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Gold-Containing and Gold-Generated 1,*n*-Dipoles as Useful Platforms toward Cycloadditions and Cyclizations

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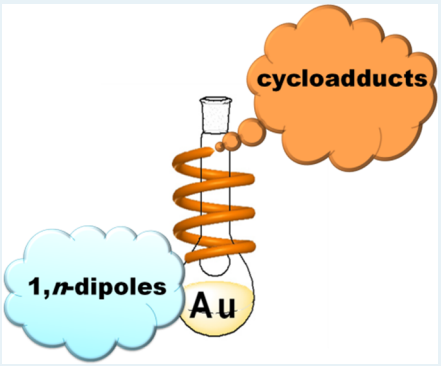
ABSTRACT: Some of the most synthetically useful methods to construct molecular complexity include Diels–Alder, [1,3]-dipolar- and [*m*+*n*]-cycloadditions. In this context, the efficient generation of 1,*n*-dipoles plays a key role. Dipoles have been usually described as transient, difficult to harness species toward cycloaddition reactions. This review highlights the development of new methodologies for the efficient generation of these valuable intermediates by means of gold catalysis, and their application in the construction of small-medium size carbocycles. The mechanistic rationale underlying these transformations is also presented here.



KEYWORDS: *gold, 1,n-dipoles, zwitterions, cycloaddition, annulations, cyclization*

1. INTRODUCTION

In recent years, gold catalysis has emerged as an extraordinary tool to create molecular complexity because of the unique ability of gold(I) and gold(III) complexes to activate carbon–carbon π-systems.[1] A broad array of gold-catalyzed cyclizations and cycloisomerizations have been disclosed offering access to complex cyclic motifs in a highly efficient manner.[2−4] Gold π-coordinated alkenes, alkynes or allenes, gold carbenes, and gold-stabilized carbocations have been invoked as likely reaction intermediates in these transformations.[5] Until recently, a much less explored area in gold catalysis involved the generation of 1,*n*-dipoles and their use as reaction partners in cycloaddition processes. Both, inter- and intramolecular cycloaddition/annulation reactions have been recognized as powerful methods to access polycyclic scaffolds in a highly regio- and stereocontrolled fashion.[6] Although these processes are mechanistically well understood, the instability of the required dipole intermediates has oftentimes limited the extension of these transformations to new systems or the development of more elaborated synthetic applications. Late transition metals (e.g., Rh, Ru, Pd) have been successfully employed to trigger the formation- or to modulate the reactivity- of dipoles participating in cycloaddition reactions.[7] In recent years, the versatility and multiple activation properties of gold have enabled the development of a wide array of cycloaddition reactions mediated by this noble transition metal.[8,9] Because of the key role played by the dipole's nature in the outcome of these annulations, we decided to focus this review not only on gold-containing dipoles but also on dipoles that are effectively generated in situ by gold-catalyzed reactions. In some cases though, it is difficult to be precise about the specific nature of these reaction intermediates, which might be better described as zwitterions or zwitterionic resonance forms rather than 1,*n*-dipoles. In this context, further precision is needed, as formal charges in gold catalyzed reactions vary depending on whether the gold precatalysts are considered cationic (which is experimentally the case in some transformations) or the metal is considered neutral. In the former case, most "zwitterionic" species depicted along the catalytic cycle could be considered neutral, even if the displayed reactivity patterns clearly reflect or seem to point toward the involvement of charge-separated species. For the sake of consistency, gold species have been considered formally neutral in the schemes illustrating the mechanistic discussions, so that the zwitterionic nature of the reaction intermediates, proposed by the original authors to play a key role in the reaction outcome, are easily recognized. Furthermore, we have formally classified these species according to the number of atoms present in the fragment, and the corresponding annulation processes are also classified according to the number of atoms involved in the reaction with a suitable dipolarophile [mC+nC]. As gold-containing 1,*n*-dipoles/zwitterions can also be suitable intermediates in cyclization reactions, representative examples of these transformations have been also included here. In summary, this account will describe the recent progress on gold catalysis involving the generation of dipoles and their subsequent application in cycloadditions and cyclizations to build up molecular complexity.

2. GENERATION OF 1,3-DIPOLES

2.1. Application of 1,3-Dipoles in [3 + 2] Cycloaddition Reactions. Gold complexes have been extensively

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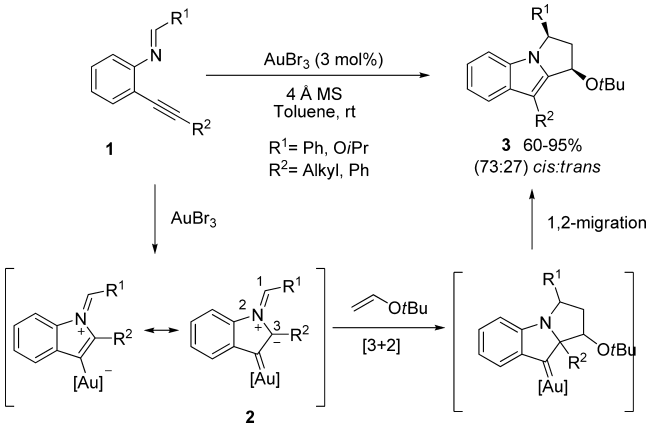
used to coordinate chemoselectively C−C triple bonds, promoting the attack of nucleophiles. Although these metal carbophilic catalysts can also coordinate alkenes and allenes, nucleophiles seem to have preference for activated alkyne systems.[1−5] On the basis of this reactivity, substrates containing both an acetylene moiety and an oxygen or nitrogen atom can be transformed into zwitterionic intermediates that undergo cycloaddition reactions with alkynes, alkenes, and so forth. A 1,3-dipole was invoked by the group of Iwasawa[10] in 2006 for the preparation of tricyclic indole derivates **3** from *N*-(*o*-alkynylphenyl)imines **1** (Scheme 1). The use of catalytic

Scheme 1. Gold-Catalyzed [3 + 2] Cycloaddition of Azomethine Ylides 2



amounts of gold tribromide generates the gold-containing azomethine ylides **2** through an electrophilic activation of the internal alkyne moiety, which induces a 5-*endo* nucleophilic attack of the imino nitrogen onto the gold-activated alkyne. A subsequent [3 + 2] cycloaddition with an external olefin followed by a 1,2-migration of the R^2 group afforded the corresponding tricyclic products **3** in 60−95% yield.

Gold azomethine ylides **6** were also invoked by Shapiro and Toste in 2008 to explain the formation of azepines **7** through a stepwise [4 + 3] annulation process between the gold carbenes **4**, generated upon 1,2-migration of the ester group in propargylic benzoates, and *α*,*β*-unsaturated imines **5** (Scheme 2).[11]

The enantioselective gold(I)-catalyzed 1,3-dipolar cycloaddition reaction of mesoionic azomethine ylides (münchones) **8**[12−14] with electron-deficient alkenes **9** to give Δ^1-pyrrolines **10** has also been recently reported (Scheme 3).[15,16]

A mechanistic rationale for this transformation is shown in Scheme 4. Deprotonation of the activated azalactone **11**, presumably by the benzoate counteranion, generates the *N*-aurated-1,3-dipole **12**. Reaction of the latter with the dipolarophile **9** produces the cycloadduct **13**. C−O cleavage and protonation followed by dissociation of the Δ^1-pyrroline **10** regenerates the gold catalyst for a new cycle (Scheme 4).

Gold azomethine ylides have been also invoked in the one-pot synthesis of azabicyclo[3.2.1]octanes **15** from 1,6-enynes incorporating a nitrone moiety **14** (Scheme 5).[17]

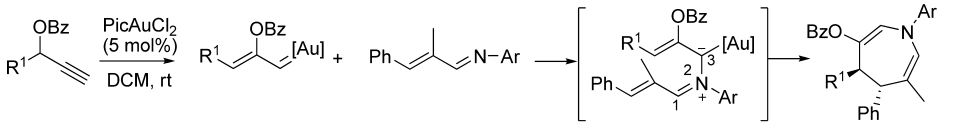
The reaction is proposed to proceed as follows: an *α*-carbonyl carbenoid **18** is formed by an internal redox reaction after the addition of the nitrone to the metal-activated alkyne (Scheme 6).[18−22] Two different plausible pathways have been proposed to explain the formation of **18**. On one hand, a nucleophilic attack of the nitrone onto the gold-activated alkyne in a 6-*exo*-*dig* fashion can generate the intermediate **16**, which has a possible neutral resonance form depicted as **17**. A retro-electrocyclization in **17** would deliver carbene **18** (path A, red). Alternatively, **18** could be generated directly from **16** without undergoing dearomatization (path B, black). Addition of the imine nitrogen to the in situ generated carbene in **18** affords the 1,3-dipole **19**, which after a [3 + 2] cycloaddition with the pendant olefin of the starting material yields the tetracyclic ketone **15**.

α-Carbonyl gold carbenes have been also proposed in related transformations aimed at the synthesis of complex azacyclic compounds. Thus, in 2011 the group of Liu reported a stereoselective synthesis of azatricyclic scaffolds **25** from *o*-alkynyl nitrobenzenes and external alkenes **24** (Scheme 7).[23] An *α*-carbonyl carbene **20** is proposed to be formed by reaction of the nitro group with the *π*-gold activated alkyne. A ketonyl oxonium intermediate **21** is subsequently generated from the nucleophilic attack of the nitroso group onto the gold carbenic carbon. A keto−enol tautomerism affords the enol form **22**, which is also characterized by the resonance structure **23**. A concerted [3 + 2] cycloaddition reaction between the in situ-generated zwitterion **23** and an external olefin affords the observed tricyclic products **25** in moderate to excellent yields.

Gold can also mediate the formation of nitrone 1,3-dipoles as reported by Shin and co-workers in 2011.[24] Dihydroisoxazoles **28** were efficiently synthesized from *N*-sulfonyl hydroxylamines **26**, which in the presence of catalytic amounts of gold afford the corresponding nitrones **27**. In the presence of different dipolarophiles, [3 + 2] cycloaddition products **28** were stereoselectively obtained in up to 89% yield (Scheme 8).

The formation of the nitrone **27** was proposed to proceed via 5-*endo*-*dig* nucleophilic attack of the nitrogen onto the gold-activated alkyne in **26** to give intermediate **29**, which after 1,3-*N*-sulfonyl migration leads to the 1,3-gold containing dipole **30**. The turnover of the gold catalyst generates the corresponding vinyl hydroxylamine that tautomerizes into the more stable nitrone **27** (Scheme 9). The use of stochiometric amounts of gold in the synthesis of gold(I)- and gold(III)-nitrone complexes has been also described.[25] These novel gold anionic salts also mediate in the 1,3-dipolar cycloaddition between *N*-benzyl-C(2-pyridyl)nitrones and methyl acrylate, affording the corresponding [3 + 2] cycloadducts.

Scheme 2. Gold-Catalyzed Synthesis of Azepines 7



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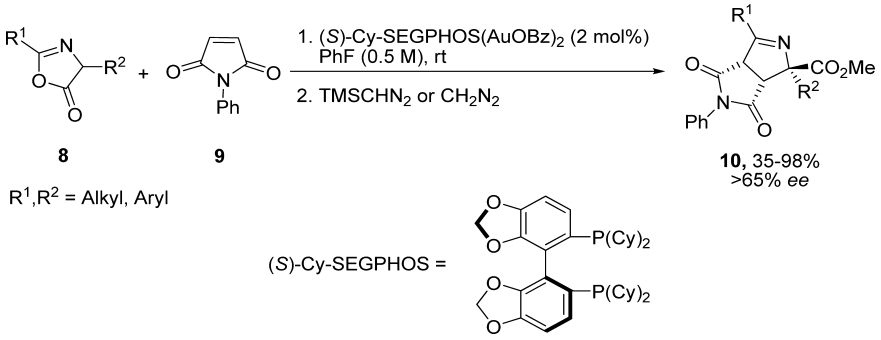
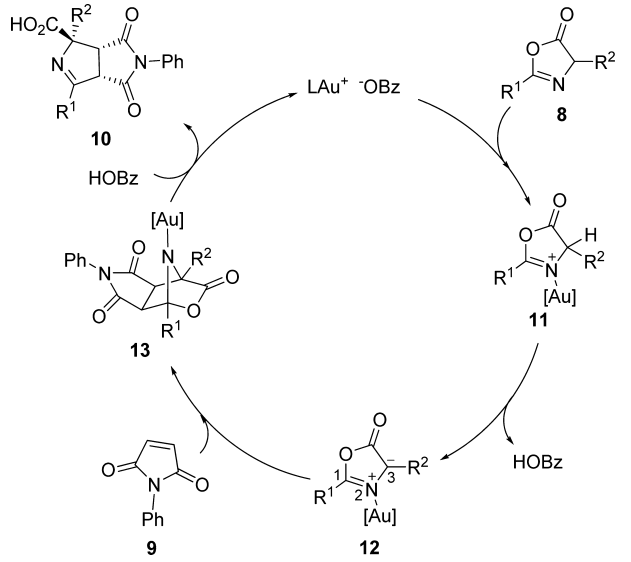
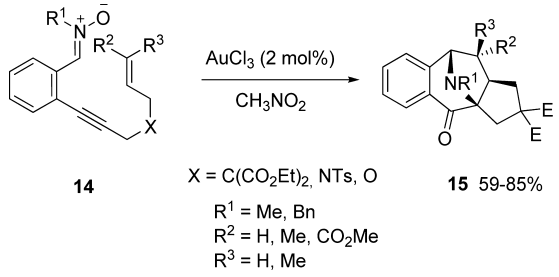
Scheme 3. Gold-Catalyzed 1,3-Dipolar Cycloaddition between Münchones 8 and Alkenes



Scheme 4. Proposed Mechanism



Scheme 5. Synthesis of Azabicyclo[3.2.1]octanes 15



In 2005, the group of Oh developed a new gold-catalyzed cycloisomerization of diynals and enynals for the formation of [6.7.*n*]-tricyclic compounds **33** (Scheme 10).[26] This type of structure is found in a variety of natural products including barbatusol, pisiferin, faveline, and xochitlolone.[27] The reaction might occur through the carbonyl addition onto the gold-activated triple bond to generate zwitterionic intermediate **32**. An intramolecular [3 + 2] cycloaddition takes place with the second alkyne moiety followed by fragmentation to give the desired product **33** while regenerating the catalyst for a new cycle. This mechanism is analogous to the one proposed by the same authors in a related Rh-catalyzed [3 + 2] cycloaddition of enynes bearing aldehyde groups.[28]

An application of this strategy for the racemic synthesis of the B and C rings of a chrysenone derivate (**35**) and of 3-desoxyequilenin (**37**) in just one preparative step was published by Dyker and co-workers in 2006 (Scheme 11).[29] The key step in these transformations is the gold-catalyzed formation of a benzopyrylium 1,3-dipole **34**, generated by a double benzannulation process resulting from the nucleophilic attack of the carbonyl oxygen of the aldehyde onto the gold-activated-alkyne moiety. A subsequent intramolecular Huisgen-type [3 + 2] cycloaddition with the second alkyne present in the molecule followed by a rearrangement leads to the aromatized *rac*-chrysenone (**35**) in 75% yield. In a similar process, compound **36** can be easily transformed into an inmediate precursor of *rac*-3-desoxyequilenin (**37**).

Another example of 1,3-dipole generated through the nucleophilic attack of a carbonyl moiety onto a gold-activated alkyne was reported by Liming Zhang et al. in 2008.[30] The reaction takes place on 1-(1-alkynyl)cyclopropyl ketone substrates, starting by a 5-*endo-dig* cyclization of the carbonyl group in **38** to form oxocarbenium intermediates **39**. These carbonyl-ylides undergo a 1,3-dipolar cycloaddition with ethyl vinyl ether, forming the bridged bicycles **40**. These compounds could be efficiently transformed into highly functionalized bicycle [3.2.0]heptanes **41** (Scheme 12).

This concept was further applied in a highly regio- and diastereoselective gold(I)-catalyzed tandem heterocyclization/[3 + 2] cycloaddition for the synthesis of cyclopenta[*c*]furans **44** from α,β-unsaturated alkynyl ketones **42** reported in 2011 by Junliang Zhang et al. (Scheme 13).[31] Variations of both the 3-styrylindole **43** and the conjugated ketone counterpart were well tolerated, affording the highly substituted cyclopenta[*c*]-furan products **44** in 68−96% yield and >20:1 diastereomeric ratio.

The effects of the dipolarophile **43** on the stereochemistry of the final product were also tested. *E* and *Z* olefins afforded the same compounds under the reaction conditions, indicating that the reaction proceeds through a stepwise formal [3 + 2] cycloaddition pathway as shown in Scheme 14. The gold(I)-catalyzed heterocyclization of the ketone **42** afforded the furanyl gold dipole **45**. Nucleophilic attack of the alkene moiety of the 3-styrylindole **43** onto **45** in a diastereo- and regioselective fashion afforded two consecutive intermediates **46** and **47**. Steric interactions disfavor **47** leading to intermediate **46**, which upon cyclization delivers the formal [3 + 2] cycloaddition products **44**.

1,3-Dipoles can also be generated by nucleophilic attack of epoxides onto activated alkynes, adding up to the strategies already disclosed in Schemes 6 and 7 for the generation of α-carbonylcarbenoids. Thus, an intramolecular redox reaction of an alkyne-epoxide **48** with gold generates the α-carbonylcarbene **49** avoiding the use of potentially hazardous

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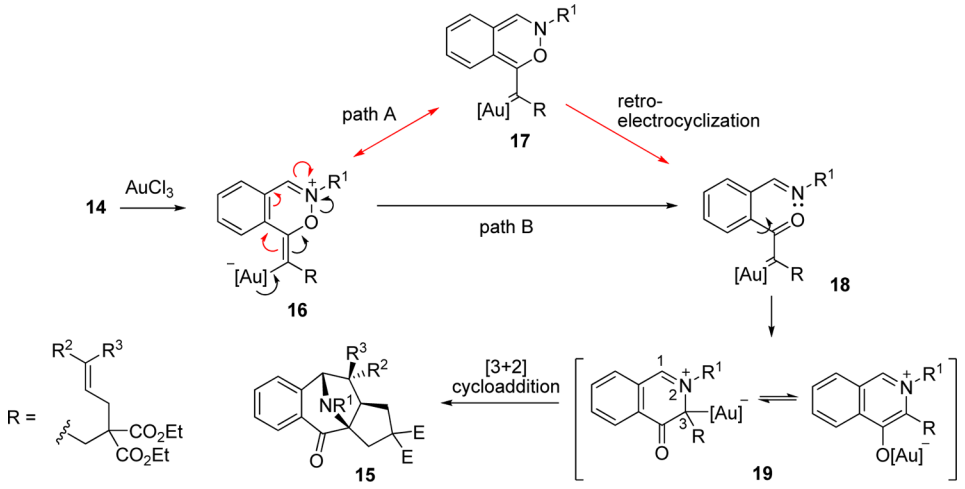
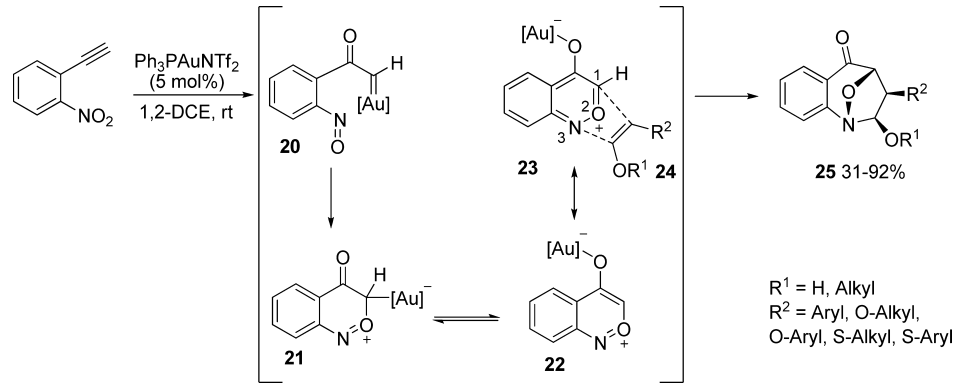
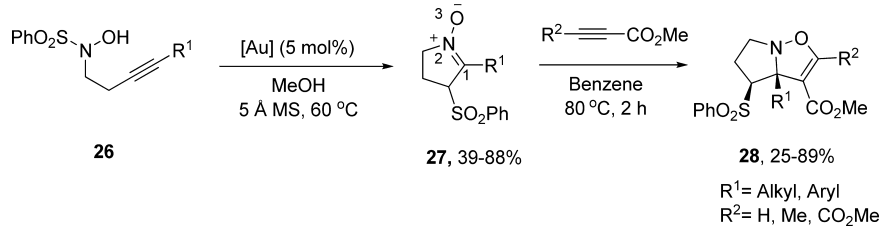
Scheme 6. Mechanistic Proposal



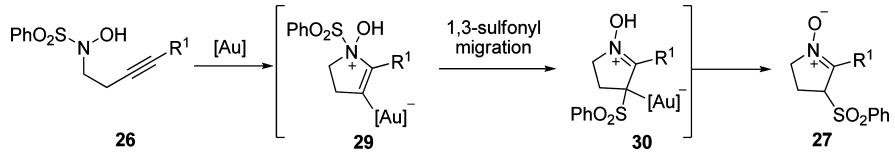
Scheme 7. Gold-Catalyzed Synthesis of Azacycles 25: Proposed Mechanism



Scheme 8. Gold-Catalyzed Nitrone Formation and [3 + 2] Cycloaddition



Scheme 9. Gold-Catalyzed Nitrone Formation



diazocarbonyl precursors (Scheme 15).[32−36] In the presence of an external olefin, a 1,3-zwitterionic intermediate **50** was proposed to be the responsible of a rapid ring closure to give the 2,3-dihydrofuran species **51** with the deuterium cis to the neighboring aryl group. Because of the slow rotation of the C−C bond, a small portion of dipoles **50′** afford the final 2,3-dihydrofuran **51′** with the deuterium atom trans to the aryl group after the ring closure step.

Allenes have been proven to be very flexible synthetic motifs in the development of novel cycloaddition[37] and cyclization[38−43] reactions upon activation in the presence of gold catalysts. Particularly, oxyallenes have also been used as effective precursors of 1,3-dipoles in the presence of gold. A pioneering example was reported by Zhang in 2007 showing that a MOM-protected allenyl carbinol **52** could be used in a highly diastereoselective formal [3 + 2] cycloaddition toward cyclopentanones enol ethers **53** (Scheme 16).[44] The mechanism operating in this transformation involves the selective gold activation of the enolic double bond of the allenyl ether moiety to trigger the corresponding oxocarbenium

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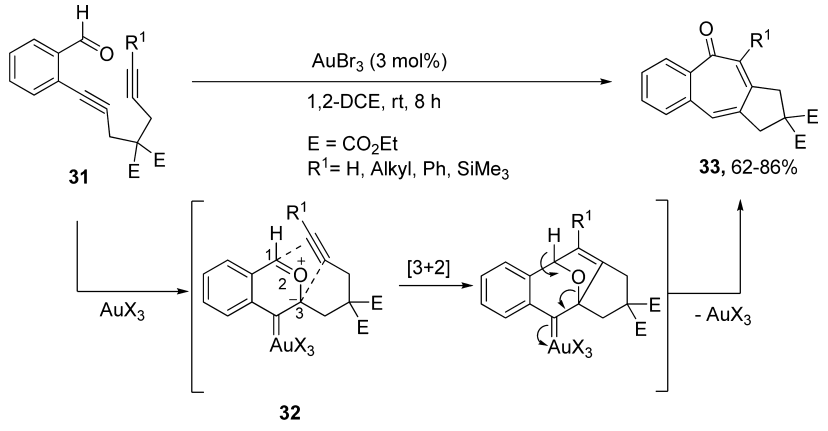
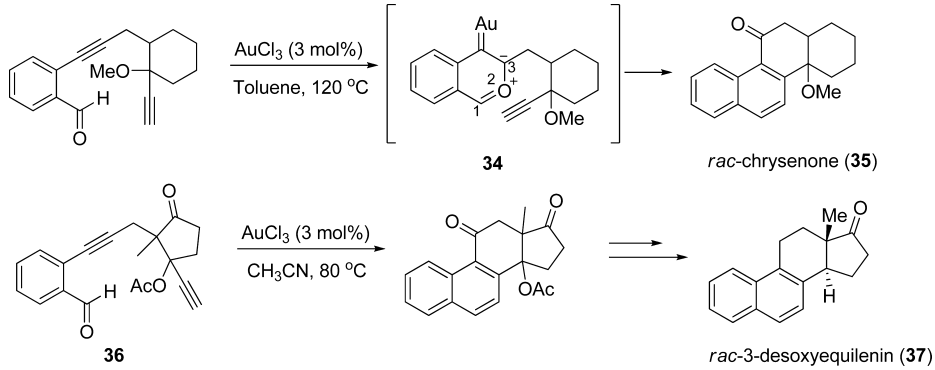
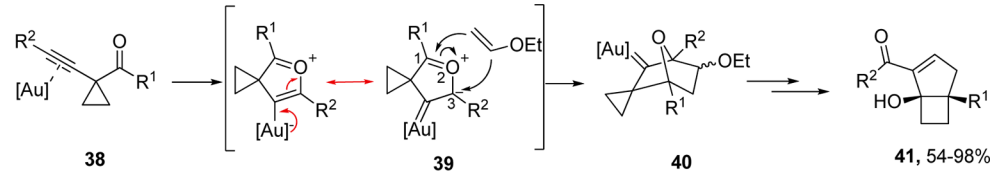
Scheme 10. Gold-Catalyzed [3 + 2] Cycloaddition of *o*-Alkynylbenzaldehydes 31



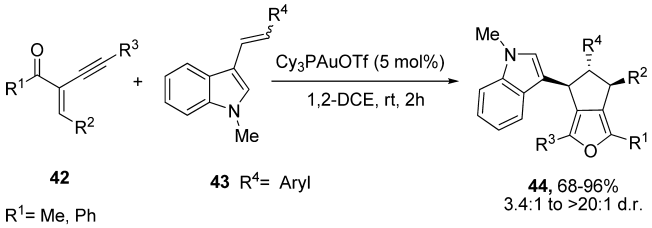
Scheme 11. Gold-Catalyzed Synthesis of *rac*-Chrysenone (35) and *rac*-3-Desoxyequilenin (37)



Scheme 12. Gold-Catalyzed 1,3-Dipolar Cycloaddition between Ethyl Vinyl Ether and an Oxocarbenium Cation 39



Scheme 13. Diastereoselective Synthesis of Cyclopenta[*c*]furans 44



54, which is in resonance with the 1,3-dipole **55**. An intramolecular [3 + 2] cycloaddition with the internal olefin delivered strained bicyclo[3.1.0]hexane gold carbene **56**. Fragmentation of the cyclopropane ring with the help of the OH group and protiodeauration forms the corresponding cyclopentanones enol ethers **53** in good yields and excellent diastereoselectivities.

The same group published in 2008 how gold-containing all-carbon 1,3-dipoles could be obtained via migration-fragmentation of ketals/acetals **57** and **60** (Scheme 17).[45] A facile [3 + 2] cycloaddition of the in situ generated 1,3-dipoles **59** and **62** with various electron-rich aromatic aldehydes and *N*-benzylindoles at room temperature led the rapid formation, with excellent diastereoselectivities, of highly functionalized 2,5-dihydrofurans **58** and cyclopentenes **61**, respectively.

In 2011, She et al. reported the formation of piperidines **65** using a gold-catalyzed tandem acyloxy migration on the enynyl ester **63** to form in situ a 1,3-dipole **64**, which had been previously reported with platinum.[46] An intramolecular [3 + 2] cycloaddition provides then an efficient approach for the synthesis of polyfunctionalized piperidines **65** in high yields with good stereoselectivities (Scheme 18). When dried CH_2Cl_2 was used as solvent to prevent hydrolysis, 1,2-disubstituted

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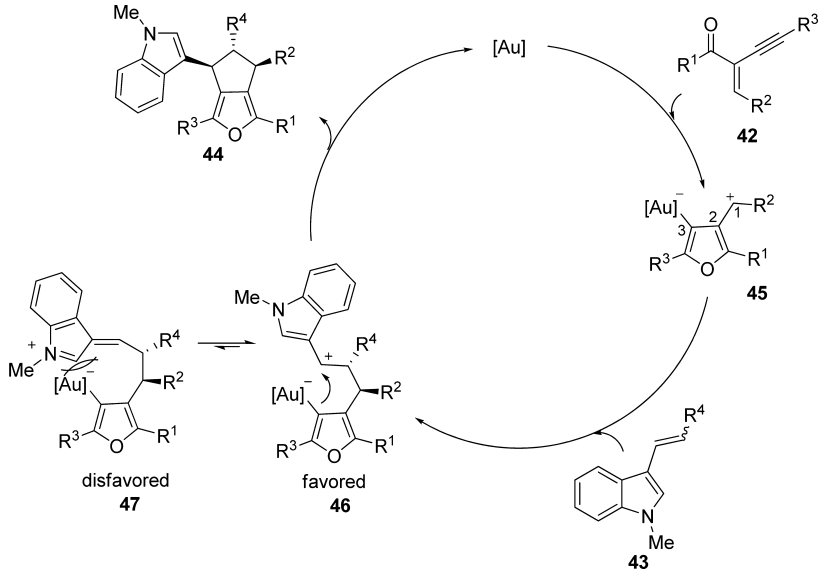
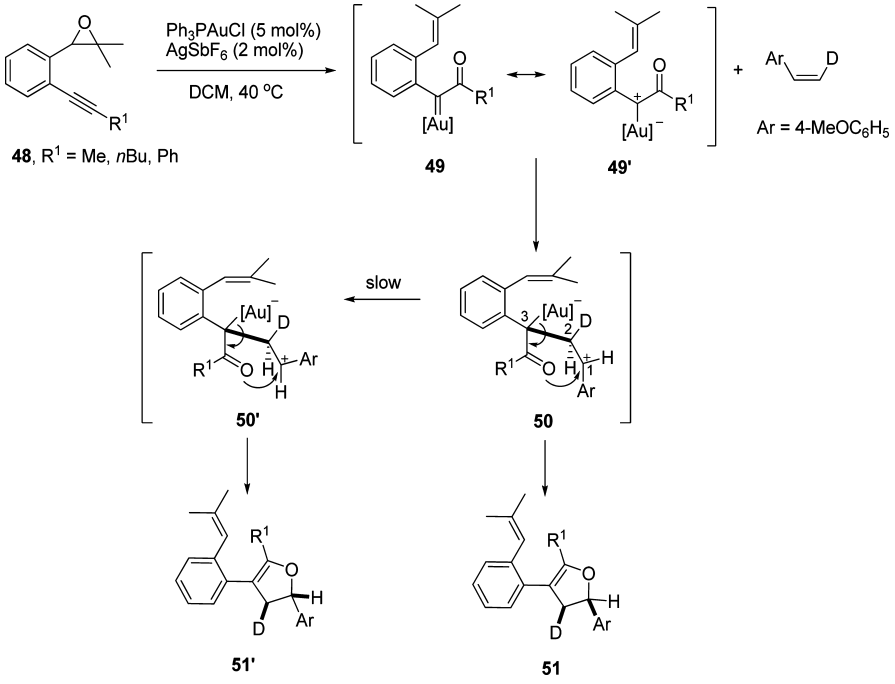
Scheme 14. Proposed Mechanism



Scheme 15. Gold-Catalyzed Synthesis of 2,3-Dihydrofurans 51 and 51′



olefins **66** led the exclusive formation of dihydrofurans **67** in good yields.

Almost simultaneously, the goup of Wang reported a gold-catalyzed [3 + 2] cycloaddition/hydrolytic Michael addition/retro-aldol reaction of propargyl esters **68** for the preparation of dihydrofuran-fused cyclohexenones **69** and **70** (Scheme 19).[47] The reactions appeared to be stereospecific because of the formation of the corresponding products as single diastereomers. When the reactions were carried out under moist air, bicyclic products **69** were obtained in 70−92% yield after 8 h (eq 1). However, when the reactions were run in dry conditions under inert atmosphere, the corresponding dihydrofuran-fused cyclohexenones **70** were isolated in good to excellent yields (eq 2). The presence of $Cu(OTf)_2$ as a cocatalyst in the last transformation significally shortened the reaction times.

The authors proposed a rare gold-promoted [3 + 2] cycloaddition/hydrolytic Michael addition/retro-aldol reaction sequence for the formation of the observed products (Scheme 20). The cascade process is triggered by gold-electrophilic activation of the alkyne in **68**, which generates the gold-coordinated allene **71** through a [3,3]-sigmatropic rearrangement of the arylcarboxy group. The addition of the carbonyl moiety to the allene in **71** followed by allylic elimination of the gold catalyst affords the 1,3-dipole **72**, which undergoes an intramolecular [3 + 2] cycloaddition with the enone double bond to give the vinyl ketal **73**. Fragmentation of **73**, driven by the strain release, generates a zwitterionic intermediate **74**, in which a rapid proton transfer delivers the dihydrofuran-fused cyclohexenones **70**. The formation of **69** requires moisture and the presence of the gold catalyst. Activation of **70** likely

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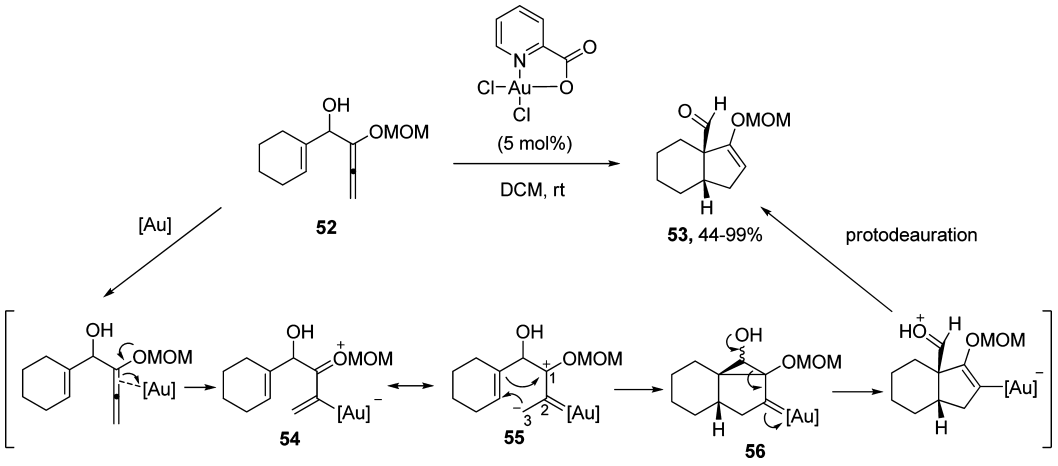
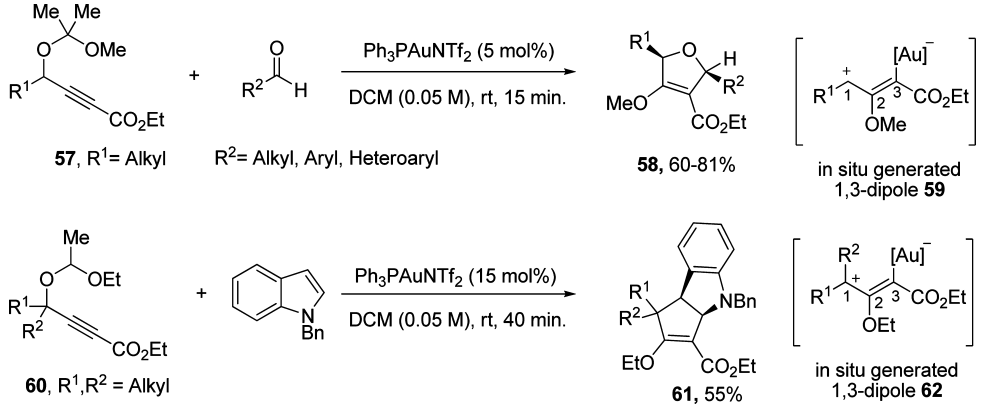
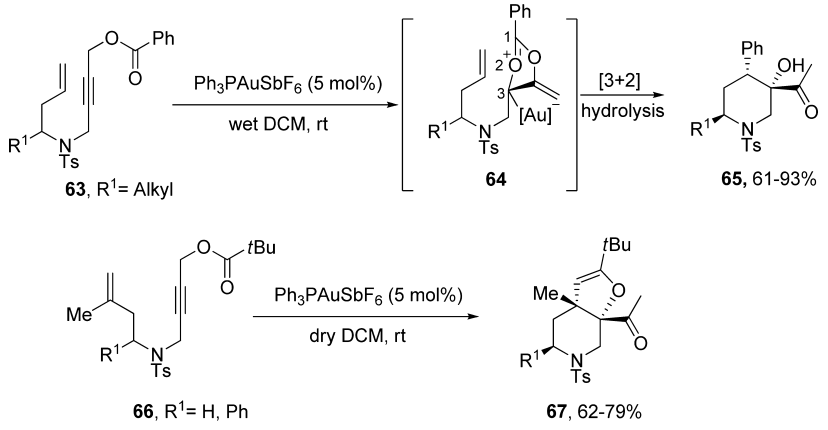
Scheme 16. Gold-Catalyzed Synthesis of Cyclopentanone Enol Ethers 53: Proposed Mechanism



Scheme 17. Formation of Functionalized 2,5-Dihydrofurans 58 and Cyclopentenes 61



Scheme 18. Gold-Catalyzed Synthesis of Piperidines 65 and Dihydrofurans 67



proceeds through the complexation of the gold catalyst to the π system of the enone. Nucleophilic attack of a molecule of water yields the labile hemiketal **75**, which affords the final compound **69** through a retro-aldol process.

2.2. Application of 1,3-Dipoles in [3 + 3] Cycloaddition Reactions. Zhang's group has further exploited oxocarbenium ion **54** and its resonance form, the 1,3-dipole **55** (see Scheme 16)[44] in a formal [3 + 3] cycloaddition reaction for the formation of benzyl-protected substituted phenols **77** (Scheme 21).[48]

The mechanism proposed for this transformation is similar to the one shown in Scheme 16 but now the presence of the acyloxy group in **76** must retard the proposed bond breaking, allowing two competitive processes (Scheme 22): (i) an homoallylic cation **78** can be formed because of the heterolytic cleavage of the ring fusion bond in **81** (path a). This cation undergoes E1-type elimination and protiodeauration affording the 1,4-cyclohexadiene intermediate **79**. The formation of the homoallylic cation **78** can also be explained through a 1,3-dipole **80** via cyclization of the alkene to the gold-activated allene (path b); (ii) Alternatively, the gold-carbenoid **81** can

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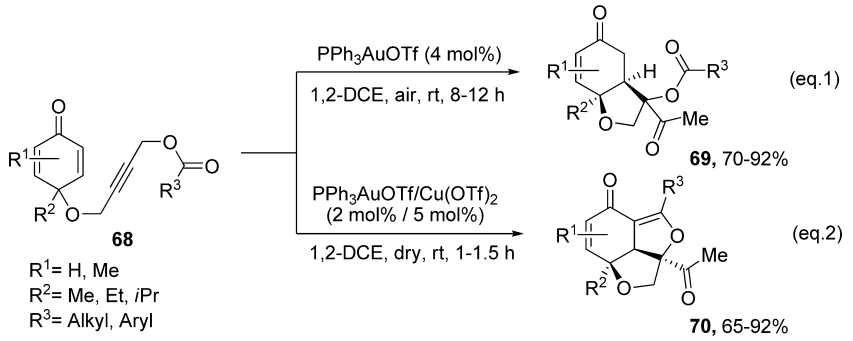
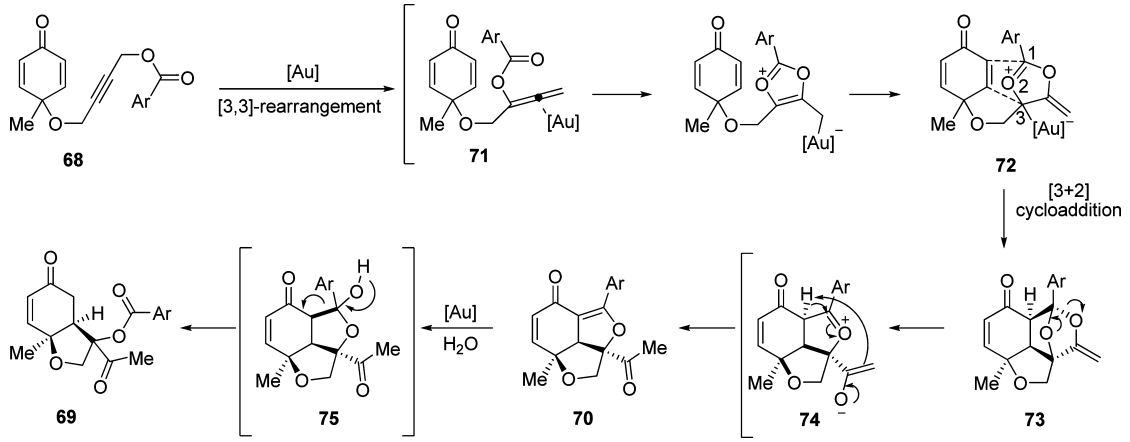
Scheme 19. Gold-Catalyzed Preparation of Dihydrofuran-Fused Cyclohexenones 69 and 70

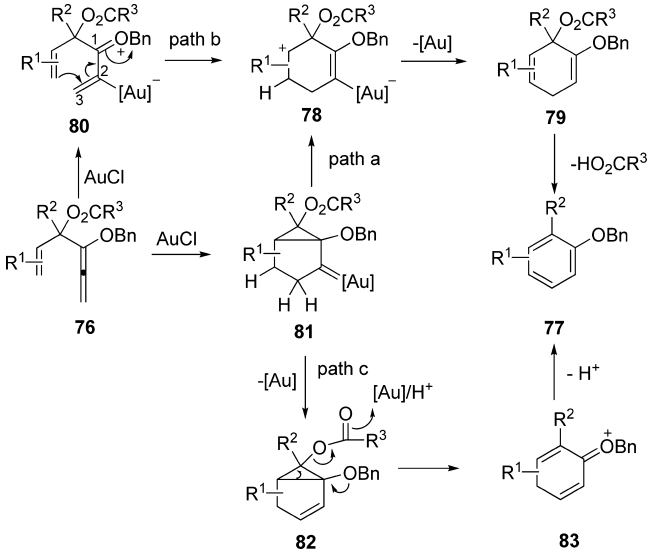


Scheme 20. Mechanistic Proposal for the Formation of 69 and 70



Scheme 21. Gold-Catalyzed Synthesis of Benzyl-Protected Substituted Phenols 77

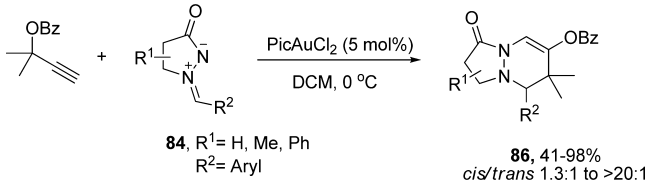
Scheme 22. Reaction Mechanism



undergo a 1,2-hydride shift and elimination forming the bicycle [3.1.0]hexane **82** (path c); coordination of the acetoxy group will trigger electrocyclic ring-opening of the cyclopropane moiety affording cyclohexadienyl cation **83**, which yields the benzyl-protected phenol **77** after proton loss. Although this transformation is described as a formal [3 + 3] cycloaddition, it could also be described as a dipole cyclization looking at the reaction profile through intermediate **80**.

In 2009, the group of Toste[49] reported a gold(III)-catalyzed [3 + 3] cycloaddition of tertiary propargyl esters and azomethine imines **84** for the synthesis of diazabicycles **86** (Scheme 23).

Scheme 23. Gold-Catalyzed [3 + 3] Cycloaddition between Propargyl Esters and Azomethine Imines 84



Steric interactions between the methyl groups of the propargyl ester and the β-substituent in the ring closing transition states **85** and **85′** were proposed to be the responsible for the cis selectivity observed in these transformations (Scheme 24). This process highlights the difference in reactivity between the alkenyl Fischer carbenes and the alkenyl Au-carbenoids, which are formed from the rearrangement of propargyl esters.

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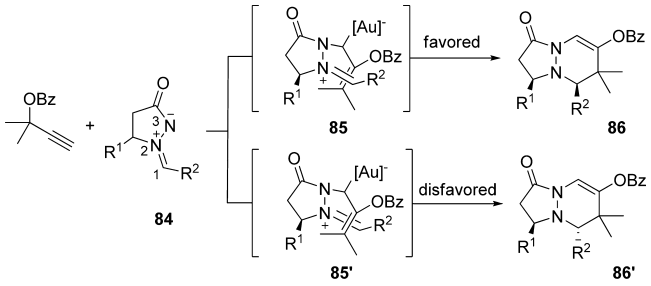
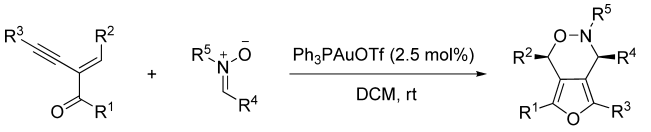
Scheme 24. Rationalization of the Steric Interactions in Transition States 85 and 85′



Highly substituted fused heterobicyclic furo[3,4-*d*][1,2]-oxazines **88** can be synthetized via [3 + 3] cycloaddition reaction between 2-(1-alkynyl)-2-alken-1-ones **42** and nitrones **87** (Scheme 25).[50] The reaction tolerates different groups on

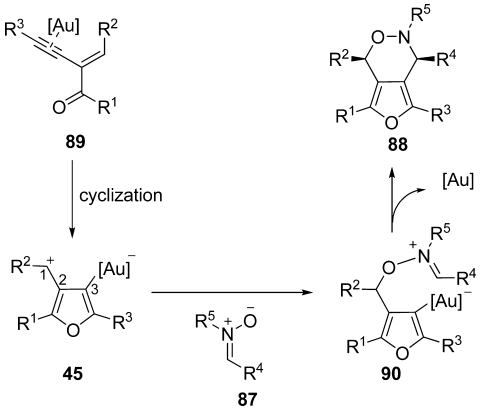
Scheme 25. Gold-Catalyzed [3 + 3] Cycloaddition Reaction between 2-(1-Alkynyl)-2-alken-1-ones 42 and Nitrones 87



both reacting partners affording the corresponding [3 + 3] cycloadducts **88** in good yields and high diastereoselectivities. [3 + 2] Cycloaddition adducts were not observed in the reaction mixture, which seems to indicate that this transformation is not only regio- but also chemospecific.

A plausible mechanism is shown in Scheme 26. Coordination of the gold complex to the alkyne moiety in **42** gives **89**, which

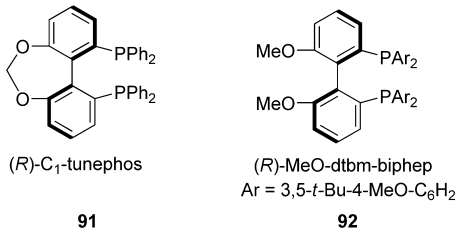
Scheme 26. Mechanistic Proposal



undergoes the addition of the carbonyl group to generate a 1,3-dipole **45** (as previously described in Scheme 14). In this case, the dipole is rapidly trapped by the nucleophilic oxygen atom of the nitrone **87** affording intermediate **90**, which cyclizes yielding the corresponding oxazines **88** and regenerating the gold catalyst in a stepwise, rather than in a concerted manner.

High enantioselectivities (up to 98% *ee*) could be achieved using two chiral ligands: (*R*)-C_1-tunephos **91** and (*R*)-MeO-dtbm-biphep **92** (Scheme 27) in these transformations.[51]

Scheme 27. Chiral Ligands for the Asymmetric Synthesis of Furo[3,4-*d*][1,2]oxazines 88



2.3. Application of 1,3-Dipoles in [4 + 2] Cycloaddition Reactions. As described in the previous section, allenes, upon coordination to a gold complex, have become suitable precursors of "formal" 1,3-C-dipoles. Interestingly these zwitterionic intermediates can be used as 2C-partners in stepwise rather than concerted cycloadditions. Thus, an intermolecular [4 + 2] annulation was reported by Mascareñas et al. in 2011 using allenamides **93** and acyclic dienes **94** (Scheme 28).[52] The generation of a formal 1,3-C-dipole **95** can be explained by gold-activation of the corresponding alleneamide **93**, which cyclizes in a stepwise manner through intermediate **96** affording the corresponding formal [4 + 2] cycloadducts **97** in good to excellent yields.

As shown in Scheme 22, allenyl ethers **98** are also suitable motifs for the formation of 1,3-C-dipoles. The group of Goeke reported in 2011 a cationic gold-catalyzed intermolecular [4 + 2] annulation between allenyl ethers **98** and dienes (Scheme 29).[53] Supported by density functional theory (DFT) calculations, coordination of the gold catalyst onto the terminal double bond of the allene is proposed to give complex **99**, from which the gold-stabilized allylic cation **100** is formed. Because of the conjugation of the alkoxy group with the allyl cation system, 1,3-dipole **101** can be proposed as a significant resonance contributor. The vinyl gold moiety of this zwitterionic intermediate **101** reacts in presence of the cyclopentadiene in a formal [4 + 2] cycloaddition delivering preferentially the *Z*-exocyclic alkene in the product **102**.

Earlier examples were available starting from unactivated allenes as reported by Gung's group,[54] based on preliminary studies performed with palladium as catalyst.[55] Gold complexes bearing bulky phosphine ligands trigger a transannular [4 + 2] cycloaddition reaction at room temperature of the 14-membered furanophane **103** with an allene function located across the ring (Scheme 30).

The authors proposed a stepwise mechanism (Scheme 31). Activation of the allene by the gold catalyst generates the 1,3-dipole intermediate which reacts with the furane ring to give zwitterionic intermediate **106**. The latter can undergo either a [4 + 2] cycloaddition reaction from trapping of the carbocation with the carbon−gold bond generating the intermediate **107** or alternatively a [4 + 3] cycloaddition via the cationic intermediate **108**, which is stabilized as the carbenoid resonance structure **109**. Interestingly, a 1,2-hydride shift and elimination of the gold catalyst in **108** lead the transannular [4 + 3] cycloaddition product **104**. Further examples of [4 + 3] cycloadditions using 1,3-dipoles are described in the next section.

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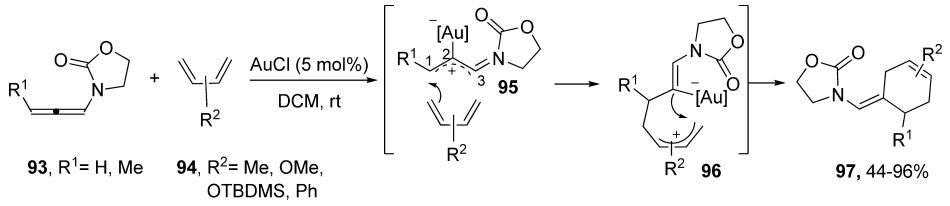
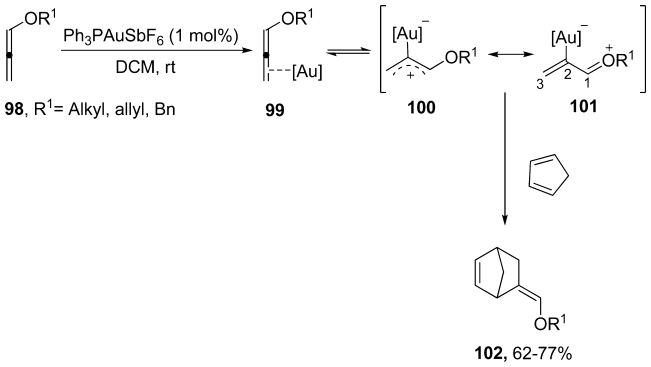
Scheme 28. Gold-Catalyzed Formal [4 + 2] Cycloaddition between Allenamides 93 and Acyclic Dienes 94



Scheme 29. Gold-Catalyzed Formal [4 + 2] Cycloaddition of Allenyl Ethers 98 and Dienes



2.4. Application of 1,3-Dipoles in [4 + 3] Cycloaddition Reactions. The gold-catalyzed [4 + 3] intramolecular cycloaddition of allenedienes **110** has been simultaneously reported by the groups of Malacria and Toste (Scheme 32). In contrast to the examples presented in the previous section, the 1,3-dipole generated by means of coordination of the allene to the gold complex functions as a 3C partner in these transformations. Intermediate **111** participates in a intramolecular [4π+2π] cycloaddition with the corresponding diene to provide the cycloheptene skeleton. A 1,2-hydride shift on the resulting carbene yields the final adduct **112** and regenerates the catalyst.[56,57] An enantioselective version of these transformations was also reported using chiral phosphoramidite ligands.[58] The reaction provides a straightforward route to optically active, synthetically relevant bicycle [5.3.0]decadienes and bicycle [5.4.0]undecadiene skeletons (>93% *ee*).

As described in Scheme 26, 1,3-furanyl gold-dipoles **45** can be generated by the attack of the carbonyl onto the gold-activated alkyne in 2-(1-alkynyl)-2-alken-1-ones **42**.[50] These intermediates were used to build polyheterocycles in a catalytic tandem heterocyclization/formal [4 + 3] cycloaddition with 1,3-diphenylisobenzofuranes **113** in the presence of gold or silver salts as reported by Juliang Zhang and co-workers in 2010 (Scheme 33).[59] In general, under gold catalysis the reaction gives the *exo* cycloadducts **114** (88−96% yield), while the *endo* products **114** are the major isomers under silver catalysis (70−93% yield). The phosphine ligand of the catalyst seems to have a strong effect in the reaction outcome, although the way in which it does is still unclear.

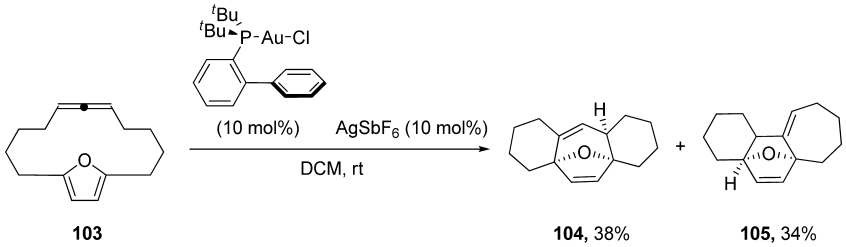
In these transformations, 1,3-furanyl gold-cation **45** undergoes a [4 + 3] cycloaddition with the 1,3-diphenylisobenzofurane **113** affording the *exo* product **114** through the more favored transition state **115**. In contrast, the silver intermediate reacts through transition state **115′** giving the *endo* cycloadduct **114** (Scheme 34).

3. GENERATION OF 1,4-DIPOLES

3.1. Application of 1,4-Dipoles in [2 + 2] Cycloaddition Reactions. The [2 + 2] cycloaddition reaction represents a powerful tool for the synthesis of substituted cyclobutanes and cyclobutenes, which are useful building blocks in organic synthesis problems.[60−67] Four membered rings were first obtained in a tandem gold-catalyzed [3,3]-acyloxy rearrangement/[2 + 2] cycloaddition of propargyl esters **116**. Highly functionalized 2,3-indoline-fused butanes **120** were obtained in this reaction (Scheme 35).[68] Indole-3-acetates **116** undergo a gold-catalyzed 1,3-migration of the acyloxy moiety to deliver allenic esters **117**. This allene moiety is further activated in presence of the metal resulting in the formation of the thermodynamically more favored *E*-oxonium cation **118**. The formation of the cyclobutane product **120** can be explained through a [2 + 2] cycloaddition reaction via 1,4-zwitterionic intermediate **119**.

A gold-catalyzed cycloisomerization of allenenes **121** to give alkylidene-cyclobutanes **122** was reported by Toste and co-workers in 2007 using a formal [2 + 2] cycloaddition reaction catalyzed by Ph_3PAuBF_4 and chiral biarylphosphinegold(I) complexes (Scheme 36).[69] The reaction tolerates a variety of aryl-substituted alkenes, distal-substitution of the allene and substitution in the olefin counterpart furnishing alkylidene-cyclobutanes **122** in 80−92% yield. The diastereoselectivity of this process was also examined showing a 6:1 d.r. in substrates having an allylic methyl group whereas a single diastereoisomer was obtained for allenes having a methyl goup at the allenic position. The use of (*R*)-DTBM-SEGPHOS as chiral ligand provided a wide range of cycloadducts with excellent

Scheme 30. Gold-Catalyzed Transannular [4 + 3] and [4 + 2] of Furanophane 103



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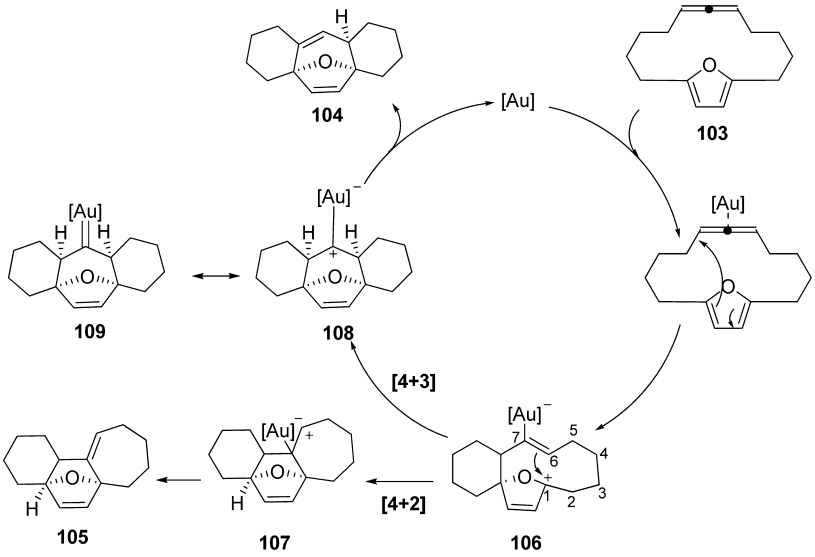
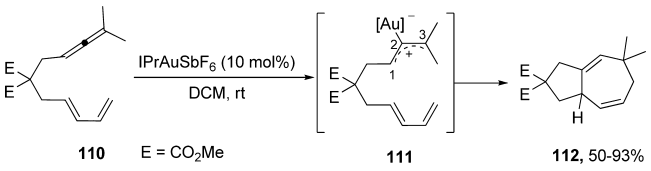
Scheme 31. Proposed Mechanism



Scheme 32. Gold-Catalyzed [4 + 3] Cycloaddition of Allenedienes 110

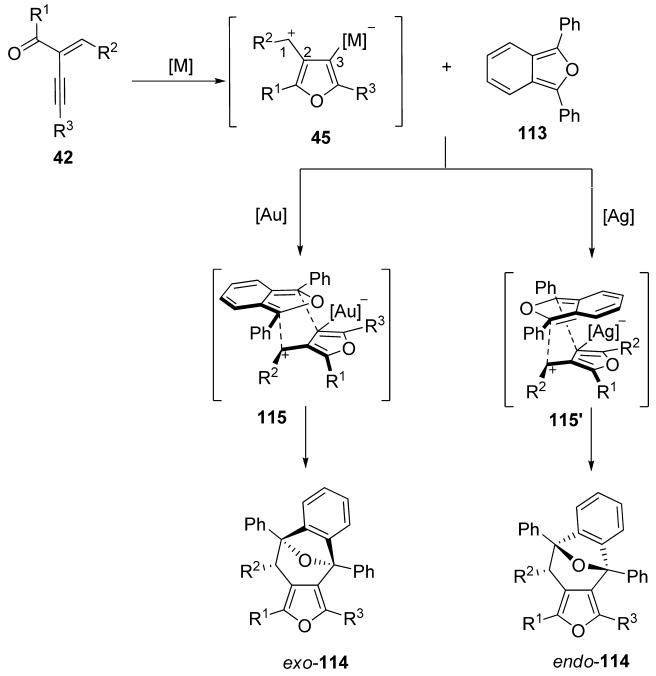


enantioselectivities (>92% *ee*). An alternative approach involves the use of chiral phosphoramidite gold complexes that have a TADDOL subunit with an acyclic backbone.[70]

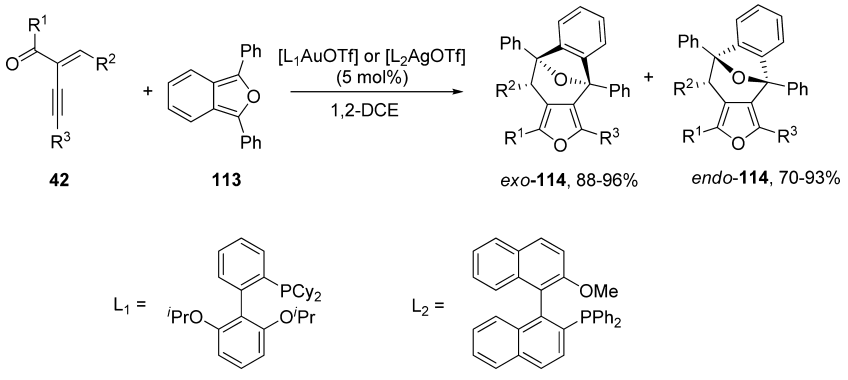
The mechanistic hypothesis to explain this transformation involves a preferential *anti* addition of the alkene moiety onto the gold(I)-activated allene **123** affording zwitterionic intermediate **124**. In absence of an external nucleophile, the cyclobutane **122** is formed from a intramolecular reaction between the vinyl-gold with the benzylic carbocation (Scheme 37).

In 2011, the group of Chan[71] reported the use of propargylic benzoates **125** for the synthesis of azabicyclo[4.2.0]oct-5-enes **128** in the presence of a cationic [(2-biphenyl)di-*tert*-butylphosphine]gold(I) complex (Scheme 38). A diverse set of 1,7-enyne substrates **125** containing thiophene, cyclopropane, OTBS, and $MeSO_2$ moieties could be transformed

Scheme 34. Mechanistic Proposal



Scheme 33. Gold-Catalyzed Synthesis of Polyheterocycles 114



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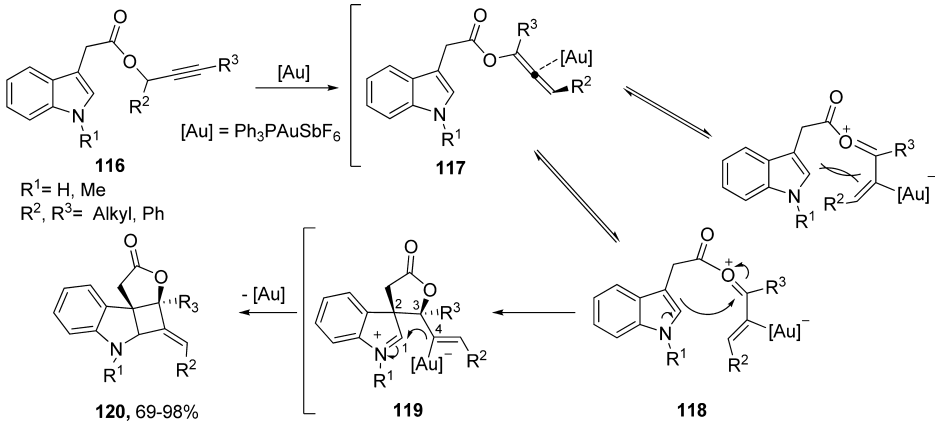
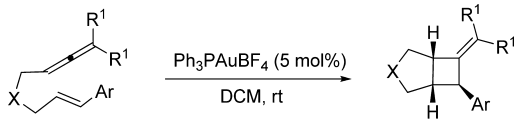
Scheme 35. Gold-Catalyzed Synthesis of 2,3-Indoline-Fused Butanes 120: Proposed Mechanism



Scheme 36. Gold(I)-Catalyzed [2 + 2] Cycloaddtition of 121

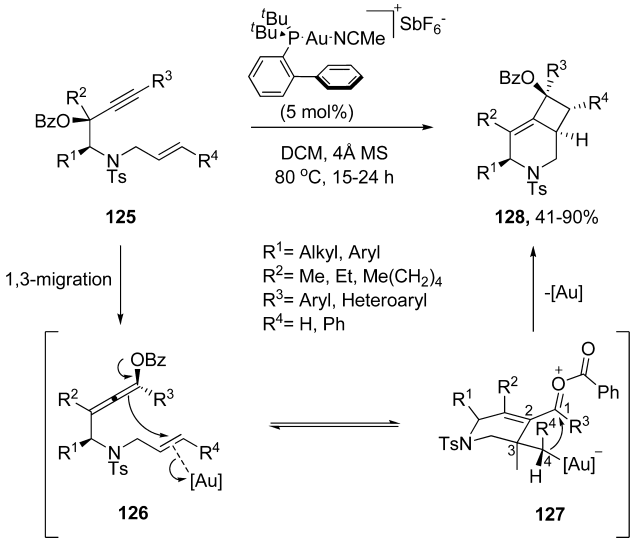


under the reaction conditions. The reaction of substrates containing an activated alkene was also found to proceed in good yields. After the well-known gold-catalyzed [3,3]-sigmatropic rearrangement of the propargyl benzoate **125** to deliver the corresponding allene intermediate **126**, the gold catalyst selectively coordinates to the alkene bond avoiding unfavorable steric interactions between the gold complex and the substituents on the allene moiety. These activated species undergoes a stepwise [2 + 2] cycloaddition involving the *anti* addition of the allenic group affording intermediate **127**. Nucleophilic attack of the Au−C(sp^3) bond onto the carbonyl group deliver the corresponding azabicyclo[4.2.0]oct-5-enes **128**.

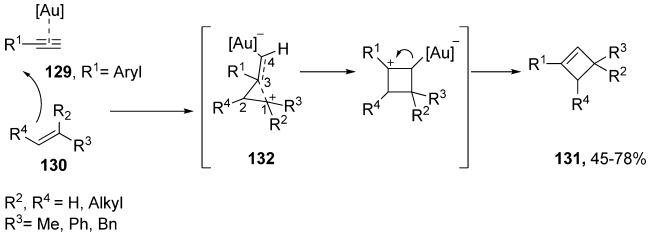
The first example of an intermolecular gold-catalyzed a formal [2 + 2] cycloaddition was reported by Echavarren and co-workers in 2010 (Scheme 39).[72] The reaction of terminal alkynes **129** with alkenes **130** affords substituted cyclobutanes **131** via [2 + 2] cycloaddition, which in addition to gold cyclopropyl carbenes as intermediates can be also explained via 1,4-zwitterion **132**. The key for the success in this transformation is the use of gold(I)-complexes with bulky ligands that selectively activate alkynes in presence of alkenes. The reaction proceeds satisfactory with alkynes bearing both electron-donor and electron-withdrawing substituents affording the cyclobutanes **131** in good yields.

The group of Corma[73] found that, under the reaction conditions, isolable digold-phenylacetylene adducts were formed. Digold complexes when isolated and used as catalysts give almost the same results than the initial gold(I) phosphine complex used by Echavarren and co-workers.

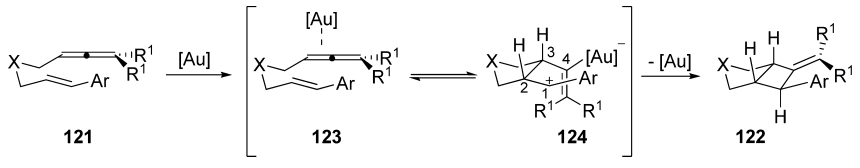
Scheme 38. Gold-Catalyzed Tandem 1,3-Acyloxy-Migration/ [2 + 2] Cycloaddition to Azabicyclo[4.2.0]oct-5-enes 128



Scheme 39. Gold-Catalyzed [2 + 2] Cycloaddition of Alkynes 129 with Alkenes 130



Scheme 37. Mechanistic Proposal of [2 + 2] Cycloaddition of Allenenes 121



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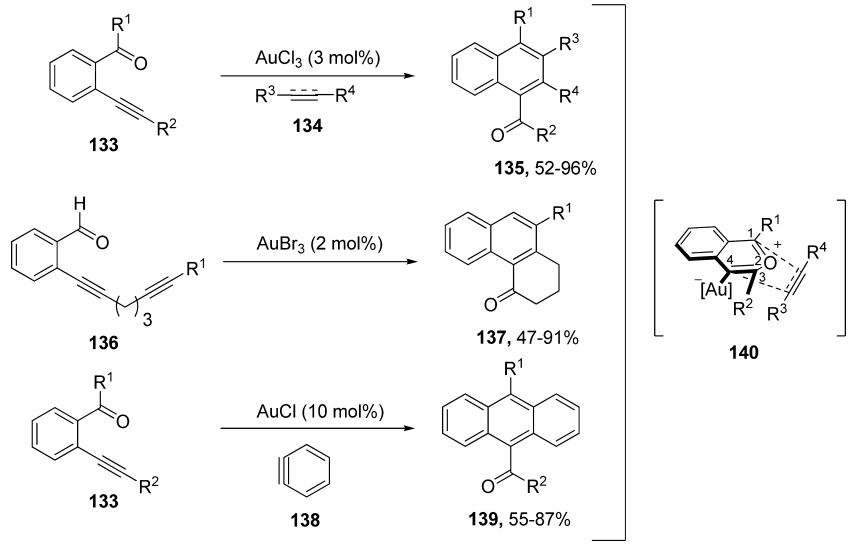
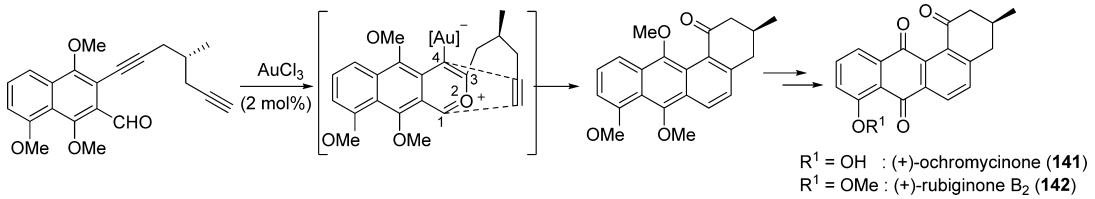
Scheme 40. Reactivities of Benzopyrylium 1,4-Dipole



Scheme 41. Total Synthesis of (+)-Ochromycinone (141) and (+)-Rubiginone B_2 (142)



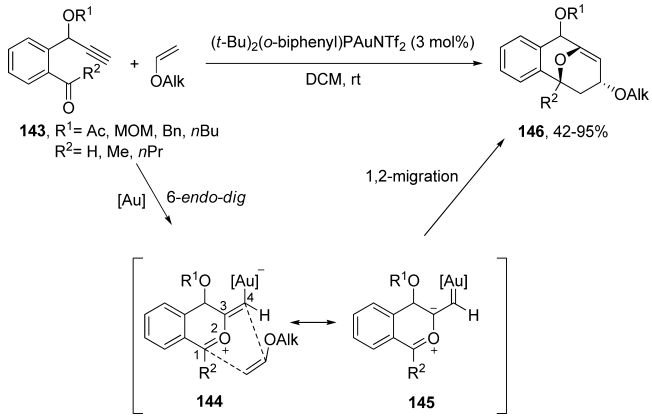
3.2. Application of 1,4-Dipoles in [4 + 2] Cycloaddition Reactions. As it was mentioned in Scheme 10, the addition of a carbonyl moiety onto a gold-activated alkyne generates a benzopyrylium 1,3-dipole **32**, which can be involved in subsequent [3 + 2] cycloadditions with pendant or external unsaturations. However, benzopyrylium 1,4-dipole reactivities have also been observed for this type of substrates (Scheme 40).

Thus, Yamamoto's group applied this strategy for the construction of naphthyl ketone derivates **135** using an intermolecular gold-catalyzed [4 + 2] cycloaddition reaction of *o*-alkynylbenzaldehydes **133** and enynals (not shown) with alkynes **134**.[74,75] The same group reported a gold and copper-catalyzed intramolecular [4 + 2] cycloaddition of substrates **136** for the synthesis of functionalized polycyclic hydrocarbons **137**.[76] Also on the basis of this idea, the group of Sato reported a gold-catalyzed [4 + 2] benzannulation reaction between *o*-alkynyl benzaldehyde **133** and benzyne (**138**), which was in situ generated from the corresponding benzenediazonium 2-carboxylate precursor for the synthesis of anthracene derivates **139**.[77] The group of Liu has also reported a stereocontrolled gold-catalyzed oxacyclization/[4 + 2] cycloaddition cascade reaction of ketone-allene substrates in the presence of external olefins.[78] A common feature of all these transformations involves the gold 1,4-dipole **140**, formed through a *6-endo-dig* cyclization of the carbonyl group onto the π-activated triple bond.

A beautiful application of this concept was reported by Yamamoto in the key step of the synthesis of (+)-ochromycinone (**141**) and (+)-rubiginone B_2 (**142**) (Scheme 41).[79]

The possibility of generating new zwitterionic intermediates through an *exo-dig* cyclization using *ortho*-propargylacetate substituted benzaldehydes **143** has also been exploited for the synthesis of 9-oxabicyclo[3.3.1]nona-4,7-dienes **146** (Scheme 42).[80] A mechanism is proposed starting with a *6-exo-dig*

Scheme 42. Gold-Catalyzed Synthesis of 9-Oxabicyclo[3.3.1]nona-4,7-dienes 146



cyclization of the carbonyl moiety onto the alkyne affording the 1,4-dipole **144**, which is in resonance with the gold-carbene intermediate **145**. A subsequent [3 + 2] cycloaddition between the carbonyl ylide **144** and an external olefin, followed by a ring expansion assisted by the oxy group and elimination, affords the oxabicyclo compounds **146** in good to excellent yields.

With similar substrates as those described in Scheme 12, the group of Zhang reported the generation of gold-containing all carbon 1,4-dipoles **147** and its application in a [4 + 2] annulation process for the formation of carbo-/heterocycles.[81] 1-(1-Alkynyl)cyclopropyl ketones **148**, previously used by

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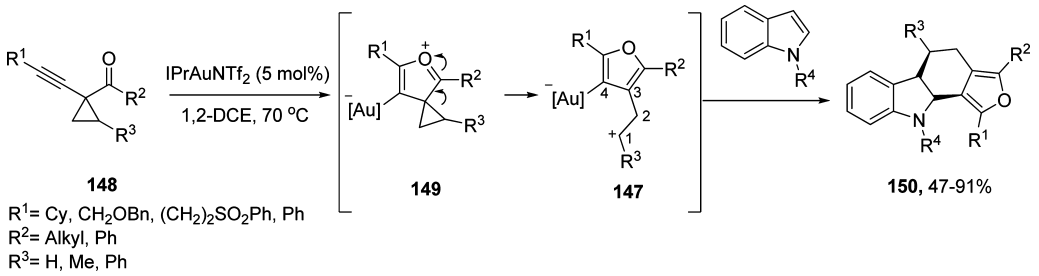
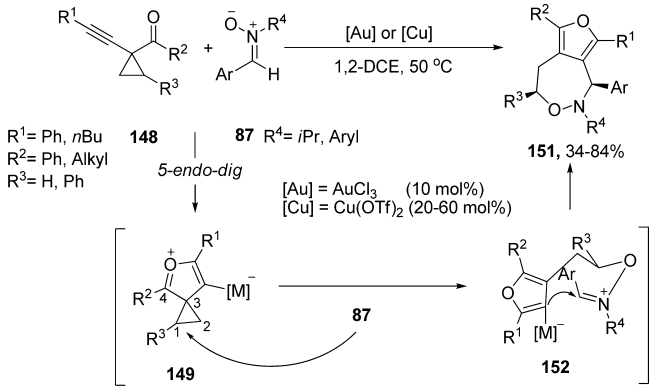
Scheme 43. Gold-Catalyzed Synthesis of Polycyclic, Fully Substituted Furans 150



Zhang and Schmalz[82] for gold-catalyzed formation of trisubstituted furans, are also used to generate the corresponding furanyl 1,4-dipole **147**. A [4 + 2] annulation process using indoles and ketone/aldehydes enables the formation of 6-membered rings **150** in good yields and excellent regioselectivities (Scheme 43).

3.3. Application of 1,4-Dipoles in [4 + 3] Cycloaddition Reactions. Wang and co-workers envisioned a formal gold- (or copper) catalyzed [4 + 3] cycloaddition of 1-(1-alkynyl)cyclopropyl ketones **148** and nitrones **87** for the construction of 1,2,4,5-tetrahydrofuro[3,4-*d*][1,2]oxazepines **151**, which are present in several bioactive compounds (Scheme 44).[83] The reaction tolerates a wide variety of *N*-

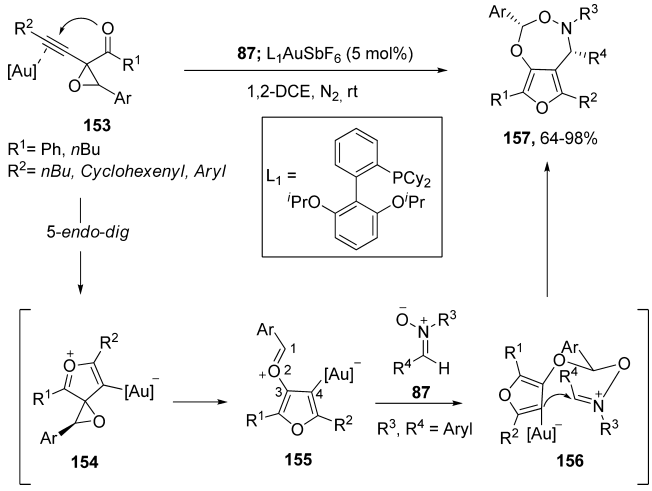
Scheme 44. Gold-Catalyzed [4 + 3] Cycloaddition of 1(1-Alkynyl)cyclopropyl Ketones 148 and Nitrones 87



aryl and *N*-isopropyl nitrones and several cyclopropyl ketones were also employed showing high diastereoselectivities in all cases. The proposed mechanism begins by a 5-*endo-dig* cyclization of the carbonyl group onto the gold-activated alkyne in **148** to give 1,4-dipole **149** followed by ring-opening of the cyclopropane ring by nucleophilic attack of the nitrone **87**. The high diastereoselectivity may be a result of the favored conformation of intermediate **152**. Thus, cis isomers **150** were obtained from the acyclic *Z* nitrones **87**, and the cyclic *E* nitrones **87** gave corresponding the trans isomer **151**.

A variation of this concept was reported by the group of Zhang in a gold-catalyzed [4 + 3] cycloaddition reaction between 1-(1-alkynyl)oxiranyl ketones **153** and nitrones **87** (Scheme 45).[84] This strategy is the first example of a metal-catalyzed, selective C−C bond cleavage of epoxy ketones by introducing an alkyne that can be activated by gold complexes. A plausible mechanism involves the nucleophilic attack of the carbonyl moiety in **153** to the alkyne to give the oxonium-containing vinyl-gold intermediate **154**. Aromatization through C−C bond cleavage of the epoxide produces the 1,4-dipole

Scheme 45. Gold-Catalyzed [4 + 3] Cycloaddition of 1-(1-Alkynyl)oxiranyl Ketones 153 and Nitrones 87



furanyl-gold intermediate **155** bearing an oxygen-stabilized carbocation. This 1,4-dipole reacts with the corresponding nitrone **87** generating the furanyl-gold intermediate **156**, which upon ring closure through the favored chairlike conformation, affords the formal [4 + 3] cycloadduct **157** in good yields and diastereoselectivities.

4. GENERATION OF 1,5-, 1,6-, AND 1,7-DIPOLES

On the basis of the first studies of Rautenstrauch with propargyl carboxylates and palladium for the synthesis of 2-cyclopentenones,[85] the groups of Nevado and Goeke decided to explore the chemistry of 1-cyclopropyl propargyl esters (**158**, **159**) in a new gold-catalyzed homo-Rautenstrauch rearrangement reaction to give five- and six-membered-ring vinyl acetates (**160**, **161**) depending of the substitution pattern of the alkyne (Scheme 46).[86,87] Internal alkynes **158** undergo [3,3]-sigmatropic rearrangement of the acetoxy group generating the cyclopropylalkyl carbenium ion **162**, which is a mesomeric form of 1,5-zwitterion **163**. Cyclization of these species afforded the trienyl acetates **160** in almost quantitative yield as a mixture of cis and trans isomers (Scheme 46, eq 1). If terminal alkynes **159** were used, the formation of the cyclohexadienyl acetates **161** could be explained by a 1,2-acyl migration of the acetate moiety onto the activated alkyne via gold-carbenoid intermediate **164** and 1,6-zwitterion **165** (Scheme 46, eq 2). A key factor in these transformations is the presence of a substituent at the cyclopropyl ring able to stabilize the positive charge developed during the cyclopropyl ring-opening process. Related 1,6-zwitterionic intermediates were previously reported by Wang and Zhang in the synthesis

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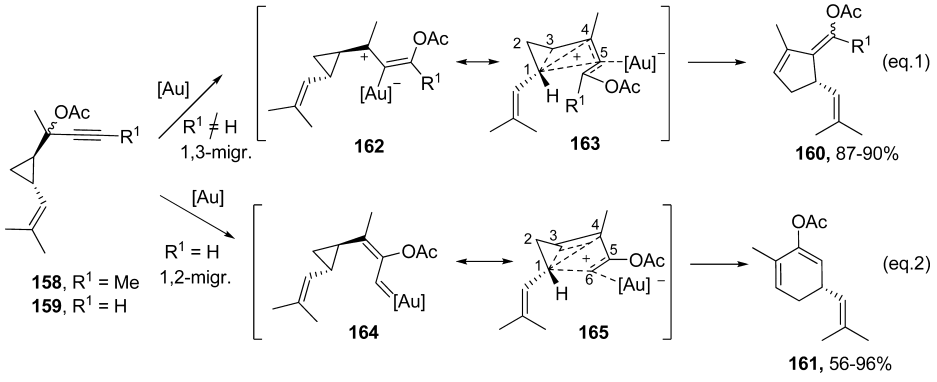
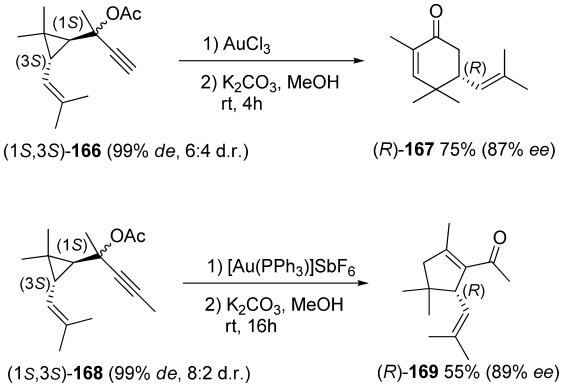
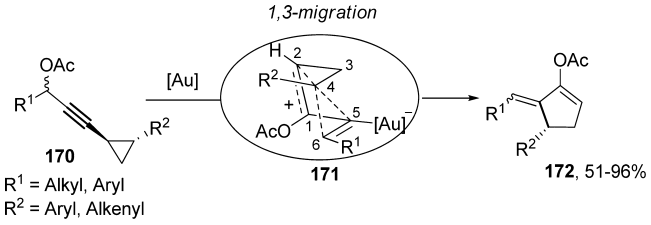
Scheme 46. Au-Catalyzed Homo-Rautenstrauch Rearrangement of 1-Cyclopropyl Propargyl Acetates 158 and 159



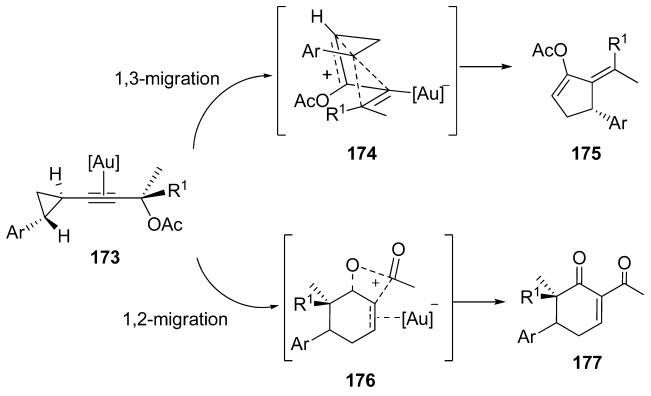
Scheme 47. Stereochemical Information Transfer of Compounds 166 and 168 to 6- and 5-Membered Rings Products



Scheme 48. Cycloisomerization of 3-Substituted Cyclopropyl Propargyl Acetates 170

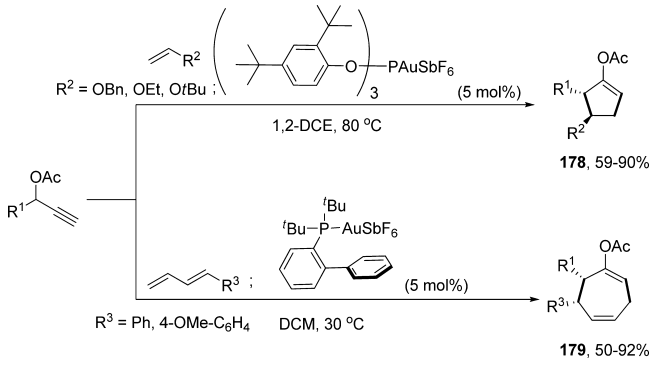


Scheme 49. Mechanistic Dichotomy for the Tertiary Propargyl Acetates 173



of 1-carboxycyclohexa-1,4-dienes from 1,5-enynes incorporating an homopropargyl acetate moiety.[88]

Scheme 50. Gold-Catalyzed 1,2-Acyloxy-Rearrangement/Cyclopropanation/Cycloisomerization Cascades



The interesting question of a possible stereochemical configuration transfer in these systems was addressed using optically active substrates **166** and **168**, which are easily available from optically pure (1*S*,3*S*)-(-)-*trans*-chrysanthemum acid (99% *ee*; Scheme 47). Using gold trichloride as catalyst, cycloisomerization of **166** cleanly afforded (*R*)-**167** after methanolysis with an effective retention of the enantioselectivity (87% *ee*). In contrast, $[Au(PPh_3)]SbF_6$ effectively promoted cycloisomerization of compound **168** delivering the acetylcyclopentenone (*R*)-**169** with good enantioselectivity (89% *ee*). The high enantiomeric excess measured in the reaction products suggests that the carbocationic centers in the polarized reaction intermediates **163** and **165** entitle a large degree of configurational stability.

In 2010, the group of Nevado extended this chemistry to 3-cyclopropyl propargyl carboxylates **170** (Scheme 48).[88] In this case, (*E*)-alkylidenecyclopentenyl acetates **172** were exclusively obtained via [3,3]-sigmatropic rearrangement of the carboxylic moiety followed by cyclopropyl ring-opening forming the 1,5-zwitterion **171** and subsequent cyclization. A complete study, supported by DFT calculations, shed light on the key gold-stabilized nonclassical carbocationic intermediates involved in these and the above-mentioned transformations.[89] In contrast to the reactivity of **166** and **168**, the stereochemical configuration transfer in these cyclopentannulations was not complete. Computational and experimental evidence support a gold-promoted cyclopropyl ring-opening/epimerization/ring closure in both *cis*- and *trans*-cyclopropyl settings, which competes with the cyclization event, thus eroding the stereochemical information transfer. The stereoselective formation of the exocyclic alkenes is kinetically controlled.

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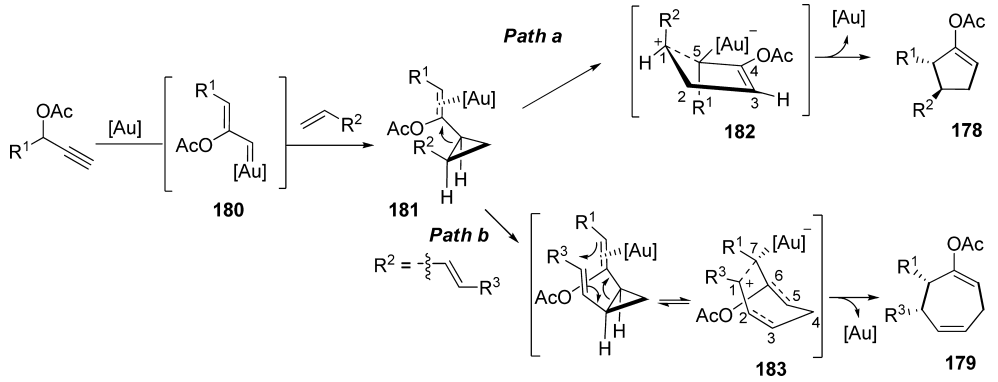
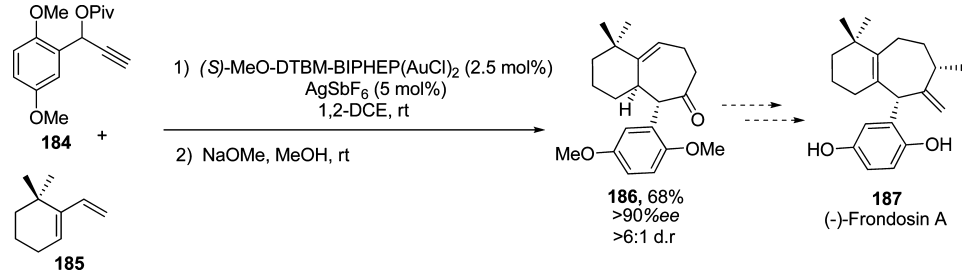
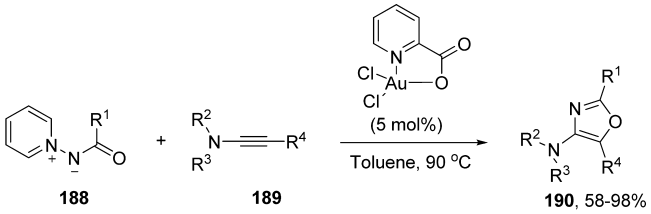
Scheme 51. Mechanistic Proposal



Scheme 52. Formal Enantioselective Synthesis of (-)-Frondosin A (187)



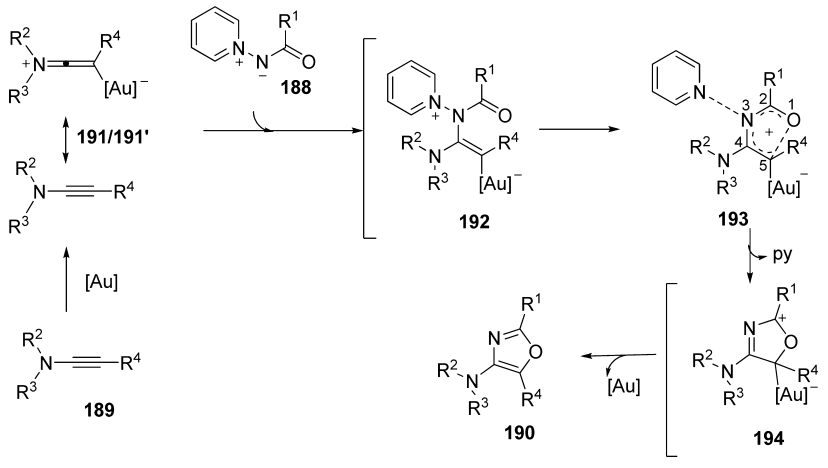
Scheme 53. Gold-Catalyzed Oxazole Cycloaddition



When tertiary acetates **173** were used, products from both 1,2- and 1,3-acyloxy migration processes could be isolated (**175**, **177**), supporting a competitive coexistence of these two pathways along the reaction profile (Scheme 49). The steric hindrance caused by the presence of the two substituents at the propargyl position raises the activation energy along the 1,3-migration migration pathway to a level comparable to the 1,2-migration one. The product composition will depend on the difference in energies between the respective transition states (**174**, **176**). Using a π-acceptor phosphite ligand on the gold center, the cyclopentannulation products **175** were obtained selectively, whereas strong σ-donor ligands, like IPr (1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene) afforded mixtures of the cyclopentenyl acetates **175** and diketones **177** in different ratios.

A reaction sequence involving propargyl esters and alkenes or dienes to give five or seven member rings **178** and **179** has also been developed via gold 1,5- and 1,7-zwitterionic intermediates, respectively (Scheme 50).[90,91]

Scheme 54. Proposed Mechanism for the Formation of 1,3-Oxazoles 190



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A possible mechanism for these transformations is proposed in Scheme 51. The gold-mediated isomerization of the propargyl ester leads to gold carbene **180**, which reacts with the olefin forming a *cis*-cyclopropane **181** intermediate.[92] Subsequent gold reactivation of the vinyl acetate moiety triggers the cyclopropyl ring-opening forming intermediate **182**. An envelope conformation is proposed for the transition state in which the substituents are disposed in a trans-pseudodiaxial fashion to minimize torsional/steric interactions yielding the *trans*-2,3-disubstituted cyclopentannulation products **178** (Scheme 51, pathway a). In contrast, when 1,4-dienes are used, the cyclopropyl system undergoes a gold-catalyzed Cope rearrangement to deliver the *cis*-2,3-disubstituted cycloheptenyl acetates **179** (Scheme 51, pathway b). A boatlike polarized transition state **183** was proposed in this case to account for the observed cis relative stereochemistry.

The latter method was also applied in a formal enantioselective synthesis of frondosin A (**187**), a marine norsesquiterpenoid with promising biological activities (Scheme 52). Treatment of acetate **184** and 6,6-dimethyl-1-vinyl cyclohexene (**185**) with (*S*)-OMe-DTBM-BIPHEP-gold-(I) complex afforded, quantitatively, the corresponding bicyclic cycloheptenyl pivaloate. In situ hydrolysis and subsequent equilibration with NaOMe/MeOH yielded thermodynamically favored ketone **186** in 68% yield and >90% ee. Since this bicyclic enone has been recently elaborated to frondosins A (**187**) and B[93,94] this approach represents a streamlined formal enantioselective synthesis of both molecules.

In 2011, the group of Davies[95] reported a regioselective gold-catalyzed intermolecular [3 + 2] cycloaddition for the synthesis of 2,4,5-trisubstituted oxazoles **190** employing conjugated *N*-ylides **188** as *N*-nucleophilic *N*-acyl nitrene/1,3-*N*,*O*-dipole equivalents and ynamides **189** (Scheme 53). The application of [3 + 2] cycloaddition across C−C π systems for the preparation of 1,3-oxazoles is extremely limited[96,97] whereas it has been widely employed for the preparation of other heterocycles.[98,99]

A rational mechanism was proposed by the authors (Scheme 54). Nucleophilic attack of the aminide **188** onto the gold-activated ynamide **191**/**191′** affords the intermediate **192**. The formation of **194** can be viewed after elimination of pyridine, forming a 1,5-dipole between the gold catalyst and the acyl oxygen, and cyclization with a capture of the electrophilic carbon center by the acyl oxygen in **193**. Elimination of the gold catalyst in **194** affords the 1,3-oxazoles **190** in good yields.

5. CONCLUSION

Gold catalyzed cycloadditions and cyclizations involving 1,*n*-dipoles as well as 1,*n*-zwitterionic intermediates have become a rapidly developing field. These processes enable the construction of elaborated polycyclic motifs in a highly regio- and stereocontrolled manner from rather straightforward starting materials under mild reaction conditions. It is thus easy to foresee the application of these methodologies in the synthesis of complex organic molecules and natural products in the near future. In addition, because of the rapid development of chiral gold catalysts, asymmetric versions of these transformations will certainly arise, thus increasing the synthetic utility of these methodologies.

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Notes

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