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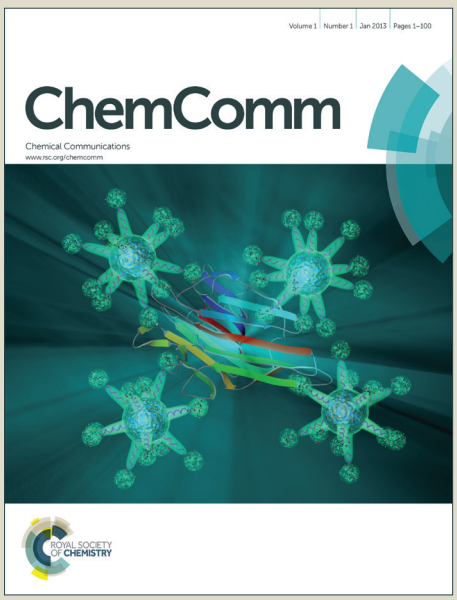

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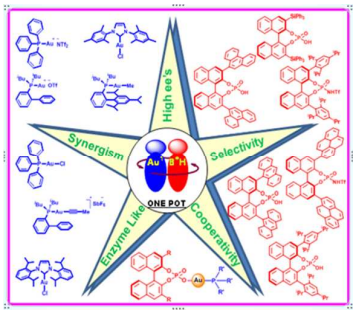

When Gold Meets Chiral Brønsted Acid Catalysts: Extending the Boundaries of Enantioselective Gold Catalysis

Suleman M. Inamdar, Ashok Konala and Nitin T. Patil*

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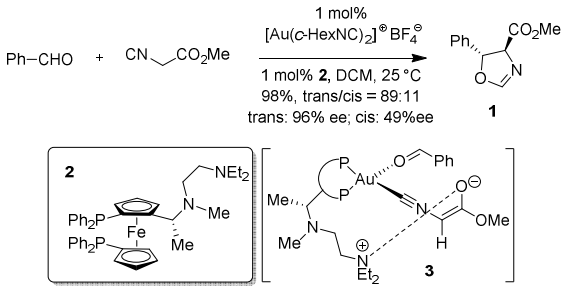
This review describes the development in the use of Au(I)/Brønsted acid binary catalytic systems to enable an enantioselective transformation in one-pot that cannot be achieved by gold catalysts alone. The examples discussed herein are promising since apart from using chiral ligands there exist a possibility of using chiral Brønsted acids. Clearly, the horizons for enantioselective gold catalysis has been expanded as there exists more options to make the gold-catalyzed reactions enantioselective.

1 Introduction

The asymmetric catalysis is one of the important branches in organic synthesis to produce enantio-pure organic compounds. The most important aspect to introduce chirality in organic molecules involves the ability of a catalyst to differentiate the enantiotopic faces of a prochiral functional group in the substrate. The ability of a catalyst to differentiate the enantiotopic faces is depends on the steric and electronic environment present in the catalyst as well as substrate/s. These criteria rarely meets and therefore the realization of the catalytic asymmetric variant of the reaction presents a significant challenge and hence there exists only a few catalytic systems which are general and works well over a broad range of substrates. This is the reason why generally racemic versions of the organic transformation appear first before the enantioselective varients. On contrary, the field of gold catalysis did not follow this trend. In fact, one of the first examples on the use of homogeneous gold catalysis in organic synthesis was actually a highly enantioselective reaction. In 1986, the Ito research group reported highly enantio- and diastereoselective synthesis of 5-alkyl-2-oxazoline-4-carboxylate **1** via aldol reaction between isocyanoacetate and benzaldehyde catalyzed by chiral Au complex (cf. **3**) (Scheme 1).[1]

Very surprisingly, the discovery made by the Ito's research group was ignored by the scientific community as evident by the absence of reports on homogeneous gold catalysis in the literature. In the beginning of this century, the potential of homogenous gold catalysis has been recognized and it has emerged as important sector of catalysis research.[2] This is mainly due to the unique ability of gold(I) and gold(III) salts to act as soft carbophilic Lewis acids towards C-C multiple bonds which, after this activation, undergo a variety of transformations that lead to formation of new carbon–carbon or carbon–heteroatom bonds. Despite its utility, however, applications of homogeneous gold catalysis in enantioselective organic transformation are still rare. Phosphine gold(I) complexes are attractive catalysts for these transformations due to their inherent chemo-selectivity for activation of C-C multiple bonds. However, the preferred linear geometry of gold(I) complexes places the chiral phosphine ligand distant from the reactive center, rendering enantioselective catalysis challenging.[3] This situation is circumvented by the use of chiral dinuclear gold(I)-phosphine complexes for the gold-catalyzed

enantioselective transformations. Similarly, several new chiral bulky monodentate phosphoramidite ligands were developed and applied successfully for gold-catalyzed enantioselective transformations.[4] In parallel, the efforts to develop chiral NHC–Au(I) catalysts have also been documented.[5] In recent years, gold-catalyzed reactions that involved chirality transfer and memory of chirality have emerged as a powerful tool in enantioselective synthesis.[6] Very recently, Zhang and coworkers introduced a novel ligand design based on the privileged (1,1′-biphenyl)-2-ylphosphine framework which turned out to be highly efficient in catalyzing the addition of acid to alkynes with very high turnover number.[7]



Scheme 1 Enantioselective gold catalyzed aldol reaction

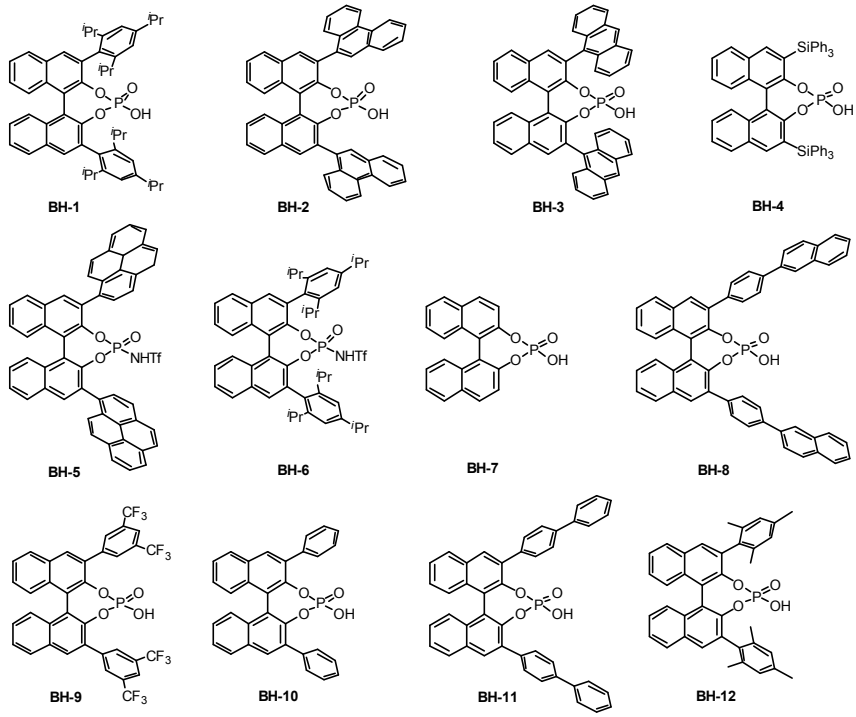


Figure 1 Structures of chiral Brønsted acids

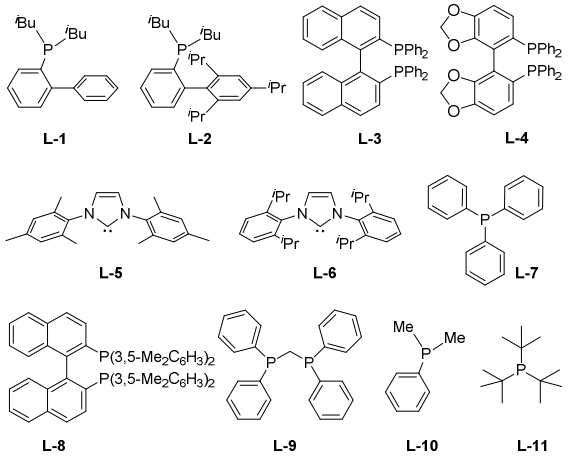
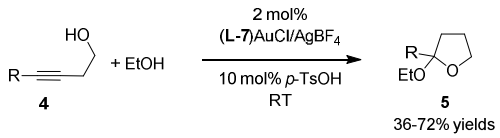


Figure 2 Ligands on Au-center (LnAuB)

Just imagine, a binary system involving gold(I)- and Brønsted acid catalyst (Fig 1 and Fig 2), mediates the reaction to give the product which is not possible to obtain with the use of a single gold(I) catalyst alone. In a view of the plethora of reactivities exhibited by gold(I) species 2[-3] and Brønsted acid catalyst,[8] several new reactions can be envisioned. The important feature of this type of gold/chiral Brønsted acid is that there exists more options to make the reaction enantioselective either by using a single chiral catalyst or by using both chiral catalysts provided that they work in synergy.[9] In 2010, Hashmi and Hubbert, for the first time highlighted the importance of merging gold catalysis with Brønsted acid catalysis.[10] Within four years of period, the area has matured enough to compile in the form of review. Herein, we discuss in detail the development in the use of Au(I)/Brønsted acid binary catalytic systems to enable an asymmetric transformation in one-pot. When both the catalysts, i.e. Au(I) and Brønsted acid, exists in one-pot, a clear understanding of their roles, generation of catalytically active species, enantioinduction is necessary.[11] Efforts have been made to discuss these issues and to illustrate how this technique can be used to graft molecular complexity from easily available starting materials.

To the best our knowledge, the first example of a binary catalyst system, consisting of a gold catalyst and a Brønsted acid, was reported by Belting and Krause in 2006. They developed cycloisomerization-hydroalkoxylation cascade for the synthesis of tetrahydrofuranyl ethers **5** from homopropargylic alcohols **4** and alcohols under the catalysis of Au(I) and *p*-TsOH binary catalytic system (scheme 2).[12]



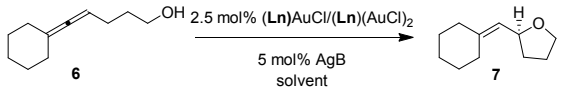
Scheme 2 Au(I)/*p*-TSA catalyzed tandem cycloisomerization-hydroalkoxylation of homopropargylic alcohols

In 2007, Toste and coworkers reported the use of chiral gold phosphate (**Ln**)AuB, derived from (**Ln**)AuCl and silver phosphate AgB.[13] The silver phosphate was conveniently prepared in situ from chiral Brønsted acids (BH) by the reaction with Ag_2O. The phosphates were utilised as catalysts for the intramolecular hydroalkoxylation of allenol **6** to produce tetrahydropyran derivative **7**. As shown in Scheme 3A, the use of a chiral ligands and chiral counter-ion on Au-center provided desired product **7** in good ee's (up to 97%) (entries 1-3). On the contrary, the use of a single chiral ligand on gold center is not satisfactory and poor ee was observed in such cases (entry 4-6). The same phenomenon was observed for hydrocarboxylation reaction of **8** to obtain enantio-pure lactone **9** (Scheme 3B). A strong matched-mismatched pairing effect between ligands and counter-ions was observed - the mismatched combination (*R*)-**L-3**$(AuCl)_2$/Ag-(*R*)-**BH-1** provided nearly racemic product on the other hand a combination of (*S*)-**L-3**$(AuCl)_2$/Ag(*R*)-**BH-1** gave **9** with 82% ee. The concept was further extended for the hydroamination of allene tethered sulfonamides **10** to afford the cyclic-sulfonamides **11** in good yields with high level of ee's (Scheme 3C).

The above mentioned discovery made by the Toste's research group is very promising. They have shown that the high ee was conferred by a chiral counterion. In addition, they have shown that the chiral counterion can be combined additively with chiral ligands to enable an asymmetric transformation that cannot be achieved by either method alone. Later, the concept of relaying chiral information via an ion pair is turned out be applicable not only for gold catalysis but also for other metal-mediated processes.[14]

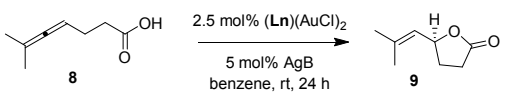
Two years later, Dixon et al. reported Au(I)/chiral Brønsted acid-catalyzed formal hydroamination/hydroarylation of alkynes tethered with carboxylic group (Scheme 4).[15] They utilized alkynoic acids **13** and aminoaromatics **12** as starting material and the process led to an efficient synthesis of enantiopure multi-ring heterocyclic compounds **14**. The reaction was initiated with Au(I)-catalyzed 5-*endo-dig* cyclization to form five membered enol lactones **15**. In presence of chiral Brønsted acid, the enol lactone **15** was attacked by the amine moiety of **12** to form keto-amide (isolable) **16** which underwent a dehydrative cyclization through *N*-acyliminium intermediates **17**. The presence of the chiral counteranion allowed stereocontrol in the nucleophilic attack of the indole to provide the polycyclic indole derivatives **14** in good to excellent yields and ee's. While no rationales were described, we assumed that the low catalyst loading of (**L-7**)AuCl/AgOTf is necessary for the obtaining the products in high ee's. Excess of (**L-7**)AuCl/AgOTf might generate residual TfOH in the reaction mixture which could be responsible for the background non-enantioselective reaction leading to the products with poor ee's.

(A)



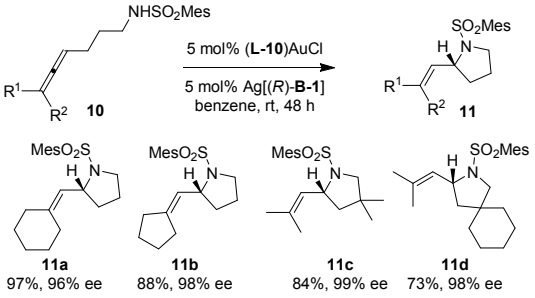
entry		solvent	Ln	B	yield, ee (%)
1	chiral counterion	DCM	L-7	(*R*)-BH-1	89%, 48% ee
2	chiral counterion	DCM	L-9	(*R*)-BH-1	76%, 65% ee
3	chiral counterion	benzene	L-9	(*R*)-BH-1	90%, 97% ee
4	chiral ligand	DCM	L-3	BF_4^-	52%, 6% ee
5	chiral ligand	DCM	L-8	BF_4^-	68%, 0% ee
6	chiral ligand	DCM	L-4	BF_4^-	79%, 2% ee

(B)

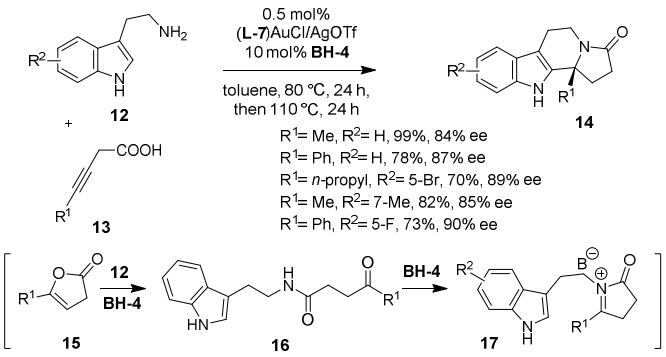


entry		Ln	B	yield, ee (%)
1	chiral ligand	(*R*)-L-3	OPNB	80%, 38% ee
2	chiral counterion	L-9	(*R*)-BH-1	89%, 12% ee
3	both (mismatched)	(*R*)-L-3	(*R*)-BH-1	91%, 3% ee
4	both (matched)	(*S*)-L-3	(*R*)-BH-1	88%, 82% ee

(C)

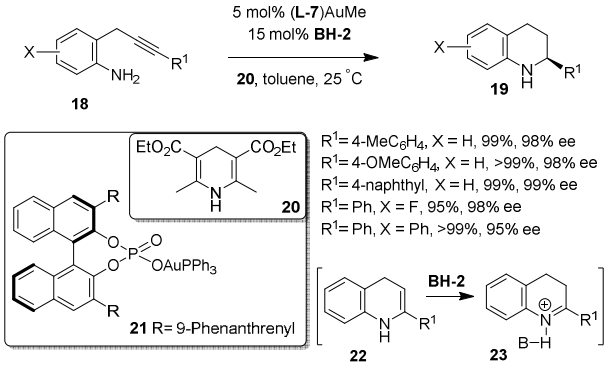


Scheme 3 Chiral Au-phosphate catalyzed enantioselective hydroalkoxylation, hydroamination and hydrocarboxylation reactions



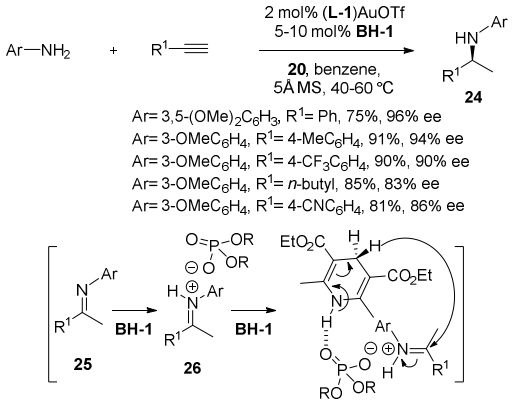
Scheme 4 Au(I)/chiral Brønsted acid catalyzed iminium ion cascade

In 2009, Gong and coworkers reported gold (I)/chiral Brønsted acid catalyzed synthesis of tetrahydroquinolines **19** from *ortho*-aminoalkyne **18** *via* intramolecular hydroamination followed by enantioselective transfer hydrogenation in good to excellent yields and ee's (Scheme 5).[16] During the optimization studies, they found that the catalyst (**L-7**)$AuCH_3$ in combination with chiral Brønsted acid **BH-2** gives the best results. The reaction proceeded through gold phosphate catalyzed intramolecular hydroamination to form 1,4-dihydroquinoline **22** that underwent **BH-2** catalyzed isomerization to form 3,4-dihydroquinoline **23**. Under the catalysis of **BH-2**, the enantioselective transfer hydrogenation in the presence of Hantzsch ester **20** took place to form tetrahydroquinolines **19**. Control studies revealed that the gold phosphate had little effect on the enantioselective transfer hydrogenation, while chiral Brønsted acid dominantly controlled the enantioselectivity.



Scheme 5 Gold(I)/chiral Brønsted acid catalyzed intramolecular hydroamination-hydrogenation cascade

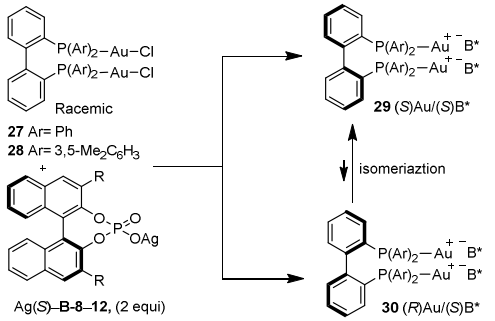
Soon after, Che and coworkers reported analogues example based on consecutive hydroamination/transfer hydrogenation reaction between terminal alkynes and aromatic amines (Scheme 6).[17] The proposed mechanism is similar to that reported by Gong and coworkers. Mechanistically, the formation of Au-phosphate took place which catalyzes intermolecular hydroamination of alkyne with amine to generate the imine **25**. This imine is then activated by Brønsted acid catalysis to generate the iminium salt **26** which subsequently undergoes enantioselective transfer hydrogenation in the presence of Hantzsch ester **20** to afford secondary amines **24** in good yields and ee's.



Scheme 6 Gold(I)/chiral Brønsted acid catalyzed intermolecular hydroamination-hydrogenation cascade

The report by Gong is very important because the catalyst (**Ln**)AuMe reacts with chiral Brønsted acid to generate gold phosphates with the liberation of methane gas. Hence the reactive species in the reaction is chiral gold phosphate and chiral Brønsted acid (if used in excess). Hence, the possibility of formation of residual achiral Brønsted acid [such as TfOH in the case of (**Ln**)AuOTf], which could be the culprit for background reactions, does not exist. It is surprising to note that the preparation of LnAuMe is known for last 20 years; however, the application in gold catalysis[18] and especially in asymmetric gold catalysis[19] is not known. The reports by Gong and Che have led good foundation for preparation of chiral gold phosphate in one-pot in contrary to Toste's procedure[13] wherein two-step processes are required.

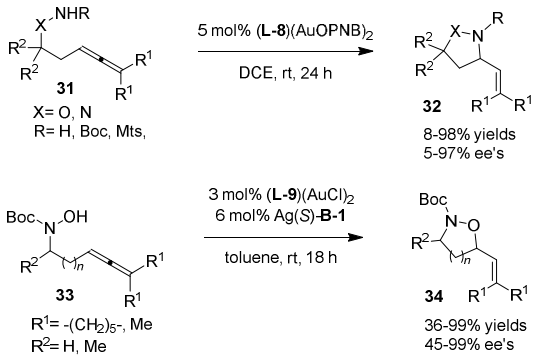
Later, Mikami et al. reported the preparation of series of gold phosphates by controlling the axial chirality using silver phosphate derivatives (Scheme 7).[20] Treatment of a racemic gold–biphep complexes **27**/**28** with two equivalents of the silver phosphate complex Ag(*S*)-**B-8** to Ag(*S*)-**B-12** delivers two diastereomers of gold phosphate **29** and **30** in quantitative yields (dr 52:48). Upon optimization of reaction conditions followed by tuning the various substituents on the silver phosphates, isomerization of gold phosphates **30** took place to afford exclusively the thermodynamically favoured single diastereomer of Au-phosphate **29**. The authors have not reported the application of those Au-phosphates in asymmetric catalysis. However, it is apparent that such a kind of optically active gold phosphates can be used as catalysts in enantioselective gold catalyzed reactions.



Solvent	*rac*-Au	Ag(B*)	T (°C)	t (h)	dr **29**:**30** (%)
acetone	**27**	Ag(*S*)–**B-9**	RT	1	52:48
acetone	**27**	Ag(*S*)–**B-9**	80	14	75:25
acetone	**27**	Ag(*S*)–**B-9**	100	14	75:25
benzene	**27**	Ag(*S*)–**B-9**	100	12	53:47
THF	**27**	Ag(*S*)–**B-9**	80	12	71:29
acetone	**27**	Ag(*S*)–**B-10**	100	14	96:04
acetone	**27**	Ag(*S*)–**B-11**	100	14	99:01
acetone	**27**	Ag(*S*)–**B-12**	100	14	100:0
acetone	**27**	Ag(*S*)–**B-8**	100	14	100:0
acetone	**28**	Ag(*S*)–**B-9**	80	14	87:13
acetone	**28**	Ag(*S*)–**B-10**	100	12	89:11
acetone	**28**	Ag(*S*)–**B-11**	100	12	100:0
acetone	**28**	Ag(*S*)–**B-8**	100	6	100:0

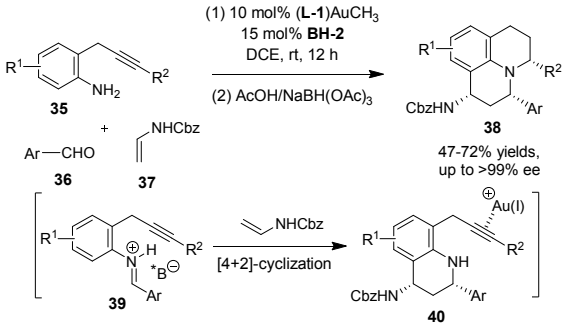
Scheme 7 Generation of gold phosphate and isomerization to thermodynamically favourable isomer.

Pioneering work from Toste's laboratory disclosed an enantioselective synthesis of pyrazolidines and tetrahydro-oxazines **32** using gold(I)/bis(*p*-nitrobenzoate) complexes catalyzed intramolecular hydroamination of **31** in moderate to good yields and ee's. Surprisingly, gold(I)/bis(*p*-nitrobenzoate) complexes proved to be ineffective catalysts for the intramolecular hydroalkoxylation of allenes **33**. The problem was overcome by the use of gold phosphate complexes, generated in situ from Ag(*R*)-**B-1** and (**Ln**)$(AuCl)_2$, to give **34** in good yields and ee's (Scheme 8).[21]



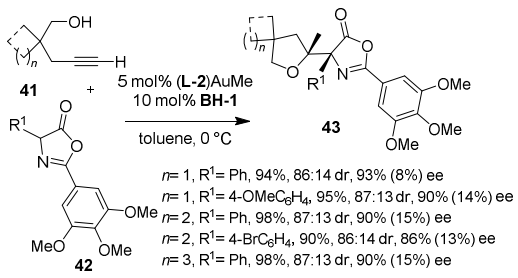
Scheme 8 Gold phosphate catalyzed intramolecular hydroamination and hydroalkoxylation of allenes

In 2010, Gong et al. described an interesting example of Au(I) and chiral Brønsted acid catalyzed enantioselective three component cascade reaction between 2-(2-propynyl) anilines **35**, aldehydes **36** and enamide **37** for the preparation of optically pure julolidine derivatives **38** (Scheme 9).[22] Mechanistically, a Brønsted acid-catalyzed [4+2] cycloaddition reaction between the iminium species **39**, derived from **35** and **36**, with enamide **37** took place to generate enantiopure amino-alkyne **40** which subsequently undergoes intramolecular hydromination catalyzed by a gold phosphate. The stable julolidine derivatives **38** were isolated after reduction with $AcOH/NaBH(OAc)_3$. Control experiments revealed that gold phosphate (generated in situ from (**L-1**)AuMe and **BH-2**) was unable to catalyze the [4+2] cycloaddition reaction - the chiral Brønsted acid served as real catalyst for this step; while, gold phosphate in combination with **BH-2** catalyses the intramolecular hydroamination of **40.**

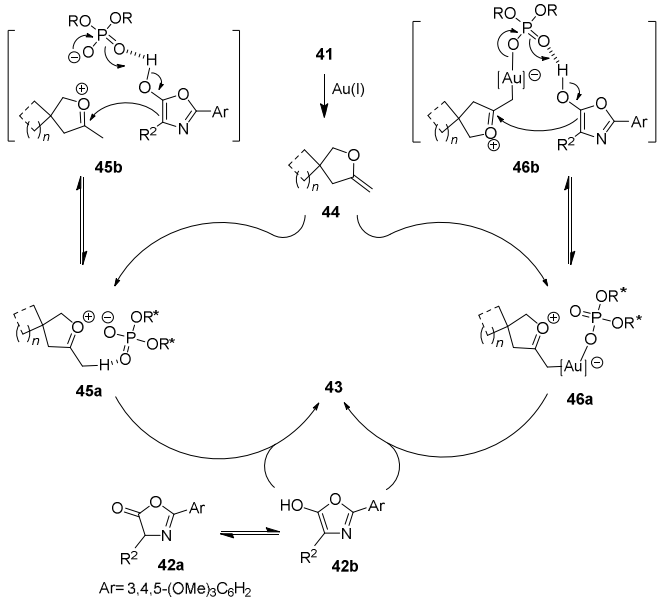


Scheme 9 Gold(I)/chiral Brønsted acid catalyzed cascade reaction for the synthesis of julolidine derivatives

Pioneering work in Gong's laboratory later disclosed the utility of Au(I)/chiral Brønsted acid catalyst system for the synthesis conformationally restricted amino acid precursors **43** bearing vicinal quaternary stereogenic centers by the reaction of alkynols **41** with azlactone **42** (Scheme 10).[23] The reaction proceeded through Au-catalyzed intramolecular hydroalkoxylation to obtain cyclic enol ether **44**. The cyclic enol ether **44** is attacked by the azlactone to furnish the product **43** through two possible intermediates a) ion pair of chiral conjugate base through oxonium ion **45a-b** or b) coordination of the chiral gold phosphate to the double bond of the enol ether **46a-b** (Scheme 11). The controlled experiment between enol ether **44** and azlactone **42** provided **43** in similar yield and stereoselectivity in the presence of either chiral Brønsted acid or gold phosphate suggesting that both the mechanistic pathways are operating simultaneously.

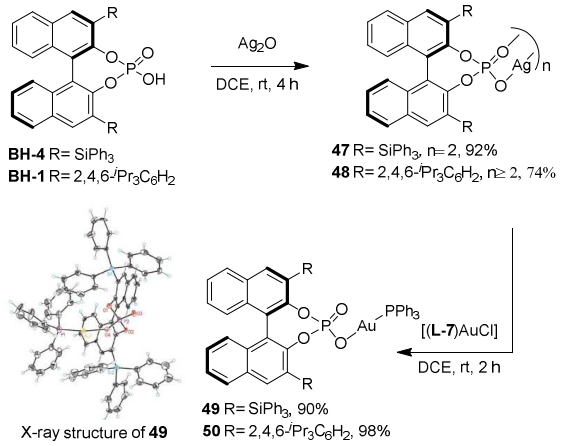


Scheme 10 Gold(I)/chiral Brønsted acid catalyzed synthesis of amino acid precursors bearing quaternary stereogenic centers



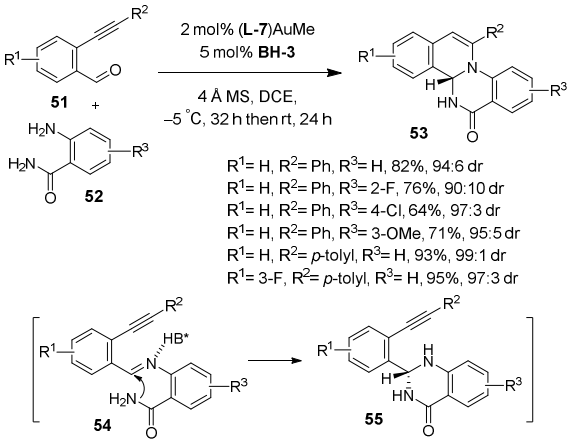
Scheme 11 A proposed mechanism for gold(I)/chiral Brønsted acid catalyzed synthesis of amino acids

It is evident that the gold phosphates are efficient catalysts which are generated in situ from the corresponding gold catalysts and chiral Brønsted acids. However, until recently, no reports exist on the isolation and characterization of gold phosphates. In 2012, Echavarren et al. reported the preparation, isolation and characterization of Au-phosphate complexes **49**/**50**. These Au-phosphate complexes were prepared in two steps following the procedure reported by Toste and coworkers[13] which involves the treatment of Brønsted acid **BH-1**/**BH-4** with Ag_2O to afford silver phosphate complex **47**/**48** followed by displacement of silver by gold with [(**L-7**)AuCl] (Scheme 12).[24] The gold phosphates thus obtained are very robust and can be purified by flash chromatography on SiO_2. These complexes **49**/**50** were well characterized by ^{31}P NMR and X-ray diffraction techniques. The authors examined the catalytic activities of gold phosphates for the cyclization of 1, 6-enynes.



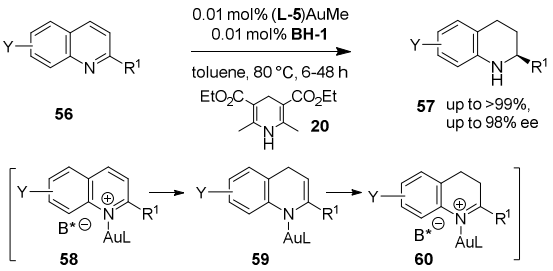
Scheme 12 Synthesis of chiral gold phosphates

Recently, our research group developed an enantioselective reaction utilizing achiral Au(I) complexes and chiral Brønsted acids for the synthesis of optically pure fused 1,2-dihydroisoquinolines (Scheme 13).[25] For instance, the treatment of 2-alkynyl benzaldehydes **51** with 2-aminobenzamides **52** in the presence of 5 mol% **BH-3** and 2 mol% (**L-7**)AuMe and MS 4Å in DCE (–5 ºC → rt) afforded enantiopure 1,2-dihydroisoquinolines **53** in high yield and up to 99% ee. Mechanistically, the reaction proceeds *via* the formation of chiral aminals **55**, by the reaction between **51** and **52** under the catalysis of chiral Brønsted acid,[26] which after intramolecular hydroamination catalyzed by gold phosphate (generated in situ from (**L-7**)AuMe and **BH-3**) afforded fused optically pure 1,2-dihydroisoquinolines **53**. The gold phosphate was characterized by ^{1}HNMR, ^{13}C NMR, HRMS and finally by ^{31}P NMR spectroscopy.



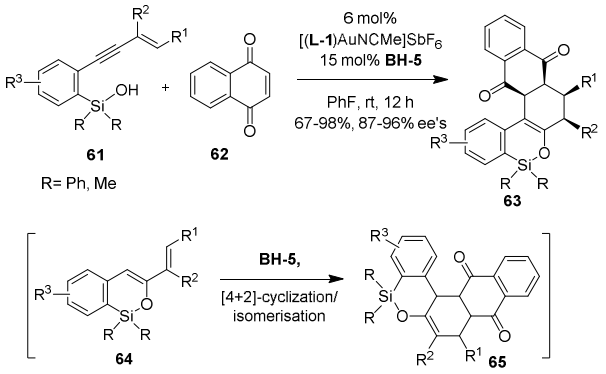
Scheme 13 Gold(I)/chiral Brønsted acid catalyzed enantioselective synthesis of fused 1,2-dihydroisoquinolines

The enantioselective hydrogenation of quinolines represents an important topic in organic synthesis because of the prevalence of 1,2,3,4-tetrahydroquinolines in a number of pharmaceutically important compounds. Transition metal catalyzed enantioselective hydrogenation of quinolines is the best known approach for this purpose. This technique relies on the use of chiral ligands to control the stereochemistry. For the first time, it is reported that the ee's of the reaction can be controlled by the chiral ion and the role of achiral ligand was proposed to modulate the catalytic performances.[27] Gold phosphate **50** (generated in situ from (**L-5**)AuCl/chiral Brønsted acid **BH-1**) served as highly efficient catalysts for the enantioselective transfer hydrogenation of quinolines **56** using with Hantzsch ester **20** to afford tetrahydroquinolines **57** in good to excellent yields and ee's (Scheme 14). The reaction initiated with the coordination of the gold phosphate to quinolines to form complex **58** which undergoes enantioselective transfer hydrogenation with a Hantzsch ester to generate intermediate **59**. Consequently protonation of this intermediate occurs to produce dihydroquinolines **60** which again undergoes enantioselective transfer hydrogenation with Hantzsch ester **20** to generate the tetrahydroquinolines **57**. Only 0.01 mol% of the gold phosphate is needed to effectively afford the enantioselective transfer hydrogenation of quinolines. These results are unusual to metal catalyzed and chiral Brønsted acid catalyzed[28] enantioselective transfer hydrogenation since such low catalyst loading has never been reported for these both types of catalysis.



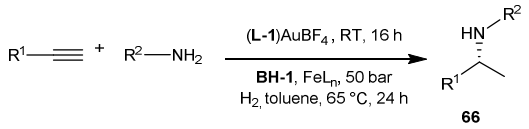
Scheme 14 Gold(I)/chiral Brønsted acid catalyzed enantioselective transfer hydrogenation of quinolines

Later, the same research group reported [(**L-1**)AuNCMe]SbF_6 with **BH-5** catalyzed synthesis of highly enantioenriched polycyclic compounds from enynylsilanol **61** (Scheme 15).[29] The reaction proceeded through gold-catalyzed intramolecular hydrosilylation of enynylsilanol **61** to generate an active silyloxydiene intermediate **64** which could subsequently participate in a chiral Brønsted acid catalyzed asymmetric Diels-Alder reaction with an electron deficient olefin **62** to generate the polycyclic compound **65**. Further an isomerization occurred presumably due to the conjugated stabilization energy between the aryl group and carbon-carbon double bond to afford the final product **63**. The Diels Alder reaction between silyloxydiene **64** and **62** did not occur in the presence of [(**L-1**)AuNCMe]SbF_6 alone which indicates that the reaction was solely accelerated by **BH-5**.

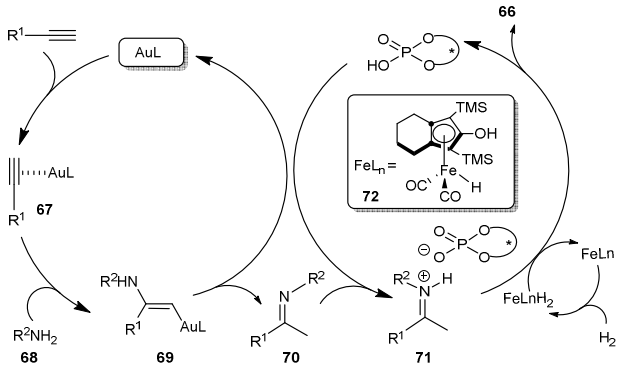


Scheme 15 Gold(I)/chiral Brønsted acid catalyzed intramolecular hydrosiloxylation/asymmetric Diels−Alder reaction

In the same year, Beller et al. reported an enantioselective reductive hydroamination of terminal alkynes with primary amines **68** to yield chiral amines **66** by utilizing gold(I) complex, Knolker's iron complex and a chiral Brønsted acid ternary catalyst system (Scheme 16).[30] The protocol is applicable for the variety of terminal alkynes and primary aromatic amines to afford chiral secondary amines in excellent yields and ee's. The reaction was initiated by Au-catalyzed hydroamination to generate ketimine **70** (cf. **69**) as intermediates.[31] Subsequently, the formation of iminium ion **71** took place from **70** in the presence of chiral Brønsted acid catalyst. Finally, the iminium ion **71** was reduced with Knolker's iron complex **72** to form the chiral amine **66** (Scheme 17).

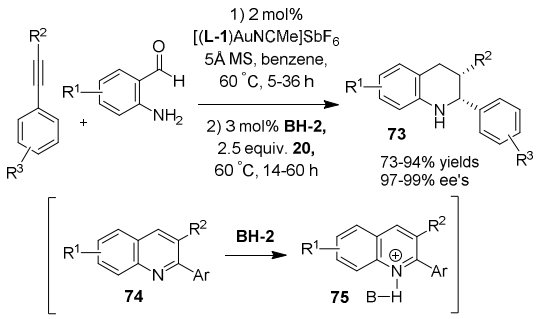


Scheme 16 Gold(I)/Fe/chiral Brønsted acid ternary catalyst system for enantioselective reductive hydroamination of terminal alkynes with primary amines



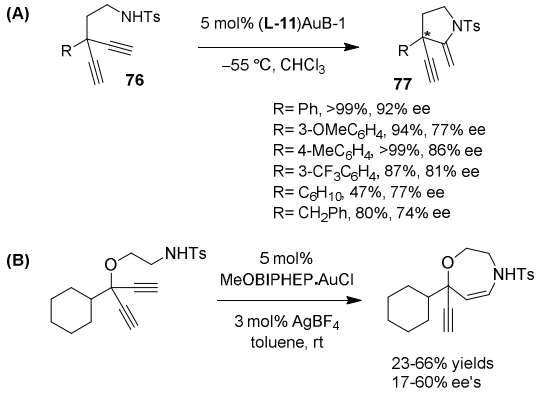
Scheme 17 A Proposed Mechanism for enantioselective reductive hydroamination of terminal alkynes

In the same context, Che et al. reported a cascade reaction catalyzed by achiral Au(I)-complex with chiral Brønsted acid binary system for regio-, diastereo-, and enantioselective synthesis of tetrahydroquinolines **73** from the reaction of 2-aminobenzaldehyde or aminophenones with alkynes (scheme 18).[32] A proposed mechanism involved Au-catalyzed intermolecular hydroamination of amine with alkyne followed by chiral Brønsted acid catalyzed enantioselective transfer hydrogenation with Hantzsch ester **20** to give optically active tetrahydroquinolines **73** in good to excellent yields. A control experiment revealed that gold(I) complex can catalyze non-enantioselective transfer hydrogenation of the corresponding quinoline intermediate with Hantzsch ester to give the desired product. In order to minimize this non enantioselective reaction catalyzed by the gold(I) complex, appropriate amount of triethylamine was employed to deactivate the gold catalyst after completion of the first step.



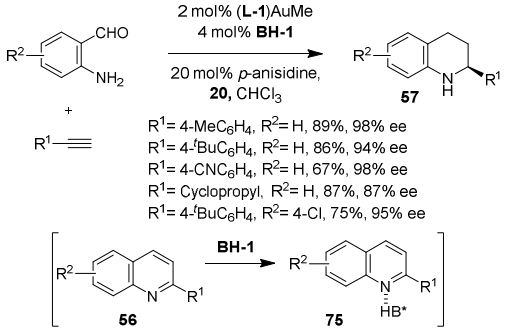
Scheme 18 Gold(I)/chiral Brønsted acid catalyzed regio-, diastereo-, and enantioselective synthesis of tetrahydroquinolines

In 2012, Czekelius and coworkers reported an entirely different approach based on the desymmetrization triggered by hydroamination reaction.[33] When 1,4-diynamides **76** were treated with chiral gold-phosphate catalyst (derived from (**L-11**)AuCl and **BH-1**), pyrrolidine derivatives **77** were obtained in fairly good yields and ee's (Scheme 19A). The reaction was found to be the most selective at lower temperatures in nonpolar solvents confirming the assumption that a contact ion pair is formed by the cationic gold-alkyne complex and the anionic chiral phosphate. It should be noted that the reaction has been reported by the authors previously using cationic chiral gold complexes; however, the reaction was not efficient in terms of yields and ee's (Scheme 19B).[34] Therefore, the authors work presented in Scheme 19A demonstrates the potential application of gold complexes bearing chiral phosphate counterion in enantioselective gold catalyzed reactions.



Scheme 19 Gold(I) phosphate catalyzed enantioselective desymmetrization of 1,4-diynamides

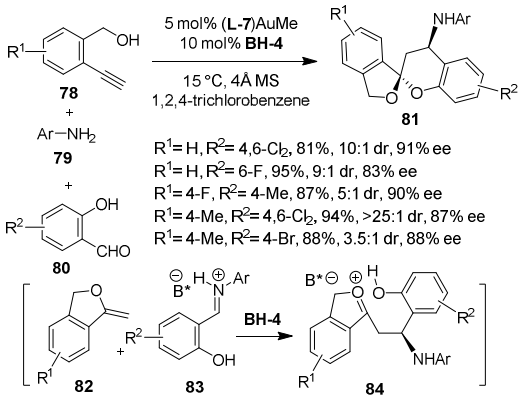
We recently reported an enantioselective cooperative triple catalysis system consisting of **Ln**AuMe/*p*-anisidine/chiral Brønsted acid catalysts for the synthesis of 2-substituted tetrahydroquinolines **57** from the reaction of 2-aminobenzaldehydes, terminal alkynes and Hantzsch ester **20** (Scheme 20).[35] The reaction worked well with a wide range of substituent on both starting materials to afford the desired optically pure 2-substituted tetrahydroquinolines in good yield with excellent ee's (up to 99%). Several controlled experiments have been performed to understand the role of each catalyst. The study indicate that all three catalysts *p*-anisidine, **BH-1**, gold phosphate (generated in situ from (**L-1**)AuMe and **BH-1**) are necessary to obtain 2-substituted quinolines **56** while chiral Brønsted acid catalyses the enantioselective transfer hydrogenation of the intermediate 2-substituted quinoline **56** with Hantzsch ester **20** to afford 2-substituted tetrahydroquinolines **57**. We believe that this is a nice demonstration of triple catalysis system wherein not only gold and Brønsted acid functions in the presence of each other but also an additional catalyst assists the overall reaction.



Scheme 20 Gold(I)/*p*-anisidine/chiral Brønsted acid ternary catalysts system for synthesis of 2-substituted tetrahydroquinolines

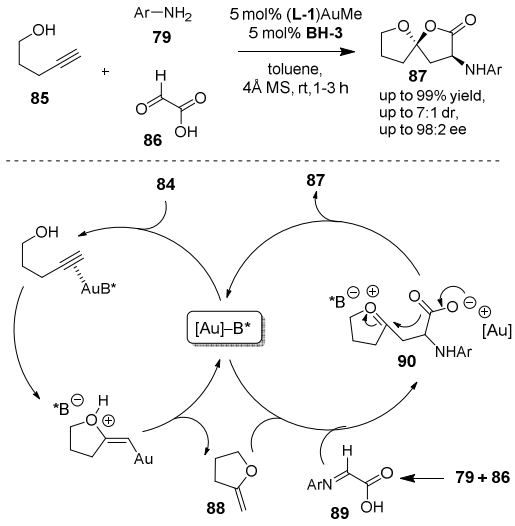
In 2013, Gong and coworkers reported a highly stereoselective three component reaction of salicylaldehydes **80**, anilines and alkynols **78** to give aromatic spiroacetals **81** in high yields and stereoselectives using (**L-7**)AuMe and **BH-4** (Scheme 21).[36] The

reaction proceeds through a Au-catalyzed intermolecular hydroalkoxylation of alkynol **78** to afford exocyclic enol ether **82**. The enol ether **82** participates in the asymmetric Mannich-type reaction with salicylaldehydimines **83**, generated in situ from the condensation reaction between salicylaldehydes and anilines under the catalysis of **BH-4** to generate oxonium ion **84** which subsequently undergoes acetalization to deliver the spiroacetals **81**. Control experiment shows that both gold phosphate and chiral Brønsted acid can catalyze the cascade reaction, but **BH-4** plays a dominant role in the control of enantioselectivity in Mannich- type reaction.



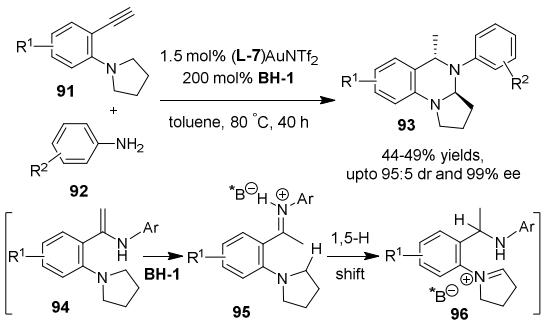
Scheme 21 Gold(I)/Brønsted acid catalyzed asymmetric synthesis of spiroacetals

Another example of merging gold catalysis [(**L-1**)AuMe] with chiral Brønsted acid (**BH-3**) was demonstrated by Fañanas, Rodríguez and coworkers for the catalytic asymmetric synthesis of [5,5]-spiroacetals **87** via three-component reaction between alkynols **85**, anilines **79** and glyoxylic acid **86** (Scheme 22).[37] Mechanistically, the reaction could have initiated by the gold phosphate catalyzed intermolecular hydroalkoxylation of **85** to generate exocyclic enol ether **88**. At the same time, the condensation reaction between glyoxylic acid **86** and anilines **79** under the catalysis of **BH-3** affords imine **89**. Subsequent co-ordination of the imine **89** with gold phosphate leads to an activated species which undergo nucleophillic addition by the cyclic enol ether **88** (cf. **90**) followed by intramolecular cyclization to deliver the desired [5,5]-spiroacetals **87** with the liberation of the catalyst. Thus, the main role of the (**Ln**)AuB catalyst in the hydroalkoxylation reaction is played by its cationic part $(Ln)Au^{+}$; while the anionic part of the catalyst (B) creates the appropriate chiral environment to produce the final enantioenriched products **87**.



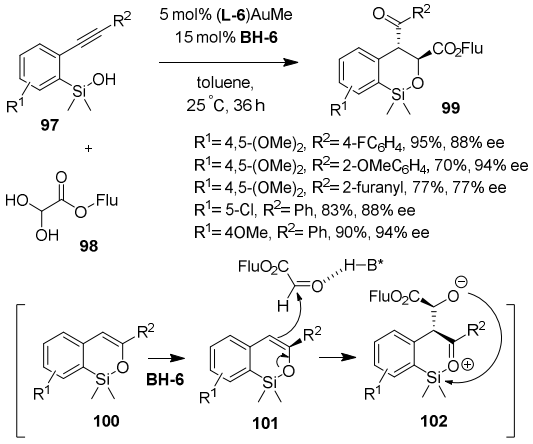
Scheme 22 Gold(I)/Brønsted acid catalyzed approach to enantiopure spiroacetals

Recently, Gong et al. reported (**L-7**)AuNTf$_2$/CF_3SO_3H as Brønsted acid catalyzed relay catalytic system for the synthesis of racemic cyclic aminals **93** utilizing tertiary amine derivatives **91** and amines **92** *via* cascade hydroamination/redox reaction. In the same publication, the author also demonstrated the catalytic enantioselective version with Au(I)-phosphate generated in situ from (**L-7**)AuNTf$_2$ and excess of chiral Brønsted acid **BH-1** to afford enantioenriched cyclic aminals (Scheme 23).[38] A proposed mechanism involves Au-catalyzed intramolecular hydroamination of terminal alkynes **91** with anilines **92** to afford enamine intermediate **94**. Chiral Brønsted acid might coordinate with intermediate **94** to form iminium species **95** which undergo 1,5 hydride shift to generate a transient intermediate **96** followed by cyclization to give cyclic aminals **93**. Optimization conditions revealed that an enhancement in enantioselectivity observed when chiral Brønsted acid was used in very excess, this might be due to the fact that chiral Brønsted acid would complete the Au(I)-catalyzed non-selective background reaction.



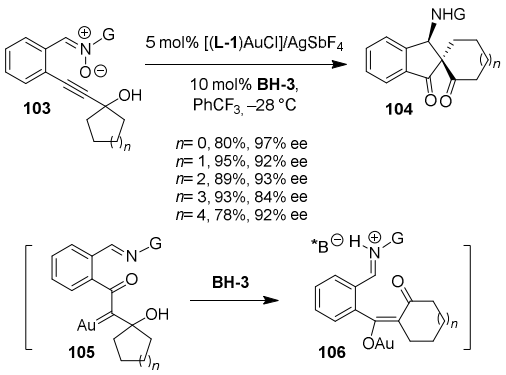
Scheme 23 Gold/chiral Brønsted acid catalyzed cascade hydroamination/redox reaction for the synthesis of cyclic aminals

In the same year, Gong and coworkers reported intramolecular hydrosiloxylation - Mukaiyama aldol reaction under the catalysis of (**L-6**)AuMe/**BH-6**. The gold phosphate generated in situ is responsible for intramolecular hydrosiloxylation of aryl acetylenes **97** (cf. **100**) while BH-6 catalyzes the asymmetric Mukaiyama aldol reactions of **100** (cf. **101**) with **98** (scheme 24).[39] The use of *N*-heterocyclic carbene (NHC) (**L-7**) as a ligand turned out to be crucial for obtaining products with good yields and ee's. The reaction tolerates both electron-withdrawing as well as -donating groups on aryl silinols to afford aldol adduct. The higher enantioinduction was observed with bulkier substrate such as fluorenyl glyoxylate (Flu) and the less bulky ethyl glyoxylate gave inferior results.



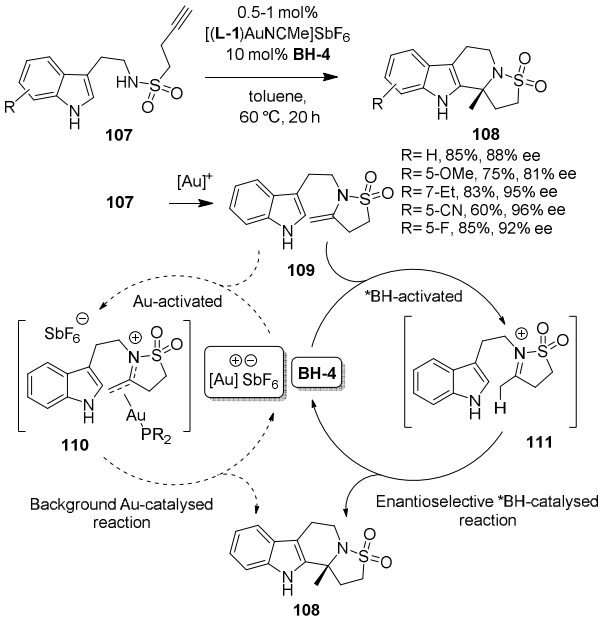
Scheme 24 Gold(I)/chiral Brønsted acid catalyzed cascade *hydrosiloxylation*/ Mukaiyama aldol reaction

Zhang et al. reported the use of gold(I)/chiral Brønsted acid binary catalytic system for the enantioselective synthesis of β-amino spirocyclic and quaternary diketone derivative **104** through a redox-pinacol-Mannich cascade (Scheme 25).[40] The mechanism of the cascade reaction involves the formation of reactive gold α-oxo carbenoid intermediates **105** from the nitro-alkyne **103**.[41] The carbenoid intermediates **105** undergo **BH-3** catalyzed rearrangement through ring expansion to get imine intermediate **106** which accelerate direct Mannich-type reaction in an enantioselective fashion to afford spirocyclic diketones **104**. It is proposed that the rate of Mannich addition promoted by chiral Brønsted acid **BH-3** is faster than that of the background reaction catalyzed by gold complex and hence **BH-3** served as the real catalyst for the enantio-determining step.



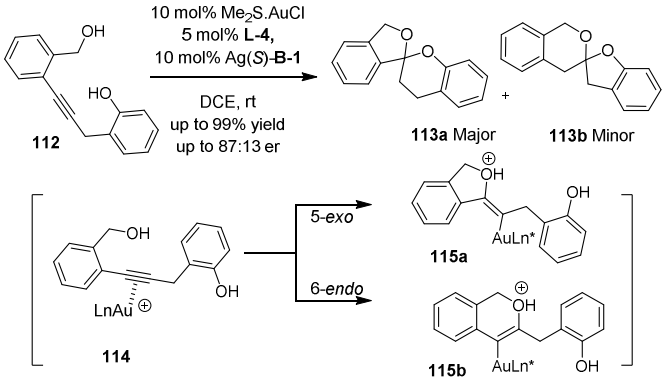
Scheme 25 Gold(I)/chiral Brønsted acid catalyzed redox-pinacol-Mannich cascade reaction

Dixon et al. developed highly enantioselective hydroamination/N-sulfonyliminium cyclization cascade for the synthesis of indole-sulphonamide hybrid scaffolds **108** from **107** under the catalysis of (**L-1**)AuNCMe/**BH-4** (Scheme 26).[42] Mechanistic studies revealed that the reaction proceeds through two sequential and independent steps. The alkynyl sulphonamide **107** undergo Au(I) catalyzed intramolecular hydroamination to obtain the five membered cyclic intermediate **109** which undergo enantioselective cyclization through *N*-sulfonyliminium intermediate **111** to form the enantiopure product **108**. The high enantioselective of the product is expected if the cyclization is triggered by the **BH-4**; the involvement of achiral gold complex would have caused non-enantioselective background reaction.



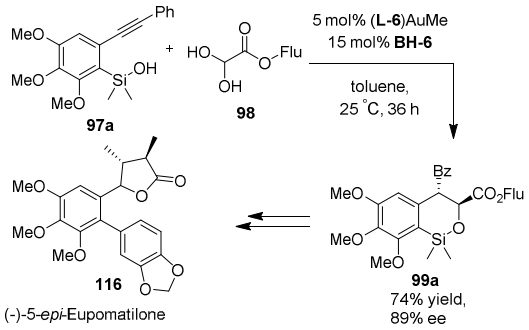
Scheme 26 Gold(I) phosphate catalyzed synthesis of complex sulphonamide scaffolds

Brimble and coworkers developed Au-phosphate (generated in situ from **L-4,** Me_2S.AuCl with Ag(*S*)-**B-1**) catalyzed asymmetric intramolecular formal double hydroalkoxylation approach for the synthesis of spiroacetal ring system **113a-b** from alkyne-diol **112** (Scheme 27).[43] The optimization studies suggested that chiral gold phosphine complex [(**L-4**)AuCl] alone does not induce the chirality, however, with the addition of Ag(*S*)-**B-1** spiroacetals were obtained in good ee's. Among all the chiral ligands and counterions tested only Ag(*S*)-**B-1** in combination with chiral gold phosphine complex [(**L-4**)AuCl] afforded spiroacetals in good yields and excellent ee's. The reaction involve gold catalyzed hydroalkoxylation of **112** *via* 5-*exo*-*dig* cyclization to obtain gold-bound oxonium ion **115a** which is trapped by the tethered phenol to afford **113a**; while, hydroalkoxylation of **112** *via* 6-e*ndo*-*dig* cyclization gives gold-bound oxonium ion **115b** which after cyclization to afford **113b**.



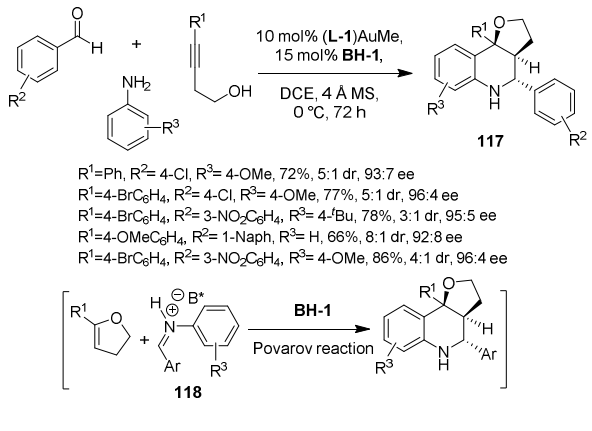
Scheme 27 Gold(I)/chiral Brønsted acid catalyzed asymmetric spirocyclization

Following the earlier report,[39] Wu et al. recently reported the application of enantioselective intramolecular hydrosiloxylation/Mukaiyama aldol reaction cascade for the synthesis of (−)-5-epi-eupomatilone-6 **116** (Scheme 28).[44] For instance, the treatment of 2,3,4-trimethoxy-6-(phenylethynyl)phenyl dimethyl-silanol **97a** with fluorenyl glyoxylate **98** afford the intermediate **99a** under the catalysis of (**L-6**)AuMe/chiral Brønsted acid in 74% yield with 89% ee. The intermediate, thus obtained, was converted into (−)-5-epi-eupomatilone-6 **116** via conventional methods. This is the first report which shows that merging gold catalysis with Brønsted acid catalysis technique might be useful for the enantioselective total synthesis of natural products and their analogues.



Scheme 28 Synthesis of (−)-5-epi-eupomatilone-6

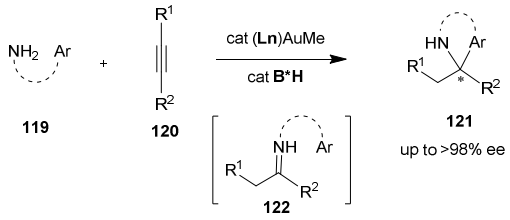
Fañanas, Rodríguez and coworkers reported the use of gold(I)/chiral Brønsted acid binary catalytic system for three component coupling reaction between alkynols, aldehydes and aryl amines for the diastereo- and enantioselective synthesis of hexahydrofuro-[3,2-c]quinolines **117** (Scheme 29).[45] The reaction initiates through the gold phosphate (generated in situ from (**L-1**)AuMe and **BH-1**) catalyzed intramolecular hydroalkoxylation of alkynol to generate cyclic enol ethers. The enol ether would then react with imines **118**, generated in situ by the condensation of aldehydes with anilines, under the catalysis of chiral Brønsted to afford desired quinoline derivatives **117**. Overall, the role of gold phosphate is to catalyze the hydroalkoxylation reaction while the function of chiral Brønsted acid is to affect enantioselective Povarov reaction. The computational studies of the Povarov reaction revealed the important role of chiral Brønsted acid catalyst **BH-1** in decreasing the activation energy of the process.



Scheme 29 Gold(I)/chiral Brønsted acid catalyzed enantioselective synthesis of hexahydrofuro-[3,2-c]quinolines

We recently discovered the catalytic enantioselective hydroamination-hydroarylation of alkynes using binary catalyst system involving (**Ln**)AuMe and **B*H** (cf. **122**). The method turned out to be very general with respect to aminoaromatics; thus, providing

access to optically active fused heterocyclic scaffolds bearing chiral quaternary carbon centre (Scheme 30) in ee's up to 99%.[46]



Scheme 30 Gold(I)/chiral Brønsted acid catalyzed enantioselective hydroamination-hydroarylation of alkynes

2 Summary and Outlook

The examples presented in this review demonstrates that merging Au(I) catalysis with Brønsted acid catalysis have evolved as a powerful technique for achieving enantioselective transformations that are triggered by the activation of C-C multiple bonds. The technique appears to be a powerful synthetic tool for accessing enantio-pure organic molecules starting from relatively simple substrates. The concept demonstrates the power of exploring the complementary advantages of gold(I) and chiral Brønsted acid catalysis to access structures or activation modes where the products obtained are not accessible by using one of the catalysts alone. Since there exist a possibility of using either of the catalyst chiral and/or both catalysts chiral, the options are more to make the reactions enantioselective. This is very appealing for Au(I) catalysis, given the inherent difficulties of transferring chiral information from a ligand disposed 180° from the substrate.

Essential for the success of the reaction is the role of gold phosphate (**Ln**)AuB, generated in situ (or prepared separately) from (**Ln**)AuMe and Brønsted Acid (B-H). In certain cases, the counter-ion has been shown to play a major role in controlling the reactivity and enantioselectivity of the process and this observation suggests that counter-ion engineering may offer further opportunities for the development of novel reactions. In metal catalysis, the synergism between chiral ligand and chiral counterion to control the stereoselectivity has been relatively established; however, this phenomenon has rarely been reported for Au(I)-catalysis.[13] It is hoped that this review will provide sufficient foundation for the development of aforementioned unexplored areas. It is author's belief that the significant progress in the field of cyclization triggered by the catalytic hydroamination of alkynes[47] is anticipated as the organic transformations based on the activation of imines with chiral Brønsted acids are well documented.8 The inference can therefore be drawn that the potential exploration of merged gold/Brønsted acids catalysis has just begun and will continue to gain momentum over the coming years.

3 Acknowledgements

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Suleman M. Inamdar received his M.Sc. degree in organic chemistry from University of Pune in 2001. He joined CSIR-NCL Pune as a Project assistant and worked for about two years. Later, in May 2004, he moved to Aditya Birla Science & Technology Centre, Mumbai and worked for about five years in R & D division as a Sr. Research Associate. In 2009, He has joined for his Ph. D. programme at CSIR-NCL, Pune. After completion of his Ph. D degree, he joined Dr. Nitin T. Patil's as a research associate. His research interests are focused on the development of new organic transformation based on π-acid catalysis.

Ashok Konala was born in 1985 in a small town Ramachandrapuram near to Visakhapatnam, India. After obtaining his B.Sc. degree in 2005 from V.S.M. College, Ramachandrapuram, he moved to GITAM College, Visakhapatnam, where he completed his masters with a specialization in organic chemistry in 2007. Later in 2008, he joined Dr. Nitin T. Patil research group for his doctoral studies. His research interests are focused on the development of new and useful synthetic methodologies based on the design of novel chiral Brønsted acid catalysts as well as the utilization of transition metal catalysts.

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