Review

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Buchwald-Type Ligands on Gold(I) Catalysis

Giuseppe Zuccarello[+],[a] Margherita Zanini[+],[a] and Antonio M. Echavarren*[a]

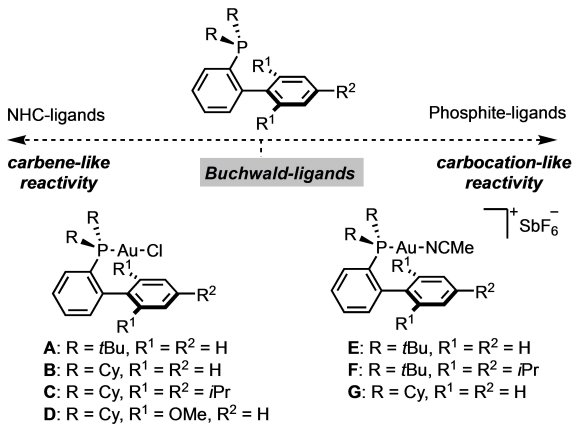
Abstract: Dialkyl biarylphosphine ligands, presented in the context of Pd-catalyzed cross-coupling reactions, have been extensively applied in gold(I) catalysis giving rise to numerous transformations and reaction pathways otherwise inaccessible under the action of other gold(I) catalysts. This review emphasizes how this privileged ligand class, as well as recent modifications on the biarylphosphine motive, have triggered the discovery of new reactivities in our research program. Finally, the introduction of chiral information on the ligand scaffold provides new solutions to challenging gold(I)-catalyzed enantioselective transformations.

Keywords: Gold(I) catalysis · Biarylphosphines · cyclizations · asymmetric catalysis · alkynes

1. Introduction

For many years gold was considered to be catalytically inactive and therefore overviewed from the chemical community until the first report on gold(I)-catalyzed transformations by Ito and Hayashi[1] marked a starting point in the field of homogenous gold(I) catalysis. Later, the preparation of ketones by addition of alcohols or water to alkynes reported by Teles[2] and Tanaka[3] respectively, as well as the gold(III)-catalyzed phenol synthesis by Hashmi[4] unrevealed the potential of gold catalysts as carbophilic π-acids in synthetic organic chemistry. The groups of Toste,[5] Fürstner[6] and our own group[7] identified cationic phosphine gold(I) catalysts [R_3PAuX] (X = labile anionic ligand) formed *in situ* from [R_3PAuCl] by chloride abstraction with AgX or by protolysis of [R_3PAuCH_3], to be the most active and selective in the cyclization of 1,*n*-enynes and other C–C[8–11] and carbon-heteroatom[12–14] bond-forming reactions. In the first decade of the current century, homogeneous gold(I) catalysis has experienced a "gold rush" during which numerous transformations were developed for the assembly of complex molecular settings,[15–20] that were also applied in the context of natural product total synthesis.[21,22] Gold(I) carbenes were invoked as key intermediates in many of these transformations whereby their reactivity is strongly determined by the ancillary ligand.[23] According to the binding model described by Toste and Goddard,[24] gold(I) binds linearly via backdonation of its electrons in the filled 5d orbitals into the empty π orbitals of the ligand and the carbene. Hence, more σ-donating ligands such as *N*-heterocyclic carbenes (NHC) result in more carbene-like intermediates with according reactivity whereas a carbocation-like behavior is obtained with π-acidic phosphite ligands (Scheme 1).[23]

Between these two extremes, bulky dialkyl biarylphosphine ligands introduced by Buchwald in 1998 for Pd-catalyzed coupling reactions,[25] provide electronically and sterically an intermediate alternative. Due to their stability with respect to oxidation[26] and synthetic accessibility,[27] this class of ligands has been employed in numerous Pd-catalyzed



Scheme 1. Dialkyl biarylphosphine-supported gold(I) complexes.

C–C[28,29] and C–X (X=N, O, F)[30–33] bond-forming reactions as well as in combination with other transition metals such as Ag,[34] Rh,[35,36] Ru[37] and Cu.[38]

Our group introduced the use of dialkyl biarylphosphine ligands in the context of gold(I) catalysis[39] resulting in a new family of highly electrophilic gold(I) complexes **A**–**D** which were found to catalyze diverse transformations upon chloride

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abstraction. Importantly, cationic complexes **E**–**G** are easily accessed from their gold chloride precursors by treatment with $AgSbF_6$ and are bench-stable white solids that can be directly used in catalysis without pre-activation.

In this account we review the impact of biarylphosphine ligands on our program on gold(I) catalysis, spanning from their first appearance in the field to several different transformations including cyclizations of 1,*n*-enynes, cascade reactions of 1,6-dienynes and the generation of gold(I) carbenes by decarbenation of 7-substituted cycloheptatrienes. Hereby, the differences in reactivity and selectivity arising from the use of complexes **A**–**G** and other gold(I) catalysts will be compared and highlighted. Additionally, unprecedent reactivities that have been disclosed upon modification of the biaryl framework, including efforts from the Zhang group on the design of bifunctional biarylphosphine ligands featuring a remote basic site, are summarized. Finally, the particular geometry and rigidity of the biaryl scaffold has provided the optimal platform for the design of chiral modifications allowing for their implementation in asymmetric gold(I) catalysis.

2. Reactivity and Structure of Buchwald-type ligands-supported Gold(I) Complexes

2.1 Access to new Reactions

2.1.1 Formal [4+2] Cycloadditions of 1,n-enynes

In the presence of a cationic gold(I) complex, 1,*n*-enynes can follow diverse reaction pathways depending on their substitution pattern on the alkene and the alkyne.[5–7,40–42] Even though most of these transformations are catalyzed by $[PPh_3AuCl]$ upon chloride abstraction, enynes containing internal alkynes, particularly arylenynes, display a reduced reactivity.[43] Hence, in 2005 our group introduced dialkyl biaryl phosphine supported gold(I) complexes **A**-**D** in the context of the formal [4+2] cycloaddition of 1,6-arylenynes **1** forming 2,3,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalenes **5** (Scheme 2).[39] The bulkier Buchwald-type ligands provided an enhanced catalytic activity compared to NHC-gold(I) complexes and afforded the target compounds in shorter reaction times and higher chemical yield. Experimental and theoretical studies support the reaction mechanism to proceed via 5-*exo*-dig formation of *anti*-cyclopropyl gold(I)-carbene **2** which is then

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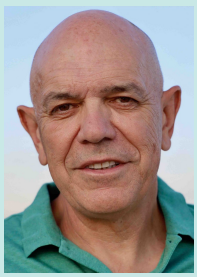

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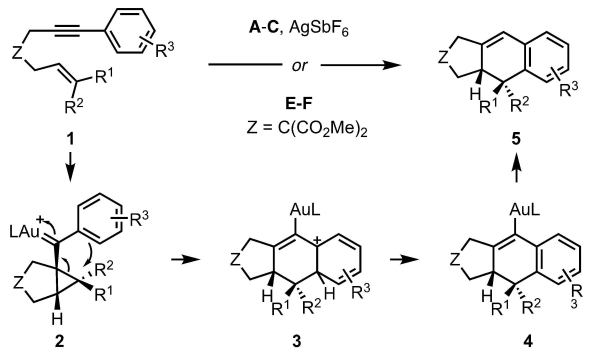
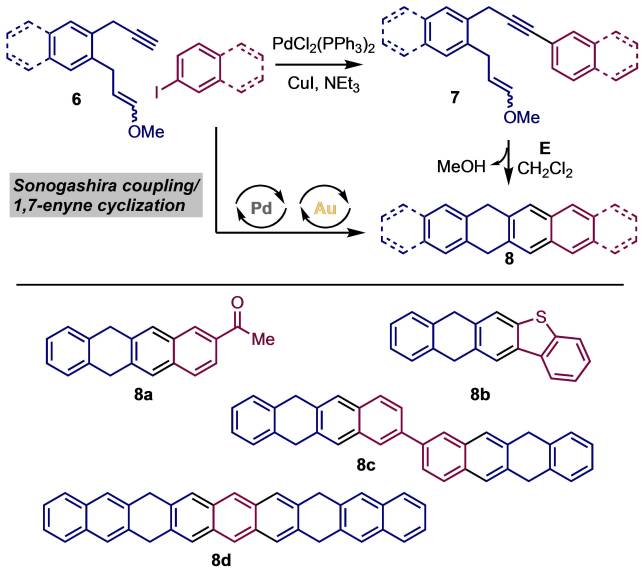


Scheme 2. Formal [4 + 2] cycloaddition of 1,6-arylenynes **1**.

opened by a Friedel-Crafts-type reaction to form Wheland intermediate **3**. Sequential proton loss and final protodeauration from **4** affords **5**.[44]

The formal [4 + 2] cycloaddition of 1,7-enyne **7** where the alkene is replaced by an enol ether leads to the formation of dihydrotetracenes **8** (Scheme 3). This reaction proceeds similarly *via* 6-*endo*-dig cyclization pathway and the concomitant aromatization by loss of one molecule of methanol.[45] Dihydroacenes are hydrogen-masked, precursors[46] for the *in situ* formation of acenes,[47] a class of linear polycyclic hydrocarbons that find their application in organic electronics[48,49] and as organic semiconducting materials.[50] However, the isolation of oligoacenes becomes more difficult with increasing length (n > 6) because of their air- and photo-instability and reduced solubility. Thus, we disclosed a sequential Sonogashira coupling/gold(I)-catalyzed cyclization sequence for the synthesis of higher hydroacenes and polyhydroacenes. Again, cationic JohnPhos-gold(I) catalyst **E**



Scheme 3. Access to hydroacenes via sequential Sonogashira coupling/gold(I)-catalyzed 1,7-enyne cyclization.

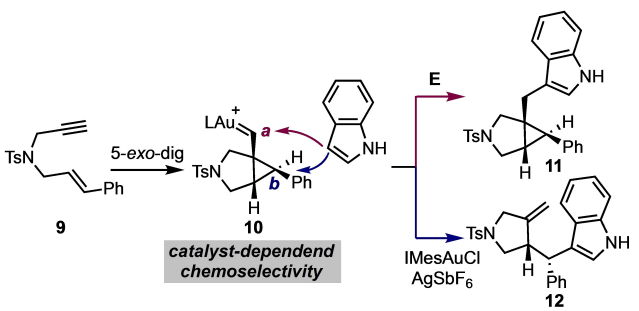
outcompeted catalysts supported by NHC- and phosphite ligands resulting in the cleanest reactions.

Starting from readily available iodoarenes a broad scope of hydroacenes were accessed spanning from functionalized dihydrotetracenes **8a** and partially saturated heteroacenes **8b** to extended dihydrotetracenes **8c** and polyhydroacenes **8d**, formed *via* multiple gold(I)-catalyzed cyclization and aromatization reaction. Shortly after, the entire series of higher acenes from heptacene to undecacene has been successfully synthesized stepwise on a Au(111) surface through dehydrogenation from their corresponding partially saturated precursors.[51,52]

2.1.2 Comparison of Catalyst-dependend Reactivities in Cyclizations of 1,n-enynes and Cascade Reactions

Buchwald ligand-supported gold(I) catalysts not only stand out for being robust and highly reactive but can display different chemo- and regioselectivities compared to other catalysts giving access to compounds otherwise difficult to synthesize. 1,6-Enyne **9** undergoes 5-*exo*-dig cyclization to form cyclopropyl gold(I)-carbene intermediate **10** which was found to be a bifunctional electrophile (Scheme 4).[53] Depending on the catalyst of choice, in the presence of an external nucleophile such as indole or electron-rich arenes intermediate **10** reacts either at the carbene carbon ***a*** or at the cyclopropyl carbon ***b***. The use of cationic catalyst **E** afforded a 4 : 1 mixture of **11** and **12** arising from the preferential reaction at carbon ***a***, whereas different selectivity was found using IMesAuCl and $AgSbF_6$ slightly in favor of **12** (1:0.8).

A comparable switch in selectivity was observed in the gold-catalyzed hydroarylation of alkynes[54–56] reported by our group (Scheme 5).[11,57] The reaction outcome of the intramolecular hydroarylation of alkynyl indoles **13** was found to be strongly dependent on the catalyst employed. In general, the use of $AuCl_3$ or AuCl salts lead to the selective formation of indoloazocine **14**, whereas cationic complex **E** afforded exclusively azepino[4,5-*b*]indole **15**. The isolation of a spiro derivative indicates that a stepwise reaction mechanism takes place in this process. First, intermediates **15** and **16** are respectively formed *via* a 7-*endo*-dig and 6-*exo*-dig aromatic electrophilic substitution at the more nucleophilic C-3 carbon.



Scheme 4. Bifunctional electrophilic reactivity of intermediate **10**.

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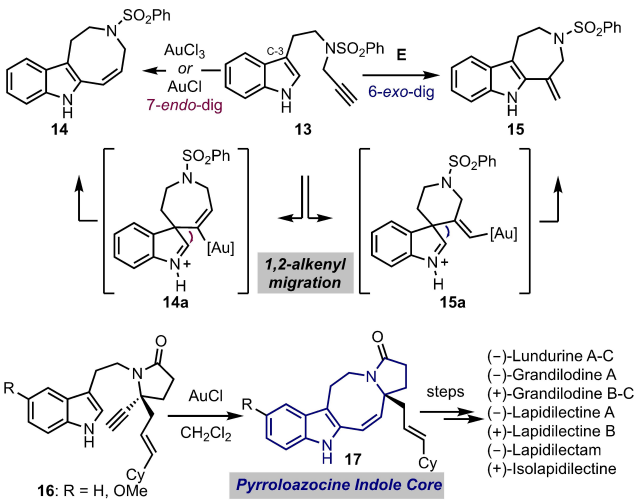


Scheme 5. Gold-catalyzed hydroarylation of alkynyl-indoles and synthetic application in total synthesis of *Kopsia* indole alkaloids.

Sequentially, a 1,2-alkyl shift[58,59] leads to the corresponding products.[60] Interestingly, catalyst **E** proved superior to $[PPh_3AuCl]/AgSbF_6$ giving **14** and **15** as a 1 : 4 mixture.

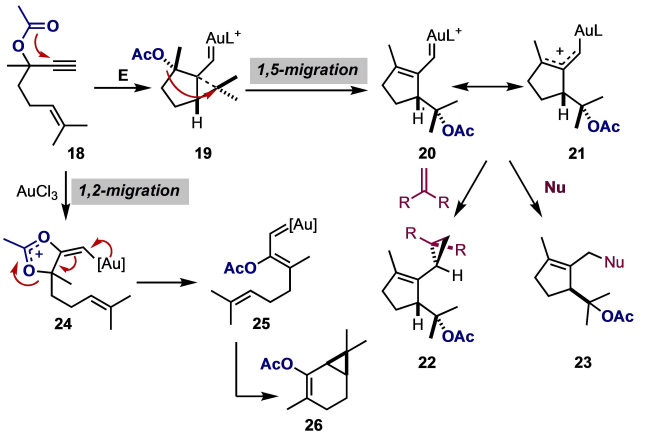
Recently, our group has demonstrated the potential of the gold-catalyzed intramolecular hydroarylation of indoles to construct the pyrroloazocine indole core in **17**[61] which was later applied in the total syntheses of *Kopsia* alkaloids[62] (−)-lundurines A-C[63] and seven members of the lapidilectine/grandilodine family.[64]

Analogously, gold(I) complexes supported by Buchwald-type phosphines are able to modulate the reactivity of 1,6-enyne bearing propargylic alcohols, ethers or silyl ethers. In fact, enynes with a propargyl acetate such as **18** react in presence of gold(I) catalyst **E** *via* cyclopropyl gold(I) carbene **19** to form an intermediate that can be represented as an α,β-unsaturated gold(I)-carbene (**20**) or a gold(I) stabilized allyl cation (**21**) *via* 1,5-migration of the OAc group (Scheme 6).[65,66] Intermediates **20**/**21** can react with 1,3-diketones as nucleophiles to give products of α-alkylation,[66] as well as with electron rich heterocycles such as indole[65] or furans.[67]

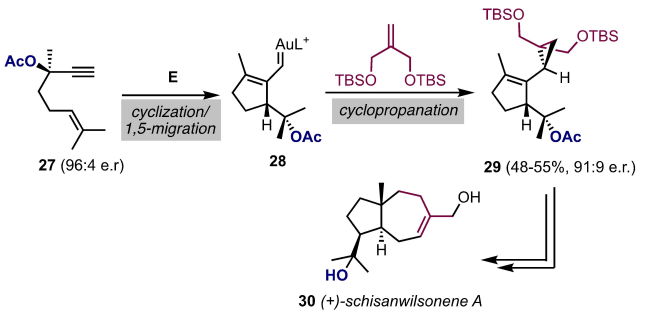
The carbene nature of intermediate **20** is revealed in the reaction with electron rich alkenes to form the corresponding cyclopropane.[65,66] In contrast, in presence of $AuCl_3$ enyne **18** undergoes initial 1,2-acyl migration to form α,β-unsaturated gold(I)-carbene **25** followed by cyclopropanation of the appended double bond.[68]

We applied these findings in the first enantioselective total synthesis of (+)-schisanwilsonene A starting from enantioenriched enyne **27** (Scheme 7).[69] The partial racemization during the key gold(I)-catalyzed 1,5-acyl migration is ascribed to the competing 1,2-acyl migration. However, in this case this process is *ca.* 20 time slower than the desired reaction.

In the effort to involve gold(I) in cascade reaction for the rapid construction of complex carbon skeletons, we discovered



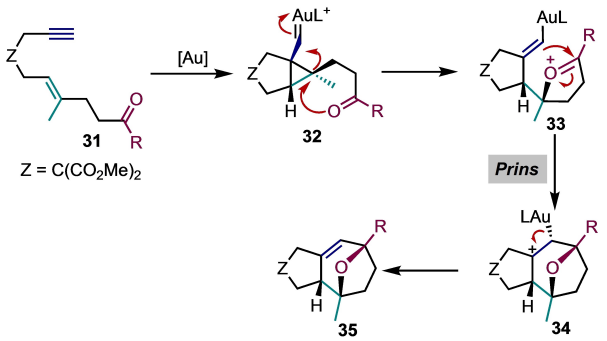
Scheme 6. Gold(I) catalyzed reactions of 1,6-enyne functionalized with propargyl acetate.



Scheme 7. Enantioselective total synthesis of (+)-schisanwilsonene A.

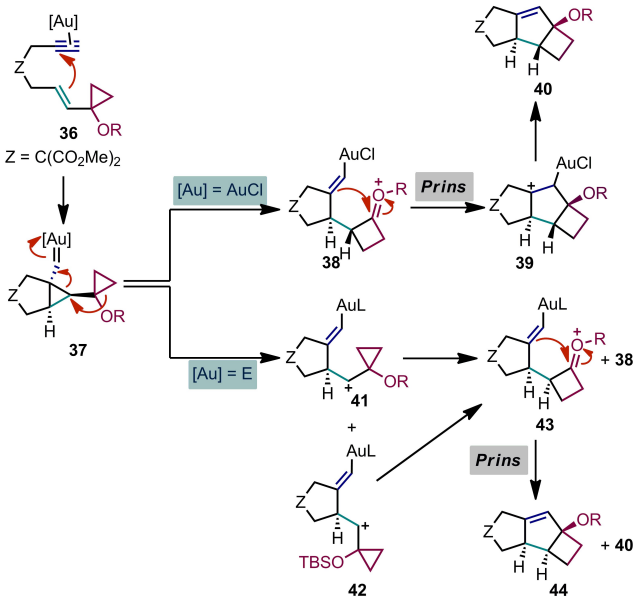
the formal [2+2+2] cycloaddition of 1,6-enyne bearing a keto group[70] (Scheme 8). The reaction begins with the formation of cyclopropyl gold(I) carbene **32**. Upon intramolecular attack of the carbonyl, the oxonium cation **33** is formed. Prins-type cyclization followed by demetalation leads to the assembly of the oxatricycle **35** from linear precursor **31**.

Interestingly, protected cyclopropanols such as **36** can act as masked activated ketones that are revealed upon a gold(I)

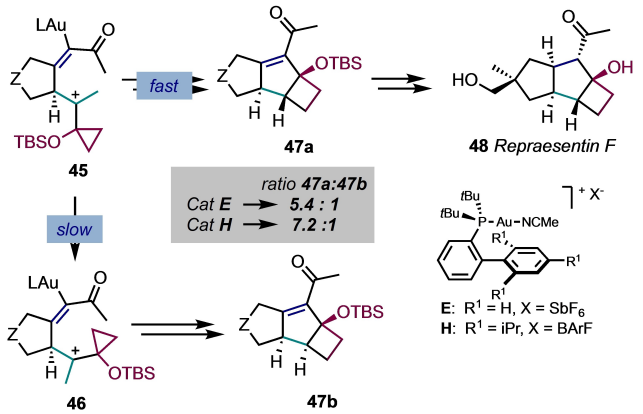


Scheme 8. Gold(I)-catalyzed [2+2+2] cycloaddition of 1,6-enynes.

catalyzed cyclization/ring expansion cascade (**38** and **41**, Scheme 9). Again, the sequence is closed via a Prins-type reaction to form a tricyclic product featuring an octahydralcyclobutane[*a*]pentalene skeleton occurring in a number of protoilludane-related sesquiterpenes. During the optimization of the reaction, AuCl outperformed other catalysts in the formation of the *anti*-diastereomer. However, the *syn*-diastereoisomer is obtained selectively with **E** as catalyst. This result can be rationalized taking into account the different stability of the intermediates in presence or in absence of the ligand. Once **37** is formed, it evolves rapidly into **38** oxonium cation with AuCl as catalyst, resulting into a diasteroselective reaction. On the other hand, catalyst **E** favors a non-concerted mechanism for the ring expansion through **41** and **42**, in which the stereochemical information is lost.



Scheme 9. Different diasteroselectivtiy in the gold(I)-catalyzed [2+2+2] cycloadditon of 1,6-enyne functionalized with cyclopropanols.



Scheme 10. Totals synthesis of natural sesquiterpene repraesentin F.

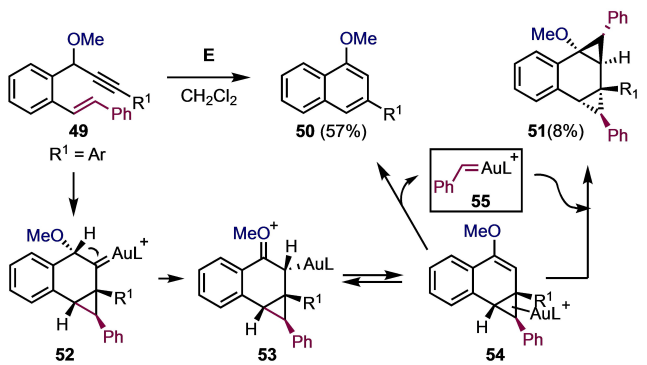
It is important to note that when the steric hindrance around the carbocation increases by addition of a methyl as in the case of **45** (Scheme 10), the equilibration between the two cations is blocked with a gold complex bearing a bulky phosphine and the ring expansion occurs stereospecifically. We took advantage of this reactivity in the total synthesis of repraesentin F (**48**),[71] in which the core skeleton is assembled in a single step via a diasteroselective gold(I)-catalyzed enyne cyclization/ring expansion/Prins cyclization cascade. The increase in the steric hindrance on the second aromatic ring of the ligand of catalyst **H** results in an improved diastereomeric ratio in the formation of **47a** and **47b**.

2.1.3 Formation of Gold Carbenes via Retro-Cyclopropanation and Retro-Buchner Reaction

Interested in broadening the scope of the tandem 1,*n*-enyne cyclization/(1,*n*-1)-migration,[65] our group studied the reactivity of arene-tethered 1,6-enyne **49** containing a propargyl ether (Scheme 11).[72] To our surprise, in presence of catalyst **E** we observed the formation of 3-aryl-1-methoxynaphtalenes **50** accompanied by biscyclopropane **51** as a minor compound.

We hypothesized that, after formation of cylopropyl gold (I)-carbene **52** by 6-*endo*-dig cyclization, followed by a [1,2]-hydrogen shift[73] giving alkenylgold(I) intermediate **54** via **53** a retro-cyclopropanation was taken place to form naphthalenes **50** and gold(I)-carbene **55**, which reacts with a molecule of **54** to afford **51**. Beside disclosing a new synthesis of 1,3-substituted naphtalenes which are otherwise not readily available, we recognized the synthetic potential to generate gold(I)-carbenes from benzofused norcaradiene derivatives **54** by retro-cyclopropanation.[74]

However, the preparation of derivatives **54** is not straightforward. Hence, our group implemented the use of 7-substituted-1,3,5-cycloheptatrienes **56** for the generation of gold(I)-carbenes **58** (Scheme 12).[75] Cycloheptatrienes **56** are in equilibrium with their norcaradiene tautomers **57**,[76,77] which react with electrophilic gold(I) complexes by a stepwise retro-cyclopropanation[78] to generate gold(I)-carbene **58** together with one molecule of benzene resulting in an overall



Scheme 11. Synthesis of naphthalenes via retro-cyclopropanation.

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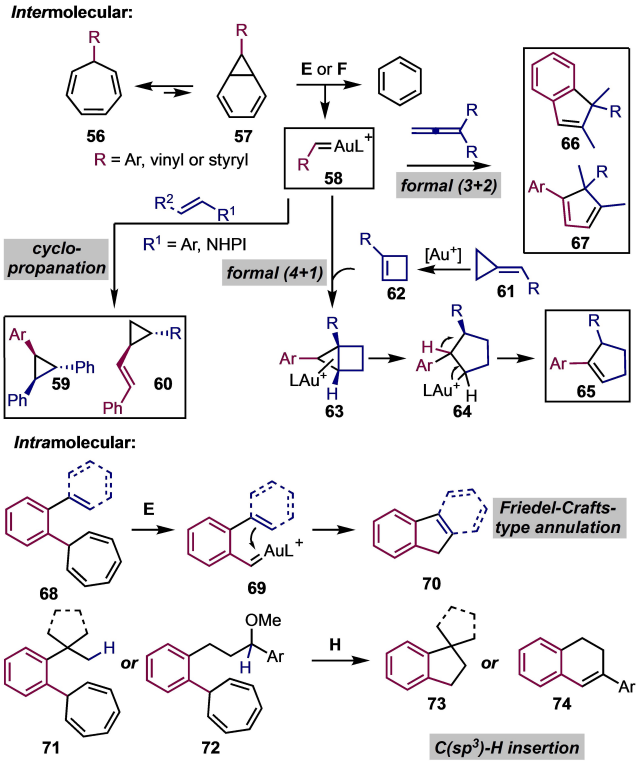


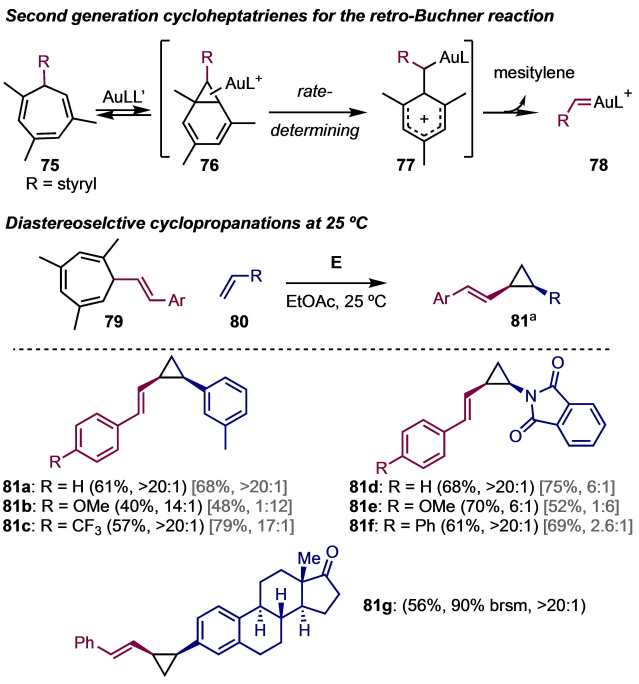
Scheme 12. Diverse reactivity of gold(I)-carbenes generated by retro-Buchner reaction.

retro-Buchner process. Gold(I)-carbene **58** can then be trapped inter- and intramolecularly with different alkenes giving rise to a number of synthetically useful transformations.[75] The use of cycloheptatrienes as carbene precursors represents a much safer alternative compared to the more conventional generation of metal carbenes from diazo compounds due to their thermal stability. Furthermore, the starting materials are easily accessible in multigram scale by addition of the corresponding organolithium or Grignard reagent to commercially available tropylium tetrafluoroborate or via Julia-Kocienski olefination.[79,80]

The reaction of the gold(I) carbenes generated by the retro-Buchner reaction with alkenes leads to a broad scope of di-, tri-aryl- and vinyl cyclopropanes **59** and **60** (Scheme 12)[79,81,82] Highly substituted cyclopentenes **65** are formed through a formal (4+1) cycloaddition by reaction of methylenecyclopropanes **61** or cyclobutenes **62** as 1,3-dienes equivalents.[83] The overall transformation is particularly intriguing since the gold(I)-catalyst is involved in three different catalytic steps. Beside generating gold(I)-carbene **58**, methylenecyclopropane **61** is isomerized to cyclobutene **62**, which is cyclopropanated giving bicyclo[2.1.0]pentanes **63**. Cleavage of the internal C–C bond is also promoted by gold(I) to form **64**, which undergoes a [1,2]-hydrogen shift to afford **65**. Allenes also react with aryl- and styryl-gold(I)-carbenes **58** giving indenes **66** and cyclopentadienes **67**, respectively, by a formal (3+2) cycloaddition.[84] The potential of these transformations was demonstrated in the total synthesis of (±)-laurokamurene B[85,86] and in the assembly of the tetracyclic carbon skeleton of the cycloaurenones[87] and dysiherbols[88] family of natural products.

Similarly, 7-aryl-cycloheptatreienes of type **68** react intramolecularly through generation of gold(I)-carbene **69** to give indene and fluorene derivatives **70** following a Friedel-Crafts-type mechanism.[82] Finally, gold(I)-carbenes generated by retro- Buchner reaction also undergo C(sp^3)–H insertion to give substituted indanes **73** and 3-aryl-1,2-dihydronaphtalenes **74** from **71** and **72**, respectively. In these transformations, cationic NHCgold(I)-complex were found to be superior catalysts.[89]

In spite of the numerous transformations streamlined by the gold(I)-catalyzed retro-Buchner reaction, their set-ups require relatively elevated temperatures (75–120 °C) diminishing stereo control and functional group tolerance. Recently, our group addressed this limitation designing a second generation of 7-styryl-1,3,5-trimethyl-cycloheptatrienes **75** (Scheme 13).[80] The electron-donating substituents stabilize Wheland-type intermediate **77** formed upon cleavage of the first C–C bond in norcaradiene **76**, which is the rate-determining step of the retro-Buchner process.[79,81] After releasing one molecule of mesitylene, gold(I)-carbene **78** is generated. In comparison with the first generation of cycloheptatrienes,[79] compounds **79** react in presence of catalytic amounts of catalyst **E** at 25 °C with a broad range of alkenes giving vinyl cyclopropanes **81** with improved *cis*-



Scheme 13. Second generation 7-styryl-1,3,5-trimethyl-cycloheptatrienes. Isolated yield and *cis*/*trans* ratio of diastereosiomers in parentheses. In grey: yield and diastereoselectivity obtained with first gen. of cycloheptatriene.

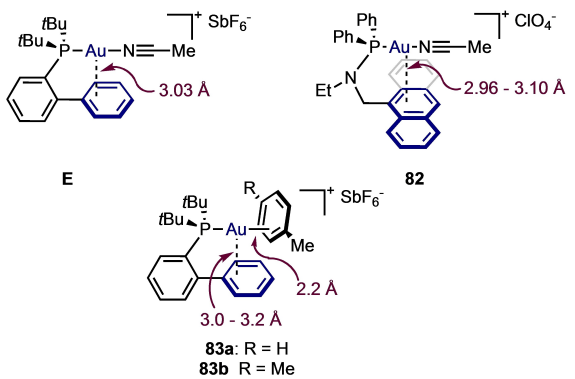
diastereoselectivity. Importantly, this new generation of cycloheptatrienes underwent retro-Buchner reaction also in presence of zinc-and and rhodium-based catalysts.[90]

2.2 Structural Considerations and Variation of the Biaryl Scaffold

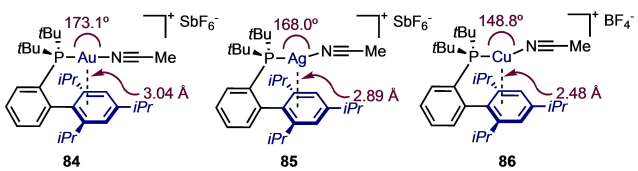
When coordinated to palladium, bulky biphosphine ligands display a Pd-arene interaction considered to be key for the successful reactivity in cross-coupling reactions.[91–93] Since these ligands also demonstrated to be privileged scaffolds in the context of gold(I) catalysis, it was important to determine if an analogue metal-arene interaction was actually taking place and was playing a role in the enhanced reactivity demonstrated by these complexes.

For cationic complex **E**, the distance between the second aromatic ring of the ligand and the gold atom is 3.03 Å,[94] similar to the one observed in anthracene complex **82** (Au–C distances of 2.958 Å and 3.097 Å) (Scheme 14).[95] These values are above the limit of significant interaction for Au and an arene calculated to be of 2.95 Å.

By crystallization of complex **E** in toluene or *p*-xylene, the aromatic solvent displaces acetonitrile as ligand forming complexes **83 a** and **83 b** with a η^1/η^2 coordination of the arene to gold(I) (Scheme 14).[94] In these cases, the distance between the aromatic plane and the metal is of 2.20–2.24 Å, which corresponds to a stronger arene-gold(I) interaction. According to these data, the M-arene interaction, which is key for palladium, does not occur in the analogues Au(I) complexes.



Scheme 14. Structure of cationic gold(I) complexes with very weak and strong arene-metal interactions.



Scheme 15. Cationic gold(I), silver(I) and copper(I) complexes with *t*BuXPhos as ligand.

We also studied the structural differences of the isoleptic family of complexes **84–86** having *t*BuXPhos as ligand (Scheme 15).[30] As already observed with JohnPhos supported complexes, Au(I) displays an almost linear coordination with a P–M–N angle of 173.1°, whereas Ag(I) and Cu(I) congeners are more bendt showing P–M–N angles of 168.0° and 148.8°, respectively. As expected, the metal-ligand distance follows the order Cu < Au < Ag. The interaction with the parallel aromatic ring in the phosphine ligand is again above the limit for a significance bonding interaction in the case of gold (observed M–C_{ispo} 3.04 Å). In contrast, Ag(I) and Cu(I) display a strong interaction with the aromatic ring (the limit for a meaningful metal-arene interaction for Ag(I) and Cu(I) are 3.03 Å and 2.83 Å, respectively). It is also important to remark that computational studies on the natural population of these complexes indicate the absence of electron transfer from the arene to the metal, which excludes a covalent character for this interaction.

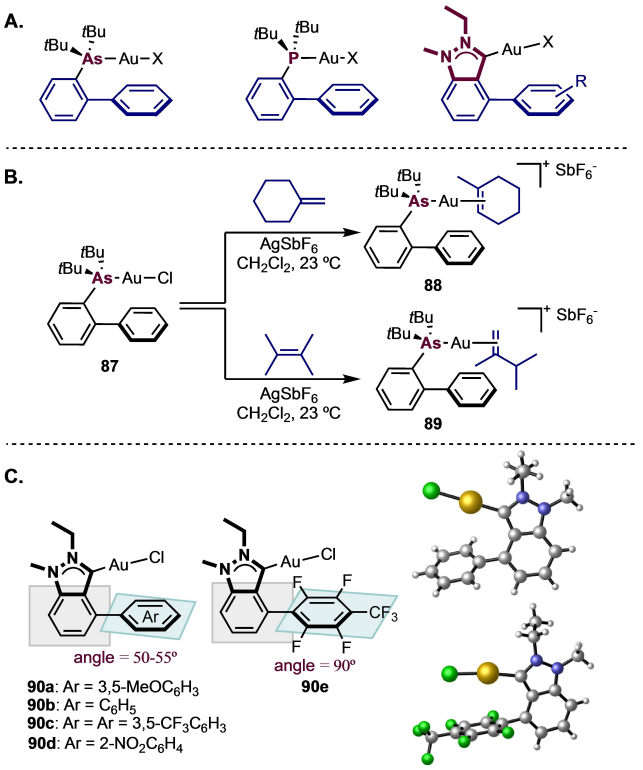
Many other studies on the structure and the nature of cationic gold π-coordinated complexes with alkenes, alkynes, dienes, allenes, arenes and heteroatom substituted π-ligands have been performed.[96] What it emerges from those studies is that the these electron-donating bulky ligands stabilizes neutral and cationic linear gold π-complexes and can be also responsible of a certain stabilization of the metal carbene, or cationic-like intermediate, generated in the catalytic activation of unsaturated C–C bonds.

2.2.1 Electronic Tuning of the Biaryl Scaffold

Despite the success of *o*-biphenyphosphines as ligands and the extensive studies performed on the structural features of the related gold(I) complexes, the variation of the electronic properties of this ligand motif has been neglected until recently.

The group of Fernández and Lassaletta[97,98] reported the synthesis of a series of ligands in which the privileged biaryl scaffold is incorporated into an imidazole core to give rise to a new family of chiral NHC–Au(I) complexes. Our group also reported the synthesis, structural analysis and the exploration of the catalytical activity of a new family of Au(I) complexes with ligands structurally inspired on JohnPhos, but with significantly altered electronic characteristics (Scheme 16).[99] On one side, we synthesized the As-based analogous of JohnPhos, that displays a stronger π-acceptor character, on the other, we incorporated the 4-aryindazole scaffold into the biaryl system of a small library of ligands with high σ-donating character (Scheme 16).

The structure of the As-based dialkyl-biphenyl gold(I) complexes are in line with what already reported for other As based gold(I) complexes.[100–102] Compared to the phosphorous analogous, the Au–Cl or Au–N distance is shorter, in line with the expected increased electrophilicity of the complexes. In the attempt of synthesizing the cationic gold(I) π-complexes with simple alkenes starting from complex **87**, we isolated



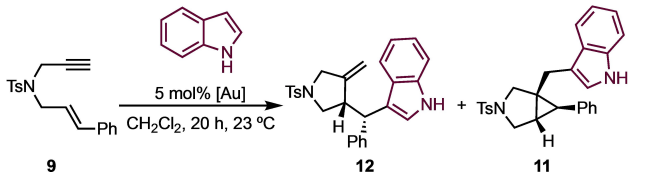
Scheme 16. Structure and reactivtiy of dialkyl-biaryl arsine gold(I) complexes and 4-arylindazole gold(I) complexes.

quantitatively complexes **88** and **89**, in which the double bonds of the original alkenes have undergone migration (Scheme 16). This 1,3-hydrogen migration probably occurs by Brønsted acid catalysis outside the coordination sphere of the metal and can be induced also in preformed complexes both with arsine or phosphine ligand. The alkene is closer to the metal center in the arsine complexes compared to the phosphine analogues in agreement with the observed higher electrophilicity of the arsine complexes. The enhanced steric congestion around the metal center is also probably responsible for the counter-intuitive isomerization of the internal double bond to the terminal one in **89**.

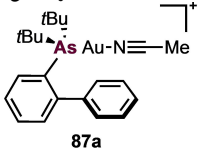
Structurally, the 4-arylindazole family of gold(I) resemble the structure of gold(I) complexes with a simpler similar ligand already reported.[103] Notably, complex **90e**, with a very electron-poor second aromatic ring, showed the C_{ipso}–Au distance to be 0.2–0.3 Å shorter than that found in the rest of the family. The angle between the two aromatic rings of **90e** is around 90°, instead of 50–55° in the other complexes. In this way, the ligand of complex **90e** resembles more the *o*-biarylphosphine skeleton of JohnPhos.

This difference in structure causes also a drastic change in reactivity in homogeneous gold(I) catalyzed reaction. As an example, we tested the library of new complexes in the addition of indole to 1,6-enyne **9** (Table 1). As mentioned before (see Scheme 4), the outcome of this addition reaction depends on the nature of the catalyst and can be correlated

Table 1. Gold(I) catalyzed addition of indole to 1,6-enyne **9**.



Entry	Catalyst	Yield [%] (**12**:**11** ratio)
1	**87a**	95 (69:31)
2	**90a**/$AgSbF_6$	21 (20:80)
3	**90b**/$AgSbF_6$	42 (25:75)
4	**90c**/$AgSbF_6$	73 (40:60)
5	**90d**/$AgSbF_6$	41 (33:67)
6	**90e**/$AgSbF_6$	61 (75:25)

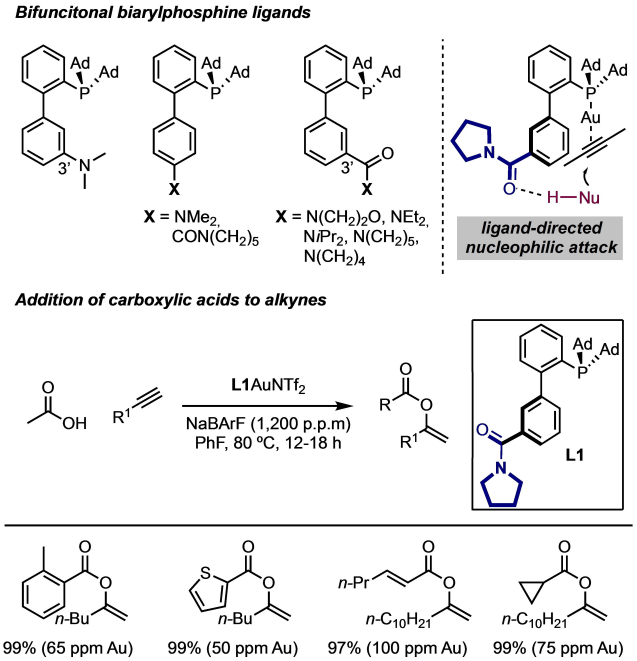


with its electrophilicity.[53] As expected, the arsine gold(I) complex **87** gave **12** as the major product (Table 1, entry 1) whereas the indazole gold(I) complexes **90a–d** led preferentially to **11** (Table 1, entries 2–5). However, complex **90e** differentiates from the rest of its congeners and leads **12** as the major product (Table 1, entry 6) stressing the similar behavior of this complex with *o*-biarylphosphine gold(I) complexes.

2.2.2 Functionalized Biphenyl Scaffolds in Gold(I) Catalysis

The bulky biarylphosphine ligands have attracted interest also from the geometrical point of view. Functionalization on the rigid biphenyl scaffold has led to the uncovering of new reactivities and to improve the selectivity of known transformations. In this context, the group of Zhang has introduced a family of ligands based on the biarylphosphine framework allowing for ligand-directed anti-nucleophilic additions to alkynes.[104] In their design, the second aryl ring is functionalized at the 3'-position with hydrogen-bond acceptor functional groups such as amines and amides (Scheme 17). In view of the outer-sphere reaction mechanism in gold(I)-catalyzed transformations, the rigid biphenyl scaffold represents the optimal platform to place a distal functional group assisting the nucleophilic attack onto a coordinated alkyne substrate. Thus, for example, the intermolecular reaction becomes a partially intramolecular process where the remote amide in ligand **L1** pre-orientates the nucleophile acting as a general base in the first place, and secondly as a general acid catalyst, promoting a rapid intramolecular protodeauration. This results in an increased reaction rate and overall reaction efficiency.

In general, additions of carboxylic acids, anilines and water to alkynes could be performed in high yields and turnover numbers (TONs) (up to 99,000) with ppm level of catalyst loadings.[104] Importantly, this class of ligands outcompetes

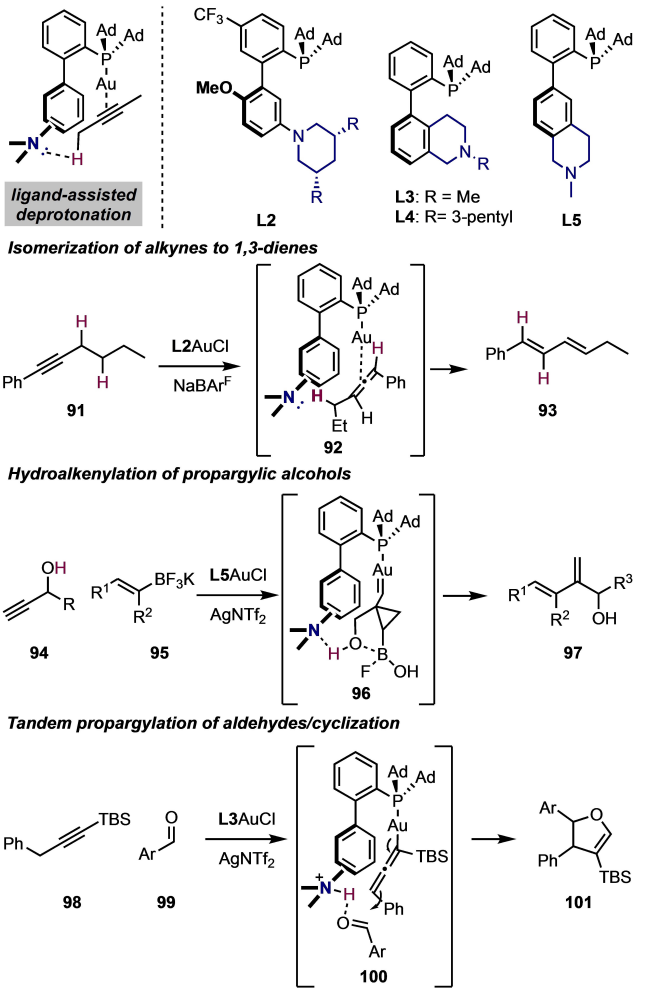


Scheme 17. Bifunctional biarylphosphine ligands and application in the addition of carboxylic acids to alkynes.

more conventional ligands employed in these transformations such as JohnPhos and NHC ligands.

This soft deprotonation strategy has streamlined the synthesis of a library of dialkyl biarylphosphine ligands **L2–L5** which bear a remote amine leading to the discovery of new reactivities in gold(I) catalysis (Scheme 18). Thus, the group of Zhang reported the isomerization of alkynes **91** to 1,3-dienes **93**.[105] In this reaction, the propargylic hydrogen is acidified upon activation of the alkyne by gold(I) and the strategically positioned weak Brønsted base functions as a proton shuttle in the isomerization process, which leads to the formation of allenyl intermediate **92**. Similarly, the isomerization of ynamides and allenamides,[106] propargylic esters[107] and allyl ynoates[108] has been reported.

This class of ligands has enabled the development of intermolecular processes such as the hydroalkenylation of propargylic alcohols **94** with alkenyltrifluoroborates **95** (Scheme 18).[109] In this transformation, the hydrogen-bond between the basic site and the propargylic alcohol increases the nucleophilicity of the oxygen, which in turn facilitates reaction with an alkenylboronate forming cyclopropylgold(I) carbene intermediate **96**, and subsequently dienol **97**. Finally, silylated alkynes **98** also undergo an isomerization reaction to generate an intermediate σ-allenylgold **100** that is stabilized by a β-silicon effect rather than undergoing fast protodeauration.[110] This allowed the reaction with electrophiles such as aldehydes **99** via 1,2-addition, followed by cyclization with concomitant 1,2-silyl migration yielding silylated dihydrofuranes **101** (Scheme 18).[111]



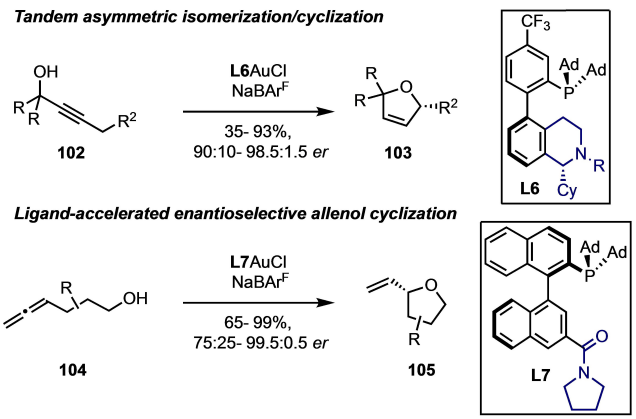
Scheme 18. Versatility of biaryl phosphine ligands **L2–L5** with remote basic functional groups in gold(I) catalysis.

2.2.3 Buchwald-type Ligands in Enantioselective Gold (I)-catalysis

In contrast to the broad scope of gold(I)-catalyzed transformations reported over the last 15 years, the enantioselective counterparts have experienced much slower development.[112–114] The associated difficulties are mainly attributed to the preferred linear dicoordination adopted by gold(I), which places the ancillary chiral ligand and the substrate opposite to each other, resulting in poor enantioinduction. In addition, gold(I)-catalyzed addition reactions to unsaturated functional groups such as alkynes take place by outer sphere mechanisms, thus enhancing the degree of difficulty in developing enantioselective processes. Despite significant progress using axially chiral digold complexes,[43,115,116] phosphoramidite ligands,[117] the combination of non-chiral gold(I) complexes with chiral counterions[118] and other emerging strategies,[119–124] the asymmetric activation of alkynes which are not prochiral still presents an important challenge.

In line with their pioneering studies, the group of Zhang reported bifunctional ligand **L6** which enables the synthesis of chiral 2,5-dihydrofuranes **103** *via* enantioselective isomerization of propargylic alcohol **102** to axially chiral allenes followed by stereospecific cyclization (Scheme 19).[121] Additionally, the same group reported a ligand-accelerated enantioselective cyclization of allenols.[122] Key to this transformation was the use of axially chiral ligand **L7** with a remote amide group whereby hydrogen-bonding between ligand and substrate asymmetrically pre-orientates allenol **104** for nucleophilic attack giving vinyl tetrahydrofuranes **105**.

In view of the general applicability of Buchwald ligands in gold(I)-catalysis, our group introduced a new family of chiral mononuclear gold(I) complexes **106**–**112** supported by modified JohnPhos-type ligands containing a remote C_2-symmetric

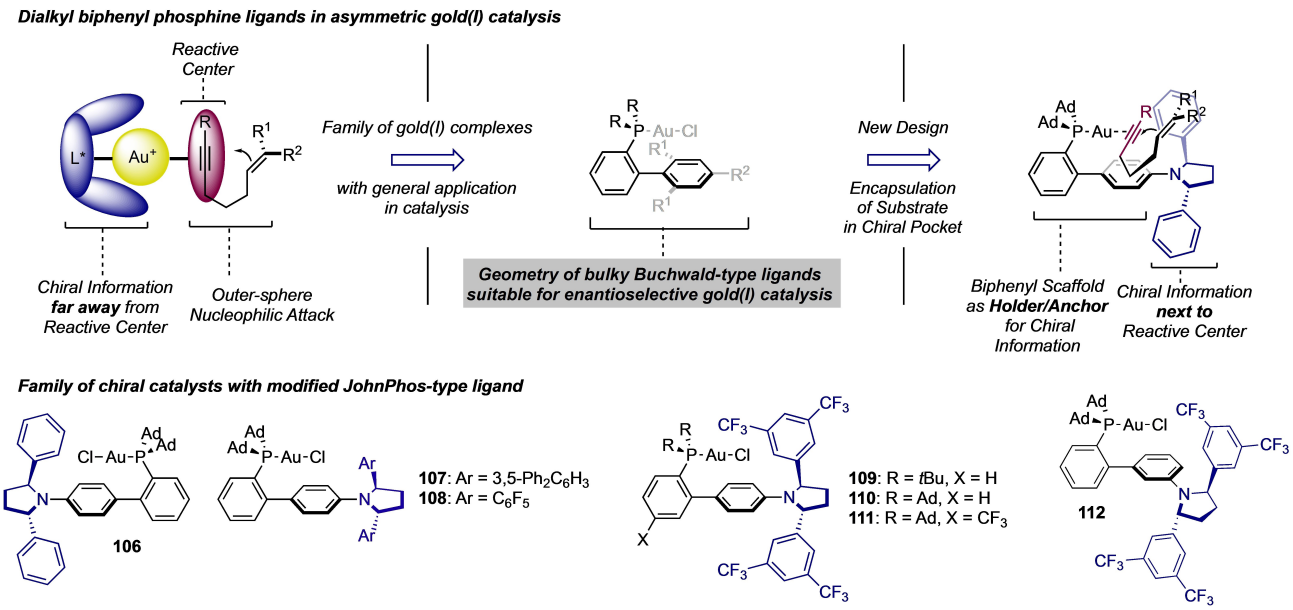


Scheme 19. Application chiral biarylphosphine ligands with remote functional group.

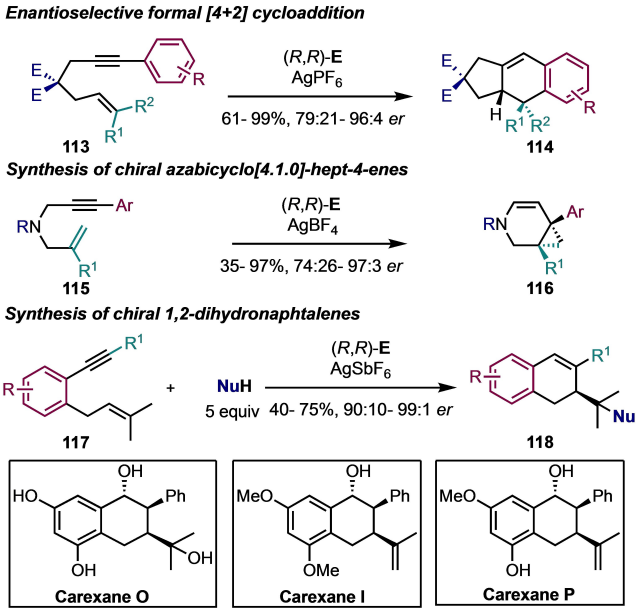
2,5-diarylpyrrolidines (Scheme 20).[125] The design of this class of ligands was streamlined by the challenge of placing the chiral information around the reactive center (substrate). To overcome this difficulty, we recognized that the geometry of the bulky dialkyl biphenyl-phosphine ligands was suitable to address the limitations presented by the particular coordination mode of gold(I). In our design, the rigid biaryl scaffold connects the chiral element and the coordinating phosphine encapsulating the gold(I) nucleus in a chiral pocket. The bulky dialkyl phosphines are crucial to prevent rotation around the C_{aryl}-P bond and force the P–Au–Cl axis to be parallel to the biphenyl scaffold and point towards the chiral information

We applied these chiral complexes in three different cyclizations of 1,6-enynes **113**, **115** and **117** giving products of formal [4+2] cyclization **114**, azabicyclo[4.1.0]hept-4-enes **116** and 1,2-dihydronaphtalenes **118** in high yields and enantioselectivities (Scheme 21).[125] Additionally, we demonstrated the synthetic utility of products **118** for the first asymmetric total synthesis of three members of the carexane family of natural products.

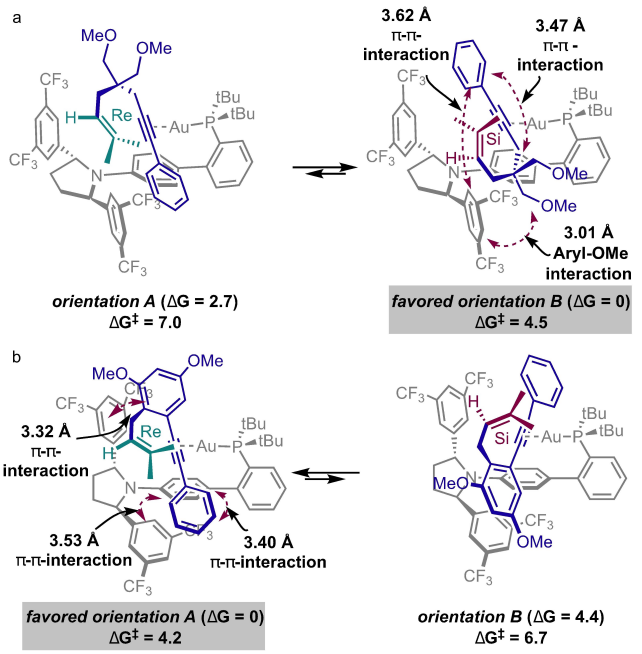
The simple design of the mononuclear complexes facilitated the systematic investigation of their mode of action.[125] Remarkably, despite the structural similarity of 1,6-enynes **113** and **117** opposite enantioselectivites were obtained arising respectively from the reaction of the *Si* or *Re* faces of the alkene, which indicates that a totally distinct folding of the unsaturated substrates takes place inside the chiral pocket. Theoretical and experimental evidence showed that attractive non-covalent interactions between the aromatic moieties of the substrates and the aromatic substituent of the distal pyrrolidine are responsible for substrate recognition favoring one specific binding orientation (**A** or **B**) and in turn the reaction of one face of the alkene over the other (Scheme 22). Additional π-π-



Scheme 20. Family of chiral mononunclear gold(I) catalysts **106**–**112**.



Scheme 21. Application of chiral complex **110** in catalysis and total synthesis.



Scheme 22. Most favorable binding orientations for a)1,6-enynes **113** and b) 1,6-enyne **117**.

interactions with the biphenyl scaffold of the ligand provided further stabilization of the transition states and, in case of 1,6-enynes **113**, aryl-OMe interactions were also identified to be important to define the stereocontrol.

3. Summary

Bulky dialkyl biarylphosphines, developed by Buchwald as ligands for Pd-catalyzed reactions, are also privileged ligands in homogeneous gold(I) catalysis. However, there are some important differences in the metal-arene interaction between palladium and gold with these ligands, since in the case of gold, the metal does not bind to the second aryl ring. The resulting gold(I) complexes are at the same time robust and highly active and, for these reasons, are among the most commonly used catalysts in homogeneous gold(I) catalysis. The rigid biaryl scaffold also allows the introduction of distal functional groups that assist the catalysis in new ways as well as chiral elements that control the folding of unsaturated substrates.

Acknowledgements

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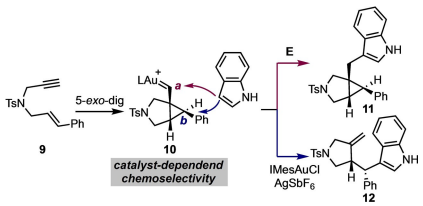

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