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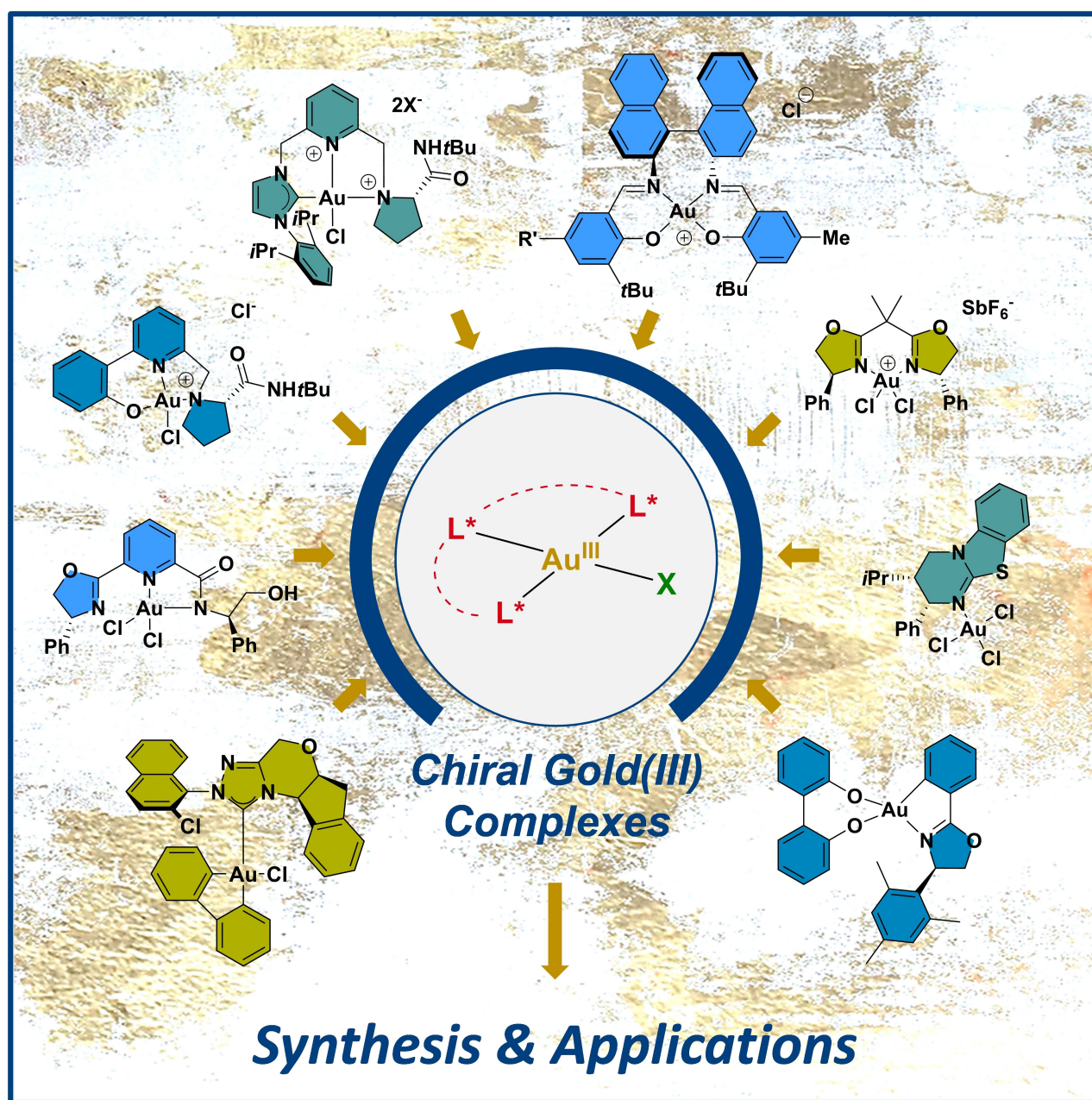
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Chiral Gold(III) Complexes: Synthesis, Structure, and Potential Applications

Rémi Jouhannet,^[a] Samuel Dagorne,^[a] Aurélien Blanc,^{*,[b]} and Pierre de Frémont^{*,[a]}



Abstract: Since the beginning of the 2000's, homogeneous gold catalysis has emerged as a powerful tool to promote the cyclization of unsaturated substrates with excellent regioselectivity allowing the synthesis of elaborated organic scaffolds. An important goal to achieve in gold catalysis is the possibility to induce enantioselective transformations by the assistance of chiral complexes. Unfortunately, the linear geometry of coordination for gold usually encountered in complexes at the +1 oxidation states renders this goal very

challenging. In consequence, the interest toward the synthesis of chiral gold(III) complexes is steadily growing. Indeed, the square planar geometry of the gold(III) cation appears more suitable to promote chiral induction. Beside catalysis, gold(III) complexes have also shown promising potential in the field of pharmacology. Herein, syntheses and applications of well-defined gold(III) complexes reported over the last fifteen years are summarized.

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Introduction

Beside its fiducial value, gold is extensively used today in the microelectronics and aerospace industries. The chemistry of gold features a large panel of available oxidation states ranging from -1 to $+V$. The $+1$ and $+III$ oxidation states provide the most stable complexes or clusters, while nanoparticles are agglomerations of bare gold atoms at the $+I/+0$ oxidation states, often stabilized by external ligands.^[1] Coordination chemistry (including organogold chemistry) is dominated by gold(I) compounds which tend to aggregate to form clusters *via* aurophilic ($d^{10}-d^{10}$) interactions.^[2] Gold complexes have generally a linear geometry with two ligands around the gold(I) cation (sp hybridization).^[3] The best stability is achieved with soft ligands such as phosphanes, carbenes, thiolates, cyanides. They form bonds with a pronounced degree of covalency due to the high Pauling electronegativity of gold.^[4] Interestingly, many gold(I) complexes are not air/moisture sensitive and can be handled as regular organic reagents. Gold(III) complexes are also well known and generally have a square planar geometry with four ligands around the gold(III) cation (dsp^2 hybridization). Compared to gold(I) complexes, they clusterize to a lesser extent through metallophilic (d^8-d^8) interactions.^[5] More importantly, they are more prone to thermal- or photo- induced decomposition *via* reductive elimination which can be prevented using chelating ligands.^[6] With monodentate ligands, the best stabilities are achieved with aryls, pyridines, imines, dithiocarbamates.^[7]

Since the beginning of the 2000's, gold chemistry has witnessed a resurgence of interest from the community of researchers. Two factors can explain this fact: 1) in 1998, the group of Teles reported a striking example of efficient homogeneous catalysis (hydration of alkynes) mediated by a phosphane gold(I) complex,^[8] thus shattering the long-lasting assumption that gold was too noble (not enough reactive) to be an effective metal for homogeneous catalysis; 2) new families of two electrons donor ligands with or without chirality were developed yielding organogold species with exceptional stabilities. One can think immediately of *N*-heterocyclic carbenes (NHC) and cyclic (alkyl)(amino)carbenes (CAAC) respectively first isolated in 1991 and 2005 by Arduengo^[9] and Bertrand^[10] while more classical ligands such as phosphanes or aryls still had to offer. Beyond homogeneous catalysis, gold chemistry has found applications for luminescence materials (*e.g.* light emitting devices),^[11] pharmacology (anti-cancer drugs)^[12] and heterogeneous catalysis (nanoparticles).^[13] Compared to cheaper metals (*e.g.* zinc, iron) the expensiveness of gold is often overcome by the straightforward experimental conditions and cheap equipment needed to perform gold chemistry. Generally, gold catalysis takes advantages of the Lewis acid behavior of the gold(I) and gold(III) cations which make them keen to activate multiple carbon bonds (carbonyls, alkenes, alkynes, allenes...) toward the addition of nucleophiles (alcohols, amines, electron enriched alkenes or alkynes).^[14,15] The catalysts usually display an excellent tolerance with substrates bearing common organic functions such as esters, tertiary amines, ethers, halogens. Whereas gold(I) catalysis has become a powerful tool in synthetic chemistry, gold(III) catalysis is less implemented and often involves simple inorganic salts such as $AuCl_3$.^[16] Indeed, the coordination chemistry of gold(III) can be challenging due to reductive eliminations. In the meantime, reaction of electron rich ligands, such as NHCs or phosphanes, with inorganic gold(III) salts often result in the oxidation of the ligands and formation of gold(I) species (*e.g.* $PR_3 + AuCl_3 \rightarrow PR_3Cl_2 + PR_3AuCl$).^[17,18] Access to gold(III) complexes by oxidation of gold(I) precursors is possible but often requires harsh conditions relying on halogenated reagents such as Br_2 , Cl_2 , $PhICl_2$ or Selectfluor®. Interestingly, with naphthyl-phosphanes, aryl-diphosphanes or biphenylene ligands, various gold(III) complexes were made by oxidative insertion of gold(I) into $C_{sp^2}-X$ bonds ($X=I, Br, C$) to create $C_{sp^2}-Au(III)-X$ bonds.^[19-21] Similar insertions were also achieved with $Si-Si$, $S-S$ or $Sn-Sn$

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σ -bonds.^[22–24] Finally, access to gold(III) complexes was possible under mild conditions starting from a geometrically constrained tricoordinate gold(I) diphosphanocarborane complex.^[25] Currently, cyclometalated gold(III) complexes featuring bidentate- or tridentate- chelating ligands with C,N- coordination sites are particularly studied for catalysis and photo-luminescence purposes.^[26] Their excellent stability against reduction elimination has enabled the isolation of unusual hydride-, alkenyl-, alcoholate- gold(III) species.^[27,28] However, they have to be prepared by transmetalation between inorganic gold(III) salts and highly toxic cyclometalated Sn(IV), Hg(II) or Tl(III) complexes. Usually, Li(I) or Mg(II) reagents are not suitable and act as reducing agents to lead to the formation of gold(I) complexes or colloidal gold(0). An important driving force toward the development of new gold(III) complexes is the promise to perform more efficient homogeneous enantioselective catalysis than with gold(I) complexes.^[29,30] Similarly to known chiral palladium(II) or platinum(II) catalysts, the gold(III) cation features a square planar sphere of coordination which provides more flexibility and opportunity to control the position of a chiral fragment in the catalyst structure in order to create match/mismatch effects with the substrates.^[31] In 2011, Michelet summarized the progress made in asymmetric gold catalysis, which then mostly focused on gold(I) complexes along with

few existing examples based on gold(III).^[32] More recently, two reviews focusing on asymmetric gold catalysis have been published: one on the recent advances in the field and the other on the use of chiral NHC-type ligands,^[33,34] both mixing gold(I) and (III) compounds. However, there is no review dedicated to the synthesis of chiral gold(III) complexes despite an increasing amount of published reports in the last years. In consequence, we wish to provide a short and comprehensive overview of this field covering all well-defined chiral gold(III) complexes and, when it is the case, the associated applications reported between 2005 and 2020.

C-Ligands

N-Heterocyclic Carbenes

In 2013, Michon *et al.* reported for the first time the preparation and the catalytic application of chiral C₂-symmetric NHC gold(III) complexes.^[35] The carbene gold(III) trichloride complexes **1** and **2** were made in five steps (Scheme 1). First, the Buchwald coupling between the commercial (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (**3**) and 1-bromo-2-methoxybenzene or bromodiphenylmethane provides the chiral *N*-substituted diamines **4**

Rémi Jouhannet was born in Alençon, France, in 1997. In 2017, he received a technical university degree from Le Mans Institut Universitaire de Technologie and got his first experience in material chemistry under the supervision of Dr. Alain Demourgues in Bordeaux. He received his B.Sc. in chemistry in 2018 and his M.Sc. in organic chemistry in 2020 from Le Mans Université. His work focused on synthesis of organometallic chiral gold compounds. He is interested in organometallic and organic chemistry. He enjoys sailplane in French countryside during his spare time.



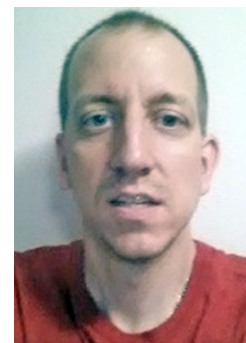
Samuel Dagorne obtained his undergraduate degree at the University of Rennes (France) in 1994. In 1995, he joined the group of Professor Richard F. Jordan at the University of Iowa (Iowa City, USA) and graduated with a Ph.D. working on chiral zirconocenes and Group 13 compounds. In 1999, he joined Professor Richard R. Schrock's group (MIT, USA) as a postdoc working on molybdenum alkylidenes. Back in France, he joined the C.N.R.S. in 2000 as a researcher and is currently a senior research scientist at the Université de Strasbourg (France). His research interests include organometallic chemistry, related fundamental reactivity, and use in catalysis.

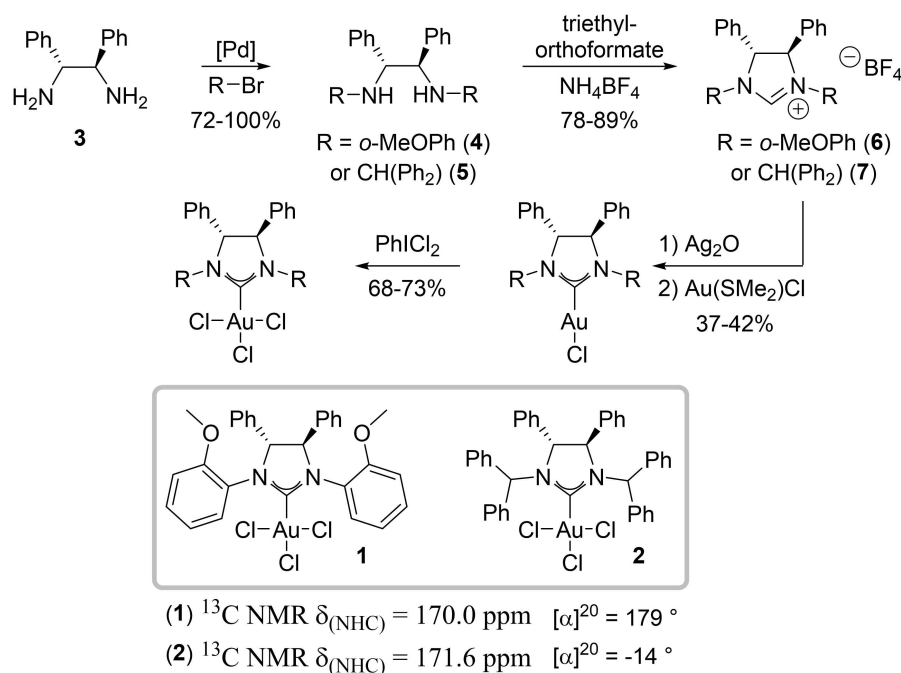


Aurélien Blanc was born in Aubenas, France, in 1976. He studied chemistry at the Joseph Fourier University in Grenoble (France). He received his Ph.D. in organic photochemistry in 2004 from the University of Geneva (Switzerland) under the supervision of Prof. Christian Bochet. After a postdoctoral stay in the group of Prof. F. Dean Toste at the University of California, Berkeley (USA), he joined the Pale's group in 2006 as a CNRS Fellow at the University of Strasbourg (France). His research mainly focuses on the development of synthetic methods catalyzed by gold.



Pierre de Frémont received his M.Sc. degree, in 2003, from Le Mans Université and his Ph.D., in 2007, from the University of New Orleans, in Prof. Steven P. Nolan's group. In 2008, he was a postdoctoral fellow at the IBM Almaden centre with Dr. James Hedrick; and in 2009, at the Université de Rennes 1 with Prof. Jean-François Carpentier. He was hired by the CNRS in 2009 and appointed to the University of Strasbourg. His research focuses mainly on the synthesis of metal NHC complexes for catalysis purpose, with a special interest on gold chemistry.

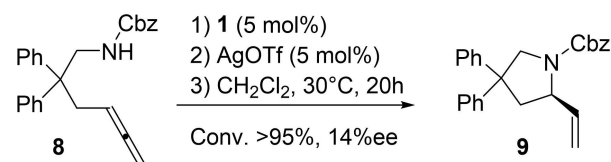




Scheme 1. Synthesis of the chiral NHC gold(III) complexes **1** and **2**.

and **5** with respectively 100% and 72% yields. Further cyclization of each chiral diamine with triethylorthoformate and NH_4BF_4 produces the imidazolium tetrafluoroborate pro-ligands **6** and **7** with 78% and 89% yields. Following a one-pot protocol described by Lin,^[36] both pro-ligands react with Ag_2O to form the corresponding cationic *bis*-NHC silver(I) tetrafluoroborate complexes which undergo transmetalation in the presence of $\text{Au}(\text{SMe}_2)\text{Cl}$ to yield the mono-NHC gold(I) chloride complexes with 37% and 42% yields. Finally, oxidation of both gold(I) complexes with dichloriodobenzene, following a protocol described by Nolan,^[37] provides the chiral NHC gold(III) trichloride complexes **1** and **2** with 68% and 73% yields. Upon oxidation, the carbene signals associated with both parent gold(I) complexes are shifted upfield by approximately 22 ppm, in line with a more Lewis acidic Au(III) metal center.^[38] Importantly, the gold(III) complexes are purified by gel chromatography (eluant: petroleum ether/acetone), prior the catalytic tests, to avoid any contamination with residual traces of silver(I) or gold(I) species which might also be potential catalysts.

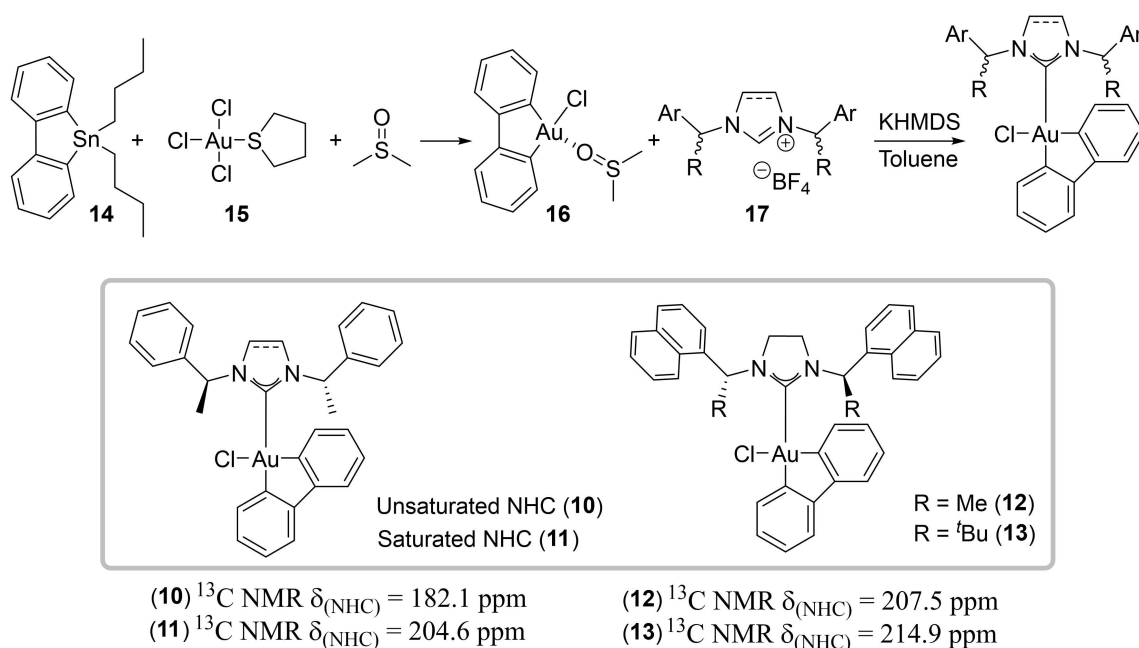
Both complexes **1** and **2** were tested for the asymmetric intramolecular hydroamination of allenes, along with some NHC and phosphoramidite gold(I) complexes. Silver triflate (AgOTf) was employed as co-catalyst to promote the substitution of chloride ligand by a less coordinating triflate, forming this way the catalytically active gold species. The tests were made in dichloromethane at 30°C with 5 mol% of catalyst and silver(I) co-catalyst. Preliminary studies made with $(\text{IPr})\text{AuCl}$ [$(\text{IPr}) = N,N'$ -(2,6-diisopropylphenyl)imidazolylidene] indicated that the hydroamination proceeds best with allenes bearing an electron deficient amine. Aminoallene **8** was used as model substrate to assess the reactivity of the chiral gold(I) and gold(III) complexes (Scheme 2). Catalysis using complex **1** provides a 95% substrate



Scheme 2. Catalytic hydroamination reaction of amine functionalized allene with complex **1**.

conversion with formation of the desired pyrrolidine **9**, while complex **2** is completely inactive. The presence of methoxy-groups on the NHC ligand supporting **1** seems to greatly enhance the activity of gold(III) center. Compared to the best enantioselectivities achieved with phosphoramidite gold(I) complexes (*ee* values up to 47%) and obtained under similar reaction conversions, complex **1** only affords 14% *ee*, and was not used further for this study.

In 2017, Toste reported a series of four chiral NHC biaryl gold(III) complexes **10–13** made in four steps.^[39] (Scheme 3) First, dibenzostannole **14** is obtained by reaction of a Grignard reagent generated *in situ* from 2,2'-dibromo-1,1'-biphenyl and magnesium, with dibutylchlorostannane. Then, the stannole **14** reacts with $\text{Au}(\text{tth})\text{Cl}_3$ **15** (tth = tetrahydrothiophene) *via* transmetalation to afford a dimeric gold(III) biphenyl chloride species. In the presence of DMSO, both chloride bridges are cleaved to afford a monomeric gold(III) biphenyl chloride **16** as a DMSO adduct. The latter reacts with chiral C2-symmetric imidazolium tetrafluoroborate pro-ligands **17**, in the presence of KHMDS to afford the desired NHC biphenyl gold(III) chloride complexes **10–13**. Unfortunately, the reaction yields are not disclosed.



Scheme 3. Synthesis of the chiral NHC biphenyl gold(III) complexes 10–13 (First generation).

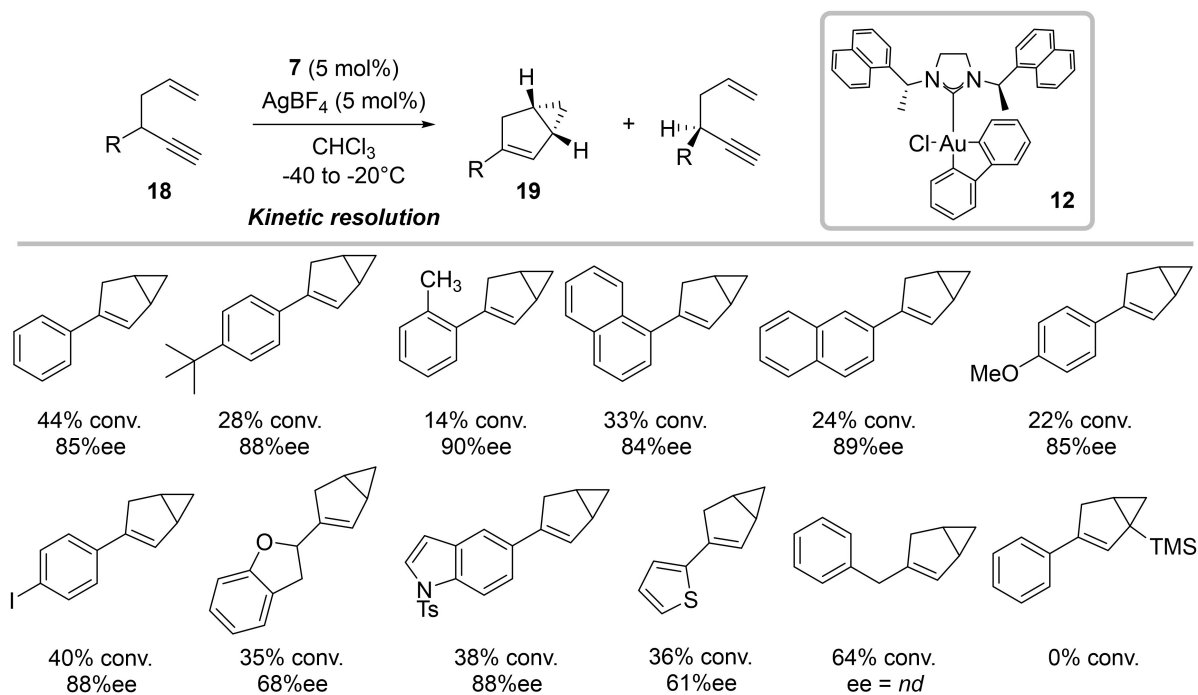
Complexes were tested for the enantioselective cycloisomerization of 1,5-enynes **18**. Optimization of the experimental conditions and mechanistic studies were carried out with the model substrate i.e., the hex-5-en-1-yn-3-ylbenzene. Silver hexafluoroantimonate (AgSbF_6) was employed to form a catalytically active cationic gold species. The tests were made in dichloromethane at 30°C , for 3 hours, with 5 mol% of catalyst and silver(I) co-catalyst. Complexes **10**–**13** allow 100% substrate conversion with formation of the desired bicyclo[3.1.0]hexene **19**. The use of saturated or unsaturated NHC ligands seems to play a role on the enantioselectivity and catalysts **10** and **11** provide respectively -24 and -34% *ee* values. Complex **12**, also supported by an unsaturated NHC but with a larger naphthyl group, offers 37% *ee*. Increasing the steric hindrance around the gold center results in a substantial loss of catalytic activity without improving the enantioselectivity, as evidenced by the 4% conversion and -2% *ee* obtained with complex **13** as catalyst. The role of the silver co-catalyst was also monitored. The use of complex **11** and AgBF_4 leads to 91% conversion and 53% *ee*. By contrast with gold(I) catalysis, the use of a triflate salt is detrimental and the conversion drops to 31%. This is likely due to the oxophilic behavior of the gold(III) cation which renders the triflate less labile. In the same line, the reaction conversions are best in dichloromethane or chloroform whereas they drastically decrease in the presence of coordinating solvents such as THF (68%), MeCN (8%), DMF (0%) without any gain for the *ees*. In toluene, the reaction conversion also decreases, however the *ee* increases to 73%. Importantly, the cycloisomerization is enantioconvergent, meaning that even at high conversion racemization does not occur, and one enantiomer of 1,5-enyne **18** remains in majority. Kinetic studies with catalyst **12**, suggest an enantioconvergent parallel kinetic

resolution which is best achieved at -40°C . The scope of the reaction was extended to enynes bearing *ortho*-substituted phenyls, or potentially coordinating *O*-, *N*-, *S*- groups. Overall, enantioselective cyclization is maintained with formation of the bicyclo[3.1.0]hexenes **19** even though higher temperatures are required (-20 or -30°C). The only noticeable exception accounts for the substrate bearing an alkyne protected by a trimethylsilyl group on the bridgehead carbon which utterly inhibits the catalyst activity (Scheme 4).

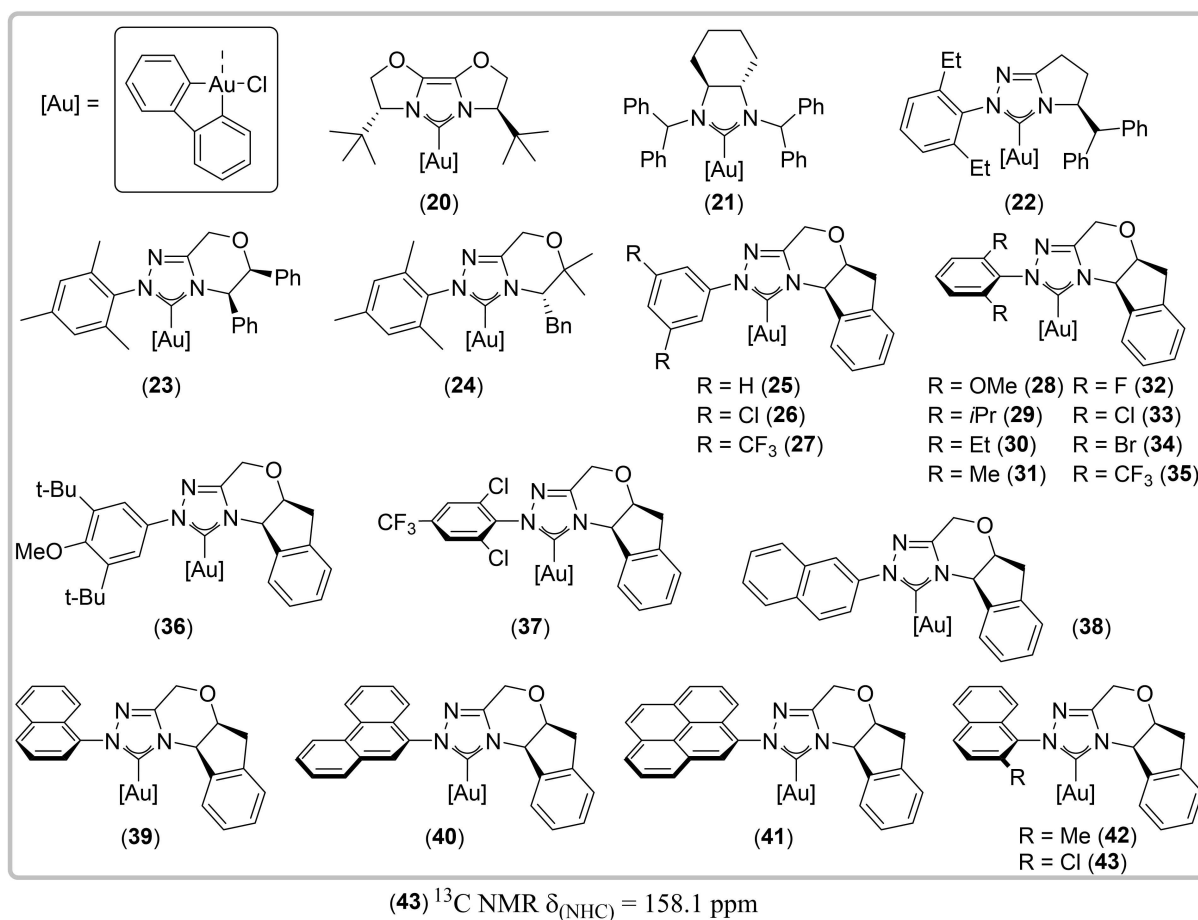
In 2020, Reid and Toste described the second generation of chiral biphenyl gold(III) complexes **20**–**43** supported by imidazolylidene- or triazolylidene- ligands, and prepared similarly to **10**–**13**: i.e. metalation of the azolium pro-ligands with a biphenylene gold(III) chloride dimer, in the presence of K_2CO_3 or potassium *bis*(trimethylsilyl)amide (KHMDS).^[40] All syntheses were deemed successful even though the authors did not provide any yields or spectroscopic data to characterize the 24 new complexes (Scheme 5).

The complexes were tested for the enantioselective γ - δ -Diels-Alder reaction of 2,4-dienals with cyclopentadiene. The conditions were set with the model substrate **44**, 10 mol% of gold(III) complexes, 10 mol% of AgNTf_2 , dissolved in a 4:1 blend of toluene and nitromethane, in the presence of molecular sieves. The reactions were performed at room temperature with time ranging from 5 to 21 h. The reaction is fully regioselective toward the formation of bicycloheptene **45** which comes as a mixture of *endo/exo*-diastereoisomers owing to the presence of two chiral carbon atoms (Scheme 6).

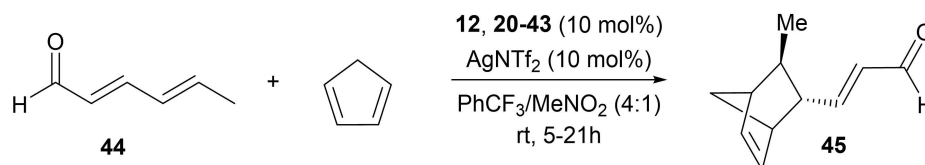
The previously reported complex **12** (see Scheme 3) and the new complexes **20**–**21** supported by symmetrical imidazolylidene ligands provides only 5 to 12% yields of bicycloheptene **45**. The *ees* are low comprised between 11% and 26%.



Scheme 4. Enantioselective cyclization of enynes mediated by complex 12.



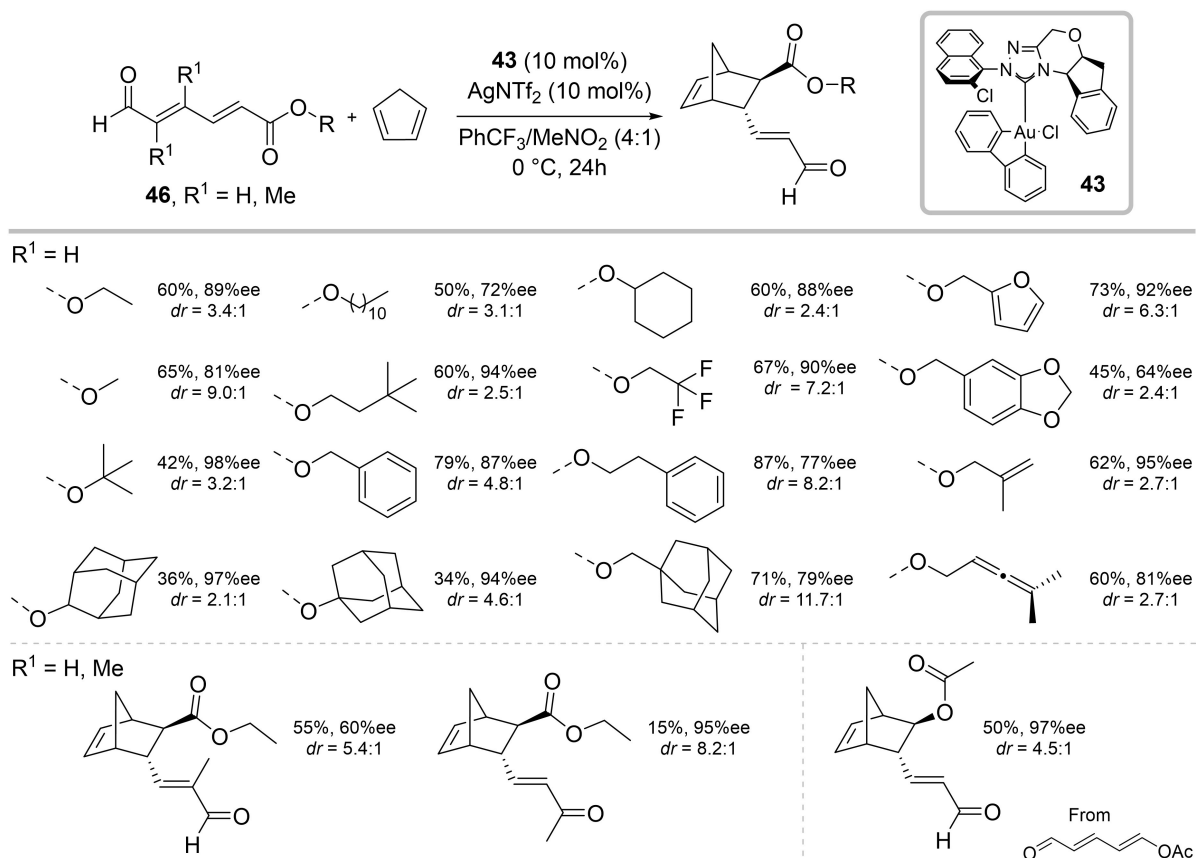
Scheme 5. Chiral NHC biphenyl gold(III) complexes 20–43 (Second generation).

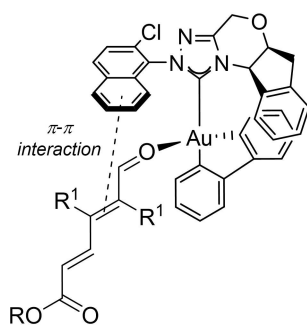
Scheme 6. Formation of the bicycloheptene **45** via Diels-Alder reaction.

Complexes **22–43** supported by unsymmetrical triazolylidene ligands incorporating a rigid fused morpholine scaffold led to an increase of the asymmetric induction. Their efficiency is further enhanced by the presence of *N*-groups comprised of substituted aryl groups for **22–37**, or polyaromatic groups for **38–43** which brings a steric constraint close from the gold cation. Following this strategy, a maximum 56% yield along with 77% ee is obtained with catalyst **43**. Further adjustments of the reaction conditions reveal that lowering the temperature to 0 °C is beneficial, yielding higher ees without sacrificing the catalyst activity. The catalytic performance is also retained in the presence of the silver salt (arising from the co-catalyst). The scope of the reaction was done with various 2,4-dienesters derivatives **46** as those electron deficient substrates result in higher yields than with **43**, while retaining similar ees (Scheme 7).

Mechanistic studies support the coordination of gold to the carbonyl moiety to initiate the catalytic cycle. Interestingly, intramolecular cyclization, as a possible side-reaction, does not occur in the presence of ester groups bearing additional unsaturations. The origin of the high stereoselection observed was attributed to attractive non-covalent interactions between the catalyst and the substrate, notably a putative π - π interaction between the proximal double bond of **46** and the aromatic group of catalyst **43** is an essential feature for high enantioselectivity (Scheme 8).

From a historical point of view, the first occurrence of enantioselective transformation mediated by chiral NHC gold (III) complexes was disclosed by Corma *et al.* in 2010 (Scheme 9).^[41] Four chiral gold(III) complexes **47–50** supported by unsymmetrical *C,N,N*-pincer ligands with the objective of stabilizing the metal center were prepared in 4 or 5 steps. Their

Scheme 7. Scope of the cycloaddition of cyclopentadiene with catalyst **43**.



Scheme 8. Putative π - π interaction between at the origin of the high enantioselectivity.

synthesis started by two successive nucleophilic substitutions carried out on 2,6-bis(bromomethyl)pyridine (**51**) with 1-aryl-1*H*-imidazole **52** and (*S*)-*N*-(*tert*-butyl)pyrrolidine-2-carboxamide (**53**) with overall yields of 80%. Following the Lin's method,^[36] both pro-ligands **54** react with Ag_2O to form the corresponding NHC silver(I) bromide complexes **55** which undergoes transmetalation in the presence of KAuCl_4 to provide the chiral cationic chloride gold(III) complexes **47** and **48** in >90% yield. Silver hexafluorophosphate (AgPF_6) was employed to generate complexes **49** and **50**, *via* a salt metathesis route.

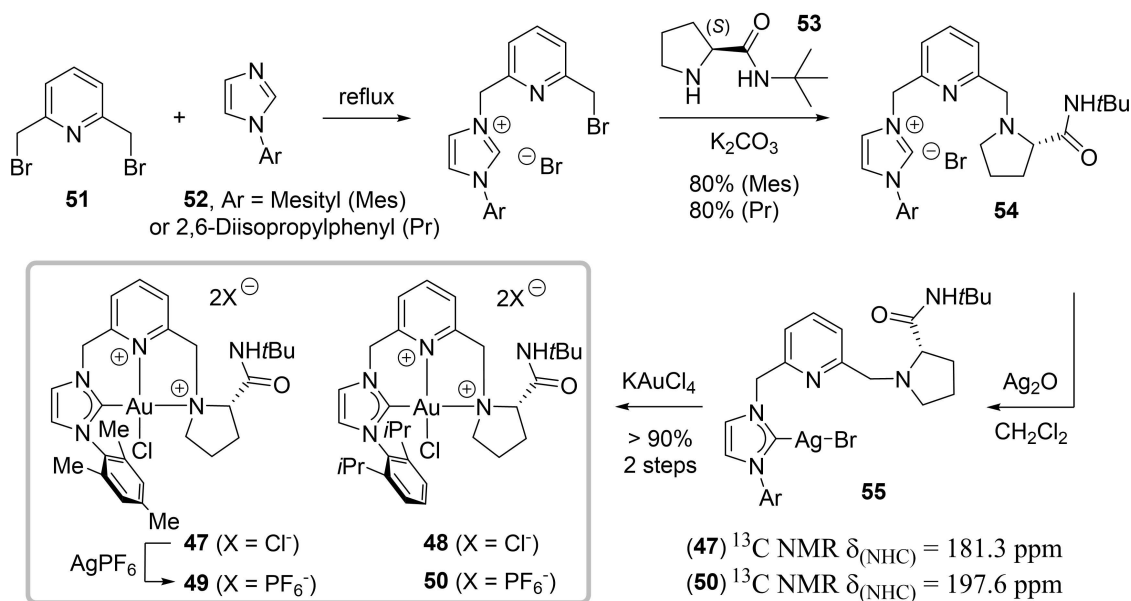
Of note, the coordination of the pyrrolidine moiety on gold atom generated a new chiral center with the diastereoselective formation of complexes **47** and **48**.

The catalytic activity of cationic hexafluorophosphate complexes **49** and **50** was tested for the hydrogenation of diethyl itaconate (**56**, $\text{R}=\text{H}$) and diethyl 2-benzylidenesuccinate (**56**, $\text{R}=\text{Ph}$) (Scheme 10). Despite the high TOF observed for both catalysts in the hydrogenation of diethyl itaconate, low enantiomeric excesses were obtained. However, the hydrogenation of the bulkier diethyl 2-benzylidenesuccinate led to excellent ees up to 90% with only 0.1 mol% of catalyst.

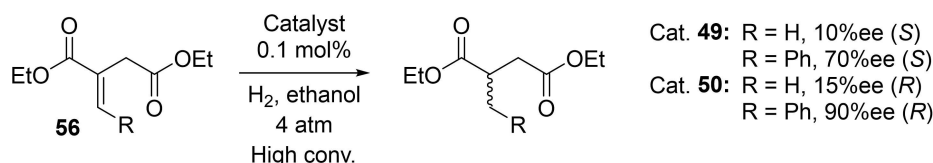
C,N-Pincer Ligands

In 2017, Quayle *et al.* prepared efficiently (*S*)-(2-(1-(dimethylamino)ethyl)phenyl)gold(III) chloride complex (**57**) (Scheme 11).^[42] The synthesis of the C,N-pincer ligand started by *ortho*-lithiation of the chiral tertiary amine **58** with *tert*-butyllithium. Then addition of dichlorodimethylstannane led to a stannanyl complex **59** (58% over 2 steps) which further underwent transmetalation with NaAuCl_4 to afford the chiral gold(III) complex **57** in 85% yield.

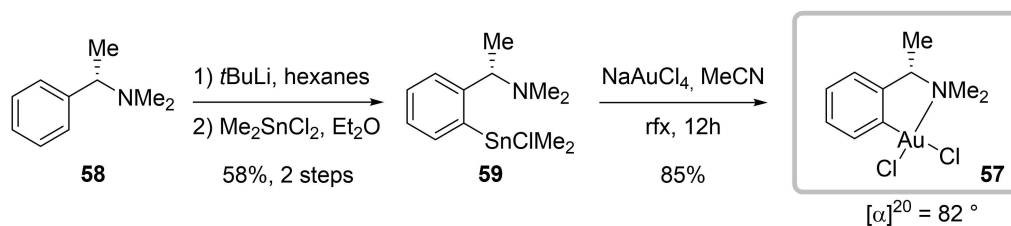
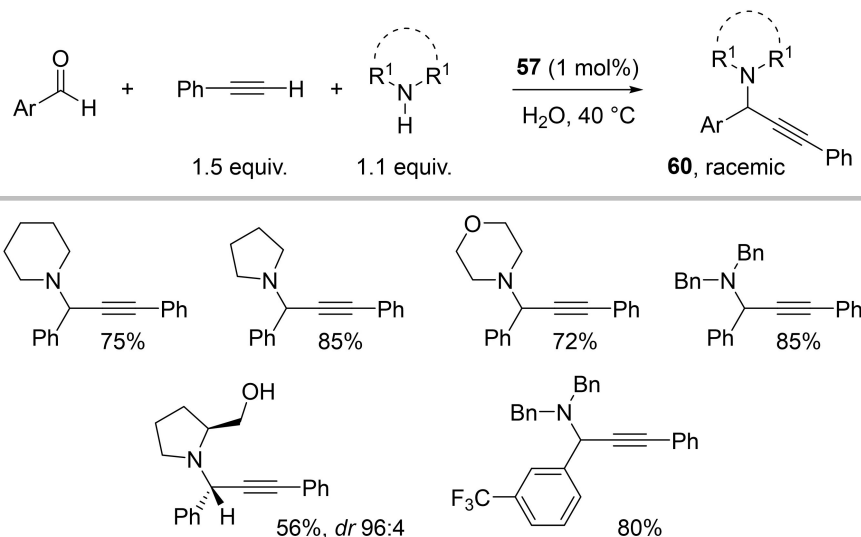
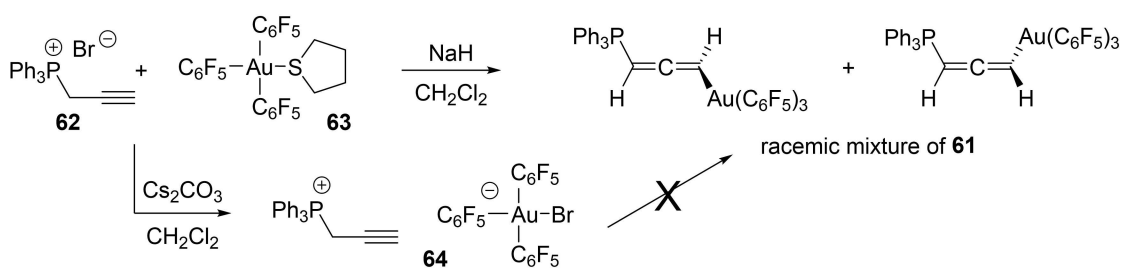
Chiral complex **57** was applied to A^3 -coupling reactions in water. Propargylamines **60** were obtained in good yields



Scheme 9. Synthesis of chiral NHC-N,N-pincer gold(III) complexes **47**–**50**.



Scheme 10. Application of **49**–**50** to asymmetric hydrogenation.

Scheme 11. Synthesis of chiral gold(III) complex **57** supported by C,N-pincer ligand.Scheme 12. Examples of racemic propargylamines **60** formed by A³ coupling catalyzed by **57**.Scheme 13. Synthesis of the gold(III) allenyl complex **61**.

starting mainly from benzaldehydes and phenylacetylene along with various secondary amines using 1 mol% of catalyst, but without any asymmetric induction (Scheme 12).

Allene Ligands

In a contribution published in 2015, Gimeno *et al.* reported the synthesis of **61** as first example of gold(III) allenyl complex which also incorporates an axis of chirality.^[43] The reaction of propargylphosphonium bromide **62** with Au(C₆F₅)₃(tht) **63** in the presence of sodium hydride, in dichloromethane, produces **61** with 65% yield as a racemic mixture. The reaction does not

proceed with the weaker base Cs₂CO₃ yielding to phosphonium/bromoaurate ion pair **64** (Scheme 13).

The allenic nature of **61** is evidenced by ¹³C NMR spectrometry with three characteristic signals at 65.6, 86.4 and 205.6 ppm. It is important to note that the phosphorous ylide ligand can exist as internal or external alkyne mesomers in polar solvents or allene mesomers in non-polar solvents. Contrary to analogous gold(I) allenyl complexes which feature a σ-gold-carbon bond located at the α-carbon atom of the ylide, the characterization of **61** by ¹H NMR and single crystal X-ray diffraction (SC-XRD) reveals the formation of a σ-gold-carbon bond located at the γ-carbon atom of the ylide. The complex crystallizes in the non-chiral P2₁/c space group with both (S)

and (*R*) enantiomers in the asymmetric unit. The carbon/carbon bond lengths range from 1.276 to 1.322 Å, in agreement with the presence of an allene moiety. This difference of regioselectivity is explained by the bulkiness of [Au(C₆F₅)₃(tbt)] (compared to [Au(C₆F₅)₃(tbt)] which prevents the coordination at the α-position. The complex **61** is thermally stable and retains its allenic form along with η¹-gold coordination at low or high temperature. The authors did not test the allenyl gold complexes for catalysis, even though they are likely involved as gold intermediates in various catalytic cycles.

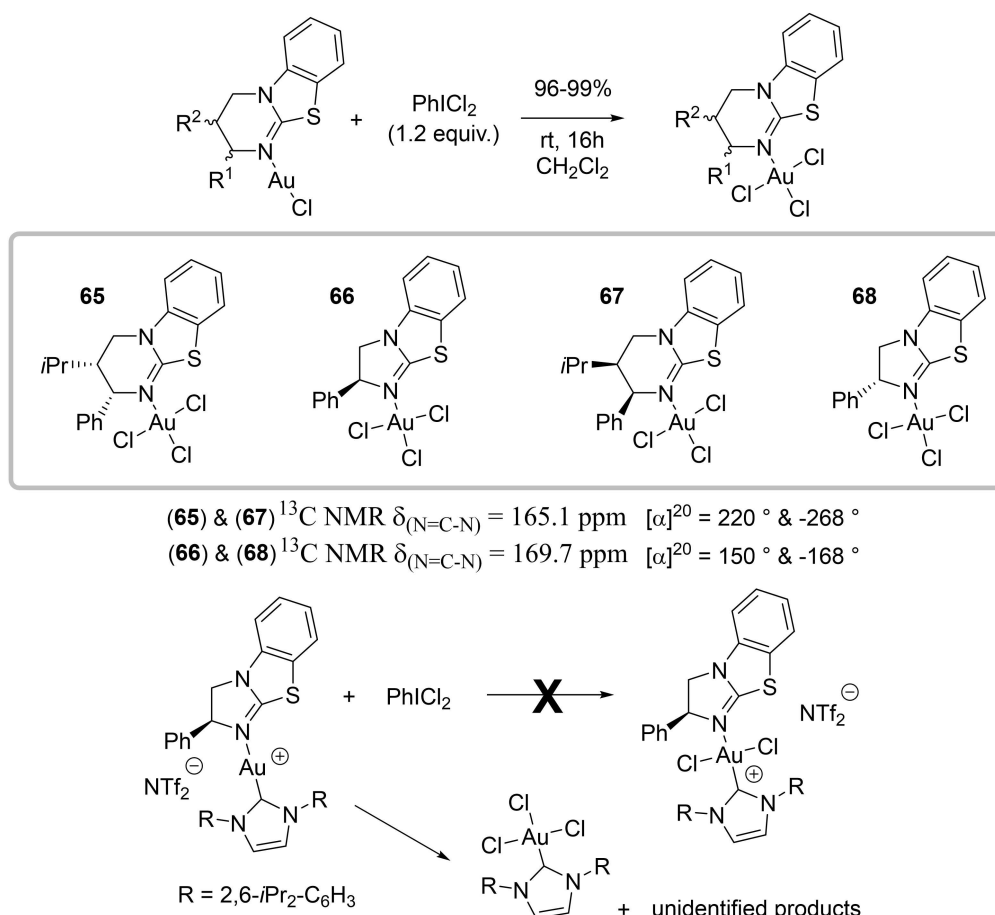
N-Ligands

Isothioureas

In 2019, while synthesizing a series of chiral isothiourea gold(I) complexes supported by NHC- and phosphane- ligands, Smith and Nolan reported the chiral thiazolopyrimidine gold(III) trichloride **65** and **66** complexes as well as their opposite enantiomers **67** and **68**, with yields above 96% and synthesized by oxidation of neutral isothiourea gold(I) chloride complexes with dichloriodobenzene (PhICl₂), at room temperature, in dichloromethane.^[44] No oxidation at the sulfur position was

observed. Other oxidants such as elemental bromine or (diacetoxyiodo)benzene (PhI(OAc)₂) led to untraceable mixtures of products. Importantly, attempts to oxidize a parent NHC gold(I) isothiourea complex was unsuccessful, yielding mainly (NHC) AuCl₃ among some other unidentified gold(I)/(III) species (Scheme 14). Formation of the complexes was monitored by NMR and FTIR spectroscopies. Upon coordination, the N=C–N moieties of **65** and **66**, feature ¹³C chemical shifts and vibration bands respectively shift by +6.6, +3.1 ppm and –53, –33 cm⁻¹, compared to free isothioureas.

Upon activation with NaBAR₄, complexes **65** and **66** promote the quantitative conversion of propargylic alcohol (1,3-diphenylprop-2-yn-1-ol) and mesitylene into the allene (1-mesitylpropa-1,2-diene-1,3-diy) dibenzene, at room temperature in dichloroethane. The reaction is completely regioselective with no formation of alkyne side products resulting from addition at the C1 position of the mesitylene. However, it fails to induce enantioselectivity, and pure racemates of allenes are obtained (Scheme 15). Finally, complex **66** is potent against cervical and breast cancer cell lines. Compared to the most potent gold(I) isothiourea complexes which are also cytotoxic (for healthy cells), the gold(III) complex **66** features similar potency; but without any cytotoxicity. Interestingly, the enantiomer **68** is not biologically active. Other tests to inhibit various



Scheme 14. Synthesis of chiral gold(III) isothiourea complexes **65**–**68** and attempt to oxidize a parent NHC gold(I) isothiourea complex.

enzymes show a specific activity of **66** with the β -glucuronidase found in cell lysosomes.

Dihydropyrroles

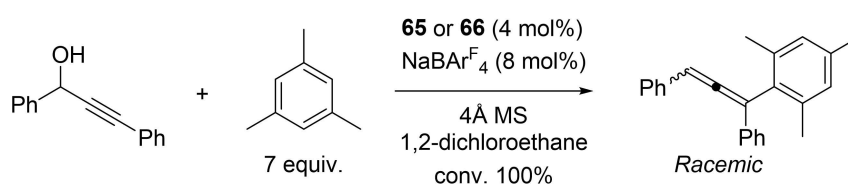
In 2020, Uriac studied the coordination of the ligand chiral dihydro-2*H*-pyrrole **69** in the presence of gold(III) salts. In chloroform with AuCl₃ or in methanol with NaAuCl₄, the pyrrole gold(III) trichloride complex **70** (*N*-coordination), or the vinyl-gold(III) trichloride complex **71** (*C*-coordination) were respectively made with 49% and 38% yields (Scheme 16, top).^[45] Complex **71** reacts further with an excess of gold(III) trichloride to form the aurocycle **72** with 26% yield. It was characterized by NMR, MS spectroscopies and SC-XRD. The aurocycle is quasi-planar due the coordination geometry of the gold(III) center. Finally, complex **72** dimerizes quantitatively in the presence of K₂CO₃ in acetone to afford a mixture of two diastereoisomers of homodimeric complexes **73** and **74** (Scheme 16, bottom).

The dimerization proceeds *via* the deprotonation of the pyrrolidinium site which further substitutes a chloride ligand at the gold cation along with HCl release. At room temperature, complex **73** is formed with 20% of diastereoisomeric excess (*de*). At -50°C , it increases to 50%. The solid-state structure of

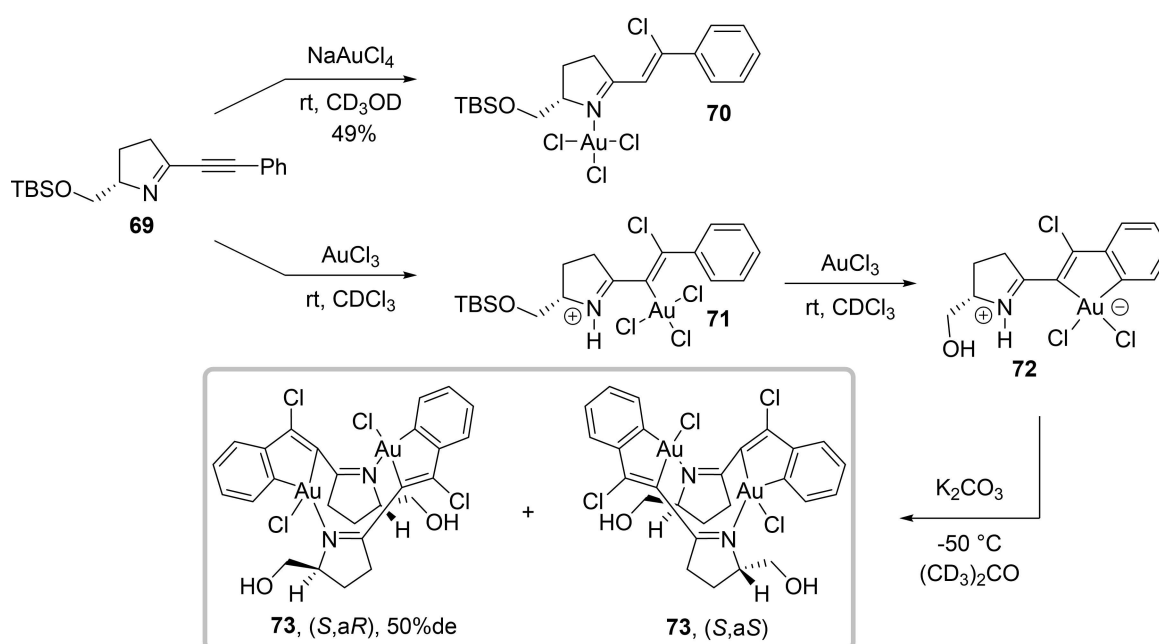
73 was confirmed by SC-XRD studies. The catalytic activity of **73** and **74** was briefly assessed for the cyclization of the *N*-Boc protected amino-ynone substrate **75**. In dichloromethane, at room temperature, 5 mol% of a 60:40 mixture of **73**:**74** along with 5 mol% of AgSbF₆ promote the formation of pyrrolidinone **76** quantitatively after 12 hours (Scheme 17).

Diamines (*N,N*-pincers)

In 2013, Isab *et al.* reported the racemic mixtures of the cationic complexes *cis*- and *trans*-1,2-diaminocyclohexane gold trichloride (**77** and **78**), as potential anticancer drugs.^[46] In 2015, they also described the enantiopure cationic complexes (1*R*,2*R*)-(–)-1,2-diaminocyclohexane gold trichloride (**79**) and *bis*-(1*R*,2*R*)-(–)-1,2-diaminocyclohexane gold trichloride (**80**).^[47] In absolute ethanol, direct complexation of sodium tetrachloroaurate with the chiral *N,N*-ligand afford all complexes as crystalline powder (Scheme 18). Their formation is confirmed by NMR spectroscopy with characteristic shifts upfield from both proton- and carbon-atoms in the vicinity of the gold cation. FTIR spectroscopy also confirms the formation of N–Au bonds with characteristic bands around 395 cm⁻¹, while the bands associated to N–H vibrations in the range of 3200–3500 cm⁻¹ undergo a blue-shift compared



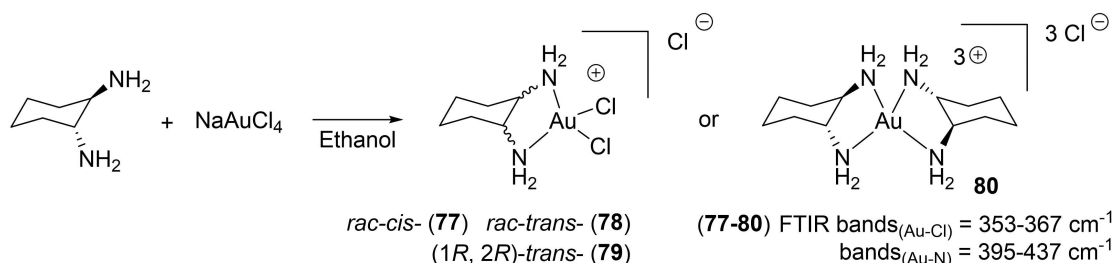
Scheme 15. Formation of the allene catalyzed by **65–66**.



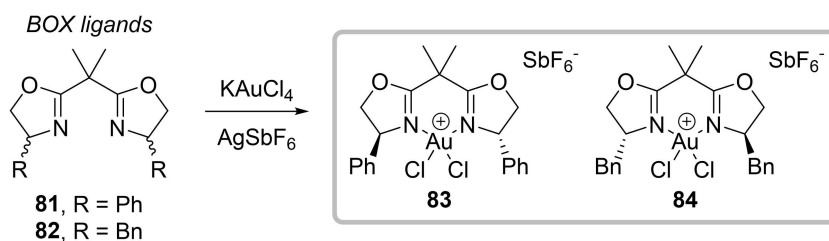
Scheme 16. Synthesis of chiral pyrrole- or vinyl-gold(III) complexes **70–71** and subsequent transformation of **71** into aurocycle **72** and homodimers **73–74**.



Scheme 17. Cyclization of amino-ynone **75** catalyzed by a mixture of the complexes **73–74**.



Scheme 18. Synthesis of chiral diamine gold(III) complexes **77–80**.



Scheme 19. One pot synthesis of chiral BOX gold(III) complexes **83–84**

to those of the free ligand. The solid-state structures of **77–80** confirmed by SC-XDR feature a gold(III) cation with a classic square planar coordination sphere. The complexes are potent against ovarian carcinoma derived cells, human gastric cancer cells, and prostate cancer cells, some of them being *cis*-platin resistant. The *cis*-complexes display the highest cytotoxicity (compared to *trans* isomers). However, the associated high IC₅₀ values should preclude any possible use as drug.

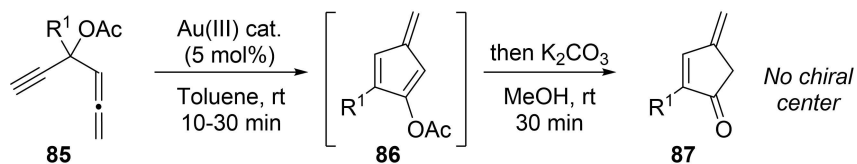
Oxazolines (N,N-Pincers)

In 2008, Akita et al. reported the one-pot reaction of commercially available and chiral C₂-symmetric bisoxazoline ligands (BOX) **81** and **82** with KAuCl₄, in the presence of AgSbF₆ (Scheme 19).^[48] Unfortunately, no yields have been disclosed for the preparation of the cationic hexafluoroantimonate gold complexes **83** and **84**.

Complexes **83** and **84** were tested as catalysts for the rearrangement of 1-allenyl-1-ethynyl acetates **85** into unstable fulvenes **86** which were *in situ* methanolized to 4-methylene-2-cyclopentenones **87** in 60–69% yields (Scheme 20). No attempt to promote asymmetric induction with these complexes has been reported.

A decade later, Fiksdhal *et al.*^[49] extended the scope of the preparation of chiral BOX gold(III) complexes using the same conditions described by Akita.^[48] In the presence of various silver salts (AgSbF₆, AgBF₄, AgBARF, or AgNTf₂) at room temperature and in acetonitrile, a series of five new cationic complexes **88–92** along with the previously described complex **83** were obtained with yields ranging from 28 to 85% (Scheme 21).

The complexes were briefly characterized by NMR and mass spectroscopy prior to further use in cyclopropanation catalysis of terminal propargylic esters with alkenes. Most of the tests were made with 5 mol% of hexafluoroantimonate gold complexes **83** and **88**, and the influence of the anion appeared marginal. After 15 min, at room temperature, both catalysts provide full conversion of aryl propargyl esters **93** and styrene into cyclopropane derivatives **94** (Scheme 22). Despite the chiral nature of the catalyst, all cyclopropyl products obtained are racemic mixtures. However, fast isomerization from *cis*- to *trans*-cyclopropyl occurs during catalysis. Upon prolonged reaction times (up to 24 h), the ratio *trans/cis* increases to 99:1, whereas decreasing the catalyst loading to 1 mol% results in lower ratios. Finally, at room temperature, complexes **83** and **88** also promote the conversion of *cis*-cyclopropanes into the corresponding *trans*-cyclopropanes with ratio up to 95:5 after 2–5 h.



with **83** or **84**: R¹ = (CH₂)₂Ph, 60% over 2 steps

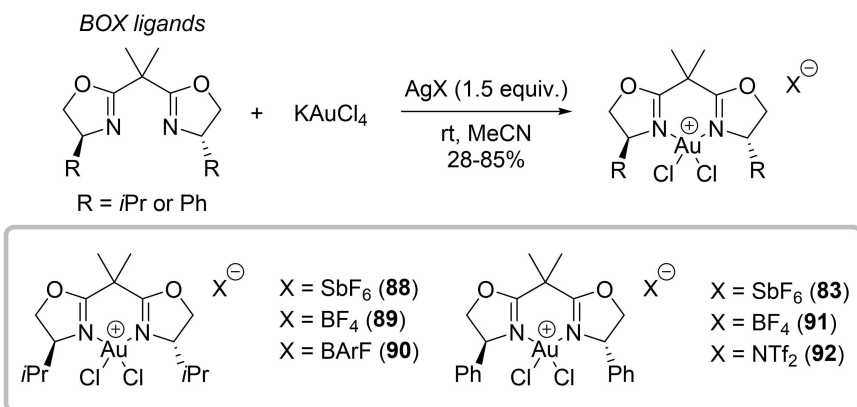
with **83**: R¹ = (CH₂)Ph, 69%

R¹ = Nonyl, 66%

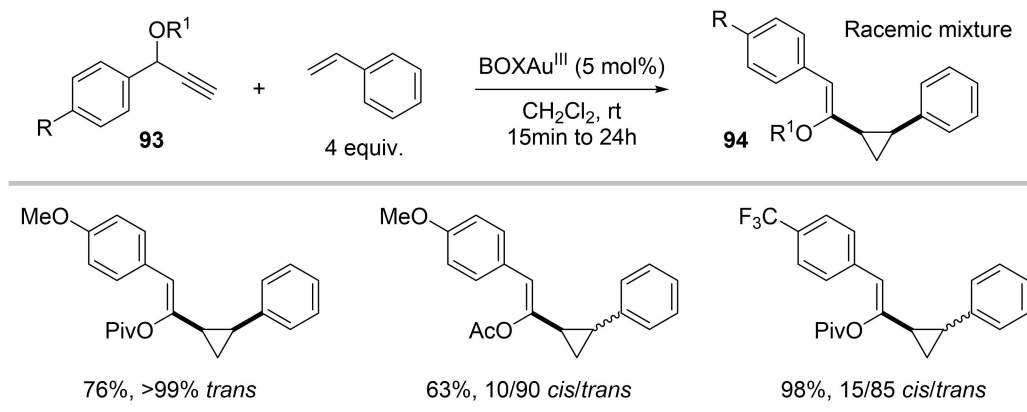
R¹ = Octyl, 63%

R¹ = CH₂CHMe(CH₂)₂CH=CMe₂, 60%

Scheme 20. Cycloisomerization of 1-allenyl-1-ethynyl acetate derivatives **85** catalyzed by bisoxazoline gold(III) complexes **83** or **84**.



Scheme 21. One pot synthesis of the chiral BOX gold(III) complexes **83**, **88**–**92**.

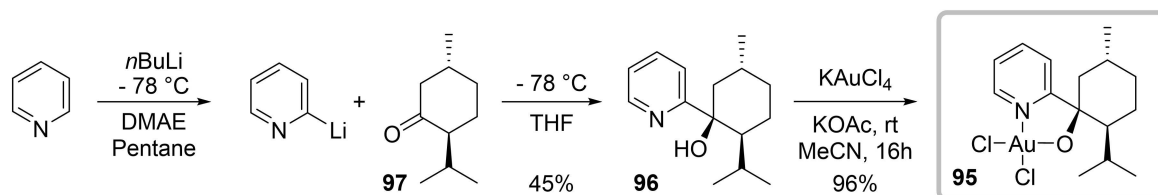
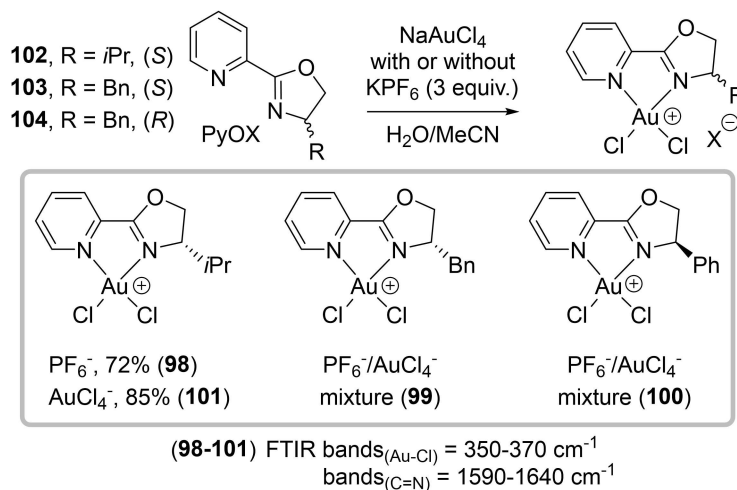
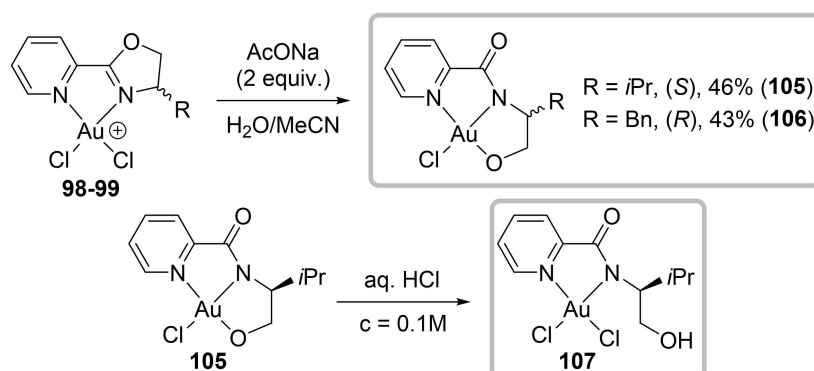


Scheme 22. Cyclopropanation of propargylic esters and styrenes catalyzed by (BOX)Au(III) species.

Fiksdhal also reported the synthesis of the neutral complex pyridinyl(–)-mentholate gold(III) dichloride **95** with 96% yield, along with the BOX complexes previously described.^[49] The chiral pyridinyl-*N,O*-pincer **96** was synthesized first by diastereoselective addition of lithiated pyridine to (–)-menthone **97**, then reacted with KAuCl₄ in the presence of potassium acetate in acetonitrile (Scheme 23). Compared to **83** and **88**, under similar catalysis conditions, complex **95** features only a modest

activity providing 16% of cyclopropanes after 24 h. It was not studied further.

In 2009, chiral pyridine-oxazoline ligands (PyOX) were used by Cinellu *et al.* to prepare cationic gold(III) complexes **98**–**101** (Scheme 24).^[50] PyOX **102**–**104** in the presence of NaAuCl₄ in acetonitrile/water, with or without KPF₆, provided chiral gold(III) complexes **98**–**101**. With an excess of KPF₆, only the well-defined cationic hexafluorophosphate gold(III) complex **98** was obtained in 72% yield while the two other complexes **99**–**100**

Scheme 23. Synthesis of the pyridinyl-(–)-menthol gold(III) complex **95**.Scheme 24. Synthesis of chiral PyOX gold(III) complexes **98–101**.Scheme 25. Preparation of neutral chiral gold(III) complexes **105–107** from PyOX-Au(III) complexes **98** and **99**.

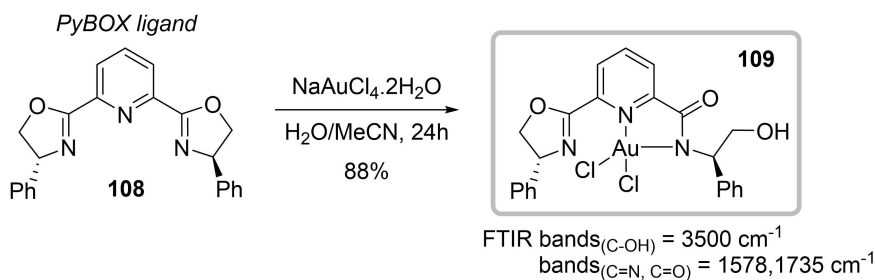
were isolated as a mixture of two anions $\text{PF}_6^-/\text{AuCl}_4^-$. In the absence of KPF_6 , tetrachloroaurate salts were formed but only the complex **101** have been characterized.

The potential catalytic activity of PyOX gold(III) complexes **98–101** was not tested in catalysis but their reactivity was explored. In the presence of water and 2 equivalents of sodium acetate, **98** and **99** afforded two new neutral gold(III) complexes **105** and **106** supporting *O,N,N*-pincer ligands, which arise from the ring-opening of the oxazoline rings, in respectively 46 and 43% yields (Scheme 25). The reaction of the so-formed complex **105** with aqueous HCl at room temperature provided complex

107 by protonation of the alkoxy oxygen atom and the coordination of the chloride anion (Scheme 25).

Finally, the polymerization of styrene or methoxystyrene was briefly investigated using 5 mol% of complex **107** activated by AgPF_6 or $\text{HBF}_4 \cdot \text{Et}_2\text{O}$, to afford atactic polystyrene materials.

The same year, Corma *et al.* tried to use a tridentate chiral PyBOX ligand to prepare the corresponding gold(III) complex supporting *N,N,N*-pincer ligand.^[51] However, the reaction of oxazolyropyridine **108** with $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ did not afford the expected gold(III) complex but the formation in good yield of the neutral ring-opened complex **109** due to the hydrolysis of

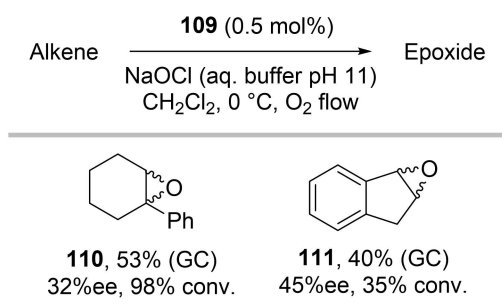


Scheme 26. Preparation of chiral gold(III) complex **109** from PyBOX ligand.

one oxazoline ring (Scheme 26) such as described by Cinellu with PyOX ligands (Scheme 25).

Complex **109** was tested for the enantioselective epoxidation of activated olefins (Scheme 27). The oxidation of 1-phenylcyclohexene was realized with only 0.5 mol% of catalyst with sodium hypochlorite as oxidant in a biphasic system under oxygen flux affording the corresponding epoxide **110** with a moderate selectivity and 32% ee. The best enantiomeric excess

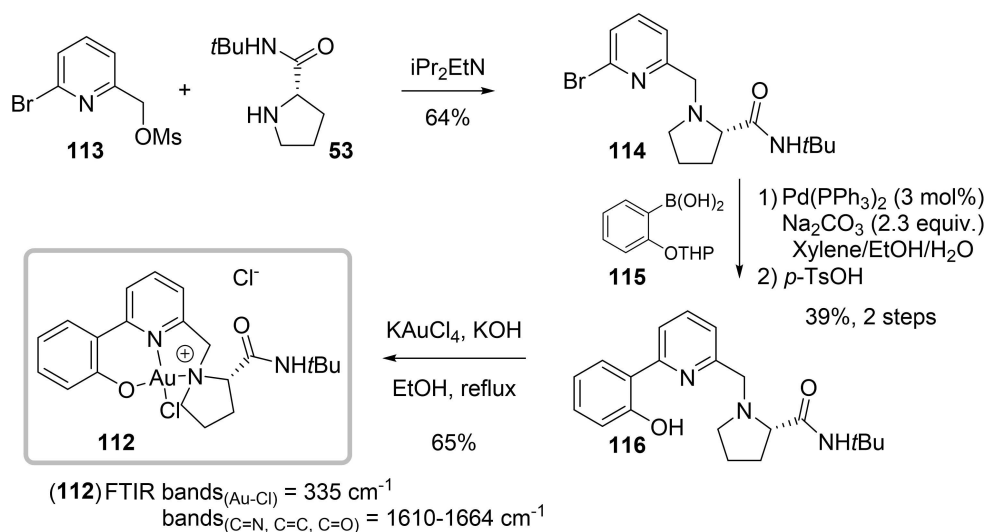
(45% ee) was obtained for the epoxidation of indene (**111**) under the same conditions.



Scheme 27. Asymmetric catalytic epoxidation of prochiral olefin with **109** using NaOCl as oxidant.

N,N,O-/N,N,O,O-Pincers

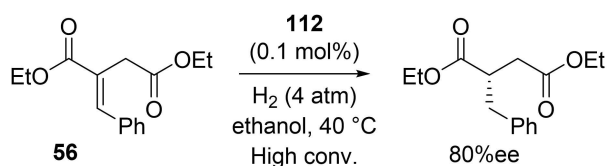
In 2007, Sánchez *et al.* prepared cationic chiral gold(III) complex **112** supported pyridine *N,N,O*-pincer (Scheme 28) and applied it to asymmetric hydrogenation.^[52] The synthesis of the complex began by nucleophilic substitution of (6-bromopyridin-2-yl) methyl methanesulfonate (**113**) with chiral pyrrolidine **53** conducted in acetonitrile in the presence *N,N*-diisopropylethylamine yielding the 2-bromopyridinyl derivative **114** in 64%. Subsequent Suzuki cross-coupling with phenylboronic acid derivative **115** catalyzed by Pd(PPh₃)₄ and acid deprotection of the THP protecting group resulted in the formation of the tridentate pro-ligand **116** in 39% over 2-steps. Complexation of gold(III) (KAuCl₄) was achieved in hot ethanolic solution in the presence of KOH with 65% yield. As for chiral NHC-*N,N*-pincer gold(III) complexes **47** and **48** reported by the same group (Scheme 9), the coordination of the pyrrolidine moiety was completely stereospecific.



Scheme 28. Synthesis of chiral pyridine *N,N,O*-pincer gold(III) complex **112**.

Complex **112** was tested for the asymmetric hydrogenation of diethyl 2-benzylidenesuccinate **56** (Scheme 29). Diethyl (*S*)-2-benzylsuccinate was obtained in 80% *ee* along with an excellent conversion using only 0.1 mol% of catalyst. It is noteworthy that this complex was also active in hydrosilylation reactions of acetophenone or benzaldehyde with diphenylsilane.

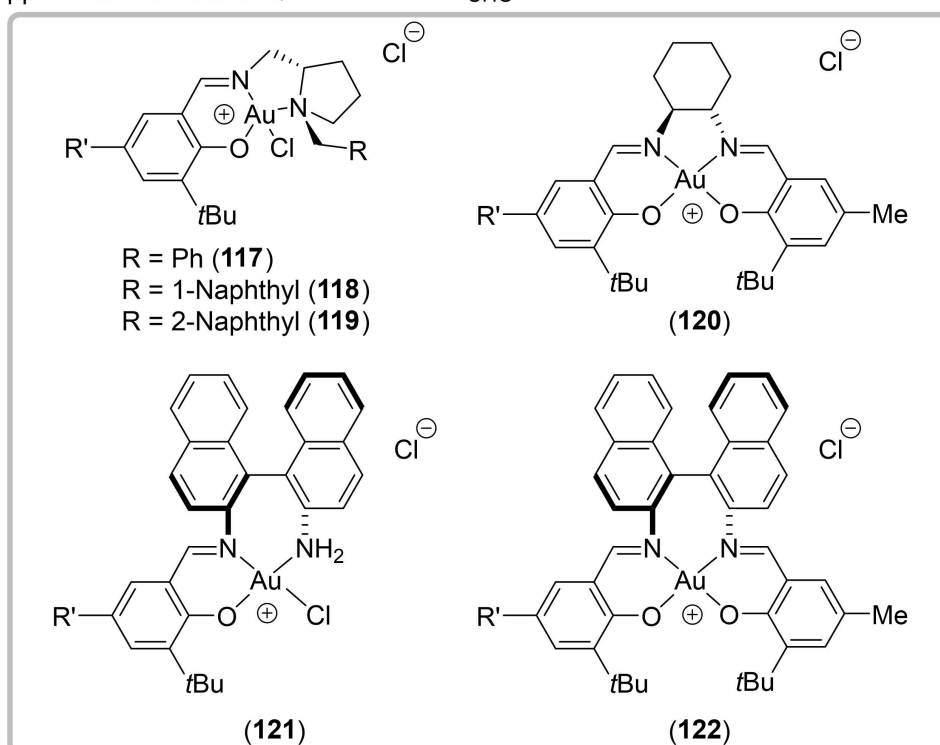
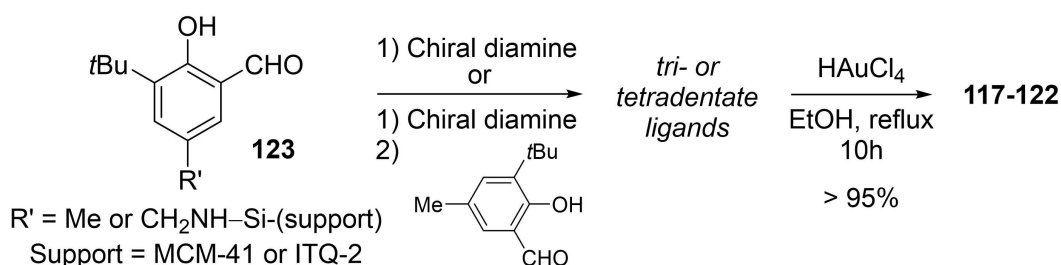
In 2005, Corma *et al.* have also reported the preparation of chiral gold(III) Schiff base-complexes in homogeneous or



Scheme 29. Application of **112** to asymmetric hydrogenation catalysis of diethyl 2-benzylidenesuccinate **56**.

heterogeneous versions.^[53] The general synthetic pathway is depicted on Scheme 30 for complexes **117–122** and their versions supported on mesoporous silica (MCM-41) or deaminated zeolitic material (ITQ-2). The preparation of *N,N,O*-tridentate pro-ligands was based on imine formation between chiral diamines and the 3-(*tert*-butyl)-2-hydroxy-5-methylbenzaldehyde (**123**) or its corresponding supported version while the *N,N,O,O*-tetradentate salen pro-ligands required a second condensation of **123** on the remaining free amine. The complexation of gold(III) was achieved in nearly quantitative yields by refluxing pro-ligands and HAuCl_4 in ethanol for 10 h.

Only complexes **117**, **120** and **122** were tested as catalyst for the homocoupling of several boronic acids (Scheme 31). Using 30 mol% of soluble gold(III) catalyst, aryl boronic acids dimerized with high yields, in xylene, at 130 °C in the presence of potassium carbonate. The reactivity is not affected by the electron donating- or electron withdrawing- nature of the R substituents. The supported versions of the catalysts **117** and **122** gave the same range of yields while the supported



(**117–122**) FTIR bands_(Au-OH) = 500–600 cm^{-1} ^{13}C NMR $\delta_{(\text{C}=\text{N})}$ = 162 ppm
bands_(C=N, C=C) = 1590–1600 cm^{-1}

Scheme 30. Synthesis of homogeneous and heterogeneous chiral gold(III) Schiff base-complexes **117–122**.

complex **120** was superior to its homogeneous version with yields > 94%.

In 2007, Corma *et al.* studied the catalytic activity of homogeneous and heterogenized complexes **119** and **122** for the asymmetric hydrosilylation of α -methylstyrene (Scheme 32). Despite good conversions, the enantiomeric excesses did not exceed the 25%.^[54]

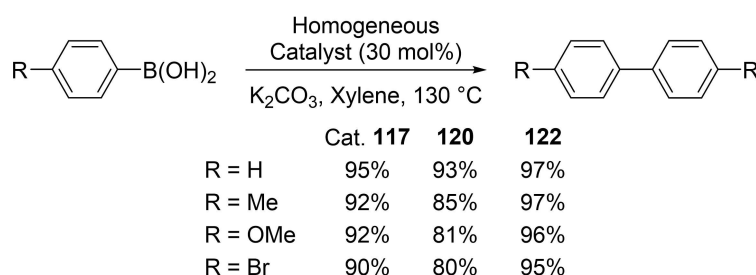
O-Ligands

BINOLs

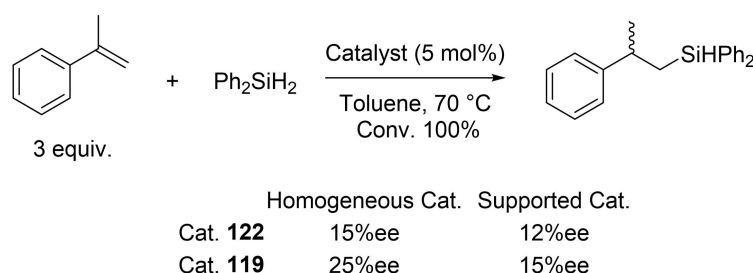
In 2017, Wong reported the synthesis of oxazolyphenyl gold(III) dichloride **124** with 87% yield *via* transmetalation between an

aryl mercury(II) precursor and KAuCl_4 . Capitalizing on the good stability of **124** against reductive elimination provided by *C,N*-chelation, it was then reacted with (*S*)-BINOL in the presence of cesium carbonate, in acetonitrile to afford complex **125**, with 85% yield (Scheme 33).^[55]

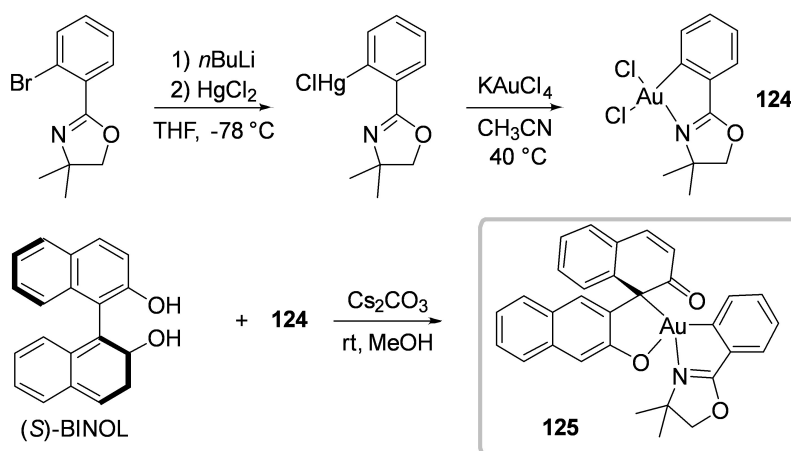
The synthesis features two remarkable aspects: 1) under basic conditions, the pro-ligand BINOL tautomerizes into the enol-keto form which undergoes complexation *via* $\kappa^2\text{-C,O}$ -chelation, due to the high carbophilic character of gold. Even though, a *O,O*-chelation was initially anticipated, *C,O*-chelations of BINOLs are reported for palladium(II) and platinum(II) complexes which feature the same electronic configuration d^8 and square planar geometry of coordination than gold(III); 2) complete transfer from axial- to central- chirality occurs providing **125** as (*R*)-enantiomer with 100% ee. By extension,



Scheme 31. Self-coupling of boronic acids catalyzed by homogeneous complexes **117**, **120** and **122**.



Scheme 32. Asymmetric hydrosilylation of α -methylstyrene catalyzed by homogeneous complexes **119** and **122** and supported versions.

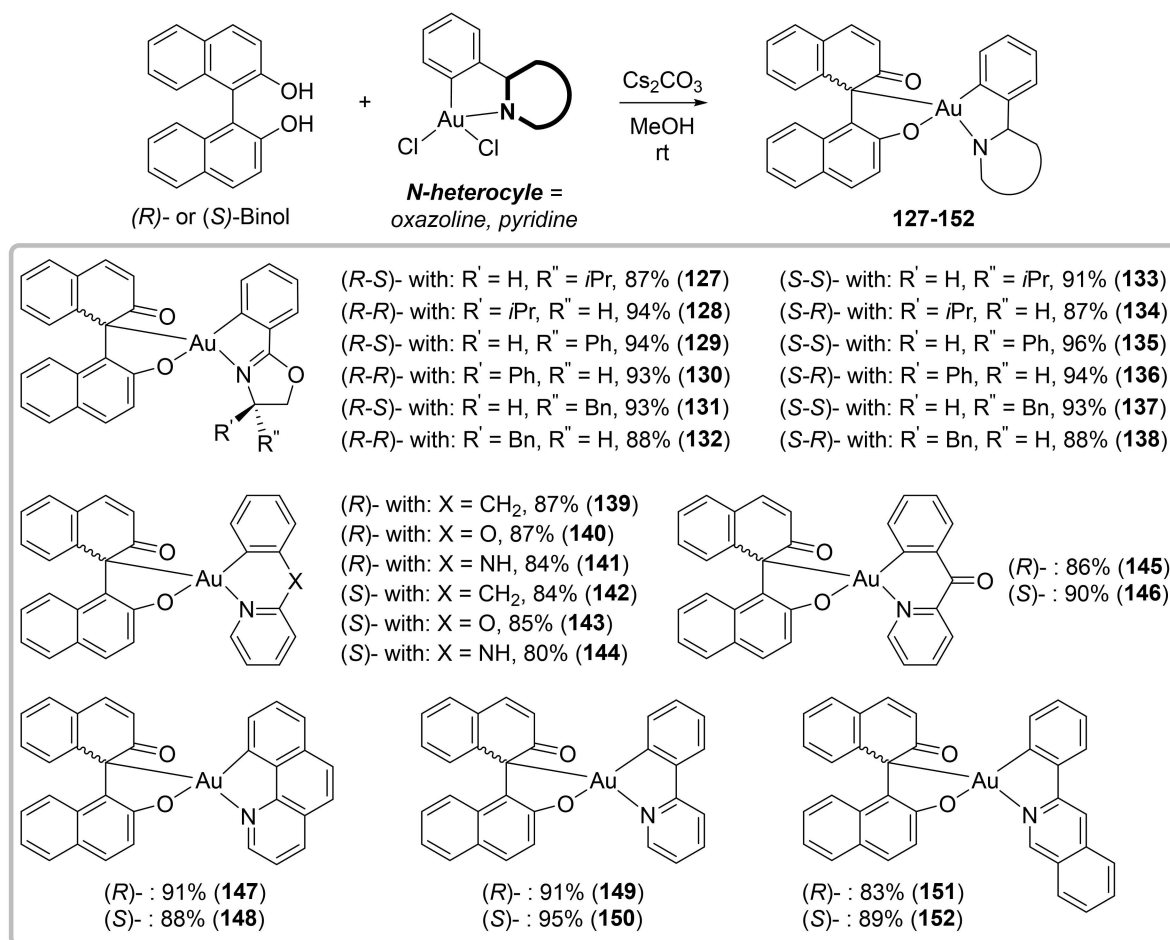


Scheme 33. Preparation of **124** and synthesis of chiral complex **125** upon tautomerization of the (*S*)-BINOL pro-ligand.

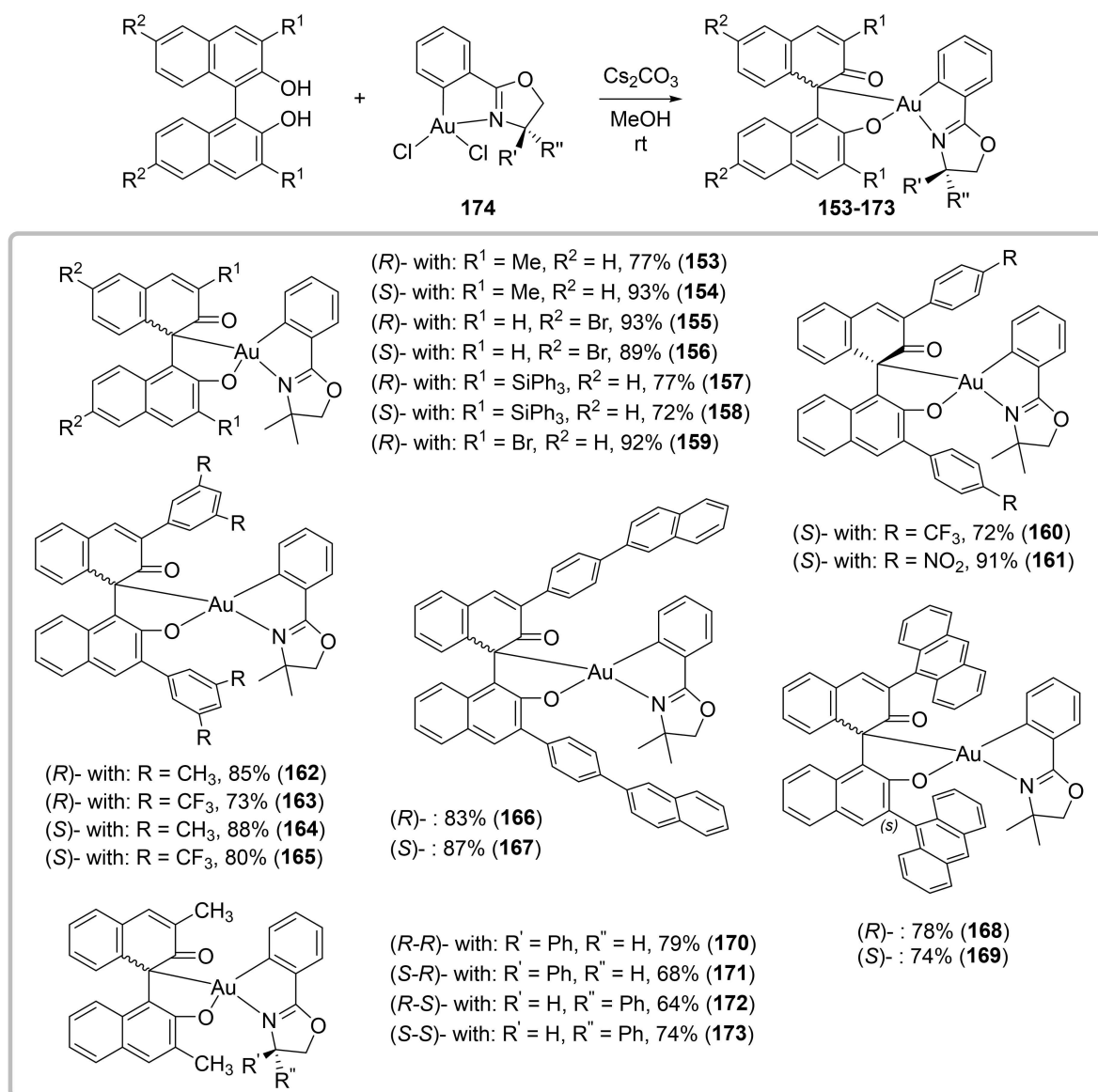
with the (*R*)-BINOL ligand, the enantiomer (*S*)-(**126**) is formed with 88% yield and 100% ee. Both complexes were characterized by NMR and circular dichroism spectroscopies. In solution, the *C,O*-chelation is confirmed with the presence of unsymmetrical protons and carbon nuclei observed by NMR. The solid-state structure of **125** established by SC-XRD also confirms the *C,O*-chelation while the gold(III) cation exhibits a classic square environment. Following the protocol described for **125**, the synthesis of complexes **127–152** was successfully achieved starting from (*R*) or (*S*)-BINOL in combination with various gold(III) fragments supported by *C,N*-ligands such as 2-benzylpyridine, 3-phenylisoquinoline, phenyl(pyridin-2-yl)methanone, benzo[*h*]quinoline (pyridine type), and 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole, (*S*)- or (*R*)-2,4-diphenyl-4,5-dihydrooxazole, (*S*)- or (*R*)-4-isopropyl-2-phenyl-4,5-dihydrooxazole, (*S*)- or (*R*)-4-benzyl-2-phenyl-4,5-dihydrooxazole (oxazoline type) (Scheme 34). The latter oxazoline gold(III) dichloride derivatives **174** were also combined with BINOLs *ortho*-substituted with methyl-, aryl, bromo- and silyl- groups affording complexes **153–173** in high yields (Scheme 35).

Overall, an impressive number of 47 new complexes were prepared with yields ranging from 64% to 96%. In all cases, complete transfer from axial to central chirality yields enantio-

pure complexes. In the presence of chiral *C,N*-ligands, and chiral BINOLs, single diastereoisomers with 2 well-defined chiral centers are obtained. Thus, with chiral *C,N*-ligands, it is possible to extend the synthesis to cheaper *rac*-BINOL ligands to afford mixtures a diastereoisomers {(*S,S*) and (*S,R*) or (*R,S*) and (*R,R*)} which are easily separated by flash chromatography. For instance, complexes **131** and **137** were accessed in 46% and 44% yield, respectively, from *rac*-BINOL and (*S*)-2-(4-benzyl-4,5-dihydrooxazol-2-yl)phenyl gold(III) dichloride. Finally, the synthesis of the racemic version of **125:126** was achieved on a gram scale starting from *rac*-BINOL with 95% yield. It was further tested in catalysis. The treatment of various *ortho*-alkynylbenzaldehydes with trialkyl orthoformates, in the presence of 2.5 mol% of **125:126**, in DCE, at 50 °C for 12 h, affords a series of 2,3-substituted isochromenes **175** with yields ranging from 62 to 96%, *via* tandem acetalization/cycloisomerization reactions (Scheme 36, Eq. 1). By contrast, the addition of 20 mol% of *D*-(+)-10-camphorsulfonic acid triggers a complete change of stereoselectivity toward the formation of a series of indenones **176** obtained with yields ranging from 56 to 87%, at room temperature. (Scheme 36, Eq. 2) In both cases, the reactions are fully regioselective, tolerating *ortho*-alkynylbenzaldehydes incorporating EWGs or EDGs. However, the formation



Scheme 34. Synthesis of chiral gold(III) complexes **127–152** supported by (*R*)- or (*S*)-BINOL and *C,N*-ligands.



Scheme 35. Synthesis of chiral gold(III) complexes 153–173 supported by substituted BINOLs and C,N-oxazoline ligand.

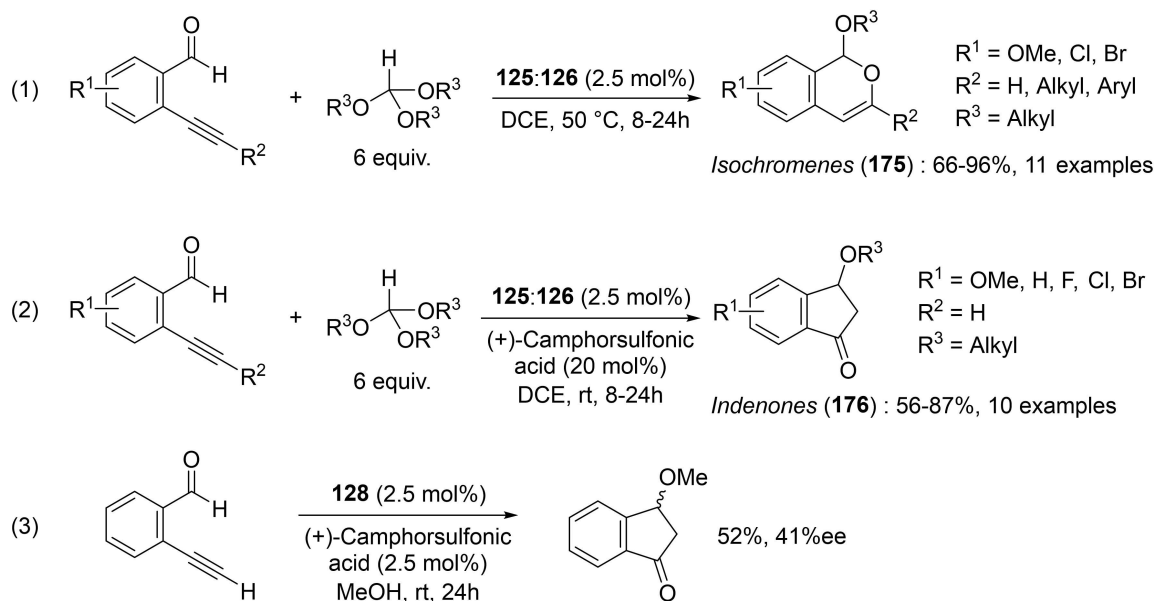
of 5-membered ring does not occur with triisopropyl orthoformate and is likely sensitive to the steric bulk of the substrates.

Finally, a single attempt to perform the carboalkoxylation of *ortho*-alkynylbenzaldehyde with methanol with the chiral complex **128** provides the desired 3-methoxy-2,3-dihydro-1*H*-inden-1-one with 52% yield and 41% *ee* (Scheme 36, Eq. 3).

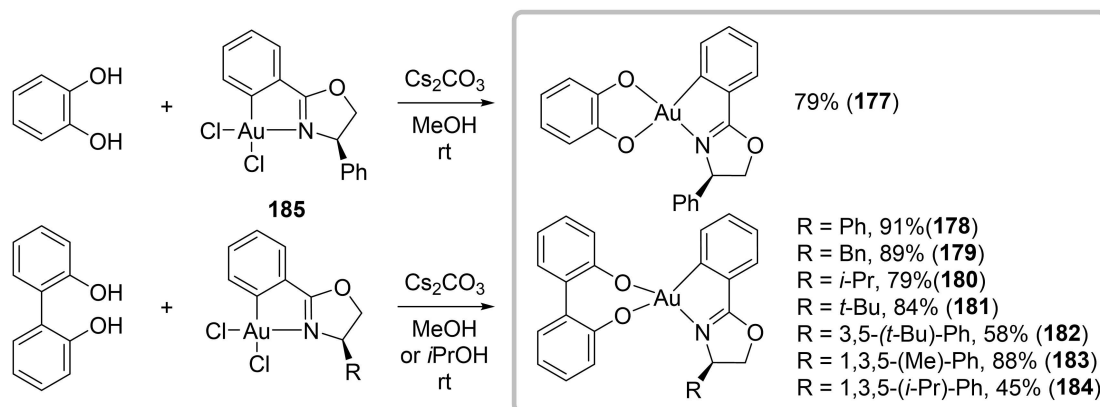
Capitalizing on their results previously described, in 2019, Wong studied the enantioselective carboalkoxylation of benzaldehyde dialkyl acetals in the presence of 9 gold(III) complexes **177–184** supported by chiral (*R*)-4-alkyl/aryl-2-phenyl-4,5-dihydrooxazole C,N-ligands and *O,O*-ligands such as 4,4'-biphenol, pyrocatechol and complex **130** previously prepared for comparison (Scheme 37).^[56] Their syntheses were achieved with yields ranging from 45 to 95%, by reacting the chiral gold(III) dichloride precursors **185** with the phenol-type *O,O*-pro-ligands, in the presence of cesium carbonate, in methanol, at room

temperature, overnight. All complexes were characterized by NMR, mass spectrometry and circular dichroism spectroscopy.

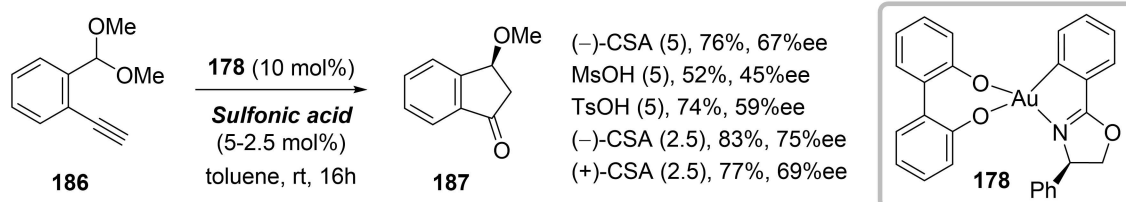
Preliminary carboalkoxylation reaction, in toluene, with 10 mol% of complex **178**, 5 mol% of *L*-(-)-10-camphorsulfonic acid and the model substrate 1-(dimethoxymethyl)-2-ethynylbenzene (**186**) gave the desired dihydroindenone **187** in 76% yield with 67% *ee* (Scheme 38). The use of methanesulfonic acid, toluenesulfonic acid, or (*S*)-binaphthyl-2,2-diyl hydrogen phosphate leads to lower yields and similar *ees*. Chloroform and particularly acetonitrile solvents lead to lower yields and lower *ees*. Finally, a maximum yield of 83% and 75% *ee* is achieved using 10 mol% of **178** and 2.5 mol% of (-)-camphorsulfonic acid (ratio equal to 4:1). Importantly the chirality of the sulfonic acid has a marginal influence on the reaction enantioselectivity.



Scheme 36. Acetalization/cycloisomerization of alkynylbenzaldehydes with trialkyl orthoformates mediated by **125:126** and asymmetric carboalkoxylation of ortho-alkynylbenzaldehyde catalyzed by **128**.



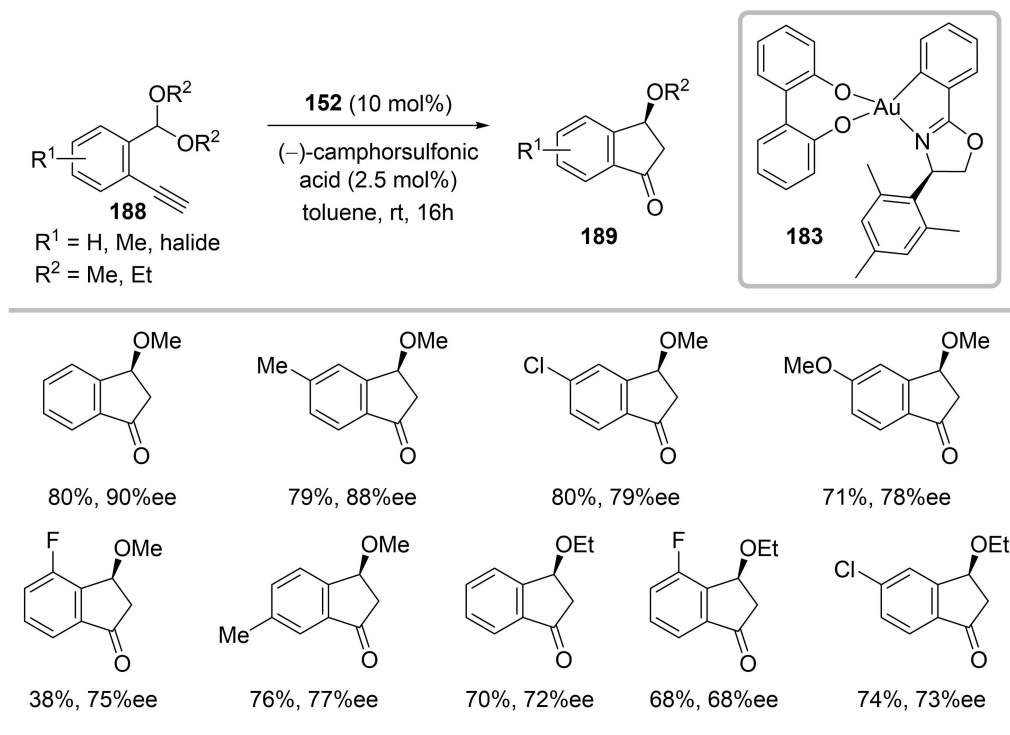
Scheme 37. Synthesis of the chiral gold(III) complexes **177–184** supported by C,N- and O,O-ligands.



Scheme 38. Effect of sulfonic acid on the carboalkoxylation reaction catalyzed by **178**.

Complexes **130** and **177**, with different O,O- or C,O-ligands provide respectively only 25% and 31% yields, with 70% and 71% ees. Reducing the bulkiness of the substituents on the chiral oxazoline in the C,N-ligands, as in complexes **179–181**, result in lower ees ranging from 19 to 28% without improving the yields. By contrast, employing complexes **178** and **182–184**

with more sterically hindered oxazolines leads systematically to higher ees, ranging from 73% to 90%. In parallel, the catalysis yields also increase over 80%, except for **182** which features only 22% yield. The best performance is achieved with **183** which is used further to assess the reaction scope with different alkynes. Compared to **186**, aromatic alkynes with EWGs or



Scheme 39. Scope of the carboalkoxylation reaction catalyzed by the complex **183**.

EDGs, or diethyl acetal **188** are well tolerated providing dihydroindenones **189** with yields ranging from 38 to 80% with ees above 68% (Scheme 39). Finally, catalysis does not proceed with internal alkynes such as 1-(dimethoxymethyl)-2-(phenylethynyl)benzene.

Mechanistic studies performed with **183** reveal that the sulfonic acid promotes the protodeauration of one oxygen site of the *O,O*-ligand in *trans*-position from the carbon site of the *C,N*-ligand, due to a larger *trans*-effect of carbon compared to nitrogen. The result is an elusive intermediate with an uncomplete coordination sphere of gold which can accommodate the alkyne close to the chiral center of the oxazoline ring, a favorable situation to induce enantioselectivity (Scheme 40). Finally, the chiral gold(III) dichloride precursors **185** used to

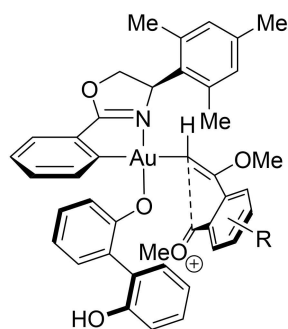
synthesize **130** and **177–184** also efficiently promote the enantioselective cyclization of **186**, with yields ranging from 50 to 81% and ees above 48%, highlighting the importance of the *C,N*-ligand (over the *O,O*-ligand) to promote chiral induction. The best results are obtained in chloroform, at room temperature, with 10 mol% of gold(III) precursors, 10 mol% of (*L*)-(-)-camphorsulfonate and 10 mol% of silver tetrafluoroborate used as halide abstractors.

P-Ligands

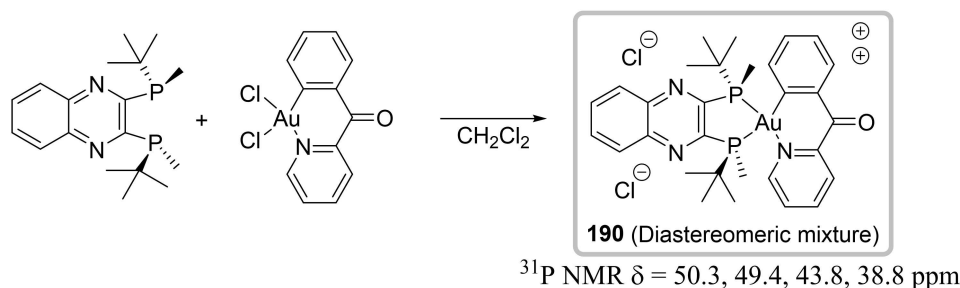
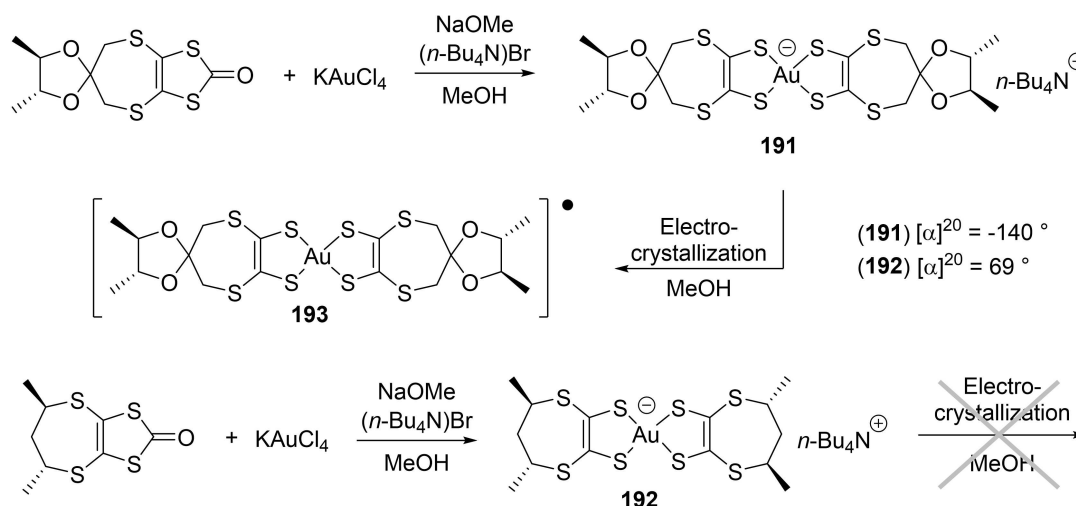
Phosphanes

While synthesizing a series of phosphane gold based anticancer drugs, Kim *et al.* reported the synthesis of chiral chelate complex **190** in 74% yield, in chloroform, by reaction of the diphosphane ligand with previously synthesized 2-benzoylpyridine gold(III) dichloride (Scheme 41).^[57]

The coordination of gold is evidenced by ³¹P NMR spectroscopy with four signals at 50.3, 49.4, 43.8 and 37.8 ppm corresponding to a mixture of two diastereoisomers: each bearing two magnetically inequivalent phosphorous atoms. The complex is fully soluble in water and stable in phosphate-buffered saline solutions mimicking physiologic media, at temperatures up to 80 °C. Cyclic voltammetry studies (in DMSO) unveil an irreversible reduction peak at -0.85 V and a reversible peak at -1.46 V, respectively attributed to the reductions of **190** to phosphane gold(I) species and colloidal gold(0). Under



Scheme 40. Favored transition state for the enantiodetermining step of the carboxylation of alkyne **188** with catalyst **183**.

Scheme 41. Synthesis of the complex **190** from a cyclometalated gold(III) precursor.Scheme 42. Synthesis of chiral anionic complexes **191**–**192**, and neutral radical complex **193**.

physiological conditions, complex **190** does not bind with bovine serum albumin which shares homology with human serum albumin. This fact is important in pharmacology implying that the gold complex **190** might be delivered structurally unaltered to the targeted cancer cells *via* the blood circulation system. Complex **190** features a cytotoxicity 2- to 10-fold higher than *cis*-platin with various lines of cancer cells (e.g., lung, ovaries...). It triggers cell apoptosis by inhibiting the reactive oxygen species (ROS) cycle of mitochondria used to generate ATP during the respiratory cycle, while it is unlikely interacting with genomic DNA.

S-Ligands

Dithiolenes

In 2016, Fourmigué *et al.* reported the one-pot synthesis of the chiral *tetra-n*-butylammonium gold(III) dithiolate complexes **191** and **192** with 44% and 19% yields, as potential precursors of chiral molecular conductors with electrical magneto-chiral anisotropy properties.^[58] In absolute methanol, the dithiolate ligands were generated *in situ* from dithiocarbonate precursors in the presence of sodium methanolate and reacted further

with a mixture of KAuCl_4 in the presence of ammonium salts (Scheme 42). The complexes were precipitated and washed with water and methanol after 24 h and further crystallized from a solution of dichloromethane/methanol. They were fully characterized by NMR spectroscopy, SC-XRD and cyclic voltammetry. Both complexes reversibly oxidize to the neutral and cationic forms at potentials equal to approximately +0.5 V and +1.0 V (versus SCE). The electrocrystallization of **191**–**192** was attempted but only produced in the case of **191** a small amount of crystals of the neutral radical complex **193** (Scheme 42). The solid-state structure of **193** features shortened C–S bonds along with elongated C=C bonds compared to **191**, suggesting a strong delocalization of the radical through both dithiolene ligands. The too small and brittle crystals of **193** precluded any conductivity measurement. However, preliminary studies based on DFT calculations and solid-state hints at the formation of an insulating material.

Conclusion

Since 2005, around a hundred well-characterized chiral gold(III) complexes have been isolated. Chelating ligands provide a significant gain of stability against the natural trend of reductive

elimination encountered with gold(III) complexes. Applications with chiral gold(III) complexes are still limited, but show tremendous potential in the fields of pharmacology with the synthesis of potent anti-cancer drugs featuring specific mechanism of actions compared to platinum(II) and gold(I). In asymmetric catalysis, gold(III) complexes exhibit a reactivity/stereoselectivity different than gold(I) complexes, even though Au(III)-catalyzed reactions are essentially limited to nucleophilic attacks on multiple C–C bonds. High conversions and yields are generally reached under very mild conditions, but the *ee* values are rarely above 90%. Despite recent encouraging results obtained by Toste and co-workers^[39,40] and Wong and co-workers,^[55,56] the development of ligands to access versatile complexes, which can ensure outstanding enantioselectivity over different classes of reaction and reagents remain to achieve. Thus, we hope that our Minireview will prompt more fellow chemists to join their effort toward the development of the growing field of organogold(III) chemistry.

Author Information

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: catalysis · chiral ligands · enantioselectivity · gold

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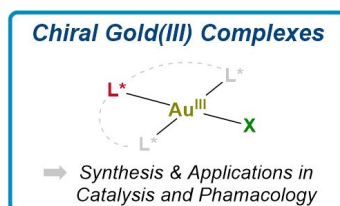
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MINIREVIEW

Golden story: Recent progresses achieved in the synthesis of well-defined chiral gold(III) complexes have been summarized. Applications that encompass homogeneous catalysis, medicinal and material chemistry, are also described.



R. Jouhannet, S. Dagorne, A. Blanc*, P. de Frémont*

1 – 25

Chiral Gold(III) Complexes: Synthesis, Structure, and Potential Applications



This Minireview highlights the synthesis of well-defined chiral gold(III) complexes and their applications mostly in catalysis during the last fifteen years. ■■■ Dear Author, please provide a longer text (ca. 500 characters); also note that this text should be different from TOC. ■■■



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