CHEMICAL REVIEWS

Review

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Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity

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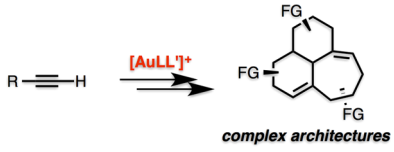

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1. INTRODUCTION

1.1. General Reactivity of Alkyne-Gold(I) Complexes

For centuries, gold had been considered a precious, purely decorative inert metal. It was not until 1986 that Ito and Hayashi described the first application of gold(I) in homogeneous catalysis.[1] More than one decade later, the first examples of gold(I) activation of alkynes were reported by Teles[2] and Tanaka,[3] revealing the potential of gold(I) in organic synthesis. Now, gold(I) complexes are the most effective catalysts for the electrophilic activation of alkynes under homogeneous conditions, and a broad range of versatile

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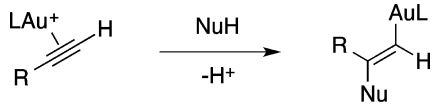
synthetic tools have been developed for the construction of carbon−carbon or carbon−heteroatom bonds.

Gold(I) complexes selectively activate π-bonds of alkynes in complex molecular settings,[4−10] which has been attributed to relativistic effects.[11−13] In general, no other electrophilic late transition metal shows the breadth of synthetic applications of homogeneous gold(I) catalysts, although in occasions less Lewis acidic Pt(II) or Ag(I) complexes can be used as an alternative,[9,10,14,15] particularly in the context of the activation of alkenes.[16,17] Highly electrophilic Ga(III)[18−22] and In(III)[23,24] salts can also be used as catalysts, although often higher catalyst loadings are required.

In general, the nucleophilic Markovnikov attack to η^2-$[AuL]^+$-activated alkynes **1** forms *trans*-alkenyl-gold complexes **2** as intermediates (Scheme 1).[4,5a,9,10,12,25−29] This activation

Scheme 1. Anti-Nucleophilic Attack to η^2-[AuL]$^+$-Activated Alkynes



1 **2**

mode also occurs in gold-catalyzed cycloisomerizations of 1,*n*-enynes and in hydroarylation reactions, in which the alkene or the arene act as the nucleophile.

Structurally, Au(I) predominantly forms linear two-coordinate complexes, although higher coordination numbers are also possible.[30] A significant number of alkyne-gold complexes have been characterized[31,32] and studied either in solution[32,33] or theoretically.[34] This selective activation of the alkyne moiety can explain a vast majority of the results experimentally observed for gold(I)-catalyzed cyclization of 1,*n*-enynes. Nevertheless, complexes of gold(I) with the alkene moiety of the enynes are also formed in equilibrium with the alkyne-gold complexes.[35] Indeed, well-characterized complexes of gold(I) with alkenes have been reported,[36] as well as with allenes[37] and 1,3-dienes.[38]

Despite the fact that simple gold salts such as $NaAuCl_4$ or AuCl are active enough to catalyze several transformations, gold(I) complexes bearing phosphines or N-heterocyclic carbenes as ligands have found more wide-ranging applications.[39] The active species are often generated in situ by chloride abstraction from [LAuCl] upon treatment with a silver salt bearing a weakly coordinating anion.

Complexes [LAuY] only exist as neutral species when Y^- is a coordinating anion (halides, carboxylates, sulfonates, and triflimide). The corresponding complexes with less coordinating anions, such as SbF_6^-, PF_6^-, or BF_4^-, are in most of the cases not stable. Although, species $[AuL]^+$ (also known as "naked gold complexes") are often suggested in mechanistic proposals, structural proof for their existence as stable, isolable species is still lacking. Here, for the sake of simplicity in mechanistic schemes throughout this review, LAu^+ is used as a surrogate of $[LAuL']^+$ complexes, where L′ states for a relatively weakly bound ligand such as the substrate (alkyne or alkene), product, or solvent molecule.

It is important to remark that when the catalytically active species are generated in situ by chloride abstraction from complexes [LAuCl] in the absence of the alkyne or other unsaturated substrate, much less reactive chloride-bridged dinuclear species [LAuClAuL]Y are readily formed.[40] Formation of these dinuclear complexes could explain, at least partly, the erratic results that have been ascribed as the "silver effects" in reactions in which Ag(I) salts are used in situ to activate neutral gold(I) complexes [LAuY].[41]

Often, the most convenient catalysts for the activation of alkynes are complexes [LAuL′]X or [LAuX] bearing weakly coordinating neutral (L′)[42] or anionic ligand (X^-).[43] These complexes can enter catalytic cycles by ligand exchange with the unsaturated substrate, which proceed by associative mechanisms as observed for Au(I) and other diagonal d^{10} metal centers.[44] Thus, large negative activation entropies characteristic of associative mechanisms have been determined for the rate determining ligand exchange reactions of substituted alkyne[45,46] and alkenes[36o] on commonly used Au(I) catalysts. Although nitriles are frequently used as weakly coordinating neutral ligands, 1,2,3-triazole[46,47] or other related ligands[48] have also been employed.

The properties of gold(I) complexes can be easily tuned sterically or electronically depending on the ligand, consequently modulating their reactivity in the activation of alkynes, alkenes, and allenes.[27,29f,49] Thus, complexes containing more donating N-heterocyclic carbenes (**3**) are less electrophilic than those with phosphine ligands (**4**, **5**) (Figure 1).[28] Complexes with less donating phosphite ligands (**6**) and related species are the most electrophilic catalysts.

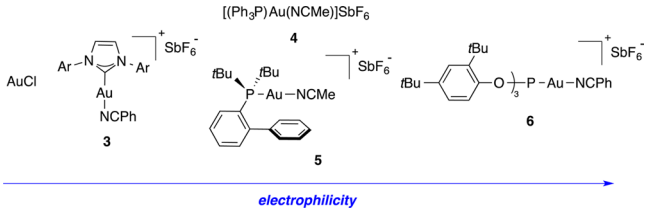


Figure 1. Increase in electrophilicity with decreased donating ligand ability in gold(I) complexes.

Gold(I) complexes bearing weak-coordinated ligands such as Me_2S, thiodiglycol, or tetrahydrothiophene (tht) have been widely used for the preparation of soluble gold(I) complexes, commonly starting from a gold(III) source.[50] Complex $[Au(tmbn)_2]SbF_6$ (tmbn = 2,4,6-trimethoxybenzonitrile), in which gold(I) is supported by two nitrile ligands, can be used for the in situ preparation of a variety of chiral and achiral cationic complexes $[LAu(tmbn)]SbF_6$, including complexes immobilized on a polymeric support.[42a] Other immobilized gold(I) complexes have also been prepared.[51] The use of gold complexes bearing chiral ligands has led to the development of efficient asymmetric gold-catalyzed transformations.[52] Less common precatalysts used in gold(I)-catalyzed transformations are gold hydroxo complex IPrAuOH, which is activated in the presence of Brønsted acids,[53] open carbenes,[39c,54] and other related complexes,[55] which give rise to selective catalysts of moderate electrophilicity. Cyclopropenylylidene-stabilized phospenium cations, which behave similarly to classical triaryl- and trialkylphosphines, have also been used as ligands in gold-catalyzed reactions.[56]

The effect of the counteranion has been studied in detail for several gold(I)-catalyzed transformations.[57,58] Thus, for the intermolecular reaction of phenylacetylene with 2-methylstyrene catalyzed by [*t*-BuXPhosAu(NCMe)]Y, it was found that yields increase depending on the counteranion in the order Y =

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$OTf^- < NTf_2^- < BF_4^- < SbF_6^- <$ BARF (BARF = 3,5,bis(trifluoromethyl)phenylborate). By using the bulky and noncoordinating anion BARF, yields are increased by 10−30% compared to those obtained when Y = SbF_6^-, probably due to a decrease in the formation of the unproductive σ,π-(alkyne)-digold(I) complexes from the initial alkyne.[57]

1.2. Scope and Organization of the Review

Homogeneous gold(I)-catalysis has experienced an outbreak in the past decade leading to the discovery of a remarkable amount of new synthetically useful transformations. Thus, in recent years many groups have used gold catalysis in key steps of total synthesis taking advantage of the unique catalytic ability of gold to build molecular complexity under mild reaction conditions.

Several reviews have been published on gold(I)-catalyzed reactions of alkynes, enynes, and related substrates,[5,7,25−28,59] as well as on gold(I)-catalyzed reactions of allenes[60] and cascade gold-catalyzed reactions.[61] Moreover, specific reviews focused on gold-catalyzed carbon-heteroatom bond formation[62] and on the use of gold catalysis in total synthesis[63] have also been published. In this review, we will cover reactions of alkynes activated by gold(I) complexes, including recent applications of these transformations in the synthesis of natural products. According to the aim of this thematic issue, the main focus is on the application of gold(I)-catalyzed reactions of alkynes in organic synthesis, although reactions are organized mechanistically. Reactions of gold(I)-activated alkenes and allenes, as well as gold(III)-activated alkynes, will not be covered.

The discussion has been primarily organized based on the different reactions catalyzed by gold(I) complexes that alkynes can undergo. When possible, inter- and intramolecular processes, as well as the applications in total synthesis, are treated in specific subsections.

2. ADDITION OF HETERONUCLEOPHILES TO ALKYNES

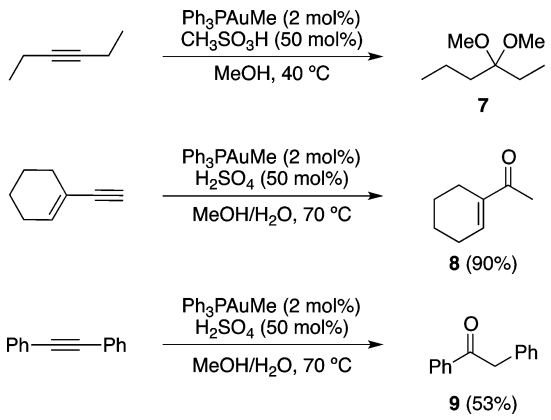
2.1. Addition of O-Nucleophiles to Alkynes

The effectiveness of gold(I) complexes for the activation of alkynes toward inter- and intramolecular nucleophilic attack has been demonstrated for a variety of heteronucleophiles. Due to relativistic effects, cationic gold complexes possess, besides a high π-acidity, a low oxyphilicity,[7,8] and therefore they are able to activate unsaturated C−C bonds in the presence of H_2O, alcohols, or any other oxygen-containing functional groups. Hence, once the alkyne is activated, the nucleophilic oxygen can attack forming a new C−O bond.

2.1.1. Intermolecular Addition of O-Nucleophiles to Alkynes. Hydration and alkoxylation of alkynes are industrially important processes for the synthesis of carbonyl compounds. A well-known method for the addition of water and alcohols to alkynes uses toxic Hg(II) salts under acidic conditions.[64] Other less harmful although expensive transition-metal-based catalytic systems have also been described,[65] including the use of Au(III) salts.[66]

The first examples of gold(I)-catalyzed addition of alcohols and water to alkynes were reported by the groups of Teles[2] and Tanaka,[3] respectively, employing air stable gold complexes [AuMe(L)] (L = phosphine, phosphite or arsine), which were activated in situ by protic acids to form acetals such as **7** or ketones **8** and **9** (Scheme 2). Markovnikov-type addition was observed in all cases, being reactive under these reaction conditions both terminal and internal alkynes. Despite its

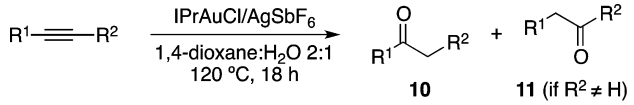
Scheme 2. Hydration and Acetalization of Alkynes with Ph_3PAuMe and Protic Acids



efficiency, this method suffers from several drawbacks, including the use of concentrated solutions of strong acids and relatively high catalyst loadings.

Although the catalytic hydration of alkynes with neutral N-heterocyclic carbene gold(I) chlorides or carboxylates in the presence of $B(C_6F_5)_3$ was already demonstrated in 2003,[67] later in 2009 it was found that the use of gold(I) complexes bearing bulkier N-heterocyclic carbene ligands allowed to catalyze this process at loadings as low as <10 ppm under acid-free conditions (Scheme 3).[68] This catalytic system showed wide

Scheme 3. Hydration of Alkynes with Low-Catalyst Loadings

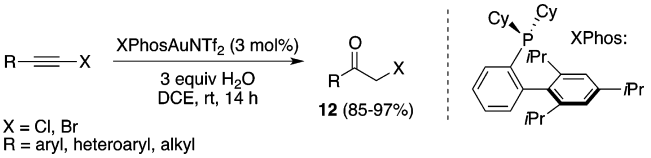


R1 = aryl, alkyl, alkenyl; R2 = aryl, alkyl, H (72-100%)

versatility, since both terminal and internal alkynes possessing any combination of alkyl and aryl substituents were suitable substrates. However, the reaction required high temperatures to proceed and for unsymmetrical internal alkynes only moderate regioselectivities were obtained. Alkynes can also be hydrated at room temperature without any acidic cocatalyst in the presence of gold(I)-phosphine complexes.[69]

The regioselective hydration of haloalkynes was recently reported to afford α-halomethylketones **12** in excellent yields under very mild reaction conditions (Scheme 4).[70] This

Scheme 4. Hydration of Haloalkynes



X = Cl, Br
R = aryl, heteroaryl, alkyl

procedure was applied on the gram-scale, and the catalyst loading could be decreased up to 2 mol % with little effect on the yield. However, *ortho*-substituted arylacetylenes provided only trace amounts of the carbonyl compounds.

Cyclic acetals are important building blocks present in many natural occurring biologically active compounds, and, moreover, they are very useful as protecting groups.[71] They are usually obtained by the addition of a diol to the corresponding

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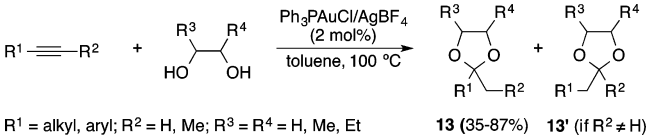
aldehyde or ketone under Brønsted acid conditions. When diols are added to alkynes in the presence of a gold(I) catalyst, cyclic acetals **13** are regioselectively formed instead of the unprotected carbonyls (Scheme 5). This reaction proceeds

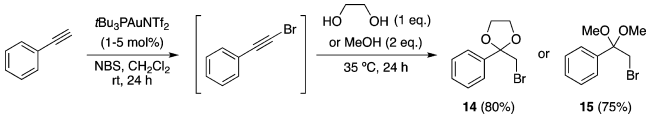
Scheme 5. Acetalization of Alkynes



with complete regioselectivity in the case of terminal alkynes and with moderate selectivity for internal alkynes, yielding a mixture of cyclic acetals **13**/**13′**.[72] The reaction can also be expanded to the preparation of acetals from 1,5-diols.

In a more recent example, *α*-bromo cyclic and acyclic acetals **14** and **15** were obtained from terminal alkynes and NBS (Scheme 6).[73] The reaction proceeded via formation of bromoacetylenes followed by addition of the *O*-nucleophiles to the triple bond.

Scheme 6. Bromo-Acetalization of Alkynes

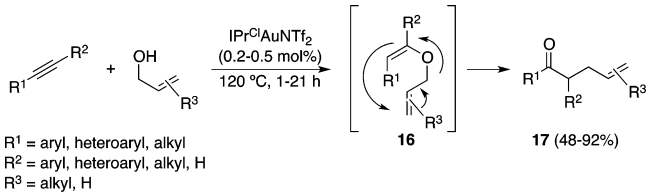


The role of the anion in the intermolecular alkoxylation of alkynes catalyzed by N-heterocyclic carbene-based gold(I) complexes [(NHC)AuX] (X = $BARF^-$, BF_4^-, OTf^-, OTS^-, TFA^-, AcO^-) has recently been dissected, with the conclusion that both coordination ability and basicity have a great impact on this transformation.[74] The most important factor seems to be the ability to abstract the proton from the alcohol during the nucleophilic attack, which is directly related to the anion basicity.

Gold(I)-catalyzed intermolecular additions of alcohols to alkynes can be coupled with other tandem reactions, therefore increasing the degree of molecular complexity in the final product.[75] The addition of allylic alcohols to alkynes followed by a Claisen rearrangement of the resulting intermediates (**16**) has recently been developed, leading to the formation of *γ*,*δ*-unsaturated ketones **17** in an efficient one-pot procedure from simple starting materials (Scheme 7).[76]

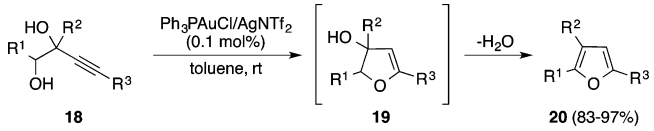
2.1.2. Intramolecular Addition of O-Nucleophiles to Alkynes. The high activity of gold(I) salts and complexes for C−O bond formation has been widely exploited intramolecularly to construct oxygen containing heterocycles. In this context, one of the most studied transformations is the intramolecular gold(I)-catalyzed cyclization of unactivated

Scheme 7. Synthesis of Homoallylic Ketones by Nucleophilic Addition-Claisen Rearrangement



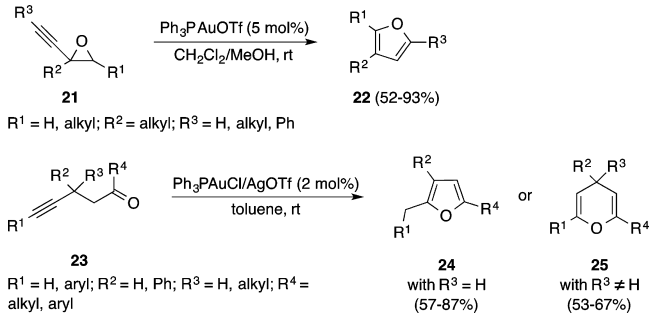
alkynols.[60b,77] As an example, alkynediols **18** underwent a gold(I)-catalyzed cyclization leading to furans **20** after elimination of H_2O from intermediate **19** in the presence of very low catalyst loadings (Scheme 8).[78] The alcohol moiety

Scheme 8. Synthesis of Furans by Cyclization of Alkynediols



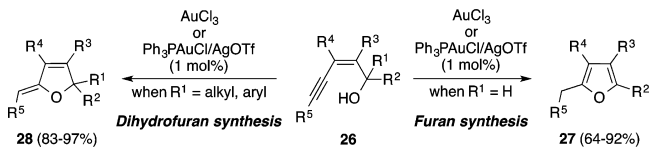
may already be present in the precursor of the gold(I)-catalyzed transformation[79] or may be generated in situ from epoxides by ring opening.[80] Carbonyls can also act the nucleophiles.[81] Thus, alkynyloxiranes **21** were converted into trisubstituted furanes **22**,[80b] and alk-4-yn-1-ones **23** gave rise to 2,4,5-trisubstituted furans **24** or substituted 4*H*-pyranes **25** depending on the substitution pattern of the substrate (Scheme 9).[81b]

Scheme 9. Cyclization of Epoxy and Ketoalkynes



Furan derivatives were obtained from *Z*-enynols **26** (Scheme 10).[82] Enynols bearing a secondary alcohol afforded substituted

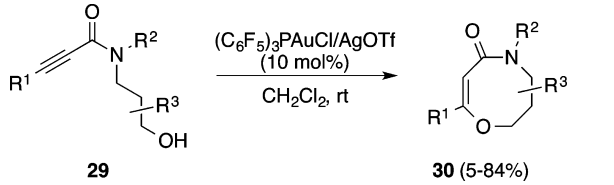
Scheme 10. Synthesis of Furan Derivatives from *Z*-Enynols



furans **27**, and those containing a tertiary alcohol gave dihydrofurans **28**. In the presence of gold(I) catalysts bearing N-heterocyclic carbene ligands these substrates were also converted into furan structures allowing the use of low catalyst loadings and very mild reaction conditions.[83]

Oxazocenones **30** have been recently synthesized via gold(I)-catalyzed 8-*endo*-dig hydroalkoxylation of alkynamides **29** (Scheme 11).[84]

Scheme 11. Synthesis of Oxazocenones



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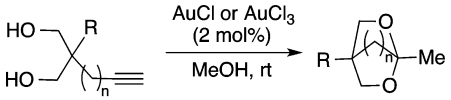
The reaction of alkynediols to give bicyclic acetals by gold(I)-catalyzed intramolecular hydroalkoxylation of terminal alkynes using bis-homopropargylic alcohols **31** was first described in 2005, opening a door to an interesting family of strained acetals **32** (Scheme 12).[85] Notably, the addition of

Scheme 12. Intramolecular Acetalization of Alkynes



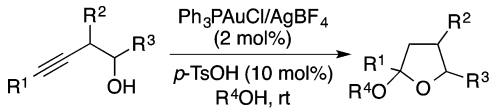
31 **32** (74-99%)

n = 1, 2
R = *n*-Bu, Bn, Ph, allyl, cinnamyl, cyclohex-2-enyl, 3-methylbut-2-enyl

methanol to alkene intermediates did not occur under the reaction conditions. Recently, the selective conversion of acetonide-tethered alkynes into bridged acetals through an analogous process using Ph_3PAuCl and AgOTf in the presence of water was reported.[86]

As described for intermolecular additions of *O*-nucleophiles, the intramolecular version can also be combined with subsequent tandem reactions in order to increase molecular complexity of the resulting products. One of the simplest examples is the tandem cycloisomerization/hydroalkoxylation of homopropargylic alcohols in the presence of an external alcohol to form tetrahydrofuranyl ethers **33** (Scheme 13).[87]

Scheme 13. Tandem Cycloisomerization/Hydroalkoxylation of Homopropargylic Alcohols



R^1 = aryl, alkyl, TMS
R^2 = H, Ph
R^3 = H, Ph, Me
R^4 = alkyl

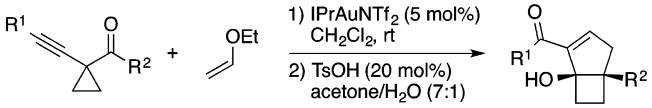
33 (36-72%)

Bishomopropargylic alcohols also react with gold(I) in a similar fashion, giving rise to methylene tetrahydrofuran motifs, which in the presence of an external nucleophile are the entry to a variety of structurally different products.[88]

The formation of bicyclo[3.2.0]heptenes **35** was reported involving an intramolecular addition of an oxygen-containing nucleophile to a cyclopropyl alkyne **34** activated by gold(I) (Scheme 14).[89] The same group also developed an unprecedented gold(I)-catalyzed tandem reaction to form polysubstituted dihydrofurans from acetal-protected propargylic alcohols and carbonyl compounds.[90]

The synthesis of tricyclic cage-like structures was described starting from diyne-diols by trapping the intermediate dienol

Scheme 14. Synthesis of Bicyclo[3.2.0]heptenes by Intramolecular Addition to a Cyclopropyl Alkyne

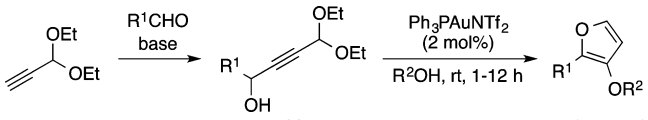


34 **35** (54-98%)

ether, which results from a double intramolecular hydroalkoxylation with external nucleophiles.[91]

The synthesis of 3-alkoxyfurans **37** from acetal-containing propargylic alcohols **36** has recently been reported.[92] Thus, these synthetically useful substrates can be easily prepared in two steps from readily available aldehydes, alcohols, and 3,3-diethoxypropyne (Scheme 15).

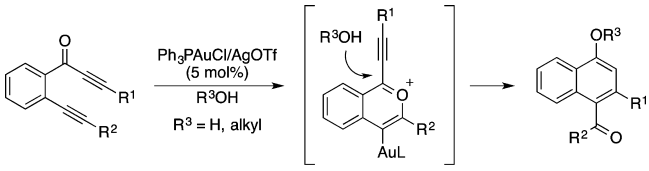
Scheme 15. Synthesis of 3-Alkoxyfurans from Acetal-Containing Propargylic Alcohols



36 **37** (68-95%)

In the case of alkynylketones or esters, the mechanism of the gold(I)-catalyzed hydration or alkoxylation involves the anchimeric assistance of the carbonyl group forming an intermediate that is opened back by one water or alcohol molecule leading to the final carbonyl compounds.[93] Diethynylketones **38** were converted into naphthol derivatives **40** by this ketone-assisted hydration followed by cyclization (Scheme 16).

Scheme 16. Synthesis of Naphthol Derivatives from Diethynylketones

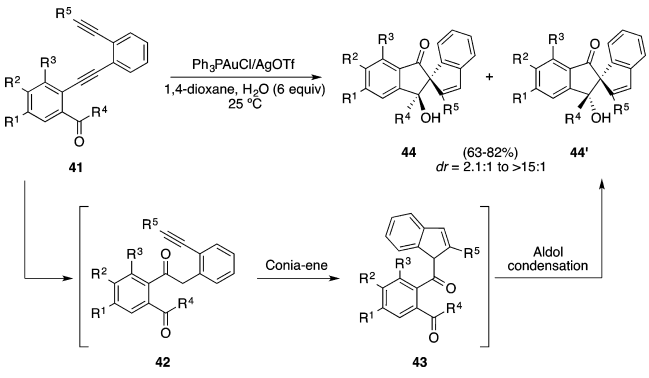


38 **39** **40** (11-93%)

In the formation of tricyclic spiroketones **44**/**44′** by tandem hydration/Conia-ene/aldol condensation,[93b] the first step also takes place via anchimeric assistance of the carbonyl moiety to give intermediate **42** and not through direct addition of H_2O to **41** (Scheme 17).

2-Alkynyl-1,5-diketones **45** undergo intramolecular oxygen transfer in the presence of AuCl via [4 + 2] cycloaddition to form cyclopentenylketones **48** (Scheme 18).[94] The mechanism of this transformation was proposed based on DFT calculations and also demonstrated by isotopic labeling experiments,

Scheme 17. Synthesis of Tricyclic Spiroketones by Tandem Hydration/Conia-Ene/Aldol Condensation



41 **44** (63-82%) *dr* = 2.1:1 to >15:1 **44′**

42 **43**

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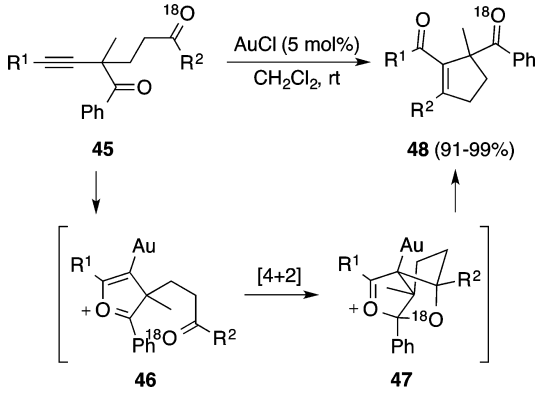
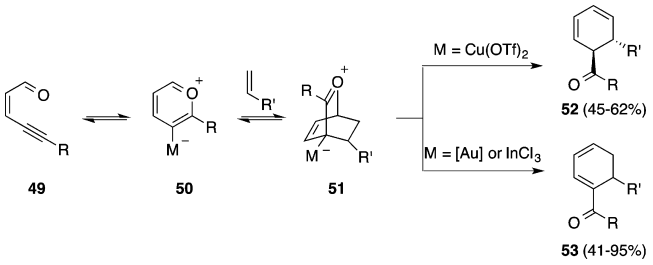
Scheme 18. Synthesis of Cyclopentenylketones from 2-Alkynyl-1,5-diketones



determining that the reaction proceeds via tandem oxycyclization/[4 + 2] cycloaddition.

A metal-dependent catalytic method has been developed for the synthesis of cyclohexadienes from enynals **49** and alkenes (Scheme 19).[95] When $Cu(OTf)_2$ was used as the catalyst, 2,4-

Scheme 19. Catalyst-Dependent Synthesis of 1,3-Cyclohexadienes

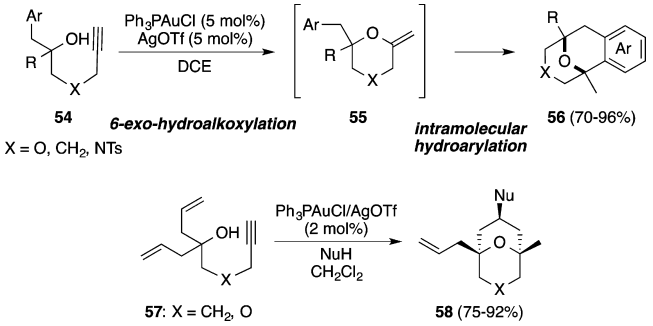


cyclohexadienes **52** were formed, whereas in the presence of $InCl_3$ or gold(I) complexes, 1,3-cyclohexadienes **53** were obtained instead. The gold(I)-catalyzed transformation proceeds via intramolecular addition of the carbonyl to the alkyne, followed by a Diels–Alder reaction between the resulting pyrylium intermediate **50** and the alkene, and final demetalation.

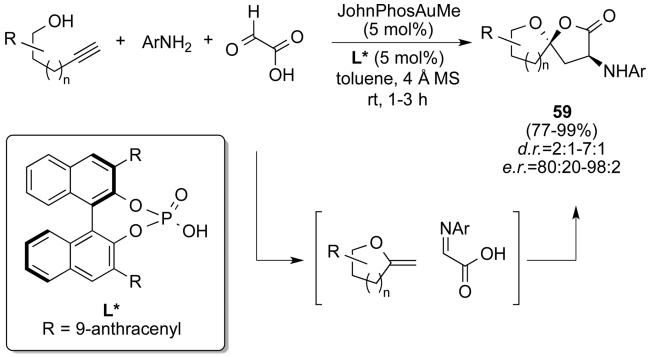
Cascade-type sequences have also led to the formation of pyrane derivatives.[96] Tricyclic 2,3-benzopyranes **56** were synthesized by a tandem intramolecular hydroalkoxylation/hydroarylation to obtain benzo-fused cyclic ethers.[97] Shortly later, a gold(I)-catalyzed tandem intramolecular hydroalkoxylation/Prins-type cyclization was described, affording oxygen-containing [3.3.2] bicyclic compounds **58** diastereoselectively (Scheme 20).[98]

Spiroketals, which are key structural units in many biologically active natural products, can also be obtained by gold(I)-catalyzed intramolecular hydroalkoxylation of alkynediols and alkynetriols.[79,99] The use of an acetonide moiety to function as a regioselectivity regulator in the spiroketalization process has been proposed to address the possible regioselectivity issues in the formation of monounsaturated spiroketals.[100] The first multicomponent enantioselective gold(I)-catalyzed synthesis of spiroketals **59** has been recently described using a gold-phosphate catalytic system in a three-component coupling between alkynols, anilines, and glyoxylic acid (Scheme 21).[101] More recently, another synthesis of

Scheme 20. Synthesis of Oxygen-Containing [3.3.2] Bicyclic Compounds by Cascade Sequences Involving Intramolecular Hydroalkoxylations



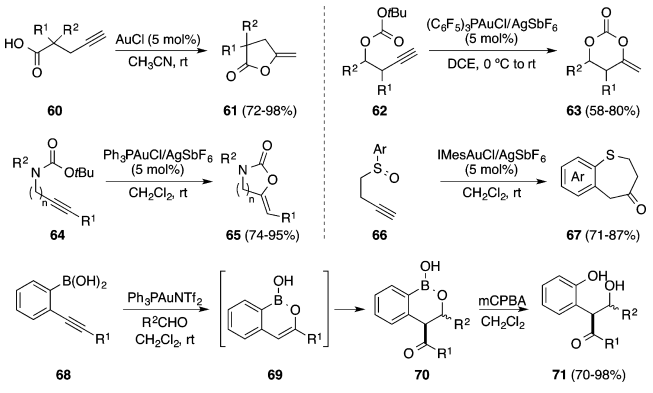
Scheme 21. Enantioselective Synthesis of Spiroketals by Coupling of Alkynols, Anilines, and Glyoxylic Acid



spiroketals has been reported combining a gold(I)-catalyzed cycloisomerization of an alkynol with an inverse-electron-demand hetero Diels–Alder mediated by $Y(OTf)_3$.[102]

Carboxylic acid derivatives,[103] carbonates,[104] carbamates,[105] sulfoxides,[106] boronic acids,[107] and related *O*-nucleophiles[108] can also add to alkynes (Scheme 22). Acetylenic carboxylic

Scheme 22. Intramolecular Addtion of *O*-Nucleophiles to Alkynes



acids **60** undergo selectively an *exo*-cyclization providing functionalized γ-lactones **61**.[103a] Analogously, *tert*-butyl carbonates derived from homopropargyl alcohols **62** cyclize to afford cyclic enol carbonates **63**[104b] and *N*-Boc propargylamines **64** yield 1,3-oxazin-2-ones **65**.[105b] Gold(I) also promotes the rearrangement of homopropargyl sulfoxides **66** to give benzothiepinones **67**[106a] and the formation of boron enolates

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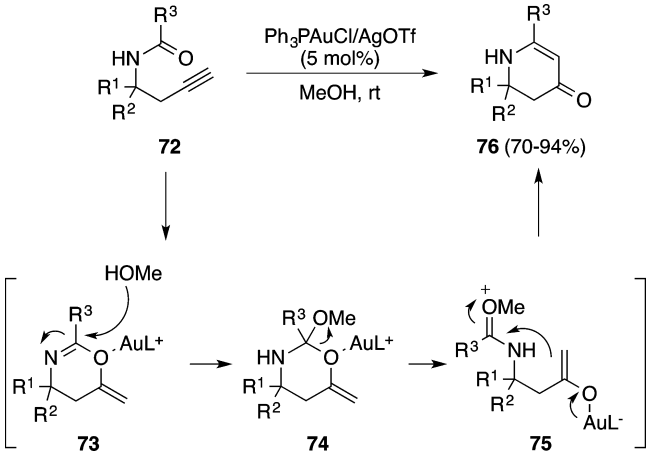
70 from alkynes, which can be further transformed into other derivatives such as diols **71**.[107]

A gold(I)-catalyzed tandem sequence has been developed for the synthesis of dihydropyridones **76** from homopropargylic carboxamides **72** (Scheme 23).[109] After an intramolecular

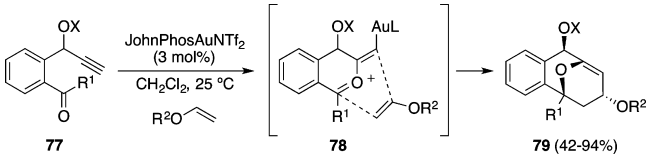
Scheme 23. Synthesis of Dihydropyridones by Intramolecular Addition of Homorpropargylic Amides to Alkynes



carbonyl addition of the homopropargylic amide to the alkyne, the formation of a σ-complex of the gold salt with the intermediate oxazine **73** promotes a nucleophilic addition of an external alcohol to form **74** followed by a Petasis-Ferrier rearrangement via **75**. Based on this concept, a new protocol for the synthesis of benzyl alcohols has been described generating the benzylating agent upon treatment of *N*-Cbz-*N*-benzyl-propargylamine with $IPrAuNTf_2$.[110] This reaction takes place under very mild conditions and eliminates the need of base additives.

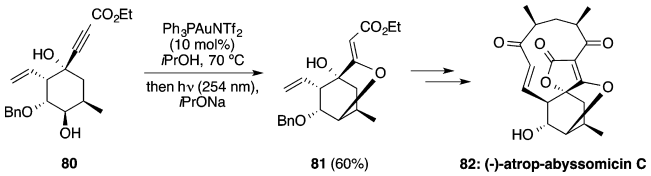
1-Oxo-4-oxy-5-ynes **77** react with gold(I) to form *s-trans*-methylene(vinyl)oxonium intermediates **78**, which in the presence of an external alkene undergo a formal [4 + 2] cycloaddition giving rise to 9-oxabicyclo[3.3.1]nona-4,7-dienes **79** (Scheme 24).[111]

Scheme 24. Reaction of 1-Oxo-4-oxy-5-ynes with Alkenes To Form 9-Oxabicyclo[3.3.1]nona-4,7-dienes

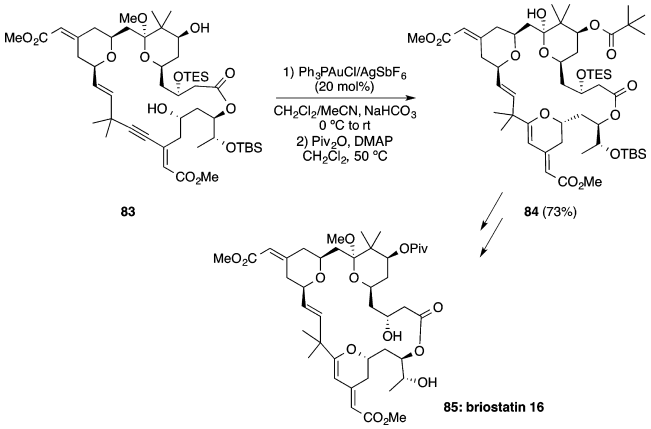


2.1.3. Addition of O-Nucleophiles to Alkynes in Total Synthesis. The gold(I)-catalyzed formation of *O*-heterocycles is a powerful tool in the field of total synthesis of natural products. In the synthesis of (−)-atrop-abyssomicin C (**82**),[112] the bridged bicycle **81** was obtained via intramolecular 6-*exo*-dig cyclization of alkynol **80** (Scheme 25). Another remarkable example is found in the total synthesis of bryostatin 16 (**85**),[113] in which a gold(I)-catalyzed oxycyclization of alkynol **83** generates the dihydropyran cycle present in the natural product (Scheme 26). In the formal total synthesis of didemniserinolipid B, a gold(I)-catalyzed 6-*endo*-dig alkynol-cycloisomerization was considered as the key step to construct the bicyclic

Scheme 25. Synthesis of (−)-atrop-Abyssomicin C



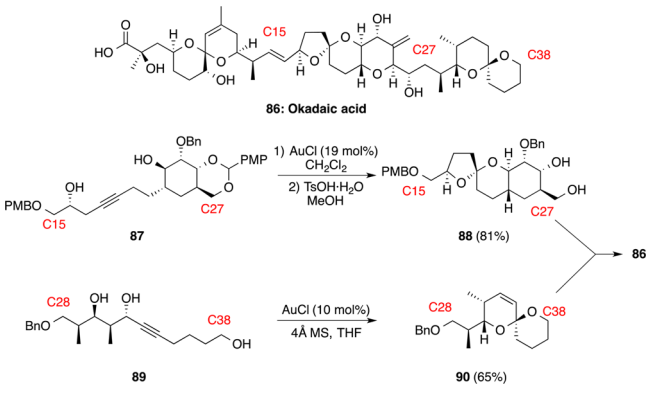
Scheme 26. Synthesis of Bryostatin 16



acetal skeleton.[114] Another example of gold(I)-promoted cycloisomerization of alkynols was recently reported in the total synthesis of (±)-cafestol.[115] In this work, the furan ring is constructed in a late-stage of the synthesis via intramolecular 5-*endo*-dig cycloisomerization followed by dehydration.

The formation of spiroketal skeletons catalyzed by gold(I) has also been successfully applied in several total syntheses.[116] Okadic acid (**86**) is a natural occurring polyether containing three spiroketal motifs. The C15−C38 fragment was synthesized taking advantage of the high activity and selectivity of AuCl for the synthesis of spiroketals starting from alkynediols (Scheme 27).[117]

Scheme 27. Construction of the Spiroketal Fragments in the Total Synthesis of Okadic Acid



The ability of carboxylic acid derivatives to add to alkynes in the presence of gold(I) complexes was exploited in the first total synthesis of neurymenolide A (**94**)[118] (Scheme 28) and in the synthesis of psymberin (**97**)[119] (Scheme 29).

A gold(I)-catalyzed tandem reaction of 1,7-diynes bearing a propargylic carboxylic acid was developed for the total synthesis of drimane-type sesquiterpenoids,[120] involving a first intra-

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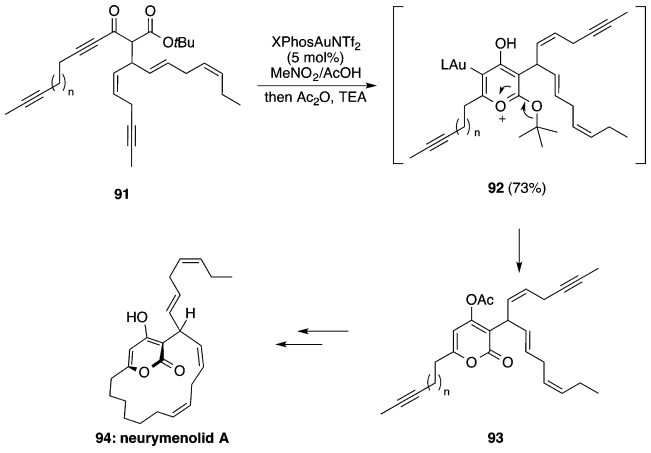
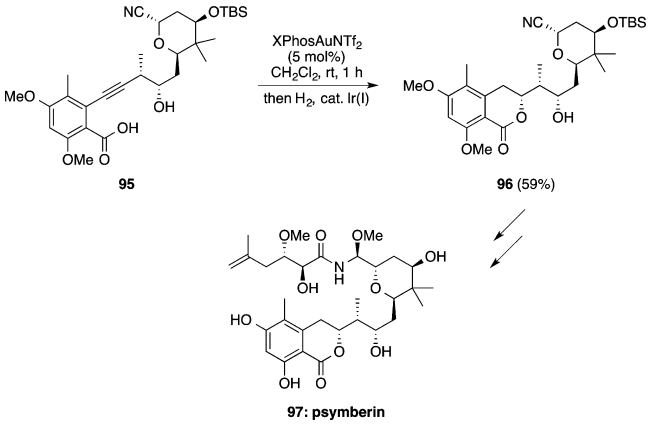
Scheme 28. Synthesis of Neurymenolide A



Scheme 29. Synthesis of Psymberin

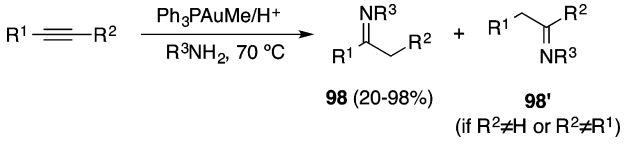


molecular alkoxylation to give a furanone intermediate that undergoes an alkoxycyclization with benzyl alcohol. A similar tandem alkoxylation/alkoxycyclization sequence was also recently used in the synthesis of cladiellins.[121]

2.2. Addition of N-Nucleophiles to Alkynes

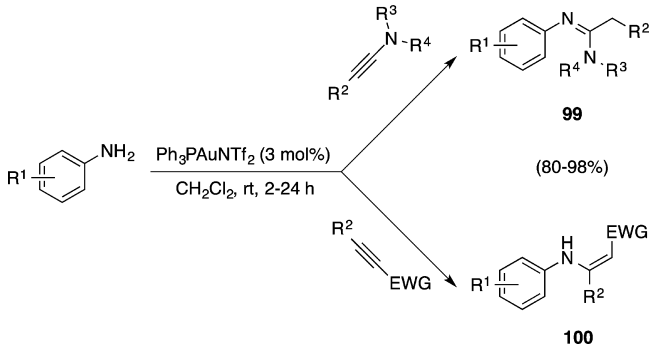
2.2.1. Intermolecular Addition of N-Nucleophiles to Alkynes. Despite the fact that gold(III)-catalyzed hydroamination of terminal alkynes had been known since 1987,[122] it was not until 2003 that Hayashi and Tanaka developed the first gold(I)-catalyzed intermolecular amination of alkynes with anilines to form imines **98**/**98′** (Scheme 30).[123] Another more

Scheme 30. Intermolecular Amination of Alkynes to Form Imines



recent example was developed using gold(I) complexes bearing 1,2,4-triazole-based N-heterocyclic carbene ligands for the formation of the corresponding ketimines from terminal alkynes and aniline derivatives.[124] A different approach for the formation of imines was based on gold(I)-phosphine complexes bearing a low coordinating bis(trifluoromethanesulfonyl) imidate counterion, namely SPhosAuNTf$_2$.[125] These complexes are active catalysts for the regioselective intermolecular hydroamination of both internal and terminal alkynes under mild reaction conditions, showing a regioselectivity based on electronic rather than steric factors. This electronic control on the regioselectivity of alkyne hydroamination reactions had earlier been reported for the hydroamination of unsymmetrical electron-poor and electron-rich alkynes with anilines (Scheme 31).[126] More challenging

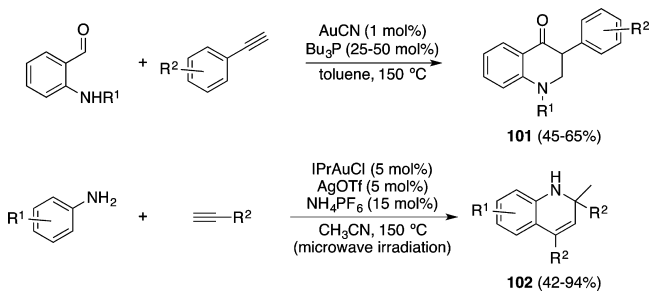
Scheme 31. Regioselective Hydroamination of Unsymmetrical Alkynes



hydroaminations of less-reactive internal alkynes an unprotected aliphatic amines could be performed using a novel series of 1,2,3-triazole-based cationic gold(I) complexes,[47a] which turned out to have a superior thermal stability than other catalysts previously reported.

Nowadays, as happens for the addition of *O*-nucleophiles to alkynes, gold(I)-catalyzed hydroamination of alkynes is not limited to the synthesis of imine or enamine products by formal addition of N−H reagents onto triple bonds.[123,127] Instead, a number of tandem sequences involving alkyne-hydroamination steps have been reported leading to the formation of more complex structures such as azaflavanones **101**[128] or quinoline derivatives **102**[129] (Scheme 32). Another example refers to a

Scheme 32. Synthesis of Azaflavanones and Quinoline Derivatives



tandem intermolecular hydroamination/transfer hydrogenation catalyzed by gold(I) combined with a chiral Brønsted acid to form enantioenriched secondary amines **103** (Scheme 33).[130] This methodology tolerates a wide range of aryl, alkenyl, and aliphatic alkynes, as well as a range of anilines with different electronic properties.

An enantioselective tandem hydroamination/hydroarylation of alkynes has recently been reported using a gold(I)/chiral Brønsted acid binary system as catalyst.[131] In this transformation, the gold(I)-activated alkynes react with a range of pyrrole-based aromatic amines to give pyrrole-embedded aza-

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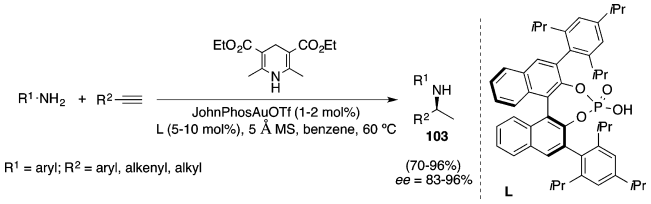
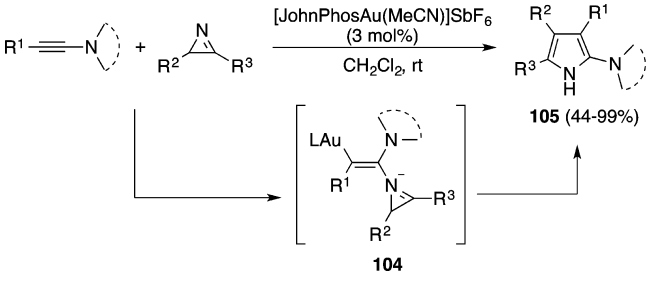
Scheme 33. Enantioselective Hydroamination/Transfer Hydrogenation Synthesis of Secondary Amines



heterocyclic scaffolds bearing a quaternary center. Isoxazoles can also add to ynamides in the presence of gold(I) in a formal [3 + 2] cycloaddition to give polysubstituted 2-amino-pyrroles.[132]

The gold(I)-catalyzed intermolecular reaction between 2*H*-azirines and ynamides provides highly substituted pyrroles **105** in a formal [3 + 2] cycloaddition (Scheme 34).[133]

Scheme 34. Synthesis of Polysubstituted Pyrroles from 2H-Azirines and Ynamides

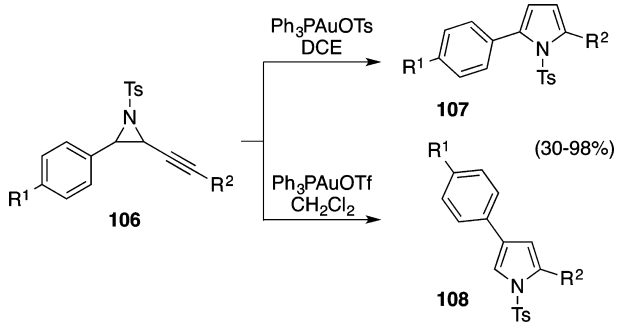


2.2.2. Intramolecular Addition of N-Nucleophiles to Alkynes. The intramolecular hydroamination of unactivated alkynes is a very useful tool to construct nitrogen-containing heterocycles. An efficient method to obtain pyrroles comes from the intramolecular dehydrative cyclization of amino-3-alkyn-2-ols mediated by gold(I).[78b] A similar catalytic system catalyzed a tandem direct amination/cycloisomerization from (*Z*)-2-en-4-yn-1-ols in the presence of an external amine to give substituted pyrroles under mild reaction conditions.[134] Alkynyl amidoalcohols undergo a gold(I)-catalyzed spiroamidoketalization giving rise to spiro-*N*,*O*-ketals with 5- and 6-membered rings presumably via tandem intramolecular 5-*exo*-dig hydroamidation/intramolecular oxycyclization.[135]

Aryl-substituted *N*-tosyl alkynylaziridines **106** are prone to undergo a gold(I)-catalyzed ring expansion to form 2,5- (**107**) or 2,4-disubstituted pyrroles (**108**) depending on the solvent and the counterion of the gold complex (Scheme 35).[136] Similarly, the system $Ph_3PAuCl/AgOTf$ is able to catalyze the rearrangement of propargylic aziridines forming trisubstituted and cycloalkane-fused pyrroles.[137] This transformation involves an unusual tandem cyclization-opening/Wagner-Meerweein sequence. The selective formation of 2,5-disubstituted pyrroles catalyzed by the same Au(I)/Ag(I) system from acetylenyl aziridines was also described using THF as solvent,[138] finding that the presence of protic species such as MeOH increased the reaction rate and the yield of the pyrrole products.

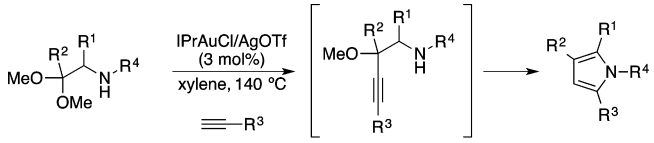
A new method for the synthesis of substituted pyrroles **111** based on an intermolecular hydroamination process has recently been reported.[139] The reaction takes place by a tandem process consisting of an initial addition of a gold-acetylide to an acetal moiety to form intermediate **110** followed

Scheme 35. Synthesis of 2,5- or 2,4-Disubstituted Pirroles from Aryl-Substituted *N*-Tosyl Alkynylaziridines



by a gold(I)-catalyzed 5-*endo*-dig cyclization and final aromatization (Scheme 36).

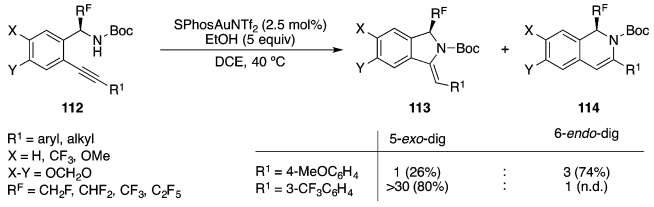
Scheme 36. Synthesis of Substituted Pyrroles by an Intermolecular Hydroamination



The synthesis of *N*-heterocycles bearing −CN and $-CF_3$ groups at the α-position has been reported by intramolecular hydroamination coupled with the addition of external nucleophiles to the resulting enamine intermediate.[140]

Depending on the relative position of the alkyne and the nucleophilic nitrogen, the cyclization can proceed by 5-*exo*-dig and 6-*endo*-dig pathways. In general, the electronic properties of the substituent of the alkyne play a crucial role in the control of regioselectivity. The presence of electron-donating substituents on the alkyne tends to favor 6-*endo*-dig cyclization pathway, whereas electron-withdrawing substituents favor the 5-*exo*-dig cyclization. One example of this regioselectivity reversal was reported in the cyclization of *o*-alkynylbenzyl carbamates **112** (Scheme 37).[141] However, other factors such as steric

Scheme 37. Cyclization of *o*-Alkynylbenzyl Carbamates



interactions have to be taken into account to predict the regiochemical outcome of intramolecular hydroaminations of internal alkynes having these two competing reaction pathways. In the case of terminal alkynes, most of the heterocyclizations afford 5-*exo*-dig products as a consequence of the better stabilization of the positive charge on the internal carbon of the triple bond.

Another example of exclusive formation of the 6-*endo*-dig cyclization product gave isoquinoline derivatives by a gold(I)-mediated hydroamination of (2-alkynyl)benzyl carbamates.[142] Moreover, the hydroamination of alkynyl carbamates bearing

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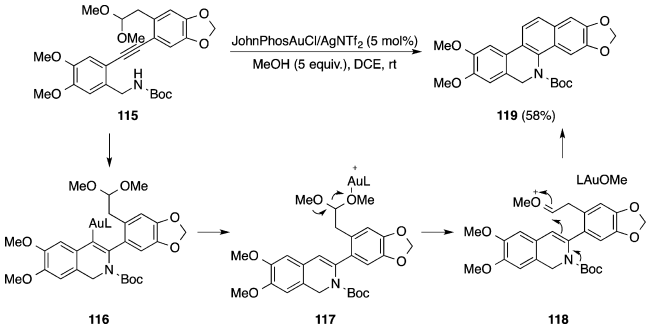
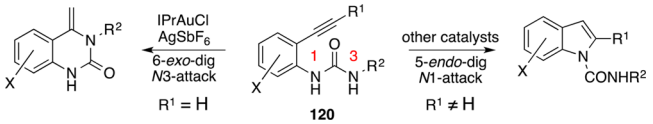
an acetal or enone was applied to the synthesis of tetracyclic heterocycles such as **119** via a gold(I)-catalyzed tandem hydroamination/cyclization (Scheme 38).

Scheme 38. Tandem hydroamination/Cyclization of Alkynyl Carbamates



Alkynylureas can also undergo intramolecular hydroamination processes in the presence of gold(I) catalysts. In general, *o*-ethynylarylureas bearing an internal alkyne lead to *N*1-attack-5-*endo*-dig cyclizations, regardless of the gold(I) complex employed. In the case of 3-substituted 1-(*o*-alkynylphenyl)ureas **120**, indole derivatives are formed (Scheme 39). *O*-

Scheme 39. Regiodivergent Cyclization of *o*-Ethynylarylureas



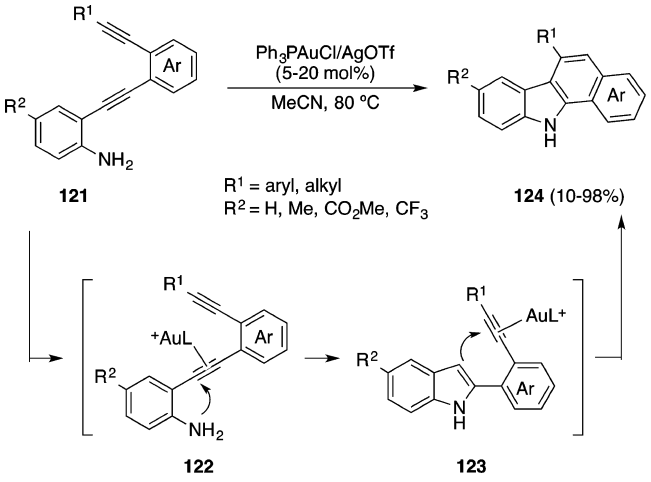
Ethynylphenylureas can selectively undergo *N*3-attack-6-*exo*-dig cyclization when NHC-stabilized gold(I) complexes are used.[143] In contrast, in a similar gold(I)-catalyzed reaction previously reported, 1-(*ortho*-ethynylaryl)ureas bearing a terminal alkyne in aqueous media led exclusively to the corresponding indole under microwave heating through *N*1-5-*endo*-dig cyclization.[144] This method provided indole-1-carboxamides in moderate yields tolerating a variety of functional groups. 1*H*-Imidazol-[1,5-*a*]indol-3(2*H*)-ones were also prepared in the presence of a gold(I) catalyst starting from urea derivatives.[145]

On the other hand, acyclic alkynylureas undergo *O*-attack-5-*exo*-dig cyclization in the presence of gold(I).[146] This feature was exploited for the development of an asymmetric three-component tandem reaction from imines, terminal alkynes, and sulfonylisocyanates in which a single gold(I) species can catalyze both the alkynylation of aryl−aryl imines and the subsequent 5-*exo*-dig cyclization to afford enantioenriched five-membered carbamimidates.

Indenyl-fused and 2,3-disubstituted indoles have been obtained from 2-tosylaminophenylpro-1-yn-3-ols in the presence of gold(I) through a common vinyl gold intermediate.[147] Furthermore, aniline-substituted diethynylarenes **121** give aryl-annulated carbazoles **124** by a hydroamination/hydroarylation cascade in the presence of gold(I) complexes (Scheme 40).[148]

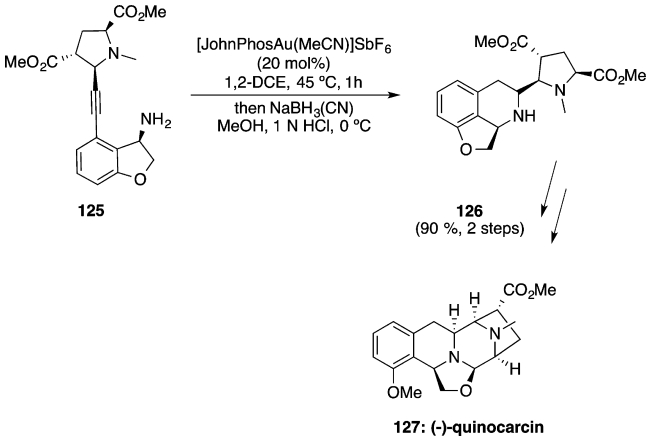
Spiro-*N*,*O*-ketals with 5- and 6-membered rings have been recently synthesized under mild conditions via gold(I)-catalyzed spiroamidoketalization of alkynyl amidoalcohols.[149] The analogous intramolecular hydroamidation of the corresponding alkynylamide leading to a seven-membered ring was not successful.

Scheme 40. Synthesis of Aryl-Annulated Carbazoles by Hydroamination/Hydroarylation



2.2.3. Addition of N-Nucleophiles to Alkynes in Total Synthesis. The potential of gold(I) to construct nitrogen containing heterocycles has been demonstrated in several total synthesis. The intramolecular gold(I)-catalyzed alkyne hydroamination reaction provides an efficient entry to tetrahydroisoquinolines, as highlighted in the total synthesis of (−)-quinocarcin (**127**).[150] In the presence of [JohnPhosAu(MeCN)]SbF_6, **125** undergoes regioselectively a 6-*endo*-dig hydroamination forming the corresponding dihydroquinoline, which after reduction with $NaBH_3(CN)$ formed the desired tetrahydrosioquinoline **126** (Scheme 41). In another remarkable example, the key step in the total synthesis of (−)-rhazinicine (**132**) and (−)-rhazinilam (**133**)[151] was a gold(I)-catalyzed cascade cyclization of **128** initiated by an intramolecular 6-*exo*-dig nucleophilic addition of the nitrogen atom of the amide to the gold-activated alkyne to build the highly substituted indolizinone skeleton **131** (Scheme 42).

Scheme 41. Synthesis of (−)-Quinocarcin



2.3. Addition of Other Heteronucleophiles to Alkynes

The gold(I)-catalyzed addition of heteronucleophiles to alkynes other than oxygen and nitrogen is by far a less developed transformation. Nevertheless, it has been described the attack of the sulfur atom of aryl thioethers to alkynes affording

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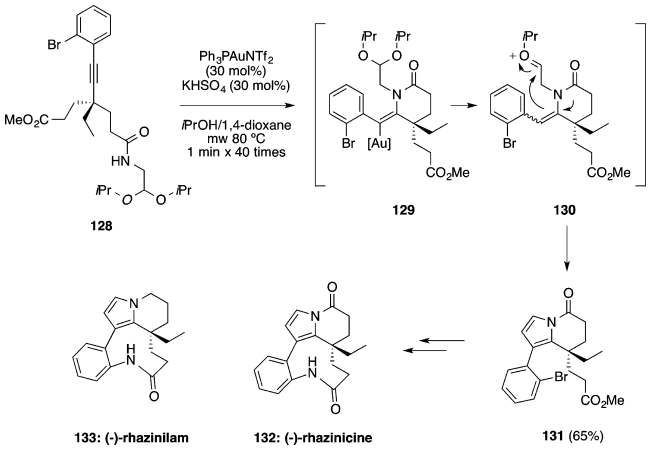
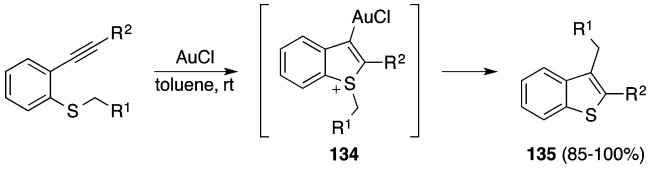
Scheme 42. Synthesis of (−)-Rhazinicine and (−)-Rhazinilam



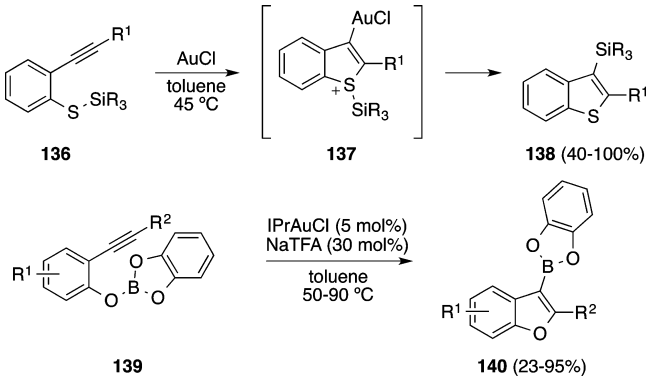
benzothiophenes **135** (Scheme 43).[152] This transformation has also been described in the presence of gold(III).[153] It was

Scheme 43. Synthesis of Benzothiophenes by Cyclization of Aryl Thioethers



shown that aryl thiosilanes **136** can act as both sulfur nucleophiles and silicon electrophiles capturing the vinyl-gold intermediate in the gold(I)-catalyzed intramolecular reaction to afford 3-silylbenzothiophenes **138** (Scheme 44).[154] When

Scheme 44. Synthesis of 3-Silylbenzothiophenes and *O*-Heterocyclic Boronic Acid Derivatives

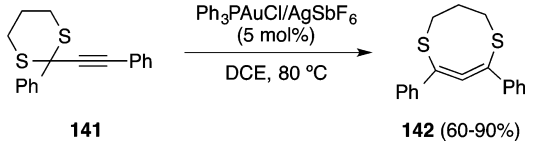


enantiomerically pure *o*-alkynylphenyl-1-aryl ethyl sulfides were used as substrates for this transformation, complete chirality transfer was observed.[155] In an analogous transformation, the gold(I)-catalyzed alkoxyboration of alkynes provides a method for the preparation of *O*-heterocyclic boronic acid derivatives **140**.[156]

Moreover, in the presence of gold(I) complexes, dithiols can also add to alkynes to form cyclic thioacetals,[72] and homopropargylthiols bearing a propargylic alcohol lead to thiophenes after addition of the thiol to the gold-activated alkyne followed by dehydration.[78]

A novel rearrangement was described for propargylic 1,3-dithianes **141** when they were heated in the presence of $Ph_3PAuCl/AgSbF_6$. In this transformation, eight-membered dithiosubstituted cyclic allenes **142** were formed with good yields and remarkable stability (Scheme 45).[157]

Scheme 45. Synthesis of Eight-Membered Cyclic Allenes



N-Heterocyclic carbene gold(I) bifluoride complexes have been shown to be efficient catalysts in the hydrofluorination of symmetrical and unsymmetrical alkynes.[158] This reaction proceeds in good to excellent yields with high stereo- and regioselectivity to afford fluorinated stilbene derivatives and fluorovinyl thioethers.

3. GOLD(I)-CATALYZED REACTIONS OF ALKENES WITH ALKYNES

3.1. Cycloisomerization of Enynes

3.1.1. General Mechanistic Aspects. Cycloisomerizations of 1,*n*-enynes are probably one of the most illustrative carbon−carbon bond forming reactions catalyzed by electrophilic metal complexes. These transformations are very useful in synthetic organic chemistry, since they provide access to complex molecular architectures from readily assembled starting materials through mechanistically complex, fully intramolecular processes.

The first example of electrophilic activation of enynes was reported back in the 1980s using palladium catalysts,[159] which promoted an intramolecular Alder-ene reaction. The Alder-ene cycloisomerization of enynes requires simultaneous coordination of both the alkyne and the alkene to the metal, followed by a two-electron oxidation of the metal, which is favorable for palladium(II) and also platinum(II).[160] However, the oxidation of gold(I) to form a gold(III) metallacycle is highly improbable under ordinary conditions.[161] In addition, $[AuL]^+$ cations are isolobal to H^+, which makes the simultaneous coordination of the alkene and the alkyne highly unlikely. Therefore, in contrast to Pd(II)[159] and Pt(II),[162] gold(I)-catalyzed cycloisomerizations of enynes do not proceed via Alder-ene reaction. Instead, activation of the alkyne by gold(I) forms a (η^2-alkyne)metal complex **143** that reacts as an electrophile with the alkene moiety either by 5-*exo*-dig or 6-*endo*-dig pathways to form the corresponding cyclopropyl gold carbenes **144** or **145** (Scheme 46),[45,163] which, in the absence of internal and external nucleophiles, evolve by different skeletal rearrangements. It is important to emphasize that these species show highly delocalized structures, which are intermediate between cyclopropyl gold(I) carbenes and gold(I)-stabilized cyclopropylmethyl/cyclobutyl/homoallyl carbocations. In general, π-back-donation from gold(I) to the carbene center is poor,[164,165] although it becomes more significant in complexes $[LAuCR_2]^+$ with highly donating N-heterocyclic carbene ligands.[166] Indeed, a few complexes with carbene-like structures showing relatively short Au(I)−C bonds have been structurally characterized.[167]

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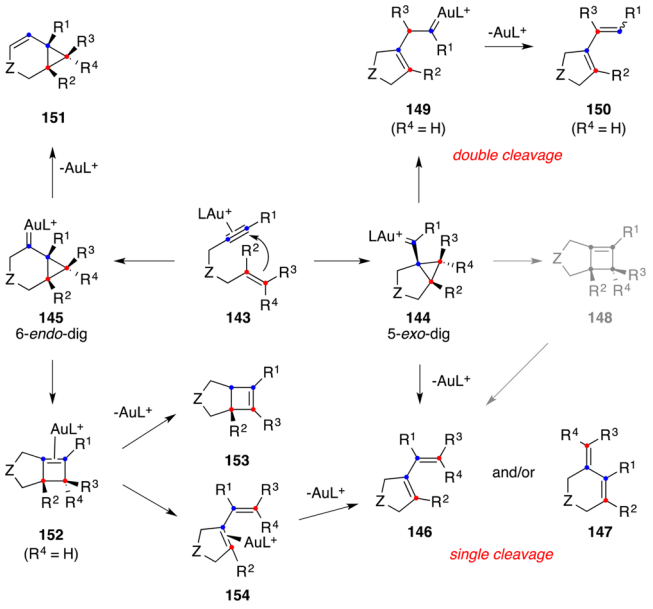
Scheme 46. General Pathways for the Cycloisomerization of 1,6-Enynes



The best-studied gold(I)-catalyzed reactions from a mechanistic point of view are cycloisomerizations of 1,6-enynes, which have often been used as model substrates for the discovery of new reactions and new catalysts activity. According to DFT calculations, the single-cleavage skeletal rearrangement occurs via opening of **144** to form η^2-diene **146**-gold(I) complexes in a single step by a 1,3-migration of the terminal carbon of the alkene to C(1) of the alkyne.[163b] Six-membered ring compounds **147** arise from an alternative *endo*-type single-cleavage rearrangement in which the internal carbon of the double bond migrates toward C(1) of the alkyne.[168] Although formation of 1,3-dienes by single cleavage in metal-catalyzed cycloisomerization of enynes could also be explained by a conrotatory ring opening of cyclobutene intermediates **148**, experimental evidence and theoretical calculations suggest that for enynes with di- and trisubstituted alkenes this transformation takes place by a direct reaction of cyclopropyl gold(I) carbenes bypassing the formation of cyclobutene intermediates.[163b] Thus, the rearrangement of 1,6-enynes with two methyl groups at the alkene terminus proceeds smoothly at temperatures as low as −40 to −60° using cationic catalysts $[(R_3P)Au(MeCN)]SbF_6$, which would imply an abnormally low activation energy for the hypothetical conrotatory opening of a cyclobutene.[163b]

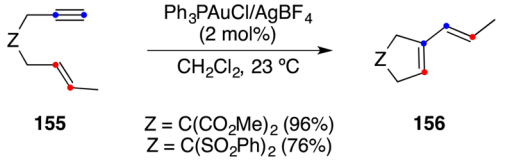
For the double-cleavage rearrangement, intermediates **144** can evolve by a formal insertion of the terminal carbon of the alkene into the alkyne carbons. These new carbenes **149** undergo α-proton elimination to afford dienes **150**. In this process, both the alkene and the alkyne are cleaved in an intramolecular transformation.

On the other hand, intermediates **145** from 6-*endo*-dig cyclization can lead to bicyclo[4.1.0]hept-2-ene derivatives **151** by protodeauration, which are the products of an intramolecular cyclopropanation of the alkene by the alkyne.[161a,169] Alternatively, isomerization of gold(I) carbene **145** by ring expansion of the cyclopropane gives (η^2-cyclobutene)-gold(I) complexes **152**, which can isomerize to give cyclobutenes **153**. Gold(I)-complexes of **152** have been observed by NMR spectroscopy,[170] and a bicyclo[3.2.0]hept-5-ene formed gold(I)-catalyzed by cycloisomerization has been characterized by X-ray diffraction.[163c] The opening of these gold(I) complexes can also form complexes **154**, which are direct precursors of 1,3-dienes **146**, the product of a single cleavage rearrangement. Analogously, 1,5-[171] and 1,7-enynes undergo gold(I)-catalyzed rearrangements through somewhat related pathways.[163b,172]

3.1.2. Cycloisomerization of 1,6- and Higher Enynes.

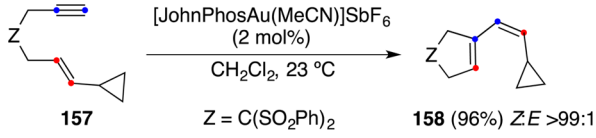
The pathway followed by a particular enyne is highly influenced by its substitution pattern. DFT calculations[173] support that the formation of 5-membered cyclic compounds is generally kinetically favored for terminal alkynes, while the formation of 6-membered rings becomes preferred for internal alkynes together with the ones with heteroatoms at the tether. Gold(I)-catalyzed single-cleavage rearrangements of enynes proceed under very mild conditions to form 1,3-dienes.[43,161a,163a,b,174] Hence, enynes **155** bearing a terminal alkyne and a disubstituted alkene undergo a cycloisomerization reaction in the presence of Ph_3PAuCl and $AgBF_4$ to give exclusive formation of single-cleavage rearrangement 1,3-dienes **156** (Scheme 47).[163a,b] In most of the cases, these rearrangements

Scheme 47. Single-Cleavage Rearrangement of 1,6-Enynes

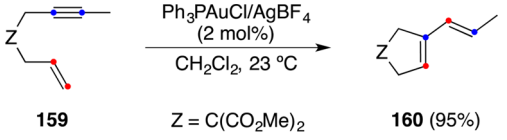


are stereospecific processes in which the configuration of the alkene is retained. However, 1,6-enynes such as **157** bearing strongly electron-donating groups at the terminal alkene carbon lead to *Z*-configured 1,3-dienes **158** regardless the configuration of the starting enynes (Scheme 48).[175] 1,6-Enynes **159** containing alkyl-substituted alkynes undergo double-cleavage rearrangements in the presence of Ph_3PAuCl and $AgBF_4$ (Scheme 49).[161a,163b]

Scheme 48. Single-Cleavage Rearrangement of 1,6-Enynes with Electron-Donating Groups at the Alkene



Scheme 49. Double-Cleavage Rearrangement of 1,6-Enynes with Alkyl-Substituted Alkynes



1,6-Enynes bearing a terminal alkene and/or tethered with heteroatoms such as **161** and **164** provide six-membered rings **162** and **165** by *endo*-type single-cleavage rearrangement as the major products (Scheme 50).[161a] 1,6-Enynes boronated at either the alkyne or the alkene react in a similar vein with Ph_3PAuCl and $AgSbF_6$.[176]

Regarding gold(I)-catalyzed 6-*endo*-dig cyclizations, when 1,6-enynes are tethered by an ether or a sulfonamide group,

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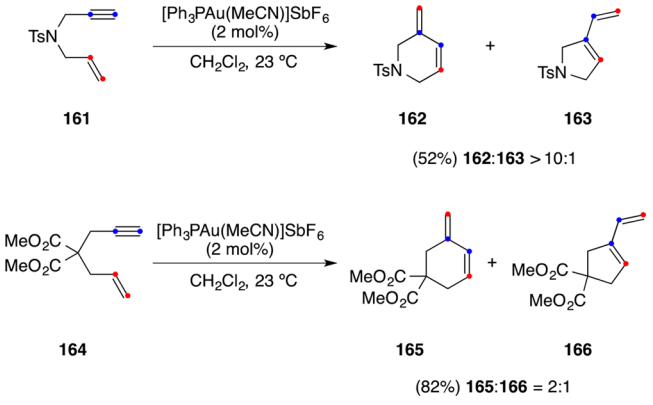
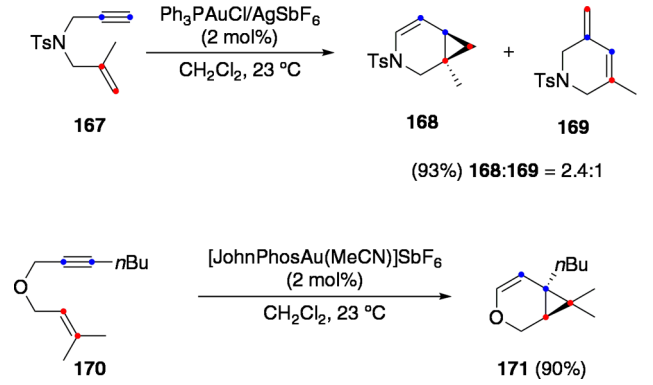
Scheme 50. *Endo*-Type Single-Cleavage Rearrangement



oxa- or aza-bicyclo[4.1.0]hept-4-ene derivatives **168** and **171** are formed as the major products as a result of a formal intramolecular cyclopropanation of the alkene by the alkyne (Scheme 51).[161a,177]

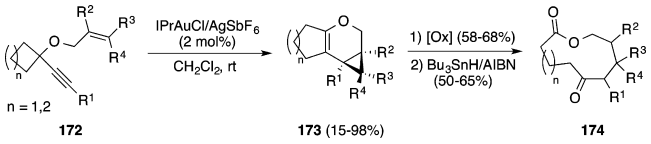
Scheme 51. Synthesis of Oxa- and Aza-Bicyclo[4.1.0]hept-4-enes by Cycloisomerization of 1,6-Enynes



A tandem allylation/cycloisomerization has been developed for the synthesis of 3-oxabicyclo[4.1.0]hept-4-ene derivatives using gold(I) catalysts.[178] The enantioselective synthesis of bicyclo[4.1.0]hept-4-enes has also been described with excellent enantioselectivities using (*R*)-DTBM-MeO-biphep-$(AuCl)_2$/AgOTf[179] (DTBM = 4-MeO-3,5-$(t\text{-Bu})_2C_6H_2$) or more recently gold(I) complexes with chiral phosphoramidite ligands.[52b,180] NHC-capped cyclodextrins coordinated to AuCl also catalyze the formation of 3-azabicyclo[4.1.0]hept-4-enes, although this catalyst provides only modest enantioselectivities.[181]

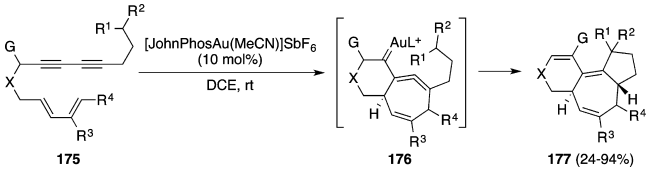
3-Alkoxy-1,6-enynes in the presence of gold(I) form 1,4-cycloheptadienes by a nucleophilic attack of the alkoxy group onto the alkyne presumably followed by a [3,3]-sigmatropic rearrangement.[182] O-Tethered 1,6-enynes **172** that contain a strained ring react with gold(I) by cycloisomerization followed by a 1,2-alkyl carbocationic shift resulting in ring expansion (Scheme 52).[183] A two-step method involving this transformation was developed for the synthesis of ketomacrolactones **174**, which are scaffolds present in several natural products. The tricyclic skeleton of natural products crotobarin and crotogoudin has very recently been obtained via a 1,6-enyne gold(I)-catalyzed cycloisomerization followed by intramolecular trapping of the resulting gold(I) carbene by a carboxylic acid.[184]

Scheme 52. Cycloisomerization Followed by a 1,2-Alkyl Carbocationic Shift



A gold(I)-catalyzed polycyclization of linear dienediynes **175** has been developed for the construction of fused 5,7,6-tricyclic ring systems **177** in one step with high diastereocontrol (Scheme 53).[185] The polycyclization takes place through

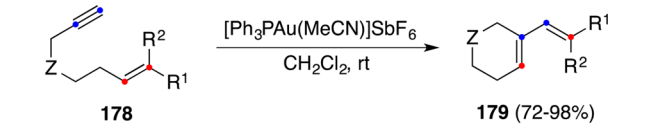
Scheme 53. Polycyclization of Dienediynes To Form 5,7,6-Tricyclic Ring Systems



gold(I)-catalyzed intramolecular cyclopropanation of the diene with the diyne followed by Cope rearrangement to give strained allene intermediate **176**, which subsequently undergoes a C−H activation, followed by 1,2-H and G- (H- or AcO) shifts.

The skeletal rearrangements of 1,7-enynes have been much less studied than those of 1,5- and 1,6-enynes. Gold(I) complexes are in general the best catalysts for the cycloisomerization of these substrates, leading to 1,3-dienes **179** through a single-cleavage process (Scheme 54).[172] Related

Scheme 54. Single-Cleavage Rearrangement of 1,7-Enynes

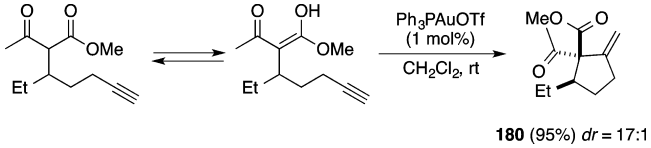


Z = $C(CO_2Me)_2$, $C(SO_2Ph)_2$, NTs
R^1 = H, Me, Ph
R^2 = H, Me

enynes bearing aryl substituents at the alkene give mixtures of products of single-cleavage along with seven-membered ring compounds by an *endo*-type single-cleavage rearrangement.[186]

Gold(I) complexes also catalyze Conia-ene reactions, which can be considered as cyclizations of 1,6-enynes via the corresponding enol tautomers (Scheme 55).[187] Thus, cyclopentane derivatives **180** were obtained in excellent yields and good diastereoselectivities. The reaction has also been efficiently carried out using a gold catalyst bearing a bulky phosphine ligand[188] or a catalyst generated in situ from a cyclic

Scheme 55. Formation of 5-Membered Rings by Conia-Ene Cyclization



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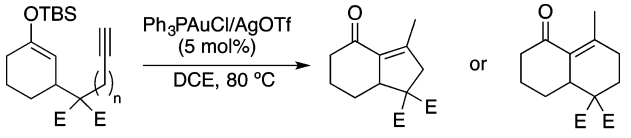
thiourea-AuCl complex and a silver salt.[189] The cyclization of aldehydes with alkynes in the presence of secondary amines proceeds analogously via the corresponding enamines generated in situ.[190]

Silyl enol ether derivatives react with alkynes in a similar way.[191] Substrates featuring a 1,6- or 1,7-relationship between the silyl enol ether and the alkyne such as **181** undergo an *exo*-cyclization to form five- (**182**) or six-membered rings (**183**), respectively (Scheme 56).[192] However, it was found that it is

Scheme 56. *Exo*-Cyclization of Silyl Enol Ethers with Alkynes



181 n=1,2 E = CO_2Me, CN
182 n=1 (87%)
183 n=2 (80%)

possible to tune the *exo*- or *endo*-selectivity by changing the ligand on gold.[193] Thus, gold(I) complexes containing very bulky phosphine ligands favor the 6-*endo*-dig cyclization, whereas complexes with NHC ligands lead to 5-*exo*-dig cyclization products preferentially. Enantioselective versions of this reaction have been developed using chiral gold(I) complexes.[194]

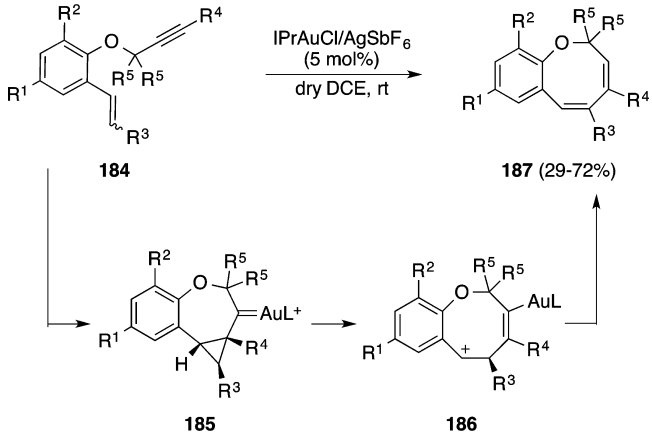
Conia-ene cyclizations have also been performed starting from 1,6-diynes that react first with methanol of another alcohol in the presence of gold(I) to form in situ the corresponding enol ethers, which then undergo the cycloisomerization process to afford the corresponding 5-membered-ring products.[195] An analogous process has been developed by the intramolecular addition of other nucleophiles such as carboxylic acids or nitrogen nucleophiles to 1,6-diynes.[196]

Gold(I)-complexes with a semihollow-shaped triethynylphosphine ligand promote a 7-*exo*-dig cyclization of 1,7-enynes bearing silyl enol ethers.[197] Related 1,8-enynes also give seven-membered-ring products in the presence of this catalyst as a result of a 7-*exo*-dig cyclization.[198] The 8-*endo*-dig pathway to form eight-membered carbocycles could be promoted by using a modified triethynylphosphine-based ligand.

1,7-Enynes **184** also undergo a formal gold(I)-catalyzed 8-*endo*-dig cyclization to give benzoxocines **187** (Scheme 57).[199] It has been proposed that the reaction proceeds through a 7-*endo*-dig cyclization, followed by ring expansion to form the benzylic carbocation **186** that after elimination and protodeauration leads to the final product. As a proof of this mechanism, tricyclic compounds deriving from the protodeauration of **185** have been isolated in some cases as the minor products.

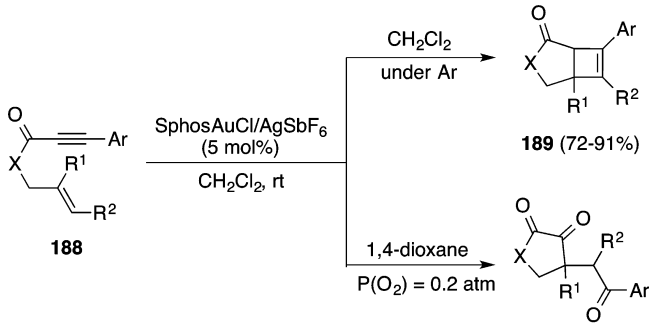
Certain 7-aryl-1,6-enynes undergo gold(I)-catalyzed cycloisomerization reactions leading to bicyclo[3.2.0]hept-6-enes.[163c,169c,170,200] In the case of 7-aryl-1,6-enynes **188** having an amide or an ester at the tether, gold(I) promotes the exclusive formation of cyclobutenes **189** that result from a formal [2 + 2] cycloaddition between the alkene and the alkyne followed by isomerization of the double bond (Scheme 58).[201] It has been recently found that, when these reactions are carried out in the presence of air, tricarbonyl compounds **190** are formed instead.[202]

Scheme 57. Synthesis of Benzoxocines by Cyclization of 1,7-Enynes



184 **187** (29-72%)
185 **186**

Scheme 58. Formal [2 + 2] Intramolecular Cycloaddition Between Alkene and Alkyne

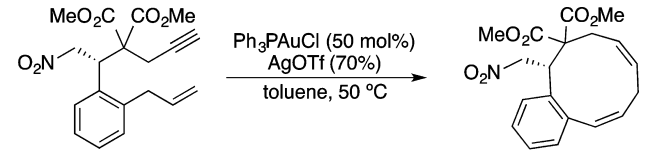


188
189 (72-91%)
190 (41-86%)

1,6-Ene-ynamides undergo highly diastereoselective gold(I)-catalyzed cycloisomerizations forming cyclobutanones or carbonyl compounds containing a 2-azabicyclo[3.1.0]hexane subunit, depending on the substitution pattern.[203]

1,7-[163b] and 1,8-enynes[204] also form cyclobutene derivatives in the presence of gold(I) catalysts. In the case of 1,9-enyne **191**, 10-membered-ring **192** was obtained in the presence of large amounts of gold(I) (Scheme 59).[205]

Scheme 59. Synthesis of a 10-Membered-Ring Compound by Cycloisomerization of a 1,9-Enyne



191 **192** (58%)

The macrocyclization of higher 1,*n*-enynes (*n* = 10−16) affords benzene-fused 9- to 15-membered rings incorporating a cyclobutene ring as a result of a formal [2 + 2] cycloaddition (Scheme 60).[206]

3.1.3. Cycloisomerization of 1,5-Enynes. In general, 1,5-enynes react by endocyclic pathways. This tendency can be rationalized in terms of the more favorable formation of a bicyclo[3.1.0]hexane system in the *endo*-cyclization, which is less strained than the bicyclo[2.1.0]pentane system that would

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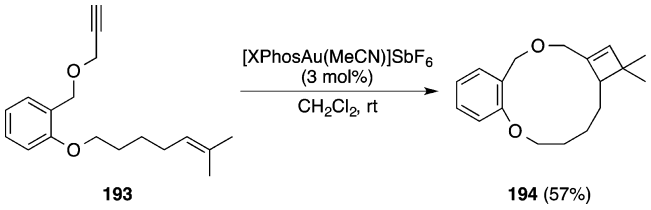
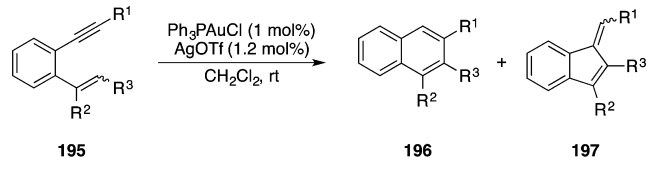
Scheme 60. Macrocyclization of 1,*n*-Enynes



result from the *exo*-cyclization.[244b] The first example of a cyclization of 1,5-enynes was described for the gold(III)-catalyzed synthesis of pyridines from ketones and propargyl amines via in situ generated enamine.[207]

1-Alkynyl-2-alkenylbenzenes **195** in the presence of gold(I) mainly undergo *endo*-dig cyclizations affording substituted naphthalenes **196** (Scheme 61).[208] The formation of products

Scheme 61. Synthesis of Naphthalenes by *endo*-dig Cyclization of 1,5-Enynes



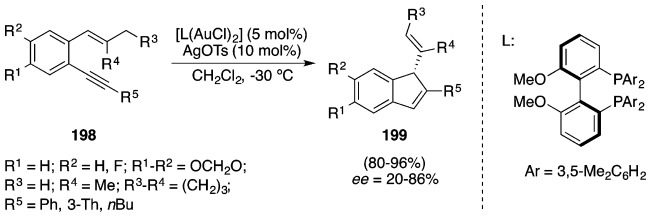
R^1 = Ph, CH_2OR, CH_2NMeTs, *n*-Bu
R^2 = Me, Ph
R^3 = H, Me

197 through *exo*-cyclization becomes more relevant when R^1 = H or I.[208a] In an analogous reaction, (*Z*)-hexa-1,3-dien-5-ynes lead to highly substituted benzene derivatives through a gold(I)-catalyzed *endo*-cyclization followed by a 1,2-alkyl shift.[209]

The selectivity of the cyclization of 2-(alkynyl)-*α*-methylstyrenes could be switched from 6-*endo*-dig to 5-*exo*-dig by adding an alcohol to the reaction media.[210] Moreover, 2-alkynylstyrenes disubstituted at the *β*-position of the styrene moiety selectively afford 1*H*-indene derivatives via 5-*endo*-dig cyclization. An enantioselective cycloisomerization of 2-alkynylstyrenes **198** has been described using a chiral dinuclear gold(I) catalyst with the (*S*)-3,5-xylyl-MeO-biphep ligand.[211] In this particular case, only *exo*-cyclization products were observed, providing access to 1-alkenyl-1*H*-indenes **199** in excellent yields and with good enantioselectivities (Scheme 62).

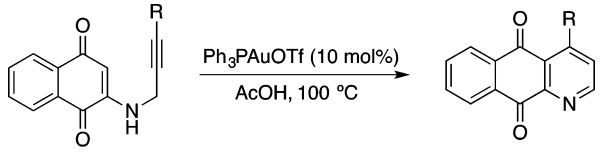
Nitrogen-tethered 1,5-enynes have been used to form *N*-heterocycles. The synthesis of 4-aryl-2-pyridones was reported by gold(I)-catalyzed *endo*-cyclization of 1,5-enynes bearing an amide at the tether.[212] Analogously, azaanthraquinones **201** were assembled from *N*-propargylaminoquinones **200** (Scheme 63).[213] The same strategy was later employed for the synthesis

Scheme 62. Enantioselective Cycloisomerization of 2-Alkynylstyrenes



R^1 = H; R^2 = H, F; R^1-R^2 = OCH_2O;
R^3 = H; R^4 = Me; R^3-R^4 = $(CH_2)_3$;
R^5 = Ph, 3-Th, *n*Bu

Scheme 63. Synthesis of Azaanthraquinones from *N*-Propargylaminoquinones

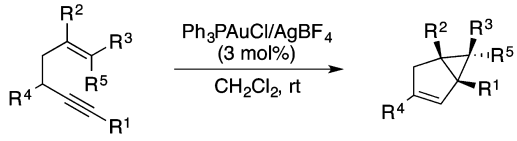


R = aryl, alkyl, H

of pentacyclic pyrido[4,3,2-*mn*]acridin-8-ones.[214] Alkyne-tethered dihydropyrimidones undergo an *endo*-cyclization in the presence of AuCl yielding pyridopyrimidones.[215]

Alkyl- and aryl-substituted 1,5-enynes undergo gold(I)-catalyzed *endo*-dig cycloisomerization to afford bicyclo[3.1.0]-hexene derivatives **202** in a stereospecific manner (Scheme 64).[216] Under these reaction conditions, substrates bearing a

Scheme 64. Synthesis of Bicyclo[3.1.0]hexenes by *endo*-dig Cycloisomerization of 1,5-Enynes

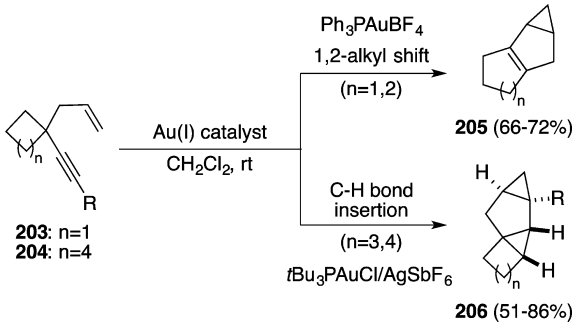


R^1 = H, Ph; R^2 = H, alkyl; R^3 = H, alkyl
R^4 = aryl, H; R^5 = H, alkyl

202
(61-99%)
dr=10:1 to >99:1

quaternary center at the propargylic position evolve differently. Thus, cycloalkyl-substituted enyne **203** undergoes a ring expansion by 1,2-alkyl shift to give tricyclic compound **205**, whereas **204** bearing a larger cycloalkyl substituent goes through C−H bond insertion to afford tetracyclic compound **206** (Scheme 65).[217]

Scheme 65. *endo*-dig Cycloisomerization of 1,5-Enynes Followed by Ring Expansion and C−H Insertion



In the presence of gold(I), 1,5-enynes **207** bearing a cyclopropylidene moiety undergo an enantioselective ring-expanding cycloisomerization providing bicycle[4.2.0]octanes **210** (Scheme 66).[218]

The gold(I)-catalyzed cycloisomerization of 3-hydroxylated-1,5-enynes may follow divergent reaction pathways depending on their substitution pattern (Scheme 67).[219] The reaction of nonprotected 3-hydroxy-1,5-enynes with gold(I) gives bicyclo[3.1.0]hexan-3-ones **211**, whereas those benzyl-protected give the analogous product **212** together with the product of skeletal rearrangement **213**. Boc-protected 3-

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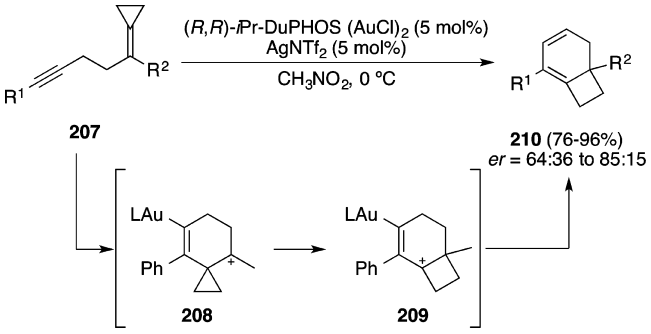
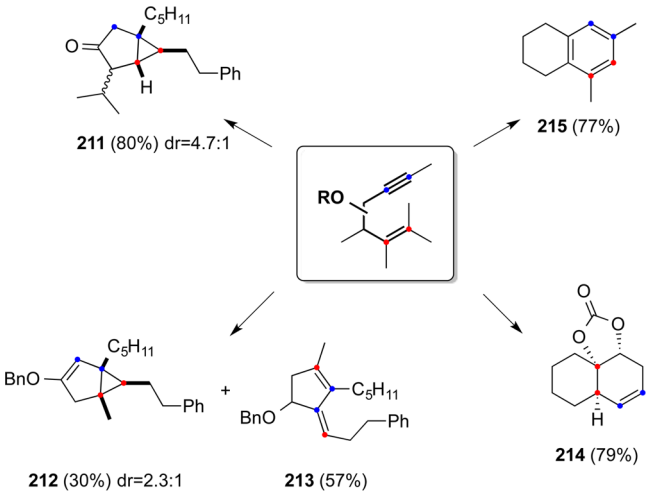
Scheme 66. Enantioselective Ring-Expanding Cycloisomerization of Cyclopropylidene 1,5-Enynes



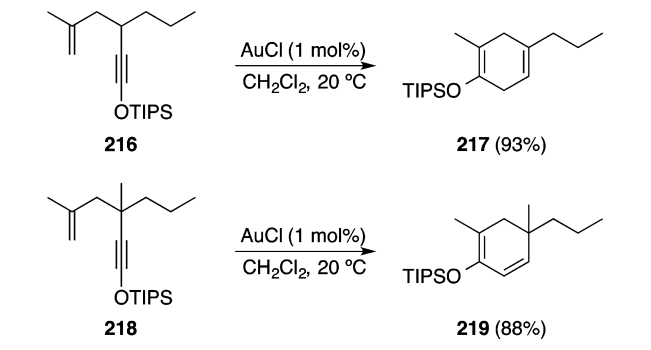
Scheme 67. General Pathways for the Cycloisomerization of 3-Hydroxylated-1,5-Enynes



hydroxy-1,5-enynes form cyclohex-4-ene-1,2-diol derivatives **214**.[220] Gold(I) complexes also catalyze formation of benzene derivatives **215** from 3-hydroxy-1,5-enynes,[221] which can also be generated in situ by the addition of allylsilanes to alkynals.[222]

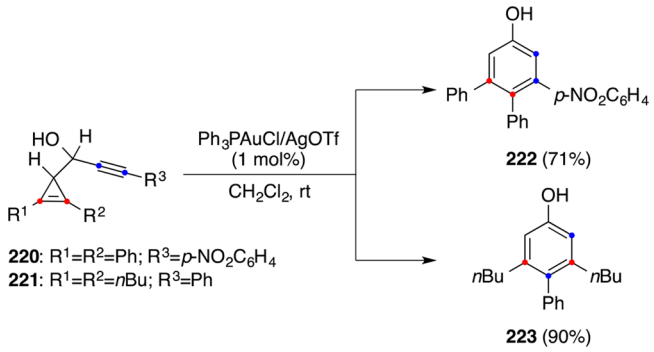
The gold(I)-catalyzed cyclization of 3-silyloxy-1,5-enynes proceeds with concomitant semipinacol rearrangement leading to carbonyl compounds.[223] 6-Silyloxy-1,5-enynes such as **216** and **218** react with AuCl by an *endo*-pathway to give 1,4- (**217**) or 1,3-cyclohexadienes (**219**) depending on the substitution at the propargylic position (Scheme 68).[171] Analogously, chiral 1,5-enynes were used to construct tricyclic structures bearing a spirofused 1,3-cyclohexadiene ring.[224]

Scheme 68. *endo*-dig Cycloisomerizations of 6-Silyloxy-1,5-enynes



Propargyl cyclopropenes react with gold(I) to form substituted benzene derivatives (Scheme 69).[225] In this

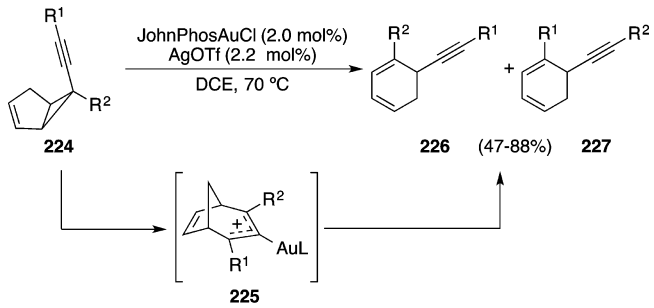
Scheme 69. Synthesis of Substituted Benzenes by Cycloisomerization of Propargyl Cyclopropenes



transformation, the substituents in the cyclopropane ring have a crucial effect on the reaction pathway and therefore on the regiochemical outcome. Thus, cyclopropenes bearing larger substituents such as aryl groups (**220**) lead to rearranged products in which neither the alkene nor the alkyne is cleaved (**222**). In contrast, those cyclopropenes bearing smaller hydrogen or alkyl groups (**221**) favor a double cleavage pathway. According to DFT calculations, the mechanism of this reaction involves an unprecedented two consecutive 1,3-cationic alkylidene migrations of nonclassical carbocation intermediates.[226]

Alkynylcyclopropanes **224** undergo a gold(I)-catalyzed rearrangement to afford alkynyl cyclohexadienes **226** and **227** (Scheme 70).[227] The mechanism of this rearrangement has

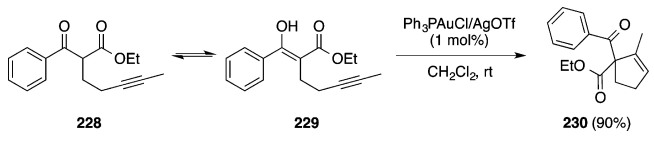
Scheme 70. Synthesis of Alkynyl Cyclohexadienes by Rearrangement of Alkynylcyclopropanes



been recently revised experimental and theoretically, giving clear evidence for the involvement of η^1-allylic gold(I) cationic intermediate **225**.[228]

Enols such as **229** deriving from β-keto esters can also participate in gold(I)-catalyzed 1,5-enyne cycloisomerizations, namely Conia-ene carbocyclizations (Scheme 71).[229] Silyl enol ether derivatives react similarly with alkynes.[191] As for 1,6-enynes, enantioselective versions of this reaction have been

Scheme 71. Conia-Ene Carbocyclizations of β-Keto Esters



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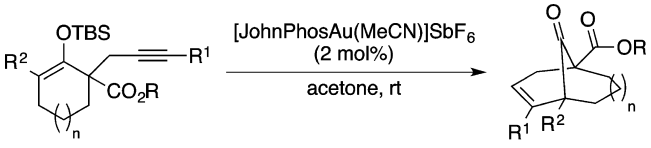
described.[194] Bicyclo[*m.n.*1]alkenone frameworks **232** with a bridged ketone were synthesized through a Conia-type reaction of 1,5-enynes **231** (Scheme 72).[230]

Scheme 72. Synthesis of Bicyclo[*m.n.*1]alkenone Frameworks by Conia-type Cyclization

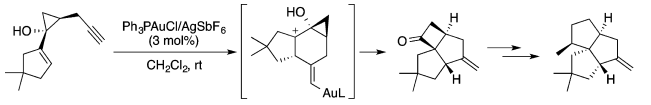


231 **232** (78-98%)

3.1.4. Cycloisomerization of 1,*n*-Enynes in Total Synthesis. Cycloisomerizations of 1,*n*-enynes, generally coupled with tandem reactions, allow for an increase of molecular complexity in one step under very mild conditions. Therefore, these transformations have been widely used in the field of total synthesis.[63]

The total synthesis of sesquiterpene ventricosene **236** was accomplished through a key gold(I)-catalyzed cyclization of 1,6-enyne **233**, which proceeds with concomitant ring expansion via **234** to form cyclobutanone **235** (Scheme 73).[231]

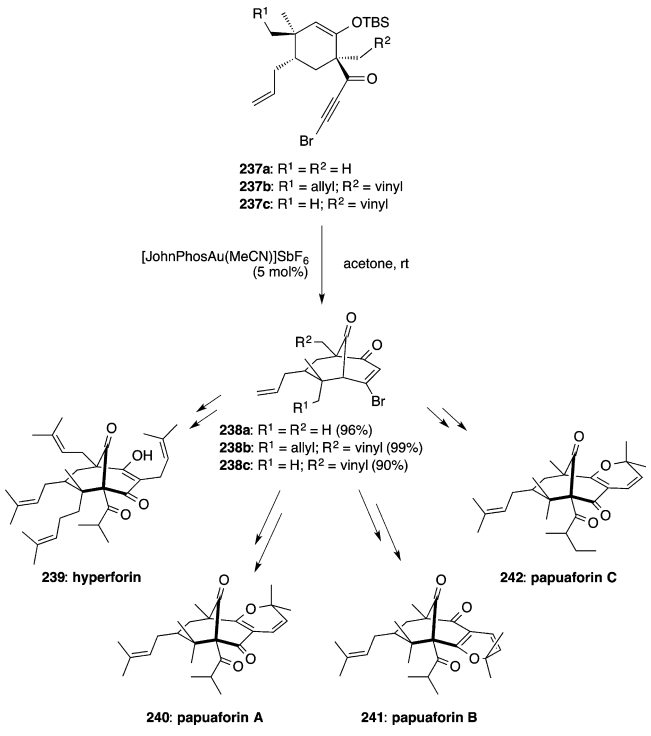
Scheme 73. Synthesis of Ventricosene



233 **234** **235** (87%) **236: ventricosene**

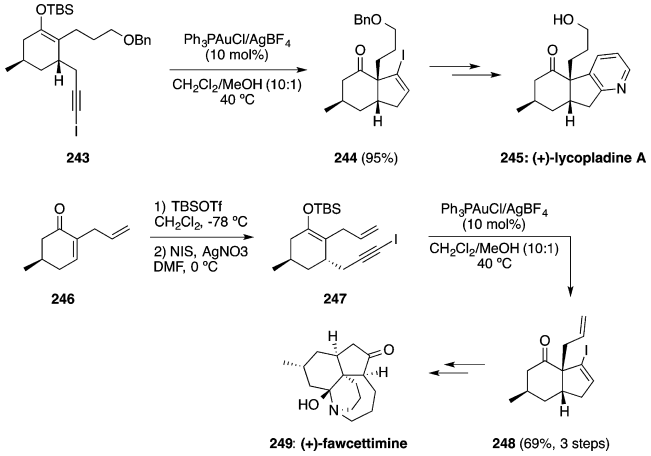
The total syntheses of hyperforin (**239**) and papuaforins A-C (**240**-**242**) have been achieved by using a gold(I)-catalyzed Conia-type reaction from 1,5-enynes **237** (Scheme 74).[232]

Scheme 74. Syntheses of Hyperforin and Papuaforins A−C



Similar cyclizations were used in the syntheses of the alkaloids (+)-lycopladine A (**245**)[233] and (+)-fawcettimine (**249**) (Scheme 75),[234] as well as in the total synthesis of platencin.[235]

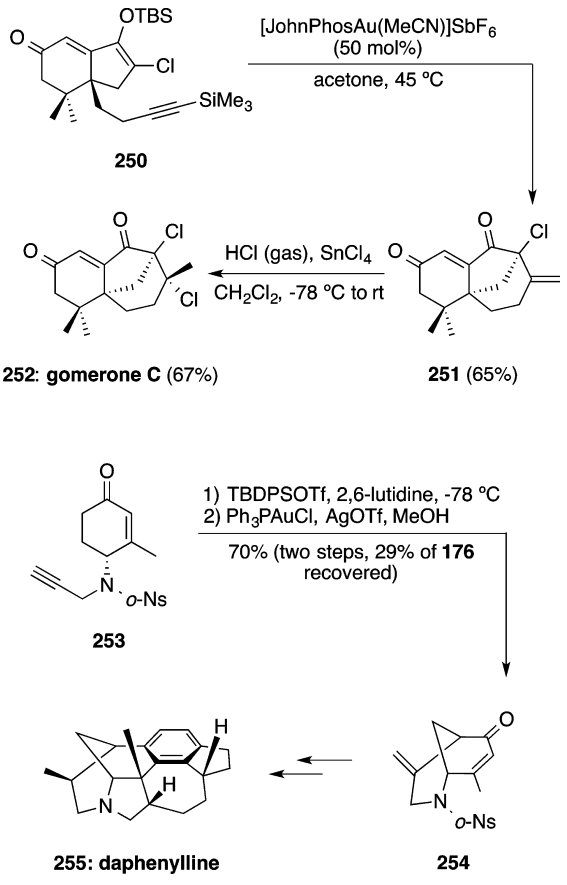
Scheme 75. Synthesis of Alkaloids (+)-Lycopladine and Fawcettimine



This reaction has also been applied to the cyclization of 1,7-enynes in the total synthesis of the marine sesquiterpene (±)-gomerone C **252**[236] and also in the total synthesis of *Daphniphyllum* alkaloid daphenylline **255** (Scheme 76).[237]

The cyclization of 3-silyloxy-1,5-enyne **256** followed by semipinacol rearrangement was used to construct the

Scheme 76. Syntheses of the Sesquiterpene (±)-Gomerone C and Alkaloid Daphenylline



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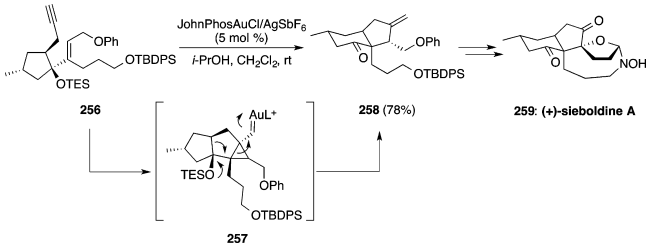
hexahydro-1*H*-inden-4(2*H*)-one core of (+)-sieboldine A (**259**), which contains an unprecedented *N*-hydroxyazacyclononane ring (Scheme 77).[238]

Scheme 77. Synthesis of (+)-Sieboldine A

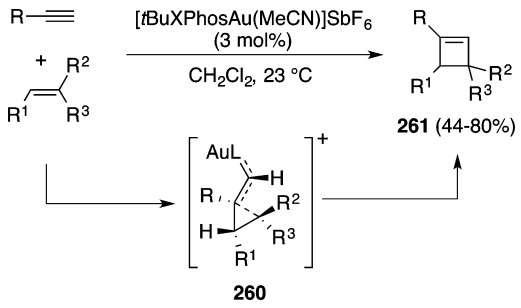


3.2. Intermolecular Reactions of Alkenes with Alkynes

Gold(I)-catalyzed intermolecular reactions between alkenes and alkynes constitute a real challenge since all the conceivable products are by themselves potential substrates for gold(I), which in consequence may compete with the initial alkene leading to oligomerization products.[59]

The first reaction developed in this area was a formal [2 + 2] cycloaddition between terminal alkynes and substituted alkenes that led to the formation of cyclobutenes **261** (Scheme 78).[239]

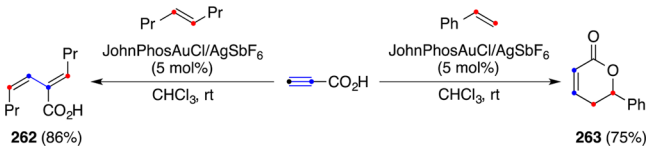
Scheme 78. [2 + 2] Cycloaddition of Alkynes with Alkenes



The regiochemical outcome of this process is in agreement with a reaction pathway through highly distorted cyclopropyl gold(I) carbenes **260** that finally undergo a ring expansion.

Interestingly, the intermolecular reaction of propiolic acid with alkenes does not form cyclobutenes. Instead, this reaction leads to 1,3-dienes (**262**) or lactones (**263**) depending on the nature of the alkenes (Scheme 79).[240] Asymmetrically

Scheme 79. Formation of Lactones or Dienes by Reaction of Propiolic Acid with Alkenes

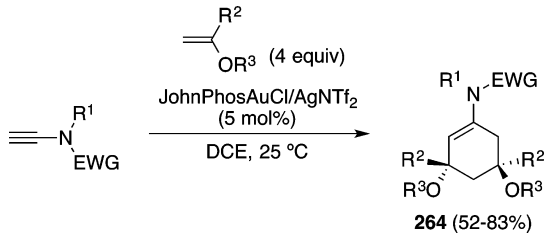


substituted alkenes lead to the formation of lactones by attack of the carboxylic acid to the most substituted carbon of the alkene. On the other hand, alkenes with two electronically identical or very similar substituents afford stereospecifically 1,3-dienes by 1,3-migration, following a pathway that is similar to the one occurring in the single-cleavage rearrangement of 1,6-enynes.

Propiolic esters[241] and sulfonylacetylenes[242] react in a different manner with allylic ethers to provide 1,4-dienes by nucleophilic addition of the ether oxygen onto the alkynes, followed by [3,3]-sigmatropic rearrangement. The presence of α-substituents in the allyl ether promotes a competing [1,3]-sigmatropic rearrangement concomitant with the [3,3]-rearrangement.

Terminal ynamides react intermolecularly with enol ethers in the presence of gold(I) to give enamines **264** as a result of a [2 + 2 + 2] cycloaddition (Scheme 80).[243] Arylynamides react

Scheme 80. [2 + 2 + 2] Cycloaddition between Ynamides and Alkenes



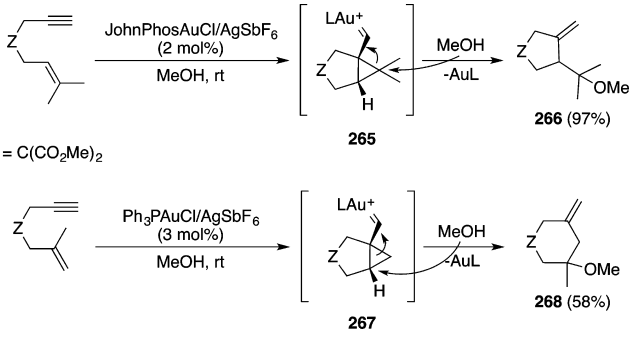
intermolecularly with alkenes forming a cyclopropyl gold(I) carbene, which is opened by a Friedel−Crafts attack of the aryl group forming 1,2-dihydronaphthalenes.[243]

3.3. Addition of Heteronucleophiles to Enynes

Gold(I) complexes catalyze the addition of amines, alcohols, or water to enynes leading to products of amino-, alkoxy-, or hydroxycyclization under much milder conditions than other metal catalysts.[161a,163a,211,244] The overall process is an *anti*-addition of an electrophile (alkyne-gold(I) complex) and a heteronucleophile to a double bond in a stereospecific process.

3.3.1. Intermolecular Addition of Heteronuclephiles to Enynes. In the presence of an external heteronucleophile, the cyclopropyl gold(I) carbenes generated as intermediates in the cycloisomerization of 1,*n*-enynes are opened by attack to the cyclopropane ring. These additions take place following the Markovnikov regiochemistry, giving rise to products of *exo*-trig (**266**) or *endo*-trig cyclization (**268**) (Scheme 81).[161a,163a]

Scheme 81. Alkoxycyclization of 1,6-Enynes



Similar results have been obtained using NHC-gold(I) or gold(III)-complexes as catalysts.[174a,244a,245] The enantioselective hydroxy- and alkoxycyclization of 1,6-enynes catalyzed by a chiral biphosphine-gold complex[246] or by NHC-gold(I) complexes[247] proceeds with moderate to good enantioselectivities. 1,5-Enynes also react with alcohols or water in the presence of gold(I) catalysts to give the corresponding adducts.[244c] The hydroxy- and alkoxycyclization of 1,7-enynes

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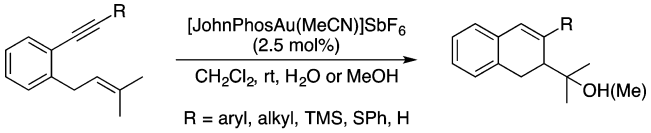
takes place similarly.[172] It is remarkable that the hydroxycyclization process is usually much faster than the direct addition of water to terminal alkynes to form the corresponding methyl ketones.

7-Substituted-1,6-enynes **269** bearing a fused aromatic ring at the tether undergo predominantly gold(I)-catalyzed hydroxycyclization by a 6-*endo*-dig pathway instead of the 5-*exo*-dig pathway usually observed for 1,6-enynes with trisubstituted alkenes to afford bicyclic compounds **270** (Scheme 82).[248]

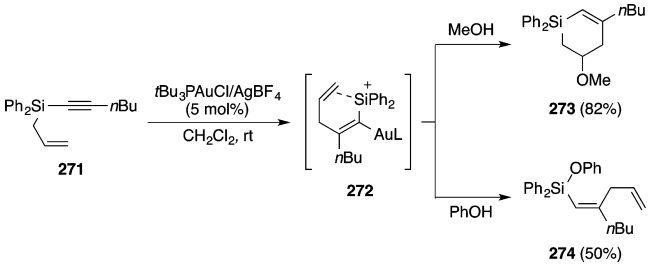
Scheme 82. Alkoxy or Hydroxycyclization of 1,6-Enynes by 6-*endo*-dig Pathway



269 **270** (55-82%)

The reaction of allylsilylalkynes such as **271** catalyzed by gold(I) in the presence of external alcohols gives vinylsilanes.[249] Depending on the choice of the nucleophile, either cyclic or acyclic vinylsilanes were obtained (Scheme 83). DFT

Scheme 83. Synthesis of Vinylsilanes from Allylsilylalkynes

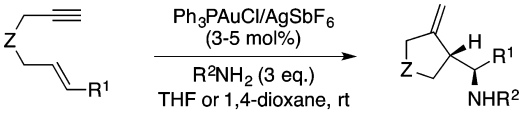


271 **272** **273** (82%) **274** (50%)

calculations suggest that this transformation takes place through silicenium cations **272** formed by a pericyclic reaction of the allylsilylalkynes coordinated to gold(I).[250] The attack of methanol to these intermediates gives cyclic vinylsilanes **273**, whereas the attack of a weaker nucleophile such as phenol takes place at the silicon leading to acyclic vinylsilanes **274**.

Propargyl vinyl ethers in the presence of gold(I) and water or alcohols undergo a Prins-type reaction affording dihydropyrans.[251] Furthermore, *N*-heteronucleophiles such as carbamates and anilines also react intermolecularly with 1,6-enynes to form amino-functionalized carbo- or heterocycles **275** (Scheme 84).[252]

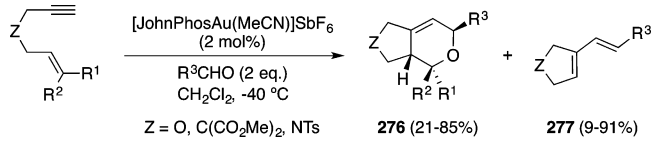
Scheme 84. Aminocyclization of 1,6-Enynes



Z = O, $C(CO_2Me)_2$, $C(SO_2Ph)_2$ **275** (46-93%)

1,6-Enynes also react with aldehydes to give products of formal [2 + 2 + 2] cycloaddition **276** together with a metathesis-type reaction of the enyne with the aldehyde that forms 1,3-dienes **277** (Scheme 85).[253] 1,7-Enynes also undergo a [2 + 2 + 2] cycloaddition with carbonyl compounds in the presence of gold(I) giving rise to analogous heterocyclic products.[254]

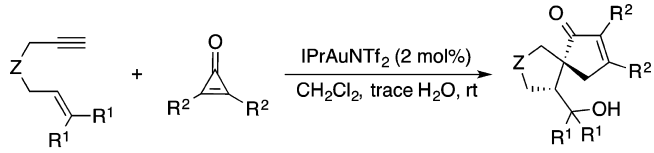
Scheme 85. [2 + 2 + 2] Cycloaddition of 1,6-Enynes with Carbonyl Compounds and Formation of Metathesis-Type Products



Z = O, $C(CO_2Me)_2$, NTs **276** (21-85%) **277** (9-91%)

Cyclopropenones react with enynes in a ring-expanding spiroannulation incorporating a molecule of water to afford spirocyclic cyclopentenones **278** by a mechanistically related process (Scheme 86).[255]

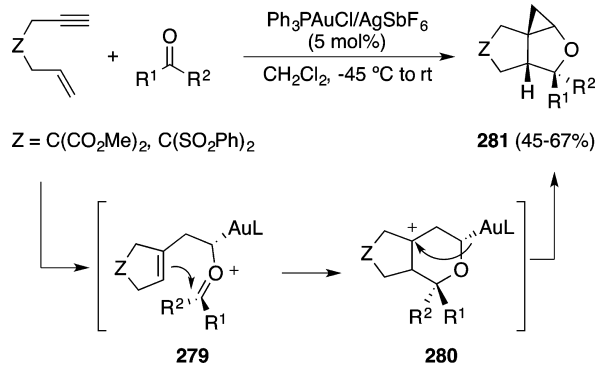
Scheme 86. Reaction of 1,6-Enynes with Cyclopropenones



Z = O, $C(CO_2Me)_2$, NTs **278** (11-97%)

1,6-Enynes bearing a monosubstituted alkene react with aldehydes and ketones in a different way, presumably via trapping of the rearranged carbene that results from the enyne to give intermediate **279**, followed by Prins reaction, to afford tricyclic compounds **281** (Scheme 87).[256] In a similar vein, 1,5-enynes also undergo intermolecular reactions with carbonyl compounds.[253]

Scheme 87. Reaction of 1,6-Enynes with Carbonyl Compounds via Rearrangement



Z = $C(CO_2Me)_2$, $C(SO_2Ph)_2$ **281** (45-67%)

279 **280**

3.3.2. Intramolecular Addition of Heteronuclephiles to Enynes.

The alkoxycyclizations can also take place intramolecularly starting from hydroxyl-1,6-enynes,[161a,244d] and the resulting adducts may further evolve increasing molecular complexity. As an example, the synthesis of 4-oxa-6-azatricyclo[3.3.0.$0^{2,8}$]octanes **285** was reported by a complex gold-catalyzed cycloisomerization of alkynyl hydroxyallyl tosylamides **282** in the presence of Ph_3PAuCl and $AgSbF_6$ (Scheme 88).[257]

The intramolecular amino- or alkoxycyclization of amino- or hydroxyl-1,5-enynes **286** yields spirofused heterobicyclic compounds **287** (Scheme 89).[258] 1,5-Enynes bearing carba-

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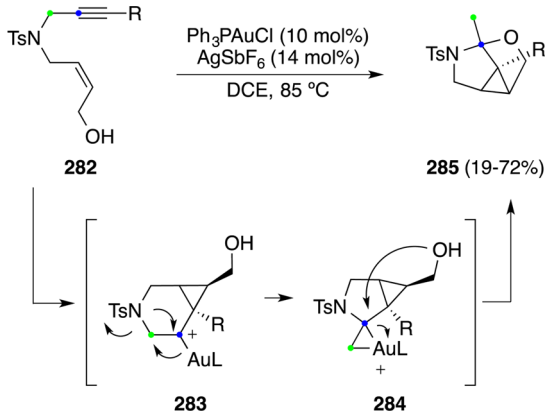
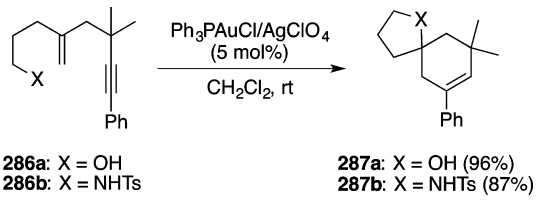
Scheme 88. Synthesis of 4-Oxa-6-azatricyclo[3.3.0.0^{2,8}]octanes from Alkynyl Hydroxyallyl Tosylamides

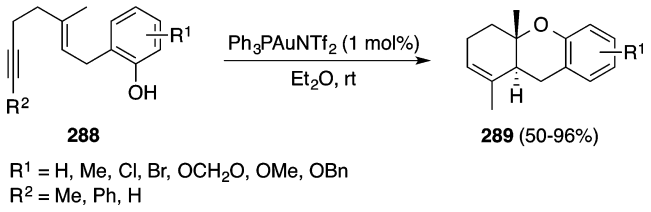


Scheme 89. Intramolecular Amino- or Alkoxycyclization of 1,5-Enynes



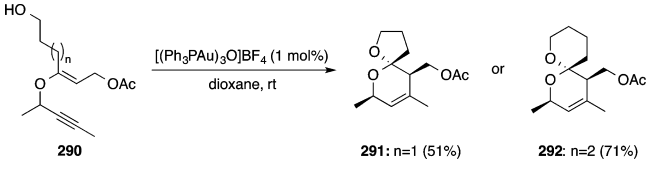
mates[259] or carbonates[260] also undergo gold(I)-catalyzed tandem cyclizations in a mechanistically related transformation. The analogous reaction of 1,6-enynes bearing a carboxylic acid leads stereospecifically to lactones.[244d,261] Phenols can also add to 1,5-enynes in substrates of type **288** with a gold(I) catalyst to give tricycles **289** stereospecifically (Scheme 90).[262] The

Scheme 90. Intramolecular Addition of Phenols to 1,5-Enynes



enantioselective version of the addition of phenols to 1,6-enynes has also been described.[261] Similarly, the intramolecular reaction of hydroxypropargyl vinyl ethers **290** catalyzed by a trinuclear gold(I)-oxo complex leads to 5,6- and 6,6-spiroketals **291** and **292** with good stereocontrol (Scheme 91).[251] This transformation constrasts with the reactivity previously shown

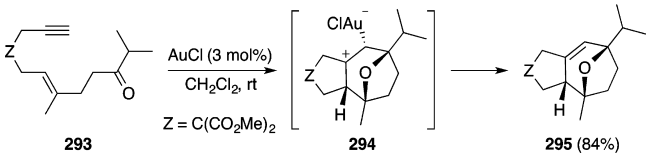
Scheme 91. Synthesis of 5,6- and 6,6-Spiroketals from Hydroxypropargyl Vinyl Ethers



for propargyl vinyl ethers, which in the presence of the same trinuclear gold(I)-oxo complex underwent a Saucy-Marbet rearrangement giving rise to allenes.[263]

Oxo-1,6-enynes such as **293** also react in the presence of gold(I) complexes to give oxatricyclic compounds **295** by a tandem sequence in which two C−C bonds are formed together with one C−O bond (Scheme 92).[264] This formal [2

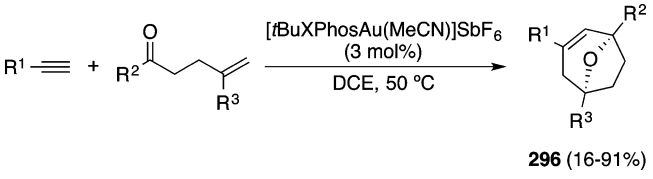
Scheme 92. Cyclization of Oxo-1,6-enynes by [2 + 2 + 2] Alkyne/Alkene/Carbonyl Cycloaddition



+ 2 + 2] alkyne/alkene/carbonyl cycloaddition proceeds by attack of the carbonyl to the cyclopropyl gold carbene intermediate followed by Prins cyclization to give **294**, which forms the final oxatricyclic derivative after deauration. Oxo-1,5-enynes also undergo an intramolecular reaction to give tricyclic derivatives.[265]

Terminal alkynes and oxoalkenes undergo an analogous [2 + 2 + 2] cycloaddition reaction by intermolecular cyclization of the alkyne and the alkene followed by intramolecular attack of the carbonyl group to form 8-oxabicyclo[3.2.1]oct-3-enes **296** (Scheme 93).[266]

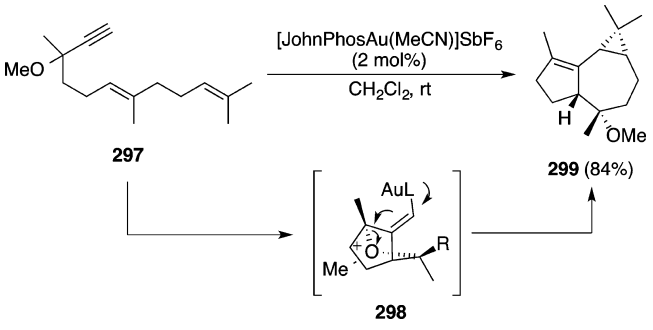
Scheme 93. Intermolecular [2 + 2 + 2] Cycloaddition of Terminal Alkynes with Oxoalkenes



Dienynes with a methoxy or other OR group at the propargylic position such as **297** react with gold(I) by an intramolecular 1,5-OR migration to form tricyclic compounds **299** (Scheme 94).[267] Substrates substituted with other OR groups at the propargyl position also undergo this 1,5-migration.

3.3.3. Addition of Heteronucleophiles to Enynes in Total Synthesis. Gold(I)-catalyzed intramolecular [2 + 2 + 2] alkyne/alkene/carbonyl cycloadditions[264] have been exploited for the synthesis of several oxygen-bridged sesquiterpenoids.

Scheme 94. Cyclization of 1,6-Enynes via 1,5-OR Migration



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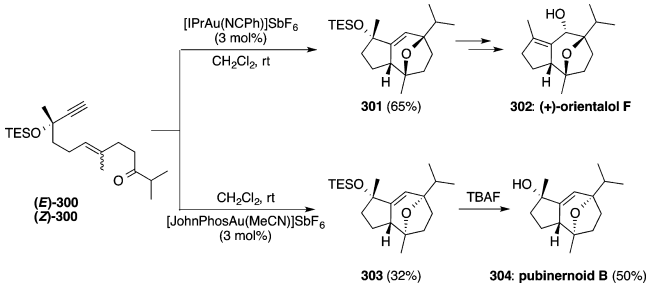
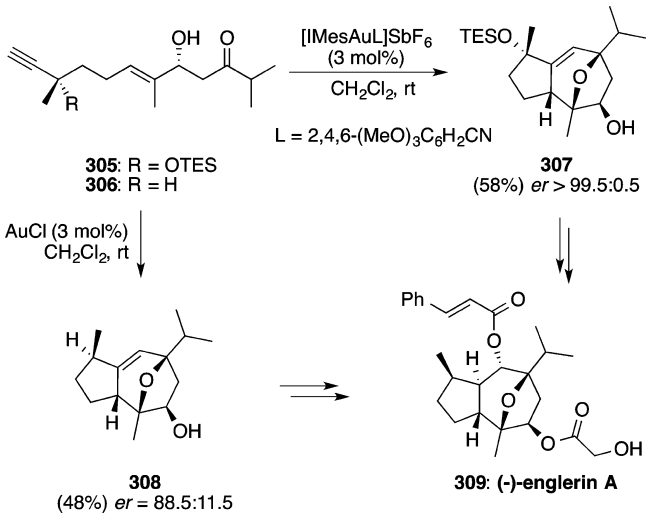
Ketoenyne (*E*)-**300** in the presence of gold(I) reacted intramolecularly to give oxatricyclic compound **301**, which was converted into (+)-orientalol F (**302**) in three additional steps (Scheme 95).[268] The key step of the synthesis of pubinernoid B (**304**) proceeded analogously starting from (*Z*)-**300**.

Scheme 95. Syntheses of (+)-Orientalol F and Pubinernoid B



The stereospecific [2 + 2 + 2] alkyne/alkene/carbonyl cycloaddition was also applied to the synthesis of antitumor sesquiterpene (−)-englerin A (**309**) in two independent syntheses (Scheme 96).[269] It is remarkable that in both approaches an unprotected aldol subunit could be used as the substrate for the gold(I)-catalyzed reaction.

Scheme 96. Synthesis of (−)-Englerin A

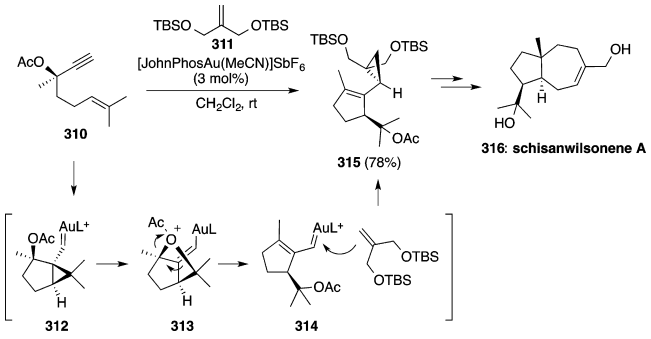


The formation of alkenylsilanes from allylsilylalkynes in the presence of an external alcohol[249] was used in the total synthesis of (−)-amphidinolide V.[270]

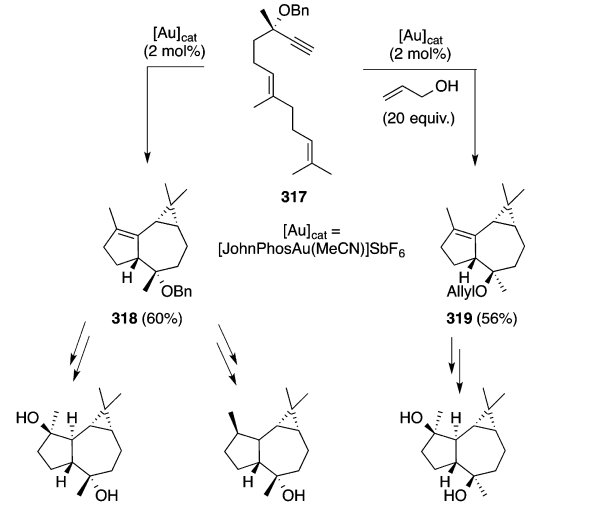
Gold(I)-catalyzed reaction of 1,6-enyne **310** by cyclization followed by 1,5-acetoxy migration from **312** forms an α,β-unsaturated carbene **314**,[267] which reacts intermolecularly with alkene **311** to afford **315** with only 5% loss of enantiomeric excess (Scheme 97).[271] This transformation was reported as part of the total synthesis of antiviral sesquiterpene (+)-schisanwilsonene A (**316**). It is interesting that the cyclization/1,5-acetoxy migration is faster than the alternative 1,2-acyloxy migration, which would lead to racemization.

The total syntheses of three sesquiterpenes, namely (−)-4β,7α-aromadendranediol (**320**), (−)-epiglobulol (**321**), and (−)-4α,7α-aromadendranediol (**322**), have been accomplished by a stereodivergent gold(I)-catalyzed reaction from a single precursor **317** (Scheme 98).[272] The reaction can take

Scheme 97. Synthesis of (+)-Schisanwilsonene A



Scheme 98. Synthesis of Aromadendrane Sesquiterpenes

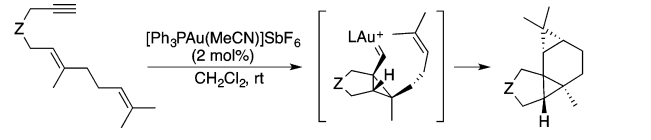


place intramolecularly by 1,5-migration of OBn giving **318** or intermolecularly in the presence of allyl alcohol as an external nucleophile, obtaining allyl ether **319**.

3.4. Addition of Carbonucleophiles to Enynes

3.4.1. Cyclopropanation of Enynes. The gold(I)-catalyzed cyclization of dienynes **323** leads stereoselectively to tetracyclic compounds **325** by cyclopropanation of intermediate gold(I) carbenes **324** (Scheme 99).[163a,169a]

Scheme 99. Intramolecular Cyclopropanation of 1,6-Enynes



These intramolecular cyclopropanations afford very complex ring systems when the starting dienynes are cyclic substrates.[273] Intramolecular cyclopropanations of 1,5-enynes take place similarly through an *endo*-carbene.[274]

Intermediate cyclopropyl gold carbenes resulting from the cyclization of 1,6-enynes can also be trapped intermolecularly

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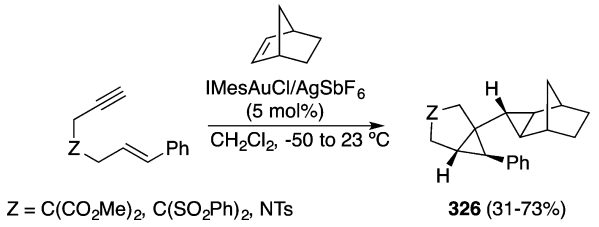
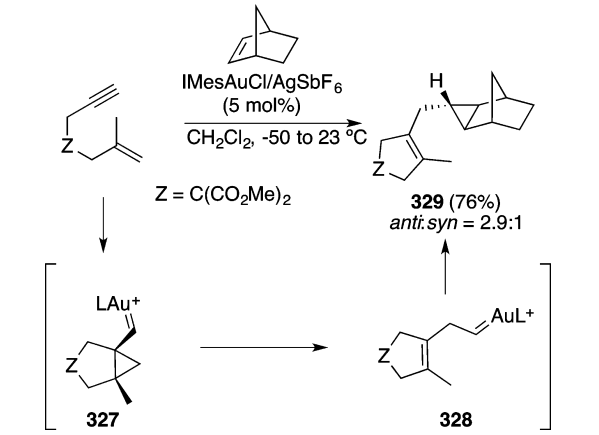
by cyclic or acyclic alkenes to form adducts **326** stereoselectively (Scheme 100).[275]

Scheme 100. Intermolecular Cyclopropanation of 1,6-Enynes



1,6-Enynes bearing a terminal alkene react by a different mechanism through rearrangement of the initially formed cyclopropyl gold(I) carbene **327** to form **328**, which reacts with an external alkene to afford **329** (Scheme 101).

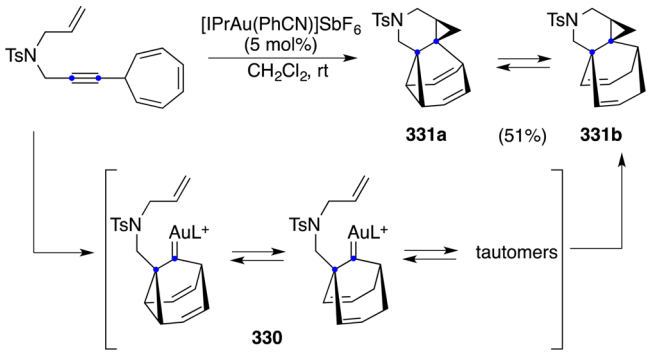
Scheme 101. Intermolecular Cyclopropanation of 1,6-Enynes via Rearrangement



In the presence of gold(I), 7-alkynylcyclohepta-1,3,5-trienes generate highly fluxional barbaralyl gold(I) cations **330**, which can be intercepted intramolecularly with alkenes to form **331a–b** (Scheme 102).[276] These two species are in equilibrium by Cope rearrangement both in the solid state and in solution.

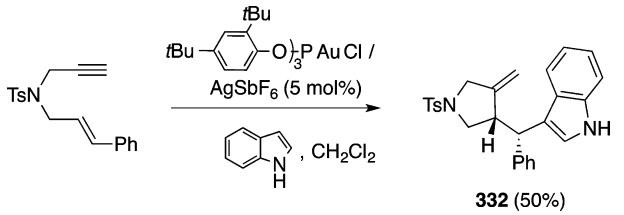
3.4.2. Friedel-Craft Arylation of Enynes. Electron-rich aromatic and heteroaromatic compounds such as indoles can undergo a stereospecific intermolecular addition to 1,6-enynes

Scheme 102. Intramolecular Cyclopropanation from 7-Alkynylcyclohepta-1,3,5-trienes



in the presence of gold(I) catalysts (Scheme 103).[252,265,277] This transformation proceeds by opening of the intermediate

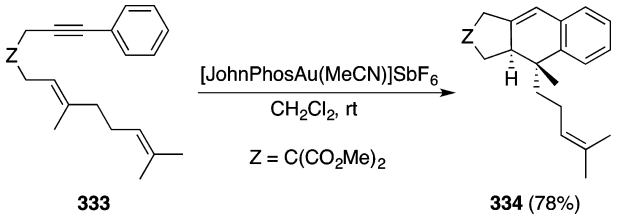
Scheme 103. Intermolecular Addtion of Indole to 1,6-Enynes



cyclopropyl gold(I) carbene in a process mechanistically related to the hydroxy- and alkoxycyclization of 1,6-enynes. The enantioselective version of this reaction has also been reported.[278] The enantioselective intramolecular addition leads to enantiomerically enriched complex ring systems in a single step.[261]

1,6-Enynes bearing an aryl substituent at the alkyne such as **333** react stereospecifically with gold(I) in a formal [4 + 2] cycloaddition reaction under very mild reaction conditions (Scheme 104).[169b,244a,279] This reaction proceeds via initial *exo*-

Scheme 104. Intramolecular [4 + 2] Cycloaddition of Arylalkynes with Alkenes



cyclization followed by opening of the cyclopropyl gold(I) carbene by a Friedel–Crafts-type reaction to provide **334**. Related 1,6-enynes with 1-thienyl and 1-indolyl groups at the alkyne also undergo formal [4 + 2] cycloadditions catalyzed by gold(I) complexes bearing bulky biphenyl phosphine ligands.[280] In the presence of chiral phosphine gold(I) complexes[281] or gold(I) phosphite complexes[282] these [4 + 2] cycloadditions can be performed enantioselectively. Related cyclizations of alkynes with allenes[283] and diynes[284] have also been described. The *endo*-cyclization also takes place in certain cases, being the major pathway in the platinum(II)- or gold(I)-catalyzed cycloaddition of related arylalkynes bearing enesulfonamides or enamines.[285]

1,5-Enynes **335** with an aryl substituent at the alkyne react with gold(I) to form dihydrobenzofluorenes **339** in a formal [3 + 3] cycloaddition by a 1,2-H shift in intermediate **337**, followed by a Friedel–Crafts alkylation (Scheme 105).[286]

3.4.3. Addition of Other C-Nucleophiles. 1,3-Dicarbonyl compounds can add to 1,6-enynes as *C*-nucleophiles through their enol tautomers, although some of them such as cyclohexane-1,3-dione and 2-oxocyclohexanecarboxaldehyde behave as *O*-nucleophiles.[277a] In the presence of 1,3-diketones, *N*-tethered 1,6-enynes bearing an internal alkyne afford tetrahydropyridines **340** as a result of an *endo*-cyclization (Scheme 106). In contrast, analogous 1,6-enynes bearing a terminal alkyne undergo an *exo*-cyclization and in the presence of the nucleophile giving adducts **341** and/or **342** depending

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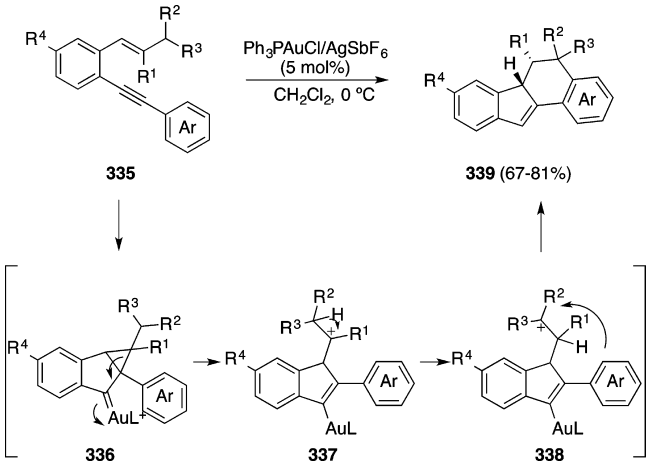
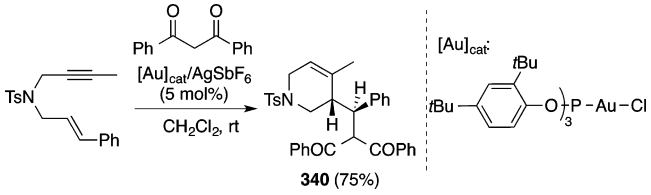
Scheme 105. Synthesis of Dihydrobenzofluorenes by Cycloisomerization and Friedel-Crafts Alkylation

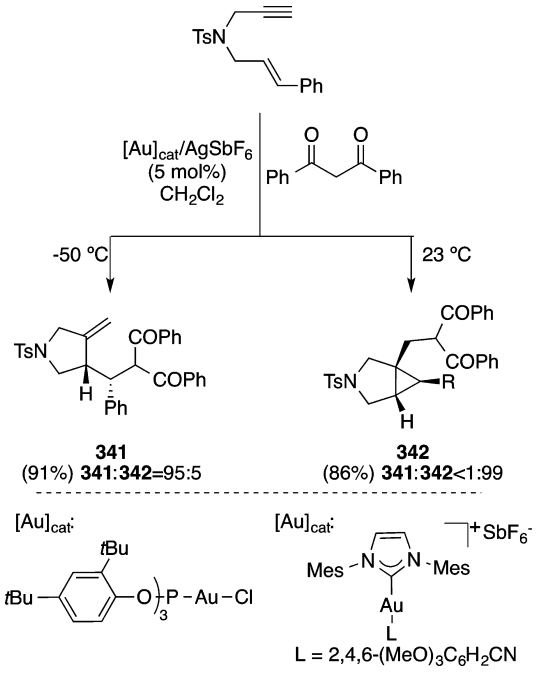


Scheme 106. Addition of 1,3-Diketones to 1,6-Enynes by endo-Cyclization



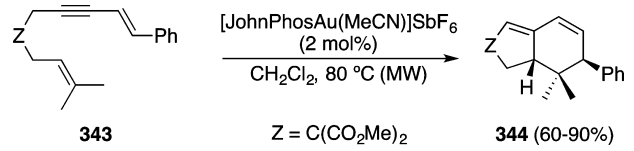
on the nature of the gold(I) catalyst (Scheme 107). Products **341** are favored with the most electrophilic gold(I) catalysts, whereas less electrophilic complexes with more donating ligands favor the formation of **342**. Gold(I) complexes also catalyze the addition of allylic silanes to 1,6-enynes.[277a]

Scheme 107. Ligand-Controlled Addtion of 1,3-Diketones to 1,6-Enynes



1,3-Dien-8-ynes undergo a formal intramolecular gold(I)-catalyzed [4 + 2] cycloaddition reaction.[287] Dienynes **343** cyclize similarly in the presence of gold(I) and heating by microwave irradiation to form stereoselectively hydrindanes **344** (Scheme 108).[169b,244a,288]

Scheme 108. Intramolecular [4 + 2] Cycloaddition of 1,3-Dien-8-ynes

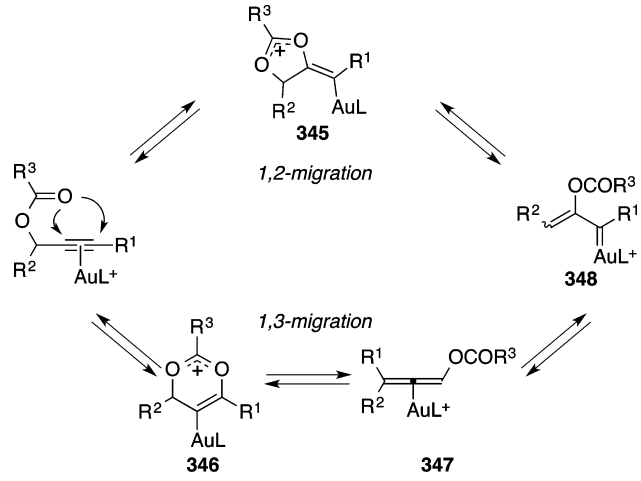


4. GOLD(I)-CATALYZED REACTIONS OF PROPARGYLIC CARBOXYLATES

4.1. Reactions of Propargylic Carboxylates

Propargylic carboxylates react with gold(I) complexes undergoing 1,2- or 1,3-acyloxy migrations through 5-*exo*-dig or 6-*endo*-dig cyclizations to form α-acyloxy-α,β-unsaturated carbenes **345** or allene-gold complexes **347**, which are in equilibrium (Scheme 109).[46,289] Similar transformations have been described for propargyl acetals,[290] as well as by using other metal catalysts.[291]

Scheme 109. General Pathways in the Isomerization of Propargylic Carboxylates



Species **348** have been trapped in intermolecular reactions with alkenes,[52a,292] ynamides,[293] carbon nucleophiles,[294] imines,[295] and sulfides.[296] Although the reaction of intermediates **348** with alkenes usually affords vinylcyclopropanes, in the case of propargyl acetals such as **349**, products of [3 + 2] cycloaddition **352** are obtained (Scheme 110).[290b,c] In this transformation, gold(I) carbene **351** is formed by 1,2-OMe shift. Intermediate **351** undergoes an intermolecular cyclopropanation with vinyl acetate to form **350**, which reacts with **351** in a Michael-type addition, followed by a Prins cyclization to form **352**.

The gold(I)-catalyzed synthesis of benzopyrans **356** has been described from propargyl carboxylates **353** by intramolecular trapping of gold(I) carbenes **354** by an ether group followed by rearrangement of the resulting allylic oxonium ylides **355**

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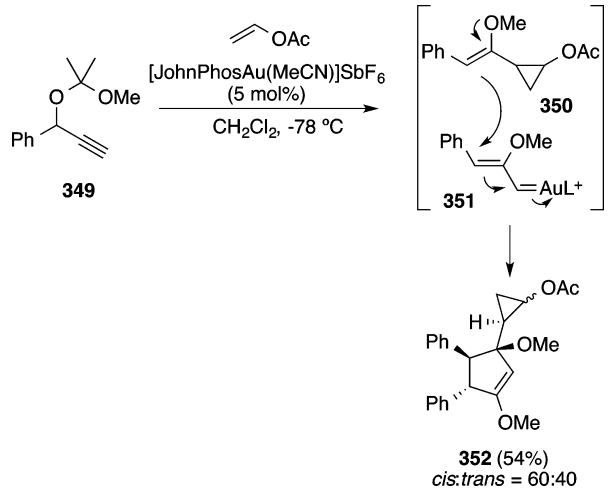
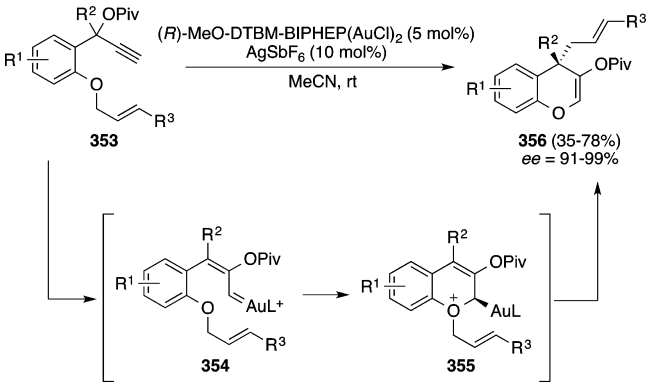
Scheme 110. [3 + 2] Cycloaddition of Propargyl Acetals with Alkenes



(Scheme 111).[297] The synthesis of substituted naphthalenes has been reported from propargylic esters by a gold(I)-

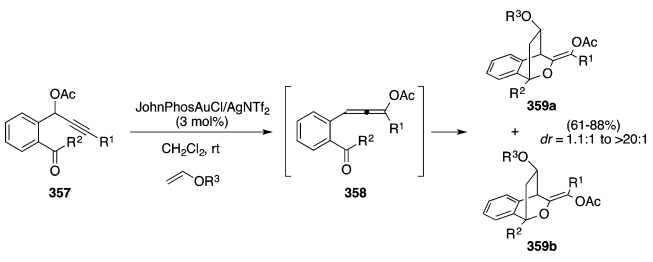
Scheme 111. Synthesis of Benzopyrans from Propargyl Carboxylates



catalyzed sequence involving a 1,3-acyloxy migration followed by a 1,2-alkyl or aryl migration and subsequent hydroarylation.[298]

Gold allenic intermediates **347** derived from 1,3-acyloxy migration (see Scheme 109) can be trapped by other functional groups to give of a range of different compounds.[299] In situ generated ketone-allene substrates **358** were used as substrates for a gold(I)-mediated tandem oxacyclization/[4 + 2] cycloaddition cascade to afford highly substituted oxacycles **359** with excellent stereocontrol (Scheme 112).[300] Nucleophilic allenes

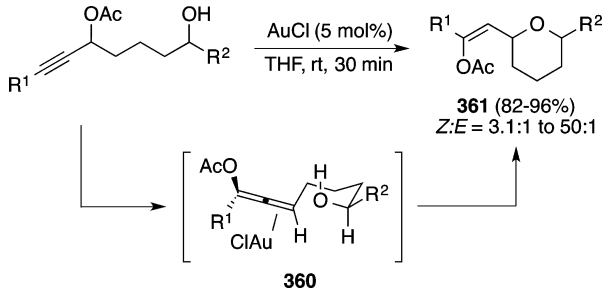
Scheme 112. Tandem Oxacyclization/[4 + 2]-Cycloaddition from in Situ Generated Ketoallene Substrates



have also been generated in situ by a gold(I)-catalyzed rearrangement of propargylic esters and then used for intermolecular $C(sp^3)-C(sp^2)$ bond formation reactions.[301]

In the presence of AuCl, ω-hydroxy propargylic acetates undergo a 1,3-acetoxy migration to form allenyl acetate **360**, which is trapped intramolecularly to form tetrahydropyranes **361** containing an exocyclic enolacetate (Scheme 113).[302] This

Scheme 113. Synthesis of ω-Hydroxy Propargylic Acetates via 1,3-Acetoxy Migration



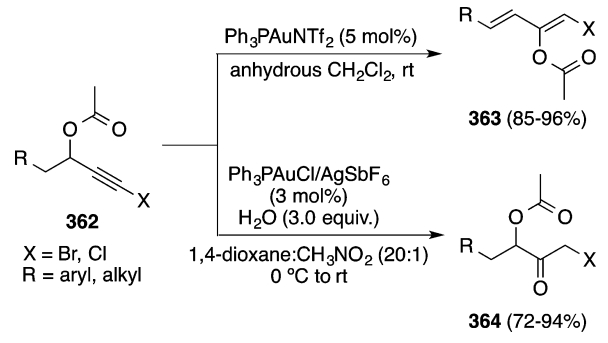
transformation proceeds with remarkable high *Z*-selectivity in the final alkenes and the retention of the configuration of diastereomerically pure substrates. 1,6-Diyne esters also react with gold(I) forming allenyl gold(I) intermediates, which can react with the pendant alkyne giving a variety of cyclized products.[303]

The gold(I)-catalyzed acyloxy migration has been applied to the synthesis of 1-acetoxy-1*H*-indenes.[304] The mechanism of this transformation involves a 1,3-migration to form the allenyl intermediate that undergoes an intramolecular hydroarylation, followed by another final 1,3-acyloxy migration to generate a more stable substituted indene. The same reaction in the presence of water leads to α,β-unsaturated ketones.

Terminal halo-substituted propargyl carboxylates **362** react with $Ph_3PAuNTf_2$ in anhydrous CH_2Cl_2 to form 1-halo-2-carboxy-1,3-dienes **363** by 1,2-migration of the ester (Scheme 114).[289f] It has been recently reported that the same substrates in the presence of $Ph_3PAuCl/AgSbF_6$ and H_2O undergo a regioselective hydration to give α-acyloxy α'-halo ketones **364**.[305]

Gold(I) catalyzes the formation of alkenyl enol esters or carbonates from trimethylsilylmethyl-substituted propargyl esters/carbonates with excellent *E*-selectivity.[306] Alkynyloxiranes **365** bearing a propargylic ester rearrange to form divinyl ketones **366** (Scheme 115).[307] The mechanism of this transformation seems to proceed via anchimeric assistance of

Scheme 114. Migration or Hydration of Halo-Substituted Propargyl Carboxylates



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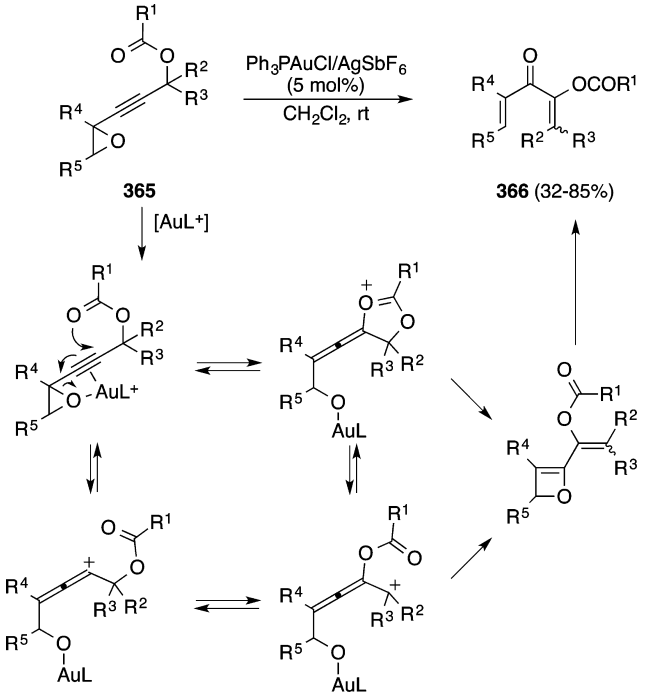
Scheme 115. Synthesis of Divinyl Ketones from Alkynyloxiranes Bearing a Propargylic Carboxylate



the propargyl ester moiety, although DFT calculations predict a complex mechanism involving several equilibriums.

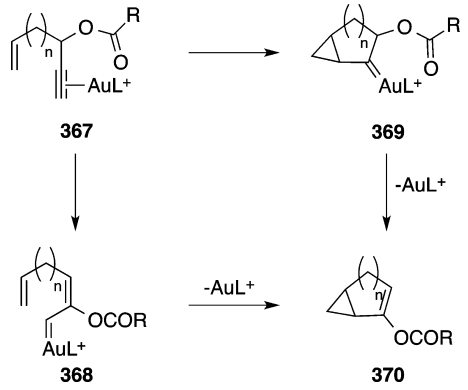
α-Iodoenones can be accessed by 1,3-migration of propargylic acetates in the presence of gold(I) and NIS.[308] α-Trifluoromethyl enones have been synthesized by a tandem 1,3-acyloxy migration/trifluoromethylation from 1-arylpropargyl esters with excellent stereoselectivity.[309] Propargylic 3-indoleacetates undergo a gold(I)-catalyzed tandem [3,3]-rearrangement/[2 + 2] cycloaddition to afford 2,3-indoline-fused cyclobutanes.[310] Other structures have also been accessed by reactions of propargyl carboxylates with gold(I), such as dihydrofurans,[311] aromatic ketones,[312] allenes,[313] or polyconjugated δ-diketones.[314]

4.2. Cycloisomerizations of Enynes Bearing Propargylic Carboxylates

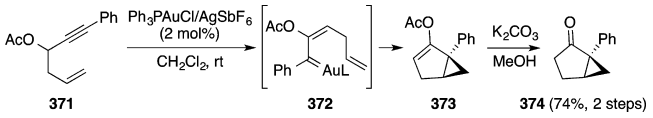
Enynes bearing propargylic α-acyloxy substituents can react with gold(I) by two parallel pathways, depending on the order of attack of the acyloxy group or the alkene onto the alkyne in complexes **367** (Scheme 116). This transformation is known as the Ohloff-Rautenstrauch (or simply Rautenstrauch) rearrangement, following the original discovery of the reaction catalyzed by zinc(II) or palladium(II).[315] If the alkene reacts first, then the cyclopropyl gold carbene **369** can suffer an intramolecular attack of the acyloxy group on the carbene, followed by elimination of AuL^+ to give **370**. On the other hand, the acyloxy group can first undergo a 1,2-migration to form carbene **368**, which leads to **370** by intramolecular cyclopropanation. Annulations of enynes **367** may also proceed via the acyloxy allene formed by 1,3-migration.[316]

The gold(I)-catalyzed cyclization of 1,5-enynes containing propargylic carboxylates affords bicyclic structures **373**, which form the corresponding ketones **374** after methanolysis (Scheme 117).[317] The cyclization of 1,7- and 1,8-enynes with propargylic acetates affords analogous products by a tandem 1,2-acyloxy migration/cyclopropanation.[318] This process allows

Scheme 116. Parallel Reaction Pathways of Enynes Bearing Propargylic Carboxylates



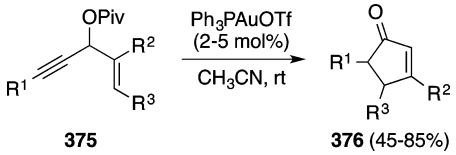
Scheme 117. Synthesis of Bicyclo[3.1.0]hexan-2-ones by Cyclization of 1,5-Enynes with Propargylic Carboxylates



the enantioselective synthesis of 7- and 8-membered-ring compounds by using chiral gold(I) catalysts.[319]

In a mechanistically related transformation, 1,4-enynes **375** bearing propargylic carboxylates in the presence of gold(I) form cyclopentenones **376** via 1,2-acyloxy migration (Scheme 118).[320] In this Rautenstrauch rearrangement, enantiomerically

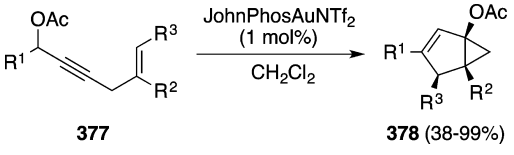
Scheme 118. Synthesis of Cyclopentenones from 1,4-Enynes with Propargylic Carboxylates



enriched propargyl carboxylates give enantioenriched cyclopentenones. The cycloisomerization of 1,6-enynes with acyloxymethyl substituents at the alkyne also proceeds by 1,2-migration to produce bicyclic derivatives with an exocyclic enol acetate group.[321]

1,3-Enynes bearing propargylic carboxylates also lead to cyclopentenones in the presence of gold(I).[322] This transformation takes place through 1,3-migration of the carboxylate followed by a Nazarov-type cyclization.[289d] Propargylic acetates **377** also react via 1,3-acyloxy migration to afford bicyclo[3.1.0]-hexenes **378** (Scheme 119), which can be converted into cyclopentenones ($R^2 \neq H$) or cyclohexenones ($R^2 = H$) by methanolysis.[316,323]

Scheme 119. Synthesis of Cyclopentenes from 1,3-Enynes with Propargylic Carboxylates



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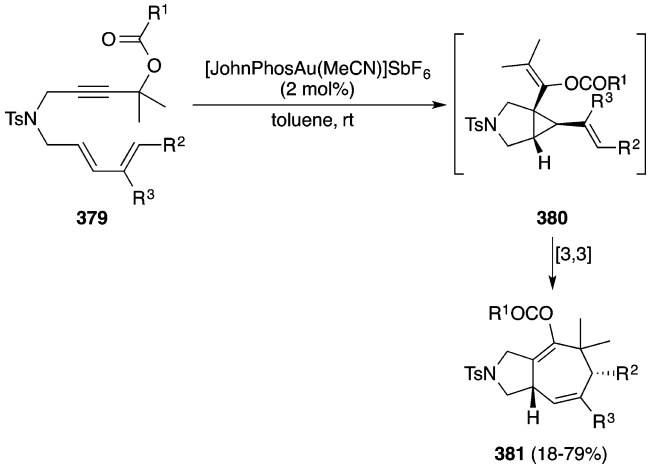
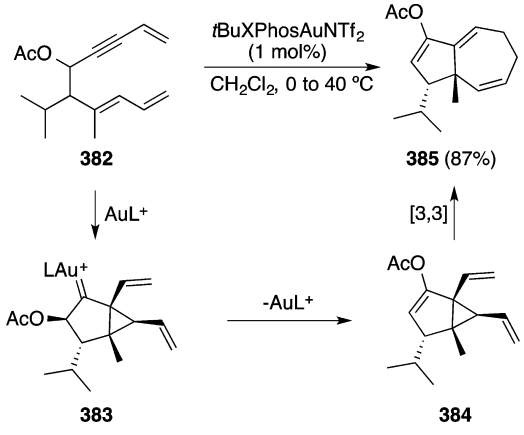
The gold(I)-catalyzed cycloisomerization of 1,6-dien-8-yne carbonates and esters **379** has been reported to yield *cis*-cyclohepta-4,8-diene-fused pyrrolidines **381** by a tandem process involving a 1,2-acyloxy migration/cyclopropanation to form **380** and a final [3,3] sigmatropic rearrangement (Scheme 120).[324]

Scheme 120. Synthesis of *cis*-Cyclohepta-4,8-diene-Fused Pyrrolidines from 1,3-Dien-8-yne Carbonates and Esters



Trienyne **382** cyclizes following a 5-*endo*-dig pathway through cyclopropyl gold(I) carbene **383**, which gives **384** by 1,2-acyloxy migration followed by a Cope rearrangement to afford hydrozulenic derivative **385** (Scheme 121).[325]

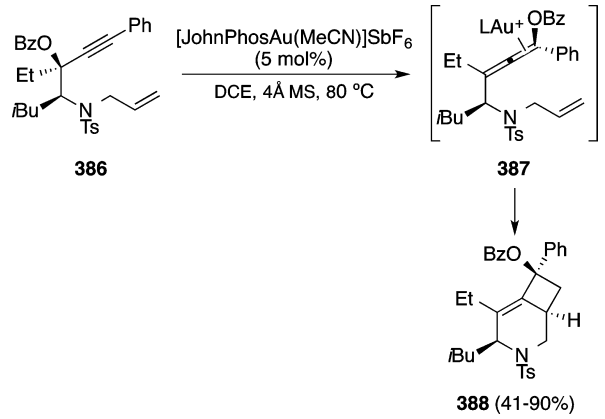
Scheme 121. Synthesis of Hydroazulenes by Cycloisomerization of 1,5-Enynes and Cope Rearrangement



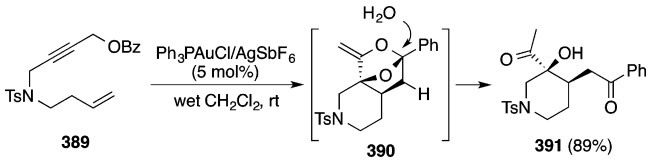
N-Tethered 1,7-enyne benzoates such as **386** bearing a substituent at the alkyne react with gold(I) by 1,3-acyloxy migration to form azabicyclo[4.2.0]oct-5-enes **388** by a formal [2 + 2] cycloaddition of the alkene with the in situ generated 1-acyloxyallene **387** (Scheme 122).[326]

Enynes **389** form hydroxy dicarbonyl compounds **391** in wet dichloromethane (Scheme 123).[327] This reaction presumably proceeds by two consecutive 1,2-acyloxy migrations, followed by a 1,3-dipolar cycloaddition of the carbonyl ylide to form acetal **390**, and final hydrolysis. A similar mechanism is involved in the gold(I)-catalyzed reaction of propargylic esters tethered to cyclohexadienones.[328]

Scheme 122. Synthesis of Azabicyclo[4.2.0]oct-5-enes from *N*-Tethered 1,7-Enyne Benzoates



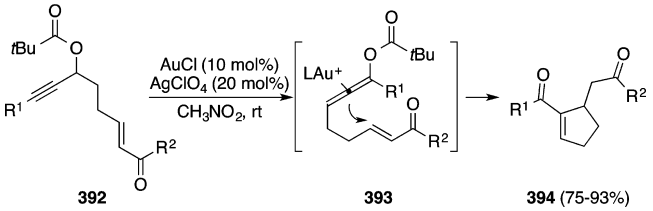
Scheme 123. Synthesis of Hydroxy Dicarbonyl Compounds by Two 1,2-Acyloxy Migrations



Cyclopropyl alkynyl acetates without any substituent at the alkyne undergo a gold(I)-catalyzed rearrangement to form cyclohexenones with high degree of enantiospecificity through gold-stabilized carbocations.[329] Cyclopropyl alkynyl acetates with a substituent at the alkyne terminus react differently by a 1,3-acyloxy shift, whereas the ones substituted at the internal position of the alkene follow a different reaction pathway to give cyclohexenones disubstituted at the 4-position.[330]

1,*n*-Enynes **392** with a conjugated enone react by a different mechanism involving a 1,3-acyloxy migration to form acyloxyallenes **393**, which undergo a Michael addition to form cyclic products **394** (Scheme 124).[331]

Scheme 124. Cyclization of 1,*n*-Enynes by 1,3-Acyloxy Migration and Michael Addition



α,β-Unsaturated ketones can be efficiently prepared by a gold(I)-catalyzed Meyer-Schuster-like rearrangement from propargyl carboxylates[332] or alcohols.[333] In contrast, *γ*-hydroxy-*α,β*-acetylenic esters in the presence of alcohols undergo a gold(I)-catalyzed alkoxylation/lactonization to form 4-alkoxy-2(5*H*)-furanones.[334] The gold(I)-catalyzed reaction of alkynylcyclopropanols and cyclobutanols proceeds through ring expansion to give *α*-alkylidene cyclobutanones.[335]

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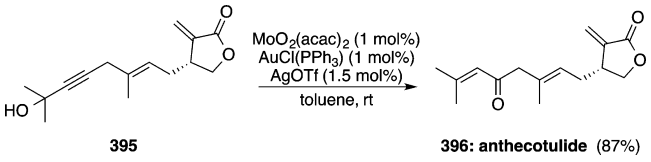
4.3. Reactions of Propargylic Carboxylates in Total Synthesis

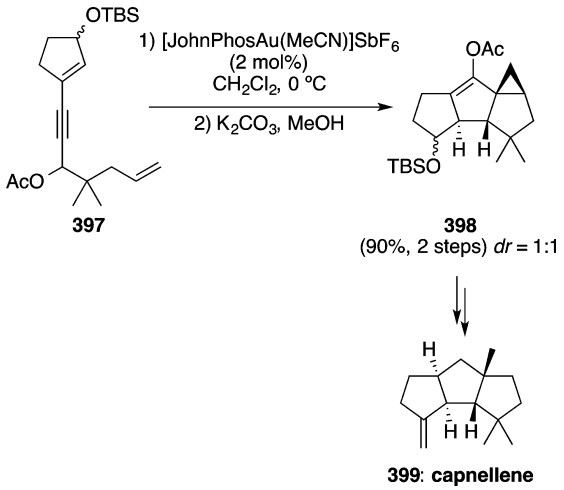
The gold(I)-catalyzed Meyer-Schuster rearrangement was applied in the total synthesis of (+)-anthecotulide **396** (Scheme 125).[336]

Scheme 125. Synthesis of Anthecotulide



The cyclization of an acetoxy-1,6-enyne by 1,3-acyloxy migration, followed by a Nazarov-type electrocyclization, was used in the total synthesis of the marine triquinane sesquiterpene capnellene **399** (Scheme 126).[337]

Scheme 126. Synthesis of Capnellene



5. HYDROARYLATION AND HYDROHETEROARYLATION OF ALKYNES

5.1. Cyclizations of Arylalkynes

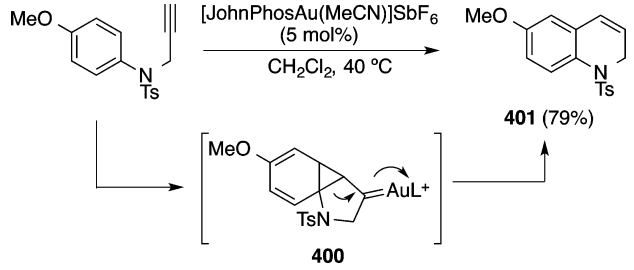
Electrophilic metal catalysts form, upon coordination to an alkyne, electrophilic complexes that undergo electrophilic aromatic substitution reactions with arenes. Gold(I)-complexes generally promote reactions according to this pathway.[338]

The direct auration of electron-rich arenes and heteroarenes by gold(I)[339] and gold(III)[340] is a well-known process, but the resulting aryl-gold complexes are apparently not involved in subsequent C−C bond forming reactions with alkynes. The auration of electron-deficient arenes has also been achieved.[341] Aryl-gold(I) complexes only react with alkynes in the presence of a palladium(0) catalysts, or a palladium(II) precatalyst, to afford products of carboauration.[341c]

The gold-catalyzed intermolecular hydroarylation of alkynes leads to 1,1-disubstituted alkenes or 1,2-disubstituted derivatives in the case of alkynes bearing electron-withdrawing groups.[342]

According to experimental and computational work on the cyclization of arylalkynes catalyzed by platinum(II), two pathways with very similar activation energies compete in intramolecular hydroarylations: a Friedel−Crafts alkenylation and a reaction proceeding through metal cyclopropyl carbenes.[343] However, comparing the results obtained for platinum(II)-catalyzed hydroarylation reactions such as the cyclization of *N*-propargyl-*N*-tosyl anilines, better yields and milder reaction conditions are obtained with cationic gold(I) catalysts (Scheme 127).[344] A detailed theoretical analysis of the

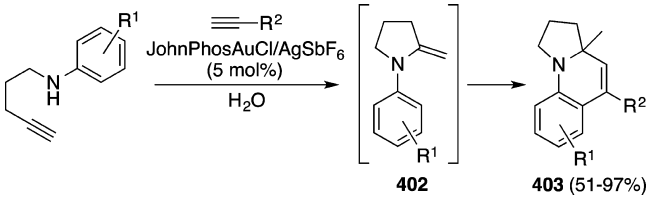
Scheme 127. Synthesis of 1,2-Dihydroquinolines from *N*-Propargyl Anilines



cycloisomerization of phenyl propargyl ethers catalyzed by a Au_{38} cluster has recently been reported.[345] *N*-Butynyl anilines also form 1,2-dihydroquinolines by 6-*exo*-dig cyclization followed by a proton-catalyzed isomerization of the exocyclic double bond.[346] These products could be rearranged into functionalized indole derivatives under photochemical conditions. The intramolecular hydroarylation of *N*-propargyl-*N*′-phenylhydrazines gives cinnoline derivatives.[347]

N-Aryl-2-alkenylpyrrolidine derivatives **402** formed in situ give rise to pyrrolo[1,2-*a*]quinolones **403** through a tandem sequence involving the attack to an external alkyne followed by an intramolecular hydroarylation (Scheme 128).[348] Unpro-

Scheme 128. Synthesis of Pyrrolo[1,2-*a*]quinolones by Intramolecular Hydroarylation



tected propargylic and homopropargylic aniline derivatives in the presence of terminal alkynes undergo a tandem hydroamination/hydroarylation to give dihydroquinolines or quinolones.[129a,349]

The hydroarylation of iodo-substituted propargyl anilines **404** gives selectively 4-iododihydroquinolines **405** with more electrophilic gold(I) complexes, whereas 3-iododihydroquinolines **406** are obtained with more electron-rich gold(I) catalysts bearing NHC ligands (Scheme 129).[350] The cyclization of bromo- and iodopropargyl aryl ethers with $IPrAuNTf_2$ also proceeds with 1,2-halogen migration to give 3-halo-2*H*-chromenes.[351]

The cyclization of propargyl aryl ethers takes place analogously yielding 2*H*-chromenes, even in the cases in which the aromatic ring bears electron-withdrawing groups.[163a,343,344b,c,352] However, in the case of substrates containing both a 1,6-enyne and an aryl propargyl ether, the enyne cycloisomerization is favored, and no hydroarylation takes place.[353]

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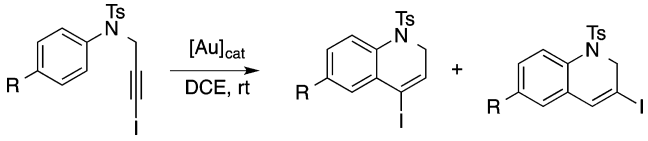
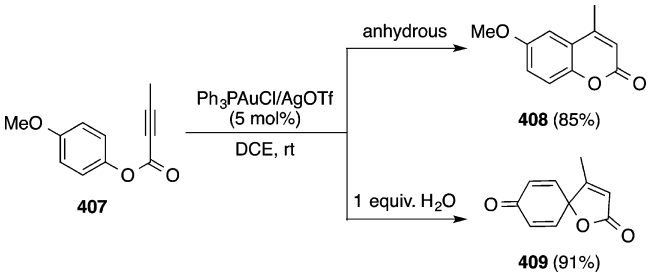
Scheme 129. Hydroarylation of Iodo-Substituted Propargyl Anilines



$[Au]_{cat}$	R	405:406
$(ArO)_3PAuCl/AgBF_4$	Me	7.9:1
$IPrAuNTf_2$	Me	1:4.8
$(ArO)_3PAuCl/AgBF_4$	COMe	3.5:1
$IPrAuNTf_2$	COMe	1:23

Aryl alkynoate esters **407** afford coumarin derivatives **408** in the presence of gold(I) by intramolecular hydroarylation under anhydrous conditions (Scheme 130).[342b,344b,354] It has been

Scheme 130. Synthesis of Coumarins or Spirolactones from Aryl Alkynoate Esters



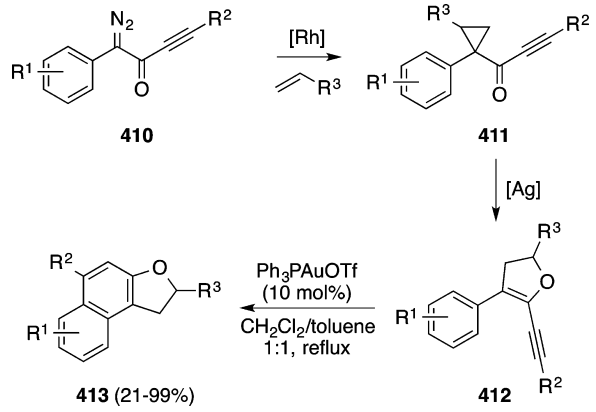
recently reported that the same substrates under the same reaction conditions swapping from anhydrous to wet solvent undergo a gold(I)-catalyzed spirocyclization under mild conditions, giving spirolactones **409** in high yields.[355] Spiro[4.5]cyclohexadienones have been also obtained by a gold(I)-catalyzed carbocyclization of phenols with a terminal alkyne via intramolecular *ipso*-Friedel–Crafts.[356] Aryl alkynylphosphonates also undergo intramolecular gold(I)-catalyzed hydroarylation to give phosphacoumarins.[357]

The intramolecular hydroarylation has also been applied in a complex transformation initiated by a rhodium(II)-catalyzed intramolecular cyclopropanation of α-aryldiazo ketones with alkenes to give products **411** that react with silver(I) to form alkynylhydrofurans **412**, which in the presence of gold(I) afford benzo-fused dihydrofurans **413** (Scheme 131).[358] Alkynylaziridines with an aryl group rearrange in the presence of gold(I) to form spiro[isochroman-4,2′-pyrrolines] via allenylidene intermediates.[359]

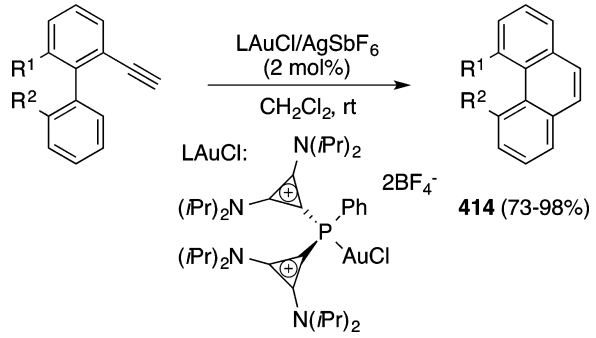
The cyclization of *o*-alkynyl biphenyl derivatives with gold(I), as happens with gold(III), platinum(II), and other metal catalysts,[360] proceeds preferentially by the *endo*-pathway leading to phenanthrenes **414**. The use of a new strongly π-acidic phosphine-bound gold(I) catalyst has allowed to broaden the scope of this transformation, leading to excellent yields in short reaction times, even for 4,5-disubstituted phenanthrenes (Scheme 132).[361]

Interestingly, *o*-haloalkynebiaryls react with AuCl to give phenanthrenes in which the halide has suffered a 1,2-shift.[360c] This type of transformation has been applied to the synthesis of 5,8-diiodo- and 6,13-diiodobenzo[*k*]tetraphenes **415** (Scheme 133),[362] as well as to the synthesis of benzo[*a*]phenanthridines from 3-alkynyl-4-arylisoquinolines.[363] It has been proposed that

Scheme 131. Synthesis of Benzo-Fused Dihydrofurans from Alkynylhydrofurans



Scheme 132. Synthesis of Phenanthrenes from *o*-Alkynyl Biphenyls



Scheme 133. Synthesis of Diiodobenzo[*k*]tetraphenes

the most favored reaction pathway features an initial 6-*endo*-dig hydroarylation of the alkyne followed by 1,2-H shift and formation of a gold-carbene intermediate, which then undergoes a 1,2-halogen shift to finally give the rearranged product after deauration.[364] The reaction of (*o*-arylphenyl)-alkynylselenides in the presence of gold(I) and gold(III) affords rearranged phenanthrenyl selenides very efficiently by migration of the selenide from the terminal to the internal position of the alkyne.[365]

Gold(I)-catalyzed 6-*exo*-dig hydroarylation reactions are much less common. The synthesis of substituted anthracenes in the presence of gold(I) by *exo*-cyclization was achieved from *o*-alkynyldiarylmethanes.[366] In a mechanistically related transformation, the synthesis of functionalized phenanthrenes **416** has been described from *o*-propargylbiaryls (Scheme 134).[367] Dibenzocycloheptatrienes were obtained by a related transformation through a 7-*exo*-dig hydroarylation.[368]

The gold(I)-catalyzed hydroarylation of alkyne-tethered fluorenes was applied to the synthesis of fluoranthenes and more complex polyarenes.[22] A gold(I)-catalyzed formation of

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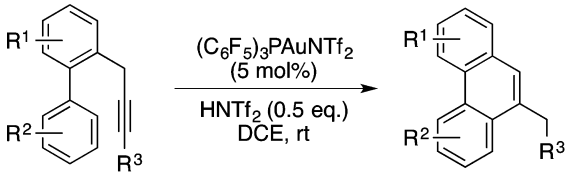
Scheme 134. Synthesis of Phenanthrenes by 6-*exo*-dig Hydroarylation



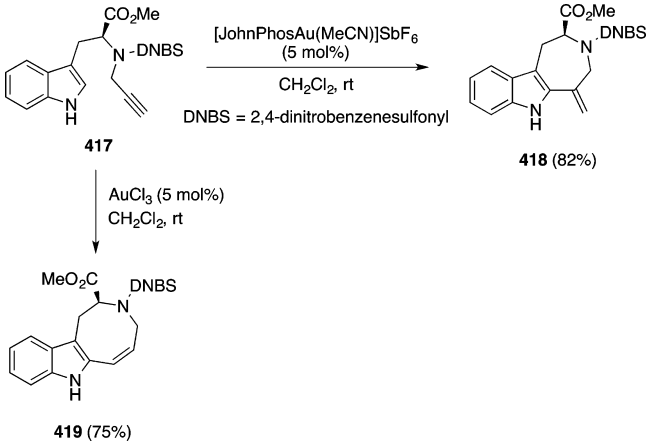
416 (43-96%)

benzofurans has been coupled with intramolecular hydroarylations to form polyaromatic ribbons.[369]

5.2. Cyclizations of Heteroarylalkynes

5.2.1. Reactions of Indoles with Alkynes. The reaction of *N*-propargyl tryptophans or tryptamines **417** catalyzed by gold(I) or gold(III) leads to seven- and eight-membered rings, respectively (Scheme 135).[370] Eight-membered-ring products

Scheme 135. Formation of Seven- and Eight-Membered Rings from Alkynyl Indoles by 7-*exo*-dig or 8-*endo*-dig Cyclization



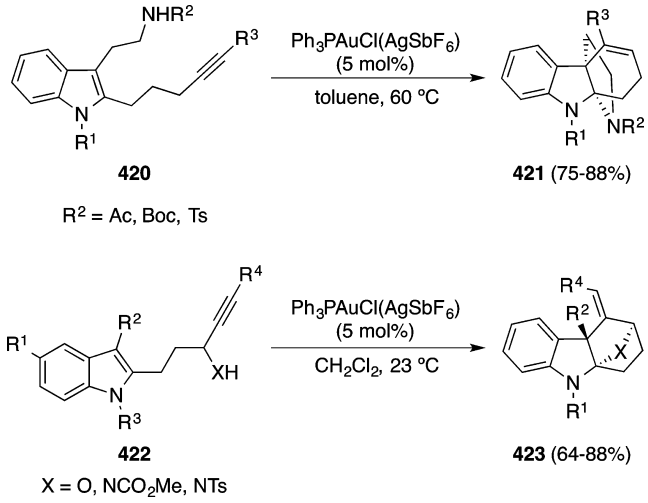
419 are formed by an 8-*endo*-dig process, a type of cyclization that had not been observed in any other hydroarylation of alkynes or cyclization of enynes. These cyclizations have been coupled with other tandem reactions to obtain polycyclic indole-based structures.[371]

The intermolecular reaction of indoles with (*Z*)-pent-2-en-4-yn-1-ols gives intermediate (*Z*)-3-(pent-2-en-4-ynyl)indoles, which undergo a similar cyclization to afford seven-membered-ring products.[372] Tetracyclic indole derivatives were synthesized enantioselectively by coupling a organocatalytic process with a gold(I)-catalyzed 7-*endo*-dig cyclization.[373]

Indoles with the alkynyl chain tethered at the 2-position can undergo a gold(I)-catalyzed cyclization to form carbazoles.[374,375] The formation of indoles in situ by intramolecular hydroamination coupled with an intramolecular hydroarylation has been applied to the preparation of benzo-fused carbazoles,[148a,376] 1,2,3,10-tetrahydroazepino[3,4-*b*]indoles, and related cyclic compounds.[148b] Other gold(I)-catalyzed transformations that yield functionalized carbazoles are the gold(I)-catalyzed deactylative cyclization of 3-acylindole/ynes[377] and the tandem hydroarylation/6-*endo-dig* cyclization of alkynes with 2-alkynylindoles.[378]

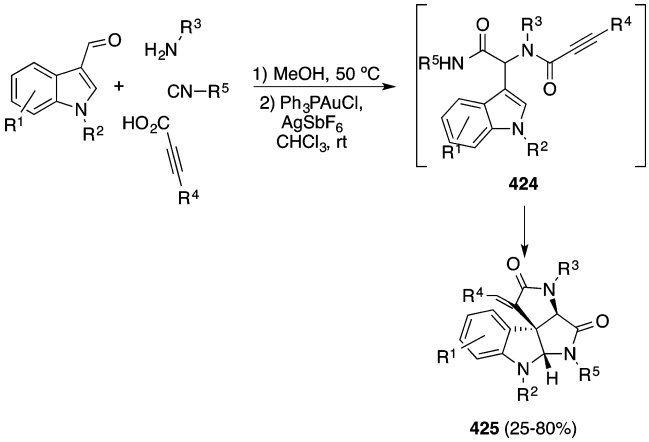
In the case of indoles bearing a nucleophilic functional group, either at the 3-position (**420**) or on the alkynyl chain (**422**), the reaction leads to tetracyclic indolines (Scheme 136).[371,379] Other cascade processes initiated by cyclizations of indoles with alkynes have also been reported.[380]

Scheme 136. Synthesis of Tetracyclic Indolines by Hydroarylation and Intramolecular Nucleophilic Addition



An Ugi four-component reaction of propargylamines with 3-formylindoles, acids, and isonitriles can be coupled with a gold(I)-catalyzed cyclization of the resulting adducts **424** to furnish substituted spiroindolines **425** (Scheme 137).[381]

Scheme 137. Synthesis of Substituted Spiroindolines from Ugi Four-Component Adducts



The intramolecular gold(I)-catalyzed hydroarylation of alkynes with indole-3-carboxamides **426** proceeds by 1,2-acyloxy shift to form dihydroindoloazepinones **428** (Scheme 138).[382] An unusual 1,2-indole migration has been observed in the gold(I)-catalyzed reaction of 3-propargylindoles.[383]

The intermolecular reaction of homopropargyl alcohols with indoles in the presence of gold(I) catalysts proceeds differently forming first 2,3-dihydrofurans, which undergo the addition of two equivalents of the indole to the resulting enol ether to give bis(indolyl)alkanes **429** (Scheme 139).[384]

5.2.2. Reactions of Furans with Alkynes. In contrast to the usual Friedel–Crafts type reaction of arenes with alkynes,

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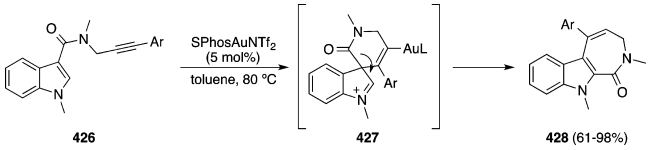
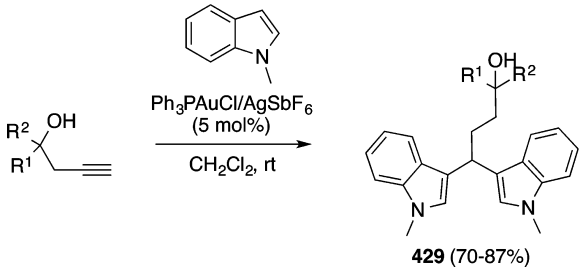
Scheme 138. Synthesis of Dihydroindoloazepinones from Indole-3-carboxamides

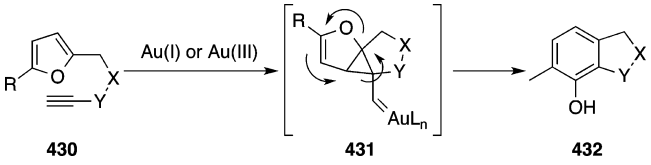


Scheme 139. Intermolecular Reaction of Homopropargyl Alcohols with Indoles



furans usually undergo gold(I)- or gold(III)-catalyzed intramolecular reactions with alkynes to form phenols in good to excellent yields (Scheme 140).[91,385] According to experimental

Scheme 140. Intramolecular Phenol Synthesis from Alkynyl Furans



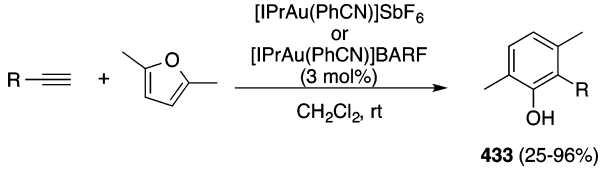
and theoretical studies, the phenol synthesis proceeds initially by a mechanism similar to that of the cyclization of 1,*n*-enynes from furans **430** giving intermediates **431** that evolve by ring opening, cyclization of the resulting carbene, demetalation, and final rearrangement to afford phenols **432**.[385f,g,p,s,386]

Furans generated in situ from endiynes also undergo cyclization with alkynes to form phenols that feature the hydroxyl group at the *meta* position with respect to the ring junction.[387]

The first example of synthesis of phenols by intermolecular reaction of a furan with an alkyne was reported using cationic binuclear complex $[(Mes_3PAu)_2Cl]BF_4$ as the catalyst, albeit the reaction is very slow and the resulting phenol was obtained in low yield.[388] Later it was reported that phenols **433** can be obtained by intermolecular reaction of furans and alkynes using gold(I) complexes bearing NHC ligands (Scheme 141).[389]

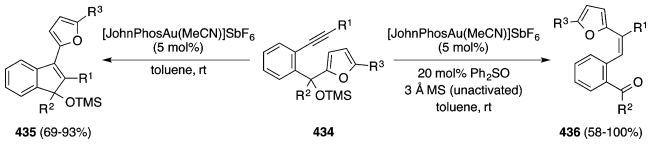
Furan-yne systems **434** with aromatic tethers react with gold(III) to form phenol derivatives. However, in the presence

Scheme 141. Intermolecular Phenol Synthesis from Alkynyl Furans



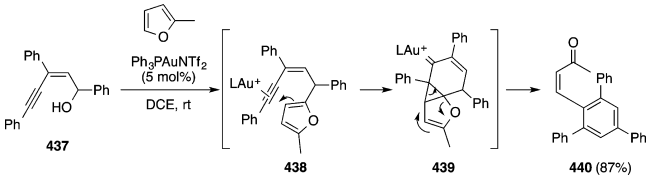
of gold(I) these substrates react to form indene derivatives **435** by *exo*-cyclization followed by 1,4-furanyl migration and cyclization.[390] It has been recently described that the same substrates undergo an *endo*-selective cyclization with concomitant 1,5-migration of the furan group in the presence of unactivated molecular sieves to yield trisubstituted alkenes **436** (Scheme 142).[391]

Scheme 142. Divergent Reactions of Furan-ynes To Form Indenes or *cis*-Stilbene-Type Derivatives



Arylated (*Z*)-enones **440** are obtained by intramolecular reaction of in situ formed intermediates **438** to give **439**, which undergo ring opening and final aromatization (Scheme 143).[392]

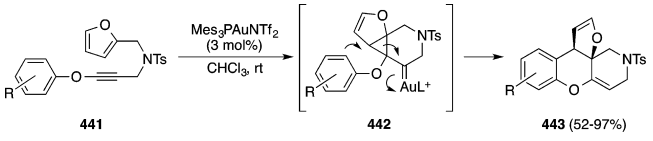
Scheme 143. Synthesis of Arylated (*Z*)-Enones from Furanyl *Z*-1,3-Enynes



A related transformation leads to functionalized fulvenes with an enone or an enal moiety starting from furanynes with a two-carbon tether between the furan and the triple bond.[393]

Furans **441** containing an alkynyl ether moiety in the presence of gold(I) undergo a furan-yne cyclization by a different reaction pathway by which, instead of phenols, tetracycles **443** containing two heteroatoms and two new stereocenters are formed (Scheme 144).[394] A more complex gold-catalyzed process initiated by an intermolecular reaction between 1,6-diyn-4-en-3-ols and furans leads to phenanthrene derivatives.[395]

Scheme 144. Furan-yne Cyclization and Friedel-Crafts Annulation



The gold(I)-catalyzed reaction of 4-silyloxy-4-furyl alkynes leads to benzofurans by a Friedel–Crafts mechanism.[396] This cyclization has been expanded for the synthesis of substituted benzo[*b*]-furans **445** by reaction with various external nucleophiles (Scheme 145).[397] Similarly, propargylic alcohol-tethered furans are converted into benzofuran derivatives in moderate yields.[398]

Internal alkynes **446** tethered to a furan through a protected benzylic alcohol react with gold(I) giving protected 1-naphthol derivatives **448** via formation of a cationic intermediate **447**, followed by ring-opening of the furan ring and aromatization (Scheme 146).[399] It was recently reported that, when furan-

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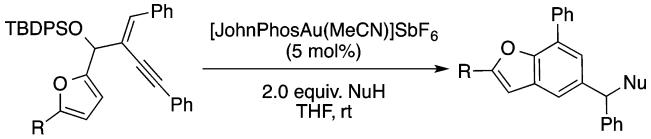
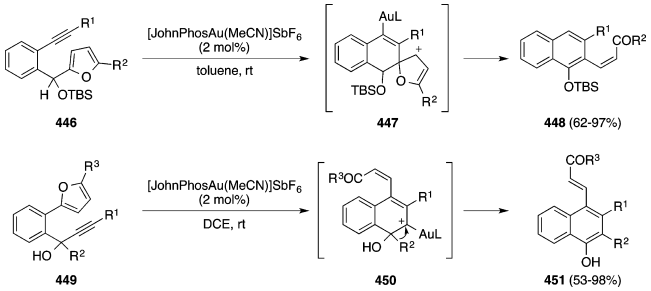
Chem. Rev. 2015, 115, 9028–9072

Scheme 145. Synthesis of Benzofurans by Friedel-Crafts Reaction of 4-Silyloxy-4-furyl Alkynes



444 **445** (47-96%)

Scheme 146. Synthesis of Naphthols by Furan-yne Cyclization



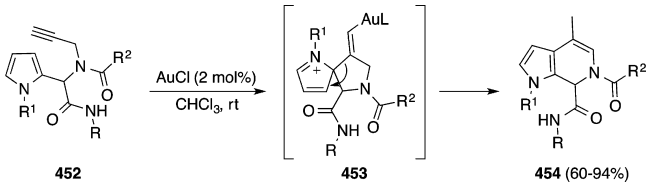
446 **447** **448** (62-97%)

449 **450** **451** (53-98%)

ynes **449** bearing a propargylic alcohol moiety were subjected to an analogous reaction, an additional 1,2-rearrangement takes place, leading to substituted 1-naphthols **451** bearing an enal or enone moiety at the C-4 position.[400]

5.2.3. Reactions of Pyrroles with Alkynes. The gold(I)-catalyzed intramolecular post-Ugi hydroarylation of internal alkynes with pyrroles was developed for the synthesis of pyrrolopyridinones.[401] In the presence of platinum(II)-catalysts this reaction affords selectively pyrroloazepinones. Ugi-adducts **452** bearing a terminal alkyne give pyrrolopyridines **454** by 5-*exo*-dig cyclization followed by 1,2-shift under very mild reaction conditions (Scheme 147).[402]

Scheme 147. Synthesis of Pyrrolopyridines by Intramolecular Hydroarylation of Pyrroles

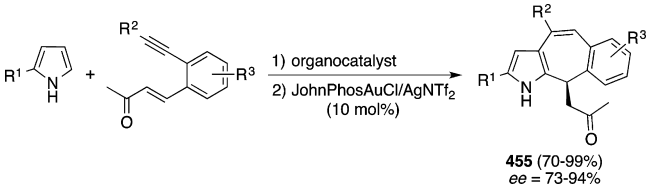


452 **453** **454** (60-94%)

The one-pot asymmetric synthesis of annulated pyrroles **455** has recently been reported combining cinchona-alkaloid-derived primary amine and gold(I) catalysts (Scheme 148).[403]

The analogous intramolecular reaction for β-yne-pyrrole derivatives provides access to fused cycloheptapyrroles in the case of internal alkynes and six-membered-ring fused pyrroles

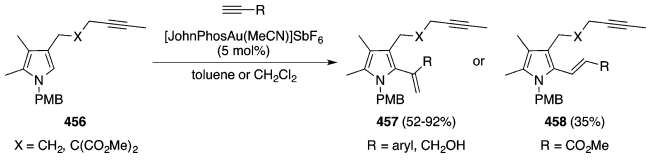
Scheme 148. Synthesis of Annulated Pyrroles via Hydroarylation



455 (70-99%)
ee = 73-94%

in the case of terminal alkynes via *endo*- and *exo*-selective cyclizations, respectively.[404] The intermolecular reaction of alkynes with pyrroles was also developed to form functionalized pyrrole derivatives **457** or **458** depending on the nature of the alkyne substituent, which could be useful scaffolds for additional annulation processes (Scheme 149).

Scheme 149. Intermolecular Hydroarylation of Pyrroles



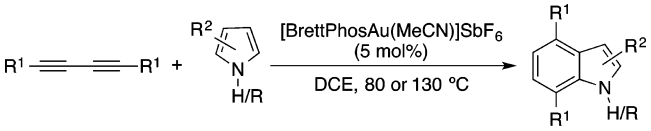
456
X = CH_2, $C(CO_2Me)_2$

457 (52-92%)
R = aryl, CH_2OH

458 (35%)
R = CO_2Me

A new synthesis of indoles **459** proceeds by formal gold(I)-catalyzed intermolecular [4 + 2] cycloaddition between 1,3-diynes and pyrroles (Scheme 150).[405] This reaction involves

Scheme 150. Synthesis of Indoles by Cycloaddition between 1,3-Diynes and Pyrroles



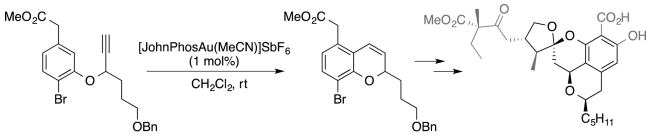
459 (11-85%)

the hydroarylation of one of the alkyne moieties of the diyne with the pyrrole, followed by intramolecular hydroarylation to give 4,7-disubstituted indole. Carbazoles could also be obtained when indoles were used as the nucleophiles instead of pyrroles.

5.3. Hydroarylation and Hydroheteroarylation Reactions in Total Synthesis

An application of the formation of 2*H*-chromenes by intramolecular hydroarylation is found in the synthesis of the tetracyclic core of berkelic acid (**462**) (Scheme 151).[406]

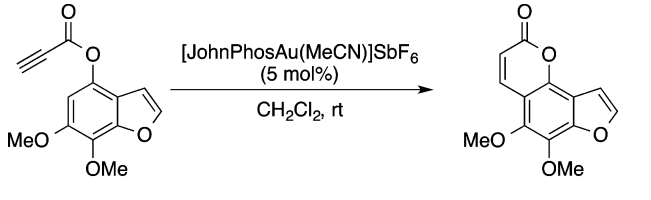
Scheme 151. Synthesis of the Tetracyclic Core of Berkelic Acid



460 **461** (81%) **462: (-)-berkelic acid**

The cyclization of aryl propiolates gives coumarin derivatives, including the natural products pimpinellin (**464**), fraxetin, and purpurasol (Scheme 152).[407]

Scheme 152. Synthesis of Pimpinellin



463 **464: pimpinellin** (72%)

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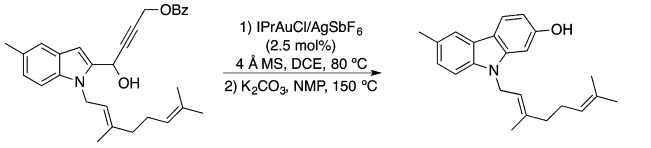
The cyclization of alkynylindoles bearing a nucleophile at the 3-position has been used in the formal total synthesis of the indole alkaloid minfiensine.[379a] The gold(I)-catalyzed synthesis of carbazoles has recently been applied to the first total synthesis of naturally occurring alkaloid karapinchamine A **466** (Scheme 153).[375b]

Scheme 153. Synthesis of Karapinchamine A



465 **466: karapinchamine A** (68%, 2 steps)

An intramolecular gold(I)-catalyzed hydroarylation of a 3-substituted furan is used as the key step of the total synthesis of furanosesquiterpenes crassifolone and dihydrocrassifolone.[408]

6. OXIDATIVE REACTIONS

6.1. Oxidative Reactions of Alkynes

The inter- or intramolecular oxidation of alkynes has been described using sulfoxides,[409] pyridine *N*-oxides,[410] nitrones,[411] nitroso- and nitrobenzenes,[412] as well as epoxides,[413] as the oxidizing agent. These processes have been proposed to proceed via α-oxo gold(I) carbenes **468**,[414] although most likely gold(I) carbenoids **469** are involved by attack of the nucleophile to the highly reactive gold(I) carbene (Scheme 154).[415] The reaction of alkynes with pyridine-*N*-amidines to

Scheme 154. Generation of α-Oxo Gold(I) Carbenes and Gold(I) Carbenoids by Oxidation of Alkynes

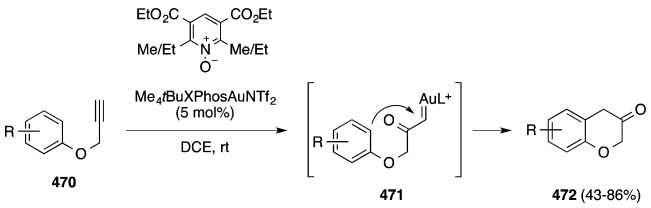
467 **468** **469**

give 2,4,6-oxazoles has also been proposed to proceed through α-oxo gold(I) carbenes.[416] Nevertheless, a mechanism involving β-alkoxy alkenylgold(I) intermediates of type **467** rather than α-oxo gold(I) carbenes has been proposed in some of these oxidative reactions of alkynes.[417]

In the case of terminal alkynes, the gold(I) carbene is always positioned at the terminal carbon of the alkyne. However, regioselectivity becomes a major challenge with internal alkynes. A highly regioselective oxidation of internal alkynes to α,β-unsaturated ketones was developed using $IPrAuNTf_2$ as the catalyst and 8-isopropylquinoline *N*-oxide as the oxidant.[410c]

The intermediate α-oxo gold(I) carbenes can be trapped intramolecularly by a nucleophile present in the starting alkyne increasing the molecular complexity of the final products. As an example, propargyl aryl ethers **470** in the presence of gold(I) and a pyridine *N*-oxide presumably form α-oxo gold(I) carbene **471**, which undergoes an intramolecular Friedel–Crafts-type reaction to afford chroman-3-ones **472** (Scheme 155).[418] In a related transformation, propargylic and homopropargylic alcohols react with gold(I) in the presence of pyridine *N*-oxides to give dihydrofuranones and oxetan-3-ones, respectively.[419] The related oxidative reaction of *o*-ethynylanilines

Scheme 155. Synthesis of Chroman-3-ones by Oxidative Cyclization

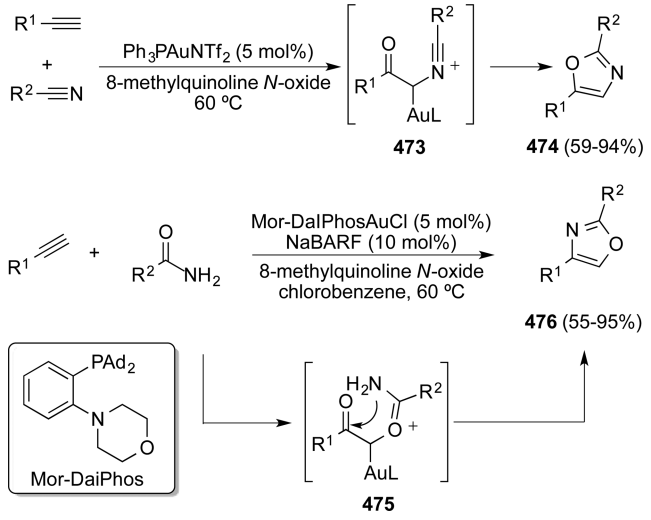


470 **471** **472** (43-86%)

gives 3-oxyindoles by intramolecular trapping of the intermediate gold(I) carbene.[420]

The strong electrophilicity of the α-oxo gold(I) carbene also allows its intermolecular trapping. 2,5-Disubstituted oxazoles **474** were obtained by a formal [2 + 2 + 1] annulation using nitriles as the solvent via intermediates **473**.[421] When carboxamides were used as the nucleophilic partners, 2,4-disubstituted oxazoles **476** were obtained by a formal [3 + 2] annulation between terminal alkynes via intermediates **475** (Scheme 156).[422] Carboxylic acids are also suitable trapping agents for the in situ generated α-oxo gold carbenes, giving rise to carboxymethyl ketones.[423]

Scheme 156. Synthesis of 2,5- and 2,4-Disubstituted Oxazoles by Oxidative Cyclization



473 **474** (59-94%) **476** (55-95%) **475**

The intermolecular trapping of α-oxo gold(I) carbenes by external nucleophiles such as indoles and anilines in aqueous media has been reported, revealing that water can dramatically suppress the undesired overoxidation of the alkyne.[424] A gold(I)-catalyzed tandem cycloisomerization/intermolecular trapping of an in situ generated α-oxo gold(I) carbene involving this transformation has been described to form functionalized indoles **477** from *o*-alkynyl anilines and ynamides (Scheme 157).[425] In this transformation, gold(I) serves dual catalytic roles to mediate both the cycloisomerization of *o*-alkynyl anilines and the intermolecular oxidation of ynamides.

Diynes bearing one terminal and one triarylmethyl-substituted alkyne were converted into benzofluorenone derivatives via a one-pot process involving a gold(I)-catalyzed generation of an α-oxo carbenoid at the terminal alkyne, followed by a photocyclization/oxidation.[426]

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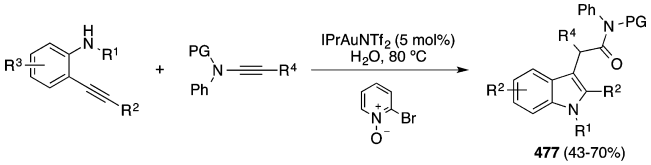
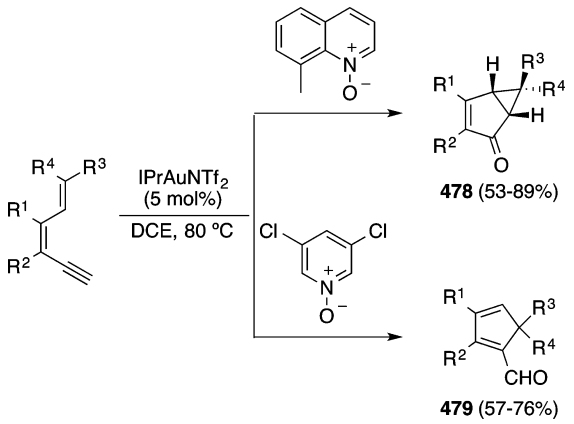
Scheme 157. Synthesis of Indoles from *o*-Alkynyl Anilines and Ynamides



6.2. Oxidative Cyclizations of Enynes

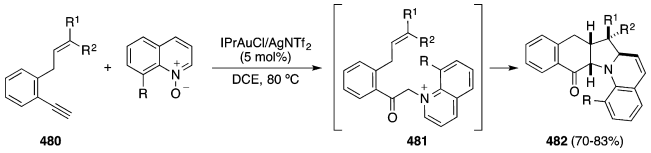
The oxidative cyclization of 1,5-enynes in the presence of gold(I) and a range of oxidants is a well documented process. Thus, the reaction of 3,5-dien-1-ynes with pyridine *N*-oxides leads to cyclopropa[*a*]inden-6(1*H*)-ones **478**[427] or cyclopentadienyl aldehydes **479**[428] depending on the structure of the starting substrate or the particular oxidant used (Scheme 158). In a similar cyclization, *N*-allylyamides are converted into 3-aza-bicylo[3.1.0]hexan-2-ones.[429]

Scheme 158. Oxidative Cyclization of 3,5-Dien-1-ynes



The gold(I)-catalyzed reaction of 3,5- and 3,6-dienynes (**480**) with 8-alkylquinoline *N*-oxides results in an oxidative cycloaddition in which a quinoline framework is activated (Scheme 159).[430] The mechanism of this transformation

Scheme 159. Synthesis of Quinoline Frameworks by Oxidative Cycloaddition



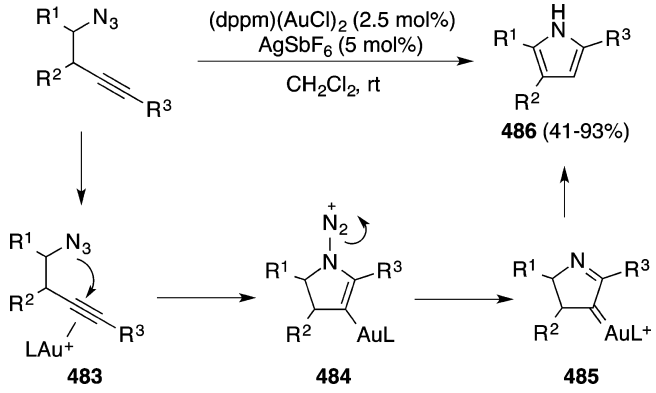
probably involves an intermediate α-oxo pyridinium ylide **481**, which undergoes a concerted [3 + 2] cycloaddition with the tethered alkene to form **482**. Cycloalkanone-fused cyclopropanes have been recently obtained by a gold(I)-catalyzed oxidative cyclization from 1,5-ene-ynes.[431]

Sulfoxides can also be employed in oxidative cyclization of enynes to afford rearranged products bearing a carbonyl moiety via gold(I)-carbenoid intermediates.[432]

Enantiomerically enriched bicyclo[3.1.0]hexan-2-ones have recently been obtained by a tandem alkyne oxidation/cyclopropanation in the presence of gold(I) complexes bearing a chiral phosphoramidite ligand.[433] Similarly, an enantioselective alkyne oxidation/cyclopropanation sequence of 1,5-enynes by gold(I) complexes bearing a P,N-bidentate ligand affords bicyclic cyclopropane products.[434]

The intramolecular additions of azides to alkynes are somewhat mechanistically related transformations that give rise to pyrroles **486** (Scheme 160).[435,436] This reaction

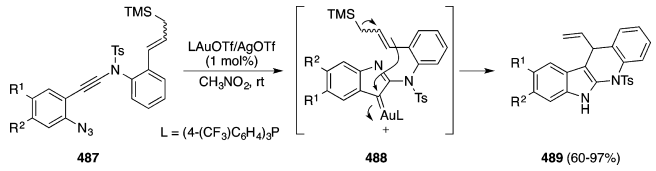
Scheme 160. Synthesis of Pyrroles by Acetylenic Schmidt Reaction



proceeds by nucleophilic attack of the azide in **483** to form intermediates **484**, which loses N_2 in a processs reminiscent of the Schmidt reaction to form cationic α-imino gold(I)-carbene **485.** Final 1,2-H shift and tautomerization lead to substituted pyrroles. In a similar reaction, 2-alkynyl arylazides have been converted into indoles,[437] whereas similar substrates bearing propargylic carboxylates give quinolines.[438]

o-(Azido)ynamides **487** were efficiently converted into indoloquinolines **489** in the presence of gold(I) via α-imino gold(I)-carbenes **488** (Scheme 161).[439] Ynamides bearing a simple alkene instead of an allyl silane gave cyclopropane-fused derivatives.

Scheme 161. Synthesis of Indoloquinolines from *o*-(Azido)ynamides

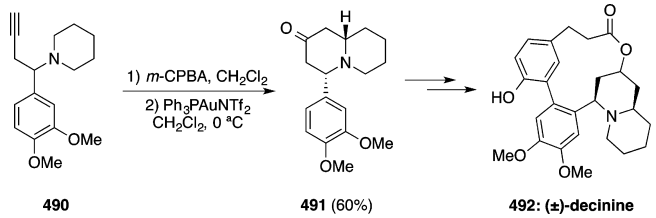


6.3. Oxidative Reactions in Total Synthesis

An intramolecular oxidation of **490** through its *N*-oxide forms 4-piperidone **491**, an intermediate in the total synthesis of the alkaloid (±)-decinine **492** (Scheme 162).[440]

The gold(I)-catalyzed synthesis of optically active γ-lactams by tandem cycloisomerization/oxidation of homopropargyl

Scheme 162. Synthesis of (±)-Decinine



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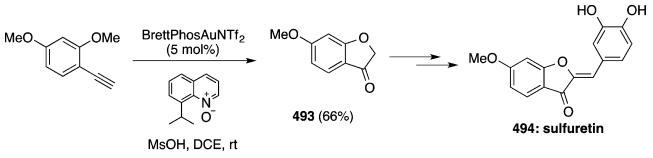
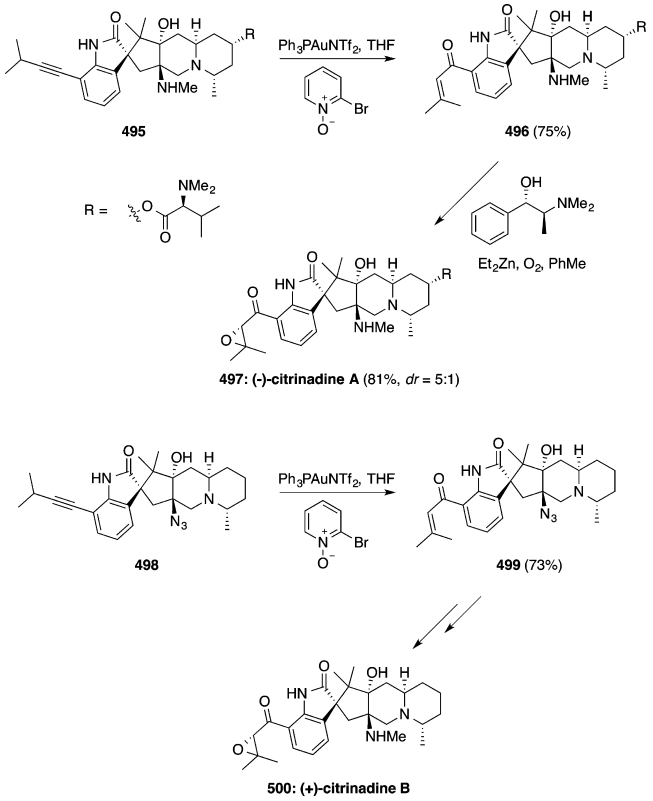
amides was applied in the synthesis of (−)-bgugaine.[441] A similar strategy has been used in the total synthesis of (−)-irniine.[442] Interestingly, 3-coumaranones such as **493** can also be obtained by gold(I)-catalyzed oxidative cyclization of *o*-ethynylanisoles, which has been applied in the total synthesis of sulfuretin (**494**) (Scheme 163).[443]

Scheme 163. Synthesis of Sulfuretin



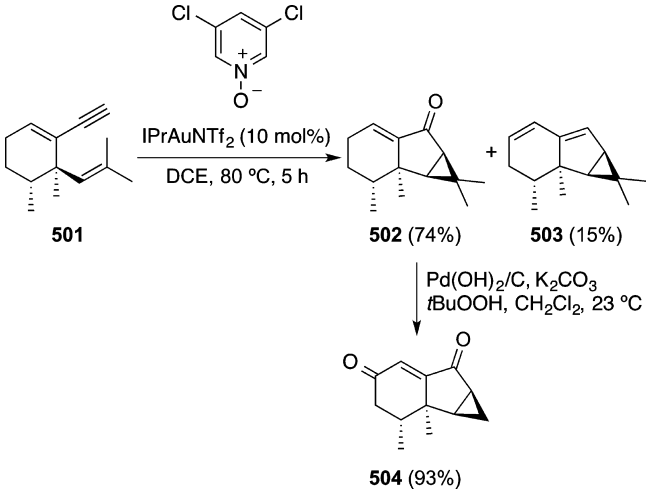
The gold(I)-promoted regioselective oxidation of alkynes[410c] was applied on the total synthesis of alkaloids (−)-citrinadin A (**497**)[444] and (+)-citrinadin B (**500**) (Scheme 164).[445]

Scheme 164. Total Syntheses of (−)-Citrinadine A and (+)-Citrinadine B



The gold(I)-catalyzed oxidative cyclization of 1,5-enynes[427] has been recently used as the key step for a concise enantioselective total synthesis of the sesquiterpene (−)-nardoaristolone B (**504**) by reaction of dienyne **501** with $IPrAuNTf_2$ in the presence of 3,5-dichloropyridine *N*-oxide to form enone **502**, along with the product of cycloisomerization **503** (Scheme 165).[446]

Scheme 165. Synthesis of (−)-Nardoaristolone B by Oxidative Cyclization



7. CONCLUSIONS

Work carried out during the past decade has demonstrated that gold(I) complexes and, in particular, cationic complexes bearing bulky phosphines and NHC ligands are the most active and selective catalysts for the activation of enynes, even in complex polyfunctional settings. Mechanistically, reactions catalyzed by gold(I) are similar to those catalyzed by other electrophilic metal complexes or even Brønsted acids and resemble carbocation-mediated processes. However, gold(I) provides unique control on complex transformations by very selectively activating alkynes and by stabilizing the key carbocationic intermediates by weak, but still significant, metal to carbene π-back-donation. Although many gold-catalyzed reactions of alkynes and, in particular, enynes appear to proceed through gold(I) carbene-like species, the implication of α-oxo gold(I) carbenes in oxidative cyclizations has been recently questioned in several contexts. Further work on the mechanism of these reactions should shed light into the structure of the species involved in these transformations. Most of the work has been carried out in intramolecular processes leading to five- or six-membered ring compounds, although smaller or larger ring systems can also be accessed by using gold(I)-catalysis. However, the regiochemical control in many cases is still essentially dependent on the substrate substitution pattern and not on the ligands on the gold(I) catalyst. Additionally, the structural characteristics of linear two-coordinated gold(I) complexes, in which the ligand is very distant from the nucleophilic addition site to the π-bound substrate, explains the slow development of general enantioselective transformations of alkynes. Finally, the developing of broad-scope intermolecular reactions of alkynes for the formation of carbon−carbon bonds still remains an important challenge in homogeneous gold(I) catalysis,

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Notes

The authors declare no competing financial interest.

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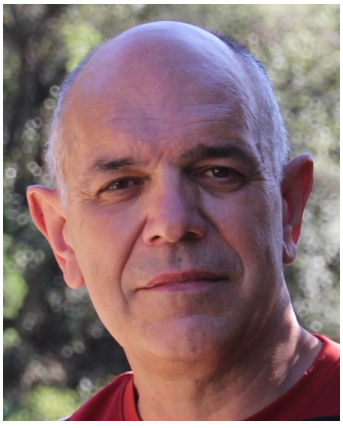
Ruth Dorel was born in Zaragoza (Spain) in 1989. She graduated in Chemistry at the Universidad de Zaragoza in 2012. In 2013, she was awarded the Master of Synthesis and Catalysis Extraordinary Prize at the Universitat Rovira i Virgili (Tarragona, Spain). Since 2013, she has been carrying out her Ph.D. studies at the Institute of Chemical Research of Catalonia (ICIQ) under the supervision of Prof. Antonio M. Echavarren working on the synthesis of natural products and polycyclic aromatic hydrocarbons.



Antonio M. Echavarren was born in Bilbao in 1955 (Basque Country, Spain) and obtained his Ph.D. at the Universidad Autónoma de Madrid (UAM, 1982) with Prof. Francisco Fariña. After a postdoctoral stay in Boston College with Prof. T. Ross Kelly, he joined the UAM as an Assistant Professor (1984−1986). Following a two year period as a NATO-fellow in the group of Prof. John K. Stille in Fort Collins (Colorado State University), he joined the Institute of Organic Chemistry of the CSIC in Madrid, where he stayed until 1992. That year he returned to the UAM as a Professor of Organic Chemistry. He is also Professor of Research of the CSIC since 2004. He moved in 2004 to Tarragona as a Group Leader at the Institute of Chemical Research of Catalonia (ICIQ). He has been a Liebig Lecturer (Organic Division, German Chemical Society, 2006), an Abbot Lecturer in Organic Chemistry (University of Illinois at Urbana—Campaign, 2009), a Schulich Visiting Professor (Technion, Haifa, 2011), a Sir Robert Robinson Distinguished Lecturer (University of Liverpool, 2011), Bristol-Myers Squibb Lecturer (The Scripps Research Institute, 2012), and a Novartis Lecturer in Organic Chemistry (Massachusetts Institute of Technology, 2015). In 2012 he received a European Research Council Advanced Grant, and in 2014 he was president of the 49th EUCHEM Conference on Stereochemistry (Bürgenstock conference). Prof. Echavarren is a member of the International Advisory Board of *ChemSusChem* (2007−), *Organic Biomolecular Chemistry* (2008−), *Advanced Synthesis and Catalysis* (2011−), and *Organic Letters* (2014−), a member of the Editorial Board of *ChemCatChem* (2009−) and *Chemistry European Journal* (2014−), Associate Editor of *Chemical Communications* (2011−), and Fellow of the Royal Society of Chemistry. He received the 2004 Janssen-Cylag Award in Organic Chemistry and the 2010 Gold Medal of the Royal Spanish Chemical Society. In 2015 he received an Arthur C. Cope Scholar Award from the ACS.

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