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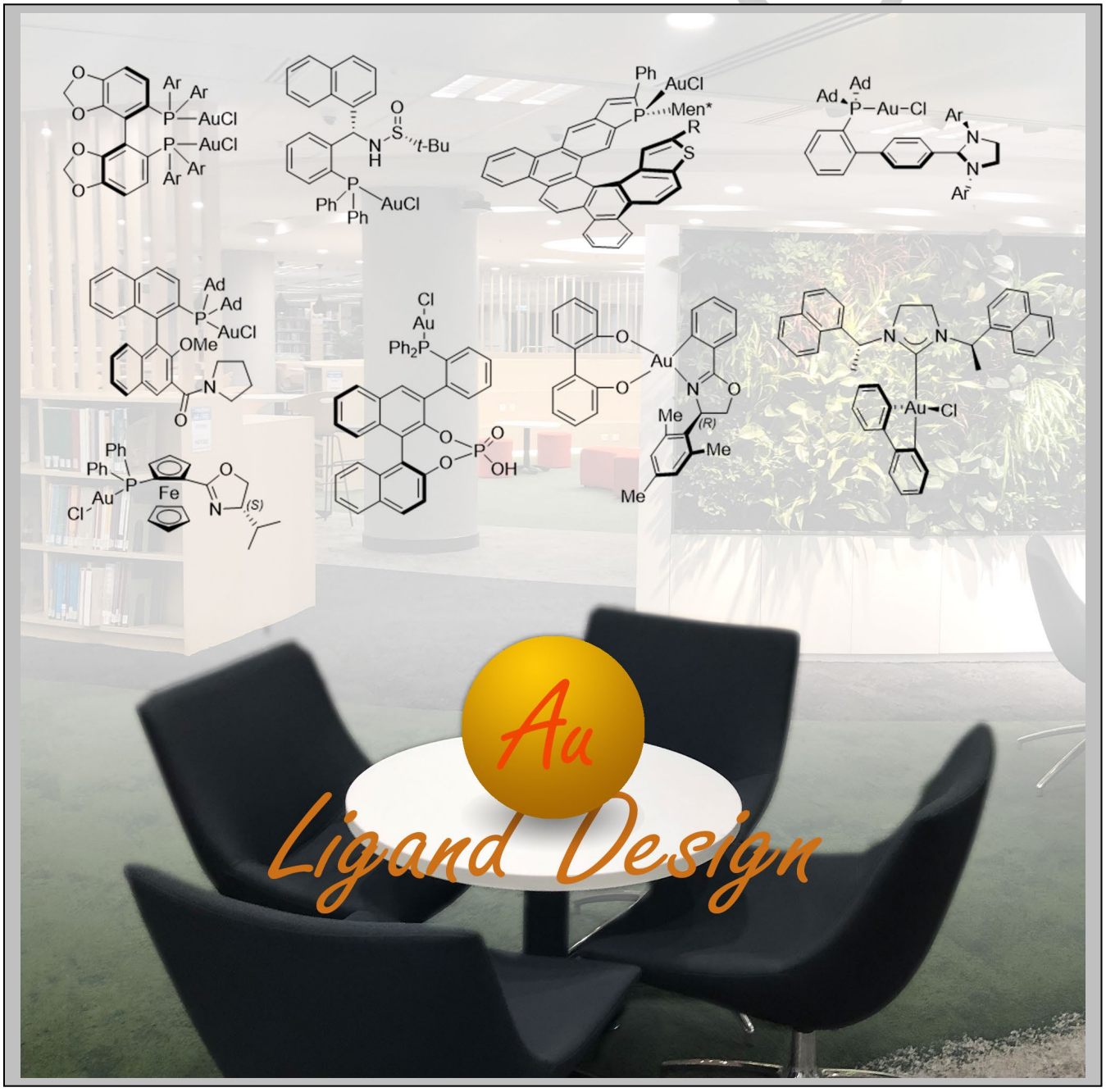
# Recent Advances in the Development of Chiral Gold Complexes for Catalytic Asymmetric Catalysis

Jia-Jun Jiang[a] and Man-Kin Wong*[a]



[a] Mr. J.-J. Jiang, Dr. M.-K. Wong
State Key Laboratory of Chemical Biology and Drug Discovery
Department of Applied Biology and Chemical Technology
The Hong Kong Polytechnic University
Hung Hom, Hong Kong
E-mail: mankin.wong@polyu.edu.hk

**Abstract:** Asymmetric gold catalysis has been rapidly developed in the past ten years. Breakthroughs had been made by rational design and meticulous selection of chiral ligands. This review summarizes newly developed gold-catalyzed enantioselective organic transformations and recent progress in ligand design (since 2016), organized according to different types of chiral ligands, including bisphosphine ligands, monophosphine ligands, phosphite-derived ligands, and N-heterocyclic carbene ligands for asymmetric gold(I) catalysis as well as heterocyclic carbene ligands and oxazoline ligands for asymmetric gold(III) catalysis.

## 1. Introduction

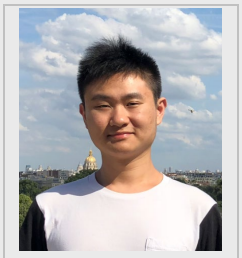
Homogenous gold catalysis has been underdeveloped for a long period of time until a "gold rush" since the beginning of the 21st century. The past decade has witnessed significant progress in the development of homogeneous gold catalysis.[1] However, in the early period of the "gold rush", homogeneous gold catalysis largely relies on the use of simple gold salts, and the development of asymmetric gold catalysis remains slow. In the past few years, a series of novel strategies have been developed for asymmetric gold-catalyzed reactions. One of the strategies is chirality transfer from substrates to products in gold-catalyzed reactions, which enables obtaining enantioenriched compounds utilizing memory of chirality in organic synthesis.[2] Another important strategy is adopting gold catalysts with chiral ligands, obtaining chiral compounds by chiral resolution or constructing new chiral centers from achiral substrates.[1r, 1v, 1x-z, 3] Merging organocatalysis and gold catalysis, using chiral auxiliaries including Brønsted acids (e.g., chiral phosphoric acids), primary/secondary amines, and hydrogen-bonding reagents (e.g., sulfonamides), is also a promising strategy.[1u, 4]

Gold(I) and gold(III), the two common oxidation states of cationic gold species, are widely used in homogenous gold catalysis. They both serve as carbophilic Lewis acids towards C-C multiple bonds and present similar reactivity in many reactions. To date, most of the enantioselective reactions are achieved by gold(I) catalysts. For the strategy adopting chiral gold(I) catalysts, the challenge in chiral ligand design mainly comes from their linear two-coordinated geometry. As a Lewis acid used to activate C-C multiple bonds, one of the coordination sites of gold(I) is required for π-coordination of a substrate, with another site for ligand binding. The distance between the ligand and substrate causes extra difficulty in ligand design. Nonetheless, in the recent years, a variety of chiral phosphine ligands and N-heterocyclic carbene ligands have been developed for gold(I) catalysts, enabling efficient chiral induction.

Asymmetric catalysis using gold(III) remains largely unexplored due to the easy reduction of gold(III) to gold(I) or gold(0) species. Most of the electron-rich tertiary phosphine and amine ligands are not suitable for gold(III) ion because of the possible reduction. Electron-deficient nitrogen-containing ligands such as pyridines, Schiff bases, N-heterocyclic carbenes and triazole derivatives, were adopted for stable gold(III) complexes.[1w-y] On the other hand, too stable gold(III) complexes tend to exhibit poor catalytic activity. An appropriate balance between stability and activity is the main challenge for the development of efficient chiral gold(III) catalysts. Despite the required meticulous choice of ligands for gold(III) catalysts, the gold center has four coordination sites with square-planar geometry, enabling easy construction of chiral environment for chiral induction. Although recent pioneering works have indicated the great potential of gold(III) catalysts, the examples of asymmetric gold(III) catalysis are still very rare.

In this mini-review, enantioselective gold catalysis that has been achieved using different chiral gold complexes in the past four years (since 2016) have been summarized. The reviewed works are organized according to the ligand designs, in the order of bisphosphine ligands, monophosphine ligands, and phosphite-derived ligands, and N-heterocyclic carbene ligands for asymmetric gold(I) catalysis, and N-heterocyclic carbene ligands and oxazoline ligands for asymmetric gold(III) catalysis.

Jia-Jun Jiang received his B.Sc. degree from The Hong Kong Polytechnic University in 2016. Afterwards, he joined the research group of Dr. Man-kin Wong for his doctoral studies. His research interest includes development of gold(III) complexes and their applications.

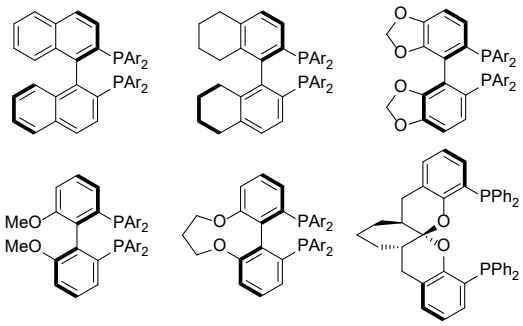


Man-kin Wong obtained his B.Sc. degree from The University of Hong Kong in 1993. He obtained his PhD degree in 1997 and finished his postdoctoral training in 1999 under the supervision of Prof. Dan Yang. He joined the research group of Prof. Chi-Ming Che as Research Assistant Professor in 1999. In 2008, he moved to The Hong Kong Polytechnic University, where he is currently an Associate Professor in the Department of Applied Biology and Chemical Technology. His research interests are catalysis and bioconjugation.

## 2. Recent Development of Enantioselective Gold(I) Catalysis

### 2.1. Catalysis by Chiral Bis(phosphine)Digold(I) Complexes

Enantioselective gold(I) catalysis largely relies on the use of chiral phosphine ligands, in which chiral bisphosphines are the most widely adopted (Scheme 1). For chiral bis(phosphine)digold(I) catalysts, the second phosphine gold center is essential for chiral induction at the long intermediate-ligand distance brought by gold(I) linear geometry. The recent advances in the reactions induced by chiral bisphosphine ligands are shown herein.

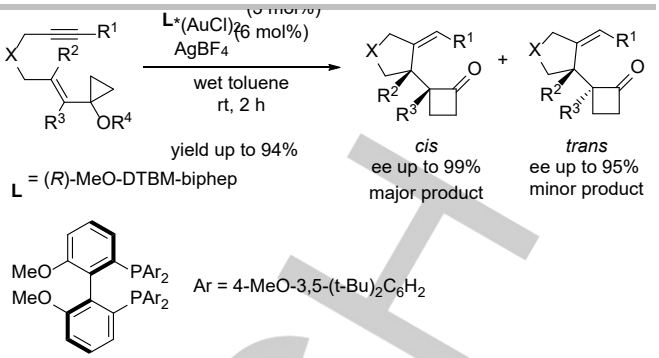


**Scheme 1.** Common Structures of Chiral Bisphosphine Ligands for Asymmetric Gold(I) Catalysis.

Chiral bis(phosphine)digold(I) complexes are frequently used in diverse gold-catalyzed asymmetric organic transformations. Asymmetric reactions including cycloisomerization of alkynes and allenes, along with asymmetric coupling reactions catalyzed by chiral bis(phosphine)digold(I) complexes have been recently demonstrated.

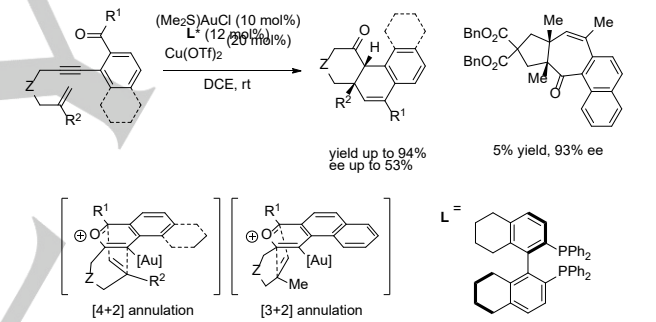
### 2.1.1 Asymmetric Transformations of Alkynes Catalyzed by Bis(phosphine) Digold(I) Catalysts

Enynes, as one of the most versatile substrates in asymmetric gold catalysis, could undergo various cycloisomerizations that rapidly build up molecular complexity and chiral centers. Among these enyne substrates, the enynes featuring cyclopropane units have been successfully developed for gold-catalyzed ring expansion-based rearrangements.[5] However, for these gold-catalyzed ring expansion-based rearrangements, the enantioselective versions are still rare.[5b, 5g, 6] In 2017, Voituriez's group[7] reported an enantioselective reaction involving 1,6-enynes with cyclopropyl esters as substrates (Scheme 2). By using (*R*)-MeO-DTBM-Biphep$(AuCl)_2$ as catalysts, products with cyclobutanone structure were obtained, which were different from using JohnPhos as the ligand that was previously reported by Echavarren's group. Interestingly, the use of wet solvent is important to ensure good yield (up to 94%) and excellent enantioselectivity (up to 99% ee) for this reaction.



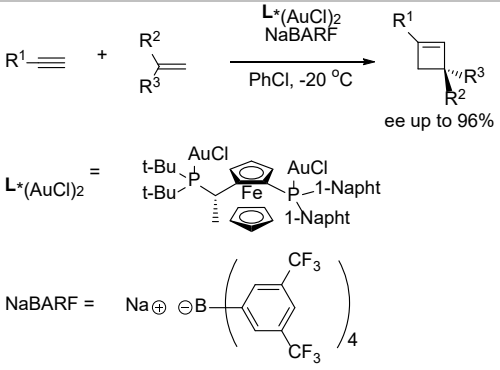

**Scheme 2.** Enantioselective Cycloisomerization/Ring Expansion Transformation.

In 2019, Tanaka and co-workers[8] reported enantioselective [4+2] annulation of enyne-carbonyl substrates. In this work, Tanaka and co-workers adopted a 2-substituted terminal alkene moieties to afford stable non-aromatizable tricyclic compounds with two stereogenic centers. By adopting chiral (*R*)-$H_8$-Binap$(AuCl)_2$ catalyst, moderate enantioselectivity (up to 53% ee) was resulted. In the meantime, a small amount of [3+2] annulation product was also observed with excellent enantioselectivity (93% ee) for one of the substrates.



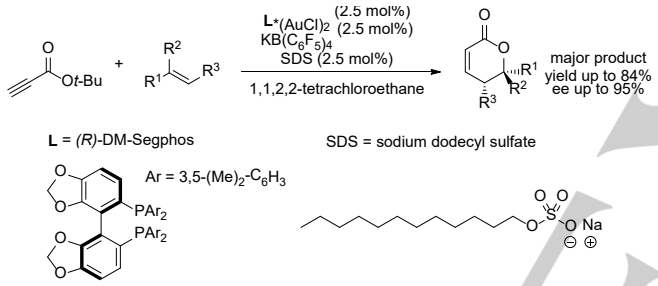

**Scheme 3.** Enantioselective [4+2] Annulation of Benzene-linked Ene-yne-carbonyls.

For a long period of time, asymmetric gold(I) catalysis based on alkyne catalysis was limited in intramolecular 1,n-enyne cycloisomerizations until a recent breakthrough demonstrated by Echavarren and co-workers[9] with intermolecular [2+2] annulation of arylacetylenes and alkenes (Scheme 4). In this work, the authors screened a series of chiral gold catalysts and found that the Josiphos ligand family achieved high enantioselectivity (ee up to 96%) and yield (up to 9 2%).



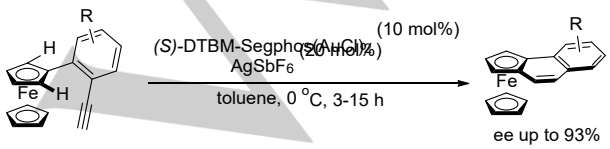

**Scheme 4.** Josiphos Digold(I)-catalyzed Intermolecular Enantioselective [2+2] Cycloaddition.

In 2018, Shin and co-workers[10] reported another intramolecular example of annulation between alkynes and alkenes. Adopting (*R*)-DM-Segphos(AuCl)$_2$ as the catalyst, they demonstrated intermolecular [4+2] annulation of propiolates and alkenes affording dihydropyranones as the major product (Scheme 5). Interestingly, the addition of a catalytic amount of SDS significantly increased the chemoselectivity of this reaction.



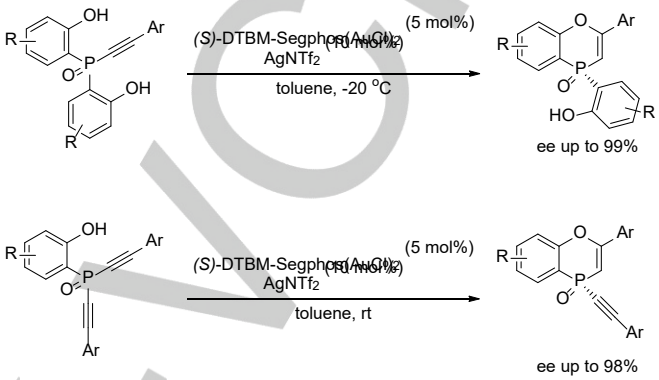

**Scheme 5.** Enantioselective Aryl–aryl Coupling Facilitated by Chiral Binuclear Gold Complexes.

Except for the bis(phosphine)digold(I)-catalyzed enantioselective cycloisomerization of alkynes, asymmetric hydrofunctionalizations of alkynes have also been advanced in recent years. In 2016, Carreno and co-workers[11] demonstrated enantioselective hydroarylation of alkynes with ferrocenes structure to afford planar-chiral products (Scheme 6). Although asymmetric ferrocene C-H activations were previously achieved by chiral Cu, Pd and Rh catalysts, Carreno and co-workers firstly adopted chiral gold catalysts for the intramolecular reaction of ferrocene C-H with tethered alkyne. (*S*)-DTBM-Segphos(AuCl)$_2$ was adopted to catalyze the hydroarylation of alkyne with a ferrocene unit to form C-C bond, affording the products with planar-chiral in good enantioselectivity (up to 93% ee)




**Scheme 6.** Gold-catalyzed C-H Cycloisomerization of Alkynes Constructing Planar-chiral Ferrocenes.

In the hydrofunctionalizations of alkynes, the formation of Csp$^2$-O and Csp$^2$-N bond cannot directly provide stereocenters. Therefore, adopting prochiral substrates is one of the strategies to develop enantioselective reactions. In 2018, Zi and co-workers[12] managed to use phosphorus atom as the stereocenters of newly developed prochiral structures. Adopting (*S*)-DTBM-Segphos(AuCl)$_2$ as the catalyst, excellent yield (up to 97%) and enantioselectivity (up to 99% ee) can be achieved for the desymmetrization of prochiral bisphenols and prochiral dialkynes with P‑stereogenic centers (Scheme 7).

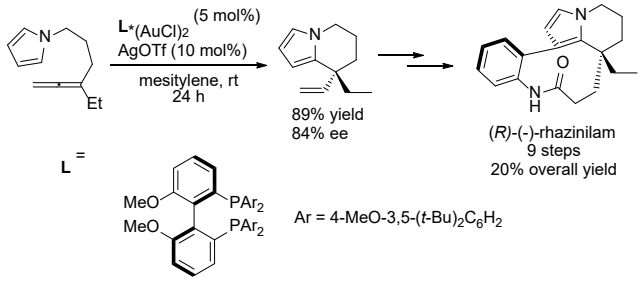



**Scheme 7.** Construction of P-chiral Molecules by Gold-Catalyzed Desymmetrization of Prochiral Phenols with P‑Stereogenic Centers.

### 2.1.2 Asymmetric Catalysis of Allenes Catalyzed by Bis(phosphine) Digold(I) Catalysts

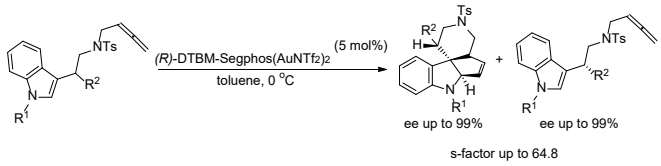
The enantioselective reactions based on allene activation by gold(I) mainly include hydrofunctionalizations forming C-O, C-N and C-C bonds, and cycloisomerizations enabling rapid assembling of molecular complexity. The newly developed enantioselective transformations of allenes catalyzed by bis(phosphine)digold(I) catalysts are presented as follows.

In 2017, Voituriez's group[13] demonstrated the enantioselective cycloisomerization of allene-functionalized pyrrole, as a key step of their newly developed strategy for the total synthesis of (*R*)-(-)-rhazinilam (Scheme 8). Using (*R*)-MeO-DTBM-Biphep(AuCl)$_2$ as the catalyst, the cycloisomerization of pyrrole-allene afforded 2-oxocyclobutylcyclopentane with good yield (89%) and enantioselectivity (84% ee). Adopting this newly developed enantioselective cycloisomerization of allene as the first step, the total synthesis of (*R*)-(-)-rhazinilam can be accomplished in 9 steps with 20% overall yield.




**Scheme 8.** Gold(I)-Catalyzed Cycloisomerization of Allene-Functionalizedpyrrole for the Total Synthesis of (-)-Rhazinilam.

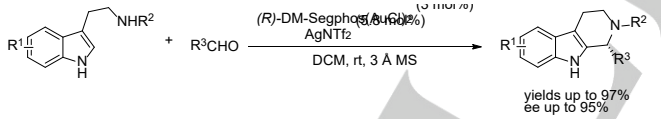
In 2019, Shi and co-workers[14] reported kinetic resolution of indole-allene substrates resulting in chiral polycyclic indoline skeletons (Scheme 9). Employing (R)-DTBM-Segphos(AuNTf$_2$)$_2$ as the catalyst, the racemic indole-allene substrates were resolved by [3+2] cycloaddition reaction of allene affording polycyclic indoline products (ee up to 99%) in high selectivity (s-factor up to 64.8). In most cases of gold-catalyzed asymmetric intramolecular cycloisomerizations or cycloadditions, the allenes were used as 2C synthons for [2+n] reaction. In this example, the allene moieties act as 3C synthons, which is relatively more challenging and less reported.




**Scheme 9.** Gold-catalyzed C-H Cycloisomerization of Alkynes Constructing Planar-chiral Ferrocenes.

### 2.1.3 Enantioselective Gold-catalyzed Pictet-Spengler Reaction Catalyzed by Bis(phosphine) Digold(I) Catalysts

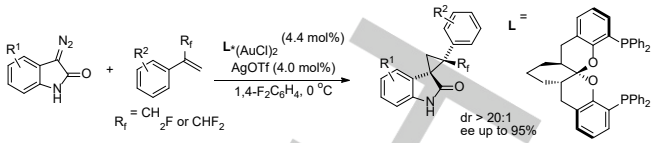
Recently, in 2019, Guinchard and co-workers[15] disclosed an enantioselective gold-catalyzed Pictet-Spengler reaction (Scheme 10). The Pictet-Spengler reaction is an acid-catalyzed condensation between β-arylethylamines and aldehydes affording tetrahydroisoquinolines or tetrahydro-β-carbolines, through iminium intermediates. As the enantioselective Pictet-Spengler reactions were previously achieved by enzymes and Brønsted acid organocatalysis, this work demonstrated the first enantioselective example adopting organometallic catalysis. Using (*R*)-DM-Segphos(AuCl)$_2$ as the catalyst, the resulting tetrahydro-β-carbolines were obtained with high yield (up to 97%) and high enantioselectivity (up to 95%).




**Scheme 10.** Enantioselective Gold-catalyzed Pictet−Spengler Reaction.

### 2.1.4 Enantioselective reactions of diazo compounds catalyzed by Bis(phosphine) Digold(I) Catalysts

While transition metals such as Fe, Cu and Rh have been intensively studied in the application of metal carbenoid intermediates generated from diazo compounds[16], the gold(I) carbenoid chemistry of diazo compounds remains to be developed, especially for the gold-catalyzed enantioselective transformations of diazo compounds. In 2018, Zhou and Ma[17] demonstrated an enantioselective olefin cyclopropanation forming all-carbon quaternary stereocenters with a $CH_2F$ group (Scheme 11). Before this work, the enantioselective synthesis of cyclopropane bearing a $CH_2F$ group at the chiral center, which can be found in biologically active molecules, remains unexplored. Interestingly, Ma and Zhou observed a significant acceleration of reaction when PhF was employed as a solvent in place of PhCl, which was proposed due to the possible C–F···H–N interactions between substrate and solvent.

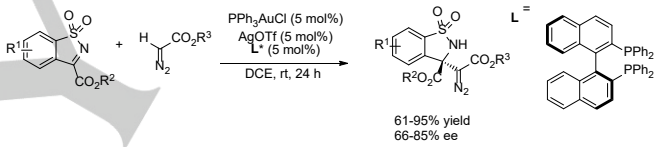



**Scheme 11.** Gold-catalyzed Enantioselective Cyclopropanation.

### 2.1.5 Bis(phosphine) Digold(I) Catalysts as σ-Lewis acids

In most of the gold-catalyzed enantioselective reactions, gold catalysts serve as π-Lewis acids. Relatively few examples demonstrated the use of gold catalysts as σ-Lewis acids in asymmetric catalysis.

In 2018, He and Wang[18] demonstrated a gold-catalyzed asymmetric Mannich reaction of α-diazocarbonyl compounds and N-sulfonyl cyclic ketimines (Scheme 12). In this work, the gold catalysts served as σ-Lewis acids instead of forming gold carbenoid intermediates in the presence of the diazo compounds. The preservation of the diazo group enables further synthetic elaboration to construct molecular complexity.

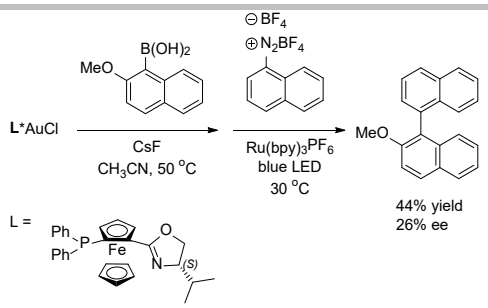



**Scheme 12.** Asymmetric Mannich Reaction of α-Diazocarbonyl Compounds and N-Sulfonyl Cyclic Ketimines Catalyzed by Bis(phosphine) Digold(I) Catalysts as σ-Lewis Acids.

### 2.1.6 Bis(phosphine) Digold(I)-Catalyzed Enantioselective Coupling Reactions

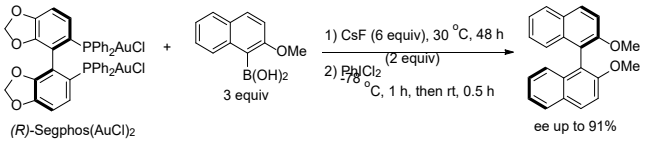
As Pd-based catalysts are widely used in metal-catalyzed cross-coupling reactions, gold catalyzed coupling reactions are much less developed. The high potential barrier between gold(I) and gold(III) makes the oxidative addition/reductive elimination cycle highly challenging. In recent years, advances have been made in redox gold(I)/gold(III) catalysis.[19] Under oxidative[20] (e.g. the use of hypervalent iodine reagents) or photoredox conditions[19a, 19h] (photocatalyzed oxidative addition to gold(I) species), the barrier between gold(I) and gold(III) can be crossed, enabling gold(I)/gold(III) catalyzed cross-coupling reactions. Oxidant free strategies such as ligand-enabled gold(I)/gold(III) catalysis have also been demonstrated.[19b, 21] However, asymmetric versions are still rare.

In 2018, Hermange and Fouquet[22] reported an example of gold-catalyzed photo-induced enantioselective cross-coupling between aryldiazonium salts and arylboronic acids (Scheme 13). In this work, the non-enantioselective cross-coupling reaction only requires a catalytic amount of achiral gold catalyst to afford moderate yield, while a stoichiometric amount of chiral gold catalyst is needed to achieve moderate yield (44%) and enantioselectivity (26% ee).




**Scheme 13.** Enantioselective Aryl–aryl Coupling Facilitated by Chiral Binuclear Gold Complexes.

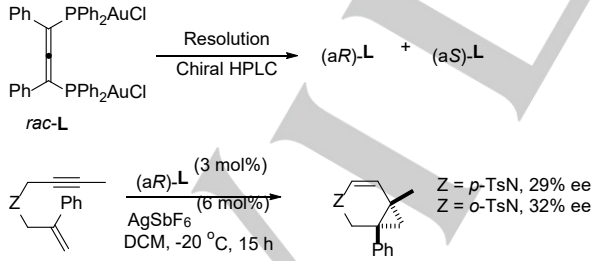
In 2019, Kramer and co-workers[23] firstly demonstrated a highly enantioselective aryl-aryl coupling facilitated by (*R*)-Segphos(AuCl)$_2$ (ee up to 91%), despite a stoichiometric amount of chiral gold catalyst was still required (Scheme 14).




**Scheme 14.** Enantioselective Aryl–aryl Coupling Facilitated by Chiral Binuclear Gold Complexes.

### 2.1.7 Bis-Phosphine Ligand Design Based on Allene

In 2016, Mouries-Mansuy and Fensterbank[24] developed a new type of bis-phosphine allene ligands, which are capable of coordinating to transition metals including Pd, Pt and Au. The racemic bis-phosphine allene digold(I) complex was stable enough to be resolved to the enantiomers by chiral HPLC. Employing the axial chirality of the bis-phosphine allene ligand, the gold-catalyzed enantioselective cycloisomerization affording azabicyclo[4.1.0]heptenes can be achieved with moderate ee (32%) (Scheme 15).



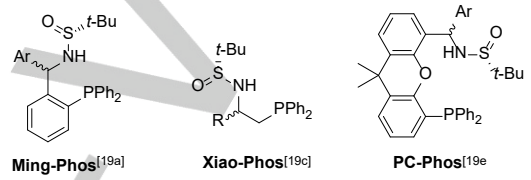

**Scheme 15.** Asymmetric Cycloisomerisation of 1,6-enynes Catalyzed by Bisphosphine Allene Digold(I) Complex.

## 2.2. Recent Development of Chiral Monophosphine Gold(I) Catalysts

Although atropisomeric biaryl bisphosphine ligands are one of the most successful ligand types in asymmetric gold(I) catalysis, they are expensive and difficult to modify. Therefore, new ligand types have also been developed for enantioselective gold(I) catalysis in recent years. Some of the novel monophosphine gold(I) catalysts are described herein.

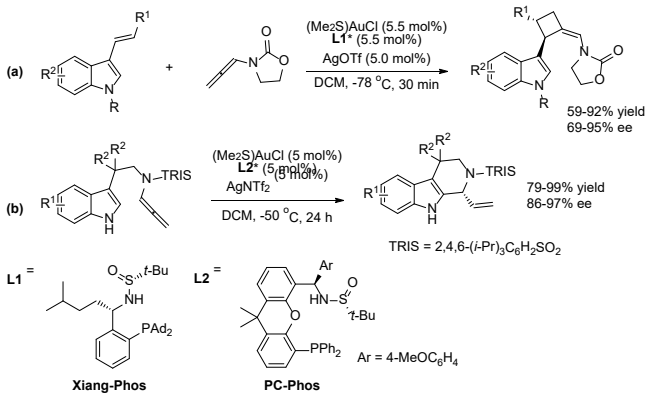
### 2.2.1 Chiral Sulfinamide Monophosphine Ligands for Enantioselective Gold(I) Catalysis

In recent years, Zhang et al designed a series of chiral sulfinamide monophosphine ligands, Ming-Phos family (Scheme 16).[25] The essential role of the second gold center in bis(phosphine)digold(I) catalysts has been frequently indicated, possibly due to a steric hindrance or second interaction with substrates. Aiming to simulate this interaction to control the enantioselectivity in catalysis, Zhang's group designed the monophosphine ligands with sulfinamide moiety, which can be modularly synthesized. The sulfinamide monophosphine ligands were proved to be efficient for various gold-catalyzed enantioselective reactions.[25]




**Scheme 16.** Chiral Sulfinamide Monophosphine Ligands.

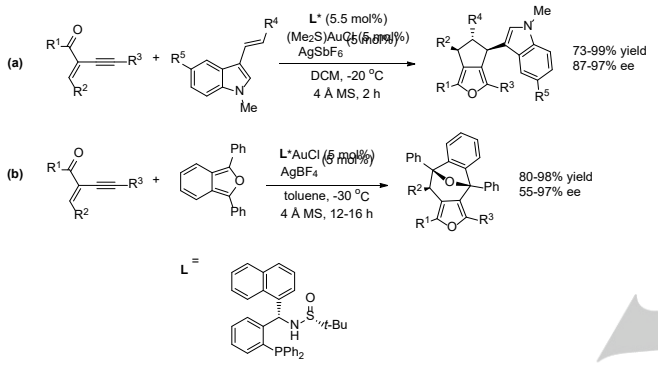
In 2016, Liu and Zhang[25d] reported an enantioselective intermolecular [2+2]-cycloaddition between 3-styrylindoles and N-allenamides affording a chiral cyclobutene scaffold (Scheme 17a). The authors adopted a new variant of Ming-Phos bearing two bulky adamantyl groups on phosphorus atom (named as Xiang-Phos). The application of the Xiang-Phos provided a good yield (up to 92%) and enantioselectivity (up to 95% ee) in the enantioselective intermolecular [2+2]-cycloaddition. In 2017, the Zhang et al[25e] demonstrated the gold-catalyzed enantioselective intramolecular cyclization of N-allenamides induced by another chiral sulfinamide monophosphine ligands (PC-Phos), featuring the first example of highly enantioselective intramolecular cyclization of N-allenamides (Scheme 17b).




**Scheme 17.** Intermolecular and Intramolecular Cycloaddition of N-allenamides Catalyzed by Sulfinamide Monophosphine Gold(I) Catalysts.

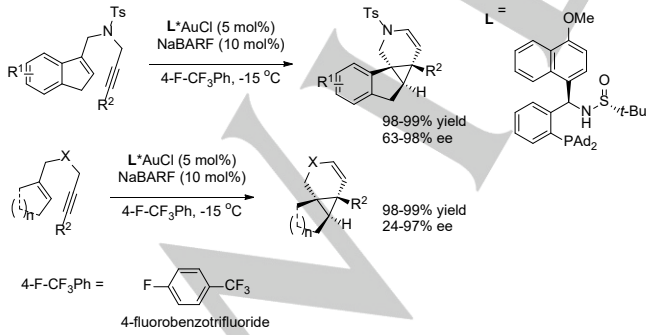
In 2018, He and Zhang[25f] reported the application of Ming-Phos on enantioselective heterocyclization/cycloaddition of 2-(1-

alkynyl)-2-alken-1-ones with 3-stylindoles (Scheme 18a). Although 2-(1-alkynyl)-2-alken-1-ones have been intensively studied as the substrates for the synthesis of 3,4-fused bicyclic furans whose scaffold is common in natural products and pharmaceuticals, the asymmetric version is still challenging to achieve. Adopting Ming-Phos/gold(I) as catalyst, the annulation afforded cyclopenta[c]furans in good yield (up to 99%) with high diastereoselectivities (>20:1) and enantioselectivities (up to 97% ee). In 2019, Li and Zhang[25h] reported another work featuring gold-catalyzed tandem heterocyclization/cycloaddition of 2-(1-alkynyl)-2-alken-1-ones and 1,3-diphenylisobenzofuran with highly exo- and enantioselectivity that catalyzed by Ming-Phos/gold(I) catalyst (Scheme 18b). In this work, the heterocyclization/[4+3]cycloaddition reaction afforded fused furan with seven-membered oxa-bridged rings in good yield (80-98%) with high exo-selectivity (exo/endo up to 50:1) and up to 97% ee.



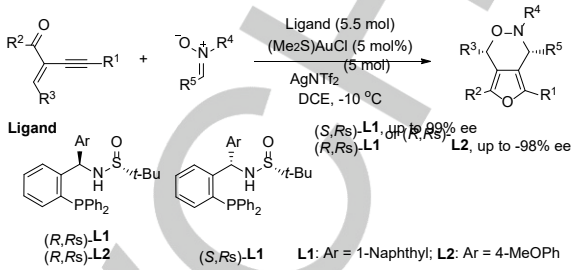

**Scheme 18.** Enantioselective Tandem Heterocyclization/cycloaddition of 2-(1-Alkynyl)-2-alken-1-ones.

In 2018, Zhang's group[25g] demonstrated the first intramolecular enantioselective cyclopropanation of indenes and trisubstituted alkenes catalyzed by Xiang-Phos/gold(I) catalyst (Scheme 19). The [5−3−6] fused-ring compounds with two vicinal all-carbon quaternary stereogenic centers, whose scaffold is common among pharmacological products and bioactive compounds, were afforded in high yield (>97%) with excellent enantioselectivity (up to 98% ee).




**Scheme 19.** Intramolecular Enantioselective Cyclopropanation of Indenes and Trisubstituted Alkenes.

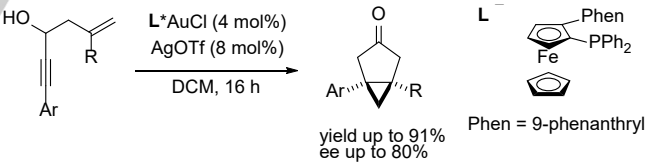
In 2020, Zhang and Zhang[26] applied Ming-Phos in asymmetric [3+3] cycloaddition of 2-(1-alkynyl)-2-alken-1-ones with nitrones. (Scheme 20) Using a pair of diastereoisomeric Ming-Phos, the enantiodivergent synthesis of chiral furo[3,4-d]-[1,2]oxazines can be achieved with high enantioselectivity (up to 99% ee and -98% ee respectively). Notably, high enantioselectivity could be obtained for the aliphatic alkyne moiety of 2-(1-alkynyl)-2-alken-1-ones ($R^3$), which was reported affording low ee in previous study using axially chiral bisphosphine ligands.[27]




**Scheme 20.** Asymmetric [3+3] Cycloaddition of 2-(1-Alkynyl)-2-alken-1-ones with Nitrones Catalyzed by Ming-Phos Gold(I) Catalysts.

### 2.2.2 Cycloisomerization of 3-Hydroxylated 1,5-Enynes Catalyzed by Aryl-monophosphino Ferrocene gold(I) Catalysts

In 2016, Voituriez and Marinetti[28] demonstrated asymmetric cycloisomerization of 3-hydroxylated 1,5-enynes catalyzed by planar chiral ferrocenylphosphine-gold(I) complexes. As aryl-monophosphino ferrocenes (MOPF) were previously adopted for Pd-MOPF and Cu-MOPF catalysts[29], the use of Au-MOPF complexes for asymmetric catalysis remains rare.[30] Using the Au-MOPF complexes as catalysts, the authors demonstrated the first gold-catalyzed enantioselective cycloisomerization of 3-hydroxylated 1,5-enynes affording cyclopropane fused cyclopentanone scaffold in good yield (up to 91%) with moderate to good enantioselectivity (up to 80% ee) (Scheme 21).

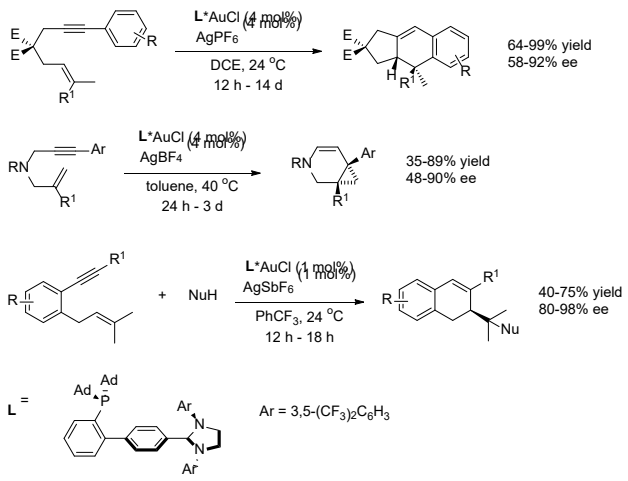



**Scheme 21.** Asymmetric Cycloisomerization of 3-Hydroxylated 1,5-Enynes Planar Chiral Ferrocenylphosphine-Gold(I) Complexes.

### 2.2.3 JohnPhos-type Ligands Bearing Remote C2-Chiral Element

In 2019, Echavarren and co-workers[31] disclosed a new ligand design of a remote $C_2$-chiral element (Scheme 22). In the new design, a $C_2$-2,5-diarylpyrrolidine moiety was introduced to the biphenyl scaffold of the JohnPhos ligand, constructing a chiral envelope-type cavity around the gold center. To demonstrate the stereocontrol ability of the newly ligand design, the annulation of several types of 1,6-enyne substrates catalyzed by the newly developed gold(I) catalyst was studied. The products were afforded in good yield (up to 99%) with high enantioselectivity (up to 98%). Interestingly, starting from the substrates with and without benzene moieties, opposite enantioselectivities have

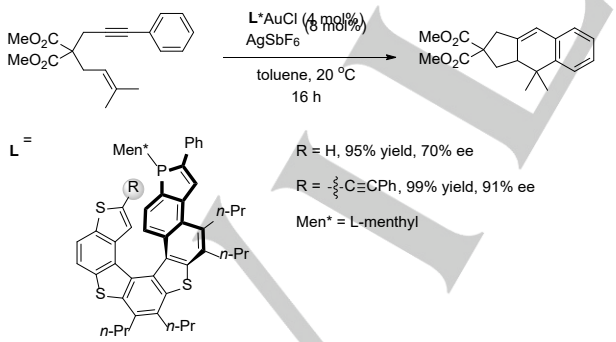
been achieved, indicating the existence of aryl-aryl interactions between ligand and substrates with a benzene ring.




**Scheme 22.** Enantioselective Folding of Enynes by Johnphos Gold(I) Complexes with Distal $C_2$-2,5-Diarylpyrrolidine.

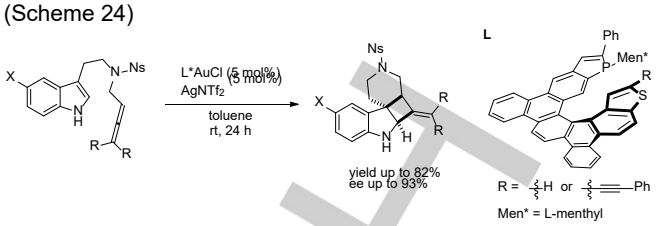
### 2.2.4 Chiral Helicene Monophosphine Ligand for Enantioselective Gold Catalysis

In recent years, helical chiral scaffolds have been successfully used as chiral ligands and organocatalysts in enantioselective catalysis, while the application of helical ligands in asymmetric gold catalysis remains relatively unexplored.[32] In 2014, Voituriez and Marinetti[33] firstly adopted phosphahelicenes as the chiral ligand of gold catalysts to achieve enantioselective cycloisomerization of enynes. In 2016, Voituriez and Marinetti[34] contributed another work featuring enantioselective [4+2] cycloaddition of hept-6-en-1-ynylbenzene derivatives. Employing modified phosphathiahelicenes as chiral ligands, the enantioselective cycloaddition afforded polycyclic dihydro-cyclopenta[b]naphthalene derivatives in excellent yield (up to 99%) with high enantioselectivity (up to 91% ee) (Scheme 23).




**Scheme 23.** Enantioselective [4+2] Cycloaddition of Hept-6-en-1-ynylbenzene Derivative Catalyzed by Substituted Phosphathiahelicenes Gold(I) Complexes.

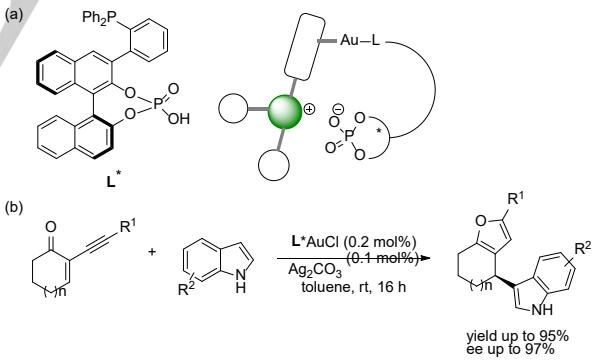
In 2020, Guinchard and Voituriez[35] improved a synthetic approach of phosphathiahelicenes, enabling gram scale synthesis and structure fine tuning. The obtained phosphathiahelicenes was successfully used as chiral ligand in enantioselective gold(I)-catalyzed [2 + 2] cycloadditions of N–homoallenyl tryptamines, affording polycyclic indole derivatives with high good enantioselectivity (up to 93% ee). (Scheme 24)




**Scheme 24.** Enantioselective Gold(I)-Catalyzed [2 + 2] Cycloadditions of N-homoallenyl Tryptamines Catalyzed by Phosphathiahelicene Gold(I) Catalyst.

### 2.2.5 Tethered Counterion-Directed Enantioselective Gold Catalysis

In 2020, Marinetti and Guinchard[36] demonstrated a new design tethering phosphine ligands and chiral phosphate counterion. Except for adopting chiral ligands, utilizing chiral counterions is another strategy in enantioselective gold catalysis. However, the drawbacks in stereochemical control of chiral counterion strategies largely come from the flexible steric relationship between the chiral phosphate and the carbocation intermediates during chiral induction. To solve this problem, Marinetti and Guinchard's group tethered the phosphine ligand and the phosphate counterion moiety, aiming to better constrain the chiral counterion and carbocation intermediate moieties (Scheme 25a). The newly designed ligand was able to catalyze enantioselective tandem cycloisomerization/nucleophilic addition reaction of 2-alkynylenones in good yield (up to 95% yield) and enantioselectivity (up to 97% ee) with a low catalyst loading (0.2 mol%) (Scheme 25b).

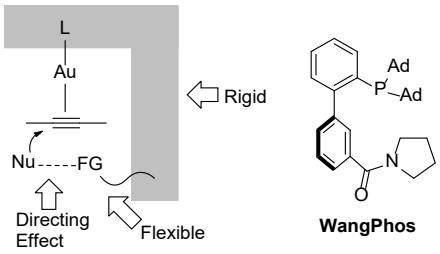



**Scheme 25.** (a) The Design of Tethered Counterion-Directed Catalysis (b) The Enantioselective Tandem Cycloisomerization/nucleophilic Addition Reaction of 2-Alkynylenones.

### 2.2.6 Monophosphine Ligands Harnessing Ligand-Directing Effects

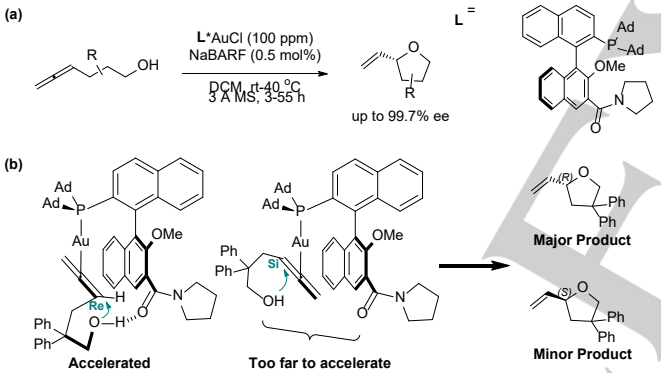
In the commonly used model of gold-catalyzed reactions, the gold(I) center serves as a π-Lewis acid to activate the unsaturated C-C bond (mostly alkyne or allene) toward nucleophilic attack. In 2014, Li and Zhang[37] disclosed the ligand design to direct the nucleophile by inducing an electrostatic interaction between nucleophile and ligand (Scheme 26). The ligand design was based on the JohnPhos structure modified

with an amide moiety (named as WangPhos). The newly developed ligands were proved to significantly accelerate the hydrofunctionalization of alkynes.[37-38]



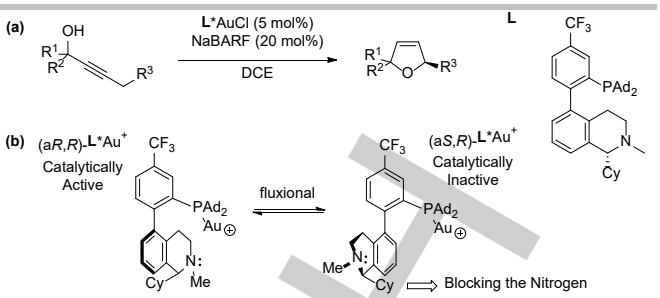

**Scheme 26.** Ligand Design of WangPhos that Directs the Nucleophile Attack to Unsaturated C-C Bonds.

In 2017, Zanoni and Zhang[39] demonstrated the axially chiral design based on WangPhos, which could accelerate and catalyze intramolecular cyclization of 4-allen-1-ols that affords 2-vinyltetrahydrofurans in high yields (up to 99%) and excellent enantioselectivity (up to 99.7% ee) (Scheme 27a). The enantioselectivity was proposed to be achieved by the hydrogen bonding-directed acceleration of the nucleophilic attack pathway that affords the major product, with another pathway leading to the minor product unaccelerated (Scheme 27b).




**Scheme 27.** Ligand Accelerated Enantioselective Cyclization of 4-Allen-1-ols.

In 2019, Zhang and co-workers[40] described the chiral bifunctional phosphine ligand that enabling the gold-catalyzed asymmetric isomerization of alkynes to allenes, followed by the cycloaddition that affords 2,5-dihydrofuran products with high enantioselectivity (up to 97%) (Scheme 28a). Notably, despite the fluxional conversion between the two atropisomers of the catalyst, the enantioselectivity are only affected by the chiral cyclohexanyl group (Cy), because one of the catalyst atropisomers are catalytically inactive due to the blocking effect of the Cy group (Scheme 28b).

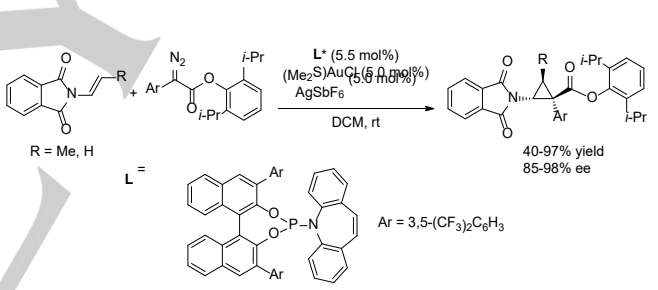



**Scheme 28.** Chiral Bifunctional Phosphine Ligand Catalyzed Asymmetric Isomerization/cycloaddition Affording 2,5-Dihydrofuran.

## 2.3. Enantioselective Gold(I) Catalysis Induced by Phosphite-derived Ligands

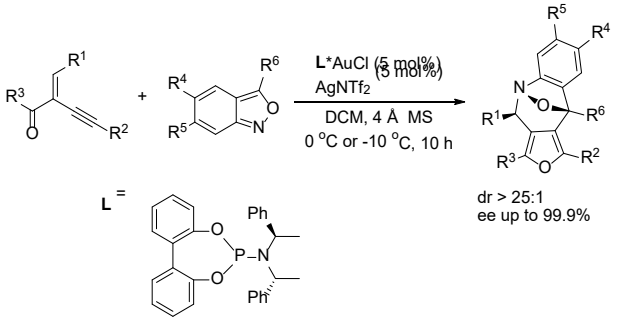
Except for chiral phosphine ligands, phosphite-derived ligands are also the successful chiral ligands that have been widely adopted in the gold-catalyzed organic enantioselective transformations.

Recently, in 2019, employing chiral monodentate phosphoramidite ligands, Li, Wu and Zhang[41] disclosed enantioselective gold-catalyzed cyclopropanation of enamides with α-diazoarylacetate compounds (Scheme 29). The cyclopropane product was resulted in good yield (up to 97%) with high enantioselectivity (up to 98%) and diastereoselectivities.



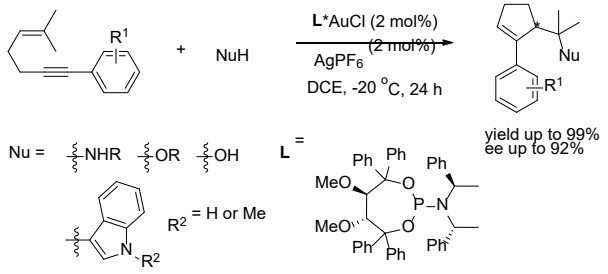

**Scheme 29.** Enantioselective Cyclopropanation of α‑Aryl Diazoacetates with Enamides Catalyzed by Phosphoramidite Gold(I) Catalyst.

In 2020, Cheng and Liu[42] adopted chiral phosphoramidite ligand to obtain high diastereoselectivity (dr > 25:1) and enantioselectivity (up to 99.9% ee) in gold(I)-catalyzed annulation between 2-(1-alkynyl)-2-alken-1-ones and anthranils (Scheme 30). This work is the first use of anthranils in asymmetric gold catalysis.



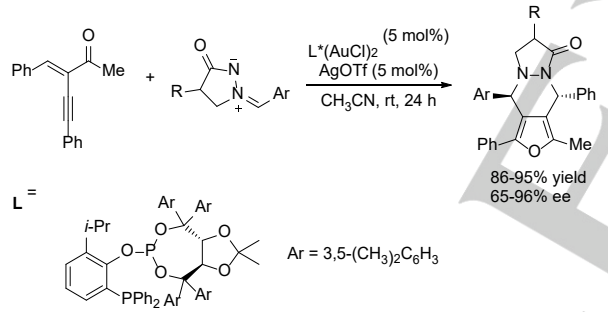

**Scheme 30.** Enantioselective Gold(I)-catalyzed Annulation between 2-(1-Alkynyl)-2-alken-1-ones and Anthranils.

In 2020, Gandon and Voituriez[43] reported enantioselective gold(I)-catalyzed cyclization/intermolecular nucleophilic additions of 1,5-enyne using TADDOL phosphoramidite-AuCl catalysts. (Scheme 31) A broad scope of O-, N-, and C-nucleophiles was achieved, affording moderate to high yields (up to 99%) and good enantioselectivity (up to 92% ee).



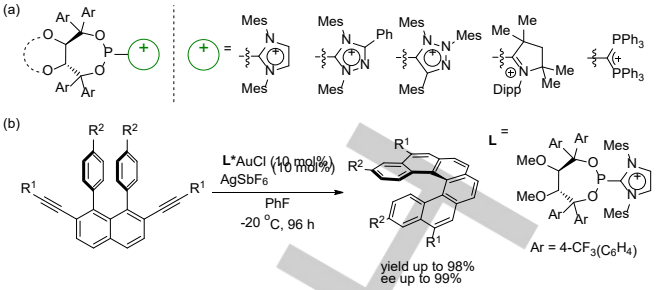

**Scheme 31.** Enantioselective Gold(I)-catalyzed Cyclization/intermolecular Nucleophilic Additions of 1,5-enyne.

In 2018, Schmalz's group[44] employed a phosphine-phosphite ligand in gold-catalyzed enantioselective heterocyclization/cycloaddition between 2-(1-alkynyl)-2-alkene-1-ones and furo[3,4-d]tetrahydropyridazines (Scheme 32). The phosphine-phosphite ligand was previously developed by the same group[45] and was firstly adopted for asymmetric gold catalysis in this work. Using the phosphine-phosphite ligand, the furo[3,4-d]tetrahydropyridazine products were afforded with high yield (up to 94%) and enantioselectivity (up to 96% ee).



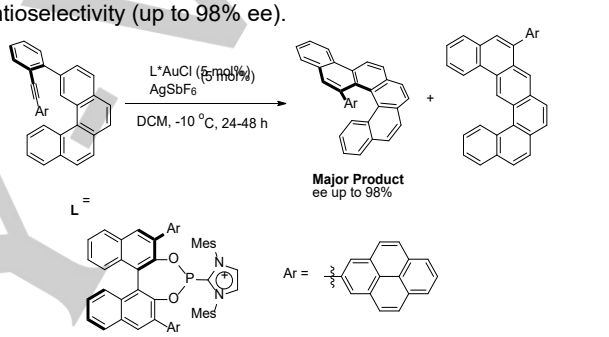

**Scheme 32.** Enantioselectivity Cycloaddition Reaction between 2-(1-Alkynyl)-2-alkene-1-ones and Furo[3,4-d]tetrahydropyridazines Catalyzed by Chiral Phosphine-phosphite Digold(I) Catalyst.

Recently, Alcarazo's group[46] disclosed the ligand design of TADDOL-derived α-cationic phosphonites. By inducing a cationic group onto the phosphorus atom of the phosphine ligands, electron density from the coordinated metals could be depleted, leading to an increase of Lewis acidity and catalytic efficiency.[47] Alcarazo and co-workers adopted this strategy in designing the novel cationic phosphonite ligands. Diverse cationic N-heterocycle groups can be utilized to modify the well-precedented TADDOL-derived structures, enabling the tuning of ligand structure in a modular approach (Scheme 33a). The ligands were applied to the gold-catalyzed intramolecular hydroarylation leading to chiral [6]carbohelicenes in high enantioselectivity (up to 99% ee) and good yield (up to 98% yield) (Scheme 33b), which well demonstrated the transfer of central chirality to helical chirality.



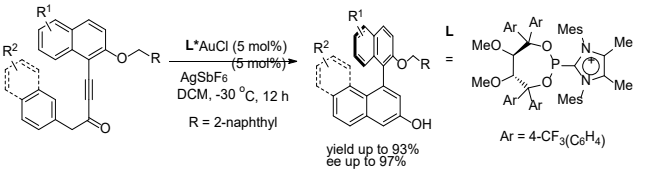

**Scheme 33.** (a) TADDOL-derived α-Cationic Phosphonites (b) TADDOL-derived α-Cationic Phosphonite Gold(I)-Catalyzed Hydroarylation.

In 2020, Alcarazo's group[48] further developed a new type of BINOL-derived cationic phosphonites ligands (Scheme 34). By fine-tuning the size of 3,3'-substitution of BINOL moiety, the intramolecular enantioselective hydroarylation could be optimized to afford helical 1-aryl benzo[5]helicenes in high enantioselectivity (up to 98% ee).




**Scheme 34.** Enantioselective Hydroarylation Affording 1-Aryl Benzo[5]helicenes Catalyzed by BINOL-derived Cationic Phosphonite Gold(I) Catalyst.

In 2020, Alcarazo and co-workers[49] demonstrated atroposelective synthesis of 1,1'-binaphthalene-2,3'-diols catalyzed by TADDOL-derived α-cationic phosphonite gold(I) catalysts. The gold-catalyzed hydroarylation reaction afforded chiral 1,1'-binaphthalene-2,3'-diols in high yield (up to 93% yield) and enantioselectivity (up to 96% ee) (Scheme 35).

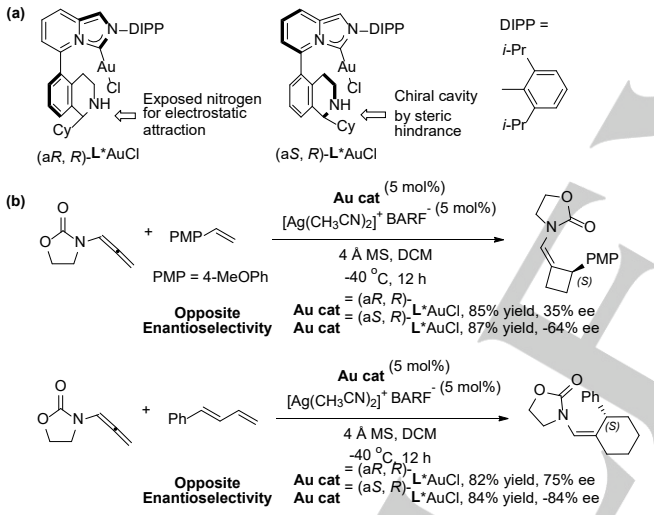



**Scheme 35.** Atroposelective Synthesis of 1,1'-Binaphthalene-2,3'-diols.

### 2.3. Enantioselective Gold(I) Catalysis Induced by N-Heterocyclic Carbene Ligands

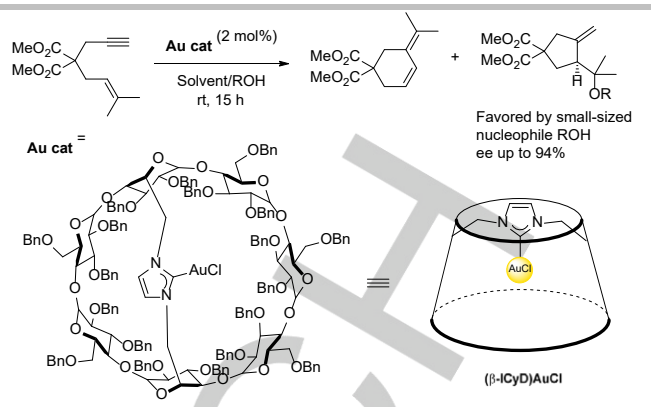
In enantioselective homogenous gold catalysis, N-heterocyclic carbenes have been adopted for gold(I) catalysts[1x, 50] and gold(III) catalysts[51]. Apart from NHC ligands, acyclic diaminocarbenes (ADC) have also proved its high potential in asymmetric gold catalysis.[1v, 1x, 52]

For recent developments, Zhang's group[53] reported the design of chiral bifunctional gold catalysts in 2019 (Scheme 36). In this work, the gold(I) center was coordinated by an N-heterocarbene moiety, forming an axially chiral bifunctional catalyst. Unlike the precedented chiral bifunctional phosphine gold catalysts with fluxional atropisomerism that demonstrated by the same group[40], the epimerization between the two atropisomers in this work are only observed at elevated temperature, enabling the separation of two atropisomers and storage at low temperature (on or below 0 °C) (Scheme 36a). The two atropisomers can be adopted respectively for asymmetric organic transformations. Interestingly, the two atropisomers of the catalyst, (a*R*, *R*)-**L***AuCl and (a*S*, *R*)-**L***AuCl, induced opposite enantioselectivities in the gold-catalyzed cyclization of N-allenamides, which is proposed due to the different chiral induction modes of the two atropisomers (Scheme 36b). In the catalysis of (a*R*, *R*)-**L***AuCl, the electrostatic attraction between the partially negatively charged nitrogen and the cationic intermediates effectively induces the product chirality. On the other hand, in the catalysis of (a*S*, *R*)-**L***AuCl, the chiral environment brought by the steric hindrance of the chiral cyclohexanyl group mainly contributes to the product chirality.




**Scheme 36.** Chiral Bifunctional NHC Ligands and Their Utilities in Asymmetric Gold Catalysis.

In 2020, Sollogoub, Fensterbank and Mouriès-Mansuy[54] reported enantioselective alkoxycyclization reactions catalyzed NHC-capped β-cyclodextrin (β-ICyD) gold(I) catalyst. (Scheme 37) The cyclodextrin moiety assisted the construction of a size-exclusive chiral cavity, allowing only small-sized nucleophiles to enter and participate in gold(I)-catalyzed enantioselective alkoxycyclization with high enantioselectivity (up to 94% ee). Note that large-sized nucleophiles cannot enter the cavity, where 1,6-enyne substrates would undergo intramolecular 6-endo-dig cyclization without nucleophiles.

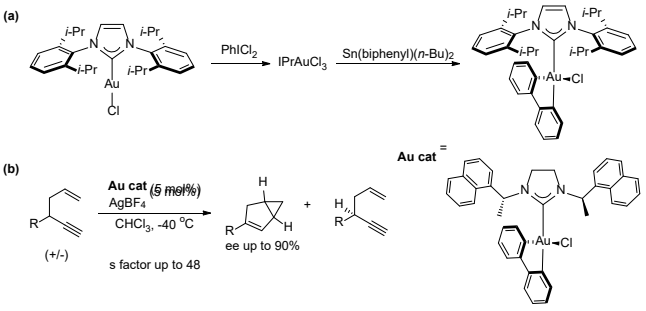



**Scheme 37.** Enantioselective Alkoxycyclization Reactions Catalyzed NHC-capped β-cyclodextrin (β-ICyD) Gold(I) Catalyst.

## 3. Recent Development of Enantioselective Gold(III) Catalysis

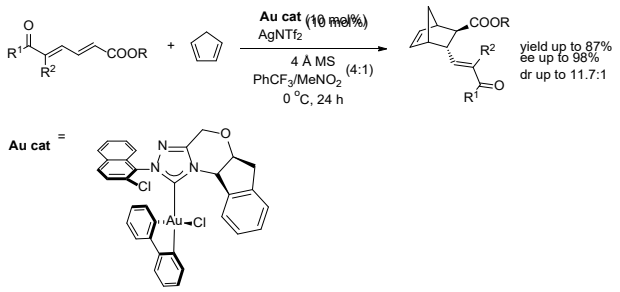
Despite gold(I) catalysis has received intense studies in the past decades, the use of gold(III) species for catalysis were mostly limited in inorganic gold(III) salts for a long time. Although some gold(III) complexes have been successfully designed as the catalysts for organic transformations, asymmetric catalysis achieved by gold(III) remains unexplored. Recently, several pioneering works developing chiral gold(III) complexes for asymmetric catalysis have been reported, opening up a new research direction of asymmetric gold(III) catalysis.

In 2015, Toste and co-workers[51a] designed novel N-heterocarbene (NHC) biphenyl gold(III) catalysts (Scheme 38a). As one of the main disadvantages of gold(I) catalysts is the linear geometry that brings a long distance between ligand and substrates, Toste and co-workers oxidized the NHC-gold(I) complex to gold(III) and stabilized it with biphenyl group, successfully synthesized new NHC-biphenyl-gold(III) complexes. The newly developed complex has a chloride group coordinating to gold(III) nucleus, which can be deprived to release the cationic vacant site for substrate binding. Comparing with the original NHC-gold(I) complex, the chloride is much closer to the NHC ligand and is more easily incorporated into the chiral environment constructed by the latter. In 2017, the same group adopted the chiral NHC-biphenyl-gold(III) catalysts to successfully catalyze a direct enantioconvergent kinetic resolution of 1,5-enynes (Scheme 38b).[51b, 55] The bicyclo[3.1.0]-hexenes were resulted with enantioselectivities up to 90% ee, which marks the first highly enantioselective transformation catalyzed by gold(III) catalyst.



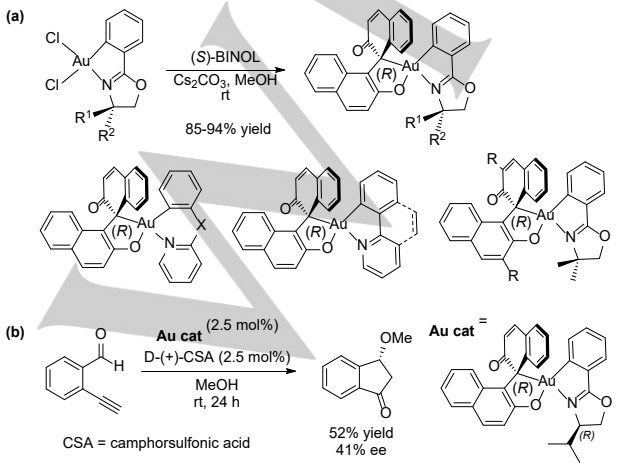
**Scheme 38.** (a) Synthesis of N-heterocarbene Biphenyl Gold(III) Catalysts (b) Enantioconvergent Kinetic Resolution of 1,5-Enynes Catalyzed by Chiral NHC-Biphenyl-gold(III) Catalysts.

Recently, Toste's group demonstrated an enantioselective γ,δ-Diels-Alder reaction catalyzed by the chiral NHC-biphenyl-gold(III) complexes (Scheme 39).[51c] The product was afforded with good yield (up to 87%), enantioselectivity (up to 98%) and diastereoselectivity (up to 11.7:1). The computational study indicated a π-π interaction between substrate proximal double bond and the catalyst aromatic group, which would be the rationale of the high enantioselectivity.



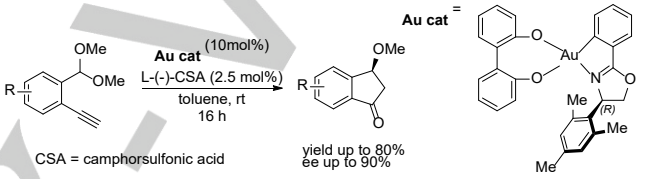

**Scheme 39.** γ,δ-Enantioselective Diels-Alder Reaction Catalyzed by Chiral NHC-Biphenyl-Gold(III) Complexes.

In 2017, Wong and co-workers synthesized a series of chiral C,O-chelated BINOL/C,N-cyclometallated oxazoline gold(III) complexes for gold catalysis (Scheme 40).[55-56] Based on the previous design of C,N-cyclometallated gold(III) complexes, the authors used BINOL ligands to replace the two chloride atoms, aiming to develop a new type of more stable tetracoordinate gold complexes as catalysts. Interestingly, they observed a rare tautomerized structure of BINOL ligands that coordinates to the gold center in a C,O-chelation mode, with originally axial chirality transformed into the central chirality on the newly generated chiral carbon center (Scheme 40a). The newly developed gold catalysts presented higher stability than the traditional C,N-cyclometallated gold(III) dichloride compounds, and also showed catalytic activity at raised temperature or in the presence of camphorsulfonic acid. In this work, one example of gold-catalyzed enantioselective carboalkoxylation of 2-ethynylbenzaldehyde with moderate enantioselectivity (41% ee) was disclosed (Scheme 40b).




**Scheme 40.** (a) Synthesis of C,O-chelated BINOL/C,N-Cyclometallated Oxazoline Gold(III) Complexes (b) (C,O)/(C,N)-gold(III) Catalyzed Enantioselective Carboalkoxylation of 2-Ethynylbenzaldehyde.

In 2019, Wong's group reported another work of asymmetric gold(III) catalysis by using chiral O,O-chelated biphenol/C,N-cyclometallated oxazoline gold(III) complexes (Scheme 41).[57] When biphenol was employed as the ligand in replace of BINOL, the O,O-chelation mode was adopted without tautomerization. By screening of a series of (O,O)/(C,N)-gold(III) catalysts and (C,O)/(C,N)-gold(III) complexes, the authors found the chirality of BINOL or biphenol ligands contribute little to the reaction enantioselectivity, while the enantioselectivity is mainly related to the chiral substituent group on the oxazoline ligand. By using the (O,O)/(C,N)-gold(III) catalyst with 1,3,5-trimethylphenyl substituent on the chiral oxazoline ligand, enantioselective carboalkoxylation afforded 3-methoxyindanone in moderate yield (up to 80%) with high enantioselectivity (up to 90% ee).




**Scheme 41.** (O,O)/(C,N)-gold(III) Catalyzed Enantioselective Carboalkoxylation of 2-Ethynylbenzaldehydes.

## 4. Summary and Outlook

Although the rapid growth of enantioselective gold catalysis has been witnessed in the past few years, there are still interesting research directions that remain largely unexplored, especially for asymmetric gold(III) catalysis. The recent advances provide some clues that may help to expand the boundary of this field:

(a) Although the selection of chiral ligands is still limited to several well-precedented chiral phosphine and phosphite-derived ligands, various novel chiral ligand designs have been disclosed in recent years, which enriches the toolbox and may hopefully achieve new types of reactions.

(b) In most of the examples of enantioselective gold catalysis, the chiral gold catalysts serve as π-Lewis acid to activate C-C unsaturated bonds. Several examples have been disclosed featuring new catalytic properties of chiral gold catalysts, such as coupling and σ-Lewis acidity, disclosing new possibilities for enantioselective gold catalysis.

(c) The chiral gold catalyst loading varies in the range of 2-10% in most of the literature reports. Several recent studies demonstrated new strategies that enable lowering the catalyst loading to below 1%, which may hopefully meet the requirements for future industrial applications by further improvement.

(d) The recent breakthrough of enantioselective gold(III) catalysis has opened up a new research direction for asymmetric gold catalysis. Considering the unique square-planar geometry of gold(III) complexes, it is envisioned that more achievements will be accomplished in asymmetric gold(III) catalysis that may complement the advanced development in asymmetric gold(I) catalysis.

(e) Redox gold(I)/gold(III) catalysis has made significant progress in the recent years, overcoming the energy barrier between gold(I) and gold(III), which enabled gold catalyzed cross-coupling reactions. Developments in redox gold(I)/gold(III) catalysis include the use of photo activation[19a, 19h] or oxidants such as hypervalent iodine reagents[20]. Recently, oxidant free strategies such as ligand-enabled gold(I)/gold(III) catalysis have also been disclosed.[19b, 21] The Ligand-enabled gold(I)/gold(III) catalysis could promisingly pave a way for chiral-ligand enabled enantioselective versions. Although the enantioselective versions of gold(I)/gold(III) catalysis are still rare, it is envisioned more enantioselective examples will be disclosed in the near future.

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**Keywords:** asymmetric catalysis • homogeneous catalysis • gold • enantioselectivity • ligand design

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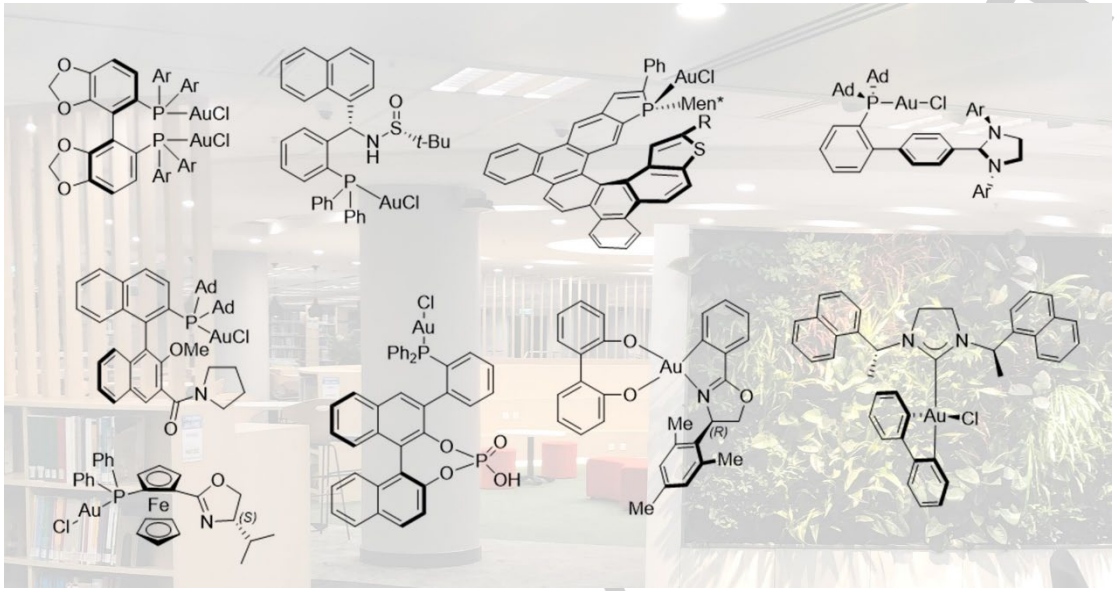
**Recent Advances in the Development of Chiral Gold Complexes for Catalytic Asymmetric Catalysis**

Jia-Jun Jiang, Man-Kin Wong



Enantioselective gold catalysis has been rapidly developed in the past ten years. Breakthroughs had been made by rational design and meticulous selection of chiral ligands. This review summarizes enantioselective gold catalysis that has been achieved using different chiral gold complexes in the past four years (since 2016).