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Recent Developments in Enantioselective Gold(I) Catalysis

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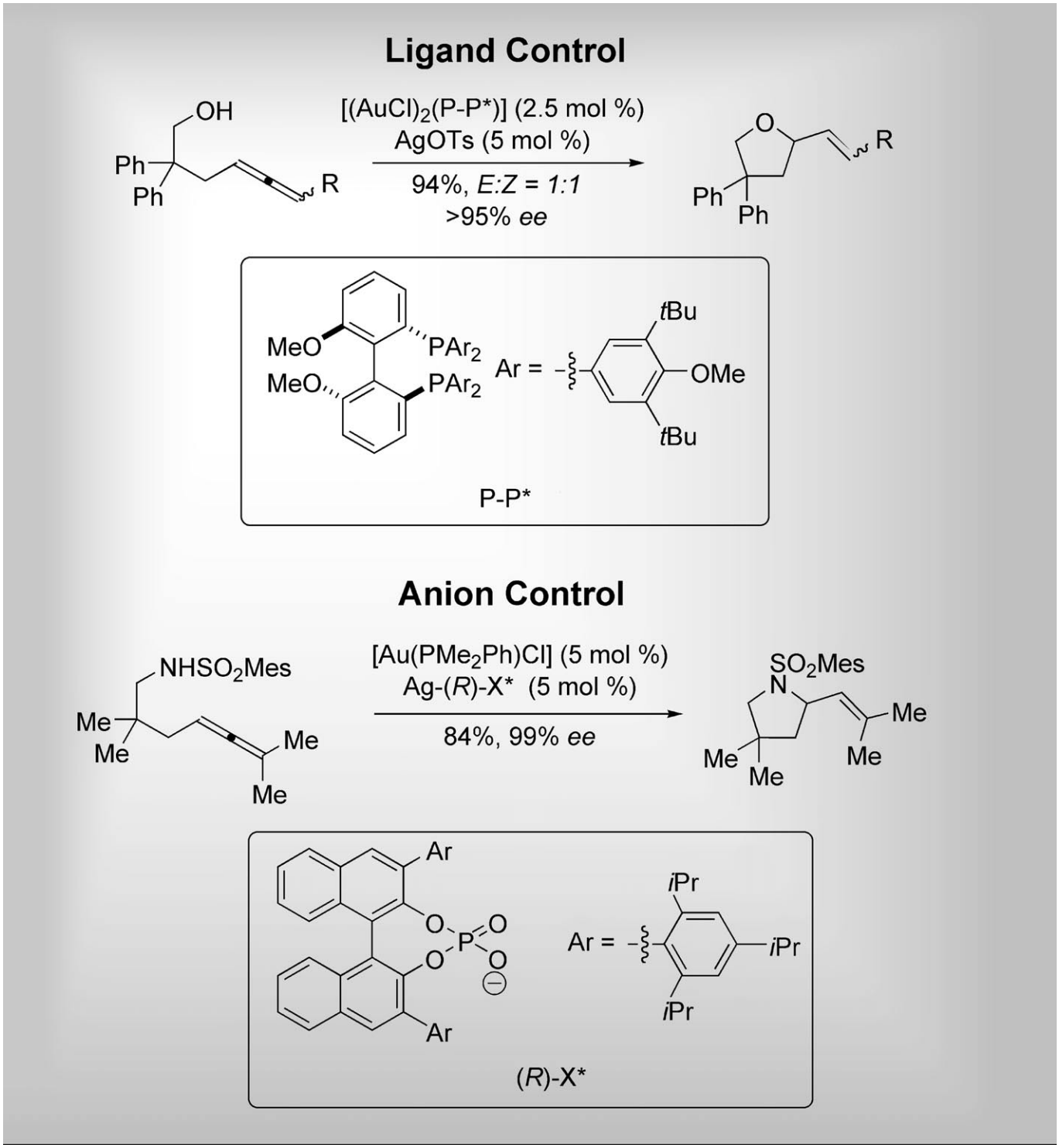

Abstract: The use of gold(I) complexes as catalysts for organic transformations has become increasingly common over the past decade, leading to the development of a number of useful carbon–carbon and carbon–heteroatom bond-forming processes. In contrast, enantioselective catalysis employing gold(I) complexes was, until recently, exceedingly rare, due in large part to the pronounced tendency of gold(I) to form linear, two-coordinate complexes. However, new approaches and strategies have emerged over the past two years, leading to the development of a number of effective gold(I)-catalyzed enantioselective transformations, most notably the enantioselective hydrofunctionalization of allenes. Outlined herein is an overview of enantioselective gold(I) catalysis since 2005.

Keywords: allenes · gold · heterocyclic compounds · homogeneous catalysis · transition metals

Introduction

The application of soluble gold complexes as catalysts for organic transformations has become increasingly common over the past decade.[1] Early work in this area focused on the use of simple gold(III) halides as catalysts, but effort has increasingly shifted toward cationic gold(I)–phosphine complexes. Although a diverse range of transformations have been reported, gold(I) complexes have demonstrated particular utility as catalysts for the metathesis and/or cycloisomerization of enynes and related substrates,[2] and for the hydrofunctionalization of alkenes, allenes, and alkynes with carbon heteroatom nucleophiles.[3] Common to these transformations is the π-activation of a C–C multiple bond of the substrate toward nucleophilic attack, a process for which gold(I) is particularly well suited. The 14-electron $[AuL]^+$ fragment is a highly electrophilic, soft Lewis acid that renders gold(I) highly carbophilic but relatively nonoxophilic.[1] As a result, gold(I) displays good chemoselectivity and good functional group compatibility, traits that are crucial for application in complex molecular environments. Importantly, weak 5d→π* metal-to-ligand back bonding further predisposes a gold(I)–π-alkene/alkyne complex toward outer-sphere nucleophilic attack.[4] Furthermore, although both the Au^I and Au^{III} oxidation states are stable, gold(I) is not prone to air oxidation and does not readily participate in potentially deleterious redox-based processes.[5]

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Enantioselective catalysis based on the π-activation of C–C multiple bonds represents an unsolved problem in organo–transition-metal chemistry,[6] and the emergence of gold(I) as an effective π-activation catalyst presents new opportunities in this area.[7] However, the rapid development of gold(I) catalysis has not extended to enantioselective catalysis. Telling is that prior to 2005, the lone example of an enantioselective gold(I)-catalyzed transformation was the enantioselective coupling of aldehydes with isocyanoacetate esters catalyzed by a gold(I)–ferrocenylphosphine complex, in which gold(I) behaves as a traditional Lewis acid through carbonyl-group activation.[8] The dearth of enantioselective gold(I)-catalyzed transformations can be traced to the propensity of gold(I) to form linear two-coordinate complexes,[9] in which the reacting substrate is positioned far from the potential source of ligand-centered chirality. The problems associated with ligand/substrate proximity are further exacerbated by the outer-sphere nature of π-activation catalysis that bypasses nucleophile–metal interaction prior to C–X bond formation.[10] The preferred linear coordination mode of gold(I) also precludes approaches based on bidentate coordination of chiral bis(phosphines) and related ligands that have become the cornerstones of enantioselective catalysis employing four-, five-, and six-coordinate transition-metal complexes.[7]

For the reasons outlined in the preceding paragraph, development of enantioselective catalytic process involving gold(I) represents a new challenge in homogeneous catalysis. The catalysis community has responded to this challenge with new approaches and new strategies, and since 2005 examples of enantioselective gold(I)-catalyzed transformations have increased markedly. Key to the development of enantioselective gold(I) catalysis has been the identification of enantiomerically pure bis(gold)–phosphine complexes of the form $[(AuX)_2(P–P)]$ (P–P = chiral bis(phosphine), X = anionic ligand or counterion) as catalysts for enantioselective transformations. Also crucial to the development of enantioselective gold(I) catalysis has been recognition of the pronounced effect of the counterion on the efficiency and selectivity of these transformations. Summarized herein is the development of enantioselective gold(I) catalysis since 2005 with an emphasis on the enantioselective hydrofunctionalization of allenes.

Addition of Carbon Nucleophiles to Alkynes

Enyne alkoxycyclization: In early 2005, Echavarren reported the gold(I)-catalyzed enantioselective alkoxycyclization of 1,6-enynes to form methylenecyclopentanes.[11] Although inefficient, these transformations represent both the first examples of enantioselective gold(I) catalysis involving π-activation and the first successful application of chiral bis(gold) complexes in enantioselective catalysis. For example, a 1:1.25 mixture of $[(AuCl)_2\{(R)$-tol-binap$\}]$ ((*R*)-**1**; Figure 1)

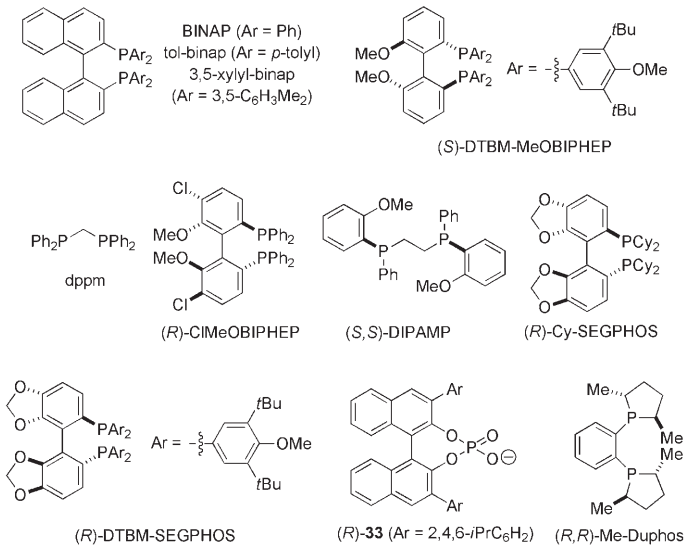
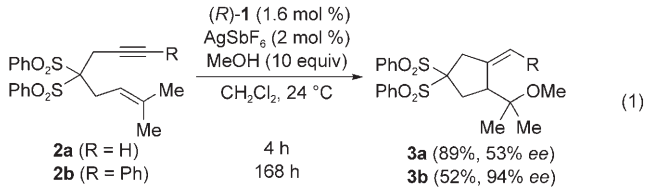


Figure 1. Bis(phosphine) ligands and anions employed in enantioselective gold(I) catalysis.

and $AgSbF_6$ catalyzed the alkoxycyclization of enyne **2a** with methanol (10 equiv) at room temperature for 4 h to form methylenecyclopentane **3a** in 89% yield with 53% enantiomeric excess (*ee*) [Eq. (1)]. In comparison, phenyl-substituted enyne **2b** underwent slow alkoxycyclization to form **3b** with high enantioselectivity, but modest yield [Eq. (1)]. Gold(I)-catalyzed enantioselective alkoxycyclization was sensitive to the Au/Ag ratio. For example, alkoxycyclization of **2a** catalyzed by a 1:2 ratio of (*R*)-**1** and $AgSbF_6$ required 30 h to reach completion and formed **3a** in only 14% *ee* with the opposite sense of stereoinduction relative to the reaction employing a 1:1.25 mixture of (*R*)-**1** and $AgSbF_6$. These and related experiments pointed to a monocationic bis(gold) complex as the most active and most selective catalyst for these transformations.



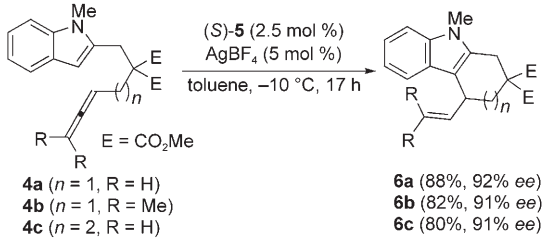
(1)

Enantioselective π-Activation of Allenes

C–C Bond formation in the gold(I)-catalyzed enantioselective alkoxycyclization of enynes presumably occurs via outer-sphere attack of the electron-rich alkene moiety on a gold π-alkyne intermediate.[11] The modest enantioselectivities realized via gold(I)-catalyzed alkoxycyclization are therefore not surprising as the newly formed sp^3 stereocenter originates from the attacking alkene moiety rather than from the metal-bound alkyne. Although nucleophilic attack on a π-alkene complex generates an sp^3 carbon atom, the low reactivity of simple alkenes relative to alkynes renders enantioselective catalysis based on the π-activation of alkenes particularly challenging. In this context, allenes represent attractive substrates for enantioselective gold(I) π-activation catalysis. Allenes, like alkynes, are more reactive than are simple alkenes[12] and, like simple alkenes, nucleophilc attack at the terminal carbon atom of a π-allene complex generates an sp^3 carbon atom. Indeed, a number of research groups have investigated the gold(I)-catalyzed enantioselective π-activation of allenes and from these efforts, a range of effective transformations have been developed.

Addition of Carbon Nucleophiles to Allenes

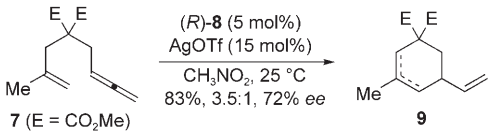
Allene hydroarylation: As an extension of their work with achiral gold(I) catalysts,[13] Widenhoefer and co-workers reported the enantioselective intramolecular hydroarylation of 2-(allenyl)indoles to form substituted, polycyclic, indole derivatives.[14] For example, reaction of 2-(γ-allenyl)indole **4a** with a catalytic 1:2 mixture of [$(AuCl)_2$\{(*S*)-DTBM-MeOBIPHEP\}] ((*S*)-**5**; Figure 1) and $AgBF_4$ in toluene at −10 °C for 17 h led to isolation of tetrahydrocarbazole **6a** in 88% yield with 92% *ee* [Eq. (2)]. The enantioselectivity of intramolecular hydroarylation was dependent on solvent, counterion, and phosphine ligand. For example, cyclization of **4a** catalyzed by a 1:2 mixture of [$(AuCl)_2$\{(*S*)-binap\}] and AgOTf in dioxane at room temperature gave **6a** in only 32% *ee*. Although the scope of the reaction was limited, the optimized protocol was effective for the hydroarylation of 2-(γ-allenyl)indole **4b** that possessed a terminally disubstituted allenyl group and for the cyclization of 2-(δ-allenyl)indole **4c** to form the seven-membered ring of **6c** [Eq. (2)].[14]



(2)

Cycloisomerization of enallenes: Gagné has reported the gold(I)-catalyzed enantioselective cycloisomerization of γ-eneallenes to form substituted vinylcyclohexenes. Treatment of the malonate derivative **7** with a catalytic 1:3 mixture of [$(AuCl)_2$\{(*R*)-3,5-xylyl-binap\}] ((*R*)-**8**; Figure 1) and AgOTf in nitromethane at room temperature led to isolation of cyclohexene **9** in 83% yield as a 3.5:1 mixture of regioisomers with 72% *ee* [Eq. (3)].[15] Enantioselective enallene cycloisomerization required substitution at the internal carbon of the alkene moiety and did not tolerate substitution at either the internal or terminal allenyl carbon atoms. Enantioselectivities were modest (≤77% *ee*) and regioisomers were typi-

cally generated. Interestingly, the sterically hindered DTBM-MeOBIOHEP and DTBM-SEGPHOS ligands (Figure 1) used to good effect for related enantioselective transformations were ineffective for this transformation. Also surprising was that employment of [(AuOTf)$_2${(*R*)-3,5-xylyl-binap}] as a catalyst led to low enantioselectivities and low reaction rates. Cyclization of **7** catalyzed by [(AuOTf)$_2${(*R*)-3,5-xylyl-binap}] in the presence of either AgOTf (15%) or AgCl (15%), restored the activity of the catalyst, but gave **9** with $\leq$34% *ee*. Although the origin of these unusual counterion/Ag effects has not been identified, this behaviour is perhaps related to the counterion effects more thoroughly delineated by Toste (see below).



(3)

X-ray crystallographic analysis of the catalyst precursor (*R*)-**8** revealed the presence of a π-stacking interaction between two P-bound xylyl groups with a plane-to-plane distance of 3.7 Å and a Au–Au distance of 5.5 Å (Figure 2).

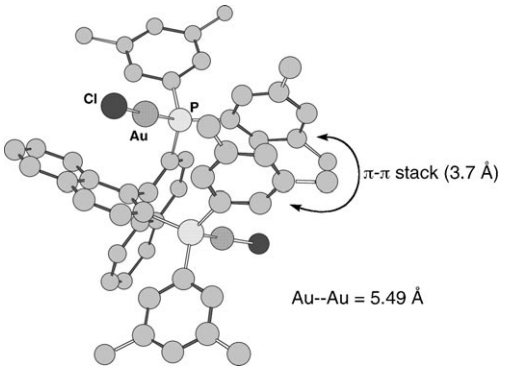
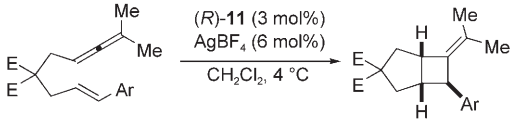


Figure 2. ORTEP diagram of the X-ray crystal structure of [(AuCl)$_2${(*R*)-3,5-xylyl-binap}] [(*R*)-**8**].[11]

Not unexpectedly, a similar solid-state conformation was observed for [(AuCl)$_2${(*R*)-tol-binap}] ((*R*)-**1**).[11] Gagné suggests that similar solution-state π-stacking interactions may be a general phenomenon that assist in creating an effective chiral environment for enantioselective catalysis employing bis(gold)–phosphine complexes.

[2+2] Cycloaddition of enallenes: Toste has developed an effective gold(I)-catalyzed protocol for the enantioselective [2+2] cycloaddition of γ-eneallenes to form [4.3.0]bicycloheptanes.[16] For example, reaction of eneallene **10a** with a 1:2 mixture of [(AuCl)$_2${(*R*)-DTBM-SEGPHOS}] ((*R*)-**11**) and $AgBF_4$ in CH_2Cl_2 at 4°C led to isolation of the [4.3.0]bicycloheptane **12a** in 92% yield as a single disastereomer with 95% *ee* [Eq. (4)]. Key to the realization of [2+2] cycloaddition rather than 6-*endo* cycloisomerization was aryl substitution at the terminal alkenyl carbon atom, but within this constraint, a number of aryl groups were tolerated in the transformation [Eq. (4)]. Effective [2+2] cycloaddition also required a terminally disubstituted allenyl moiety and disubstitution at the homoallylic carbon atom, which presumably facilitates cyclization through the Thorpe–Ingold effect.

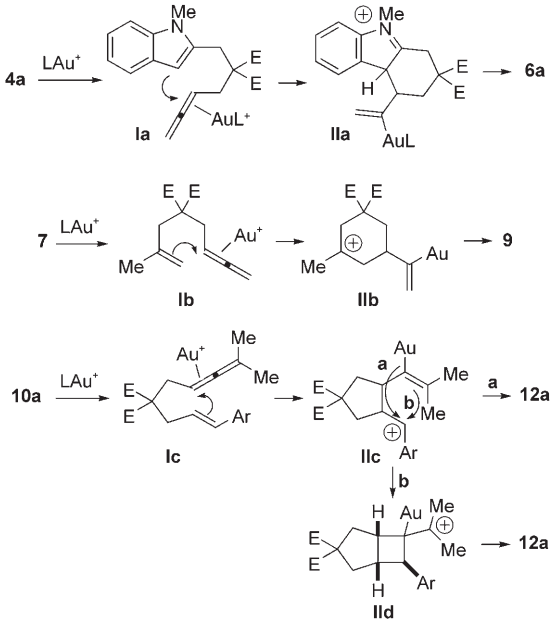


(4)

(E = CO_2Me)

10a (Ar = Ph) **12a** (92%, 95% *ee*)
10b (Ar = 2-naphthyl) **12a** (81%, 97% *ee*)
10c (Ar = *p*-ClC_6H_4) **12a** (80%, 96% *ee*)
10d (Ar = *p*-tolyl) **12a** (78%, 91% *ee*)

Mechanisms of hydroarylation and hydroalkenylation: Although mechanistic studies are lacking, C–C bond formation in the gold(I)-catalyzed enantioselective hydroarylation of 2-allenyl indoles and in the cycloisomerization and [2+2] cycloaddition of γ-enallenes presumably occurs through outer-sphere attack of the pendent arene or alkene moiety on gold π-allene intermediates **Ia–Ic** respectively (Scheme 1).



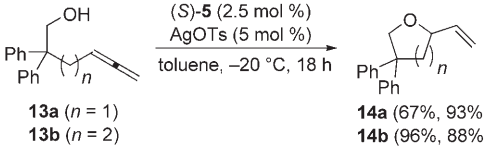
Scheme 1. Proposed mechanisms of gold(I)-catalyzed C–C bond forming processes.

In the case of hydroarylation, deprotonation of the initially formed iminium ion **IIa** followed by protonolysis of the Au–C bond with retention of configuration[17] would form the tetrahydrocarbazole **6a** (Scheme 1). In the case of cycloisomerization, competetive β-elimination of the secondary or tertiary hydrogen atom from the initially formed carbocation **IIb** followed by protonolysis of the Au–C bond

would form cyclohexenes **9**. The most direct pathway that accounts for cyclobutane formation in the [2+2] cycloaddition of **10a** is attack of the Au–C σ bond of **IIc** on the proximal benzylic carbocation **IIc** to form bicycloheptane **12a** (Scheme 1, path a). Alternatively, attack of the proximal C=C bond on the benzylic carbocation of **IIc** followed by elimination of gold from carbocation **IId** would also form **12a** (Scheme 1, path b).

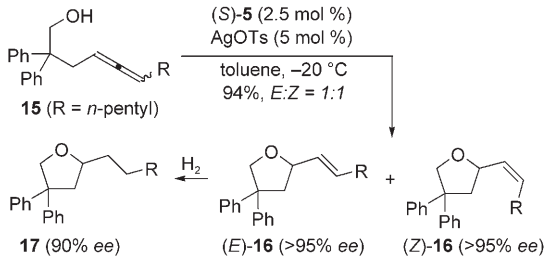
Carbon–Heteroatom Bond Formation

Intramoleclar hydroalkoxylation allenes: In early 2007 Zhang and Widenhoefer reported the gold(I)-catalyzed, enantioselective, intramolecular, hydroalkoxylation of γ- and δ-hydroxy allenes to form oxygen heterocycles.[18] For example, reaction of 2,2-diphenyl-4,5-hexadienol (**13a**) with a catalytic 1:2 mixture of (*S*)-**5** (2.5 mol%) and AgOTs at −20°C in toluene for 18 h led to isolation of **14a** in 67% yield with 93% *ee* [Eq. (5)].[18] Similarly, gold(I)-catalyzed hydroalkoxylation of 2,2-diphenyl-5,6-heptadienol (**13b**) formed 2-vinyl tetrahydropyran **14b** in 96% yield with 88% *ee* [Eq. (5)]. Several points are worth noting regarding the optimization of the protocol, which illustrate the strong dependence of this transformation on catalyst and counterion composition. Under comparable conditions (dioxane, room temperature, 125 mM in **13a**), the enantioselectivity of the conversion of **13a** to **14a** decreased from 86 to 28% *ee* upon substitution of AgOTs with $AgClO_4$ and from 86 to 19% *ee* upon substitution of (*S*)-**5** with [$(AuCl)_2$\{(*S*)-binap\}].



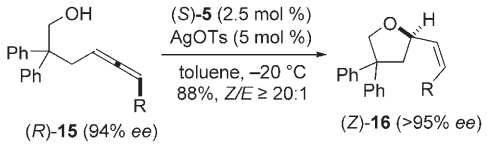
(5)

Enantioselective hydroalkoxylation of γ-hydroxyallenes that possessed an axially chiral allenyl moiety occurred with high enantioselectivity/low diastereoselectivity in a catalyst-controlled process. For example, reaction of *rac*-**15** with a catalytic 1:2 mixture of (*S*)-**5** and AgOTs led to isolation of a 1:1 mixture of (*E*)-**16** (>95% *ee*) and (*Z*)-**16** (>95% *ee*) in 94% combined yield (Scheme 2). The homochirality of (*E*)-**16** and (*Z*)-**16** was established by hydrogenation of the mixture to form 2-heptyltetrahydrofuran **17** with 90% *ee*. These results suggested that one enantiomer of **15** formed (*E*)-**16** and the second enantiomer of **15** formed (*Z*)-**16**. Indeed, gold-catalyzed enantioselective hydroalkoxylation of (*R*)-**15** (94% *ee*) led to isolation of (*Z*)-**16** in 88% yield with >95% *ee* and ≥20:1 diastereoselectivity [Eq. (6)]. In comparison, gold(I)-catalyzed hydroalkoxylation of **18**, which lacked substitution along the alkyl backbone, underwent enantioselective hydroalkoxylation to form a 1.5:1 mixture of (*E*,*R*)-**19** and (*Z*,*R*)-**19** in high yield but with low



Scheme 2. Gold-catalyzed hydroalkoxylation of an axially chiral γ-hydroxyallene.

enantioselectivity [Eq. (7)]. Nevertheless, conversion of **18** to (*R*)-**19** served to establish the absolute sense of stereoinduction from (*S*)-**5**.



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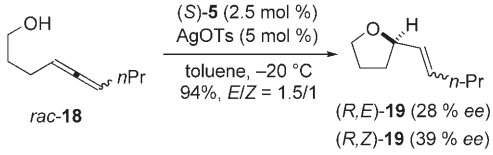
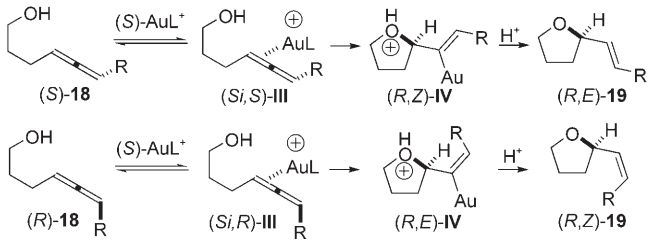


(7)

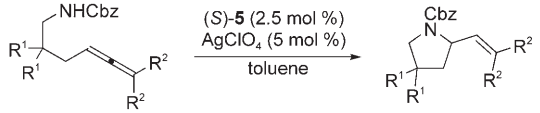
The experiments described in the preceding paragraph support a catalyst-controlled outer-sphere mechanism for the Au-catalyzed enantioselective hydroalkoxylation of *rac*-**18** (Scheme 3). In the major pathway for enantiomer (*S*)-**18**,



Scheme 3. Proposed mechanism of the gold(I)-catalyzed enantioselective hydroalkoxylation of *rac*-**18**.

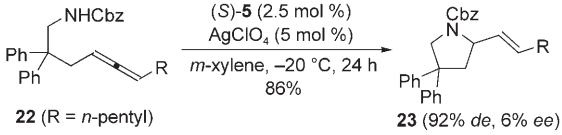
complexation of gold to the *Si* face of the internal allenyl C=C bond would form gold-allene complex (*Si*,*S*)-**III**. Outer-sphere cyclization followed by deprotonation/protonolysis of (*R*,*Z*)-**IV** with retention of stereochemistry[17] would form (*R*,*E*)-**19** (Scheme 3). In the case of (*R*)-**18**, outer-sphere cyclization of gold π-allene complex (*Si*,*R*)-**III** followed by deprotonation/protonolysis of (*R*,*E*)-**IV** would form (*R*,*Z*)-**19** (Scheme 3).

Hydroamination of *N*-allenyl carbamates: With subtle modification, the catalyst system employed for enantioselective hydroalkoxylation of allenes was also effective for the enantioselective hydroamination of *N*-(γ-allenyl)carbamates.[19] As an example, reaction of **20a** with a catalytic 1:2 mixture of (*S*)-**5** and $AgClO_4$ in *m*-xylene at 0–23 °C for 48 h led to isolation of **21a** in 83% yield with 91% *ee* [Eq. (8)]. The enantioselectivity of allene hydroamination was sensitive to substitution of the *N*-allenyl carbamate. Enantioselective hydroamination of the terminally unsubstituted *N*-allenyl carbamate **20b** formed pyrrolidine **21b** in 97% yield with 81% *ee*, while enantioselective hydroamination of the unsubstituted *N*-allenyl carbamate **20c** gave pyrrolidine **21c** in near quantitative yield but with only 34% *ee* [Eq. (8)]. The rate of reaction was highly sensitive to the nature of the counterion and substitution of $AgClO_4$ with AgOTs led to a ≈1000-fold decrease in reaction rate accompanied by a small decrease in enantioselectivity.



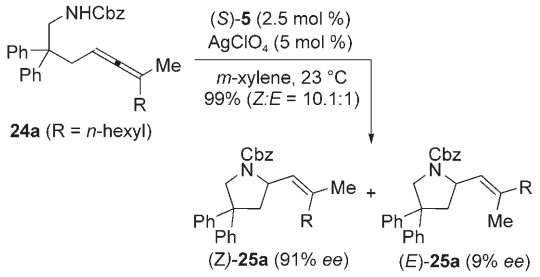
(8)

In sharp contrast to the gold(I)-catalyzed enantioselective hydroalkoxylation of axially chiral γ-hydroxy allene **15**, enantioselective hydroamination of the axially chiral *N*-(γ-allenyl) carbamate **22** formed pyrrolidine **23** with high diastereoselectivity, but with negligible enantioselectivity in a substrate-controlled process [Eq. (9)]. Because both reactions presumably involve similar gold π-allene intermediate(s), the divergent behaviour of these two transformations suggests that absolute configuration is not determined by selective formation of a gold allene π-complex, but rather by the selective attack of the nucleophile on one of a mixture of equilibrating gold π-allene complexes.



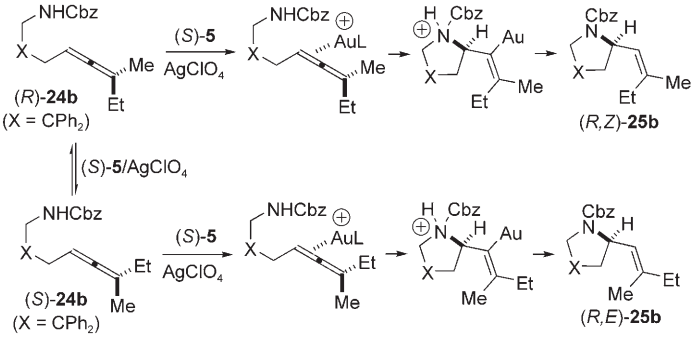
(9)

Dynamic kinetic enantioselective hydroamination: Although cationic gold(I) complexes racemize allenes,[20] there was no evidence of dynamic behaviour in either the hydroalkoxylation or hydroamination of 1,3-disubstituted allenes catalyzed by (*S*)-**5**/AgX.[18,19] In contrast, *N*-(γ-allenyl) carbamates that possessed a trisubstituted allenyl group underwent dynamic kinetic enantioselective hydroamination (DKEH) to form predominantly one of four possible 2-vinyl pyrrolidine stereoisomers.[21] For example, reaction of benzyl 6-methyl-2,2-diphenyl-4,5-dodecadienyl carbamate (**24a**) with a catalytic 1:2 mixture of (*S*)-**5** (2.5 mol%) and $AgClO_4$ (5 mol%) in *m*-xylene at room temperature for 24 h led to isolation of a 10.1:1 mixture of (*Z*)-**25a** and (*E*)-**25a** in 99% combined yield with 91 and 9% *ee*, respectively [Eq. (10)].



(10)

Stereochemical analysis of the DKEH of *N*-(γ-allenyl) carbamate **24b** catalyzed by (*S*)-**5**/$AgClO_4$ established 1) the rapid racemization of **24b** under reaction conditions, 2) the conversion of (*R*)-**24b** to (*R*,*Z*)-**25b** in the matched reaction manifold, and 3) conversion of (*S*)-**24b** to (*R*,*E*)-**25b** in the mismatched reaction manifold (Scheme 4). These experiments were in accord with the outer-sphere mechanism depicted in Scheme 4 that is analogous to that proposed for the enantioselective hydroalkoxylation of **18**. The only significant difference between the two mechanisms is the facile racemization of starting material in the case of DKEH.

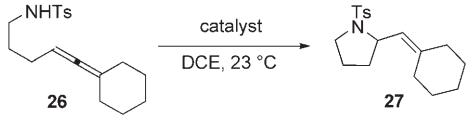


Scheme 4. Proposed mechanism for the DKEH of **24b** catalyzed by (*S*)-**5**/$AgClO_4$.

Hydroamination of allenyl sulfonamides: Toste has reported an effective enantioselective protocol for the intramolecular hydroamination of γ- and δ-allenyl sulfonamides catalyzed by bis(gold)–3,5-xylyl-binap complexes.[22] Development of this chemistry relied heavily on the recognition of the pronounced effect of the counterion on the efficiency and enantioselectivity of hydroamination. For example, the enantioselectivity of the hydroamination of γ-allenyl tosylamine **26** catalyzed by a mixture of [$(AuCl)_2${(*R*)-3,5-xylyl-binap}] ((*R*)-**8**) and $AgBF_4$ increased from 1 to 51% *ee* as the (*R*)-

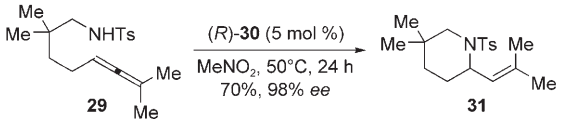
8:$AgBF_4$ ratio increased from 1:2 to 1:1 (Table 1). Increasing the steric bulk of the counterion led to a dramatic increase in enantioselectivity and reaction of **26** with a catalytic 1:2

Table 1. Effect of counterion in the gold-catalyzed enantioselective hydroamination of allenyl sulfonamide **26**.



Catalyst	*t* [h]	Yield [%]	*ee* [%]
(*R*)-**8** (3 mol %)/$AgBF_4$ (6 mol %)	0.5	80	1
(*R*)-**8** (3 mol %)/$AgBF_4$ (3 mol %)	0.5	89	51
(*R*)-**8** (3 mol %)/AgOPNB (6 mol %)	24	76	98
(*R*)-**28** (3 mol %)	17	88	98

mixture of (*R*)-**8** and AgOPNB (OPNB = *p*-nitrobenzoate) formed **27** in 76% yield with 98% *ee*, albeit with reduced reaction rate (Table 1). The low activity of this catalyst system was traced, in part, to incomplete formation of [(AuOPNB)$_2${(*R*)-3,5-xylyl-binap}] ((*R*)-**28**) from (*R*)-**8** and AgOPNB under reaction conditions. Consistent with this observation, reaction of **26** with a catalytic amount of preformed (*R*)-**28** led to an increase in both the rate and yield of the reaction without decrease in enantioselectivity (Table 1). δ-Allenyl sulfonamides also underwent effective enantioselective hydroamination employing a slightly modified protocol. As an example, treatment of **29** with [(AuOPNB)$_2${(*R*)-ClMeOBIPHEP}] ((*R*)-**30**; 5 mol %; Figure 1) in nitromethane at 50 °C for 24 h formed 2-alkenyl piperidine **31** in 70% yield with 98% *ee* [Eq. (11)]. Enantioselective hydroamination of γ- and δ-allenyl sulfonamides was sensitive to substitution along the alkyl tether and both disubstitution at the terminal allenyl carbon atom and employment of a sulfonamide nucleophile were required to achieve effective enanatioselective hydroamination.

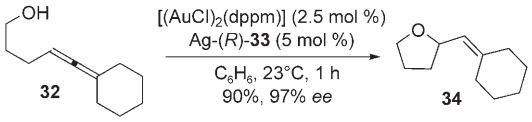


(11)

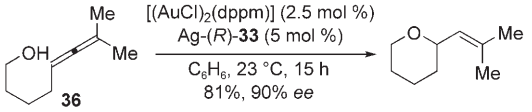
It is worth noting the disparate behaviour with respect to substrate scope of allene hydroamination catalyzed by AuOPNB complexes (*R*)-**28** or (*R*)-**30** relative to (*S*)-**5**/$AgClO_4$. For example, enantioselective allene hydroamination catalyzed by (*R*)-**28** or (*R*)-**30** was restricted to *N*-allenyl sulfonamides that possessed a terminally disubstituted allene moiety. In contrast, enantioselective allene hydroamination catalyzed by (*S*)-**5**/$AgClO_4$ was most effective with carbamate nucleophiles and was effective for terminally unsubstituted allenes, albeit with diminished enantioselectivity. Similarly, high enantioselectivity in the hydroamination and hydroalkoxylation of allenes catalyzed by (*S*)-**5**/AgX was realized only for substrates that possessed *gem*-dialkyl substitution along the alkyl chain. In contrast, the hydroamination of *N*-allenyl sulfonamides catalyzed by (*R*)-**28** or (*R*)-**30** displayed higher enantioselectivity for substrates that lacked substitution along the alkyl backbone than for the corresponding *gem*-disubstituted allenyl sulfonamides.

Hydrofunctionalization with Chiral Anions

Building from their observations regarding the pronounced counterion effects in the gold(I)-catalyzed hydroamination of allenyl sulfonamides, Toste and co-workers developed an effective protocol for the intramolecular hydroalkoxylation of γ- and δ-hydroxy allenes that utilized chiral, enantiomerically pure anions to convey stereochemical information.[23] For example, reaction of γ-hydroxy allene **32** with a catalytic 1:2 mixture of the achiral bis(gold) complex [(AuCl)$_2$(dppm)] and chiral, non-racemic silver phosphonate Ag-(*R*)-**33** (Figure 1) in benzene at room temperature led to isolation of 2-alkenyl tetrahydrofuran **34** in 90% yield with 97% *ee* [Eq. (12)]. Similarly, hydroalkoxylation of δ-hydroxy allene **36** catalyzed by a mixture of [(AuCl)$_2$(dppm)] and Ag-(*R*)-**33** formed 2-(2-methyl-1-propenyl)tetrahydropyran in 81% yield with 90% *ee* [Eq. (13)]. The enantioselectivity of the conversion of **32** to **34** decreased significantly when polar solvents were employed (18% *ee* in nitromethane), pointing to the importance of a gold/phosphonate ion-pair in the transfer of chiral information during cyclization.



(12)

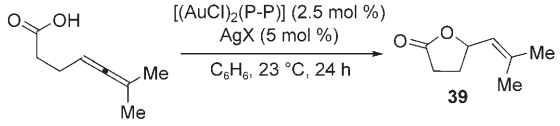


(13)

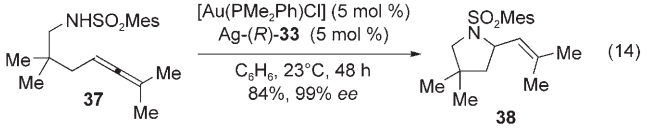
The chiral anion strategy was also applied to good effect for the enantioselective intramolecular hydroamination and hydroacetoxylation of allenes.[23] As an example of the former, treatment of γ-allenyl sulfonamide **37** with a catalytic 1:1 mixture of the achiral mono(gold)–phosphine complex [Au(PMe$_2$Ph)Cl] and Ag-(*R*)-**33** (5 mol %) in benzene at room temperature for 48 h led to isolation of 2-alkenyl pyrrolidine **38** in 88% yield with 98% *ee* [Eq. (14)]. Enantioselective intramolecular hydrocarboxylation proved a particularly effective showcase for the power of combining a chiral counterion with a chiral bis(phosphine) ligand. Hydroacetoxylation of 6-methyl-4,5-heptadienoic acid catalyzed by a mixture of either [(AuCl)$_2${(*R*)-binap}] and AgOPNB or [(AuCl)$_2$(dppm)] and Ag-(*R*)-**33** gave lactone **39** in good

yield but with $<40\%$ *ee* (Table 2). In comparison, reaction of 6-methyl-4,5-heptadienoic acid with catalytic mixture of [$(AuCl)_2$\{(*S*)-binap\}] and Ag-(*R*)-**33** gave **39** in 88% yield with 82% *ee*.[23] In contrast, the mismatched combination of [$(AuCl)_2$\{(*R*)-binap\}] and Ag-(*R*)-**33** gave **39** in $<5\%$ *ee*, establishing the cooperative effect of chiral phosphine and chiral counterion in achieving stereoinduction (Table 2).

Table 2. Effect of ligand and anion chirality on the catalytic enantioselective hydrocarboxylation of 6-methyl-4,5-heptadienoic acid.



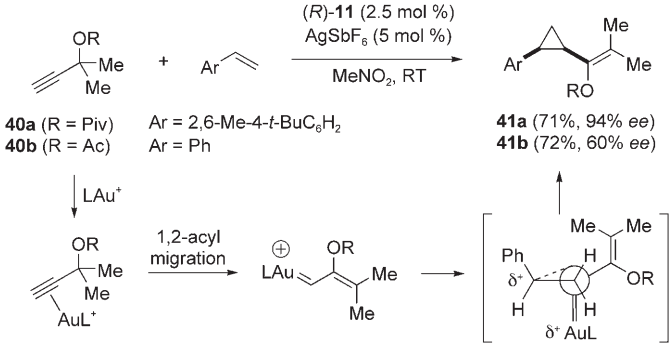
P–P	AgX	Yield [%]	*ee* [%]
(*R*)-binap	AgPNB	80	38
dppm	Ag-(*R*)-**33**	89	12
(*R*)-binap	Ag-(*R*)-**33**	88	82
(*S*)-binap	Ag-(*R*)-**33**	91	3



(14)

Cyclopropanation of Vinyl Arenes

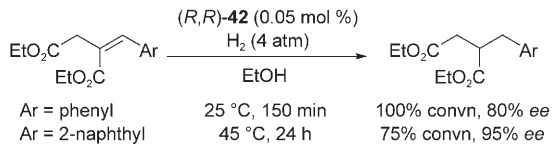
Toste has reported a gold(I)-catalyzed protocol for the enantioselective cyclopropanation of vinyl arenes with propargyl esters. For example, reaction of pivaloate ester **40a** with 4-*tert*-butyl-2,6-dimethylstyrene catalyzed by a 1:2 mixture of (*R*)-**11** and $AgSbF_6$ led to isolation of *cis*-cyclopropane **41a** in 71% yield with 94% *ee* as a single diastereomer (Scheme 5).[24] The enantioselectivity of cyclopropanation decreased with the decreasing steric bulk of the propargyl ester and/or the vinyl arene. As a point of comparison, gold-catalyzed cyclopropanation of propargyl acetate **40b** with styrene gave cyclopropane **41b** in 72% yield with only 60% *ee* (Scheme 5). Gold(I)-catalyzed cyclopropanation presumably occurs through π-activation of the C≡C bond of **40** followed by 1,2-acyl migration to form a gold carbenoid intermediate that is stabilized by 5d→2p back donation (Scheme 5).[25] Concerted transfer of the gold(I) carbenoid to the vinyl group of the arene would then form **41**. It should be noted that although π-activation is involved in the generation of the key gold carbenoid intermediate, absolute configuration is set by the transfer of the carbene to the vinyl arene.



Scheme 5. Gold(I)-catalyzed cyclopropanation of vinyl arenes.

Enantioselective Hydrogenation of Alkenes

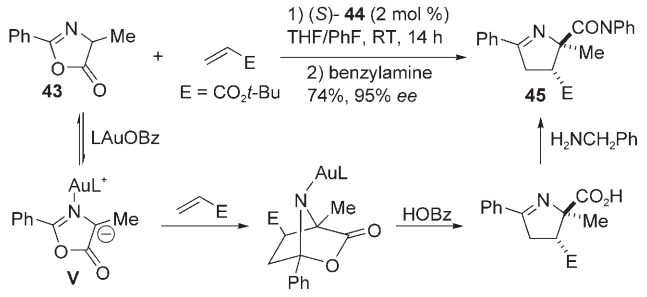
Shortly after Echavarren's initial disclosure of enantioselective alkyoxycyclization of enynes catalyzed by bis(gold) complexes, Corma and co-workers reported the enantioselective hydrogenation of functionalized alkenes and imines catalyzed by [$(AuCl)_2$\{(*R*,*R*)-Me-DUPHOS\}] ((*R*,*R*)-**42**; Figure 1).[26] For example, treatment of diethyl benzylidenesuccinate with a catalytic amount of (*R*,*R*)-**42** (0.05 mol%) under H_2 (4 atm) at 25°C for 15 min led to 100% conversion to form diethyl 2-benzylsuccinate with 80% *ee* [Eq. (15)]. The corresponding reaction with diethyl 2-naphthylidenesuccinate formed diethyl (2-naphthyl)methylsuccinate with 95% *ee*, but the reaction was considerably slower [Eq. (15)]. The authors proposed a mechanism for gold(I)-catalyzed hydrogenation initiated by hydrogenolysis of a Au–Cl bond of (*R*,*R*)-**42** to form an active gold(I)–hydride species. Hydrometalation of the alkene followed by protonolysis of the resulting gold(I)–alkyl species would release the chiral alkane. It is worth noting that the inner-sphere nature of this mechanism differs fundamentally from the outer-sphere pathways proposed for allene hydrofunctionalization.



(15)

Enantioselective 1,3-Dipolar Cycloaddition

Despite the pronounced carbophilicity of cationic gold(I) complexes, cationic bis(gold)–phosphine complexes also function as chiral Lewis acids. As an extension of the work of Tepe,[27] Toste and co-workers have exploited the Lewis acidity of gold(I) through development of an enantioselective protocol for the 1,3-dipolar cycloaddition of Münchnones to electron-deficient alkenes.[28] As an example, reaction of azalactone **43** with *tert*-butyl acrylate catalyzed by [$(AuOBz)_2$\{(*S*)-Cy-SEGPHOS\}] ((*S*)-**44**; Figure 1) in a 3:1 THF/fluorobenzene mixture at room temperature followed by in situ amination gave Δ^1-pyrroline **45** in 74% yield as a single regio- and diastereoisomer with 95% *ee* (Scheme 6). The transformation was effective for the cycloaddition of **43** with a range of cyclic and acyclic electron-deficient alkenes



Scheme 6. Gold(I)-catalyzed enantioselective 1,3-dipolar cycloaddition.

and for the cycloaddition of *N*-phenylmaleimide with a number of aryl-substituted azalactones. The mechanism of Lewis acid catalysis presumably involves complexation of gold to the nitrogen atom of the azalactone followed by deprotonation with benzoate to form the gold imine derivative **V**. *exo*-Selective 1,3-cycloaddition with alkene followed by C–O bond cleavage and aminoloysis forms **45** (Scheme 6).

Conclusions and Outlook

Following the pioneering report of Echavarren in 2005 describing the gold(I)-catalyzed enantioselective alkoxycyclization of 1,6-enynes, the application of gold(I) complexes in enantioselective catalysis has increased dramatically. The bulk of the effort in this area has been directed toward the intramolecular hydrofunctionalization of allenes with carbon and heteroatom nucleophiles to form carbocyclic and heterocyclic compounds with up to 99% *ee*. Where available, mechanistic data for these transformations support classic π-activation pathways involving outer-sphere attack of the nucleophile on a gold allene π-complex. However, enantioselective gold(I) catalysis is not restricted to π-activation processes as enantioselective transformations involving σ-activation, hydrogenation, and carbene transfer have also been developed.

With few exceptions, enantioselective gold(I)-catalysis has employed bis(gold)–phosphine complexes of the form $[(AuX)_2(P–P)]$ (P–P = chiral bis(phosphine), X = anionic ligand or counterion) as catalysts that are typically generated in situ by treatment of gold chloride precatalysts with an appropriate silver salt. The most common bis(phosphine) ligands are binap or MeOBIPHEP derivatives (see Figure 1) that contain sterically hindered P-bound aryl groups. Despite the widespread use of bis(gold) complexes in enantioselective catalysis, there is no evidence to support the participation of both gold centers in the bond-forming/bond-breaking processes involved in catalysis. However, a growing body of evidence, most notably the pronounced effect of the counterion on the enantioselectivity of a number of gold(I)-catalyzed transformations, points to the importance of nonbonding interactions between the ancillary AuX group and the reactive gold center. The first documentation of this behaviour was the reversal of absolute steroinduction observed for the gold(I)-catalyzed alkoxycyclization of 1,6-enynes when the (*R*)-**1**:$AgSbF_6$ ratio was changed from 1:1.25 to 1:2.[11] Counterion effects in enantioselective gold(I) catalysis were harnessed and exploited by Toste, who demonstrated the control of absolute configuration with chiral anions in the catalytic hydrofunctionalization of allenes.

An intriguing question regarding the effectiveness of bis(gold)–phosphine complexes in enantioselective catalysts is whether intramolecular, noncovalent bonding interactions facilitate internal organization of the catalyst. For example, π–π stacking interactions in both $[(AuCl)_2$(tol-binap)] and $[(AuCl)_2$(3,5-xylyl-binap)] lead to formation of a well-defined chiral environment in the solid state.[11,15] However, the persistence of these interactions in solution or in the case of cationic bis(gold) complexes has not been established. A second noncovalent bonding interaction that may facilitate internal organization of bis(gold)–phosphine complexes is the formation of aurophilic Au–Au interactions. Gold(I) complexes form short (≈3 Å), weak (5–10 kcal mol^{-1}) Au–Au bonds perpendicular to the main coordination vector through relativistically enhanced electronic correlation of the closed-shell d^{10} fragments.[29] Although Corma noted that models of $[(AuCl)_2${(*R*,*R*)-Me-DUPHOS}] were consistent with the presence of an Au–Au interaction, no experimental evidence was provided to support this contention.[26]

Although much has been accomplished in the past two years, it appears likely that we have only begun to scratch the surface of enantioselective gold(I) catalysis. Even within the realm of the most well studied transformations, enantioselective allene hydrofunctionalization, many limitations exist. All of the reported procedures suffer from limited scope, particularly with respect to substitution along the alkyl chain and at the allenyl carbon atoms. Yet to be demonstrated is the intermolecular enantioselective functionalization of allenes or the enantioselective hydrofunctionalization of simple alkenes. Likewise, a single example of a gold(I)-catalyzed dynamic kinetic asymmetric transformation has been documented, and diastereoselectivities were modest. Aside from some scattered stereochemical investigations, mechanistic data relating to enantioselective gold(I)-catalyzed transformations is lacking, as is a reliable model for steroinduction. This latter limitation represents a significant challenge given the synergistic role of ligand and counterion in the control of enantioselectivity in these transformations. To date, enantioselective gold(I) catalysis has relied heavily on a small family of bis(phosphine) ligands and it appears likely that identification of new ligands will, in turn, lead to the development of new enantioselective transformations. As a final note, in contrast to the recent surge in enantioselective gold(I) catalysis, enantioselective catalysis employing gold(III) complexes has not been demonstrated, which probably stems from the paucity of transformations catalyzed by gold(III) complexes that contain donor ligands.[30] It remains to be seen whether chiral gold(III) complexes represent viable catalysts for enantioselective transformations.

Acknowledgements

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