

Gold-Catalyzed Synthesis of Small Rings

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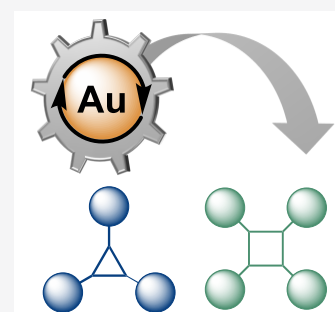
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ABSTRACT: Three- and four-membered rings, widespread motifs in nature and medicinal chemistry, have fascinated chemists ever since their discovery. However, due to energetic considerations, small rings are often difficult to assemble. In this regard, homogeneous gold catalysis has emerged as a powerful tool to construct these highly strained carbocycles. This review aims to provide a comprehensive summary of all the major advances and discoveries made in the gold-catalyzed synthesis of cyclopropanes, cyclopropenes, cyclobutanes, cyclobutenes, and their corresponding heterocyclic or heterosubstituted analogs.



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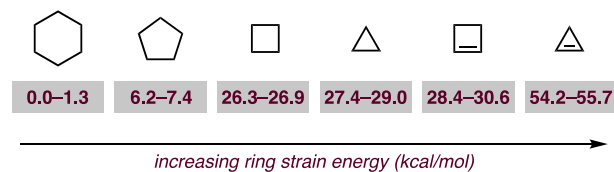
1. INTRODUCTION

Cyclopropane was first synthesized by August Freund in 1882 (via Wurtz coupling of 1,3-dibromopropane), who already proposed its correct structure,¹ whereas cyclobutane was first prepared by hydrogenation of cyclobutene in 1907.² The structure and properties of these highly strained carbocycles and their derivatives have fascinated chemists ever since.^{3–6} As a result, huge efforts have been made over the years to gain access to diverse small ring-containing molecules and to study their special reactivity patterns.

Due to their inherent strain (60° C–C bond angles compared to 109.5° for typical C_{sp³}–C_{sp³} bonds), the reactivity of cyclopropanes often resembles more closely that of alkenes

than that of alkanes.^{7,8} Strikingly, the strain energy of cyclobutane and cyclopropane is rather similar (Scheme 1).^{9–13} This has been rationalized by taking both C–C and

Scheme 1. Estimated Ring Strain Energy Ranges for Selected Cyclic Hydrocarbons



C–H bond energy components into consideration: the total C–C bond strain of cyclopropane is 10 kcal/mol higher than that for cyclobutane, but this is largely compensated by the stronger C–H bonds of cyclopropane (8 kcal/mol).^{14,15} Stabilizing effects increase when substituents are placed on the backbone of these rings.^{16,17}

As a consequence of the uphill thermodynamics, methods for the assembly of highly strained small rings differ significantly from those employed to build medium or large rings. For example, many classical methods to obtain cyclopropanes rely on passing through highly energetic intermediates, such as carbenes or carbenoids.^{18,19} General strategies based on direct ring-closing cyclizations are rare for the construction of small rings.

1.1. The Importance of Small Rings

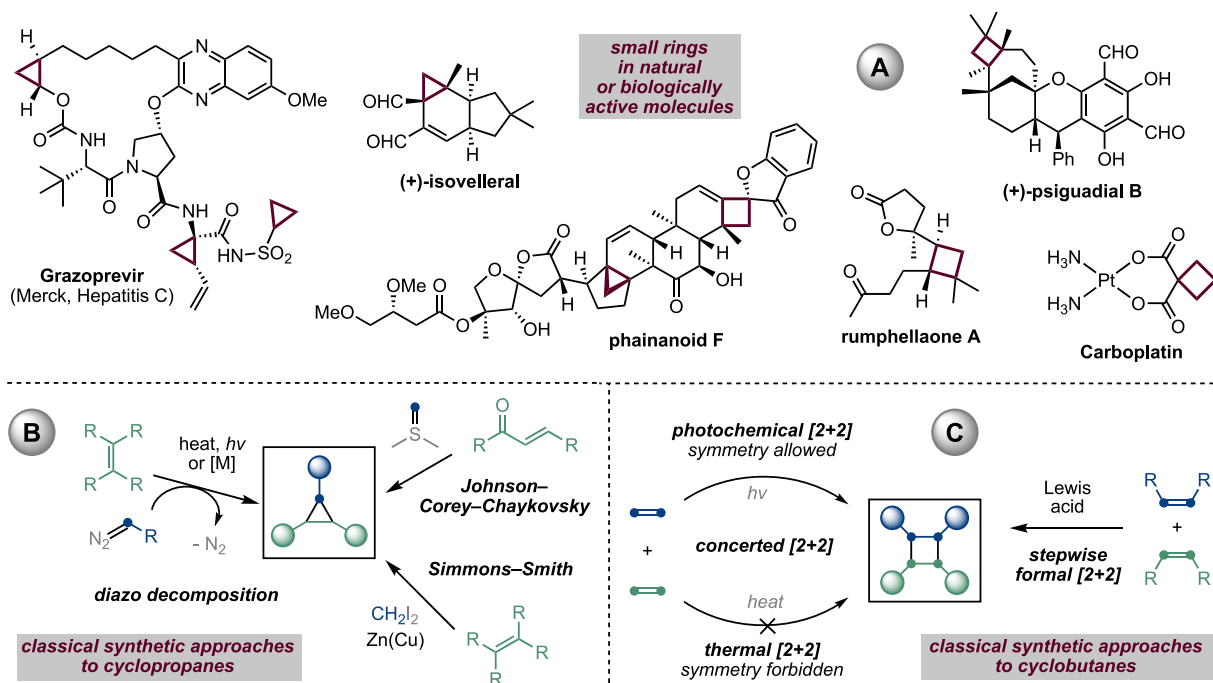
The importance of small rings to the scientific community goes far beyond purely academic reasons. The cyclopropane unit is considered a privileged motif in medicinal chemistry.²⁰ Thus, more than 10 cyclopropane rings can be found among the 220 drugs approved by the U.S. FDA between 2015 and 2019.^{21–24} This does not come as a surprise, since 3-membered rings appear in a wide range of naturally occurring, biologically active molecules (Scheme 2A).^{25–27} Although less widespread, cyclobutanes and cyclobutenes are also present in small molecules isolated from natural sources^{28–30} and have been explored as drug candidates.^{31–33} Biosynthetically, both cyclopropanes and cyclobutanes are commonly proposed to form by ring closure of homoallyl cation intermediates, among other pathways.^{34–36} Furthermore, countless applications of 3-membered^{37–42} and 4-membered carbocycles^{43–46} as reactive intermediates have been developed. These strategies have been widely applied in the context of synthetic methodology development and natural product synthesis.^{47–50}

1.2. An Overview of the Synthetic Methods to Assemble Small Rings

The synthesis of cyclopropanes has been traditionally approached by methodologies such as the Simmons–Smith reaction (through metal carbenoids)^{51–56} or the Johnson–Corey–Chaykovsky reaction (also developed for the assembly of epoxides or aziridines)^{57–60} or via metal carbenes through decomposition of diazo compounds (Scheme 2B).^{61–63} Some alternative methods for the synthesis of cyclopropanes involve the use of different types of ylides,^{64–67} free dihalocarbenes,⁶⁸ direct cyclizations,^{69,70} ring contractions,^{71–73} radical pathways,^{74–77} or the Kulinkovich reaction,^{78–80} among others.^{81–84}

The most classical approach for the synthesis of cyclobutanes is the photoexcitation of alkenes, which can engage in concerted [2 + 2] cycloaddition pathways, thermally forbidden by

Scheme 2. Structures of Natural or Bioactive Compounds Containing Small Rings (A) and Selected Classical Approaches for the Assembly of Cyclopropanes (B) and Cyclobutanes (C)



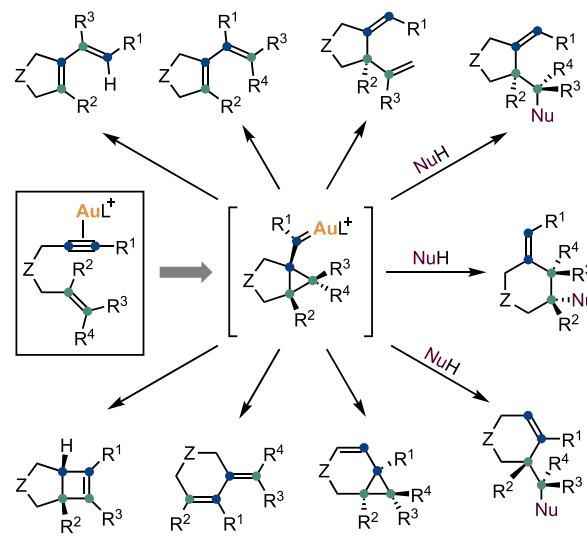
symmetry (Scheme 2C).^{85–87} These transformations have found a broad range of applications in organic synthesis over the years.^{88–91} Apart from direct photoexcitation pathways,⁹² cyclobutanes have also been assembled via formal [2 + 2] cycloadditions with the aid of photoredox^{93,94} or Lewis acid catalysis.^{95–97} The use of highly polarized cycloaddition partners is a general theme in this context, but metal-catalyzed [2 + 2] cycloadditions of unbiased alkenes and alkynes have also been achieved.^{98,99} Non-cycloaddition strategies for the synthesis of 4-membered rings include ring expansion,^{100–103} ring contraction,^{104,105} strain release opening,^{106,107} hydroalkylation,¹⁰⁸ or hydroacylation reactions¹⁰⁹ among others.^{110,111}

1.3. Gold Catalysis in the Construction of Small Rings

The origins of homogeneous gold catalysis date back to 1986, when Ito et al. described an asymmetric aldol reaction catalyzed by a chiral ferrocenylphosphine–gold(I) complex.¹¹² In 1987, the first homogeneous gold-catalyzed addition of nucleophiles to alkynes was realized by the group of Utimoto using sodium tetrachloroaurate dihydrate.^{113,114} One decade later, Teles et al.¹¹⁵ and Tanaka et al.¹¹⁶ demonstrated the possibility of activating alkynes using gold(I) complexes. From that point, the field of gold(I) catalysis started to gain momentum year after year and still today remains one of the most active areas of research in organometallic chemistry.^{117,118} This comes as a consequence of the ability of gold(I) complexes to activate π bonds in a very selective manner.^{119–135} Its potential, attributed partially to relativistic effects,¹³⁶ is illustrated by the wide molecular complexity^{137–184} that can be built through the gold(I)-catalyzed cycloisomerization of enynes (Scheme 3).

Arising from complex mechanistic scenarios, the generated cyclopropyl gold carbenes can oftentimes evolve or be trapped to form isolable products containing 3- or 4-membered carbocycles.^{185–206}

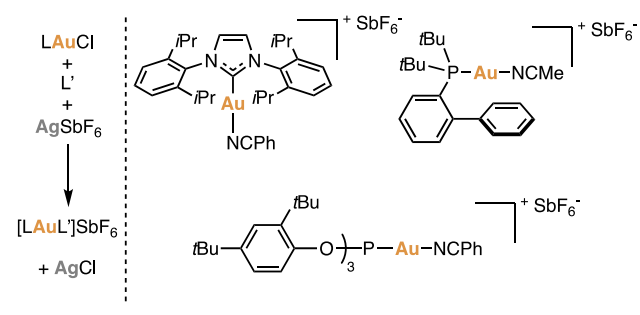
Scheme 3. Fate of Cyclopropyl Gold(I) Carbenes Generated by 1,6-Enyne Cyclization



The discovery of novel chemical transformations catalyzed by gold grows together with the development of new and more active catalysts, such as highly electrophilic cationic gold(I) complexes.^{207–210} These species can be either generated in situ by chloride abstraction (Scheme 4, left)^{211–213} or synthesized and handled as bench-stable solids (Scheme 4, right).^{214,215} Design and selection of the main ligand (L) allows tuning the reactivity of the complex^{216–222} or achieving highly enantioselective transformations.^{223–234}

Hand in hand with this explosive development, gold catalysis has emerged a powerful and versatile tool to assemble 3- and 4-membered rings.

Scheme 4. Activation of Gold(I) Chloride Complexes (Left) and Stable Cationic Gold(I) Complexes (Right)



1.4. Scope of the Review

In this review, we cover all the major developments in the field of small ring assembly using homogeneous gold catalysis. We include under the denomination of “small rings” all 3- and 4-membered carbocycles (cyclopropanes, cyclopropenes, cyclobutanes, and cyclobutenes) and their corresponding heterocyclic or heterosubstituted analogs.

The review is divided in two major parts: the first one discusses the synthesis of 3-membered rings, and the second one covers the preparation of 4-membered rings. The different gold-catalyzed transformations are organized based on the nature of the reaction substrates employed or the reaction products obtained in each of them. For most of the discussed reactions, a brief selection of the scope of the methodology is presented, as well as an overview of its mechanistic rationale when appropriate.

For the sake of simplicity in some mechanistic schemes throughout this review, “AuL⁺” is used as a surrogate of $[AuLL']^+$ complexes, where L' is a relatively weak ligand such as a bound substrate (alkyne or alkene), product, or donor solvent molecule. However, it is important to stress that the existence of “naked” gold(I) species “AuL⁺” in solution has not yet been demonstrated.

2. CONSTRUCTION OF 3-MEMBERED RINGS CATALYZED BY GOLD

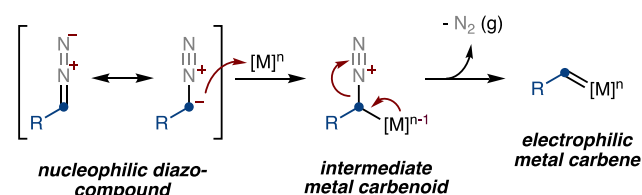
Most of the gold(I)-catalyzed transformations that give rise to 3-membered carbocycles are proposed to involve the intermediacy of gold(I) carbenes.^{235,236} Apart from the classical decomposition of diazo compounds,^{237,238} different precursors of gold(I) carbenes or carbenoids have been developed for the assembly of 3-membered rings.^{239,240} A few previous reviews have covered the gold-catalyzed synthesis of 3-membered rings until 2016.^{237–240}

2.1. Decomposition of Diazo Compounds

The most common application of diazo compounds²⁴¹ is their decomposition to generate either free carbenes or metal carbenes, through downhill release of nitrogen (Scheme 5).^{242,243}

The resulting intermediates can take part in a wide range of transformations, among which the assembly of 3-membered rings, through either concerted or stepwise (2 + 1) cycloaddition pathways, is probably the most studied one.^{61–63,237,238} More recently, the use of hydrazones as precursors for the in situ generation and decomposition of diazo compounds has allowed the development of safer procedures involving these potentially hazardous reagents.^{244,245}

Scheme 5. Mechanistic Rationale for the Generation of Metal Carbenes from Diazo-Compounds

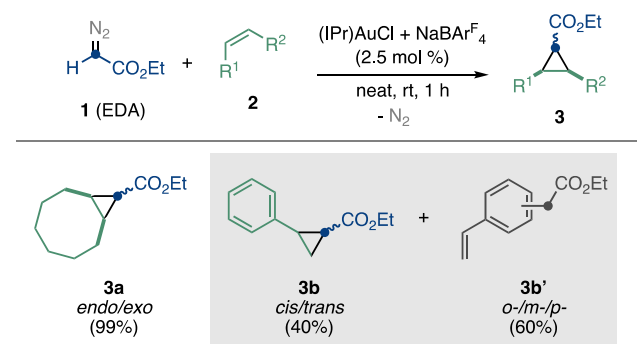


2.1.1. Gold-Catalyzed Cyclopropanation with Diazo Compounds.

The metal-catalyzed carbene transfer reaction from diazo compounds is the best-established method for the assembly of acceptor or donor–acceptor cyclopropanes. Gold(I) catalysts are one type of several metal complexes that are able to promote this transformation.²⁴⁶ Some of the most often used metals in this type of cyclopropanation of alkenes are rhodium,^{247,248} ruthenium,^{249–252} copper,^{253,254} cobalt,^{255–257} and palladium.^{258–260} Over the past 15 years, several gold(I) complexes have been employed to promote carbene transfer reactions to different nucleophiles.²⁶¹

Pérez and co-workers disclosed the first example of the use of a gold(I) catalyst for a carbene transfer reaction from ethyl diazoacetate (EDA).²⁶² Reaction of EDA with a large excess of cyclooctene in the presence of $[(IPr)AuCl]$ activated with $NaBARF_4$ led to quantitative formation of a mixture of the corresponding *endo/exo* cyclopropanes (Scheme 6). The same

Scheme 6. Gold(I)-Catalyzed Cyclopropanation of Cyclooctene and Styrene with Ethyl Diazoacetate



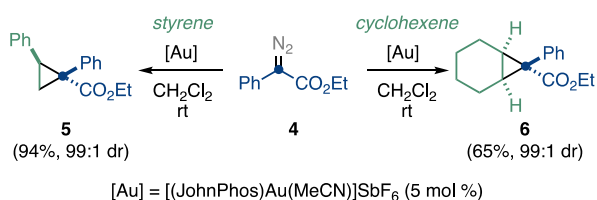
reaction with styrene gave a mixture of products of cyclopropanation (*cis/trans*) and formal aryl C–H insertion (*ortho*-, *meta*-, and *para*-). The generated acceptor gold(I) carbenes also undergo C–H, N–H, or O–H insertion reactions in the presence of alkanes,²⁶³ primary amines, or alcohols, respectively.

The same group reported the synthesis and characterization of cationic NHC–Au(I) complexes, which in the original report were generated in situ by chloride abstraction.²⁶² Such catalysts (e.g., $[(IPr)Au(MeCN)]PF_6$) proved to be active also in the cyclopropanation of styrene with EDA, giving quantitative conversion after 3 days to the products of cyclopropanation, 3b, exclusively. These cationic complexes did not require activation but were slower at promoting the carbene transfer process.²⁶⁴

The groups of Echavarren and Pérez studied this carbene transfer cyclopropanation with other cationic gold(I) catalysts, different alkenes, and donor–acceptor diazo compounds (Scheme 7).²⁶⁵

In this work, a range of cationic gold(I) complexes bearing phosphine, phosphite, and NHC ligands were tested, among

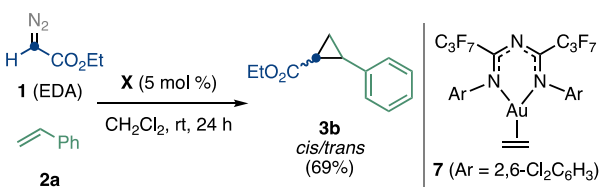
Scheme 7. Cyclopropanation Catalyzed by a Cationic Phosphine Gold(I) Complex



which [(JohnPhos)Au(MeCN)]SbF₆ performed best. In contrast to the original reports with EDA,²⁶² these reactions were remarkably efficient, allowing the use 1.1 equiv of the alkene partner while still maintaining significant yields. The products of cyclopropanation with these carbenes were obtained as single (*trans*- or *exo*-) diastereoisomers, following the general trend for donor–acceptor metal carbenes.²⁶⁶ In 2019, Pérez reported the cyclopropanation of ethylene, the simplest alkene, using ethyl diazoacetate in the presence of an NHC–gold(I) catalyst.²⁶⁷

A carbene transfer reaction from EDA was also carried out using gold(I) complexes bearing a polyhalogenated triazapentadienyl group and ethylene as ligands (7, Scheme 8). The reaction gives good yield of cyclopropane 3b, with only 2% C–H insertion side products.²⁶⁸

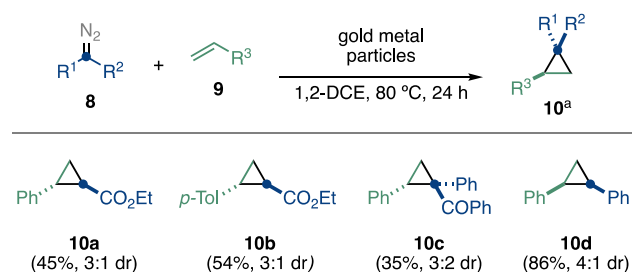
Scheme 8. Gold(I) Ethylene Complexes with Triazapentadienyl Ligands in Cyclopropanation



Besides gold(I) complexes, bulk gold metal has also been used to carry out similar transformations, with moderate yields and diastereoselectivities. The size of the gold particles, together with the morphology and composition of the metal surface, influenced the outcome of the carbene transfer reactions. For instance, the authors found that a freshly prepared urchin morphology (with incorporated carbon) is less active than smoother gold powder that is formed during the catalytic diazo-transfer processes themselves (Scheme 9).²⁶⁹

Corma and co-workers demonstrated the possibility of using simple salts such as NaAuCl₄ or KAu(CN)₂ in combination with ionic liquids for the same transformations.²⁷⁰ These salts rapidly

Scheme 9. Diazo–Carbene Transfer Cyclopropanation Promoted by Metallic Gold Particles

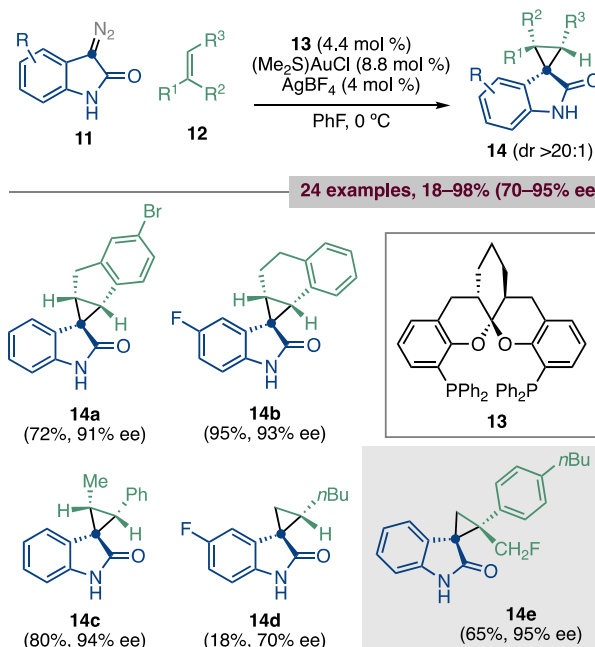


^aMajor diastereoisomer (*cis/trans*) depicted for each cyclopropane.

decompose and afford Au(0) nanoparticles, which remain stabilized in the ionic liquid and can be recovered after the reaction. Furthermore, the same group showed that gold-containing metal–organic frameworks (MOFs) can be employed to promote diazo-carbene transfer cyclopropanations.²⁷¹ This allowed the assembly of different acceptor cyclopropanes in moderate to good yields and moderate to excellent diastereoselectivities.

The field moved one step further when Zhou and co-workers reported the first general gold(I)-catalyzed enantioselective cyclopropanation via carbene transfer using diazooxindoles 11 (Scheme 10).²⁷² This method proved to be superior to the ones

Scheme 10. Enantioselective Gold(I)-Catalyzed Cyclopropanation with Diazooxindoles

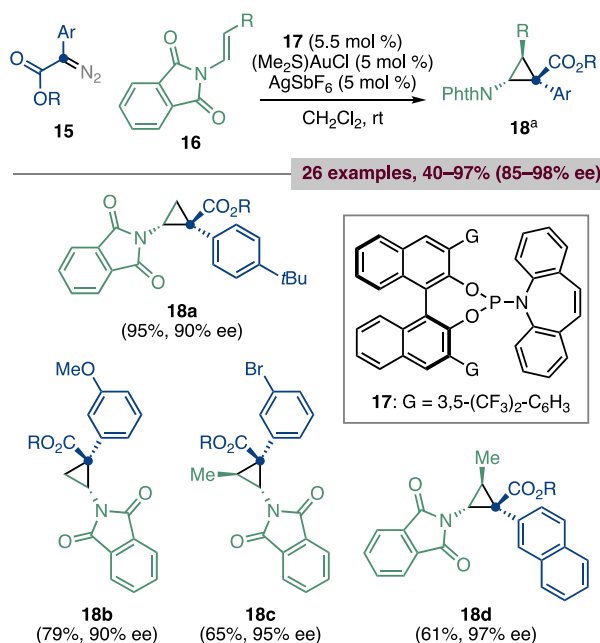


previously reported based on rhodium(II) (up to 74% ee)²⁷³ or mercury(II) catalysis (scope limited to simple styrene).²⁷⁴ In this work, a monoactivated digold complex derived from a spiroketal biphosphine (13) generated in situ was used to prepare a range of cyclopropanes in good yields, short reaction times, and excellent diastereo- and enantioselectivity with styrene-type alkenes. However, the yield and enantioselectivity dropped significantly when nonactivated alkenes such as 1-hexene (14d) were used. More recently, the system was expanded to the highly enantioselective cyclopropanation of interesting mono- and difluoromethylated styrenes, affording products such as 14e.²⁷⁵

A gold(I)-catalyzed enantioselective cyclopropanation of enamides using donor–acceptor diazo compounds was reported by the group of Zhang (Scheme 11).²⁷⁶ This transformation used Carreira ligand²⁷⁷ 17 for the synthesis of a range of densely substituted donor–acceptor cyclopropanes with high diastereo- and enantioselectivity. The presence of an additional β -methyl on the starting vinyl-phthalimide further improved the stereoselectivity of the transformation (18c,d). Remarkably, the reaction could be carried out with a moderate excess of the diazo-compound (1.5 equiv) on gram scale.

2.1.2. Cyclopropanation of Aromatic Rings: The Buchner Ring Expansion. The Buchner ring expansion

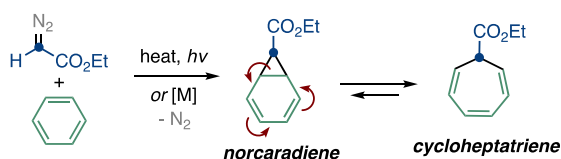
Scheme 11. Enantioselective Gold(I)-Catalyzed Cyclopropanation of Enamides^a



^aR = 2,6-*i*-Pr₂C₆H₃. Products obtained as the depicted *trans* single diastereoisomer.

reaction is used to assemble 1,3,5-cycloheptatrienes.^{278–280} It involves the cyclopropanation of an aromatic ring by a carbene (generated from a diazo compound with the aid of light, heat, or a metal catalyst), giving rise to a norcaradiene, which is in equilibrium with the corresponding cycloheptatriene through a 6-electron disrotatory electrocyclic process (valence tautomerism, Scheme 12).²⁸¹

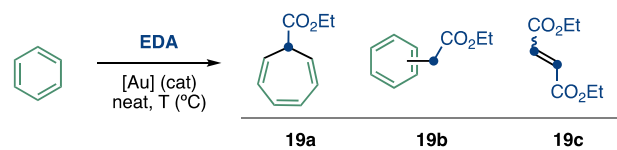
Scheme 12. Buchner Reaction



The first example of gold(I)-catalyzed cyclopropanation–ring expansion of benzene was described by the group of Pérez using EDA and an NHC–Au(I) complex as catalyst (Scheme 13, top). However, the main product of the reaction was 19b, due to formal insertion of the carbene into the C–H aromatic bonds (1:3 cyclopropanation/insertion ratio). The cyclopropanation/insertion ratio was moderately higher (2:3) when toluene was used instead of benzene.²⁶² Complementary to this reactivity, He and co-workers reported that gold(I) complexes bearing a terpyridine ligand (*t*-Bu₃tpy) promote selectively the Buchner ring expansion of benzene, without formal insertion, giving an equimolar mixture of diethyl maleate/fumarate (19c) as the only side products (Scheme 13, bottom).²⁸²

The reactivity of acceptor metal carbenes generated from EDA was studied using gold(I) complexes bearing several NHC ligands in addition to IPr.²⁸³ This, together with later reports,^{284–286} proved the ability of these coinage metal carbenes to engage not only in cyclopropanation/Buchner reactions but also in the C–H functionalization of saturated

Scheme 13. Gold(I)-Catalyzed Buchner Ring Expansion versus C–H Insertion



2005 (Pérez)

[Au] = (IPr)AuCl (5 mol %) + NaBAR₄^F (5 mol %) rt, 1 h

25%	75%	n/d
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2006 (He)

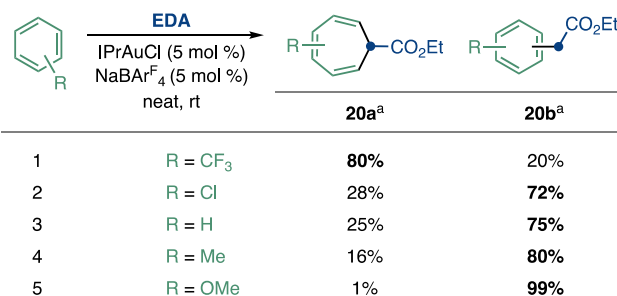
[Au] = [(*t*-Bu₃tpy)AuOTf]^a (3 mol %) 80 °C

57%	n/d	43%
-----	-----	-----

^a*t*-Bu₃tpy = 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine.

hydrocarbons. Thorough mechanistic investigations on the Buchner ring expansion versus C_{sp³}-H insertion of acceptor metal carbenes catalyzed by Au(I), Ag(I), and Cu(I) NHC complexes were disclosed showing a clear correlation between the electronics of the aromatic ring and the ratio of Buchner/insertion products (Scheme 14).²⁸⁷

Scheme 14. Buchner versus Insertion Reaction of Acceptor Gold(I) Carbenes

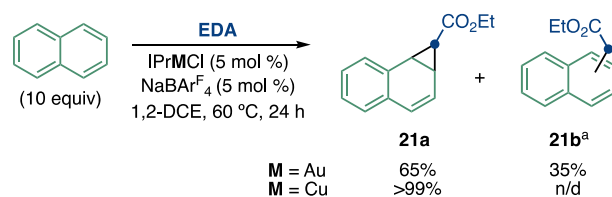


^aCombined amount of all possible regioisomers. In all cases, the total yield for the carbene transfer from EDA was at least 94%.

Finally, the cyclopropanation of a more extended aromatic system, naphthalene, was also achieved by the use of EDA in the presence of either Au(I) or Cu(I) NHC/chloride complexes (activated with NaBAR₄^F), the latter being the most effective and selective (Scheme 15).²⁸⁸

2.1.3. Cyclopropanation with Diazo Compounds. The most direct approach for the synthesis of cyclopropenes is the reaction of alkynes with metal carbenes generated from diazo compounds, which has been developed using complexes of different metals.^{289–294}

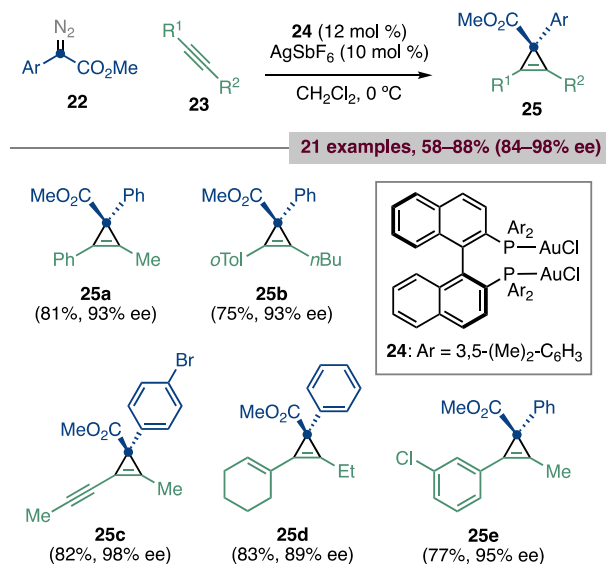
Scheme 15. Cyclopropanation of Naphthalene



^aObtained as a mixture of the two possible regioisomers.

Cyclopropanes are known to react in the presence of electrophilic gold(I) complexes, generating carbene intermediates (see section 2.3).²⁹⁵ In spite of this fact, the group of Davies successfully developed a highly enantioselective cyclopropanation of alkynes based on the use of donor–acceptor diazo compounds via gold-catalyzed carbene transfer (Scheme 16).²⁹⁶

Scheme 16. Gold(I)-Catalyzed Enantioselective Cyclopropanation of Internal Alkynes



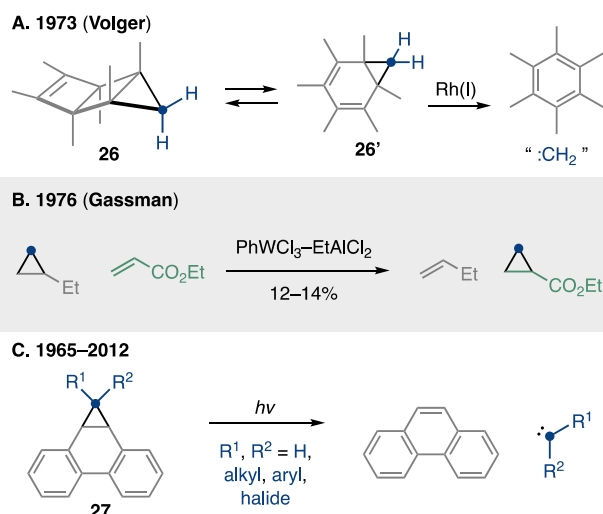
This is the asymmetric version of a transformation previously developed by the same group using silver(I) catalysis.²⁹⁷ Similar reactivity was previously achieved for less challenging terminal alkynes by chiral rhodium(II) catalysis.²⁹⁸ In this work, chiral digold phosphine complexes such as **24** were employed in combination with AgSbF₆. Internal alkynes with a broad range of substituents (alkyl, aryl, alkenyl, and alkynyl) were cyclopropanated in good yields and excellent enantioselectivities.

All the examples covered in this first section illustrate how diazo-carbene transfer reactions catalyzed by gold, along with other metals,^{247–260} are one of the most straightforward ways of assembling acceptor or donor–acceptor three-membered carbocycles. However, when it comes to assembling non-acceptor cyclopropanes via carbene intermediates, diazo compounds are usually not the reagents of choice for several reasons. Even though it is possible to prepare nonstabilized diazo compounds with only H (such as poisonous²⁹⁹ and hazardous diazomethane), aryl, vinyl, or alkyl substituents,⁶³ these are usually challenging to make, inherently unstable, explosive in pure form,³⁰⁰ difficult to store for long periods of time,^{244,245} and prone to diazo dimerization. For these reasons, great attention has been given recently to the development of alternative methods for the generation of donor metal carbenes.³⁰¹

2.2. Retro-Cyclopropanation or Decarbenation Reactions

A general method for accessing nonacceptor carbenes relies on retro-cyclopropanation or decarbenation reactions, in which the driving force is the release of an unstrained unsaturated organic fragment, usually aromatic, instead of gaseous nitrogen.³⁰² Volger reported that tricycle **26**, which is in equilibrium with its norcaradiene tautomer **26'**, reacts in the presence of [Rh(CO)₂Cl]₂ to give hexamethylbenzene quantitatively (Scheme 17A).³⁰³ Later, Gassman described the possibility of using

Scheme 17. Retro-Cyclopropanation Reactions: Historical Perspective

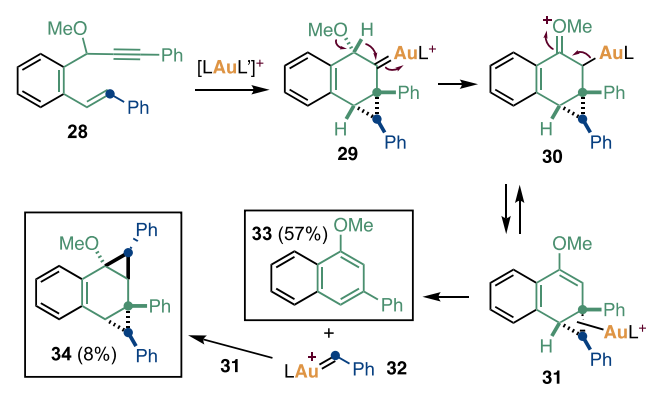


highly electrophilic PhWCl₃–EtAlCl₂ to carry out a cyclopropane–alkene metathesis via retro-cyclopropanation of simple ethylcyclopropane (Scheme 17B).^{304,305} Furthermore, several groups disclosed the photolytic decarbenation reaction of phenanthrene derivatives **27** (Scheme 17C).^{306–309}

Despite these and a few other observations,^{310–312} the possibility of using carbenes released by retro-cyclopropanation in a synthetically useful manner was not clear at the time. It was not until gold(I) catalysis was brought into play that decarbenation reactions emerged as a general and safe alternative to assemble nonacceptor cyclopropanes.³⁰²

2.2.1. Decarbenation or Retro-Buchner Reaction of Cycloheptatrienes. The group of Echavarren disclosed the formation of free aryl gold(I) carbenes in the context of cycloisomerization of enynes such as **28** (Scheme 18).

Scheme 18. Retro-Buchner or Decarbenation Reaction of Cycloheptatrienes

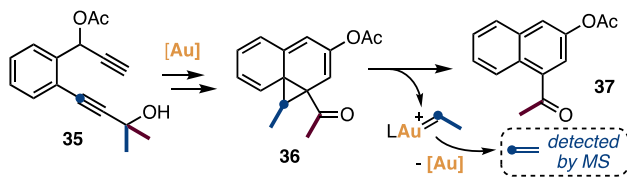


Cyclization results in the formation of electron-rich benzo-fused norcaradienes **31**, which undergo a retro-cyclopropanation or decarbenation process to give naphthalene derivatives **33**, while releasing free aryl carbenes **32**. The presence of these intermediates was confirmed by the formation of **34** via cyclopropanation of another molecule of **31** (Scheme 18).³¹³

The group of Hashmi later proposed a retro-Buchner pathway for the formation of a naphthalene by a gold(I)-catalyzed diyne cycloisomerization (Scheme 19).³¹⁴ Extrusion of a carbene unit

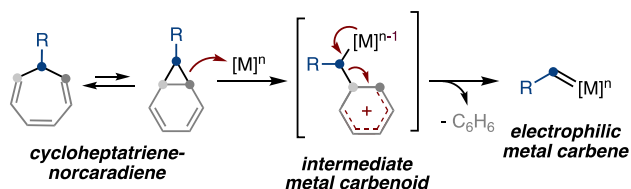
from benzo-fused norcaradiene **36**, which results in the release of ethylene (detected by MS), would be the driving force of the process.

Scheme 19. Formation of Naphthalenes by Retro-Cyclopropanation of a Benzo-fused Norcaradiene



Mechanistically, these reactions proceed analogously to the formation of metal carbenes by diazo decomposition (see Scheme 5 and Scheme 20).³¹⁵ Breaking the first C–C bond of

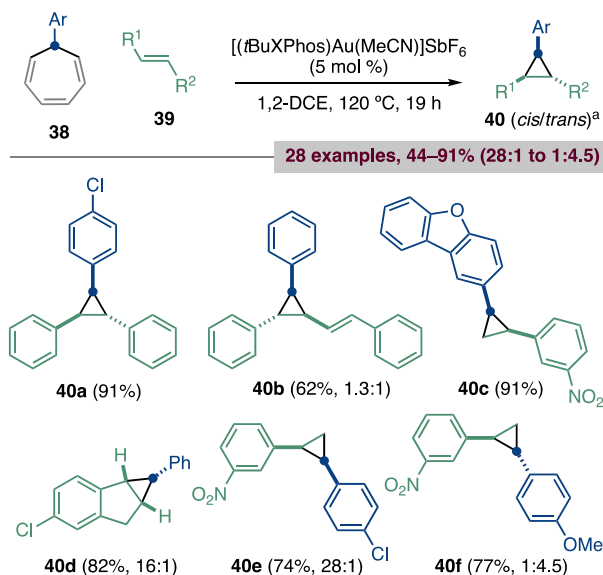
Scheme 20. Retro-Buchner or Decarbenation Reaction of Cycloheptatrienes



the norcaradiene tautomer leads to a carbenoid-like Wheland intermediate, which evolves by release of the aromatic fragment (e.g., benzene), generating the corresponding metal carbene.

This concept, discovered through the retro-cyclopropanation of benzo-fused norcaradienes such as **31**, led to the development of 7-aryl-1,3,5-cycloheptatrienes **38** as precursors of aryl gold(I) carbenes, which were used to cyclopropanate a range of styrenes and stilbenes with moderate to high diastereoselectivities (Scheme 21).³¹⁶ This allows the easy assembly of trisubstituted nonacceptor cyclopropanes (**40a,b**), which would be challeng-

Scheme 21. Aryl Cyclopropanation by Decarbenation or Retro-Buchner Reaction

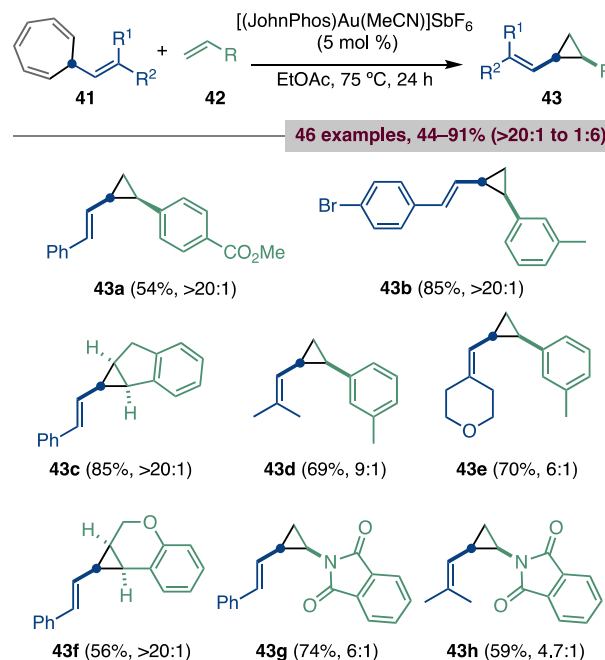


^aYield and *cis/trans* ratio between parentheses.

ing synthetic targets by other methods involving the use of potentially dangerous aryl diazo compounds.^{244,245} In this case, 7-aryl cycloheptatrienes are used, which can be prepared in one step by reaction of aryl lithium or Grignard reagents with commercially available tropylium tetrafluoroborate.

This method was extended to a broad-scope gold(I)-catalyzed *cis*-vinylcyclopropanation of alkenes using 7-vinyl and 7-styryl-1,3,5-cycloheptatrienes **41** as carbene precursors, which are more reactive than their corresponding 7-aryl analogs (requiring 75 °C instead of the 120 °C from the original work) (Scheme 22).³¹⁷

Scheme 22. Synthesis of *cis*-Vinylcyclopropanes



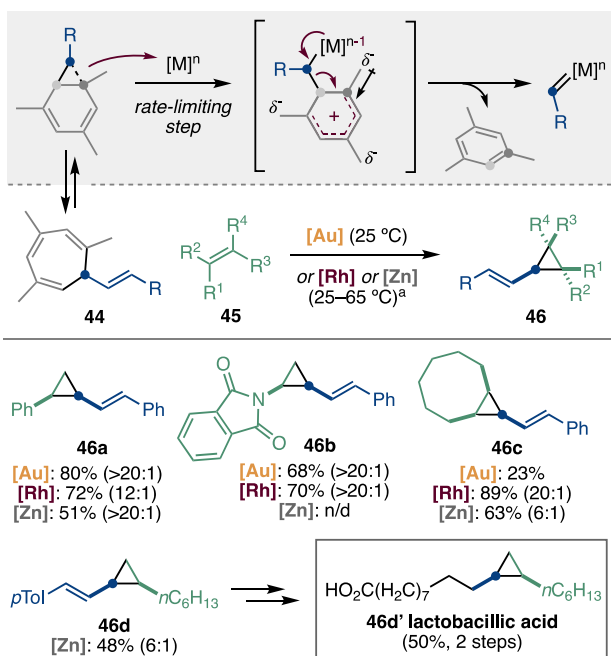
A new design, based on the hypothesis that electron-donating groups in the cycloheptatriene ring would lower the energy required to reach the cationic Wheland-type intermediate involved in the rate-limiting step of the decarbenation reaction, led to the development of a second generation of more reactive carbene precursors³¹⁸ (Scheme 23, top). Thus, 7-substituted 1,3,5-trimethyl-1,3,5-cycloheptatrienes **44** undergo the gold(I)-catalyzed retro-Buchner reaction at 25 °C. Importantly, these reagents allowed researchers to carry out, for the first time, efficient decarbenation reactions catalyzed by zinc(II) salts (such as inexpensive ZnBr₂)³¹⁸ or rhodium(II) complexes (unlocking new reactivity).³¹⁹

This kind of vinyl gold(I) or rhodium(II) carbenes can also be trapped efficiently by enol ethers (Scheme 24), assembling densely substituted cyclopropyl ethers.³²⁰ Under rhodium(II) catalysis, nonacceptor cyclopropanes **49** can be opened to give all-*E* trienes, upon release of methanol.

Based on the same concept of release of an aromatic molecule, benzo-fused norcaradienes derived from naphthalene (**51**) and phenanthrene (**52**) were also developed.³²¹ These persistent cyclopropanes can be retro-cyclopropanated under gold(I) catalysis, and the corresponding carbenes can be trapped with alkenes to afford cyclopropanes (Scheme 25).

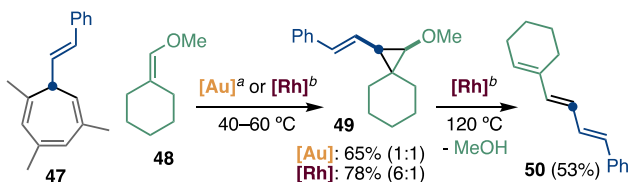
Besides cyclopropanation reactions, metal carbenes generated by retro-Buchner reaction of cycloheptatrienes have been employed to develop new formal cycloadditions^{322,323} and C–

Scheme 23. Second Generation of Cycloheptatrienes as General Metal Carbene Precursors



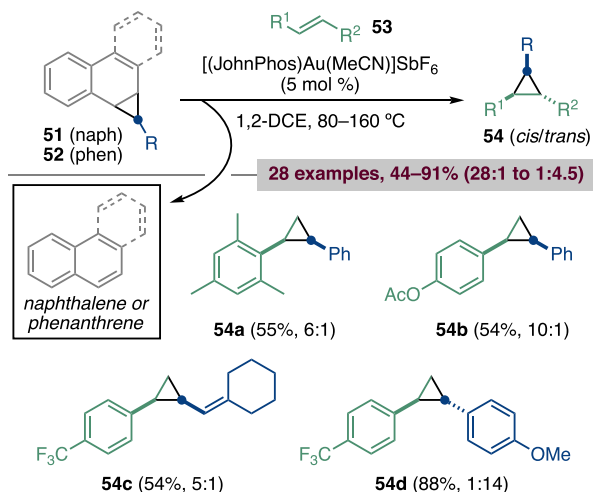
^a[Au] = [(JohnPhos)Au(MeCN)]SbF₆ (5 mol %) in EtOAc at 25 °C. [Rh] = Rh₂TFA₄ (3 mol %) in 1,2-DCE at 25–60 °C. [Zn] = ZnBr₂ (10 mol %) in 1,2-DCE at 65 °C.

Scheme 24. Au(I)- or Rh(II)-Catalyzed Cyclopropanation of Enol Ethers



^a[Au] = [(JohnPhos)Au(MeCN)]SbF₆ (5 mol %) in 1,2-DCE at the specified temperature. ^b[Rh] = Rh₂TFA₄ (5 mol %) in 1,2-DCE at the specified temperature.

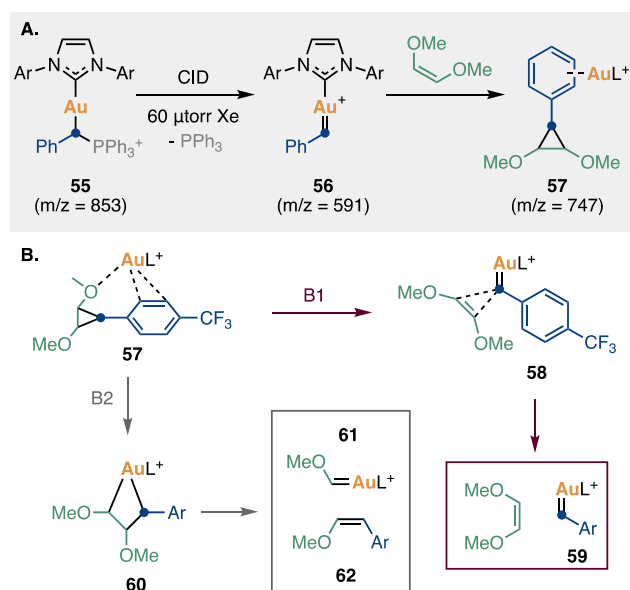
Scheme 25. Gold(I)-Catalyzed Decarbenation of Persistent Cyclopropanes



H/X–H insertion reactions^{319,324} and in the total synthesis of natural products.^{318,319,323}

2.2.2. Gold Carbenes in Gas Phase by Retro-Cyclopropanation. The group of Chen reported the first the gas-phase generation of an aryl gold(I) carbene complex. This was accomplished by collision-induced dissociation (CID) of phosphonium ylide gold complexes such as **55** (Scheme 26).^{325–329} These highly energetic intermediates show the

Scheme 26. Gold(I)-Carbenes by Retro-Cyclopropanation in Gas Phase



expected reactivity for gold(I) carbenes, cyclopropanating alkenes (Scheme 26A). This process is reversible (Scheme 26B), and the same cyclopropanes can give back the original metal carbene and alkene (pathway B1). Alternatively, a different alkene (**62**) and carbene units (**61**) can be released (pathway B2), resulting in an overall cross-metathesis-type process.

2.3. Cyclopropane Opening Followed by Cyclopropanation

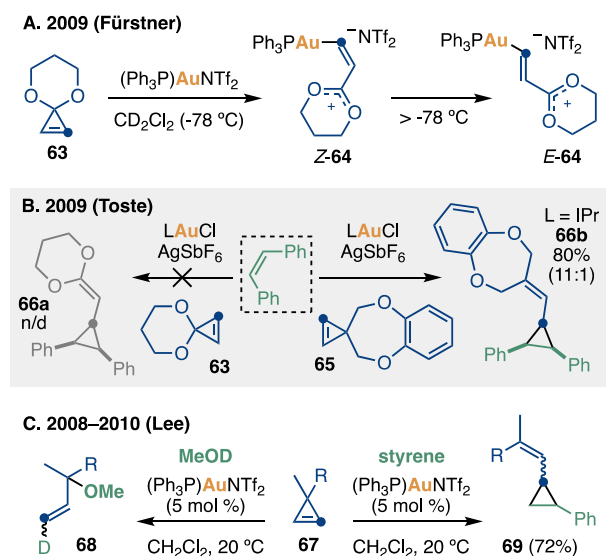
Cyclopropanes have also been established over the past decade as a safe and reliable source of metal carbenes.²⁹⁵ Long after cyclopropanes were discovered to be reactive under metal catalysis,^{40,330} it was reported that in the presence of cationic gold(I) complexes cyclopropanes can be opened, generating vinyl carbenes **64** (or gold-stabilized carbocations), which can be characterized spectroscopically (Scheme 27A)³³¹ or trapped by organic nucleophiles, such as alkenes, alcohols, arenes, or carbonyl groups, among others (Scheme 27B).^{295,332–338}

Analogously to other gold(I) carbene sources, cyclopropanes react with alkenes to give cyclopropanes, as first revealed by the groups of Lee,³³⁴ and Toste³³² (Scheme 27B,C). The opening process promoted by gold has also been studied computationally.^{339,340}

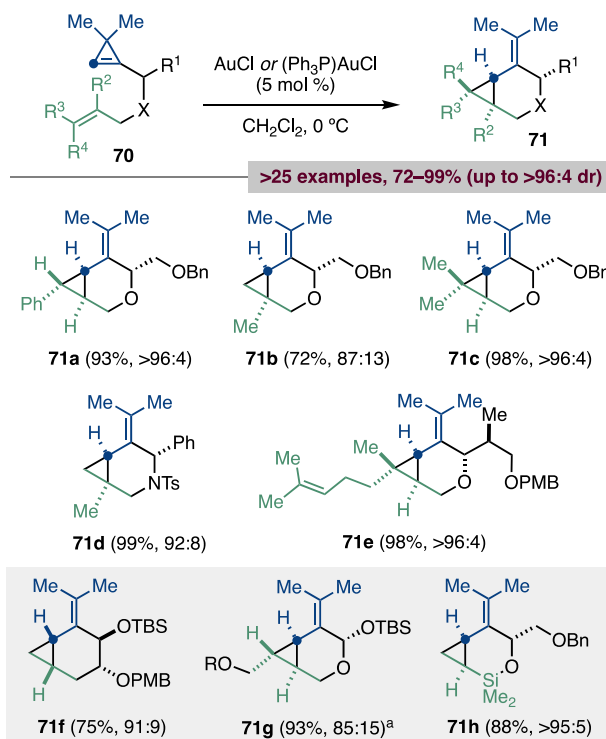
The group of Cossy reported an intramolecular approach for the synthesis of fused cyclopropanes by gold(I)-catalyzed disassembly of cyclopropanes. This allowed access to densely functionalized 3-oxa- and 3-azabicyclo[4.1.0]heptanes **71** in excellent yields and diastereoselectivities (Scheme 28, top).³⁴¹

This method was extended to the synthesis of a diverse range of bicyclic structures (Scheme 28, bottom), which could be elaborated to assemble synthetically complex cyclopro-

Scheme 27. Characterization and Reactivity of Gold(I) Carbenes via Cyclopropenes

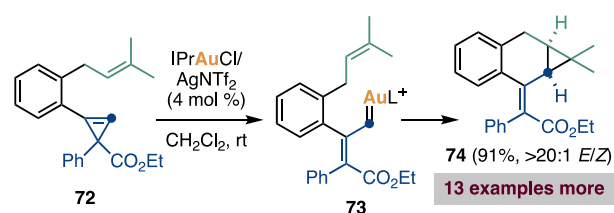


Scheme 28. Cyclopropene Opening and Intramolecular Vinylcyclopropanation of *O*- and *N*-Tethered 1,6-Cyclopropene-enes



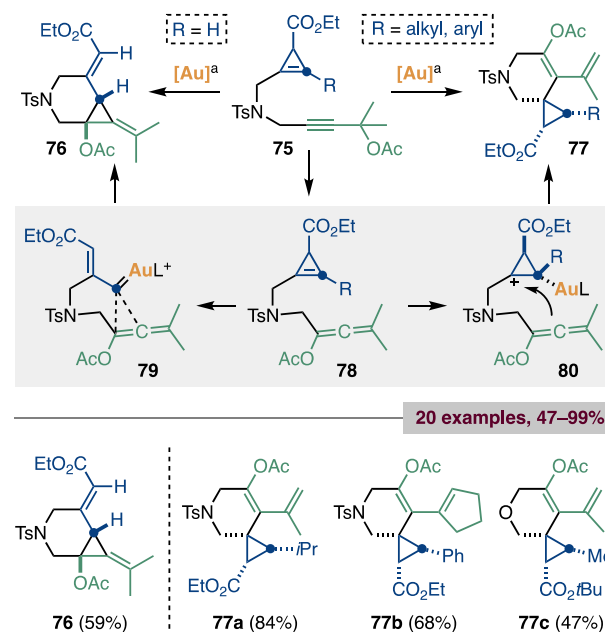
panes.^{342,343} Following a similar strategy, Liu and co-workers reported the cyclization of cyclopropene-enes such as **72** under gold catalysis to assemble cyclopropanes **74** in good yields and high *E/Z* ratios. The starting cyclopropenes were prepared by rhodium(II)-catalyzed cyclopropanation of the corresponding alkynes. Further treatment with a gold(I) complex triggers the cyclopropene opening, generating a vinyl carbene that undergoes intramolecular cyclopropanation (Scheme 29).

Scheme 29. Cyclopropene Opening and Cyclopropanation of Benzene-Tethered 1,6-Cyclopropene-enes



Two different scenarios were explored by Tang and co-workers using propargyl esters as the nucleophilic component (after isomerization to the corresponding allene) (Scheme 30).³⁴⁵ When 1,3-disubstituted cyclopropenes **75** were

Scheme 30. Cyclopropene Opening and Substrate-Dependent Divergent Cyclopropanation



employed (R = H), the cyclopropene ring opens under gold(I) catalysis generating vinyl carbene **79**, which cyclopropanates the proximal double bond of the allene, giving 3-azabicyclo[4.1.0]heptanes such as **76**. On the other hand, 1,2,3-trisubstituted cyclopropenes **75** give spirocyclic cyclopropanes **77**, presumably through cationic intermediate **80**.

The vinylcyclopropanation of furans through gold(I)-catalyzed opening of cyclopropenes results in the direct disassembly of the corresponding intermediates to afford conjugated trienyl-ketones.³⁴⁶ In a complementary manner, the cyclopropane intermediates can be isolated when performing the same reaction under Zn(II) catalysis.³⁴⁷ In heterogeneous phase, gold metal particles were also employed for the opening of 3,3-diphenylcyclopropene and subsequent trapping with styrene.²⁶⁹ Beyond cyclopropanations, many other methods have been recently developed based on the use of cyclopropenes as carbene sources under catalysis of different metals,^{348–353} but they fall out of the scope of this review.

2.4. Enynes, Allenynes and Diynes Cycloisomerization Terminated with Cyclopropanation

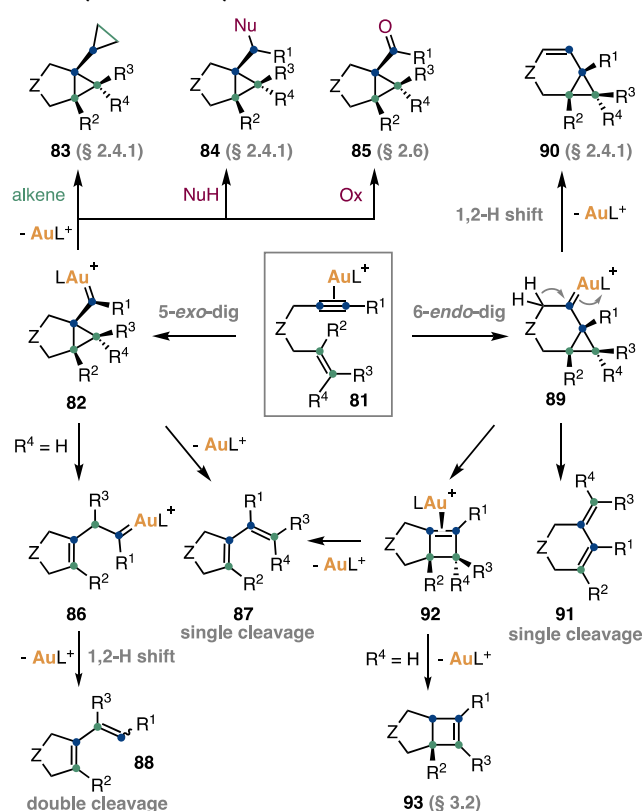
Reactions forming cyclopropyl-containing scaffolds are presented in this section divided by substrate type: enynes (1,6-enynes, 1,5-enynes, and other kinds of enynes), allenynes and diynes.

2.4.1. Cycloisomerization of Enynes. 2.4.1.1. 1,6-Enynes.

Gold complexes are selective carbophilic π acids for the activation of multiple C–C bonds,^{119–135} such as those of alkynes, alkenes, and allenes. Gold-catalyzed cycloisomerizations of enynes have been studied extensively since the beginning of the XXI century.^{185–206,354} When interacting with an enyne, Au(I) can form η^2 -complexes with either the triple or the double bond.^{355,356} The higher affinity for alkynes in front of alkenes (termed alkynophilicity) is a kinetic effect driven by the lower LUMO of the η^2 -alkyne gold complex, hence its higher propensity to undergo nucleophilic attack.³⁵⁷

The cycloisomerizations of Au(I)-activated 1,6-enynes **81** lead to cyclopropyl gold carbenes **82** and **89** by 5-*exo*-dig and 6-*endo*-dig cyclizations, respectively (Scheme 31). The pathway

Scheme 31. Main Au(I)-Catalyzed Cycloisomerization Pathways for 1,6-Enynes

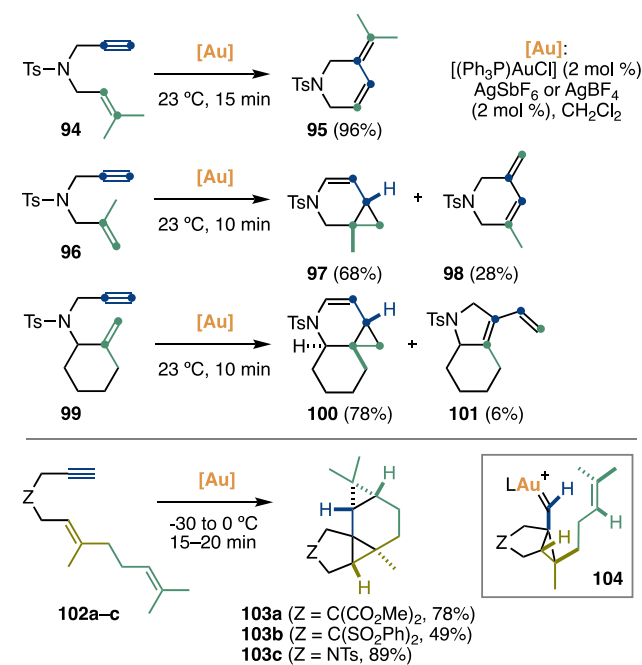


followed by a given enyne depends mostly on its substitution pattern; thus 5-*exo*-dig cyclization is kinetically favored for terminal alkynes, while enynes with internal alkynes or heteroatoms at the tether generally undergo 6-*endo*-dig cyclizations.^{358,359} Cyclopropyl gold carbenes have highly delocalized structures, to which the resonance forms of gold(I)-stabilized cyclopropylmethyl, cyclobutyl, and homoallyl carbocations contribute to a greater or lesser extent depending on substitution and the ancillary ligand on gold.^{235,236,331–333,360–362} They can be trapped by alkenes, C-nucleophiles, or oxidants affording bicyclo[3.1.0]hexanes **83**,

84, and **85**, whose preparation is described in this section (compounds **85** are covered in section 2.6 on α -oxo gold carbenes, as they can be obtained also via alkyne oxidation followed by cyclopropanation). Alternatively, cyclopropyl gold carbenes **82** can evolve to dienes **87** and **88** through single cleavage and double cleavage rearrangements, respectively. Gold carbenes **89** lead to bicyclo[4.1.0]heptenes **90** after 1,2-H shift and deauration. On the other hand, they could also undergo single-cleavage rearrangements to dienes **91** or isomerize with ring expansion to (η^2 -cyclobutene)Au(I) complexes **92**. The latter evolve to cyclobutenes **93** by gold decoordination (see section 3.2) or to dienes **87** by ring opening. 1,6-Enynes with an ester or amide tether (i.e., with a carbonyl rather than a CH₂ unit between the alkyne and the heteroatom linker Z) proceed via a different mechanism to fused cyclobutene products (see section 3.2).³⁶³

The first study on gold(I)-catalyzed rearrangements and alkoxy cyclizations of a variety of 1,6-enynes was reported by the group of Echavarren (Scheme 32).^{364,365} Compared to the other

Scheme 32. Au(I)-Catalyzed Cycloisomerizations of 1,6-Enynes and Intramolecular Cyclopropanation of Diynes

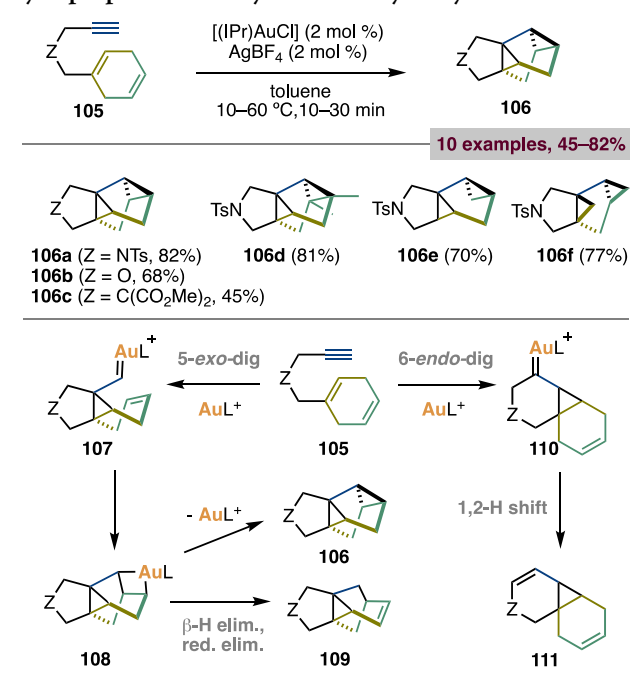


metal catalysts known at the time for enyne activation,^{185–206,366–379} Au(I) complexes stood out for their high activity even at low temperatures and for their ability to trigger different mechanisms. The alkoxy cyclizations of 1,6-enynes proceed more readily under Au(I) than Pt(II) catalysis,^{358,359} and indeed lower energy barriers were computed for the 5-*exo*-dig and 6-*endo*-dig cyclizations of model enyne (*E*)-6-octen-1-yne catalyzed by the [AuPH₃]⁺ fragment with respect to *trans*-[Pt(H₂O)Cl₂].³⁸⁰ The high substrate dependence of the cycloisomerization pathways for *N*-tethered 1,6-enynes is evident from the selected examples reported in Scheme 32: substrates **94**, **96**, **99** preferentially underwent 6-*endo*-dig cyclizations,³⁸¹ whereas diynes **102a–c** cyclized in a 5-*exo*-dig mode. Cyclopropyl gold carbene **104**, with antiperiplanar arrangement of the cyclopropane and metal carbene, was then trapped by the pendant alkene affording tetracycles **103a–c** as single diastereomers. The scope of the intramolecular bis-

cyclopropanation of dienynes was expanded, and DFT computations indicated that the second cyclopropanation proceeding through *anti*, rather than *syn*, gold carbene intermediates such as **104** is kinetically and thermodynamically more favorable.³⁸²

Chung and co-workers reported the bis-cyclopropanation of dienynes **105**, possessing a 1,4-diene moiety, to give compounds **106** with a tetracyclo[3.3.0.0^{2,8}.0^{4,6}]octane skeleton (Scheme 33).³⁸³ A tentative mechanism, depicted as proposed by the

Scheme 33. Au(I)-Catalyzed Intramolecular Cyclopropanation of Cyclohexadienyl Alkynes

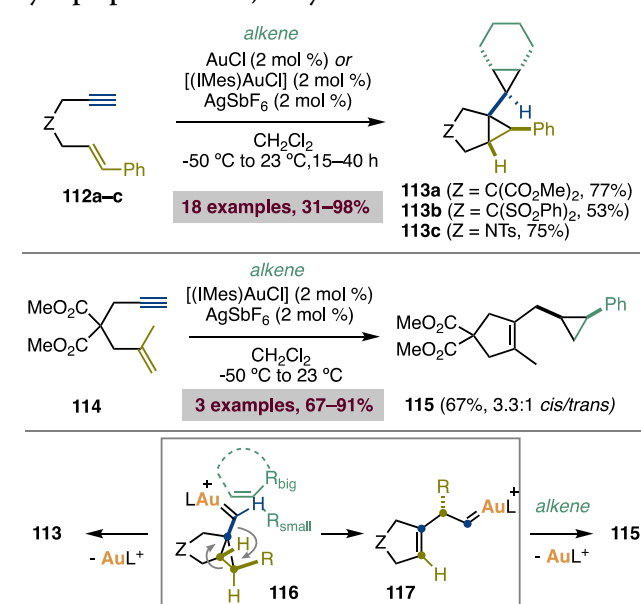


authors, accounts also for the formation of products **109** and **111**, obtained using other Au(I) complexes. The same group later described the formal [4 + 2] cycloaddition of *N*-tethered enynes with a 1,3-diene unit³⁸⁴ and prepared related 4-oxa-6-azatricyclo[3.3.0.0^{2,8}]octanes by cycloisomerization of *N*-tethered internal 1,6-enynes bearing an allylic alcohol.³⁸⁵ *O*-Tethered 1,6-enynes with an enol ether as the alkene component delivered similarly complex cage structures.³⁸⁶

The intermolecular version of these reactions was developed trapping with external alkenes two different cyclopropyl gold carbene intermediates (**116** and **117**) generated from 1,6-enynes (Scheme 34).^{387,388} Cyclopropyl gold carbene **116** can convert to intermediate **117** in a stepwise or concerted manner, namely via a 1,2-shift of the carbene C atom of **116** with concomitant cleavage of the cyclopropane distal C–C bond and double bond formation.²¹⁴ 1,3-Metallotropic shift of the Au(I) carbene along a conjugated alkyne, followed by intramolecular cyclopropanation by the transposed carbene, was also observed.

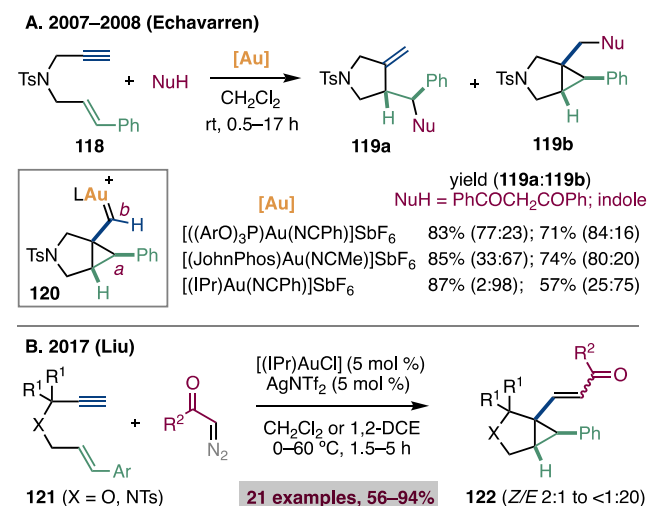
Additional experimental and computational investigations revealed that the cyclopropanation of alkenes with 1,6-enynes is a process proceeding via electrophilic cyclopropyl gold carbenes, which can occur both in a concerted (for aliphatic, electronically unbiased alkenes) and in a stepwise fashion (for polarized alkenes such as styrenes or enol ethers).^{320,388,327} Regardless, the reaction remains stereospecific with respect to the alkene geometry because the second C–C bond formation has a very low barrier.

Scheme 34. Au(I)-Catalyzed Intermolecular Cyclopropanation of 1,6-Enynes with Alkenes



Cyclopropyl gold carbenes generated from 1,5- and 1,6-enynes were trapped also by other nucleophiles, such as electron-rich arenes and dicarbonyl compounds (Scheme 35A).^{389,390} With some exceptions, phosphite ligands directed

Scheme 35. Trapping of Cyclopropyl Gold Carbenes Generated from 1,6-Enynes^a

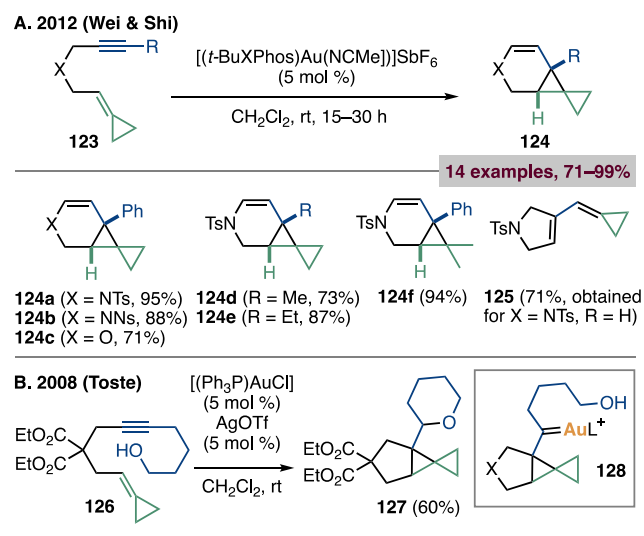


^a(ArO)₃P = (2,4-(*t*-Bu)₂C₆H₃O)₃P

nucleophilic attack at the cyclopropyl carbon *a* in intermediate **120** yielding predominantly exocyclic alkenes **119a**, whereas more electron-donating ligands favored attack at the carbene carbon *b* delivering products **119b**. Later, Liu and co-workers reported that cyclopropyl gold carbenes generated in a 5-*exo*-dig fashion from 1,6-enynes can be trapped by aryl diazo ketones (Scheme 35B).³⁹¹

Wei and Shi reported that the cycloisomerizations of *N*- and *O*-tethered alkylidenecyclopropanes **123** deliver tricyclic compounds **124** in high yields via the expected 6-*endo*-dig pathway, as long as the alkyne is internal (Scheme 36A).³⁹² An enyne with a terminal triple bond proceeded instead to diene

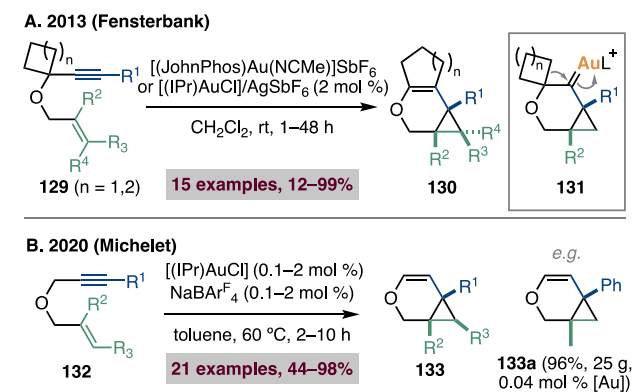
Scheme 36. Au(I)-Catalyzed Cycloisomerization of Alkylidencyclopropanes



125 via 5-*exo*-dig cyclization. This reactivity contrasts with the rare 6-*exo*-dig cyclization previously observed by the group of Toste for a C-tethered 1,6-enyne (Scheme 36B),³⁹³ highlighting once again the substrate dependence of gold(I)-catalyzed enyne cycloisomerizations. Indeed, from *O*- and *C*-tethered 1,6-enynes, allene products have also been prepared using gold catalysis.³⁹⁴

Fensterbank and co-workers combined the cycloisomerizations of 1,6-enynes with ring expansion, preparing a range of enol ethers **130** (Scheme 37A).³⁹⁵ The key step involves a

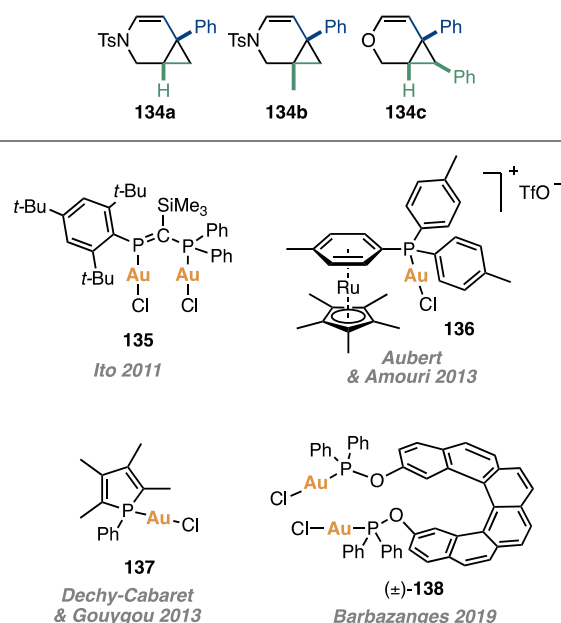
Scheme 37. Cycloisomerization of *O*-Tethered 1,6-Enynes



Wagner–Meerwein transposition onto the carbene center of intermediate **131**. The group of Michelet recently exploited the cycloisomerization of *O*-tethered 1,6-enynes for the efficient preparation of relatively volatile enol ethers with distinctive olfactory properties (Scheme 37B).³⁹⁶

All in all, the 6-*endo*-dig cycloisomerizations of *O*- and *N*-tethered 1,6-enynes to products **134a**, **134b**, and **134c** have become standard reactions to test the performance of new gold complexes, such as **135**,³⁹⁷ **136**,³⁹⁸ **137**,³⁹⁹ and **138**⁴⁰⁰ (Scheme 38). Enantioselective variants have been achieved employing chiral mono- or dinuclear Au(I) complexes **139**,^{401,402} **140**,^{403,404} **141**,⁴⁰⁵ **142**,⁴⁰⁶ **143**,⁴⁰⁷ **144**,⁴⁰⁸ **145**,⁴⁰⁹ **146**,⁴¹⁰ and **147**⁴¹¹ (Scheme 39). Phosphoramidite gold complex **140** was used for the asymmetric synthesis of antidepressant candidate

Scheme 38. Gold Complexes for Non-asymmetric Cycloisomerizations of *O*- and *N*-Tethered 1,6-Enynes



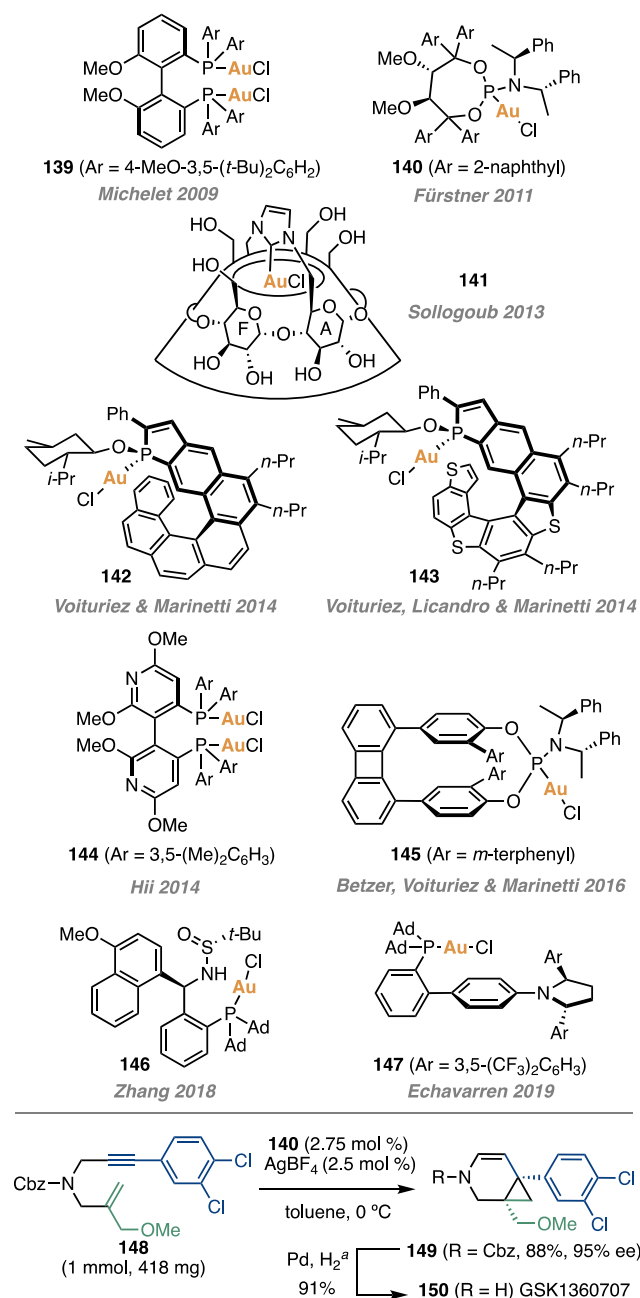
150,⁴⁰³ performing significantly better than commercially available chiral phosphines (Scheme 39, bottom).⁴¹²

Under gold(I) catalysis, *C*-tethered 1,6-enynes deliver cyclopropane-containing products in some particular instances: (i) upon trapping the gold carbene intermediates with alkenes intra-^{364,365,382} or intermolecularly^{387,388} (as discussed above); (ii) upon reaction with carbonyl compounds,^{413,414} and (iii) upon 1,5-OR migration of propargylic groups.⁴¹⁵ The group of Helmchen disclosed that the addition of aldehydes and ketones to terminal 1,6-enynes yields 2-oxabicyclo[3.1.0]hexanes **153** stereoselectively (Scheme 40).^{413,414} The mechanism, supported by DFT calculations, begins with the formation of cyclopropyl gold carbene **154** by 5-*exo*-dig cyclization, followed by a double-cleavage rearrangement to intermediate **155**. Attack by the carbonyl O atom, ring closure, and finally cyclopropane formation deliver the product and regenerate the active species.

Under Au(I) catalysis, dienynes carrying a propargylic alcohol, ether, silyl ether, or ester react by tandem 5-*exo*-dig cyclization/1,5-OR migration/intramolecular cyclopropanation (Scheme 41).⁴¹⁵ Cyclopropyl gold carbene **161** was found to undergo 1,5-OR migration via nearly barrierless transition state **162**, delivering gold-substituted allylic carbocation/ α,β -unsaturated gold carbene **163**.⁴¹⁶ The 1,5-OR migration was faster than the intramolecular cyclopropanation and even of 1,2- and 1,3-acetoxy shift (see section 2.5), thus avoiding racemization of propargylic stereocenters.

This cascade reaction was performed on enantioenriched dienyned **164** as the key step in the synthesis of three aromadendrane sesquiterpenes, prepared in 12–17% overall yields from (*E,E*)-farnesol (Scheme 42).⁴¹⁷ Compounds **165** and **166** with epimeric stereocenters were obtained either by 1,5-OBn migration or intermolecular nucleophilic attack on cyclopropyl Au(I)-carbene-like intermediate **167**.

1,6-Enynes **168** followed the same reactivity pattern. In this case, after 1,5-OR migration, intermolecular cyclopropanation occurred (Scheme 43).^{415–418} From compounds **170b** and **170c**, first-⁴¹⁸ and second-generation⁴¹⁶ syntheses of sesquiterpene (+)-schisanwilsonene **A** were accomplished.

Scheme 39. Gold Complexes for Enantioselective Cycloisomerizations of *O*- and *N*-Tethered 1,6-Enynes

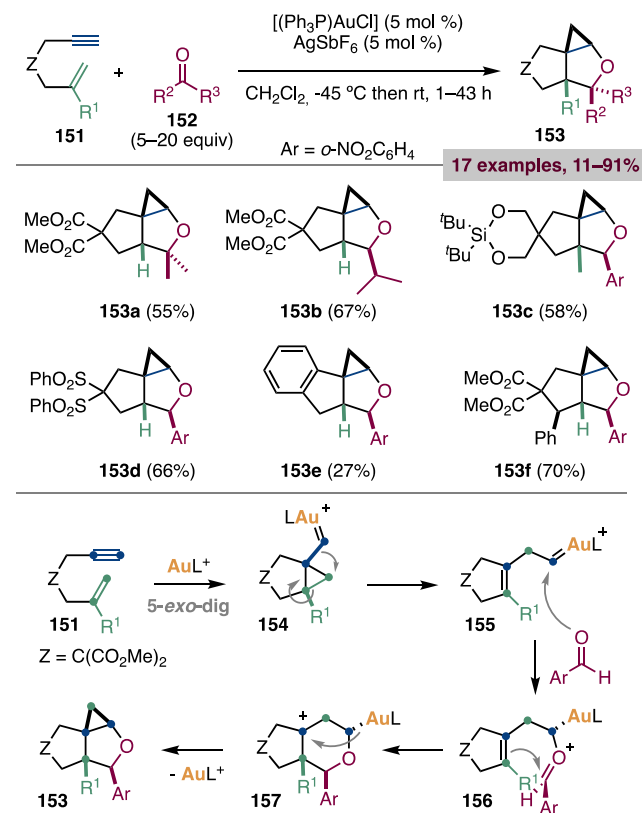
^aPd black (2.5 mol %), H₂ (1 atm), Na₂CO₃, EtOAc/MeOH (1:1).

A special class of 1,6-enynes with an ynamide tether and a propargylic alcohol follows yet another pattern when treated with gold. Thus, the group of Cossy described the AuCl-catalyzed formation of azabicycles 173 in moderate yields, through 5-*exo*-dig cyclization and 1,2-H shift onto gold carbene 174 (Scheme 44).^{419,420}

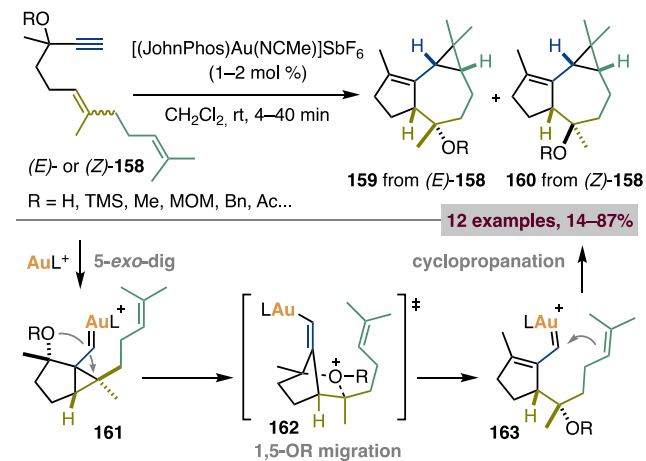
2.4.1.2. 1,5-Enynes. Gold-activated 1,5-enynes typically react by 5-*endo*-dig cyclization to give bicyclo[3.1.0]hexane systems, as 4-*exo*-dig cyclization would afford strained bicyclo[2.1.0]-pentanes.

The groups of Fürstner²¹² and Malacria⁴²¹ independently reported that 3-hydroxylated 1,5-enynes such as 175 cyclisomerized to bicyclo[3.1.0]hexanones 176 using Au(I) complexes at room temperature or PtCl₂ upon heating (Scheme

Scheme 40. Synthesis of 2-Oxabicyclo[3.1.0]hexanes

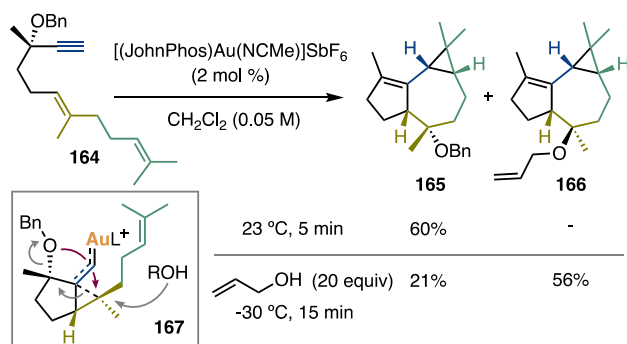


Scheme 41. Tandem Cyclization/1,5-OR Migration/Intramolecular Cyclopropanation of Dienynes

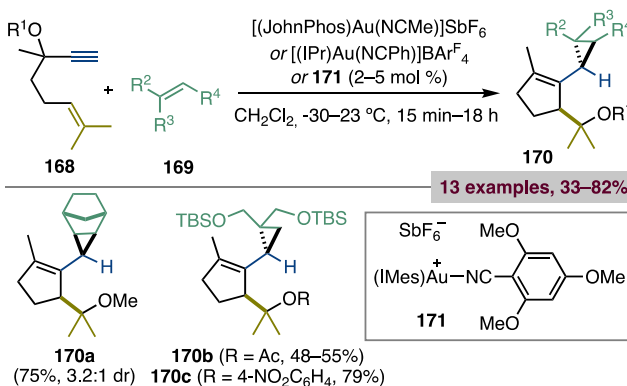


45). As already noted for the alkoxycyclizations of 1,6-enynes,^{364,365} the use of Au(I) rather than Pt(II) catalysts allowed the reaction to proceed under milder reaction conditions (lower temperature and reduced catalyst loading). The initially formed cyclopropyl Au(I) carbene 177 collapses by 1,2-hydride shift and loss of gold(I). Further studies by Gagosz probed the generality of the transformation on 3-hydroxy, 3-benzyloxy, and 3-acetoxy 1,5-enynes, highlighting the substrate dependence of the reaction manifold.⁴²² Various gold(I) precatalysts combined with chloride scavengers are effective in this transformation.⁴²³ However, only one asymmetric gold-catalyzed version has been developed to date using a planar chiral ferrocenylphosphine gold(I) complex to induce moderate enantioselectivity.^{424,425}

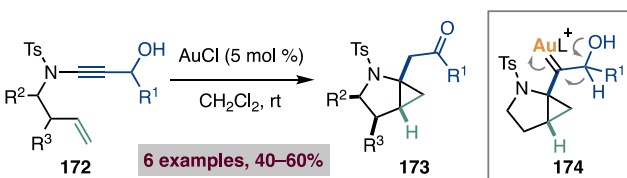
Scheme 42. Gold-Catalyzed Formation of the Tricyclic Cores of Aromadendranes



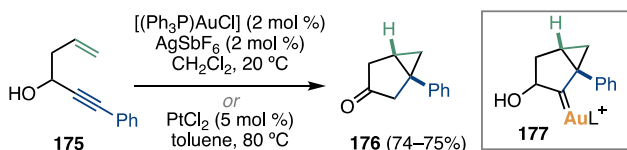
Scheme 43. Tandem Cyclization/1,5-OR Migration/Intermolecular Cyclopropanation of 1,6-Enynes



Scheme 44. Cycloisomerization of 1,6-Ene-Ynamides



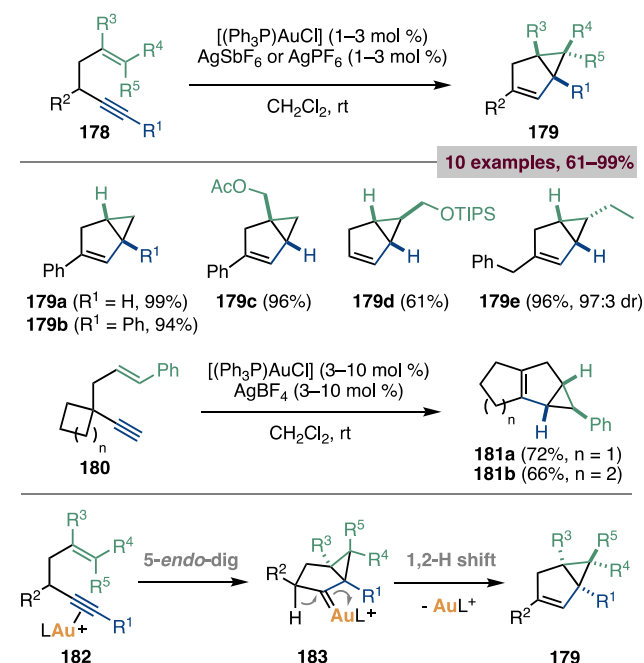
Scheme 45. Gold(I)- or Pt(II)-Catalyzed Cycloisomerization of 3-Hydroxy-1,5-enynes



The group of Toste disclosed that Au(I) and Au(III) complexes greatly outperformed Pt(II), Pd(II), and Ag(I) catalysts in the cycloisomerization of 1,5-enynes **178** to bicyclo[3.1.0]hexanes **179** (Scheme 46).⁴²⁶ Cyclopropanation, which was found to be stereospecific, occurs by attack of the alkene to the gold-activated alkyne **182** via half-chair transition states, affording cyclopropyl gold-carbene like intermediate **183**. Then, 1,2-H shift (or alkyl shift in the case of **181a** and **181b**) onto the carbene center takes place.^{427,428} Similarly, Zhang and Kozmin disclosed that the AuCl-catalyzed cycloisomerizations of 1-siloxy-1,5-enynes afforded instead cyclohexadienes.^{429–431}

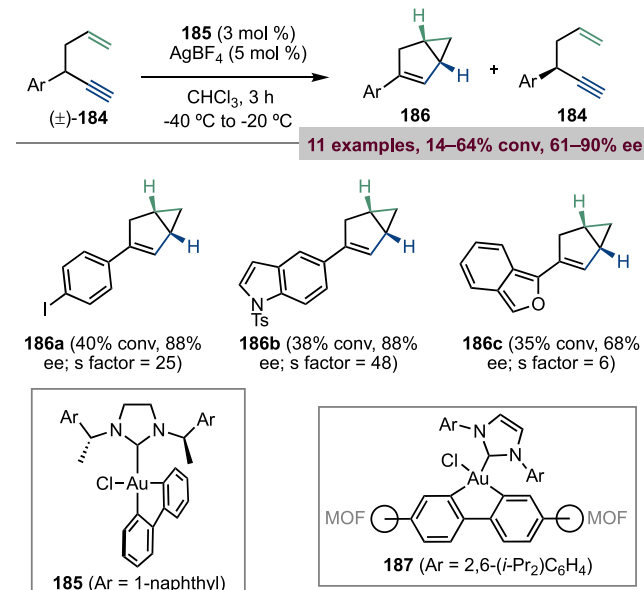
Transfer of chirality has been observed with certain enantioenriched substrates.^{213,432} Toste and co-workers em-

Scheme 46. Gold(I)-Catalyzed Cycloisomerization of 1,5-Enynes



ployed a well-defined square-planar chiral Au(III) catalyst to realize a nondynamic, yet enantioconvergent, kinetic resolution of 1,5-enynes with moderate *s* factors (Scheme 47).^{433,434} In a

Scheme 47. Gold(III)-Catalyzed Enantioconvergent Kinetic Resolution of 1,5-Enynes

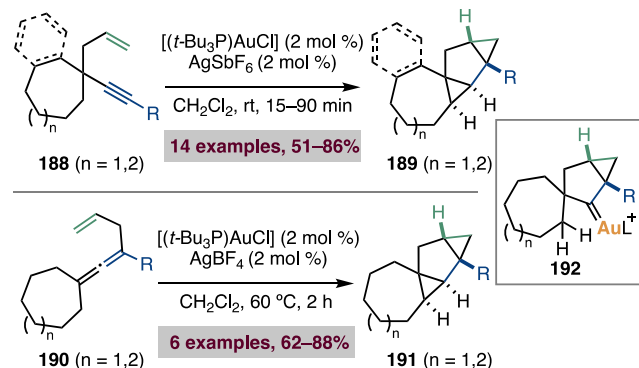


related work, an achiral NHC–gold(III) complex, **187**, anchored into a rigid metal–organic framework to geometrically prevent undesired decomposition via reductive elimination of biphenylene, was active in the cycloisomerization of a model 1,5-enyne after chloride abstraction by TIPF_6 .⁴³⁵

The group of Toste also described a sequential cycloisomerization/ sp^3 C–H bond functionalization of 1,5-enynes **188** and 1,4-enallenes **190**, providing all-carbon tetracycles **189** and **191** through cyclopropyl gold(I) carbene-like intermediates

192 (Scheme 48).^{436,437} The observed inverse primary KIEs were tentatively explained by the formation of a σ complex

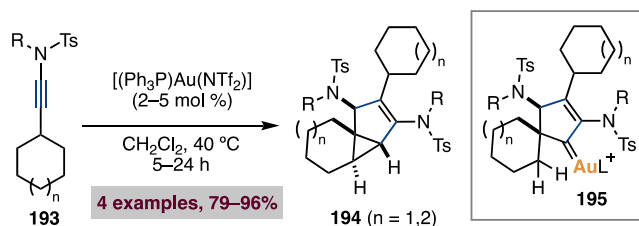
Scheme 48. Gold(I)-Catalyzed Cycloisomerization/C–H Insertion of 1,5-Enynes and 1,4-Enallenes



between the hydrogen atom and the gold(I) center before the hydrogen transfer event.

Gagosz, Skrydstrup and co-workers observed a mechanistically related gold-catalyzed dimerization of ynamides, leading to tricyclic compounds **194** by a final intramolecular C–H insertion of gold(I) carbene **195** (Scheme 49).⁴³⁸

Scheme 49. Gold(I)-Catalyzed Dimerization of Ynamides



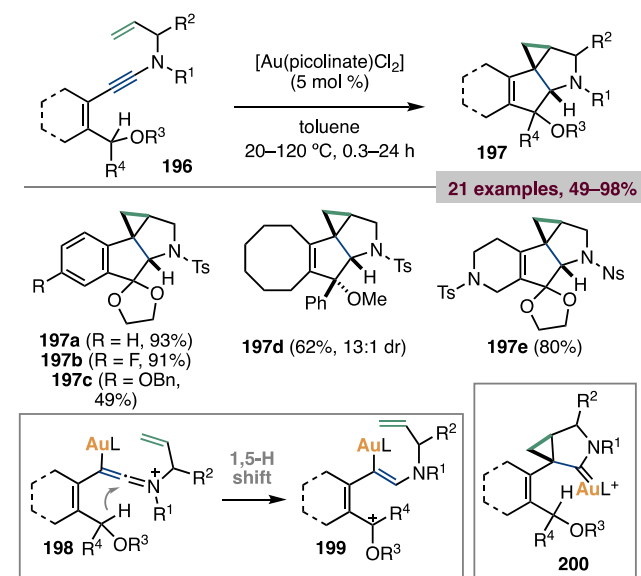
Davies and co-workers reported the Au(III)-catalyzed formal intramolecular insertions of cyclopropyl gold carbenes into activated C(sp³)–H bonds, affording compounds **197** (Scheme 50).⁴³⁹ The mechanism can be rationalized invoking as the first step the 1,5-H migration on gold keteniminium complex **198**, followed by cyclization and cyclopropanation. The alternative initial cyclopropanation to afford **200** and subsequent C–H insertion was considered less likely.

The initially formed gold carbenes in cyclizations of 1,5-enynes could be trapped by external C-nucleophiles^{389,390,440} as well as by pendant alkenes in a concerted reaction (Scheme 51, top).⁴⁴¹ When trapped with aldehydes, in certain cases tricyclic compounds formed by C–H insertion of the carbene into neighboring C–H bonds (Scheme 51, bottom).⁴⁴²

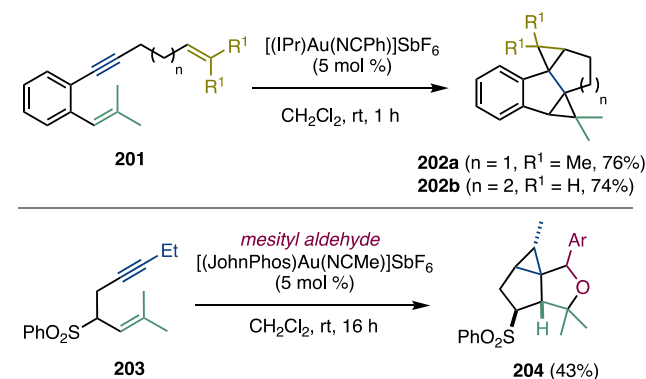
Finally, Wei, Tang, Shi, and co-workers observed the formation of polycyclic products containing both 3- and 4-membered rings in the Au(I)-catalyzed cycloisomerization of 1,5-enynes containing a 3-cyclopropyl group (see Scheme 119D in section 3.1.1.1).⁴⁴³

2.4.1.3. Other Enynes. Gold-catalyzed cycloisomerizations of 1,7- and higher enynes very rarely lead to cyclopropane-containing products, because the initially formed cyclopropyl gold carbene rearranges. Treatment of 1,7-enynes with Au(I) catalysts can afford linear or cyclic 1,3-dienes,^{444,445} 1,4-dienes,⁴⁴⁶ or hydroacenes,⁴⁴⁷ depending on enyne tether and substitution at the termini. Kumar and Waldmann observed the

Scheme 50. Au(III)-Catalyzed C–H Insertion/Cyclization Cascade of Ynamides



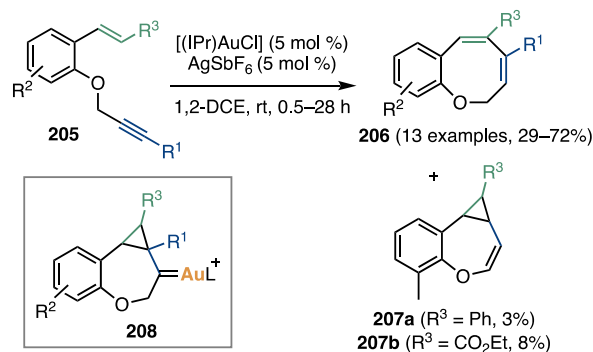
Scheme 51. Evolution of Cyclopropyl Au(I) Carbenes Generated from 1,5-Enynes



formation of cyclopropyl-fused compounds **207** in very low yields during the 8-*endo*-dig cyclization of 1,7-enynes **205** (Scheme 52).⁴⁴⁸ From 1,7- and higher enynes, cyclobutenes can be obtained via intramolecular [2 + 2] cycloadditions (see section 3.2.1.2),^{449,450} and occasionally other macrocycles.⁴⁵¹

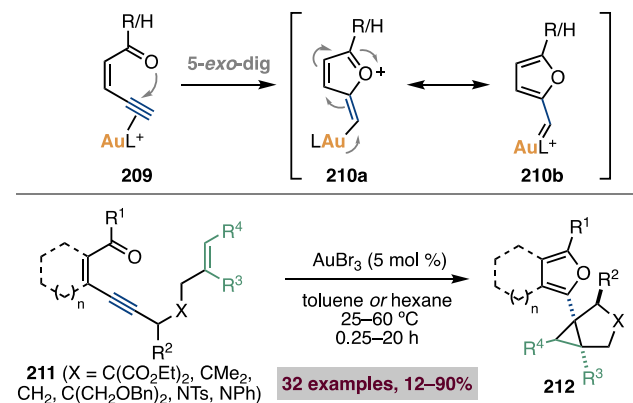
Special 1,3-enynes such as ynenals and ynenones can be used to access 2-furyl gold carbenes **210** by 5-*exo*-dig cyclization

Scheme 52. Au(I)-Catalyzed 8-*endo*-dig Cyclization of 1,7-Enynes



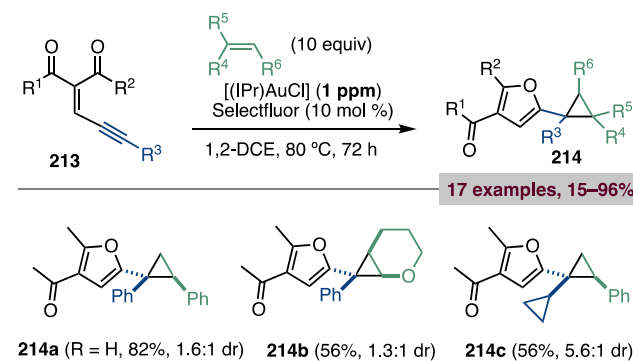
under gold(I) or gold(III) catalysis, as outlined in Scheme 53.^{168,452} These species can participate in several reactions, including intramolecular cyclopropanations as described by Oh (Scheme 53).^{453,454}

Scheme 53. Intramolecular Furanylation–Cyclopropanation Using Ynenals and Ynenones



A first, single example of intermolecular cyclopropanation using styrene for the synthesis of **214a** was disclosed by Zhang and co-workers.⁴⁵⁵ The generality and the efficiency of the transformation were later demonstrated by the group of Zhu, employing a combination of $[(\text{IPr})\text{AuCl}]$ and Selectfluor (Scheme 54).⁴⁵⁶ A putative cationic Au(III) species $[(\text{IPr})\text{AuClF}]^+$ was deemed responsible for the high catalytic activity.

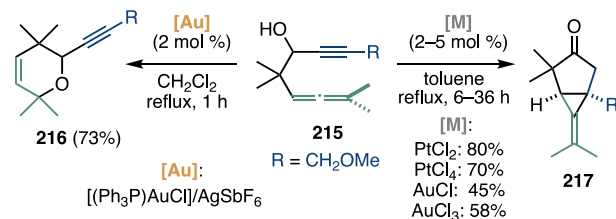
Scheme 54. Intermolecular Furanylation–Cyclopropanation Using Ynenones



2.4.2. Cycloisomerization of Allenynes. Using gold catalysis, allenynes have proven to be valuable building blocks for the synthesis of complex molecules.^{130–132} Allenynes undergo various types of carbocyclizations such as $[2 + 2]$ cycloadditions (see section 3.1) and other annulations.^{133–135} Acetoxyallenes can be generated from propargyl carboxylates via 1,3-acyloxy shift and take part in several reactions (see section 2.5).^{457,458}

Gold-catalyzed carbocyclization of allenynes can proceed either with the allene attacking a gold-activated alkyne or vice versa, with the triple bond attacking the activated allene and delivering a vinyl cation. Fensterbank, Malacria, and co-workers studied the alkyne versus allene activation in platinum- and gold-catalyzed cycloisomerizations of hydroxylated 1,5-allenynes, which proved to be both substrate and catalyst dependent (Scheme 55).⁴⁵⁹ Chloride salts of Pt(II), Pt(IV), Au(I), and

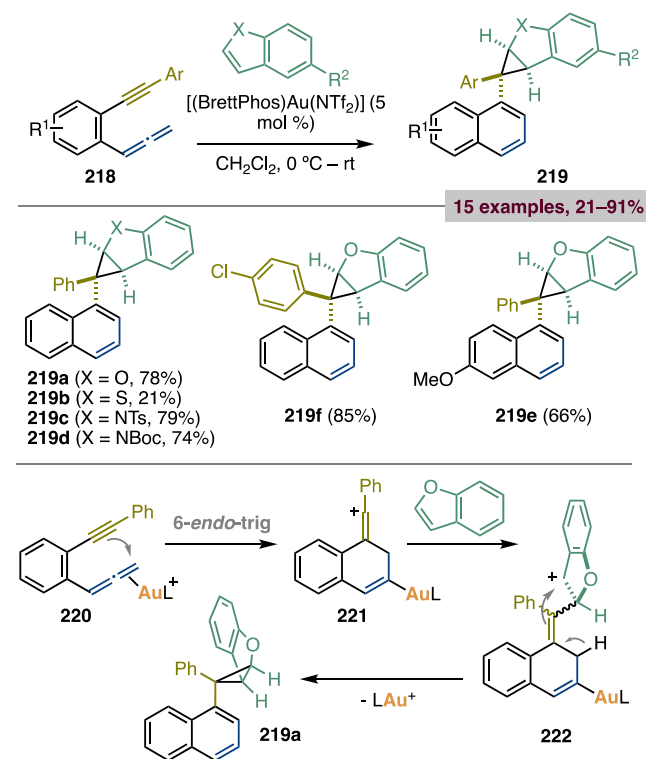
Scheme 55. Pt- or Au-Catalyzed Cyclization of 1,5-Allenynes



Au(III) converted allenyne **215** to 6-methylenebicyclo [3.1.0]-hexan-3-one **217** by attack of the allene onto a metal-activated alkyne, while $\text{PPh}_3\text{AuCl}/\text{AgSbF}_6$ yielded exclusively **216** by intramolecular allene hydroalkoxylation.

The group of Ohno reported that benzene-tethered 5-allenynes react with benzoheterocycles to give 1-naphthyl cyclopropane derivatives **219** (Scheme 56).⁴⁶⁰ In this trans-

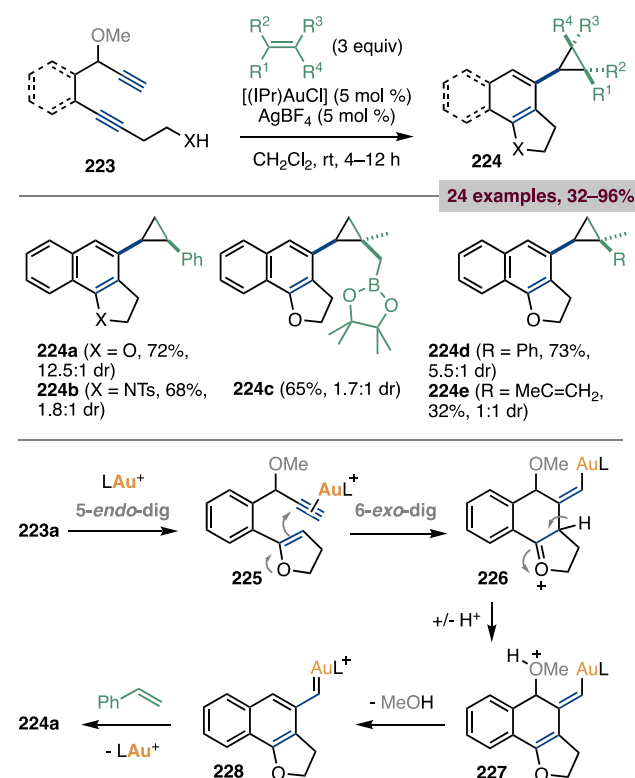
Scheme 56. Au(I)-Catalyzed Cyclization of 1,5-Allenynes



formation, the initially formed vinyl cation **221** is attacked by the 2-position (or 3-position) of benzofuran, and (*E*)-**222** or (*Z*)-**222**, with the heterocycle in the less hindered axial position, undergoes ring closure/aromatization/protodeauration to afford regioselectively product **219a**.

2.4.3. Cycloisomerization of Diynes. Diyne substrates have been used in gold-catalyzed methodologies especially to prepare 5-membered or larger fused carbo- and heterocycles.^{127–129} The few gold-catalyzed examples where diynes give rise to cyclopropanes are mostly initiated by 1,2-acyloxy migration on propargylic esters (see section 2.5). As an exception, Zhu and co-workers reported the intermolecular cyclopropanation of aryl gold(I) carbenes such as **228**, generated from 1,6-diynes **223** by gold-catalyzed tandem cyclizations and aromatization (Scheme 57).⁴⁶¹

Scheme 57. Au(I)-Catalyzed Intermolecular Cyclopropanation of 1,6-Diynes



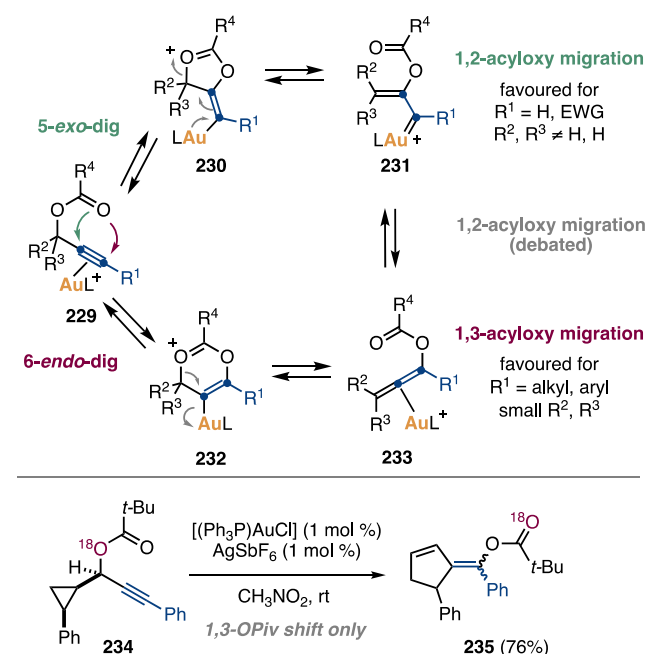
2.5. 1,2- and 1,3-Acyloxy Migration

2.5.1. General Mechanistic Considerations. Propargylic carboxylates are prone to metal-catalyzed rearrangements.^{462–464} Seminal works by Ohloff⁴⁶⁵ and Rautenstrauch⁴⁶⁶ showed that propargyl acetates underwent 1,2-acyloxy migration using ZnCl₂ or [PdCl₂(CH₃CN)₂], respectively. Later studies focused on the use of Ru,^{467–469} Cu,^{470,471} Ag,^{470,471} Pt,⁴⁷² Au,^{473–476,457} and Rh.⁴⁷⁷ In the presence of gold, propargylic carboxylates can undergo either a 1,2-acyloxy migration^{473–476} to deliver vinyl gold(I) carbenes **231** in a process known as Rautenstrauch–Ohloff rearrangement or a 1,3-acyloxy migration^{457,458} via a stepwise^{478–480} 3,3-sigmatropic rearrangement to afford gold-activated allenyl esters **233** (Scheme 58).

Computations^{481,482} and experimental observations^{483–485} indicate that intermediates **231** and **233** are in equilibrium, because the steps are reversible, so 1,2- and 1,3-acyloxy migration pathways are in competition. In some cases, it was suggested that a net 1,3-OAc migration could result from 2 consecutive 1,2-OAc shifts.^{481,483} However, studies by Toste and co-workers using isotopically labeled substrate **234** ruled out this possibility in their specific case, as no scrambling of the ¹⁸O atom was detected (Scheme 58, bottom).⁴⁷⁹ The 1,2-shift takes place preferentially for alkynes where R¹ is a H or electron-withdrawing group, and for substrates with a substituted propargylic C atom. The nature of the gold ligand, the presence of other functional groups on the substrates and reaction partners (hence downstream reactivity from **231** or **233**), and the reaction conditions also influence the preferred pathway.^{473–485}

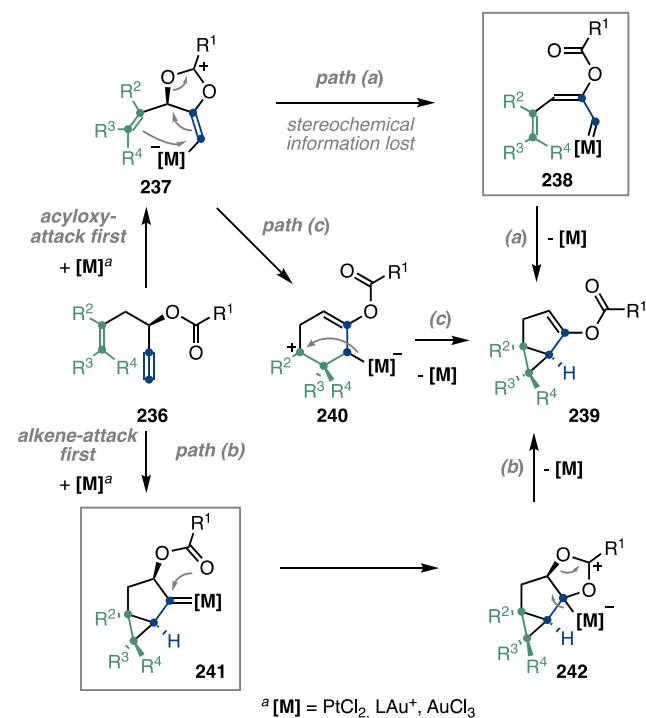
In this section, the focus will be exclusively on Au-catalyzed rearrangements of propargylic carboxylates resulting in cyclopropanation.⁴⁷⁵ When the cyclopropanation occurs intramolecularly, that is, for enynes, three mechanisms are possible

Scheme 58. 1,2- vs 1,3-Acyloxy Migration of Au-Activated Propargylic Carboxylates



(Scheme 59): (a) complete 1,2-acyloxy migration, followed by alkene cyclopropanation by vinyl carbene intermediate **238**; (b)

Scheme 59. Reaction Mechanisms for Enynes Bearing a Propargylic Carboxylate



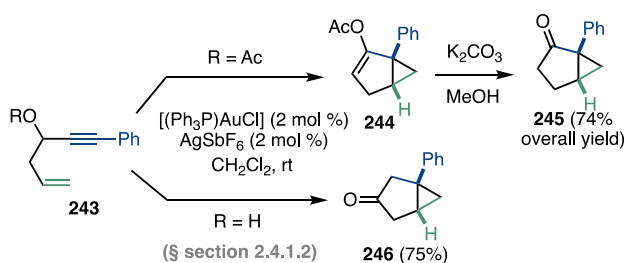
cycloisomerization, followed by 1,2-acyloxy shift onto the α -cyclopropyl carbene **241**; (c) an intermediate case where cyclopropanation occurs on a nonplanarized vinyl gold species **240**.

Computations with PtCl₂ show the different mechanistic routes to be close in energy, with pathway c slightly favored.⁴⁸⁶

Based on these studies and experimental investigations, the same scenario has been proposed for gold catalysis.^{487–489} Partial transfer of chirality, often observed under both Pt and Au catalysis with certain substrates carrying a propargylic stereocenter,⁴³² rules out the exclusive intermediacy of mechanism a, since the stereochemical information at the propargylic position would be entirely lost, and supports instead pathways b and c.^{490–492}

2.5.2. Intramolecular Cyclopropanations via 1,2-Acyloxy Migration. During their studies on Pt(II)- and Au(I)-catalyzed rearrangements of 3-hydroxylated 1,5-enynes, Fürstner and co-workers reported that propargylic acetate **243** underwent smooth transformation into compound **244** under Au(I) catalysis (Scheme 60).²¹² Methanolysis of **244** to

Scheme 60. Au(I)-Catalyzed Intramolecular Cyclopropanations of 3-Acetoxy versus 3-Hydroxy 1,5-Enyne



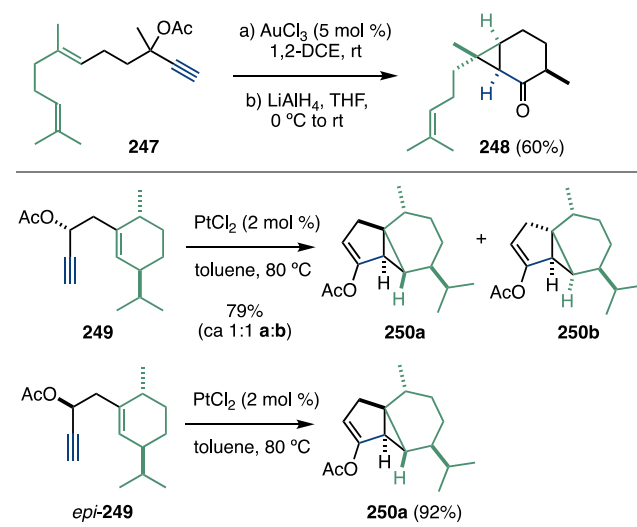
[3.1.0]bicyclic ketone **245** highlighted the role of propargylic acetates as convenient precursors of α -oxo gold carbenes upon 1,2-acetoxy migration. The group of Gagosz found that the air-stable gold catalyst $[(\text{Ph}_3\text{P})\text{Au}(\text{NTf}_2)]$ was particularly active in this type of cycloisomerization too.⁴⁹³

The group of Fürstner exploited the AuCl_3 -catalyzed cycloisomerizations of various propargylic acetates for the diazo-free synthesis of several carene terpenoids.^{490,494} The synthetic studies established that (i) the cyclopropanation step proceeded stereospecifically, with the alkene configuration dictating the configuration of the cyclopropane, (ii) the closer alkene reacted preferentially (Scheme 61, top), and (iii) under PtCl_2 catalysis pathways b and c were operative (see Scheme 59), since a propargylic stereocenter influenced the reaction outcome (Scheme 61, bottom).

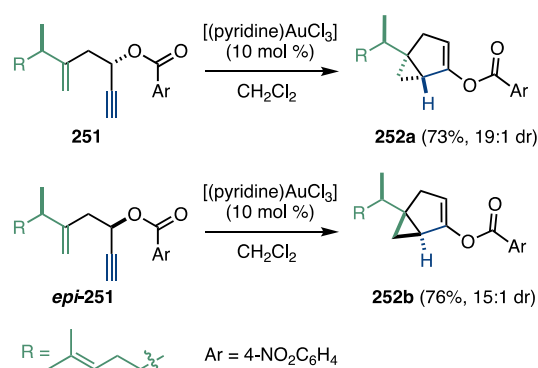
Similar stereochemical observations on chirality transfer were made by Fehr and co-workers when performing Au-, Pt-, and Cu-catalyzed enyne cycloisomerizations for the synthesis of (–)-cubebol.⁴⁹¹ Similarly, the Fürstner group realized the asymmetric total synthesis of sesquisabinene terpenes based on gold(III)-catalyzed Ohloff–Rautenstrauch-type cycloisomerizations of enantiopure enynes.⁴⁹² A propargylic *p*-nitrobenzoate group allowed a more efficient transfer of the stereochemical information than an acetate ester ($\geq 15:1$ versus 5:1 dr, Scheme 62).

Nolan and co-workers reported the Au(I)-catalyzed rearrangement of more complex dienynes **253** bearing an acetate group at the fully substituted propargylic position (Scheme 63, top).⁴⁹⁵ Mixtures of cyclopropane-containing products were obtained, stemming from both possible cyclopropanation of the two alkenes and competitive 1,2- and 1,3-acetate migration. As evidenced also by later works, the product ratio was highly ligand-, counterion-, metal-, and solvent-dependent, with bulky NHC ligands necessary to obtain high ratios of **256c**.^{496,497} Products arising from both 1,2 and 1,3-OAc migration were

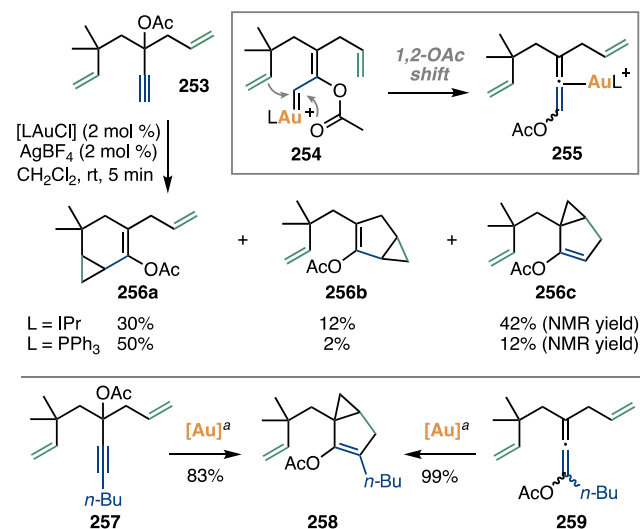
Scheme 61. AuCl_3 - and PtCl_2 -Catalyzed Cycloisomerizations in the Synthesis of Terpenoids



Scheme 62. Au(III)-Catalyzed Cycloisomerizations in the Synthesis of Terpenoids



Scheme 63. Au(I)-Catalyzed Rearrangements of Dienynes



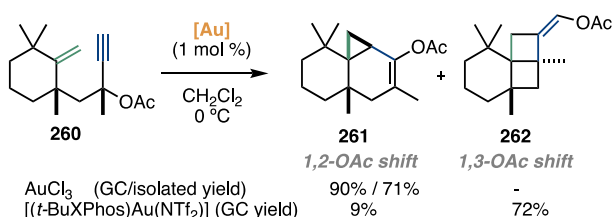
^a $[(\text{IPr})\text{AuCl}]$ (2 mol %), AgBF_4 (2 mol %), CH_2Cl_2 , rt, 10 min

observed also in the gold-catalyzed cyclization of cyclohexyl-tethered 3-acetoxy 1,6-enynes.⁴⁹⁸

Thorough DFT calculations painted a complex landscape with numerous reaction pathways of similar energy (“golden

carousel").^{496,497} In the most likely one, initial 1,2-acetate shift delivers vinyl gold carbene **254**, which can be attacked by the distal alkene affording **256a** or undergo a second 1,2-OAc shift delivering gold-activated allene **255** (Scheme 63, top). From this intermediate, allene-ene cyclization and retro 1,2-OAc shift produced **256c**. Indeed, cycloisomerizations of allenyl ester **259** provided **258** in better yield than when starting from diene **257** (Scheme 63, bottom). Cycloisomerization of other allenyl esters, delivering a mixture of cyclopropane-containing products, were also studied.^{496,497} Synthetic studies by the group of Fehr again highlighted that 1,2-OAc and 1,3-OAc cycloisomerization pathways often coexist and are catalyst-dependent (Scheme 64).⁴⁹⁹ Indeed, cyclobutane product **262** likely arises by [2 + 2] cycloaddition of an allenene formed in situ.⁵⁰⁰

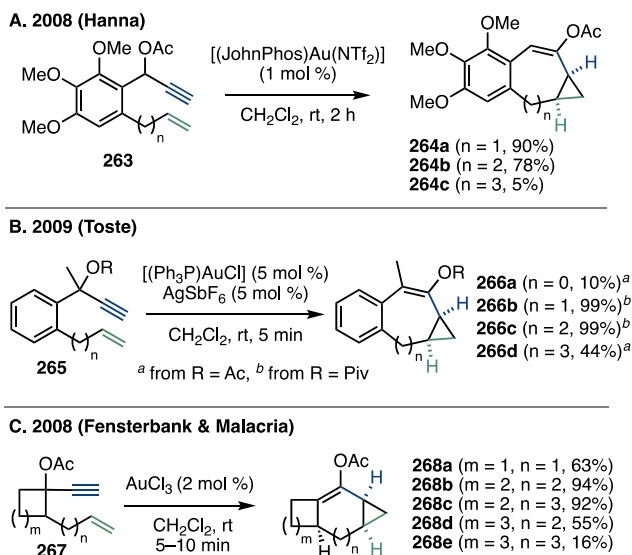
Scheme 64. Catalyst-Dependent 1,2- and 1,3-OAc Migrations on 1,6-Enynes



The group of Gagosz described the Au(I)-catalyzed tandem cycloisomerization/1,2-OAc shift of trienynes bearing a propargylic ester to give divinyl cyclopropanes, which underwent subsequent thermal Cope rearrangement.⁵⁰¹

The Ohloff–Rautenstrauch rearrangement of 1,7- and higher enynes was used to prepare medium-size rings. Hanna and co-workers synthesized tricyclic compounds **264** and used them in the synthesis of an allocolchinoid (Scheme 65A).⁵⁰² The group of Toste later studied the substrate scope extensively (selected examples in Scheme 65B).⁵⁰³ Fensterbank and Malacria reported similar cycloisomerizations catalyzed by PtCl₂, AuCl₃, or Au(I) affording tricyclic compounds **268** as single diastereomers (Scheme 65C).⁵⁰⁴ The higher activity of AuCl₃ and Au(I) catalysts in front of PtCl₂ in enyne rearrangements

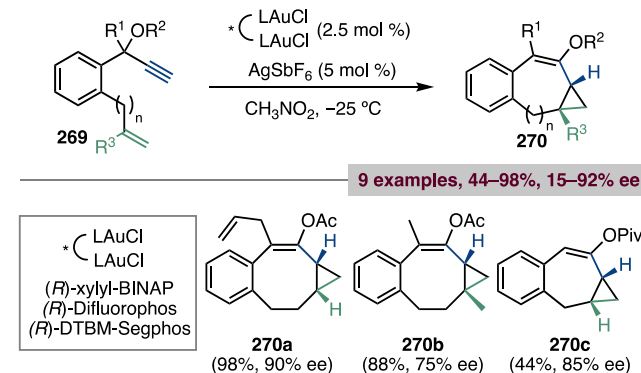
Scheme 65. Cycloisomerizations of 1,7- and Higher Enynes for the Formation of Medium-Size Rings



was observed once again, with comparable yields for products **268** obtained either in 2 h at 80 °C when employing 5 mol % PtCl₂ or in 5–10 min if using 2 mol % gold catalysts at room temperature. The latter reaction was carried out successfully on a *trans*-cyclopentyl-tethered 1,7-enyne as the key step to access neomeran skeletons.⁵⁰⁰

Toste and co-workers also developed an enantioselective version of these reactions using dinuclear gold(I) complexes with chiral diphosphine ligands (Scheme 66).⁵⁰³ Mechanistic

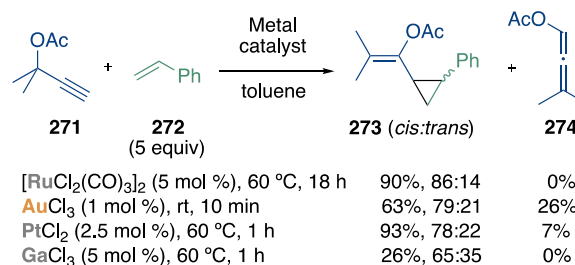
Scheme 66. Asymmetric Synthesis of Medium-Size Rings by Intramolecular Cyclopropanation



experiments discarded a cyclopropanation-first pathway (i.e., path b in Scheme 59) and highlighted the fluxional (*E*)/(*Z*)-alkene geometry of the vinyl gold(I) carbene intermediate.

2.5.3. Intermolecular Cyclopropanations via 1,2-Acyloxy Migration. Uemura and co-workers reported the first intermolecular cyclopropanations effected by vinyl carbene intermediates generated from propargylic acetates using Ru, Pt, or Au catalysis (Scheme 67).^{467,468} Vinyl cyclopropane **273**

Scheme 67. First Gold-Catalyzed Intermolecular Cyclopropanation via 1,2-OAc Migration

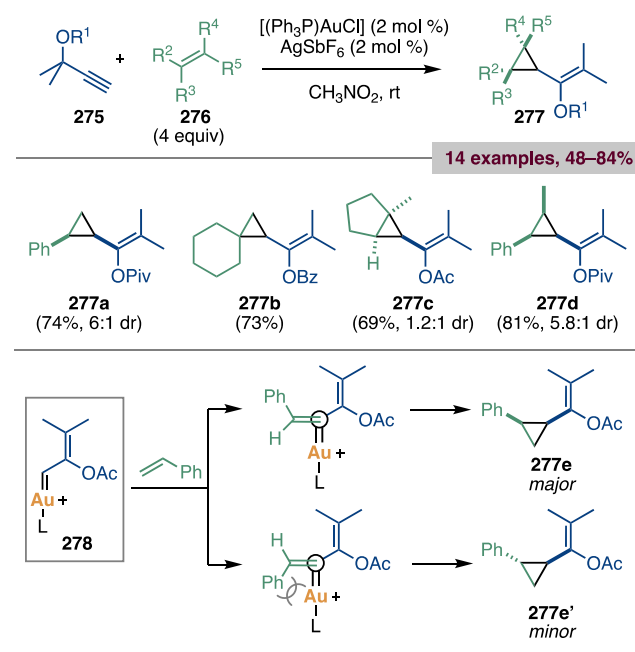


formed via 1,2-OAc migration followed by cyclopropanation, while allenyl ester **274** resulted from competitive 1,3-OAc migration. AuCl₃ showed the highest activity for both cyclopropanation and allene formation but with a lower product selectivity.

Toste and co-workers developed a general Au(I)-catalyzed cyclopropanation of a broad range of alkenes with propargyl esters (Scheme 68).⁵⁰⁵ The reaction was stereospecific with respect to the alkene configuration and yielded cyclopropanes **277** with moderate to excellent *cis* selectivity when using styrenes, as rationalized by stereochemical models (Scheme 68, bottom).

The intermediacy of a planar vinyl gold carbene such as **278** was supported by the complete loss of stereochemical information when using enantioenriched propargyl acetates as

Scheme 68. General Au-Catalyzed Alkene Cyclopropanation Using Propargylic Esters



substrates. This observation, which stands in contrast with the transfer of chirality observed in intramolecular cyclopropanations (see section 2.5.2), derives from the entropic preference for a complete intramolecular acyloxy migration before cyclopropanation of a nontethered alkene.⁵⁰⁶ Replacing PPh₃ with axially chiral bisphosphine **282** allowed the enantioselective synthesis of vinyl cyclopropanes **281** with high *cis* selectivity (Scheme 69).

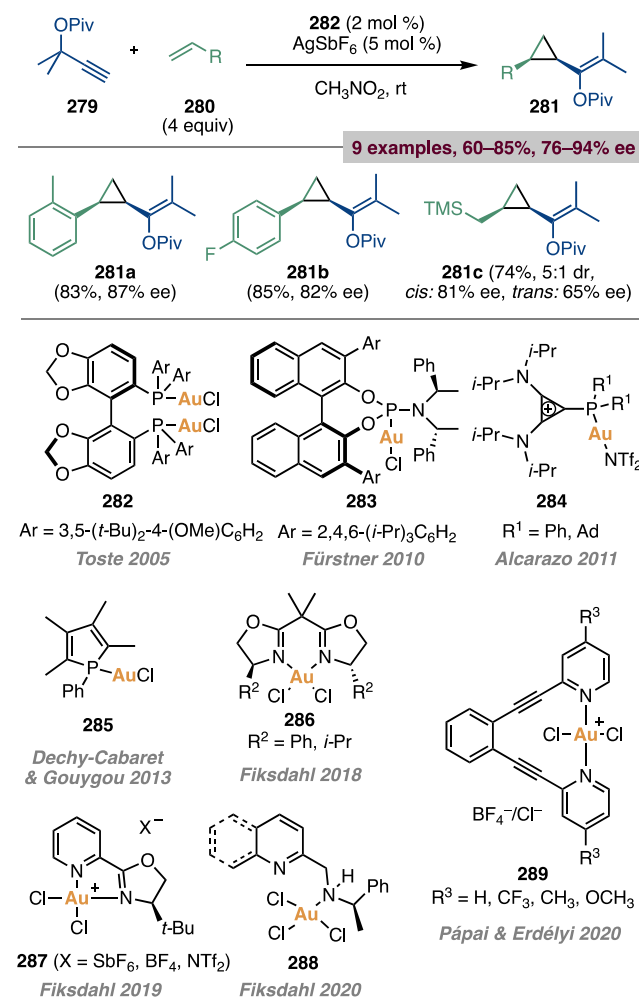
This transformation has since become a benchmark reaction to test new chiral and achiral gold complexes, such as Au(I) complexes **283**,⁵⁰⁷ **284**,⁵⁰⁸ and **285**.³⁹⁹ Notably, catalytically active Au(III) complexes **286**,⁵⁰⁹ **287**,⁵¹⁰ and **288**⁵¹¹ did not induce any enantioselectivity, despite their chiral backbone. Complexes **286** were effective catalysts for the intramolecular cyclopropanation and subsequent *in situ cis* to *trans* isomerization of vinyl cyclopropanes at room temperature.⁵⁰⁹ Recently, *trans* bis(pyridine)gold(III) complexes **289** have been found to exhibit a strain-modulated reactivity in this transformation.⁵¹²

Toste and co-workers investigated the effect of structural variations of the two substrates, appending an additional triple bond to either the vinyl carbene precursor or the alkene. Using 1,3-diynes **290**, they developed a styrene cyclopropanation–hydroarylation cascade for the synthesis of benzenorcaradienes **291** (Scheme 70).⁵¹³ The proposed mechanism involves cyclopropanation by gold(I) carbene **294**, delivering cyclopropane intermediate **295**, which can be isolated as **291'**. The latter then undergoes a gold-catalyzed intramolecular hydroarylation.

When the triple bond was attached to the alkene, the annulation between 1,3-enynes **298** and propargylic pivalates afforded *cis*-vinyl-alkynyl-cyclopropanes, together with styrene or fluorene products derived from their rearrangement (illustrative examples in Scheme 71).⁵¹⁴ Few additional examples of intramolecular cyclopropanations were reported in related studies.⁵⁰³

Nevado and co-workers described the synthesis of cyclopentenes **307** or cycloheptadienes **308** by net (3 + 2) and (4 + 3) annulations, respectively, via ring-opening of vinyl cyclopropane

Scheme 69. Enantioselective Au(I)-Catalyzed Styrene Cyclopropanation Using Propargylic Esters

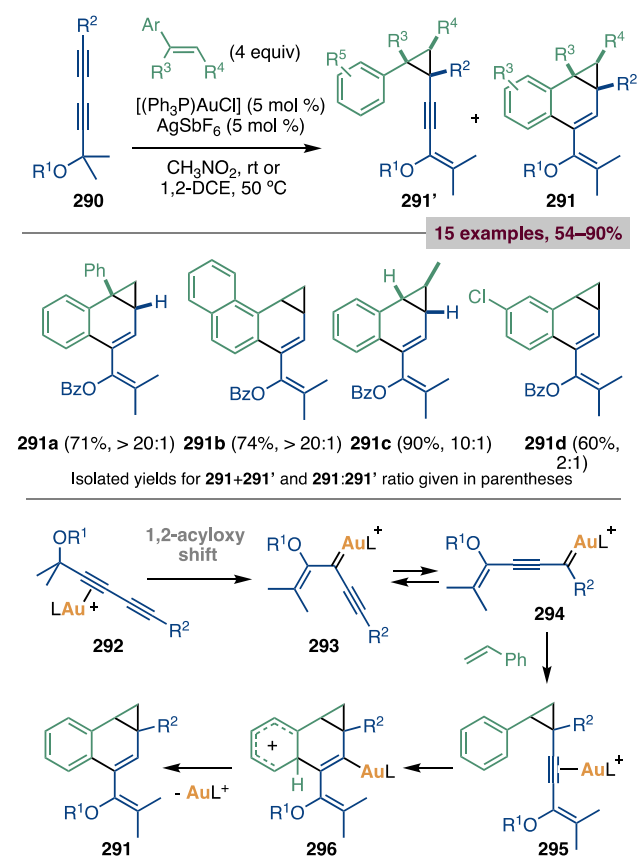
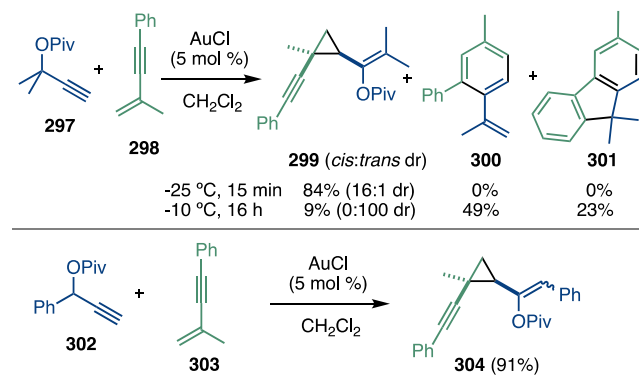


intermediates **309** (Scheme 72A).⁵¹⁵ The preferred outcome (cyclopropanation vs cyclopentane formation) of these reactions is very sensitive to the sterics and electronics of the substrates, particularly of the alkene partner.^{516–519} In this regard, the group of Fiksdahl investigated various substrate combinations in the intermolecular cyclopropanation reaction. It was established that vinyl esters and vinyl sulfonamides,⁵¹⁶ as well as protected indoles and certain vinyl ethers,^{517,518} furnish vinyl cyclopropanes when used in combination with propargylic esters as gold carbene precursors (Scheme 72B). When propargylic acetals were used instead, (3 + 2) cycloaddition products were obtained.⁵¹⁷ Reacting propargylic acetals with vinyl esters resulted instead in sequential (2 + 1) and (3 + 2) cycloadditions, affording cyclopropyl-substituted cyclopentenes.⁵¹⁹

Barbazanges, Fensterbank, Goddard, Stoffelbach, and co-workers employed vinyl gold carbenes generated from bifunctional monomers **315** under Au(I) or Au(III) catalysts to prepare oligomers (Scheme 73).⁵²⁰

Gold(I) carbenes **318a** generated by 1,2-acyloxy shift of a propargylic ester group can be transferred over a tethered alkyne, generating homologated gold carbenes **318b** (Scheme 74A). These intermediates, which were described by the groups of Chan,^{521,522} Oh,⁵²³ and Hashmi⁵²⁴ in intramolecular reactions involving the tethered group R², can also be trapped intermolecularly with alkenes. The first example of this kind was

Scheme 70. Synthesis of Benzenorcaradienes by Cyclopropanation–Hydroarylation Cascade

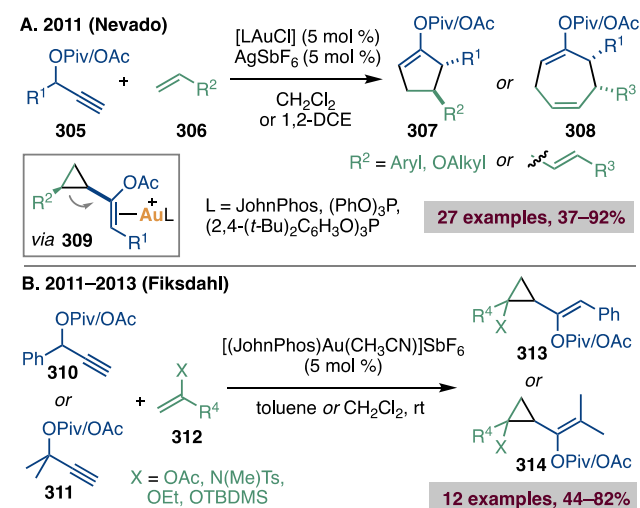
Scheme 71. Synthesis of *cis*-Vinyl-alkynyl-cyclopropanes, Styrenes, and Fluorenes

disclosed by the group of Chan as a mechanistic proof for the formation of **321** (Scheme 74B).⁵²¹ Following work by Hashmi and co-workers showed that removal of the R² group at the alkyne terminus reduced side reactions available to the carbene intermediate, thus allowing intermolecular cyclopropanations to be carried out with only one equivalent of alkene to obtain 1-naphthyl cyclopropanes **323** in good yields (Scheme 74C).⁵²⁵

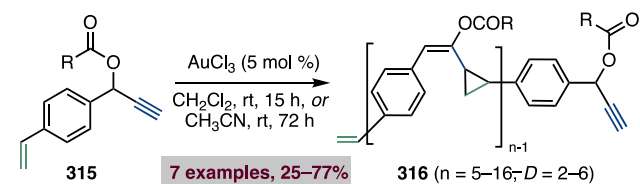
2.5.4. Cyclopropanations via 1,3-Acyloxy Migration.

1,3-Acyloxy shifts via stepwise [3,3]-sigmatropic rearrangement are favored for propargyl acetates possessing alkyl-substituted triple bonds and deliver Au-activated allene intermediates (see section 2.5.1),^{457,458} which can evolve in a variety of ways.^{130–135} The presence of a suitably positioned tethered alkene allows stepwise intramolecular cyclopropanation, as

Scheme 72. (2 + 1), (3 + 2), and (4 + 3) Cycloadditions Using Propargylic Esters as Gold Carbene Precursors



Scheme 73. Au(III)-Catalyzed Polymerization Using Styrene–Propargylic Ester Monomers



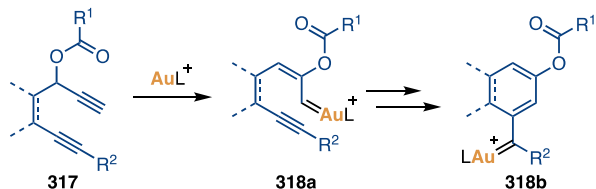
demonstrated by Buzas and Gagosz.⁵²⁶ His group reported the formation of bicyclo[3.1.0]hexenes **325** by Au(I)-catalyzed cycloisomerization of 1,4-enynes **324** bearing a propargylic acetate group (Scheme 75). Chirality transfer from a propargylic stereocenter was observed (product **326**, absolute configuration not determined), and the products could be further transformed in various 2-cycloalken-1-ones. The proposed mechanism involves formation of gold allene complex **328**, which is attacked intramolecularly by the alkene, affording the cationic vinyl gold species **329**. Attack to the carbocation assisted by electron donation from gold gives cyclopropyl gold carbene **330**, which undergoes 1,2-hydride shift and protodeauration delivering product **325**.

Rao, Chan, and co-workers built upon the reactivity of 1,4-enynes bearing a propargylic ester to access several tetracyclic compounds **332** (Scheme 76)⁵²⁷ and phenol derivatives.⁵²⁸

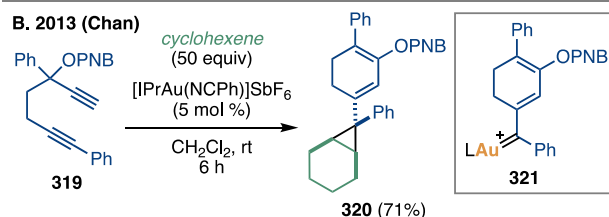
Malacria, Fensterbank, and Gandon and their co-workers studied experimentally and computationally the Au-catalyzed cycloisomerizations of related substrate classes, namely, 1,3-enynes and allenynes carrying a propargylic ester group.^{529,530} They developed an efficient preparation of polycyclic compounds **334** (Scheme 77, top), which was applied in total synthesis.^{530,531} In order to suppress the formation of cyclopentadiene side products, the internal position of the 1,3-enyne framework had to be substituted (group R in Scheme 77, bottom). Several mechanistic pathways were computed, and the lowest energy one was found to proceed through [3,3]-sigmatropic rearrangement of propargyl acetates **333** into allenyl acetates **335**, followed by metallaNazarov reaction of gold complex **337**. The resulting cyclopropyl gold carbene **338** then effected intramolecular cyclopropanation.

Scheme 74. Intermolecular Cyclopropanations Using 1,6-Diynes with a Propargylic Ester Group

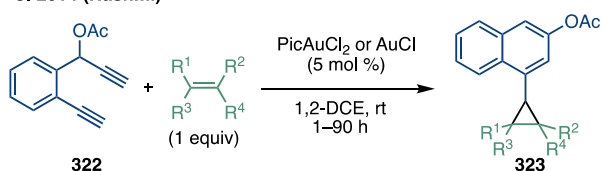
A. 2013 (Chan, Oh, Hashmi)



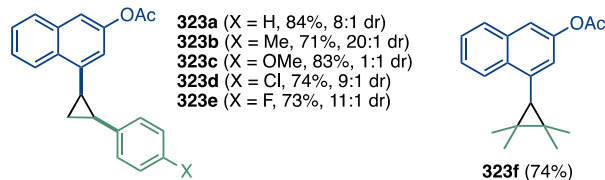
B. 2013 (Chan)



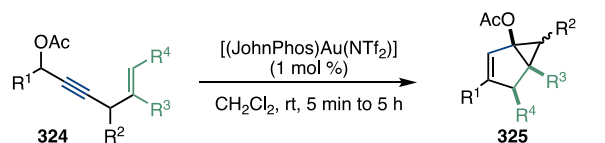
C. 2014 (Hashmi)



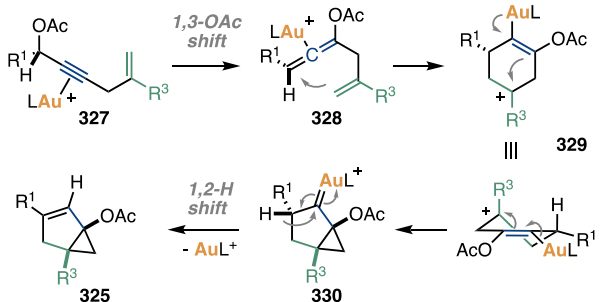
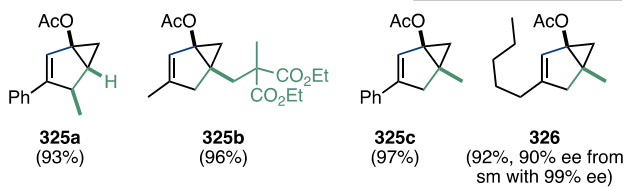
13 examples, 65–87%



Scheme 75. Cycloisomerization of 5-En-2-yn-1-yl Acetates

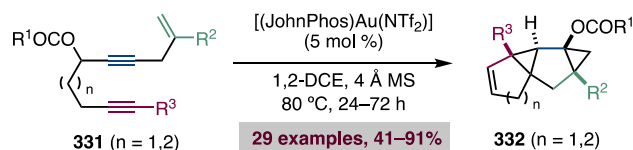


10 examples, 38–99%

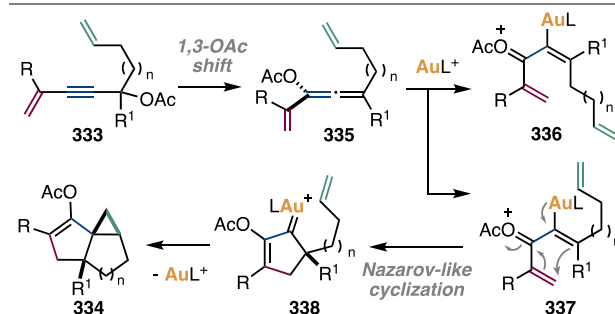
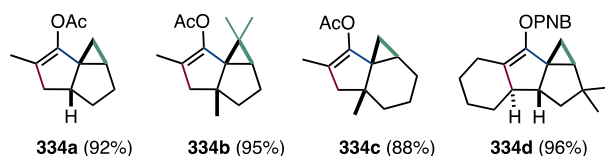
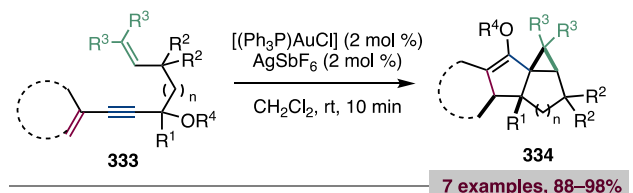


Efficient transfer of chirality was observed at low temperature and attributed to the formation of a bent-allene gold complex such as 341, which retained the stereochemical information

Scheme 76. Gold-Catalyzed Tandem 1,3-Migration/Double Cyclopropanation of 1-Ene-4,n-diyne Esters

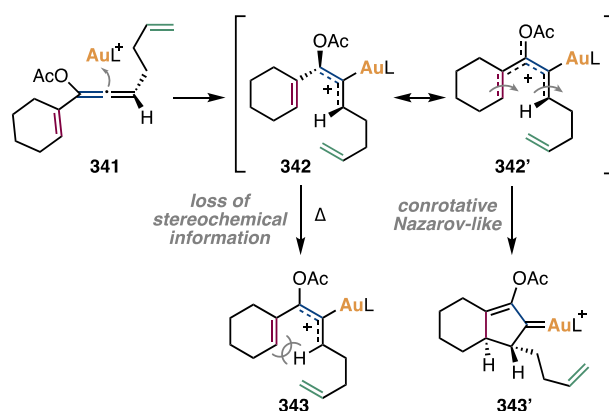
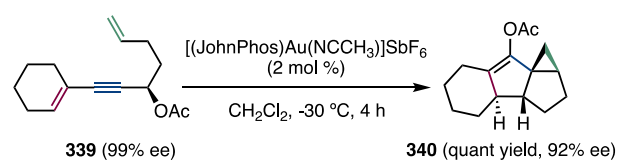


Scheme 77. Cycloisomerization of 4-En-2-yn-1-yl Acetates



the allene, in turn derived from the propargylic acetate (Scheme 78).⁵³² With a trisubstituted allene, racemization via planar allene gold complex 343 was disfavored. Conrotatory cyclization

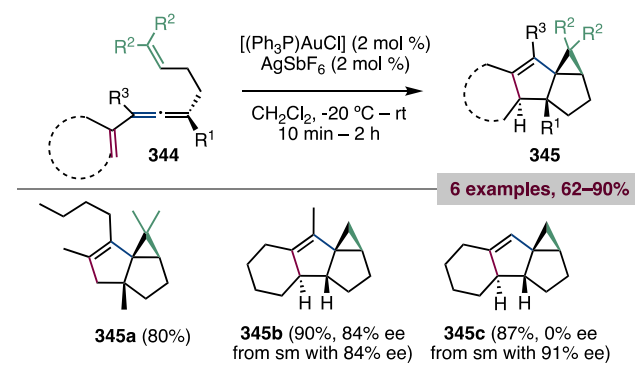
Scheme 78. Chirality Transfer via Bent-Allene Gold Complexes



gave rise to intermediate **343'** with the expected relative and absolute configuration.

Based on the mechanisms presented above, it was hypothesized that the same reaction would proceed directly from vinyl allenenes, with chirality transfer in the case of trisubstituted allenenes, which was experimentally demonstrated (Scheme 79).^{529,532}

Scheme 79. Cycloisomerization from Vinyl Allenenes



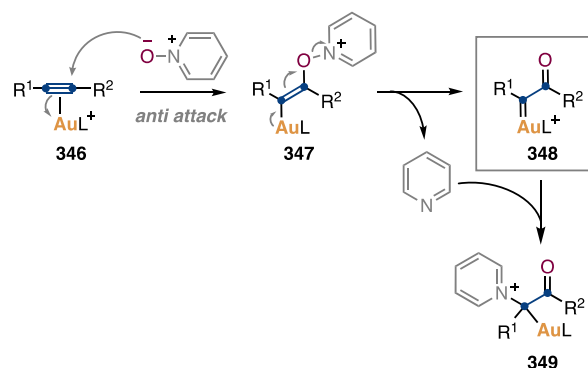
The mechanistic intricacies of Pt- and Au-catalyzed cycloisomerization of enynyl and allenynyl esters were also studied by Cavallo, Fensterbank, Malacria, and Nolan and their co-workers, as shown in Scheme 63.⁴⁹⁶ The two metals can catalyze divergent reaction pathways, which was also noted in the course of synthetic efforts toward lindenane and myliol cores: treatment of a *trans*-cyclohexyl-tethered 1,5-enyne with AuCl₃ resulted exclusively in 1,3-OAc migration, while also products derived from 1,2-OAc shift were obtained using PtCl₂.^{533,534}

In summary, 1,2- and 1,3-acyloxy migrations of propargylic ester substrates are well-established platforms for the generation of vinyl gold carbenes and gold-activated allene intermediates, and as such have been fruitfully employed in the cyclopropanation arena. Intermolecular cyclopropanations via 1,2-acyloxy migration pathways can be performed stereo- and enantioselectively with styrenes. Intramolecular cyclopropanations via 1,2- and 1,3-acyloxy migration can leverage instead transfer of chirality from enantioenriched substrates. However, given the complex mechanistic scenario of this golden carousel, catalyst- and substrate-dependent reaction outcomes remain the norm.

2.6. Oxidation of Alkynes with Oxygen-Transfer Reagents

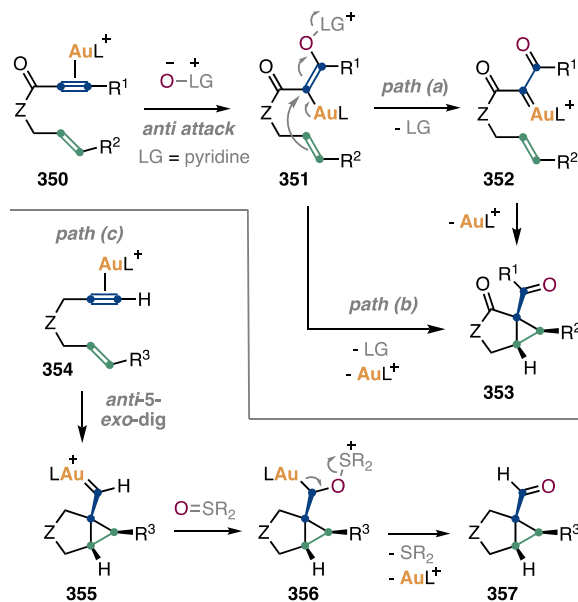
2.6.1. General Considerations on α -Oxo Gold Carbenes. The gold-catalyzed oxidation of alkynes takes place with reagents with a polar LG⁺–O[–] bond, such as sulfoxides and amine *N*-oxides (Scheme 80).^{535–544} These oxidants attack the π -alkyne gold(I) complex in an *anti* fashion at the C atom better able to accommodate the partial positive charge (e.g., positions that are benzylic, α to N atoms, or β to electron-withdrawing groups). The initially formed vinyl gold complex **347** eliminates the leaving group delivering transient α -oxo gold carbene **348**.⁵⁴⁵ Computational and experimental gas-phase studies have shown that these intermediates react rapidly with the expelled pyridine to form more stable gold(I) carbenoids **349**.^{546,547} Attack of the pyridine to the carbene C atom or its coordination to Au can be prevented by using acidic additives and by choosing less nucleophilic pyridines with bulky or electron-withdrawing substituents.

Scheme 80. Formation of α -Oxo Gold Carbenes by Oxidation of Gold-Activated Alkynes



This oxidation strategy provides very electrophilic α -oxo gold carbenes from readily available alkynes,^{535–544} circumventing the use of dangerous and toxic α -diazocarbonyl precursors. Since the group of Zhang reported their generation by intermolecular alkyne oxidation,⁵⁴⁸ α -oxo gold carbenes have enjoyed a rich chemistry.^{535–544} When they are involved in cyclopropanations, enynes are used in most cases as substrates. Thus, after alkyne oxidation, cyclopropanation occurs intramolecularly with the pendant alkene, delivering bicyclo[3.1.0]hexane skeletons (Scheme 81, pathways a and b). A related

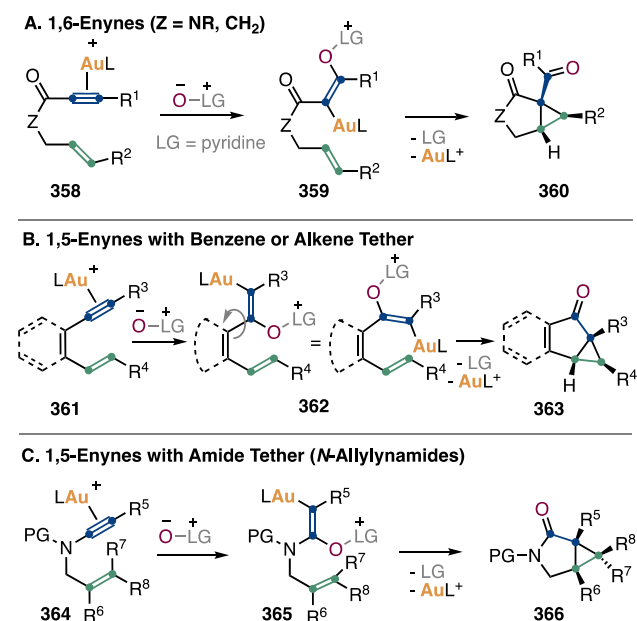
Scheme 81. Mechanisms for the Formation of Bicyclo[3.1.0]hexane Skeletons via Oxidation of 1,6-Enynes



approach to bicyclo[3.1.0] compounds had been described by the Toste group (Scheme 81, pathway c).⁵⁴⁹ In this case, 5-*endo*-dig cyclization of 1,6-enynes of type **354** precedes oxidation of the intermediate cyclopropyl gold carbene **355** (see section 2.4.1.1). In these oxidative cycloisomerizations, typically sulfoxides are more efficient oxidants than *N*-oxides.

Both 1,5-enynes and 1,6-enynes deliver [3.1.0] bicyclic compounds upon oxidative intramolecular cyclopropanation (Scheme 82). 1,6-Enynes give products **360** with exocyclic incorporation of the oxygen atom from the oxidant, as a pendant aldehyde or ketone, depending, respectively, on the presence of a terminal or internal alkyne in the substrate (Scheme 82A).

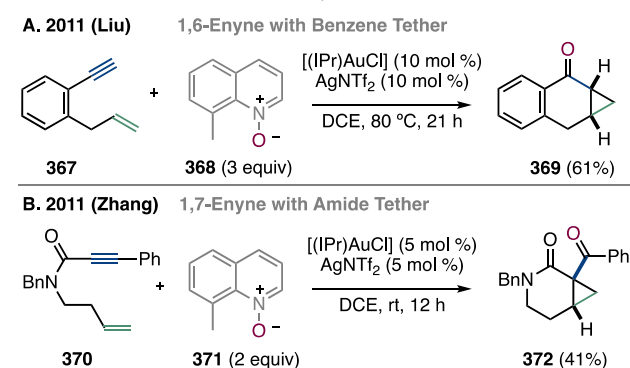
Scheme 82. Comparison between Oxidative Cyclopropanations of 1,5- and 1,6-Enynes



Instead, 1,5-enynes afford compounds **363** or **366** with an endocyclic oxidant-derived carbonyl group (Scheme 82B,C). Regardless of the exact mechanism involved, in the majority of the cases these gold-catalyzed oxidative cyclopropanations occur stereospecifically with respect to the alkene configuration.

While nearly all gold-catalyzed oxidative intramolecular cyclopropanations of enynes afford bicyclo[3.1.0] compounds, there have been two illustrative cases where bicyclo[4.1.0] compounds formed instead (Scheme 83).

Scheme 83. Formation of Bicyclo[4.1.0] Skeletons

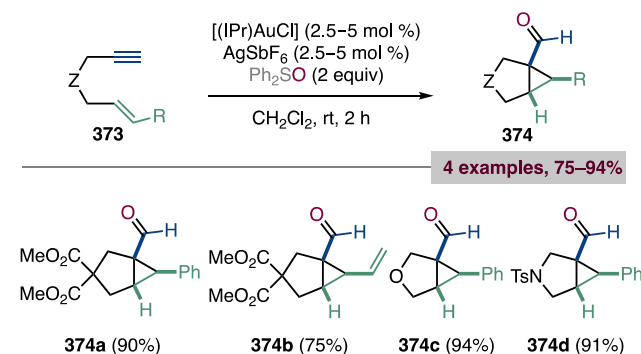


The first example, disclosed by Liu and co-workers, consists in the cyclization of benzene-tethered 1,6-enyne **367** using excess 8-methylquinoline oxide as oxidant (Scheme 83A).⁵⁵⁰ The second one, reported by Zhang, involves the cyclization of amide-tethered 1,7-enyne **370**, using the same oxidant and catalytic system ([[(IPr)AuCl]/AgNTf₂, Scheme 83B).⁵⁵¹ The lower temperature and catalyst loading of the second example can be ascribed to the higher reactivity of the electron-deficient alkyne, and the higher electrophilicity of the corresponding doubly activated putative gold carbene intermediate.

2.6.2. Oxidative Intramolecular Cyclopropanations of 1,6-Enynes. Seminal work by the Toste group demonstrated the interception of gold(I) carbene intermediates by oxidation

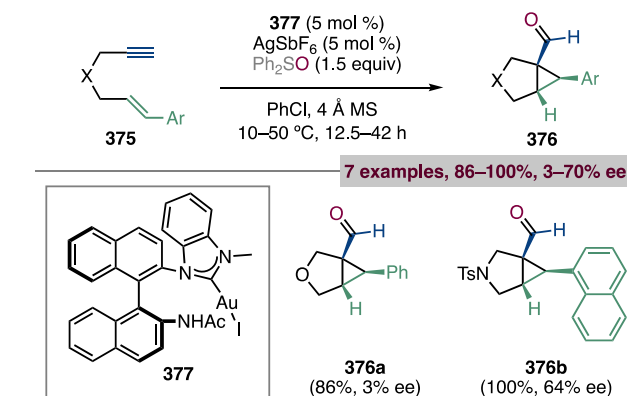
with sulfoxides, which were generated under gold(I) catalysis from a variety of precursors.⁵⁴⁹ Among these, α -diazoketones, propargylic esters, and 1,6-enynes were used. Specifically, the first oxidative cycloisomerizations of 1,6-enynes **373** using stoichiometric diphenylsulfoxide afforded cyclopropyl aldehydes **374** in good to excellent yields (Scheme 84).

Scheme 84. Oxidative Cycloisomerization of 1,6-Enynes



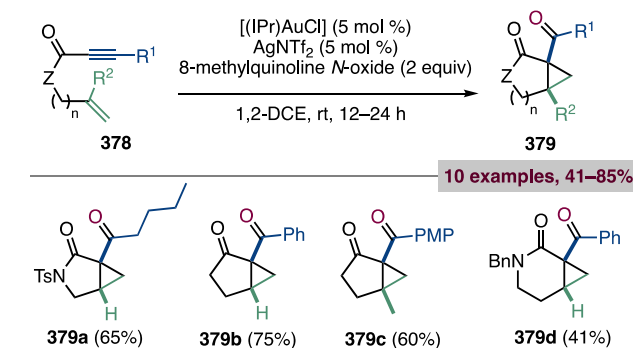
An asymmetric version of this reaction was reported by Shi and co-workers employing chiral NHC–gold complex **377** (Scheme 85), providing cyclopropanes **376** with moderate enantioselectivities.⁵⁵²

Scheme 85. Enantioselective Oxidative Cycloisomerization of 1,6-Enynes Using a Carbene Ligand



Qian and Zhang described the gold-catalyzed oxidative cyclization of amide- or ketone-tethered 1,6-enynes **378** to prepare hetero- and carbo[3.1.0]bicyclic ketones **379** (Scheme 86).⁵⁵¹ Similar oxidative cyclopropanations of amide- or ester-

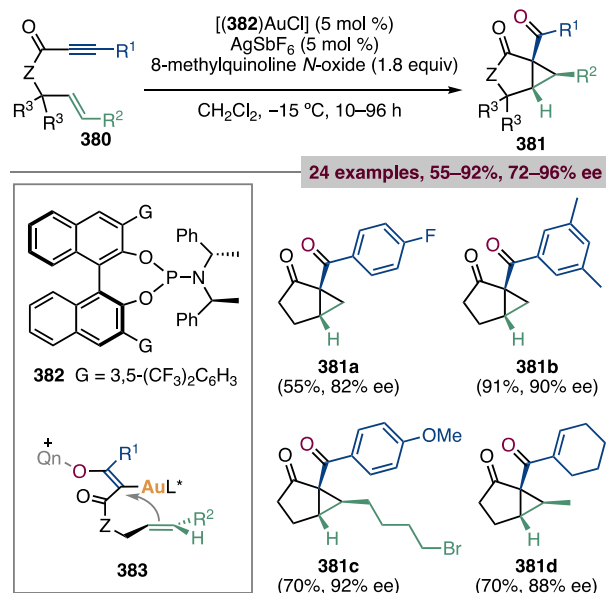
Scheme 86. Oxidative Cyclization of 1,6-Enynes



tethered 1,6-enynes had been reported using catalytic $\text{Pd}(\text{OAc})_2$ and stoichiometric $\text{PhI}(\text{OAc})_2$.^{553,554} Yeom and Shin later showed that this methodology could be extended to propiolamide-derived 1,6-enynes with a terminal triple bond, using SPhos as Au(I) ligand and diphenyl sulfoxide as oxidant.⁵⁵⁵

The group of Zhang developed an enantioselective version of the oxidative cyclization of 1,6-enynes using BINOL-derived phosphoramidite ligand **382** (Scheme 87).⁵⁵⁶ Crucial for the

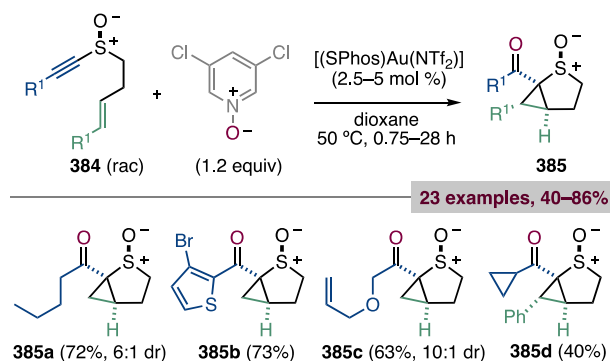
Scheme 87. Enantioselective Oxidative Cyclization of 1,6-Enynes Using a Phosphoramidite Ligand



high enantioselectivity were the 3,3'-groups on the binaphthol ligand backbone, the use of activated α -keto or α -amide alkynes (as they allowed for low reaction temperatures) and the presence of vinyl or electron-rich aromatic groups on the alkyne terminus. Based on control experiments and on the observed dependence of the enantioselectivity on the structure of the oxidant, the authors proposed the intermediacy of β -vinyl-oxyquinolinium species **383** rather than an α -oxo gold carbene.⁵⁵⁷

1,6-Enynes with aromatic ketones,⁵⁵⁷ sulfones, and sulfoxides⁵⁵⁸ as linkers are also viable substrates for oxidative cycloisomerizations (Scheme 88). Davies and Grainger observed that the sulfoxide group did not interfere with the oxidation of the alkyne, carried out by 3,5-dichloropyridine *N*-

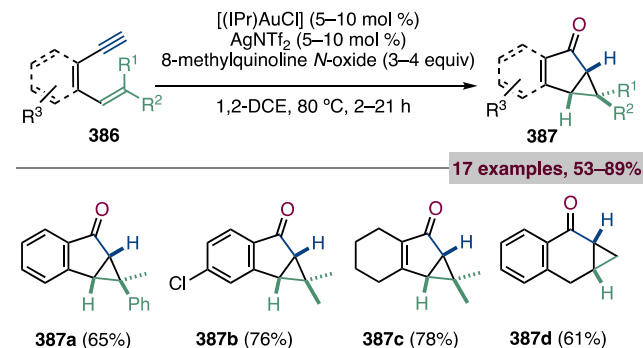
Scheme 88. Oxidative Cyclization of Alkynyl Sulfoxides



oxide in the presence of bulky $[(\text{SPhos})\text{Au}(\text{NTf}_2)]$. Bicyclo[3.1.0] ketones **385** with the cyclopropyl ring on the same side of the sulfoxide were obtained as the major or only diastereomers.

2.6.3. Oxidative Intramolecular Cyclopropanations of 1,5-Enynes. The group of Liu reported the first oxidative cyclization of 1,5-enynes, featuring the proposed intermediacy of α -oxo gold carbenes.⁵⁵⁰ Under gold catalysis and in the presence of 8-methylquinoline *N*-oxide, 1,5-enynes **386** with an aromatic or alkenyl linker provided cyclopropyl ketones **387** in good yields (Scheme 89). While 5 mol % catalyst loading and

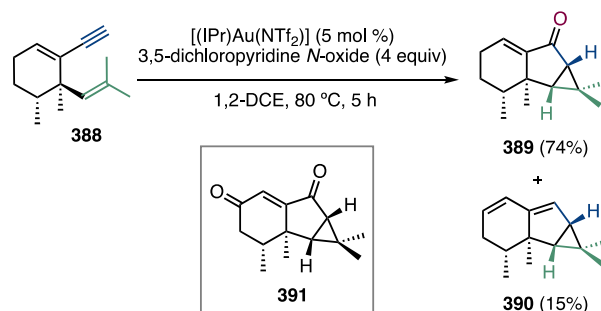
Scheme 89. Oxidative Cyclization of 1,5-Enynes



short reaction times sufficed for most enynes, slightly more forcing conditions were required for a substrate bearing an internal alkyne and for a 1,6-enyne to afford **387d**.

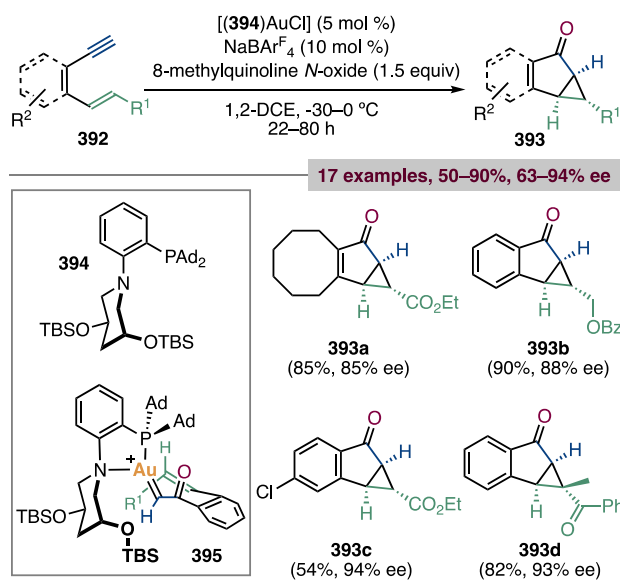
The exact structure of the *N*-oxide was shown to influence the chemoselectivity for the reaction of 1,3-dien-5-yne substrates, delivering either products like **387c** or cyclopentadienyl aldehydes.⁵⁶⁰ This methodology was applied by the Echavarren group to entioenriched 1,5-enyne **388** for the total synthesis of (–)-nardoaristolone B (**391**) (Scheme 90).⁵⁶¹

Scheme 90. Oxidative Cyclization of a 1,5-Enyne in the Synthesis of (–)-Nardoaristolone B



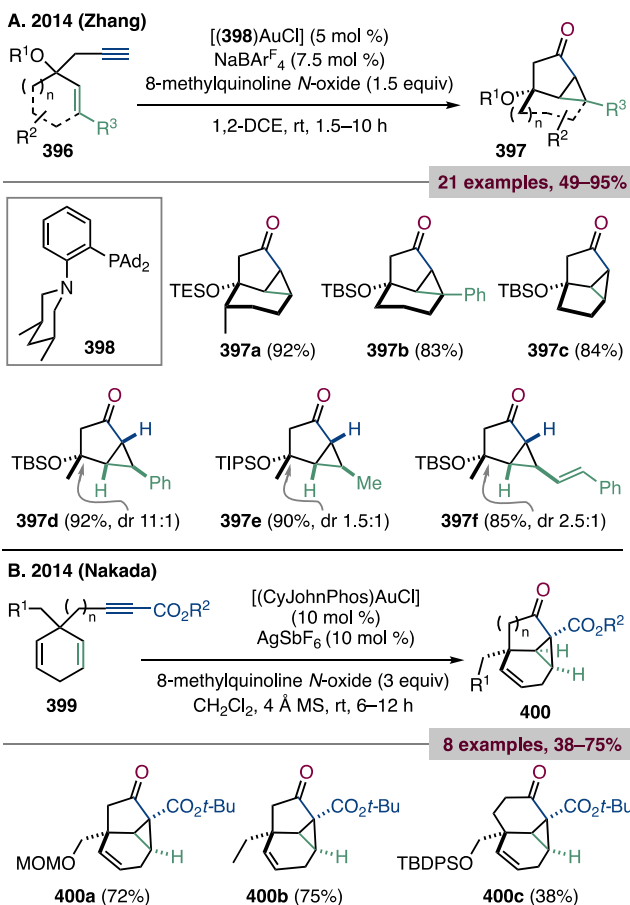
Zhang and co-workers disclosed an enantioselective version of the oxidative cyclization of 1,5-enynes (Scheme 91).⁵⁶² The design of hemilabile P,N-ligand^{563,564} **394** endowed with a C₂-symmetric piperidine ring was key to achieve good enantiocontrol. It was proposed that coordination of the N atom to the metal center and steric shielding temper the high reactivity of the very electrophilic α -oxo gold carbene intermediate **395**,^{565,566} while the piperidine provides a suitable chiral environment. Previous attempts to perform this reaction using axially chiral diphosphine ligands resulted in very low levels of enantioselectivity.⁵⁶⁷

Scheme 91. Enantioselective Oxidative Cyclization of 1,5-Enynes Using a P,N-Ligand



The groups of Zhang⁵⁶⁸ and Nakada⁵⁶⁹ reported the formation of complex tricyclic products starting from specific enynes. The Zhang group reported the synthesis of bi- and tricyclic cyclopropyl ketones **397** in 3 steps from cyclic enones and linear enals, respectively (Scheme 92A; major diastereomers

Scheme 92. Preparation of Bi- and Tricyclic Cyclopropyl Ketones via Oxidative Cyclizations

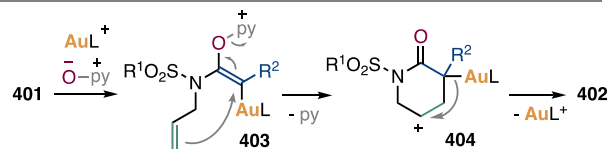
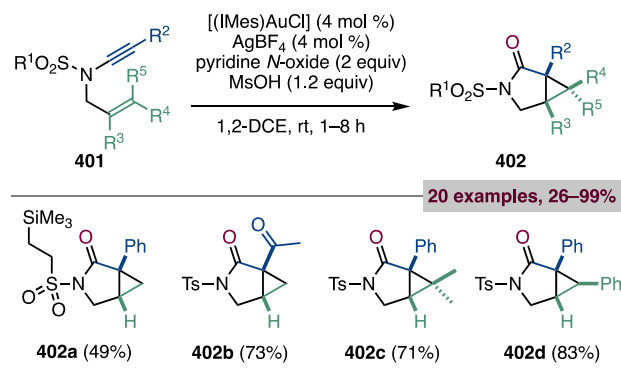


shown).⁵⁶⁸ This work highlighted once again the importance of a conformationally rigid P,N-bidentate ligand such as **398** to tame the reactivity of α -oxo gold carbenes. Nakada described the synthesis of similar tricyclic compounds **400** as single diastereomers starting from dienynes **399** (Scheme 92B).⁵⁶⁹

2.6.4. Oxidative Intramolecular Cyclopropanations of Ynamides.

Ynamides^{570–575} are easy-to-make^{576–580} electron-rich alkynes, that after activation by Lewis-acidic transition metals (or by Brønsted acids)⁵⁸¹ undergo facile addition of nucleophiles at the C_α .⁵⁸² Li and co-workers described the first gold-catalyzed oxidative cyclopropanation of *N*-allyl ynamides leading to various 3-aza-bicyclo[3.1.0]hexan-2-one derivatives **402** using $[(\text{IMes})\text{AuCl}]/\text{AgBF}_4$ as the catalyst and pyridine *N*-oxide as the oxidant (Scheme 93).⁵⁸³ Mechanistic studies excluded the intermediacy of an α -oxo gold carbene, pointing to attack of the alkene onto the electrophilic β -oxyppyridinium vinyl gold(I) species **403**.

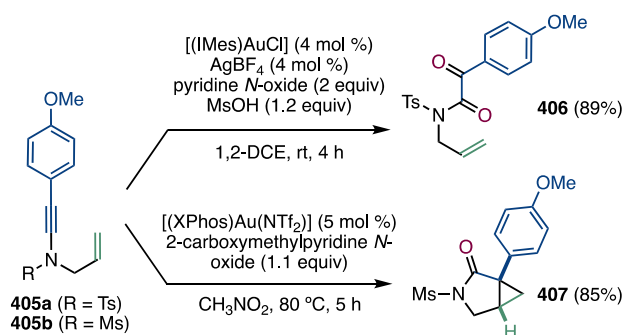
Scheme 93. Oxidative Cyclopropanation of *N*-Allyl Ynamides



In this protocol, electron-rich aromatic substituents at the alkyne terminus were not tolerated because of overoxidation (Scheme 94, top), a problem that was later solved by the group of Davies employing different reaction conditions (Scheme 94, bottom).⁵⁸⁴

Tang and co-workers showed that products **407** could be accessed from ynamides also using a Rh(I) catalyst and 3,5-dichloropyridine *N*-oxide, likely via a concerted cyclopropanation.

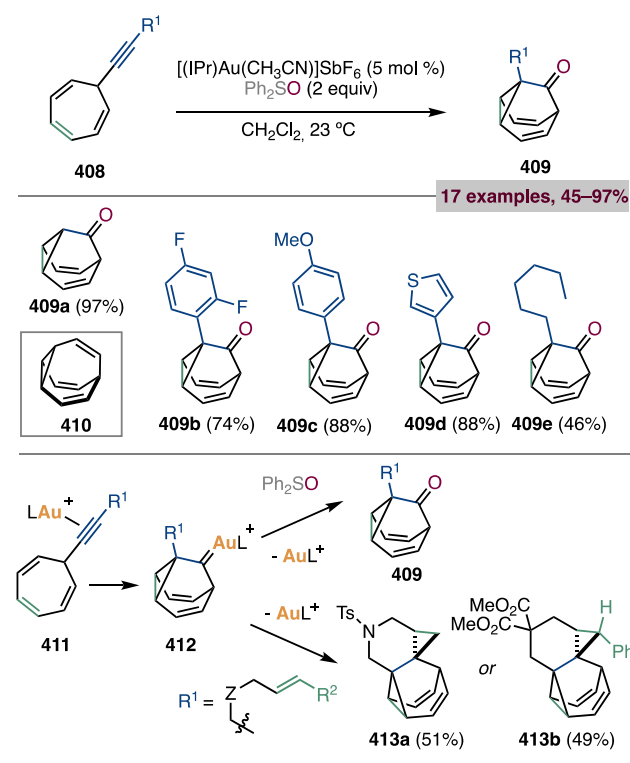
Scheme 94. Gold-Catalyzed Oxidation of Electron-rich Ynamides



tion of the pendant alkene by an α -oxo Rh(I) carbene.⁵⁸⁵ The group of Hashmi recently reported one case of Au(I)-catalyzed yne-ynamide cyclization/oxidation/intramolecular cyclopropanation cascade using diphenyl sulfoxide.⁵⁸⁶

2.6.5. Oxidative Intramolecular Cyclopropanation of Other Substrates. Gold-catalyzed oxidative cyclizations were applied by the group of Echavarren for the synthesis of highly fluxional molecules such as bullvalene (**410**) and analogues (Scheme 95).^{587,588} Several barbaralones **409** were prepared by

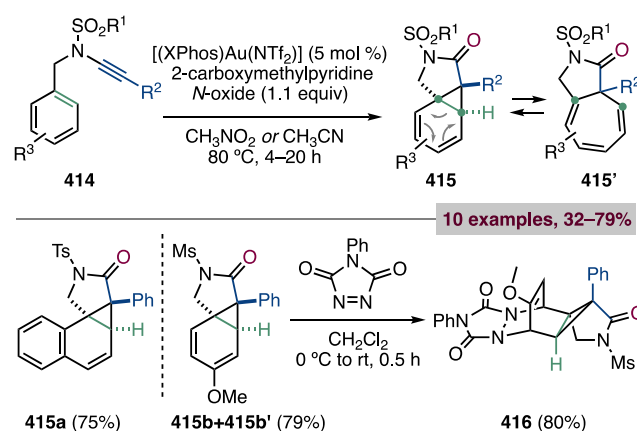
Scheme 95. Oxidative Cyclization of 7-Ethynyl-1,3,5-cycloheptatrienes



oxidative gold-catalyzed cycloisomerization of 7-ethynyl-1,3,5-cycloheptatrienes **408**. From barbaralone **409a**, bullvalene **410** could be accessed in only 3 steps and overall 16% yield, comparing favorably with previous syntheses. Most likely the reaction takes place via oxidation of barbaralyl gold(I) intermediates **412**, rather than by alkyne oxidation, as otherwise the opposite regioselectivity should be observed with aryl alkynes. Moreover, the optimal reaction conditions using diphenylsulfoxide suggest oxidation of a cyclopropyl-gold carbene-like intermediate, in line with the seminal report by Toste.⁵⁴⁹ The foundations of this work were laid by a previous study on the gold-catalyzed generation of fluxional barbaralyl cations (Scheme 95, bottom).⁵⁸⁹ Barbaralyl-gold complex **412** formed from activated alkyne **411** through a formal 6-*endo*-dig cyclization, which, according to calculations, actually involved the norcaradiene tautomer. The carbene center of **412**, which was oxidized for the synthesis of barbaralone, could be trapped by intramolecular cyclopropanation.

While all examples presented so far involve the reaction of an α -oxo gold carbene intermediate with a pendant alkene, there are also examples of cyclopropanation of a tethered aromatic ring. The group of Davies reported the oxidative Buchner-type reaction of *N*-benzyl ynamides **414** to afford [5.3.0] azabicycles **415'** (Scheme 96).⁵⁸⁴ A dynamic cycloheptatriene–norcaradiene

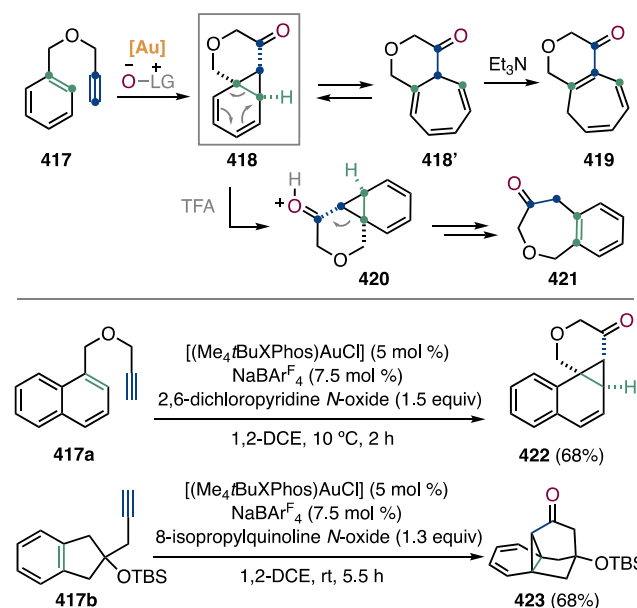
Scheme 96. Oxidative Intramolecular Cyclopropanation of Benzene Rings in *N*-Benzyl Ynamides



equilibrium was evident by NMR. Norcaradiene tautomer **415b** was trapped in a Diels–Alder reaction affording polycycle **416**, while **415a** was obtained exclusively as the norcaradiene product.

Similarly, Zhang and co-workers reported the intramolecular cyclopropanation of benzene rings by oxidatively generated α -oxo gold carbenes starting from benzyl propargyl ethers **417** (Scheme 97).⁵⁹⁰ In two instances, products with an intact

Scheme 97. Oxidative Intramolecular Cyclopropanation of Benzene Rings in Benzyl Propargyl Ethers

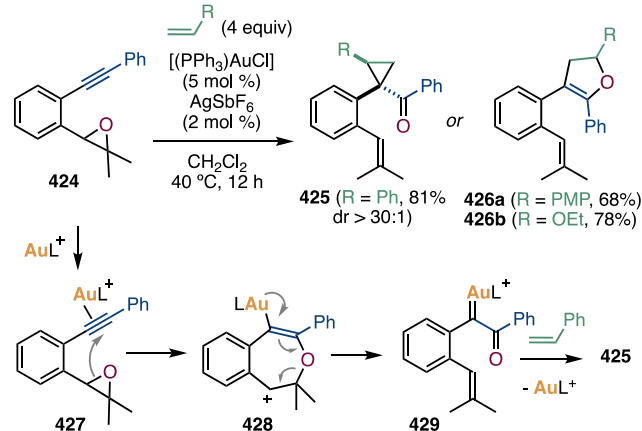


cyclopropane ring were obtained: whereas generally norcaradienes **418** underwent ring expansion to products **419** or **421** under basic or acidic conditions, respectively, vicinal benzo-fused norcaradiene **422** and propellane-type norcaradiene **423** were obtained as final products.

2.6.6. Oxidative Intermolecular Cyclopropanations.

Intermolecular cyclopropanations have proven much harder to develop. Liu and co-workers reported the first case of trapping with styrene an α -oxo gold carbene generated by intramolecular alkyne oxidation (Scheme 98).⁵⁹¹ An epoxide functionality in the substrate acted as sacrificial alkyne oxidant to deliver gold carbene **429**, which then effected the cyclopropanation of

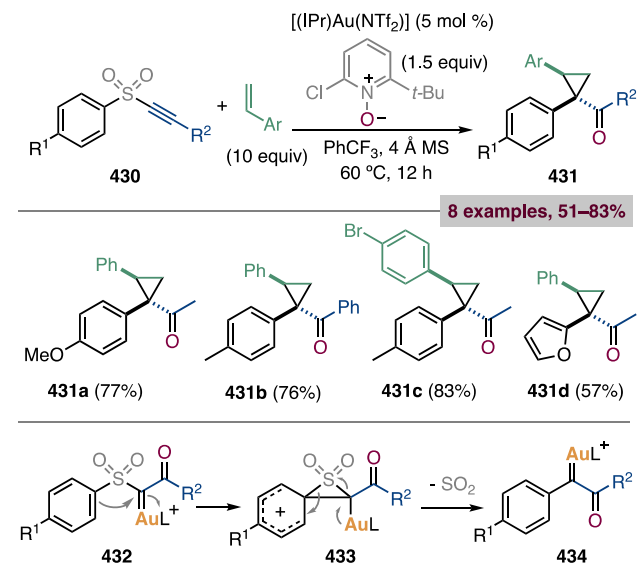
Scheme 98. Trapping of an α -Oxo Gold Carbene Intermediate by Styrene



styrene in 81% yield. When using electron-rich alkenes such as 4-methoxystyrene and ethyl vinyl ether, the major products were (3 + 2)-adducts **426a** and **426b**, respectively.

A more general approach was described by the group of Zhang, who generated the putative α -oxo gold carbene using an external oxidant, 2-(*tert*-butyl)-6-chloropyridine *N*-oxide⁵⁹² (Scheme 99).⁵⁹³ A plausible reaction mechanism involves at

Scheme 99. Oxidative Intermolecular Cyclopropanation of Styrenes



first the formation of carbene **432** with the expected regioselectivity, that is, oxidation at the alkyne C atom β to the electron-withdrawing group. Friedel–Crafts-type attack onto the very electrophilic carbene center then would afford episulfone **433**, which would fragment with SO_2 extrusion to α -oxo gold carbene **434**. It is worth noting that the latter carbene would be accessible only as the minor regioisomer by the oxidation of an internal aryl alkyne.

The alkene scope was limited to electronically unbiased styrenes, which were used in 10-fold excess. Electron-rich alkenes such as 4-methoxystyrene or ethyl vinyl ether were not suitable reaction partners. When using α -methylstyrene as a solvent, instead of the cyclopropane, a (3 + 2) cycloaddition product was obtained. Overall, whereas intramolecular oxidative

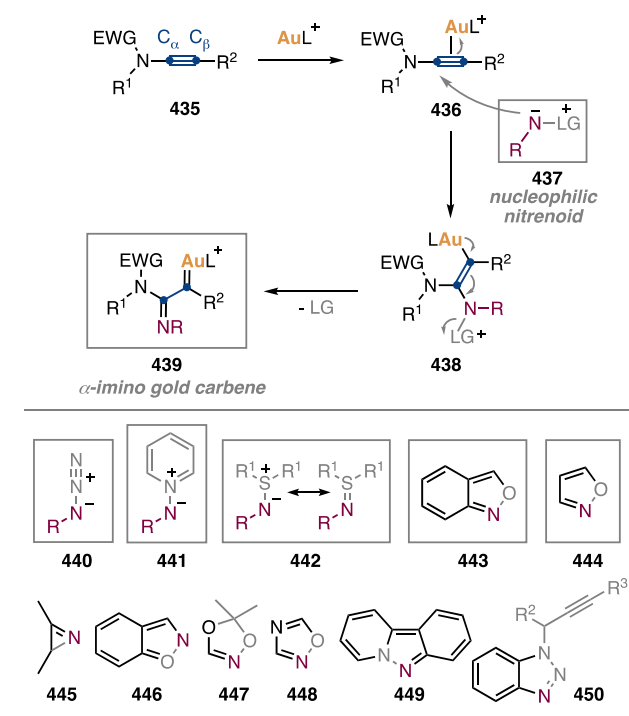
cyclopropanation of various enynes are well developed (see sections 2.6.2–2.6.5), there is still room for improving the more challenging intermolecular cyclopropanation of alkenes by oxidatively generated α -oxo gold carbenes.

2.7. Oxidation of Alkynes with Nitrogen-Transfer Reagents

2.7.1. General Considerations on α -Imino Gold Carbenes

In the same way as α -oxo gold carbenes can be accessed from gold-activated alkynes by oxygen transfer using *N*-oxides and sulfoxides (see section 2.6), α -imino gold carbenes **439** can be obtained employing nitrogen-based nucleophiles **437** that bear a leaving group on the N atom (Scheme 100).^{594–600} These reagents are also termed nucleophilic

Scheme 100. Formation of α -Imino Gold Carbenes from Gold-Activated Alkynes



nitrenoids,⁵⁹⁴ because they perform a net nitrene transfer to the alkyne. Their *anti* addition to a gold(I) or gold(III) activated alkyne delivers vinyl gold species **438**. The regioselectivity of addition depends on the polarization of the triple bond, that is, the nucleophile attacks the C atom where a higher build-up of partial positive charge occurs upon gold coordination. In the case of highly polarized ynamides^{570–575} such as **435**, the addition of the nucleophile is thus generally directed at C_α .⁵⁸² Subsequent gold retrodonation triggers the expulsion of the leaving group, affording α -imino gold carbene complex **439**.

As in the case of α -oxo gold carbenes, there is still mechanistic ambiguity on whether the competent catalytic intermediates are vinyl gold species **438** or α -imino gold carbenes **439**, particularly because the latter have not yet been isolated nor characterized spectroscopically.⁵⁹⁵ In fact, since both species are electrophilic, reaction with a nucleophilic partner can be envisaged either alongside or after elimination of the leaving group.⁵⁹⁴

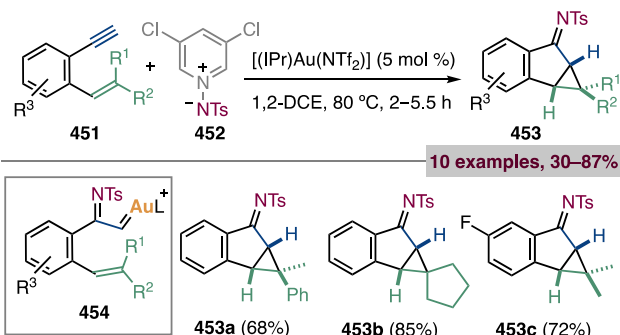
All cyclopropanations reported so far using α -imino gold carbenes **439** (or equivalent electrophilic species such as **438**) are intramolecular reactions, performed on substrates possessing a pendant alkene in the group R^1 (Scheme 100, top). Among the several nitrogen-based nucleophiles used for the generation of α -

imino gold carbenes (Scheme 100, bottom), azides 440,⁶¹² iminopyridinium ylides 441,⁶⁰¹ sulfilmines 442,⁶¹³ anthranils 443 (benzo[*c*]isoxazoles or 2,1-benzisoxazoles),⁶¹⁴ and isoxazoles⁶⁰² 444 have been employed to deliver cyclopropanes. The first three reagents take advantage of the presence of dinitrogen, pyridine, and thioethers as leaving groups, respectively. Anthranils and isoxazoles capitalize instead on the lability of the N–O bond.

As a final comparison between α -imino and α -oxo gold carbenes, it can be noted that α -imino gold carbenes are less electrophilic than their oxygen counterparts, due to the lower electronegativity of the N atom. An obvious structural difference is that α -imino gold carbenes allow the preparation of molecules incorporating N rather than O atoms (most notably, N-heterocycles).⁵⁹⁴ Moreover, an additional group (R) is necessarily transferred together with the N atom (Scheme 100). This substituent, apart from modulating the reactivity of the intermediate complexes, can participate in intramolecular reactions.

2.7.2. Cyclopropanations Involving α -Imino Gold Carbenes. The first example of intermolecular nitrene transfer to gold-activated alkynes, reported by Zhang,^{603,604} popularized the use of iminopyridinium ylides such as 452 as nucleophilic nitrenoids. These reagents are the nitrogen analogues of pyridine N-oxides, common oxidants in the field of α -oxo gold carbenes.^{535–544} Combining the use of iminopyridinium ylides and their previously reported oxidative cyclopropanation of 1,5-enynes (see Scheme 89),⁵⁵⁰ Liu and co-workers described the first cyclopropanation involving α -imino gold carbene intermediates, yielding cyclopropane-fused indanimines 453 (Scheme 101).⁶⁰¹

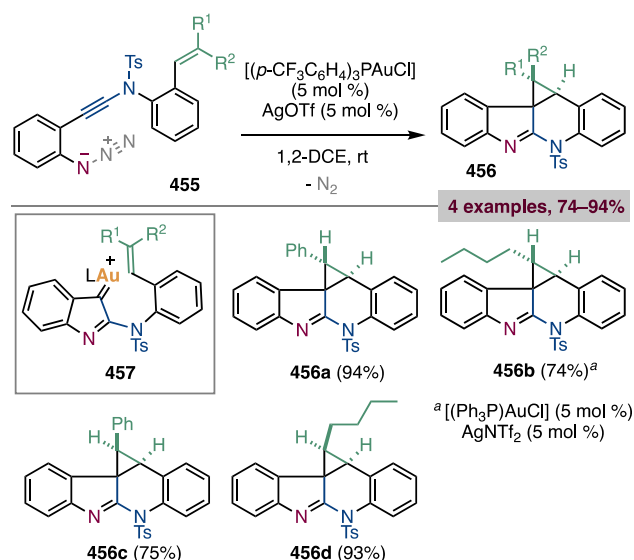
Scheme 101. Intramolecular Cyclopropanation of 1,5-Enynes Using Iminopyridinium Ylides



Ohno and co-workers described the reaction of (azido)-ynamides 455 with tethered alkenes to deliver cyclopropane-fused indoloquinolines 456 (Scheme 102).⁶¹² Intramolecular attack of the azide onto the ynamide, followed by nitrogen loss, delivered the key α -imino gold carbene 457, which then effected cyclopropanation of the pendant alkene. The use of azides as intramolecular nitrogen-transfer reagents for gold-activated alkynes became commonplace^{605,606} after the first report by the group of Toste for the synthesis of pyrroles.⁶⁰⁷

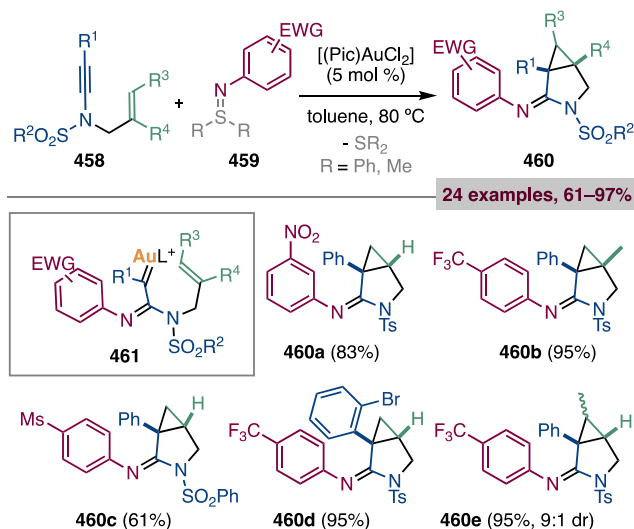
Due to the very specific ynamide substrates used, however, the generality of this approach was rather limited. Hashmi and co-workers improved the applicability of α -imino gold carbenes in intramolecular cyclopropanations of ynamides by using external nitrene transfer reagents. They employed *N*-arylsulfilmines 459 for the formation of α -imino gold carbenes 461 through intermolecular attack on gold-activated ynamides followed by

Scheme 102. Intramolecular Cyclopropanation of (Azido)ynamides



N–S cleavage (Scheme 103).⁶¹³ The intermediates could be trapped in a number of ways,⁵⁹⁹ including by a tethered alkene to

Scheme 103. Intramolecular Cyclopropanation of Ynamides Using Sulfilmines

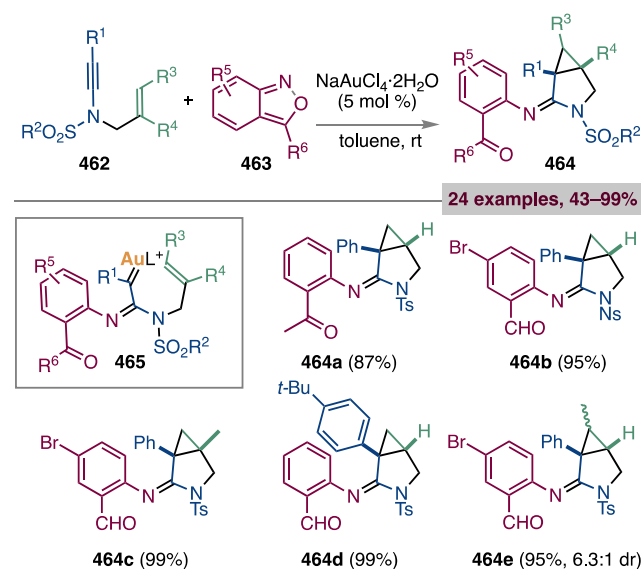


deliver 3-azabicyclo[3.1.0]hexan-2-imines 460 in good to excellent yields. In order for the reaction to proceed efficiently, more Lewis acidic gold(III) rather than gold(I) catalysts were beneficial, a temperature of 80 °C was required, and the sulfilmines had to carry a strong electron-withdrawing group on the arene. Sulfilmines⁵⁹⁹ are the nitrogen counterpart of sulfonium ylides, previously used by Maulide and co-workers in gold-catalyzed cyclopropanations (see section 2.9.3).^{608–611}

The group of Hashmi later showed the possibility of obtaining 3-azabicyclo[3.1.0]hexan-2-imines 464 from ynamides under milder conditions using alternative nucleophilic nitrenoids, namely anthranils (Scheme 104).⁶¹⁴ The reaction in this case could proceed with catalytic amount of NaAuCl₄ dihydrate at room temperature.

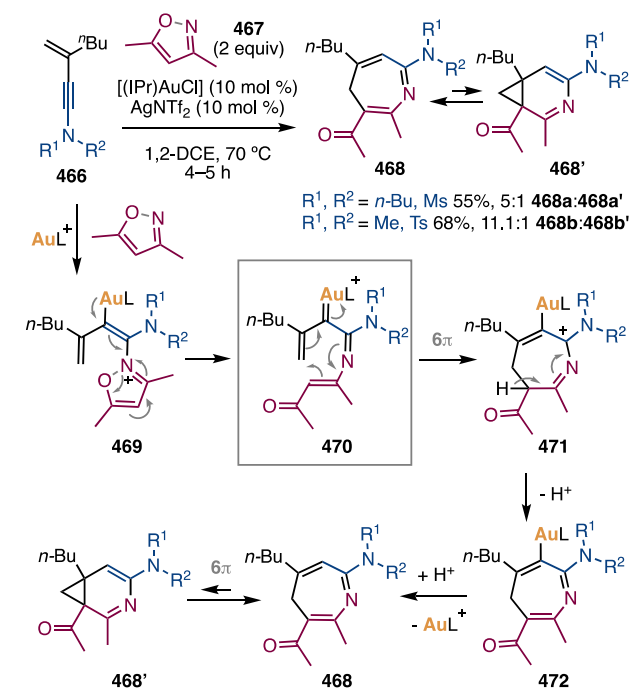
It is worth mentioning a related work involving α -imino gold carbenes, which in special cases allowed the generation of

Scheme 104. Intramolecular Cyclopropanation of Ynamides Using Anthranils



cyclopropane-fused bicyclic compounds **468'** (Scheme 105).⁶⁰² Liu and co-workers studied the gold(I)-catalyzed formation of

Scheme 105. (4 + 3) Annulation of 3-En-1-ynamides with Isoxazoles



azepine derivatives **468** starting from 3-en-1-ynamides **466** and isoxazoles⁵⁹⁵ **467** through a formal (4 + 3) cycloaddition process. In the proposed mechanism, α -imino gold carbene **470**, whose resonance form can be visualized as a gold-stabilized 3-azaheptatrienyl cation, underwent a 6π electrocycloaddition to deliver compound **471**, which after proton loss and proto-deauration afforded 4*H*-azepine **468**. Since these products contain a triene conjugated with a ketone, their 6π electrocycloaddition to deliver 3-azanorcaradienes **468'** is thought to be disfavored due to loss of conjugation. When the ynamides bore

an *n*-butyl group in the internal alkene position, Liu and co-workers observed the presence of the 3-azanorcaradiene **468a'** as minor isomer.

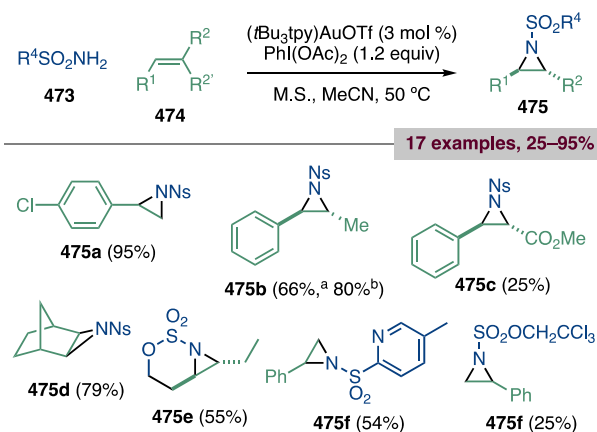
Despite this recent progress, there is still ample room to further develop the use of α -imino gold carbenes in the realm of cyclopropanations, as all examples reported to date are intramolecular, non-enantioselective reactions and, with only one exception, use activated alkynes (ynamides)^{612–614} as substrates.

2.8. Assembly of Heteroatom-Containing 3-Membered Rings

Gold(I) catalysis was also employed in different mechanistic scenarios to prepare heterocyclic 3-membered rings, namely, aziridines and epoxides.

2.8.1. Gold-Catalyzed Synthesis of Aziridines. Metal-catalyzed nitrene transfer reactions are analogous to carbene transfer processes. These reactions are a typical procedure to assemble aziridines from alkenes and are often carried out under rhodium, copper, or ruthenium catalysis, among others.⁶¹⁵ The first report on gold(I)-catalyzed nitrene transfer reaction for the synthesis of aziridines was reported by the group of He (Scheme 106).²⁸² This reaction is proposed to proceed through $\text{PhI}=\text{N}$

Scheme 106. Gold(I)-Catalyzed Nitrene Transfer for Aziridine Synthesis



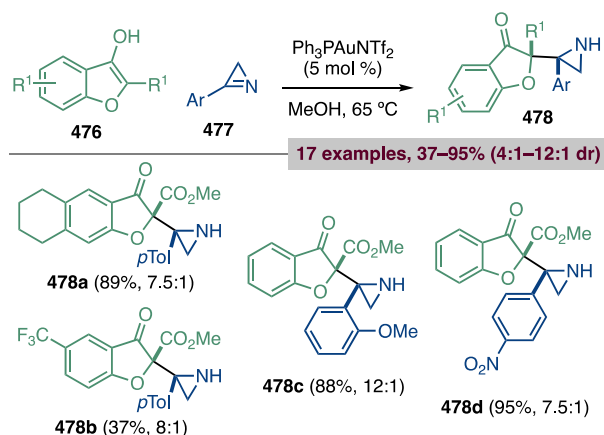
^aStarting from *E*- β -methylstyrene. ^bStarting from *Z*- β -methylstyrene.

NNs-type nitrenoid intermediates, which are generated in situ by combining commercially available sulfonamides with iodine(III) oxidant PhI(OAc)₂. This is a stereoconvergent reaction, in which both *E* or *Z* disubstituted alkenes **474** lead to the same *trans*-aziridine **475**, which strongly suggests a stepwise nature for the nitrene aziridination process.

The same group showed how a similar gold-catalyzed transfer process promoted by an iodine(III) reagent could be applied to carry out nitrene insertions into aromatic and benzylic C–H bonds.⁶¹⁶ Aziridines **478** have been also assembled by addition of 3-hydroxybenzofurans **476** to 2*H*-azirines **477** catalyzed by gold(I) complexes (Scheme 107).⁶¹⁷

Heterogeneous gold catalysis has also been successfully employed in the assembly of aziridines. For example, gold nanoparticles were reported to transfer nitrogen from ammonia to styrene, giving 2-phenylaziridine.⁶¹⁸

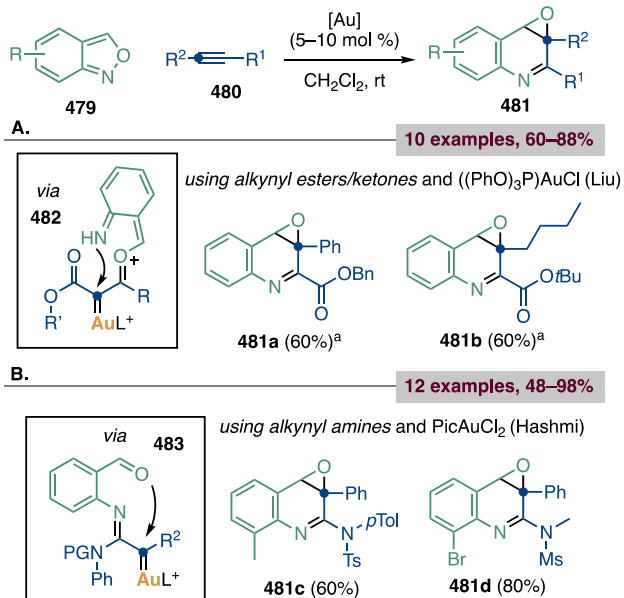
2.8.2. Gold-Catalyzed Synthesis of Epoxides. Under gold catalysis, epoxides have been often used as reactive units that can act both as electrophiles (upon Lewis-acid activation) and as nucleophiles (attacking other functional groups activated

Scheme 107. Aziridines from 2*H*-Azirines

by gold, such as alkynes) taking part in complex tandem processes.^{619–622,591} However, a few cascade cyclizations that result in the formation of epoxides based on gold catalysis have been recently reported.

Sahani and Liu reported for the first time a gold-catalyzed intermolecular (4 + 2) cycloaddition of electron-poor alkynes with benzisoxazoles that results in the assembly of highly oxygenated tetrahydroquinolines (**481a,b**), containing an epoxide group (Scheme 108A).⁶²³ Some of these products undergo an epoxide rearrangement affording 4-quinolones.

Scheme 108. Formal (4 + 2) Cycloaddition of Alkynes with Benzisoxazoles



^aUsing AgSbF₆ as chloride scavenger.

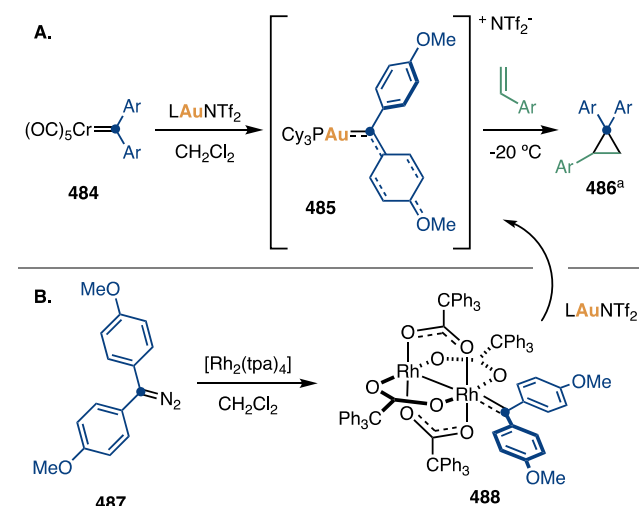
The group of Hashmi employed a similar strategy, using electron-rich alkynyl amines.⁶²⁴ This resulted in the development of a new switchable methodology, in which by choosing the appropriate gold catalyst, either 6-acylindoles (with a gold(I) complex) or quinoline epoxides such as **481c,d** (with a gold(III) complex) could be obtained from the same two substrates (Scheme 108B).

Besides homogeneous catalysis, supported gold nanoparticles have been reported to be active in the oxidation of alkenes by oxygen to yield epoxides.^{625,626}

2.9. Miscellaneous Precursors

2.9.1. Stable Gold Carbenes via Transmetalation. Seidel and Fürstner reported the solid-state characterization of a reactive gold(I) carbene, **485**, which was prepared by formal chromium-to-gold transmetalation of chromium carbonyl **484**. Besides being a historical landmark in the understanding of the bonding model of gold(I) carbene complexes, this species was found to react readily with styrenes to afford cyclopropanes (Scheme 109A).⁶²⁷ The same group disclosed the synthesis and

Scheme 109. Synthesis, Characterization, and Reactivity of Metal Carbenes



^aAr = *p*-Methoxyphenyl.

first X-ray characterization of analogous rhodium(II) carbenes (**488**) that led to the development of a versatile method for the preparation of gold(I) carbenes by rhodium-to-gold transmetalation (Scheme 109B).⁶²⁸

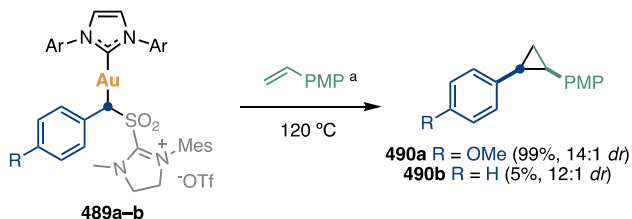
Through careful ligand design, Borissou and co-workers reported the isolation and solid-state characterization of a tricoordinated α -oxo gold(I) carbene complex generated from ethyl diazo(phenyl)acetate at -40 °C, which was competent in the cyclopropanation of styrene when generated in situ from the diazo-compound.⁵⁶⁶ Other groups have also contributed to the characterization of gold(I) carbenes, using different strategies to stabilize the otherwise reactive species.^{629–633}

2.9.2. Gold Carbenoids as Precursors of Gold Carbenes in Solution. Metal carbenoids are organometallic species of the type (X)(M)C(R¹)(R²), where an sp³ carbon atom C (for which R¹ and R² can be H or organic groups) is bound to both a metal M and a leaving group X. These species can evolve or be in equilibrium with the corresponding carbenes (M)CR¹R² upon release of the leaving group X and display analogous reactivity patterns, such as cyclopropanation of alkenes. The most studied type of metal carbenoid is the proposed intermediate for metal-catalyzed diazo decomposition reactions, in which X = N₂ (see section 2.1).^{236,634} Alternative types of gold(I) carbenoids have been prepared and employed as carbene equivalents in gas phase and solution.

2.9.2.1. Sulfone-Imidazolium Salt as Leaving Group in Gold(I) Carbenoids. The group of Chen reported the synthesis

of carbenoid-type gold(I) complexes such as **489**, based on their previous work on gas phase generation of carbenes (see section 2.2.2). These complexes release SO₂ and a free NHC (Scheme 110, in gray) upon heating, generating free gold carbenes that

Scheme 110. High Temperature Cyclopropanation Using Sulfone–Imidazolium Gold(I) Carbenoids

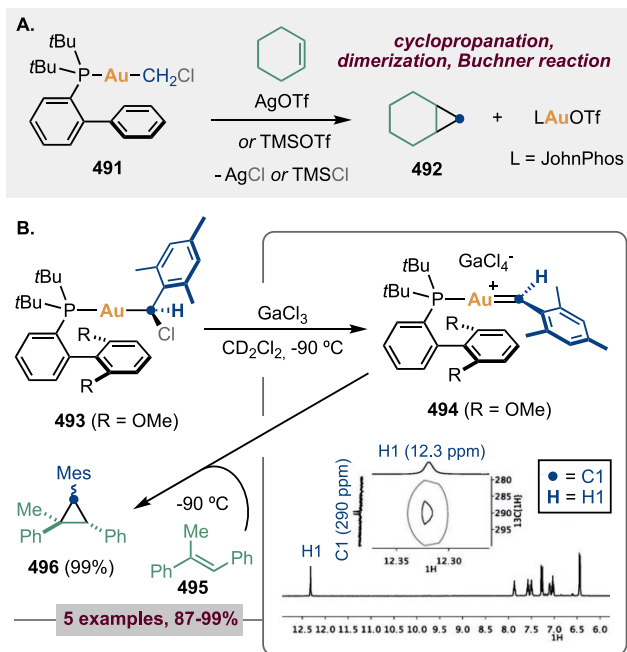


^aPMP = *p*-Methoxyphenyl.

can be trapped by electron-rich *p*-methoxystyrene to afford efficiently *cis*-cyclopropane **490a**. A catalytic version of this transformation was developed adding stoichiometric amounts of an external imidazolium salt.^{635,636}

2.9.2.2. Chloride as Leaving Group in Gold(I) Carbenoids. The group of Echavarren reported an alternative type of gold(I) carbenoid **491** bearing chloride as leaving group, which can act as methylene carbene equivalent. These carbenoids, upon activation with TMSOTf or AgOTf, display the typical reactivity patterns of metal carbenes: cyclopropanation of alkenes, dimerization, and Buchner reaction (Scheme 111A).⁶³⁷

Scheme 111. Gold Carbenes from Chloromethyl Gold(I) Carbenoids

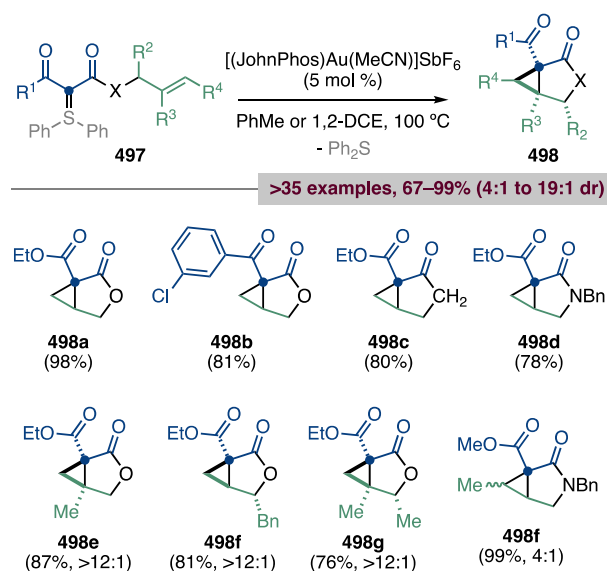


The [(JohnPhos)AuCH₂]⁺ species has only been detected by ESI-MS under very energetic conditions. In contrast, further study of these complexes revealed that chloro(aryl)methylgold(I) carbenoids such as **493** allowed the controlled generation of gold(I) carbenes in solution upon treatment with GaCl₃, even at cryogenic conditions. This allowed the NMR characterization of the corresponding carbenes, which are lacking heteroatom

stabilization. These carbenes undergo cyclopropanation, C–H insertion, oxidation, and dimerization reactions under very mild conditions (Scheme 111B).⁶³⁸ Similarly, Fürstner and co-workers reported the preparation of gold(I) difluorocarbenoid complexes, which also react with alkenes to assemble difluorocyclopropanes.⁶³⁹

2.9.3. Sulfonium Ylides. The group of Maulide disclosed for the first time the use of sulfonium ylides as gold(I) carbene equivalents that react with alkenes to form cyclopropanes. Rather than by metal carbene formation, these cyclopropanations occur via alkene activation by gold, an unusual pathway in gold(I) catalysis.⁶¹¹ Using this strategy, a highly stereoselective intramolecular cyclopropanation was developed, allowing the preparation of a wide range of cyclopropane-fused lactones **498** in high yields (Scheme 112).⁶⁰⁸

Scheme 112. Intramolecular Cyclopropanation through Catalytic Alkene Activation with Sulfonium Ylides

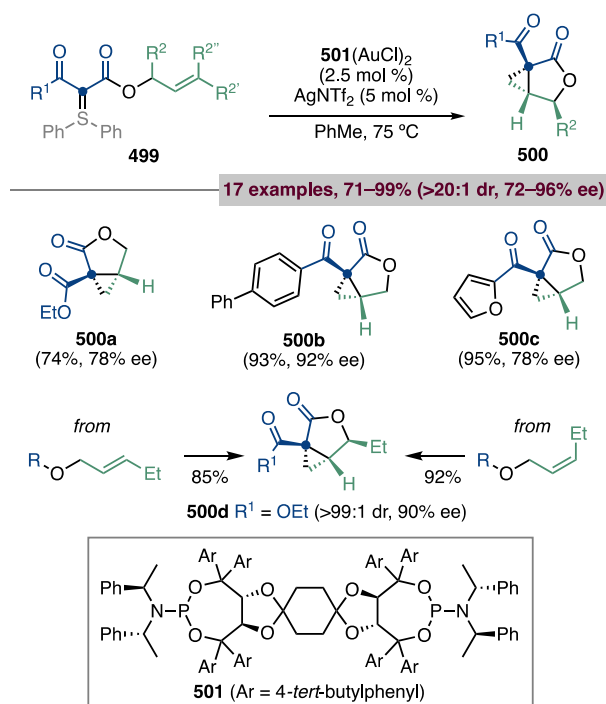


An asymmetric version of this reaction was reported by the same group.⁶¹⁰ In this work, the use of a digold complex with dimeric TADDOL phosphoramidite ligand **501** was key to the overall enantioselectivity, in a process featuring not only a diastereo- and enantioselective cyclopropanation but also an initial dynamic deracemization for chiral racemic substrates (where R² differs from H). This reaction was also found to be regio- and stereoconvergent in terms of the position of the alkene substituents (Scheme 113, colored in green): regardless of the position of R² in **499**, the substituent ends up in the same position in products **500**.

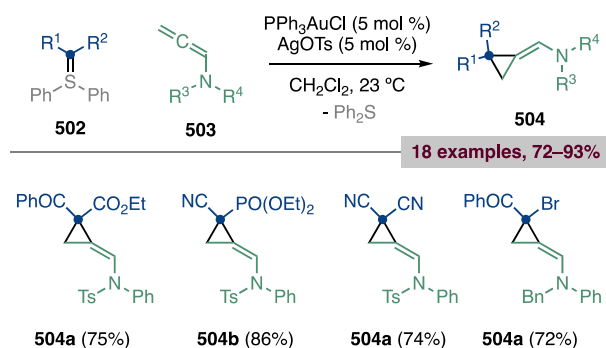
Maulide and co-workers also developed an intermolecular version of this gold(I)-catalyzed cyclopropanation reaction to afford methylenecyclopropanes **504** (Scheme 114).⁶⁰⁹ Mechanistic studies supported the hypothesis of allene activation by gold instead of the classical “carbene generation” pathway.

2.9.4. Acetylene as Dicarbene Precursor. Recently, Echavarren and co-workers reported the gold(I)-catalyzed activation of acetylene, as the simplest dicarbene equivalent (Scheme 115).⁶⁴⁰ By careful selection of the gold(I) complex, good yields of several biscyclopropanes **508** derived from stilbenes can be obtained. The same reaction can be carried out in the presence of cyclooctene, giving biscyclopropane **507**. Alternatively, if the reaction is carried out in the presence of a

Scheme 113. Asymmetric Intramolecular Cyclopropanation with Sulfonium Ylides



Scheme 114. Cyclopropanation of Allenamides with Sulfonium Ylides



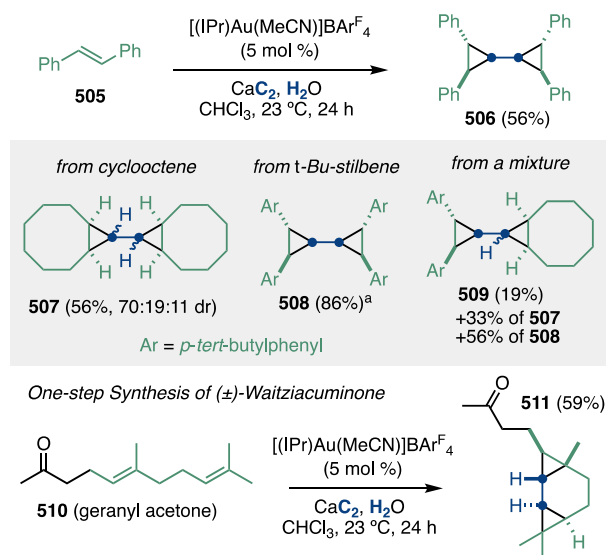
mixture of alkenes, a moderate amount of cross-biscyclopropanation product **509** can be obtained (Scheme 115, above). This biscyclopropanation strategy performs best by reacting acetylene with dienes. This is clearly illustrated by the intramolecular biscyclopropanation of geranyl acetone with acetylene, which affords directly natural product waitziacuminone (**511**) in one step, as a single diastereoisomer (Scheme 115, below).

3. CONSTRUCTION OF 4-MEMBERED RINGS CATALYZED BY GOLD

3.1. Synthesis of Cyclobutanes

The first synthesis of 4-membered rings using gold(I) catalysis was discovered in the context of the preparation of indoline-fused cyclobutanes.⁶⁴¹ Since then, the implementation of an impressive number of gold(I)-catalyzed protocols, mostly based on ring expansions and stepwise [2 + 2] cycloadditions, has rapidly expanded the field.^{41,119–126,207–210,449,450,642–645} These novel methods enable construction of compounds ranging from

Scheme 115. Acetylene as Dicarbene Precursor



^aUsing $[(t\text{BuXPhos})\text{AuCl}]/\text{NaBARF}_4$ (5 mol %) as catalyst.

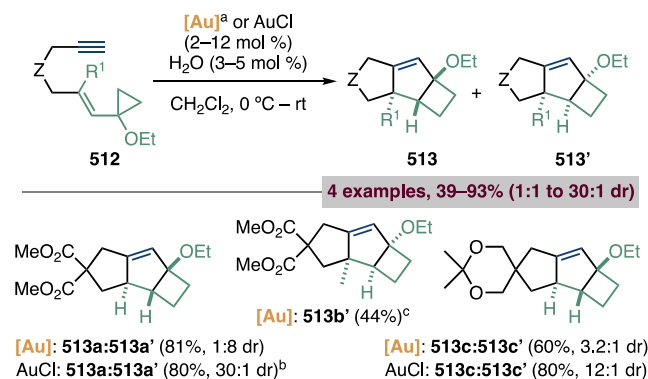
simple rings to complex skeletons of natural products in an atom-economical manner.

This section covers all the advances on the gold-catalyzed synthesis of 4-membered cycles from the outset of the field. The section will be divided by the type of ring formed and each subsection will be structured based on mechanistic considerations.

3.1.1. Gold(I)-Catalyzed Cyclopropane Ring Expansions. The strain release derived from cyclopropane expansion has been extensively used to thermodynamically favor the construction of 4-membered cycles.^{7,8,41,646} Under gold(I) catalysis, a wide range of cyclopropane-embedded frameworks can undergo ring expansion to efficiently assemble substituted cyclobutanes.^{41,644,645,647,648}

3.1.1.1. Gold(I)-Catalyzed Cycloisomerization of Cyclopropyl Enynes. The group of Echavarren disclosed the cascade gold(I)-catalyzed transformation involving the ring expansion of a cyclopropyl moiety to build a cyclobutane by the tandem enyne cyclization/ring expansion/Prins cyclization sequence of cyclopropyl 1,6-enynes **512** to form tricyclic compounds **513**, as mixtures of diastereoisomers (Scheme 116).⁶⁴⁹

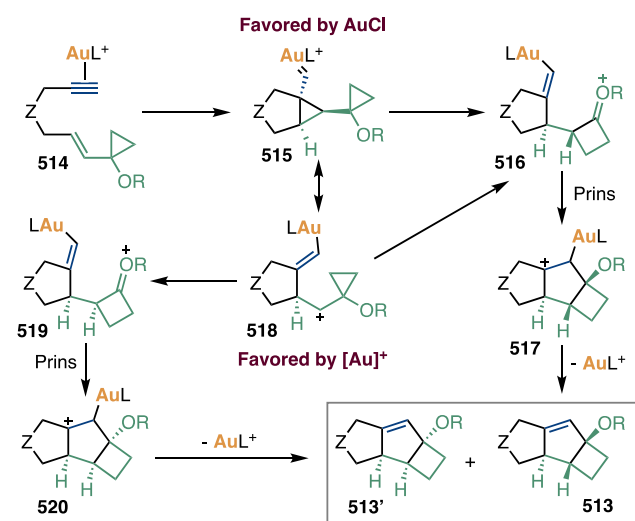
Scheme 116. Gold(I)-Catalyzed Cycloisomerization of Cyclopropyl 1,6-Enynes



^a $[(\text{JohnPhos})\text{Au}(\text{MeCN})]\text{SbF}_6$. ^b $E/Z = 1:1$. ^cReaction without H_2O .

Interestingly, the diastereoselectivity varied according to the gold(I) catalyst employed. Thus, using AuCl, cyclopropyl gold(I) carbene **515**, generated via 5-*exo*-dig cyclization, undergoes ring expansion to form alkenyl gold(I) complex **516**. Subsequent 5-*exo*-dig Prins cyclization and deauration steps release tricycles **513** (Scheme 117). For cationic gold(I)

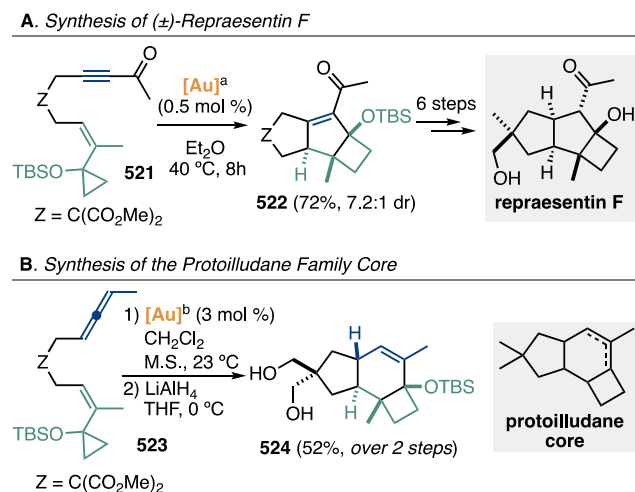
Scheme 117. Mechanistic Proposal for Gold(I)-Cycloisomerization of Cyclopropyl 1,6-Enynes



catalysts, the cyclopropyl cation (**518**) resonance form is favored, which evolves through a non-stereospecific ring expansion to give mixtures of diastereoisomers **513'** and **513** after Prins cyclization (Scheme 117).

The synthetic utility of this gold(I)-cyclization cascade was demonstrated with the diastereoselective one-pot construction of the tricyclic skeleton **522** of repraesentin F, which was further converted into the natural product in 6 steps (Scheme 118A).⁶⁵⁰ A related gold(I)-catalyzed allene–vinylcyclopropane cycloisomerization gave access to the tricyclic core of the protoilludanes family in a single step (Scheme 118B).⁶⁵¹

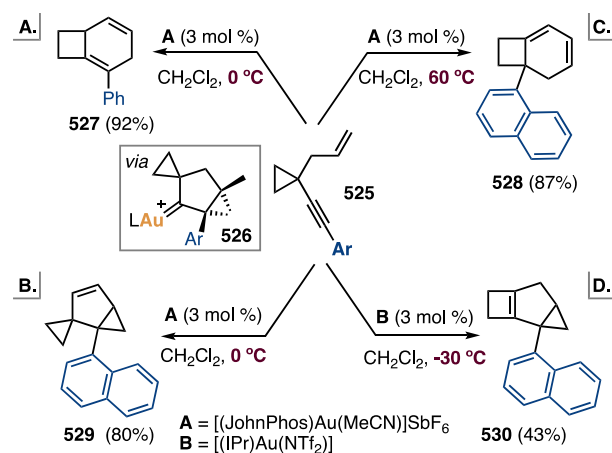
Scheme 118. Access to Repraesentin F and the Protoilludane Family Core



^a[(*t*-BuXPhos)Au(MeCN)]BAR^F₄, ^b[(JohnPhos)Au(MeCN)]SbF₆.

Shi reported the divergent gold(I)-catalyzed cycloisomerization of cyclopropyl-tethered 1,5-enynes **525** (Scheme 119).⁴⁴³

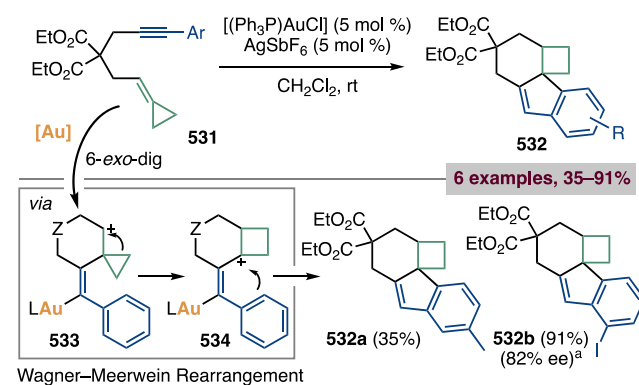
Scheme 119. Gold(I)-Catalyzed Cycloisomerization of Cyclopropyl 1,5-Enynes



When the aryl group was not *ortho*-substituted, cyclobutane-fused 1,4-cyclohexadienes **527** were obtained (Scheme 119A). The *ortho*-substitution of the aryl group resulted in the development of a switchable protocol, in which, by choice of the appropriate gold catalyst, three different polycyclic scaffolds were obtained under temperature control, namely, spiro compound **529**, fused-cyclobutane conjugated cyclohexadiene **528**, and tricyclic cyclobutene **530** (Scheme 119B,C,D, respectively). Computational and labeling experiments pointed to the initial formation of common bicyclopropane gold(I) carbene intermediate **526**, whose evolution toward the different products was controlled by the *ortho*-substituent effect.

3.1.1.2. Gold(I)-Catalyzed Cycloisomerization of Cyclopropylidene Enynes. Toste and co-workers developed a methodology to construct diastereomerically pure fused cyclobutanes **532** via Wagner–Meerwein skeletal rearrangement of cyclopropylcarbanyl cations **533**. These intermediates were generated in situ from the gold(I)-catalyzed 6-*exo*-dig cyclization of cyclopropylidene 1,6-enynes **531** (Scheme 120).³⁹³ Enantioenriched tetracycle **532b** could be obtained in 82% ee using [((*R*)-Xyl-SDP)(AuCl)₂] as gold(I) precatalyst (Scheme 120).

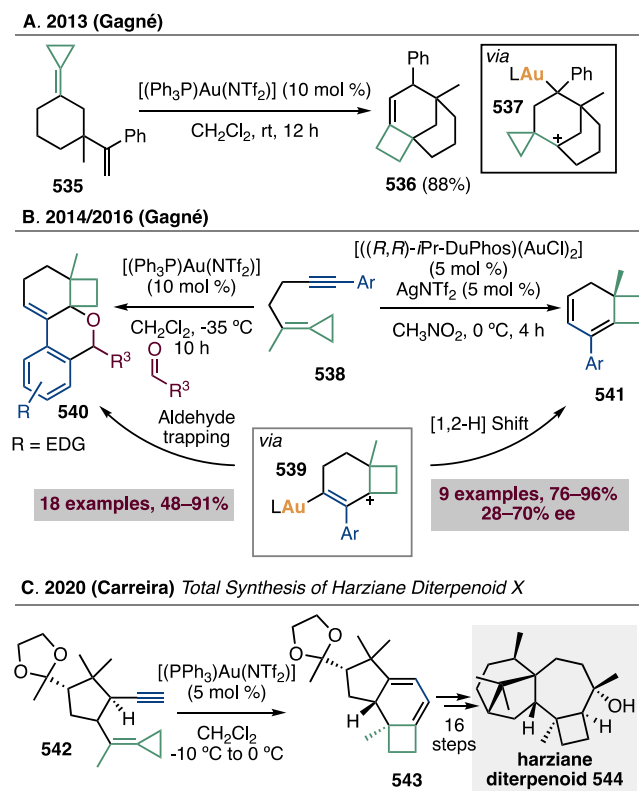
Scheme 120. Gold(I)-Catalyzed Cycloisomerization of Cyclopropylidene 1,6-Enynes



^aReaction using [((*R*)-Xyl-SDP)(AuCl)₂] as precatalyst.

This work by Toste inspired several subsequent studies in which the ring strain relief of cyclopropylidene fragments was key for the assembly of cyclobutanes under gold(I) catalysis. Thus, the group of Gagné reported a gold(I)-catalyzed Cope rearrangement and cyclopropane ring enlargement of cyclic 1,5-dienes **535** leading to tricyclic compounds **536** (Scheme 121A).⁶⁵² The same group disclosed the gold(I)-catalyzed

Scheme 121. Gold(I)-Catalyzed Cycloisomerization of Cyclopropylidene-Tethered Frameworks



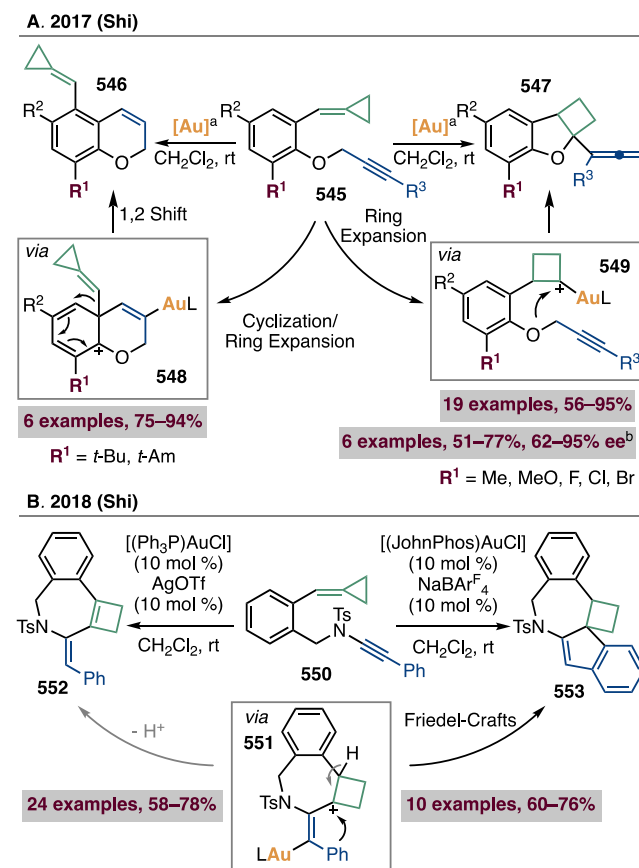
enantioselective cycloisomerization/ring-expansion sequence of cyclopropylidene-bearing 1,5-enynes **538** that led to enantio-enriched bicyclo[4.2.0]octanes **541** in up to 70% ee (Scheme 121B, right).⁶⁵³ Mechanistically, the ring-expanding cycloisomerization begins with a gold(I)-catalyzed 6-endo-dig cyclization and subsequent cyclopropane ring expansion toward the more stable allylic carbocation **539**, which undergoes 1,2-hydrogen shift to yield fused cyclobutane product **541**. In a follow-up report by the same group, gold(I)-stabilized allyl cation intermediates **539** were trapped by aldehydes, leading to oxo-carbenium cations, which suffer Friedel–Crafts annulation to form polycyclic structures **540** in a highly diastereoselective cascade reaction (Scheme 121B, left).⁶⁵⁴

Inspired by the protocol developed by the group of Gagné,⁶⁵³ Hönig and Carreira recently designed the key step of the first total synthesis of the unnamed harziane diterpenoid **544** (Scheme 121C).⁶⁵⁵ The target cyclobutane (**543**) was prepared with high diastereocontrol via gold(I)-catalyzed cycloisomerization of cyclic cyclopropylidene 1,5-enynes **542** bearing a terminal alkyne. The key cyclobutane was further transformed into harziane diterpenoid **544** in 16 steps.

Methylenecyclopropanes are known to undergo isomerization to form cyclobutenes in the presence of Pt(II),⁶⁵⁶ Pd(II),⁶⁵⁷ and Au(I)³²² catalysts. The group of Shi found that

treating “(propargyloxy)arenemethylenecyclopropanes **545** with an electrophilic gold(I) catalyst, [(*p*-CF₃C₆H₄)₃PAuCl], produced chemodivergent results, depending on the nature of the *ortho*-substituents on the phenyl group (R¹) (Scheme 122A).⁶⁵⁸ Specifically, when bulky substituents, such as *t*-Bu and

Scheme 122. Regiodivergent Gold(I)-Catalyzed Cycloisomerizations of Cyclopropylidene 1,7-Enynes



^a[(*p*-CF₃C₆H₄)₃PAuCl] (2.5 mol %) and AgSbF₆ (2.5 mol %).
^b[(DTBM-SegPhos)(AuCl)₂] (10 mol %), NaBAR₄^F (20 mol %), toluene, rt, 96 h.

t-Am are used, the methylenecyclopropane group migrates, rather than expands, leading to the formation of bicyclic products **548** (Scheme 122A, left). Nonbulky substituents (Me, MeO, or halogens) favor the gold(I)-catalyzed ring expansion and subsequent migration of the propargyl group to form 2,3-dihydrobenzofuran cyclobutane fused allene derivatives **547** (Scheme 122A, right). The asymmetric version of this transformation using DTBM-SegPhos ligand was also reported with a good level of enantioinduction, but a narrow substrate scope (Scheme 122A, right).

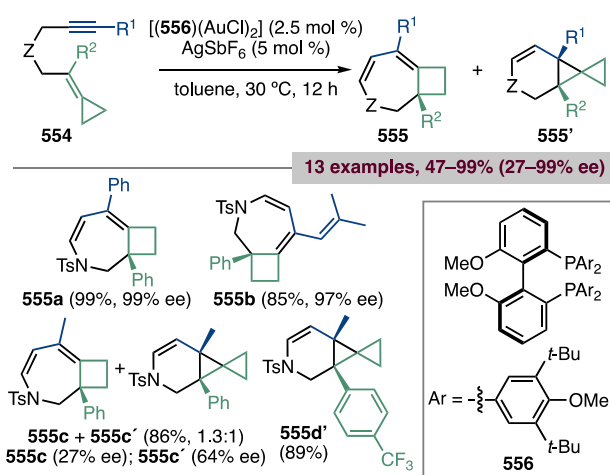
Shi also developed a regiodivergent gold(I)-catalyzed cyclization/ring opening sequence from alkynylamide-tethered alkylidenecyclopropanes **550** (Scheme 122B). In this case, two different types of fused 4-membered rings, cyclobutanes **553** and cyclobutenes **552**, were obtained depending on the gold(I) catalysts employed.⁶⁵⁹ Both the ligand and the counteranion of the cationic gold(I) catalyst were found to play an important role in the product distribution. When [(Ph₃P)AuCl] was used in combination with AgOTf, cyclobutenes **552** were exclusively obtained (Scheme 122B, left). Instead, the use of JohnPhos as

ligand with BAR_4^- counteranion led to cyclobutanes **553** as the only product (Scheme 122B, right). Using [(JohnPhos)Au(OTf)] as catalyst, a mixture of both carbocycles was obtained. The regiodivergent outcome was rationalized based on the mechanistic proposal. After ring expansion, the gold(I)-stabilized carbocation **551** can undergo Friedel–Crafts annulation leading to spirocyclic cyclobutanes **553**. Alternatively, intermediate **551** can be deprotonated affording cyclobutenes **552**.

Initial attempts to develop a gold(I)-catalyzed asymmetric synthesis of cyclobutanes via cyclopropylmethyl cation ring expansion were met with either only moderate levels of enantioinduction or limited substrate scope.^{653,658} In particular, in the context of the cycloisomerization of cyclopropylidene-tethered 1,6-enynes, the first asymmetric variant was disclosed by Toste (Scheme 120, 82% ee).³⁹³

Building upon this work, the groups of Li and Yu developed a general asymmetric synthesis of azepine-fused cyclobutanes **555** by means of a gold(I)-catalyzed cyclization/C–C cleavage/Wagner–Meerwein rearrangement sequence from cyclopropylidene 1,6-enynes **554** (Scheme 123).⁶⁶⁰ Here, the authors

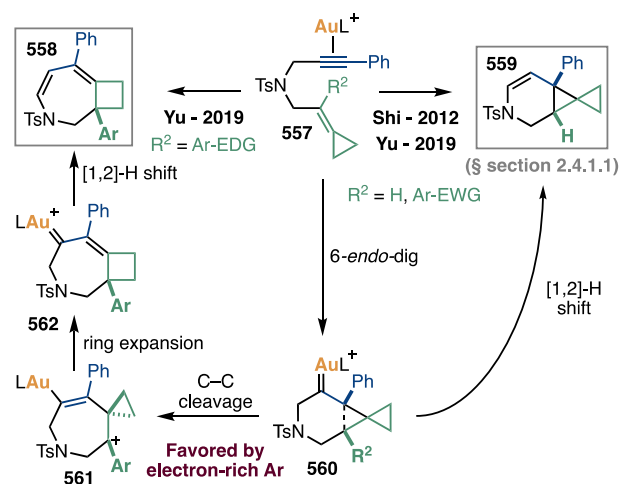
Scheme 123. Enantioselective Gold(I)-Catalyzed Cycloisomerization of Cyclopropylidene 1,6-Enynes



found that both solvent and counterion played an important role in enhancing enantioinduction. Notably, when [(*(R)*-4-MeO-3,5-(*t*-Bu)₂-MeOBIPHEP)(AuCl)₂], AgSbF₆, and toluene were used, the enantioselectivity for cyclobutane products **555** could be boosted up to 99% ee.

Interestingly, when electron-poor aryl groups were attached to the cyclopropylidene moiety, the reaction delivered spirocyclic compound **555'** with complete chemoselectivity. The same outcome had been previously reported by Shi using 1,6-enynes bearing monosubstituted cyclopropylidene fragments (Scheme 36A, section 2.4.1.1).³⁹² Using DFT calculations, the authors proposed a chemodivergent mechanism to explain this dichotomy (Scheme 124). Here, upon 6-*endo*-dig cyclization, cyclopropyl gold(I) carbene **560** can undergo either 1,2-hydrogen shift to spirocyclic compounds **559** or C–C cleavage, followed by ring expansion and 1,2-hydrogen shift, to azepine-fused cyclobutanes **558**. The latter pathway proceeds through carbocation **561**, which therefore will be stabilized by adjacent electron-rich aryl groups. The authors define intermediate **561** as a “carbocation with memory of chirality”,

Scheme 124. Mechanistic Proposal for the Gold(I)-Catalyzed Cycloisomerization of Cyclopropylidene 1,6-Enynes



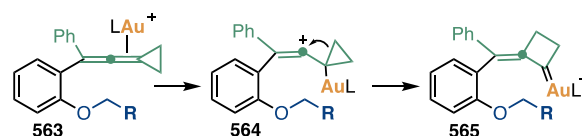
through which the chirality of the initially formed cyclopropane is transferred to the final product.

3.1.1.3. Gold(I)-Catalyzed Cycloisomerization of Vinylidenecyclopropanes. Shi and co-workers disclosed a new mode for gold(I) carbene generation based on the ambiphilic nature of vinylidenecyclopropanes. Upon gold(I) activation, a vinylidenecyclopropane such as **563** generates cyclopropyl gold(I) intermediate **564**, which leads to gold(I) carbene **565** by ring expansion (Scheme 125A).⁶⁶¹

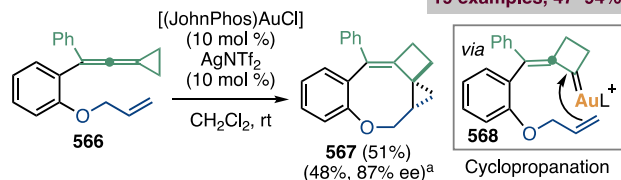
When vinylidenecyclopropane-enes of type **566** were submitted to this procedure, the transient gold(I) carbenes **568** cyclopropanated the pendant alkene moiety, building 3-, 4-, and 8-membered fused rings in a formal single step (Scheme 125B).⁶⁶¹ Only vinylidenecyclopropane-enes tethered to non-

Scheme 125. Gold(I)-Catalyzed Cycloisomerization of Vinylidenecyclopropanes

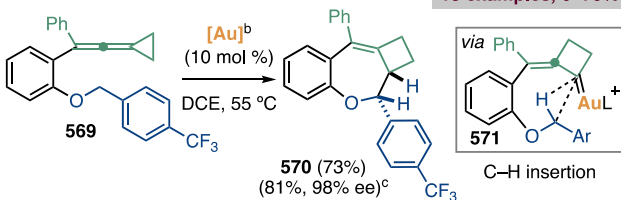
A. Gold(I) Carbene Generation Mode Developed by Shi



B. 2015 (Shi)



C. 2016 (Shi)

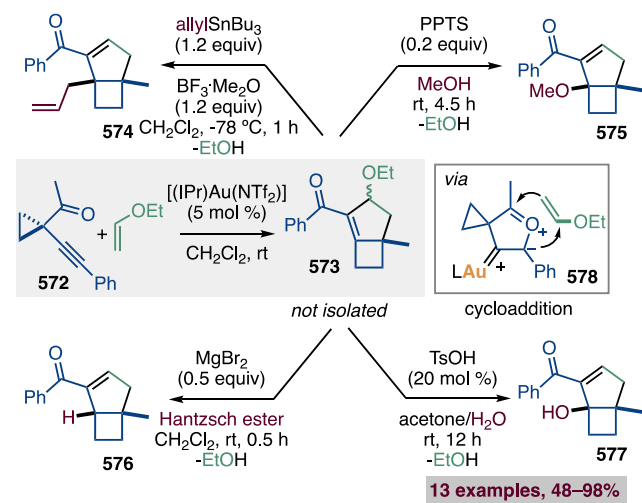


^a[(*(R)*-Xyl-BINAP)Au₂(MeCN)₂](SbF₆)₂ (10 mol %), toluene, rt.
^b[(Me₄-*t*BuXPhos)Au(MeCN)]NTf₂ (10 mol %).
^cSee refs 661 and 662 for details.

ortho-substituted aromatic rings were suitable substrates. By carefully modifying the pendant chain of vinylidenecyclopropanes, they developed a novel approach in which the in situ generated gold(I) carbene was involved in an intramolecular C(sp³)-H insertion (Scheme 125C).⁶⁶² Here, only scaffolds bearing *p*-CF₃ substituted aryl (**569**) gave the desired fused cyclobutane products such as **570** with high diastereocontrol. Enantioselective variants of these transformations were also developed using bidentate chiral phosphine-supported gold(I) catalysts (Scheme 125B,C).^{661,662}

3.1.1.4. Gold(I)-Catalyzed Oxo-Cyclization/Ring Expansion/Cycloaddition Sequences. Zhang disclosed the gold(I)-catalyzed intermolecular [4 + 2] annulation of alkynyl cyclopropyl ketones **572** with dipolarophiles, such as aldehydes, ketones, indoles, imines, and silyl ethers, to easily access polycyclic furans.⁶⁶³ In the course of their investigation, they found that when ethyl vinyl ether was employed as dipolarophile the reaction outcome switched to deliver a mixture of strained bicyclic cyclobutanes (Scheme 126).⁶⁶⁴ The authors proposed

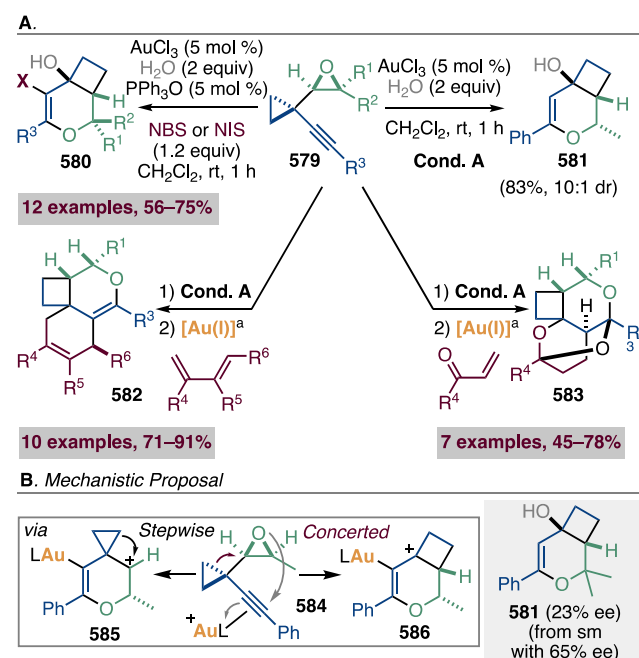
Scheme 126. Three-Component Reactions for the Synthesis of Bicyclo[3.2.0]heptanes



that enone **573** was initially formed by means of oxo-cyclization and 1,3-dipolar cycloaddition. However, this acid sensitive compound decomposed during purification, thus preventing isolation (Scheme 126). Varying the conditions, they developed a series of chemoselective one-pot three-component protocols in which unstable intermediates such as **573** were treated before purification with different nucleophiles, such as H₂O, MeOH, hydride, and allyl groups, to furnish substituted bicyclic enones **574**–**577** in high yield.

Liu reported the gold(III)-catalyzed cyclization of 1-epoxy-1-alkynylcyclopropanes **579**, in which the epoxide acts as a nucleophile attacking intramolecularly the alkyne fragment (Scheme 127A).⁶⁶⁵ When the gold(III)-catalyzed electrocyclic cyclization of **579** was performed in the presence of NBS or NIS, the replacement of the gold(III) fragment by Br⁺ or I⁺ led to halogenated products **580** in good yields and complete diastereoselectivity (Scheme 127A, top left).⁶⁶⁶ In addition, the oxocyclic alcohol products **581** could engage in a [4 + 2] cycloaddition with enones and dienes to deliver polycyclic compounds **583** and **582**, respectively, as single diastereoisomers (Scheme 127A, bottom).⁶⁶⁵ Originally, it was proposed that the gold(III)-catalyzed oxo-cyclization occurs

Scheme 127. Gold(I)-Catalyzed Cyclization of 1-Epoxy-1-alkynylcyclopropanes

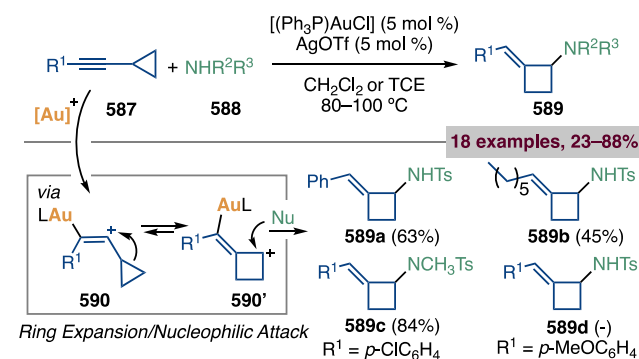


^aSiO₂ filtration, [(Ph₃P)AuCl] (10 mol %), AgSbF₆ (10 mol %), CH₂Cl₂, rt.

simultaneously to a cyclopropane ring expansion, in a concerted electrocyclic cyclization to form exocyclic alcohols **581** in a diastereoselective manner (Scheme 127B). However, experiments using enantioenriched epoxyalkynes **579** demonstrated that the chiral information was mostly lost during the gold(III)-catalyzed cyclization and, thus, a stepwise oxo-cyclization/ring expansion sequence could not be discarded (Scheme 127B).

3.1.1.5. Gold(I)-Catalyzed Synthesis of Cyclobutanamines. Ye and Yu disclosed the gold(I)-catalyzed synthesis of 2-alkylidenecyclobutanamines **589** with complete *E*-selectivity, taking place via ring enlargement of nonactivated alkynylcyclopropanes **587** and subsequent intermolecular sulfonamide trapping (Scheme 128).⁶⁶⁷ Other common Lewis Acids such as PtCl₂ and Sc(OTf)₃ led to low reactivity. Aryl- and alkyl-alkynylcyclopropanes **587** were suitable substrates, whereas terminal alkynes underwent ring expansion instead. A DFT study of this reactions was also carried out.⁶⁶⁸

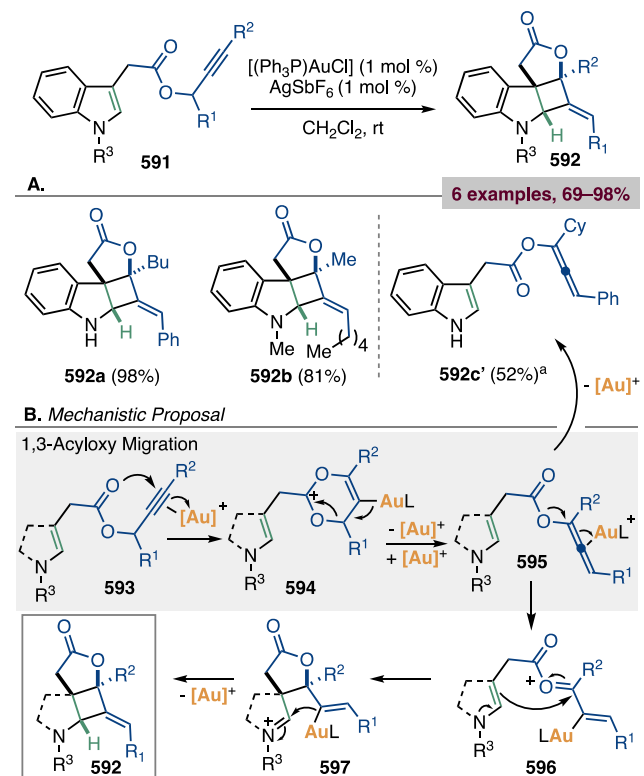
Scheme 128. Gold(I)-Catalyzed Synthesis of Cyclobutanamines



A heterogeneous gold(I)-catalyzed version of this transformation was developed using $\text{Fe}_3\text{O}_4@\text{SiO}_2\text{-PPh}_2\text{-AuOTf}$ supported on magnetic nanoparticles that could be recycled up to 10 times, maintaining a catalytic activity comparable to the previous homogeneous version.⁶⁶⁹

3.1.2. Gold(I)-Catalyzed 1,3-Acyloxy Migration of Propargylic Carboxylates. Zhang disclosed a tandem gold(I)-catalyzed 1,3-acyloxy migration/[2 + 2] cycloaddition sequence from indole-tethered propargylic carboxylates to furnish indole-fused cyclobutanes **592** with complete diastereoselectivity (Scheme 129A).⁶⁴¹ This work is not only

Scheme 129. Intramolecular Gold(I)-Catalyzed 1,3-Acyloxy Migration/[2 + 2] Cycloaddition Sequence



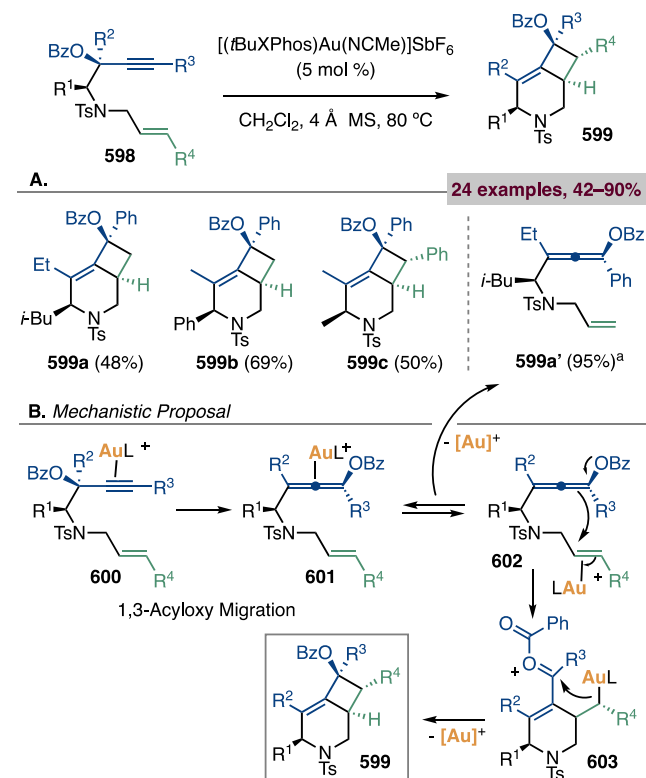
^a AuCl_3 (10 mol %), CH_2Cl_2 , rt.

significant for being the first example of gold(I)-catalyzed synthesis of cyclobutanes, but also because it laid the foundations for the, nowadays well-explored, field of gold(I)-catalyzed [2 + 2] cycloadditions of allenes and alkenes, which will be further detailed in section 3.1.3 of this review. The author proposed that the initial gold(I)-catalyzed 1,3-acyloxy shift proceeds through a 6-*endo*-dig oxo-cyclization to form oxocarbenium intermediate **594**, which undergoes ring opening to carboxyallene **595** in an overall [3,3]-sigmatropic rearrangement (Scheme 129B, gray square).^{479,641} The in situ generated allene can be subsequently activated by gold to participate in further transformations. In this particular case, the indole moiety present on the original scaffold **591** engages in a formal [2 + 2] cycloaddition via two consecutive intramolecular trapping events. Interestingly, the carboxyallene-indole product **592c'** could be isolated, supporting their mechanistic proposal (Scheme 129A). Calculations by Cavallo et al. suggested an alternative pathway in which a gold(I) vinylidene could be

formed via two sequential 1,2-acyloxy migrations (see also section 2.5 on 1,2- and 1,3-acyloxy shift).⁴⁸¹

The group of Chan reported another gold(I)-catalyzed 1,3-acyloxy shift/[2 + 2] cycloaddition sequence from 1,7-enyne benzoates **598** (Scheme 130).⁶⁷⁰ This transformation gave

Scheme 130. Intermolecular Gold(I)-Catalyzed [3,3]-Rearrangement/[2 + 2] Cycloaddition Sequence of 1,7-Enynes

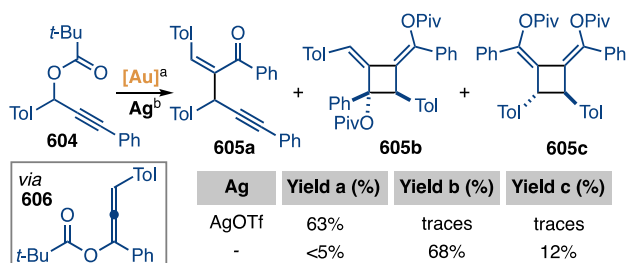


^aReaction performed in acetonitrile.

access to azabicyclo[4.2.0]oct-5-enes **599** in a regioselective and stereoconvergent manner (Scheme 130A). In addition, the chirality could be transferred from enantiopure substrates to the products. Interestingly, the authors proposed a different activation mode, in which gold coordinates preferentially to the alkene in 1,7-allenene **602**, which can be formed in situ via 1,3-acyloxy shift (Scheme 130B). This η^2 -(alkene)gold(I) species **602** undergoes a subsequent stepwise [2 + 2] cycloaddition leading to the product. The solvent and the optimal catalyst were essential to promote the last step and prevent the exclusive formation of the 1,7-allenene intermediate, as occurred for **599a'** (Scheme 130A).

The gold(I)-catalyzed 1,3-acyloxy migration of 1,3-diarylpargyl carboxylates has been considered challenging due to the formation of uncharacterized mixtures. While investigating the nature of the multiple products, Shi and co-workers developed a chemo- and regioselective silver-free protocol for the intermolecular gold(I)-catalyzed synthesis of cyclobutanes **605b** from highly reactive scaffolds **604** (Scheme 131).⁶⁷¹ Here, the in situ generated allenes undergo intermolecular gold(I)-catalyzed [2 + 2] cycloaddition between themselves. In the presence of silver, 1,4-enyne **605a** was formed exclusively (Scheme 131). In contrast, under silver-free conditions, the cyclobutane isomer **605b** could be obtained as the major

Scheme 131. Intermolecular Gold(I)-Catalyzed 1,3-Acyloxy Shift/[2 + 2] Cycloaddition Sequence



^a[(Ph₃P)Au(N-methyl benzotriazole)]OTf (1 mol %), CH₂Cl₂, rt.
^bAgOTf (2 mol %).

product depending on catalyst choice and substitution pattern of the carboxylate moiety.

An isolated example of this reactivity was recently reported by Fiksdahl in the context of gold(I)-catalyzed [2 + 2 + 2] cyclootrimerizations.⁶⁷²

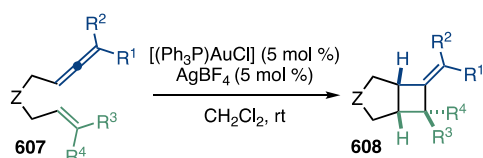
3.1.3. Gold(I)-Catalyzed [2 + 2]-Cycloadditions of Allenes and Alkenes. A seminal publication by Toste and co-workers disclosed the formation fused cyclobutanes **608** via diastereoselective [2 + 2] cycloaddition of 1,6-allenenes **607** (Scheme 132A).⁶⁷³ In the same work, the original racemic protocol was expanded using [(*R*)-DTBM-SEGPHOS]-(AuCl)₂ **609** as precatalyst to obtain *cis*-cyclobutanes with excellent enantioselectivity (Scheme 132B).

The gold(I)-catalyzed [2 + 2] cycloaddition of 1,6-allenenes **607** became a benchmark reaction to explore the utility of new chiral ligands in asymmetric gold(I) catalysis. For instance, it was employed by Fürstner and co-workers to study the performance of a library of chiral phosphoramidite ligands in gold(I) asymmetric catalysis.^{404,507} Complex **610**, with a ligand based on an acyclic TADDOL, gave even better results than the bidentate phosphine SEGPHOS used in the original work by Toste (Scheme 132B, **609**). In another publication by the group of Toste, spirobiindane-derived phosphoramidite gold(I) complex **611** was reported to mediate the asymmetric [2 + 2] cycloaddition efficiently in terms of both catalytic activity and enantioselectivity (Scheme 132B, **611**).⁶⁷⁴ Likewise, the group of Marinetti developed gold(I) complex **612**, bearing a phosphahelicene ligand, which was applied to the synthesis of enantioenriched cyclobutanes **608** (Scheme 132B, **612**).⁶⁷⁵

In the original work by Toste,⁶⁷³ the *cis*-cyclobutane **614** was obtained from the gold(I)-catalyzed [2 + 2] cycloaddition of both *E*- and *Z*-1,6-allenene **613** (Scheme 133A). Interestingly, when *E*-1,6-allenene **613** was exposed to a gold(I) catalyst in the presence of methanol, *trans*-cyclopentane **615** was formed (Scheme 133A).⁶⁷³ These preliminary mechanistic studies pointed toward the stepwise formation of carbocationic intermediates.

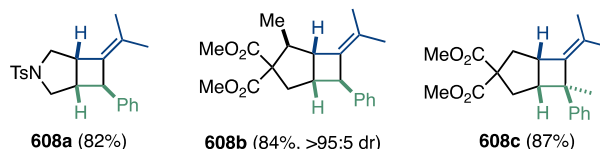
To clarify the mechanistic scenario, DFT studies were performed on the gold(I)-catalyzed [2 + 2] cycloaddition of a 1,6-allenene using a model phosphoramidite-gold(I) catalyst (Scheme 133B).⁶⁷⁴ This study showed that the reaction starts by intramolecular alkene addition to the gold(I)-coordinated allene **617**, which can occur through two competitive pathways leading to *cis*- and *trans*-vinyl gold(I) complexes **618**. In the presence of methanol, the kinetically favored carbocation *trans*-**618** is intermolecularly trapped by MeOH to furnish cyclopentane *trans*-**615** (Scheme 133B, left). In the absence of nucleophiles, carbocations *trans*-**618** and *cis*-**618** are

Scheme 132. Gold(I)-Catalyzed [2 + 2] Cycloaddition of 1,6-Allenenes

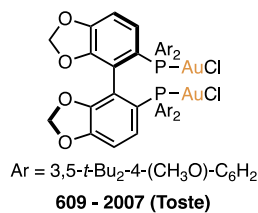
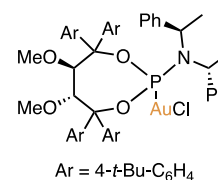
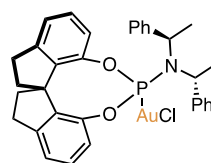
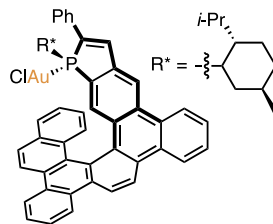


A. 2007 (Toste)

11 examples, 57–92%



B. Asymmetric Synthesis of Cyclobutanes

**609** - 2007 (Toste)7 examples
(70–92%, 54–97% ee)**610** - 2010/2012 (Fürstner)10 examples
(60–94%, 81–99% ee)**611** - 2011 (Toste)9 examples
(52–87%, 14–97% ee)**612** - 2015 (Marinetti)7 examples
(72–93%, 82–90% ee)

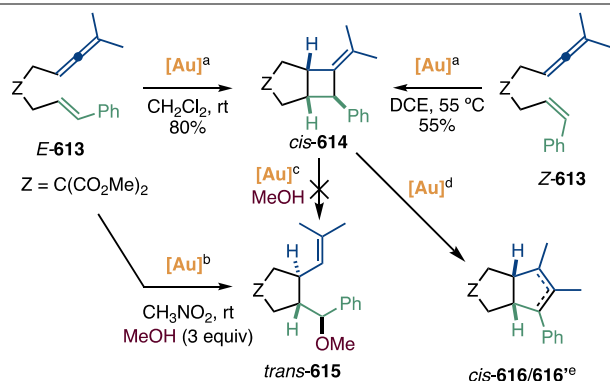
in equilibrium, and the later undergoes intramolecular carbocation trapping to form the thermodynamically more stable *cis*-cyclobutane **614** (Scheme 133B, right). The reverse ring-opening from *cis*-**614** to generate carbocation *cis*-**618** was not energetically feasible, as proven by experimental data (Scheme 133A). However, in an independent work by Fürstner, this pathway was found to be effective during the gold(I)-catalyzed rearrangement of *cis*-**614** to the ring-expanded scaffolds **616/616'** (Scheme 133A).⁶⁷⁶ Remarkably, this reaction only takes place using NHC ligands with the appropriate electronic properties.

Under gold(I) catalysis, larger 1,7-allenenes **619** gave variable mixtures of 5- and 4-membered carbocycles, **620a** and **620b**, respectively (Scheme 134).^{677–682} The product ratio was dependent on the ligand, although the formation of cyclopentene scaffolds **620a** was always favored. The ligand effect on this transformation was investigated using multivariate analysis, concluding that the selectivity-determining step, which was proposed to be a concerted cyclization to form both rings, was significantly affected by the steric properties of the ligand. Based on a detailed computational study, Liu et al. suggested that the two fused rings were formed via a stepwise cyclization.⁶⁸³

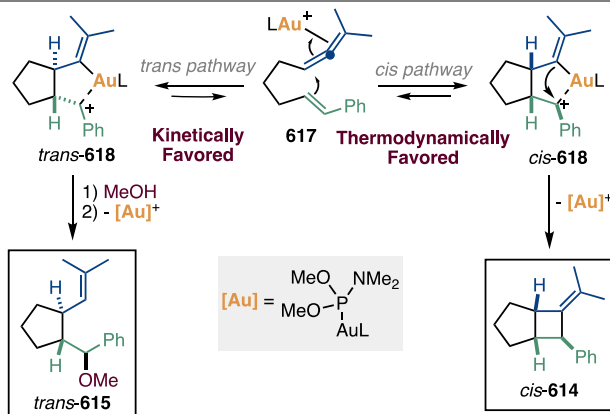
A similar regiodivergent scenario was found independently by the groups of Toste and Mascareñas in the gold(I)-catalyzed intermolecular cycloadditions of allenedienes **621**.^{677–681} These

Scheme 133. Experimental and Computational Mechanistic Studies on the Gold(I)-Catalyzed [2 + 2] Cycloaddition of 1,6-Allenenes

A. Mechanistic Studies

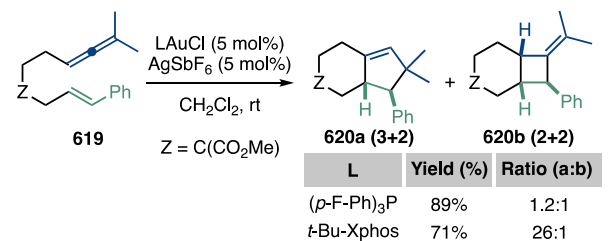


B. Mechanistic Proposal (DFTs)



^a[(Ph₃P)AuCl] (5 mol %), AgBF₄ (5 mol %). ^b[(Ph₃P)Au]BF₄ (5 mol %). ^c[(PhO)₃P]Au]BF₄. ^d[(NHC)AuCl] (5 mol %), AgSbF₆ (5 mol %), CH₂Cl₂, -5 °C, NHC = imidazopyridine-2-ylidene derivative. ^eA mixture of **616** (56% ee) and **616'** (52% ee) was obtained from enantioenriched **613** (>99% ee).

Scheme 134. Gold(I)-Catalyzed Cycloadditions of 1,7-Allenenes

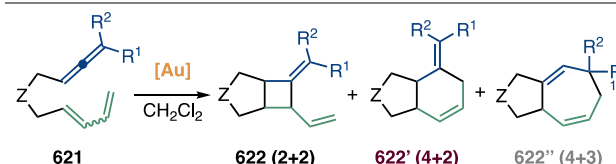


substrates can undergo either (4 + 2) or (4 + 3) cycloadditions to form 6- or 7-membered carbocycles, respectively, via a ligand-controlled bifurcated mechanism from intermediate **623** (Scheme 135A).^{678,682} Interestingly, two specific allenediene evolve by means of gold(I)-catalyzed [2 + 2] cycloaddition to release fused cyclobutanes **622** and **622'** instead of forming larger rings (Scheme 135B).⁶⁷⁸

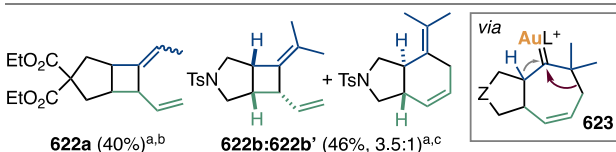
Contributions by the groups of Chen,⁶⁸⁴ González,⁶⁸⁵ and López and Mascareñas⁶⁸⁶ set the foundations for the development of the intermolecular gold(I)-catalyzed [2 + 2] cycloaddition of alkenes and allenes (Scheme 136). The catalytic methods developed by these groups gave access to densely

Scheme 135. Gold(I)-Catalyzed Cycloadditions of Allenediene

A.

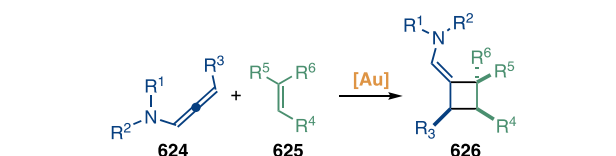


B.



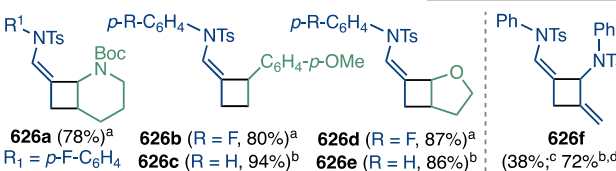
^a[(2,4-(*t*-Bu)₂-C₆H₃O)₃P]AuCl] (10 mol %), AgSbF₆ (10 mol %), 0 °C. ^b**622a** was obtained from *trans*-**621**. ^c**622b** and **622b'** were obtained from *cis*-**621**.

Scheme 136. Gold(I)-Catalyzed [2 + 2] Cycloaddition of Alkenes and Allenamides



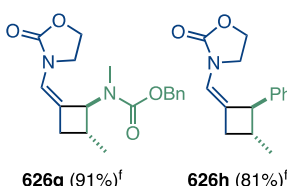
A. 2012 (Chen^a and González^b)

32 examples, 25–94%



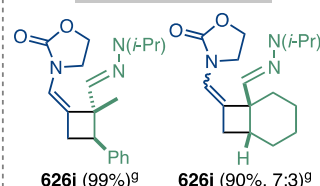
B. 2012 (Mascareñas^f)

17 examples, 33–96%

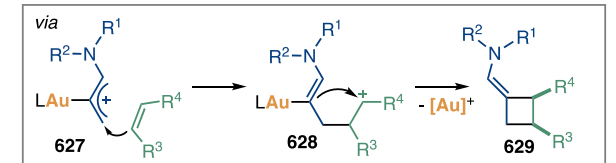


C. 2014 (Mascareñas^g)

19 examples, 41–99%



D. Mechanistic Proposal



^a[(JohnPhos)AuCl] (2 mol %), AgSbF₆ (2 mol %), CH₂Cl₂, 4 Å MS, 25 °C. ^b[(2,4-(*t*-Bu)₂-C₆H₃O)₃P]Au(NTf₂)] (0.5 mol %), CH₂Cl₂, rt. ^c[(Ph₃P)AuCl] (5 mol %), AgSbF₆ (2 mol %), CH₂Cl₂, 4 Å MS, 25 °C. ^dNorbomene (15 mol %). ^eReaction without alkene partner. ^f[(2,4-(*t*-Bu)₂-C₆H₃O)₃P]AuCl] (2 mol %), AgSbF₆ (2 mol %), CH₂Cl₂, 4 Å MS, -15 °C. ^g[(JohnPhos)Au(MeCN)]SbF₆ (5 mol %), DCE, rt to 85 °C.

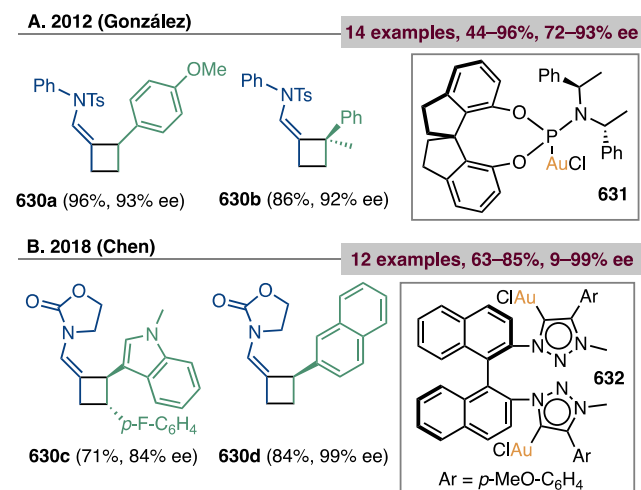
substituted cyclobutanes bearing an exocyclic *Z*-double bond as single regio- and diastereoisomers. In the course of their investigations, they found a competitive dimerization of *N*-allenylsulfonamides that could be optimized to selectively obtain cyclobutanes **626f** (Scheme 136A).^{684,685}

N-allenylsulfonamide and *N*-allenylloxazolidinone as allene partners and electron-rich alkene counterparts, such as enol ethers, cyclic enamines, styrene derivatives, and enamides participated in the reactions (Scheme 136A,B).^{684–686} The use of bisalkenes led to a mixture of [2 + 2] product and *N*-allenylloxazolidinone dimer.⁶⁸⁷ Mascareñas and López and co-workers reported a follow-up work in which the alkene scope was expanded to include *N,N*-dialkyl hydrazones (Scheme 136C). Platinum complexes were found to be poorer catalysts for this transformation.⁶⁸⁸

Mechanistically, these gold(I)-catalyzed [2 + 2] cycloadditions start by the regioselective attack of the alkene to the γ -carbon of a σ -type allenamide gold(I) complex (**627**) to generate carbocation intermediate **628**, which undergoes C–C bond formation to complete the formal [2 + 2] cycloaddition (Scheme 136D).⁶⁸⁹

The group of González disclosed the asymmetric version of the intermolecular gold(I)-catalyzed [2 + 2] cycloaddition of vinyl arenes and *N*-allenylsulfonamides (Scheme 137A),⁶⁹⁰

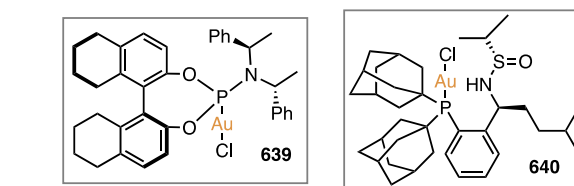
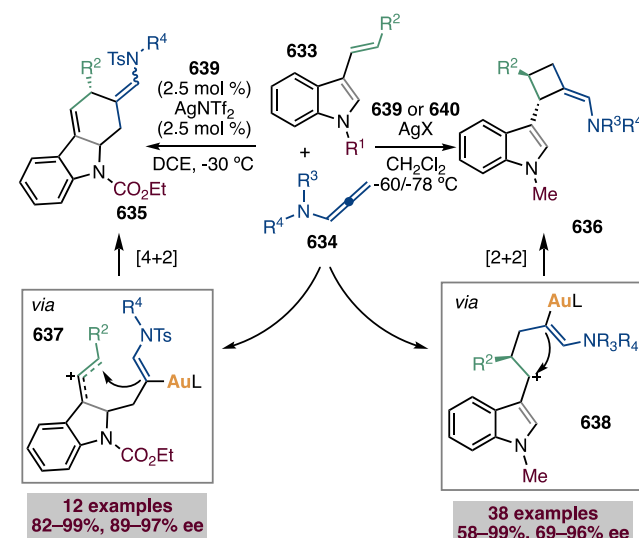
Scheme 137. Asymmetric Gold(I)-Catalyzed [2 + 2] Cycloaddition of Alkenes and Allenamides



which also represents one of the leading enantioselective methods using allene scaffolds in gold(I) catalysis.⁶⁹¹ Here, a family of chiral phosphoramidite gold(I) complexes gave excellent results in the construction of enantioenriched cyclobutanes. Recently, Chen and co-workers found that chiral bis-1,2,3-triazol-5-ylidene digold(I) complex **632** was also an ideal catalyst for the enantioselective synthesis of cyclobutanes by [2 + 2] cycloaddition.⁶⁹² The use of this ligand allowed extension of the scope to several alkene and allenamide partners (Scheme 137B).

Zhang and co-workers reported the asymmetric gold(I)-catalyzed cycloadditions of 3-styrylindoles **633** and *N*-allenylsulfonamides **634** (Scheme 138).⁶⁹³ Here, it was found that the cycloaddition mode was switched by the electronic properties of the *N*-substituents. Specifically, electron-donating substituents favored the formation of 3-cyclobutylindole **636** via [2 + 2] cycloaddition (Scheme 138, right), whereas electron-poor substituents facilitated the [4 + 2] cycloaddition to form tetrahydrocarbazole scaffolds **635** (Scheme 138, left). Remarkably, both pathways were found to be diastereo- and highly enantioselective when using the same chiral phosphoramidite gold(I) catalyst. Later, a new protocol was developed using a

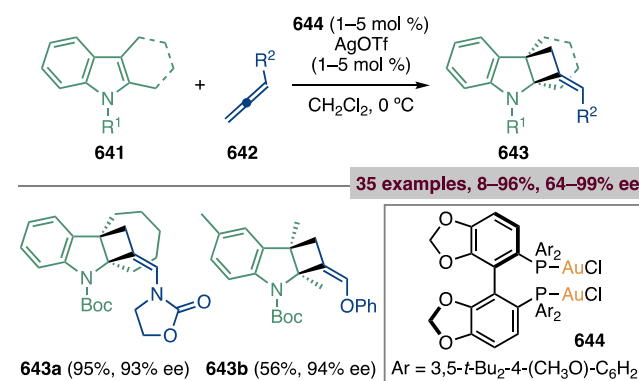
Scheme 138. Asymmetric Gold(I)-Catalyzed [2 + 2] and [4 + 2] Cycloaddition of 3-Styrylindoles and Allenamides



monophosphine Xiang-Phos chiral gold(I) catalyst, **640**, which allowed the use of *N*-allenyl oxazolidinone as electrophilic partner in the [2 + 2] cycloaddition.⁶⁹⁴

The group of Bandini developed an asymmetric protocol for the gold(I)-catalyzed dearomative [2 + 2] cycloaddition of 1,2-substituted indoles **641** and allenamides **642** (Scheme 139).^{689,695} The use of electron-rich phosphine-based gold

Scheme 139. Asymmetric Gold(I)-Catalyzed [2 + 2] Cycloaddition of Indoles and Allenes

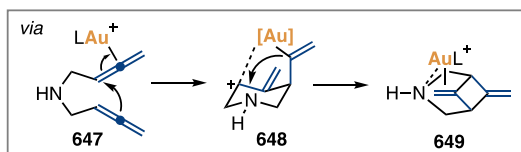
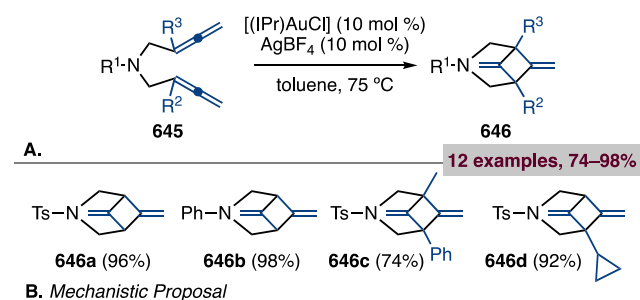


catalyst **644** was key to furnish indolincyclobutanes **643** with high chemo-, diastereo-, and enantioselectivity. The same group had previously reported that treatment of similar scaffolds with a highly electrophilic gold(I) catalyst led to selective C3-functionalization of indoles.⁶⁹⁶

3.1.4. Other Strategies for the Gold(I)-Catalyzed Synthesis of Cyclobutanes. **3.1.4.1. Gold(I)-Catalyzed Cycloisomerization of Bisallenes.** Chung and co-workers reported the gold(I)-catalyzed cycloisomerization of 1,5-

bisallenes **645** to form azabicyclo[3.1.1]heptanes **646**, in which the cyclobutane bears two exocyclic double bonds (Scheme 140).⁶⁹⁷ Only substituents in the proximal carbon atoms of the

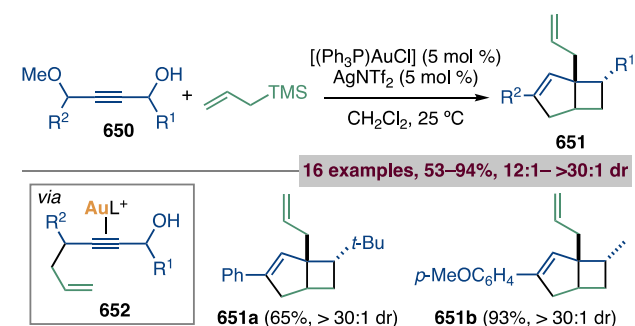
Scheme 140. Gold(I)-Catalyzed Cycloisomerization of Bisallenes



allenes were tolerated (Scheme 140A). DFT studies were performed to clarify the preference for the twisted head-to-head cycloaddition over other plausible mechanistic scenarios, which showed that the most favorable pathway begins with an initial attack from the middle carbon in the nonactivated allene to the internal carbon of the gold(I)-coordinated allene to generate six-membered cyclic intermediate **648**. From the latter, the formation of the second C–C bond is facilitated by the stabilizing interaction of the gold atom with both carbons.

3.1.4.2. Gold(I)-Catalyzed Formal (3 + 2)/(2 + 2)-Annulation of Allylsilane with 4-Methoxybut-2-yn-1-ols. An alternative protocol to construct strained bicyclo[3.2.0]heptane scaffolds under gold(I) catalysis was reported by Liu et al.⁶⁹⁸ Here, the formal intermolecular (3 + 2)/(2 + 2)-annulation of allylsilane with 4-methoxybut-2-yn-1-ols **650** gave access to fused cyclobutanes **651** in high yield and diastereoselectivity (Scheme 141). Their mechanistic proposal suggests the

Scheme 141. Gold(I)-Catalyzed Formal (3 + 2)/(2 + 2)-Annulation



formation of 1,5-enynes **652**. These intermediates can be further activated by gold to furnish cyclobutanes by annulation with allylsilane.

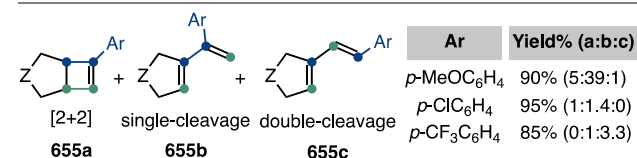
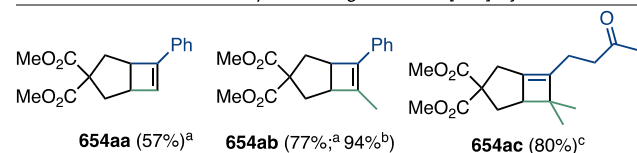
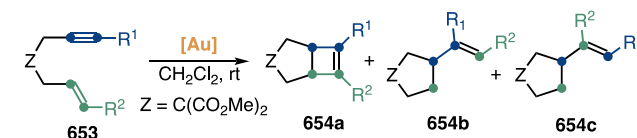
3.2. Synthesis of Cyclobutenes

3.2.1. Gold(I)-Catalyzed Cycloisomerization of Enynes.

3.2.1.1. Gold(I)-Catalyzed [2 + 2] Cycloaddition of 1,6-Enynes. Echavarren and co-workers found that fused cyclobutenes **654a**

could be obtained via gold(I)-catalyzed [2 + 2] cycloaddition only when 7-phenyl-1,6-enynes possess terminal or disubstituted alkenes, leading to **654aa** and **654ab**, respectively (Scheme 142A).²¹¹ Remarkably, bicyclo[3.2.0]hept-5-enes of

Scheme 142. Gold(I)-Catalyzed Cycloisomerization of 1,6-Enynes



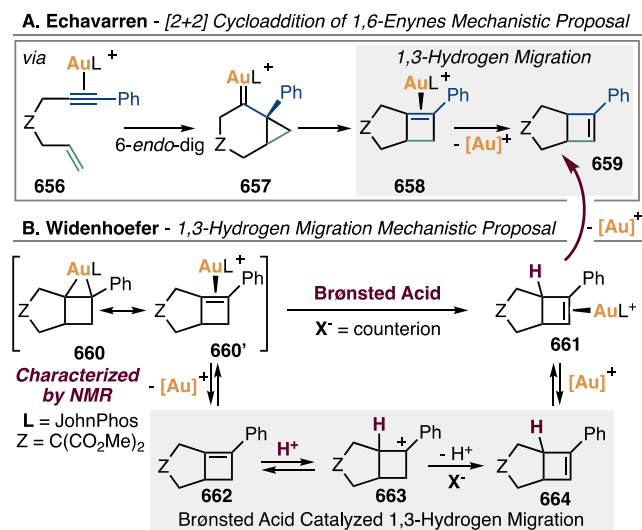
^a[(CyJohnPhos)AuCl] (2 mol %), AgSbF₆ (2 mol %). ^b[(Ph₃P)Au(NTf₂)] (2 mol %). ^c[(IPr)Au(PhCN)]SbF₆ (5 mol %). ^d[(JonhPhos)Au(MeCN)]SbF₆ (5 mol %), CH₂Cl₂, 80 °C.

type **654ac** was formed from an alkyl-1,6-enyne bearing a trisubstituted alkene.⁶⁹⁹ However, these were isolated examples, and in most of the cases, the gold(I)-catalyzed [2 + 2] cycloaddition of 1,6-enynes competes with other skeletal rearrangements, which prevent the selective formation of cyclobutenes (Scheme 142B).^{643,699,700} The ligand employed was found to affect the regioselectivity of these transformations.⁶⁹⁹

Regarding the mechanism for the formation of cyclobutenes, computational studies revealed that the most favorable pathway begins with a 6-*endo*-dig cyclization to form cyclopropyl gold(I) carbene **657** (Scheme 143A).⁶⁹⁹ This species evolves via ring expansion toward η²-(cyclobutene)gold(I) intermediate **658**. The final cyclobutene product was proposed to be formed through double bond isomerization, although the transition state for this step was not located. Interestingly, η²-(cyclobutene)gold(I) intermediates **658** can also open up to form 1,3-dienes via single-cleavage rearrangement.

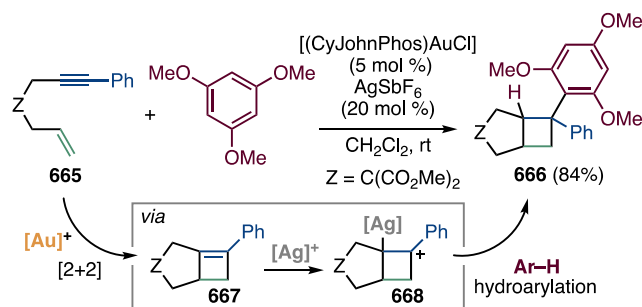
In several consecutive reports, Widenhofer and co-workers studied in detail the double bond isomerization step in the gold(I)-catalyzed [2 + 2] cycloaddition of 7-aryl-1,6-enynes **656**.^{701–703} In this work, it was found that cyclobutene **662** evolves to the final product by means of a Brønsted acid-catalyzed formal 1,3-hydrogen migration that does not involve the intermediacy of the gold(I) catalyst (Scheme 143B).⁷⁰² Thus, after deauration, cyclobutene **662** can be rapidly protonated leading to benzylic carbocation **663**, which undergoes a rate-determining deprotonation to give rise to the final product. Further studies showed that the counterion, from which the Brønsted acid is generated in situ, can influence the skeletal rearrangement pattern, modifying the final outcome of the reaction.⁷⁰³

Scheme 143. Mechanistic Proposal for the Gold(I)-Catalyzed [2 + 2] Cycloaddition of 7-Aryl-1,6-enynes



Inspired by their mechanistic findings, the group of Widenhoefer developed a protocol in which bicyclo[3.2.0]-hept-1-ene scaffolds **667** were trapped by electron-rich arenes, to furnish cyclobutanes of type **666** (Scheme 144).⁷⁰⁴

Scheme 144. Gold/Silver-Catalyzed [2 + 2] Cycloaddition/Hydroarylation Sequence of 7-Aryl-1,6-enynes



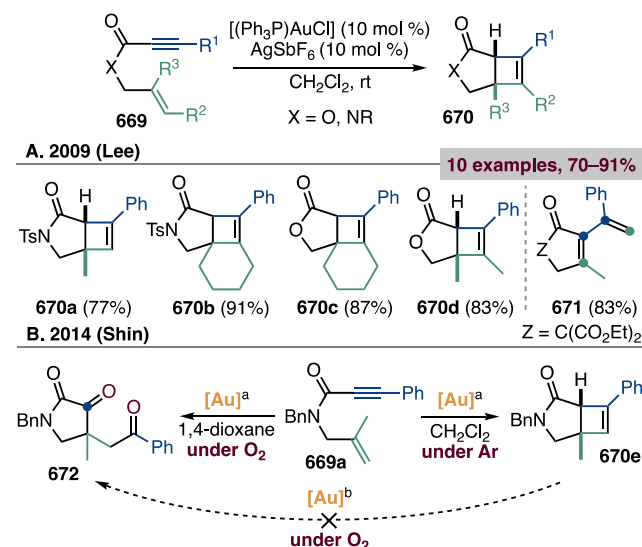
Mechanistic investigations suggest that an initial gold(I)-catalyzed [2 + 2] cycloaddition of 7-aryl-1,6-enynes is followed by a silver-catalyzed hydroarylation of cyclobutenes **667** (Scheme 144).^{701–703}

Chung and co-workers developed a general synthesis of cyclobutenes **670** from 1,6-enynes bearing a carbonyl group frame (Scheme 145).³⁶³ While amide- and ester-tethered 7-aryl-1,6-enynes gave the corresponding cyclobutenes in excellent yield, C-tethered 1,6-enyne led to 1,3-diene **671** (Scheme 145A). The group of Shin found that when the reaction was performed under oxygen, a tricarboxyl compound of type **672** was exclusively obtained via cycloisomerization/oxidation sequence in a formal C–C triple bond oxygenerative cleavage outcome⁷⁰⁵ (Scheme 145B, left).

The group of Yeh found that bicyclic lactams of type **675** could be prepared by a tandem gold(I)-catalyzed [2 + 2] cycloaddition/oxidation sequence of 1,6-enynes **673** (Scheme 146). In some specific cases, the highly constrained cyclobutene intermediates **674** could be isolated, and the bicyclic lactams **675** could be obtained by treatment with NMO/OsO₄.⁷⁰⁶

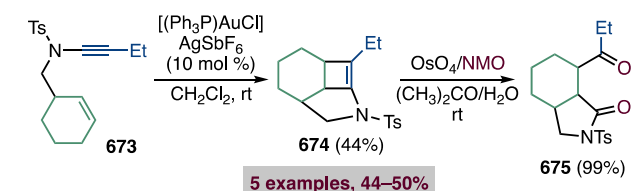
3.2.1.2. Gold(I)-Catalyzed [2 + 2] Cycloaddition of Large 1,*n*-Enynes (*n* ≥ 7). As for 1,6-enynes, the gold(I)-catalyzed

Scheme 145. Gold(I)-Catalyzed [2 + 2] Cycloaddition of Carbonyl-Tethered 1,6-Enynes



^a[(SPhos)AuCl] (5 mol %), AgSbF₆ (5 mol %), rt. ^b[(SPhos)AuCl] (5 mol %), AgSbF₆ (5 mol %), CF₃CH₂OH, rt.

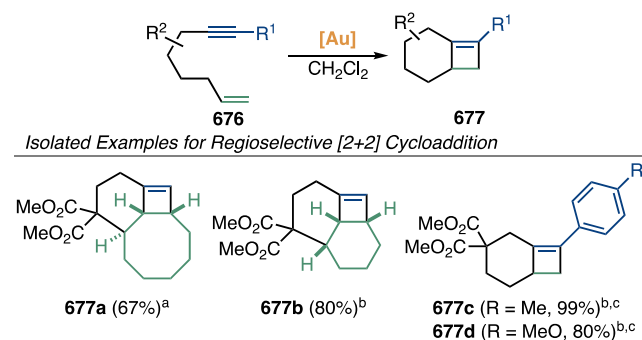
Scheme 146. Gold(I)-Catalyzed [2 + 2] Cycloaddition of 1,6-Enynes and Subsequent Oxidation



cycloisomerization of larger 1,7-enynes can lead to a diverse range of products via divergent mechanistic pathways. Among them, cyclobutene-fused 6-membered carbocycles can be obtained by means of a formal [2 + 2] cycloaddition from very specific substrates with high regioselectivity (Scheme 147).⁷⁰⁰

Another example of cyclobutene synthesis from 1,7-enynes was reported by the group of Liu.⁷⁰⁷ Here, cyclobutenes were initially obtained as side products in the gold(I)-catalyzed [2 +

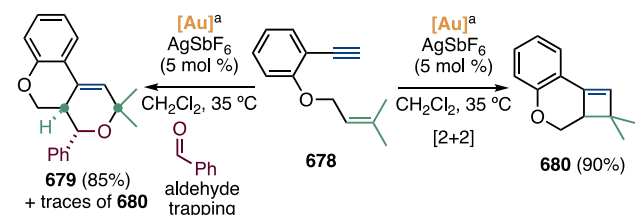
Scheme 147. Gold(I)-Catalyzed [2 + 2] Cycloaddition of 1,7-Enynes



^a[(CyJohnPhos-OMe)AuCl] (2 mol %), AgSbF₆ (2 mol %), CH₂Cl₂, rt. ^b[(JohnPhos)Au(NCMe)]SbF₆ (2 mol %), CH₂Cl₂, rt. ^c80 °C, MW.

2+2] cycloaddition of *O*-tethered 1,7-enynes with aldehydes (Scheme 148, left). Performing the reaction in the absence of aldehyde led to the exclusive formation of four-membered carbocycle **680** (Scheme 148, right).

Scheme 148. Gold(I)-Catalyzed [2 + 2] Cycloaddition of 1,7-Enynes

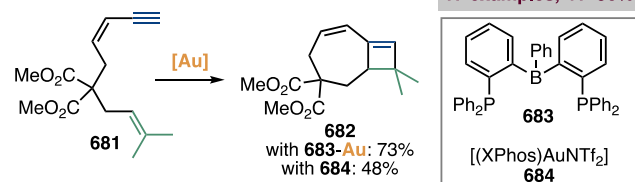


^a[(JohnPhos)AuCl] (5 mol %).

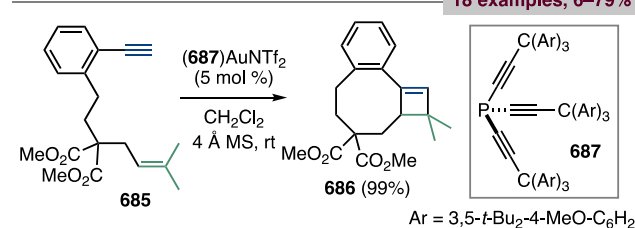
Odabachian and Gagosz developed a general [2 + 2] cycloaddition reaction of 1,8-enynes **681** leading to carbocycles **682** bearing a bicyclo[5.2.0]nonane framework (Scheme 149A).⁷⁰⁸ When these 1,8-enynes were treated with gold(I)

Scheme 149. Gold(I)-Catalyzed [2 + 2] Cycloaddition of 1,8- and 1,9-Enynes

A. 2009/2015 (Gagosz and Inagaki) - 1,8-enynes



B. 2018 (Sawamura) - 1,9-enynes



catalysts at higher temperatures, products of fragmentation, ene reaction, and isomerization were obtained. Inagaki found that gold(I) complexes with uncommon Z-type ligand also catalyze this transformation (Scheme 149A).⁷⁰⁹ The regioselective gold(I)-catalyzed [2 + 2] cycloaddition of 1,9-enynes **685** has been enabled by a gold complex bearing hollow-shaped triethynylphosphine ancillary ligand **687** (Scheme 149B).⁷¹⁰

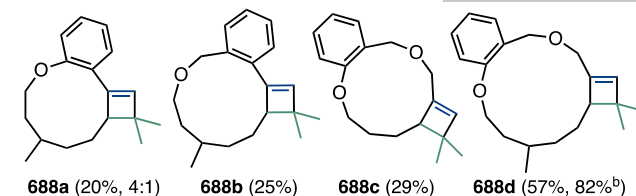
Echavarren and co-workers developed the macrocyclization of larger 1,*n*-enynes ($n > 9$) that leads to cyclobutene-fused macrocycles of type **688** (Scheme 150A).⁷¹¹ Besides the essential role played by sterically hindered phosphines on regioselectivity, the use of $\text{BAR}_4^{\text{F}^-}$ counterion significantly improved the yield.⁷¹² Other metals, such as Pt and Ag, did not catalyze the macrocyclization.⁷¹¹ The same group applied this reaction for the construction of the cyclobutane moiety present in the skeleton of rumpbellaone A and (+)-hushinone from 1,10-enyne **689** (Scheme 150B).⁷¹³

3.2.2. Gold(I)-Catalyzed [2 + 2]-Cycloaddition of Alkynes with Alkenes. The group of Echavarren disclosed the first intermolecular gold(I)-catalyzed [2 + 2] cycloaddition

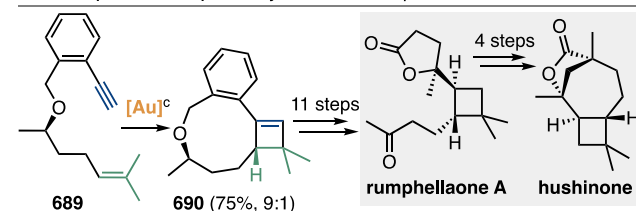
Scheme 150. Gold(I)-Catalyzed [2 + 2] Cycloaddition of Large 1,*n*-Enynes ($n \geq 10$)

A. 2013 (Echavarren)^a - 1,*n*-enynes ($n = 10-15$)

8 examples, 20–71%



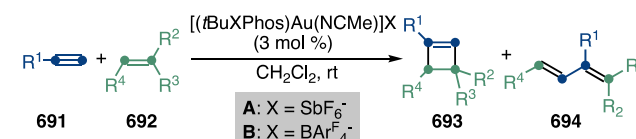
B. 2016 (Echavarren) Total Synthesis of Rumpbellaone A and Hushinone



^a[(*t*-BuXPhos)Au(MeCN)]SbF₆ (3 mol %), CH₂Cl₂, 23 °C. ^b[(*t*-BuXPhos)Au(MeCN)]BAR₄^F (3 mol %), CH₂Cl₂, 23 °C. ^c[(IPr)Au(PhCN)]BAR₄^F (3 mol %), CH₂Cl₂, 25 °C.

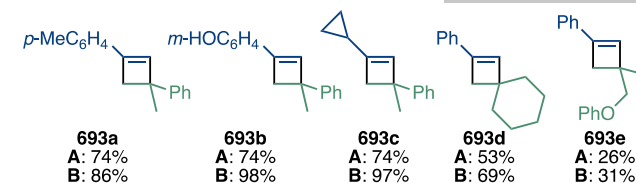
of terminal alkynes **691** with alkenes **692** to furnish nonfused cyclobutenes **693** in a regioselective manner (Scheme 151).⁷¹⁴

Scheme 151. Gold(I)-Catalyzed [2 + 2] Cycloaddition between Alkynes and Alkenes



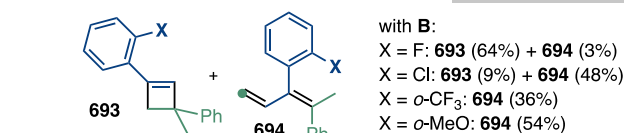
A. 2010/2013 (Echavarren) - [2+2] cycloaddition

24 examples, 21–99%



B. 2017 - *ortho*-effect: [2+2] vs rearrangement

20 examples, 3–54%



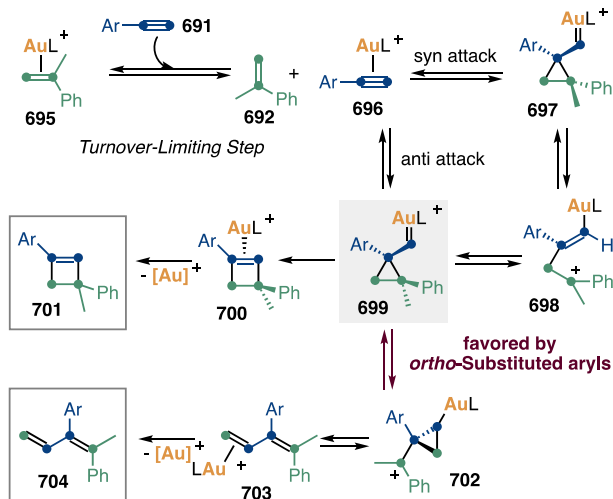
The use of a cationic gold(I) complex that bears a sterically crowded phosphine ligand was essential for this reaction.⁷¹⁵ It was later found that the replacement of counterion SbF_6^- by $\text{BAR}_4^{\text{F}^-}$ improved the yield of the cycloaddition (Scheme 151A).⁷¹² Regarding the scope, aryl alkynes and electron-rich di- and trisubstituted alkenes were successful reaction partners (Scheme 151A).

Interestingly, under the same reaction conditions, *ortho*-substituted aryl alkynes led also to a variable mixture of cyclobutenes **693** and 1,3-dienes **694** (Scheme 151B).⁷¹⁶ Deuteration experiments confirmed an insertion process of the alkyne moiety between the alkene C atoms in the formation of 1,3-dienes **694**.

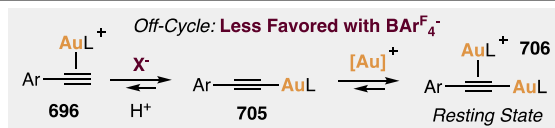
For the competitive formation of cyclobutenes **701** and 1,3-dienes **704**, computational investigations revealed a complex divergent scenario, highly dependent on the alkyne substituents (Scheme 152A).⁷¹⁶ Initially, a turnover-limiting alkene–alkyne

Scheme 152. Mechanistic Proposal for the Formation of Cyclobutenes and 1,3-Dienes

A. Pathways for the Formation of Cyclobutenes and 1,3-Dienes



B. Counteranion (X^-) Dependent Off-Cycle Pathway



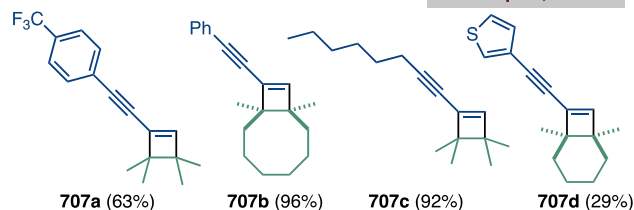
associative ligand exchange leads to η^2 -(alkyne)gold(I) species **696**. From this intermediate, cyclopropyl gold(I) carbenes **697** and **699**, which are in equilibrium through ring opening, can be generated via electrophilic addition to the alkene. In particular, gold(I) carbene **699**, generated by anti attack of the alkene, can evolve through cyclopropane ring expansion to furnish 4-membered carbocycles **701**. In the case of *ortho*-substituted aryl alkynes, gold(I) carbene **699** is in equilibrium via carbon migration with carbocationic intermediate **702**, which undergoes ring opening to liberate 1,3-dienes **704** in a formal single-cleavage skeletal rearrangement. The divergent evolution pathways of the key cyclopropyl gold(I) carbene **699** have similar activation energies, thus explaining the marked *ortho*-effect. Kinetic and NMR investigations supported the existence of an off-cycle pathway, in which η^2 -(alkyne)gold(I) species **696** is in equilibrium, via counteranion-assisted deprotonation, with alkyngold(I) complexes **705**, which can further react with a cationic gold(I) complex to form σ,π -digold(I) alkyne **706** (Scheme 152B).⁷¹² The latter was found to be an unproductive resting state of the catalytic cycle and its formation was less favored with $\text{BAR}_4^{\text{F}^-}$ than with SbF_6^- .

Alkenes bearing carbonyl groups react with alkynes to form 8-oxabicyclo[3.2.1]oct-3-enes by a [2 + 2 + 2] cycloaddition process in which two C–C bonds and one C–O bond are formed.⁷¹⁷ On the other hand, 1,3-butadiynes (Scheme 153A) and 1,3-enynes (Scheme 153B) react with alkenes to form cyclobutenes selectively.⁷¹⁸ With respect to 1,3-dienes, the reaction proceeds selectively at the most electron-rich double bond.

Scheme 153. Gold(I)-Catalyzed [2 + 2] Cycloaddition of 1,3-Diynes, 1,3-Enynes, and 1,*n*-Dienes ($n = 3,5$)

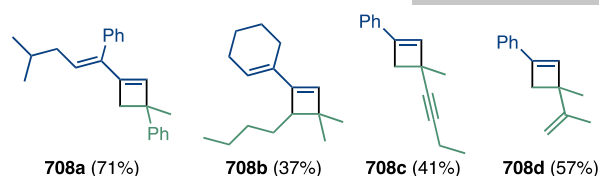
A. 2017^a (Echavarren) - 1,3-Diynes

16 examples, 29–99%



B. 2018^b - 1,3-Enynes and 1,*n*-Dienes ($n = 3,5$)

28 examples, 14–98%



^a[(IPr)Au(PhCN)]BAR₄^F (5 mol %), CH₂Cl₂, 23 °C. ^b[(*t*-BuXPhos)-Au(MeCN)]BAR₄^F (5 mol %), CH₂Cl₂, 23 °C.

The asymmetric intermolecular gold(I)-catalyzed [2 + 2] cycloaddition between allenes and alkenes is a versatile method to build highly enantioenriched saturated 4-membered carbocycles (section 3.1.3).^{690,692,695} This becomes particularly challenging when alkynes⁷¹⁹ are used in place of allenes.^{720,721} This approach has been developed using Co,⁷²² Zn,⁷²³ Ni,⁷²⁴ Cu,^{725–729} Ru,^{730–733} Rh,⁷³⁴ Pd,⁷³⁵ and Ir^{736,737} catalysts using either cyclic alkenes or alkenes substituted with electron-withdrawing groups. In this context, Echavarren and co-workers reported the enantioselective gold(I)-catalyzed synthesis of cyclobutenes by [2 + 2] cycloaddition between alkynes and alkenes using non-C₂ symmetric Josiphos chiral ligands (Scheme 154).⁷³⁸ With these ligands, cyclobutenes **709** could be obtained from terminal aryl alkynes and di- or trisubstituted alkenes in good enantioselectivities (Scheme 154A).

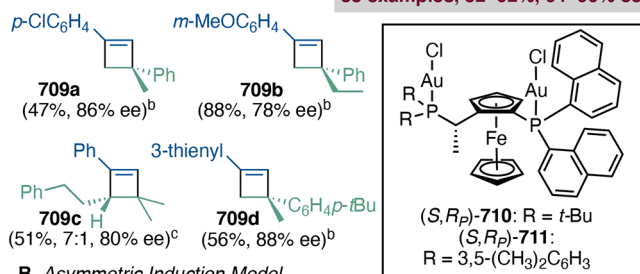
Kinetic investigations suggested a complex mechanistic scenario in which the turnover-limiting step switches depending on the electronic properties of the alkene. In addition, DFT calculations revealed that the enantio-discriminating step consisted in the electrophilic addition of the η^2 -(alkyne)gold(I) species to the alkene. The enantiomeric discrimination arises from unfavorable steric clashes in TS_S and stabilizing face-to-face π -stacking interactions in TS_R, which decrease the free energy of this transition state (Scheme 154B).

This methodology was applied to a concise, second-generation⁷¹³ asymmetric synthesis of rumphellaone A (Scheme 155).⁷³⁸ In this new approach, the skeleton of this natural product was obtained via enantioselective intermolecular [2 + 2] cycloaddition between phenylacetylene and trisubstituted alkene **712**.

The groups of Gao and Zhang contributed to the field of intermolecular gold(I)-catalyzed [2 + 2] cycloadditions using chloroalkynes **714** instead of terminal aryl alkynes (Scheme 156).⁷³⁹ This new protocol allowed the use of unactivated mono- and disubstituted alkenes to build chlorocyclobutenes **716** in high yield with excellent levels of regioselectivity. The authors also reported that bromoalkynes can undergo [2 + 2] cycloaddition with cyclopentene (Scheme 156, **717**). In contrast, the group of Echavarren found that the gold(I)-catalyzed reaction of bromoalkynes with allylsilanes led to 1,4-enynes by formal cross-coupling via a rearrangement process.⁷⁴⁰

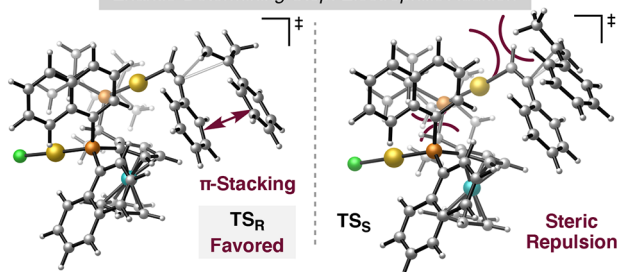
Scheme 154. Asymmetric Gold(I)-Catalyzed [2 + 2] Cycloaddition of Alkenes with Alkynes^a

A. 2017 (Echavarren)^a **38 examples, 32–92%, 64–96% ee**



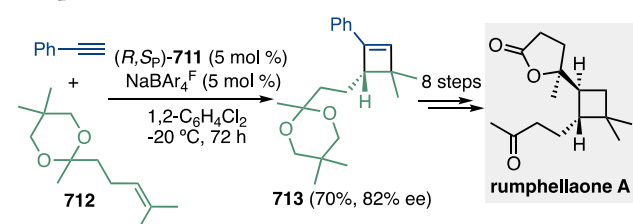
B. Asymmetric Induction Model

Enantio-Determining Step: Electrophilic Addition

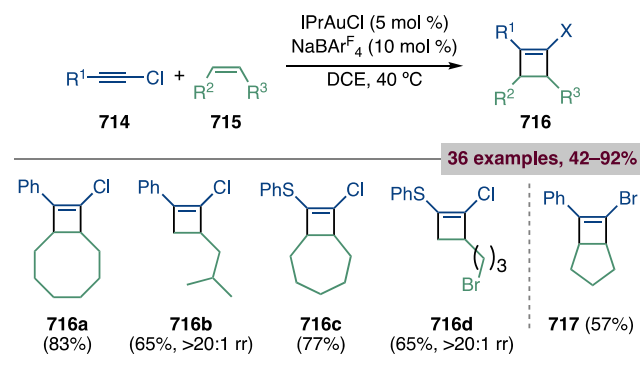


^aC₆H₅Cl, -20 °C. ^b(*S,R*_p)-710 (2.5 mol %), NaBAR₄^F (2.5 mol %). ^c(*R,S*_p)-711 (5 mol %), NaBAR₄^F (5 mol %).

Scheme 155. Enantioselective Total Synthesis of Rumphellaone A



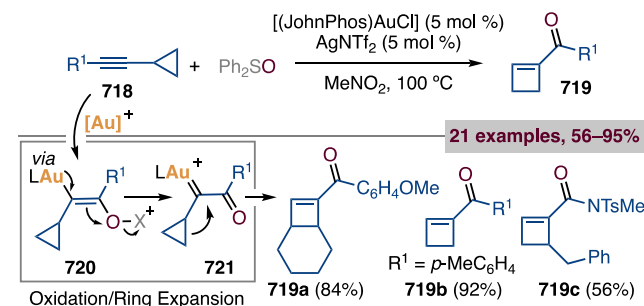
Scheme 156. Gold(I)-Catalyzed [2 + 2] Cycloaddition between Haloalkynes and Alkenes



3.2.3. Gold(I)-Catalyzed Cyclopropyl Ring Expansions.

The group of Liu reported a novel approach to construct cyclobutenylketones **719** by gold(I)-catalyzed oxidative ring expansion of cyclopropylalkynes **718** (Scheme 157).⁷⁴¹ Here, the ketone functionality was introduced by diphenylsulfoxide via regioselective intermolecular oxidation. The protocol was expanded to unactivated cyclopropylalkynes with different substitution patterns. However, under the same conditions, donor–acceptor cyclopropylalkynes undergo oxidative ring

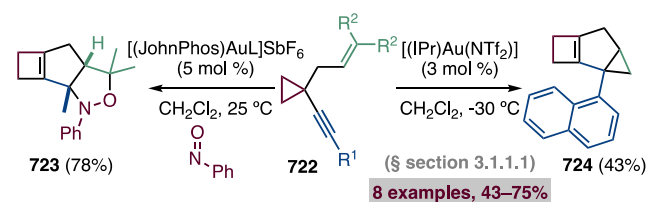
Scheme 157. Gold(I)-Catalyzed Oxidative Ring Expansion



cleavage. Mechanistically, the reaction begins with a regioselective O-attack to the β -carbon of the coordinated alkyne, forming cyclopropyl gold(I) carbene **721** (Scheme 157). As proposed for [2 + 2] cycloadditions,^{699,700,716} this intermediate evolves by means of ring expansion leading to cyclobutene products **719**. The same scenario was suggested for cyclopropylalkynes embedded into diyne scaffolds.⁷⁴² Alternatively, the carbene can suffer a second oxidation to furnish a diketone. This side reaction was prevented by careful optimization of the reaction conditions.⁷⁴³

As depicted in Scheme 119 (section 3.1.1.1), the gold(I)-catalyzed cycloisomerization of cyclopropyl-tethered 1,5-enynes is a versatile transformation.⁴⁴³ The product distribution is controlled by both the reaction conditions and the *ortho*-effect. In particular, when the reaction took place at -30 °C using *ortho*-substituted aryl-tethered 1,5-enynes, fused cyclobutenes were selectively obtained via a cyclization/ring expansion sequence (Scheme 119D and 158, right). The construction of

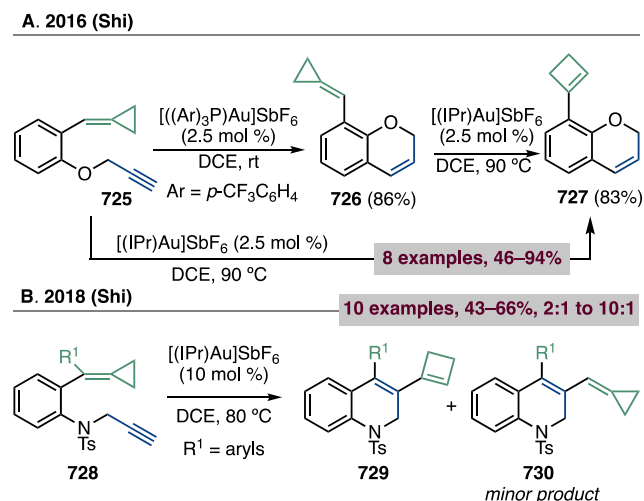
Scheme 158. Gold(I)-Catalyzed Cycloisomerization of Cyclopropyl 1,5-Enynes



fused cyclobutenes was also reported in the context of the oxidative (2 + 2 + 1) cycloaddition of similar cyclopropyl-tethered 1,5-enynes and nitrosobenzenes (Scheme 158, left).⁷⁴⁴

The group of Shi reported a temperature-controlled divergent gold(I)-catalyzed cycloisomerization of cyclopropylidene 1,7-enynes **725** (Scheme 159A). In contrast, no reactivity was found in the presence of Pt(cod)Cl₂.⁷⁴⁵ Here, 2*H*-chromene derivatives **726** were obtained at room temperature via intramolecular hydroarylation. At 90 °C, the hydroarylation was followed by a ring expansion leading to the corresponding cyclobutenes **727**. Interestingly, scaffolds with the same skeleton and *ortho*-substituted aryl groups evolve through a different pathway, affording cyclobutenes instead, as depicted in Scheme 122A (section 3.1.1.2).⁶⁵⁸ On the other hand, 1,2-dihydroquinolines containing cyclobutenes **729** were obtained as the major product when aniline-tethered cyclopropylidene 1,7-enynes **728** were exposed to gold(I) catalysts (Scheme 159B).⁷⁴⁶ The reaction was proposed to take place through two consecutive cyclopropyl gold(I) carbene intermediates, but only one expands to form the 4-membered carbocycle. In this protocol,

Scheme 159. Gold(I)-Catalyzed Cycloisomerization of Cyclopropylidene 1,7-Enynes



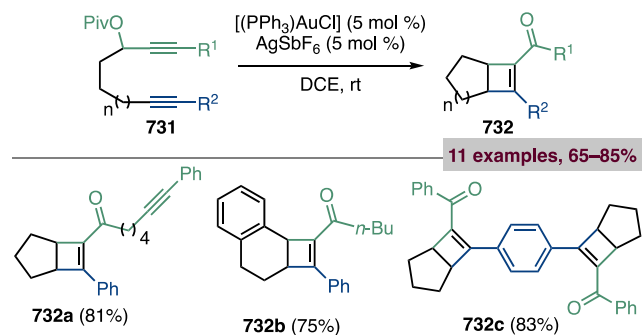
different amounts of adduct **730**, in whose formation the ring expansion does not take place, were also detected. The product distribution was highly dependent on the aryl substituents.

Similar alkynylamide-tethered cyclopropylidene 1,7-enynes gave direct access to cyclobutanes and cyclobutenes in a ligand-dependent regiodivergent process, as shown in [Scheme 122B](#) (section 3.1.1.2).⁶⁵⁹ In this case, the mechanistic bifurcation occurs just after the ring expansion step.

3.2.4. Gold(I)-Catalyzed 1,3-Acyloxy Migration/[2 + 2] Cycloaddition of Diynes. The gold(I)-catalyzed 1,3-acyloxy shift of propargylic carboxylates is a widespread approach to generate allenes in situ that can be engaged in further transformations, among which the construction of cyclobutenes by subsequent [2 + 2] cycloaddition will be outlined here.

In this context, the group of Kim disclosed the gold(I)-catalyzed cycloisomerization of 1,7-diyne pivalates **731**, which gives access to cyclobutenylketones **732** ([Scheme 160](#)). The

Scheme 160. Gold(I)-Catalyzed Cycloisomerization of 1,7-Diyne Pivalates

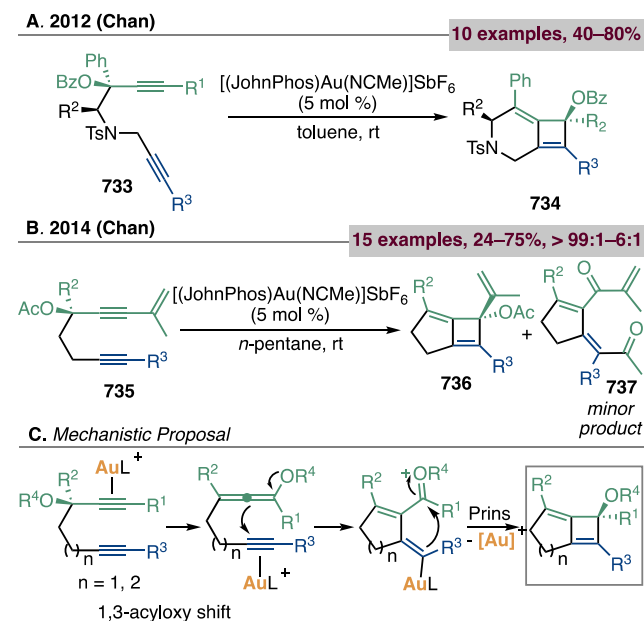


reaction did not proceed under Pt catalysis.⁷⁴⁷ The authors proposed that the propargylic pivalate fragment undergoes 1,3-acyloxy shift followed by a [2 + 2] cycloaddition between the alkyne and the in situ formed allene. The obtained products were isolated upon hydrolysis. Under the same conditions, when two 1,7-diyne pivalate scaffolds were linked by a phenyl moiety, dimeric bicycles of type **732c** were obtained by a 2-fold 1,3-acyloxy shift/[2 + 2] cycloaddition sequence. The same group

broadened the scope of dimeric bicycles by using 1,7-diyne pivalates linked by a variety of other aryl rings.⁷⁴⁸

The group of Chan developed a gold(I)-catalyzed cycloisomerization of *N*-tethered 1,7-diyne benzoates **733**. Here, substrates bearing terminal alkynes afforded *N*-heterocycle-containing cyclobutenes **734** in a regio- and diastereoselective manner ([Scheme 161A](#)).⁷⁴⁹ In addition, the chiral information

Scheme 161. Gold(I)-Catalyzed Cycloisomerization of 1,*n*-Diyne Benzoates



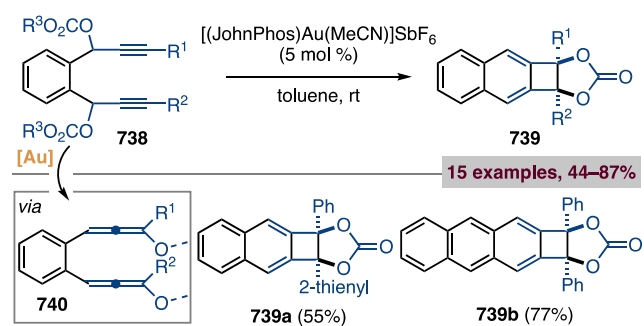
was effectively transferred from the starting diynes to the cyclobutene products. In this protocol, internal alkynes were essential to promote the 1,3-acyloxy migration that generates the corresponding allene intermediates ([Scheme 161C](#)). These species undergo a stepwise [2 + 2] cycloaddition via 6-*exo*-dig cyclization, followed by subsequent Prins cyclization to liberate the cyclobutene product.

As part of their investigations on the reactivity of diyne carboxylates, the group of Chan also developed a method for the 1,3-acyloxy migration/[2 + 2] cycloaddition sequence of 1,6-diyne carboxylates **735** ([Scheme 161B](#)).⁷⁵⁰ Accordingly, under gold(I) catalysis, 1,6-diyne bearing a vinyl substituent led to cyclopentene-fused cyclobutenes **736** preferentially. In this method, variable amounts of diketones **737** were also detected. For cyclobutenes, the authors proposed a similar mechanistic scenario as for 1,7-diyne,⁷⁵⁰ in which the tandem [3,3]-rearrangement/5-*exo*-dig/Prins-type cyclization sequence was the most plausible pathway ([Scheme 161C](#)).

The group of Liu reported the gold(I)-catalyzed cycloisomerization of 1,7-diyne biscarboxylates **738** that gave access to naphthocyclobutenes **739** with *cis*-stereoselectivity ([Scheme 162](#)).⁷⁵¹ The authors proposed that bis(allenyl carbonates) **740** were generated via double 1,3-acyloxy shift of the propargyl carbonates.

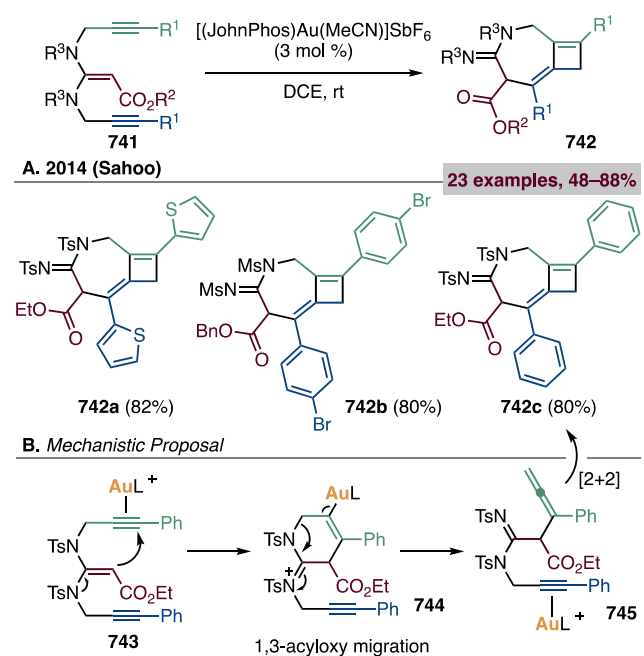
Sahoo and co-workers designed stable alkyne-tethered ketene *N,N*-acetals **741**, which, under gold(I) catalysis, underwent 1,3-acyloxy migration to form allenes **745** in situ ([Scheme 163](#)).⁷⁵² Cyclobutene fused azepine heterocycles **742** were obtained selectively from symmetric ketene *N,N*-acetals **741** ([Scheme 163A](#)). Based on NMR studies, the authors proposed that the

Scheme 162. Gold(I)-Catalyzed Cycloisomerization of Diynes



^a $[(\text{Ph}_3\text{P})\text{Au}(\text{N-methyl benzotriazole})]\text{OTf}$ (1 mol %), CH_2Cl_2 , rt.
^b AgOTf (2 mol %).

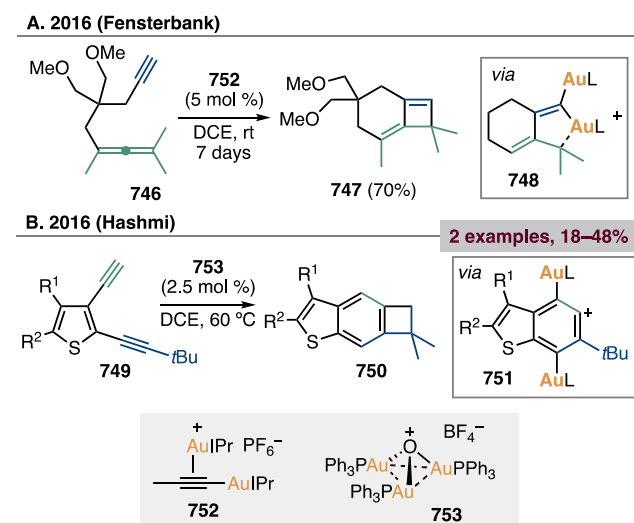
Scheme 163. Gold(I)-Catalyzed Cycloisomerization of Alkyne-Ketene *N,N*-Acetals



terminal carbon of the enamine attacks the gold(I)-activated alkyne via 6-*endo*-dig cyclization to form 6-membered iminium-gold-vinyl species **744** (Scheme 163B). The 6-membered ring intermediate rearranges leading to an allene functionality that further engages in a formal [2 + 2] cycloaddition with the second activated alkyne.

3.2.5. Dual Gold(I)-Catalyzed Synthesis of Cyclobutenes. Substrates bearing a terminal alkyne can occasionally experience dual activation gold catalysis through the formation of gold acetylides.^{753–755} Although this field has been studied extensively in the last decade, only few particular substrates have led to cyclobutene products. This is the case for 1,6-allenynes **746**, which was selectively converted into bicyclo[4.2.0]-octadiene **747** using complex **752** via dual gold(I)-catalyzed [2 + 2] cycloaddition (Scheme 164A).⁷⁵⁶ For this transformation, the intermediacy of digold species **748** was supported both by deuteration experiments and computational studies. In addition, the catalyst used was previously reported to foster this activation mode.^{757,758}

Scheme 164. Dual Gold(I)-Catalyzed Synthesis of Cyclobutenes

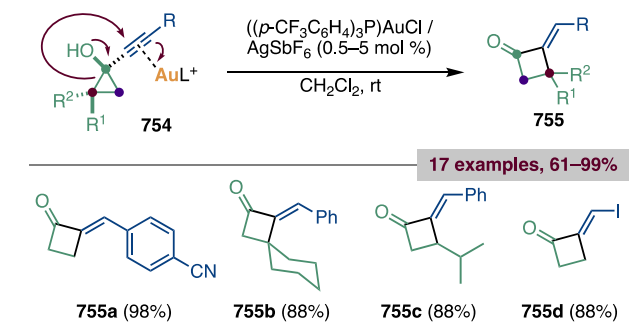


In another example, cyclobutenes **750** were obtained by means of dual gold(I)-catalyzed cyclization of thiophene-tethered diynes **749** (Scheme 164 B).⁷⁵⁹ However, this reaction could be applied only to two substrates, and with very low efficiency. Other similar diynes evolved through alternative pathways forming norbornene or fulvene derivatives. Mechanistically, a 6-*endo*-dig cyclization was proposed to lead to intermediate **751**, which subsequently undergoes an intramolecular C(sp³)-H insertion to furnish cyclobutene products **750**.

3.3. Synthesis of Cyclobutanones

3.3.1. Ring Expansion of Cyclopropanols. The best-explored strategy for the synthesis of cyclobutanones using gold(I) catalysis is the ring expansion of cyclopropanols. This area was pioneered by the group of Toste, who disclosed a gold(I)-catalyzed ring expansion of 1,1-alkynylcyclopropanols **754** (Scheme 165).⁷⁶⁰ The reaction proceeds by selective

Scheme 165. Ring Expansion of 1,1-Alkynylcyclopropanols

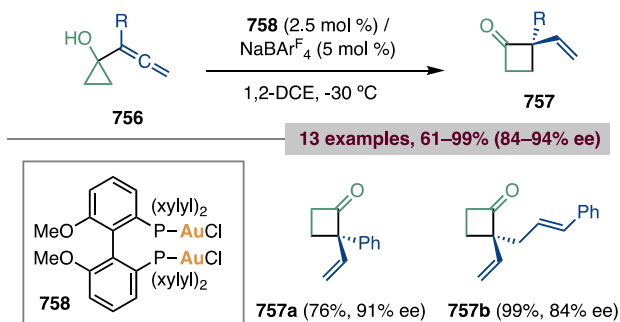


migration of the more substituted carbon of the cyclopropane giving alkylidene cyclobutanones **755** in excellent yields and perfect stereoselectivity. Theoretical mechanistic studies on this ring-expansion process were performed afterward by a different group, and the results were in agreement with the experimental observations.⁷⁶¹ It is worth highlighting that this reaction also proceeds satisfactorily when using silyl-protected cyclopropanols. Allyl ethers derived from cyclopropanol react by the intramolecular transfer of the allyl through a [3,3]-sigmatropic rearrangement followed by a [1,2]-allyl shift.⁷⁶²

Hashmi and co-workers reported that the treatment of a 1,1-alkenylcyclopropanol with pyridine *N*-oxide in the presence of a gold(I) catalyst leads to the formation of an α -ketocyclobutanone.⁷⁶³ On the other hand, Trost and co-workers explored the use of ruthenium catalysts to promote similar processes.⁷⁶⁴

Kleinbeck and Toste reported an asymmetric variant of this transformation using 1,1-allylencyclopropanols to furnish 2-allyl-cyclobutanones **757** in high yields and enantioselectivities (Scheme 166).⁷⁶⁵

Scheme 166. Enantioselective Ring Expansion of 1,1-Allylencyclopropanols



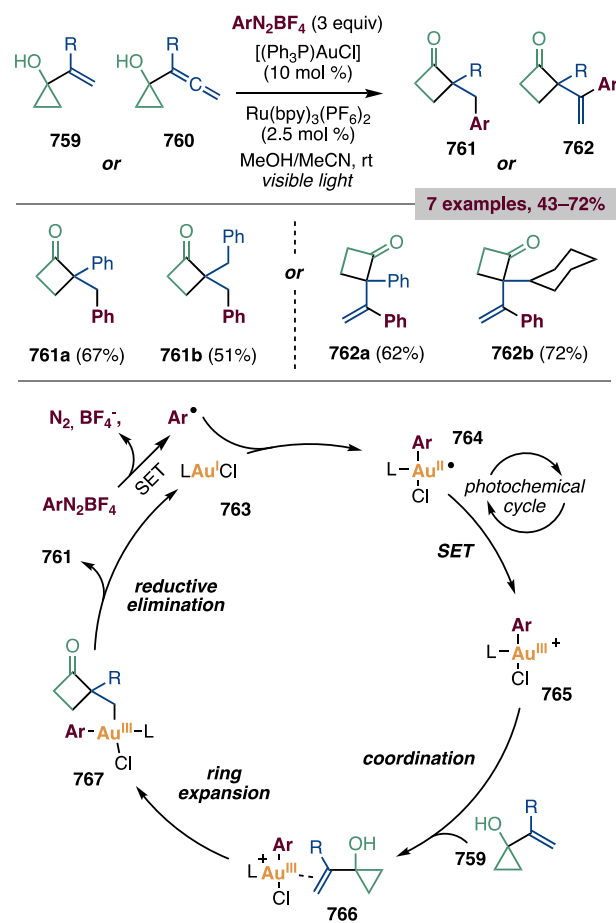
The same group combined these last two approaches with photoredox catalysis to develop a gold-catalyzed arylation ring expansion.⁷⁶⁶ This method relies on the use of aryl diazonium salts as a source of aryl radicals under photoredox conditions, which leads to the generation of aryl-gold(III) intermediates (Scheme 167). The latter promote the ring expansion of cyclopropanols **759** or **760**, giving rise to alkyl-aryl-gold(III) species that afford, after reductive elimination, benzyl- (**761**) or vinyl-cyclobutanones (**762**) in moderate to good yields. This arylation ring expansion was also used to transform cyclobutanols into cyclopentanones.

When studying 1,1-alkenylcycloalkanol, Chen and co-workers observed a divergent reactivity under gold(I) and zinc(II) catalysis.⁷⁶⁷ When treating **768** with $[(\text{Ph}_3\text{P})\text{AuCl}]/\text{AgSbF}_6$, alkenyl cyclobutanone **769** was obtained (Scheme 168). Larger cycloalkanol also undergo this gold(I)-catalyzed ring-expansion process. In contrast, ZnBr_2 catalyzes the transformation of substrates **768** into 2,5-dihydrofurans.

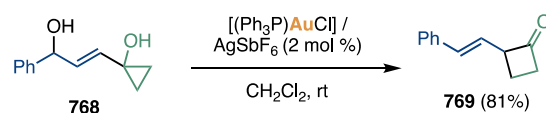
Gandon, Marinetti, Voituriez, and co-workers reported an enantioselective gold(I)-catalyzed rearrangement of cyclopropyl-substituted 1,6-enynes **770** into 2-oxocyclobutylcyclopentanes **771** (Scheme 169),⁷⁶⁸ reminiscent of that previously developed by the group of Echavarren for the synthesis of tricyclic systems (see section 3.1.1.1.).^{649,650} This cycloisomerization proceeds in high yields, moderate to good *syn/anti* selectivity, and very high enantioselectivity for both isomers. This method was applied for the construction of the tricyclic skeleton of natural product russujaponol D.

Vinylidene cyclopropanes are precursors of alkylidene cyclobutanones.⁷⁶⁹ Thus, reaction of **773** with 2 equiv of a pyridine *N*-oxide in the presence of $[(\text{Ph}_3\text{P})\text{AuCl}]/\text{AgSbF}_6$ afforded cyclobutanones **775** by stepwise ring expansion and oxidative trapping of the corresponding gold(I) carbene **774** (Scheme 170).⁷⁷⁰ Cyclobutanones were also found as side products in a gold(I)-catalyzed oxidative rearrangement of homopropargylic ethers with pyridine *N*-oxides to give α,β -unsaturated carbonyl compounds.⁷⁷¹

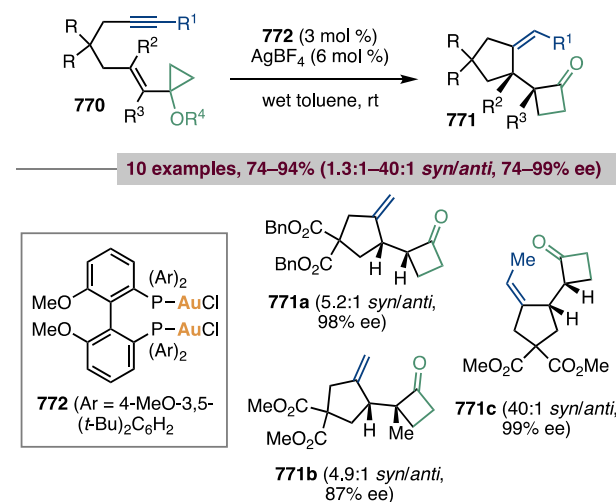
Scheme 167. Photoredox and Gold-Catalyzed Arylation Ring Expansion



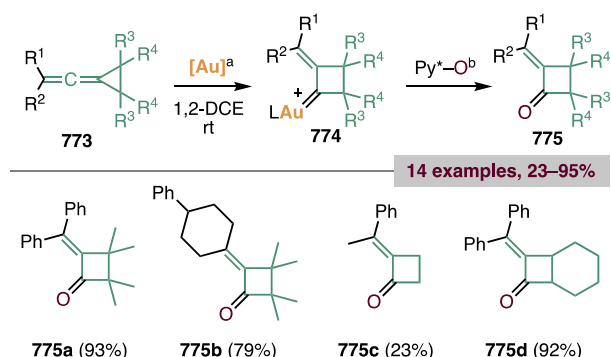
Scheme 168. Ring Expansion of a 1,1-Alkenylcyclopropanol



Scheme 169. Asymmetric Cycloisomerization of Cyclopropyl-Substituted 1,6-Enynes



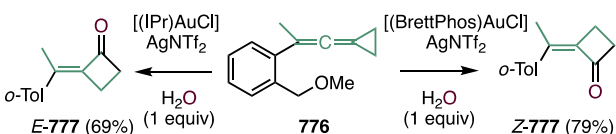
Scheme 170. Oxidative Ring-Expansion of Vinylidene Cyclopropanes



^a[Au] = [(Ph₃P)AuCl] (5 mol %)/AgSbF₆ (10 mol %). ^bPy*–O = 3,5-dibromopyridine *N*-oxide.

Shi and co-workers developed an intramolecular approach, in which a tethered methoxy group acts as oxygen transfer agent to the vinylidene cyclopropane. This concept was used to develop a catalyst-controlled stereodivergent synthesis of alkylidene cyclobutanones: [(IPr)AuCl] gave exclusively *E*-777, whereas [(BrettPhos)AuCl] gave diastereoisomer *Z*-777 (Scheme 171).⁷⁷²

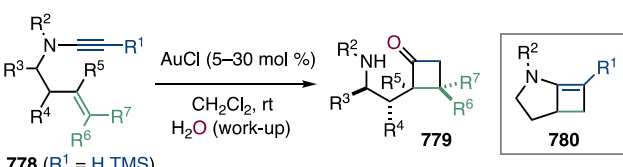
Scheme 171. Stereodivergent Synthesis of Alkylidene Cyclobutanones



3.3.2. Synthesis of Cyclobutanones by Other Methods.

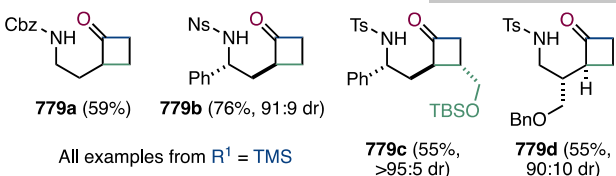
Cossy and co-workers reported that the gold-catalyzed cycloisomerizations of 1,6-ene-ynamides 778 possessing a terminal or trimethylsilyl-substituted alkyne provided cyclobutanones 779 in moderate to good yields (Scheme 172).^{419,420} A mechanism

Scheme 172. AuCl-Catalyzed Cycloisomerization of 1,6-Ene-ynamides



778 (R¹ = H, TMS)

9 examples, 47–77%

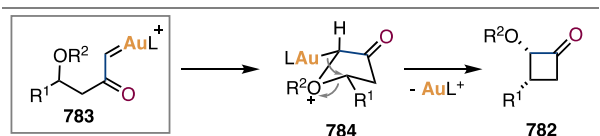
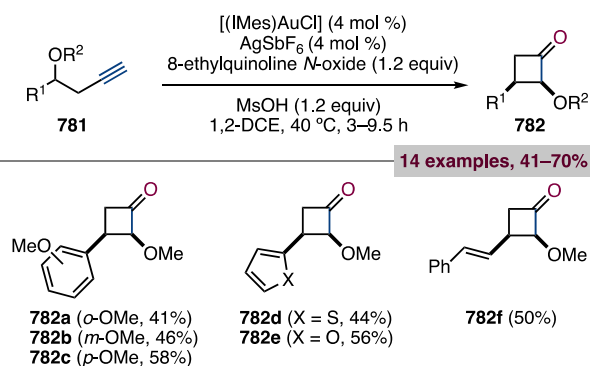


involving gold-catalyzed cycloisomerization to cyclobutenes 780 followed by hydrolysis during the work-up was proposed. The high diastereoselectivity observed with substrates bearing a stereocenter at the position α or β to the N atom (779b–d) was rationalized with chair-like transition states for the formation of

the cyclopropyl gold carbene intermediates, in analogy with cationic cyclizations of *N*-acyliminium ions.

Li and co-workers disclosed that homopropargylic ethers 781 bearing electron-rich aromatic or alkenyl R¹ groups afforded *cis*-cyclobutanones 782 in the presence of a gold(I) catalyst and 8-ethylquinoline *N*-oxide (Scheme 173).^{773,774} In the proposed

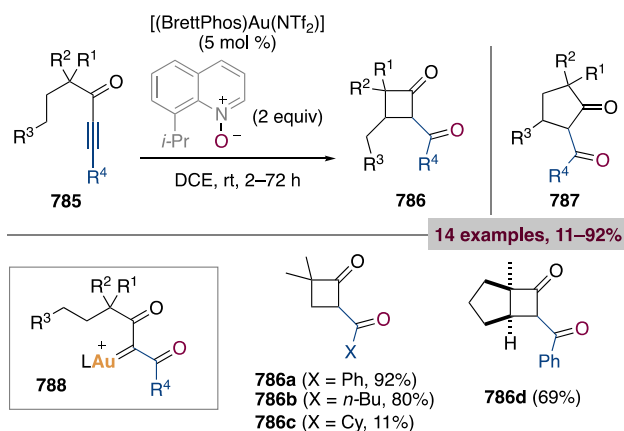
Scheme 173. Au(I)-Catalyzed Oxidative Rearrangement of Homopropargylic Ethers to *cis*-Cyclobutanones



mechanism, α -oxo gold carbene 783 is trapped by the tethered ether group to afford oxonium ylide 784, which rearranges in a concerted process to *cis* product 782. Under acidic conditions, the latter converts into the *trans* isomer.

The group of Zhang developed methods for the selective formation of cyclobutanones 786 and cyclopentanones 787 depending on the ligand and substrate structures through the intramolecular insertion into C(sp³)–H bonds by oxidatively generated β -diketone- α -gold carbenes 788 (Scheme 174).^{775,776}

Scheme 174. Au(I)-Catalyzed Oxidative Synthesis of Cyclobutanones

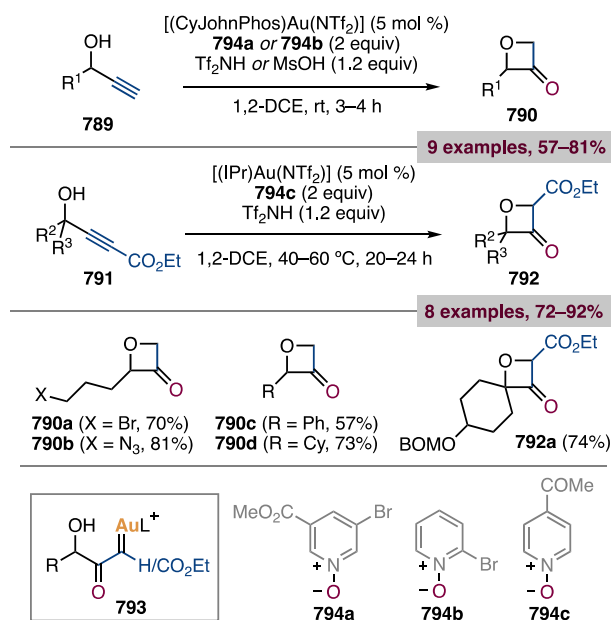


3.4. Synthesis of Heteroatom-Containing 4-Membered Rings

Zhang and co-workers devised the synthesis of O- and N-containing 4-membered rings based on the propensity of α -oxo gold carbenes, generated from alkynes by Au(I)-catalyzed intermolecular oxidation (see section 2.6),⁵³⁷ to effect intramolecular insertion into N–H and O–H bonds. A practical

synthesis of oxetan-3-ones⁷⁷⁷ **790** and **792** was developed from readily available propargylic alcohols,⁷⁷⁸ and carried out under air using pyridine *N*-oxides as oxidants and catalytic amounts of gold(I) complexes (Scheme 175).⁷⁷⁹ With tertiary propargylic

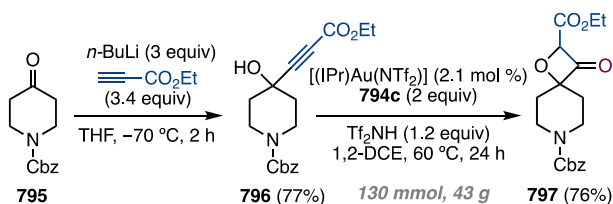
Scheme 175. Au(I)-Catalyzed Oxidative Synthesis of Oxetan-3-ones



alcohol substrates **791**, an electron-withdrawing group had to be installed at the alkyne terminus to avoid side reactions, arising presumably from the formation of propargylic cations under acidic conditions.

This method was employed for the synthesis of a drug discovery library of 419 spirocyclic oxetane–piperidine scaffolds (Scheme 176),⁷⁸⁰ which are relevant motifs in medicinal chemistry.^{781,782}

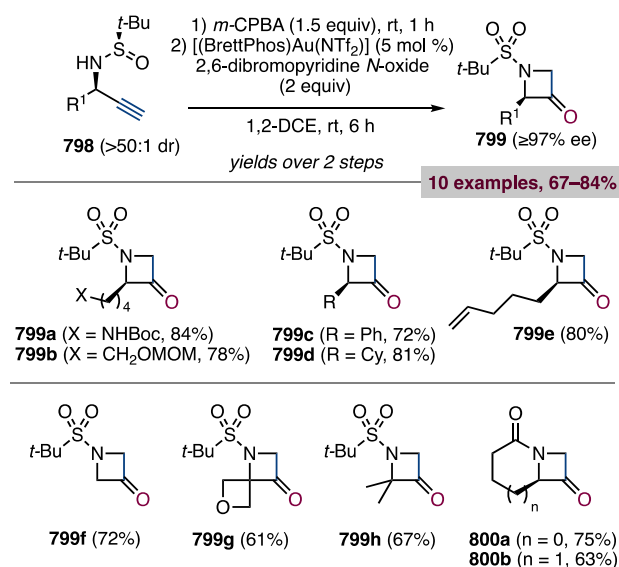
Scheme 176. Large-Scale Au(I)-Catalyzed Synthesis of an Oxetane–Piperidine Building Block



Zhang and co-workers applied the same strategy to prepare azetidine-3-ones **799** from *N*-*tert*-butylsulfonyl propargylamines (Scheme 177).⁷⁸³ The use of a bulky Buchwald ligand and of an electron-poor, hindered pyridine *N*-oxide obviated the need for acidic additives with secondary propargyl amine substrates, improving functional group compatibility (products **799a**, **799b**). By carefully tuning the reaction conditions, azetidin-3-ones with different substitution patterns and protecting groups could be obtained. It was later shown that several other sulfonyl-protecting groups were tolerated in this reaction.⁷⁸⁴ Notably, the *tert*-butanesulfinamide group allowed preparation of enantioenriched products by employing the chemistry of Ellman.⁷⁸⁵

Although the formation of oxetan-3-ones and thietane-3-ones under oxidative gold catalysis has been sporadically re-

Scheme 177. Au(I)-Catalyzed Oxidative Synthesis of Azetidin-3-ones



ported,^{786,787} the only gold-catalyzed preparative methods for the synthesis of heteroatom-containing 4-membered rings remain the two protocols developed by the group of Zhang.

4. OUTLOOK AND FINAL REMARKS

In less than two decades, gold(I) catalysis has emerged as one of the most powerful tools to build molecular complexity in a single reaction step. Many of the transformations that take place through gold(I) π -bond activation proceed via gold(I) carbene intermediates, which can often evolve, inter- or intramolecularly, to assemble three- or four-membered carbocycles. This strategy has been widely applied to develop a plethora of methodologies that allow the assembly of small rings efficiently and selectively. One of the main general challenges of this field is developing versatile methods that do not rely on the use of excessively complex or specific starting materials, which may introduce potentially undesired functional groups in the reaction products. In many cases, due to the complex mechanistic scenarios of these reactions, simple variations on the substitution pattern of the substrates or on the reaction conditions lead to completely different outcomes. Furthermore, even though the field of asymmetric gold(I) catalysis has experienced significant growth over the past ten years, the development of enantioselective versions of certain transformations remains an important challenge. In particular, gold(I)-catalyzed intermolecular reactions that afford enantioenriched three- or four-membered rings are still scarce and often highly dependent on the nature of the substrates employed.

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Author Contributions

[§]M.M., A.F., and C.G.-M. contributed equally.

Notes

The authors declare no competing financial interest.

Biographies

Mauro Mato completed his B.Sc. in Chemistry at the University of A Coruña (Spain) in 2016 and his M.Sc. in Synthesis and Catalysis at the Rovira i Virgili University (Tarragona, Spain) in 2017, receiving for both degrees the Extraordinary Award. Then he started his Ph.D. studies under the supervision of Prof. Antonio M. Echavarren at the Institute of Chemical Research of Catalonia (ICIQ), where he works on the generation and reactivity of metal carbenes. During this period, he carried out a short project at Scripps Research (San Diego, CA) under the supervision of Prof. Phil S. Baran and received a RSEQ–Lilly Award for Ph.D. students in 2020.

Allegra Franchino studied for her B.Sc. and M.Sc. degrees in Chemistry at the University of Milan (2008–2013), including an Erasmus semester at RWTH Aachen and research work in the group of Prof. Cesare Gennari. She continued her training in homogeneous asymmetric catalysis, particularly using transition metals, during her Marie Skłodowska-Curie Ph.D. program at the University of Oxford (2013–2017, Prof. Darren Dixon group). After a brief stint in an international API chemical company, in September 2018 she joined the laboratories of Prof. Antonio M. Echavarren at ICIQ as a Marie Skłodowska-Curie COFUND postdoctoral fellow.

Cristina García-Morales received her B.Sc. in chemistry from Universidad de Huelva (Spain), including an Erasmus year at the University of Strathclyde (U.K.), and her M.Sc. from Universitat Rovira i Virgili (Spain). She earned her Ph.D. in 2019 under the guidance of Prof. Antonio M. Echavarren and joined the group shortly after for a postdoctoral stint. During her doctoral and postdoctoral studies, she worked on enantioselective gold(I) catalysis and the characterization of highly reactive catalytic intermediates. Alongside experimental efforts, she gained expertise in DFT analyses, which she employed in deciphering Au- and Rh-catalyzed transformations.

Antonio M. Echavarren got his Ph.D. at the Universidad Autónoma de Madrid (UAM, 1982). After postdoctoral stays at Boston College and Colorado State University, he joined the Institute of Organic Chemistry (CSIC) in Madrid. In 1992, he moved to the UAM as a Professor, and in 2004, he was appointed Group Leader at the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona. In 2012, he got an ERC

Adv grant to develop gold catalysis and, in 2019, another ERC Adv grant on biomimetic catalysis. Prof. Echavarren is a member of the Advisory Boards of *Organic & Biomolecular Chemistry*, *Chemical Society Reviews*, *Advanced Synthesis and Catalysis*, and *Chemical Communications*, a member of the Editorial Board of *Chemistry—European Journal*, and a Fellow of the Royal Society of Chemistry. He received the 2004 Janssen-Cytag Award in Organic Chemistry and the 2010 Gold Medal of the Spanish Royal Society of Chemistry and, in 2015, the Arthur C. Cope Scholar Award from the ACS. Since January 2018, he has been the President of the Spanish Royal Society of Chemistry.

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