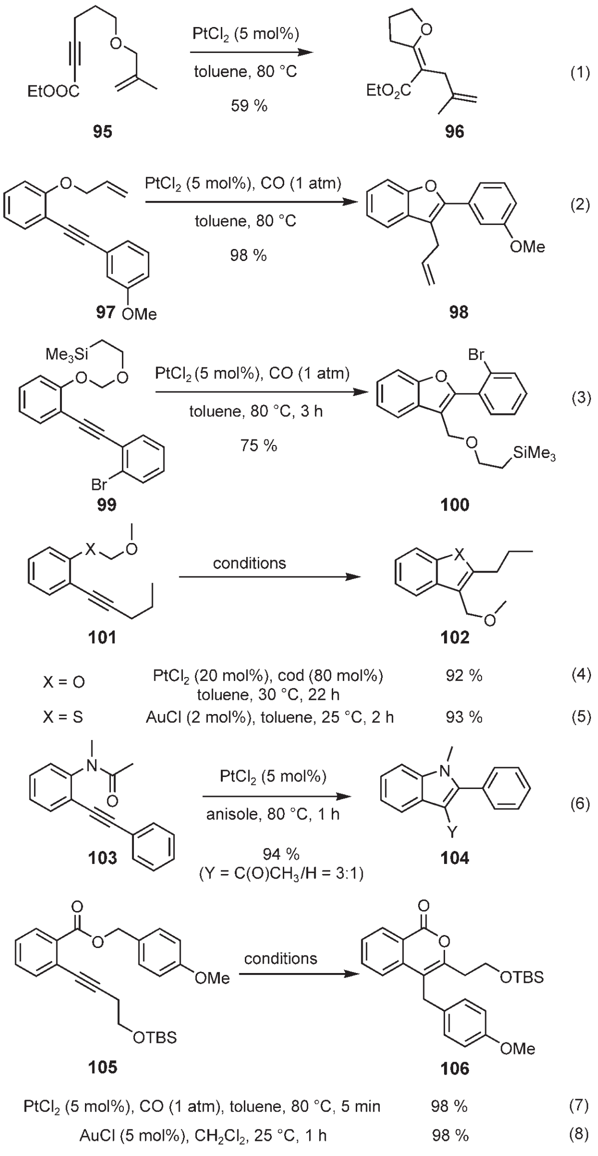
The dihydrofuran **93** initially formed from cyclization of substrate **92**,[157] in the presence of molecular oxygen, undergoes gold-catalyzed aerobic oxidation to give the corresponding butenolide **94** (Scheme 20).[158,159]



Scheme 20. Synthesis of butenolides.

4.3.2. *Carboalkoxylation Processes*

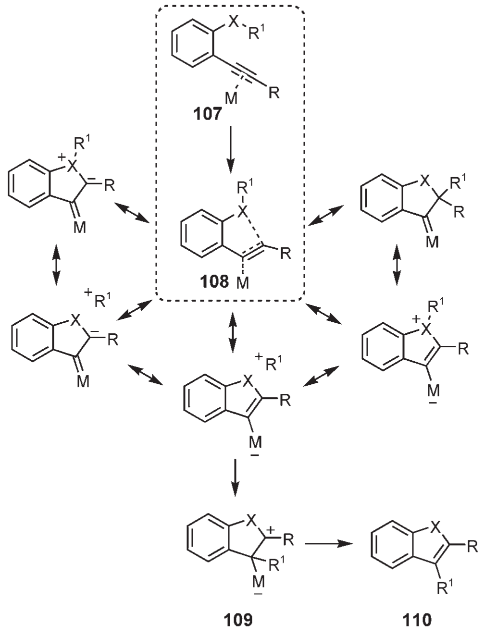
Whilst the hydroamination and related reactions mimic classical π-activation chemistry, albeit with a vastly improved reaction profile, the use of nucleophiles with no proton attached demonstrates the further dimensions of these catalytic processes. Mixed acetals and thioacetals, as well as allyl and benzyl ethers and amines, react with alkynes by this method, thus providing valuable heterocyclic scaffolds such as furans, benzofurans, benzothiophenes, and indoles (Scheme 21).[147,151,160,161] Furthermore, *N*-acylanilines with adjacent alkyne groups are amenable to related cyclizations that result in an N→C acyl shift during the *trans*-carboamination [Scheme 21, Eq. (6)].[162] The example of the formation of an isochromenone by an analogous route suggests a wider scope for transformations of this type in the realm of heterocycle synthesis [Eqs. (7) and (8)].[151,163] The proposed mechanistic scenario involves complexation of the nucleophilic heteroatom to the metal-activated alkyne to afford an onium intermediate (Scheme 22). Consequently, one of the heteroatom substituents transfers to the metalated position to



Scheme 21. Carboalkoxylation and carboamination of alkynes.

effect an overall heteroatom→carbon shift.[160] Although the mechanism for this carboalkoxylation process remains to be fully elucidated, it is the substituent that can best stabilize a developing positive charge that undergoes the shift.

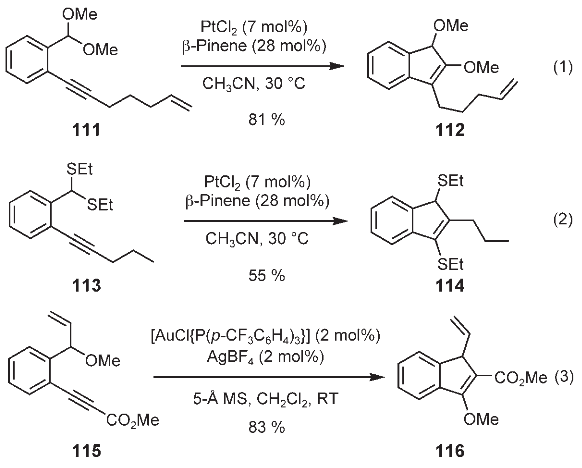
In the case of benzothiophene [Scheme 21, Eq. (5)], it was shown that $AuCl_3$, AuCl, and $PtCl_2$ gave similar yields whereas palladium- or copper-based catalysts were ineffective. For maximum efficiency, the activity of the simple metal salts can be enhanced by the use of additives such as CO[151,166] or olefins (cod, β-pinene, or benzoquinone).[164] It was proposed that cod breaks the aggregate structure of polymeric $PtCl_2$, thereby possibly increasing the number of active sites available in solution.[165] However, since the monomeric [$PtCl_2$(cod)] complex was found to be ineffective, it is currently not possible to give a conclusive answer. The use of CO as an additive should increase the electrophilicity of the metal center by virtue of its strong π-acidic character, and, hence, the cationic character of the reactive intermediate,



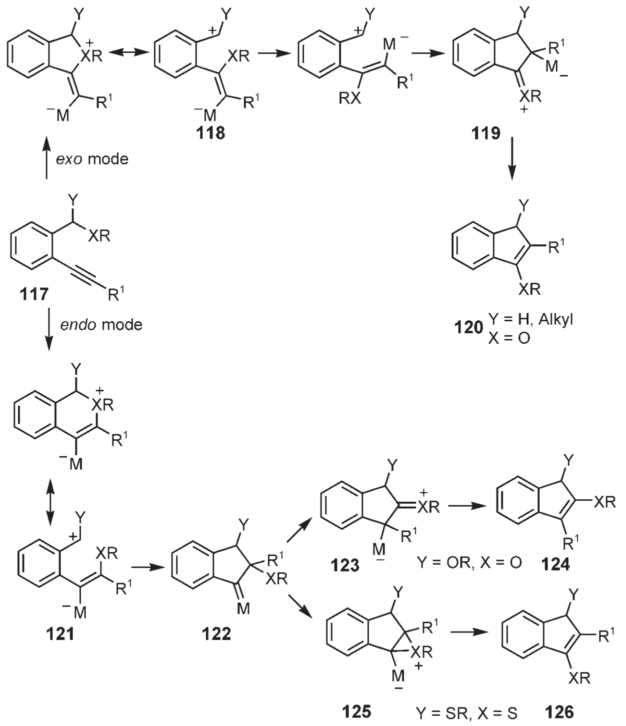
Scheme 22. Mechanism for the carboalkoxylation of alkynyl arenes.

while being sufficiently labile on the Pt^{II} template not to block the necessary coordination sites. The use of CO does not detract from the operational simplicity of the process and leaves no residue behind during the work-up.[147,151,166,167]

By virtue of the same activation, when the stabilized transferring group is within the tether linking the oxygen nucleophile to the alkyne, carboalkoxylation effected by a cationic gold catalyst occurs to form indenyl ethers [Scheme 23, Eq. (3)].[168,169] Along similar lines, *o*-alkynyl benzaldehyde acetals and thioacetals are converted into substituted indenes when treated with either $PtCl_2$/olefin or PdI_2 at 30 °C [Scheme 23, Eqs. (1) and (2)]. A possible pathway to explain the observed regiochemistries is depicted in Scheme 24, with structural divergence possibly explained by the relative proclivities of the oxygen- and sulfur-containing intermediates to promote either 1,2-alkyl shift or 1,2-heteroatom shift (**122→124** and **122→126**, respec-



Scheme 23. Carboalkoxylation of alkynes. MS = molecular sieves.



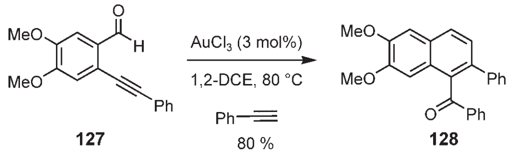
Scheme 24. Mechanistic explanation for the carboalkoxylation reactions.

tively).[170,171] A discrepancy exists when comparing the benzaldehyde acetals with benzyl ethers. In the latter case either unknown factors in this system favor the 1,2-heteroatom shift or the initial cyclization mode is *exo* (**117**→**118**). Further mechanistic studies to elucidate the exact pathway and the controlling factors in this area of chemistry are desirable.

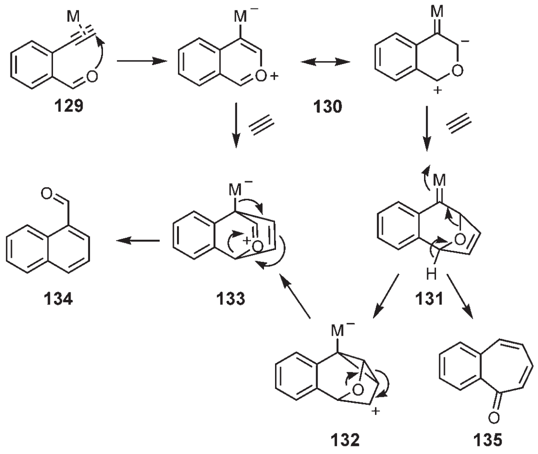
4.3.3. Platinum- and Gold-Catalyzed Cycloadditions

Whilst the previous examples have dealt with σ-bound nucleophiles, the use of π-bound systems (namely, carbonyl moieties) offers alternative reactivity. The further evolution of oxonium (iminium) species, generated from the nucleophilic attack of a carbonyl (imine) group onto a metal activated alkyne, makes this a powerful route to fused polycyclic materials (Scheme 25).

The coordination of the oxygen atom to the activated alkyne in substrates of type **129** affords a 1,3-dipole capable of reacting with an external or tethered alkyne unit to give benzannulated products after further rearrangement.[172–174] These processes were originally believed to proceed through a [4+2] mechanism, whereas recent theoretical calculations[175] suggest that a [3+2] cycloaddition with a subsequent rearrangement is more likely. However, experimental evidence suggests that this might also be substrate- and catalyst-dependent.[176] Whatever the later stages of the mechanism, both routes arise from the same nucleophilic attack on an activated alkyne (Scheme 26). Computational studies show that both Au^{I} and Au^{III} are equally capable of catalyzing this transformation, and reiterate the equivalence of the formal cationic and carbene pathways.[175] Further mechanistic studies of such transformations is thus clearly desirable.[177] As expected, esters, amides, and thioesters undergo analogous reactions.[178] Furthermore, this type of transformation has already been employed successfully in natural product synthesis, an example of which is given in Section 5.5.



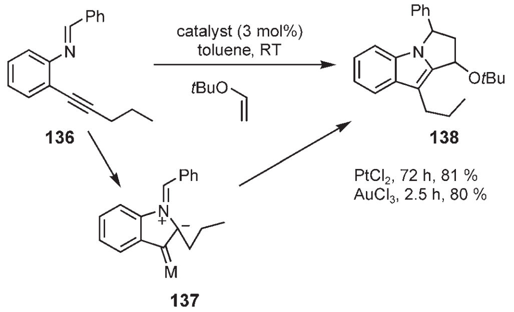
Scheme 25. Benzannulation through a formal intermolecular [4+2] cycloaddition. 1,2-DCE = 1,2-dichloroethane.



Scheme 26. [3+2] versus [4+2] mechanisms for nobel-metal-catalyzed benzannulation.

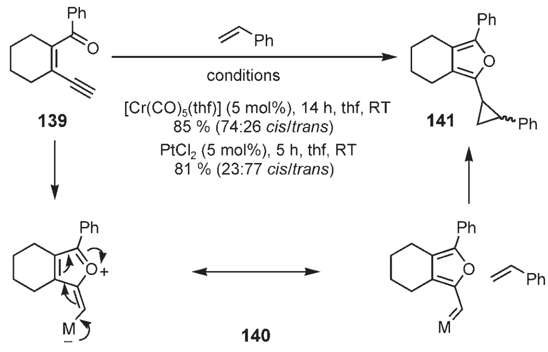
An interesting variation on the theme of [3+2] cycloaddition uses imines with inverse orientation relative to the alkyne. After activation with the catalyst, an azomethine ylide is generated which can be trapped with a suitable dipolarophile (Scheme 27).[179,180]

An alternative process takes place in cases where the π system linking the carbonyl (or imine) moiety and the alkynyl unit is not aromatic. Cyclization through the *exo*-mode pathway is favored to form a heterocyclic arene nucleus; concomitantly the distal position of the alkyne is



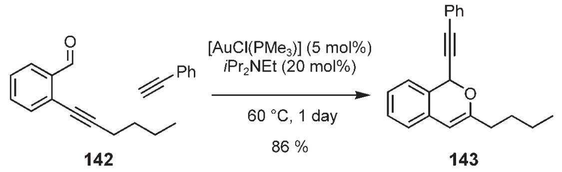
Scheme 27. Cycloaddition via an azomethine ylide.

converted into a metal carbene. This route appears to outperform any conceivable [3+2] mode so that reaction with an external olefin provides the expected cyclopropane products (Scheme 28). This overall type of transformation can be induced by various transition metals, with $PtCl_2$, $[Cr(CO)_5(thf)]$, $[Rh(OAc)_2]_2$, and cationic Ru^{II} being the most successful catalysts to date.[181–183]



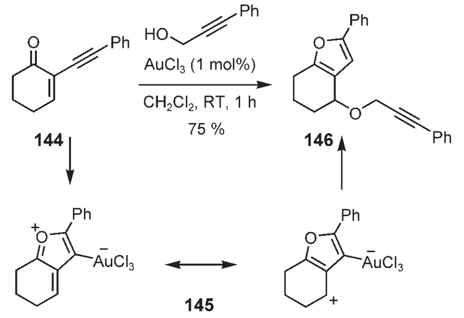
Scheme 28. Example of a cyclization-cyclopropanation cascade.

Alkynylation of the activated carbonyl unit occurs in preference to cycloaddition in the presence of base (Scheme 29). The requirement for a terminal alkyne as the external partner suggests it plays a part in the mechanism, which would be consistent with a metal acetylide adding to an oxonium species.[184–186] This proposal parallels the addition of nucleophiles to *ortho*-alkynylarylaldimines promoted by Ag^I salts.[187,188]



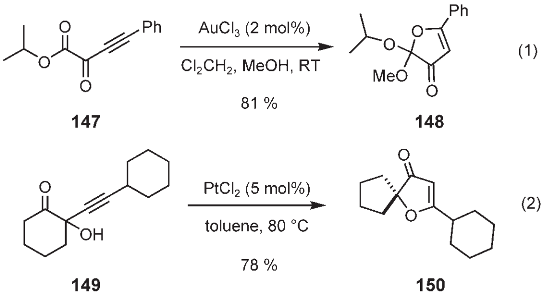
Scheme 29. Example of a gold-catalyzed cyclization-alkynylation cascade.

A continuation of the activation principle can be seen in the reaction of α-alkynyl enones with a wide range of nucleophiles. The attack of the carbonyl unit onto the gold-activated alkyne generates a benzylic carbocation which can be intercepted with various reagents such as alcohols, activated methylene compounds, and electron-rich arenes. Overall, this process constitutes a highly flexible entry to polysubstituted furans (Scheme 30).[189] The gold-catalyzed reaction of 1-(1-alkynyl)cyclopropyl ketones with nucleophiles proceeds through an analogous process, with ring opening of the cyclopropyl unit during formation of the furan resulting in a homobenzylic cation intermediate.[190] Deuterium labeling experiments are consistent with the proposed mechanism. This example further highlights that gold is merely the most effective amongst the several carbophilic π acids tested, all of which are late-transition-metal species. By the same principle, halonium ions, with their pronounced affinity toward alkenes and alkynes, have been shown to induce the same type of cyclization. However, the reaction proceeds with stoichiometric incorporation of the halogen atom.[191] When the nucleophile is a 1,3-diketone species, the fused oxabicyclic products are formed with substitution at the activated methylene group.[192]

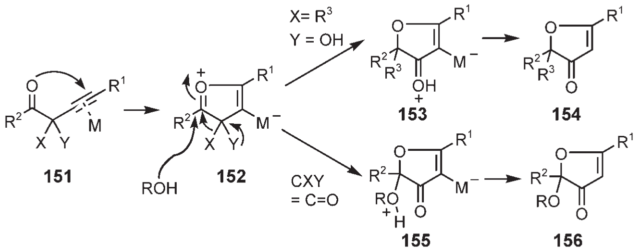


Scheme 30. Gold-catalyzed synthesis of highly substituted furans.

Depending on the reaction conditions and substrate structure, other evolutions of the putative oxonium species can also result. For example, alkynedione **147** yields 3(2*H*)-furanone **148** after nucleophilic addition of an alcohol under Au^{III} catalysis.[193] When the substrate backbone contains an α-hydroxy group, as in **149**, then an effective 1,2-shift onto the oxonium intermediate affords furanone **150** (Scheme 31 and Scheme 32).[194] Once again platinum and gold salts were shown to be the most effective of the late-transition-metal catalysts tested. The outcome of the reaction between alkynes and aldehydes to form enones under Ag^I catalysis might also be considered to be a result of π activation. In this case, the



Scheme 31. Platinum- and gold-catalyzed synthesis of furanones.

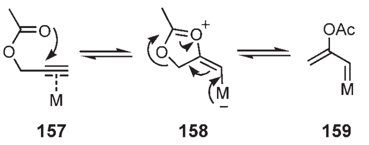


Scheme 32. Substrate-dependent divergent mechanisms for the synthesis of furanones.

reaction is thought to proceed through a formal [2+2] cycloaddition and cycloreversion pathway and thus resembles a metathesis between an alkyne and a carbonyl group.[195]

4.3.4. *Reactions of Propargylic Carboxylates*

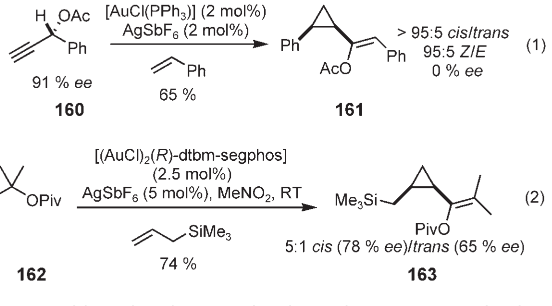
A growing area concerns the use of propargylic carboxylates in catalytic processes. The nature of such substrates is complementary to the pull-push reactivity of metal-activated alkynes. The carbonyl unit acts as a nucleophile onto the metal-activated alkyne; in doing so, its leaving-group ability at the incipient allylic position is enhanced to the extent that it is readily extruded on back-donation from the metal to the ligand. This process results in the formation of metal "carbenoid" **159** in which both the ester and the π system have migrated from their original positions (Scheme 33).



Scheme 33. Metal-induced activation of a propargyl acetate.

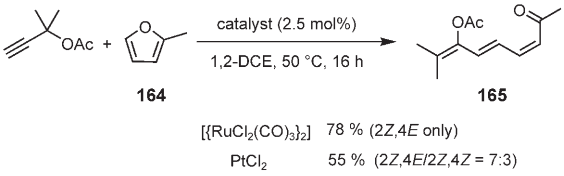
In essence, the carboxylate group serves to develop the metal–alkylidene species at the distal position of the alkyne. This mode of reactivity has been demonstrated in intermolecular reactions by trapping with external alkenes to afford vinylcyclopropanes such as **161**.[196,197] The intermediacy of a planar alkylidene of type **159** is supported by the reaction of enantiomerically enriched propargylic carboxylates, which afford racemic products.[198] However, appreciable levels of asymmetric induction can be reached when using chiral cationic gold complexes (Scheme 34).

These are the first examples in which uniformly relevant levels of enantioselectivity from a wide range of substrates were achieved under gold catalysis.[198,199] As shown in Section 2.3, part of the difficulty arises from the reluctance of Au^I to accept chelating ligands together with its strong preference for a linear geometry. The successful catalyst system is in fact a binuclear complex with individual gold units on both phosphane entities of the chosen segphos scaffold. To which extent, if any, an aurophilic interaction between these centers plays a role in obtaining the high levels of enantioselectivity remains to be elucidated.

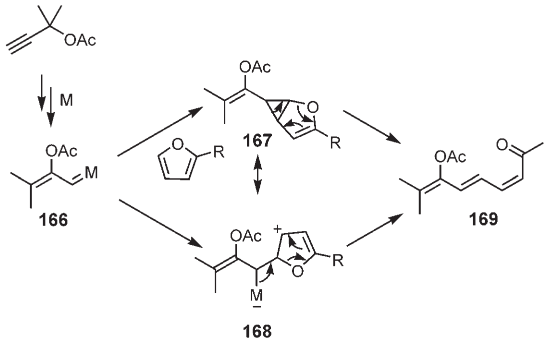


Scheme 34. Gold-catalyzed intermolecular cyclopropanations by the rearrangement of a propargylic carboxylates. Piv = pivaloyl, dtbm-segphos = (4,4′-bi-1,3-benzodioxol)-5,5′-diylbis[di-(3,5-di-tert-butyl-4-methoxyphenyl)phosphane].

Replacing the olefin with a furan or thiophene ring results in the formation of conjugated trieneones (Scheme 35). An analogous attack of the carbene on the aromatic unit is followed by a heteroatom-driven opening of the heterocyclic system (Scheme 36).[200]

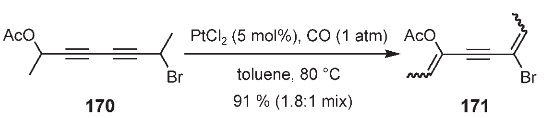


Scheme 35. Ring-opening addition to furans.



Scheme 36. Proposed mechanism for the ring opening.

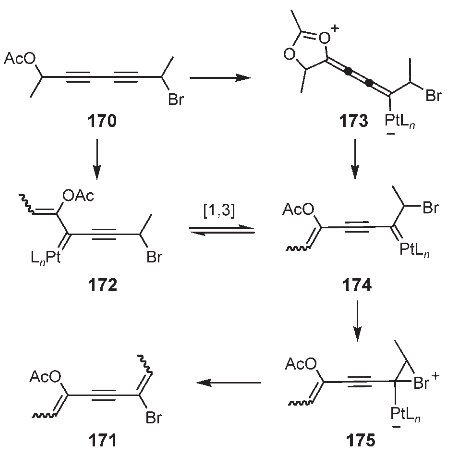
For 1,3-diyne substrates, the metal carbenoid generated on activation of a propargylic carboxylate by the metal can be relayed through a [1,3] metallotropic shift (Scheme 37).[201,202]



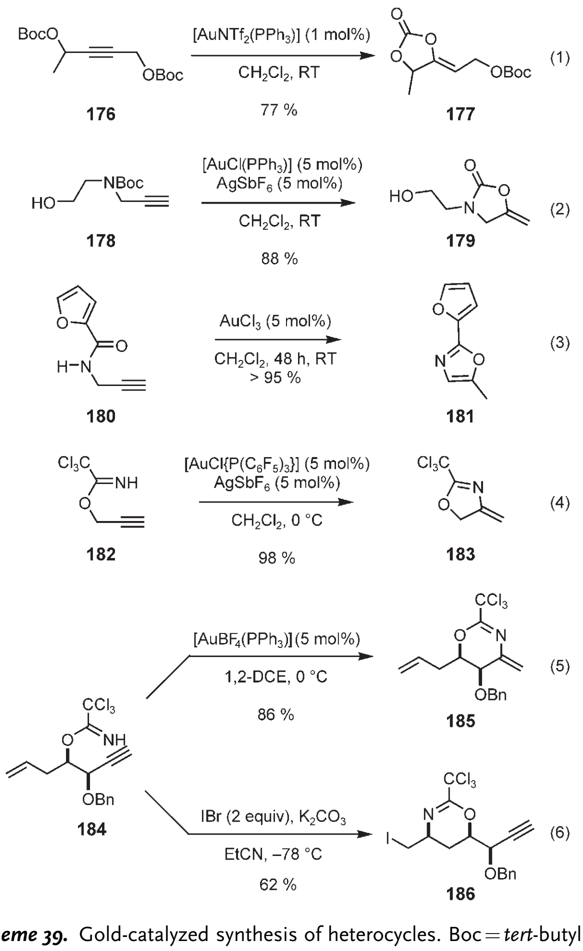
Scheme 37. Isomerization of diynes by a putative [1,3] metallotropic shift.

This process is reminiscent of similar metallotropic rearrangements using Grubbs-type catalysts, and also has precedent in stoichiometric carbene chemistry.[203] Despite this, one has to be careful in drawing final conclusions as the outcome could also be interpreted in terms of a remote activation mechanism involving intermediates of type **173** (Scheme 38).

The π-acid-induced rearrangement seen with propargylic esters is interrupted by modification of the carboxylate group. The use of a *t*Bu-carbonate or *t*Bu-carbamate yields 1,3-dioxolan-2-ones[204] or oxazolidinones,[205] respectively, as a result of the elimination of isobutene and protonation at the vinylmetal species [Scheme 39, Eqs. (1) and (2)].[206] The structurally related *N*-propargylcarboxamides are similarly cyclized and form oxazoles on proton transfer and migration of the double bond, which is driven by the enthalpic gain of aromatization [Scheme 39, Eq. (3)].[207,208] However, this is no



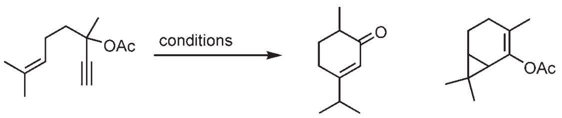
Scheme 38. Two different possible mechanisms for the observed isomerization of 1,3-diynes.



Scheme 39. Gold-catalyzed synthesis of heterocycles. Boc = *tert*-butyl oxycarbonyl.

prerequisite for the reaction to occur, as illustrated by the cyclization of propargylic and homopropargylic trichloroacetimidates to give non-aromatic heterocyclic products [Scheme 39, Eq. (4)]. A further interesting example demonstrates the chemoselectivity: the gold-catalyzed reaction occurs at the alkyne, whereas IBR activates the alkene moiety of the substrate [Scheme 39, Eqs. (5) and (6)].[209,210] These processes indicate the opportunity for orthogonal activation of π systems, which has not been fully exploited.

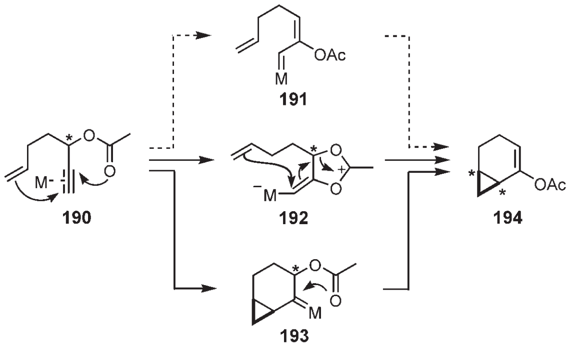
A higher level of complexity is seen in the intramolecular reactions of propargylic carboxylates with alkene units (Scheme 40). The presence of a second nucleophile raises questions as to the exact order of the individual steps. It was in such a context that this particular rearrangement of propargylic carboxylates was originally discovered.[211] Treatment of enyne **187** with a stoichiometric quantity of $ZnCl_2$ in benzene at 80 °C afforded small amounts of 2-acetoxy-2-carene (**189**; Ohloff rearrangement) as well as the major product carvenone (**188**). In contrast, the same substrate affords **189** almost quantitatively in the presence of only 5 mol% $AuCl_3$ at room temperature.[212] This comparison illustrates the superb effectiveness of noble metal salts as π-acidic catalysts.



187	188	189
$AuCl_3$ (5 mol%), 1,2-DCE		98 %
$ZnCl_2$, benzene, 80 °C	70 %	5 %

Scheme 40. Comparison of the efficacies of a gold and a zinc catalyst.

This transformation of **187** to **189** is readily explained through the formation of a carbene as the reactive intermediate, as discussed in the intermolecular case. However, very recent experimental data support a slightly more involved scenario (Scheme 41).[212,213] Chiral information from the propargylic position is transferred to the product, thus rendering a planar vinylmetal carbene of the type **191** as the actual intermediate improbable. The observed results can be explained by assuming that attack by the olefin either takes priority over the carboxylate group, thus leading to cyclopropyl carbene **193**,[212] or intercepts the vinylmetal species **192** before effective back-donation can occur.[213,214] As is evident from Scheme 41, the common theme of these mechanisms is the activation of the π system by a noble-

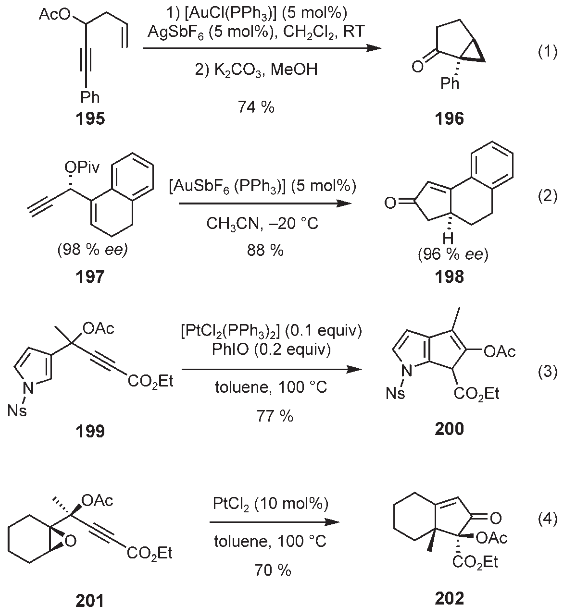


Scheme 41. Possible reaction pathways for the gold-catalyzed "Ohloff" cycloisomerization.

metal catalyst, with only subtle differences in the orchestration of the reacting components.[215]

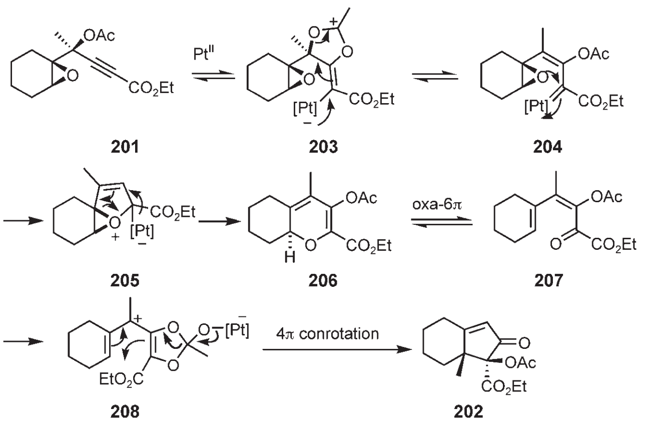
From a preparative point of view it is also relevant that the configuration of the reacting olefin translates into the stereochemistry of the resulting cyclopropane, thus showing that the reaction is stereospecific.[212,216,217] With regard to the migrating carboxylate, acetates seem to be the best compromise in terms of accessibility and price, although other esters such as pivalate and *para*-nitrobenzoates will also participate.[216,220] Remote unsaturated units are tolerated in the substrates.[217] The major limitation currently arises from the fact that only terminal alkynes undergo this rearrangement in preparatively relevant yields, whereas internal alkynes are prone to competing [3,3] sigmatropic rearrangement with formation of allenyl acetates.[218,219]

Although cyclization of 1,6-enynes is generally kinetically favored over those of 1,5-enynes,[220,221] the latter do participate effectively, and afford [3.1.0]bicyclic structures under gold or platinum catalysis [Scheme 42, Eq. (1)].[222,223] Along similar lines, 1,4-enynes can be subject to cycloisomerization [Scheme 42, Eq. (2)]. Generally referred to as the Rautenstrauch reaction,[224] this offers an attractive route to cyclopentenones[225] and offers an alternative to classical transformations such as the Nazarov cyclization[226] and Pauson–Khand [2+2+1] cyclocarbonylation.[227] If the alkene is replaced by an aromatic unit, the analogous reaction results in pentannulated products deriving from a formal C–H insertion of the putative platinum–carbene intermediate [Scheme 42, Eq. (3)].[228] As in Ohloff-type cyclizations, a high degree of chirality transfer in these rearrangements suggests that a mechanism involving C–C bond formation prior to the complete scission of the C–O bond at the stereogenic center is operative.[229]



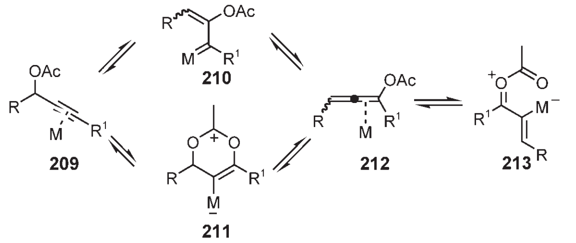
Scheme 42. Cyclization of diverse propargylic acetates.

An interesting extension has recently been outlined in which an epoxide takes the role of the olefin [Scheme 42, Eq. (4)]. On interception of the putative platinum carbenoid, a fragmentation cascade ensues which leads to the formation of pyran **206**. This subsequently undergoes an electrocyclic ring opening to dienone **207**, which in turn converts into the functionalized cyclopentenone **202** (Scheme 43).[230]



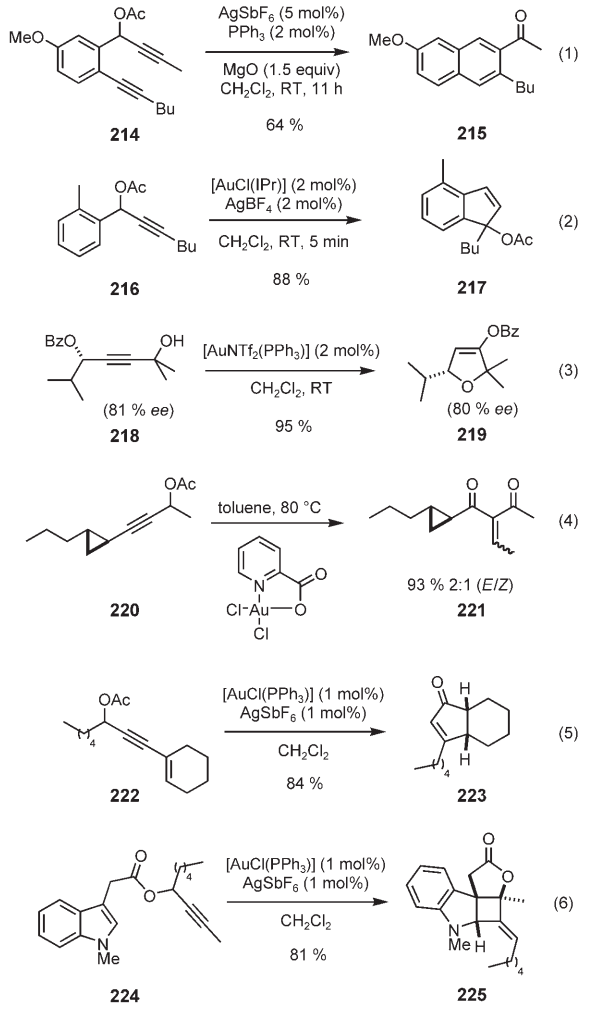
Scheme 43. Proposed mechanism for a platinum-catalyzed cyclopentenone synthesis through a fragmentation-electrocyclization cascade.

Whilst the 1,2-acetate rearrangement results in a variety of useful transformations, the corresponding 1,3-migration of propargylic carboxylates also provides valuable opportunities in a preparative context (Scheme 44). Recent examples include the reaction of the allenyl acetate initially formed with a tethered gold- or silver-activated alkyne to give aromatic ketones [Scheme 45, Eq. (1)].[231] Likewise, reactions of the incipient allenyl acetates with an adjacent benzene ring or alcohol in the presence of a gold catalyst results in the formation of substituted indenes[232] or dihydrofurans, respectively [Scheme 45, Eqs. (2) and (3)].[233,234] The former reaction requires a cationic gold source stabilized by a heterocyclic carbene ligand; other carbophilic metals just promote the first step but are ineffective at inducing cyclization. The latter reaction is reminiscent of the transformation of preformed allenes.[126]



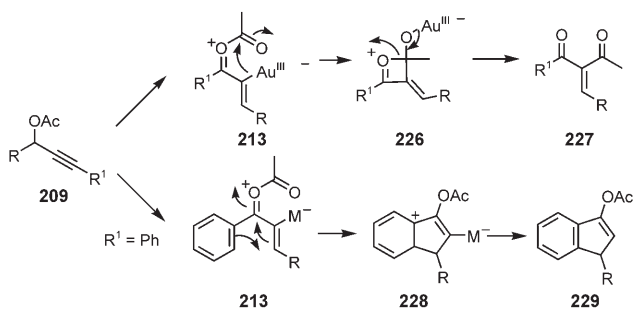
Scheme 44. Alternative routes for the noble-metal-catalyzed 1,3-acetate migration of propargyl acetates.

In the absence of viable nucleophiles, the allenyl acetates formed in situ react with gold to afford vinyl–gold intermediate **213**. Depending on the structure of the substrate, this

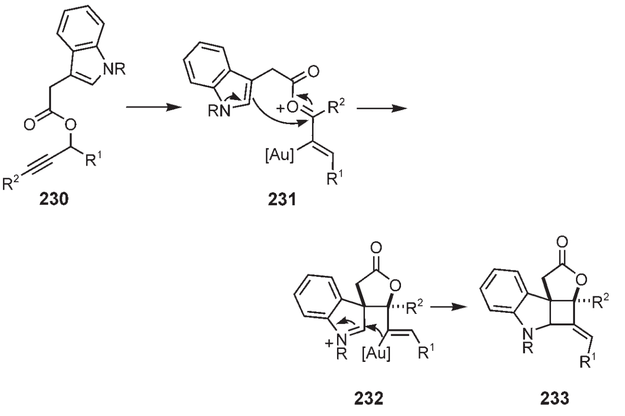


Scheme 45. Cycloisomerization of propargyl carboxylates, which possibly proceed via allenyl carboxylate intermediates.

species undergoes a number of alternate reactions, including elimination of a silyl group,[235] fission of the acetate unit,[236] Nazarov-type electrocyclization,[237] or formal [2+2] cycloadditions, with indoles (Schemes 46 and 47).[238] This latter example provides an excellent illustration of the structural complexity that can be garnered through an easily performed noble-metal catalysis.



Scheme 46. Divergent mechanisms in the transformations of propargylic acetates.

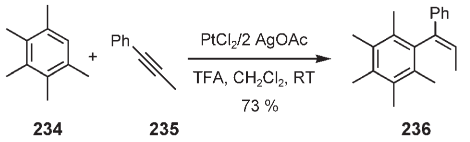


Scheme 47. Example of a gold-catalyzed isomerization leading to formation of a polycyclic framework.

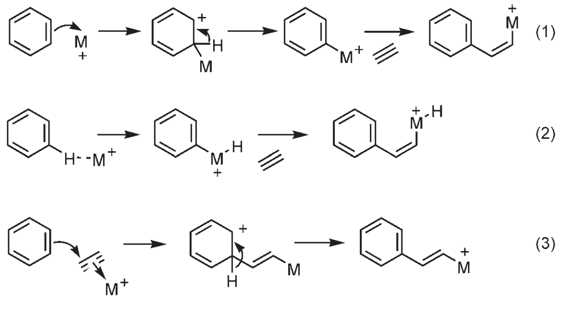
4.3.5. *Arenes and Activated Olefins*

In view of the foregoing discussion, it may not come as a surprise that alkynes activated by carbophilic Lewis acid templates react with aromatic nucleophiles, particularly if the aromatic units are electron rich. In the formal sense, this constitutes a *trans*-hydroarylation of alkynes and has been shown to be a reaction of considerable preparative potential.

In 2000, Fujiwara and co-workers reported the catalytic hydroarylation of alkynes using $Pd(O_2CCF_3)_2$ or $Pt(OAc)_2$ in trifluoroacetic acid and CH_2Cl_2 (Scheme 48) and proposed a C–H activation mechanism in which metalation of the aromatic ring was thought to constitute the key element [Scheme 49, Eq. (1)].[239] Although the metalation of arenes by electrophilic noble-metal cations is well-known,[240,241] this pathway is inconsistent with kinetic and stereochemical data.



Scheme 48. Platinum-catalyzed hydroarylation of alkynes. TFA = trifluoroacetic acid.

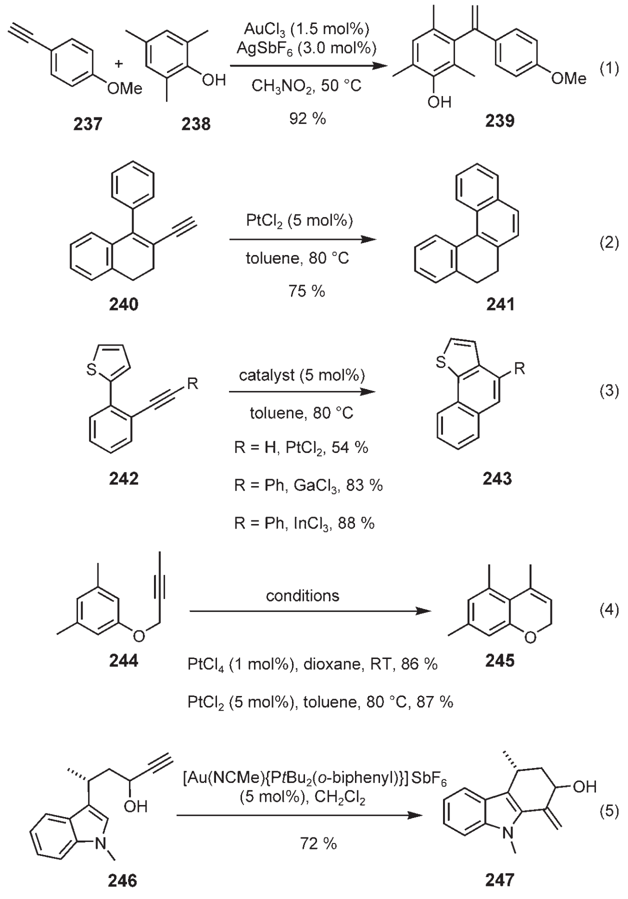


Scheme 49. Possible activation pathways for the platinum-catalyzed arylation of alkynes: 1) electrophilic substitution; 2) C–H activation; 3) activation of the alkyne.

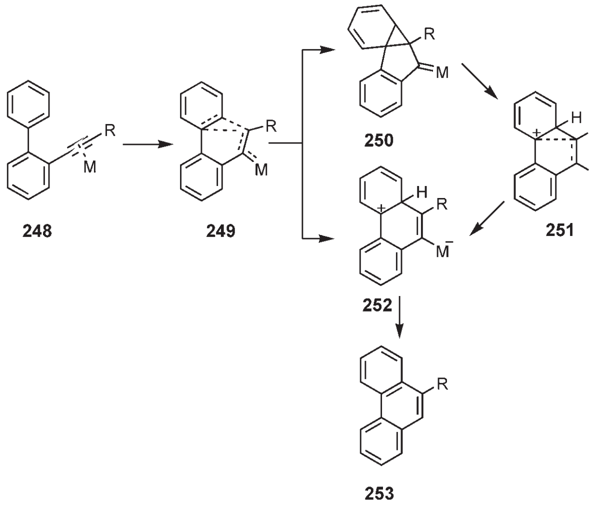
Specifically, the expected significant primary isotope effect for a C–H activation pathway was not observed and in fact an inverse kinetic isotope effect of 0.64–0.82 was measured.[242] Furthermore, the observed *trans* addition across the alkyne unit does not match the known preference for aryl platinum and aryl palladium complexes to undergo stereoselective *cis* addition. These observations make an "activation-of-alkyne"-based mechanism much more likely than a C–H activation scenario [Scheme 49, Eq. (3)].[242] The involvement of metal–vinylidene intermediates has been ruled out on the basis of deuteration experiments,[243] although they may be involved in the case of metals other than platinum.[244,245] Actually, a case in which vinylidenes most likely intervene is in the gold-catalyzed formation of 9-halophenanthrenes from alkynyl halides discussed in Section 4.2.2.[135]

The possibility remains that different reactions falling under the category "hydroarylation of alkynes" may follow alternative mechanisms. The net outcome however, invariably resembles that of a Friedel–Crafts process. These transformations make use of a relatively inert functional group which is activated under mild conditions, and therefore tolerate a wide range of functional groups, in contrast to the classical approach. They can be intra- or intermolecular, and are particularly useful in the synthesis of polycyclic aromatic and heteroaromatic systems (Scheme 50). Reactions of this type have borne scrutiny in the synthesis of several natural products, an example of which is discussed in Section 5.2. In line with the proposed electrophilic activation of the alkyne, the use of noble-metal salts in higher oxidation states or of cationic fragments is particular efficacious.[135,246–258] However, these processes are very general and a wide range of metal salts and complexes including soft non-transition metals including Ga$^{\text{III}}$[259] and In$^{\text{III}}$[135,260] are able to effect these transformations.[239,261,262] Although platinum and gold species are once again the preferred catalysts, some screening may prove necessary to find the optimum system.

The high *endo* selectivity observed in many of the cyclizations suggests that the mechanism might actually be more complex than a simple Friedel–Crafts reaction. It has been proposed that—in analogy to the carbene mechanisms implied above—the involvement of electrophilic carbenes would explain the outcome of the reaction.[8a] Recent computational studies corroborate this view, and highlight the bias of platinum compounds to form carbenoid intermediates (Scheme 51).[136] These calculations indicate that although a Friedel–Crafts mechanism and the cyclopropanation pathway via metalcyclopropyl carbenes show very similar activation energies, platinum cyclopropyl carbenes of type **250** are the stationary points with the lowest energy.[136,249]

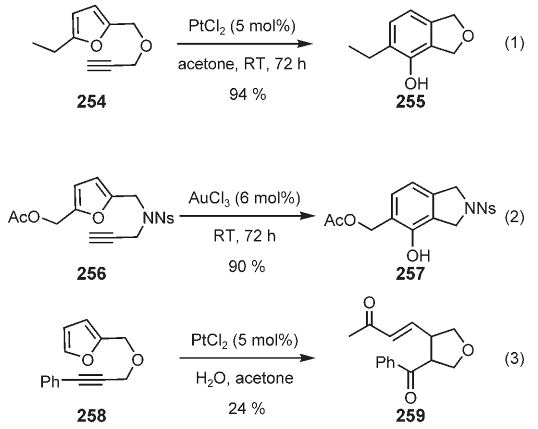


Scheme 50. Inter- and intramolecular hydroarylation of alkynes effected by platinum and gold catalyts.

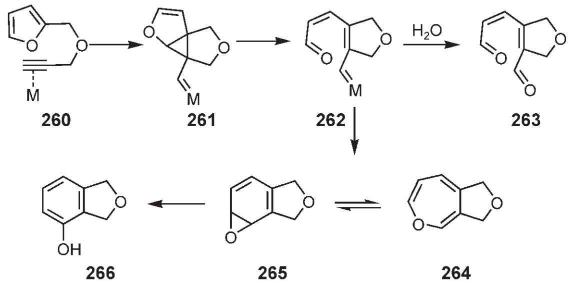


Scheme 51. Reaction pathways for phenanthrene synthesis.

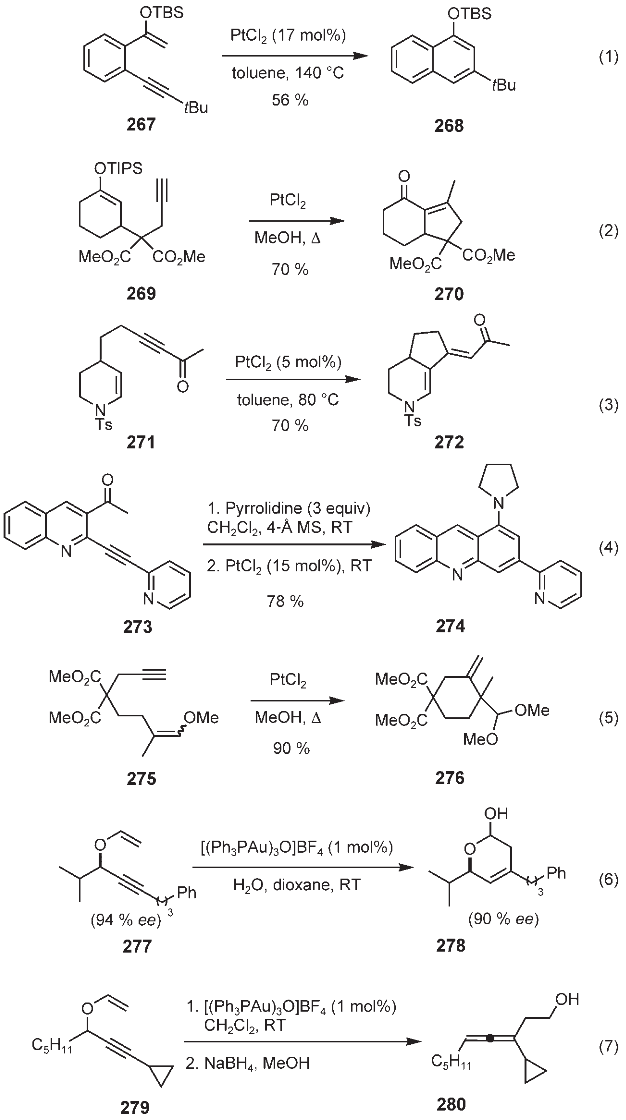
The involvement of carbene intermediates is even more apparent in some of the reactions of furans with tethered alkynes. For the representative cases shown in Scheme 52, the formation of products **255**, **257**, and **259** is best explained by invoking the generation of carbene **261** as the primary intermediate with subsequent rearrangement to the conjugated, and hence even more stabilized, metal carbene **262**. In the absence of external nucleophiles, a [2+2] addition pathway leads to the formation of phenolic products.[263,264] Whilst the exact mechanism is not fully elucidated, arene oxide **265** is a proven intermediate (Scheme 53).[265] In the presence of water, however, the carbene intermediate can evolve into the aldehyde **263**. It was possible to demonstrate that reactions of this type were able to proceed efficiently under very low



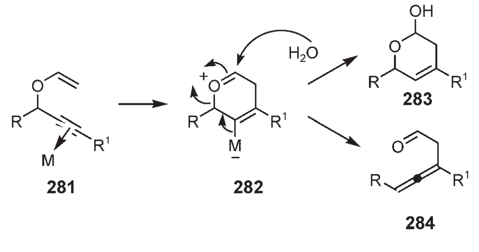
Scheme 52. Platinum- and gold-catalyzed phenol synthesis.



Scheme 53. Mechanistic explanation for the formation of phenols and aldehydes in the noble-metal-catalyzed cyclization of furans onto alkynes.



Scheme 54. Reaction of electron-rich olefins with alkynes. TIPS = triisopropylsilyl.



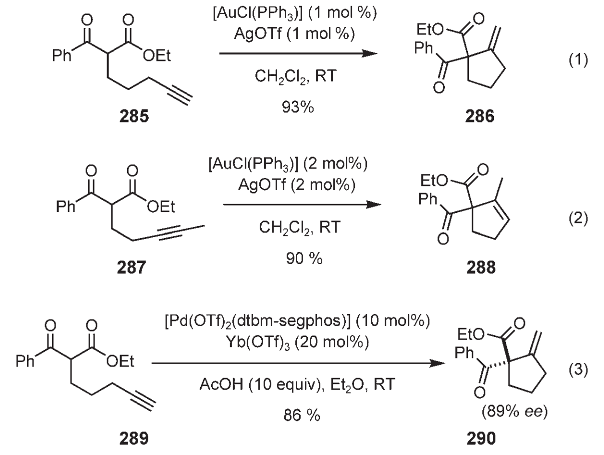
Scheme 55. Divergent synthesis of diyhdropyran and allenones through a shared intermediate.

metal loadings when modified Au^{III} complexes were employed.[97] This finding suggests that it may well be possible to reduce the loadings generally used in academic research by proper catalyst tuning, which has clear significance for potential applications.

The reaction of alkyl and silyl enol ethers with metal-activated alkynes or allenes mirrors those of electron-rich aryl groups and result in the formation of dienes or their hydrolyzed enone forms [Scheme 54, Eqs. (1) and (2)].[266–269] These reactions promise a significant degree of utility and an early example of their application in the synthesis of natural products is discussed in Section 5.4. Similarly, functionalized nitrogen heterocycles[270] and 1-aminoacridines[271] can be prepared by an analogous reaction of enamines [Scheme 54, Eqs. (3) and (4)].[272]

The associated acetals are formed from enol-alkyne cycloisomerization in the presence of an alcohol [Scheme 54, Eq. (5)],[267a] thus providing a convenient route to dihydropyrans from *O*-propargyl enol ethers [Scheme 54, Eq. (6)].[273] In the absence of an alcohol, these substrates undergo a propargyl–Claisen rearrangement, by extrusion of the catalyst from intermediate **282** (Scheme 55).[274–276]

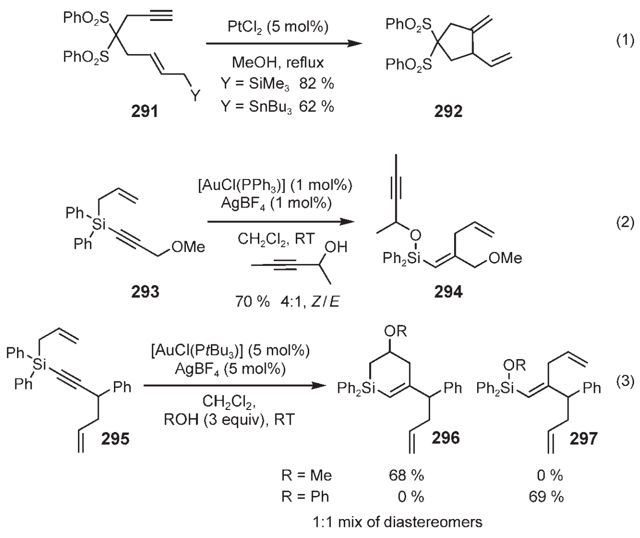
In a related manner, activated methylene compounds (malonates, β-keto-esters) act as nucleophiles toward gold-activated alkynes in a Conia–ene reaction, which has been shown to proceed through both *exo*- and *endo*-mode carbocyclizations (Scheme 56).[277,278] Although cationic gold–phosphane complexes effectively catalyze this transformation, preparatively useful levels of enantioselectivity have so far only been achieved with the aid of cationic palladium catalysts.[279] This again highlights the current lack of effective chiral platinum and gold complexes for the asymmetric activation of alkynes.[280] In mechanistic terms, there remains some ambiguity over the possible involvement of gold



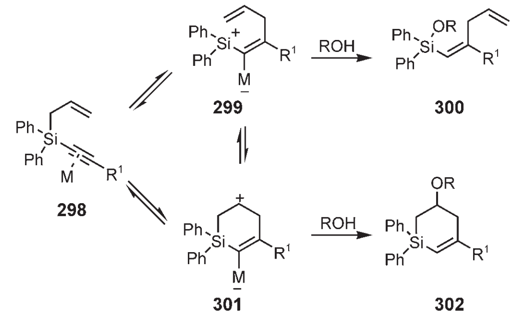
Scheme 56. Addition of activated methylene units across an alkyne.

enolates in this variant of the Conia–ene cycloisomerization.[281]

The inter- and intramolecular hydroallylation of alkynes can be achieved using allyl silanes or stannanes in the presence of a noble-metal catalyst and an alcohol additive (Scheme 57).[282,283] Incorporating a diphenylsilane unit into the tether results in a stereoselective synthesis of vinylsilanes when a secondary alcohol or phenol is employed.[284] The use of the more nucleophilic MeOH, however, leads to the addition of the alcohol to the carbocation intermediate **301**, thus affording the silacycle **302** (Scheme 58).[285]



Scheme 57. Gold- and platinum-catalyzed addition of allylsilanes and -stannanes across an alkyne.

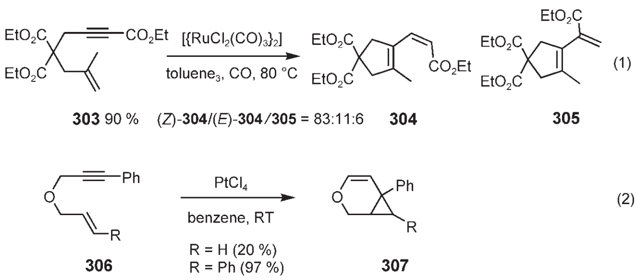


Scheme 58. Possible mechanism for the formation of vinylsilanes and silacycles.

4.3.6. *Enynes*

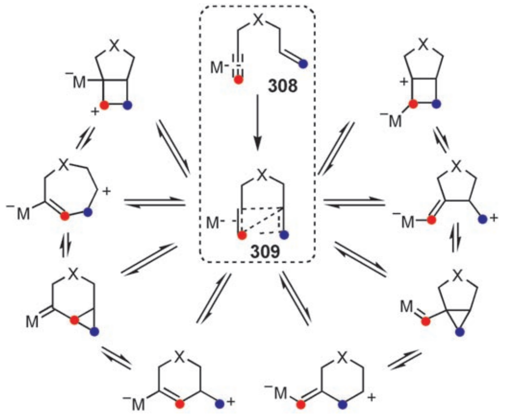
The reactivity of enynes in general arguably represents the most-widely studied substrate class in the field of cycloisomerization.[8a–d,286] Intense investigations over a number of decades have led to the development of numerous important transformations, which are distinguished examples of the concept of atom-economy in organic synthesis.[104] Despite this impressive heritage, a new journey of chemical discovery was embarked upon when platinum, and later gold catalysts were employed.[8]

Although the major field of application of palladium catalysts involved Alder–ene-type reactions,[286] early work by Trost et al. showed that enynes could also be transformed into 1,3-dienes by using palladacycles in a process formally resembling an enyne metathesis reaction.[287] This discovery was followed shortly after by Murai, Chatani, and co-workers who used ruthenium complexes and later platinum salts as the catalysts.[288,289] It soon became clear from the number of structurally interesting products obtained, however, that the mechanism of the latter systems diverged from that accepted for metathesis and Alder–ene-type reactions.[289] For example, the transformation of enyne **303** into two regioisomeric esters **304** and **305**[290] cannot be rationalized by either the Alder–ene or metathesis-type reactivity. Similarly, the unprecedented [4.1.0]bicyclic structures reported by Blum et al. at about the same time strongly suggested that an alternative explanation must be sought (Scheme 59).[289b]



Scheme 59. Examples of cycloisomerizations that diverged from the pathways known at the time of their discovery.

It was in the synthesis of the pyrrole alkoloid streptorubin (see Section 5.1) that a different explanation was proposed which was able to explain the range of products produced (Scheme 60).[291] In this investigation an analogy to the reactivity of nonclassical carbocations was drawn, taking up the motif that alkynes coordinated to Pt^{II} had been shown to have carbocation character. This analogy was enforced by the fact that some transformations of this type can also be bought about by ordinary Lewis acid or even Brønsted acid

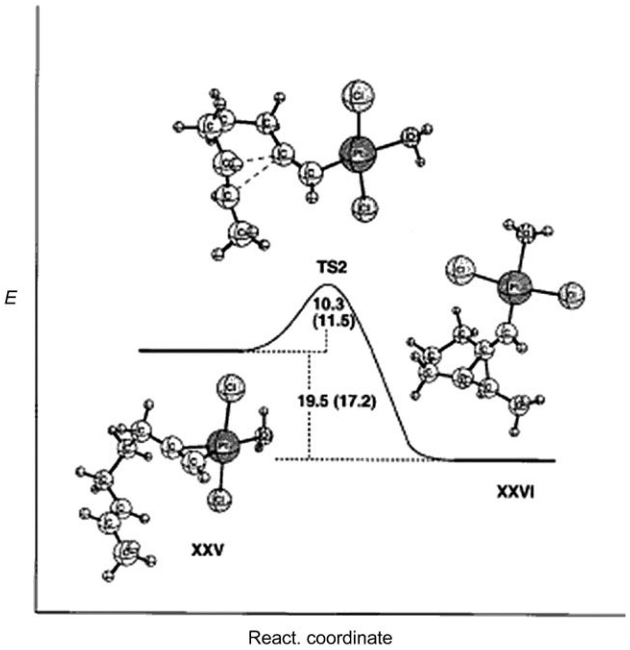


Scheme 60. Interpretation of metal-activated enynes in the sense of a "nonclassical" carbocation rendition.

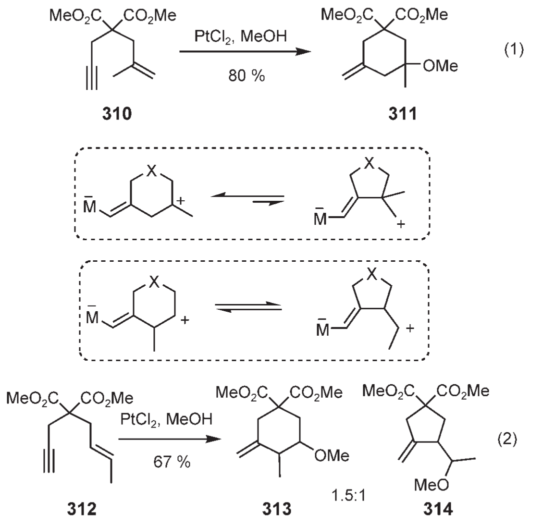
catalysis.[291] For the platinum case though, it was concluded that the reactive intermediate had substantial carbenoid character.[160,291] Simultaneous coordination of the alkene and the alkyne to the metal center is not required;[292] the route requires only that the alkyne be coordinated to initiate.[293] This proposal has since been widely adopted and confirmed by numerous computational and experimental studies which provide insights into the details of the reaction coordinate.[294–302] Whilst the carbenoid nature is perhaps the most apposite description for the reactive intermediates in the platinum series (Scheme 61), theoretical studies show that they should also be viewed as exhibiting considerable cationic character (compare also the quotations in Ref. [73]). This view reflects the "split personality" displayed in the structure of the late-transition-metal "carbenes" discussed in Section 2. The cationic nature appears to be more pronounced for the more-electrophilic gold species. It will be interesting to see whether the successful use of carbon monoxide in certain platinum-catalyzed transformations is due to an increase in the cationic nature of the intermediates.[147,151,166]

As this research field has developed, it is striking how the initial mechanistic hypothesis[160,291] has been able to account for more and more diverse transformations by extension of the underlying principles. This hypothesis seems to hold true for a fairly diverse range of carbophilic catalysts that were successfully screened, most notably based on Ga^{III},[303] In^{III},[304] Ir^{I},[305] and Ru[306,316] Since an up-to-date review on the exact pathways and structure of the putative intermediates is available,[8e] it suffices to point out here that in practice only the potential cationic resonance structures need be considered to allow the most likely outcome of these reactions to be predicted.

The reactions of substrates **310** and **312** in the presence of $PtCl_2$ and an alcohol illustrate this notion (Scheme 62). The reaction intermediates are trapped with methanol, with the position determined by the relative stabilization of the positive charge. With **310**, the alkoxylated product **311** results from the stabilization of the most substituted (tertiary) carbocation, whereas both of the tautomeric forms of activated substrate **312** are secondary cations. Therefore, it can be foreseen that substrate **312** is likely to react less regioselectively, as mirrored in the experimental results.[307–311]

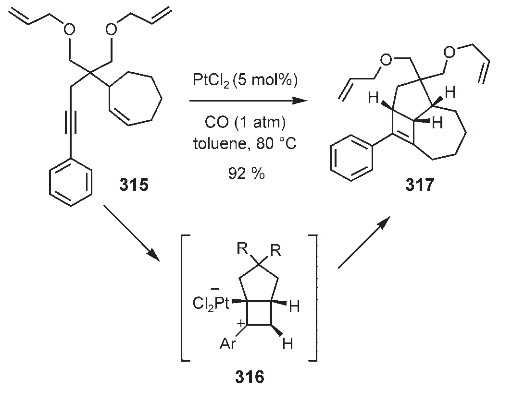


Scheme 61. Computed reaction coordinate for the cycloisomerization of an 1,6-enyne which nicely shows that the transformation commences through coordination of the alkyne to the electron-withdrawing Pt^{II} template to afford an electrophilic platinum carbenoid adjacent to a cyclopropyl ring. This particular arrangement imparts some cyclopropylmethyl↔homopropargyl↔cyclobutyl cation character upon this putative intermediate. The computed transition state illustrates the "1,2-dicarbene" character of the former alkyne moiety, as is evident from the incipient cyclopropanation process. *E* values are given in kcal mol^{-1}. Reprinted with permission. Copyright 2001, American Chemical Society.[294]

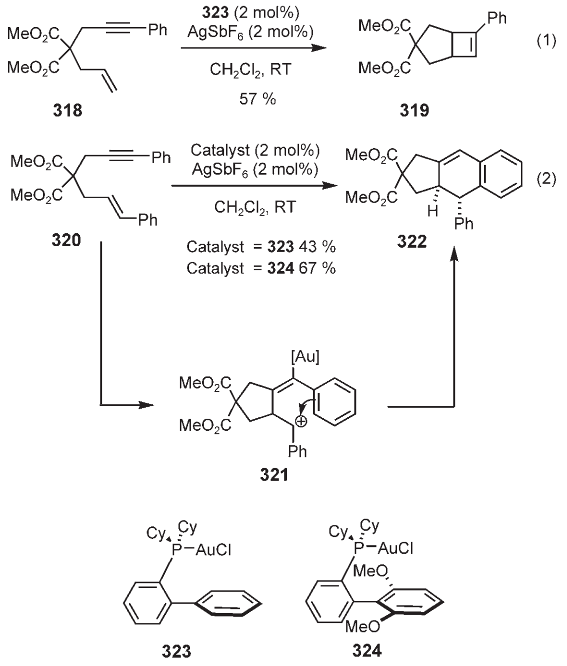


Scheme 62. Platinum-catalyzed alkoxycyclization of enynes to explore the likely stability of cationic intermediates and explain the regioselectivity of the reaction.

On equal grounds, deviation from the usual reaction pathway leading to the formation of 1,3-diene products is seen when arylated enynes are used as substrates.[166] Once again this could be predicted by considering the relative stabilities of the possible mesomeric forms of the nonclassical carbocation. The stabilizing effect of the aromatic substituent results in the putative cyclobutyl cation **316** becoming favored over the other conceivable resonance structures, and so an unfavorable pathway for simpler enynes now predominates (Scheme 63).[163] These compounds thus lead in one simple operation to highly strained cyclobutene derivatives that are difficult to obtain otherwise.[166,312–314] By enhancing the cationic character of the catalytic platinum species by coordination of π-acidic carbon monoxide, a gradual move from a carbenoid-dictated outcome towards a more polarized character is engendered, which has an impact upon both the yield and rate of the reaction.[166] This effect appears to move the reactivity of Pt^{II} towards that of the highly electron-deficient cationic gold systems that were found to effect the same and other closely related transformations (Scheme 64).[315]

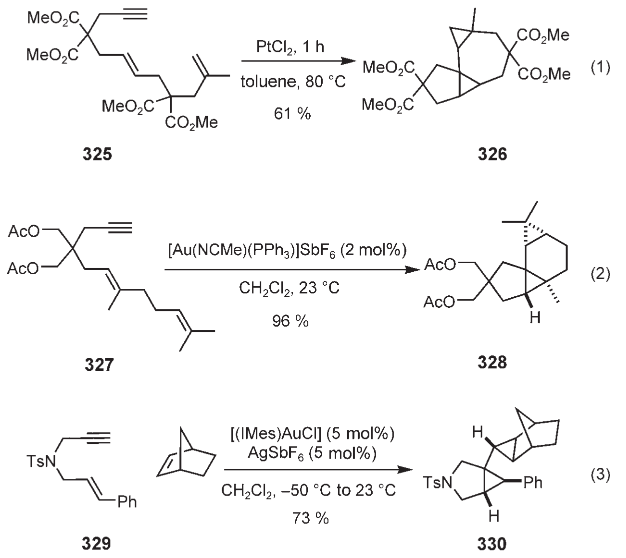


Scheme 63. Platinum-catalyzed cycloisomerization of arylated enynes.



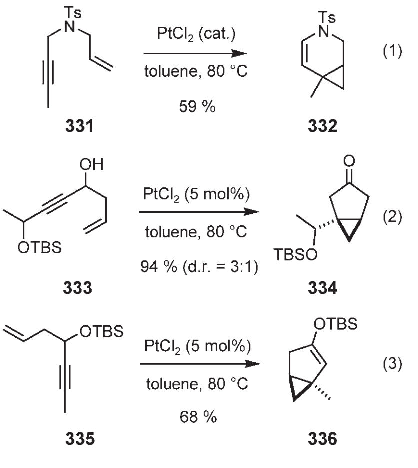
Scheme 64. Gold-catalyzed cycloisomerization of arylated enynes.

Whilst the previous examples invoke the "cationic rendition" of the key reactive intermediates in platinum- and gold-catalyzed enyne cycloisomerizations, their complementary "carbenoid" nature is particularly evident from polycyclization reactions. A representative example demonstrating two intramolecular cyclopropanations with platinum is depicted in Scheme 65.[316] Other π-acidic catalysts, most notably cationic gold species[317] and $[\{RuCl_2(CO)_3\}_2]$ are equally effective, and extensions to intermolecular systems have recently been reported.[318]



Scheme 65. Involvement of a triple bond in two vicinal cyclopropanations, illustrating the "carbenoid" nature of alkynes activated by noble-metal π acids. IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.

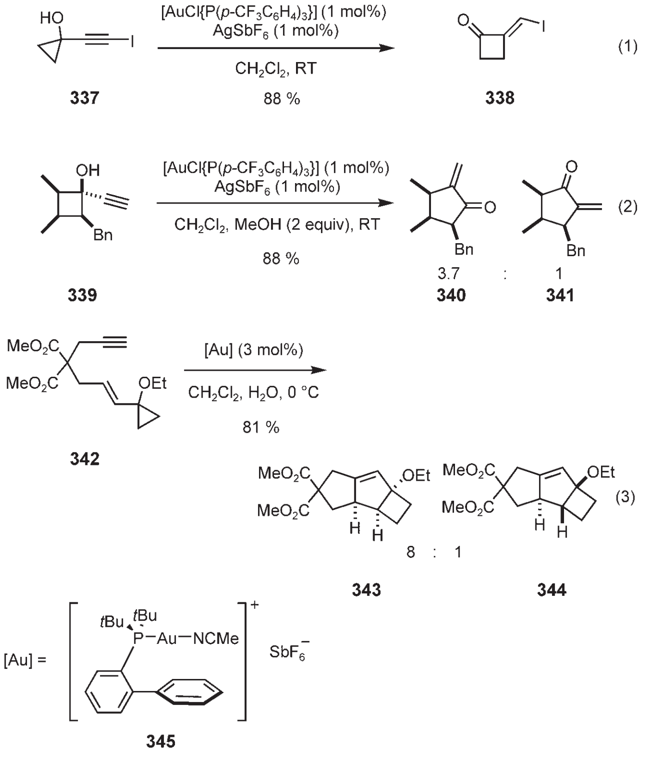
Further support for considering metal-activated alkynes as "1,2-biscarbene synthons" comes from the reactions of 1,5- and 1,6-enynes bearing heteroatoms at the propargylic position (Scheme 66). In both cases the 1,2-hydrogen shift and metal elimination that terminates the reaction is charac-



Scheme 66. Cycloisomerization of enynes bearing heteroatoms at the propargylic position.

teristic of metal–carbene chemistry,[222,223a,319] as proven by deuterium labeling experiments. The product structures emanating from these reactions are common in nature. It is significant to note that the cyclic ketones derived from the unprotected enynols are complementary in regiochemical terms to those obtained from the very same substrates in acetylated form [compare Scheme 42, Eq. (1)].[222,223]

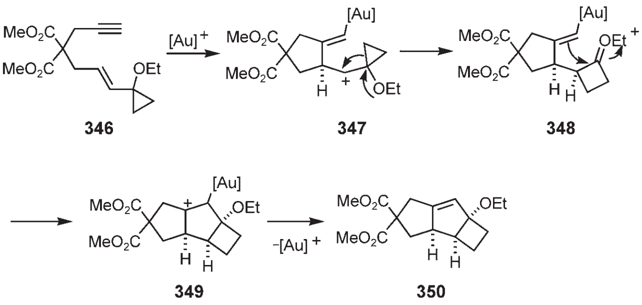
The heteroatom-assisted 1,2-shift to an adjacent metal-activated alkyne can be uncoupled from the cycloisomerization manifold as witnessed by the highly successful ring expansion of cyclopropanols and cyclobutanols. The transformation of iodoalkyne **337** illustrates that no conventional oxidative insertion/reductive elimination cycle interferes (Scheme 67).[320] This type of reactivity has been elegantly combined with enyne cycloisomerization to give complex tricyclic frameworks (**350**, Scheme 68) that resemble the core structures of various elaborate terpenes such as fascicularone B.[309b]



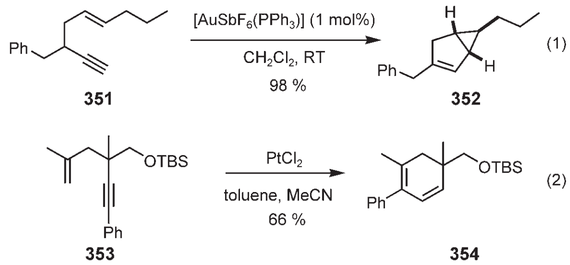
Scheme 67. Cycloisomerization involving heteroatom-driven ring expansions.

The same process occurs with the more constrained 1,5-enyne systems even in the absence of the propargylic heteroatom, as a 1,2-hydride or 1,2-alkyl shift can outperform the limited alternative processes in stabilizing the intermediates (Scheme 69).[321,322]

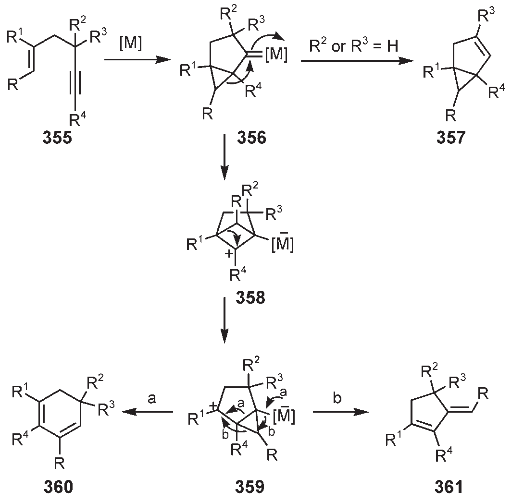
When the newly formed cyclopropyl unit participates in these processes [Scheme 69, Eq. (2)], a [2.1.1]bicyclic intermediate of type **358** is formed and a subsequent alkyl shift/ring expansion process is triggered (**358**→**360**, Scheme 70), which ultimately yields a highly functionalized cyclohexadiene.[323] The cyclopentenes observed in the cycloisomerization of some 1,5-enynes also derive from this 1,2-alkyl shift by scission of an alternative bond during the ring opening of the cyclopropyl unit (**359**→**361**).[324] Similar approaches were used to construct aromatic rings from related 1,6-enynes that contain an olefin between the reacting alkene units.[325]



Scheme 68. Proposed mechanism for the cycloisomerization cascade.

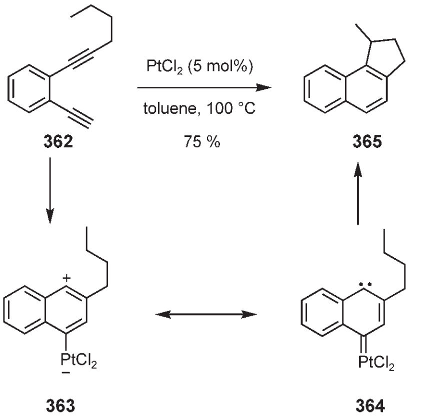


Scheme 69. Cycloisomerization of 1,5-enynes involving a hydride [Eq. (1)] or alkyl shift [Eq. (2)].



Scheme 70. Mechanistic diversity in the cycloisomerization of 1,5-enynes.

1,5-Diyne units linked by an aryl or alkenyl spacer undergo an interesting platinum-catalyzed cyclization, the fused polycyclic products of which once again support the formation of a metal–carbenoid intermediate. Initial cyclization results in the biscarbenoid species capable of C–H insertion into a tethered alkyl unit (Scheme 71).[326]



Scheme 71. Platinum-catalyzed bicyclization incorporating C–H insertion.

4.4. Miscellaneous Reactions

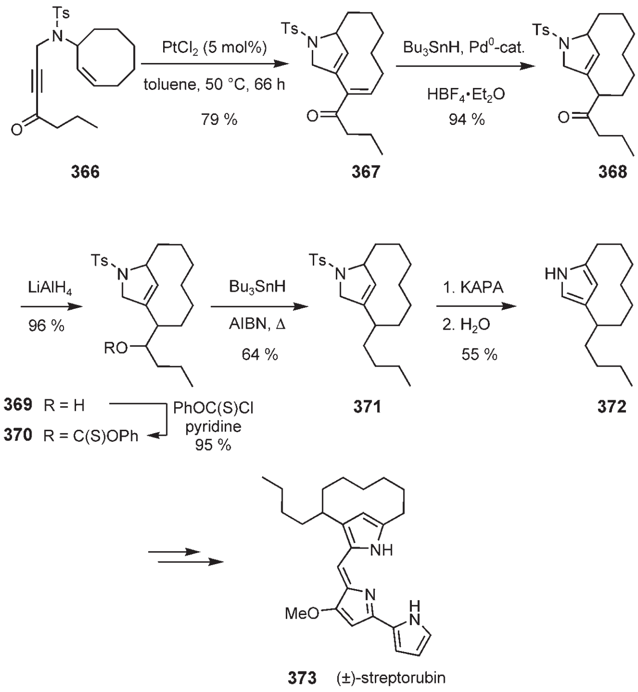
Further interesting transformations initiated by metal-activated alkynes include various reactions that result in the formation of polycyclic aromatic skeletons[327–332] as well as Nicholas-type propargylic substitution by a selection of carbon and heteronucleophiles.[93d,333] Isoxazoles may be synthesized from alkynes and nitric acid.[334] Yet another way to exploit the peculiarities of Pt^{II} takes advantage of its propensity to form platinate complexes. This approach has led to a "halophilic activation" concept manifested in Hosomi–Sakurai reactions, which are catalytic and at the same time stereodivergent.[335]

5. Selected Applications in the Total Synthesis of Bioactive Natural Products

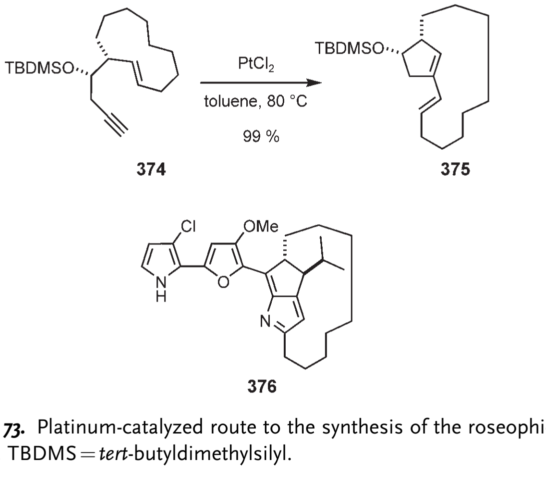
The simplicity, mild conditions, and functional-group tolerance associated with platinum catalysis, and therefore its suitability for use within a natural product synthesis program were recognized at an early stage. The initial application was in the synthesis of streptorubin. This application is particularly noteworthy, as it led to the elucidation of key insights into the mechanism (see Section 4.3.6) and formed the basis from which the field has continued to evolve.[291] Subsequently, a diverse range of transformations based on the catalytic carbophilic activation of π systems have started to be used in the syntheses of natural products, representative examples of which are discussed below.

5.1. (±)-Streptorubin, Roseophilin, and (±)-Salviasperanol

The synthesis of the antibiotics (±)-streptorubin and (±)-metacycloprodigiosin centered around a platinum-catalyzed cycloisomerization that was used to construct the highly strained bicyclic cores.[291,336] For streptorubin (**373**), cyclization of the cyclooctene derivative **366** with PtCl$_2$ afforded the bridged bicyclic structure **367** in excellent yield (Scheme 72). A range of platinum salts were shown to be capable of inducing this transformation (PtCl$_2$, PtBr$_2$, PtCl$_4$, PtBr$_4$), and even conventional Lewis and Brønsted acids (ZnCl$_2$, TiCl$_4$, AlCl$_3$, SnCl$_4$, BF$_3$·Et$_2$O, HBF$_4$) can be used, but are somewhat less effective. A series of by-products could be isolated when the cycloisomerization was performed on a larger scale. These two factors led to the proposal that reactions of this type may involve intermediates with some "nonclassical carbocation" character, which is masked in the form of an electrophilic "carbenoid" if platinum salts are used as catalysts.[160,291] Subsequent reduction of the enone unit followed by a deoxygenation, elimination, and rearrangement strategy afforded the *meta*-bridged pyrrole core of **372** in nine steps from cyclooctene. This building block was then converted into the antibiotic **373** by following literature methods.



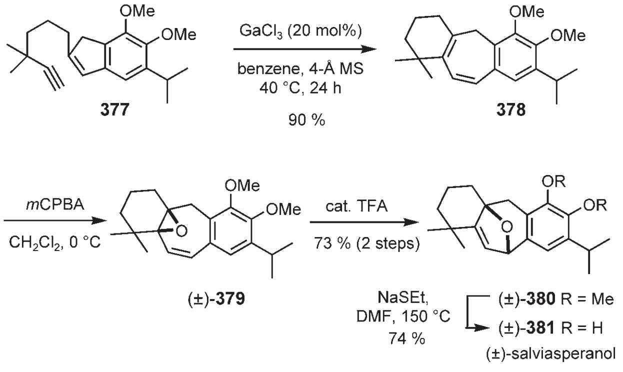
Scheme 72. Synthesis of (±)-streptorubin by a platinum-catalyzed cycloisomerization. AIBN = azobisisobutyronitrile, KAPA = potassium salt of 1,3-diaminopropane.



Scheme 73. Platinum-catalyzed route to the synthesis of the roseophilin core. TBDMS = *tert*-butyldimethylsilyl.

The utility of platinum-mediated cycloisomerizations was later further underscored by an asymmetric synthesis of the roseophilin core **375** by following a similar logic. The formal synthesis of roseophilin (**376**) was completed by elaborating **375** into an advanced intermediate previously used in a racemic synthesis of the cytotoxic natural product (Scheme 73).[337,338]

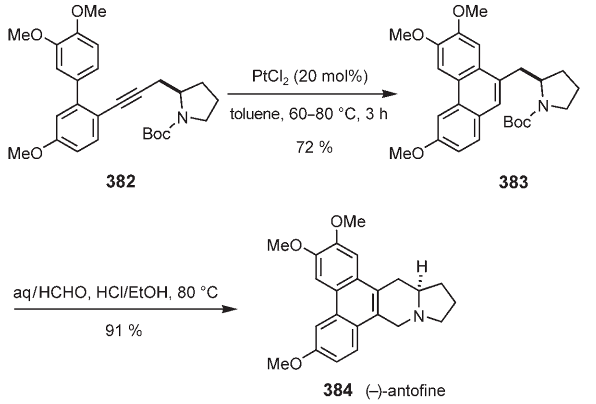
The $GaCl_3$-catalyzed cyclization of enyne **377** in the synthesis of (±)-salviasperanol (**381**) further highlights the fact that whilst platinum and gold catalysts are generally privileged for this area, other metal species are capable of mediating related transformations and may be more suitable in particular cases (Scheme 74).[339]



Scheme 74. Synthesis of (±)-salviasperanol by a $GaCl_3$-catalyzed enyne cycloisomerization. *m*CPBA = *meta*-chloroperbenzoic acid.

5.2. (−)-Antofine

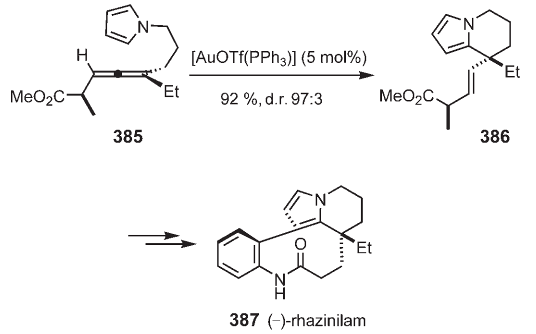
The synthesis of various tylophora alkaloids was recently realized by an efficient and flexible route based around an intramolecular alkyne hydroarylation.[340] The modular nature of the cyclization precursors, accessed by palladium-catalyzed coupling reactions, allows for ready application of the same retrosynthetic strategy to related natural products or analogues by the systematic modification of their basic skeletons. In the case of (−)-antofine, the polysubstituted *o*-alkynylbiaryl **382** undergoes cyclization with $PtCl_2$ in toluene to afford the fully functionalized phenanthrene core **383** in good yield. A one-pot deprotection/Pictet–Spengler reaction results in the natural product **384** (Scheme 75). This strategy was also employed in the synthesis of the related alkaloids (±)-cryptopleurin, (−)-tylophorine, and (−)-ficuspetine C.[340] Whilst $PtCl_2$ proved the optimum metal salt in this case, the synthesis of the aporphine alkaloid 7,7′-bisdehydro-*O*-methylisopiline, centered on an $InCl_3$-mediated hydroarylation,[135,260] further demonstrates that a variety of metal species are able to effect these types of transformations.[247]



Scheme 75. Synthesis of (−)-antofine by a platinum-catalyzed hydroarylation of an alkyne.

5.3. (−)-Rhazinilam

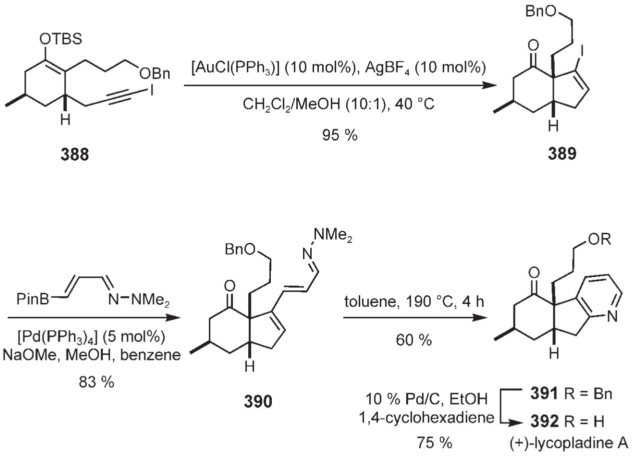
The hydroarylation of allenes similarly represents an attractive tool for target-oriented synthesis. In a recent approach to (−)-rhazinilam (**387**), the gold-catalyzed reaction of an enantioenriched allene **385** and a tethered pyrrole ring leads to the construction of the key tetrahydroindolizidine structure **386**.[341] The introduction of the quaternary carbon center proceeds with high diastereoselectivity by efficient transfer of chiral information from the allene (Scheme 76). Whilst the cationic gold complex $[Au(OTf)(PPh_3)]$ was shown to be the most efficient, simpler cationic gold salts were also effective catalysts.



Scheme 76. Diastereoselective synthesis of (−)-rhazinilam by a gold-catalyzed hydroarylation of an allene.

5.4. (+)-Lycopladine A

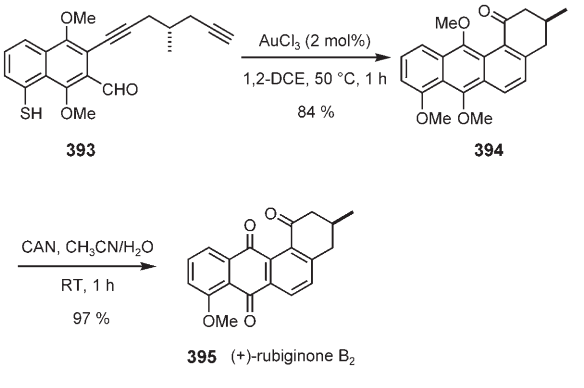
A quaternary carbon atom was similarly prepared during the gold-catalyzed construction of the hydrindanone core of the cytotoxic alkaloid (+)-lycopladine A (**392**).[269] The use of a silyl enol ether as the nucleophile to the alkyne, activated by the π-acidic gold catalyst, defines the α-stereocenter of the fused ring junction in **389** (Scheme 77). The stereoselective formation of a vinyl iodide from the alkynyl iodide in the same step highlights the orthogonal nature of these catalysts to standard "redox-type" transition-metal-catalyst systems and introduces the synthetic handle central to the completion of the synthesis.



Scheme 77. Synthesis of (+)-lycopladine A by a gold-catalyzed formation of an α-keto quaternary stereocenter.

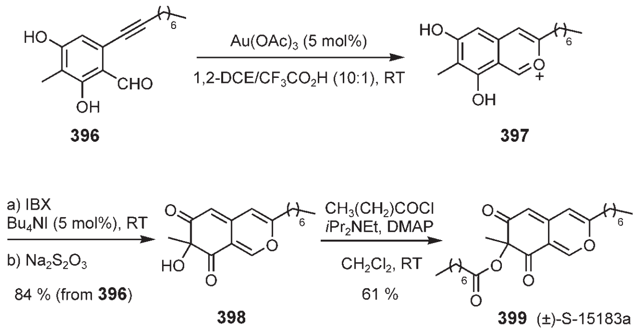
5.5. (+)-Rubiginone B$_2$

The AuCl$_3$-catalyzed intramolecular formal [4+2] benzannulation of *o*-alkynylbenzaldehydes was utilized as the key step in the synthesis of (+)-rubiginone B$_2$ (**395**), a member of the angucyclinone family of natural products (Scheme 78).[342] After the efficient formation of the tetracyclic core, oxidation of the dihydrotetraphenone derivative **394** then yields the target natural product.



Scheme 78. Synthesis of (+)-rubiginone B$_2$ by an AuCl$_3$-catalyzed intramolecular [4+2] benzannulation. CAN = cerium ammonium nitrate.

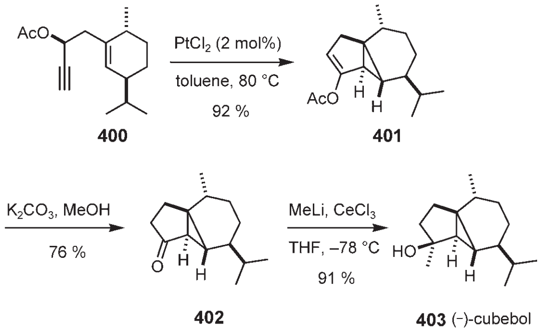
Further applications of *o*-alkynylated benzaldehyde and aryl ketone cycloisomerizations have been reported.[343,344] One example is the clever synthesis of a range of azaphilones by isolation of the oxonium species **397** when the unprotected aldehyde **396** is treated with a gold catalyst in the presence of trifluoroacetic acid (Scheme 79).[345] Subsequent oxidation of **397** with IBX under phase-transfer conditions followed by esterification completed the synthesis of (±)-S-15183a (**399**), which acts as a potent sphingosine kinase inhibitor.



Scheme 79. Synthesis of (±)-azaphilone S-15183a by a gold-catalyzed cyclization reaction. DMAP = *N*,*N*-4-dimethylaminopyridine, IBX = 2-iodoxybenzoic acid.

5.6. (−)-Cubebol and (±)-Sabinol

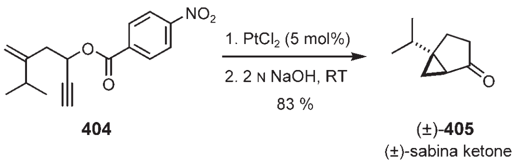
The power of the Ohloff-type reaction (see Section 4.3.4) to engender a significant increase in molecular complexity suggests a role for this process in the synthesis of natural products.[212,213,217,218,222] As hydrolysis of the resulting enol acetate yields a cyclopropyl carbonyl derivative, the propargylic acetate moiety can be considered an α-diazoketone equivalent, and thus this transformation represents an attractive and less hazardous synthetic equivalent to classical diazocarbonyl chemistry.[217] The nature of this reaction was further elucidated in the synthesis of members of the cubebane family of tricyclic sesquiterpenes.[212] The cyclization of propargylic acetate (*S*)-**400**, derived from *R*-(−)-carvone, with PtCl$_2$ (2 mol %) proceeded smoothly to give the tricyclic core of the cubebanes in excellent yield (Scheme 80).



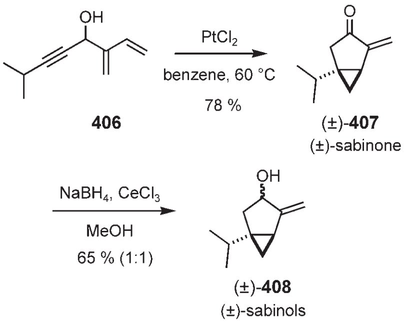
Scheme 80. Synthesis of (−)-cubebol by a platinum-catalyzed Ohloff-type cycloisomerization.

Hydrolysis affords the key intermediate from which (−)-β-cubebene, (−)-cubebol, and (−)-α-cubebene are prepared by Wittig methylenation, addition of a methyl–cerium reagent,or enol triflate formation and iron-catalyzed cross-coupling, respectively.[212] The stereoselective cyclization of (*S*)-**400** was, however, not mirrored by that of (*R*)-**400**, which gave a mixture of diastereomers. This outcome illustrates that the configuration at the stereogenic center carrying the acetate unit translates into the stereochemistry of the products, so that this position cannot become planar before cyclopropanation occurs (see Section 4.3.4).[212,213]

The related 1,5-enyne variant has been used in a concise synthesis of (±)-sabina ketone (**405**, Scheme 81),[223a] whereas the structurally similar sabinol terpenes (±)-**408** were prepared by the cyclization of enynol substrates (Scheme 82).[222]



Scheme 81. Platinum-catalyzed synthesis of (±)-sabina ketone.



Scheme 82. Synthesis of (±)-sabinone and (±)-sabinols.

6. Conclusions

The rapidly expanding fields of application highlight the enormous potential of platinum and gold catalysts for synthetic chemistry. It is evident that the basic guiding principles pertinent to π activation and the ensuing transformations have been condensed into a concise, comprehensive, and easy to use model. With the help of this model it is possible to navigate through the diverse structural space encompassed by this field.

Although the underlying concepts are fairly well established, subtleties in the behavior of individual substrates and/or catalysts remain to be fully elucidated. Whilst gold and platinum catalysts are similarly efficacious in many cases, in other examples there is a clear preference for one over the other. This finding ensures that the choice of catalyst must remain somewhat empirical at this time, although certain trends are slowly surfacing as more experimental and theoretical studies are performed.

Whilst a growing number of research groups have embraced this mode of catalysis over the last decade, as evidenced by the sharp increase in work published in this area, there remains some distance to go before it is truly adopted by the wider chemical community. However, historic precedence from organopalladium chemistry, most notably cross-coupling, is highly encouraging in this regard. If the issue of the yet underdeveloped area of asymmetric activation of π ligands, notably alkynes, can be successfully addressed, then the potential of the process will almost certainly ensure its widespread uptake.

We sincerely thank all co-workers involved in the noble-metal-catalysis project for their invaluable intellectual and experimental contributions to this fascinating field; their names appear in the references. We are also indebted to Dr. C. W. Lehmann and J. Rust for their help with the CCDC searches and the preparation of the graphics of the crystal structures depicted in this Review. Moreover, the substantial and constant financial support by the Max-Planck Society and the Fonds der Chemischen Industrie is gratefully acknowledged, as is the generous gift of various noble-metal salts from Umicore AG & CoKG, Hanau.

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[33] The mechanism of nucleophilic attack to a coordinated olefin or alkyne has been the subject of much controversy, not least in the context of elucidating the mechanism of the Wacker oxidation. Some of the ambiguity arises by the possibility that the nucleophile may first attack the metal center rather than the ligand, followed by a migratory rearrangement to the π system. Such a mechanism implies a *cis* addition, which has been proven experimentally for certain cases. However, since the currently available information shows that $\mathrm{Pt^{II}}$- and $\mathrm{Au^{I}}$-catalyzed addition reactions proceed by *trans* addition, this alternative pathway is not discussed any further in this Review.

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