A Reactivity-Driven Approach to the Discovery and Development of Gold-Catalyzed Organic Reactions

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Abstract: Approaches to research in organic chemistry are as numerous as the reactions they describe. In this account, we describe our reactivity-based approach. Using our work in the area of gold catalysis as a background, we discuss how a focus on reaction mechanism and reactivity paradigms can lead to the rapid discovery of new synthetic tools.

Key words: gold catalysis, enantioselective catalysis, cycloisomerizations, alkynes, allenes

1 Introduction

'Our scientific theories do not, as a rule, spring full-armed from the brow of their creator. They are subject to slow and gradual growth…' – Professor Gilbert N. Lewis writing in *Science* in 1909.[1]

At the time, Lewis was speaking of ionic theory, but his words resonate throughout chemistry. To an organic chemist, his words speak of the difficulty associated with the prediction of reactivity. In answer to this challenge, numerous approaches to chemical research have been devised. We have categorized these research styles into four methods that we perceive to be the most prevalent (Table 1). Historically, chemists have been motivated by problems in total synthesis or by a desire to develop reactions of broad utility. With the total synthesis of natural or unnatural compounds as the driving force, method development is typically focused on the efficient synthesis of a certain chemical motif.[2] In contrast, bond-based methodology programs focus on the transformations of specific chemical bonds.[3] A third approach employs high-throughput screening to identify reaction conditions that will allow a more general type of transformation.[4] We have undertaken an alternative approach, one that we describe as reactivity-based. Instead of focusing on specific reactions, we concentrate our efforts on understanding and expanding specific reactivity paradigms.[5]

Table 1 Approaches to Methodology Research in Organic Chemistry

Approach	Hypothesis
motif-based	New methods for the synthesis of a specific chemical motif are needed.
bond-based	The transformation of one specific set of chemical bonds into another would be a useful synthetic transformation.
high-throughput screening	High-throughput screening of reaction conditions will lead to the discovery of new reactions.
reactivity-based	Understanding and expanding reactivity paradigms will lead to the discovery of new reactions.

We do not argue that one of the approaches to reaction discovery described above is superior to the others. On the contrary, we would claim that each approach is important in and of itself, and that each complements the next. Nonetheless, this account will highlight our reactivity-based approach, using gold catalysis as a backdrop for this discussion.

We typically begin our research with a fragment of theoretical knowledge, commonly a proposed reaction mechanism or intermediate. Initially, this background was derived from the literature, although, as our research program has developed, we have frequently been able to use our own proposed mechanisms. From this theoretical

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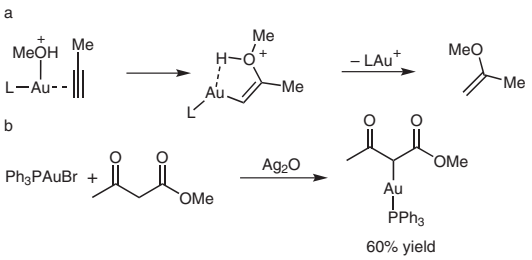
knowledge, we seek to extract a hypothesis that can be subsequently tested in the laboratory. After designing and executing the appropriate test, conclusions are drawn that can either contradict, support, or expand the initial theory. While it is not always the case, progress through this cycle frequently results in the discovery of new reactivity paradigms.

2 Addition Reactions

2.1 The Conia-Ene Reaction

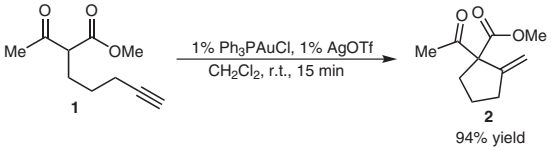
We were initially attracted to the area of gold catalysis by the pioneering report of Teles and co-workers showing that cationic gold(I) complexes can activate alkynes towards nucleophilic attack from alcoholic nucleophiles.[6] Based on a series of calculations, the authors proposed a *cis*-addition mechanism in which the gold(I) catalyst is coordinated to both the alcohol and the alkyne (Scheme 1, part a). A subsequent survey of the literature led us to a report from 1974 describing the stoichiometric auration of β-keto esters (Scheme 1, part b).[7] Combining this report with Teles and co-workers' proposed mechanism led to the simple hypothesis that gold(I) complexes might be employed as catalysts for the addition of β-keto esters to alkynes, and this prompted us to investigate such gold-catalyzed additions.

To test this hypothesis, we designed a simple substrate **1** containing an alkyne tethered with a β-keto ester



Scheme 1 (a) The mechanism, which has subsequently been disproved, originally proposed by Teles and co-workers for the addition of alcohols to alkynes mediated by gold(I) complexes; (b) a reaction reported in 1974 showing the carboauration of β-keto esters

(Equation 1).[8] To our delight, gold(I) complex $Ph_3PAuOTf$ (formed in situ from Ph_3PAuCl and AgOTf) catalyzed the desired carbon–carbon bond forming event rapidly at room temperature. Thus, by testing a simple hypothesis, we had discovered a mild method for effecting carbon–carbon bond formation.[9,10] Furthermore, we were able to contribute to the database of knowledge surrounding gold catalysis.[11]



Equation 1

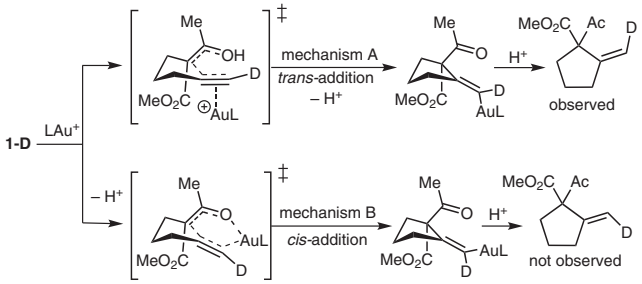
Biographical Sketches

Nathan Shapiro was born and raised in Milwaukee, Wisconsin. After graduating from Shorewood High School, he moved to Cambridge to attend the Massachusetts Institute of Technology. In 2005, he graduated with a B.S. in chemistry and biology, and moved to the University of California, Berkeley, where he joined the laboratory of Professor F. Dean Toste. As a graduate student his research has focused on the development of new gold-catalyzed methodologies and understanding their mechanistic subtleties. Upon completion of his doctoral studies, he will be joining Professor George M. Whitesides at Harvard University as an NIH postdoctoral fellow.

Dean Toste was born in Terceira, Azores, Portugal, but soon moved to Toronto, Canada. He received his B.Sc. and M.Sc. degrees in chemistry from the University of Toronto, where he worked with Professor Ian W. J. Still. In 1995, he began his doctoral studies at Stanford University, USA, under the direction of Professor Barry M. Trost. Following postdoctoral studies with Professor Robert H. Grubbs at Caltech, he joined the faculty at the University of California, Berkeley, in July of 2002, and was promoted to Associate Professor in 2006. Current research in his group is aimed towards the design of metal catalysts and metal-catalyzed reactions and the application of these methods to chemical synthesis. He has received numerous awards including the Camille and Henry Dreyfus New Faculty Award (2002), the Alfred P. Sloan Research Fellowship (2005), the National Science Foundation CAREER Award (2005), the Cope Scholar Award (2006), and the E. J. Corey Award (2008) from the American Chemical Society, the BASF Catalysis Award (2007), the OMCOS Award (2007) from IUPAC, and the Thieme–IUPAC Prize (2008).

This discovery also allowed us to postulate additional hypotheses. One of the simplest was that this reaction should be applicable to internal alkynes. To our surprise, these substrates were mostly unreactive even under more-forcing conditions. This contradiction to our hypothesis prompted us to test the validity of the *cis*-addition mechanism that had been proposed by Teles and co-workers.

When deuterium-labeled alkyne **1-D** was subjected to the reaction conditions, the deuterium was selectively incorporated *syn* to the keto ester (Scheme 2). This result supports a mechanism involving *trans*-addition of the keto ester to a pendant gold-activated alkyne.[12] Furthermore, this mechanism provides an explanation for the poor reactivity of internal alkynes, which would experience severe 1,3-allylic strain in the cyclization transition state. Further support for this mechanism, including the isolation and characterization of related vinylgold intermediates, has accumulated.[13]

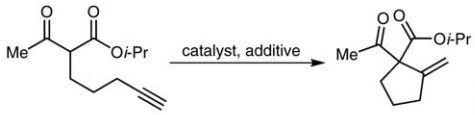


Scheme 2 Mechanistic proposals for the gold(I)-catalyzed Conia-ene reaction; experimental results support a mechanism involving *trans*-addition

Our initial attempts to render this reaction enantioselective were frustrated by the consequences of a *trans*-addition mechanism. Employing chiral phosphinegold(I) complexes in the Conia-ene reaction induced very little enantioselectivity (Scheme 3, part a). This is not too surprising; gold(I) complexes typically adopt a two-coordinate linear geometry, which places the prochiral nucleophile more than 5 Å from the chiral phosphine in the cyclization transition state. This can be seen in the X-ray crystal structure of (*R*)-BINAP(AuCl)$_2$ [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; Scheme 3, part b], where the distance between the phosphine and the chloride ligands is 4.58 Å. In the catalytic reaction, the alkyne of the substrate would replace the chloride, and the prochiral keto ester would approach the alkyne from a position *trans* to the gold atom (as in Scheme 2, mechanism A).

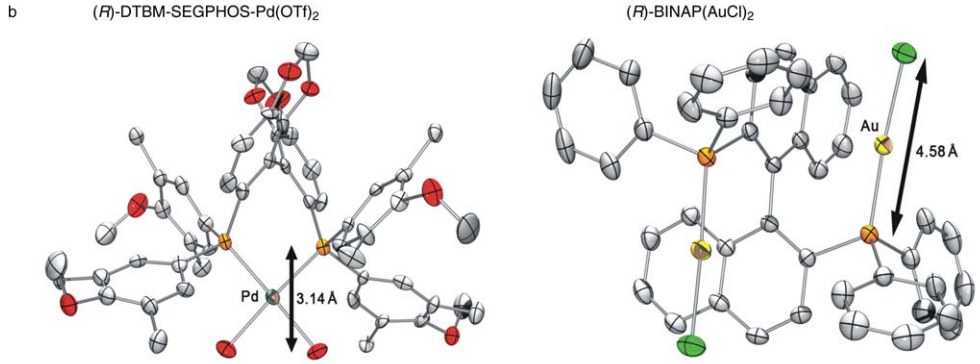
To render the Conia-ene reaction enantioselective, we surveyed other π-acidic metal complexes that are not confined to a linear geometry. While chiral copper(II), nickel(II), and platinum(II) complexes gave poor selectivity, we were satisfied to find that the square-planar BINAP-Pd(OTf)$_2$ complex provided the desired product with moderate enantiomeric excess (68% ee), albeit in low yield (Scheme 3 part a). Further investigation revealed that the yield could be increased through the addition of Brønsted and Lewis acids,[14] while the enantioselectivity was improved by replacing (*R*)-BINAP with (*R*)-DTBM-SEGPHOS (up to 89% ee). For comparison, the X-ray crystal structure of (*R*)-DTBM-SEGPHOS-Pd(OTf)$_2$ is illustrated in Scheme 3, part b. In this case, the distance between the phosphine and substrate-binding sites is decreased to 3.14 Å [versus 4.58 Å for the gold(I) catalyst]. Following this, we applied the principles we had learned in developing the gold(I)- and palladium(II)-catalyzed Conia-ene reactions to transformations employing silyl enol ethers as nucleophiles.[15] This methodology was subsequently applied to the total synthesis of (+)-lycopladine A and (+)-fawcettimine.[16]

a



Catalyst	Additive	Yield (%)	ee (%)
(*R*)-BINAP(AuOTf)$_2$	–	85	0
(*R*)-BINAP-Pd(OTf)$_2$	–	low	68
(*R*)-DTBM-SEGPHOS-Pd(OTf)$_2$	–	18	81
(*R*)-DTBM-SEGPHOS-Pd(OTf)$_2$	10 equiv AcOH, 20% Yb(OTf)$_3$	84	89

b



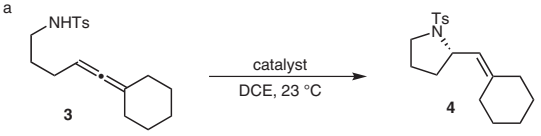
Scheme 3 Transition-metal-catalyzed enantioselective Conia-ene reaction; (a) effect of the transition metal and ligand on enantioselectivity; (b) a comparison of (*R*)-DTBM-SEGPHOS-Pd(OTf)$_2$ and (*R*)-BINAP(AuCl)$_2$ complexes showing the effect of metal geometry on the proximity of the ligand and substrate (for clarity, *tert*-butyl groups and triflate counteranions in the palladium complex are not fully shown)

2.2 Asymmetric Hydroamination

Despite our success using palladium(II) catalysts to render the Conia-ene reaction enantioselective, we soon returned to the challenge of asymmetric gold catalysis. We quickly realized that the requirement for a prochiral nucleophile in enantioselective additions to alkynes greatly limits the scope of possible transformations. To overcome this problem, we have subsequently employed a number of strategies.

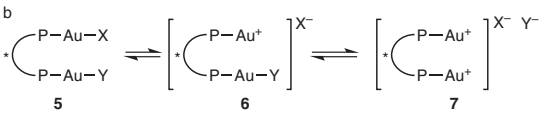
The first of these strategies involves the gold-catalyzed addition of various nucleophiles to achiral allenes, which are prochiral electrophiles.[17] In the hydroamination of allene **3**, we were initially frustrated by variable enantioselectivities (1–51% ee) when (*R*)-xylyl-BINAP(AuCl)$_2$ was employed as the precatalyst (Scheme 4, part a).[18] After some experimentation, we found that the amount of silver(I) tetrafluoroborate ($AgBF_4$) was crucial in determining the enantioselectivity of the transformation, with lower equivalents of silver relative to gold providing higher enantiomeric excesses. This suggested that the monocationic species **6** was providing the enantioenriched product, while the dicationic species **7** was providing the product with lower enantiocontrol (Scheme 4, part b). The ^{31}P NMR spectroscopic analysis of a solution containing a 2:1 mixture of (*R*)-xylyl-BINAP(AuCl)$_2$ and $AgBF_4$ revealed that all three species **5**–**7** are present. By replacing the non-coordinating tetrafluoroborate counteranion with a more-coordinating benzoate anion (OBz), we were able to shift the equilibrium towards **5** and **6**, resulting in a large increase in enantioselectivity (98% ee, Scheme 4, part a). Ultimately, the benzoate anion proved to be too coordinating, providing only low yields of the product, even after extended reaction times. Fortunately, the reactivity could be increased, without any decrease in selectivity, by switching to the 4-nitrobenzoate (OPNB) counteranion. The resulting gold–OPNB complexes proved to be bench-stable white solids, the direct use of which further improved the yield of the reaction (88%).

a



Catalyst	Time (h)	Yield (%)	ee (%)
3% (*R*)-xylyl-BINAP(AuCl)$_2$ + 6% $AgBF_4$	0.5	82	1
3% (*R*)-xylyl-BINAP(AuCl)$_2$ + 3% $AgBF_4$	0.5	81	51
3% (*R*)-xylyl-BINAP(AuCl)$_2$ + 6% AgOBz	24	27	98
3% (*R*)-xylyl-BINAP(AuCl)$_2$ + 6% AgOPNB	24	76	98
3% (*R*)-xylyl-BINAP(AuOPNB)$_2$	17	88	98

b



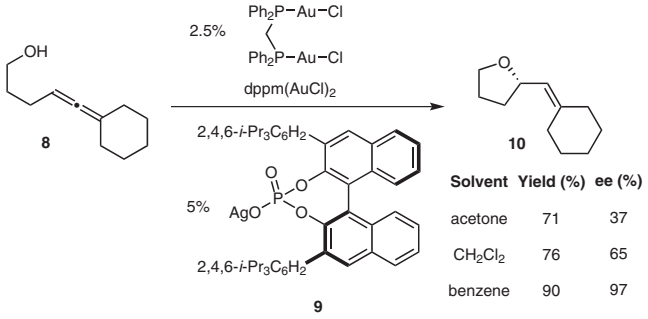
Scheme 4 (a) Development of a gold(I)-catalyzed asymmetric hydroamination reaction; (b) a possible rationale for the observed counteranion effects

2.3 Chiral Counteranions

We initially hypothesized that gold(I) benzoates provide increased enantioselectivity in the formation of cyclic product **4** by preventing the formation of the dicationic complex **7** and also by increasing the size of the remaining coordinated anion in the active catalyst (Y^- in **6**) (see Scheme 4). Another possible explanation is that the counteranion (X^- in **6**) influences the relative rate of the cyclization of the diastereomeric gold(I)-coordinated allene complexes. We predicted that if this were true, it should also be the case that chiral counteranions should be able to influence the relative rate of the cyclization of enantiomeric gold(I)-coordinated allene complexes.[19] To test this third hypothesis, we prepared a set of chiral silver phosphates.

Treatment of dppm(AuCl)$_2$ [dppm = 1,1-bis(diphenylphosphino)methane], an achiral gold(I) complex, with silver phosphate **9** provided a complex that catalyzed the enantioselective hydroalkoxylation of allene **8** (Scheme 5).[20] Further optimization revealed that less-polar solvents provided higher enantioselectivity, a result that is consistent with an ion-pair model for enantioinduction. This result is particularly remarkable in light of the fact that we were never able to achieve even moderate enantioselectivities for this transformation when chiral phosphines were employed. We have subsequently expanded the scope of these transformations to include both N- and O-linked hydroxylamine nucleophiles.[21] As a group, these reactions provide access to a diverse range of enantioenriched heterocycles, including pyrazolidines, isoxazolidines, tetrahydrooxazines, tetrahydrofurans, tetrahydropyrans, pyrrolidines, and butyrolactones.

As an approach to asymmetric transition-metal catalysis, the use of chiral counteranions is complementary to the use of chiral ligands.[22,23] It therefore has the potential to significantly expand the scope of reactions that can be rendered asymmetric.

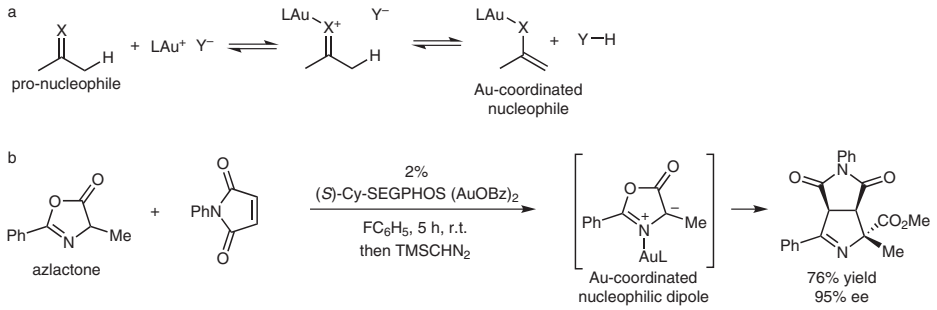


Solvent	Yield (%)	ee (%)
acetone	71	37
CH_2Cl_2	76	65
benzene	90	97

Scheme 5 The first report of a highly enantioselective, chiral counteranion controlled asymmetric reaction

2.4 Exploiting Basic Counteranions

The observation that the reactivity of cationic gold(I) complexes can be modulated through the basicity of the counteranion prompted us to investigate the potential of these catalysts to activate pro-nucleophiles. In this scenar-



Scheme 6 (a) A potential mechanism for pro-nucleophile activation by gold(I) catalysts; (b) gold(I)-catalyzed enantioselective 1,3-dipolar cycloaddition initiated by the formation of a gold-coordinated Münchnone intermediate

io, more-basic counteranions should favor the formation of the gold-coordinated nucleophile and the conjugate acid of the counteranion (Scheme 6, part a).[24] We employed this strategy to activate azlactones for cycloaddition with electron-deficient olefins (Scheme 6, part b).[25] Using (*S*)-Cy-SEGPHOS(AuOBz)$_2$ as the catalyst, this reaction provides an attractive route to enantioenriched proline derivatives.[26]

2.5 Ring Expansion Reactions

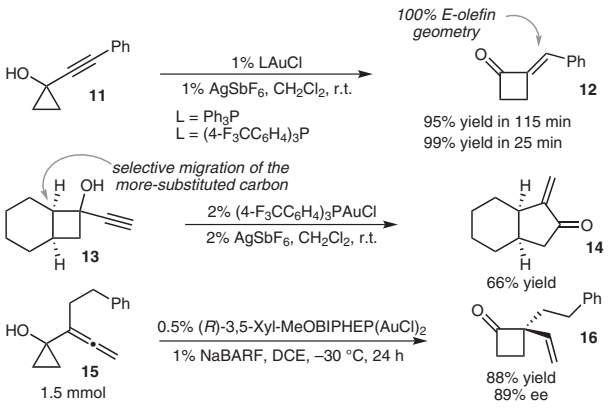
In the addition reactions described above, gold(I) coordination to an unsaturated carbon–carbon bond is proposed to induce the *trans*-addition of a tethered nucleophile. This stands in contrast to nucleophile-activation-based mechanisms that have been proposed for early transition metals, lanthanides, and actinides.[27] Based on this precedence, we hypothesized that gold(I) should also catalyze the addition of nucleophiles that lack metal-coordination sites (i.e., a carbon–carbon σ-bond). Thus, treatment of alkynylcyclopropanol **11** with 1% of a cationic phosphinegold(I) complex provided cyclobutanone **12** as a single olefin isomer (Scheme 7).[28] Higher yields and shorter reaction times were obtained when electron-deficient arylphosphines were employed as ligands.[29] Alkynylcyclobutanols, such as compound **13**, were also found to be viable substrates for gold(I)-catalyzed ring expansion (Scheme 7). The formation of the *E*-olefin and the selective migration of the more-substituted cycloalkanol carbons are consistent with a mechanism in which coordination of the gold(I) catalyst to the alkyne induces a 1,2-alkyl shift.[30,31] A vinylogous variant of this reaction was applied to the total synthesis of ventricosene.[32]

Ring expansion of allenylcyclopropanols, e.g. compound **15**, provides access to cyclobutanones possessing a vinyl-substituted quaternary center. This reaction can be rendered enantioselective by employing (*R*)-3,5-Xyl-MeO-BIPHEP as the ancillary ligand (Scheme 7).[33,34]

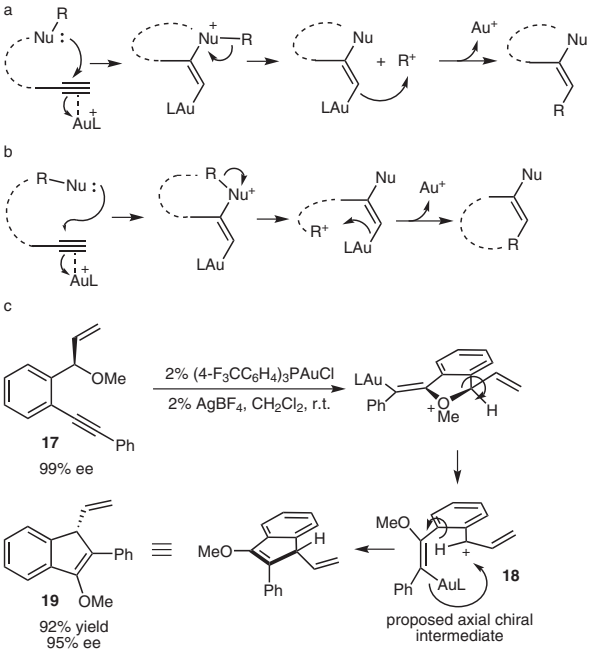
2.6 Intramolecular Carboalkoxylation

The research described in the previous sections illustrates that gold(I)-mediated electrophilic activation of carbon–carbon multiple bonds provides an opportunity for mild carbon–carbon and carbon–heteroatom bond formation. In addition, through the scrupulous choice of chiral ligand and/or chiral counteranion, many of these reactions can be rendered enantioselective. Nevertheless, these reactions fall under the reactivity paradigm encompassed by Markovnikov's rule.[35] An important expansion beyond these transformations would be to trap the proposed vinylgold intermediates with electrophiles other than a proton. This would allow the formation of additional bonds and the rapid generation of molecular complexity. Towards this goal, we envisaged that the protonation of the vinylgold intermediate could be avoided via in situ generation of an alternate electrophile. Thus, the addition of a neutral, aprotic nucleophile to a gold-coordinated alkyne leads to an increase in positive charge on the nucleophile (Scheme 8, parts a and b). Fragmentation of a single bond attached to this nucleophile generates a reactive electrophile (R^+), which can be trapped by the vinylgold moiety.[36]

Towards this end, treatment of methyl ether **17** with a cationic gold(I) catalyst generated carboalkoxylation product **19** (Scheme 8, part c).[37] The surprising observation that the chirality in the starting material is transferred to the product with inversion led us to propose the mechanism outlined in Scheme 8, part c. Following the addition of the methoxy moiety to the gold(I)-coordinated alkyne, fragmentation of the carbon–oxygen bond is expected to occur in such a way that maximizes overlap of the developing p orbital with the aromatic π-system. By also minimizing steric interactions of the benzylic substituent (vinyl in this case) with the developing enol ether, axial chiral intermediate **18** is formed. Subsequent trapping of the carbocation



Scheme 7 Gold(I)-catalyzed cyclopropanol and cyclobutanol ring expansion reactions



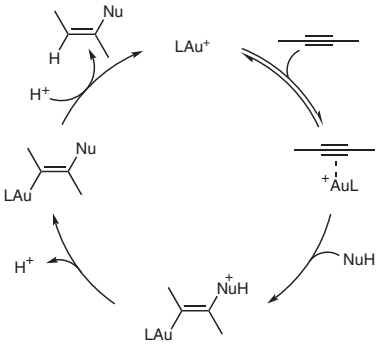
Scheme 8 (a) and (b) Mechanistic possibilities for the in situ generation of reactive electrophiles and their subsequent trapping by vinylgold moieties; (c) application to the synthesis of enantioenriched indenyl ethers

by the vinylgold moiety must be faster than racemization to maintain efficient chirality transfer.[38]

2.7 Rationalizing the π-Acidity of Cationic Gold(I) Complexes

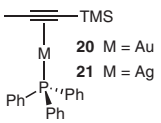
The gold(I)-catalyzed Conia-ene reaction of β-keto ester **1** provides cyclopentane **2** in 15 minutes in 94% yield with only 1% catalyst loading (see Section 2.1). In contrast, the silver(I) triflate (AgOTf) catalyzed reaction requires 10% catalyst loading and proceeds to only 50% conversion after 18 hours.[39] Furthermore, while an ancillary phosphine accelerates the gold-catalyzed synthesis, the addition of triphenylphosphine to the AgOTf-catalyzed reaction eliminates all catalytic activity. To further understand these differences, we considered a prototypical catalytic cycle for the addition of a protic nucleophile to an alkyne (Scheme 9). In doing this, we made the assumption that coordination of the cationic gold(I) catalyst to the alkyne is reversible and that nucleophilic addition is, therefore, rate determining. Thus, we reasoned that further study of gold(I)-coordinated π-bonds would lead to a better understanding of gold(I) catalysis.[40]

We noted that there was minimal literature presence for the isolation and characterization of cationic phosphine-gold(I) π-complexes. We hypothesized that these difficulties might be overcome by tethering a coordinatively stable phosphine ligand to the more-labile alkyne.[41] Using this strategy, we were able to obtain X-ray quality crystals of analogous cationic gold(I)- and silver(I)-coordinated alkynes. These structures allowed a comparative analysis, which was further augmented with density functional theory calculations. Second-order perturbative analysis revealed that σ-donation from the alkyne π-bond to the metal center is the most-important bonding interaction for both gold and silver (Table 2).[42] However, the magnitude of this interaction is significantly larger for gold (56.6 vs 38.5 kcal/mol for Ag). This interaction is primarily responsible for augmenting the electrophilicity of the coordinated alkyne. Interestingly, back-donation from gold to π* of the coordinated alkyne is also larger in magnitude (13.3 vs 6.4 kcal/mol for Ag). While this interaction is expected to decrease the electrophilicity of the coordinated alkyne, it suggests that back-donation from gold may be important for other aspects of gold(I) catalysis, as described below.



Scheme 9 A typical catalytic cycle for the gold(I)-catalyzed addition of protic nucleophiles to alkynes

Table 2 Natural Bond Order Orbital Interaction Energies

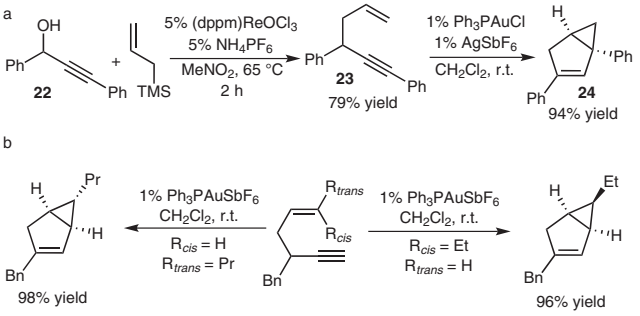
Parameter	Energy (kcal/mol)	
	 **20** M = Au **21** M = Ag	
	Gold complex **20**	Silver complex **21**
π → M	56.6	38.5
M → π*	13.3	6.4
difference	43.3	32.1

3 Reactions Involving Carbenoid Intermediates

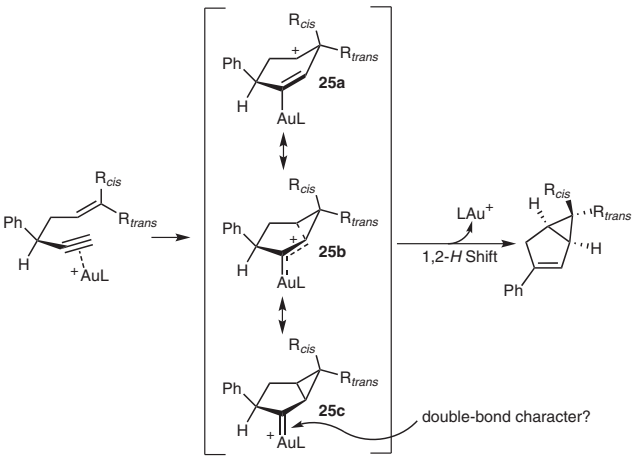
A reactivity-based approach to organic synthesis requires that reaction mechanisms are constantly proposed and tested. As described throughout Section 2, even in our forays into enantioselective catalysis, the testing of mechanistic proposals has frequently produced the most-important advances. This testing process plays an even more pivotal role in the development of new, mechanistically distinct reactions. In this section, we describe a series of reactions that are linked by a stream of mechanistic proposals.

3.1 1,5-Enyne Cycloisomerization

Following our success with the gold(I)-catalyzed Conia-ene reaction, we decided to explore the intramolecular addition of less-activated carbon nucleophiles to alkynes. A simple monosubstituted olefin constitutes the simplest of these nucleophiles. Coincidentally, we had at that time developed a rhenium-catalyzed synthesis of 1,5-enynes from propargyl alcohols.[43] Thus, the treatment of propargyl alcohol **22** with an allylsilane and catalytic (dppm)$ReOCl_3$ produced 1,5-enyne **23** in 79% yield (Scheme 10, part a). Subsequent gold(I)-catalyzed cycloisomerization effected this compound's clean conversion into bicyclo[3.1.0]hexene **24**.[44–46]



Scheme 10 (a) Rhenium-catalyzed synthesis of 1,5-enynes and their subsequent gold-catalyzed cycloisomerization; (b) stereospecific cycloisomerizations

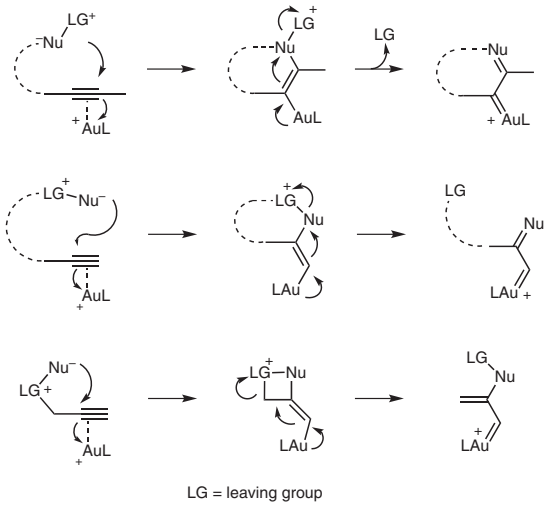


Scheme 11 Proposed 1,5-enyne cycloisomerization mechanism

The formation of bicyclic product **24** suggested a new mode of reactivity in gold catalysis. This prompted us to further investigate the reaction mechanism. As illustrated in Scheme 10, part b, the reaction of substrates containing 1,2-disubstituted olefins proceeded stereospecifically. We also found that a propargyl deuterium label is selectively incorporated in the vinyl position of the product. Based on these observations, we proposed the mechanism that is partially illustrated in Scheme 11. The initial coordination of the alkyne by the cationic gold(I) catalyst induces the cyclization of the pendant olefin, producing cationic intermediate **25**. The electronic structure of this intermediate can be represented by a number of resonance forms ranging from carbocation **25a** to gold–carbenoid **25c**. The degree of bonding from gold to carbon is further discussed in Section 3.5. A 1,2-hydrogen shift produces the desired product and liberates the gold catalyst.

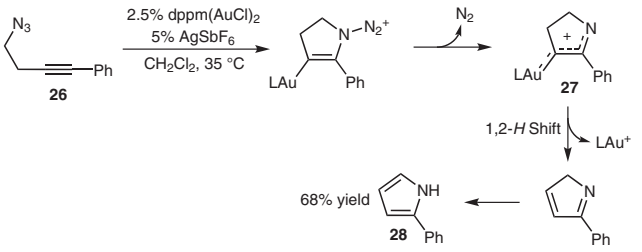
3.2 Intramolecular Addition of Dipolar Nucleophiles to Alkynes

The postulate that gold can stabilize the positive charge in intermediate **25** (see Scheme 11) was initially the matter of some debate. Nevertheless, the concept that gold can act as both a π-acid and as an electron donor has been useful in predicting new reactivity. We hypothesized that we could exploit this behavior in the gold-catalyzed addition of ylide-like nucleophiles to alkynes (Scheme 12).



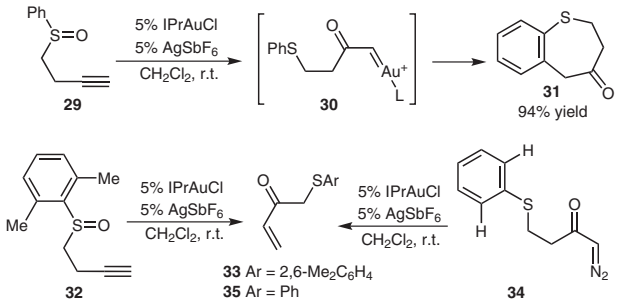
Scheme 12 A few possible routes to gold–carbenoids from ylide-tethered alkynes

For example, following the gold-catalyzed nucleophilic addition of the azide moiety in **26** to the pendant alkyne, back-donation from gold is sufficient to effect the loss of dinitrogen (Scheme 13).[47] The resulting intermediate **27** is similar to compound **25** in appearance and again raises questions as to the nature of the gold–carbon bond in these types of intermediates. The observed pyrrole product **28** is produced following 1,2-hydrogen migration and subsequent tautomerization.



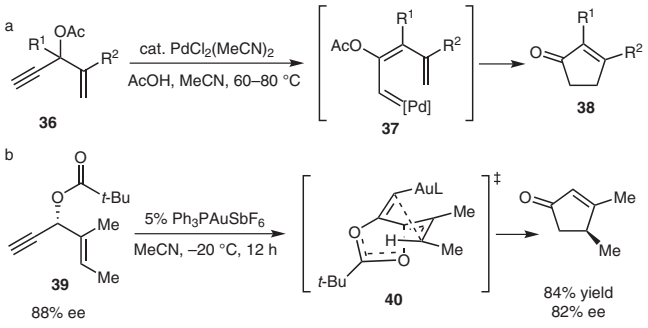
Scheme 13 Gold(I)-catalyzed intramolecular acetylenic Schmidt reaction

This concept was further expanded in the reaction of alkynyl sulfoxides (Scheme 14).[48] The gold(I)-catalyzed rearrangement of substrate **29** provides an alternative route to a carbenoid intermediate, i.e. **30**, that would traditionally be accessed via the transition-metal-catalyzed decomposition of α-diazocarbonyl compounds.[49,50] In this particular case, the proposed carbenoid intermediate undergoes a formal intramolecular C–H insertion to provide benzothiepinone **31**. An internal competition inverse kinetic isotope effect suggests that the formal C–H insertion proceeds via a Friedel–Crafts-type mechanism. When the *ortho*-positions of the aromatic ring are blocked, as in substrate **32**, sluggish conversion into enone **33** is observed. Surprisingly, when *S*-phenyl-substituted α-diazo ketone **34** is subjected to the same reaction conditions, enone **35** is produced instead of benzothiepinone **31**. This suggests that the gold-catalyzed rearrangement of alkynyl sulfoxides provides a route to intermediates that are actually inaccessible from the corresponding α-diazocarbonyl compounds. An explanation of this divergent reactivity remains an area for future exploration.



Scheme 14 Gold(I)-catalyzed sulfoxide rearrangements

In 1984, Rautenstrauch reported the palladium(II)-catalyzed isomerization of propargyl acetates **36** to give cyclopentenones **38** (Scheme 15, part a).[51] This reaction is proposed to proceed via palladium–carbenoid **37**. Based on the similarity of this reaction mechanism to those discussed above, we postulated that propargyl ester rearrangement could provide a third route to gold–carbenoid intermediates. To our delight, gold(I) catalysis allowed the substrate scope of this transformation to be significantly expanded.[52] To confirm the proposed reaction mechanism, we subjected enantioenriched propargyl ester **39** to our gold-catalysis conditions (Scheme 15, part b). To our surprise, we observed excellent chirality transfer. This suggests that an achiral gold–carbenoid intermediate is not present in the catalytic cycle. As an alternative mechanistic proposal, we suggested that a cyclic transition state, e.g. **40**, would account for chirality transfer. Subsequent calculations supported a similar hypothesis, in which a helical intermediate allows for efficient chirality transfer.[53] However, as is discussed below, these results do not imply that carbene-like behavior cannot be accessed from propargyl esters.

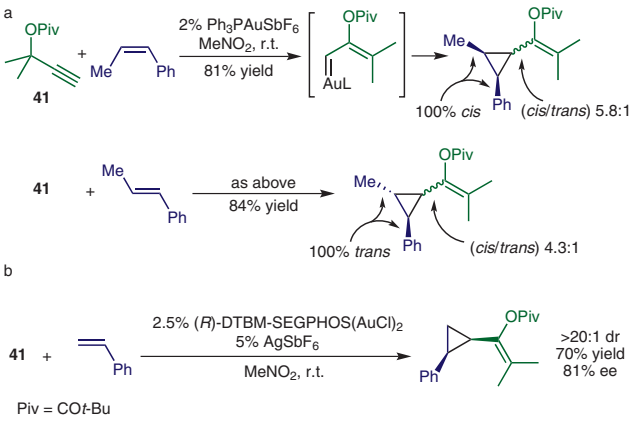


Scheme 15 (a) Palladium-catalyzed Rautenstrauch rearrangement; (b) the gold-catalyzed variant and our initially proposed cyclic transition state

3.3 Stereospecific Cyclopropanation

The term 'carbenoid' is defined as a 'description of intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species'.[54] Therefore, for carbenoid to be an apt descriptor of gold-stabilized cationic intermediates, such as **25**, these compounds must exhibit reactivity that is similar to that of a free carbene.

Of the reactions that typify free singlet carbenes, the stereospecific cyclopropanation of olefins is one of the most indicative.[55] We therefore sought to test the ability of the proposed gold–carbenoid intermediates in the cyclopropanation of olefins.[50,56] For this task, we employed propargyl esters, which had been previously reported to be convenient precursors to carbenoid intermediates.[57] Accordingly, we found that the cyclopropanation of *cis*- and *trans*-β-methyl-substituted styrenes with propargyl ester **41** occurs stereospecifically in the presence of a catalytic amount of a gold(I) complex (Scheme 16, part a). In addition, and in contrast to the Rautenstrauch rearrangements discussed above, we found that chirality was not transferred from enantioenriched propargyl esters to the cyclopropane products.



Scheme 16 (a) Demonstrating that gold(I)-catalyzed cyclopropanation is stereospecific; (b) an enantioselective variant

Encouraged by these results, we sought to develop an enantioselective variant of this reaction. Successful transmission of chiral information from the ancillary ligand of the gold complex to the cyclopropane product would provide further evidence for the participation of the gold catalyst in the cyclopropanation step. In the event, (*R*)-DTBM-SEGPHOS(AuCl)$_2$ catalyzed the asymmetric cyclopropanation of styrene to provide the product in 81% enantiomeric excess (Scheme 16, part b).[58] This concept was subsequently applied to the asymmetric synthesis of seven- and eight-membered rings via intramolecular gold(I)-catalyzed cyclopropanation.[59]

3.4 Gold–Carbon Bonding in Cationic Intermediates and Relativistic Effects

We were initially hesitant to define the exact nature of the bonding between gold and carbon in intermediate **25** (see Scheme 11). We wrote, 'Cyclopropylcarbinyl cation [**25b**] may have some gold(I)–carbene character ([**25c**]). The bicyclo[3.1.0]hexene product is generated by a 1,2-hydrogen shift onto a cation or gold(I)–carbene.' Even the boldness of this statement was based on literature precedence.[60] However, as evidence for gold–carbenoid reactivity accumulated (*vide supra*), we sought to provide a theoretical explanation for this behavior.

Previous experimental and theoretical reports[61] suggested that gold–carbenoid behavior is indeed plausible and can be ascribed to the relativistic expansion of the 5d orbitals of gold (Figure 1).[62] This expansion allows the delocalization of the electrons in these orbitals into carbon-based orbitals of sufficiently low energy (in particular an unoccupied p orbital of a carbocation). This provides an explanation for why gold–carbenes display behavior that is reminiscent of the reactivity of other transitional metal–carbene complexes. On the other hand, the relativistic contraction of the 6s orbital provides an explanation for the increased π-acidity of gold, as this orbital is the primary acceptor of electron density from ligands and substrates.[63] Thus, cationic gold complexes are typically stronger π-acids compared with silver and copper, yet also retain the ability to stabilize adjacent carbocations via back-donation.

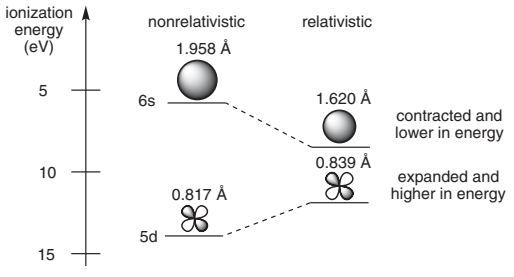


Figure 1 A comparison of the calculated sizes and energies of the 6s and 5d orbitals of gold with and without consideration of relativistic effects

3.5 A Bonding Model for Gold(I)–Carbene Complexes

Consideration of relativistic effects allows carbenoid reactivity in gold catalysis to be rationalized; however, we postulated that a more-specific description of the bonding in gold–carbene complexes would allow improved prediction and explanation of reactivity.[64] With this in mind, in collaboration with the Goddard group, density functional theory calculations were used to determine the effect of both carbene substituents (R^1, R^2) and the ancillary ligand (L) on bonding in gold–carbene complexes **42**. In agreement with previous calculations, we found that the gold–carbon bond in complexes **43**–**45** is composed mainly of π-type bonding (Figure 2).[65] Furthermore, the degree of π-back-donation from gold to the carbene is largely dictated by the carbene substituents. For example, π-bonding between gold and the carbene fragment is decreased relative to σ-bonding in **45**, a species that is stabilized by two oxygen atoms.

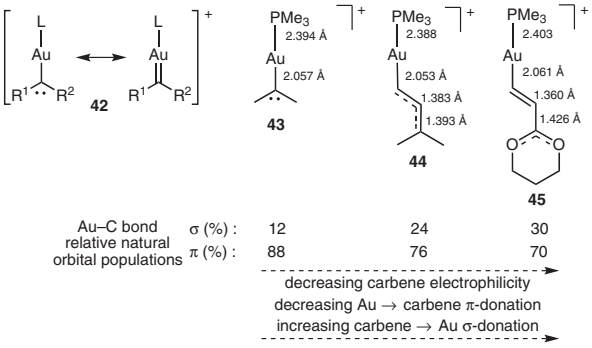


Figure 2 Calculated bond distances and relative natural orbital populations for three cationic gold(I)–carbene complexes

The ligand–gold–carbene bonding triad can be divided into three components (Figure 3). The σ-bonding is mainly composed of a three-center/four-electron hyperbond[66] (where hyperbond refers to bonding beyond the reduced 12-electron valence space and can be represented by the resonance forms L:Au–C ↔ L–Au:C). As a result, strongly σ-donating ligands decrease the gold–carbon bond order (*trans* influence). The π-bonding consists of electron donation of two orthogonal d orbitals of gold into π-acceptor orbitals of the ligand and the carbene. These two π-bonds compete for electron density and, therefore, have an indirect effect on each other. Overall, this bonding model suggests that the formation of a gold–carbene complex from a vinylgold intermediate occurs with an increase in gold to carbon π-bonding and a decrease in carbon to gold σ-bonding. Thus, the depiction of a gold–carbon double bond should be understood to mean that both π and σ components to the bond are present, but not that the gold–carbon bond has a bond order of two.[67] Indeed, the calculated natural bond orders for compounds **43** (1.14), **44** (0.91), and **45** (0.53) are all significantly less than two.

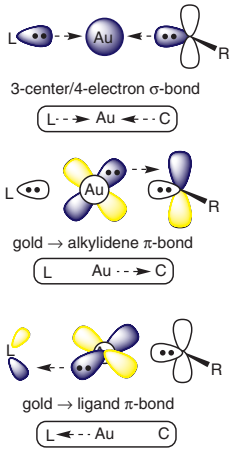
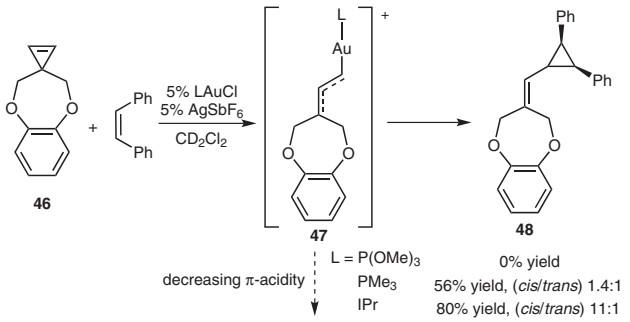


Figure 3 A bonding model for gold–carbene complexes

This bonding model can be used to predict the effect of ancillary ligands on reactivity.[29] Strongly σ-donating ligands increase the gold–carbon bond length, thereby increasing 'free carbene' like behavior. In contrast, π-acidic ligands are expected to decrease σ-donation from gold to carbene, thereby increasing carbocation-type reactivity. As a result, carbene-like reactivity is favored for ancillary ligands that are π-donating or π-neutral and strongly σ-donating. This trend is demonstrated by the yield of cyclopropanation product **48** obtained from the gold-catalyzed decomposition of cyclopropene **46** (Scheme 17). This reaction is expected to proceed via a gold–carbene intermediate, i.e. **47**, that is similar to compound **44** (see Figure 2). The highest yield was obtained when the N-heterocyclic carbene (NHC) ligand 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) was employed (NHC ligands are strongly σ-donating and only weakly π-acidic). In contrast, trimethyl phosphite, a strongly π-acidic ligand, provided none of the desired product.

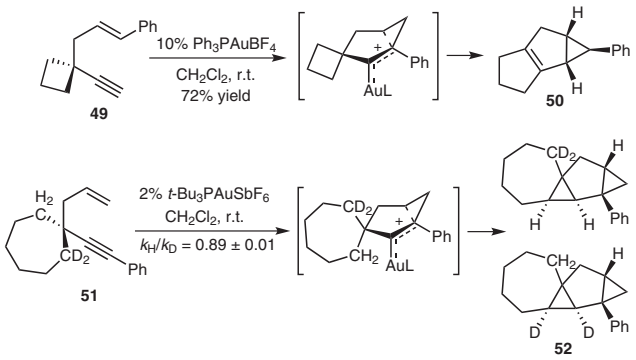


Scheme 17 The effect of the ancillary ligand on the reactivity of gold(I)–carbene complexes

4 Further Insights into Reactivity from Gold-Catalyzed Cycloisomerization Reactions

4.1 Intramolecular Rearrangements of 1,5-Enynes

In the absence of an available hydrogen for a 1,2-hydride shift, a given gold–carbenoid intermediate can undergo several other types of rearrangement. For example, a gold–carbene intermediate related to **25** (see Scheme 11) will also undergo an intramolecular 1,2-alkyl shift/ring expansion to produce tricyclic compound **50** (Scheme 18)[44] Interestingly, gold-catalyzed cycloisomerization of the related enyne **51** produces tetracycle **52** via an intramolecular C–H bond insertion (Scheme 18).[68] In this case, we hypothesize that the seven-membered ring allows the adjacent carbon–hydrogen bonds to adopt an optimal position for insertion.[69,70]



Scheme 18 Observed products resulting from intramolecular rearrangement of cationic intermediates

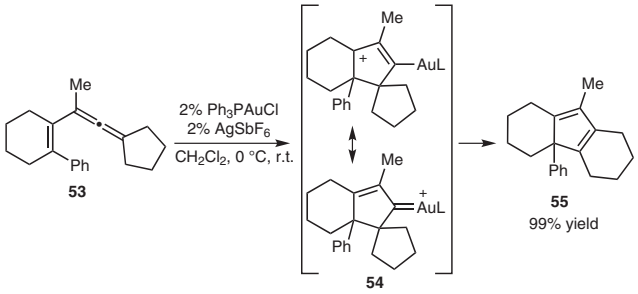
We performed several kinetic isotope effect experiments to gain further insight into the mechanism of this C–H insertion. The results suggest that a mechanism involving simple hydride transfer to the carbenoid intermediate is unlikely.[71]

4.2 Ligand- and Substrate-Controlled Access to [2+2], [3+2], [4+2], and [4+3] Cycloadditions in Gold-Catalyzed Reactions of Allene–Enes

We had developed a number of reactions suggesting that gold-containing cationic intermediates of the type **42** (see Figure 2) can display either carbene- or carbocation-like reactivity. To further understand this divergence in reactivity, we sought to quantify the degree of carbocation stabilization in gold(I)–carbene complexes.

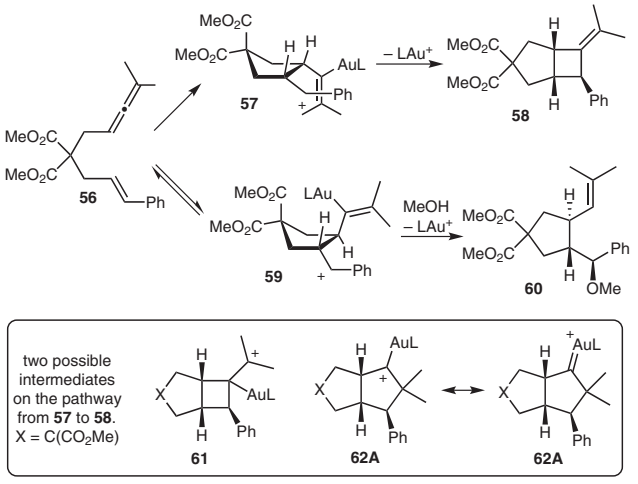
To identify a platform for these investigations, we considered the reactivity of 1,3-allene–enes, such as substrate **53** (Scheme 19).[72] Our investigations suggested that the gold(I)-catalyzed cycloisomerization to give cyclopentadiene **55** proceeds via allyl cation/gold–carbene complex **54**.[73] While we could not devise a method to quantify the degree of carbocation stabilization from gold for this particular reaction, we reasoned that the analogous 1,6-allene–ene **56** (Scheme 20) might provide a path towards this type of insight.

The initial coordination of a cationic gold(I) catalyst to the allene moiety of substrate **56** induces the addition of the pendant olefin (Scheme 20).[74] The resulting carbocation can subsequently be trapped in one of two ways. In the absence of an external nucleophile, *cis*-bicyclic compound **58** is produced,[75] while *trans*-cyclopentane **60** is formed



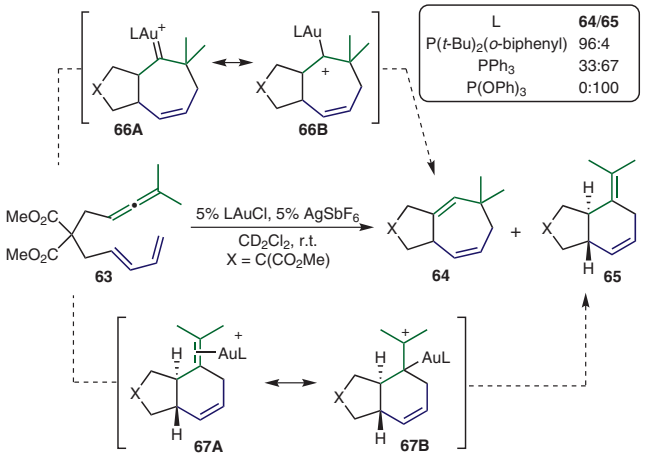
Scheme 19 Gold(I)-catalyzed 1,3-allene–ene cycloisomerization

in the presence of methanol. Furthermore, when these reactions are catalyzed by (*R*)-DTBM-SEGPHOS(AuCl)$_2$, compound **58** is produced in 92% yield and 95% enantiomeric excess, while **60** is produced in 75% yield, but as a racemic mixture. Based on these results, we proposed that the initial addition of the olefin to produce **59** is fast and reversible. When an external nucleophile is present, intermediate **59** is trapped; however, in the absence of such a nucleophile, the reaction funnels through compound **57**. The formation of **57** from **56** may or may not be reversible. The exact mechanism of the conversion of carbocation **57** into product **58** has remained somewhat unclear. We initially hypothesized that the reaction most likely proceeds via trapping of the carbocation in **57** either by the pendant olefin to produce intermediate **61** or by the gold–carbon bond to directly produce **58**. However, as the results below suggest, the ring contraction of gold–carbene intermediate **62** may be more likely.



Scheme 20 Observed reaction products and possible reactive intermediates in the gold-catalyzed reactions of a 1,6-allene–ene

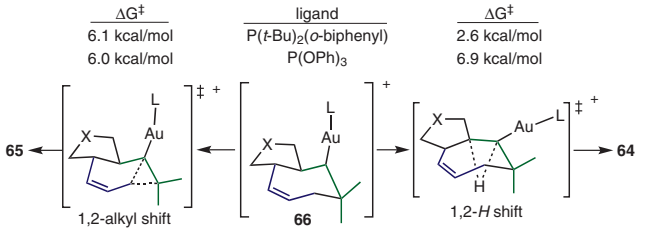
In light of these results, we were intrigued to find that the (triphenylphosphine)gold(I) cation catalyzed cycloisomerization of allene–diene **63** produced a 33:67 mixture of [4+3] and [4+2] cycloadducts **64** and **65**, respectively (Scheme 21).[76,77] We considered that this ratio might be altered by varying the ancillary ligand on gold. To our delight, electron-rich phosphines, including *o*-biphenyl(di-*tert*-butyl)phosphine, provided the [4+3] product **64** in high yield, while π-acidic ligands, including triphenyl phosphite, provided exclusively the [4+2] adduct **65**. This is one of the few examples of ligand-controlled divergent reactivity in gold catalysis.[29,78] Furthermore, by employing chiral, nonracemic phosphites and phosphoramidites it is possible to fully control the chemo-, diastereo-, and enantioselectivity of this reaction.[79]



Scheme 21 Initial experimental observations and mechanistic hypothesis for ligand-directed, gold-catalyzed [4+3] and [4+2] cycloadditions

Based on the results from the [2+2] cycloadditions described above, we initially assumed that this reaction would also proceed via a stepwise addition/trapping mechanism. This would indeed explain the observed ligand effect, with electron-rich ligands stabilizing gold–carbene complex **66** and π-acidic ligands disfavoring this pathway.

In collaboration with the Goddard group, we initiated a theoretical study of this reaction to further elucidate the differences in bonding that lead to this divergent reactivity.[80] These calculations suggest that both products **64** and **65** are actually formed through an initial concerted [4+3] cycloaddition, producing gold–carbene intermediate **66** (Scheme 22). A subsequent 1,2-alkyl shift (ring contraction) or 1,2-hydride shift produces the observed products.



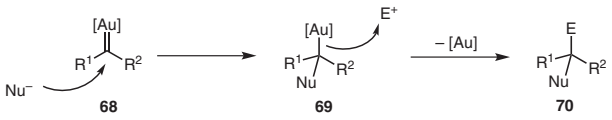
Scheme 22 Calculated structures and transition state energies for the intermediates in gold-catalyzed [4+3] and [4+2] cycloadditions

Elucidating how the ancillary ligand controls product selectivity has led to some interesting insights. Because of

steric interactions, the gold moiety in intermediate **66** is puckered out of the plane of the bicycle. In addition, larger ligands cause the phosphine–gold–carbon bond to distort from 180° [169° for P(*t*-Bu)$_2$(*o*-biphenyl) vs 178° for P(OPh)$_3$]. Thus, π-donation from gold to carbon is actually reduced using the bulky, electron-rich *o*-biphenyl(di-*tert*-butyl)phosphine ligand, and this result suggests that it is also important to consider sterics when attempting to predict the ability of a gold(I) complex to stabilize an adjacent carbocation. In this reaction, increased occupation of the p orbital of the carbon in intermediate **66** disfavors the 1,2-hydride shift. As a result, the 1,2-alkyl shift prevails with triphenyl phosphite as the ancillary ligand, while the 1,2-hydride shift is faster with *o*-biphenyl(di-*tert*-butyl)phosphine (Scheme 22).

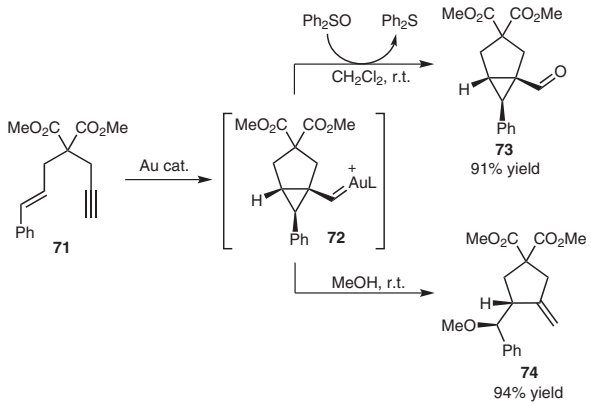
5 Intermolecular Annulation Reactions

Several additional experiments aimed at trapping proposed gold–carbenoid intermediates have been successful. Nucleophilic addition to gold–carbenoid intermediates **68** generates a gold–carbon σ-bond. In the case of protic nucleophiles, the gold catalyst is typically regenerated by proto-deauration (equation 2, $E^+ = H^+$).[81]



Equation 2

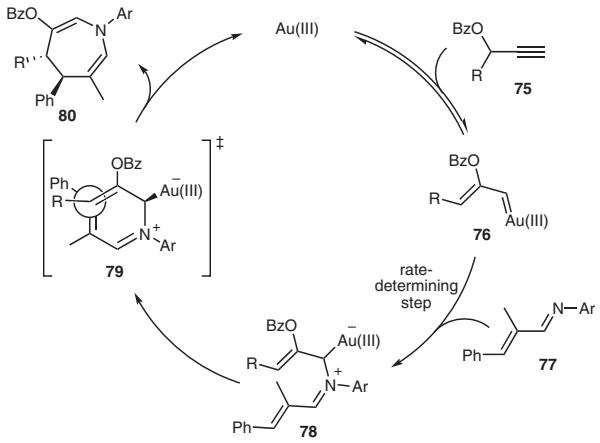
As an example, when the reaction of enyne **71** is conducted in methanol, the cationic intermediate **72** is trapped, producing methyl ether **74** (Scheme 23).[82] In the case of aprotic nucleophiles, the gold–carbon bond may be trapped by electrophiles other than a proton. Thus, trapping of the intermediate carbenoid with diphenyl sulfoxide produces aldehyde **73** after release of diphenyl sulfide.[83] In addition to these reactions, Echavarren and co-workers have also reported these intermediates can be trapped with olefins to produce cyclopropanation products.[84] Considering these results, we hypothesized that tethering the nucleophile and electrophile in equation 2 would allow an intermolecular annulation reaction.[85]



Scheme 23 Observed products resulting from intermolecular trapping of a gold–carbenoid intermediate

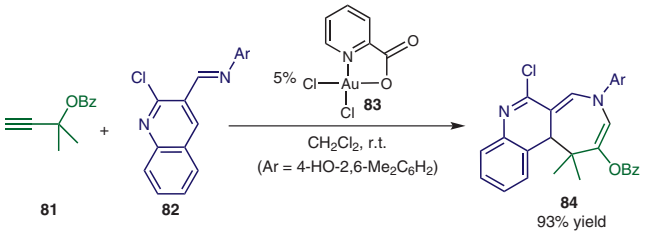
5.1 A [4+3] Annulation Approach to Azepines

In analogy to related reactions of rhodium-stabilized carbenoids,[86] we reasoned that α,β-unsaturated imines could serve as appropriate coupling partners. Based on this hypothesis, we were pleased to find that gold(III) catalysts[87] efficiently promote the formation of azepines **80** from carbenoid precursors **75** and imines **77** (Scheme 24).[88] Based on the *trans* diastereoselectivity observed with the reaction from secondary propargyl esters, we proposed that the cyclization occurs via transition state **79**. Overall, this transformation constitutes the reactivity paradigm that we had initially set out to observe, i.e. trapping of a gold–carbenoid complex with a tethered nucleophile–electrophile pair.



Scheme 24 Proposed mechanism of gold(III)-catalyzed azepine synthesis

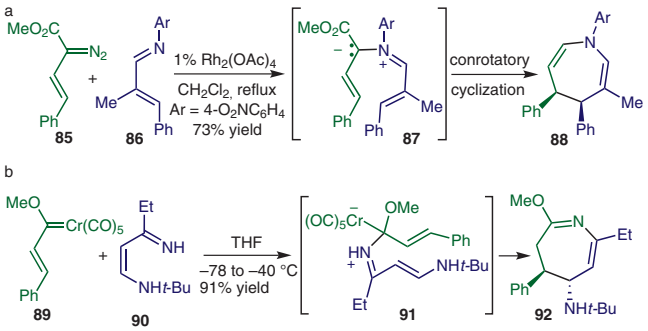
Further insight into this reaction was acquired through a Hammett analysis, which showed that the rate of the reaction is enhanced by electron-donating substituents on the *N*- and β-aryl groups.[89] This supports our stepwise mechanism and suggests that the formation of compounds **78** from carbenoid intermediates **76** is rate determining. In addition, this result implies that nucleophilic addition of *C*-aryl imines to complexes **76** should occur despite the absence of a double bond for subsequent seven-membered-ring formation. We were therefore curious to investigate potential dearomatization/annulation reactions. To



Equation 3

our delight, heteroaromatic imines (i.e., **82**) could indeed be dearomatized via this methodology (equation 3).

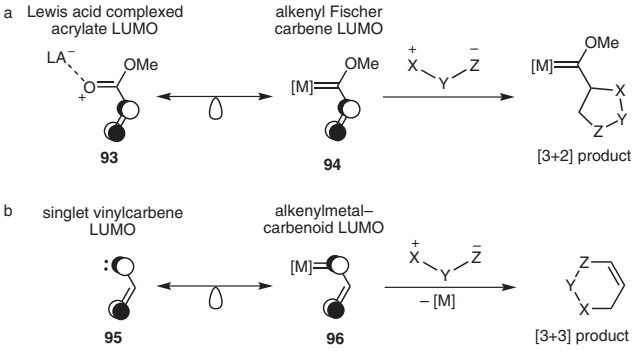
The proposed reaction mechanism for this transformation is particularly interesting in comparison with those that have been suggested for the related reactions of rhodium–carbenoids and Fischer carbenes. The $Rh_2(OAc)_4$-catalyzed decomposition of vinyl-containing diazo ester **85** in the presence of imine **86** is proposed to generate free ylide **87**, which undergoes a thermally allowed eight-electron electrocyclization to produce *cis*-substituted azepine **88** (Scheme 25, part a).[86a] In contrast, the stoichiometric reaction of 4-amino-1-azabuta-1,3-diene **90** with Fischer carbene **89** is proposed to produce *trans*-substituted azepine **92** via transition state **91**, which is quite similar to that proposed for the gold(III)-catalyzed reaction, i.e. **79** (Scheme 25, part b).[86d] In this respect, the gold-catalyzed reaction can be considered a valuable alternative to the use of stoichiometric amounts of chromium reagents. On the other hand, it should be noted that these three reactions, i.e. rhodium-catalyzed, gold-catalyzed, and chromium-mediated, provide access to azepines with complementary substitution patterns.



Scheme 25 (a) Transition-metal-catalyzed and (b) -mediated annulations of α,β-unsaturated imines

5.2 Orbital Considerations in [3+3] Annulations

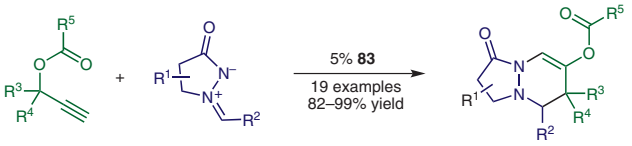
In light of these comparisons, we were curious to investigate gold-catalyzed annulation reactions of 1,3-dipoles, a type of transformation that is well-known for alkenyl Fischer carbenes,[90] but remains unprecedented for both free and metal-coordinated electrophilic alkenylcarbenes.[91,92] The reaction of alkenyl Fischer carbenes with 1,3-dipoles typically proceeds via concerted asynchronous [3+2] cycloaddition. The regioselectivity of this reaction can be rationalized by considering the molecular orbitals involved (Scheme 26, part a). The lowest unoccupied molecular orbital (LUMO) of Fischer carbene **94** is isolobal with that of Lewis acid complexed acrylate **93**.[90c] As such, the reaction with 1,3-dipoles proceeds via [3+2] cycloaddition with the alkenyl fragment. In contrast, the LUMO of alkenylmetal–carbenoid **96** can approximate that of free singlet vinylcarbene **95**.[93] Given this analogy, a [3+3] cycloaddition between 1,3-dipoles and carbenoid **96** would be predicted (Scheme 26, part b). However, as mentioned



Scheme 26 Isolobal structures of (a) alkenyl Fischer carbenes and (b) alkenylmetal–carbenoids lead to predictions of distinct regioselectivity in the reaction of these species with 1,3-dipoles

previously, this type of reactivity had not been reported at the time we began our investigations.

We were, therefore, delighted to find that the picolinic acid derived gold(III) complex **83** efficiently catalyzes the [3+3] annulation of azomethine imides and propargyl esters (equation 4).[94] Mechanistic investigations suggest a stepwise mechanism similar to that proposed for the gold-catalyzed [4+3] annulation of imines and propargyl esters (*vide supra*).[88] In addition, this reaction serves to highlight the differences in the reactivity of alkenyl Fischer carbenes and alkenylgold–carbenoids.



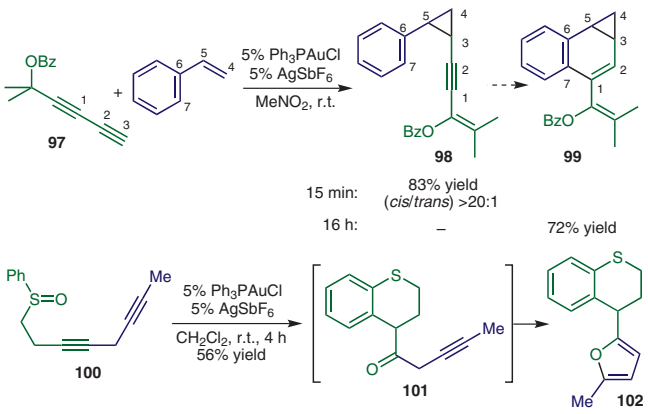
Equation 4

6 Tandem Reactions

The ability to effect multiple, mechanistically distinct, bond-forming events into a single reaction sequence allows the rapid and efficient construction of complex molecular structures.[95] The design of tandem reactions requires an intricate understanding of reactivity. Each reaction must occur in the proper order and with high fidelity to ensure a high yield of the product. In our own research, we have developed several tandem reactions and, in doing so, have used many general strategies to ensure that these requirements are met.

One strategy is to employ sequential intramolecular/intermolecular reactions. As an example, in what is overall a [4C+3C] annulation, the intermolecular cyclopropanation of styrene with ester-containing diyne **97** can be coupled with an intramolecular hydroarylation (Scheme 27).[96] This sequence uses the knowledge that the gold(I)-catalyzed intermolecular cyclopropanation reaction occurs rapidly at room temperature (in this case, within 15 min).[56] This allows substrate-controlled regioselectivity in the subsequent intramolecular hydroarylation. If the

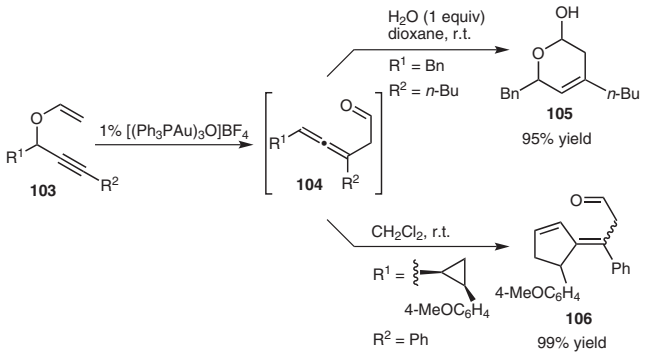
rate of intermolecular hydroarylation was faster than or similar to the rate of cyclopropanation, then controlling the regioselectivity of the hydroarylation could become problematic.[97] A similar strategy is employed in the annulation of enynes or propargyl esters to form fluorenes or styrenes.[78b]



Scheme 27 Gold(I)-catalyzed tandem cyclization reactions

An alternative strategy for the design of tandem sequences employs reactions that create functional groups that can undergo a second metal-catalyzed transformation. This strategy was employed in the bis-cyclization of diyne sulfoxide **100**; as shown in Scheme 27, the ketone created in the first cyclization is subsequently transformed into the furan moiety of product **102**.

Similarly, propargyl Claisen rearrangement of vinyl ether **103** forms allenyl-containing aldehyde **104**.[98] In the presence of water, the aldehyde moiety will undergo further cyclization with the allene, forming dihydropyran **105** (Scheme 28).[99] By excluding water from this reaction, cyclopropyl-substituted allene **104** undergoes ring expansion to form cyclopentene **106**.[100]



Scheme 28 Tandem propargyl Claisen rearrangement/cyclization reactions

7 Conclusions

In this account, we have attempted to illustrate the thought processes and experimental testing that occur throughout a reactivity-based approach to reaction discovery.[5] In practice, this 'method' of organic chemistry research frequently involves close inspection of reaction mechanisms, as well as the ability to identify and creatively expand upon reactivity paradigms. On a personal level, we have enjoyed the freedom to investigate new reactions that is afforded by this research method. But above all else, it is the potential impact of discovering new reactivity, mechanisms, and reactions that provides the driving force for this research program:

'The goal is always finding something new, hopefully unimagined and, better still, hitherto unimaginable.' – Professor K. Barry Sharpless[5a]

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