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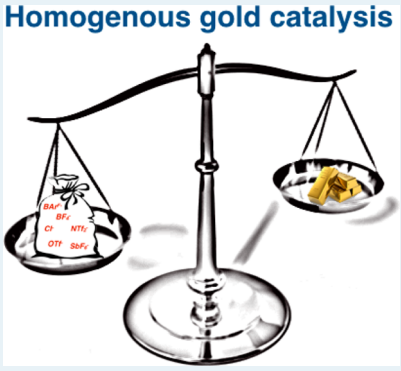
Counterion Effects in Homogeneous Gold Catalysis

Minqiang Jia and Marco Bandini*

Department of Chemistry "G. Ciamician", Alma Mater Studiorum − University of Bologna, Via Selmi 2, 40126 Bologna, Italy

ABSTRACT: Homogeneous gold catalysis has received growing attention over the past few years, enabling the replacement of consolidated organic reactions with more simple, selective, and chemically sustainable alternatives. The fine-tunability of the electronic as well as steric properties of gold catalysts contributed substantially to the popularity of the research field, with robust applications in total synthesis and asymmetric catalysis. In this context, the metal counterions proved of pivotal importance in impacting both kinetics and selectivity of gold-assisted transformations. Despite the intrinsic difficulties in properly rationalizing and predicting the role of anions in complex reaction machineries, nowadays, some general trends are available. This review aims at presenting some leading examples of counterion-controlled gold catalysis, with particular emphasis on their structure−activity relationship.



KEYWORDS: *asymmetric catalysis, catalysis, counterion, gold, reaction mechanism, selectivity*

1. INTRODUCTION

In the new millennium, a flurry of research concerning gold(I) and gold(III) species appeared in the literature with great impact on the development of organometallic catalysis and organic synthesis.[1] This astonishing credit found no comparisons within the transition metals family, pervading the field of organometallic catalysis with unprecedented inspirations toward the development of new chemical events.

Despite the rather young age of homogeneous gold catalysis, the use of [Au(0)] and [Au(I)] species in heterogeneous catalysis dates back to the last century, with peculiar emphasis on oxidative,[2] reductive,[3] and C−C-bond-forming protocols.[4] Differently, the use of gold salts/complexes under homogeneous or pseudohomogeneous conditions found only sporadic but illuminant works before the year 2000.[5] As a matter of fact, the field remained almost silent up to the rediscovery of $AuCl_3$ as an effective promoter for the synthesis of furans by Hashmi.[6] Subsequently, the scenario mutated rapidly, and the homogeneous gold catalysis was efficiently applied to access always more challenging chemical complexity/diversity in organic synthesis.

Nowadays, homogeneous gold catalysis is recognized worldwide as an established research field. Gold catalysis is currently considered a hot topic in organic synthesis with applications in the (i) total synthesis of complex molecular architectures, (ii) asymmetric synthesis,[7] (iii) C−H activation reactions and (iv) visible photoredox catalysis.[8] Moreover, there is a dedicated scientific journal for the metal's properties and its applications,[9] two monographs on the topic were recently delivered,[10] and dozens of research groups are currently engaged in studying organic transformations assisted by this noble metal.

The credit that gold catalysis has received and still continues to gain worldwide is easily ascribable to some properties that make gold (especially [Au(I)]) unique, within late-transition metals.[11] The peculiar π-affinity, functional group, and oxygen tolerance, robustness, fine-tunability, large availability in the market, and applicability to asymmetric synthesis are only a few of the major properties that have substantially contributed to the success of gold(I) and gold(III) in organic synthesis.

Among them, electronic tunability deserves a particular mention, enabling a large portfolio of electronically complementary catalysts to be accessed. The fine-tuning of gold catalysts of general formula LAuX or $LAuX_3$ can be realized primarily via permutations of three aspects, namely, the nature of the organic ligand (L), the oxidation state of the metal center, and the nature of the monovalent anion (X). A careful interplay of these components allows a range of reactivity to be covered by gold catalysis under extremely mild conditions.

A wide range of chiral as well as achiral organic ligands have been effectively coupled with gold centers in organic transformations, proving that catalytic tunability can be remarkably achieved. Currently, electronic perturbation of the reaction partners, played by the metal, are well understood and, in some cases, predictable. A clear example relies on the possibility to discriminate between the nature of gold carbenoid intermediates and the corresponding reactivity (i.e., gold-stabilized carbocations or gold carbenes, Figure 1a)[12] by means of using "little electron donating" $(2,4\text{-}t\mathrm{Bu}_2\mathrm{C}_6\mathrm{H}_3\mathrm{O})_3\mathrm{P}$ ligand with respect to electron-donating phosphine-based ligands (Figure 1b). The divergent chemical output was demonstrated in the condensation of phenols (**1**) or 1,3-dicarbonyl compounds to α-aryl-α-diazoacetates (**2**).[13]

It should be mentioned that the impact of the ligand on gold catalysis has already been comprehensively described[14] and will

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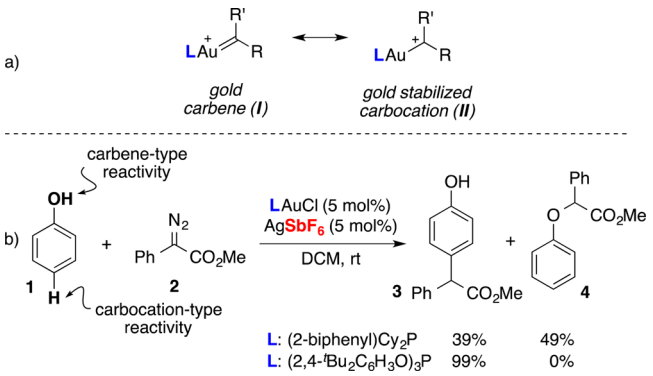


Figure 1. (a) Gold stabilized carbocation and gold carbene structures. (b) Example of ligand-controlled reactivity of gold-carbenoid intermediates (ref 13).

not be herein discussed in detail.[15] On the contrary, the role of the counterion in affecting the gold catalysis is still far from being fully rationalized.

As a general trend in chemical methodology, during the optimization of the reaction parameters, a range of mono-anionic and differently coordinating counterions is screened, by condensing gold halide precursors (commonly gold chloride species) with halide scavengers based on silver salts (Figure 2a).

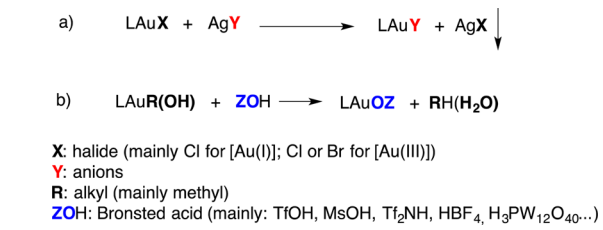


Figure 2. In situ activation modes of gold halide precatalytic species. (a) Halide metathesis. (b) Protonolysis with Brønsted acids.

Alternatively, the efficiency of the potent halophile silylium salt $[(Tol)SiEt_3][B(C_6F_5)_4]$, was also documented in preparing cationic cyclic (alkyl)(amino)carbene gold species.[16] Finally, during the revision of the review, Kirsh and co-workers documented the unprecedented use of sodium *closo*-dodecaborate $Na[Me_3NB_{12}Cl_{11}]$ as a halide scavenger and gold(I) activator in a range of π-system manipulations.[17]

Generally, the resulting insoluble silver salts are not removed from the reaction mixture being considered inert over the reaction profile. Once the best conditions are identified, control experiments are adopted to assess the role of the remaining silver salt in the reaction vessel. However, this initial chemical approximation should always be carefully verified through dedicated control experiments.[18] In many cases, cocatalysis played by silver-based contaminants was proven to be an active part in the chemical outcome of the reaction.[19] Commonly, the cationization of gold(I) and gold(III) salts/complexes enabled more electrophilic and catalytically active species to be obtained; however, in some specific cases, the abstraction of the halide can also result in the partial or total deactivation of the final complex.[20]

In this context, it is worth mentioning the seminal work published by Reetz and co-workers on gold(III)-catalyzed hydroarylation of alkynes.[21a] The authors analyzed the solid residue derived from the metathesis reaction between $AuCl_3$ (1 equiv) and AgOTf (3 equiv). The resulting chemical composition was unexpected. In particular, a solution of pure cationic $Au(OTf)_3$ was not formed,[21b] and a close inspection revealed the formation of a complex aggregate of [Au(III)], [Au(I)], and [Ag(I)] chlorides (i.e., $4AuCl_3 \cdot 5AuCl \cdot 11AgCl$), leaving in solution an unknown catalytically active gold species (Figure 3). This intriguing result pointed out also for the first time the still unsolved ambiguity on the real oxidation state in certain [Au(III)]-based catalytic transformations.[22]

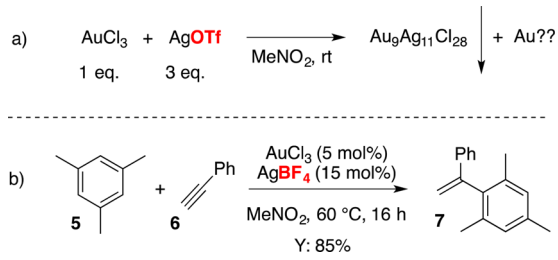
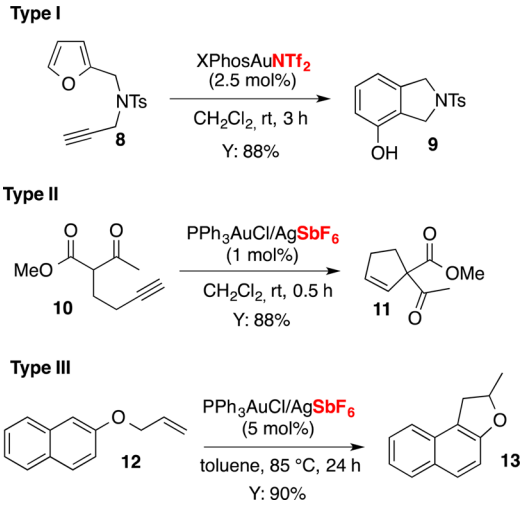


Figure 3. (a) $AuCl_3$ activation with AgOTf (ref 21a). (b) Gold-catalyzed hydroarylation of alkynes (ref 21a).

The "silver effect" on gold(I) catalysis was also recently discussed by Shi and co-workers.[23] In particular, gold-catalyzed processes were classified into three subgroups on the basis of the role of the silver salt, namely: (i) "genuine" gold catalysis, in which the silver salt exclusively makes cationic the gold halide precursor and does not participate in the reactive event; (ii) gold/silver bimetallic catalysis, in which both metal species are required for the efficiency of the chemical reaction and neither the gold nor the silver alone can promote the reaction; (iii) Ag-assisted Au catalysis; this is probably the most important and popular activation mode in gold catalysis. Here, both metal species are able to promote singularly the chemical process. However, when simultaneously present in solution, they work synergistically, providing better results. Exemplificative cases for the three possible activation modes are described in Scheme 1.

Scheme 1. Categorization of Gold Catalysis Based on the "Silver Effect" Proposed by Shi[a]



[a]Type I: phenol (**9**) synthesis via furanyne **8** rearrangement (ref 24a); type II: cyclization of acetylenic dicarbonyl compounds **10** (ref 24b); type III: synthesis of dihydrobenzofurans **13** (ref 24c). Yields and reaction conditions are referred to the Shi report. XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

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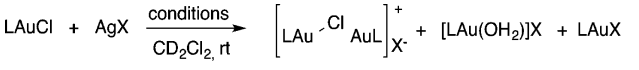
The authors sustained their discovery on the basis of titled comparative control experiments in which the resulting silver halides were removed via filtration through Celite. In this direction, the different interpretation proposed by Yu and co-workers on this phenomena should be noted.[25] They proposed that aquo- and oxo-gold complexes could exist in solution when a certain amount of water was present in the reaction system. As a matter of fact, the aquo- and oxogold complexes were isolated and fully characterized during the exchange reaction between PPh_3AuCl and AgOTf or $AgSbF_6$, followed by removal of the insoluble silver salts via filtration on Celite (reagent grade CH_2Cl_2, water content ≈ 100 ppm).

In addition to the discussed "silver effect",[26] what also emerged from these studies was the role of the counterion (i.e., "counterion effect"). In fact, although different catalytic properties were observed case-by-case in the presence of weakly coordinating anions (i.e., OTf^-, SbF_6^-, BF_4^-), when the weakly coordinating and more moisture tolerant NTf_2^- analogous was employed,[27] the role of the silver salt was less evident.

At this stage, a preliminary conclusion can be drawn: the univocal obtainment of the so-called and widely invoked "cationic naked gold species [LAu^+]",[28] via metathesis reaction of LAuCl and AgX, is a function of several aspects, such as the nature of the counterion; equivalents of AgX employed; nature of the solvent; and last but not least, the order of addition (i.e., gold, silver, and reaction substrates). As a matter of fact, gold catalysis generally deals with association/dissociation phenomena in solution between the metal center and both counterion and organic substrates. Therefore, the solvent frequently turns out to be of pivotal importance in the fine-tuning of the catalyst performances. Although a wide range of organic solvents has been adopted in gold chemistry, arenes (i.e., benzene, toluene, trifluorotoluene) and halogenated solvents (i.e., DCM, DCE, $CHCl_3$) cover the largest part of gold catalyzed transformations, with ion pair-based chemical events being of particular concern.

Order of addition is the factor of particular relevance. Very recently, this unexpected parameter was elegantly highlighted by Echavarren and co-workers.[28] The Spanish team highlighted the formation of mixtures of fully cationic, aquo, and stable chloride-bridged digold complexes in the treatment of JohnPhosAuCl and AgX (X: BF_4, NTf_2, OTf, SbF_6) in CD_2Cl_2. The ratio among the three gold complexes (See Table 1) varied significantly with the coordination capability of the counterion, leading predominantly to the corresponding dinuclear gold species in the presence of low-coordinating anions.[29] In some cases (i.e., triflate), an excess of AgOTf was necessary to cleave the less-active dinuclear species and to favor the formation of the LAuX (entry 2). In contrast, even 10 equiv of $AgBF_4$ was not sufficient to convert completely $((JohnPhosAu)_2Cl)BF_4$ into the expected $JohnPhosAuBF_4$. Putting in practice these pieces of evidence, a range of chemical reactions was investigated. From the study, what predominantly emerged was the importance of the addition order of gold, silver, and substrates during the transformation. In particular, because the cleavage of the digold species is mandatory for optimal reaction rates, when low coordinating compounds are involved (i.e., internal acetylenes), a premixing of the gold source to the organic compounds was found beneficial to minimize the $((JohnPhosAu)_2Cl)X$ upon AgX addition.

Table 1. Impact of the Coordinating Attitude of the Counterion on the Halide Exchange Reaction between JohnPhosAuCl and AgX (ref 28)[a]



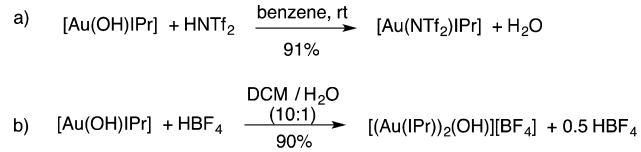
entry	AgX (eq)[b]	conditions	$(LAu)_2ClX$	LAuX	$LAu(OH_2)X$
1	AgOTf (1)	crude	100	0	0
2	AgOTf (5)	crude	0	100	0
3	AgOTf (1)	filtration Celite	67	20	13
4	$AgNTf_2$ (1)	crude	50	50	0
5	$AgBF_4$ (1)	crude	100	0	0
6	$AgSbF_6$ (1)	crude	100	0	0

[a]L = JohnPhos. [b]With respect to LAuCl (1 equiv).

It should be emphasized that the puzzling picture arising from the afore-described works, is still not completely elucidated in many instances; however, the current large availability of silver free cationic gold complexes (i.e., $LAuNTf_2$ and [LAu(NCMe)]SbF_6) represents valuable assistance to unequivocally clarify both the real nature of the active metal species and, eventually, the role of the ancillary ligands. In addition, it has being shown that cationic carbene[Au(I)] complexes can also react with the anion (i.e., BAr^F_4), delivering neutral fluorinated [Au(I)]-aryl adducts in high yields.[30]

A particularly attractive alternative to the use of silver halide scavengers relies on the cationization of alkylgold[31] or gold hydroxide[32] precursors via protonolysis with Brønsted acids (see Figure 2b). Here, volatile hydrocarbons or water are delivered as byproducts, respectively.[33,34] Nolan was extremely active in this segment, with primary attention to the obtainment of cationic *N*-heterocyclic carbene (NHC) gold adducts from the corresponding air-stable hydroxide counterparts. As an example, $[Au(NTf_2)(IPr)]$ was obtained in 91% yield by protonolysis of [Au(OH)(IPr)] with $HNTf_2$ in benzene at room temperature (Scheme 2a). Differently, when protonolysis

Scheme 2. Different Reaction Outcomes in the Protonolysis of [Au(OH)IPr] with (a) $HNTf_2$ and (b) HBF_4 (ref 32)



was operated in the presence of aqueous HBF_4, a new cationic dinuclear hydroxygold complex of general formula $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ was isolated in 90% yield (Scheme 2b).

Before addressing a selected number of gold-catalyzed organic transformations displaying a marked anion effect, it would be interesting to analyze and to eventually identify trends in the use of counterions in gold catalysis. In this direction, in addition to the early seminal works (1980s–1990s), we focus our analysis on the period of 2000–2013 that dramatically contributed to the establishment of homogeneous gold(I) and gold(III) catalysis. The key word "gold catalysis" was employed as a topic (basic search) in the *Web of Science Core Collection* as the database. Considering exclusively the sections "Chemistry Multidisciplinary" and "Chemistry Organic" resulted in almost 3000 references. This massive volume of efforts was further refined by considering exclusively organic reactions specifically promoted by gold(I) or gold(III) salts/complexes. Differently, pure mechanistic (i.e., DFT),[35]

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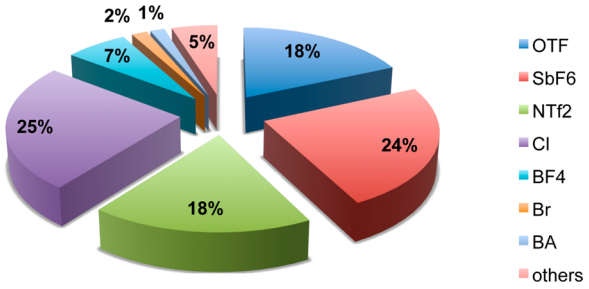
spectroscopic, and structure characterization studies were not taken into account.[36]

From Chart 1 emerged that almost 85% of the entire volume of gold(I)-/gold(III)-assisted organic transformations is based

Chart 1. Use of Counterions in Homogeneous Gold Catalysis[a]

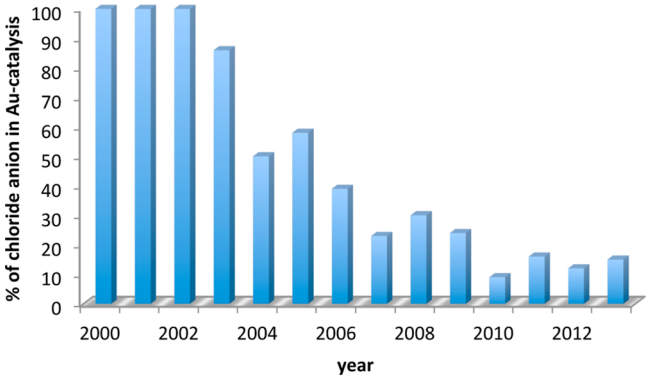


[a]*Web of Science Core Collection* (2000−2013). BA: binol-based chiral phosphates.

on four anions: chloride (Cl^-, 25%), triflate (OTf^-, 18%), hexafluoroantimonate (SbF_6^-, 24%), and bistrifluoromethanesulfonamide (NTf_2^-, 18%). The remaining 15% of the chemistry exploits a variety of monoanionic species, such as BF_4^-, Br^-, I^-, CN^-, $BAr^F{}_4^-$, BPh_4^-, $B(C_6F_5)_4^-$, ClO_4^-, OAc^-, NO_3^-, TFA^-, OTs^-, *p*NB^-, Bz^-, PF_6^-, and binol-based chiral phosphates.

It is also worth mentioning that at the early stage (2000−2005), chloride was by far the most employed anion. In particular, [Au(III)] sources such as $AuCl_3$, $HAuCl_4$, and $NaAuCl_4$ were predominant over the corresponding air-sensitive AuCl. Interestingly, the cationization of gold center via halide metathesis reactions with silver salts found growing impact on gold catalysis later on (2004/2005), as exemplified in Chart 2. Despite the initial predominant use of chloride anion,

Chart 2. Decreasing Popularity of Chloride-Based Gold Catalysis[a]

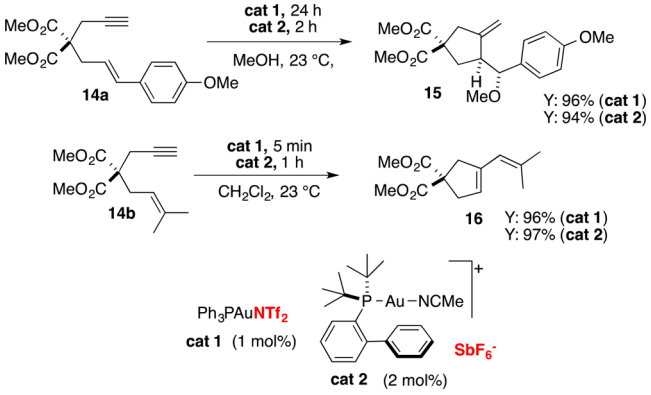


[a]*Web of Science Core Collection* (2000−2013). The analysis exclusively considers studies aimed in applying gold(I) and gold(III) species in organic transformations.

the use of halide scavengers or protonolysis for the activation of gold species becomes predominant since 2006. Interestingly, in 2010, only 10% of publications based on gold catalysis highlighted chloride as the optimal counterion. Obviously, this trend was also deeply affected by the constant development of new organic ligands in gold(I) catalysis during the past decade.

In the realm of gold catalysis, the poorly coordinating hexafluoroantimonate (SbF_6^-) rises to prominence due to a series of elegant investigations by Echavarren and co-workers. A family of gold complexes of general formula $[LAu(NCR)]SbF_6$ (i.e., R = Me, Ph) have been synthesized, characterized, and effectively employed in the cyclizations of 1,6-enynes **14**. The molecule of acetonitrile comes together to stabilize the organometallic species (i.e., moisture tolerance) with respect to the highly sensitive $LAuSbF_6$ congeners (Scheme 3).[37,38]

Scheme 3. Cyclization of 1,6-Enynes by Means of Echavarren's [JohnPhosAu(ACN)]SbF_6 (cat 2) and Gagosz's $Ph_3PAuNTf_2$ (cat 1) Complexes (refs 27a, 37)



Analogously, Gagosz and co-workers emphasized the attitude of NTf_2^- in performing a dynamic coordination with gold atom in solution, resulting in the more stable "neutral" $Ph_3PAuNTf_2$ complex (**cat 1**). This well-defined air-stable gold species proved competent in numerous organic transformations, contributing to overcome the ancient paradigm *stable = inert*. Applications to cycloisomerizations of enynes are depicted in Scheme 3.[27a] Shortly after, the same team also documented on the synthesis, structural characterization, and catalytic activity of a range of N-heterocyclic carbene gold(I) bis-(trifluoromethanesulfonyl)imidate complexes of general formula $[Au(NHC)NTf_2]$. Also in this class of complexes, the anion proved to be tightly coordinated to the metal center in the solid state (selected bond distances (Å) for $IPrAuNTf_2$: Au−C(NHC) = 1.969(2), Au−N(NTf_2) = 2.091(2)).[39]

The dichotomy in coordinating capability of SbF_6^- (BF_4^-, PF_6^-) and NTf_2^- was also rationalized in terms of relative nucleophilicity (i.e., $NTf_2^- \gg SbF_6^-$) and geometry. As a matter of fact, the spherical symmetry of SbF_6^-, BF_4^- and PF_6^- supports their lowest coordination attitude.[40]

It should be mentioned that the concept of dynamic coordination and consequent higher thermodynamic stability was elegantly and extensively developed also by Shi and co-workers through the synthesis of a series of catalytically active cationic gold(I) species of general formula $[PPh_3Au(TA)]OTf$, featuring a stabilizing triazole unit in the first coordination sphere of the metal.[41]

However, two main questions have risen to prominence:

1) What is the real affinity scale of cationic gold(I) complexes for the most commonly used anions?
(2) Where are the anions located in cationic gold complexes with the π-systems?

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(1) The coordinating attitude of several monoanionic species toward phosphine-based gold(I) complexes has been investigated and estimated both computationally and experimentally.

The dissociation energy of several PPh_3AuX complexes into the corresponding cationic $[PPh_3Au^+] + X^-$ (DCE) has been calculated by Ujaque, providing the following trend: $CF_3CO_2^- \approx Cl^- > NO_3^- > OTs^- > OTf^- > BF_4^-$.[42] Moreover, a detailed affinity scale in solution for a number of mononuclear $[LAu(NCMe)]^+$ versus a range of anions and neutral species was experimentally determined by Zhdanko and Maier via ^1H and ^{31}P NMR spectroscopy (room temperature).[43] Focusing on the widely utilized $[JohnPhosAu(NCMe)]^+$ cation, the scale of affinity depicted in Figure 4 (CD_2Cl_2) was determined. Here,

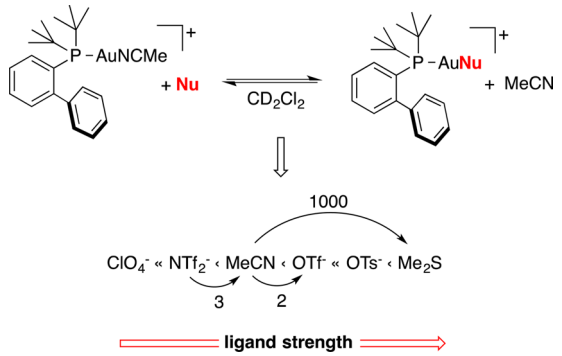

Figure 4. Scale of binding affinity of neutral and anionic ligand toward $[JohnPhosAu(NCMe)]^+$ in CD_2Cl_2 (ref 42).

the scale locates SbF_6^- as a very little coordinating anion, OTf^- and NTf_2^- showed an intermediate level of nucleophilicity, and OTs^- was one of the most coordinating anions among the ones investigated.

(2) The unambiguous spatial localization of the counterion in solution would represent a unique tool to predict reactivity and selectivity of a titled chemical event. In this direction, Macchioni and co-workers produced a number of elegant investigations combining spectroscopic and computational tools, toward the rationalization of ion-pairing structures[44] in phosphine- and carbene-based cationic gold complexes with alkenes and alkyne.[45] Interestingly, the weakly coordinating BF_4^- was unambiguously located far away from the metal center and nearby the π-system or ligand side. The final localization proved to be strongly affected by the ligand/hydrocarbon combination.

Of particular relevance are the results deriving from the analysis of complexes $[(PPh_3)Au(4\text{-Me-styrene})]BF_4$ **III** and $[(PAr^F_3)Au(2\text{-hexyne})]BF_4$ [Ar^F = 3,5-bis(trifluoromethyl) phenyl] **IV** in solution. Here, the anion locates close to the unsaturated hydrocarbon unit, interacting with the hydrogen atoms of the olefin fragment and close to the methyl group of the internal alkyne, respectively (^{19}F,^1H-HOESY NMR spectra). The analysis of the molecular charge distribution rationalized these arrangements in terms of weak but determinant Coulomb interactions between the anion and the more attractive sites of the cationic complexes (i.e., hydrogen atoms of the styryl unit and acetylenic methyl group, Figure 5).[46]

As already anticipated, the largest part of the studies addressing gold-catalyzed organic transformations have not provided specific insights into the real role of the counterion, but have simply limited the discussion on highlighting the best

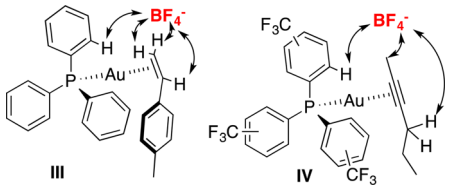

Figure 5. Proving the location of BF_4^- counterion in the cationic PAr_3Au-alkene (**III**) and -alkyne complexes (**IV**). The arrows indicate the $^{19}F-^1H$-HOESY correlations (ref 44).

performing anions for a certain process. This is also due to the intrinsic difficulty in finding the precise role of ionic species involved in cascade reactions with polyfunctionalized compounds.

These aspects make the undoubted elucidation of the counterion effect a challenging issue to be fully solved, in many circumstances. However, the interest by the chemical community for the impact of "secondary interactions" in gold catalysis is growing rapidly, and some convincing rationales have been provided. Among the numerous roles, the gold counterion has been recognized in modulating (i) the kinetics of the process due to the different coordinating properties; (ii) the real structure of the catalytically active species (i.e., formation of clusters, dimers); (iii) the chemo-, regio-, and stereoselectivity of the transformations via key interactions with reagents as well as intermediates during the reaction course.

Last but not least, the fine-tunability (steric and electronic) of the counterions enabled the development of peculiar enantioselective transformations based exclusively on the formation of tight ion pairs and weak second interactions (i.e., hydrogen bonds)[47] between the anion and electrophilic partners of the reaction. In the following sections, a selection of works addressing these intriguing aspects is presented.

2. COUNTERIONS

2.1. Counterion Effect on the Chemo-/Regio- and Stereoselectivity. The marked dichotomy in chemical outcomes (chemoselectivity and regioselectivity) of gold catalyzed reactions generally occurs when strongly coordinating anions (i.e., OTs^-, pNBz$^-$, OAc^-) are compared with weakly coordinating analogues. However, examples of chemotunability with weakly coordinating anions have also been documented.

Related to the latter case, Li succeeded in rationalizing the regiodivergent behavior of PPh_3AuOTf and PPh_3AuSbF_6 in the cycloisomerization of bromoallenyl ketones **17**,[48] originally proposed by Gevorgyan and co-workers, proceeding via halonium intermediate (Scheme 4).[49] Interestingly, although $Ph_3PAuSbF_6$ afforded exclusively the 3-Br furan **18b** via 1,2-halo shift, the use of $Ph_3PAuOTf$ generated the regioisomeric 2-Br furan **18a** via 1,2-hydrogen shift. DFT calculations provided a rationale for the unique trend. Here, although cationic metal species are known to favor halide migrations (**V** and blue pathway → **VI**), the corresponding 1,2-hydrogen shift can be assisted by the counterion (**V** and red pathway → **VII**). In this context, the OTf^--mediated hydrogen shift turned out to be far less endoenergetic (9.6 kcal/mol) than the SbF_6^- one (29 kcal/mol).

In 2009, Davies and co-workers elegantly demonstrated the pivotal role of anions in the gold(I)-catalyzed synthesis of substituted pyrrole via ring-opening of alkynyl aziridines **19**.[50] In particular, regioisomeric disubstituted *N*Ts pyrroles (**20a**,**b**) were selectively obtained when PPh_3AuOTf or PPh_3AuOTs

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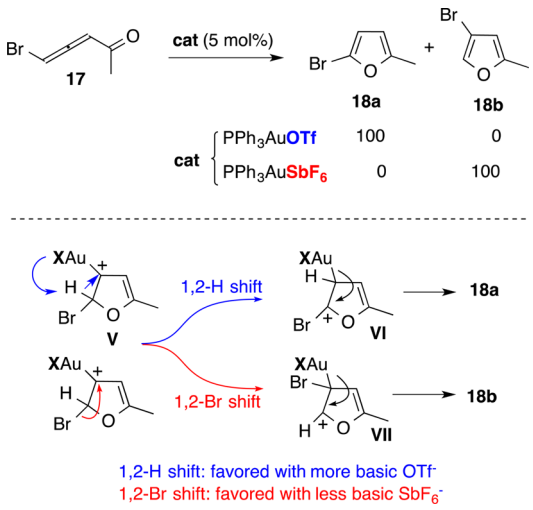
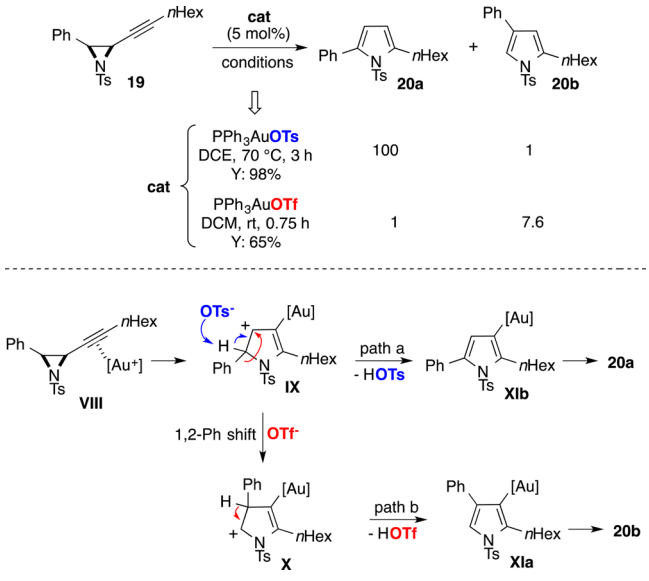
Scheme 4. Regiodivergent Behavior of Anions in Gold Promoted Synthesis of Bromofurans (ref 48)



were employed, respectively (Scheme 5). The divergent chemical pathway was rationalized in terms of different

Scheme 5. Counterion Plays the Role in the Synthesis of Disubstituted Pyrroles 20 (refs 52, 53)



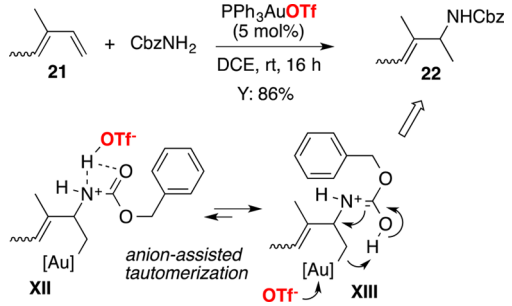
basicities (pK_a in DCE: HNO_3, −1.7; HBF_4, −10.3; TfOH, −11.4; Tf_2NH, −11.9; $HClO_4$, −13.0)[51] of the metal counterion as well as the reaction media.[52] In particular, although the basic OTs^- favored the rearomatization/protodeauration sequence (path a) with consequent obtainment of 2,5-disubstituted pyrroles (**20a**), the use of more electrophilic gold complex (i.e., X = OTf, DCM) provided the 1,2-aryl shift[53] as a competitive event (path b), with the consequent formation of 2,4-disubstituted pyrroles (**20b**) as major compounds.

This work clearly exemplified that different coordinating features of the anions can significantly affect not only the chemical profile of gold catalysis but also the overall kinetics. As a matter of fact, in solution, poorly dissociated counterions generally deliver a lower amount of catalytically active gold species with consequent reduced performances in terms of turnover frequency. Here, refluxed DCE was used to overpass this drawback.

The explication of gold counterion effect via hydrogen bond interactions was also demonstrated by Ujaque and co-workers[42] with specific reference to the intermolecular hydroamination of dienes previously documented by He.[54] In particular, the theoretical investigation focused on the Markovnikov condensation of cyclic/acyclic carbamates with 1,3-dienes in the presence of PPh_3AuOTf (5 mol %, DCE, rt to 50 °C).

The numerous reaction channels investigated enabled ascerting that the triflate can assist the tautomerization of the positively charged carbamate intermediate (**XII**, **XIII**), deriving from the initial outer-sphere hydroamination step. The resulting NH═C−OH tautomer proved competent in transferring one proton to the alkyl-gold center, providing the final protected allyl amine. Direct protodeauration steps proved to be not competitive in terms of energetic profiles with the one synthetically reported in Scheme 6.

Scheme 6. Counterion Effect in the Intermolecular Hydroamination of Dienes (ref 54)



Similar conclusions were also drawn by Liu and co-workers[55] during the computational investigation of the cyclization of aminoallenes promoted by PPh_3AuSbF_6.[56] Here, the presence of the poorly coordinating SbF_6^- proved to be beneficial in the final 1,3-H migration that restored the catalytically active species.

Kundo also documented the chemodivergent cyclization of indole-2-alkynyl-urea systems under gold catalysis.[57] The indolyl-alkynyl scaffold **23** was proved competent in delivering a library of tricyclic compounds via regioselective 6-*endo*-dig N- or O-based nucleophilic attack on the triple bond. When PPh_3AuCl (5 mol %) was combined with AgOTf (20 mol %) or $AgNO_3$ (20 mol %), a divergent output was recorded (OTf → **23b**, Y = 85%), (NO_3 → **23a**, Y = 87%, Scheme 7). In rationalizing the experimental pieces of evidence the authors invoked the different soft/hard character of N- and O-based nucleophiles in combination with the silver effect aforementioned by Shi.[23] In particular, $AgNO_3$ is proposed to cocatalyze the process by coordinating the hard oxygen atom (**XIV**). In addition, the participation of the NO_3^- anion in the deprotonation of the urea moiety and subsequent formation of **23a** cannot be ruled out.

Our group has also recently experienced a dramatic counterion effect on the site-selective functionalization of 2,3-disubstituted indoles with allenamides to give densely functionalized indolenine cores **26**.[58] The overall regiochemistry of the condensation was regulated by the nature of the gold counterion, spanning from absolute N(1)-alkylation (**27**) in the presence of $(ArO)_3PAuCl/AgOTf$,[59] to the corresponding regiospecific C(3)-functionalization (**26**) when the air-tolerant

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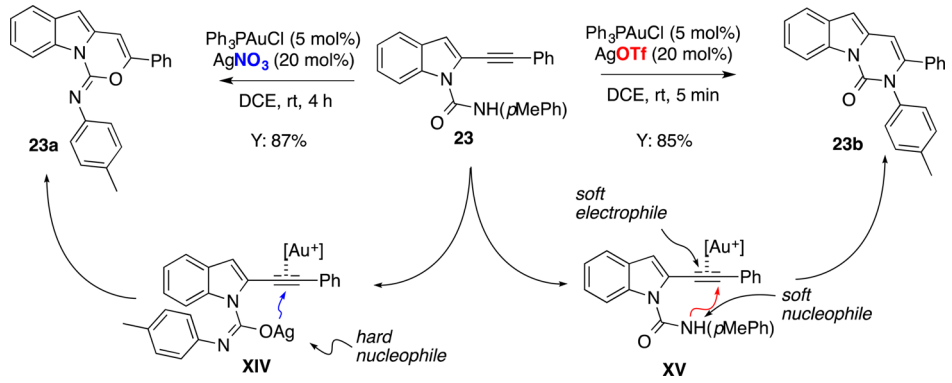
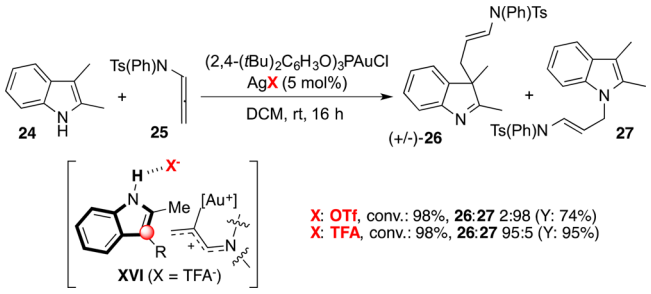
Scheme 7. Silver and Counterion Effect in the Cyclization of Indole-2-alkynylurea 23 (ref 58)



$(ArO)_3PAuTFA$ was employed (Scheme 8). A rationale for the regiodivergent profile relies on the different coordination

Scheme 8. Weak Interactions Make the Difference in Gold(I)-Catalyzed Dearomatization of Indoles with Allenamides (ref 59)



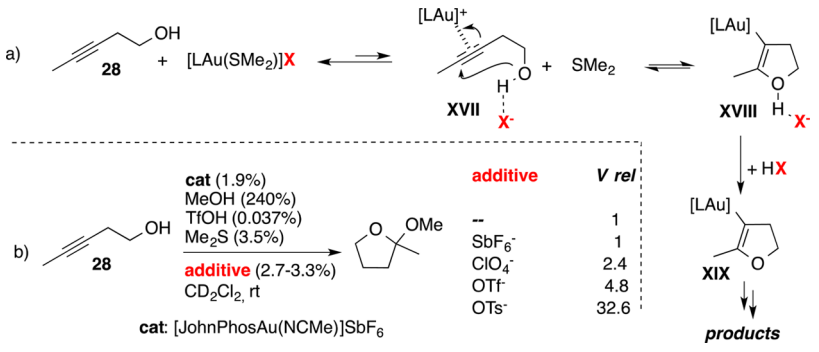
attitude/basic character of TFA^- with respect to OTf^- or NTf_2^-. As a matter of fact, with TFA^-, we envisioned the establishment of strong hydrogen bond interactions between the anion and the N(1)−H indole site, resulting in the nucleophilic activation of the hetereoaromatic nucleus (mainly at the C(3)-position, **XVI**) and concomitant "protection" of the N(1) site.

Very recently, Zhdanko and Maier were able to rationalize the effect of gold counterion on the reaction profile of the hydroalkoxylation of alkynes by means of detailed kinetic studies.[43,60] The overall process is described by a dual activation mode: coordination of the carbon−carbon triple bond to the cationic gold complex and hydrogen bond interaction between the alcohol moiety (nucleophilic agent in the present process) and the anion of the gold complex (**XVII**). Subsequently, the condensation of the activated alcohol to the unsaturated hydrocarbon would yield the protonated vinyl gold intermediate **XVIII** that can evolve into the final free vinyl gold species plus one molecule of free acid (**XIX**, Scheme 9a). Experimental findings revealed the formation of the ion pair **XVII** as the rate-limiting step of the overall transformation. The case of the addition of methanol to the pentynol **28** is depicted in Scheme 9b.

Obviously, the reactivity order displayed in Scheme 9 does not parallel the π-acidity of the corresponding gold species and aspects different from that pure metal electrophilicity should be involved in determining the experimental findings. In this direction, further insights were documented by Zuccaccia and co-workers through a combined experimental, spectroscopic and computational study.[61] In particular, the counterion of election OTs^- was demonstrated to fulfill the following roles: (i) assisting the nucleophilic attack of the alcoholic moiety to the activated alkyne via a hydrogen bond; (ii) providing an ideal spatial arrangement of the reactants for the C−O bond forming step.

In addition to hydrogen bondings formation, gold counterions have been also postulated to specifically interact with positively charged C and Si intermediates, triggering/facilitating unexpected molecular rearrangements. In this direction, Xia[62] recently got some insights into the mechanism of the synthesis 1-silaindenes **31** via alkenylsilylation of 1,6-enynes **30**, previously documented by Murakami (Scheme 10, "Non-innocent Counterion Effect").[63] Here, DFT calculations

Scheme 9[a]



[a](a) Revealing the role of anions in the gold catalyzed hydroalkoxylation of alkynes. (b) Highly coordinating species improve the reaction rate by enhancing the nucleophilic character of the alcohol in the ion pair **XVII** (ref 43).

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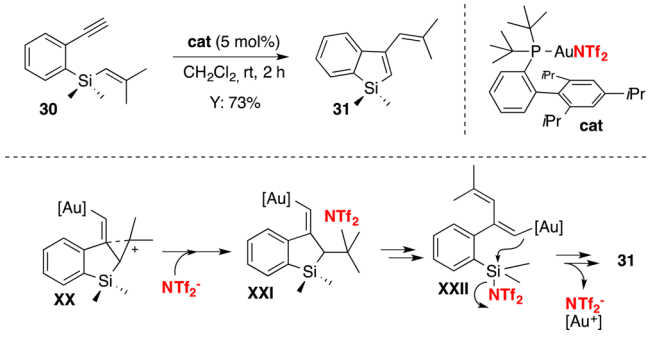
Scheme 10. Role of the NTf_2^- in Assisting the [Au(I)]-Catalyzed Alkenylsilylation of 1,6-Enynes 30[a]

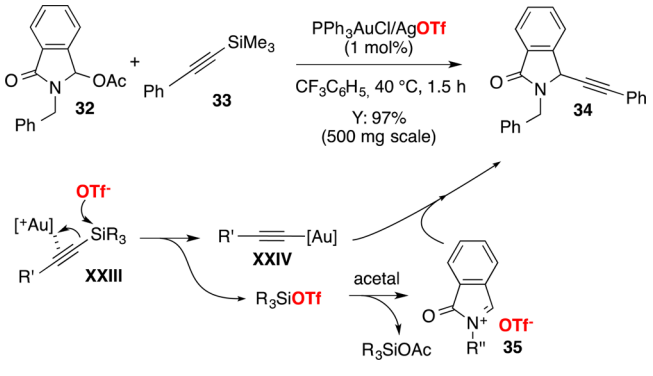


[a]Stabilization of C_β carbocations with respect to Si (**XXI**) and assistance of silyl-cation rearrangement (**XXII**); ref 63.

revealed the multiple roles exerted by the NTf_2^- anion during the reaction profile. Among the others were found direct implications in assisting the skeletal rearrangements of the carbon cationic intermediate **XX** and the silyl derivative **XXII**.

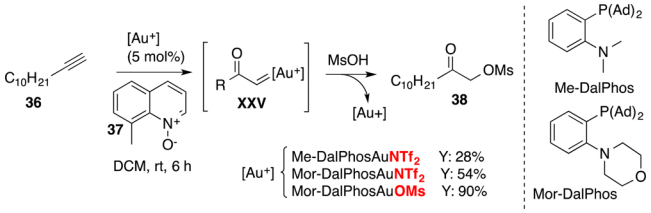
The choice of the counterion proved to be of pivotal importance also in the alkynylation of *N,O*-acetals.[64] In this regard, Dalla and co-workers reported on the direct intermolecular condensation between trialkylsilylalkynes **33** and acetals **32** under mild conditions ($CF_3C_6H_5$, 40 °C), in the presence of in-situ-formed PPh_3AuOTf (1−3 mol %). The delivered OTf^- ion was thought to participate in the auro-desilylation of the resulting silylalkyne **XXIII**. The in-situ-generated strong Lewis acid TMSOTf proved to be crucial for the economy of the protocol, consisting overall of a gold(I)/TMS cocatalysis. In contrast, Cl^-, OTs^-, I^-, and BF_4^- were by far less reactive than NTf_2^- and OTf^-, and this phenomena was ascribed to the lower tendency of the TMSX (Lewis acidity) in activating *N,O*-acetals (Scheme 11).

Scheme 11. [Au(I)]/TMSOTf(NTf_2) Co-Catalysis in the Alkynylation of *N,O*-Acetals 32 (ref 65)



A specific case in which the counterion proved to be fundamental in gold(I)-mediated processes, documented by Zhang and co-workers, employed the gold counterion as one of the reaction partners in the synthesis of methanesulfonyloxymethyl ketones **38**.[65] The protocol involves the oxidation of terminal alkynes with quinoline *N*-oxide derivatives **37**,[66] delivering the corresponding α-oxo gold carbenes **XXV** that were trapped by MsO^-. Although the use of "bidentate" phosphine ligands such Me-DalPhos and Mor-DalPhos enabled the isolation of the desired MsO-ketone, the resulting isolated yields were not synthetically useful (max 54%) in the presence of NTf_2^- as the metal counterion. To address this issue, the authors envisioned the possibility of employing MsO^- as the counterion of the gold center, as a result of the positive effect played by the proximity effect. Interestingly, the use of Mor-DalPhosAuOMs (5 mol %), combined with higher concentrations, led to a full conversion of the terminal alkynes delivering **38** in 90% yield (Scheme 12).

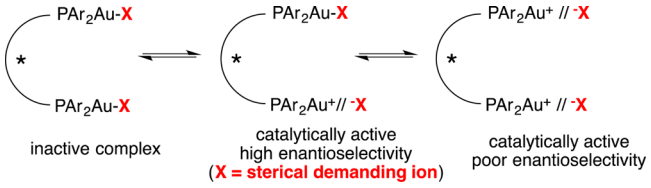
Scheme 12. Counterion Acts As the Nucleophile in the Synthesis of Methanesulfonyloxymethyl Ketones 38 via α-oxo Gold Carbenes (XXV, ref 66)



Enantioselective gold catalysis has rapidly become a mature reality within the field of asymmetric synthesis. Chiral *C*1-symmetric mononuclear and *C*2-symmetric binuclear gold complexes have been proven competent in controlling the stereochemical profiles of numerous organic transformations involving π-systems under mild conditions. In addition, extraordinary results in terms of stereochemical differentiations have been reached, also by using gold complexes featuring chiral anions as the only source of stereochemical information.[7] The latter approach will be specifically addressed in section 2.2; here, we summarize a selection of stereoselective transformations in which an achiral counterion has been demonstrated to control both the kinetics and the stereochemistry of the process.

Toste in 2007 highlighted the impact of the size of the counterion in the intramolecular enantioselective hydroamination of allenes **39**.[67,68] In particular, on the basis of experimental pieces of evidence, the authors proposed the monocationic $[xylyl\text{-}binap(Au)_2X]^+//X^-$ as the real active species for the C−N bond-forming process that is obtained in situ through the corresponding equilibrium with neutral $[xylyl\text{-}binap(AuX)_2]$ (Scheme 13). The remaining coordinated

Scheme 13. Catalytically Active Monocationic Binuclear Gold Complexes[a]



[a]*p*-Nitrobenzoate fulfills both steric requirements and coordination attitude to guarantee high stereoinduction (ref 67).

anion X^- was believed to come together in enhancing the enantioselectivity of the process due to steric reasons. On that basis, the rather coordinating *p*-nitrobenzoate anion (OPNB) was chosen as the best anion satisfying both steric properties and coordinating capability (entries 4 and 5, Table 2). Accordingly, the more coordinating benzoate (Bz) performed similarly in terms of the optical outcome (entry 3) but provided

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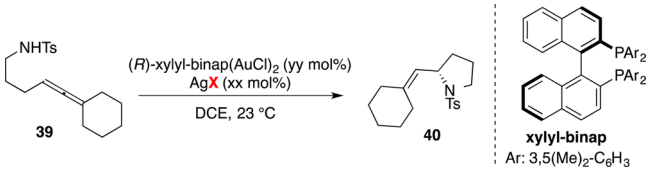
Table 2. Counterion Dramatically Amplifies the Stereocontrol in the Gold Catalyzed Intramolecular Hydroamination of Allenes (ref 70)[a]



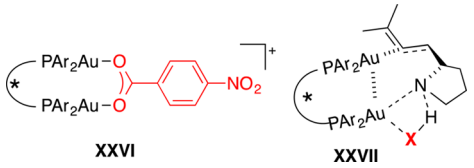
Entry	yy [b]	X (xx)	Yield (%)	Ee (%)
1[a]	3	BF_4 (6)	82	1
2[a]	3	BF_4 (3)	81	51
3[a]	3	Bz (6)	27	98
4[a]	3	OPNB (6)	76	98
5[b]	xylyl-binap(AuOPNB)$_2$ (3)[b]		88	98

[a]Complex prepared in situ. [b]With preformed catalyst.

lower yields as a result of the lower concentration of monocationic active species in solution (Table 2).[69] Subsequently, the present approach found applicability in numerous asymmetric gold catalyzed protocols.[70]

Furthermore, the enantioselective intramolecular hydroamination of allenes was also investigated by means of computational tools by Lee and Kang.[71] Interesting conclusions were drawn on the structure of the monocationic [xylyl-binap(Au_2OPNB)$^+$//OPNB$^-$] that was found to bind the gold center via a chelating mode (**XXVI**). This arrangement was addressed as a major driving force for the dissociation in solution of the binuclear neutral precursor. Moreover, combined theoretic and experimental evidence enabled the authors to propose an unusual *syn*-nucleophilic (inner-sphere) attack of the amino group to the allene on the basis of the key role of weak interactions, such as Au−Au aurophilic contact and NH···X hydrogen bond interaction in providing the correct substrate preorganization for the enantioselective ring-closing protocol (Scheme 14).

Scheme 14[a]

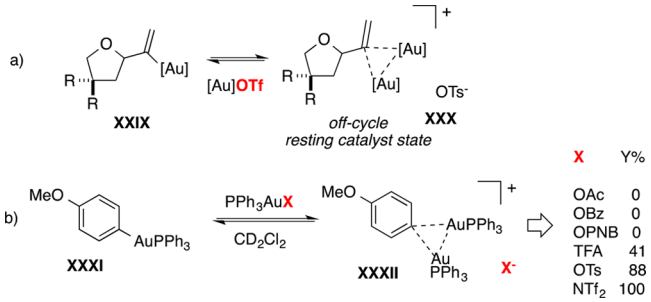


[a]*p*-Nitrobenzoate is proposed to chelate the binuclear gold complex (left). An inner-sphere mechanism is proposed (right, ref 72).

It is important to mention that the gold(I)-catalyzed enantioselective hydroxyalkylation of allenes was reported almost simultaneously by Widenhoefer in 2007 in the presence of DTBM-MeObiphep(AuCl)$_2$/AgOTs (1:2 ratio).[72] The corresponding reaction machinery was elegantly investigated by Widenhoefer and Gagné years later, highlighting (1) the reversibility of the C−O bond-forming step; and (2) the presence of the three-center, two-electron bis(gold) vinyl species **XXX** as an off-cycle reservoir of the catalytically active cationic monogold-vinyl species **XXIX** (Scheme 15a).[73,74]

Subsequently, Gagné and co-workers investigated the formation and reactivity of geminal-digold species by

Scheme 15[a]



[a](a) The "A_2C" off-cycle species in the gold alkoxylation of allenes (ref 74). (b) The counterion dramatically influences the equilibrium percentage of the off-cycle species with respect to the monogold(I) precursor (ref 76).

determining the equilibrium percentage in solution of digold species **XXXII** vs readily accessible monogold aryl species **XXXI**, a function of the gold counterion (Scheme 15b).[75] The equilibrium proved to be progressively shifted toward the bisgold species when less coordinating anions were employed (100% conversion with NTf_2^-), and this trend was rationalized in terms of tightness of ion pairs ([PPh_3Au]**X**).

The role of the counterion in determining the presence of resting states of **XXX**-type (mimicked by the addition of ([PPh_3Au]**X**) was then correlated with the protodeauration rate of PPh_3AuAr in the presence of AcOH. Interestingly, the use of weakly coordinating anions led to the lower reaction rates with respect to AcO^- or $OPNB^-$ as a result of the higher concentration in solution of more-stable digold-intermediates. With respect to this, the performances of LAuOTs in the hydroalkylation of allenes can also be related to more cationic but less efficient gold complexes. Once again, these findings clearly emphasize that the "equation" "the more cationic the catalyst, the higher the reaction rate" is not always applicable in metal and, specifically, in gold catalysis.

Concerning the intramolecular process, the gold counterions were found also to be crucial for the preorganization of the acyclic precursors to speed up the reaction rate and to control the stereochemical profile. For that reason, we recently performed a combined experimental/computational investigation to obtain a mechanism rationale for the enantioselective intramolecular allylic alkylation of indoles with alcohols.[76] Along the stepwise process promoted by the dinuclear DTBM-MeObiphep(AuOTf)$_2$ complex, the ion triflate displayed multiple roles, such as the "folding effect", in which the counterion templates the indolyl-alcohols precursor in a specific folded conformation, facilitating the intramolecular hydroindolynation of the olefin fragment (**XXXIII**). The peculiar spatial arrangement of the reagent imprinted by the anion, also favored the final proton shift from the dearomatized indolyl core to the leaving hydroxyl group in the alkyl-gold intermediate (**XXXIV**, Scheme 16).

2.2. Chiral Counterions in Asymmetric Gold Catalysis.

As previously outlined, enantioselective gold catalysis is generally accomplished by complexing [Au(I)] salts with chiral monodentate/bidentate P-based ligands featuring biphenyl, binaphthyl, and ferrocenyl backbones or chiral NHC-based ligands.[7] Then the resulting precatalytic C1- or C2-symmetric gold chloride species can be activated via classic anion metathesis with silver-based halide scavengers.

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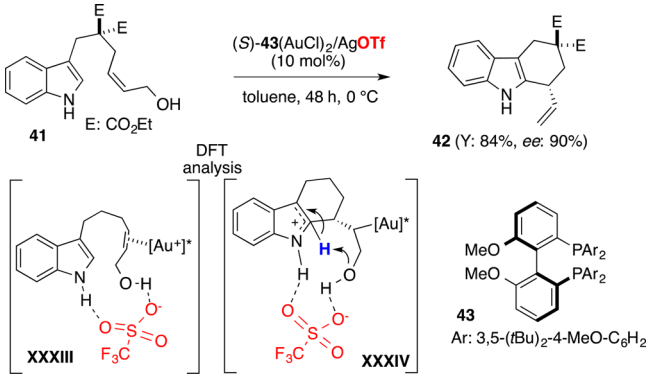
Scheme 16. Folding Effect of the OTf^- in the Enantioselective Allylic Alkylation of Indoles (refs 76a)



Despite to the numerous successful applications, this approach suffers from the intrinsic linear coordination geometry of [Au(I)] species that locates the reactive site opposite the chiral organic ligand with respect to the metal center (Figure 6a). Accordingly, sterically congested aryl

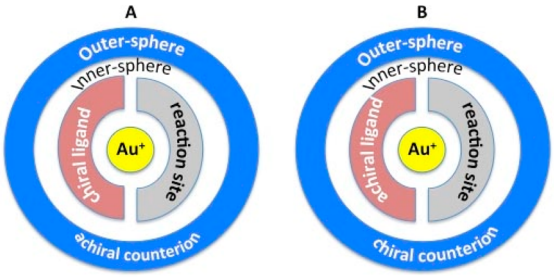


Figure 6. Schematic representation of the chiral ligand-based (A) and chiral counterion-based (B) approaches in asymmetric gold catalysis.

substituents at the phosphorus atoms (i.e., DTBM = 3,5-(*t*-Bu)$_2$-4(OMe)-C$_6$H$_2$) are frequently adopted, representing an unavoidable constraint/limitation (both economic and structural) in enantioselective homogeneous gold catalysis.

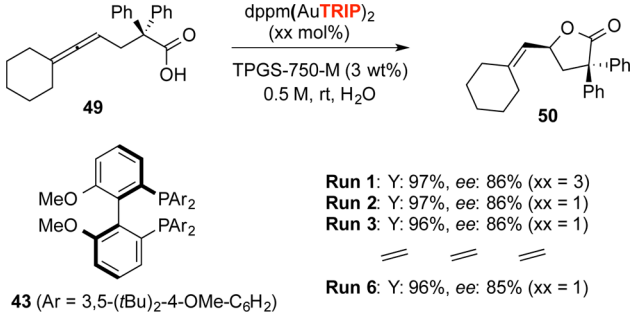
In this segment, the Toste group discovered (2007) a "complementary" strategy by locating the "chiral unit" at the gold counterion but not at the organic ligand.[77] This "outer sphere" approach deals with the ionic character associated with gold catalysis and with the consequent possibility to realize tight ion pairs between positively charged organogold species and the chiral anion (Figure 6b).[78] It should be emphasized that numerous enantioselective transformations combining chiral or achiral gold complexes and chiral organohydrogen donors have been documented.[79] However, aim of the present review is to discuss those cases in which both chiral anions and the Au center synergistically contribute to the reaction profile, excluding the metal−hydrogen bond cocatalysis.

The seminal work deals with the enantioselective intramolecular hydroalkoxylation, hydrocarboxylation/hydroamination of allenes **44** in the presence of dinuclear achiral [dppm(AuCl)$_2$] complexes (2.5 mol %) and AgX (5 mol %), in which the enantiomerically pure binol-based phosphate anion TRIP (**48**) was employed. The corresponding 5- and 6-membered heterocyclic compounds **45** were obtained in synthetically acceptable yields and high enantiomeric excesses (up to 99%, Scheme 17a).

The chiral counterion-based gold catalysis was also applied by the same team in the intramolecular C−O forming processes, involving the condensation of hydroxylamines to allenes (Scheme 17b).[80] Remarkably, a wide range of vinyl isoxazolidines and oxazine **47** was obtained in high yields and excellent enantiomeric excesses.

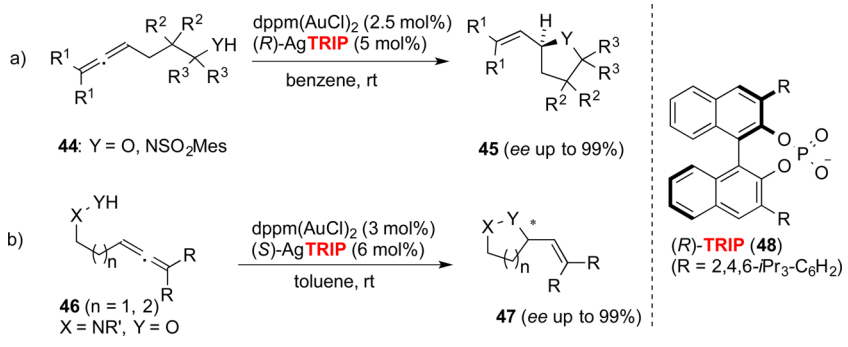
An intriguing aqueous variant of the present approach was recently presented by Lipshutz and co-workers [81] through the exploitation of in-situ-formed aqueous nanomicelles in the presence of TPGS-750-M as a designed surfactant.[82] The enantioselective lactonization of allenic acids **49** was utilized as the model reaction under the catalysis of binuclear gold complexes comprising the matched combination of (*R*)-DTBM-MeO-biphep (**43**) as the organic backbone and (*R*)-TRIP$^-$ as counterion (Scheme 18). The working plan deals

Scheme 18. Chiral Counterion Strategy in the Enantioselective Gold-Catalyzed Functionalization of Allenes (ref 81)



with the realization of much tight ion between the activated allenes and the chiral anion pairs and well-defined chiral pockets in the microenvironment generated by the nano-

Scheme 17. Chiral Counterion Strategy in the Enantioselective Gold-Catalyzed Functionalization of Allenes (refs 77, 80)



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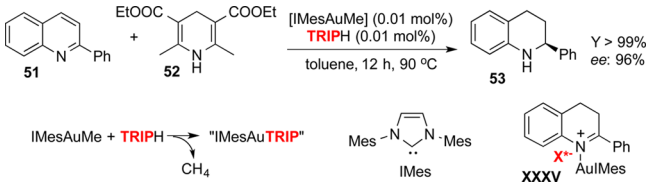
micelles. In addition to the high level of enantioselectivity obtained (ee 72−96%), the working systems enabled the recovery and reuse of both surfactant and catalyst for up to 6 times without any appreciable loss in performances.

In addition to the well documented silver-mediated [Au(I)] activation, protonolysis of alkylgold complexes was also utilized to obtain phosphine(carbene)gold species embedding chiral counterions. Related to this, Gong reported on the efficiency of chiral gold phosphate complexes in the catalytic asymmetric transfer hydrogenation of quinolines **51** with Hantzsch ester **52**. The enantioselectivity was controlled by the chiral anion (TRIP) of the gold phosphate catalyst. It should be mentioned that the achiral ligand (the carbene IMes) displayed a great impact on the catalyst performance, enabling unusually low loading of catalyst to be utilized (0.01 mol %, TON = 10 000, Scheme 19).[83]

Scheme 19. Enantioselective Transfer Hydrogenation of Quinolines Promoted by In-Situ -Formed IMesAuTRIP Complexes[a]



[a] X^{*-} = chiral phosphate anion, ref 83.

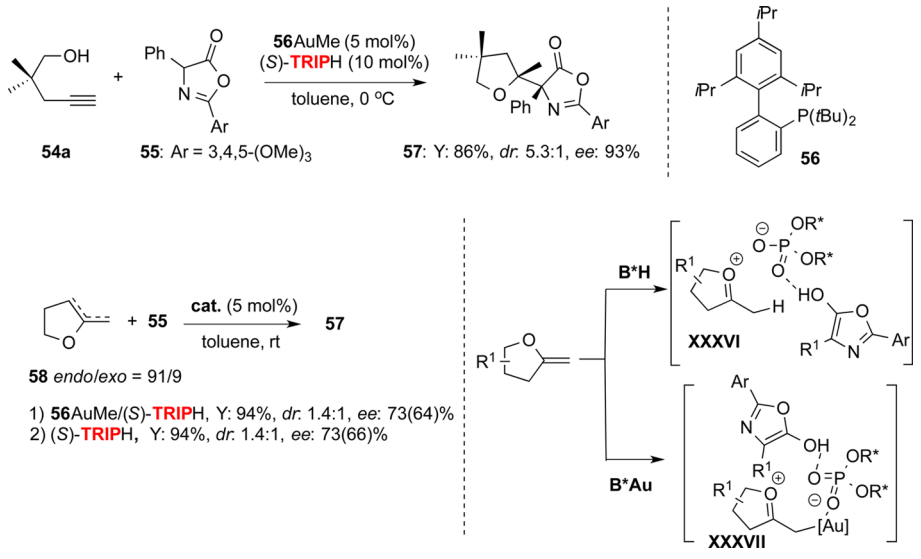
Mechanistically, although a detailed stereochemical model was not proposed, the formation of an intimate ion pair between the chiral phosphate and the cationic dihydroquinoline gold complex (**XXXV**) was hypothesized during the enantio-discriminating transfer hydrogenation.

The same group published several elegant papers on the topic also exploiting the "chiral counterion/gold relay catalysis" in stereoselective C−C bond forming cascade processes.[84] In these studies, the chiral phosphoric acid is generally employed in excess with respect to the gold species, leading to intriguing mechanistic considerations. The selected example regards the synthesis of amino acid precursors **57** bearing vicinal quaternary stereogenic centers through the condensation of alkynols **54a** with azlactones **55**.[84c] The "relay catalysis" involves the initial [Au(I)]-promoted cyclization, followed by the nucleophilic attack by the azlactones to deliver the final product **57** (Scheme 20). Interestingly, a control experiment was carried out with the preformed enol ether **58** providing the final product with similar yield and ee. This evidence suggested that the enantioselectivity of the second step was controlled either by the chiral phosphoric acid or by the cationic gold phosphate.

The covalent nature of the phosphate gold complex [AuX(L)] was unambiguously proved by Echavarren and co-workers. In particular, the synthetic pathway highlighted in Scheme 21 enabled the synthesis, isolation, and characterizing (solid state and solution) of the gold complexes **62**−**63**.[85] The chiral binol phosphates **48**,**59** were initially reacted with Ag_2O to deliver the corresponding dimeric adducts **60**−**61** in reasonable yields (74−92%). Finally, the subsequent metathesis reaction with PPh_3AuCl enabled the isolation of **62** and **63** in very high yield (up to 98%). Interestingly, conductivity measurements carried out on **63** in CH_2Cl_2, with respect to [Au(*o*-biphen*P*tBu_2)(MeCN)]SbF_6, supported its covalent structure also in solution. Nguyen and co-workers also drew similar conclusions via a detailed analysis on complex **62** via X-ray absorption fine structure spectroscopy (XAFS). In particular, the results of the EXAFS spectrum in solution showed the existence of a strong bond between the phosphate oxygen and gold cation. Moreover, the absence of any broadening of ^{31}P NMR spectra of the catalyst suggested that the bond existed during the whole catalytic cycle.[86] However, a possible partial or complete dissociation of the gold phosphate bond in solution cannot be ruled out in other processes, especially when excesses of strongly coordinating π-systems are involved in the chemical event.

The use of chiral [Au(I)] complexes, featuring phosphate anions, was also exploited by Czekelius in 2012 in the first enantioselective desymmetrization of diynamides **64**.[87] These results are remarkable because terminal alkynes were proved to

Scheme 20. Chiral Counterion/Gold Relay Catalysis Applied to the Stereoselective Synthesis of Amino Acid Precursors 57 (ref 84c)



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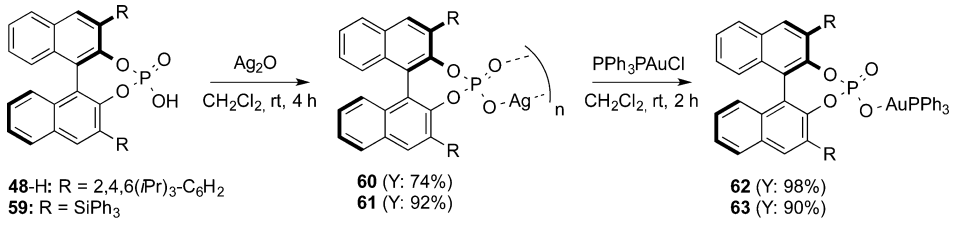
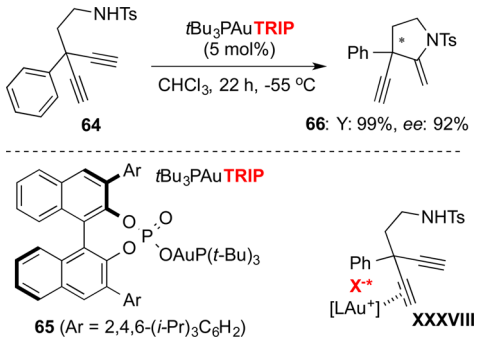
Scheme 21. Synthesis of Binol Phosphate Gold Complexes 62-63 (ref 85)



be challenging substrates in gold-mediated electrophilic activations due to the formation of rather stable alkynyl-gold(I) complexes. A library of enantiomerically enriched pyrrolidines **66** was obtained under optimal reaction parameters that involved *t*Bu$_3$PAuTRIP as chiral promoter (5 mol %) in $CHCl_3$ at −55 °C (Scheme 22). The formation of a tight ion pair

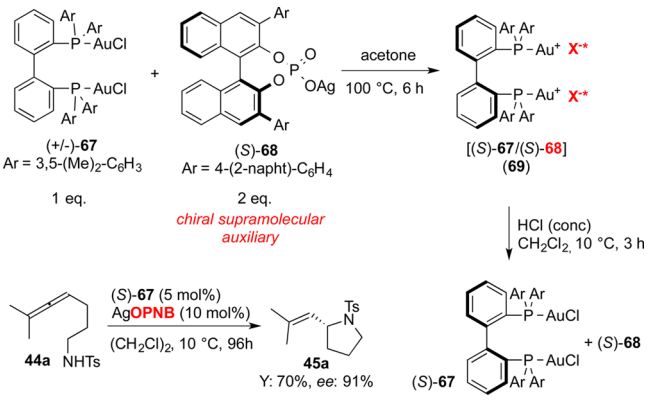
Scheme 22. Enantioselective Desymmetrization of Diynamides 64 by Means of Chiral Counterion Gold Catalysis (ref 87)



between the chiral phosphate and the cationic [Au(I)-alkyne] species (**XXXVIII**) was postulated during the enantiodiscriminating event of the catalytic process.

Chiral binol-based phosphate anions were also elegantly utilized by Mikami as a chiral auxiliary to control axial chirality in binuclear cationic [biphep(Au)$_2$]$^{2+}$ complexes. In particular, the treatment of *rac*-[biphep(AuCl)$_2$] (**67**) with 2 equiv of phosphoric silver salt (*S*)-**68** led to the diastereospecific formation of (*S*)-biphepAu/(*S*)-**68** (**69**, acetone, reflux, Scheme 23).[88] The treatment of **68** with HCl (conc.) resulted into the isolation of enantiomerically pure (*S*)-[biphepAuCl] without any traces of racemization (ee > 99%). The authors rationalized

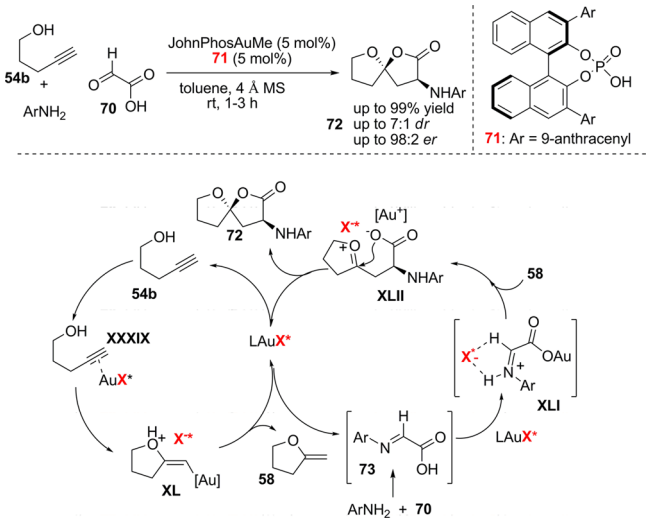
Scheme 23. Counterions as Chiral Auxiliaries to Control Axial Chirality in [Biphep(AuCl)$_2$] Complexes (ref 88)



the unusually high rotation barrier of the biphenyl scaffold with the presence of the gold centers coordinating to the phosphorus atoms that block the internal rotation as a result of the aurophilic interaction (Au−Au distance: 3.10 Å). The obtained enantiomerically pure (*S*)-[biphep(AuCl)$_2$] was also successfully employed in the stereoselective hydroamination of allenes upon activation with AgOPNB. In addition, the same group has tried some other asymmetric reactions with an axial chiral Au complex obtained by this method, and a synergistic effect was observed by introducing a chiral silver phosphate.[89]

In 2013, Fañanás and Rodríguez reported on the first multicomponent catalytic asymmetric synthesis of spiroacetals **72** via a one-pot, three-component coupling reaction.[90] Alkynols, anilines, and glyoxylic acid (**70**) were reacted in the presence of a 1:1 mixture of JohnPhosAuMe and chiral binol phosphate **71** (5 mol %, Scheme 24). The resulting gold

Scheme 24. One-Pot Multicomponent Synthesis of Spiroacetals Catalyzed by JohnPhosAuMe/71 (ref 90)



phosphate was thought to promote both stages of the reaction machinery, namely, cycloisomerization to give cyclic enol ether intermediates (**58**, [Au$^+$]) and subsequent asymmetric [3 + 2]-cycloaddition with the imine **73** (phosphate).

Conceptually similar is the dihydroalkoxylation reaction documented by Brimble in 2013, comprising the synthesis of benzannulated spiroacetal rings in the presence of chiral [Au(I)-phosphates]. The intramolecular condensation led to a range of spiroacetals in moderate enantiomeric excesses with the matched pair [(*S*)-segphos(AuCl)]/[Ag(*S*)-TRIP].[91]

3. CONCLUSIONS

Homogeneous gold catalysis has rapidly become a fascinating field of research with applications spanning asymmetric

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catalysis, total synthesis, C−H activation, and photoredox catalysis. In this scenario, an organic ligand, the gold oxidation state, and counterions represent different key pieces of a complex puzzle that, when currently assembled, enables extraordinary chemical complexity and diversity in straightforward manner. Among them, counterions are probably the least understood and predictable variables because of their multiple roles in chemical transformations.

The picture resulting from the present review reveals a still dynamic research field with substantial efforts still based on a trial and error approach. However, some general trends in the structure−activity relationship of gold anions have been delineated. As an example, the assumption "more labile = more catalytically active" can no longer be considered of general impact in gold catalysis.

In particular, although it is largely accepted that weakly coordinating anions (i.e., SbF_6^-, OTf^-, $BAr^F{}_4^-$, BF_4^-) will generate more-electrophilic gold centers with consequent stronger metal−π system interactions,[92] more-coordinating anions can positively affect late-stage catalytic events, such as sequestering the metal center from the catalyst resting state or favoring the frequently occurring protodeauration stage. In addition, basic anions (i.e., benzoates, tosylate, and acetates) can also directly interact with the reaction partners through hydrogen-bond contacts, determining optimal structural geometries for a titled transformation or controlling multiple chemo-, regio-, or stereoselective channels.

Ultimate examples of the latter cases rely on the chiral counterion-based enantioselective gold catalysis, in which chiral anions (commonly binol-based phosphates) determine the asymmetric induction in the enantiodiscriminating event of a process.

In conclusion, despite the undoubted progress, a complete and unveiled picture on the role of anion in gold catalysis is still absent, and more intriguing insights are expected in the near future.

AUTHOR INFORMATION

Corresponding Author

*E-mail: marco.bandini@unibo.it.

Notes

The authors declare no competing financial interest.

ABBREVIATIONS

ACN,acetonitrile; $BAr^F{}_4$,3,5-bis(trifluoromethyl)-phenyl borate; Bz,benzoate; DCE,dichloroethane; DCM,dichloromethane; dppm,bis(diphenylphosphinomethane); IPr,1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; LA,Lewis acid; LTM,late transition metal; NTf_2,bis((trifluoromethyl)sulfonyl)amide; OPNB,*p*-nitrobenzoate; OTf,trifluoromethanesulfonate; TA,triazole; TFA,trifluoroacetate

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