Chapter

Gold Catalyzed Asymmetric Transformations

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Abstract

In this chapter, the strategies developed to attain asymmetric reactions with gold are disclosed. Because of its preferred linear arrangement, to induce asymmetry, gold(I) needs to fulfill one of the following requirements: a) the use of bulky chiral ligands, that create a chiral pocket around the active site, b) the coordination to bifunctional ligands capable to establish secondary interactions with substrates, or c) tight ion pairing with chiral counteranions. On the other hand, gold(III) profits of a square-planar coordination mode, which approaches chiral ligands to substrates. However, its tendency to be reduced leads to difficulties for its applications in catalytic asymmetric transformations. Pioneering works using cyclometaled structures, have found the balance between stability and activity, showing its potential in asymmetric transformations.

Keywords: gold, catalysis, bulky ligands, bifunctional ligands, ion pairing

1. Introduction

Gold was long considered to be unsuitable for catalysis due to bulk gold present a high reluctance to react. Nonetheless, in the last part of the 20th century pioneering studies from different groups, showed that gold in oxidation states I and III has a big potential as catalysts specially, in reactions dealing with the activation of C-C multiple bonds [1–7]. Because gold(III) is prone to be reduced, the majority of gold catalyzed transformations described so far involves gold(I) complexes. It has been evidenced that gold(I) is able to trigger the building of complex molecular frameworks in a few steps, under soft conditions and with a high degree of functional group tolerance [8–15]. Its special properties lay on relativistic effects, that contract its 6 s and 6p orbitals and expands the 5d shell, lowering the energy level of the LUMO which in turn is traduced in a high Lewis acidity [16]. The development of unsymmetric transformations with gold(I), was hampered at the beginning because of its preferred linear coordination mode [17, 18], that keeps away the substrate being modified from the chiral ligand environment. Hopefully have been uncovered successful strategies to circumvent this problem, such us the use of chiral counter anions, or the development of suitable chiral ligand incorporating secondary interactions with substrates which achieve high asymmetric level. Conversely gold(III) has an square planar coordination mode, ideal for approaching close together the substrate being transformed and the asymmetric ligand, however as note before, its tendency to be reduced has restricted its applications. A few examples has appeared very recently arriving at a compromise between reactivity an stability and it is expected to continue growing in next years, as the chemistry of gold(III) continues to be enlarge.

This chapter is an overview of the strategies and ligands employed to achieve chiral transformations with gold. It is organized according to the type of ligands designed [19–22].

2. Gold(I) asymmetric transformations

2.1 Gold(I) asymmetric transformations with diphosphine ligands

The first asymmetric ligands that enabled moderate to good enantiomeric ratios were atropoisomeric bidentate phosphines. The most commons are depicted in **Figure 1**. The importance of these phosphines relay on their relative accessible synthetic procedures and their commercial availability. Along with them, some planar chiral diphosphines, or diphosphines containing asymmetric carbon centers has also been used, although in a minor extent.

One of the reactions more thoroughly studied in gold chemistry is the cycloisomerization of 1,n enynes. Starting from linear pools, this reaction gives access under soft conditions, to otherwise complex synthetic targets. Primary studies over the cycloisomerization of enynes, showed that the alkoxycyclization of 1,6 enynes proceeds with modest values of enantioselectivity using (*S*)-Tol-BINAP as ligand (**Figure 2**, Ec1). It was assumed that the reaction is triggered by a monocationic gold complex, generated *in situ* by halogen abstraction with a silver salt. Upon coordination to the alkyne, the catalyst would promote a 5-*exo-dig* cyclization. As a result, it would be formed a cyclopropyl gold carbene complex, which evolves to the final alkylidene cyclopentene, by nucleophilic attack of methanol to the cyclopropane moiety [23].

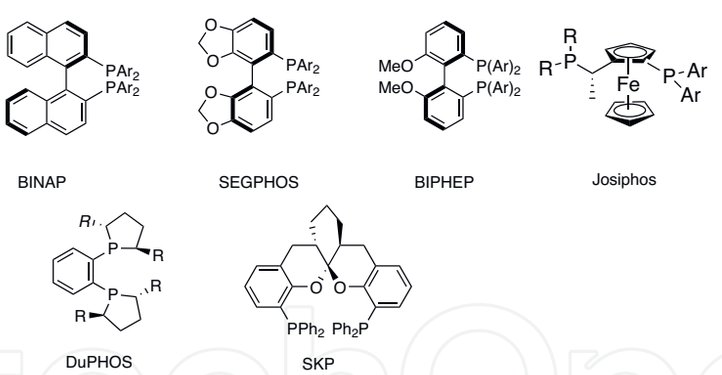

Figure 1.
Common asymmetric biphosphine ligands.

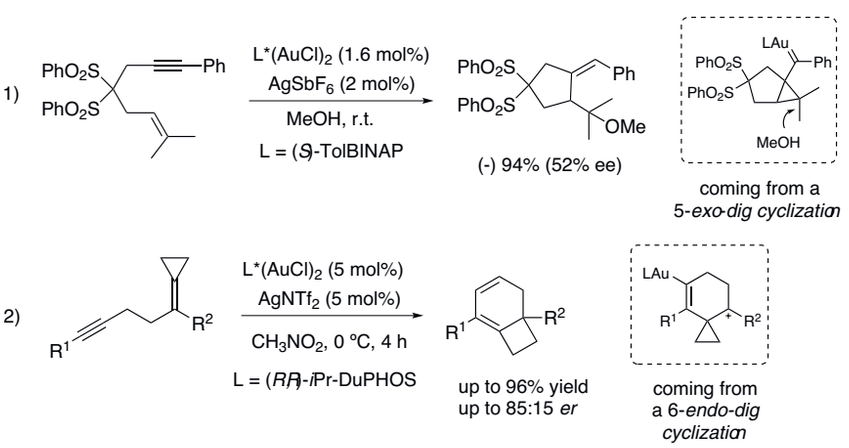

Figure 2.
Asymmetric cycloisomerization of 1,6- and 1,5-enynes.

Improved enantiomeric values were obtained in the cycloisomerization of 1,5-enynes bearing cyclopropyliden moieties (**Figure 2**, Ec2). These substrates led to challenging bicyclo[4.2.0]octanes, by a 6-*endo-dig* cyclization/ring expansion process [24, 25]. It was observed that the enantioselectivity values were importantly affected by the amount of the silver salt employed. The best results were obtained using the complex (*R,R*)-*i*Pr-DuPHOS$(AuCl)_2$ (5 mol%), and AgNTf (5 mol%) as a silver salt. It could be notice that AgNTf itself, is able to catalyze the reaction in some extension, being responsible of the decrease in the enantiomeric ratios. Related to this ring expansion procedure, 1,6-enynes containing a cycloalkoxy unit, have been shown to rearrangement to cyclopentyl-cyclobutanones with high enantioselectivities, when treated with [(*R*)-MeO-DTBM-BIPHEP-$(AuCl)_2$] (3 mol%) and $AgBF_4$ (6 mol%) [26]. On the other hand, 1-allenylcyclopropanols also undergo a cyclization/ring expansion process that affords chiral vinyl cyclobutanones, with good enantiomeric ratios, when treated with (*R*)-MeO-DTBM-BIPHEP$(AuCl)_2$ (2.5 mol%) and NaBARF (5 mol%) as chloride scavenger. The reaction is promoted by Π activation of the allene through gold coordination, and a subsequent Wagner-Meerwein shift [27]. Finally, another strategy for accessing chiral cyclobutanes consists onto an intermolecular [2 + 2] cycloaddition of alkynes and alkenes. This time higher enationomeric ratios were obtained with a Josiphos digold(I) complex (2.5 mol%) and $NaBAr_4^F$ (2.5 mol%). Interestingly, the mechanistic studies carried out in this work, revealed that only one atom of gold is involved in the activation of the alkyne, but the second one is needed to induce enantioselectivity (**Figure 3**) [28].

Chiral cyclopropanes are also amenable with gold complexes by olefin cyclopropanation with diazo compounds (**Figure 4**). Thus, cyclopropanes with vicinal all-carbon quaternary stereocenters can be assembled by reaction of diazooxindoles with α-CH_2F styrenes, using a spiroketaldiphosphine digold(I) complex. This reaction benefits from hydrogen bond interaction with the solvent, particularly fluorobencene forms a strong C-F···H-N interaction, that lower the activation barrier of

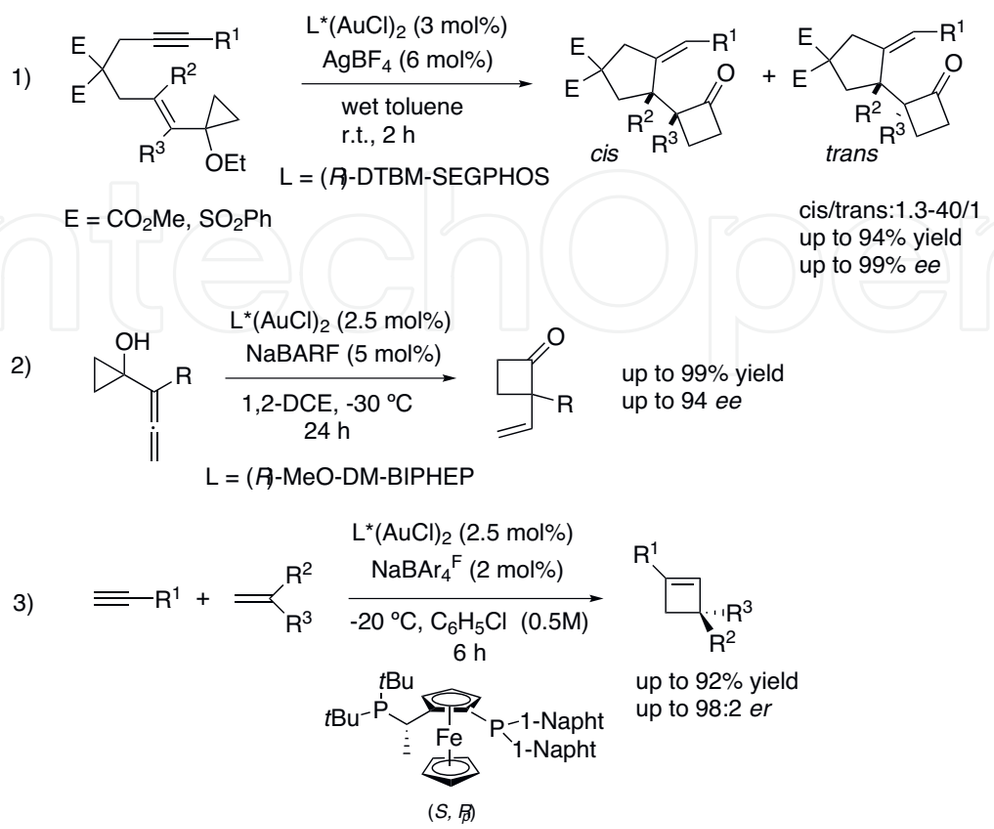

Figure 3.
Asymmetric cyclobutanes synthesis.

the reaction. Yields up to 93% were obtained, with enantioselectivities over 90% and diastereoselectivities higher of 20:1 in all cases [29].

Enantioselective hydroetherification of alkynes is possible by desymmetrization of prochiral phenols containing a P-stereogenic center (**Figure 5**, Ec.1). It has been observed that bisphenols and dialkyne phosphine oxides, undergo a 6-*endo-dig* cyclization with (*S*)-DTBM-SEGPHOS(AuCl)$_2$ complex, leading to chiral cyclic phosphine oxides. The yields of the reaction maintained up to 97% and the enantioselectivites close to 99%. This reaction is an efficient and practical tool to achieve compounds with P-sterogenic centers [30]. Notably, the same complex has been used for the synthesis of planar-chiral ring-fused ferrocenes, starting from *ortho*-alkylnylaryl ferrocenes (**Figure 5**, Ec. 2) [31]. Finally, along with this alkyne activation protocols, (*R*)-DTBM-SEGPHOS(AuCl)$_2$ has been efficiently applied in asymmetric Picted-Spengler reactions between tryptamines and arylaldehydes [32].

2.2 Gold(I) asymmetric transformations with monophosphine ligands

In some reactions catalyzed by chiral digold complexes, better performances were obtained by generation of monocationic instead of dicationic species. This fact points that in those cases the role of the second atom of gold may be just steric, or that it may be involved in secondary interactions with substrates. With this in mind, there has been an increasing interest in developing monophosphine chiral ligands. One of the monophosphines that have exerted better enantioselectivities, are

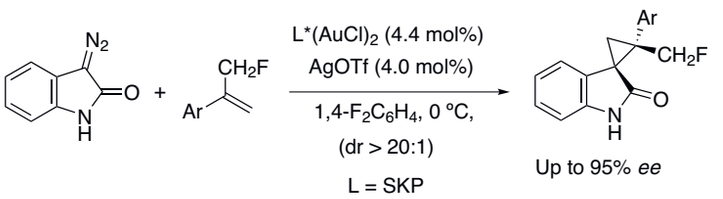

Figure 4.
Asymmetric synthesis of cyclopropanes with diazooxindoles.

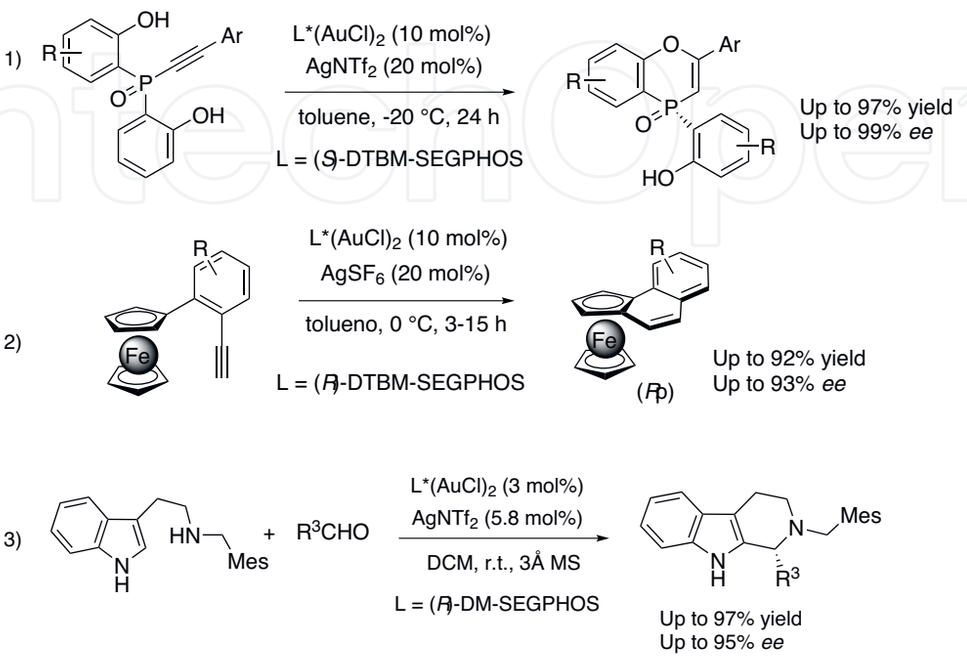

Figure 5.
Asymmetric synthesis of cyclic phosphine oxides, ring-fused planar chiral ferrocenes and tetrahydo-β-carbolines.

monophosphines bearing a chiral sulfinamide moiety that can stablish secondary interactions with the substrates. These ligands offer the advantage of being easily modified, as they can be modularly synthesized. For example, the MING-PHOS family is synthesized by a two-step sequence (**Figure 6**, Ec1), that consists in the condensation of an arylphoshine aldehyde with chiral *tert*-butylsulfinamide, followed by the stereodivergent addition of RLi or RMgX. This way diasteromeric sulfinamide monophosphines can be isolated. MING-PHOS ligands has been applied over a variety of reactions, thus they have shown to catalyze the enantioselective [3 + 3] cycloaddition of 2-(1-alkynyl)-alk-2-en-1-ones with nitrones (**Figure 6**, Ec. 1). The reaction furnished furo[3,4-*d*] [1,2]oxazines, with high diasteroselectivity (> 20:1) and stereoselectivity. Interestingly, both types of enantiomers could be isolated by using a pair of diasterosisomeric MING-PHOS [33, 34]. Replacing nitrones by 3-stylindoles, cyclopenta[c]furans were obtained with similar values of diastereo- and entioselectivities (**Figure 6**, Ec. 3) [35]. A variation of the MING-PHOS family that incorporates adamantyl groups at the phosphorous atom (XIA-PHOS

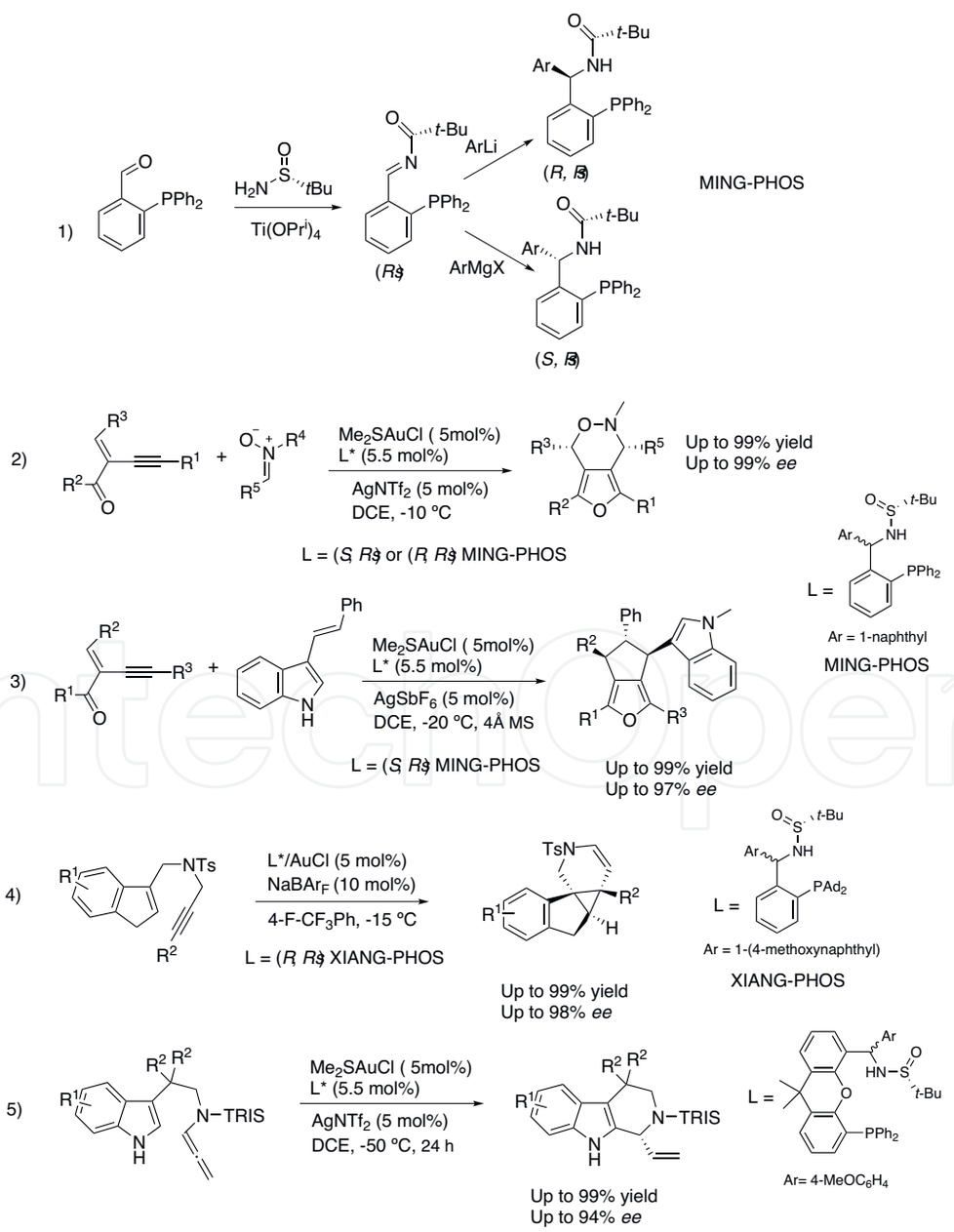

Figure 6.
(1) Synthesis of chiral sulfinamides. (2) Asymmetric reactions with chiral phosphine sulfinamides.

family), has been employed for the synthesis of fused polycycles. Thus, the intramolecular cyclopropanation of indenes or trisubstituted alkenes, led to polycyclic compounds containing two vicinal all-quaternary stereogeneic centers with excellent yields and enantioselectivities (**Figure 6**, Ec. 4) [36]. N-allenamides attached to the indol nuclei could be cyclized to chiral tetrahydrocarbolines, by using PC-PHOS family. This family of ligands combine the well-known Xant-Phos phospine with a chiral sufinamide, affording high levels of entantioselectivity (**Figure 6**, Ec.5).

Along with chiral phosphine sulfinamides, other chiral bifunctional monophosphine ligands have been described. Based on remote cooperative effects, it have been designed axially chiral monophosphines containing a chiral basic center that can stablish secondary interactions with substrates. These types of ligands have been used to obtain asymmetric 2,5-dihydrofurans with excellent values of enantio- and diasteroselectivity, starting from alkynols through isomerization to chiral allenols and subsequent cyclization (**Figure 7**) [37].

Another interesting approach that relays in secondary interactions, consists in the synthesis of phosphines containing a biphenyl scaffold connected to a C_2-chiral pyrrolidine moiety (**Figure 8**). Because of the bulky substituents at the phosporous atom, upon complexation, the P-Au-Cl axis remains parallel to the biphenyl moiety, approaching the gold center to the asymmetric unit. This way it is created a chiral pocket in which the substrate is encapsulated. These ligands have been applied to the cyclization of 1,6-enynes, giving rise to high enantiomeric ratios. DFT calculations showed that the enatioselectivity of the reaction, relays on π-π interactions between the substrate and the ligand. It could be observed opposite enantioselectivities, depending on the position of the aromatic ring in the substrate being cyclized. This chemistry has been applied to the total synthesis of tree members of the carexane family [38].

Finally, phosphahelicenes has also been used to induce asymmetry in the cyclization of 1,6-enynes. These ligands contain a menthyl at phosphorous as the chiral auxiliar. The phosphorous atom racemize at room temperature, and after complexation with a LAuCl precursor, are obtained two epimeric gold complexes; one where the gold atom is disposed toward the helical scaffold (*endo* complex) and another where the gold atom is disposed on the opposite face (*exo* complex). *Endo* isomers give higher enantioselective values since locate closer the metal to the helical moiety (**Figure 9**) [39].

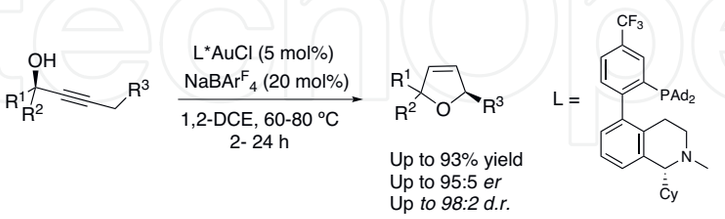

Figure 7.
Asymmetric synthesis of dihydrofuranes with axially chiral bifunctional monophosphines.

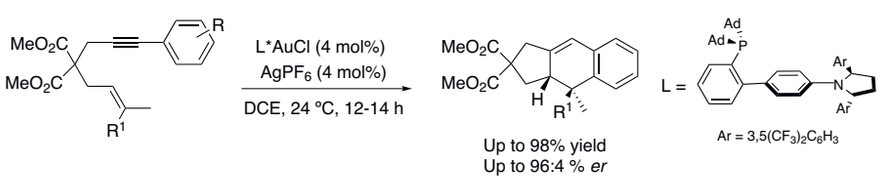

Figure 8.
Asymmetric cyclization of 1,6enynes with biphenyl C_2 chiral pyrrolidine phosphines.

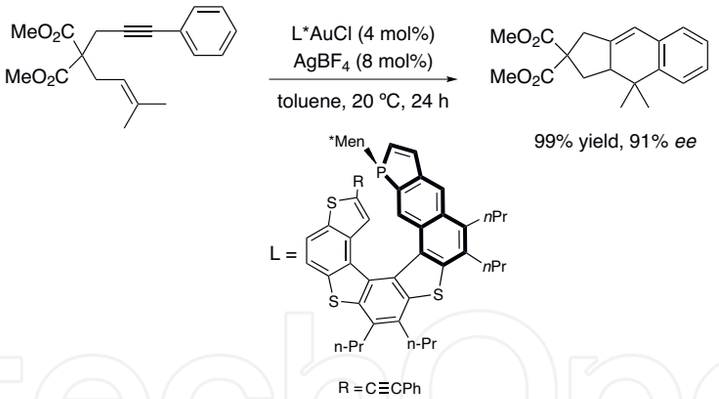

Figure 9.
Asymmetric cyclization of 1,6-enynes with phosphahelicenes.

2.3 Gold(I) asymmetric transformations with phosphoroamidites

Phosphoroamidites are modulable monodentate ligands that exerts good levels of enantiomeric ratios in gold catalysis. The firsts example of asymmetric transformations employing phosphoramidites, where applied to the cyclization of allenes. Using phoshoroamidite ligands based on BINOL scaffold, it was shown that allenedienes undergo a formal (4 + 3) cycloaddition reaction leading to bicyclic compounds via an allylic cation. The carbene derived from this cation, can evolve via a 1,2-H migration shift, affording 5,7-fused bicyclic compounds, or by a ring contraction leading to 6,7-fused bicyclic compounds. The presence of substituents at the end of the allene favors the formation of 6,7-fused bicyclic compounds. The reaction is totally diastereselective and proceeds with high values of enantioselectivity (**Figure 10**, Ec. 1) [40]. Other BINOL derived ligands have been used in the

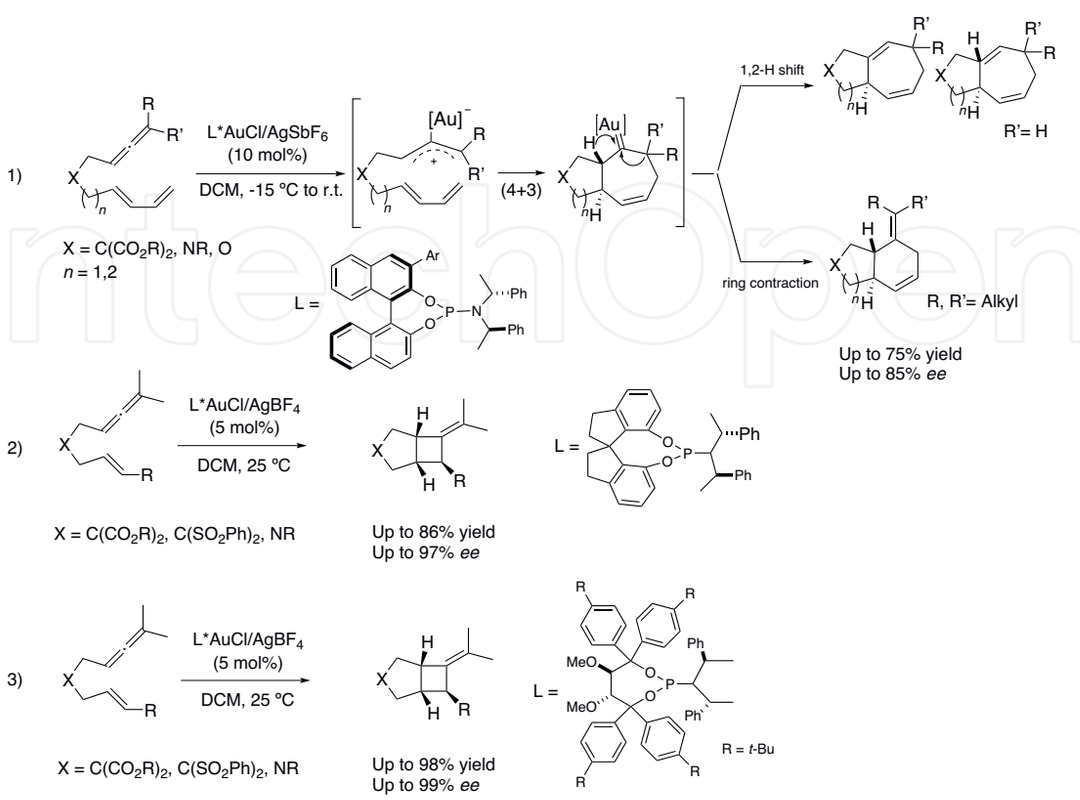

Figure 10.
Asymmetric cyclization of allendienes and allenenes with BINOL and TADDOL-derived phosphoroamidites.

cyclization of allenes. Thus, it has been shown that, allenenes undergo a (2 + 2) cycloaddition reaction furnishing 5 + 4 bicyclic compounds with excellent enantioselective values (**Figure 10**, E. 2) [41]. Along with BINOL, TADDOL-derived phosphoramidites has shown excellent performance in asymmetric reactions catalyzed by gold. This scaffold creates a conic cavity of C_3 symmetry around the gold center. One of the better TADDOL-derived phosphroamidites bears an acyclic backbone. This type of ligands exerts excellent values of enantioselectivity in a variety of gold catalyzed reactions, in particular allenenes undergo a (2 + 2) cycloaddition reaction with excellent levels of asymmetry [42].

After these initial examples, BINOL derived phosphoroamidites have been used in several relevant organic reactions, such as hetero-Diels-Alder reactions (**Figure 11**, Ec. 1), where the chiral gold(I) complex acts as a Lewis acid activating urea-based diazene dienophiles (**Figure 11**, Ec.1) [43], or in the (3 + 2) annulation of 2-(1-alkynyl)-2-alken-1-ones with *N*-allenamides (**Figure 11**, Ec. 2) [44]. This reaction is proposed to procceds by generation of an all-carbon 1,3-dipole and subsequent (3 + 2) annulation at the proximal C=C bond of the alleneamide.

Looking for more electrophilic phosphorous centers, recently TADDOL and BINOL have been used as chiral scaffolds in α-cationic phosphonites. These ligands incorporate an imidazolium, or a related cationic heterocyclic moiety, directly bounded to phosphorous. The cationic group increase the Lewis acidity character of the phosphorous increasing the activity of gold upon complexation. By far, these ligands have been used for the synthesis of helicenes via gold catalyzed alkyne hydroarylation reactions, with excelents levels of enantioselectivity (**Figure 12**) [45, 46].

2.4 Gold(I) asymmetric transformations with carbenes

Although in a minor extent than phosphine and phosphoramidites ligands, both acyclic and cyclic N-heterocyclic carbenes have been used in asymmetric gold catalyzed reactions. Acyclic diaminocarbene ligands with a pendant binaphthyl moiety, induce high enantioselective values in gold catalyzed acetalization/cycloisomerization reactions of *ortho*-alkynylbenzaldehydes (**Figure 13**, Ec. 1) [47]. According to DFT calculations, the wide N-C-N angle of the carbene, approaches the binaphthyl unit to the gold center, facilitating an Au-arene interaction, that creates the chiral environment for the enantio-discrimination. N-heterocyclic carbenes (NHC) have

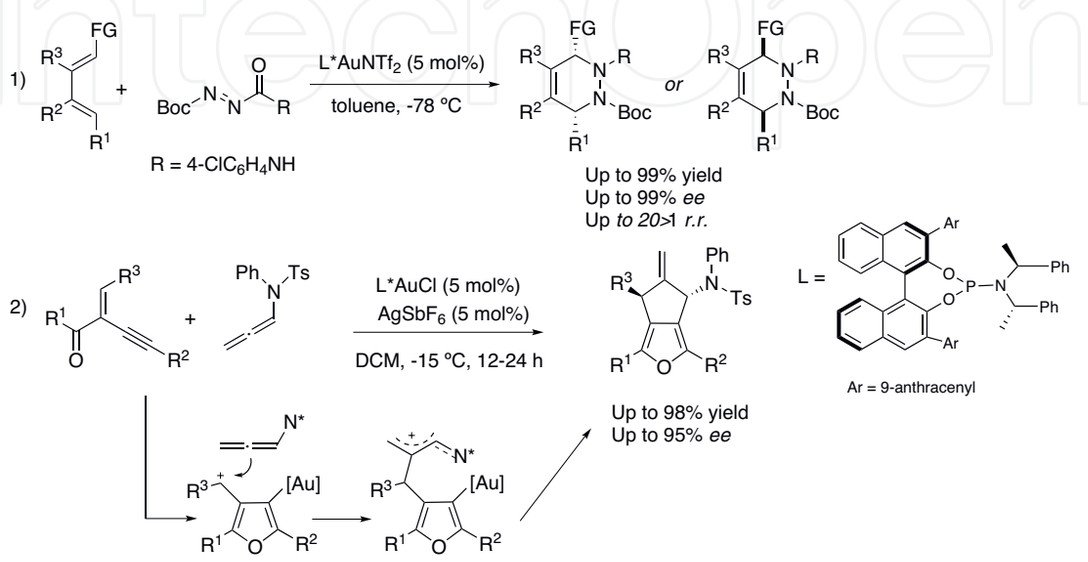

Figure 11.
(4 + 2) and (3 + 2) cyclizations with BINOL-derived phosphoramidites.

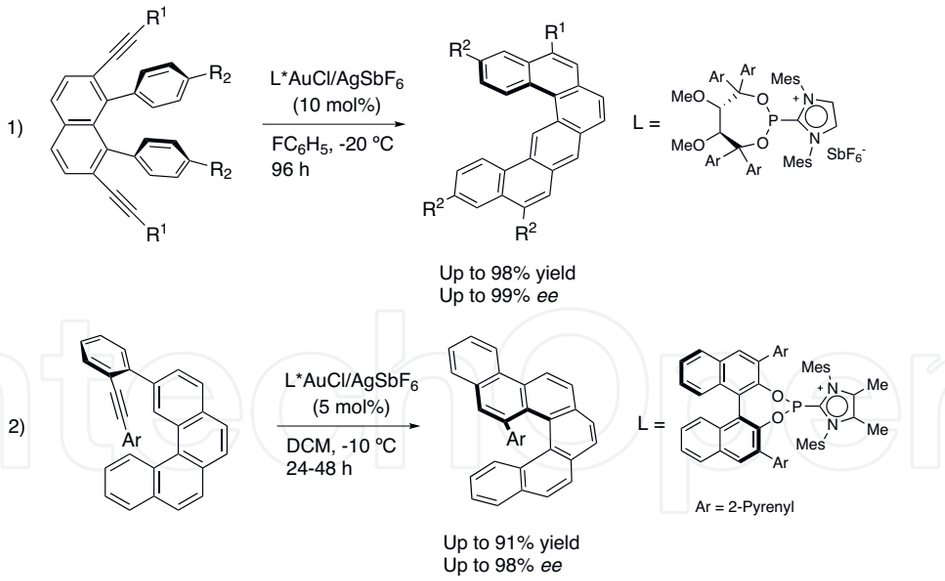

Figure 12.
Asymmetric synthesis of helices with α-cationic phosphonites

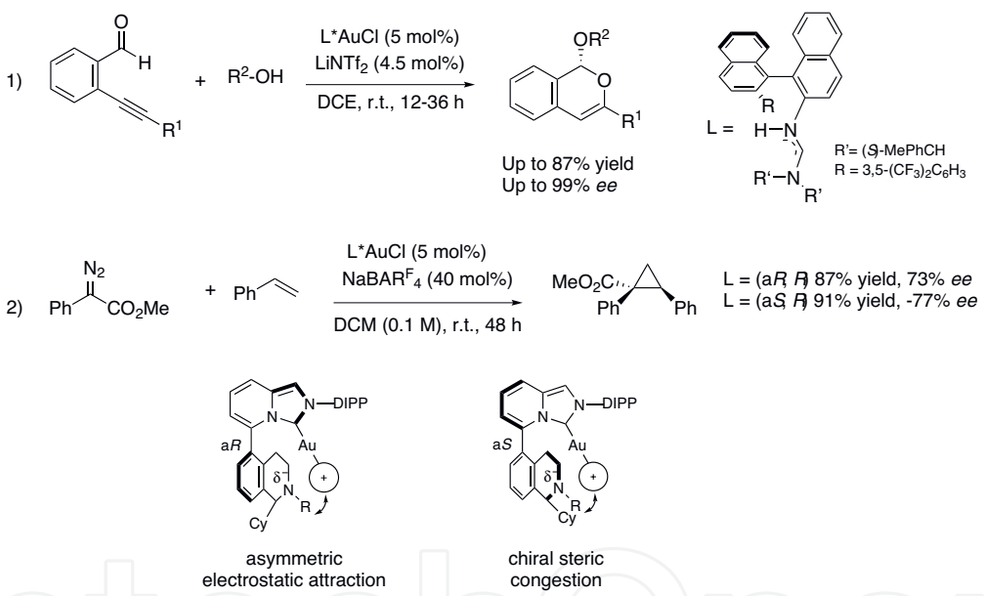

Figure 13.
Asymmetric transformations with carbene ligands.

been used in bifunctional type ligands containing chiral tetrahydroisoquinoline structures. These ligands contain a fluxional biaryl axis, that allow the aryl groups to be orientated orthogonally. After complexation with $AuCl{\cdot}SMe_2$, it was possible to separate two atropoisomer complexes generated, due to the restricted rotation of the biaryl axis in the presence of AuCl. It was observed, that each atropoisomers give rise to opposite enantiomers, as it is illustrated in the cyclopropanation of styrene (**Figure 13**, Ec. 2). In the complex with (a*R*,*R*) configuration, the enantio-discrimination come from an electrostatic attraction effect, between the partially negatively charged ligand nitrogen and the cationic gold center. On the other hand, in the case of the complex with a (a*S*,*R*) configuration, enantio discrimination was attributed to the chiral steric environment posed by the cyclohexyl group [48]. Along with these examples, gold complexes encapsulated in capped cyclodextrin cavities have also shown to catalyze several asymmetric transformations, such us the cycloisomerization of enynes, hydroarylation and lactonizations reactions [49].

2.5 Gold(I) asymmetric transformations with chiral counteranions

The difficulty in creating an asymmetric environment around gold(I), and the cationic nature of gold(I) catalyzed reactions, led to the search of alternatives strategies to induce asymmetry based on ion pairing. Generation of cationic achiral gold complexes, in the presence of chiral counterions, allow inducing asymmetry by transferring the chiral information via formation of tight ion pairs between cationic organogold species and chiral anions. It was first observed, that allenes undergo hydroalkoxylation, hydrocarboxylation and hydroamination reactions with high enantioselective values, using an achiral diphosphine digold complex in the presence of a chiral silver phosphate derived from binaphthol (**Figure 14**, Ec. 1). It was proposed that, the silver phosphate generates a cationic gold(I) complex leaving the chiral phosphate as counteranion, which is responsible for the enantioselectivity observed [50]. The same strategy was applied to the desymmetrization of 1,3-diols (**Figure 14**, EC. 2) [51].

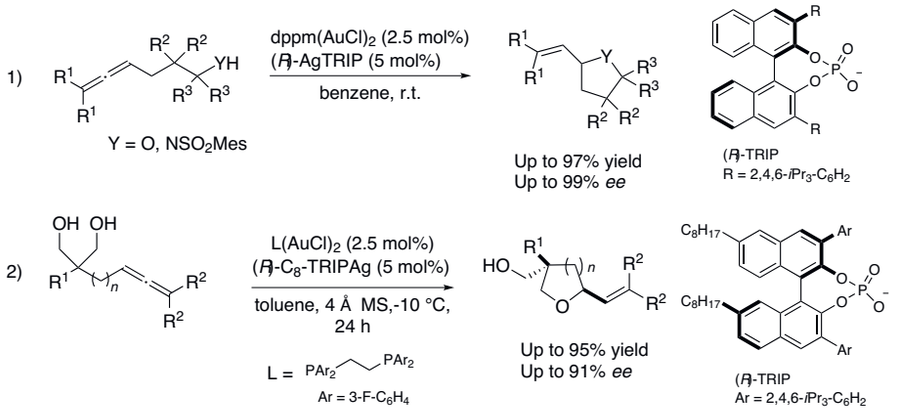

Figure 14.
Asymmetric cyclization of allenes with chiral counterions.

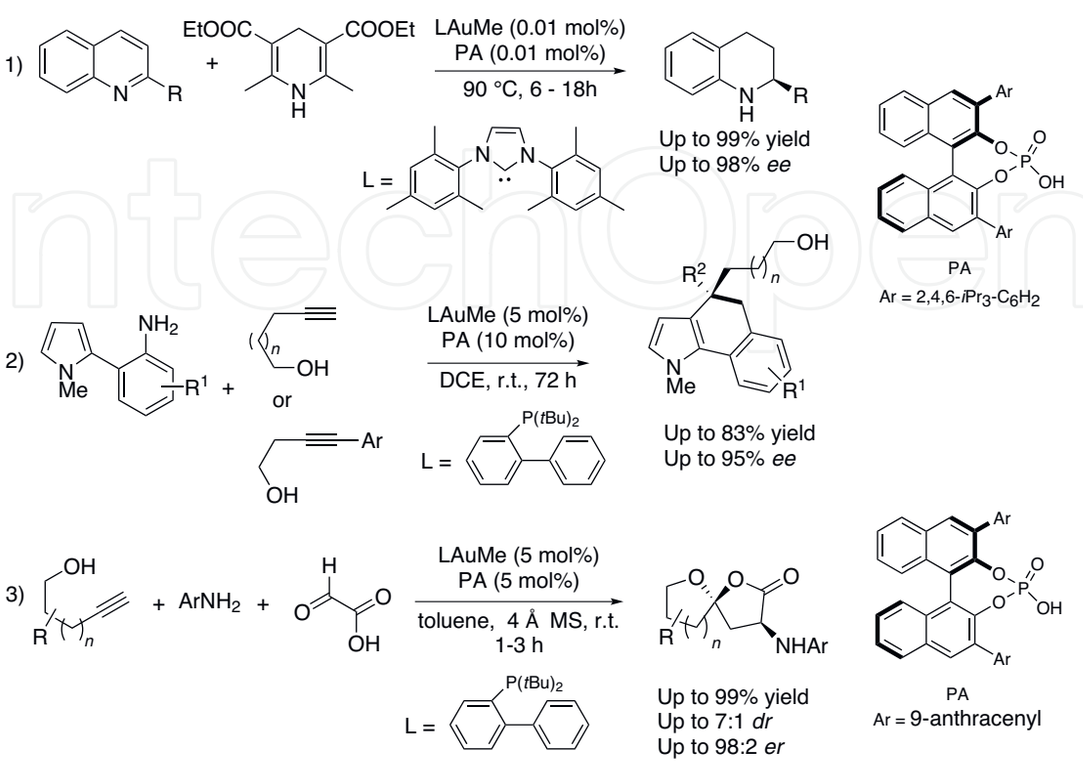

Figure 15.
Asymmetric transformations with chiral phosphoric acids.

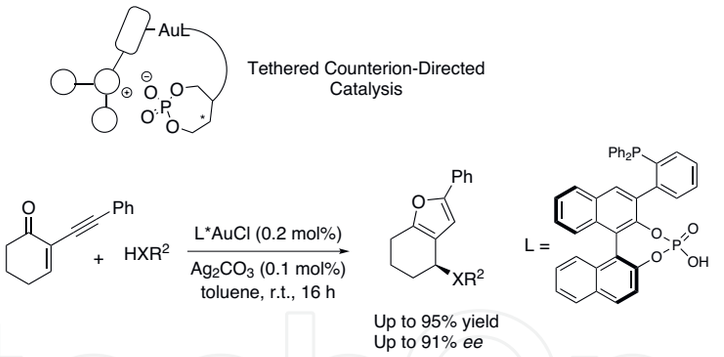

Figure 16.
Asymmetric transformations with phosphoric acid-tethered phosphines.

The cationic gold(I) specie can also be generated with chiral phosphoric acids by protonolysis of complexes precursors with an Au-Me bond. This type of asymmetric induction has been used in enantioselective transfer hydrogenation reactions of quinolines (**Figure 15**, Ec. 1) [52], in the hydroamination-hydroarylation of alkynes (**Figure 15**, Ec. 2) [53] and in the synthesis of spiroacetals among others [54].

In these approximations the degree of enantio-discrimination depends upon the proximity of the counteranion to the cationic gold center. In this sense, recently have been designed new phosphine ligands, thetered to chiral phosphoric acids, with the aim to restring the flexibility of the ion pair. The new phosphoric acid-tethered phosphines have shown excellent levels of enantioselectivity in reactions proceeding through carbocationic intermediates, such us the cyclization-addition of heteronucleophiles to enones (**Figure 16**) [55].

3. Gold(III) asymmetric transformations

Opposite to gold(I), gold(III) complexes have a square-planar geometry that allows ancillary ligands to be closer to the substrate, what made them good candidates for the development of asymmetric transformations. However, its enormous tendency to be reduced, have hampered it use in catalysis. Some recent studies have found the way to stabilize gold(III) centers, while maintaining its catalytic activity, placing them into cyclometalated frameworks. NHC-biphenyl gold(III) complexes with a cyclometalated structure, showed enough stability to catalyze an enantioconvergent kinetic resolution of 1,5-enynes (**Figure 17**, Ec. 1) [56]. In this reaction racemic 1,5-enynes are converted to bicyclo[3.1.0]hexenes with enantiomeric ratios up to 88%. Each enantiomer of the starting 1,5-enyne led to the same bicyclo with different enantioselectivity, making the overall enantioselectivity decrease with the conversion. Because of the latter, the conversions were maintained below, 50%. A related NHC-biphenylene gold(III) catalyst has been applied to enantioselective γ,δ-Diels-Alder reactions. In this occasion enantioselectivities reached 97% and yields were up to 87%. Detailed mechanistic studies revealed that the enantio- discrimination come from non-covalent π-π interactions between the substrate and an aromatic group of the complex (**Figure 17**, Ec. 2) [57].

Other cyclometalated complexes, such as cyclometalated oxazoline gold(III) complexes incorporating a biphenol ligand, have shown to be able to catalyze the asymmetric carboalkoxylation of alkynes. The corresponding 3-alcoxyindanones are obtained with moderate to good enantioselectivities. Remarkably, in this reaction camphorsulonic acid (CSA) activate the gold complex avoiding the need of adding silver salts as activators. Mechanistic studies suggested that the active catalytic specie is formed through protodeauration of one of the oxygens of the biphenol ligand (**Figure 18**) [58].

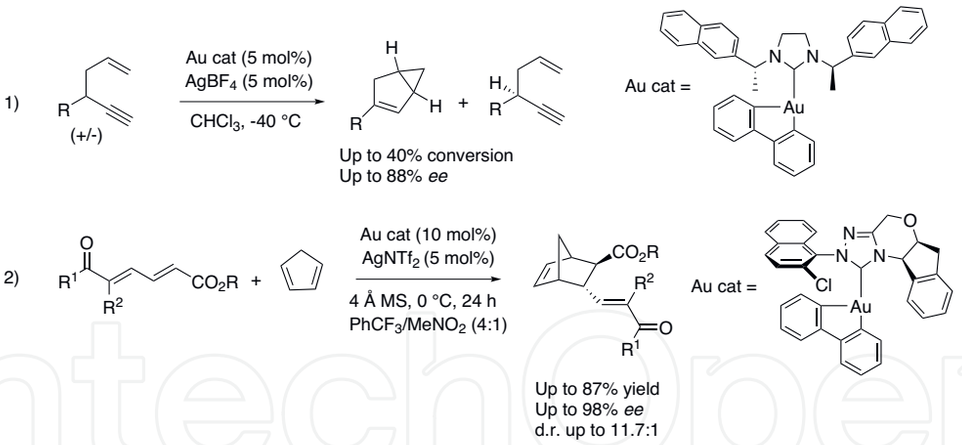

Figure 17.
Asymmetric transformations with chiral NHC-biphenyl gold(III) complexes.

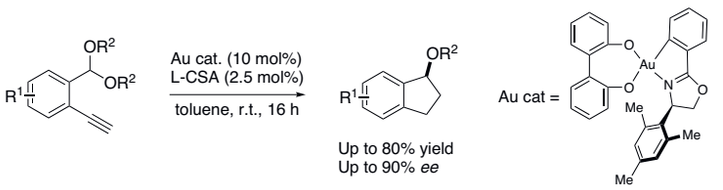

Figure 18.
Asymmetric carboalkoxylation of alkynes with gold(III) complexes.

4. Conclusions

Gold catalyzed asymmetric transformations is an emerging area. Enantioinduction with gold(I) catalysts, is a challenging task due to its preferred linear coordination mode, that place the substrate far from the chiral ancillary ligands. Nonetheless, to date several successful strategies have arose. Some are based on using sterically congested ligands, that create a chiral pocked around the active site, others use bifunctional phosphines, that stablish secondary interactions with the substrate, and finally others are based on using tight ion pairing with chiral anions. On the other hand, asymmetric catalysis with gold(III) is just beginning to be developed. When introducing ancillary ligands around gold(III), a fair balance between stability and activity must be reached. By far, cyclometalated complexes of gold(III) have shown that it is possible to undergo catalytic asymmetric reactions with gold(III), manifesting its great potential. A deeper development is expected in near future with gold(III).

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

Tol-BINAP	2,2'-bis(di-*p*-tolylphenylphosphino)-1,1′-binaphthyl
*i*Pr-DuPHOS	1,2-bis[(2S,5S)-2,5-diisopropylphospholano]benzene

DTBM-SEGPHOS	[(4*R*)-(4,4′-bi-1,3-bezodioxole)-5,5′-diyl]bis[bis(3,5-di-tert-butyl-4-methoxyphenyl)phosphine]
DM-SEGPHOS	5,5'-bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole
BIPHEP	bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
XantPhos	4,5-bis(diphenylphosphino)9,9-dimethylxanthene
TADDOL	α,α,α,α-tetraaryl-1,3-dioxo-lane-4,5-dimethanol
BINOL	1,1′-binaphthalene-2,2′-diol
CSA	camphor sulfonic acid

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