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Gold-Catalyzed Tandem Reactions of Methylenecyclopropanes and Vinylidenecyclopropanes

DI-HAN ZHANG, XIANG-YING TANG,* AND MIN SHI*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, People's Republic of China

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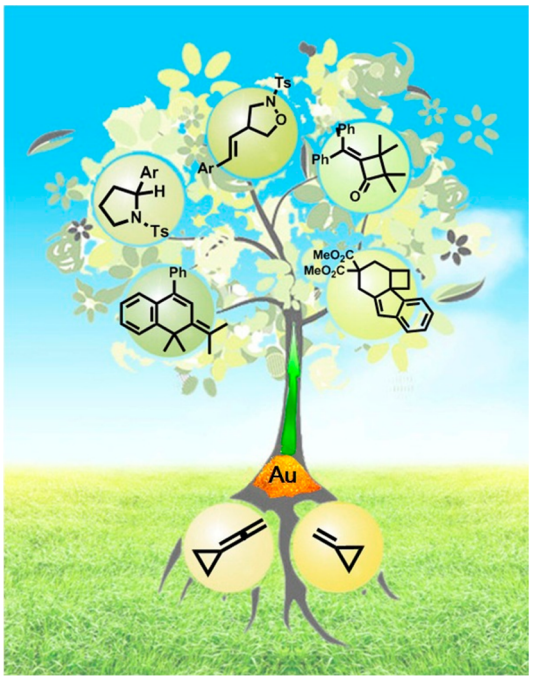
CONSPECTUS

Gold catalysis is often the key step in the synthesis of natural products, and is a powerful tool for tandem or domino reaction processes. Both gold salts and complexes are among the most powerful soft Lewis acids for electrophilic activation of carbon−carbon multiple bonds toward a variety of nucleophiles. The core of these reactions relies on the interaction between gold catalysts and π-bonds of alkenes, alkynes, and allenes. Activation of functional groups by gold complexes provides a useful and important method for facilitating many different organic transformations with high atom efficiency.

Although they are highly strained, methylenecyclopropanes (MCPs) and vinylidenecyclopropanes (VDCPs) are readily accessible molecules that have served as useful building blocks in organic synthesis. Because of their unique structural and electronic properties, significant developments have been made in the presence of transition metal catalysts such as nickel, rhodium, palladium, and ruthenium during the past decades. However, less attention has been paid to the gold-catalyzed chemistry of MCPs and VDCPs. In this Account, we describe gold-catalyzed chemical transformations of MCPs and VDCPs developed both in our laboratory and by other researchers.



Chemists have demonstrated that MCPs and VDCPs have amphiphilic properties. When MCPs or VDCPs are activated by a gold catalyst, subsequent nucleophilic attack by other reagents or ring-opening (ring-expansion) of the cyclopropane moiety will occur. However, the C−C double bonds of MCPs and VDCPs can also serve as nucleophilic reagents while more electrophilic reagents are present and activated by gold catalyst, and then further cascade reactions take place as triggered by the release of ring strain of cyclopropane. Based on this strategy, both our group and others have found some interesting gold-catalyzed transformations in recent years. These transformations of MCPs and VDCPs can produce a variety of polycyclic and heterocyclic structures, containing different sized skeletons. Moreover, we have carried out some isotopic labeling experiments and computational studies for mechanistic investigation. These reactions always give the desired products with high level control of chemo-, regio-, and diastereoselectivities, making them highly valuable for the synthesis of natural products and to the pharmaceutical industry and medicine in general.

1. Introduction

Methylenecyclopropanes (MCPs) and vinylidenecyclopropanes (VDCPs) are highly strained but readily accessible and adequately reactive molecules that can serve as useful building blocks in organic synthesis.[1,2] MCPs and VDCPs can undergo a variety of ring-opening reactions because

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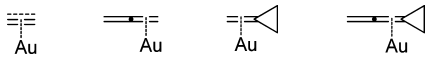
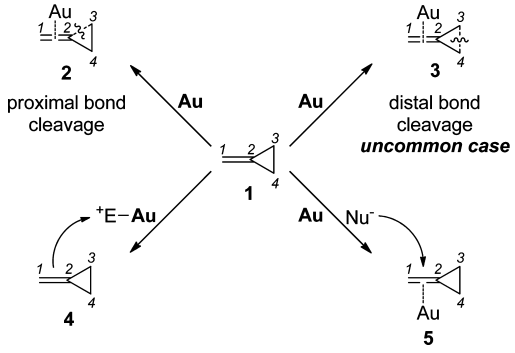
SCHEME 1. Interaction between Gold Catalyst and π-Bonds



SCHEME 2. Gold-Catalyzed Reaction Patterns of MCP **1**

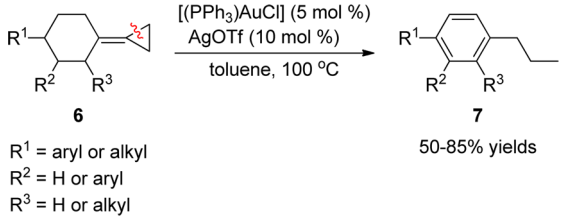


the release of cyclopropyl ring strain provides a thermodynamic driving force and the π-character of the three-membered ring bonds affords the kinetic opportunity to initiate the unleashing of the strain.[3] Over the last few decades, due to their unique structural and electronic properties, the chemistry of MCPs and VDCPs has been widely explored in the presence of transition metal catalysts.

Owing to the efficiency with which alkenes, alkynes, and allenes can be activated by homogeneous gold catalysis, this method has undergone significant developments in many organic transformations in recent years.[4] The most common reaction pattern is the addition of nucleophiles to unsaturated C−C bonds, initially activated by the gold complex acting as a powerful soft Lewis acid, to efficiently construct new carbon−carbon or carbon−heteroatom bonds. In this regard, the development of new methods that explore the scope of other functional groups in the gold-catalyzed reactions has gained momentum.

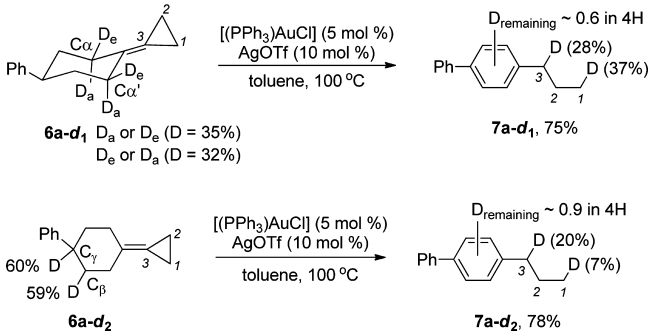
Besides alkenes, alkynes, and allenes, MCPs and VDCPs, due to the cyclopropane moiety that can increase the s-character of the C−C double bonds, are also excellent π-donation components and suitable to be used as substrates in gold-catalyzed reactions (Scheme 1). It has been disclosed that substituents on the terminus of the double bond or cyclopropyl ring of MCPs and VDCPs significantly affect the reaction pathways, and some interesting transformations have been found during the past decade by our group and others. However, this field has not been thoroughly reviewed. In this Account, we will summarize the development of various novel types of gold-catalyzed tandem reactions of MCPs and VDCPs.

SCHEME 3. Gold(I)-Catalyzed Dehydrogenated Rearrangement of MCPs **6**



R^1 = aryl or alkyl
R^2 = H or aryl
R^3 = H or alkyl

SCHEME 4. Deuterium Labeling Experiments for the Rearrangement of MCPs **6a**-d_1 and **6a**-d_2



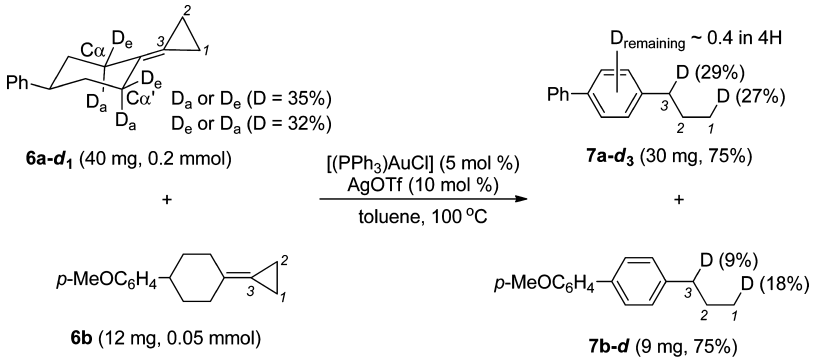
2. Gold-Catalyzed Tandem Reactions of MCPs

Gold-catalyzed reactions of MCP, **1**, can be broadly classified as four patterns depicted in Scheme 2: the proximal bond (C_2-C_3 or C_2-C_4) cleavage gives intermediate **2**, while the distal bond (C_3-C_4) cleavage gives intermediate **3** (uncommon case); alternatively, MCP, **1**, can serve as a nucleophilic species such as **4** (without ring cleavage) to react with the electrophile activated by the gold catalyst and also as electrophilic species upon activation by gold catalyst such as **5** (without ring cleavage), reacting with nucleophile.

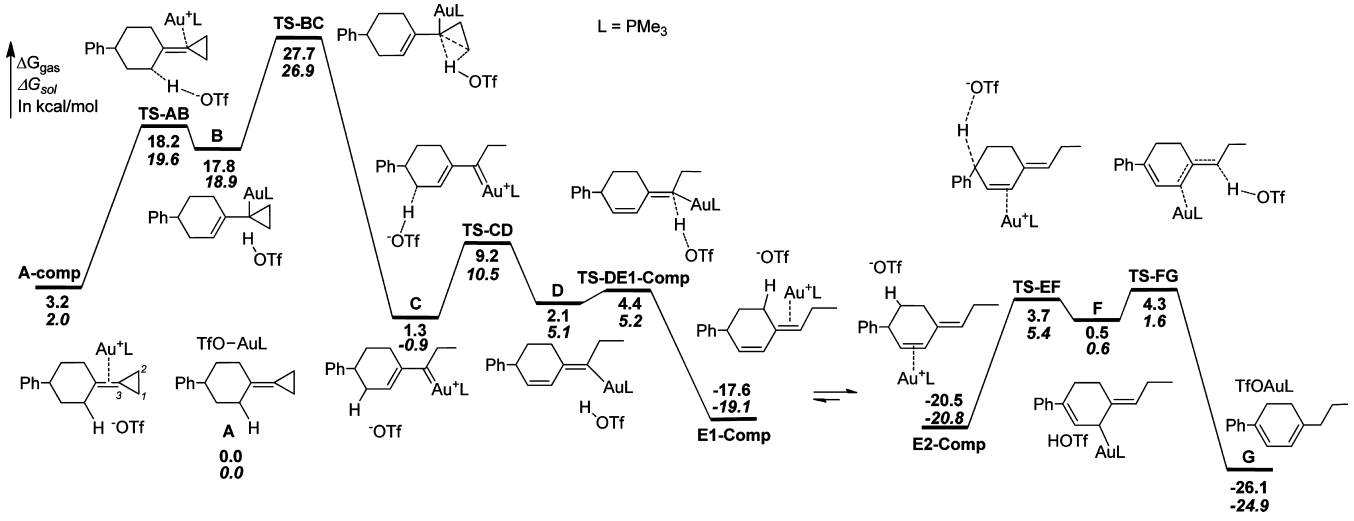
2.1. Ring-Opening Reactions along with the Proximal Bond Cleavage. More recently, catalytic processes involving C−H bond activation or C−C bond activation are highly desirable, not only because they allow the functionalization of more readily available starting materials but also because they produce clean reactions with high atom efficiency.[5] In 2010, we found that cyclohexane-containing MCPs **6**, using [(PPh_3)AuCl]/AgOTf as catalyst, could undergo tandem C−H and C−C bond activation to give multisubstituted benzene derivatives **7** in moderate to good yields (Scheme 3).[6]

Deuterium labeling experiments of MCPs **6a**-d_1 and **6a**-d_2 were carried out under standard conditions to clarify the reaction mechanism (Scheme 4). The products **7a**-d_1 and **7a**-d_2 were obtained in good yields along with D content at C_1 and C_3, suggesting that (1) the hydrogen atoms at C_α or $C_{\alpha'}$ transfer to C_1 and C_3 and (2) the hydrogen atoms at C_β or C_γ

SCHEME 5. Crossover Experiments of MCPs of **6a**-d_1 and **6b**



SCHEME 6. Proposed Mechanism of the Gold(I)-Catalyzed Tandem Reaction

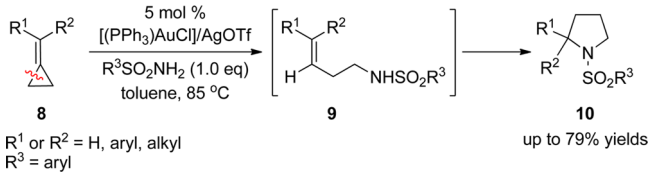


also transfer to C_1 and C_3 in the presence of gold catalyst. The crossover experiments of **6a**-d_1 and **6b** afforded products **7a**-d_3 and **7b**-*d* both with D content at C_1 and C_3, suggesting that intermolecular hydrogen transfer also takes place under the standard conditions (Scheme 5).

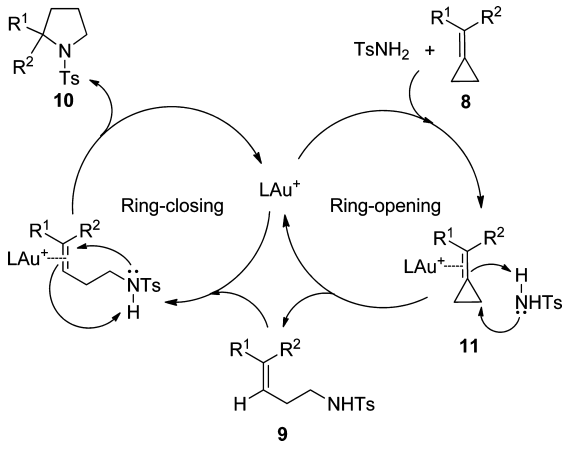
The mechanism of this novel Au(I)-catalyzed tandem C−H and C−C bond cleavage reaction has been investigated by density functional theory (DFT) studies (Scheme 6). The reaction is initiated through formation of a complex **A-comp**, in which the acidity of the α-H atom is enhanced due to the coordination of Au(I) with the double bond. Subsequently, the $^-$OTf anion abstracts an α-H atom, leading to formation of an intermediate **B**, in which Au forms a covalent bond with C_3 (2.096 Å) stabilizing the carbanion. Then the attack from the proton of HOTf results in the cleavage of the C_1-C_3 bond. The cyclopropane is opened (proximal bond cleavage), meanwhile the α-H is transferred to C_1, giving the gold carbenoid **C**. This is the rate-determining step, indicating that the whole reaction should be facilitated by the release of the strain energy of the cyclopropane ring. Passing through transition state **TS-CD** with a small energy barrier, the $^-$OTf anion next abstracts a β-H atom, yielding the alkenylgold **D**. The protonation of intermediate **D** by HOTf leads to formation of intermediate **E1-Comp**, and the [Au^+] catalyst is released. **E1-Comp** could be isomerized to **E2-Comp** via a dissociation/association process of the Au(I) catalyst and the C=C double bonds. The γ-H atom in **E2-Comp** is abstracted by the $^-$OTf anion, affording intermediate **F**, which undergoes the protonation on C_3 to give the cyclohexa-1,2-diene **G**. Based on the calculation results, the $^-$OTf/HOTf pair plays a proton-carrier role to finish up intra- and intermolecular hydrogen transfer involved in the reaction process, which is in line with the deuterium-labeling experimental results.

Nitrogen-containing saturated heterocyclic systems are important core structures in organic chemistry because of their appearance in many natural products. In 2004, upon investigation of the reactions of MCPs with sulfonamides in

SCHEME 7. Gold(I)-Catalyzed Domino Ring-Opening/Ring-Closing Hydroamination of MCPs **8**



SCHEME 8. A Plausible Mechanism for the Formation of Pyrrolidine Derivative **10**

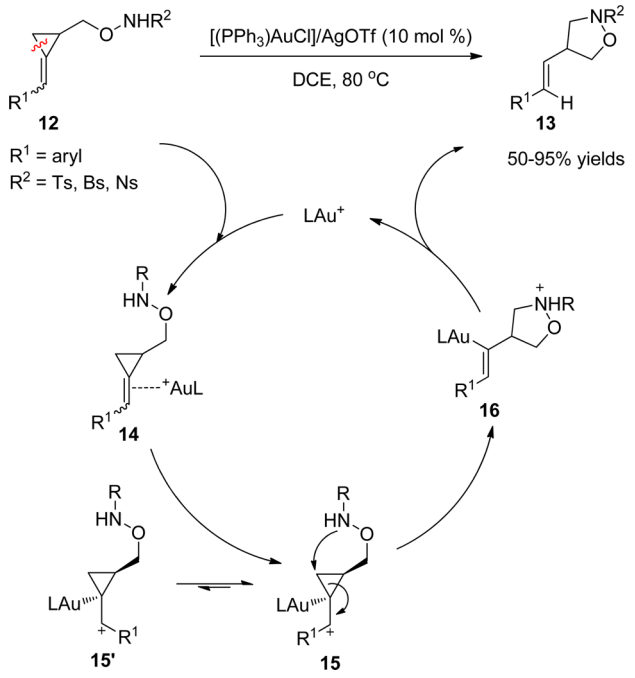


the presence of Lewis acid, we found that from alkyl-substituted starting materials, pyrrolidine derivatives **10** could be formed in low yields rather than the homoallylic sulfonamides **9**.[7] Further investigation showed that gold catalyst, a powerful soft Lewis acid, exhibited high reactivity and selectivity; thus we improved this domino ring-opening/ring-closing hydroamination of MCPs with sulfonamides to provide a facile synthetic route to pyrrolidine derivatives **10** (Scheme 7).[8]

A plausible mechanism for the formation of pyrrolidine **10** is shown in Scheme 8. Cationic Au(I) complex first coordinates to the alkene moiety of MCP **8** to give intermediate **11**. Then intermediate **11** undergoes an intermolecular hydroamination along with the ring-opening of cyclopropane (proximal bond cleavage) to give the corresponding homoallylic sulfonamides **9** and regenerate the Au(I) complex. Further activation of the alkene moiety of intermediate **9** by Au(I) complex induces a common intramolecular hydroamination to produce pyrrolidine derivative **10** (Scheme 8). It has to be mentioned that the Au(I) complex plays important roles both in the ring-opening and in the ring-closing catalytic cycles.

2-(Arylmethylene)cyclopropylcarbinols are another kind of MCP bearing an additional hydroxymethyl group and, as demonstrated by our group, can undergo a variety of

SCHEME 9. Gold(I)-Catalyzed Intramolecular Hydroamination and Ring-Opening Reaction



transformations triggered by the nucleophilic hydroxyl group. Several studies have focused on intramolecular nucleophilic addition of MCPs bearing a nucleophilic group.[9] In view of this point, we designed and synthesized a novel type of sulfonamide-substituted 2-(arylmethylene)cyclopropylcarbinol, **12**. In the presence of gold catalyst, a variety of 4-substituted isoxazolidine derivatives **13** were obtained in good to high yields with highly regioselective cleavage of C−C bond (proximal bond) cleavage of the cyclopropyl ring (Scheme 9).[10]

A plausible mechanism for the formation of this five-membered N,O-heterocycle **13** is depicted in Scheme 9. Cationic Au(I) complex first coordinates to the alkene moiety of **12** [(*E*) or (*Z*) configuration] to give intermediate **14**, which then produces a carbocationic intermediate **15**. There may be an equilibrium between intermediates **15** and **15**′, in which intermediate **15** is favored based on the formation of more stable (*E*)-configuration product. Intermediate **15** undergoes an intramolecular hydroamination along with the ring-opening of cyclopropane to give the corresponding five-membered heterocyclic intermediate **16**. Protodeauration of intermediate **16** produces the final product **13**.

An interesting structure-dependent rearrangement of MCP **17** was reported by Fensterbank and Malacria (Scheme 10).[11] They found that the length of the methylene spacer was the critical reason for the outcome of the reaction

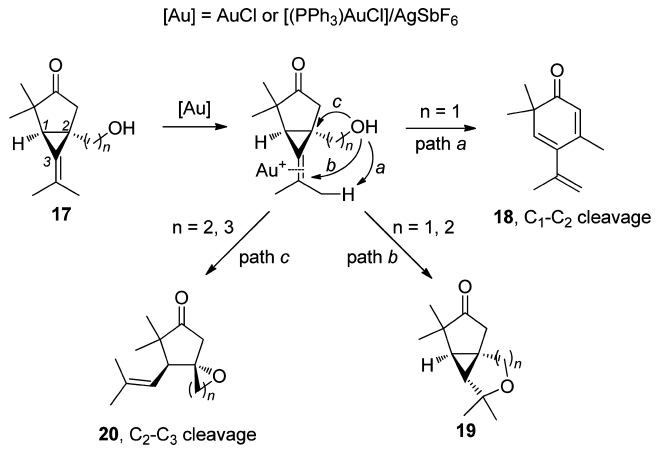
in the presence of gold catalysts. When $n = 1$, electron depletion of the methylenecyclopropane moiety induced by gold coordination promotes elimination of an allylic proton, and then this compound rearranges into the more stable $\alpha,\beta,\gamma,\delta$-unsaturated ketone **18** (distal bond cleavage). With a longer tether ($n = 2$ or 3), nucleophilic attack of the alcohol at the double bond or at the cyclopropane moiety (proximal bond cleavage) becomes faster than proton elimination, which results in tricyclic ketone **19** and spiro compound **20**, respectively.

2.2. Ring-Opening Reactions along with the Distal Bond Cleavage. In 2009, an unprecedented gold-catalyzed oxidative cross-coupling of propargylic acetates and arylboronic acid was developed involving Au(I) and Au(III) catalytic cycles in the presence of oxidants such as Selectfluor, leading to a one-step synthesis of α-arylenones.[12] On the other hand, in the process of studying the characteristics of MCPs, we also discovered an interesting diacetoxylation of MCPs in the presence of iodosobenzene diacetate via a Pd(II)/Pd(IV)[13] catalytic cycle. Inspired by these results, we then established an alternative methodology for diacetoxylation of MCPs catalyzed by Au(I)/Au(III) complexes.[14] As shown in Scheme 11, activation of MCP **21** by Au(I) induces a nucleophilic attack by AcO^- to afford intermediate **23** or allylic Au(I) species **24**, which undergoes oxidative addition with $PhI(OAc)_2$ to provide Au(III) intermediate **25**.[15] The reductive elimination of intermediate **25** produces diacetoxylated product **22**. We envisaged that the property of gold catalysts was somehow changed by $PhI(OAc)_2$ in this case. It can exclusively activate the cyclopropane ring mostly at the distal bond, leading to the distal bond cleavage by nucleophile.

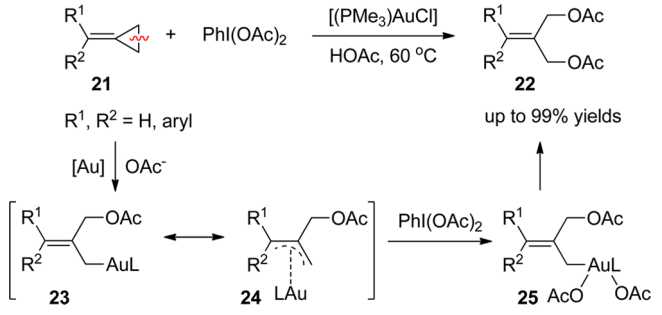
2.3. Nucleophilic Attack of the Double Bond and Ring-Expansion Reactions. Multiple-component reactions are always attractive, because they can build complex molecular structures straightforwardly in a single operation.[16] A gold-catalyzed three-component intermolecular domino reaction was investigated in our laboratory. We found that, in the presence of gold catalyst, 3-oxabicyclo[3.1.0]hexanes **29** and **29′** could be obtained in high yields and moderate diastereoselectivities when 2-(arylmethylene)cyclopropylcarbinols **26**, terminal alkynes **27**, and alcohols **28** were mixed together (Scheme 12).[17]

To confirm the mechanism of this addition reaction, we performed deuterium labeling studies with deuterated reagents. Under the standard conditions, reaction of **26a** with deuterated phenylacetylene and methanol afforded **29**-d_1 and **29′**-d_1 in 83% yield with the D atom remaining at the same carbon. Moreover, reaction of **26a** with phenylacetylene and methanol-d_4 produced **29**-d_2 and **29′**-d_2 in 90% yield with two deuterium atoms incorporated at the terminal alkynyl carbon, which indicated that the alkynyl component

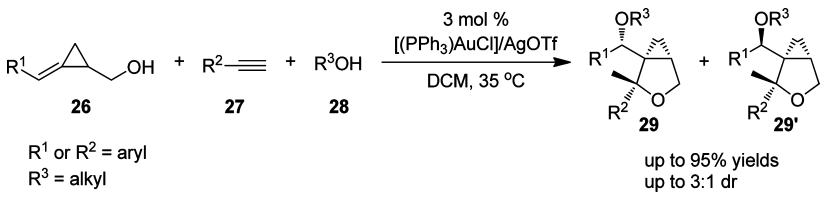
SCHEME 10. Gold(I)-Catalyzed Cycloisomerization of MCP **17**



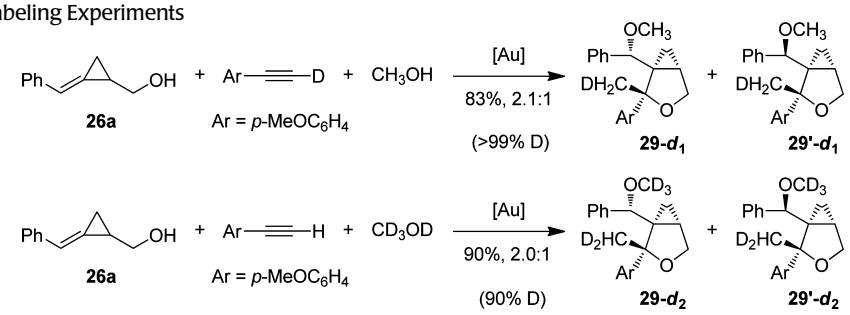
SCHEME 11. Gold-Catalyzed Diacetoxylation of MCP **21** in the Presence of $PhI(OAc)_2$



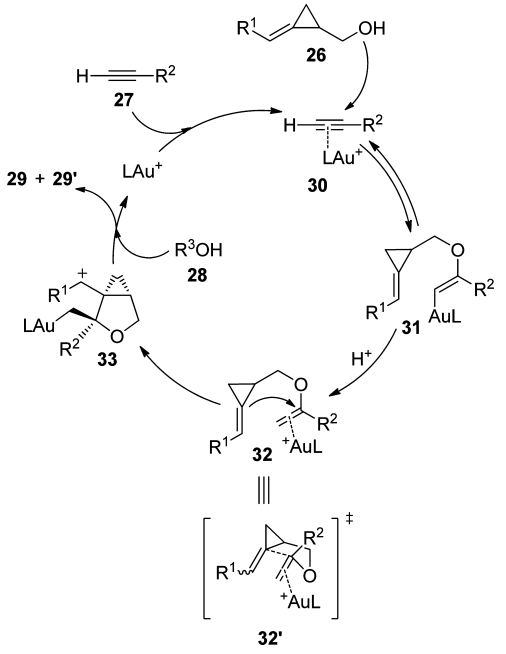
SCHEME 12. Gold(I)-Catalyzed Three-Component Intermolecular Tandem Reaction



SCHEME 13. Deuterium Labeling Experiments



SCHEME 14. A Plausible Mechanism for the Formation of 3-Oxabicyclo-[3.1.0]hexanes **29** and **29′**

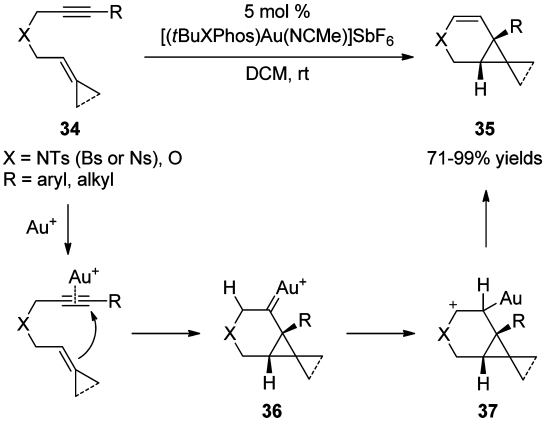


accepted twice nucleophilic attack and protodemetalation during the reaction process (Scheme 13).

A plausible mechanism involving an intermolecular tandem hydroalkoxylation/Prins-type reaction pathway has been proposed (Scheme 14). Activation of alkyne by the Au(I) complex forms intermediate **30**, which is attacked by the hydroxyl group of MCP **26** to produce vinylgold species **31**. Species **31** undergoes protodemetalation to furnish intermediate **32**. A subsequent Prins-type reaction catalyzed by gold occurred to afford intermediate **33** stereospecifically. This process may proceed via a chairlike transition state **32′**, which can account for the stereoselectivity. Trapping the organogold cation **33** with an alcohol and the following protodemetalation delivers the three-component adducts and regenerates the Au(I) catalyst.

Among these interesting gold-catalyzed reactions, cycloisomerization of enynes is one of the most important

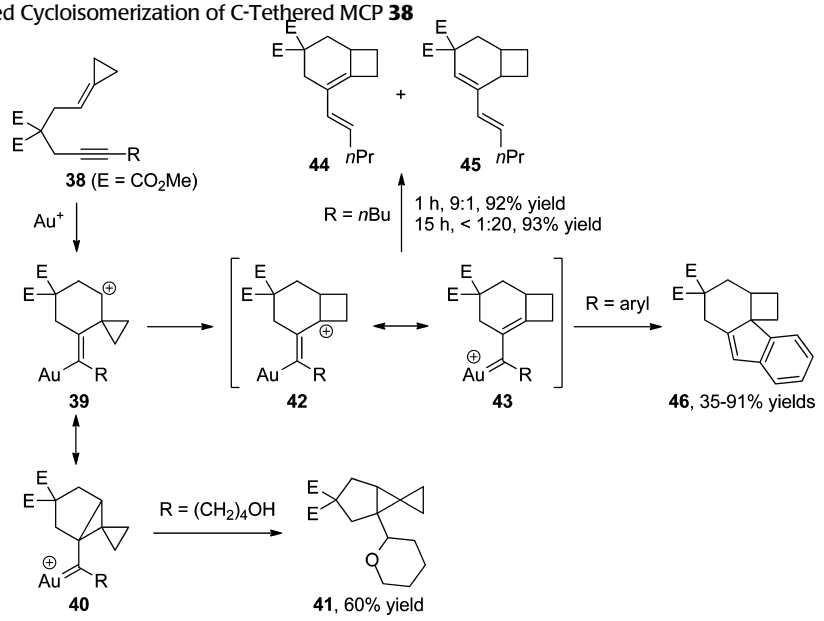
SCHEME 15. Gold(I)-Catalyzed Cycloisomerization of N- and O-Tethered MCP **34**



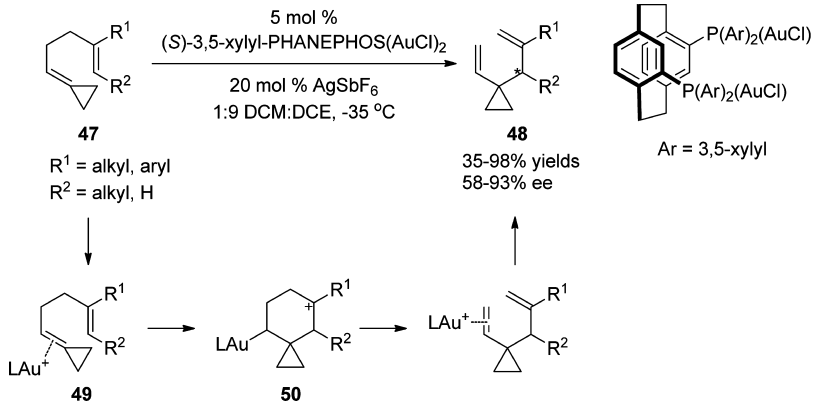
strategies for the construction of functionalized cyclic structures.[18] Nitrogen- and oxygen-bridged enynes are useful starting materials for the preparation of heterocyclic building blocks. Since Blum et al. first reported the $PtCl_4$-catalyzed cyclorearrangement of allyl propynyl ether to 3-oxabicyclo[4.1.0]heptenes in 1995,[19] this type of 6-*endo*-dig cycloisomerization has been developed by the use of transition metal catalysts such as platinum, rhodium, gold, and iridium. Recently, we reported a novel gold(I)-catalyzed cycloisomerization of nitrogen- and oxygen-tethered MCPs to provide easy access to tricyclic compounds or bicyclo-[4.1.0]heptane derivatives in high yields under very mild conditions (Scheme 15).[20] A plausible mechanism is shown in the scheme. Cationic Au(I) complex first coordinates to the alkyne moiety of MCP **34**, which evolves to give the cyclopropyl Au−carbene intermediate **36** (via 6-*endo*-dig cyclization). Intermediate **36** is expected to undergo a facile [1,2] hydride shift to generate intermediate **37**, followed by elimination of Au(I) complex to give product **35**.

In 2008, Toste et al. developed two novel gold(I)-catalyzed ring-expanding enyne cycloisomerization reactions that allow for rapid preparation of complex polycyclic ring systems (Scheme 16).[21] They found that MCPs were

SCHEME 16. Gold(I)-Catalyzed Cycloisomerization of C-Tethered MCP **38**



SCHEME 17. Gold-Catalyzed Enantioselective Cope Rearrangement of MCP **47** on the Basis of DFT Calculation



important regiocontrolling elements with latent ring-strain reactivity. In contrast to the 6-*endo*-dig cyclizations in our work, the rearrangement of carbon-tethered MCP **38** is initiated by a 6-*exo*-dig addition. The resulting intermediate **39** undergoes a ring-expansion to give cyclobutane intermediate **42** or Au−carbene intermediate **43**. When R = *n*Bu, methylene cyclobutene **44**, generated by a 1,2-hydrogen shift onto the cation or gold carbenoid, is formed as the kinetic product, which isomerizes to the thermodynamically more stable diene **45**. When R = aryl, tetracycle **46** can be afforded as a single diastereomer via a Nazarov-type electrocyclization. Alternatively, gold(I)-catalyzed cycloisomerization of alcohol (R = $(CH_2)_4OH$) results in selective formation of pyran **41** in 60% yield. In this case, intramolecular addition of the pendant alcohol to gold-stabilized cation **40** occurred faster than cyclopropane ring expansion.

Recently, a new chiral Au(I) catalyst was developed for the enantioselective Cope rearrangement of alkenyl-MCPs by Gagné and co-workers.[22] This is an interesting example of a Cope reaction in which the enantioselectivity is not provided either by a pre-existing stereocenter or through a multistep sequence. The reaction proceeds at low temperature, and the synthetically useful vinylcyclopropane products are obtained in high yields and enantioselectivities (Scheme 17). Density functional theory calculations predict that the reaction is thermodynamically driven by the relief of ring strain from the MCP moiety, and that the Au(I) catalyst greatly lowers the barriers for rearrangement. The formation of product **48** can be rationalized as in Scheme 17. Coordination of Au(I) complex to the alkene of MCP moiety forms intermediate **49**, and then vinylcyclopropane **48** can be formed via a cyclic tertiary carbenium ion intermediate **50**.

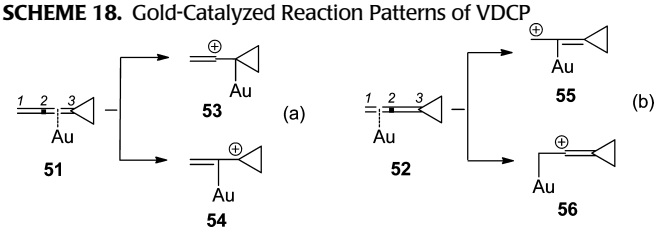
Although gold-catalyzed asymmetric reaction of MCPs is rare, we believe that more significant developments will be coming up in the near future.

3. Gold-Catalyzed Tandem Reactions of VDCPs

Vinylidenecyclopropanes (VDCPs) are another type of strained small ring molecules with even higher strained energy than that of MCPs. While containing both an allene and a cyclopropane moiety (or a methylenecyclopropane (MCP) and an alkene moieties), VDCPs are given integrated characteristics of allene and MCP together with some special reactivities, which make them excellent resources for the study of allene and cyclopropane chemistry. The chemistry of VDCPs is significantly rich and has been extensively developed by several research groups, including Mizuno,[23] Huang,[24] our group[25] and others. In this Account, we primarily focus on recent developments in gold-catalyzed transformation of VDCPs and thus bring more comprehensive understanding of gold chemistry of this unique species.

Generally, gold-catalyzed reaction modes of VDCP can be summarized as four patterns. As depicted in Scheme 18, the two C−C double bonds of allene can be coordinated by the gold catalyst to generate species **51** and **52**. Because of the regioselectivity, **51** and **52** can be further transformed to species **53** and **54** and **55** and **56**, respectively. In this Account, **56** is not included because this reaction pathway has not been reported yet. In addition, nucleophilic attack from VDCP to an electrophilic substrate, which is activated by a gold catalyst, can also take place as well and this reaction pathway will be reported in due course.

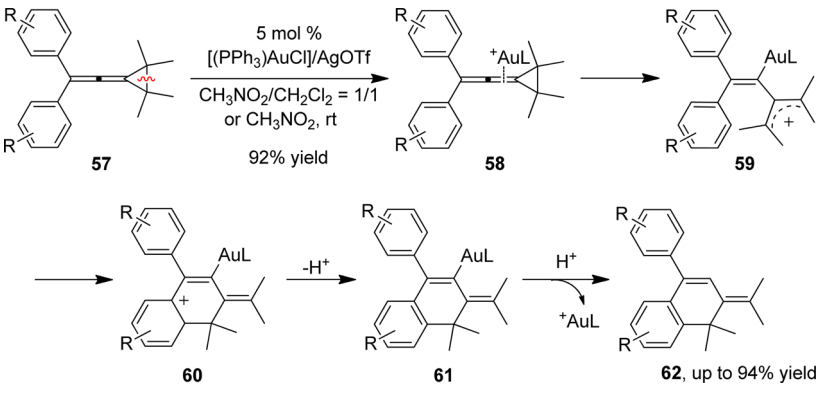
SCHEME 18. Gold-Catalyzed Reaction Patterns of VDCP



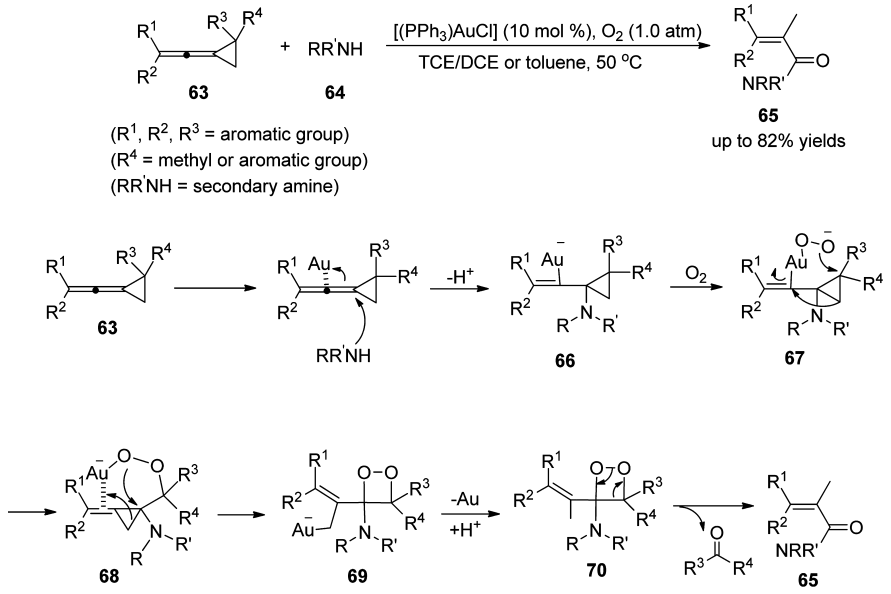
3.1. Gold-Catalyzed Intra- and Intermolecular Tandem Reactions of VDCPs. In 2008, we reported a novel gold(I)-catalyzed intramolecular rearrangement of simple VDCP **57**, selectively affording functionalized 1,2-dihydronaphthalene derivative **62** in good yield (Scheme 19).[26] A plausible mechanism is proposed. The corresponding cyclopropyl ring-opened zwitterionic intermediate **59** is formed via the initial gold-activated intermediate **58**. Next, intramolecular Friedel−Crafts reaction of the cation center with its adjacent aromatic group takes place to produce the corresponding zwitterionic intermediate **60**, which affords the corresponding intermediate **61** after aromatization. Subsequent protonation of intermediate **61** produces the corresponding 1,2-dihydronaphthalene derivative **62** and regenerates the Au(I) catalyst.

Environmentally friendly oxidative transformations catalyzed by transition metal catalyst have gained great interest of organic chemists in the past decade, many successful examples have been reported for gold-catalyzed homogeneous oxidative C−C bond cleavage/reconstruction reactions.[27] Recently, we also reported a novel gold(I)-catalyzed tandem ring-opening/C−C bond cleavage reaction of vinylidenecyclopropanes **63** with a variety of secondary amines **64** under oxygen atmosphere, leading to the corresponding fully substituted acrylamides **65** in good yields (Scheme 20).[28] Based on several control experiments, we believed that the reaction did not proceed through a radical pathway and molecular oxygen fixation catalyzed by gold catalyst happened in a quite earlier stage. The mechanism of this novel reaction is shown in Scheme 20. VDCP **63** is activated by a gold(I) complex followed by nucleophilic addition of amine to afford intermediate **66**. Subsequent

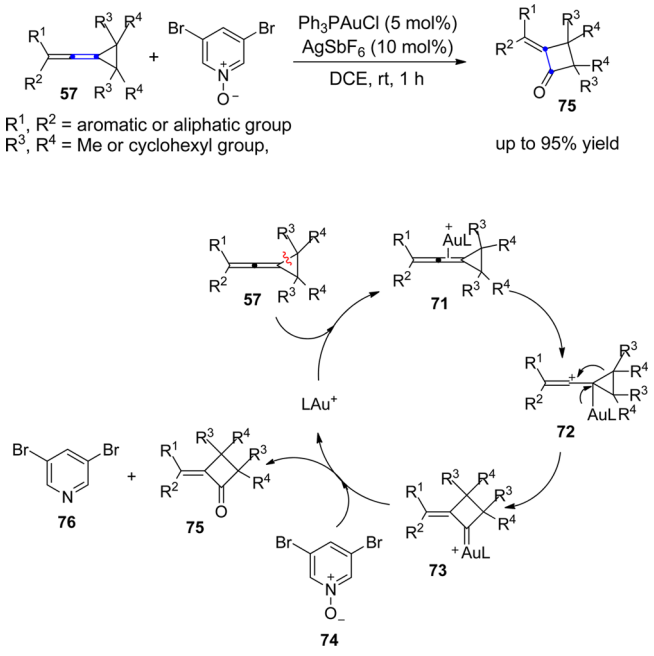
SCHEME 19. A Plausible Mechanism for the Formation of **62**



SCHEME 20. Gold(I)-Catalyzed Tandem Oxidative Ring-Opening/C−C Bond Cleavage Reaction



SCHEME 21. A Plausible Mechanism for the Formation of **75**

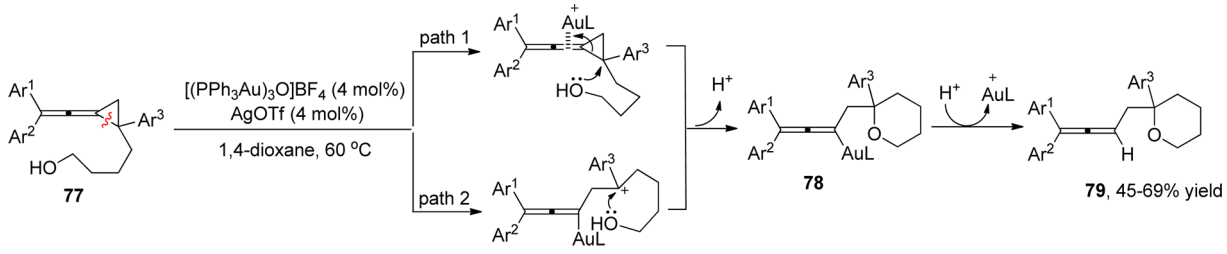


oxygen fixation forms a dioxogold intermediate **67**, and further rearrangement gives a new cyclopropane intermediate **68**, in which the C=C bond is further activated by the gold(I) complex. Then, the intramolecular nucleophilic attack along with the ring-opening of cyclopropane takes place to give the corresponding allylic gold intermediate **69**. Then, a tandem protonation and ring-opening of the dioxetane via intermediate **70** produces the final product **65** along with the release of one molecule of ketone.

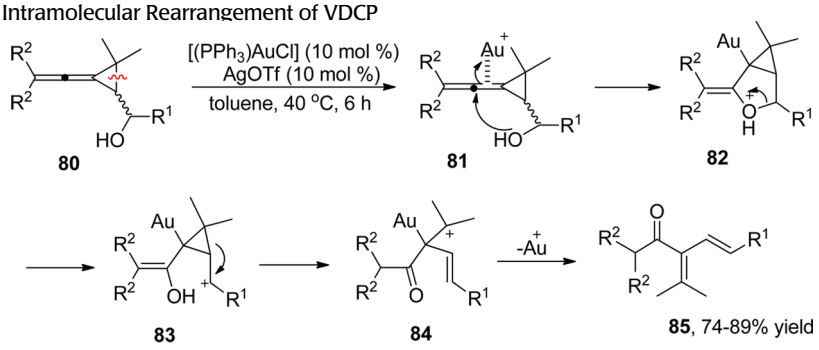
Moreover, when another strong oxidant, such as pyridine N-oxide, was used instead of oxygen, VDCPs went through a novel oxidative ring expansion rearrangement catalyzed by $[(Ph_3P)AuCl]/AgSbF_6$, giving alkylidenecyclobutanones in good yields.[29] A mechanism involving a gold−carbene intermediate was proposed (Scheme 21). Initially, VDCP **57** is activated by coordination with gold species to give intermediate **71**, in which the C−C double bond undergoes an addition process with gold catalyst, affording cationic intermediate **72**, followed by a ring expansion rearrangement to form a more stable cyclobutyl gold−carbene intermediate **73**. After an oxidation reaction by pyridine N-oxide **74**, intermediate **73** is then transformed to the corresponding alkylidenecyclobutanone **75** together with the formation of a byproduct, pyridine **76**.

3.2. Gold-Catalyzed Intramolecular Tandem Reactions of Functionalized VDCPs. Unlike simple arylvinylidenecyclopropanes, functionalized vinylidenecyclopropanes tethered with nucleophilic moieties demonstrate a quite different reactivity. For example, VDCP **77** experienced a novel tandem addition/ring-opening reaction catalyzed by $[(Ph_3PAu)_3O]BF_4$ and AgOTf to achieve the synthesis of allene-containing tetrahydropyran derivative **79** in good yield (Scheme 22).[30] This reaction can occur through two possible pathways: allene functionality activation by gold cation (path 1); gold(I) catalyzed ring-opening reaction of cyclopropane (path 2). Both pathways lead to the same intermediate **78** upon the intramolecular nucleophilic addition by the hydroxyl group, followed by protonation generating the corresponding tetrahydropyran derivative **79**.

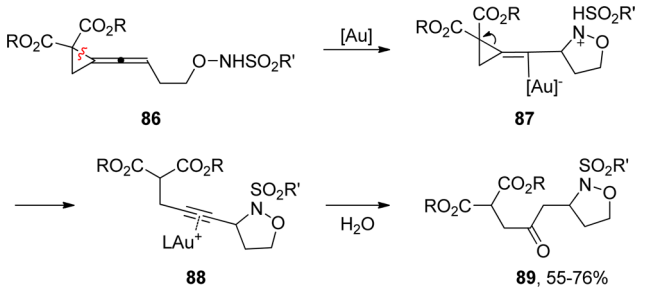
SCHEME 22. Gold-Catalyzed Tandem Addition/Ring-Opening Reaction of VDCP **77**



SCHEME 23. Gold-Catalyzed Intramolecular Rearrangement of VDCP



SCHEME 24. Gold(I)-Catalyzed Domino Intramolecular Hydroamination and Ring-Opening Reaction



Changing the length of tethered alkane chain is also possible. For example, we synthesized another type of functionalized vinylidenecyclopropane **80** in which the cyclopropane moiety bears an adjacent secondary alcohol group. In the presence of gold(I) catalyst, **80** undergoes intramolecular nucleophilic addition via gold activated intermediate **81** to form a protonated furan derivative **82**, followed by a C−O bond cleavage giving cationic intermediate **83**, and a subsequent cation-induced ring-opening of cyclopropane gives ketone intermediate **84**. After protodeauration, dienone derivative **85** is formed under mild conditions (Scheme 23).[31] This reaction mechanism is also supported by an O^{18}-labeling experiment under the standard conditions.[31]

In addition, an interesting domino transformation of sulfonamide-substituted VDCP-diester **86** was also developed in our group (Scheme 24).[32] In the presence of [(PPh_3)AuCl]/AgOTf, the allene moiety of VDCP is activated, and then intramolecular hydroamination occurs along with a ring-opening reaction of cyclopropane to give product **88** via intermediate **87**. Furthermore, the C−C triple bond of **88** can be further activated by the regenerated Au(I) catalyst, and the final ketone derivative **89** is afforded through a classical alkyne hydration with H_2O.

4. Conclusion

We have seen the research work on gold catalysis increase exponentially in the past few years. Gold-catalyzed reactions are particularly suited for the development of tandem processes for the ready formation of complex architectures. In this Account, we have collected recent advances in gold-catalyzed tandem reactions of MCPs and VDCPs. This type of gold-catalyzed process has become an established methodology for accessing a large number of carbocyclic and heterocyclic structures, containing different sized skeletons. Furthermore, these reactions always give the desired products with high level control of chemo-, regio-, and diastereoselectivities.

Despite the rapid development of new methodologies based on MCP/VDCP gold-catalyzed chemistry, many aspects still require further clarification. The presence of still quite unexplored segments, such as gold-catalyzed

asymmetric reactions, synthetic applications, and not fully elucidated mechanistic aspects, suggest that more important developments still will come in the near future.

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BIOGRAPHICAL INFORMATION

Dr. Di-Han Zhang received his B.S. degree in Chemistry from East China Normal University (2008) and Ph.D. from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the direction of Professor Min Shi (2013). He is now a research assistant in Min Shi's group working on transition metal catalyzed annulation reactions of strained molecules.

Dr. Xiang-Ying Tang received his B.S. degree in Chemistry from Huazhong University of Science and Technology (2005) and Ph.D. from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the direction of Professor Min Shi (2010). Then, he moved to Albert Einstein College of Medicine of Yeshiva University as a postdoctoral associate (2010−2012). Subsequently he joined Professor Min Shi's group at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, as an associate professor. He is currently working on development of new methodologies of organic chemistry and natural product synthesis based on those new strategies.

Dr. Prof. Min Shi received his B.S. degree in 1984 (Institute of Chemical Engineering of East China, now known as East China University of Science and Technology) and Ph.D. in 1991 (Osaka University, Japan). He had his postdoctoral research experience with Prof. Kenneth M. Nicholas at University of Oklahoma (1995−1996) and worked as an ERATO Researcher in Japan Science and Technology Corporation (JST) (1996−1998). He is currently a group leader of the State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

FOOTNOTES

*Corresponding author e-mail: siocxiangying@sioc.ac.cn.
*Corresponding author e-mail: Mshi@mail.sioc.ac.cn. Fax: 86-21-64166128.
The authors declare no competing financial interest.

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