Very Important Paper

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

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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 1,1,1-triples[7] and allenes[8],[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 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.

![Figure 1. a) Limitations associated with enantioselective gold(I) catalysis. b) Three main approaches to enantioselective gold(I) catalysis.](image-url)
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] alkynes[4e, f] and the use of chiral counterions[19] 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

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Ulysses Caniparoli received his dual Engineer- ing degree in Chemistry and MSc. in Biochem- istry 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.

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.

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).
Similarly, the synthesis of otherwise configurationally unstable chiral lower order carbohelicenes was also achieved via double gold(I)-catalyzed hydroarylation reaction introducing appropriate substituents at the 1- and 12-position to prevent racemization. Finally, the Alcarazo group also developed the enantioselective gold(I)-catalyzed hydroarylation of carbohelicenes containing a pendant substituted alkyne giving chiral carbohelicenes. However, in this transformation, the TADDOL-based $\alpha$-cationic ligands did not give satisfactory level of enantioselectivity. Hence, ligands of type containing a 3,3'-disubstituted binaphthol moiety were developed, maintaining the strong $\pi$-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 from alkylnones using xylyl-binap-supported digold(I) complexes, albeit with modest enantioselectivities (Scheme 2a). 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 containing a remote chiral 1,2,3,4-tetrahydroisoquinoline have been designed by the same group for the sequential isomerization of propargylic alcohols to allenylmethanol derivatives and in situ stereospecific cyclization to form chiral 2,5-disubstituted dihydrofuranes (Scheme 3).

2.2. Biaryl ligands

Bulky dialkyl biarylphosphine ligands have occupied a central role in the development and discovery of gold(I)-catalyzed transformations. 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.
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 \( \sigma \)-donating axial functional NHC-analogues were introduced replacing the bulky Pd\(_2\) 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 (\( > 50^\circ\mathrm{C} \)) and were therefore used separately in various asymmetric transformations including the alkoxycyclization of 1,6-enynes. 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.\(^{[39]}\) 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 \( \alpha \)-hydrogens (\(pK_a \sim 17\)) (Scheme 5).

To ensure the high efficiency of these transformations, including reaction yields, enantio- and diastereoselectivities, 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 L17AuCl. 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-trimethyltetrahydroisoquinoline 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).\(^{[30]}\) 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 cyclopental[6]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

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

**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.
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. 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
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 monodentate ligands with embedded \( \text{meta} \)-fused phospholes. Computational studies and NCI plots have identified attractive non-covalent interactions in the reaction cavity as key factor to achieve high enantioselectivities.

#### 2.4.1. Helically chiral monophosphines

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### 2.5. Chiral sulfonamide monophosphine ligands

Recent progress relies on the design of chiral ligands such as sulfonamide monophosphines. The group of Juliang Zang has contributed to the development of the so-called Ming-Phos family of ligands from commercially available sources. These bifunctional monophosphines proved to be efficient for various enantioselective inter- and intramolecular cycloadditions fixing the substrates via non-covalent interactions (Scheme 11). 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. A broad range of \( N \)-
tethered enynes 49 gave rise to the diastereo and enantioselective construction of fused tetracyclic compounds 50 in good to excellent enantioselectivities.

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. In these transformations, two independent unsaturated substrates (alkynes and alkenes) can compete for the binding to the gold center having similar association constants. Furthermore, inherently acidic gold catalysts can also promote side reactions such as the polymerization of alkenes. The complexity of inducing enantioselectivity in these reactions increases when linear alkynes react in an intermolecular fashion. 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.

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). 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, the group of Davies developed the asymmetric cyclopropagation of internal alkynes 54 with aryl diazoacetates 55 using binuclear gold(I) catalyst based on the (S)-xylylBINAP ligand (L23) (Scheme 13). The resulting cyclopropanes 56, which are important synthons, 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 \(\alpha,\beta\)-unsaturated \(\delta\)-lactones 59 by a formal \([4 + 2]\) annulation, as demonstrated by group of Shin (Scheme 14). Thus, upon the formation of the corresponding cycopropyl gold carbene Int1, the more substituted...
carbon of the alkene is attacked intramolecularly by the propionate 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.\textsuperscript{[31,32]}

Cyclobutenes of type 64 are important structural motifs occurring in many natural products and in biologically relevant compounds.\textsuperscript{[34]} Therefore, these cyclobutanes have been used as valuable synthons to access a diversity of scaffolds, such as cyclobutanes and cyclopropanes.\textsuperscript{[36]} Our group reported the gold(I)-catalyzed regioselective formation of cyclobutenes 64 from terminal alkynes 60 with alkene 61 (Scheme 15).\textsuperscript{[30a]} The reaction proceeds satisfactorily using cationic gold(I) complexes 62 with sterically hindered tBuXPhos 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.\textsuperscript{[31,32]} 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,\textsuperscript{[32]} transition metals,\textsuperscript{[33]} and photochemical processes.\textsuperscript{[34]} 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.\textsuperscript{[35]} However, cyclobutenes were obtained with low enantiomeric ratios (65:35 er).\textsuperscript{[36]}

In this context, our research group discovered that non-C$_2$ chiral Josiphas digold(I) precatalysts were optimal for the enantioselective intermolecular [2 + 2] cycloaddition of alkynes with alkenes (Scheme 16).\textsuperscript{[30c]} Enantioenriched cyclobutenes of type 64 were generally obtained in moderate to good enantiomeric ratios (65:35 er).

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The origin of the enantioselectivity is attributed to a combina-

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 (T$_{S_R}$ and T$_{S_S}$). Application to the enantioselective total synthesis of rumphellane A.
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.65

Binuclear Josiphos digold(I) complex 67 (Scheme 16) was found to be also effective for the enantioselective intermolecular thiophilalation of propiolates with allyl sulfides (Scheme 17).66 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.

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, previously developed by the same laboratory.69 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.70 With the goal of stabilizing these intermediates, the group of Zhang introduced a bidentate P,N-ligand which forms a tricoordinated gold(I) complex L25AuCl, 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).71 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. 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).72 A wide variety of enantioenriched substituted bicyclic furans 78 were obtained by the highly diastereoselective tandem heterocyclization/cycloaddition of readily available substrates 79 and 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-alkyny)-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] oxazines product 82a–b could be obtained in high enantioselectivities using either diastereomer of the chiral ligand. The proposed enantiomultiplication 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.

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

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

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). DFT calculations suggest that the high regio- and enantioselectivities originate from attractive non-covalent σ-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). The BINOL moiety underwent an interesting axial-to-central chirality transfer 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 carboxalkylation 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 99 were obtained which catalyzed the interconversion of compound 99 to analogous indanone products 101 with good to excellent yields and enantioselectivities.

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.

Acknowledgements

We acknowledge the European Research Council (Advanced Grant No. 835080), Ministerio de Ciencia e Innovación (PID2019-104815GB-I00), Severo Ochoa Excellence Accreditation2020-2023 (CEX2019-000925-S), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support.

Conflict of Interest

The authors declare no conflict of interest.

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