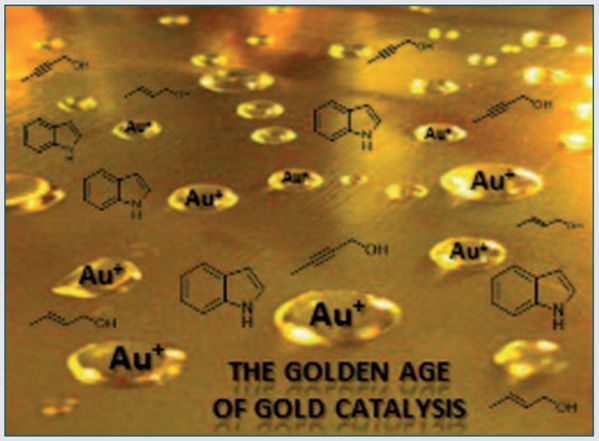

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THE "GOLDEN AGE" OF GOLD CATALYSIS IN ORGANIC SYNTHESIS

Gold catalysis has become a solid and concrete reality in the modern scenario of organic synthesis. The peculiar attitude of this coinage metal towards electrophilic activation of unsaturated unfunctionalized hydrocarbons, concurred to define gold among the most utilized transition metals in catalytic organic transformations, currently. Our group has recently contributed to this field by developing a number of gold catalyzed stereoselective manipulations of environmentally benign π-activated alcohols (i.e. allylic and propargylic). A brief summary of these achievements will be discussed here.

Over the past decade, gold is probably the transition metal that featured the most rapid growth in terms of application in homogeneous organic synthesis [1]. Gold(III) and most likely gold(I) salts/complexes triggered a revolution within the realm of modern synthetic chemistry, turning old processes into chemically, economically and environmentally acceptable organic transformations. Analogously, tremendous efforts were also devoted towards the discovery of unprecedented reactivities mainly concerning unsaturated unactivated hydrocarbons. The potential of gold catalysis in the realization of multi-step synthetic sequences, having natural compounds as final targets, has already been documented [2]. Functional group tolerance, redox stability, moisture resistance and fine-tunability via organic ligand modulation [3] are some of the most salient characteristics featuring gold(I) species. However, the crucial aspect that makes gold invaluable synthetic shortcut to complex molecular architectures is the unique π-acidity (*i.e.* carbophilicity) [4a,b] that has been also rationalized in terms of relativistic effects [4c]. Among the others, the nucleophilic addition to multiple bonds allowed for the creation of carbon-carbon as well as carbon-heteroatom connections under extremely mild manner [5]. Analogously, nowadays hot-topic in organic reactions dealing with C-H activation processes [6] and cross-coupling reactions [7] have been extensively documented through the assistance of gold(I) and gold(III) species. In parallel manner, asymmetric transformations based on the use of chiral gold complexes has recently arisen to prominence for the manipulation of hydrocarbons via enantioselective nucleophilic additions to alkynes, alkenes and allenes [8]. From a stereochemical view point, while nucleophilic additions to alkenes and allenes concur to generate new stereogenic centers at one of the carbon atoms of the hydrocarbon, in the gold catalyzed reactions involving alkynes, the incoming stereocenter is commonly installed on the nucleophilic counterpart (Fig. 1). One of the main issue that prevented a rapid growth of asymmetric gold catalysis with comparison to other late transition metal species, is

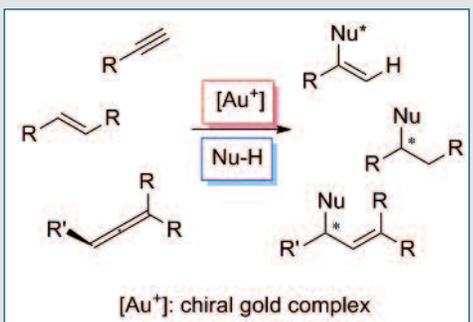

Fig. 1 - Exemplificative mechanistic pictures for gold catalyzed stereoselective functionalization of hydrocarbons

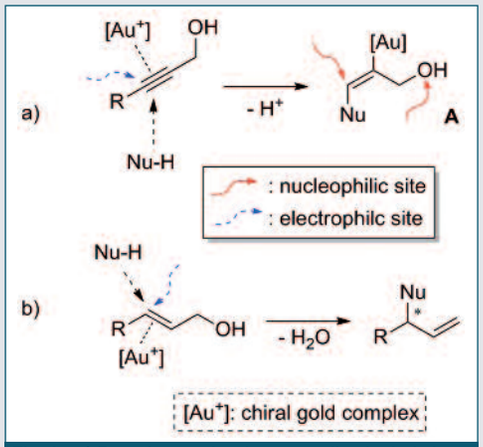

Fig. 2 - a) Reactive mode of propargylic alcohols in the presence of gold(I) catalysts; b) allylic alcohols, valuable and environmentally friendly alkylating agents under gold catalysis

ascribable to the linear bi-coordination mode commonly featured by the [Au(I)] species. Such an arrangement negatively impacted onto the transfer of "chirality information" transferring from the chiral organic ligand to the reaction site that are spatially separated by the gold atom. Very recently, the growing availability of chiral phosphorous based-ligands (*i.e.* C_2-phosphines and C_1-phosphites) bearing bulky substituents onto the phosphorous atoms, deeply contributed to the large diffusion of asymmetric [gold(I)] catalysis in C-C and C-X bond forming processes.

Despite this interest, there is still room for improvements in enantioselective gold catalysis with particular concern to [gold(III)]-catalysis that is still largely unexplored. Moreover, although stereoselective nucleophilic addition to alkynes and allenes have been extensively documented, little is known about the use of chiral gold species for the functionalization of unactivated alkenes. Having sustainability as a guideline during the development of organic transformations, the use of low-loading of catalyst along with the replacement of hazardous chemical entities with more environmental acceptable variants represent a highly desirable approach. In this direction, the use of alcohols, as reaction partners, is receiving growing attention by the chemical community due to some of their invaluable features. Firstly, alcohols are extremely flexible synthetic groups that can take part into a plethora of reaction profiles (both as electrophilic and nucleophilic reagents), then alcohols are largely available compounds that, in certain circumstances can improve mandatory aspects for a sustainable organic reaction such as: atom, redox and step economy [9]. In this scenario, alcohols are flourishing substrates also in asymmetric synthesis with particular relevance towards the so-called π-activated alcohols (*i.e.* allylic and propargylic alcohols) [10]. With this class of compounds, gold catalysts can exert their action both via electrophilic π-activation of the C-C multiple bond or through σ-coordination to the oxygen atom. Moreover, gold-catalyzed manipulation of π-alcohols are commonly embedded into cascade processes (mainly propargylic alcohols) featuring valuable nucleophilic sites in the hydroxyl group or in the vinylgold intermediate **A** (Fig. 2a).

Our group has recently documented the suitability of allylic and propargylic alcohols for creating chemical complexity in heterocyclic chemistry when reacted in the presence of chiral gold complexes. In particular, allylic alcohols proved to be valuable synthetic analogous of more reactive allylic carbonates and acetates in nucleophilic allylic substitutions. Here, along with the stereoselective formation of new C-C and C-X bonds, water would represent the only stoichiometric by-product of the reaction (Fig. 2b). In second instance, propargylic alcohols demonstrated competence in originating diversity in a new class of densely functionalized indoline-based alkaloids, when reacted in the presence of chiral cationic gold complexes.

Direct activation of allylic alcohols by enantioselective gold catalysis

Although catalytic asymmetric allylic alkylation with alcohols is attracting more and more attention, their use still represents a challenging issue [10d]. Their intrinsic low reactivity and tendency to form carbocations are the main drawbacks to face when allylic alcohols are involved in stereoselective processes.

Here we report two examples witnessing the high efficiency of chiral gold complexes in the activation of allylic alcohols in enantioselective transformations [10c]. For example indolyl alcohols of type **1** or **2** underwent intramolecular enantioselective Friedel-Crafts allylic alkylation of the indole core when a suitable gold catalyst was employed (Fig. 3) [11]. After a screening of chiral metal complexes, chiral bis(phosphine)-gold(I) complexes of general formula $[(P\text{-}P)Au_2X_2]$ emerged as unique catalysts to perform the desired transformation with high enantioselectivity. In particular chiral ligand **L1** [(*S*)-DTBM–OMe-biphep] afforded the best results in terms of enantiomeric excess, leading to the formation of 1-vinyl- and 4-vinyltetrahydrocarbazoles (**3** and **4**) with *ees* up to 96%. The nature of the silver salt, used as halide scavenger, turned out to be crucial for both reaction rate and selectivity. OTf^- (trifluoromethanesulfonate) emerged as the most suitable counterion in this transformation.

Investigation on the reaction scope demonstrated the high functional group tolerance of this methodology. Several electron donating and withdrawing groups on the indole core and different malonyl tethering groups were adequately tolerated. However, *N*-methyl protected substrates of type **1** did not undergo cyclization under standard conditions. Various experiments were carried out to establish the real coordination mode of the bimetallic catalyst with the allylic alcohol. Although such

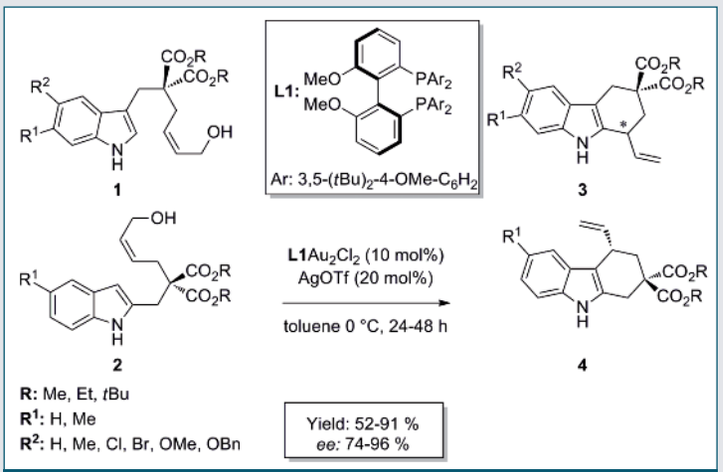

Fig. 3 - Enantioselective gold-catalyzed allylic alkylation of indoles with alcohols

experiments were not conclusive, the importance of both the configuration of the double bond and the presence of the free OH group were demonstrated. Allylic alcohols with *E* configurated double bond were completely inert toward cyclization, whilst *O*-TBDMS protected alcohols afforded the product in diminished yield and enantioselectivity.

The same strategy was applied to the stereoselective synthesis of functionalized morpholines starting from diols bearing an allylic alcohols moiety [12]. In particular, when enantiopure diols **5** and **6** were treated with binuclear complex [dppf(AuOTf)$_2$] a dehydrative intramolecular coupling took place, leading to 2-vinyl-morpholines **7**/**8** in good yield and excellent *cis* diastereoselectivity (Fig. 4a). Even in this case the configuration of the double bond turned out to play a crucial role for the stereochemical outcome of the reaction, ruling out a possible cationic pathway for the process [13]. In fact, when (*E*)-**5a** (R = Ph) was employed the *dr* dropped from 98:2 to 63:37.

The enantioselective variant of the dehydrative allylic alkoxylation was then developed by subjecting achiral diols type **9** and **10** to cyclization. Optimal conditions dealt with the use of an enantiopure gold complex comprising the enantiopure (*R*)-3,5-*t*Bu$_2$-4-OMe-segphos (**L2**) in combination with NTf_2^- counterion [NTf_2^-=bis(trifluoromethane)sulfonimide]. High enantioselectivity was generally obtained accompanied by a remarkable functional group tolerance. The experiments carried out to establish the coordination mode of the binuclear gold catalyst, pointed out a high substrate control and the prominent role played by the counterion. As an example, overall inversion of stereoinduction was recorded when isomers (*Z*)-**9a** and (*E*)-**9a** (R^1, R^2 = H, X = Ts) were subjected to best conditions. Moreover, the great impact of the counterions on the reaction profile was proved by screening a range of silver salts, leading to the conclusion that the anionic species might be directly involved in the stereodiscriminating event of the reaction.

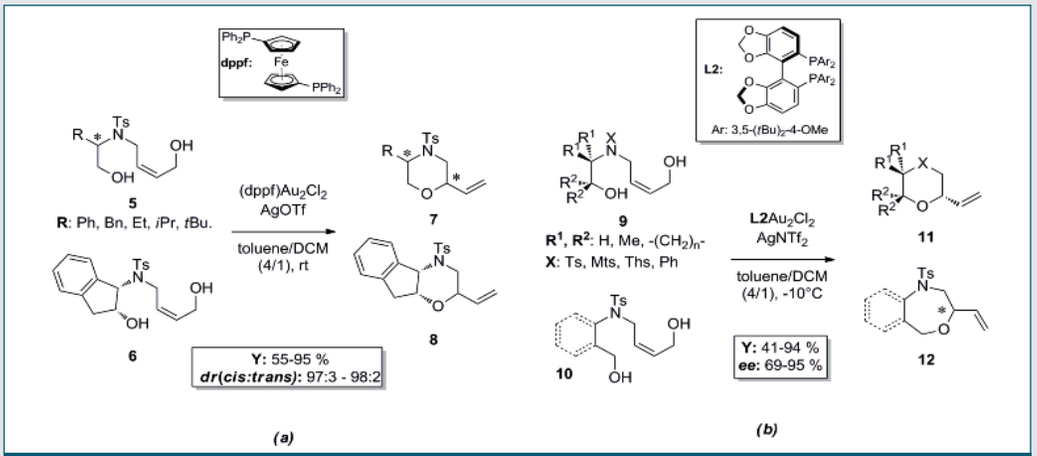

Fig. 4 - Stereoselective gold-catalyzed synthesis of 2-vinyl-morpholines; Mts = mesitylsulfonyl; Ths: = 2-thienylsulfonyl

Stereoselective gold catalyzed functionalizations of propargylic alcohols

The use of propargylic alcohols in gold catalysis has been extensively explored due to their capability in generating chemical diversity. The electrophilic activation of the triple bond could lead in principle to the addition of various external nucleophiles. Here the hydroxyl group can act as an "internal" nucleophile, trapping transient electrophilic species generated by the activation of the π-system. In accordance to the interest of our group on the stereoselective functionalization of the indole cores [14], we reasoned on the suitability of indole based propargylic alcohols (**13** and **15**) to achieve a practical synthetic strategy to structurally complex indoline alkaloids. The hypothesis relied on the use of *N*-unprotected indolyl propargylic alcohols that, after the electrophilic activation of the alkyne moiety could enter a Friedel-Crafts/iminium trapping reactive sequence leading to dihydropyranoindolines (5-*exo-dig* cyclization) and furoindolines (7-*endo-dig* cyclization). Silver-free gold complex **cat 1** (Fig. 5) proved to be the catalyst of choice providing **14** in high 5-*exo-dig* regiochemistry and excellent diastereomeric ratio (yield up to 86%, *dr*=50:1) [15]. Wide substrate scope was documented by taking into account different malonyl tethering units and indole substitutions. The protocol was further applied to the tryptamines derivatives **15** that lead to tetracyclic furoindolines **16**, through 7-*endo-dig* cyclization pathway, in moderate to good yields (up to 76%). Since overall stereochemistry of the protocol is essentially controlled by the initial gold-triggered regioselective hydroindolination of the triple bond [16], an unprecedented enantioselective variant of this protocol can be envisioned by means of chiral gold complexes [17]. A screening of reaction conditions disclosed *C*-2 symmetric xylyl-binap **L3** as the ligand of election (5 mol%) along with the use of $AgBF_4$. Under best conditions a range of (6a*R*,11b*R*)-**14** was obtained in good yield (50-75%) high diastereoselection (*dr* 50:1) and enantiomeric excess up to 86% (Fig. 6). The scope of the reaction was then expanded to indolyl alcohols **15** in the presence of ligand **L2** (5 mol%) and AgOTf, providing the corresponding furoindolines (7a*R*,12b*S*)-**16** in high enantiomeric excess (82-85%).

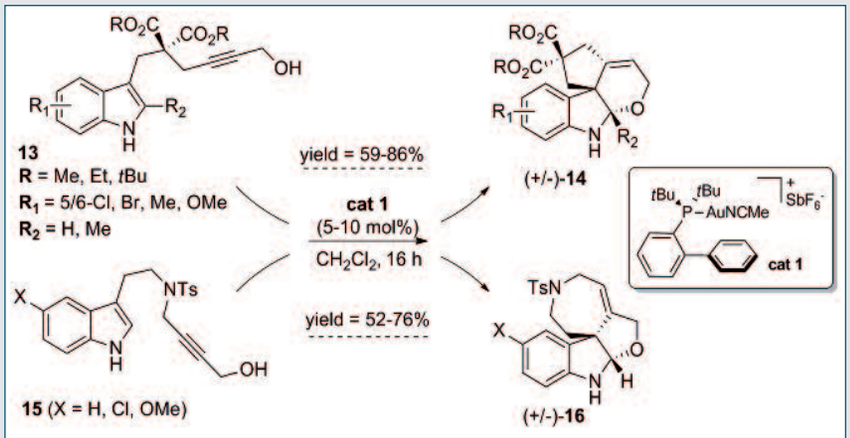

Fig. 5 - Gold-catalyzed cascade synthesis of indolines

Conclusions

Nobel Prize in Chemistry 2001 Ryoji Noyori recently ascertained that despite the extraordinary level of sophistication reached by organic chemistry, there is still room for improvements [18]. Certainly, homogeneous gold catalysis is operating in this direction as testified by the exponential growth of popularity gained over the past ten years. In this realm, the successful combination of π-activated alcohols and chiral gold complexes was recently investigated in our labs, with applications in the synthesis of aliphatic and aromatic heterocyclic scaffolds through stereoselective C-C and C-X bond forming processes.

Acknowledgments

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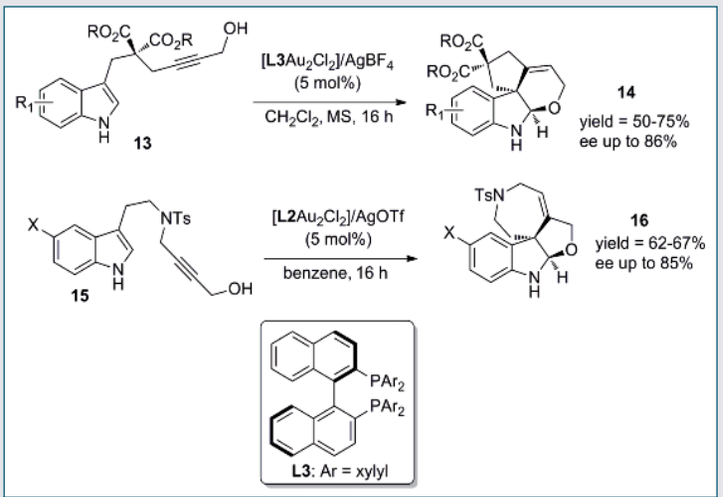

Fig. 6 - Enantioselective synthesis of tetracyclic indolines

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RIASSUNTO

La catalisi da oro in sintesi organica

La catalisi asimmetrica promossa da complessi di oro(I) rappresenta oggigiorno una concreta realtà nel panorama della moderna chimica organica di sintesi, a seguito di una crescita esponenziale registrata nell'ultima decade. Spiccata carbofilicità, tolleranza verso i più comuni gruppi funzionali e blande condizioni operative hanno reso specie cationiche di oro indispensabili sistemi catalitici per la funzionalizzazione di idrocarburi insaturi non attivati e la sintesi di composti eterociclici. L'uso combinato di complessi chirali di Au(I) e alcoli π-attivati è stato recentemente affrontato nei nostri laboratori di ricerca, al fine di sviluppare metodiche di sintesi stereoselettive caratterizzate da elevati gradi di "atom and step economy".