VIP *Very Important Paper*

New-Generation Ligand Design for the Gold-Catalyzed Asymmetric Activation of Alkynes

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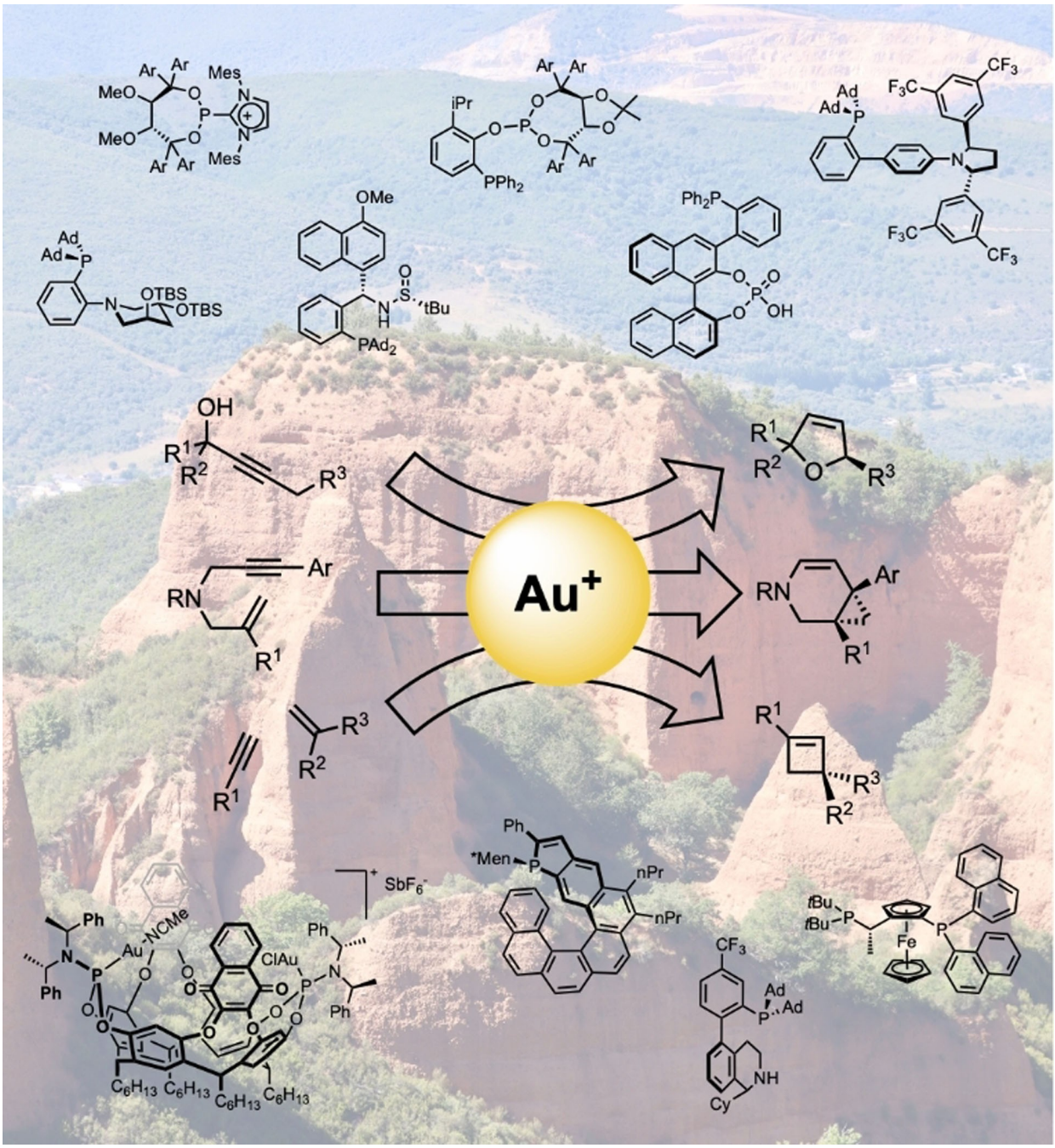

Gold(I) catalysts are ideal for the activation of alkynes under very mild conditions. However, unlike allenes or alkenes, the triple bond of alkynes cannot be prochiral. In addition, the linear coordination displayed by gold(I) complexes places the chiral ligand far away from the substrate resulting in an inefficient transfer of chiral information. This poses a significant challenge for the achievement of high enantiocontrol in gold(I)-catalyzed reactions of alkynes. Although considerable progress on enantioselective gold(I)-catalyzed transformations has recently been achieved, the asymmetric activation of non-prochiral alkyne-containing small molecules still represents a great challenge. Herein we summarize recent advances in intra- and intermolecular enantioselective gold(I)-catalyzed reactions involving alkynes, discussing new chiral ligand designs that lie at the basis of these developments. We also focus on the mode of action of these catalysts, their possible limitations towards a next-generation of more efficient ligand designs. Finally, square planar chiral gold(III) complexes, which offer an alternative to chiral gold(I) complexes, are also discussed.

1. Introduction

Gold(I) catalysts are the most efficient for the selective activation of alkynes and other C–C multiple bonds under exceptionally mild conditions.[1] Upon π-activation, a broad range of nucleophiles can engage inter- or intramolecularly in numerous cyclizations and cycloadditions providing access to molecular complexity from simple starting materials in one single transformation.[2] By means of gold(I) catalysis, diverse total syntheses of naturally occurring compounds have been completed constructing complex carbon skeletons that would be otherwise difficult to access.[3] In contrast to the fast evolution of this research field, the development of broad scope enantioselective gold(I)-catalyzed transformations has represented a more difficult task.[4] The linear binding geometry adopted by gold(I) complexes places the ancillary chiral ligand on the direct opposite side of the substrate resulting in an inefficient transfer of chiral information during the stereo-determining outer-sphere nucleophilic addition. Moreover, the relatively free rotation around the L*-Au and the Au–substrate bonds makes the fixation of the substrate in a chiral environment more challenging (Figure 1a).

Three main conceptual designs have shown successful in enantioselective gold(I) catalysis. The most studied system involves the use of axially chiral binuclear gold(I) complexes with either bisphosphines or diaminocarbene ligands (Figure 1b).[5] Thus, enantioselective intra- and intermolecular cyclopropanations,[6] cycloisomerizations of 1,*n*-enynes,[7] hydrofunctionalizations of alkenes[8] and allenes[9] and other annulations[10] have been developed. On the other hand, highly modular, and readily available one-point binding phosphoramidite ligands based on BINOL,[11] TADDOL[12] or SPINOL backbones have been particularly effective in the cyclization of allenes.[13] Analysis of the X-ray crystal structures of these last complexes reveals the importance of the chiral amine moiety to provide a chiral environment around the reactive center.[14]

Equally successful for the activation of allenes[15] has been the synergistic use of chiral or non-chiral gold(I) complexes with chiral counterions such as phosphates.[16] In this case the chiral environment is held next to the reactive center by the formation of tight ion pairs with the cationic gold complexes. However, this approach cannot be extended to the activation of terminal alkynes[17] as phosphates are basic enough to deprotonate the alkynyl proton, leading to the formation of unreactive gold(I) acetylides.[18] Although efficient for several processes, none of these approaches show sufficient broad scope. In addition, strategies for the enantioselective activation of

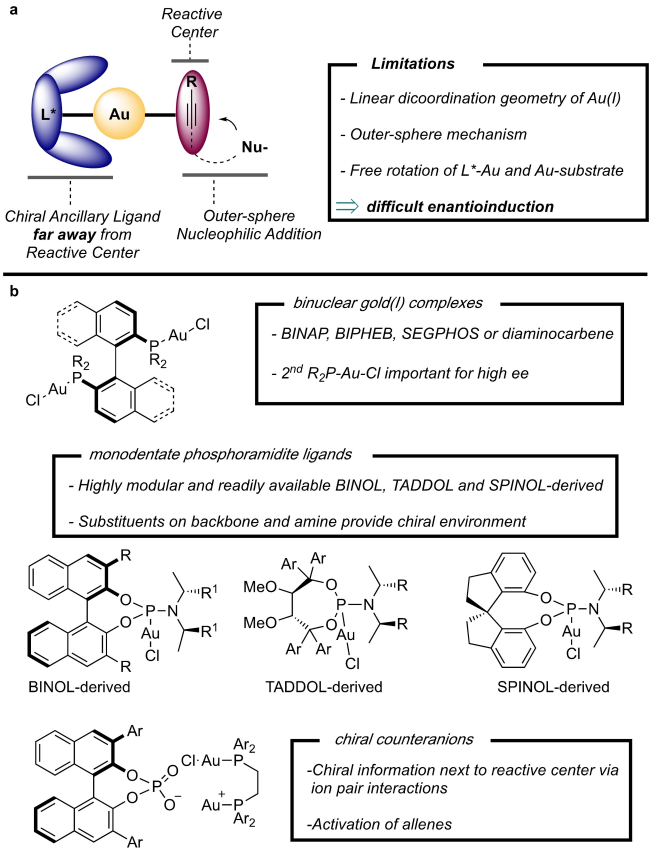

Figure 1. a) Limitations associated with enantioselective gold(I) catalysis. b) Three main approaches to enantioselective gold(I) catalysis.

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alkynes, which are not prochiral, present an additional level of difficulty and thus, remain limited.

1.1. Scope and organization

In this review we summarize recent advances towards the development of new enantioselective gold(I)-catalyzed systems with focus on the activation of alkynes (*ca.* 2014–). For the sake of completeness, selected earlier reactions will be discussed briefly. This review has been mainly divided into intra- and intermolecular transformations. In particular, we center the discussion on new ligand designs that have emerged spanning from highly π-acidic α-cationic phosphonites and chiral monophosphines to bifunctional ligands. In addition, the specific working mode of the new chiral ligands will be addressed. Finally, we will discuss important progress on gold(III)-catalyzed enantioselective transformations.

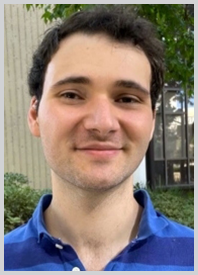
The asymmetric activation of allenes,[4a–f] alkenes[4e,f] and the use of chiral counterions[16] have been reviewed elsewhere and will not be discussed herein.

2. Intramolecular Gold(I)-Catalyzed Transformations

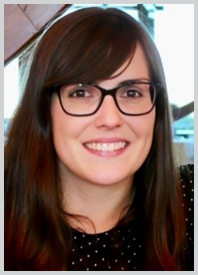
2.1. α-Cationic phosphonites: enantioselective hydroarylation reactions

Intrigued by the physical and chiroptical properties of *ortho*-fused polyaromatic molecules and their broad application in various fields of chemistry including asymmetric catalysis,[19] molecular machines,[20] and liquid crystal technologies[21] the group of Alcarazo recently reported the enantioselective synthesis of carbo[*6*]helicenes **2** via sequential gold(I)-catalyzed hydroarylation of diynes **1** introducing α-cationic[22] phosphonite ligands **L1**–**4** (Scheme 1).[23]

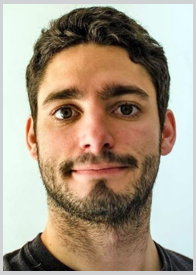
In this ligand design, the modular TADDOL backbone, previously shown to be effective in enantioselective gold(I) catalysis,[12–14] is merged with an imidazolium unit to increase the π-acceptor character of the ligands, and ultimately the π-acidity of the corresponding gold complexes. Accordingly, analogous neutral phosphoramidite gold complexes did not display catalytic activity. Shortly after, improved reactivities and enantioselectivities were obtained replacing the imidazolium unit by more electron withdrawing 1,3-dimesityl-1,2,3-triazolium and 1,4-dimesityl-1,2,4-triazolium moieties in ligands **L3**



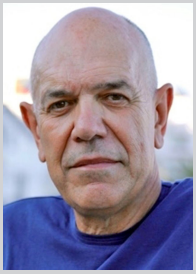
Giuseppe Zuccarello was born in Basel (Switzerland). He completed his BSc in Chemistry at the University of Basel and obtained his master's degree in Chemistry at the Swiss Federal Institute of Technology in Zürich (ETHZ) working on stereodivergent total synthesis of Δ^9-tetrahydrocannabinols under the supervision of Prof. Erick M. Carreira. In 2020 he completed his doctoral studies at the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona (Spain) under the supervision of Prof. Antonio M. Echavarren working on the design and synthesis of new chiral gold(I) complexes and their application in catalysis. In the same year he joined the research group of Prof. Gregory C. Fu at the California Institute of Technology (Caltech) in Pasadena (USA) as a SNSF postdoctoral fellow. His research interests currently focus on copper- and nickel-catalyzed enantioconvergent cross couplings.



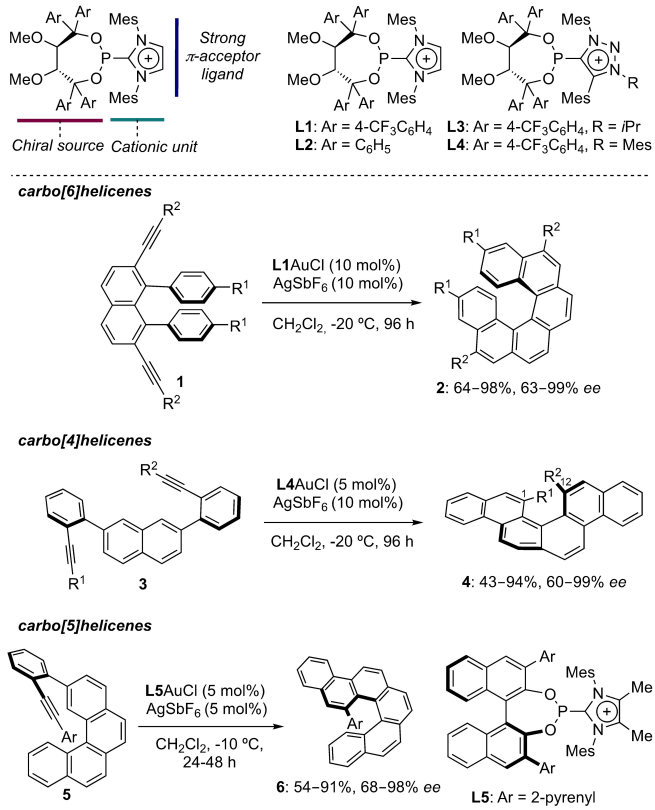
Imma Escofet was born in La Granada, in the Alt Penedès region of Catalonia (Barcelona, Spain). She studied Chemistry at the University of Barcelona (UB) and did her Bachelor Thesis at the University of Aberdeen (Scotland, UK) under the supervision of Prof. Laurent Trembleau (2010). Then, she joined the research group of Prof. Antonio M. Echavarren at the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona, as a laboratory engineer where she also completed her PhD studies (2020) working on computational mechanistic studies of gold(I) catalysis and design of new chiral ligands.



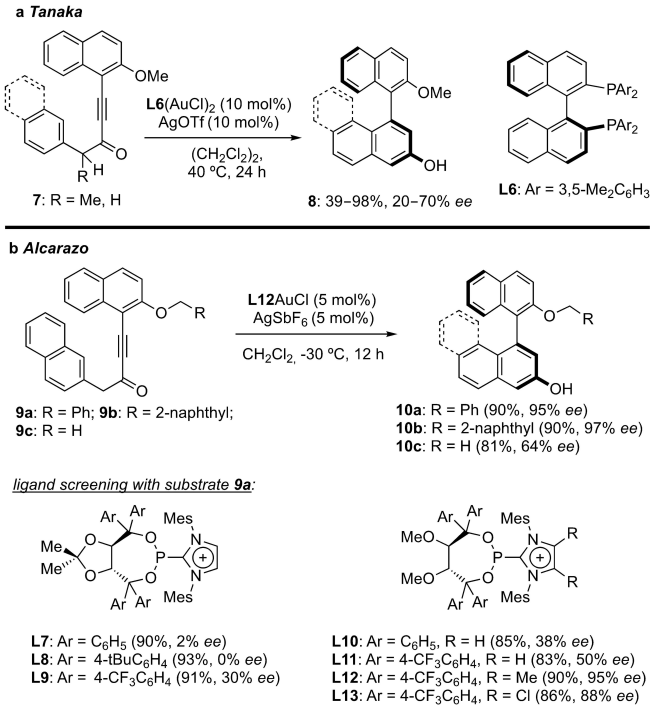
Ulysse Caniparoli received his dual Engineering degree in Chemistry and MSc. in Biochemistry from the Ecole Nationale Supérieure de Chimie de Montpellier, France. He is currently a Ph.D. candidate in ICIQ, Spain, under the supervision of Prof. Antonio M. Echavarren. His research is focused on development of new ligand designs for gold(I) asymmetric catalysis.



Prof. Dr Antonio M. Echavarren was born in Bilbao (Spain). He received his PhD at the Universidad Autónoma de Madrid (UAM, 1982). After a postdoctoral stay in Boston College and Colorado State University, he joined the Institute of Organic Chemistry of the CSIC in Madrid. In 1992 he returned to the UAM as a Professor of Organic Chemistry and in 2004 he moved to Tarragona as a Group Leader at the Institute of Chemical Research of Catalonia (ICIQ). In 2013 he got an ERC Adv. Grant to develop gold catalysis and in 2019 a second ERC Adv. Grant to develop new catalysts for the biomimetic cyclization of unsaturated substrates. He received the 2004 Janssen-Cylag Award in Organic Chemistry and the 2010 Medal of the Royal Spanish Chemical Society and an Arthur C. Cope Scholar Award from the ACS. He is the President of the Spanish Royal Society of Chemistry (RSEQ).



Scheme 1. Gold(I)-catalyzed synthesis of chiral carbohelicenes. The counter-ion SbF_6^- has been omitted for clarity.



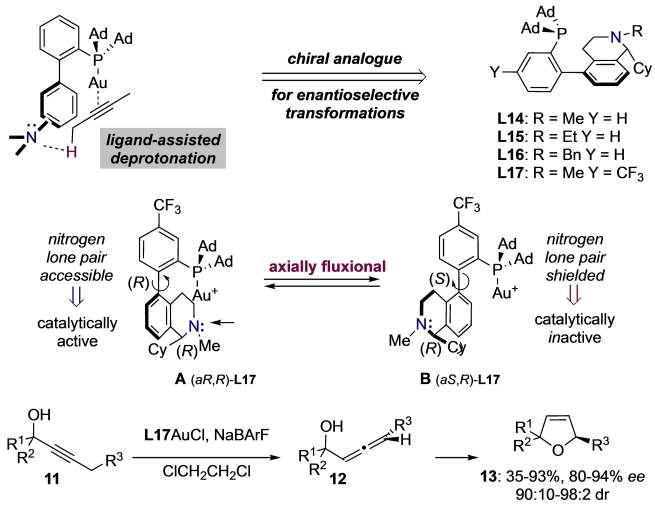
Scheme 2. Gold(I)-catalyzed atroposelective hydroarylations.

and **L4**.[24] Similarly, the synthesis of otherwise configurationally unstable chiral lower order carbo[*4*]helicenes **4** was also achieved via double gold(I)-catalyzed hydroarylation reaction introducing appropriate substituents at the 1- and 12-position to prevent racemization.[25] Finally, the Alcarazo group also developed the enantioselective gold(I)-catalyzed hydroarylation of carbo[*4*]helicenes **5** containing a pendant substituted alkyne giving chiral carbo[*5*]helicenes **6**.[26] However, in this transformation, the TADDOL-based α-cationic ligands **L1**–**4** did not give satisfactory level of enantioselectivity. Hence, ligands of type **L5** containing a 3,3′-disubstituted binaphthol moiety were developed, maintaining the strong π-acceptor character of the ligand.

In the context of enantioselective gold(I)-catalyzed hydroarylation reactions, Tanaka and his coworkers reported the synthesis of axially chiral 1,1′-naphthyl-2,3′-diols **8** from alkynones **7** using xylyl-binap-supported digold(I) complexes, albeit with modest enantioselectivities (Scheme 2a).[27] In view of the general importance of atropoisomeric biaryls, found in several natural products,[27] organocatalysts[28] and in the backbone of chiral ligands for transition metal catalysis[29] the Alcarazo group applied the pronounced π-acidity of their α-cationic phosphinite gold(I) complexes on the synthesis of this type of biaryls (Scheme 2b).[30] Among the surveyed ligands, it was found that flexible methyl ethers on the TADDOL backbone were superior to cyclic acetonides (**L7**–**9** *vs* **L10**–**13**). Moreover, additional substituents on the imidazolium ring narrow the chiral pocket and in turn lead to an increase in enantioselectivity. Finally, attractive non-covalent π-π interactions between substrate and ligand were found to play a crucial role in this transformation as product **10b** with an extended 2-naphthyl substituent gave slightly higher enantioselectivities compared to **10a**, whereas **10c** containing a methyl group was obtained with modest levels of enantioselectivity.

2.2. Biaryl ligands

Bulky dialkyl biarylphosphine ligands have occupied a central role in the development and discovery of gold(I)-catalyzed transformations.[31] Due to their electronic and steric properties this family of ligands is able to stabilize key carbo cationic- and carbene-like intermediates giving rise to unprecedented reactions. Recently, the group of Liming Zhang showed that the particular geometry of biarylphosphine ligands represents an attractive platform to introduce remote basic units on the bottom aryl ring of the biphenyl scaffold allowing for a bifunctional activation mode and in turn, for the discovery of novel selectivities and reactivities, including the propargylic deprotonation of gold(I)-activated alkynes.[32] This concept of ligand-assisted activation has been analogously exploited in the development of asymmetric reactions as the substrate is predisposed in a chiral environment. As such, axially fluxional ligands **L14**–**L17** containing a remote chiral 1,2,3,4-tetrahydroisoquinoline have been designed by the same group for the sequential isomerization of propargylic alcohols **11** to allenylmethanol derivatives **12** and in situ stereospecific cyclization to form chiral 2,5-disubstituted dihydrofuranes **13** (Scheme 3).[33]



Scheme 3. Axially fluxional biarylphosphine ligands with remote basic chiral element.

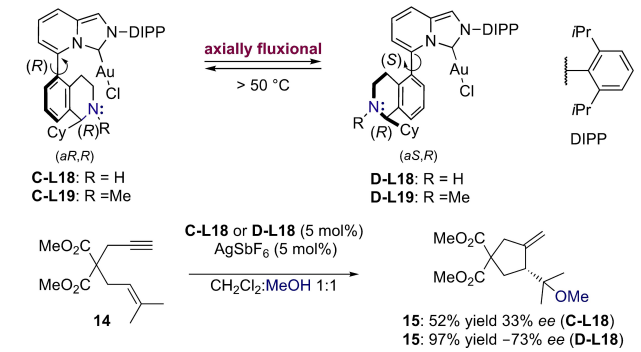
Due to the free rotation around the biaryl axis, the corresponding cationic complex of ligand **L17** would exist as a mixture of isomers **A** and **B**. In the latter however, the cyclohexyl substituent points towards the catalytic site shielding the basic nitrogen and preventing the interaction with substrates of type **11**. Thus, isomer **B** is catalytically inactive and the enantioselectivities in products **13** are attributed to reaction with isomer **A**. Shortly after, the strongly σ-donating axially fluxional NHC-analogues were introduced replacing the bulky PAd_2 moiety by the rigid imidazo[1,5-*a*]pyridine framework **L18**–**L19**.[34] Interestingly, the analogous atropoisomers **C** and **D** only interconvert at elevated temperatures (> 50 °C) and were therefore used separately in various asymmetric transformations including the alkoxycyclization of 1,6-enyne **14**. Although corresponding cycloadducts **15** were obtained with good yields, the level of enantioselectivity was modest (Scheme 4).

Very recently, the same group reported the asymmetric intramolecular net addition of propargylic C–H bonds to aliphatic aldehydes **16** for the formation of synthetically useful 5- and 6-membered-fused homopropargylic alcohols **17**.[35] Remarkably, cooperative activation of the triple bond allowed for the preferential deprotonation of the propargylic C–H bond ($pK_a > 30$) by the remotely positioned basic unit ($pK_a \sim 10$) in the presence of much more acidic aldehyde α-hydrogens ($pK_a \sim 17$) (Scheme 5).

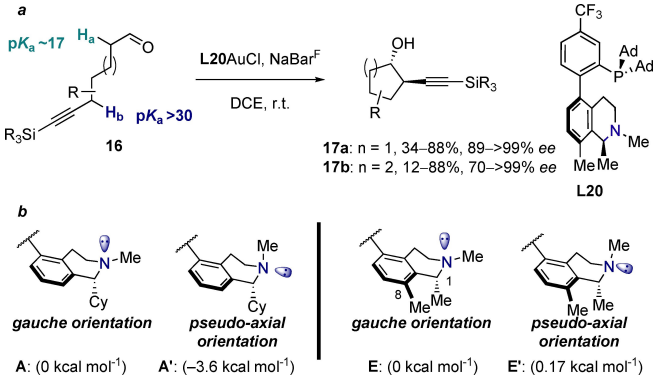
To ensure the high efficiency of these transformations, including reaction yields, enantio- and diastereoselectivites, a DFT-guided ligand design was performed (Scheme 5b). In a previously reported design (see Scheme 3), catalytically active, because nitrogen-exposed, conformer **A**-**L17** was found to be less stable than the nitrogen-buried conformer **A'** due to the gauche interactions between the cyclohexyl and the N–Me substituents in the tetrahydroisoquinoline unit. This leads to an overall lower reactivity of **L17**AuCl. To minimize the destabilizing gauche interactions, the 1-cyclohexyl substituent was replaced by a 1-methyl, and a 8-methyl moiety was introduced to maintain the pseudo axial orientation of the 1-methyl group. DFT calculations confirmed that conformers **E** and **E'** of the 1,8,N-trimethyltetrahydroquinoline unit in **L20** have comparable energies.

Our laboratory recently introduced a family of chiral modified JohnPhos-type ligands bearing a C_2-symmetric diaryl pyrrolidine at the 4′ position of the biphenyl scaffold **18**–**23** (Scheme 6).[36] The latter is employed as a geometrical holder positioning the chiral information directly next to the reactive center and thus, circumventing the inherent difficulty posed by the linear coordination in gold(I) catalysts. Moreover, the C_2-symmetric chiral element prevents the formation of rotamers and the bulky dialkyl phosphine component of the ligand design blocks rotation around the C–P bond directing the P–Au–Cl axis towards the chiral source for efficient enantioinduction. These complexes found application in three different enantioselective cyclizations of 1,6-arylenynes **24, 26** and **28** to give cyclopenta[*b*]naphthalenes **25**, azabicyclo[4.1.0]hept-4-enes **27** and 1,2-dihydronaphthalenes **29** in good yields and enantioselectivities. Additionally, products **29** were successfully employed in the first enantioselective total synthesis of three members of the carexane family of natural products **30a-c**.

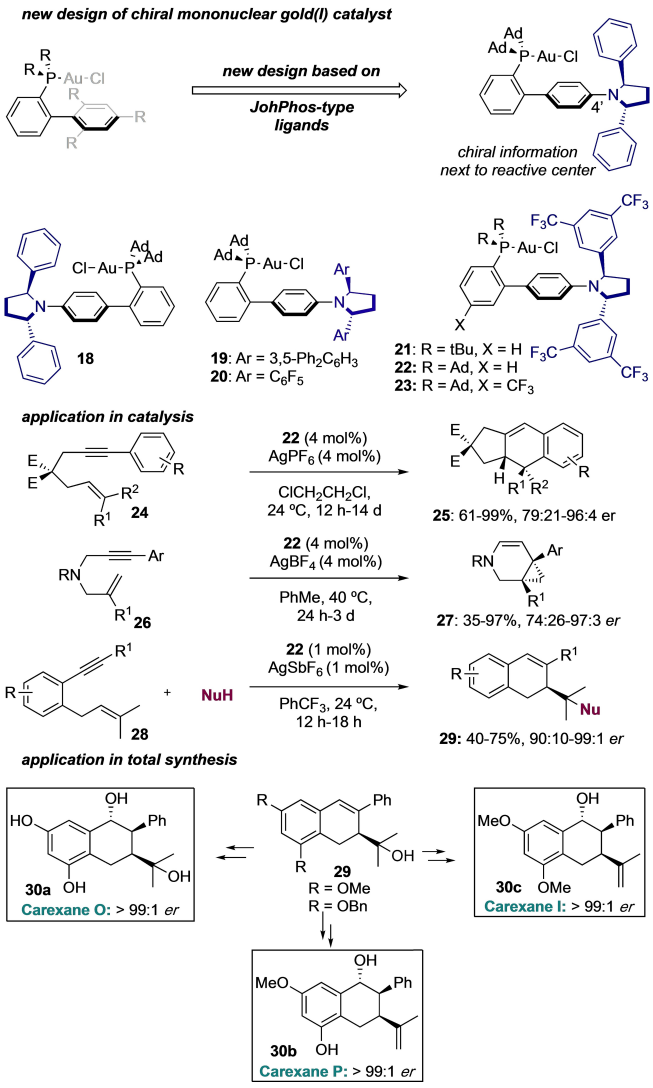
Surprisingly, although 1,6-arylenynes **24a** and **28a** are structurally related, opposite enantioselectivities were observed in the corresponding products **25a** and **29a**, arising from the



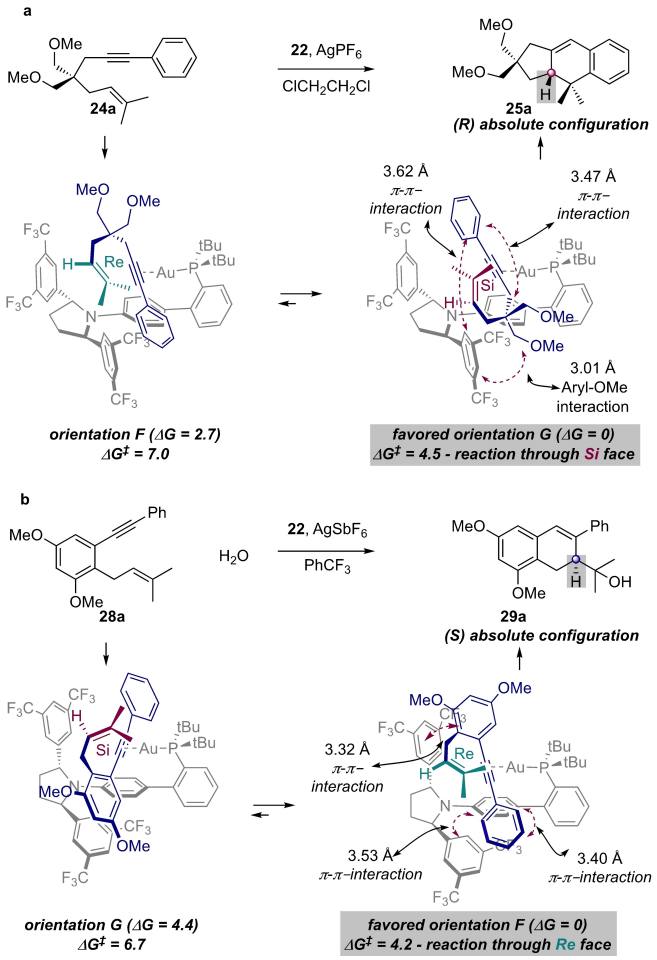
Scheme 4. Axially fluxional NHC-gold(I) complexes with remote basic chiral element.



Scheme 5. a) Asymmetric gold(I)-catalyzed construction of chiral homopropargylic alcohols **17**. b) Ligand tetrahydroisoquinoline moiety conformations and relative energies.



Scheme 6. Dialkyl pyrrolidinylbiphenylphosphine ligands.



Scheme 7. Enantioselective folding of enynes **24a** and **28a**. Two most relevant binding orientations (**F** and **G**) are shown. Energy values are given in kcal/mol relative to the most stable binding orientation.

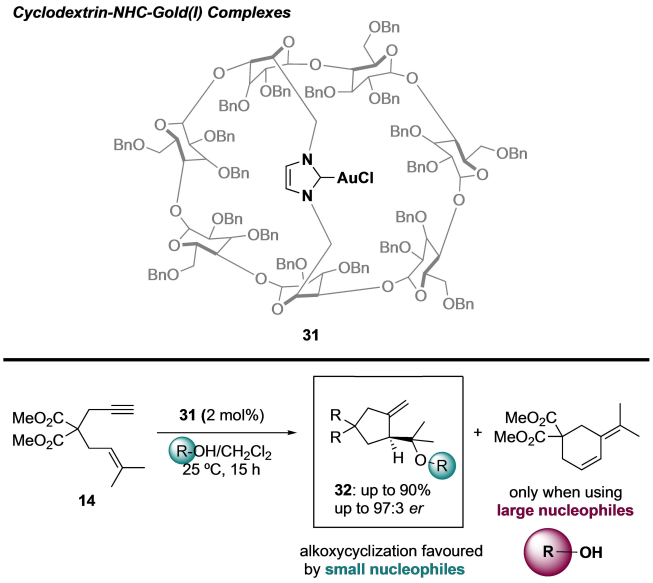
preferential reaction of the respective *Si* and *Re* faces of the alkenes (Scheme 7).

We elucidated the mode of enantioinduction of the catalysts both experimentally and computationally as arising from attractive non-covalent π-π-interactions between stereo-directing aromatic moieties of the substrates and the aromatic substituents of the chiral pyrrolidine in the ligand backbone. The absolute configuration in products **25a** and **29a** can originate from the combination of two binding orientations (**F** and **G**) of the substrate coordinated to gold through the alkyne and the reaction of the *Re* or *Si* face of the alkene. In agreement with our experimental results our computational work predicts that enyne **25a** reacts preferentially via binding orientation **G** through the *Si* face of the alkene leading to the (*R*) enantiomer of **29a** whereas the (*S*) absolute configuration in **29a** arises from reaction at the *Re* prochiral face of the alkene via binding orientation **F**. Thus, upon substrate recognition, the ligand induces a specific binding orientation that dictates the enantioselective folding inside the chiral pocket and ultimately, the absolute configuration in products **25a** and **29a**. Additional stabilization of the transition state was provided by interactions with the biphenyl scaffold of the ligand and in case of enyne **24a** aryl-OMe interactions were also found to be stereocontrolling.

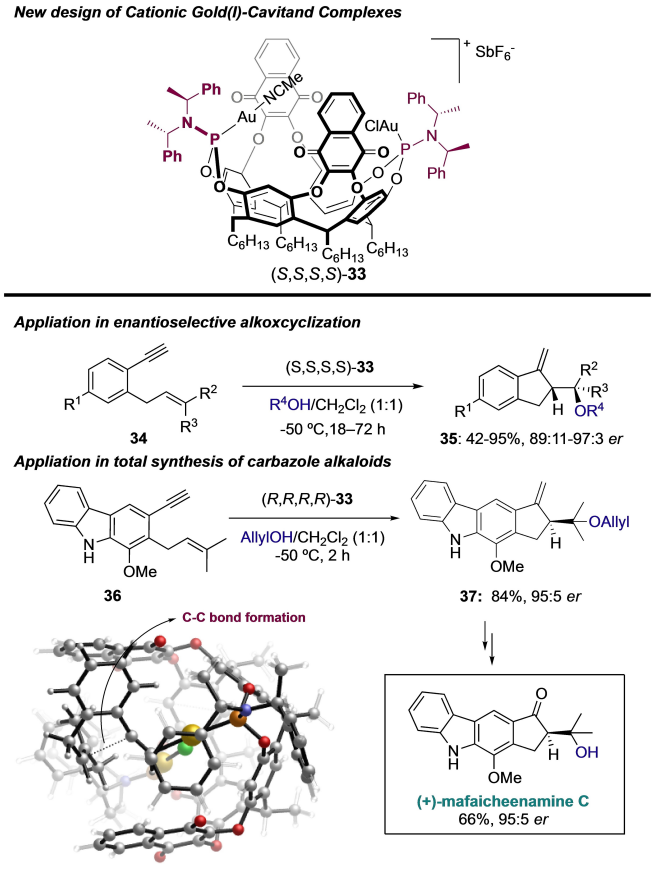
2.3. Chiral cavitand-type ligands

The groups of Sollogoub/Fensterbank and Armspach, have developed different gold catalysts confined inside of cyclodextrins.[37,38] Thus, using NHC-capped β-cyclodextrin gold (I) catalyst **31**, the Sollogoub group achieved excellent enantioselectivities (up to 94–98% *ee*) in the hydroxy- and methoxycyclization of 1,6-enynes **14** (Scheme 8).[37c,d]

Recently, a new family of chiral gold(I) complexes of type **33** have been designed in our laboratories based on cavitands.[39] These new complexes were easily prepared modularly from resorcin[4]arenes and commercially available chiral secondary amines, and proved to be active for the enantioselective alkoxycyclization of 1,6-enynes, giving excellent yields and high enantiomeric ratios (Scheme 9). This protocol has been applied



Scheme 8. Enantioselective gold(I)-catalyzed alkoxycyclization of *E*-1,6-enynes using NHC-capped β-cyclodextrin gold(I) catalysts.



Scheme 9. Enantioselective gold(I)-catalyzed alkoxycyclization of *E*-1,6-dienyne **34** using cavitand complex **33**. Application in the total synthesis of (+)-mafaicheenamine C, and its enantiomer.

for the first total synthesis of carbazole alkaloid (+)-mafaicheenamine C, and its enantiomer, assigning its absolute configuration as *R, via* **37**. Computational studies and NCI plots identified attractive non-covalent interactions in the reaction cavity as key factor to achieve high enantioselectivities.

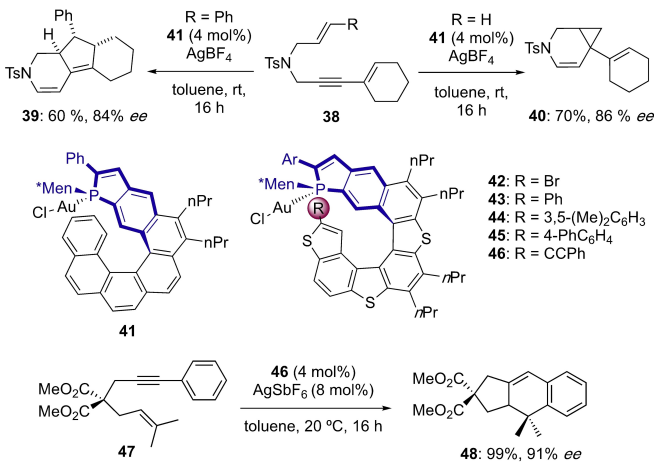
2.4. Helically chiral monophosphines

The groups of Marinetti and Voiturez introduced helically chiral monodentate ligands with embedded *meta*-fused phospholes.[40] The corresponding gold(I) complex **41** has been found to be catalytically active in the cyclization of *N*-tethered 1,6-enynes of type **38** to give fused tricyclic compounds **39** and azabicyclo[4.1.0]-hept-4-enes **40** (Scheme 10).[41]

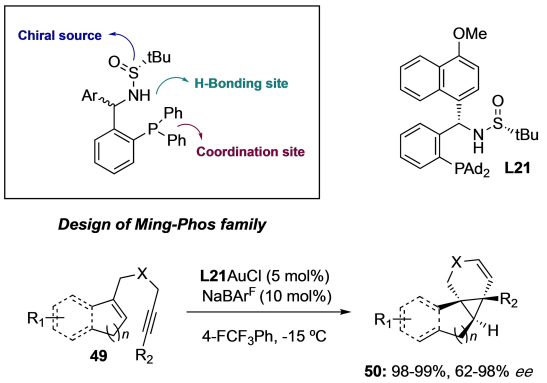
While modification of the ligand's helix have been beneficial in the enantioselective activation of allenes,[42] phosphathiohelicene-supported gold(I) complexes **42**–**45** were applied in the formal [4+2] cycloaddition of 1,6-arylenyne **47**. Importantly, the thiopehene-containing scaffold can be selectively brominated, allowing for the modular access to a broader family of complexes via Suzuki coupling.[43]

2.5. Chiral sulfinamide monophosphine ligands

Recent progress relies on the design of chiral ligands such as sulfinamide monophosphines. The group of Juliang Zang has contributed to the development of the so-called Ming-Phos family of ligands from commercially available sources.[44] These bifunctional monophosphines proved to be efficient for various enantioselective inter- and intramolecular cycloadditions fixing the substrates via non-covalent interactions (Scheme 11).[45] The first intramolecular gold(I)-catalyzed enantioselective cyclopropanation of indenes and trisubstituted alkenes allowed for the efficient formation of [5-3-6] fused-ring systems in products **50** (containing two vicinal all-carbon quaternary stereogenic centers) by using Xiang-Phos ligand **L21**.[46] A broad range of *N*-

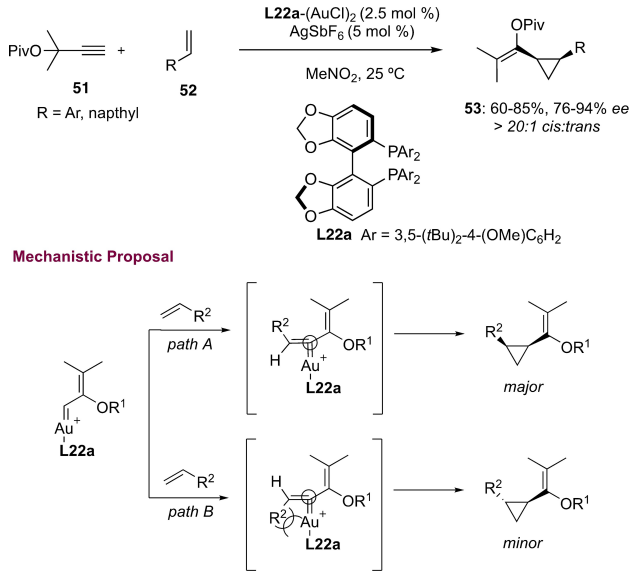


Scheme 10. Helically chiral monophosphines in enantioselective gold(I) catalysis.



Scheme 11. Gold(I)-catalyzed Intermolecular cycloaddition of indenes and trisubstituted alkenes.

tethered enynes **49** gave rise to the diastereo and enantioselective construction of fused tetracyclic compounds **50** in good to excellent enantioselectivities.



Scheme 12. Enantioselective intermolecular cyclopropanation of alkenes using pivalate ester **51**.

3. Intermolecular Gold(I) Catalyzed Reactions of Alkynes

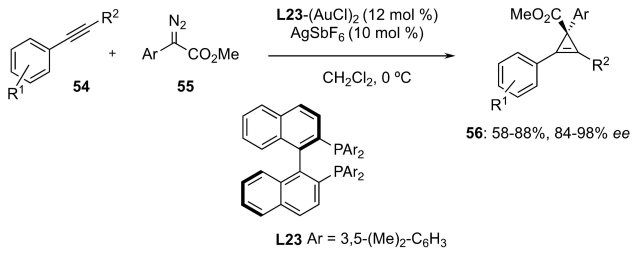
Although significant progress has been made in the intramolecular gold(I)-catalyzed reactions of alkynes to obtain complex polycyclic structures, the development of intermolecular transformations is still challenging.[47] In these transformations, two independent unsaturated substrates (alkynes and alkenes) can compete for the binding to the gold center having similar association constants.[48] Furthermore, inherently acidic gold catalysts can also promote side reactions such as the polymerization of alkenes.[49] The complexity of inducing enantioselectivity in these reactions increases when linear alkynes react in an intermolecular fashion.[50] Nonetheless, a wide range of gold-catalyzed intermolecular transformations have been developed recently, opening the door to the construction of complex molecular frameworks from simple starting materials.[51]

3.1. Binuclear gold(I) complexes

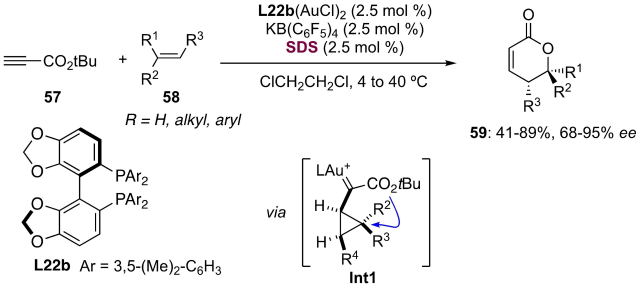
The use of DTBM-SEGPHOS ligand (**L22**) in gold(I) catalysis was disclosed by the group of Toste in the intermolecular cyclopropanation of sterically hindered propargylic pivalate **51** and styrenes of type **52** (Scheme 12).[52] The steric hindrance of the aryl substituent at the alkene in *path B* was found to be key for high enantiodiscrimination. Moreover, the proposed transition state showed an outer sphere attack of the vinyl group in a 90° angle with respect to the gold(I) carbene in *path A*, which facilitates the enantiodiscrimination giving rise to *cis*-cyclopropanes **53** in good to excellent enantioselectivities.

Later, as an extension of previous work using achiral silver catalysts,[53] the group of Davies developed the asymmetric cyclopropenation of internal alkynes **54** with aryldiazoacetates **55** using binuclear gold(I) catalyst based on the (*S*)-xylylBINAP ligand (**L23**) (Scheme 13).[54] The resulting cyclopropenes **56**, which are important synthons,[55] were obtained in moderate to excellent (up to 98% *ee*) enantiomeric ratios.

Propiolic acid and some of its derivatives can also take part in a gold(I) catalyzed intermolecular reaction with 1,1-di- or trisubstituted alkenes leading to α,β-unsaturated δ-lactones **59** by a formal [4+2] annulation, as demonstrated by group of Shin (Scheme 14).[56] Thus, upon the formation of the corresponding cyclopropyl gold carbene **Int1**, the more substituted



Scheme 13. Enantioselective cyclopropenation of internal alkynes **54**.



Scheme 14. Asymmetric gold(I)-catalyzed intermolecular [4+2] annulation.

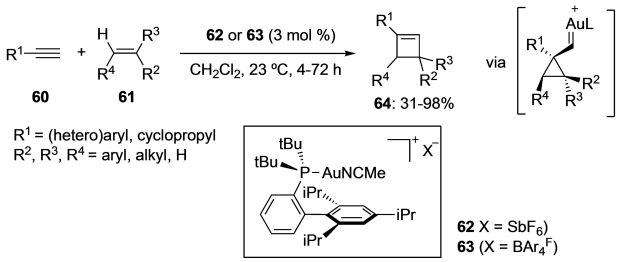
carbon of the alkene is attacked intramolecularly by the propiolate moiety. Initially, when ligand (*R*)-**L22b** was used α,β-unsaturated δ-lactones were obtained with a maximum of 65% ee. Later, under slightly different conditions and using sodium dodecyl sulphate (SDS) as an anionic surfactant, lactones **59** were obtained with better enantioselectivities.[57]

Cyclobutenes of type **64** are important structural motifs occurring in many natural products and in biologically relevant compounds.[58] Therefore, these carbocycles have been used as valuable synthons to access a diversity of scaffolds,[59] such as cyclobutanes and cyclopropanes.[60] Our group reported the gold(I)-catalyzed regioselective formation of cyclobutenes **64** from terminal alkynes **60** with alkenes **61** (Scheme 15).[50a] The reaction proceeds satisfactorily using cationic gold(I) complexes **62** with sterically hindered *t*BuXPhos ligand. Formation of the unreactive σ,π-(alkyne)digold(I) species was found as a secondary process in this transformation. Later, we found that cationic gold complexes **63** containing bulky and less acidic BAr_4^{F-} as counterion, instead of SbF_6^- (complex **62**), are superior catalysts for these reactions due to the anion effects.[61] Aryl and cyclopropyl alkynes are required to ensure high reactivities. Electron-rich alkenes, preferentially being bi- and tri-substituted, are the best reaction counterparts for the most efficient [2+2] cycloadditions.

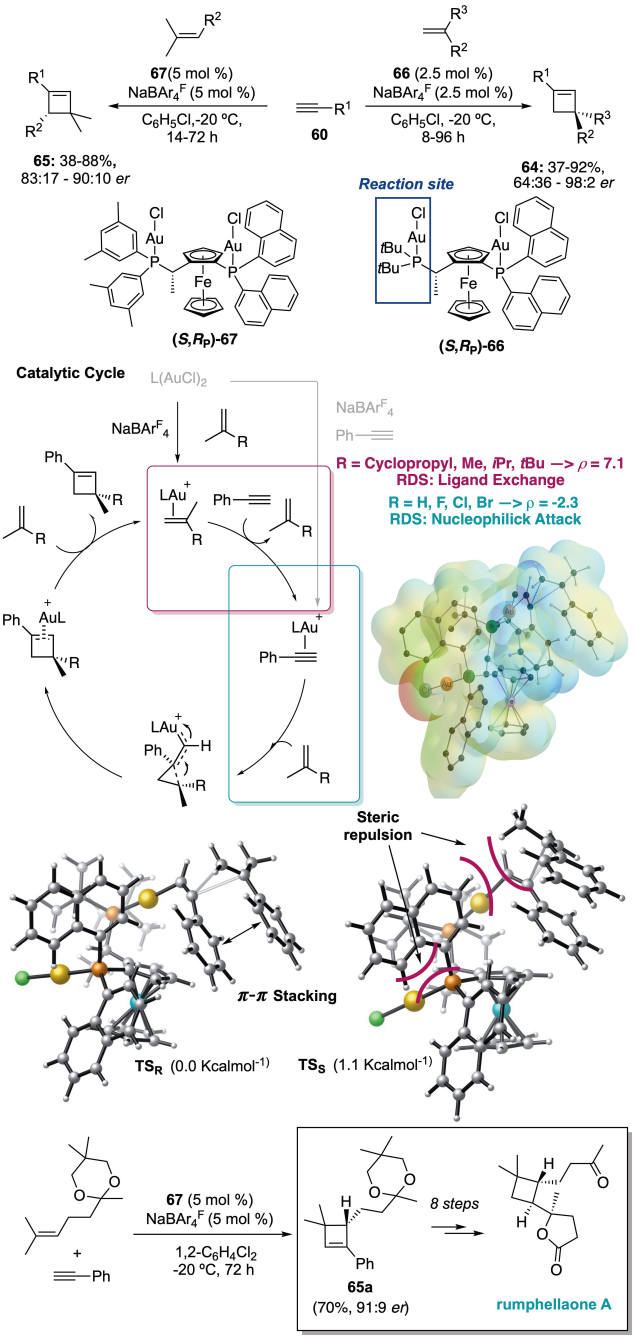
Several strategies have been designed for the efficient preparation of cyclobutenes using Lewis acids,[62] transition metals,[63] and photochemical processes.[64] Among these strategies, the gold(I)-catalyzed [2+2] cycloaddition of alkynes with alkenes is one of the most straightforward methodologies to afford enantioenriched 4-membered carbocycles.

The first example of gold(I)-catalyzed enantioselective intermolecular [2+2] cycloaddition was reported by the group of Lassaletta and Fernández using an axially chiral imidazoisoquinolin-2-ylidene as ligand.[65] However, cyclobutenes were obtained with low enantiomeric ratios (65:35 *er*).

In this context, our research group discovered that non-C_2 chiral Josiphos digold(I) precatalysts were optimal for the enantioselective intermolecular [2+2] cycloaddition of alkynes with alkenes (Scheme 16).[66] Enantioenriched cyclobutenes of type **64** were generally obtained in moderate to good enantiomeric ratios by cycloaddition of aryl alkynes **60** and α-methyl styrenes catalyzed by catalyst **66**, whereas Josiphos complex **67** allowed for the cycloaddition of trisubstituted alkenes. It was demonstrated that only one of the gold centers is directly involved in the activation of the alkyne, the second



Scheme 15. Gold(I)-catalyzed [2+2] cycloaddition of terminal alkynes with alkenes.

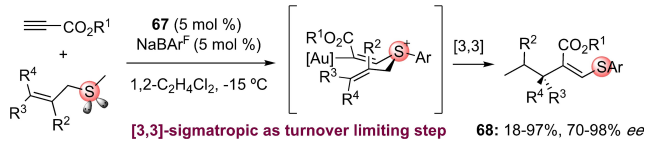


Scheme 16. Gold(I)-catalyzed [2+2] cycloaddition of alkynes with alkenes. Catalytic cycle for the reaction of phenylacetylene with α-methyl-styrene and catalyst **66** and computed two possible transition states (TS_R and TS_S). Application to the enantioselective total synthesis of rumphellaone A.

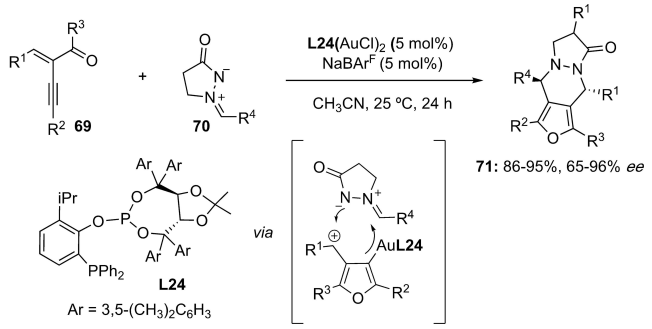
one is required to induce high enantioinduction. The rate-determining step of this transformation was highly influenced by the electronic properties of the alkene. When less electron rich alkenes were used as the cycloaddition partners, as expected, the slowest step was found to be the C–C bond formation by an electrophilic addition of the alkyne-gold(I) complex, while for more electron rich alkenes, the rate determining step is the associative ligand exchange reaction. The origin of the enantioselectivity is attributed to a combina-

tion of stabilizing π-stacking interactions and unfavorable steric effects in the most favorable transition state. This intermolecular [2+2] cycloaddition was applied in the second generation asymmetric total synthesis of rumphellaone A from **65a**.[67]

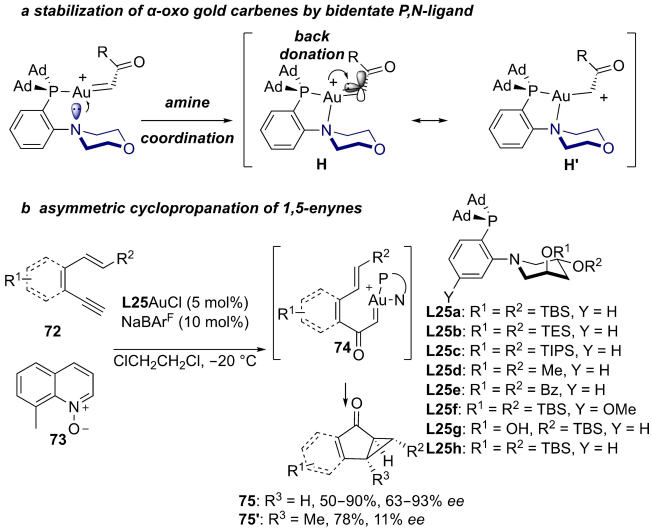
Binuclear Josiphos digold(I) complex **67** (Scheme 16) was found to be also effective for the enantioselective intermolecular thioallylation of propiolates with allyl sulfides (Scheme 17).[68] This intermolecular variant of the Claisen rearrangement led to the selective preparation of enantioenriched β-thioacrylates **68** in moderated to excellent enantiomeric excesses. Mechanistic studies revealed that sulfonium-induced asymmetric Claisen rearrangement minimizes the allyl dissociation giving rise to higher enantioselectivities. A Hammet analysis suggested the [3,3]-sigmatropic rearrangement as turnover limiting step.



Scheme 17. Gold(I)-catalyzed enantioselective Thio-Claisen rearrangement.



Scheme 18. Enantioselective gold(I)-catalyzed synthesis of furo[3,4-d] tetrahydropyridazines **71**.



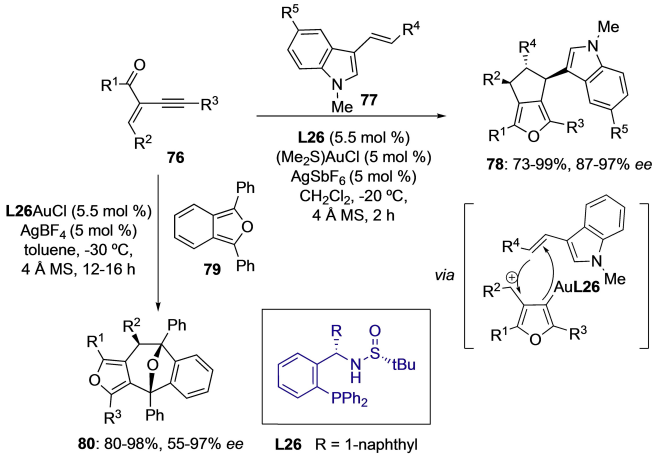
Scheme 19. Bidentate P,N-ligands in enantioselective cyclopropanations of 1,5-enynes.

The group of Schmalz reported the enantioselective gold(I)-catalyzed preparation of highly substituted furo[3,4-*d*] tetrahydropyridazines **71** by using a chiral phosphine-phosphite ligand **L24**,[69] previously developed by the same laboratory.[70] The tandem cyclization/intermolecular [3+3]-cycloaddition process between 2-(1-alkynyl)-2-alken-1-ones **69** and azomethine imines **70** allows for the regio- and diastereoselective preparation of products **71** in mild conditions with high yields and excellent enantioselectivities (Scheme 18).

3.2. Mononuclear gold(I) complexes

The gold(I)-catalyzed oxidation of alkynes involves the formation of highly electrophilic α-oxo gold(I) carbenes.[71] With the goal of stabilizing these intermediates, the group of Zhang introduced a bidentate P,N-ligand which forms a tricoordinated gold(I) complex **L25**AuCl, providing additional electron density to the gold atom. Thus, stabilization of gold carbene intermediate **H** occurs via back donation and mesomeric cationic species **H'** becomes less accessible (Scheme 19a).[72] On this basis, a chiral version of these P,N-ligands (**L25a–h**) was developed for the intramolecular enantioselective oxidative cyclopropanation of 1,5-enynes **72**.[73] In this transformation, the activated alkyne reacts with 8-methylquinoline 1-oxide **73** to give the corresponding α-oxo gold(I) carbene **74**, which reacts with the pendant olefin to give bicyclo[3.1.0]hexan-2-ones **75** in good yields and enantioselectivities up to 93 %. However, product **75'** containing all-carbon quaternary stereocenter at the cyclopropane was obtained with low enantiomeric excess (Scheme 19b).

The intermolecular [3+2] cycloaddition of 2-(1-alkynyl)-2-alken-1-ones **76** with 3-alkenylindoles **77** was achieved in high enantiomeric ratios using Ming-Phos ligand **L26**-supported gold (I) catalysts, previously designed by the group of Juliang Zhang (Scheme 20).[74] A wide variety of enantioenriched substituted bicyclic furans **78** were obtained by the highly diastereoselective tandem heterocyclization/cycloaddition of readily available



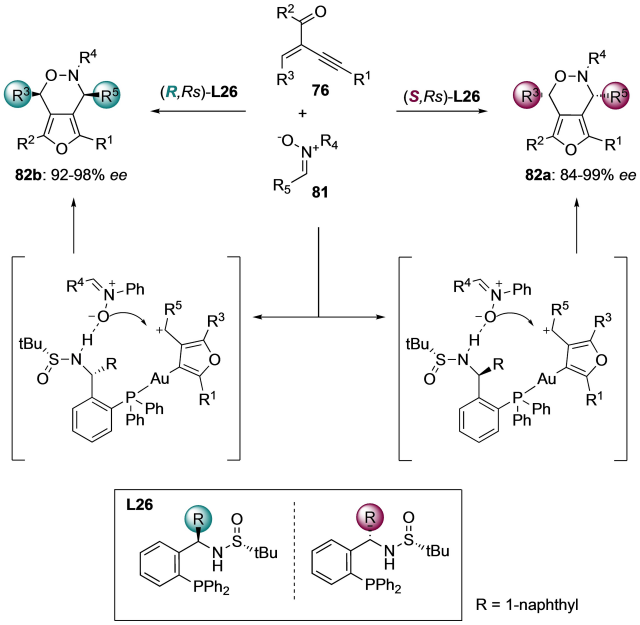
Scheme 20. Enantioselective gold(I)-catalyzed synthesis of indolyl-substituted cyclopenta[*c*]furans **78** and oxa-bridged benzocycloheptanes **80**.

starting materials. The same chiral sulfinamide ligand **L26** was later found to be efficient catalyst for the highly exo- and enantioselective synthesis of seven membered oxa-bridged rings **80** in 80–98% yield and with high exo selectivity (exo/endo up to 50:1) and up to 97% ee.[75]

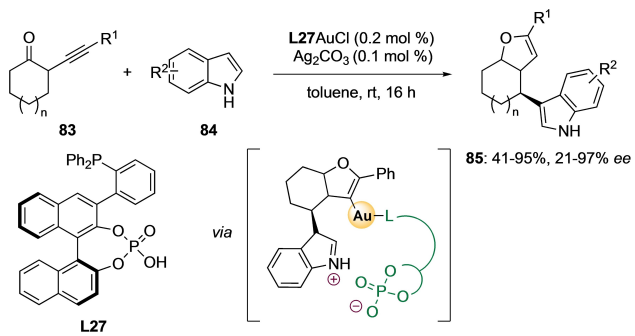
The asymmetric intermolecular tandem [3+3] cycloaddition of 2-(1-alkynyl)-2-alken-1-ones **76** with nitrones **81** was achieved using a gold(I) complex with Ming-Phos ligand **L26** (Scheme 21).[76] Both enantiomers of the furo[3,4-*d*][1,2] oxazinesin product **82a**–**b** could be obtained in high enantioselectivities using either diastereomer of the chiral ligand. The proposed enantioinduction model relies on H-bonding of the sulfinamide moiety with nitrones.

3.3. Asymmetric counteranion-directed catalysis

Recently, Marinetti and Guinchard reported a new strategy that uses a BINOL-derived chiral phosphate counterion tethered to a monophosphine ligand **L27** (Scheme 22)..[77] This design provides high enantioinduction in the tandem cycloisomerization/nucleophilic addition of 2-alkynylenones **83** at low catalyst loading. According to DFT calculations, the stereochemical control is driven by the geometrical constraints and molecular folding in the key intermediate that is stabilized by the phosphate anion group via ion-pairing.



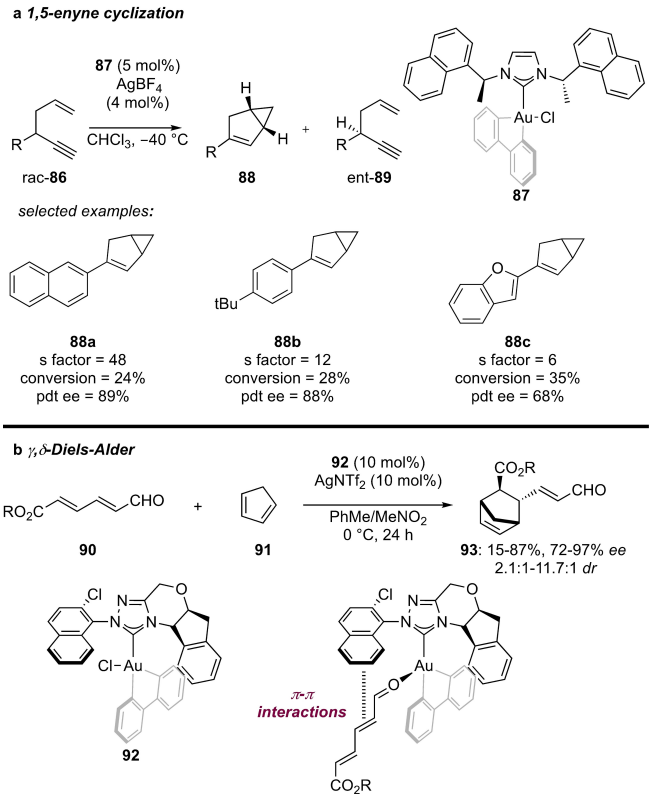
Scheme 21. A gold(I)-catalyzed asymmetric intermolecular tandem [3+3]-cyclization reaction of 2-(1-alkynyl)-2-alken-1-ones **76** with nitrones **81**.



Scheme 22. Gold(I)-catalyzed asymmetric cycloisomerization/nucleophilic addition.

4. Enantioselective Gold(III)-Catalyzed Transformations

Compared to homogeneous gold(I) catalysis, the use of high-valent gold(III) catalysts remains underdeveloped.[78] This is mainly traced back to their high redox potential that facilitates reduction to Gold(I) or formation of gold(0) species.[79] The stabilization of gold(III) complexes is commonly achieved with weak π-acceptor nitrogen-containing ligands such as pyridines,[80] Schiff bases,[81] triazoles[82] or cyclometalated biphenyls.[83] The potential of chiral gold(III) catalysts lies in their square-planar coordination geometry that brings the chiral information closer to the reactive center and therefore simplifies enantioinduction. The group of Toste reported the application of a chiral gold(III) catalyst **87** for the kinetic resolution of racemic 1,5-enynes **86** affording chiral bicyclo-[3.1.0]hexenes **88** and enantioenriched 1,5-enynes **89** in the same transformation (Scheme 23a).[84] The potential of chiral



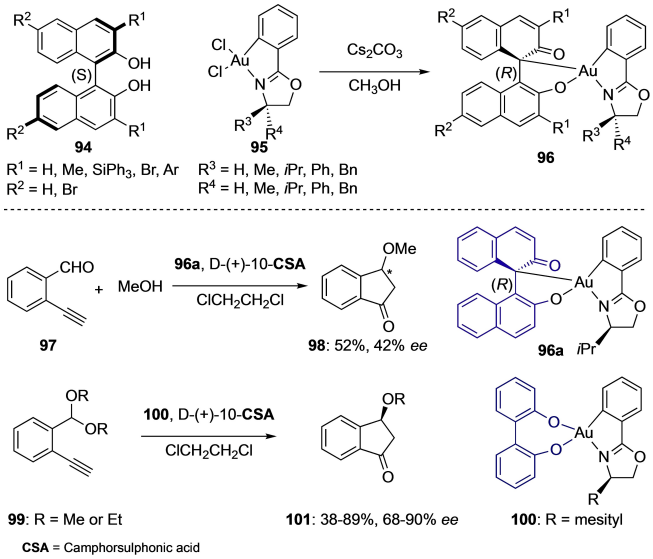
Scheme 23. Enantioselective gold(III)-catalyzed a) cyclization of 1,5-enynes and b) Diels-Alder reaction.

gold(III) catalysts lies in their square-planar coordination geometry that brings the chiral information closer to the reactive center and therefore simplifies enantioinduction. A similar chiral gold(III) complex **92** was used for the enantioselective gold(III)-catalyzed Diels-Alder reaction between 2,4-dienals **90** and cyclopentadiene **91** (Scheme 23b).[85] DFT calculations suggest that the high regio- and enantioselectivities originate from attractive non-covalent π-π interactions between the 2-chloro-naphthyl substituent of the triazolium ligand and the proximal double bond of the substrate.

The group of Wong recently reported the synthesis and catalytic activity of new gold(III) complexes formed by reaction of cyclometalated oxazoline gold(III) dichloride complexes **95** with BINOL derivatives **94** (Scheme 24).[86] The BINOL moiety underwent an interesting axial-to-central chirality transfer[87] giving the C,O-chelated gold(III) complexes **96**. Although *ca.* 50 new 3,3′- and 6,6′-substituted gold(III) complexes were synthesized, the carboalkoxylation of *ortho*-alkynylbenzenaldehydes **97** in the presence of MeOH and catalytic amounts of D-(+)-10-camphorsulfonic acid afforded indanone **98** with only modest 52% yield and 41% *ee*. Later, the same group found that replacing BINOL (complex **96**) by simple biphenol, O,O′-chelated 4,4′-biphenol cyclometalated oxazoline gold(III) complexes **100** were obtained which catalyzed the interconversion of compound **99** to analogous indanone products **101** with good to excellent yields and enantioselectivities.[88]

5. Conclusion

The stringencies imposed by the linear coordination usually adopted by gold(I) complexes have led to the development of new imaginative ligand designs to achieve good to excellent enantioselectivity levels in reactions involving alkynes as substrates. However, often limitations exist with terminally unsubstituted alkynes in reactions in which the alkyne-Au(I) complex becomes the electrophile. Thus, even under the optimized conditions, intermolecular reactions of terminal alkynes leading to α,β-unsaturated δ-lactones or cyclobutenes developed by the group of Shin[55] and our own group,[64] respectively, proceed with 90% or higher enantiomeric excess in only a few cases. A new generation of gold(I) catalysts should still be developed to achieve consistently high enantioselectivities and broad scope in cyclization and cycloaddition reactions. Finally, the examples shown in section 4 clearly highlight that there is much room for the development of new families of chiral gold(III)-catalysts for the enantioselective activation of alkynes.



Scheme 24. O,O′-cyclometalated Gold(III) complexes in enantioselective catalysis.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: alkynes · asymmetric catalysis · chiral ligands · cyclization · gold

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