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Enantioselective merged gold/organocatalysis

Chayanika Pegu,† Bidisha Paroi† and Nitin T. Patil *

Gold complexes, because of their unique carbophilic nature, have evolved as efficient catalysts for catalyzing various functionalization reactions of C–C multiple bonds. However, the realization of enantioselective transformations *via* gold catalysis remains challenging due to the geometrical constraints and coordination behaviors of gold complexes. In this context, merged gold/organocatalysis has emerged as one of the intriguing strategies to achieve enantioselective transformations which could not be possible by using a single catalytic system. Historically, in 2009, this field started with the merging of gold with axially chiral Brønsted acids and chiral amines to achieve enantioselective transformations. Since then, based on the unique reactivity profiles offered by each catalyst, several reports utilizing gold in conjunction with various chiral organocatalysts such as amines, Brønsted acids, N-heterocyclic carbenes, hydrogen-bonding and phosphine catalysts have been documented in the literature. This article demonstrates an up-to-date development in this field, especially focusing on the mechanistic interplay of gold catalysts with chiral organocatalysts.

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1. General introduction

The development of asymmetric catalysis to synthesize highly enantiopure compounds has been regarded as one of the sought-after research topics.[1] Substantial progress in the field of asymmetric synthesis has been accomplished by relying on transition metal catalysis[2] and organocatalysis.[3] Besides these conventional approaches, the concept of dual catalysis has garnered remarkable attention as an innovative tool for developing a diverse array of enantioselective transformations.[4] The foundation for dual catalysis has been laid based on the utilization of two catalysts in one-pot, working in synchronization to enable a single synthetic transformation. In this regard, several dual catalytic systems merging metal–metal,[5] organo–organo[6] and metal–organocatalysts[7] have been devised to achieve unique molecular scaffolds with excellent levels of chemo-, regio- and stereoselectivity. Among these merged catalytic systems, the strategy involving the combination of transition metals and chiral organocatalysts has been enormously applied in the realm of asymmetric organic synthesis.[7]

Gold catalysts have gained considerable interest owing to their unique π affinity for carbon–carbon multiple bonds. Leveraging the carbophilic mode of activation, a variety of reactions have been achieved under gold catalysis.[8] Primarily,

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these transformations are based on the π–complexation of gold to the C–C multiple bonds which then triggers the nucleophilic attack followed by protodeauration. Capitalizing on this carbophilic character of gold, significant efforts have been directed towards the advancement of enantioselective gold catalysis (Scheme 1a).[9] However, most of the developed strategies rely on the employment of chiral Au(I) complexes. The main challenge encountered in achieving enantiocontrol originates from the remote placement of the chiral ligand from the reaction site at the Au(I) center. As a result, imparting high enantioinduction to Au(I) catalysis usually requires (a) bulky dinuclear species;[9j] (b) mononuclear gold(I) complexes having bulky chiral ligands or helical ligands[9f,9k] and (c) chiral counterions.[10] Additionally, other enantioinducting modes involving chiral Au(III) catalysis[9k] and Au(I)/Au(III) redox catalysis[9k,11] have been developed to realize asymmetric transformations. In the ongoing pursuit of advancing asymmetric gold catalysis, the scientific community has successfully utilized the well-established concept of metal-based dual catalysis (bimetallic and metal-organocatalysis) as a powerful tool for achieving numerous enantioselective reactions.

The prospect of merging gold with organocatalysis has evolved as a promising strategy to induce enantioselectivity in gold-catalyzed asymmetric transformations (Scheme 1b). This is mainly because of the advantages, such as: (a) utilization of the complementary reactivities offered by gold and organocatalysts depending on the chemoselective activation of specific functional groups; (b) access to different reactivities and selectivities which are not possible to achieve by either of the catalysts alone. However, this strategy is associated with some challenges, such as: (a) catalyst inhibition due to undesired coordination between gold and organocatalysts; (b) synchronization between the two catalytic cycles to avoid mismatch in the individual kinetic rates of both cycles. In addition, another significant challenge lies in the identification of the reaction conditions essential for both catalysts to work in a synergistic fashion. Despite these difficulties, owing to the complementary reactivities of gold and organocatalysts, several enantioselective transformations have been reported over the years. The origin of this field can be traced back to the utilization of gold with chiral Brønsted acids and amine in the reports from the groups of Dixon,[12] Gong,[13] Che,[14] Krause and Alexakis[15] in 2009. Following these reports, a diverse array of chiral organocatalysts including amine, Brønsted acid, N-heterocyclic carbene (NHC), hydrogen-bonding and phosphine catalysts have been successfully applied in combination with gold catalysts.

As a part of our continuous research interest in the field of gold catalysis, we endeavored to provide an authoritative review on merged gold/organocatalysis. Reviews addressing the advancements in this concept have already been summarized a long back.[16] However, significant progress achieved in the subsequent period has prompted a need for an up-to-date compilation of the reports in this field. Herein, we report an overview focusing on the state of the art in the field of enantioselective merged gold/organocatalysis. It should be noted that the reports regarding the combination of gold catalysis with enzyme catalysis[17] remains out of the scope of our discussion. For a better understanding of the operating catalytic modes, the transformations are discussed based on our previous proposition on sequential, relay and cooperative catalysis (Scheme 1c).[18] This article has been categorized into five sections, according to the type of chiral organocatalysts employed, which are as follows:

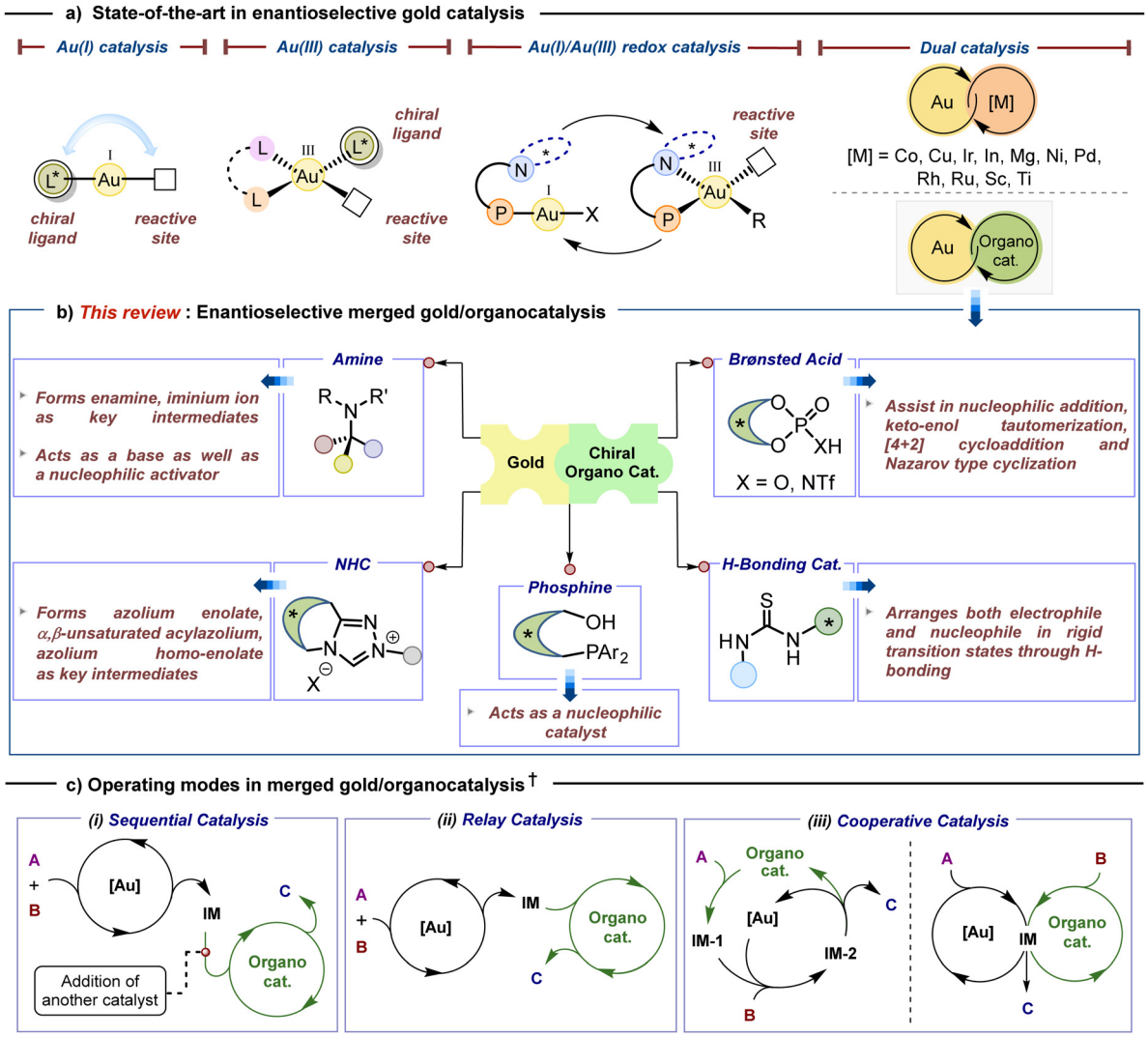
(1) Enantioselective merged gold/amine catalysis.
2) Enantioselective merged gold/Brønsted acid catalysis.
(3) Enantioselective merged gold/NHC catalysis.
4) Enantioselective merged gold/H-bonding catalysis.
(5) Enantioselective merged gold/phosphine catalysis.

2.1. Enantioselective merged gold/amine catalysis

In 2009, Krause, Alexakis and co-workers reported the merging of gold catalysis with chiral amine catalysis to carry out sequential Michael addition and acetalization/cyclization (Scheme 2).[15] At first, isovaleraldehyde **2b** undergoes Michael addition with nitroenyne **2a** in the presence of chiral pyrrolidine **2c** to deliver aldehyde **2d** with excellent diastereoselectivity (up to 97 : 3 dr for *syn* : *anti*) and enantioselectivity (up to >99% ee). After the completion of Michael addition, aldehyde **2d** undergoes gold-catalyzed tandem acetalization/cyclization in the presence of alcohol to furnish tetrahydrofuranyl ether **2e** (77–86% yield and up to 93 : 7 dr for *cis*/*trans*). Mechanistically, the cationic Au(I) complex would coordinate with the oxygen atom of aldehyde **2d** (cf. **2f**), thereby promoting the nucleophilic attack of an alcohol to form a hemiacetal intermediate **2g**. A subsequent oxyauration (cf. **2h**) generates a vinyl gold intermediate **2i**, which upon protodeauration forms **2e**. The authors mentioned that *p*-TsOH is required to prevent the quenching of the gold catalyst

Nitin T. Patil

Nitin T. Patil was born in Jalgaon (Maharashtra), India, in 1975. He completed his doctoral studies at the University of Pune in 2002 under the supervision of Prof. Dilip D. Dhavale. Subsequently, he joined Prof. Christoph Schneider's group as a postdoctoral fellow at the University of Goettingen, Germany. In November 2002, he moved to Tohoku University, Japan, as a JSPS postdoctoral fellow to work with Prof. Yoshinori Yamamoto, where later on he was appointed as an Assistant Professor. In June 2006, he joined Prof. K. C. Nicolaou's laboratory at ICES, Singapore, and later moved to The Scripps Research Institute, USA. He began his independent career in September 2008 at CSIR-IICT, Hyderabad, and subsequently moved to CSIR-NCL, Pune, in August 2013. In July 2017, he joined IISER Bhopal as an Associate Professor and he attained the rank of Professor in October 2023. His research group focuses on understanding the unique reactivities of gold complexes and their utilization in developing organic transformations.



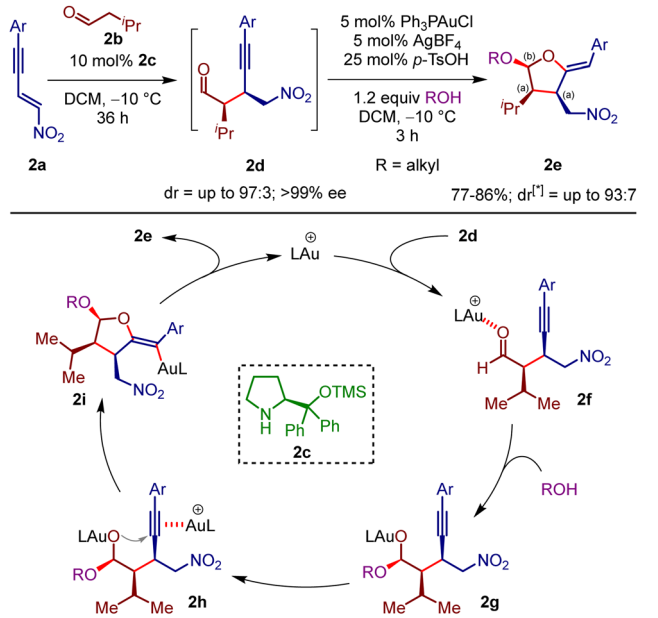
Scheme 1 (a) State of the art in enantioselective gold catalysis; (b) this review: enantioselective merged gold/organocatalysis; and (c) schematic representation of sequential, relay and cooperative modes of catalysis. † The catalytic sequence can be reversed.

by amine **2c** but using in excess (100 mol%) leads to epimerization of **2d** giving an *anti*-adduct. Usage of *p*-TsOH in slight excess (25 mol%), relative to 10 mol% **2c**, slows down the epimerization as compared to acetalization, providing the optimal result.

In 2010, Jørgensen and co-workers demonstrated the carbocyclization of enals **3a** with alkyne-tethered malononitrile **3b**, with high enantioselectivity (ee up to 96%), by exploiting mutual cooperativity of Ph_3AuNTf_2 and chiral pyrrolidine amine **3j** (Scheme 3).[19] The proposed mechanism involves the initial activation of enal **3a** by chiral pyrrolidine **3j** to deliver the corresponding iminium ion **3d** which then undergoes a nucleophilic attack from **3b**, forming **3e**. Subsequently, the alkyne activation by gold in **3e** initiates the nucleophilic attack from tethered enamine, leading to the 5-*exo-dig* cyclization. The generated vinyl gold intermediate **3g** produces the iminium ion **3h** *via* protodeauration which then undergoes hydrolysis followed by isomerization to furnish α,β-unsaturated cyclopentene carbaldehyde **3c**. This dual catalytic cascade protocol can be also achievable under Cu(I) and Cu(II) catalysis but such catalytic systems suffer from the disadvantages of requiring additional phosphine and an inert atmosphere, unlike gold catalysis.

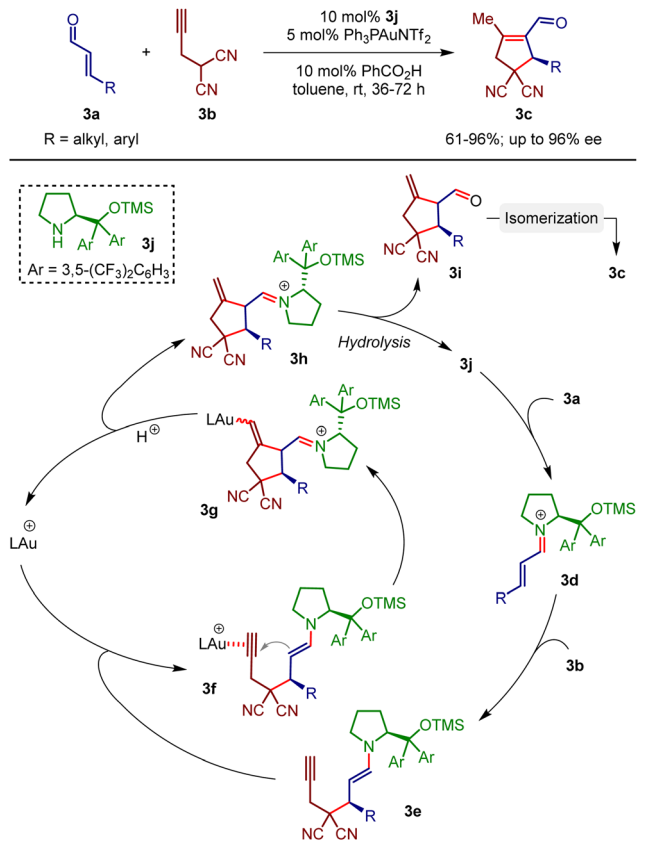
In 2012, Dixon and co-workers documented a sequential catalysis protocol utilizing the combination of Takemoto's catalyst **4d** and Echavarren's gold(I) catalyst.[20] A diastereo- and enantioselective synthesis of tetrahydropyridine derivatives **4c** *via* a nitro-Mannich/hydroamination reaction sequence between *N*-protected aldimines **4a** and nitro-alkynes **4b** has been achieved in 96% ee (Scheme 4a). At first, the nitro-Mannich reaction between **4a** and **4b** under chiral amine (**4d**) catalysis delivers chiral β-nitroamine **4e**. In the subsequent reaction, Au(I) catalyzes the intramolecular hydroamination of **4e**, resulting in 6-*exo-dig* cyclization (cf. **4f**). The generated vinyl gold intermediate **4g** on protodeauration followed by isomerization gives **4c**. After the completion of the first reaction, DPP was added to prevent the quenching of the subsequent gold catalysis process.

Later, in 2014, the same group utilized the above-mentioned sequential strategy involving a chiral amine **4d** catalyzed

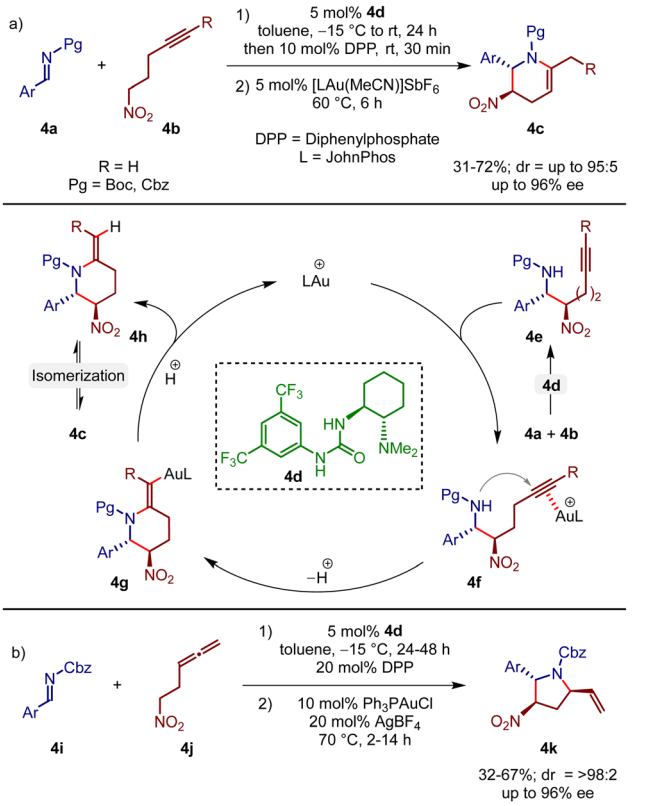


Scheme 2 Gold/chiral amine-catalyzed enantioselective Michael addition and tandem acetalization/cyclization. [*] dr value corresponds to the *cis*/*trans* relationship between the stereogenic centers labeled as (a) and (b).

asymmetric nitro-Mannich reaction followed by gold-catalyzed hydroamination to afford trisubstituted pyrrolidine derivatives



Scheme 3 Gold/chiral amine-catalyzed enantioselective carbocyclization of α,β-unsaturated aldehydes with propargylated malononitrile.

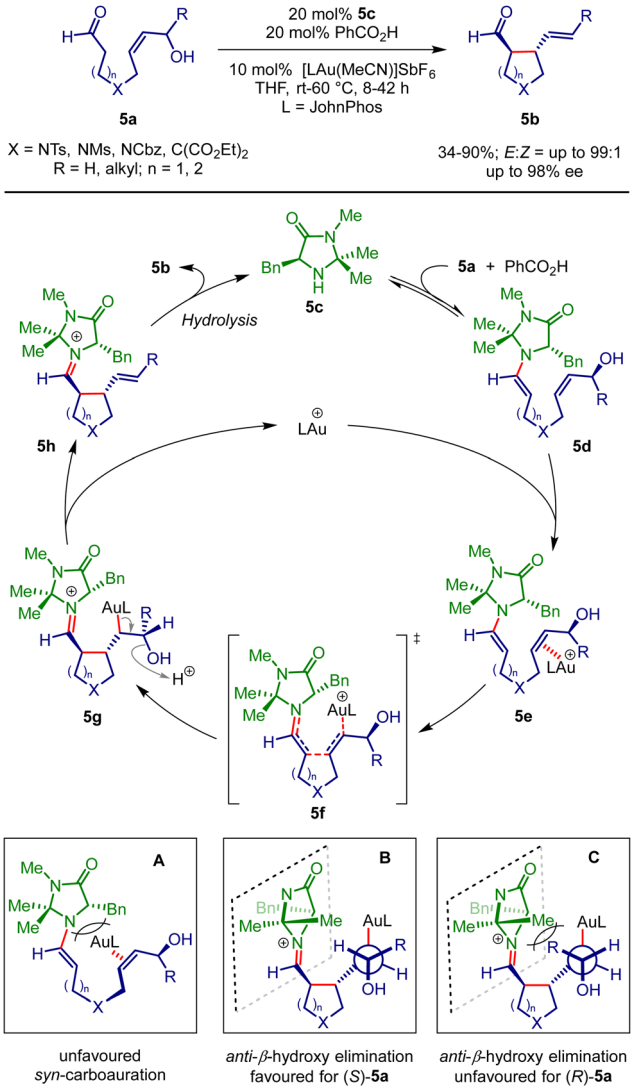


Scheme 4 Gold/chiral amine-catalyzed enantioselective nitro-Mannich/hydroamination cascade reaction.

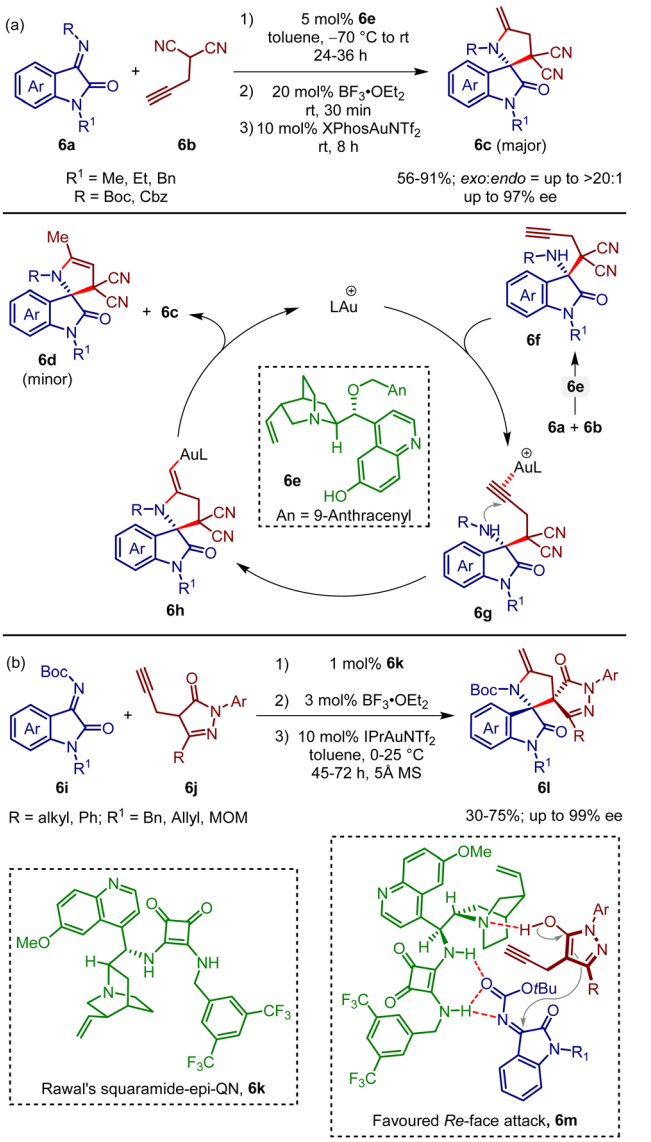
4k in 96% ee from *N*-Cbz protected aldimines **4i** and nitroallene **4j** (Scheme 4b).[21]

In 2012, Bandini and co-workers developed a cooperative catalytic system by merging [JhonPhosAu(MeCN)]SbF_6 with chiral imidazolidinone **5c** to perform enantioselective intramolecular α-allylic alkylation of enolizable aldehydes **5a** with allyl alcohols (Scheme 5).[22] In this reaction, five or six-membered cyclic aldehydes **5b** are obtained in dr up to 99 : 1 *E* : *Z* (*trans*) with excellent enantioselectivities (up to 98% ee). The mechanism was proposed to initiate with the condensation between **5a** and **5c** in the presence of benzoic acid, generating chiral enamine **5d**. For the gold-catalyzed nucleophilic allylic substitution process, a stepwise *anti*/*anti* S_N2'-mechanism was suggested by the authors. The activation of the C–C double bond (cf. **5e**) by the gold complex facilitates the intramolecular nucleophilic attack from chiral enamine, favouring *anti*-carboauration (cf. **5f**) over the sterically more hindered *syn*-carboauration (cf. **A**). Subsequently, the intermediate **5g** undergoes *anti*-β-hydroxy elimination followed by hydrolysis of the resulting iminium ion **5h** to generate **5b**. The authors proposed that in the *anti*-β-hydroxy elimination step, a steric interaction between the methyl substituent of the Re-face of the iminium intermediate and the alkyl group (R) of secondary alcohol determines the *E* : *Z* ratio of the allylic double bond (compare intermediates **B** and **C**).

Later, in 2013, Jiang, Liu and co-workers utilized the combination of the gold complex and chiral amine **6e** to synthesize



Scheme 5 Gold/chiral amine-catalyzed enantioselective intramolecular α-allylic alkylation of aldehydes.

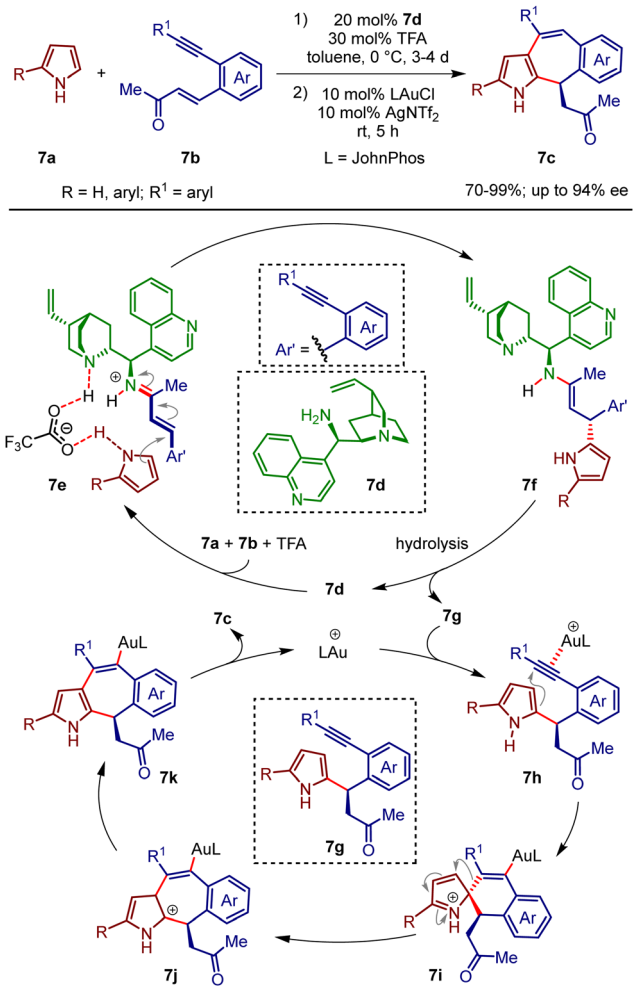


Scheme 6 Gold/chiral amine-catalyzed enantioselective Mannich/hydroamination cascade reaction.

spiro[pyrrolidin-3,2′-oxindole] derivatives **6c** in 56–91% yields with enantiomeric excess up to 97%. The protocol involves a chiral amine-catalyzed Mannich reaction and a subsequent gold-catalyzed intramolecular hydroamination reaction (Scheme 6a).[23] Under the catalysis of chiral *Cinchona* alkaloid **6e**, oxindole imines **6a** reacts with propargylated malononitrile **6b** producing adduct **6f**. Then, $BF_3{\cdot}OEt_2$ was added to quench **6e** prior to the introduction of gold catalysis. Subsequently, Au(I) activates the C–C triple bond in **6f** towards the nucleophilic attack from secondary amine (cf. **6g**). The resulting vinyl gold(I) species **6h** on protodeauration affords *exo* product **6c**.

Along the same line, Vaselý and co-workers in 2021 employed the above-mentioned sequential catalytic system for the enantioselective synthesis of bispiro[oxindole-pyrrolidine-pyrazolones] **6l** (Scheme 6b).[24] During the chiral amine **6k** catalyzed Mannich reaction, the squaramide part of **6k** activates the oxindole imines **6i** through H-bonding with the carbamate group. In addition, the basic quinuclidine moiety of **6k** increases the nucleophilic character of the enol form of the alkyne tethered pyrazolones **6j** (cf. **6m**). The observed enantioselectivity has been attributed to the sterically favourable nucleophilic attack from the activated enol on the Re-face of the imine in the H-bonded transition state. A subsequent gold-catalyzed hydroamination step leads to the construction of **6l** in 99% ee.

Enders' group, in 2014, employed a sequential catalytic system consisting of JohnPhosAuCl and chiral cinchona-alkaloid-derived primary amine **7d**, for the dialkylation of pyrrole at C-2 and C-3 positions (Scheme 7).[25] Pyrroles **7a** and enones **7b** upon treatment with amine **7d** followed by JhonPhosAuCl provide access to an enantiopure seven-membered ring containing 2,3-annulated pyrrole **7c** (up to 94% ee). Mechanistically, the reaction initiates with condensation of **7b** with amine **7d** in the presence of TFA. The generated iminium ion then binds to **7a** *via* H-bonding through



Scheme 7 Merged gold/chiral amine-catalyzed enantioselective C–H functionalization of the C-2 and C-3 positions of pyrroles.

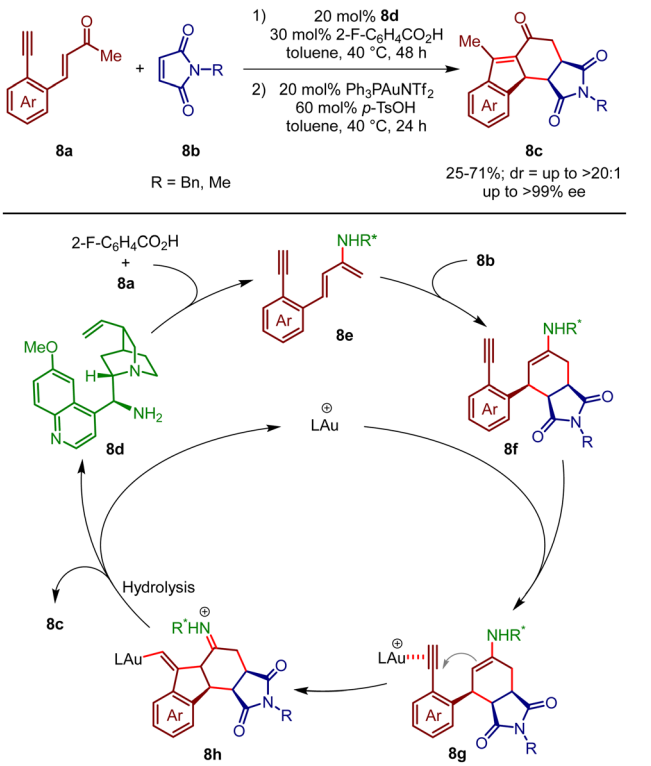
trifluoroacetate from the quinuclidine backbone (cf. **7e**). The nucleophilic attack from the C-2 position of pyrrole on the α,β-unsaturated iminium ion in the rigid H-bonded intermediate **7e** was proposed to determine the enantioselectivity of the reaction. The ensuing enamine **7f** hydrolyzes to form a ketone **7g**. Next, **7g** upon alkyne activation by gold undergoes a nucleophilic attack from the C-2 position of pyrrole, resulting in 6-*endo-dig* cyclization. The resulting non-aromatic spirocycle **7i** then rapidly rearranges to a seven-membered cationic intermediate **7j**, which after rearomatization followed by protodeauration delivers **7c** in 70–99% yields.

In the same year, by taking advantage of the mutual cooperativity of the gold(I) catalyst and Cinchona alkaloid-based amine **8d**, Wu and co-workers reported the asymmetric synthesis of [6,5,6]-carbotricyclic compounds in excellent ee up to >99% and high dr up to >20:1 (Scheme 8).[26] The reaction proceeds with the condensation between alkynylenones **8a** and amine **8d** generating dienamine **8e**, which then undergoes a formal Diels–Alder reaction with maleimide **8b** to furnish enamine **8f**. Next, intermediate **8f** engages in an intramolecular carboannulation reaction under Au(I) catalysis (cf. **8g**), forming a vinyl gold intermediate **8h**. Subsequent hydrolysis and protodeauration of **8h** leads to the generation of **8c**.

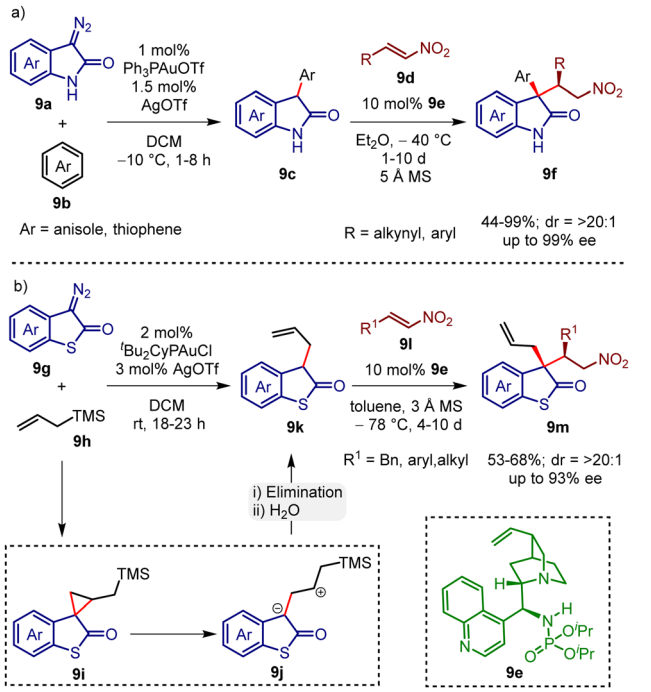
Zhou and co-workers, in 2016, developed a sequential process consisting of Au(I)-catalyzed C–H functionlizaton[27] and a chiral tertiary amine-catalyzed Michael addition reaction (Scheme 9a).[28] In the presence of 1.5 mol% $Ph_3PAuOTf$,[29] diazooxindole **9a** undergoes C–H insertion with the aromatic compounds **9b** to form 3-aryloxindoles **9c**. After the completion of aromatic C–H functionalization, nitroenynes **9d** and chiral amine **9e** were added. The activation of intermediate **9c** through deprotonation by **9e** facilitates Michael addition with **9d** to furnish the quaternary oxindoles **9f** in 44–99% yields with excellent ee (up to 99%).

In 2021, Dong, Wu, Zhou and co-workers combined Au(I)-catalyzed allylation of diazo (thio)oxindoles **9g** with chiral amine-catalyzed Michael addition in a sequential manner (Scheme 9b).[30] The authors hypothesized the mechanism to involve Au(I)-catalyzed cyclopropanation/elimination of **9g** with allyltrimethylsilane **9h** (cf. **9i** and **9j**), delivering 3-allyl (thio)oxindoles **9k**. In the next step, the asymmetric Michael addition of **9k** to nitroolefins **9l** in the presence of amine **9e**, yields chiral 3,3-disubstituted (thio)oxindoles **9m** in 93% ee.

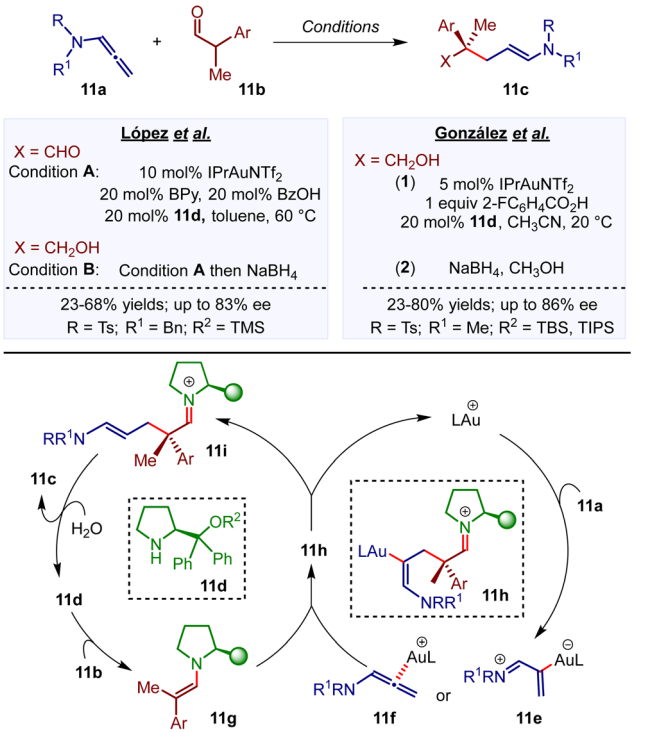
Zhou and co-workers, in 2016, demonstrated a binary catalytic system comprising gold/chiral amine to execute an enantioselective enone formation/cyanosilylation of diazooxindoles **10a** *via* a sequential mode of catalysis. Synthesis of 3-alkenyloxindole-based cyanohydrins **10d** has been achieved in 40–87% yield and up to 96% ee (Scheme 10).[31] **10a** reacts with



Scheme 8 Gold/chiral amine-catalyzed enantioselective Diels–Alder/carboannulation cascade reaction.



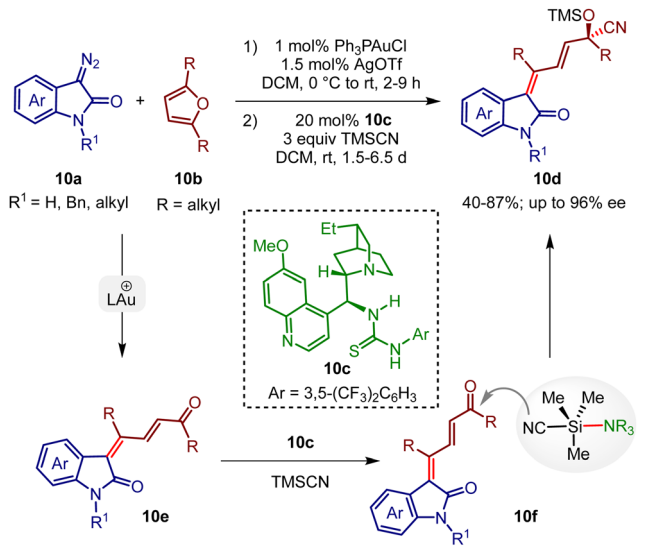
Scheme 9 Gold/chiral amine-catalyzed (a) enantioselective C–H functionalization/Michael addition reaction and (b) enantioselective formal allylation/Michael addition reaction.



Scheme 11 Gold/chiral amine-catalyzed enantioselective intermolecular α-allylation of aldehydes with *N*-allenamides.

furan **10b** in the presence of PPh_3AuCl to produce 3-alkenyl oxindole based enones **10e**. Thereafter, an asymmetric cyanosilylation of **10e** was carried out using TMSCN under the catalysis of amine **10c**, which acts as a nucleophilic activator.

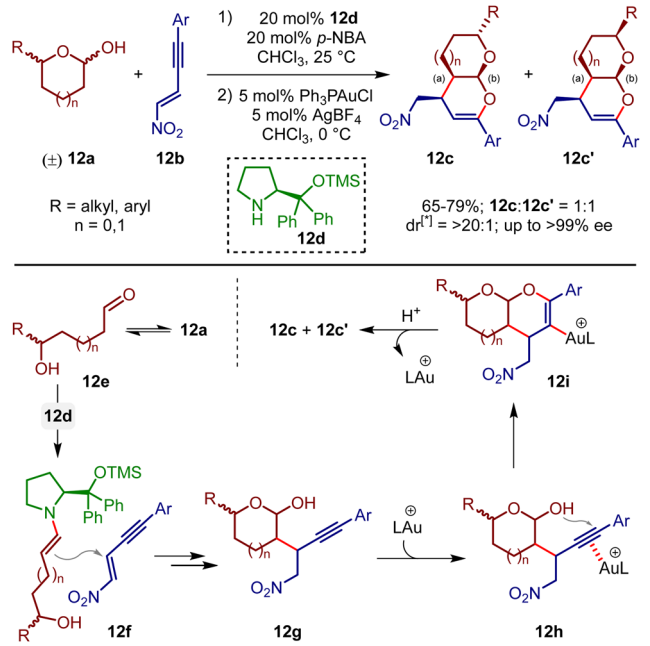
In 2016, the research groups of González and López independently demonstrated the enantioselective intermolecular α-allylation of aldehydes **11b** with *N*-allenamides **11a** under the cooperative catalysis of $IPrAuNTf_2$ and chiral diphenylprolinol silyl ether **11d** (Scheme 11).[32] In the gold(I) catalytic cycle, López and co-workers proposed the formation of a zwitterionic electrophilic species **11e** through the interaction of $IPrAuNTf_2$ and **11a**, while González proposed gold(I)-coordinated *N*-allenamide species **11f** as the key intermediate. Simultaneously, the reaction of **11b** with amine **11d** leads to enamine **11g** which subsequently captures the electrophilic **11e** or **11f**, resulting in the adduct **11h**. The protodeauration of **11h** followed by hydrolysis of the resulting **11i** forms **11c**. Of note, López and co-workers suggested that the presence of BPy (2,2′-bipyridine) can facilitate the decoordination of amine from the gold catalyst.



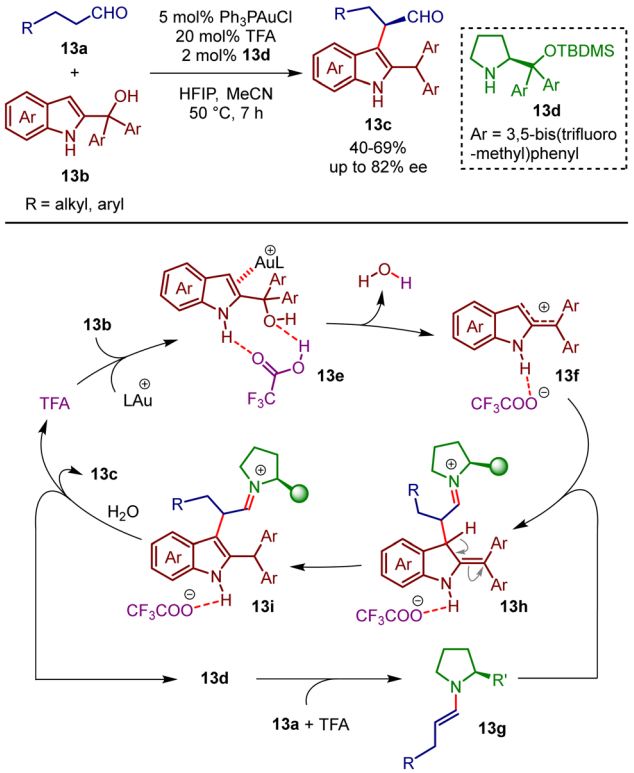
Scheme 10 Gold/chiral amine-catalyzed enantioselective enone formation/cyanosilylation cascade reaction.

In 2017, synthesis of bicyclic (5,6- or 6,6-fused) *O*,*O*-acetals was achieved in 99% ee under a sequential catalysis of gold and chiral diphenylprolinol silyl ether **12d** by the research group of Liu (Scheme 12).[33] The reaction commences with the activation of the racemic lactol **12a** by amine **12d** to form the corresponding enamine. Subsequently, the enamine undergoes a *Si*-face attack to nitroenyne **12b**, resulting in the formation of substituted lactol **12g**. Next, gold-catalyzed oxyauration of **12g** generates a vinyl gold intermediate **12i** which upon protodeauration provides two separable bicyclic acetal epimers **12c** and **12c′** in 65–79% yields with excellent diastereo- and enantioselectivity.

Shi and co-workers, in 2018, demonstrated a cooperative catalytic system comprising of the gold complex and chiral amine **13d** for the enantioselective α-arylation of aldehydes **13a** using 2-indolylmethanols **13b** as an arylating agent (Scheme 13).[34] Chiral α-arylated aldehydes **13c** were synthesized in 40–69% yield and with ee up to 82%. The Au(I) complex activates **13b** by coordinating to the double bond between the



Scheme 12 Gold/chiral amine-catalyzed enantioselective [3 + 3] process leading to bicyclic *O,O*-acetals. [*] dr value corresponds to stereogenic centers labeled as (a) and (b).



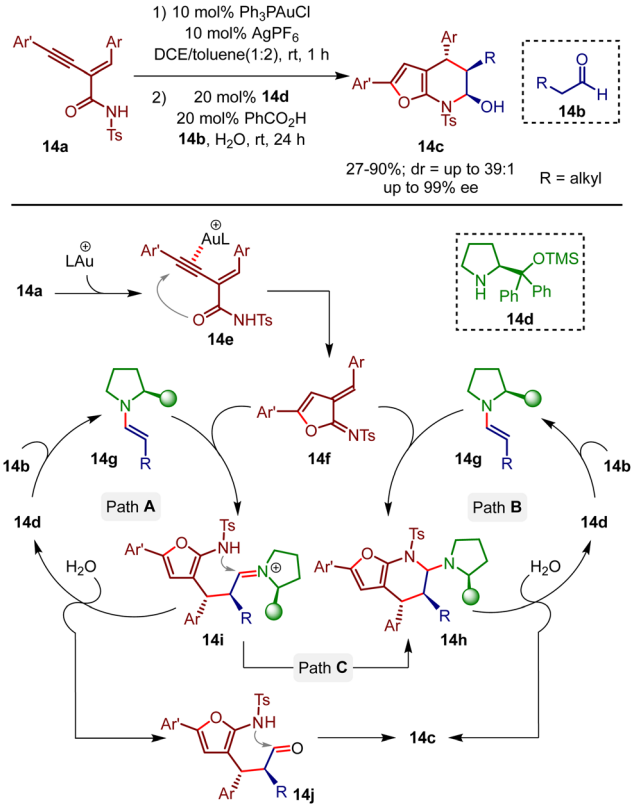
Scheme 13 Gold/chiral amine-catalyzed enantioselective α-arylation of aldehydes.

C-2 and C-3 positions. Such a metal complexation in the presence of TFA (cf. **13e**) promotes the formation of a delocalized carbocation **13f** *via* dehydration. Simultaneously, enamine **13g** was formed from **13a** in the presence of **13d** and TFA. Next, the nucleophilic attack from **13g** on the carbocation **13f** leads to the formation of adduct **13h** which on rearomatization followed by hydrolysis furnishes **13c**.

In 2021, Moreau and co-workers reported an enantioselective gold and chiral diphenylprolinol silyl ether **14d** catalyzed sequential cycloisomerization/cycloaddition strategy to synthesize 4,5,6,7-tetrahydrofuro[2,3-*b*]pyridines **14c** in 99% ee (Scheme 14).[35] The reaction begins with the gold-catalyzed 5-*endo-dig* cycloisomerization (cf. **14e**) of ynamide **14a**, leading to the formation of α,β-unsaturated *N*-sulfonyl ketimine **14f**. In the next step, **14d** undergoes condensation with α-H containing aldehydes **14b**, generating chiral enamine **14g**. At this stage, two plausible mechanisms have been proposed. Path A involves the nucleophilic attack of **14g** on intermediate **14f**, leading to the formation of a conjugate adduct **14i**. Subsequently, **14i** undergoes hydrolysis to generate aldehyde **14j**, followed by the formation of hemiaminal **14c**. In path B, **14f** and **14g** react through an Aza-Diels–Alder reaction, resulting in aminal **14h**, which upon hydrolysis, leads to the formation of **14c**. Furthermore, an alternative path C involves the direct formation of aminal **14h** from **14i**, followed by hydrolysis to yield **14c**.

In the same year, Hu, Xu and co-workers disclosed the gold/chiral amine cooperative catalysis in the asymmetric allylation of isatins **15b** and isatin-derived ketimines **15b′** by using *N*-propargylamides **15a** (Scheme 15).[36] This methodology provides an access to 2,5-disubstituted alkylideneoxazolines (**15e**/**15e′**) in 99% ee, using quinine-derived squaramides (QN-SQA) **15c** and **15d** as chiral amine catalysts. Mechanistically, the reaction commences with *5-endo-dig* cyclization (cf. **15f**) of **15a** under Au(I) catalysis, generating a (*E*)-vinyl gold intermediate **15g**. The authors proposed that **15g** transforms into the key alkyl gold species **15h** through H-shift driven by aromatization. Then, **15h** undergoes a formal hetero-ene reaction with **15b′** under the chiral QN-SQA catalysis, delivering **15e′**. Within the transition state **15i**, QN-SQA **15d** associates with **15b′** through double H-bonding with squaramide hydrogens and simultaneously coordinates to the Au(I) center of **15h** with the *N*-atom of the quinoline part of **15d**. In this transition state, nucleophilic addition occurs preferably to the Re-face of **15b′** which results in high enantioselectivity.

Next, Wennemers and co-workers developed a combination strategy of a gold catalyst with peptide catalysts (H–$_D$Pro–Pro–Glu–NHC$_{12}$H$_{25}$ **16d** and H–$_D$Pro–Pro–Asp–NHC$_{12}$H$_{25}$ **16e**) for enantioselective addition of branched alkyl-aryl and alkoxy-aryl aldehydes (**16a** and **16b**) to allenamides (**16c**) under cooperative mode of catalysis. This protocol affords various γ,δ-enamide aldehydes bearing a fully substituted benzylic stereocenter (**16f** and **16g**) in high ee up to 99% (Scheme 16).[37] The plausible mechanism depicts the formation of an enamine **16h** from **16a** in the presence of the peptide **16d**. **16h** then reacts with an electrophilic allenamide-gold(I) complex **16m**, generated through ligand exchange between Au–DMAP complex **16k** (or Au–TFA complex **16l**) and **16c**. This C–C bond-forming step is proposed to be the stereodetermining step where the reaction at **16m** takes place from the upper, less sterically hindered face



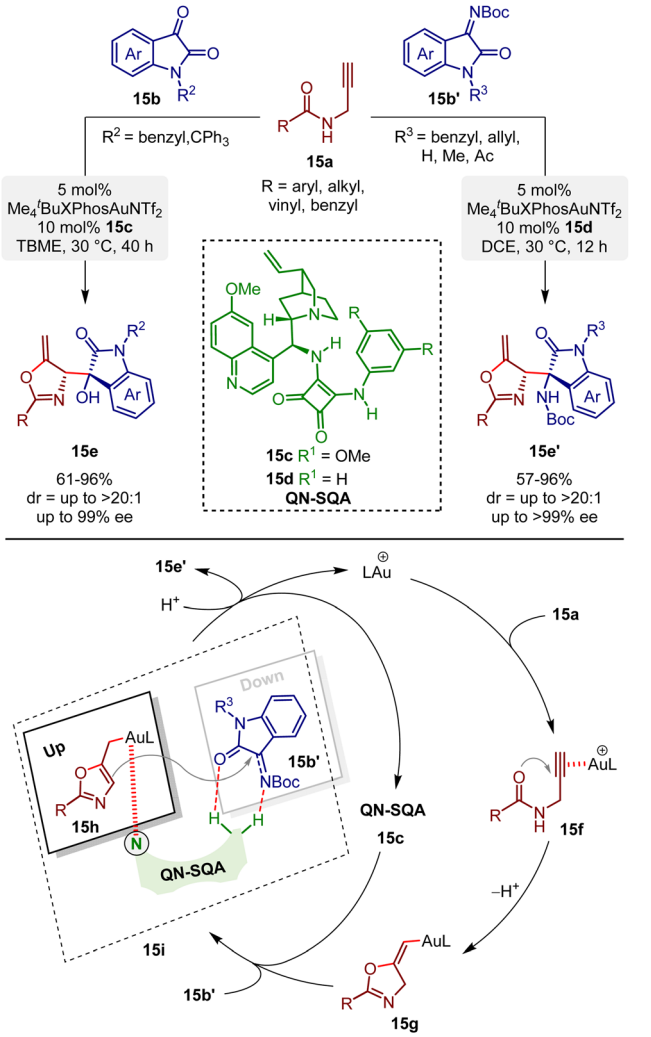
Scheme 14 Gold/chiral amine-catalyzed enantioselective cycloisomerization/cycloaddition reaction to access furan-fused tetrahydropyridines.

of **16h** (cf. **16o**). The resulting vinyl gold iminium **16i** then undergoes protodeauration followed by hydrolysis to furnish **16f**. Balancing the concentrations of DMAP and TFA is crucial for achieving the optimal reaction rate with suppression of undesired side reactions, forming **16n** and other oligomers.

2.2 Enantioselective merged gold/Brønsted acid catalysis

Chiral Brønsted acids (BH) have exhibited remarkable compatibility as an organocatalyst with the gold complexes in expanding the horizon of enantioselective merged gold/organocatalysis. In this regard, a comprehensive review on merged gold/Brønsted acid catalysis has been published by our research group in 2014.[16c] Therefore, this discussion exclusively concentrates on Au(I)/chiral BH-catalyzed enantioselective reactions reported subsequent to that period. Of note, reports regarding the asymmetric counterion directed catalysis (ACDC) *via* the formation of a gold–phosphate complex[10,38] and tethered-counterion directed catalysis (TCDC) where chiral phosphate counterion is covalently tethered to gold *via* a ligand,[39] are beyond the scope of this review.

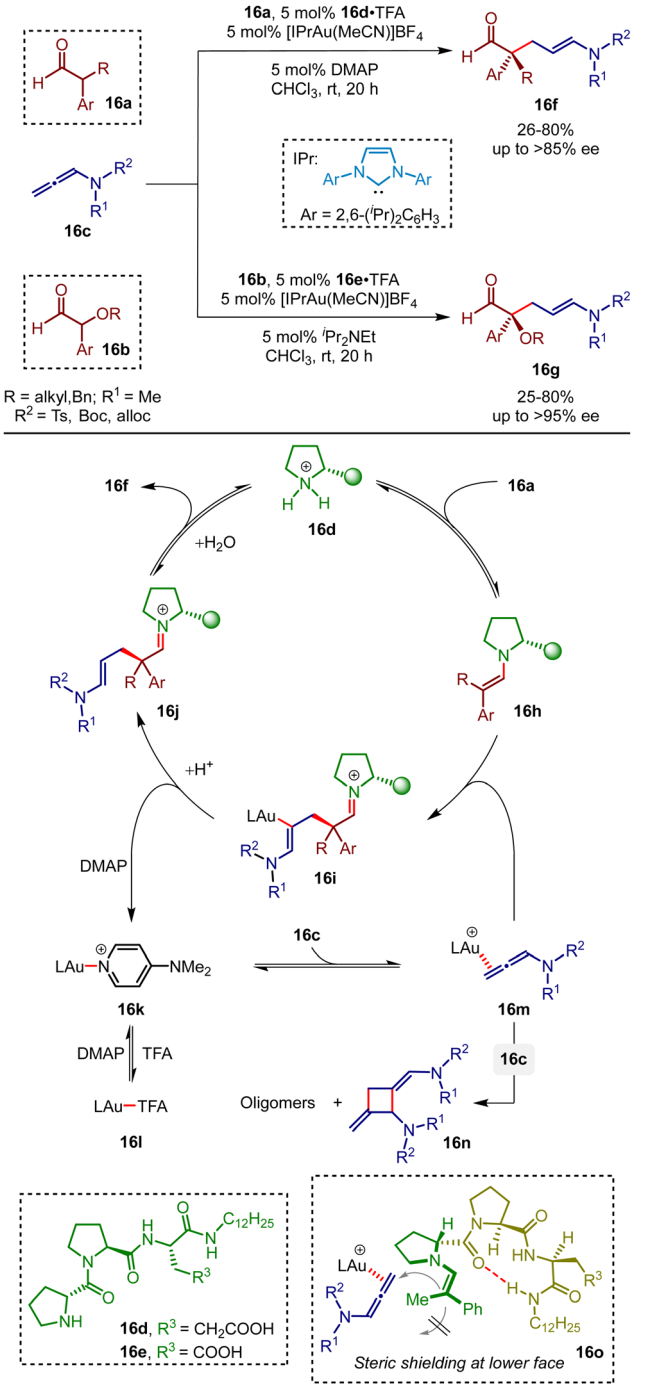
In advancing the field of merged metal/organocatalysis, the group of Gong and co-workers has contributed significantly over the years.[7a,13] In 2014, the authors developed a relay catalytic cascade hydrosiloxylation and asymmetric hetero-Diels–Alder reaction under the binary catalytic system of Au(I) and chiral *N*-triflyl BINOL-based phosphoramide **17d** (Scheme 17).[40] An efficient access to tetrahydrobenzo-pyrano-oxasiline carboxylates **17c** from enynyldiphenylsilanols **17a** and



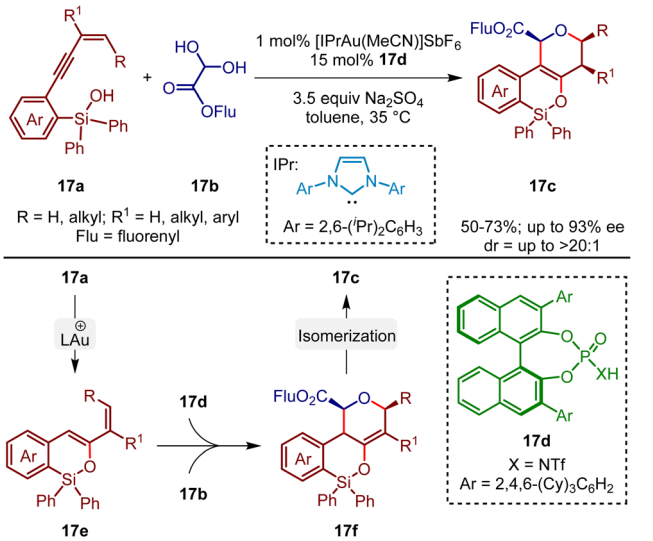
Scheme 15 Gold/chiral amine-catalyzed enantioselective allylation of isatins and isatin-derived ketimines.

fluorenyl glyoxylates **17b** has been achieved with excellent enantiomeric excess up to 93%. Mechanistically, the gold(I) complex triggers an intramolecular hydrosiloxylation of **17a**, generating diene **17e**. Next, under the stereochemical control of **17d**, an oxo-hetero-Diels–Alder reaction of **17e** with **17b** provides intermediate **17f**. Subsequent isomerization leads to the more stabilized conjugated product **17c**.

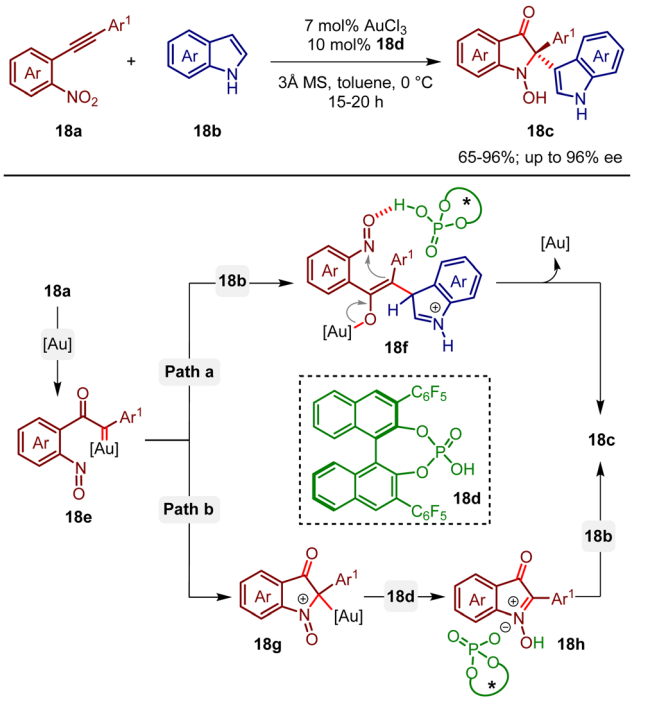
In 2015, Jia and co-workers described an enantioselective redox annulation reaction of nitroalkynes **18a** with indoles **18b** under the cooperative catalysis of gold and chiral phosphoric acid (CPA) **18d** (Scheme 18).[41] This transformation afforded indolin-3-one derivatives **18c** bearing a quaternary stereocenter at the C2 position with high enantiopurity (up to 96% ee). At first, π-activation of **18a** by the gold catalyst promotes an intramolecular nucleophilic attack from the O-atom of the nitro group, yielding α-oxo gold carbenoid intermediate **18e**. Afterwards, two mechanistic possibilities have been proposed for the formation of **18c**. The path **a** showcases the interception of **18e** with **18b**, generating a zwitterionic intermediate **18f**. Subsequent cyclization *via* intramolecular nucleophilic attack from



Scheme 16 Gold/chiral amine-catalyzed enantioselective addition of branched aldehydes to allenamides.



Scheme 17 Gold/chiral Brønsted acid-catalyzed enantioselective hydrosiloxylation/hetero-Diels–Alder cascade reaction.

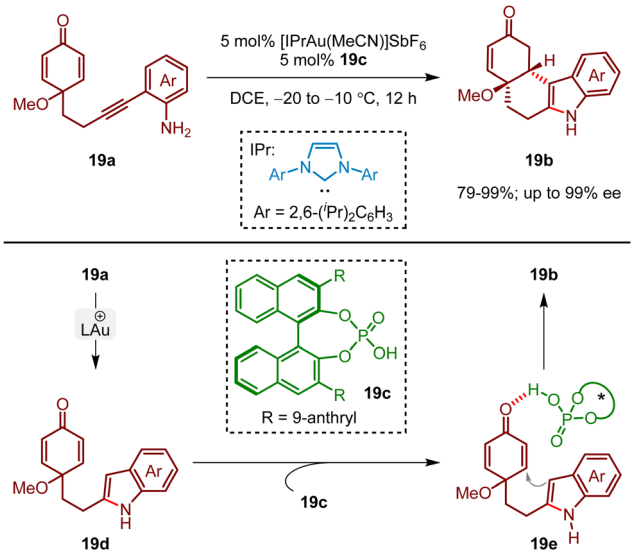


Scheme 18 Gold/chiral Brønsted acid-catalyzed enantioselective redox annulation of nitroalkynes with indoles.

the gold enolate on the nitroso group (cf. **18f**) in the presence of CPA delivers **18c**. Whereas, path **b** depicts an intramolecular trapping of the carbenoid species by the nitroso group resulting in the generation of **18g**. A subsequent protonation of **18g** with CPA **18d**, followed by the attack of **18b** delivers **18c**.

In 2016, Han and co-workers reported a hydroamination/Michael addition cascade under the relay catalysis of a gold complex and chiral Brønsted acid **19c** to afford enantiopure tetrahydrocarbazoles **19b** (Scheme 19).[42] Mechanistically, the reaction proceeds with gold(I)-catalyzed intramolecular hydroamination of 2-ethynylanilines **19a** leading to indole **19d**. Later, **19d** undergoes a CPA-catalyzed asymmetric intramolecular Michael addition reaction, yielding **19b** with excellent enantioselectivity (up to 99% ee).

In 2017, the group of Luo and Gong employed a relay catalytic system consisting of $XPhosAuNTf_2$ and chiral Brønsted acid **20d** for synthesis of γ-keto esters **20c** (Scheme 20).[43] The

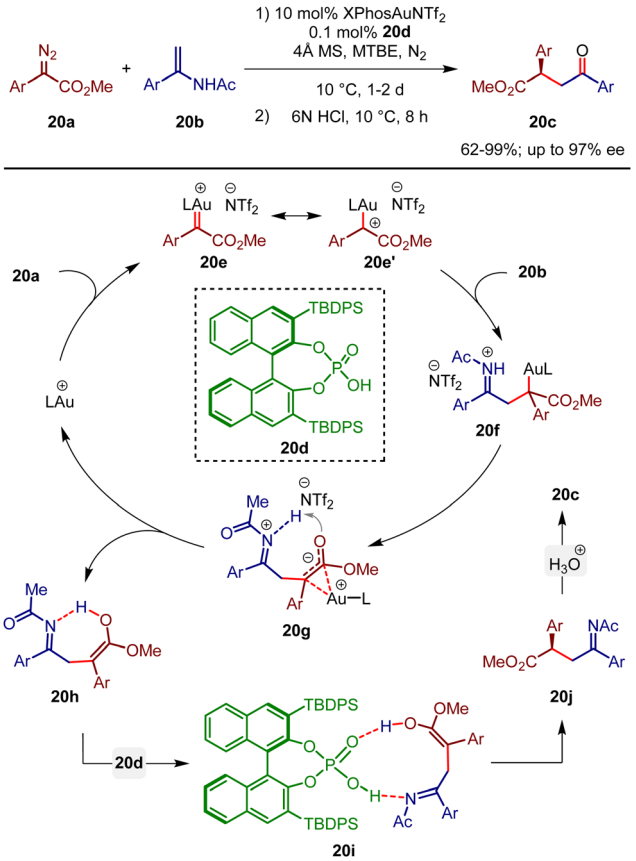


Scheme 19 Gold/chiral Brønsted acid-catalyzed enantioselective synthesis of tetrahydrocarbazoles.

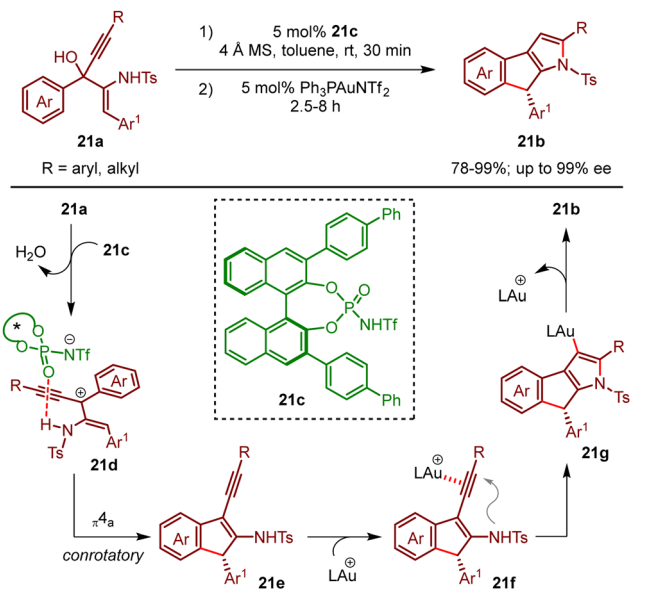
reaction mechanism initiates with the interaction between α-diazoester **20a** and $XPhosAuNTf_2$, leading to the generation of gold carbenoid species (**20e** or **20e′**). The highly electrophilic Au(I) carbenoid then engages in an aza-ene-type reaction with the nucleophilic enamide **20b**, furnishing the adduct **20f.** Next, an intramolecular proton transfer from the iminium functionality within intermediate **20f** results in the formation of an enol species **20h** *via* the gold enolate species **20g.** Subsequent stereoselective protonation of **20h** with CPA **20d** (cf. **20i**) generates imine **20j** which on hydrolysis delivers **20c** with enantiomeric excess up to 97%.

In 2018, Chan and co-workers developed a sequential chiral Brønsted acid-catalyzed dehydrative Nazarov-type electrocyclization (DNE) and gold-catalyzed hydroamination, leading to the synthesis of 1,8-dihydroindeno[2,1-*b*]pyrroles **21b** from β-amino-1,4-enynols **21a** (Scheme 21).[44] At first, chiral *N*-triflyl BINOL-based phosphoramide **21c** results in the dehydration of **21a** with the formation of an ion-pair **21d.** The precise stereochemical environment in **21d**, aided by H-bonding interactions between the amino group and CPA anion facilitates the enantioselective Nazarov-type electrocyclization, generating chiral 1*H*-indene **21e.** Next, under the gold(I) catalysis, **21e** undergoes a 5-*endo-dig* cyclization, forming vinyl gold intermediate **21g** which on protodeauration affords **21b** in 99% ee.

In 2018, Hu, Xu and co-workers developed the cooperative catalysis of gold(I) and chiral phosphoric acid (CPA) to achieve an enantioselective Mannich-type reaction of 3-butynols **22a** and nitrones **22b**, affording dihydrofuran-3-ones **22c** in 96% ee (Scheme 22a).[45] The plausible reaction mechanism involves the gold-catalyzed oxidation of **22a** in the presence of **22b**, resulting in an electrophilic α-oxo gold carbenoid **22f** formation along with the elimination of imine **22g.** Subsequently, an intramolecular attack of the tethered hydroxyl group on gold carbenoid species **22f** generates the gold associated oxonium ylide **22h** or its enolate form **22i.** Next, **22i** undergoes Mannich-type addition with the eliminated **22g** under CPA catalysis to deliver **22c.** The observed high enantioselectivity originates from the



Scheme 20 Gold/chiral Brønsted acid-catalyzed enantioselective aza-ene-type reaction of enamides with α-diazoesters.



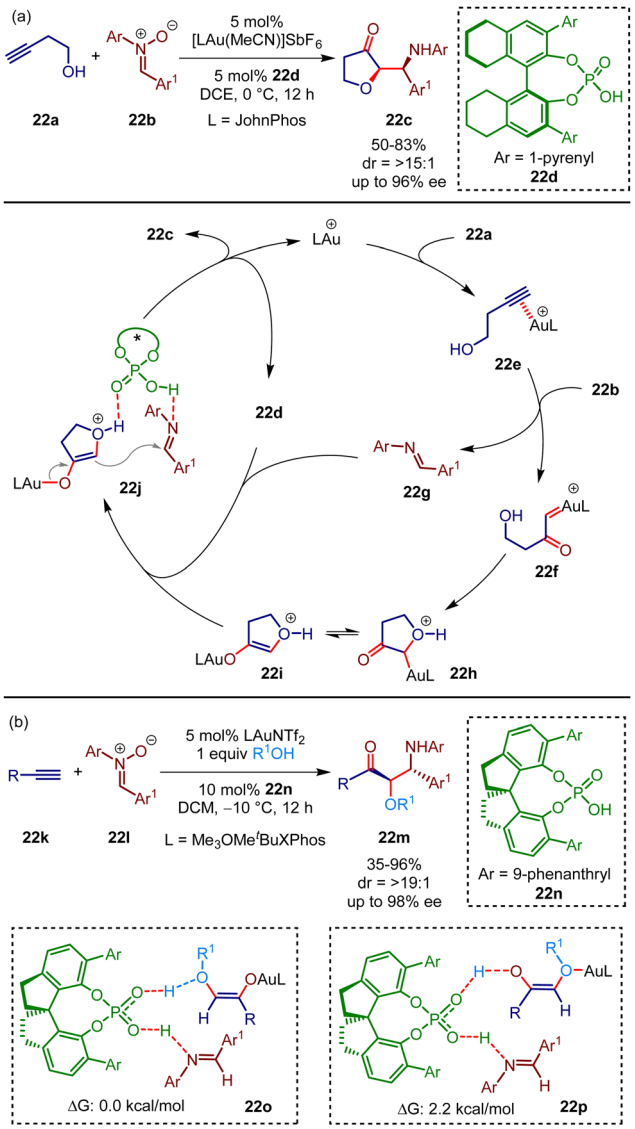
Scheme 21 Gold/chiral Brønsted acid-catalyzed enantioselective dehydrative Nazarov-type electrocyclization/hydroamination reaction.

dual H-bonding of CPA with both reactive species in the Mannich-type addition step (cf. **22j**).

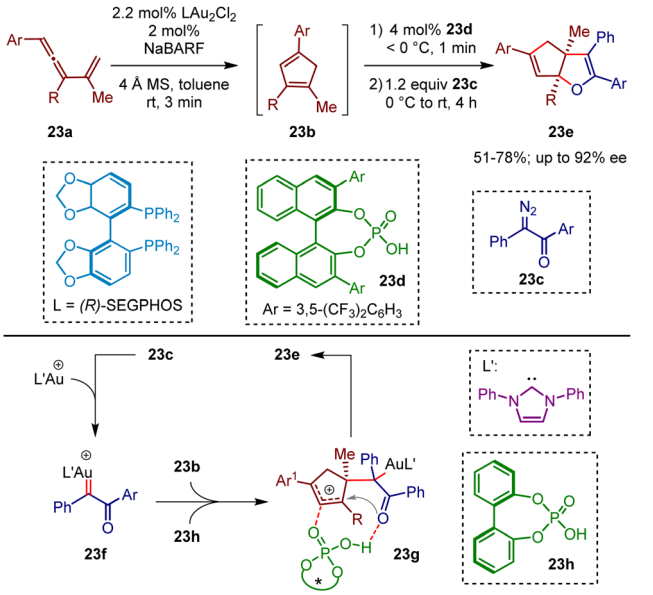
Along the same line, in 2021, the group of Hu, Ke and Xu employed the cooperative catalysis of gold/CPA **22n** to achieve the intermolecular three-component enantioselective multifunctionalization of terminal alkynes **22k** with nitrones **22l** and alcohols (Scheme 22b).[46] Of note, gold catalyzed multicomponent reactions (MCRs) have evolved as an important branch, giving access to different molecular frameworks in a single step.[47] Herein, an alkyne oxidation/ylide formation/Mannich-type addition sequence has been successfully performed, affording α-alkoxy-β-amino-ketones **22m** in 98% ee. A similar mechanistic paradigm as described in Scheme 22a has been proposed for this case as well, only differing in the ylide formation through an intermolecular attack of external alcohol on the α-oxo gold carbenoid. For the gold-associated Mannich-type addition step, the authors proposed two possible intermediates: (a) **22o**, where the gold complex binds to the initial carbonyl oxygen atom, and (b) **22p**, where gold interacts to the ether oxygen atom. DFT calculations suggested the more stable gold enolate species **22o** as the key intermediate involved in the enantioselective C–C bond formation step.

In 2021, Cheng, Liu and co-workers reported the asymmetric [3 + 2]-annulation of tetrasubstituted alkenes **23b** with α-aryl diazoketones **23c** under the cooperative catalysis of gold and chiral Brønsted acid **23d**, affording bicyclic 2,3-dihydrofurans **23e** (Scheme 23).[48] Vinyl-allenes **23a** have been utilized as precursors for **23b** under Au(I) catalysis. Using the L'AuCl catalyst and CPA **23h**, the free energy profile of the reaction has been studied through DFT calculations. Based on DFT calculations, the authors proposed the mechanism to involve the nucleophilic attack from the more substituted alkene of **23b** on the α-oxo gold carbene **23f**, generated from **23c** under Au(I) catalysis. This regioselective attack leads to the generation of gold enolate intermediate **23g** bearing a highly stabilized allylic cation. Next, the CPA associates with both gold enolate and the allylic cation part of **23g** *via* a dual H-bonding interaction. Under this rigid stereochemical environment, a subsequent ring closure affords the [3 + 2]-annulation product **23e** with high enantioselectivity (up to 92% ee).

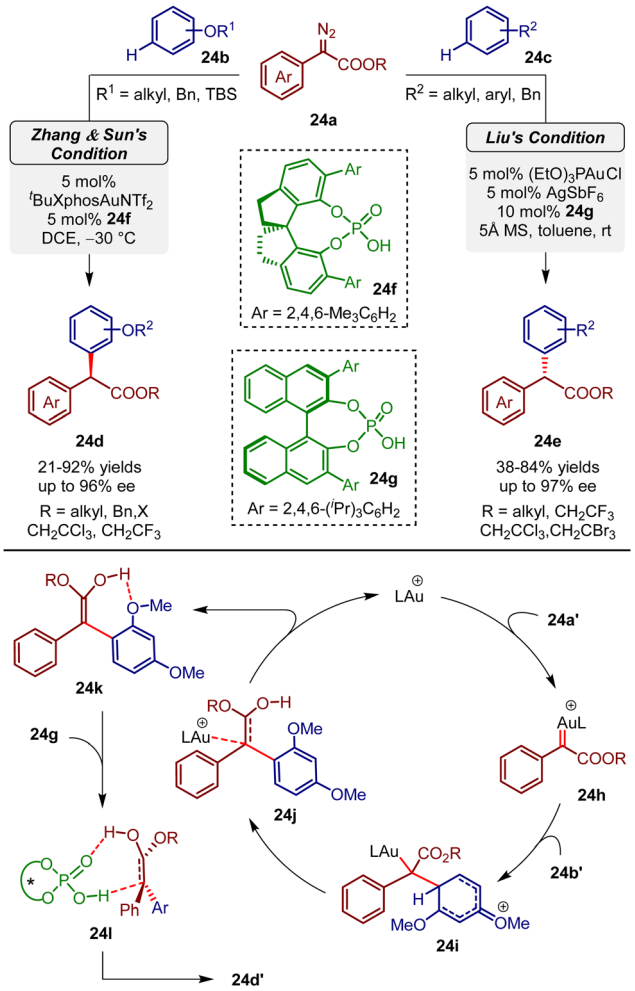
Two research groups, led by Zhang/Sun[49] and by Liu,[50] independently employed gold/chiral Brønsted acid (**24f**/**24g**) relay catalysis for an enantioselective C–H insertion reaction (Scheme 24). The two groups reported the insertion of α-aryl-α-diazoesters **24a** into the *para*-C–H bond of alkyloxy arenes **24b** and alkyl arenes **24c**, affording chiral 1,1-diaryl esters **24d** and **24e**, respectively. As per the proposed reaction mechanism by Zhang and Sun, the electrophilic Au(I) carbene **24h**, generated from the diazoester **24a**′ under gold catalysis, triggers a *para*-C–



Scheme 22 Gold/chiral Brønsted acid-catalyzed enantioselective oxidative cyclization of alkynes/Mannich-type addition cascade.



Scheme 23 Gold/chiral Brønsted acid-catalyzed enantioselective [3 + 2]-annulations of α-aryl diazoketones with cyclopentadienes.



Scheme 24 Gold/chiral Brønsted acid-catalyzed enantioselective *para*-C(sp^2)–H bond functionalization of arenes with α-aryl-α-diazoesters.

H insertion reaction of alkyloxy arene **24b′** to form cation **24i**. Subsequently, **24i** generates *E*- or *Z*-enol species **24k** through an intramolecular proton transfer (cf. **24j**). This step is indicated as the rate-determining step by DFT analysis. The energetically favorable *E*-enol species **24k** (due to the stabilized interaction between hydroxyl and methoxy groups) furnishes **24d′** with high enantioselectivity *via* a CPA assisted proton transfer process (cf. **24l**). Mechanistic investigations performed by Liu's research group also support the similar catalytic cycle.

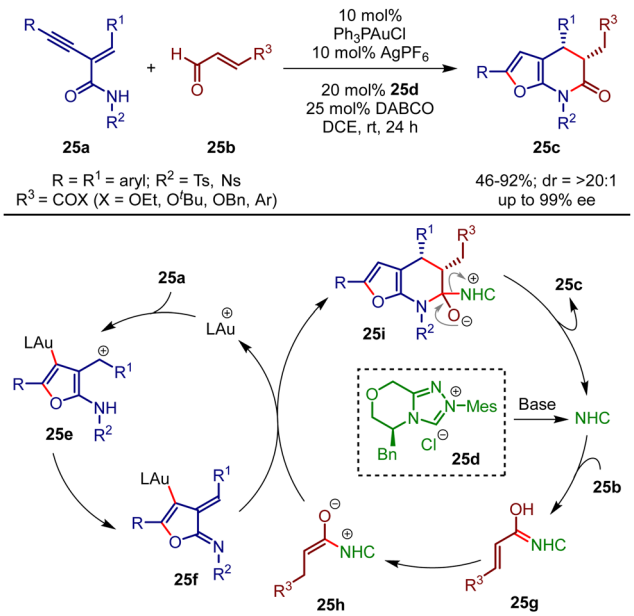
2.3. Enantioselective merged gold/N-heterocyclic carbene catalysis

In the realm of merged gold/organocatalysis, amines and Brønsted acids as organocatalysts have witnessed a significant development for the enantioselective synthesis of a diverse range of organic compounds. In contrast, reports demonstrating merged gold/N-heterocyclic carbene (NHC) catalysis are relatively scarce, probably due to the inherent strong coordinating ability of NHC ligands to gold complexes, causing catalyst inhibition.

In 2020, the first report of merging gold and chiral NHC catalysis in a diastereo- and enantioselective cycloisomerization/azadiene-Diels–Alder reaction was disclosed by the group of Pan and Chi (Scheme 25).[51] Ynamides **25a** and enals **25b** react together in the cooperative catalysis mode of the PPh_3AuCl complex and NHC precatalyst **25d** to generate furan-fused six-membered lactams **25c**. Mechanistically, Au(I) catalyzes 5-*endo*-*dig* cyclization of **25a** through an intramolecular oxyauration, resulting in the formation of vinyl gold intermediate **25e**. Next, an intramolecular proton transfer in **25e** leads to the generation of α,β-unsaturated *N*-sulfonyl ketimine **25f**. Parallelly, **25b** reacts with the active NHC catalyst to generate the Breslow intermediate **25g** which further isomerizes to an azolium enolate intermediate **25h** through a proton transfer process. Finally, the reaction between two key intermediates **25f** and **25h** furnishes **25c** in high enantiomeric excess (up to 99%).

Later, in 2022, Lu and co-workers reported the gold and NHC relay catalysis in the formal [3 + 3] cycloaddition between α-amino-ynones **26a** and enals **26b** to afford enantioenriched pyrrole-fused lactones **26c** (Scheme 26).[52] The proposed mechanism involves gold catalyzed intramolecular hydroamination to generate furyl gold intermediate **26f**. Subsequent protodeauration of **26f** leads to the formation of pyrrolin-4-one **26g**. Chiral NHC reacts with **26b**, generating Breslow intermediate **26i** which on oxidation with DQ (3,3′,5,5′,-tetra-*tert*-butyl-4,4′-diphenoquinone) produces α,β-unsaturated acylazolium **26j**. Next, an enolate **26h**, formed *via* proton abstraction from **26g**, undergoes a conjugate addition to **26j** and a subsequent alkoxide cyclization. The resulting cyclic intermediate **26k** delivers **26c** in 96% ee with the NHC elimination.

Very recently, in 2023, Lv, Zhou and co-workers utilized a relay catalysis strategy involving Au(I)/chiral NHC for the asymmetric synthesis of spirofuro[2,3-*b*]azepine-5,3′-indoline derivatives **27c** from enyne-amides **27a** and isatin-derived enals **27b** (Scheme 27).[53] Mechanistically, the alkynophilic activation (cf.



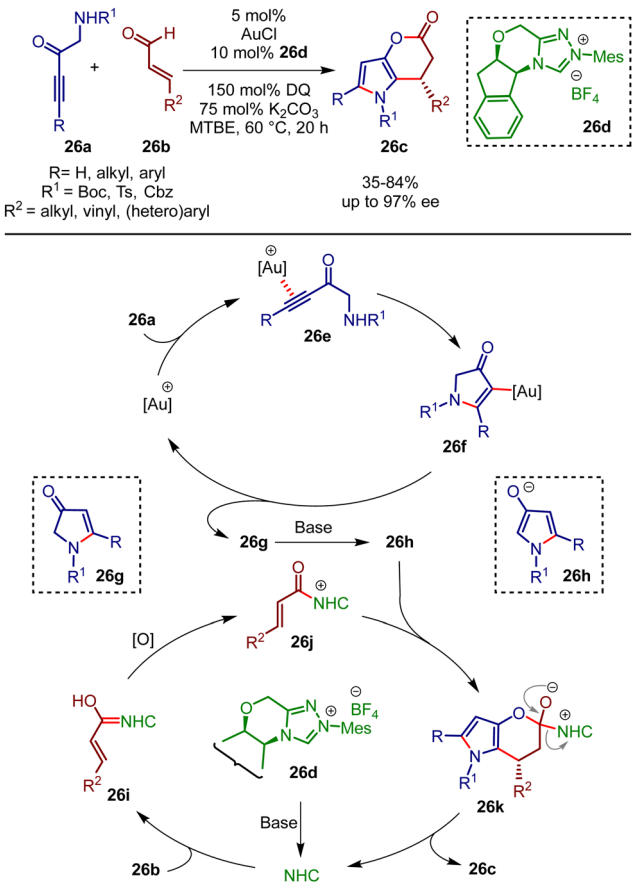
Scheme 25 Gold/chiral NHC-catalyzed enantioselective cycloisomerization/cyclization reaction of ynamides and enals.

27e) by the Au(I) species of **27a** leads to 5-*endo-dig* cyclization, thereby forming a furyl-Au(I) intermediate **27f**. Following this, dihydrofuran-fused azadiene **27g** is generated through an isomerization and protodeauration of **27f**. In another catalytic cycle, the interaction between enal **27b** and chiral NHC produces Breslow intermediate **27h**, which then isomerizes to the azolium homoenolate species **27i**. Next, **27i** undergoes conjugate addition to **27g**, leading to the formation of adduct **27j** which *via* intramolecular *N*-acylation delivers **27c** in 96% ee.

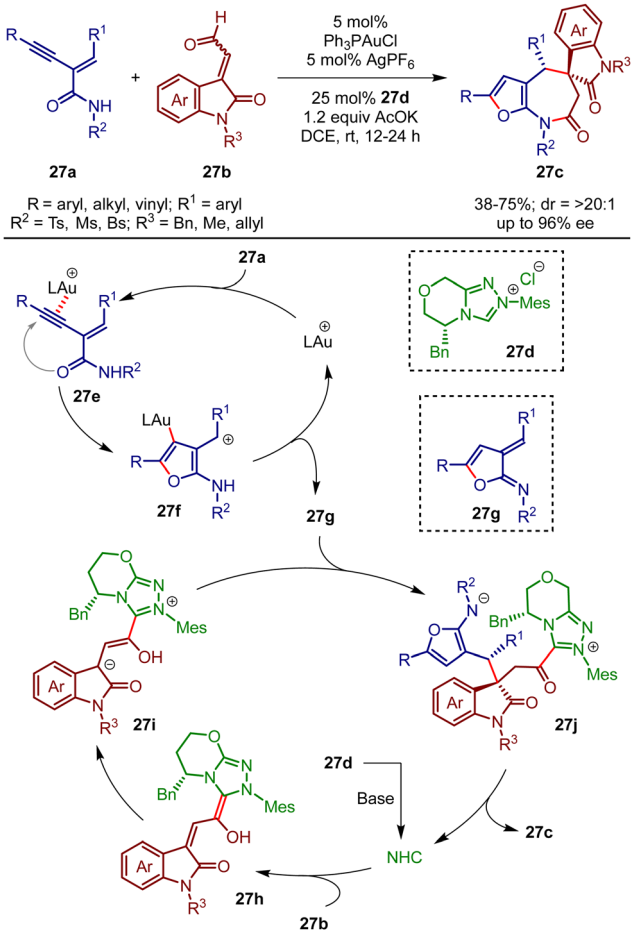
2.4 Enantioselective merged gold/hydrogen-bonding catalysis

In addition to the amine, Brønsted acid and NHC, the merger of hydrogen-bonding catalysis involving chiral bifunctional H-bonding organocatalysts with gold catalysis has appeared as an innovative tool to achieve excellent enantiocontrol. However, this strategy has seen limited development which could be due to their strong coordination tendencies to the gold center leading to catalyst deactivation.

In 2010, Jørgensen and co-workers first reported a one-pot sequential catalysis involving thiourea-based hydrogen-bonding organocatalyst **28d** and $Ph_3PAuNTf_2$. By employing this catalyst combination, 2,3,3,5-tetrasubstituted 2,3-dihydro-1*H*-pyrrole derivatives **28c** were enantioselectively synthesised from *N*-Boc protected imines **28a** and propargylated malononitriles **28b**



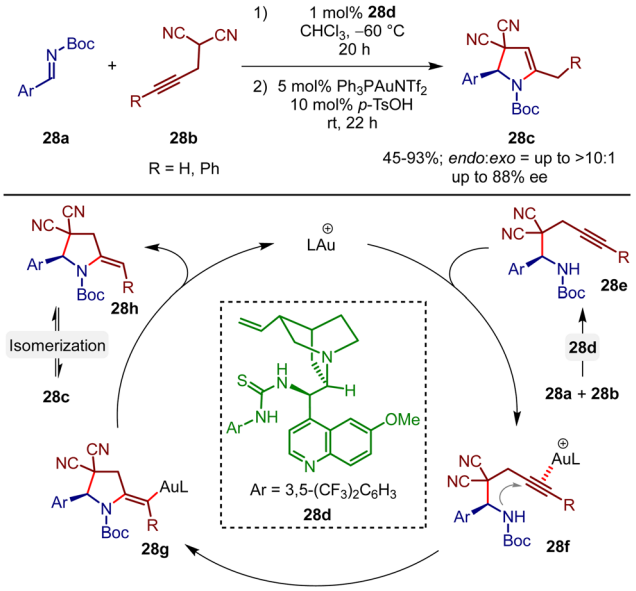
Scheme 26 Gold/chiral NHC-catalyzed enantioselective annulation of α-amino-ynones and enals.



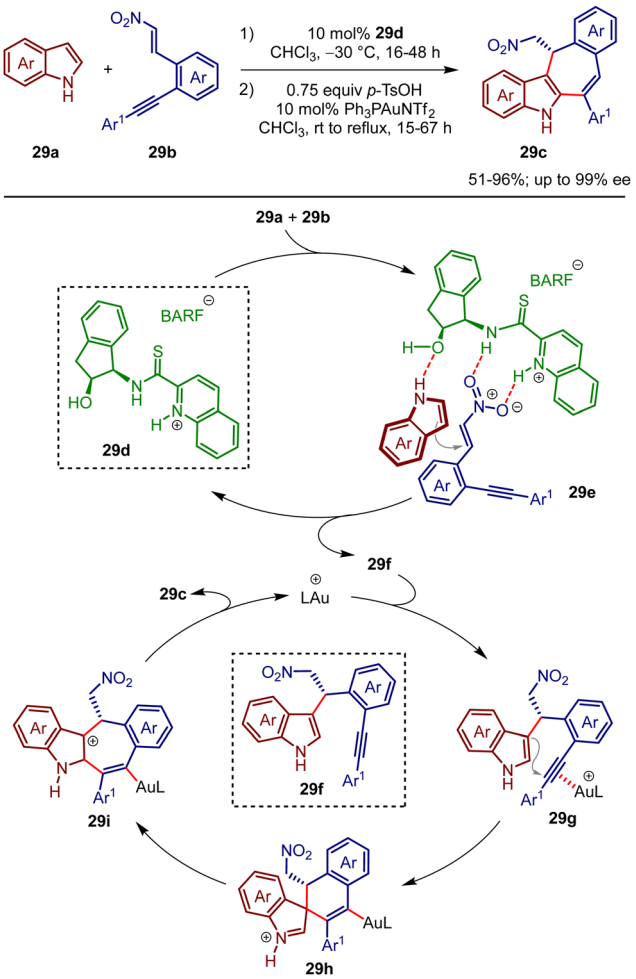
Scheme 27 Gold/chiral NHC-catalyzed enantioselective cycloisomerization/formal [4 + 3]-cycloaddition reaction of enyne-amides and isatin-derived enals.

(Scheme 28).[54] The initial step involves the Mannich-type reaction between **28a** and **28b** to generate a chiral intermediate **28e**. The authors proposed that the observed enantioselectivity stems from the simultaneous activation of **28a** *via* the H-bonding from the thiourea moiety and the activation of **28b** *via* the base-catalysis from one of the basic sites of **28d**. In the next step, Au(I) catalyzes 5-*exo-dig* cyclization of **28e**, forming a vinyl gold intermediate **28g** which then undergoes protodeauration followed by isomerization to yield **28c** in 88% ee.

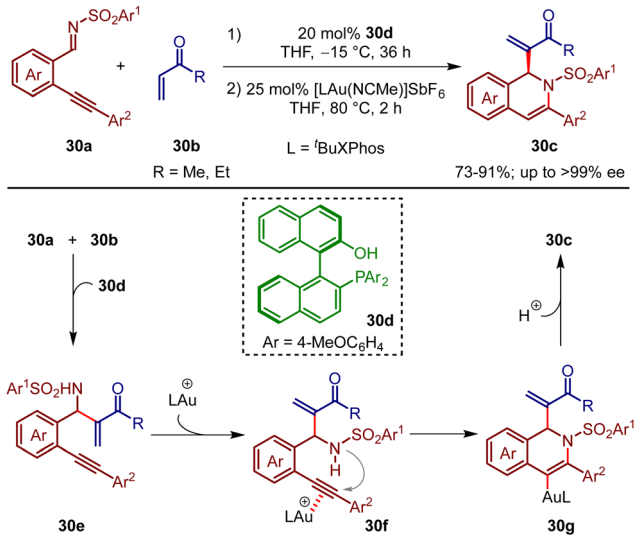
Later, in 2011, Enders and co-workers developed a H-bonding organo/gold-catalyzed double Friedel–Crafts type reaction in a sequential manner, affording an asymmetric C2/C3-annulation of indoles (Scheme 29).[55] Synthesis of tetracyclic indole derivatives **29c** has been achieved from indoles **29a** and nitrostyrenes **29b** in excellent ee up to 99%. The first Friedel–Crafts type reaction involves the simultaneous activation of **29a** and **29b** in the presence of a H-bonding organocatalyst **29d**, producing an adduct **29f**. This step exhibits excellent stereocontrol by locking both reactants with the organocatalyst in a rigid transition state (cf. **29e**) through multiple H-bonding interactions and thereby favouring the *Si*-face attack of indole on nitrostyrene **29b**. In the next step, **29f** undergoes another



Scheme 28 Enantioselective synthesis of 2,3-dihydropyrroles under gold/H-bonding catalysis.



Scheme 29 Enantioselective synthesis of tetracyclic indoles under gold/H-bonding catalysis.



Scheme 30 Gold/chiral phosphine-catalyzed enantioselective synthesis of dihydroisoquinolines.

intramolecular Friedel–Crafts type reaction under the gold catalysis. Gold-activated C–C triple bond of **29f** undergoes 6-*endo-dig* cyclization *via* the nucleophilic attack from the C3-position of indole. The generated spirocyclic intermediate **29h** then undergoes a 1,2-alkyl shift to produce a seven-membered ring containing carbocation **29i** which after rearomatization and protodeauration delivers **29c.**

2.5 Enantioselective merged gold/phosphine catalysis

Phosphine catalysis has found extensive utilization in Morita–Baylis–Hillman (MBH) and aza-Morita–Baylis–Hillman (aza-MBH) reactions, providing multiple functional groups containing complex molecular architectures from simple substrates. Despite significant advances in phosphine-mediated MBH reactions, realization of these reactions under merged gold/phosphine catalysis poses a specific challenge. The strong coordination between phosphines and gold complexes leads to the quenching of both the catalysts. In 2016, an enantioselective sequential catalysis involving a chiral phosphine catalyst **30d** and a gold catalyst was developed by Shi and co-workers to afford *enantio*-enriched dihydroisoquinoline derivatives **30c** (up to 99% ee) (Scheme 30).[56] At first, under the phosphine catalysis, the asymmetric aza-MBH reaction between aromatic sulphonated imine tethered alkynes **30a** and vinylketones **30b** delivers an intermediate **30e.** A subsequent 6-*endo-dig* cyclization of the Au(I)-activated alkyne (cf. **30f**) produces a vinyl gold intermediate **30g** which upon protodeauration affords **30c** in 73–91% yields.

3. Conclusion and Outlook

The field of gold catalysis has garnered remarkable interest capitalizing on its carbophilic activation mode; however, the developments in asymmetric gold catalysis have been comparatively modest. The linear geometry of the dicoordinated Au(I)

species poses a challenge in efficiently transferring the chiral information from the ligand to the substrate. In the continuing endeavor for developing strategies to realize enantioselective transformations, the merger of gold catalysts with chiral organocatalysts has emerged as one of the efficient techniques for achieving gold-catalyzed asymmetric synthesis. In this review, we have summarized the progress in the field of enantioselective merged gold/organocatalysis. The categorization of the reports has been made based on the type of chiral organocatalysts such as amine, Brønsted acid, N-heterocyclic carbene, H-bonding and phosphine catalysts. Through exploiting their complementary reactivities, merged gold/organo-catalyzed asymmetric transformations have unlocked the reactivities that remain beyond the reach of individual catalysts. As discussed, notable advancements have been accomplished in merging gold catalysis with amine and Brønsted acid catalysis. In contrast, the merging of gold catalysis with NHC, phosphine and H-bonding catalysis is underdeveloped which could be due to their compatibility issues with gold complexes.

It is worth noting that most of the reports on the merged gold/organocatalysis employed Au(I) catalysts for the activation of C–C multiple bonds. Considering the recent surge in the development of Au(I)/Au(III) redox catalysis,[57] the combination of this catalytic mode with chiral organocatalysis is expected to uncover new enantioselective reactions in the future. As fundamental knowledge of both gold and organocatalysts has expanded over the years, we foresee the realization of several fascinating transformations utilizing the concept of merged catalysis. It is our belief that this review will not only provide the foundation for further development of enantioselective merged gold/organocatalysis but also stimulate the interest of the scientific community in exploring different mergers to expand the horizon of dual catalysis.

Conflicts of interest

There are no conflicts to declare.

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