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Construction of Medium-Sized Rings by Gold Catalysis

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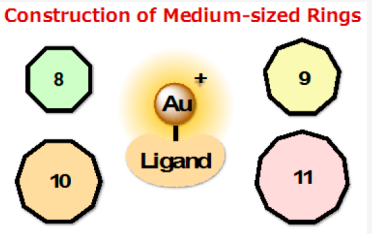
ABSTRACT: Compounds having cyclic molecular frameworks are highly regarded for their abundance and diverse utilities. In particular, medium-sized carbocycles and heterocycles exist in a broad spectrum of natural products, bioactive therapeutics, and medicinally significant synthetic molecules. Metal-mediated methods have been developed for the preparation of compounds containing a medium-sized ring (MSR) through cyclization of different classes of substrates and acyclic precursors. This review focuses on the methodologies for construction of MSRs via gold catalysis. Given the challenges in enabling the assembly of different ring sizes, we present here accounts on Au-mediated cyclization giving notable 7-membered and medium-sized (8−11-membered ring) structures. Emphasis on the pathway and mode of cyclization and the selection of precursors ranging from structurally biased compounds were outlined. Reactivity patterns and the choice of efficient Au catalysts for controlling reaction performance and selectivity in addition to mechanistic attributes are examined.



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1. INTRODUCTION

1.1. Compounds with Medium-Sized Rings

Cyclic molecular frameworks are key structural cores in diverse natural products comprised of bioactive and pharmacologically significant compounds. Development of novel methodologies for the construction of carbocyclic and heterocyclic compounds has been a central theme in organic and natural product synthesis, especially in light of the increasing demands for these compounds in recent decades. However, the ease of preparation of every ring size differs considerably. With less conformational stability compared to six-membered rings, seven-membered and medium-sized rings (MSR, 8−11-membered ring structures)[1−11] are arguably the most difficult to prepare. As a consequence of enthalpic (transannular interactions, bond and torsional strains) and entropic influences[4,12] that hamper cyclization strategies, synthesis of MSRs remains a significant challenge despite their widespread

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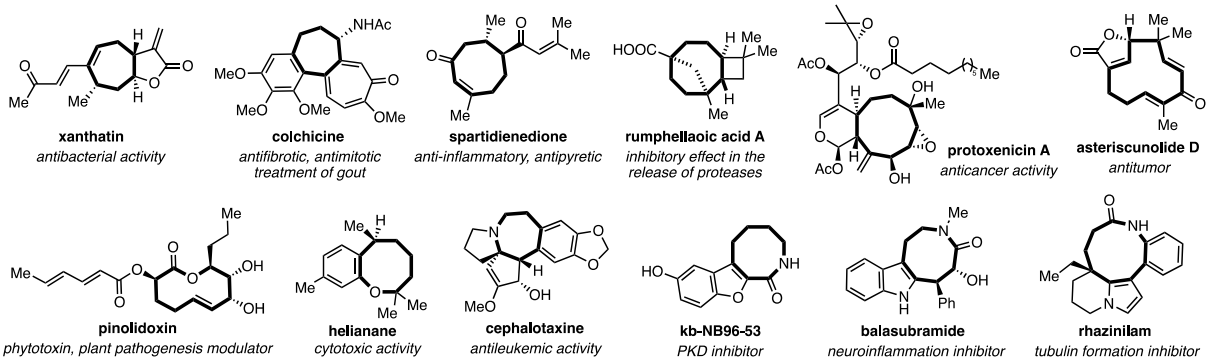

Figure 1. Representative examples of bioactive natural products with seven-membered and medium-sized rings (MSR).

abundance and potential in delivering distinct chemical functionalization for a range of applications. Remarkably, in direct comparison with small- to normal-sized rings (3−6-membered rings) and with macrocyclic (12+-membered rings) compounds, the inherent rigidity and disparity in the three-dimensional spatial characteristics of MSRs give them the advantage for inducing improved binding affinities[13,14] to a variety of biochemical receptors in different classes of organisms, heightened oral bioavailability,[15] and amplification in cellular permeability.[16,17] In fact, compounds bearing MSRs are extensively utilized for pharmaceutical purposes (Figure 1) as they exhibit a wide-ranging scope in terms of bioactivity.[18] This efficiency is observed for both medium-sized carbocycles and heterocyclic MSRs, fueling the surge in interest for their synthetic accessibility.

Generally, preparation of MSRs by metal-mediated synthetic methodologies via cyclization or transformative cycloaddition from acyclic precursors is limited. Established methods rely on substrate-controlled strategies to enable changing the size of the targeted compounds, and in most cases, generating MSRs is based on the reactivity of a fixed reaction site in the starting materials. Ligand-controlled divergent synthesis of MSRs is also rare, especially in the context of controlling regioselectivity. Consequently, compounds containing MSRs are largely under-represented in screening libraries for drug discovery and development despite their success rate as drug leads.[19,20] This challenge has continuously driven collective efforts toward a diversity-oriented synthesis to access medium-sized cyclic scaffolds featuring rapid, modular, and viable approaches.[21−26]

1.2. Gold-Catalyzed Cyclizations

Cyclization reactions catalyzed by gold (Au) have recently emerged in the literature as an effective methodology for construction of hydrocarbon rings and building up molecular complexity. The seminal contributions of Hashmi on the catalytic efficiency of gold on cycloisomerization reactions involving C−C bond formation in alkynyl-based compounds to access furans and arenes have been instrumental in sparking a wave of interest for Au-catalyzed cyclizations.[27,28] Gold, a group 11 transition metal, behaves as a soft carbophilic Lewis acid due to the ability of its complexes to activate unsaturated functional groups such as alkynes, allenes, and alkenes. The relativistic effects[29−31] of gold that promote contraction of its 6s orbital explain this unique π-acidic character and its extraordinary affinity for alkynes (alkynophilicity) in the presence of other functional groups. The alkynophilicity of gold has been the common guiding principle in designing Au-catalyzed cyclizations, cycloisomerizations, and rearrangement reactions of π-rich substrates.[32,33] Generally, the electrophilicity of alkynes or allenes dramatically increases upon coordination of gold to give an Au-activated unsaturated system which then promotes a nucleophilic Markovnikov attack leading to vinyl gold species. This activation mode is similarly operational in cycloisomerizations and hydroarylation reactions when alkenes or arenes serve as the nucleophile.[34] Skeletal rearrangements give access to a variety of carbocyclic compounds but are not limited to an all-carbon cyclization since pendant heteroaromatic nucleophiles are also known for their propensity to participate in these reactions, leading to an array of polycyclic products.[35] Gold catalysis has shown the breadth of synthetic applications in the preparation of carbocyclic and heterocyclic moieties in parallel to known metal-mediated synthesis of MSRs. Encompassing classical methodologies including Ru-based ring-closing metathesis[36] and other late transition-metal-catalyzed cyclization such as those mediated by Pt(II),[37,38] Ag(I),[39,40] Ga(III),[41,42] In(III),[43−45] and Bi(III),[46−48] catalysis using gold complexes has achieved tremendous growth in recent years in the context of reaction efficiency, functional group compatibility, scope, and extensiveness of utility in natural product chemistry.

1.3. Early Stage: Five- and Six-Membered Rings

The first example of a cyclization reaction via C−C bond formation catalyzed by gold was the asymmetric aldol reaction reported by Ito, Sawamura, and Hayashi in 1986, affording five-membered ring oxazoline derivatives.[49] Preparation of substituted six-membered tetrahydropyridines was reported by Utimoto through the intramolecular addition of amines to carbon−carbon triple bonds in alkynylamines under gold catalysis.[50] Teles also disclosed an efficient gold-catalyzed addition of alcohols to alkynes leading to six-membered dioxane derivatives.[51] In addition to these notable examples, the pioneering work of Hashmi and co-workers on homogeneous gold catalysis provided a concrete demonstration of ring formation mediated by gold.[27] In the early exploratory stages of metal-mediated ring formation, Hashmi's selective Au-catalyzed synthesis of arenes from alkynylfuran derivatives **1**, which can be viewed as a functionalized 1,6-enyne, offers an example of a ring-closing transformative cascade reaction leading to synthetically useful substituted phenols **4**, Scheme 1. Upon coordination of gold, which increases the electrophilicity of the alkyne moiety, reaction between this "yne" and the "en" moiety from the furan ring leads to the isomeric reactive gold carbene species **2** and **3**. The resulting intermediate then undergoes ring reorganizations which eventually give the aromatized phenolic derivatives.

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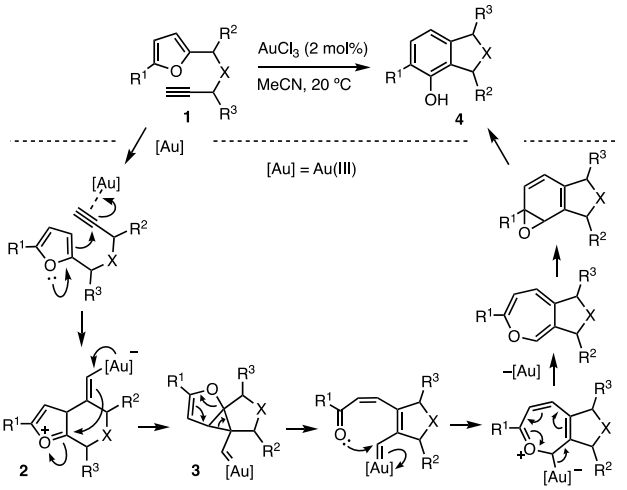
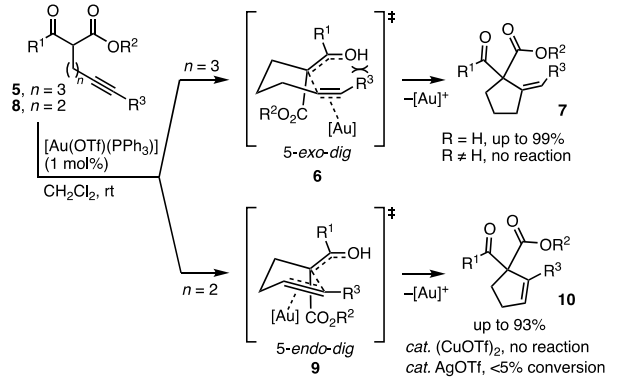
Scheme 1. Hashmi's Pioneering Work on Au-Catalyzed Ring Reorganization of Alkynyl Furans for the Synthesis of Arenes



The scarcity of C−C bond formation mediated by gold further highlights the importance of this precedent, and the synthetic blueprint from Hashmi's work has become a platform for development of methodologies utilizing homogeneous gold catalysis for cyclization and ring reorganization reactions. For example, Toste employed a cationic gold complex as a catalyst for intramolecular addition of β-ketoesters **5** to unactivated alkynes in a Conia−ene reaction under neutral conditions.[52] The methodology provided access to both monocyclic and bicyclic *exo*-methylenecyclopentanes and cyclohexanes in good yields and diastereoselectivities, Scheme 2. Mechanistically, the

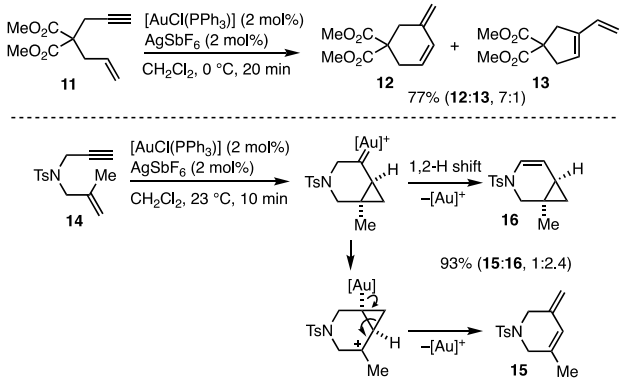
Scheme 2. Au-Catalyzed Carbocyclization of Dicarbonyl Compounds with Alkynes



reaction involved nucleophilic attack of the enol form of the ketoesters to the initially generated gold(I) alkyne complex.[52,53] This reaction, however, has been limited to terminal alkynes as carbocyclization onto nonterminal alkyne variants was unsuccessful probably due to a 1,3-allylic strain in the transition state **6** that leads to the 5-*exo*-*dig* cyclization products **7**. Correspondingly, utilization of β-ketoesters with appended nonterminal α-3′-alkynyl derivatives **8** essentially eliminates the allylic strain in the transition state **9**, promoting the Au(I)-mediated 5-*endo*-*dig* cyclization of dicarbonyl compounds onto the appended nonterminal alkynyl moieties, giving the cyclopentene products **10**, Scheme 2.[54] Use of other metal catalysts (Cu, Ag, etc.) for this reaction was unproductive.

The high alkynophilicity of gold emerged as one of its strengths in the construction of diverse functional scaffolds particularly from the ability of gold complexes to mediate the transformation of substrates with an ene−yne moiety through cycloisomerization reactions. Echavarren[32] and co-workers demonstrated this feat for the skeletal rearrangements of α,ω-enynes using cationic gold(I) complexes generated in situ from the [AuCl(PPh$_3$)]/AgX (X= BF$_4$ or SbF$_6$) system, Scheme 3. Thus, *exo*- and *endo*-cycloisomerization of enyne **11**

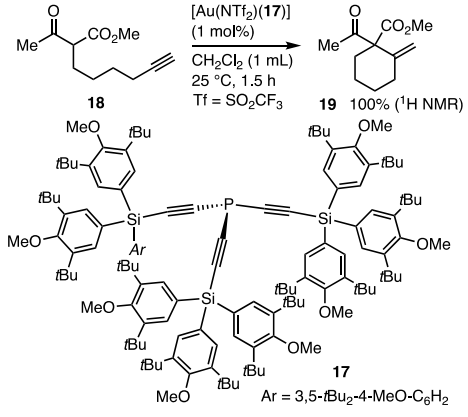
Scheme 3. Au-Catalyzed Cyclization of Enynes



was demonstrated giving the conjugated dienes **12** and **13** bearing six- and five-membered cyclized structures, respectively. Similar reactivity was observed using the methallyl sulfonamide **14** which upon single-cleavage rearrangement and 1,2-H shift/protodeauration via 6-*endo*-*dig* cyclization afforded the medicinally relevant tetrahydropyridine scaffolds **15** and **16**.

Formation of compounds with a six-membered ring has been challenging compared to the greater ease of formation of five-membered rings. In their long-standing interest with catalyst design enabling challenging transformations, Sawamura and co-workers previously reported that the gold(I) complex of the semihollow-shaped triethynylphosphine **17** enabled a markedly accelerated six-membered ring formation starting with acetylenic ketoester **18** that is difficult to access using conventionally utilized catalytic systems,[55] Scheme 4. The cavity in the ligand framework forcing the nucleophilic

Scheme 4. Au-Catalyzed 6-*exo*-*dig* Cyclization Using a Semihollow-Shaped Triethynylphosphine Ligand



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center to be in close proximity to the Au-activated alkyne is crucial to this efficient 6-*exo*-*dig*-ketoester addition, giving monocyclic methylenecyclohexane derivative **19**. The increased catalytic activity in the cyclization was proposed to emanate from the overall entropy-based enhancement enforced by the holey catalytic environment; as such, the reactivity has been extended to nonterminal alkynic β-ketoesters.[56]

Homogeneous gold catalysis has also been utilized in the field of indole functionalization.[57,58] Indoles represent one of the most intensively studied heterocyclic systems in diverse areas of research especially in pharmaceutical, agrochemical, and material sciences. Formation of indole-tethered five- and six-membered rings via Au-catalyzed transformations was likewise reported in the literature including preparation of carbazoles and its derivatives.[59−61]

1.4. Scope of This Review

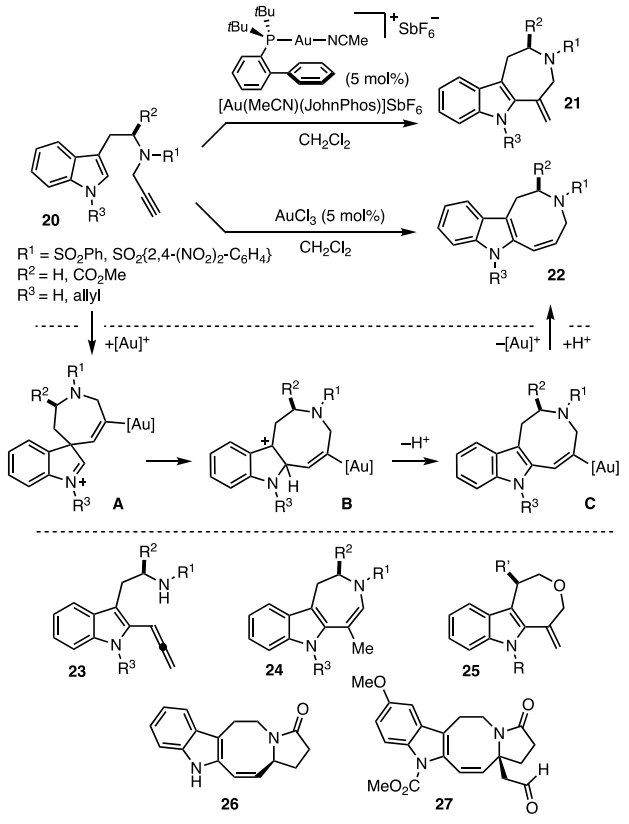
Outlined thus far are representative pioneering works exploiting the propensity of gold to mediate construction of carbocyclic and heterocyclic molecules in the early exploratory stage of gold's utility for C−C bond formation which focused primarily on the preparation of compounds bearing five- and six-membered rings. This brief enumeration sets the theme and overall flow of this review attuned to give a comprehensive account and emphasis on the construction of challenging medium-sized (8−11-membered) ring compounds through Au catalysis. Several notable strategies for construction of seven-membered ring compounds are also discussed. Several reviews have been published on Au-catalyzed transformations focusing on cyclization reactions detailing the nature of reactivity,[29−31] ligand effects,[62−66] substrate class-dependent reactivities and synthetic utilities,[33,35,67−76] and mechanistic considerations.[34,53,77] This review focuses on presenting methodologies for the preparation of MSRs organized by concisely detailing aspects of the ring-closure pathway through either stepwise or direct cyclization. Examples of Au-mediated cascade reactions of different substrate classes including indoles and related heterocycles, alkynols, allene−enones, enyne−ethers, and alkynyl ketone derivatives undergoing sequential or stepwise medium-sized ring formation through rearrangements, tandem processes, or ring expansions are given. In contrast, direct formation of seven-membered or medium-sized ring compounds operating on well-established pathways and modes upon which the cyclization reactions occur (i.e., exo or endo) are highlighted in separated sections. Given in subsections are either specific types of substrates that are successfully employed in these direct ring formations or the categories of Au-catalyzed reactions that facilitate ring closure. There is an evident lack of reports for the utility of gold nanoparticles[78−80] for the synthesis of MSRs, and recent developments in the field of photoredox catalysis in the context of Au-mediated synthesis of MSRs have been underdeveloped, while intramolecular Au-photoredox cyclization proved to be viable for five- and six-membered rings.[81,82] Thus, the present review focuses on the use of Au salts under homogeneous catalysis to achieve cyclization reactions for the preparation of medium-sized carbocyclic and heterocyclic systems. In this review we intend to cover the most representative examples and reported papers published in the years from early 2000 to present. While we try to cover all excellent reports on this topic, any omissions are unintentional.

2. STEPWISE RING FORMATION

2.1. Indole Rearrangements

Indole is an excellent nucleophile to induce sequential or cascade reactions since its C2 and C3 positions at the pyrrole ring are readily amenable for transformations most notably with activated intermediates. In particular, given the prevalence of indole-annulated medium-sized ring motifs in both natural and synthetic products, intramolecular indole/alkyne cyclization can be considered as an attractive method to fast track access to these valuable compounds starting from readily available precursors. This concept was realized successfully for the first time by Echavarren and co-workers with the Au-catalyzed intramolecular cyclization of indoles with alkynes via a stepwise cyclization manifold.[83,84] Interestingly, the cyclization reaction proved to be strongly dependent on the nature of the gold catalyst, Scheme 5. Thus, utilization of the cationic

Scheme 5. Au-Catalyzed Intramolecular Reaction of Indoles with Alkynes



Au(I) complex [Au(MeCN)(JohnPhos)]SbF_6 in the intramolecular cyclization of precursors with an alkynyl motif appended at the C3 indole position **20** led to isolation of the seven-membered azepino[4,5-*b*]indoles **21** having an exocyclic double bond.

The selectivity for this cyclization was overturned toward formation of eight-membered azocino[4,5-*b*]indoles **22** using the more electrophilic $AuCl_3$ as the catalyst, a process reminiscent of an 8-*endo*-*dig* cyclization. Formation of the eight-membered compound **22** resulted from the 1,2-shift in the initially generated seven-membered ring iminium species **A** giving intermediate **B**. Subsequent proton loss from **B** yielded **C**, which in turn underwent a protodemetalation process to form product **22**. In the reactions performed using the Au(I)

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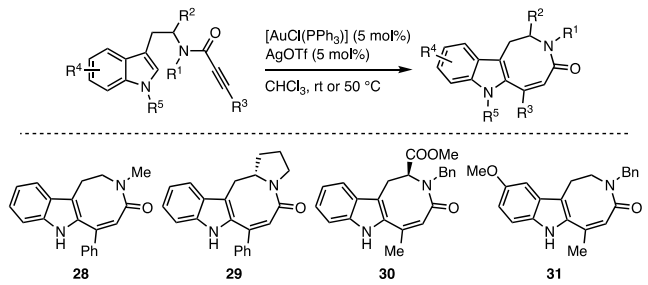
catalyst especially at prolonged reaction times, unusual allenylation of indole at the C2 position due to a fragmentation reaction of intermediate **C** to give allenes **23** was observed. On the other hand, cyclization reactions employing $AuCl_3$ also gave azepino−indoles **24** as minor products in some cases brought by migration of the exocyclic double bond in **21**. In addition to the preparation of these seven- or eight-membered indoloazepines or azocines, the Au(I)-catalyzed cyclization was also successfully applied to propargylic tryptophol derivatives giving the cyclized oxepino[4,5-*b*]indole derivatives **25**.

The synthetic utility of this method was demonstrated for the preparation of bioactive compounds. For example, to access the tetracyclic core skeleton of lundurines, a class of alkaloid with an indoline-fused polyhydropyrroloazine core, the Au-catalyzed cyclization of alkynylindole derivatives has become an effective route for facile preparation of the 1*H*-azocino[5,4-*b*]indole motif **26**.[85] In the total synthesis of lundurine A−C reported by Echavarren and co-workers,[86,87] the Au(I)-catalyzed hydroarylation was the key step to obtain the intermediate aldehyde **27** needed to construct the pyrroloazocine framework. More recently, Cheng, Xia, and Ye disclosed a cycloisomerization-initiated sequential cyclization of Boc-protected indole-tethered homopropargylic amides delivering valuable bridged aza skeletons found in distinct natural products.[88]

A similar approach for the preparation of alkaloidal eight-membered azocino[5,4-*b*]indole core was reported by Van der Eycken using a $[AuCl(PPh_3)]$/AgOTf catalytic system for the intramolecular alkyne hydroarylation of propargylic amides derived from the monoamine alkaloid tryptamine and 3-substituted-2-propynoic acids, Scheme 6.[89,90] Thus, a variety of

Scheme 6. Au-Catalyzed Intramolecular Alkyne Hydroarylation of Propargylic Amides

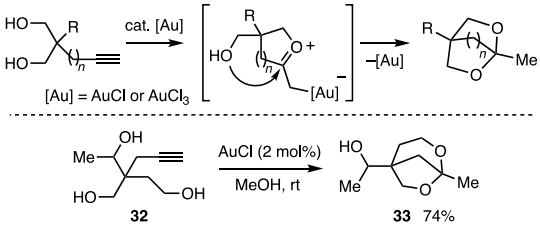


indoloazepines, previously accessible using a toxic $Hg(OTf)_2$ catalyst,[91] were prepared in excellent yields including natural product relevant derivatives **28** and **29**, amino acid tryptophan derivative **30**, and indole core-substituted azocine **31**. A closely related stereoselective synthesis of seven-membered functionalized polycylic indoline skeletons featuring four contiguous stereocenters was also described by Shi, Tang, and co-workers.[92] In this work, substrates with an alkyne moiety appended to the indoline nitrogen resulted in fused polycyclic compounds using a Feringa phosphoramidite−Au catalyst. Moreover, Van der Eycken and co-workers disclosed several strategies for the preparation of diversely substituted pyridinones, azepinones, and azepinoindoles bearing seven-membered indole-fused derivatives.[93−96]

2.2. Domino (Tandem) Reactions

Construction of architecturally complex molecules bearing cyclic structures via tandem reactions has also emerged as an attractive avenue to provide valuable cyclic compounds. Early examples by Michelet and Genêt[97] on the Au-catalyzed tandem *exo*-hydroalkoxylation/hydroalkoxylation of bis-homopropargylic diols gave access to a variety of functionalized strained bicyclic ketals, Scheme 7, with up to a seven-

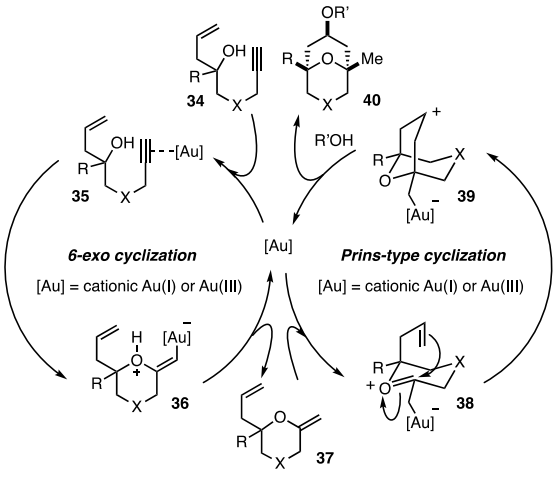
Scheme 7. Tandem Au-Catalyzed *exo*-Hydroalkoxylation/Hydroalkoxylation of Homopropargylic Alcohols



membered ring as the largest ring formed in the process. More interestingly, they demonstrated the synthesis of an unsymmetrical strained bicyclic ketal starting with the alkynyl triol **32** through a smooth chemoselective cyclization where both of the primary alcohols reacted with the alkyne moiety furnishing **33** with a dioxabicyclo[3.2.1]ketal framework. Alcaide, Almendros, and co-workers also succeeded in the direct preparation of bridged acetals under gold-catalyzed regio- and stereocontrolled bis-oxycyclization reactions.[98−101]

Barluega and co-workers reported a protocol for the Au-catalyzed tandem exohydroalkoxylation/Prins-type cyclization of allyl-substituted alkynol derivatives[102] outlined in Scheme 8.

Scheme 8. Tandem Au-Catalyzed *exo*-Hydroalkoxylation/Prins-Type Cyclization of Alkynol Derivatives



The concurrent tandem reaction is initiated by the coordination of the gold catalyst to the alkynol substrate **34** forming π-complex **35**. This is followed by the intramolecular 6-*exo* addition of the hydroxyl group to the triple bond, leading to **36**. Protodeauration of the latter affords the *exo*-cyclic enol ether **37**. From here the subsequent cyclization process (**38** to **39**), proposed to proceed through a chairlike transition state, forms the oxocarbenium ion **39**. Nucleophilic trapping of **39** by an alcohol consequently leads to the eight-membered carbocycle **40**. This cascade reaction has been later extended to include the use of oxygen-, nitrogen-, and carbon-centered nucleophiles,[103] even allowing the synthesis of enantiopure

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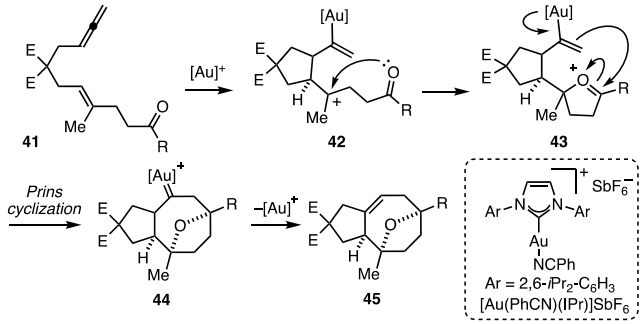
benzofused eight-membered carbo- and heterocyclic compounds.[104]

Following their success on Au-catalyzed intramolecular cyclization of oxo-1,6-enynes[105] in assembling tricyclic carbon skeletons, Echavarren and co-workers[106] invoke gold carbene complexes in the cycloisomerization of 11-oxo-1,7-allenenes **41** to afford oxygen-bridged cyclooctene derivatives, Scheme 9.

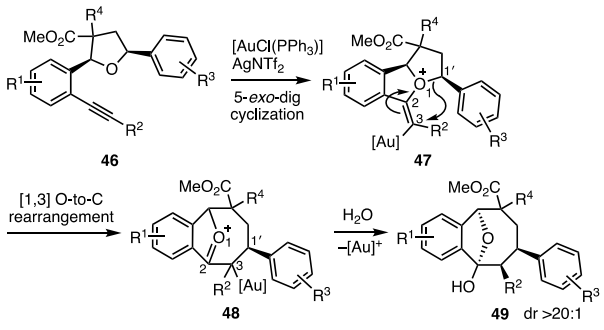
Scheme 9. Au-Catalyzed Cycloisomerization of Allene−Enones



The Au−NHC complex initially mediates the 5-*exo*-trig cyclization leading to **42**, upon which participation of the neighboring carbonyl moiety generates the oxonium ion **43**. The cascade then proceeds through quenching of **43** by 7-*endo*-trig ring closure forming the carbene complex **44**, eventually affording the bicyclo[6.3.0]undecane derivatives **45** upon deauration.

Efficient construction of bridged oxa[4.2.1] skeletons was reported by Zhu and co-workers.[107] The gold-mediated 5-*exo*-*dig* cyclization of enyne−ethers **46** forms vinyl oxonium intermediate **47**, Scheme 10. The oxonium intermediate sets

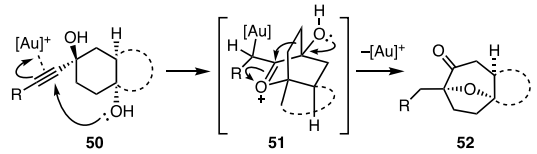
Scheme 10. Tandem Cyclization/[1,3] O-to-C Rearrangement of Enyne−Ethers Catalyzed by Gold



the stage for the sequential intramolecular [1,3] O-to-C rearrangement affording intermediate **48**, which gives the eight-membered ring scaffold in a diastereoselective fashion.

Alternatively, the reactivity demonstrated in Scheme 10 can be viewed as a process operating on a ring-expansion strategy (see section 2.3), enabling access to bridged bicyclic motifs. Yang and co-workers[108] similarly utilized an Au-catalyzed tandem *exo*-hydroalkoxylation/semipinacol rearrangement essentially leading to a diastereoselective route for the synthesis of oxabicyclo[3.2.1]octanes, a process that results from ring expansion of 1-ethynyl-cyclohexane-trans-1,4-diol derivatives **50** via an Au-catalyzed cascade reaction, Scheme 11. The reaction proceeds through the initial Au-catalyzed intramolecular nucleophilic addition of the hydroxyl group onto

Scheme 11. Au-Catalyzed Tandem *exo*-Hydroalkoxylation/Semi-Pinacol Rearrangement Reaction



the alkyne moiety followed by isomerization giving a highly strained oxonium ion intermediate **51**. The oxonium ion generated in the process is a precursor for the semipinacol rearrangement which results in the cyclized products **52**. The 1,2-alkyl migration is crucial to formation of the desired oxabicyclo[3.2.1]octanes framework as revealed by DFT calculations. The value of this methodology was demonstrated in the formal total synthesis of cortistatins, an important class of steroidal alkaloids exhibiting an antiangiogenic activity.[109]

2.3. Gold-Induced Ring Expansion

The propensity of gold to trigger ring-expansion processes has become a flexible synthetic tool to introduce molecular complexities in organic compounds. For example, Schmalz disclosed an Au-catalyzed ring expansion of alkynyl cyclopropyl ketones **53**, Scheme 12, providing access to highly substituted furans **54** under mild conditions.[109] Two mechanistic rationales were proposed for this transformation. Nucleophilic attack of the carbonyl oxygen atom to the activated alkynyl moiety in **55** results in the concomitant cyclopropyl ring opening, generating a carbocationic intermediate **56** (Scheme 12, path a). Trapping of **56** is accomplished by an external nucleophile, providing after protonolysis of the organogold intermediate **57** furan derivative **54**. An alternative plausible mechanism involves complexation of gold to the carbonyl and alkynyl moieties forming chelate complex **58** (Scheme 12, path b). Intermolecular nucleophilic attack then triggers the opening of the cyclopropyl ring in a regioselective homo-Michael-type addition, leading to the Au−enolate **59**. Finally, cycloisomerization affords **57** and upon subsequent protonolysis will give the product **54**. A range of *O*-nucleophiles, phenols, or even acetic acid was employed giving a variety of substituted furans. Moreover, substrates bearing cycloheptane motifs and derivatives of 2,3-methanochromanone are applicable, giving products with medium-sized ring furan-fused structures **60** and **61**, respectively.

Recently, Zhu also reported an Au-catalyzed ring expansion of alkynones to afford a furan-fused cycloalkanone system.[110] In this case, the reaction proceeds through 1,2-acyl migration followed by Friedel−Crafts reaction. Despite the required elevated temperature (100 °C) for the transformation to proceed, this methodology provides an appealing strategy for the synthesis of polycyclic compounds.

A novel rearrangement of propargylic dithioacetals **62** catalyzed by $[AuCl(PPh_3)]/AgSbF_6$ was reported by Wang and co-workers.[111] The reaction provides eight-membered 1,5-dithio-substituted cyclic allenes **63** through ring expansion by double-1,2-sulfur migrations (Scheme 13, **I**−**III**). This methodology provides the first example for the synthesis of stable eight-membered 1,3-bisthio-substituted cyclic allenes whose structures were confirmed by X-ray analysis. A limitation encountered, however, is the formation of diene product in cases when an alkyl substituent is present in the substrate (i.e., *i*Pr instead of Ar), which is proposed to arise

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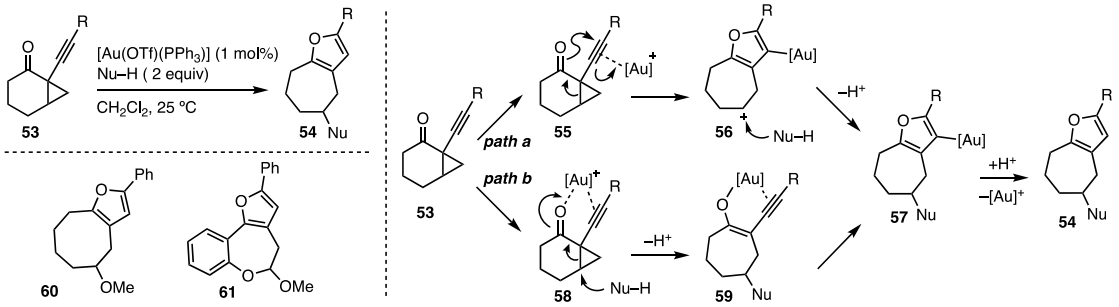
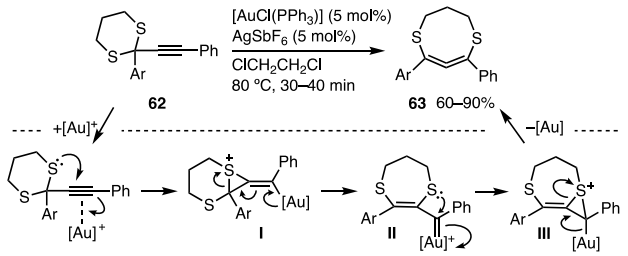
Scheme 12. Au(I)-Catalyzed Ring Expansion of Alkynyl Cyclopropyl Ketones



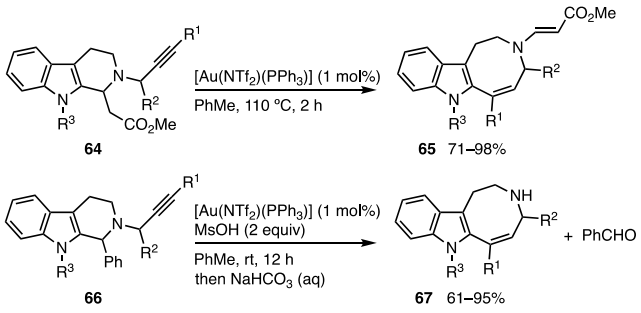
Scheme 13. Au(I)-Catalyzed Ring -Expansion for the Synthesis of Medium-Sized Sulfur-Containing Cyclic Allenes



from isomerization of the initially formed cyclic allene to relieve the high ring strain. Nonetheless, derivatization by *m*CPBA-mediated oxidation of the heterocyclic allene was also demonstrated, giving the corresponding sulfone derivative which, in view of this report, enabled detailed structural analysis of the sulfur-containing cyclic allenes.

Access to eight-membered heteroannulated azocines was reported by Wang through an Au-catalyzed ring expansion of 2-propargyl tetrahydro-β-carbolines **64** featuring an intramolecular hydroarylation, [1,2]-alkenyl migration, and carbon−carbon bond fragmentation.[112] The methodology provides an innovative strategy to deliver azocinoindole derivatives **65** by fusing the indole moiety to the generated azocine ring, Scheme 14. The reaction tolerated a variety of

Scheme 14. Au(I)-Catalyzed Ring Expansion Affording Eight-Membered Azocinoindole Derivatives



substituents both at the alkyne terminus and at the propargylic position. The methoxycarbonylmethyl group at the C1 position of the tetrahydro-β-carboline unit is requisite for the ring expansion as control experiments replacing this moiety with a phenone or either simple alkyl or phenyl groups hampered the cyclization process.

Addressing this issue, further studies have demonstrated the need for acidic additives such as methanesulfonic acid (MsOH) to allow ring expansion for both C1-unsubstituted tryptolines and phenyl or alkyl C1-substituted derivatives **66**.[113] Correspondingly, after the alkaline workup, eight-membered azocinoindoles with an unprotected secondary amines **67** can be generated in good to excellent yields. Utilization of terminal alkynes (**66**, R^1 = H), however, furnishes spiroindoline products instead, suggesting the role of the terminal group on the alkyne moiety for determining the outcome of the ring-expansion process. DFT calculations suggest that Au(I)-catalyzed cyclization contains a bifurcating potential energy surface which gives simultaneously both α- and β-alkenylation intermediates which then interconvert into each other via a [1,5]-alkenyl shift.

3. DIRECT RING FORMATION

3.1. Exo Cyclization

3.1.1. 1,*n*-Enynes. A range of reaction topologies for direct cycloisomerization of 1,*n*-enynes delivers efficiently a diverse subset of cyclic motifs. Considered as privileged substrates, 1,*n*-enynes are readily accessible and easily modifiable in terms of varying the functionalities in their structures and serve as attractive precursors in accessing cyclic skeletons with a broad selection of functional or decorative moieties for complex compound synthesis. Excellent reviews detailing different aspects of advances, strategies, and mechanisms for cyclization of these compounds have been published.[33,76,77,114−117] Exo-cyclization of enynes has been one of the most extensively studied approaches in the context of transition-metal-catalyzed cycloisomerization. Pioneering work by Echavarren and co-workers showed that skeletal rearrangements of α,ω-enynes catalyzed by Au(I) complexes[32] lead to five-membered exocyclic products (see Scheme 3). Sawamura reported a gold(I)-catalyzed cycloisomerization of 1,7-enynes using triethynylphosphines (compound **17**, see Scheme 4), affording substituted six-membered ring products with a 1,3-diene moiety through a direct exo-cyclization process.[55]

Gagosz reported the isomerization of 1,8-enynes to generate cyclobutene derivatives via an Au(I)-catalyzed formal [2 + 2] cycloaddition.[118] Seven-membered ring compounds with a bicyclo[5.2.0]nonene framework **68** were generated from functionalized 1,8-enynes **69** using a bulky XPhos−Au(I) catalyst, Scheme 15. The synthetic utility of these cyclobutene derivatives toward further isomerization, fragmentation, or ene reaction to access structurally complex molecules was also demonstrated, highlighting the importance of MSRs as handles in natural product chemistry.

Inagaki and co-workers[119] utilized a cationic Au(I) complex **70** for intramolecular cycloaddition of 1,8-enynes **71** generating compounds with a seven-membered ring fused to

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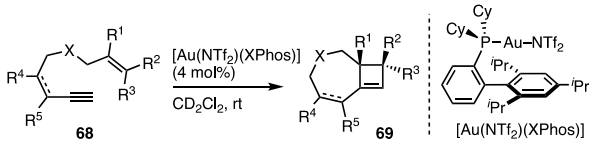
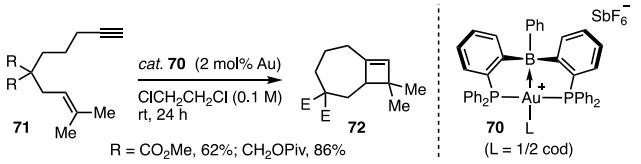
Scheme 15. Au(I)-Catalyzed Intramolecular [2 + 2] Cycloaddition of 1,8-Enynes



a cyclobutene moiety **72**, Scheme 16. Gold catalyst **70** showed better performance for the enyne cyclization as compared to

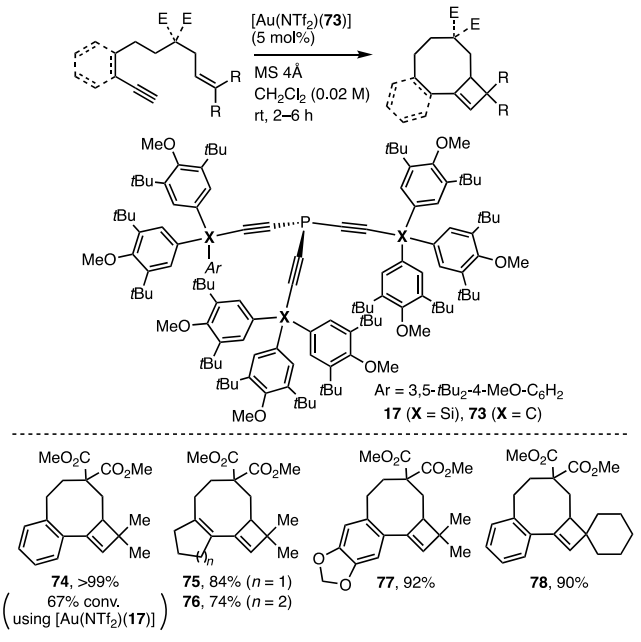
Scheme 16. Cationic Au(I)-Catalyzed Intramolecular 1,8-Enyne Cyclization



other simple cationic catalytic systems probably due to the strong σ-accepting properties of the Lewis acidic boron trans from the catalytically active site.[66,120,121]

Use of ethynyl phosphine ligands with bulky substituents proved to be efficient in assembling cyclobutene-fused eight-membered carbocycles through Au-catalyzed intramolecular enyne [2 + 2] cycloaddition of 1,9-enynes.[122] Sawamura utilized phosphine ligand **73**, a carbon analogue of ligand **17**, under gold catalysis to construct synthetically challenging eight-membered ring compounds which are inaccessible by other catalytic systems.[123] Thus, aliphatic tricyclic compounds **74**−**77** and the spiro tetracyclic scaffold in **78** were synthesized in high yields, Scheme 17. Use of the cationic gold complex [Au(NTf$_2$)(**73**)] for this transformation was critical to achieve better substrate conversion and yield. A lower reaction efficiency was observed, for example, in the synthesis of **74** using ethynyl phosphine **17**, which was used as ligand to

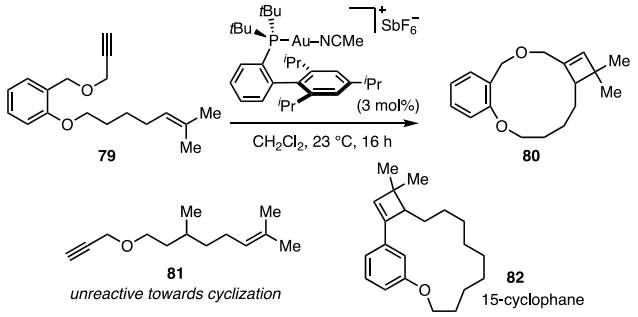
Scheme 17. Au-Catalyzed Cycloisomerization of 1,9-Enynes



generate substituted six-membered ring products through a direct exo-cyclization process.[55,56]

Utilization of higher 1,n-enynes (n = 10−16) has been demonstrated successfully by Echavarren and co-workers.[124] Enynes derived from ortho-substituted aromatic rings afforded the macrocyclic structures resulting from the formal [2 + 2] cycloaddition. Thus, the 1,13-enyne **79** gave the benzofused 12-membered ring compound **80** incorporating a cyclobutene ring, Scheme 18. The conformation of the precursor enynes is

Scheme 18. Macrocyclization of 1,n-Enynes, n = 10−16

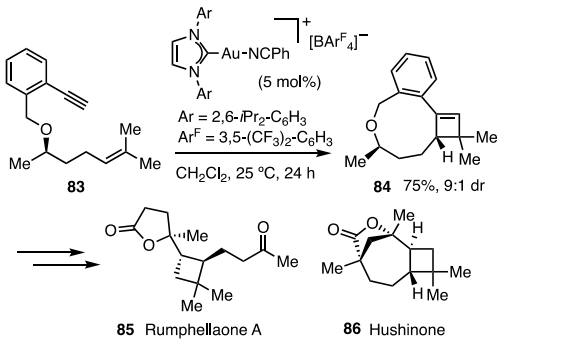


the key to the reactivity toward intramolecular macrocyclization. Cyclized products from enynes with a flexible spacer linking the alkyne and the alkene moieties, for example, enyne **81**, could not be obtained using this methodology.

This observation can be attributed to the reduction of the degrees of rotational freedom in the presence of the ortho-substituted aromatic ring orienting the two reactive sites in the same direction which favors the cyclization. This strategy was effectively utilized for preparation of 9−12-membered medium-sized ring compounds (20−71% yield) and applicable also to preparation of larger macrocyclic systems, 13−15-membered ring compounds, and even provides access to m-cyclophanes, for example **82**.

A report by Echavarren disclosed a diastereoselective intramolecular Au(I)−NHC catalyzed [2 + 2] macrocycloaddition of 1,10-enyne **83** to produce the nine-membered benzo- and cyclobutene-fused oxonine derivative **84** (Scheme 19), the

Scheme 19. Au-Catalyzed [2 + 2] Cycloaddition of 1,10-Enynes in Total Synthesis



key intermediate in the total synthesis of the sesquiterpenes Rumphellaone A and Hushinone, compounds **85** and **86**, respectively.[125] The prevalence of macrocycles in natural products makes this strategy a remarkable tool for incorporation in total synthesis platforms to access compounds with complex structural frameworks. A limitation commonly

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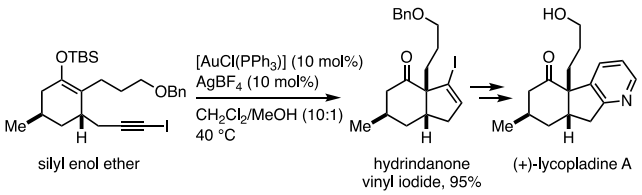
encountered, however, is that utilization of 1,*n*-enyne for $n > 8$ is scarce. The examples shown in Schemes 18 and 19 are notable precedents in the exploitation of reactivities for larger enynes.[125,126]

3.1.2. Silyl Enol Ethers. Silyl enol ether derivatives are appealing substrates for a number of different transformations because of their ease of preparation and reasonable reactivity. In the context of Au-catalyzed cyclization, silyl enol ethers with appended alkynic substituents have been employed to access carbocycles in the presence of an external proton source which is necessary for protonolysis of vinylic Au intermediates, a fundamental difference with respect to enol nucleophiles. For example, preparation of bicyclic frameworks through cationic gold(I)-catalyzed *exo-dig* cyclizations, Scheme 20, of a silyl

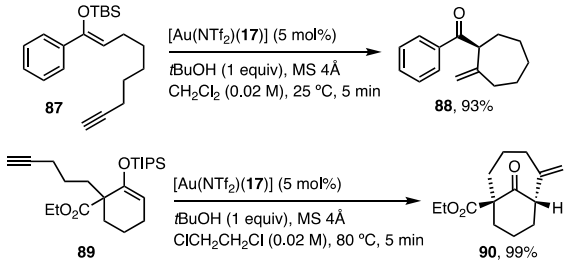
Scheme 20. Au-Catalyzed Cyclization of Silyl Enol Ethers



enol ether to alkyne has been demonstrated to give a cyclopentene hydridanone vinyl iodide derivative and was utilized to access bioactive compounds such as lycopladine A, reported by Toste and co-workers.[127]

Sawamura disclosed an efficient gold(I)−triethynylphosphine-catalyzed construction of seven-membered ring compounds through a 7-*exo-dig* cyclization of silyl enol ethers with *ω*-alkynic substituents.[128] Linear acethylenic silyl enol ether **87** cyclized to give the *β*-methylenecycloheptane derivative **88**, Scheme 21, under gold catalysis utilizing the semihollow-

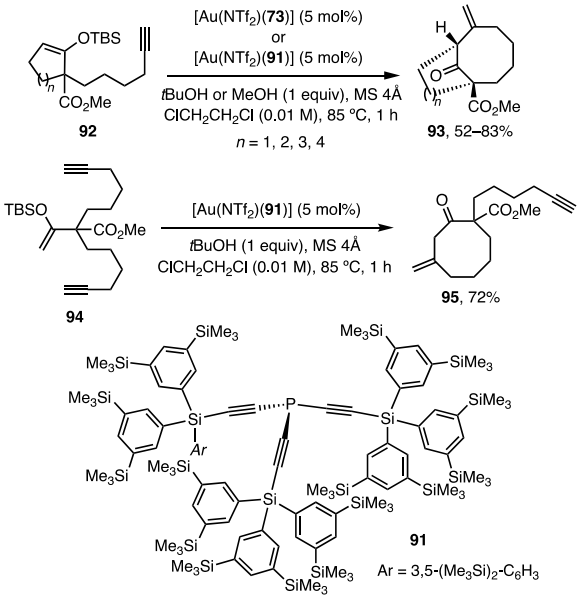
Scheme 21. Au-Catalyzed Cyclization of Acetylenic Silyl Enol Ethers



shaped triethynylphosphine ligand **17** (see Scheme 4 for the structure of the ligand). This catalytic system promoted the 7-*exo-dig* cyclization of a variety of 1,8-enynes bearing silyl enol ethers, giving seven-membered carbocycles. Related cyclic alkynyl silyl enol ethers, for example **89**, were also amenable, giving 2-methylene bicyclo[4.3.1]decane structures, **90**.

Similarly, the 8-*endo-dig* annulation in 1,8-enynes bearing silyl enol ethers to form eight-membered carbocycles with a bicyclo[5.*n*.1]alkane structures[129] could also be promoted using ligand **73** (see Scheme 17 for the structure), the modified carbon analogue of the triethynylphosphine **17**. Ligand **91** made by alteration to triethynylphosphine **73** at the acetylenyl terminus with a bis(trimethylsilyl)phenyl-based end cap also showed considerable and, in some cases, better efficiencies. Thus, several monocyclic siloxyalkenes with appended acetylenic moieties **92** underwent cyclization, providing access to compounds with eight-membered ring structures **93** within a bicyclic alkane framework, Scheme 22.

Scheme 22. Preparation of 8-Membered Carbocycles from Acetylene-Tethered Silyl Enol Ethers via Gold Catalysis



The reaction is not limited to the construction of fused ring systems but also applicable to the synthesis of nonfused eight-membered carbocycles. For example, preparation of the monocyclic compound **95** from the Au(I)-catalyzed 8-*exo-dig* cyclization of the acyclic acetylene-tethered siloxyalkane **94** was obtained in good yield using a combination of Au(I) and ligand **91**.

3.1.3. Hydroarylation. Gold complexes are also efficient catalysts in mediating hydroarylation processes,[130] which involves addition of Ar−H across the alkynyl triple bond. Construction of medium-sized ring compounds through gold-catalyzed hydroarylation has been successfully employed in the synthesis of complex natural products.

For example, Snyder reported a 9-*exo-dig* ring closure via an Au(III)-mediated reaction between the alkyne and the aryl moieties in the atropisomeric compound **96**, Scheme 23, affording a nine-membered carbocycle **97** in their work toward the total synthesis of caraphenol A.[131] The reactivity demonstrated in this transformation results from a cyclization mode requiring high conformational control. The starting material **96** exists as a mixture of atropisomers, **96a** and **96b**. Only **96b** underwent the productive hydroarylation, while **96a** was recovered untouched after the reaction, although atropisomer equilibration can be facilitated by heating the starting material in toluene favoring **96b**. Hence, the productive Au-catalyzed hydroarylation process requires that the alkyne moiety be in close proximity to the nucleophilic partner, a feature that is evident in **96b** and not in **96a**.

Hashmi and co-workers[132] developed an efficient Au-catalyzed synthesis of dibenzocycloheptatrienes via a selective 7-*exo-dig* hydroarylation of homopropargyl-substituted biarylic compounds **98**, Scheme 24. Dibenzocycloheptatrienes are a common motif in various pharmacophores, especially in molecules showing anticancer activities; thus, facile access to this class of compounds provides huge utilities in the context

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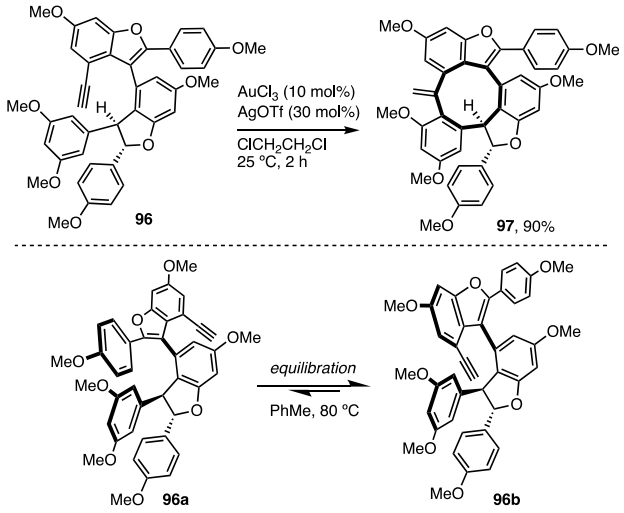
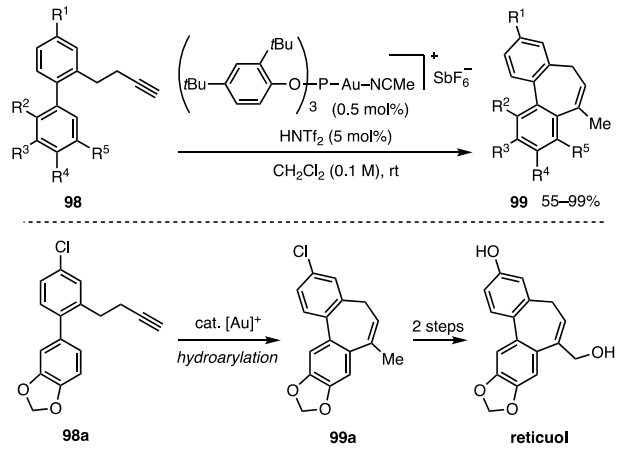
Scheme 23. Au(III)-Mediated Hydroarylation Proceeding through a 9-*exo-dig* Annulation



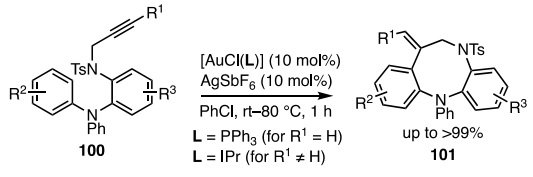
Scheme 24. Au-Catalyzed Synthesis of Dibenzocycloheptatrienes via 7-*exo-dig* Hydroarylation



of diversifying structural complexities in drug candidates. The cationic Au(I)-catalyzed intramolecular hydroarylation proceeded in good to excellent yields, giving tricyclic compounds **99**. In addition to the synthetic advantage point of using a very low catalyst loading (0.5 mol %) to enable the transformation, the strategy was applied to the first total synthesis of the tetracyclic molecule reticuol, a compound that shows inhibition of cytochrome P450 (CYP3 A4), via the intermediate dibenzocycloheptatriene derivative **99a**.

Related Au(I)-catalyzed intramolecular hydroarylation of *N*-propargyl-2-anilinoanilines **100**, Scheme 25, involving an eight-membered ring formation have been described recently by Shibata and co-workers[133] in the synthesis of dibenzo[*b*,*e*][1,4]diazocines **101**. To enable the selective 8-*exo-dig* carbocyclization the presence of an electron-withdrawing group on the nitrogen atom of the propargylamine moiety is necessary to avoid the corresponding 6-*endo-dig* cycloisomerization by decreasing the nucleophilicity at the position adjacent to the propargylamine nitrogen atom. Moreover, the choice of ligand differentiates the reactivity between terminal and internal alkynes to undergo the 8-*exo-dig* hydroarylation. While triphenylphosphine, PPh_3, showed efficiency as a ligand for terminal alkynes, the *N*-heterocyclic carbene ligand IPr was found to be more suitable in the case of substrates with internal alkynic moieties. A related regioselective synthesis of diazoninones through an Au-catalyzed intramolecular hydroarylation process was reported by Van der Eycken, providing access to diversely substituted fused nine-membered rings.[134]

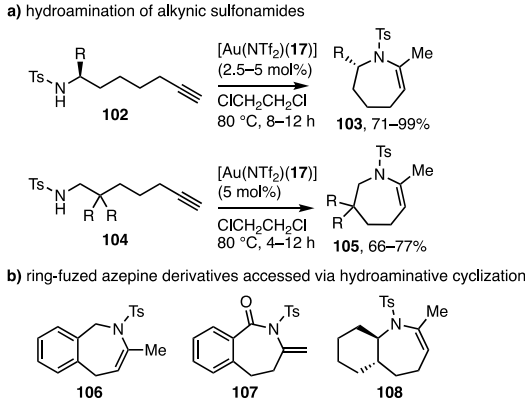
Scheme 25. Au-Catalyzed 8-*exo-dig* Hydroarylation To Access Dibenzo[*b*,*e*][1,4]diazocines



3.1.4. Hydroamination. Formal addition of a N−H bond across C−C multiple bonds in hydroamination processes has received considerable attention for expediting protocols in the preparation of nitrogen-containing molecules. Several known methodologies have been reported for the construction of *N*-heterocyclic compounds via hydroamination[68] including Au-catalyzed intramolecular hydroamination of carboxamides with unactivated alkenes,[135] trichloroacetimidates derived from propargyl and homopropargyl alcohols,[136] and spiro-*N*,*O*-ketals.[137] These hydroamination reactions gave five- or six-membered rings under exceptionally mild conditions. Preparation of compounds with a medium-sized ring through Au-mediated hydroamination is scarce and often requires substrate preorganization to enable cyclization.

Sawamura[138] disclosed a 7-*exo-dig* intramolecular hydroamination of *ω*-alkynic *N*-alkyl-*N*-sulfonamide derivatives, **102** and **104**, under gold catalysis utilizing the semihollow-shaped triethynylphosphine ligand **17**, Scheme 26a. The reaction

Scheme 26. Au-Catalyzed 7-*exo-dig* Intramolecular Hydroamination of Alkynic Sulfonamides



provides access to seven-membered *N*-containing heterocyclic compounds, **103** and **105**, in good to excellent yields. Access to compounds with bicyclic frameworks was also amenable, Scheme 26b. Thus, benzazepine derivatives **106** and **107** can be obtained from the corresponding *o*-alkynyl benzylsulfonamide and *N*-tosylbenzamide, respectively. The bicyclic compound **108** with an azabicyclo[5.4.0]decene framework can also be synthesized starting with a cyclohexane-fused sulfonamide.

The utility of the [Au(NTf$_2$)(**17**)] catalyst also proved to mediate formation of the more challenging eight-membered

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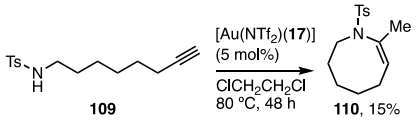
ring compound **110** starting with the acyclic ω-octanyl sulfonamide **109**. Highlighting the difficulty in the construction of eight-membered ring compounds as compared to seven-membered or smaller ring sizes, the azocine derivative **110** was isolated in 15% yield from an 8-*exo-dig* cyclization of the starting sulfonamide **109**, Scheme 27.

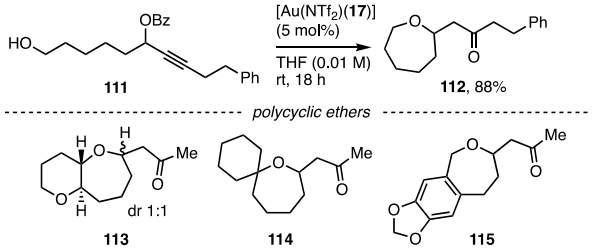
Scheme 27. Construction of an Eight-Membered Ring Compound via an 8-*exo-dig* Intramolecular Hydroamination



3.1.5. Hydroxy-Tethered Propargylic Esters. Gold catalysis has been utilized for preparation of cyclic ethers via intramolecular hydroalkoxylation of alkynyl alcohols.[139,140] Regioselective construction of functionalized bicyclic ethers has also been recently reported.[141] Beyond construction of five- or six-membered cyclic ethers under gold catalysis, an efficient route to medium-sized rings through hydroalkoxylation remains challenging.

Utilizing the semihollow-shaped triethynylphosphine ligand **17** under gold catalysis, Sawamura and co-workers[142] succeeded in the construction of not only six-membered ring ethers but also a variety of seven-membered oxepines by cyclization of hydroxy-tethered propargylic esters, Scheme 28.

Scheme 28. Au-Catalyzed Cyclization of Hydroxy-Tethered Propargylic Esters

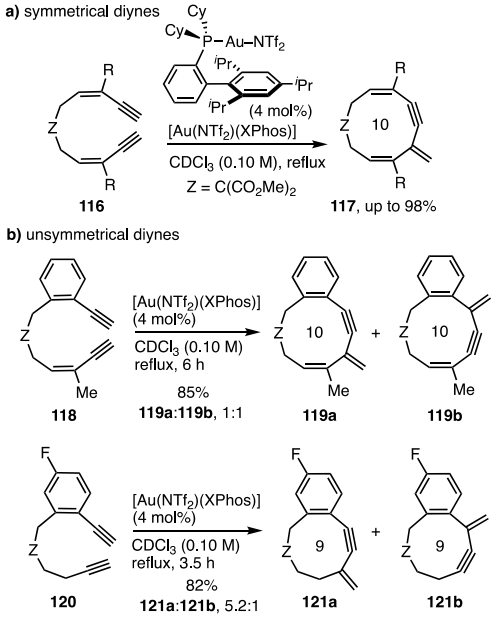


The reaction likely proceeds via the Au-catalyzed hydroalkoxylation of the intermediary allenyl ester from the corresponding hydroxy-tethered propargylic ester. Ligand **17** is thought to enhance the reaction efficiency by ensuring that the electrophilic Au-bound intermediate adopts a bent conformation, fitting into the ligand cavity or chemical space that results in a closer proximity to the nucleophilic center. Thus, cyclization of hydroxy-tethered propargylic esters such as **111** results in the seven-membered oxepine derivative **112**. The methodology also provided access to polycyclic ethers bearing seven-membered rings such as the diastereomeric tetrahydropyran-annulated 6,7-fused bicyclic diether **113**, a 5,6-spiro compound **114**, and a benzoxepine derivative **115**.

3.1.6. Diynes. Construction of compounds with medium-sized rings using dienyne derivatives has also been investigated. Gagosz and co-workers reported the utilization of bis-enynes toward 9- or 10-*exo-dig*-selective cycloisomerization providing medium-sized cycloalkynes.[143] Symmetrical diynes **116** gave 10-membered cycloalkynes **117** by Au(I)−XPhos-catalyzed 10-*exo-dig* cycloisomerization, Scheme 29a.

Likewise, unsymmetrical diynes, Scheme 29b, reacted cleanly, providing isomeric mixtures of 10-membered cyclo-

Scheme 29. Au-Catalyzed Cyclization of Hydroxy-Tethered Propargylic Esters

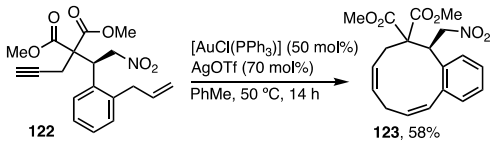


diynes such as **119** from the cycloisomerization of the benzofused diyne derivative **118**. Nine-membered cycloalkyne **121** was also furnished from substrate **120**, resulting from a 9-*exo-dig* cycloisomerization. In these transformations, the products arise from alkyne−alkyne coupling without any detectable formation of byproducts. Moreover, a dual reactivity of the gold catalyst was proposed: conventional electrophilic activation of alkyne via π-coordination and nucleophilic activation via formation of gold acetylide.[144]

3.2. Endo Cyclization

3.2.1. Enyne Cycloisomerization. In direct comparison to the gold-mediated exo cyclization of enynes, efficient syntheses of carbo- and heterocycles through endo cyclization of larger 1,*n*-enynes ($n > 7$) are limited and the preparation of compounds with medium-sized rings using this strategy are scarcely accessible. A rare example for the utility of 1,9-enynes to construct 10-membered ring structures was demonstrated by Porco and co-workers,[126] Scheme 30. Construction of the

Scheme 30. Formation of 10-Membered Ring Compound from 1,9-Enyne



10-membered ring compound **123** from the thermolysis of **122** via gold catalysis operated on an endo cyclization; however, it required the use of a high catalyst loading (50 mol %) to give a moderate yield.

Waldmann, Kumar, and co-workers[145] reported access to functionalized eight-membered ring benzoxocine derivatives **126** through an Au-catalyzed 8-*endo-dig* cyclization of 1,7-enynes **124**, Scheme 31. Activation of the acetylene unit by gold results in an 8-*endo-dig* cyclization onto the alkene and by the stereoelectronic effect of the phenoxy moiety forms an

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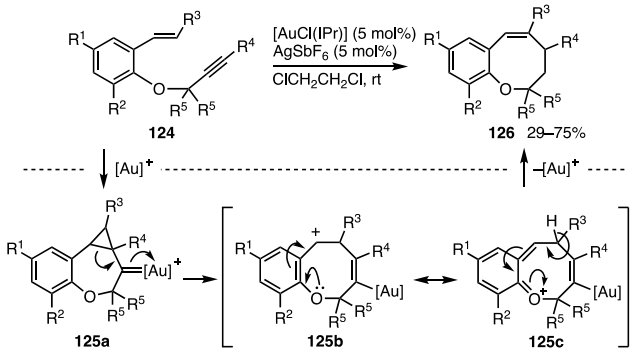
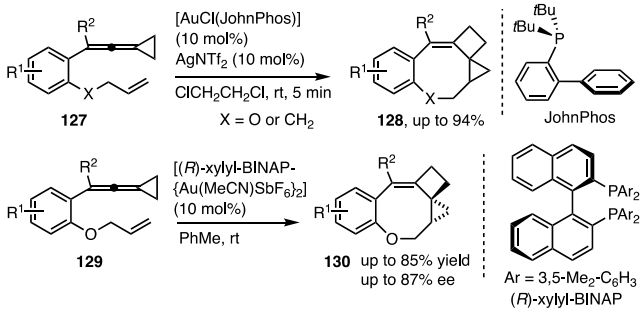
Scheme 31. Enyne Cycloisomerization Affording 8-Membered Benzoxocine Derivatives



intermediary cyclopropane species **125a**. The opening of the latter followed by protodeauration, **125b** to **125c**, gives the eight-membered cyclic ether benzoxocines **126**. It should be noted, however, that substrates lacking the phenoxy moiety failed to induce any cyclization reaction. The strategy has been useful for the synthesis of natural products bearing the benzoxocine framework, particularly the family of heliannane compounds which possess the 2*H*-1-benzoxocine structure.

3.2.2. Vinylidenecyclopropanes as Nucleophile. Vinylidenecyclopropanes, compounds with a strained cyclopropyl unit connected to an allene moiety, are thermally stable and versatile intermediates in various transition-metal-catalyzed transformations.[146] Tang, Shi, and co-workers[147] demonstrated that gold carbenoid intermediates from vinylidenecyclopropane−enes could be captured by an appended allyloxy group via cyclopropanation, Scheme 32. The vinylidenecyclopropane

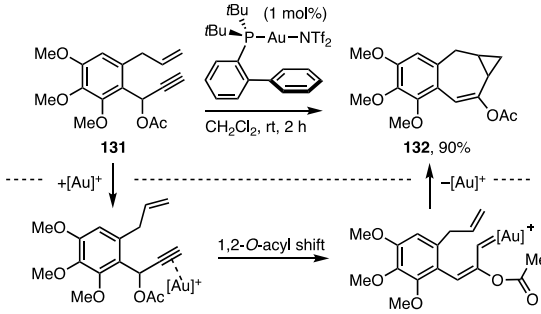
Scheme 32. Cycloisomerization of Vinylidenecyclopropanes



127 acts as a nucleophile upon alkene activation by the Au(I) complex. Subsequently, as a consequence of its amphiphilic nature to generate gold carbenoid species, the activated vinylidenecyclopropane then undergoes ring expansion as an electrophile. The reaction employing [AuCl(JohnPhos)] as catalyst smoothly delivered the fused eight-membered ring compounds **128**. An asymmetric variant of this transformation was also successfully developed using chiral xylyl-BINAP as ligand, delivering the enantioenriched products **130** from the corresponding vinylidenecyclopropane−ene **129** in good yields. Recently, Ren, Miao, and co-workers also disclosed a divergent synthesis of furan-fused N,O-heterocycles through Au-catalyzed cycloisomerizations.[148]

3.2.3. Acyloxy Rearrangement. Intramolecular migration of the acetoxy group in gold catalysis, which typically involves 1,2- or 1,3-migration of a propargyl ester, has been the subject of considerable studies in recent years.[149,150] Gold-catalyzed cyclization of 1,7-enynes with propargylic acetates leads to tricyclic derivatives usually with high stereoselectivity.[151] Hanna utilized this strategy in the synthesis of the seven-membered benzofused tricyclic compound **132** starting from the propargylic acetate **131**, Scheme 33, in their work toward

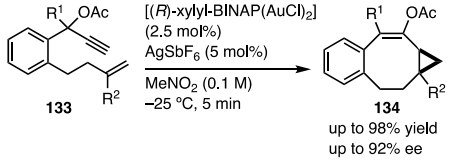
Scheme 33. Au-Catalyzed Acyloxy Rearrangement of Propargylic Acetate



the synthesis of a new class of allocolchinoids.[152] The methodology was also demonstrated to be applicable to the synthesis of eight-membered MSRs. This cyclization results from the 1,2-acyloxy migration in the polarized gold−alkyne complex, leading to formation of a gold carbene intermediate. The process continues with the intramolecular cyclopropanation of the alkenyl C=C double bond, giving the tricyclic compound. While a competing 1,3-*O*-acyl rearrangement[149] is possible to give allene acetate derivatives, in the case of substrate **131**, ring closure of the intermediate occurred exclusively, delivering the cycloheptyl compound **132**.

The enantioselective synthesis of eight-membered ring compounds can also be achieved using this strategy, Scheme 34. Toste reported the Au-mediated asymmetric intra-

Scheme 34. Au-Catalyzed Asymmetric Intramolecular Cyclopropanation



molecular alkene cyclopropanation of propargylic acetates **133** to afford medium-sized ring compounds **134** in excellent yields and enantioselectivities.[153] The reaction is similarly proposed to involve a 1,2-shift of the propargyl acetate to generate an Au-stabilized vinyl carbenoid.

Construction of medium-sized ring ethers and aza-heterocycles through a sequential cascade reaction involving a gold-catalyzed cycloisomerization coupled with cycloaddition was developed by Xie, She, and co-workers.[154−156] On the basis of their initial report on a cascade reaction that proceeds through 1,2-acyloxy migration/[3 + 2] cycloaddition of enynyl esters,[154] She and co-workers developed an Au(I)-catalyzed 1,2-acyloxy migration of dieneyne derivatives[155] such as **135** generating a gold carbene species **136**, Scheme 35. Carbonyl lone pair addition to the latter then gives a 1,3-dipole trapped with an internal alkene via an intramolecular [3 + 2] cycloaddition, **137** to **138**, leading to formation of a tricyclic acetal **138** which upon hydrolysis affords compound **139** with

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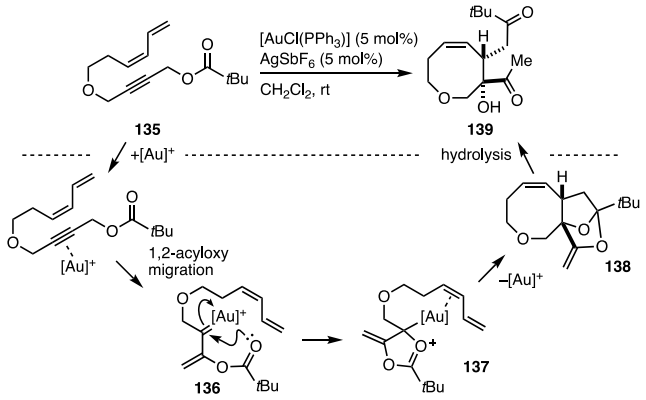
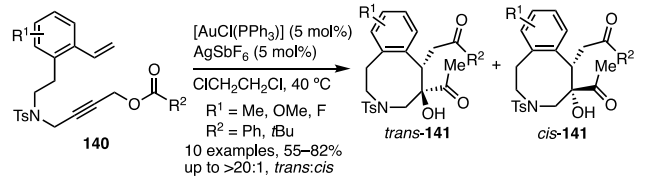
Scheme 35. Au-Catalyzed 1,2-Acyloxy Migration/[3 + 2] 1,3-Dipolar Cycloaddition of Dieneyne



an eight-membered ether ring decorated with two ketonic functionalities.

The possibility of replacing the internal alkene in **135** to further introduce molecular complexity was also demonstrated to be feasible. The transformation shown in Scheme 35 only works for *Z*-conjugated terminal dienes. Xie and co-workers[156] replaced the internal alkene in **135** with aryl moieties, such as styrene units, Scheme 36, and further expand the utilities to the

Scheme 36. Au-Catalyzed Synthesis of Benzazocines from 1,9-Enynyl Esters

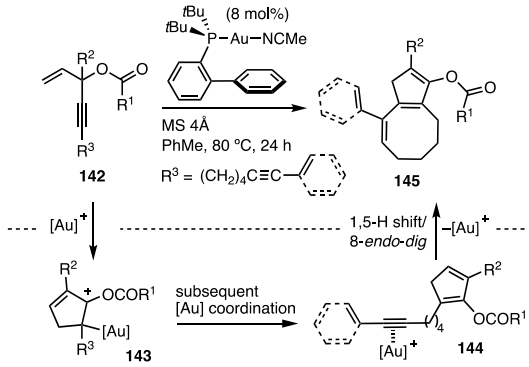


corresponding nitrogen-containing counterparts in **140**. Thus, a selection of 1,9-enynyl esters underwent the cascade reaction to give the substituted eight-membered nitrogen heterocycle benzazocine derivatives **141**. The resulting diastereoisomers were successfully isolated with the *trans*-**141** being the major product.

Recently, Chan also demonstrated a methodology for construction of cyclopenta[8]annulene frameworks including compounds with a bicyclo[6.3.0]undecane skeleton.[157] Utilizing 1-ene-4,10-diynyl esters **142** as starting materials under gold catalysis, a double cycloisomerization provides an expedient strategy for construction of both ring components of bicyclic compounds **145**, Scheme 37. Following the first alkyne activation by the gold catalyst, the remaining alkyne group in the putative cyclopentenyl gold complex **143** is believed to further coordinate with the Au catalyst to give the Au(I)-activated species **144**, which is susceptible to a sequential 1,5-hydride shift/8-*endo-dig* cyclization reaction. Upon deauration, the desired compound **145** containing a cyclooctane motif can be isolated in good yields.

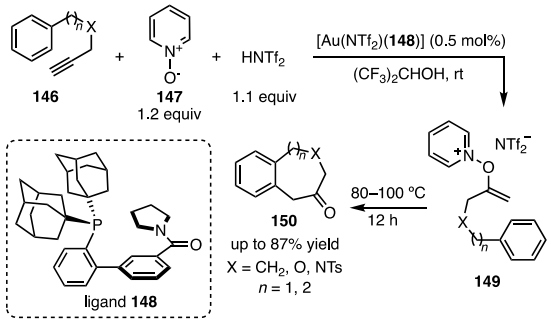
3.2.4. α-Oxocarbenium Ions. Having a core structure consists of an sp^2-hybridized carbon center and an oxygen substituent; oxocarbenium ions are reactive chemical species where the overall positive charge is delocalized to either the central carbon or the oxygen atom. These species are implicated as reactive intermediates in diverse chemical transformations, leading to formation of carbon−carbon

Scheme 37. Double Cycloisomerization of 1-Ene-4,10-diynyl Esters



bonds, especially in the synthesis of natural products. This characteristic reactivity was employed by Zhang and co-workers in the preparation of benzofused medium-sized ring ketones based on a gold-catalysis-enabled enolate umpolung reactivity.[158] Unactivated alkyne derivatives **146** in the presence pyridine-*N*-oxide **147** and triflimide $HNTf_2$ under gold catalysis incorporating ligand **148** generate adduct **149** in hexafluoroisopropyl alcohol. The *N*-alkenoxypyridinium salt **149** upon heating leads to cyclization, forming seven- and eight-membered ketones **150** in good yields, Scheme 38.

Scheme 38. Construction of Benzene-Fused Medium-Sized Ring Ketones from Unactivated Alkynes



Addition of a stoichiometric amount of triflimide was needed to retain the catalytic activity as it was assumed that the basic pyridine set free in the course of the reaction was inhibiting the gold catalyst. The acid might be involved in protonation of the pyridine, forming a weak coordinating conjugated base, thereby avoiding deactivation of the catalyst. Cyclization of **149** does not need the presence of the gold catalyst as the isolated adduct was cyclized independent of the catalyst. Adduct **149** from the alkyne and *N*-oxide is highly electrophilic and undergoes nucleophilic substitution (S_N2') at the α-position of the carbonyl product. Thus, the reactivity shown in this transformation can be considered to arise from an umpoled enolate or enolonium ion.

3.2.5. Addition to Allenes. Cyclization reactions of allenes provide efficient synthetic routes to access a variety of carbocyclic and heterocyclic molecular skeletons. Early examples of Au-catalyzed cyclizations involving allenes and its derivatives gave diverse 5−8-membered ring compounds, demonstrating their utility for the preparation of MSRs.[159−163] Alcaide, Almendros, and co-workers utilized the reactivity of aryl−allene-tethered 2-azetidones **151** for

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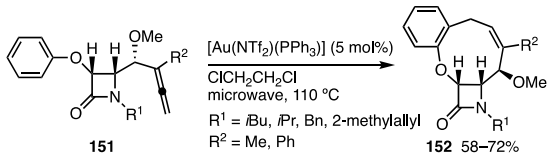
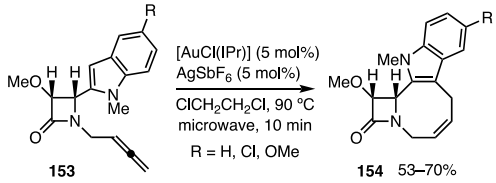
preparation of nine-membered annulated β-lactam derivatives **152** via Au-catalyzed 9-*endo*-carbocyclization,[164] Scheme 39.

Scheme 39. 9-*endo* Hydroarylation of (Aryl)allene-Tethered 2-Azetidones



Under microwave irradiation, the gold-mediated synthesis of the tricyclic system occurred efficiently, giving the fused nine-membered heterocycles in good yields. DFT calculations (PCM-M06/def2-SVP//PCM-B3LYP/def2-SVP level) support the 9-*endo* carbocyclization process as the kinetically, rate-limiting, and thermodynamically favored step over other alternative carbocyclization reactions. Utilization of β-lactam-tethered allenyl indoles **153** was also investigated for the construction of eight-membered fused tetrahydroazeto-[1′,2′:1,2]azocino[3,4-*b*]indol-2(4*H*)-ones[165] **154**, Scheme 40. The cyclization reaction mediated using an Au−IPr

Scheme 40. Intramolecular Hydroarylation of β-Lactam-Tethered Allenyl Indoles



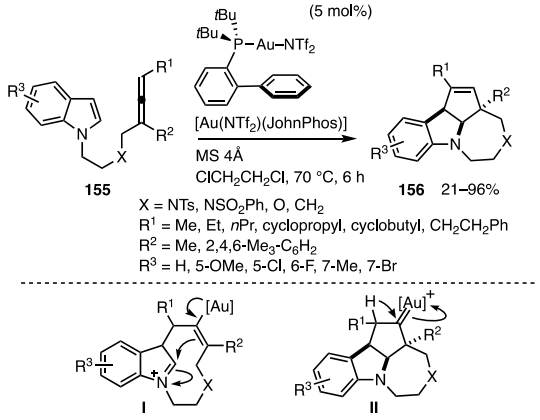
catalysts was carried out under microwave irradiation, forming regioselectively tetracyclic β-lactams by 8-*endo* carbocyclization. In a recent report, Sun and co-workers disclosed the construction of eight-membered rings through a Au-catalyzed formal cycloaddition reaction of anthranils with allenamides delivering oxa-bridged heterocycles.[166]

The [3 + 2] annulation of indolyl−allenes **155** mediated by gold has been recently described by Shi and co-workers.[167] Using a cationic gold(I) complex [Au(NTf$_2$)(JohnPhos)] as catalyst, a variety of azabenzo, oxa−azabenzo, and diazabenzo-[*a*]cyclopenta[*c*,*d*]azulene epimers **156** was isolated in good to excellent yields, Scheme 41. The proposed mechanism involves formation of heterocyclic intermediate **I**, which leads to the Au−carbene precursor **II**, overall featuring a 10-*endo*-*trig* process.

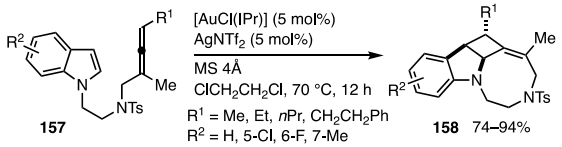
This reaction, however, is not limited to a [3 + 2] annulation as a [2 + 2] cycloaddition product **158** was also observed using an [AuCl(IPr)]/AgNTf$_2$ catalyst, Scheme 42. The resulting eight-membered diazoheterocyclic compounds were obtained in good to excellent yields. It is believed that generation of **158** results from the nucleophilic trapping of the iminium intermediate (see Scheme 41, **II**) by the carbon−Au bond. Furthermore, the ligands in the gold complex and the steric and electronic character of the R^1 and R^2 substituents were also critical to the observed product selectivities toward **156** and **158**.

3.2.6. Indoles as Nucleophile. Gold-catalyzed endo cyclizations in diynes giving indole derivative scaffolds have also been utilized for the construction of eight-membered

Scheme 41. Au-Mediated [3 + 2] Cycloaddition of Indolyl−Allenes

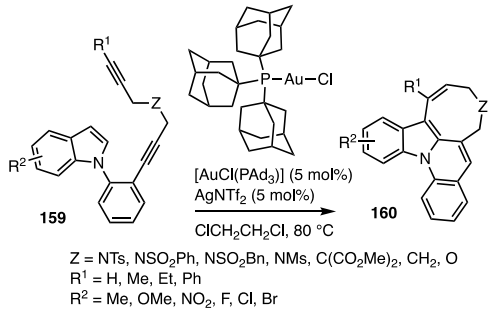


Scheme 42. Au-Mediated [2 + 2] Annulation of Indolyl-Allenes



indolizine compounds.[168] Shi and co-workers utilized *N*-substituted indoles **159** containing a tethered diyne that cycloisomerize to give eight-membered ring indoziline derivatives **160** in the presence of tri(1-adamantyl)phosphine gold complex as the catalyst, Scheme 43. This gold complex

Scheme 43. Construction of Indolizine Derivatives via Au-Catalyzed Cycloisomerization of Diynes



with the bulky phosphine ligand promotes intramolecular nucleophilic attacks of the two activated internal alkynes at the C2 and C3 positions of indole under thermal treatment. Such processes afford a variety of 1,8-disubsituted indolizines in good yields. Interestingly, the gold-mediated transformation tolerated a range of sulfonyl derivatives as nitrogen-protecting groups in cases when the alkynyl group connector (*Z*) is amine based. Ether and esters can also be used as the connector of the two alkyne moieties. Indolizines are extremely useful not just as pharmaceutical targets but also for their fluorescence properties; thus, the methodology offers potential applications to access molecular frameworks in the field of spectroscopy and OLEDs.

Available methodologies including the catalyst-controlled reactivity of (indolyl)alkyne-tethered lactams[169] and the strategic generation of bridged indole alkaloid-like hetero-

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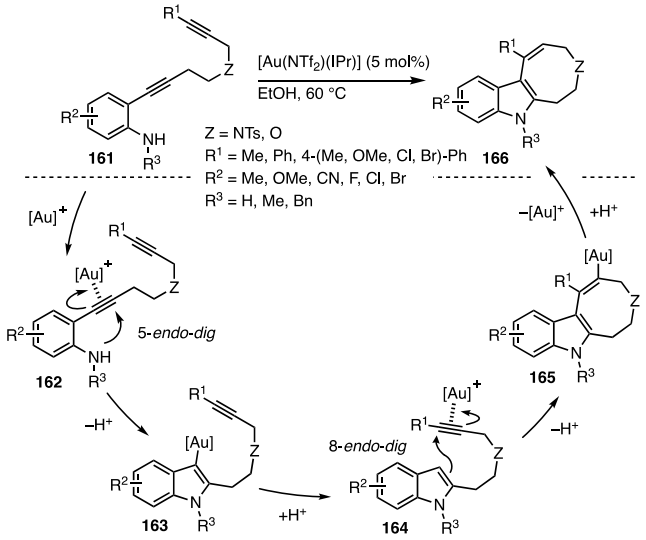
cycles[170,171] under Au catalysis paved the way for a surge of streamlined processes in accessing MSRs. More recently, access to eight-membered ring-fused indoles through a cascade cyclization of anilines with diynes via Au-catalyzed intramolecular tandem 5-*endo-dig* hydroamination/8-*endo-dig* cycloisomerization was reported by Ohno, Inuki, and co-workers.[172] Cyclization of *N*-substituted anilines **161** bearing two alkynyl moieties linked by either tosylamide or an ether functional group (*Z* = NTs or O), Scheme 44, in the presence of an Au−

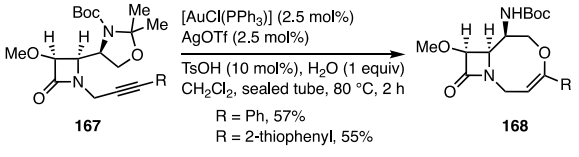
Scheme 44. Synthesis of Eight-Membered Oxocine-Fused Indoles by Au-Catalyzed Cascade Cyclizations



NHC (IPr) complex as the catalyst efficiently gives the eight-membered cyclized oxocine-fused indole derivatives **166**. The choice of gold catalyst and solvent are both crucial in this transformation as a competitive reaction giving propellane-type indolines was also observed. The cascade cyclization commences with the Au-activated alkyne **162** which has the propensity to promote a 5-*endo-dig* cyclization followed by protodeauration, **162** to **163**, giving the indole intermediate **164**. Subsequently, activation of the second alkyne moiety leads to an 8-*endo-dig* hydroarylation event to give **165**, which undergoes protodeauration to give the eight-membered ring product **166**.

3.2.7. *O*-Nucleophiles. Intramolecular *O*-nucleophilic cyclization has been investigated by Alcaide, Almendros, and co-workers in assembling eight-membered heterocycles.[173] Cyclization precursors consisting of enantiopure alkynyloxazolidine-tethered 2-azetidones **167** were transformed into annulated *β*-lactams **168** chemoselectively under mild conditions employing gold catalysis, Scheme 45. Nonterminal alkynes delivered the desired bicyclic compounds without deleterious effects on the sensitive four-membered lactam ring.

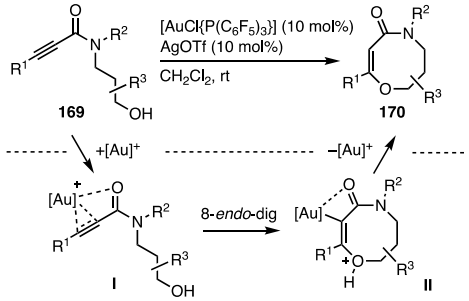
Scheme 45. Au-Catalyzed 8-*endo* Oxycyclization of Alkynyloxazalidines



Since different reactivity patterns were observed between terminal and nonterminal alkynyl substrates, with the former delivering tricyclic *N,O* aminals, it was proposed that the eight-membered ring fused with the lactam moiety was generated by participation of the oxygen atom, enabling the cyclization event. Thus, reaction of alkynyloxazalidines **167** giving the 1,5-oxazocine derivatives **168** results from an exclusive 8-*endo* oxycyclization initiated by attack of the oxygen atom to the external alkyne carbon. The stereoelectronic effect of the propargylic N atom may facilitate endo cyclization.

Intramolecular hydroalkoxylation of electron-deficient alkynes has been reported by Schreiber to generate eight-membered oxazocenone derivatives **170** from the corresponding hydroxy ynamide **169**,[174] Scheme 46. Use of an electron-

Scheme 46. Au-Catalyzed 8-*endo-dig* Cyclization Giving Oxazocenones



deficient phosphine-ligated gold complex along with AgOTf at room temperature resulted in the highly selective formation of oxazocenone in good yield. Mechanistically, the reaction may involve the dual *π* and *σ* Lewis acidic properties of the gold phosphine complex, $[AuP(C_6F_5)_3]^+$. The hydroalkoxylation reaction of **169** promoted by activation of the amide carbonyl moiety by gold, as in **I**, coupled with the proposed bidentate coordination of gold with the internal alkyne favors an 8-*endo-dig* cyclization of the alcohol, giving the cyclized intermediate **II**. The product was obtained after the subsequent protodeauration of **II**. Extension of the reactivity to terminal alkynes and secondary amides resulted in low conversions.

4. BIARYL COUPLING

An intramolecular coupling of simple arenes tethered to arylsilanes for highly selective generation of 5−9-membered ring compounds was developed by Lloyd-Jones and co-workers.[175] In the presence of the precatalyst $[(tht)AuBr_3]$ (tht = tetrahydrothiophene) and an active oxidant prepared in situ from $PhI(OAc)_2$ and camphorsulfonic acid (CSA) in $CHCl_3$/MeOH, construction of medium-sized 7−9-membered rings from the corresponding arylsilanes with a tethered arene, Scheme 47, proceeded efficiently.

For example, seven-membered dibenzoannulenes, oxepines, and azepines **171** and **172** can be constructed from the corresponding aryl group tethered to a trimethyl(phenyl)-silane. The conformational flexibility of the tethering chain connecting the two arenes can be extended to allow the synthesis of larger ring compounds including eight-membered dibenzo-oxocine **173** and nine-membered dibenzo-oxonine **174** frameworks. Extensive experimental and mechanistic studies reveal that tethering the arene to the arylsilane better promotes the C−H auration step as compared to the intermolecular variant of this reaction.[176]

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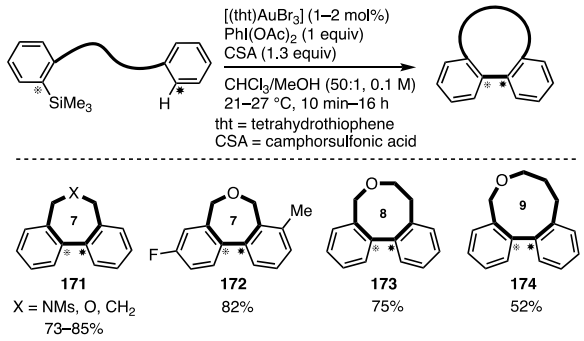
Scheme 47. Au-Catalyzed Biaryl Coupling Affording Medium-Sized Ring Compounds



5. SUMMARY AND OUTLOOK

Cyclization reactions catalyzed by gold for the preparation of compounds with seven-membered[177−184] and medium-sized ring frameworks has become an enabling tool for introducing molecular diversity and complexities. The ability of gold complexes to activate unsaturated moieties as a consequence of their relativistic effects has paved the way to utilization of diverse classes of substrates including alkynes, alkenes, and allenes. The electronic and steric nature of the ligands employed in the Au-catalyzed preparations of MSRs effectively direct unique reaction patterns in building distinct scaffolds. Gold complexes with more electron-donating *N*-heterocyclic carbenes have been utilized to induce reactivity toward cycloisomerizations in allene−enones through tandem reactions (see Scheme 9), intramolecular macrocycloadditions of enynes that lead to the preparation of significant sesquiterpenes (Scheme 19), synthesis of benzoxocine frameworks (Scheme 31), and the corresponding hydroarylation (Scheme 40) and annulation (Scheme 42) of various allenyl derivatives. On the other hand, the utility of phosphine ligands for various Au-mediated carbophilic activations has been exploited extensively to invoke greater reactivity and modulating selectivity for both stepwise and direct cyclizations. In addition to conventional triaryl- or trialkylphosphines, Buchwald ligands (JohnPhos, XPhos, etc.) and derivatives (i.e., ligand **148**) have been used broadly in Au-catalyzed preparations of MSRs encompassing a wide range of substrate classes for different cyclization processes. Gold−phosphite (Scheme 24) and other Au complexes bearing novel σ-acceptors (Scheme 16) also proved useful for this purpose. Semihollow-shaped triethynylphosphine ligands bearing a deep metal binding cavity in their frameworks (**17**, **73**, **91**) enabled the accelerated formation of MSRs that are difficult to access using commonly utilized catalytic systems, implying the importance of ligand design to achieve desirable activation.[185] Moreover, structural biases in substrates also play crucial roles in the reactivity and selectivity outcomes of the transformations. For example, the presence of multiple unsaturation sites (C═C or C≡C), geminal-disubstituted moieties, stereoelectronic effects mediated by heteroatoms in the substrates, and propensities to form cyclized intermediates through preorganization in substrates greatly influence the reactivity patterns for the synthesis of MSRs. While transannular interactions have been a major challenge in MSR formation, a survey of the reactivity presented in this review implies potential effects of sp^2-hydridized atoms or moieties (alkenes, aromatics, heteroaryls) present in the substrate or the resulting cyclized products in allowing facile ring formation. In some instances, regioselectivity reversal for the preparation of MSRs has been observed using other transition-metal catalysts,[61,177,186] further highlighting the ability of Au complexes to drive selective carbocyclization and heteroannulations.

Overall, application of gold-catalyzed cyclization in the synthesis of complex scaffolds that are challenging to access using other known methodologies has truly emphasized the utility of gold-mediated processes. The explosive development of Au-catalyzed reactions for construction of these rings can also be a starting avenue for the development of atom-economical benign green processes for creation of fine chemicals, natural products, and pharmaceuticals and aid in various industries including agrochemicals and food manufacturing. Finally, medium-sized ring compounds are underrepresented in screening and drug libraries because of the challenges associated with their synthesis. It is with ardent hope that gold catalysis will change this landscape in the next few years with the robust development of strategies to access these carbocycles and heterocyclic frameworks, eventually placing gold at the center stage of the synthetic arena.

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Notes

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ABBREVIATIONS

Ad	1-adamantyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
CSA	camphorsulfonic acid
DFT	density functional theory
IPr	1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)-imidazole-2-ylidene
JohnPhos	(2-biphenylyl)di-*tert*-butylphosphine
*m*CPBA	*meta*-chloroperoxybenzoic acid
Ms	methanesulfonyl
MSRs	medium-sized rings
Ts	*p*-toluensulfonyl
Piv	pivaloyl
Tf	trifluoromethanesulfonyl
TBS	*tert*-butyldimethylsilyl
TIPS	triisopropylsilyl
tht	tetrahydrothiophene
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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