CHEMICAL REVIEWS

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Gold-Catalyzed Nucleophilic Cyclization of Functionalized Allenes: A Powerful Access to Carbo- and Heterocycles

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CONTENTS

1. INTRODUCTION

Allenes are highly valuable synthetic precursors in preparative organic chemistry because of their ability to undergo a variety of transformations.[1] Among many different reaction modes, activation of the cumulated double bonds by treatment with a Brønsted or Lewis acid is particularly useful because it allows a nucleophilic attack, which leads to the formation of a new C−C or C−heteroatom bond in an inter- or intramolecular fashion. Because of their axial chirality, allenes can undergo this bond formation with chirality transfer, which renders the method attractive for stereoselective target-oriented synthesis.

Because of their soft and carbophilic character, gold catalysts[2] are particularly well suited for the selective activation of allenes in the presence of other reactive functionalities.[3] Compared to intermolecular additions, gold-catalyzed cyclization reactions of allenes by intramolecular nucleophilic attack have received much more attention. Here, the gold catalyst can coordinate to either allenic double bond, and the regioselectivity of the subsequent nucleophilic attack depends on the structure of the substrate, in particular the length of the tether connecting allene and nucleophile (Scheme 1). Hence, four different *endo*- or *exo*-cyclization products can be obtained, but the formation of five- or six-membered rings via σ-gold species **A** or **D**, i.e., by nucleophilic attack at a terminal allenic carbon atom, is favored in most cases, whereas products arising from nucleophilic attack at the central allenic carbon atom (via intermediates **B** and **C**) are rare. Normally, these cyclization products are chiral and can be accessed in a stereoselective manner either from chiral allenes by axis-to-center chirality transfer or from achiral allenes utilizing chiral gold catalysts.

This account comprises gold-catalyzed cyclization reactions of allenes by attack of carbon or heteroatom nucleophiles. Intermolecular addition reactions to allenes, as well as gold-catalyzed transformation of nonallenic substrates in which an allene is generated in situ (e.g., by sigmatropic rearrangement[2p]) and converted without isolation, will not be covered.

2. CYCLIZATION BY ATTACK OF HETEROATOM NUCLEOPHILES

At the end of the 20th century, Fukuda and Utimoto[4] and Teles et al.[5] found that gold salts are highly reactive catalysts for addition reactions of *O*- and *N*-nucleophiles to alkenes or alkynes. At this point, it was merely a question of time until this reaction type would also be applied to allenes. Indeed, it was subsequently shown that allenes exhibit a similar reactivity than alkynes in gold-catalyzed hydroalkoxylations and hydroaminations.

2.1. Oxygen Nucleophiles

The first gold-catalyzed addition of a heteroatom nucleophile has been accomplished by Hashmi et al.,[6] who reported the cycloisomerization of α-allenyl ketones **1** to the corresponding substituted furans **2** (Scheme 2). Previously, other transition metals like silver[7] or palladium[8] had been employed for cycloisomerization reactions of this type. In contrast to this, the use of gold entails a number of advantages such as shorter reaction times, milder conditions, and/or lower catalyst loadings. The reaction times range from >1 week (silver) to ∼1 h (palladium) to ∼1 min when gold catalysts are applied. Interestingly, variable amounts of the dimerization product **3** were also obtained; this is formed by a subsequent Michael addition of the newly formed furan to unconsumed allenic ketone.

Even though gold displays a higher reactivity than silver, the formation of the undesired dimerization product **3** (which is also generated in the corresponding silver-catalyzed cyclization) is a serious drawback. Fortunately, this side reaction can be prevented by using a modified gold catalyst as demonstrated by Che and co-workers,[9] who employed the cationic gold(III) porphyrin complex **6** for the cyclization of various mono- or disubstituted allenic ketones **4** to the corresponding furans **5** (Scheme 3). Under these conditions, no dimer could be detected, but the presence of trifluoroacetic acid and elevated temperatures are essential, which can lead to problems with acid-labile substrates. The Au(III) catalyst **6** is highly reactive (the catalyst loading can be decreased to 0.1 mol %, corresponding to turnover numbers of up to 850) and can be recovered and reused in up to nine consecutive runs with no appreciable loss of reactivity or decrease of yield.

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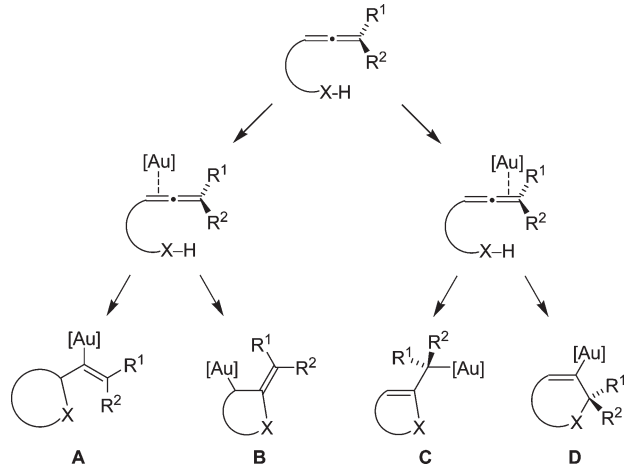
The cycloisomerization of allenic ketones with $AuCl_3$ or [Au(TPP)]Cl follows the mechanistic model shown in Scheme 4. The active gold species is coordinated to the "distal" double bond of the allene and induces a nucleophilic attack of the oxygen atom furnishing the cationic intermediate **8**, which after deprotonation affords the furyl−gold species **9**. Subsequent protodeauration (which is facilitated in the presence of an external proton donor like CF_3CO_2H) leads to the furan **5** and releases the gold catalyst into the catalytic cycle. Experimental support for this model was recently gained by Widenhoefer and co-workers[10] through the isolation of a gold π-allene complex, which was characterized by X-ray crystallography and variable-temperature NMR spectroscopy.

Besides alkyl- and aryl-substituted furans, halogenated furans are also of great interest because of a large variety of possible consecutive transformations. These functionalized heterocycles are accessible by application of the gold-catalyzed cycloisomerization to bromoallenones **10** as shown in Scheme 5. Gevorgyan and co-workers[11] demonstrated that the structure of the product is highly dependent on the gold catalyst. When a carbophilic Au(I) species (e.g., Et_3PAuCl) is used, the cycloisomerization leads to the expected 5-bromofuran **12**, whereas the more oxophilic gold(III) chloride preferentially generates the 4-bromofuran **15**. This remarkable result can be explained by formation of a bromoirenium ion **14** arising from coordination of the oxophilic Au(III) catalyst to the carbonyl oxygen atom. Chlorinated and iodinated allenes show a similar behavior and can be converted to the corresponding halogenated furans. Moreover, silyl-, thio-, or selenofurans can be obtained from the corresponding allenes by a 1,2-Si, 1,2-S, or 1,2-Se shift (Scheme 6).[12]

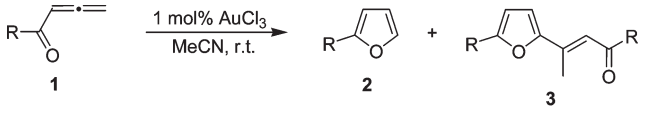
The driving force for the cycloisomerization of allenones is the formation of the aromatic heterocycle. This is even possible with allenones bearing two carbon substituents in the γ-position if one of the substituents has a pronounced tendency to migrate (Scheme 7).[13] For example, heating of allenyl ketones **18** with the cationic gold catalyst $Ph_3PAuOTf$ affords furans **21** via intermediates **19** and **20**, i.e., by ring closure and subsequent [1,5]-phenyl shift.

Even though the gold-catalyzed cycloisomerization of allenones offers an efficient and convenient access to various substituted furans, it does not take advantage of the possibility to use chiral allenes as the substrate since the products are achiral. In contrast, replacing the keto with a hydroxy group allows the formation of chiral heterocycles. Shortly after the first account on the gold-catalyzed cycloisomerization of allenones,[6] Krause and co-workers[14] reported the synthesis of chiral 2,5-dihydrofurans (±)-**23** by treatment of α-hydroxyallenes (±)-**22** with catalytic amounts of $AuCl_3$ in unpolar solvents (Scheme 8). Many

Scheme 1. Gold-Catalyzed Nucleophilic Cyclization Reactions of Functionalized Allenes

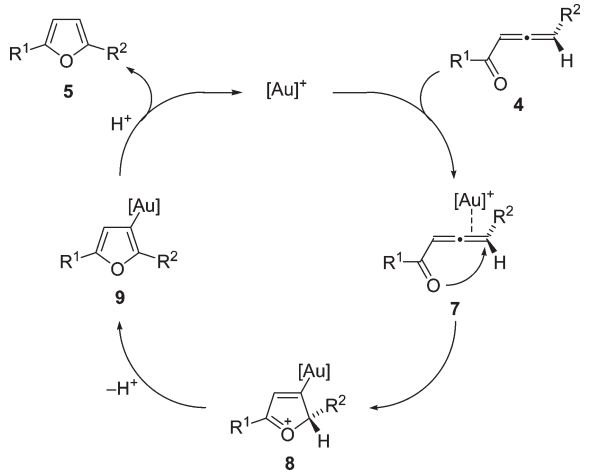


Scheme 2. Gold-Catalyzed Cycloisomerization of Allenic Ketones to Furans

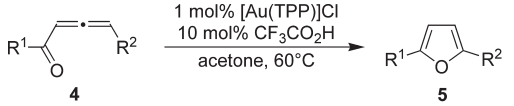


R = 4-MeOC$_6$H$_4$CH$_2$	66 : 34 (91%)
4-O$_2$NC$_6$H$_4$	96 : 4 (92%)
Me	50 : 50 (94%)

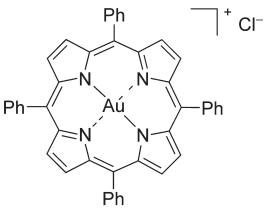
Scheme 4. Mechanistic Model for the Gold-Catalyzed Cycloisomerization of Allenic Ketones



Scheme 3. Cycloisomerization of Allenic Ketones to Furans Catalyzed by Gold Complex 6



R^1	R^2	Yield (%)
Ph	H	88
4-MeOC$_6$H$_4$CH$_2$	H	81
4-O$_2$NC$_6$H$_4$	H	91
Me	H	89
Me	*n*-C$_5$H$_{11}$	97



[Au(TPP)]Cl (**6**)

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functionalities (e.g., carbonyl groups, free alcohols, acid-sensitive protecting groups) are tolerated under these conditions. In the case of chiral allenes bearing alkyl substituents, the stereochemical information of the chirality axis is completely transferred to the newly formed stereogenic center.[15]

The mechanistic model for the gold-catalyzed cycloisomerization of α-hydroxyallenes is similar to that of allenones (Scheme 9). Thus, coordination of the carbophilic gold catalyst to the allenic double bond distal to the hydroxy group affords π-complex **25**, which undergoes a 5-*endo*-cyclization to the zwitterionic σ-gold species **26**. Protodeauration leads to the dihydrofuran **27** and regenerates the gold catalyst. The cyclization is accelerated in the presence of external proton donors (water, methanol); this suggests that the protodeauration of **26** is the rate-limiting step.

In contrast to alkyl-substituted allenes, substrates with phenyl or electron-rich aromatic substituents undergo epimerization when treated with gold catalysts. Whereas $AuCl_3$ in CH_2Cl_2 epimerizes both the allene and the dihydrofuran, only the allene but not the dihydrofuran is epimerized in the presence of gold(I) chloride in dichloromethane.[16] The epimerization probably proceeds via zwitterionic intermediates **29** (formed from π-complex **28**) and **32** (formed by ring-opening of **31**) comprising a benzyl cation substructure and an anionic aurate moiety (Scheme 10).

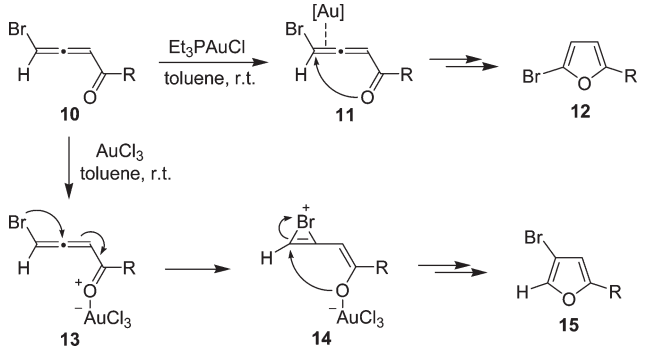
The stereochemical integrity of substrate and product is preserved by decreasing the Lewis acidity of the gold catalyst.[16] Thus, high levels of chirality transfer from allene (±)-**34** to dihydrofuran (±)-**35** were observed when the cycloisomerization was carried out in the presence of σ-donor ligands to gold, e.g., 2,2′-bipyridine (Scheme 11); alternatively, a weakly coordinating solvent like THF can be used as well. A third possibility is to conduct the reaction with the original $AuCl_3/CH_2Cl_2$ system at −30 °C instead of room temperature, giving (±)-**35** with high diastereoselectivity.

Gold(III) chloride in tetrahydrofuran (THF) is an efficient catalyst for the cycloisomerization of various functionalized allenols like α-hydroxyallenamides,[17] α,α′-bishydroxyallenes,[18] methoxyallenols,[19] and arylallenes.[20] Moreover, several applications in target-oriented synthesis have been disclosed. In a recent example published by Erdsack and Krause,[21] Garner's aldehyde **36** was used as precursor for α-hydroxyallenes **37** and **39**, which, upon treatment with 1 mol % of gold(III) chloride in THF, underwent cycloisomerization to the dihydrofurans **38** and **40** (Scheme 12). In the case of allene **37**, the cyclization was accompanied by acetal cleavage, which is apparently linked to the higher reaction temperature (room temperature (rt) instead of 0 °C). Subsequent removal of the protecting groups and oxidation afforded analogues of the antibiotic amino acid furanomycin (**41**).

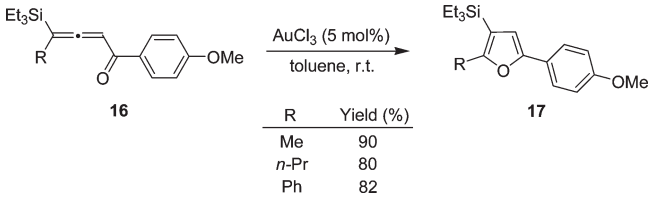
In the same year, Volz and Krause[22] reported the first total synthesis of the β-carboline alkaloids (−)-isocyclocapitelline (**44**) and (−)-isochrysotricine (**45**) by Pictet-Spengler reaction of a chiral tetrahydrofuran with tryptamine (Scheme 13). Key intermediate **43** was obtained from the corresponding α,β-dihydroxyallene **42** with complete axis-to-center chirality transfer by the use of only 0.05 mol % of gold(III) chloride in THF. Hydrogenation of the double bond, oxidation, and carbolin formation led to the enantiomerically pure natural products. An analogous gold-catalyzed cycloisomerization of dihydroxyallene **46** to 2,5-dihydrofuran **47** was employed recently by Kocienski and co-workers[23] in their synthesis of ionomycin−calcium complex **48** (Scheme 14).

The gold-catalyzed cycloisomerization of α,β-dihydroxyallenes **42** and **46** is not only stereoselective but also highly chemoselective, because no product resulting from nucleophilic attack of the β-hydroxy group was observed. The intrinsic preference of a 5-*endo*-trig over a 6-*endo*-trig cyclization can be overcome by removal or protection of the α-hydroxy group; for example, β-hydroxyallenes

Scheme 5. Gold-Catalyzed Cycloisomerization of Bromoallenones

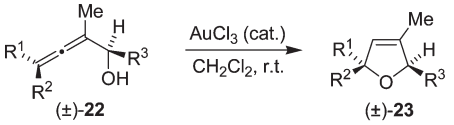


Scheme 6. Gold-Catalyzed Cycloisomerization of Silylallenes



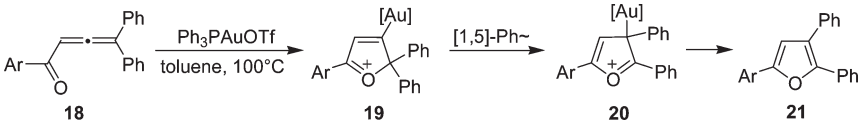
R	Yield (%)
Me	90
n-Pr	80
Ph	82

Scheme 8. Gold-Catalyzed Cycloisomerization of α-Hydroxyallenes



R^1	R^2	R^3	Yield (%)
t-Bu	Me	CO_2Et	94
t-Bu	H	CH_2OTBS	95
H	Me	CH_2OTBS	77
$H_2C{=}CHCH_2$	Me	CH_2OMe	86

Scheme 7. Gold-Catalyzed Cycloisomerization of Allenones 18



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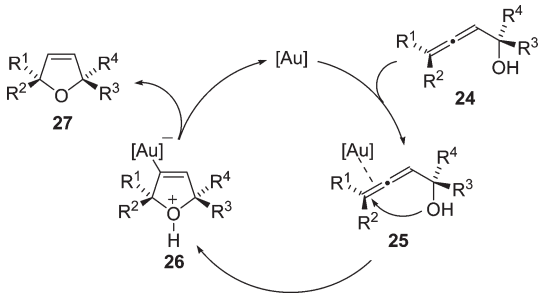
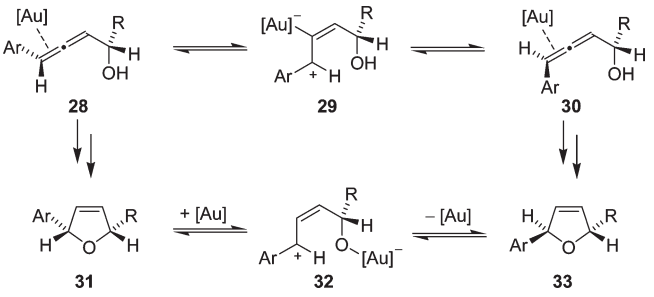
(±)-**49** are converted to the corresponding 5,6-dihydro-2*H*-pyrans (±)-**50** in the presence of a cationic gold catalyst formed in situ from Ph_3PAuCl and $AgBF_4$ (Scheme 15).[24] These cyclizations are often very slow, resulting in reaction times of several days. For example, treatment of β-hydroxyallene (±)-**51** with 5 mol % of AuCl in dichloromethane at room temperature requires 5 days for complete conversion to dihydropyran (±)-**52** (X = H). However, addition of *N*-iodosuccinimide (NIS) to the reaction mixture induces a tremendous acceleration, leading to the formation of the corresponding iodinated dihydropyran within 1 min at room temperature.[25] This effect is probably caused by a very rapid iododeauration of a σ-gold intermediate (cf. **26** in Scheme 9) by NIS, which is activated by the gold catalyst (species **53**).[26]

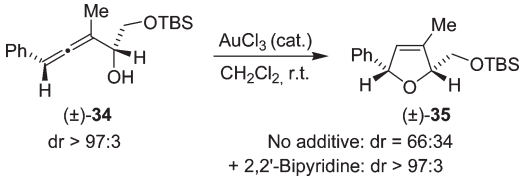
Scheme 9. Mechanistic Model for the Gold-Catalyzed Cycloisomerization of α-Hydroxyallenes



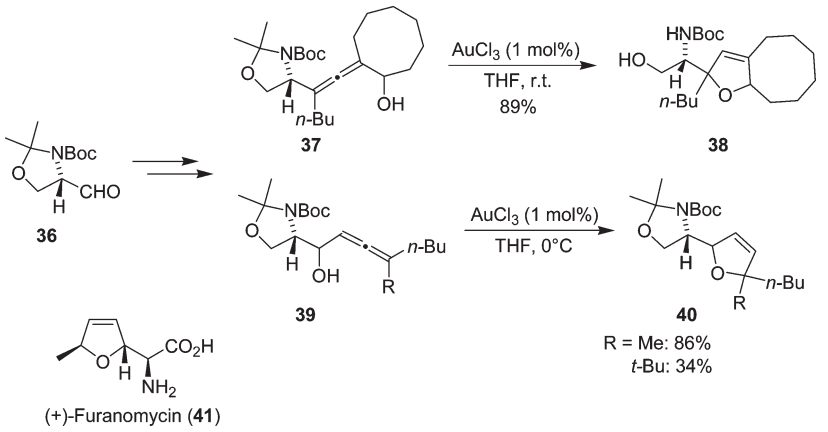
Scheme 10. Epimerization of Aryl-Substituted α-Hydroxyallenes and 2,5-Dihydrofurans



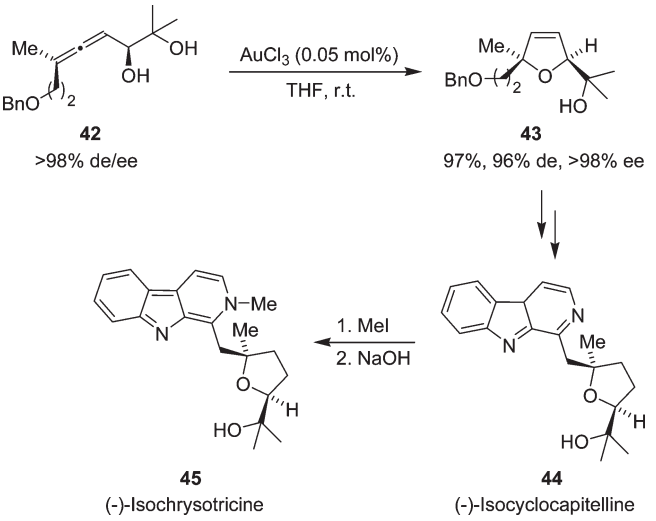
Scheme 11. Gold-Catalyzed Cycloisomerization of Phenyl-Substituted α-Hydroxyallene (±)-34



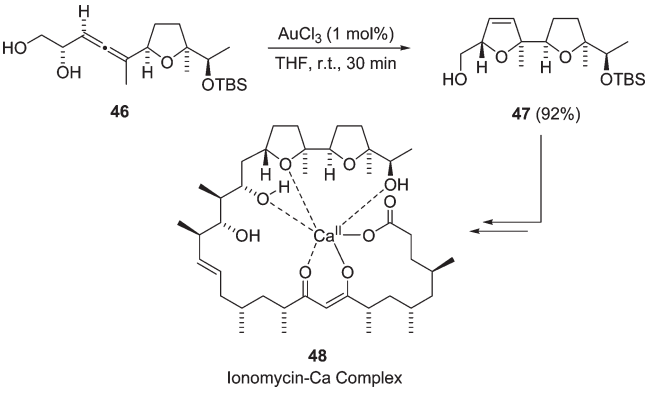
Scheme 12. Synthesis of Furanomycin Analogues



Scheme 13. Synthesis of β-Carboline Alkaloids



Scheme 14. Synthesis of Ionomycin−Calcium Complex 48



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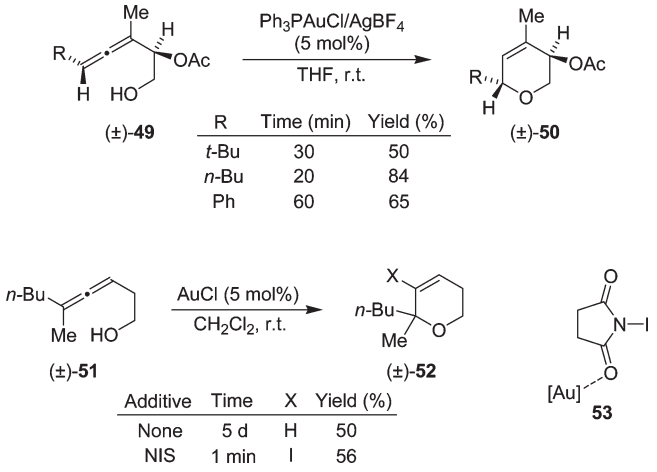
This reaction has already found application in target-oriented synthesis as well. Thus, the gold-catalyzed cycloisomerization of β-hydroxyallene **54** to the dihydropyran **55** was the key step in the first total synthesis of the naturally occurring sesquiterpenoid (*R*,*R*,*R*)-bejarol (**56**) and its (3*R*,5*S*,9*R*)-isomer (Scheme 16).[27]

An interesting example of a chemoselective gold-catalyzed transformation was reported by Kim and Lee.[28] The diol **57** bearing both an alkyne and an allene moiety can afford different cyclization products (Scheme 17); whereas gold(III) chloride activates the allene and gives dihydrofuran **59** via intermediate **58**, treatment of **57** with silver triflate yields furan **61** by activation of the triple bond (intermediate **60**). This is a rare example of the formation of different products using gold and silver catalysts.[29]

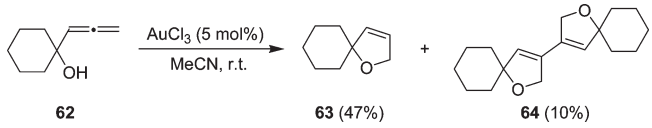
The previous examples demonstrate that both gold(I) and gold(III) salts are active (pre)catalysts for the cycloisomerization of allenols. What is the oxidation state of the catalytically active species? Investigations by Hashmi et al.[30] suggest that gold(III) chloride is reduced in situ to gold(I) in the presence of α-hydroxyallene **62**. This is concluded from the formation of the oxidative coupling product **64** together with the dihydrofuran **63** (Scheme 18). An increase of the amount of the gold(III) salt caused a raised yield of **64**, which indicates that $AuCl_3$ is indeed acting as oxidizing agent in this transformation (and is therefore reduced to gold(I)). On the other hand, it is known that gold(I) chloride can undergo dismutation to gold(III) and gold(0) in the presence of an allene.[31]

A serious drawback of homogeneous gold catalysis is that the catalyst is usually reduced to metallic gold after the reaction or upon workup, so that it cannot be recycled. This problem can be overcome by using ionic liquids as reaction medium. Thus, for the cycloisomerization of allenol (±)-**65** to dihydrofuran (±)-**66**, $AuBr_3$ in the imidazolium-derived medium [BMIM][PF_6] gives

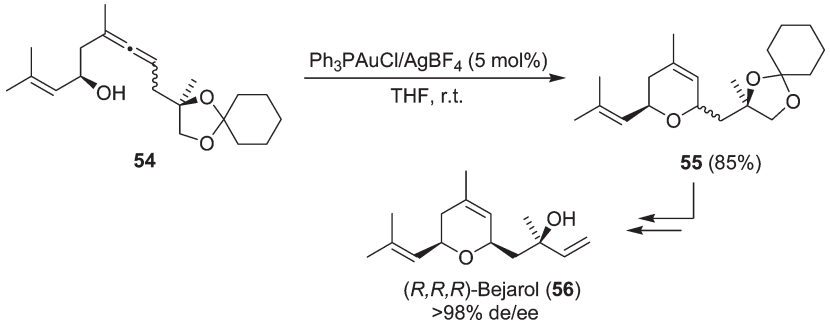
Scheme 15. Gold-Catalyzed Cycloisomerization of β-Hydroxyallenes



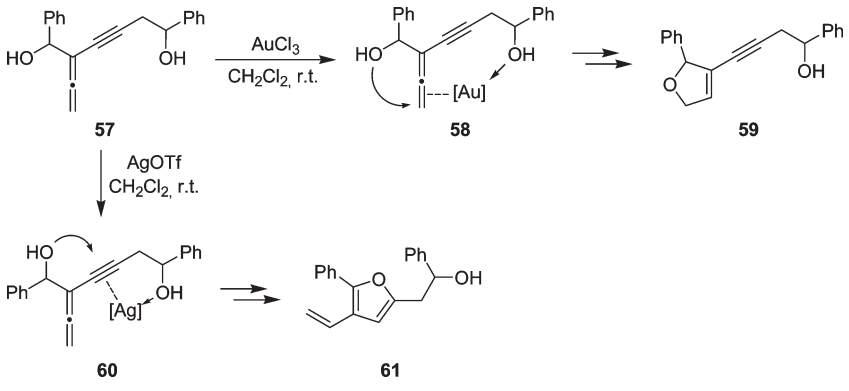
Scheme 18. Oxidative Coupling by Gold(III) Chloride



Scheme 16. Synthesis of (*R*,*R*,*R*)-Bejarol



Scheme 17. Cycloisomerization of Diol 57



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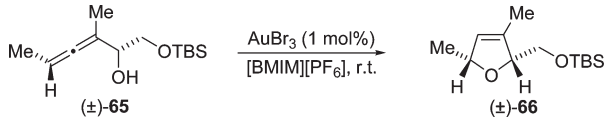
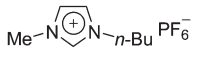
Scheme 19. Gold-Catalyzed Cycloisomerization in an Ionic Liquid

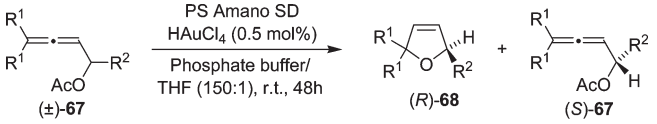




[BMIM][PF_6]

Run	Time	Yield (%)
1	10 min	84
2	3 h	74
3	3 h	81
4	3 h	84
5	3 h	84

Scheme 20. Tandem Lipase/Gold Catalysis



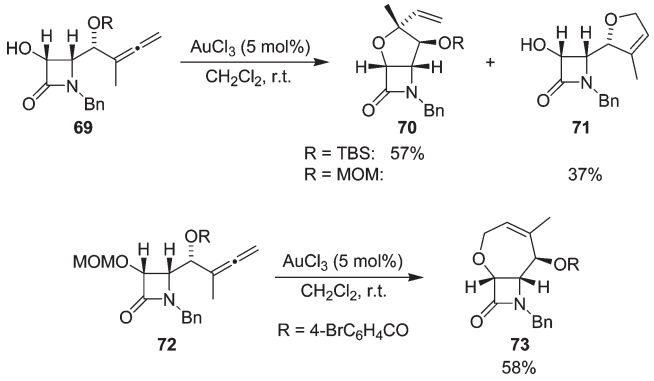
		(*R*)-**68**		(*S*)-**67**	
R^1	R^2	Yield (%)	ee (%)	Yield (%)	ee (%)
-$(CH_2)_5$-	Me	28	86	31	93
-$(CH_2)_5$-	*n*-Pr	45	95	40	>95
-$(CH_2)_4$-	*n*-Pr	38	88	33	>95
Me	*n*-C_8H_{17}	50	98	36	95

the best results (Scheme 19).[32] This catalyst system is not only stable to water and air but can also be recycled easily without loss of efficiency. Interestingly, the reactivity of the catalyst decreases after the first run but is constant after that. Over five runs, only 0.03% of the original catalyst loading is lost during extraction of the product. This almost negligible leaching makes the method attractive for the synthesis of pharmacologically active target molecules and indicates that the solution of $AuBr_3$ in [BMIM][PF_6] is potentially recyclable several thousand times.

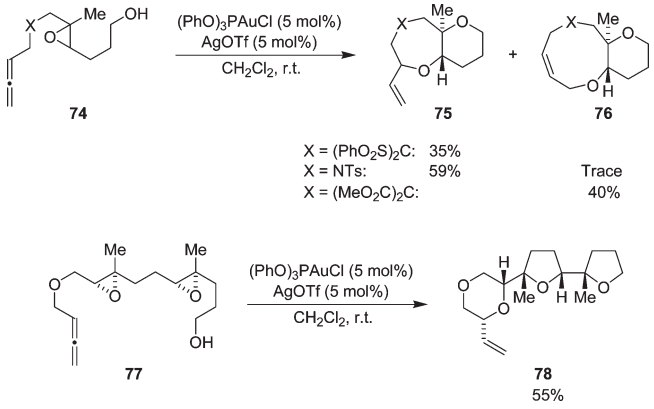
The cycloisomerization of α- or *β*-hydroxyallenes can also be carried out in water with tetrachlorogold acid as catalyst.[33] Recently, this system was utilized for the first example of a tandem lipase/gold-catalyzed transformation. The one-pot kinetic resolution/cycloisomerization of racemic allenic acetates (±)-**67** with *Burkholderia cepacia* lipase (PS Amano SD) and $HAuCl_4$ afforded 2,5-dihydrofurans (*R*)-**68**, as well as unreacted starting material (*S*)-**67**, with 28−50% isolated yield and 86−98% ee (Scheme 20).[34] The mutual tolerance of the Lewis acidic gold catalyst with the Lewis basic lipase is maintained as long as low amounts of the former are used.

Besides *endo*-cyclizations, functionalized allenes can also undergo gold-catalyzed *exo*-selective attack, in particular if the distance between the nucleophilic group and the allene moiety is large. Alcaide et al.[35] examined gold-catalyzed transformations of *β*-lactams **69** containing an α,*γ*-dihydroxyallene structure and observed the formation of three different cyclization products (Scheme 21). Whereas treatment of the TBS-protected substrate with $AuCl_3$ afforded tetrahydrofuran derivative **70** resulting from 5-*exo*-attack of the *γ*-hydroxy group, the corresponding methoxymethyl (MOM)-protected starting

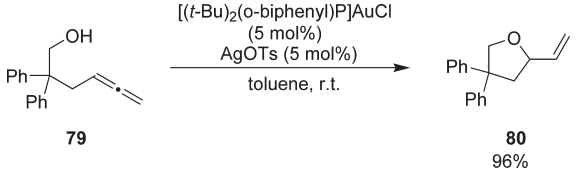
Scheme 21. Different Cyclization Modes of Allene 69



Scheme 22. Different Cyclization Modes of Allenic Epoxyalcohols



Scheme 23. *exo*-Selective Cycloisomerization of Allenol 79

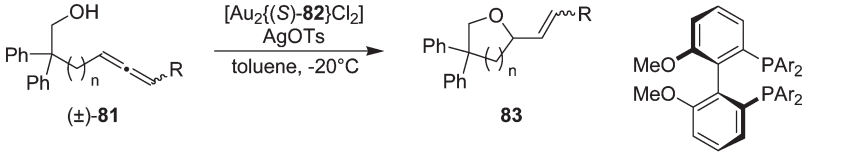


material underwent deprotection and 5-*endo*-trig cyclization to the 2,5-dihydrofuran **71** under these conditions. Moving the MOM group to the *γ*-position (substrate **72**) led to the formation of the unusual product **73** by gold-catalyzed deprotection and 7-*endo*-trig cycloisomerization.

Intriguing variable cyclization modes were also observed in the reaction of allenic epoxyalcohols with cationic gold catalysts (Scheme 22).[36] Whereas substrates **74** bearing a bis(phenylsulfonyl)methyl or sulfonamide group in the tether afforded mainly or exclusively the 7-*exo*-trig cyclization product **75**, a very unusual 9-*endo*-trig cycloisomerization to the bicyclic ether **76** was observed with the corresponding malonate derivative. The method was extended to the gold-catalyzed cascade cyclization of allenic diepoxyalcohol **77**, which furnished tricyclic ether **78** in 55% yield.

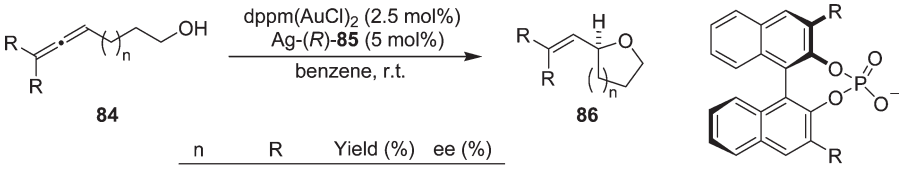
dx.doi.org/10.1021/cr1004088 |*Chem. Rev.* 2011, 111, 1994–2009

Scheme 24. Enantioselective Cycloisomerization of Allenols



n	R	Yield (%)	*E*/*Z*	*ee* (%)
1	H	67	–	93
1	Me	96	1:1	97/99
1	*n*-C_5H_{11}	94	1:1	>95/>95
2	H	96	–	88
2	*n*-C_5H_{11}	92	1.5:1	67/93

Scheme 25. Chiral Counterion in the Enantioselective Cycloisomerization of Allenols



n	R	Yield (%)	ee (%)
1	-$(CH_2)_4$-	90	97
1	Me	91	95
2	Me	81	90
2	H	96	80

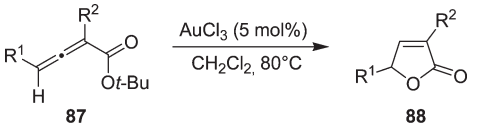
Another example for a gold-catalyzed *exo*-selective cyclization is the transformation of γ-allenol **79** to the tetrahydrofuran **80**, which was reported by Widenhoefer and co-workers[37] (Scheme 23). The corresponding 6-*exo*-dig cycloisomerization leading to a dihydropyran does not take place under these conditions but rather in the presence of a platinum catalyst. Application of this method to axially chiral allenols afforded the corresponding tetrahydrofurans with high levels of chirality transfer.

The same working group extended this method to the synthesis of enantiomerically enriched tetrahydrofurans or tetrahydropyrans **83** by using chiral phosphine ligands on the gold catalyst (Scheme 24).[38] In the presence of biphep derivative (*S*)-**82**, the attack of the oxygen atom is directed to the *Si*-side of the allene; because of the fact that racemic allenols (±)-**81** were used as starting material, the cyclization products **83** were formed as mixture of *E*/*Z*-isomers with high enantioselectivities in most cases.[39]

An alternative catalytic system reported by Toste and co-workers[40] takes advantage of a chiral counterion, which was introduced into the catalyst by a silver salt (Scheme 25). Thus, treatment of γ- or δ-allenols **84** with catalytic amounts of an achiral gold precatalyst and the chiral silver salt Ag-(*R*)-**85** afforded heterocycles **86** with high yield and excellent enantioselectivity in most cases. For the terminal allene (R = H), the enantiomeric excess could be improved from 80 to 92% by using a chiral gold catalyst together with the chiral silver salt. Application of this method to allenic carboxylic acids afforded chiral γ-lactones with up to 82% ee.[40]

Instead of allenic carboxylic acids, the corresponding esters can also be used as substrate for gold-catalyzed cyclization reactions. The first example has been reported by Shin and co-workers,[41] who obtained butenolides **88** by heating *t*-butyl allenoates **87** with gold(III) chloride in dichloromethane (Scheme 26). In a similar way, Bäckvall and co-workers[42] treated allenic malonates with gold(III) chloride and silver hexafluoroantimonate in acetic acid and obtained the corresponding δ-lactones in high yield.

Scheme 26. Gold-Catalyzed Cycloisomerization of Allenic Esters

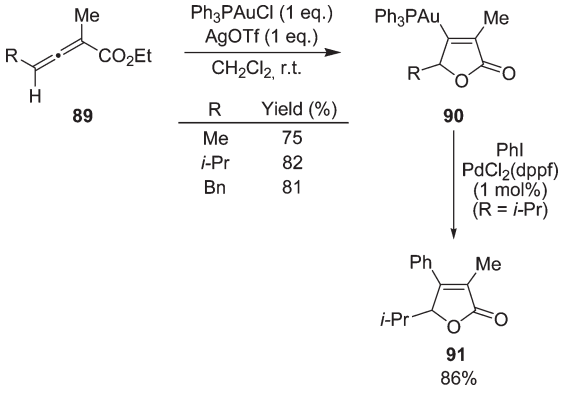


R^1	R^2	Yield (%)
Bn	H	88
Bn	Me	77
Bn	Bn	96
H_2C=$CHCH_2$	Me	71
n-C_9H_{19}	H	65

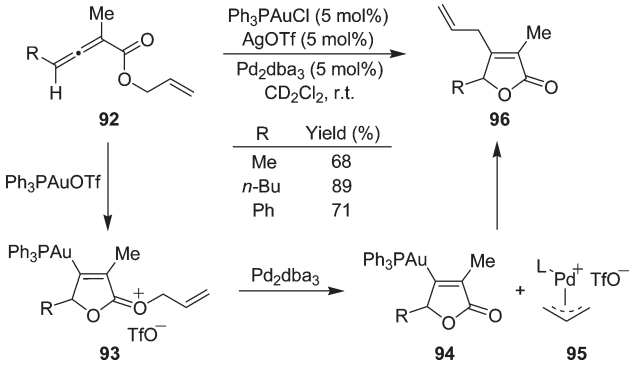
Important insight into the mechanism of this transformation was gained by the group of Hammond,[43] who isolated various stable σ-gold compounds **90** formed from allenic esters **89** and stoichiometric amounts of $Ph_3PAuOTf$ (Scheme 27). These were characterized by NMR spectroscopy and, in one case (R = Bn), also by X-ray crystallography. Thus, the mechanism of the gold-catalyzed cyclization of allenic esters is similar to that proposed for α-hydroxyallenes (cf. intermediate **26** in Scheme 9). In the presence of triflic acid or iodine, vinylgold compounds **90** undergo protodeauration or iododeauration to the corresponding butenolides. Moreover, they participate in

dx.doi.org/10.1021/cr1004088 |*Chem. Rev.* 2011, 111, 1994–2009

Scheme 27. Synthesis and Reactions of Stable σ-Gold Species 90



Scheme 28. Tandem Gold/Palladium-Catalyzed Cycloisomerization of Allyl Allenoates



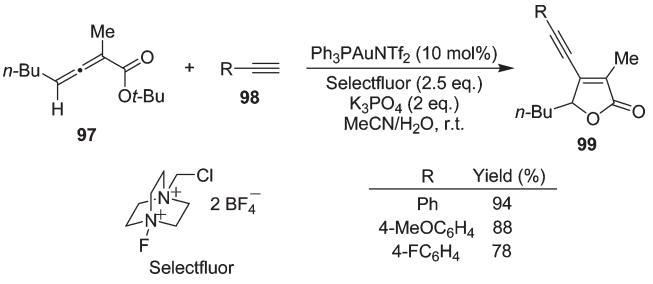
palladium-catalyzed cross-couplings; for example, treatment of **90** (R = *i*-Pr) with iodobenzene in the presence of $PdCl_2$(dppf) afforded lactone **91** with 86% yield.[44]

Products of this type can also be obtained in a tandem C−O/C−C bond formation by treating allyl allenoates **92** with catalytic amounts of $Ph_3PAuOTf$ and Pd_2dba_3 (Scheme 28).[45] Activation of the distal allenic double bond by the gold catalyst induces cyclization to allyl oxonium intermediate **93**, which undergoes deallylation in the presence of the Pd(0) catalyst. Nucleophilic attack of the resulting σ-vinylgold intermediate **94** at the π-allyl palladium species **95** and reductive elimination affords allylated butenolides **96** and regenerates both catalysts.

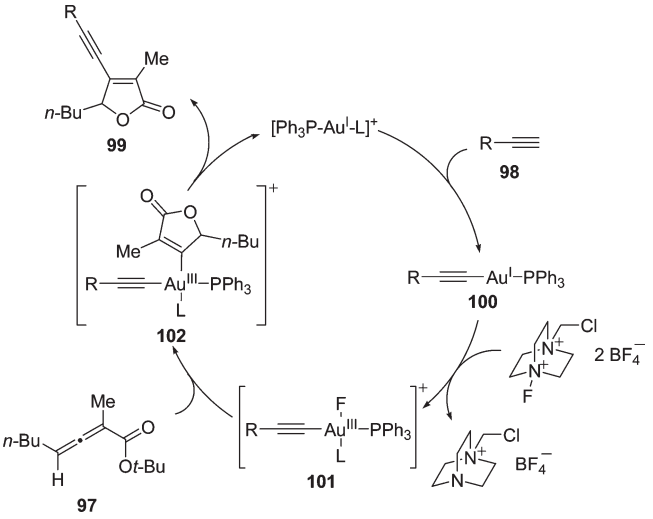
Another variation of the gold-catalyzed butenolide synthesis from allenic esters involves the use of Selectfluor for the oxidative C−C coupling of σ-gold intermediates of the type **90**. Gouverneur and co-workers[46] have developed this powerful synthetic method for the cycloisomerization of aryl-substituted allenoates to indenofuranones and further applied it to the formation of the alkynylated lactones **99** from ester **97** and terminal alkynes **98** (Scheme 29).

Mechanistically, this intriguing transformation involves a gold(I)/gold(III) redox cycle (Scheme 30).[46] Thus, deprotonation of the alkyne **98** and reaction of the acetylide with the cationic gold(I) catalyst leads to alkynylgold(I) intermediate

Scheme 29. Gold-Catalyzed Cyclization/Oxidative C−C Coupling



Scheme 30. Mechanistic Model for the Gold-Catalyzed Cyclization/Oxidative C−C Coupling



100, which then undergoes oxidation by Selectfluor to afford cationic gold(III) species **101**. Coordination to the allene **97** provides the necessary activation for nucleophilic attack of the pendant *t*-butyl ester, which leads to the gold(III) complex **102** bearing both the butenolide and alkyne substituent. After reductive elimination, this intermediate delivers the product **99** and regenerates the gold(I) catalyst. Alternatively, the cycloisomerization could take place prior to the alkyne coordination step.

2.2. Nitrogen Nucleophiles

In 2004, Morita and Krause[47] reported the first intramolecular *endo*-selective hydroamination of allenes. With gold(III) chloride, various α-aminoallenes (±)-**103** were converted to the corresponding 3-pyrrolines (±)-**104** with high levels of chirality transfer (Scheme 31).[48] Whereas short reaction times (30 min) were observed for protected aminoallenes, 5 days at room temperature are required for full conversion of the corresponding unprotected aminoallene. The diminished reactivity is probably due to deactivation of the gold catalyst by the Lewis-basic amino group; by using gold(I) chloride instead of $AuCl_3$, the reaction time was decreased to several hours at room temperature.[49] The same method was applied by Lee and coworkers,[50] who used gold(III) chloride in dichloromethane to

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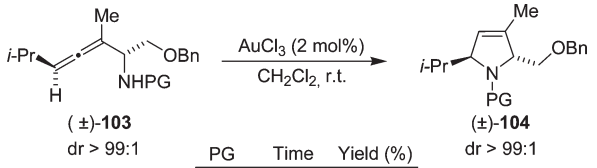
Scheme 31. Gold-Catalyzed Cycloisomerization of α-Aminoallenes

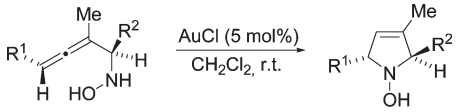


(±)-**103**
dr > 99:1

(±)-**104**
dr > 99:1

PG	Time	Yield (%)
Ms	30 min	77
Ts	30 min	93
Ac	30 min	80
Boc	30 min	69
H	5 d	74

Scheme 32. Gold-Catalyzed Synthesis of *N*-Hydroxypyrrolines



(±)-**105**
dr > 99:1

(±)-**106**
dr > 99:1

R^1	R^2	Yield (%)
n-Bu	CH_2OBn	80
Ph	CH_2OBn	73
n-Bu	CH_2OH	67

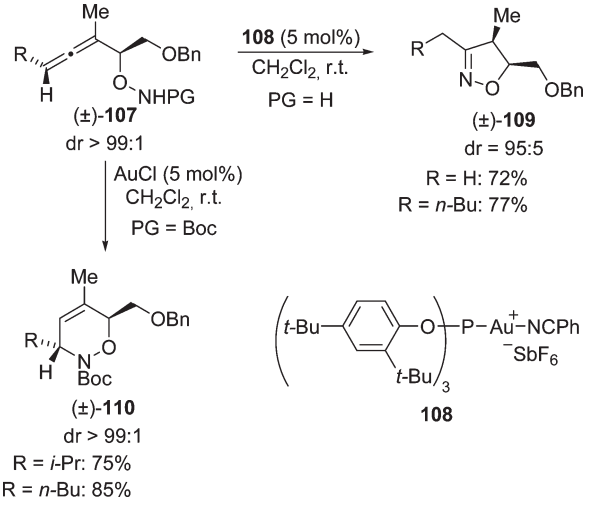
obtain bicyclic β-lactams, as well as by Reissig and co-workers[51] in a synthesis of tricyclic pyrroloisoindolones. Analoguous to β-hydroxyallenes (Scheme 15), β-aminoallenes undergo a slow gold-catalyzed 6-*endo*-cycloisomerizion to the corresponding tetrahydropyridins.[24]

Application of this method to allenic hydroxylamine derivatives proved to be particularly useful because three different chiral heterocycles can be obtained with high regio- and stereoselectivity, depending on the starting material, the gold catalyst, and the protecting group at nitrogen.[52] In all cases, the nitrogen atom acts as the nucleophile and attacks the allene in a 5- or 6-*endo* cyclization. Thus, *N*-hydroxy-α-aminoallenes (±)-**105** afforded *N*-hydroxypyrrolines (±)-**106** with complete axis-to-center chirality transfer in the presence of 5 mol % of gold(I) chloride (Scheme 32).

Under these conditions, the allenic hydroxylamine ethers (±)-**107** with exchanged positions of the heteroatoms furnished mixtures of 4,5-dihydroisoxazoles and 3,6-dihydro-1,2-oxazines. The regioselectivity can be shifted in favor of isoxazoles (±)-**109** by using the cationic gold(I) complexes Ph_3PAuBF_4 or **108** (Scheme 33).[52] In contrast to this, a selective 6-*endo*-cyclization to the oxazines (±)-**110** is possible by treatment of the *N*-Boc-protected hydroxylamine ethers with gold(I) chloride. Overall, this method is particularly versatile because the precursors (±)-**105** and (±)-**107** of the three heterocycles (±)-**106**, (±)-**109**, and (±)-**110** are all obtained in a stereoselective manner by Mitsunobu reaction from the same α-heterocycle (cf. Scheme 32).

Recently, allenic hydrazones were found to undergo a gold(I)-catalyzed cycloisomerization to substituted pyrroles (Scheme 34).[53] For example, heating of 2,4-dinitrophenylhydrazones **111** with $Ph_3PAuNTf$−toluene complex in dichloroethane to

Scheme 33. Gold-Catalyzed Cycloisomerization of Allenic Hydroxylamine Ethers



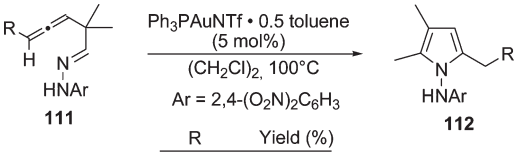
(±)-**107**
dr > 99:1

(±)-**109**
dr = 95:5
R = H: 72%
R = *n*-Bu: 77%

(±)-**110**
dr > 99:1
R = *i*-Pr: 75%
R = *n*-Bu: 85%

108

Scheme 34. Gold-Catalyzed Cycloisomerization of Allenic Hydrazones

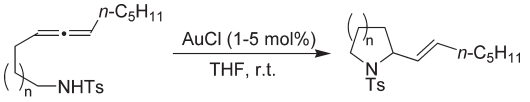


111

112

R	Yield (%)
Me	93
n-Bu	92
4-BrC_6H_4	quant.

Scheme 35. Gold-Catalyzed *exo*-Cycloisomerization of Aminoallenes



113
n = 1: 96% ee
n = 2: rac.

114
99%, 94% ee
53%, rac.

100 °C for 20 min afforded the pyrroles **112** with excellent yield. A 1,2-alkyl or aryl shift is key to the formation of the aromatic heterocycle (cf. Scheme 7).

In analogy to the corresponding allenols, γ- or δ-aminoallenes also undergo *exo*-selective hydroamination reactions in the presence of gold catalysts.[54] Thus, Yamamoto and co-workers[55] obtained 2-vinylpyrrolidines or 2-vinylpiperidines **114** by treatment of aminoallenes **113** with gold(I) chloride (Scheme 35). The low catalyst loading of 1 mol % in the case of γ-aminoallenes is revealing a high reactivity of these substrates toward the gold catalyst, whereas the formation of the six-membered ring required 5 mol % and longer reaction times (24 h at room temperature compared to 3 h for the 5-*exo*-trig cyclization). In the

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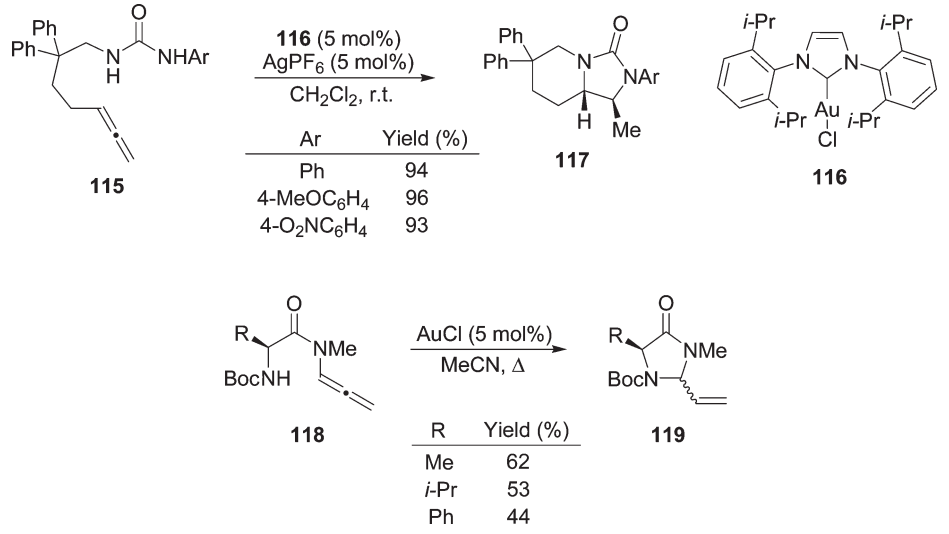
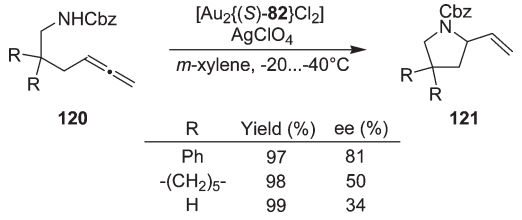
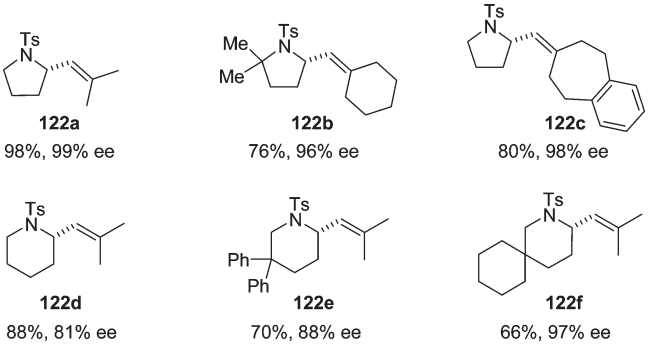
Scheme 36. Gold-Catalyzed Synthesis of Imidazolidinones



Scheme 37. Enantioselective Cycloisomerization of γ-Aminoallenes



Scheme 38. Products Obtained by Enantioselective Cycloisomerization of γ- or δ-Aminoallenes



case of the enantiomerically enriched γ-aminoallene **113**, axis-to-center chirality transfer is observed, leading to pyrrolidine **114** with high enantioselectivity. Analogous results were obtained by Widenhoefer and co-workers[37] using a phosphine-stabilized gold complex and silver triflate in dioxane at room temperature. The method was applied to a formal synthesis of swainsonine[56] and also employed for the cycloisomerization of allenic ureas **115** (using gold−NHC complex **116**)[57] or allenamides **118**[58] to the corresponding imidazolidinones **117**/**119** (Scheme 36).

The Widenhoefer group extended the method to the synthesis of enantiomerically enriched 2-vinylpyrrolidines **121** from monosubstituted γ-aminoallenes **120** in the presence of chiral gold precatalyst [Au_2{(*S*)-**82**}Cl_2] and silver perchlorate (Scheme 37).[59] Various protecting groups are tolerated under these conditions, and trisubstituted allenes can be converted to the corresponding hydroamination products as well.

Higher levels of chiral induction were achieved by Toste and co-workers[60] using (*R*)-xylyl−BINAP(Au-*p*-nitrobenzoate)$_2$ or (*R*)-ClMeOBiPHEP(Au-*p*-nitrobenzoate)$_2$ as catalyst. These allowed the smooth formation of chiral heterocycles **122** with up to 99% ee and high chemical yield from the corresponding trisubstituted tosyl-protected aminoallenes (Scheme 38). Similar to the cycloisomerization of γ- or δ-hydroxyallenes (Scheme 25), gold catalysts with a chiral counterion can also be employed for the highly enantioselective intramolecular *exo*-hydroamination of aminoallenes.[40]

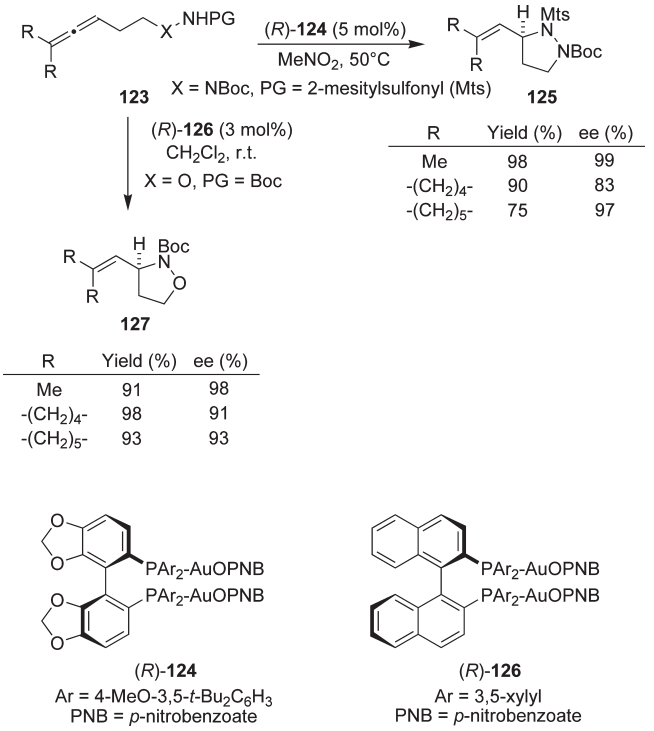
Recently, Toste and co-workers[61] expanded the scope of gold-catalyzed intramolecular *exo*-selective hydroaminations to allenic hydrazines and hydroxylamines **123**. The former substrates afforded pyrazolidines **125** in the presence of segphos-Au complex (*R*)-**124**, whereas the binap-gold catalyst (*R*)-**126** gave the best results in the cyclization of the hydroxylamine derivatives to isoxazolidines **127** (Scheme 39). Excellent chemical yields and enantioselectivities were obtained in most cases, and the method was also applied to the synthesis of chiral tetrahydrooxazines.

2.3. Sulfur Nucleophiles

The gold-catalyzed addition of a sulfur nucleophile to an allene may be considered rather exotic. After all, sulfides are known to be potent poisons for transition metal catalysts, and because of the strong Au−S bonds, gold is no exception to this rule.[62] Nevertheless, in 2006 Morita and Krause[63] reported the gold-catalyzed cycloisomerization of α-thioallenes (e.g., (±)-**128**) to the corresponding 2,5-dihydrothiophenes of type (±)-**129**

dx.doi.org/10.1021/cr1004088 |*Chem. Rev.* 2011, 111, 1994–2009

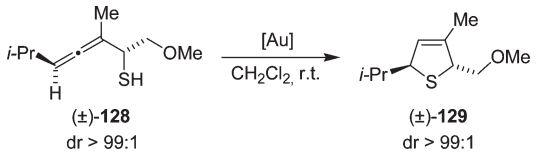
Scheme 39. *exo*-Cycloisomerization of Allenic Hydrazines and Hydroxylamines



R	Yield (%)	ee (%)
Me	98	99
-$(CH_2)_4$-	90	83
-$(CH_2)_5$-	75	97

R	Yield (%)	ee (%)
Me	91	98
-$(CH_2)_4$-	98	91
-$(CH_2)_5$-	93	93

Scheme 40. Gold-Catalyzed Cycloisomerization of α-Thioallenes



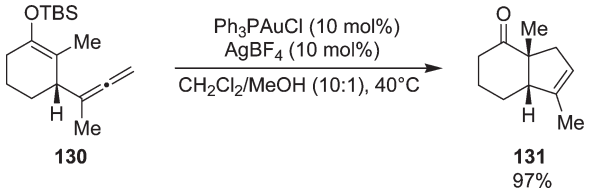
[Au]	Time (min)	Yield (%)
$AuCl_3$	180	58
AuCl	90	88
AuI	5	88

(Scheme 40), which, at the time, was the first example of a gold-catalyzed carbon−sulfur bond formation. In this transformation, gold(I) catalysts showed a higher reactivity and gave better yields than gold(III) chloride. In the latter case, the disulfide formed by oxidative coupling of thioallene (±)-**128** was isolated as side product; because $AuCl_3$ is the only oxidizing agent present in the reaction mixture, this finding indicates that it is reduced to gold(I) under the reaction conditions (cf. Scheme 18). Independent of the catalyst used, complete axis-to-center chirality transfer was observed in the cycloisomerization of α-thioallenes.[64]

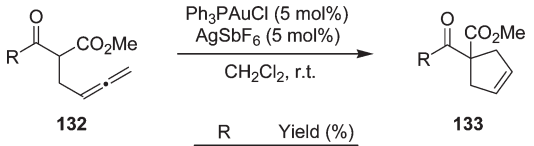
3. CYCLIZATION BY ATTACK OF CARBON NUCLEOPHILES

As described in the previous section, homogeneous gold catalysis has been widely utilized for the addition of heteroatom

Scheme 41. Gold-Catalyzed Cycloisomerization of Allenic Silyl Enol Ether 130



Scheme 42. Gold-Catalyzed Cycloisomerization of Allenic β-Ketoesters



R	Yield (%)
Me	51
Bn	71
Ph	67

nucleophiles to allenes since the beginning of this millennium. In contrast to this, addition reactions of carbon nucleophiles have been first disclosed in the year 2006, and the number of examples is still rather small. Toste and co-workers[65] used acetylenic and allenic silyl enol ethers for the gold-catalyzed intramolecular C−C bond formation; for example, substrate **130** undergoes a 5-*endo*-trig cyclization to hexahydroindenone derivative **131** in the presence of a cationic gold catalyst (Scheme 41). In these transformations, water or methanol is used as external proton source for protodeauration of an intermediate vinylgold species.

In an analogous manner, cyclopentenes **133** were obtained in good yields from allenic β-ketoesters **132** (Scheme 42).[66] In the presence of a palladium catalyst and an allyl halide, the same substrates afford functionalized 2,3-dihydrofurans.

Gold-catalyzed cyclization reactions of allenenes and allenynes usually proceed via non-nucleophilic pathways different from those outlined in Scheme 1.[67] Exceptions involve the cycloisomerization of allenenes of the type **134** in the presence of chiral gold precatalyst (*R*)-**135** and silver triflate, which afforded a mixture of chiral vinylcyclohexenes **136**/**137** with high yield and good enantioselectivity (Scheme 43).[68] The formation of these products is rationalized by nucleophilic attack of the olefinic double bond at the activated allene, followed by deprotonation and protodeauration of the resulting cyclohexyl cation. In a related study, Liao, Liu, and co-workers[69] obtained cyclic ketones of the type **139** by heating allenynes (e.g., **138**) with a cationic gold catalyst in wet 1,4-dioxane. This hydrative cyclization probably proceeds via 5-*endo*-attack of the triple bond at the activated allene. The resulting vinylcation is then trapped by water, and subsequent protodeauration closes the catalytic cycle.

Most reports on the gold-catalyzed intramolecular C−C bond formation of allenes take advantage of electron-rich aromatics or heteroaromatics as the nucleophile.[70] Interestingly, this hydroarylation has been utilized in natural product synthesis even before the method was studied extensively. Thus, Nelson

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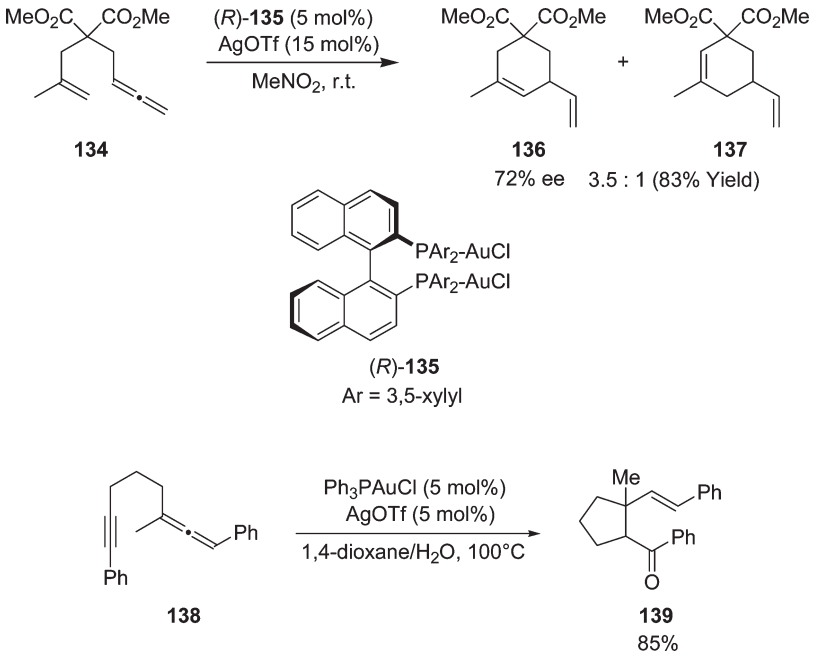
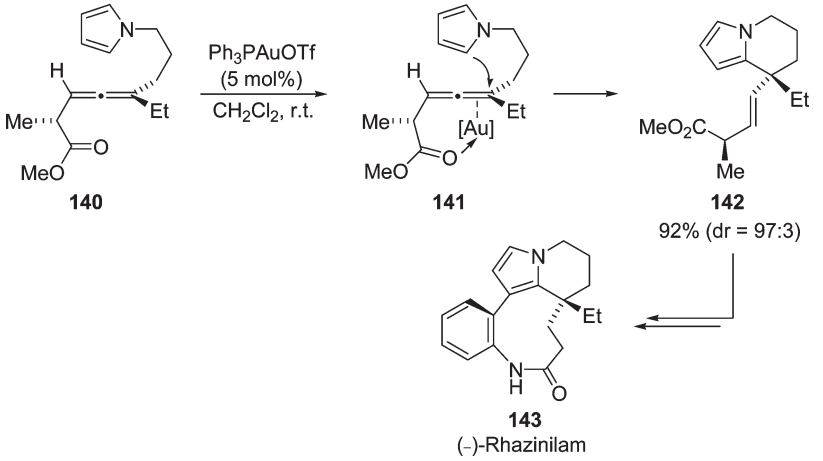
Scheme 43. Gold-Catalyzed Cycloisomerization of Allenenes and Allenynes



Scheme 44. Gold-Catalyzed Cycloisomerization of Allenic Pyrrol Derivative 140



and co-workers[71] used a cationic gold catalyst to activate allene **140** for nucleophilic attack of the pyrrole ring, which delivered tetrahydroindolizine **142** (a precursor of the alkaloid (−)-rhazinilam **143**) with high yield and excellent chirality transfer (Scheme 44). It seems reasonable to assume that coordination of the Lewis acidic gold catalyst to the carbonyl group (intermediate **141**) is key to the high diastereoselectivity. In contrast to this, palladium or silver catalysts either failed to deliver the desired cyclization product or gave poor stereoselectivities.

Other electron-rich heteroaromatics like indoles can also be used as nucleophile in gold-catalyzed hydroarylations. As in the case of *exo*-selective hydroalkoxylations and hydroaminations, it was Widenhoefer[37] who reported the first examples of the formation of tetrahydrocarbazoles and related heterocycles from allenyl indoles. Starting from achiral allenes, e.g., **144**, the hydroarylation products **145** were obtained with high ee by using chiral gold precatalyst $[Au_2\{(S)\text{-}\mathbf{82}\}Cl_2]$ (cf. Schemes 24 and 37) and silver tetrafluoroborate (Scheme 45).[72] Interestingly, this method also allows the formation of seven-membered carbocycles. Recently, *endo*-selective gold-catalyzed cycloisomerizations of *N*-(2,3-butadienyl)-substituted indol derivatives were described as well.[73]

Electron-rich phenyl rings are also competent nucleophiles for the intramolecular gold-catalyzed hydroarylation of allenes. Thus, an efficient route to dihydroquinoline and chromene derivatives has been developed by Fujii, Ohno, and coworkers,[74] who exposed allenic anilines or allenic arylethers to a cationic gold catalyst (Scheme 46). Depending on the structure of the substrate, the C−C bond is formed at the

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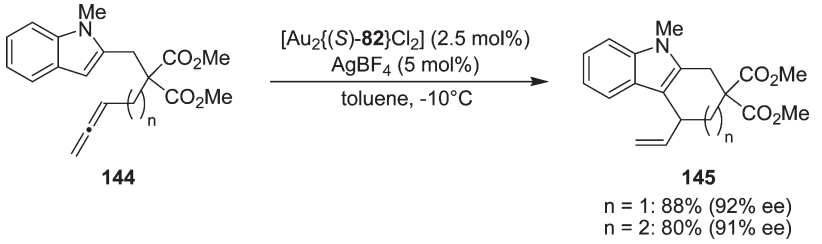
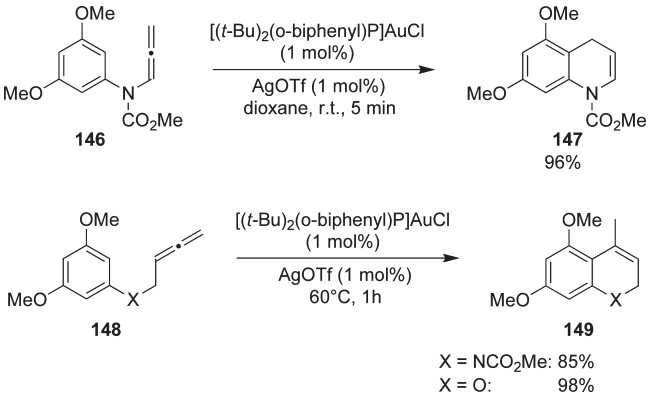
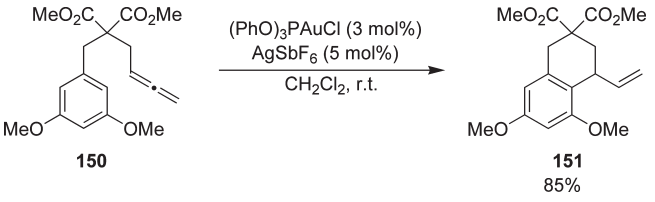
Scheme 45. Intramolecular Hydroarylation of Allenyl Indoles



Scheme 46. Intramolecular Hydroarylation of Arylallenes



Scheme 47. Intramolecular Hydroarylation of Arylallene 150

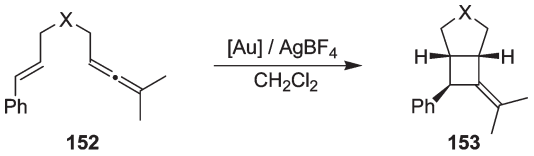


terminal or central allenic carbon atom. Thus, allenamide **146** delivers dihydroquinoline **147** with 96% yield by 6-*endo*-attack, whereas substrates **148** with an extended tether between the allene and the aryl ring undergo 6-*exo*-cyclization. Because of the lower reactivity of allenes **148**, heating and a longer reaction time are required to obtain hydroarylation products **149** in high yield.

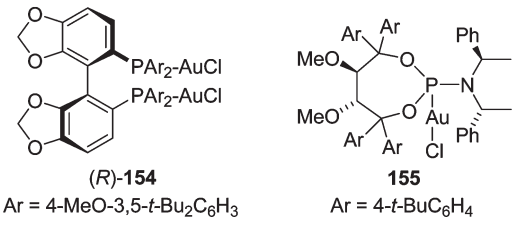
This method was applied by Gagné and co-workers[75] to arylallenes of the type **150** bearing an extended all-carbon linker between the reactive sites. In this case, a 6-*exo*-trig cyclization was induced by a mixture of triphenylphosphite gold(I) chloride (3 mol %) and silver hexafluoroantimonate (5 mol %), giving tetralin derivative **151** in high yield (Scheme 47). Extensive mechanistic studies have revealed a diaurated species as catalyst resting state, which is activated by the silver salt.[76]

Another possibility to use the activation of allenes by gold catalysts for C−C bond formation is their participation in cycloadditions.[77] Intramolecular [2 + 2]-cycloadditions of allenenes **152** were studied by Toste and co-workers,[78] who

Scheme 48. Gold-Catalyzed Intramolecular [2 + 2]-Cycloaddition of Allenenes



X	[Au]	Yield (%)	ee (%)
$C(CO_2Me)_2$	(*R*)-**154**	92	95
NTs	(*R*)-**154**	70	54
$C(CO_2Me)_2$	**155**	91	>99
NTs	**155**	52	95



obtained the bicyclic cycloadducts **153** with moderate to high enantioselectivities by using chiral biarylphosphinegold(I) catalyst (*R*)-**154** together with silver tetrafluoroborate (Scheme 48). Even better results were reported recently by Fürstner and co-workers,[79] who employed the chiral TADDOL-derived gold complex **155**. By using electron-rich NHC−gold catalysts, an alternative pathway toward [3 + 2]-cycloaddition products can be favored.[80]

Precatalyst **155** and related gold phosphoramidite complexes also promote enantioselective intramolecular [4 + 2]-cycloadditions of allenic dienes.[79,81] This transformation was previously studied by Shapiro and Toste,[77,82] who obtained Diels−Alder adduct **157** from tetraene **156** in the presence of cationic gold species formed from arylphosphite gold chlorides and silver hexafluoroantimonate (Scheme 49). In contrast to this, the [4 + 3]-cycloaddition product **158** is formed almost exclusively with gold catalysts bearing electron-rich σ-donor ligands. This is attributed to a stabilization of the gold carbenoid intermediate **159** formed in the [4 + 3]-cycloaddition.[80,82−84]

Suitably substituted allenes can also participate in (formal) [3 + 2]- and [3 + 3]-cycloadditions.[85] Because these transformations do not involve nucleophilic attack at the allene, they are not discussed in this account.

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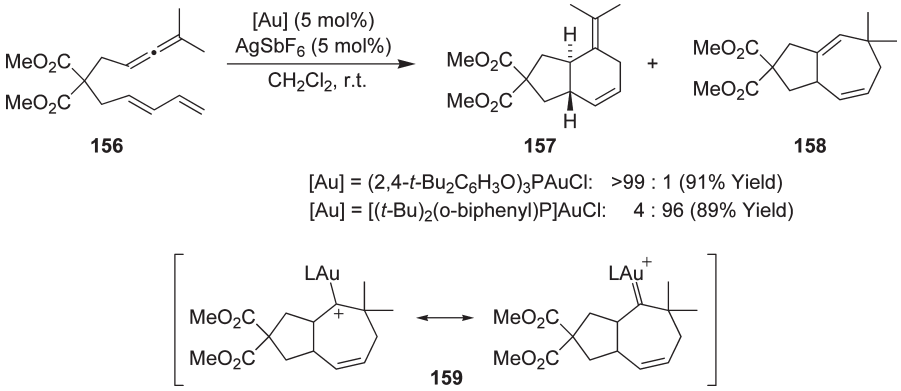
Scheme 49. Gold-Catalyzed Intramolecular [4 + 2]- and [4 + 3]-Cycloaddition of Allenic Diene 156



4. CONCLUSION

The activation of allenes with homogeneous gold catalysts sets the stage for cyclization by intramolecular attack of various nucleophiles, affording highly useful hetero- or carbocyclic products by formation of new C−O, C−N, C−S, or C−C bonds. In many transformations of this type, the stereochemical information of the allene is efficiently transferred to the product by axis-to-center chirality transfer, or it is introduced into the product with the aid of chiral gold catalysts. Several applications of these methods in target-oriented synthesis demonstrate their utility.

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Norbert Krause graduated from Technical University of Braunschweig in 1984 and received his Ph.D. in 1986. After postdoctoral stays at ETH Zürich and Yale University, he joined Technical University of Darmstadt and obtained his Habilitation in 1993. In 1994, he moved to the University of Bonn as Associate Professor, before being appointed to his present position at Dortmund University of Technology as Full Professor in 1998. He was a Fellow of the Japan Society for the Promotion of Science (2003 and 2009), and Guest Professor at the Université Catholique de Louvain, Belgium (2007), at the University of California, Santa Barbara, CA, USA (2009), and at the École Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI), France (2009). Since 2006, he is a member of the Editorial Board of the European Journal of Organic Chemistry. His review on "Recent Advances in Catalytic Enantioselective Michael Additions" was the World's Most Cited Chemistry Paper in Nov. 2002. His research focuses on the stereoselective synthesis and transformation of functionalized allenes, taking advantage of coinage metal (copper, silver, and gold) catalysis. In his free time, he enjoys snorkeling and riding his motorbike.

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