# The power of gold beyond glitter: homogeneous catalysis with Au(I)-complexes to generate a library of privileged scaffolds

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**Gold complexes have emerged in the last few years as excellent catalysts in numerous homogeneous transformations involving the activation of carbon–carbon multiple bonds towards the attack of a large variety of nucleophiles. This article gives a brief overview of this enticing subject and identifies some of the most important aspects of homogeneous gold catalysis in organic synthesis focusing on the research done in our laboratory.**

'*All that glitters may not be gold, but at least it contains free electrons.*' – John Desmond Bernal

**Keywords:** Gold, homogeneous catalysis, organic reactions, privileged scaffolds.

IN the process of evolution of organic chemistry, one can quickly judge that metal catalysed reactions are important in shaping the area of organic synthesis. Several metal-mediated processes are known to have wide applications in the synthesis of value-added products in academia and the industry. Presently, one cannot imagine contemporary organic synthesis without transition metal catalysis. The fact that the preceding subsequent three Nobel Prizes in organic chemistry (year 2001: Knowles, Noyori and Sharpless; year 2005: Chauvin, Grubbs and Schrock, and year 2010: Heck, Negishi and Suzuki) have been bagged by the organic chemists who devoted their entire career in nurturing these areas, clearly reveals the importance of such reactions. Most strikingly, during their inception, these fundamentally new reactions constituted pure basic science and it took several years to understand the importance of such processes for mankind.

Gold has been present in the collective conscience of mankind since the beginning of known history. It always exerted a deep fascination, being associated with beauty, wealth and authority probably due to its collective and unique properties such as high density, softness, malleability, ductility and most aesthetically pleasing property such as glittery. Particularly, there is special significance of gold in Indian culture; religious and societal. The importance of gold can be understood from the saying 'all that glitters is not gold'. Gold in free elemental form does not get oxidized by air or water, as is evident by its occurrence as nuggets or grains in rocks, veins and alluvial deposits[1]. Such high stability of gold in nature might have created misconceptions among the scientific community that the metal is extremely inert and therefore, its salts cannot be used as catalysts for organic reactions. This could be the reason why gold has lived in the shadow of other metals for a long time.

In the beginning of the 1970s, several examples in the area of heterogeneous catalysis appeared[2]. Some of the examples of industrial importance include hydrochlorination of ethyne to vinyl chloride[3] and the low-temperature oxidation of CO to $CO_2$ (ref. 4). Similarly, Au-NPs played an important role in the development of this discipline[5]. Homogeneous gold catalysis should have several advantages over heterogeneous catalysis in terms of many aspects such as yield, enantioselectivity (ee), much better substrate tolerance and most importantly, the use of low temperature and pressure which helps the reaction to be conducted under mild conditions. The main benefit of homogeneous gold catalysis is that the specific modification of the catalyst structure may influence the reaction paths in a controlled and predictable manner. In recent years, homogeneous gold catalysis has attracted much attention and a lot of powerful new reaction cascades for the rapid construction of molecular complexity, starting from simple key precursors, have been explored[6]. An early example of enantioselective gold-catalysed reaction is the aldol reaction of isocyano acetates/amides with aldehydes[7]. In fact, this is one of the rarest phenomena in organic chemistry, wherein the enantioselective reaction was discovered first before the discovery of relatively simple reactions. In general, the basic principle involved in gold-catalysed reactions is the coordination of C–C multiple bonds to catalysts making them electrophilic in nature and thus susceptible to attack by nucleophiles.

Privileged structures are extremely important in drug discovery programme for the identification of bioactive small molecules. In general, privileged structures are polyheterocyclic core skeletons which show binding specificity towards certain biopolymers because of the 'prepaid' entropic penalty, resulting from the limited conformational flexibility of the skeletons. A particular

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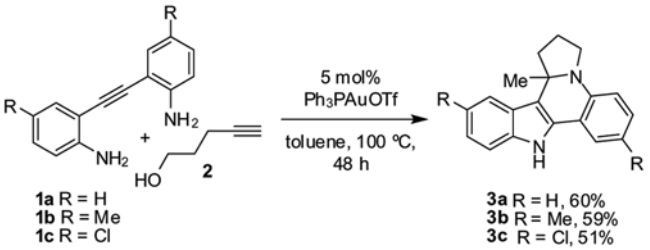
advantage is that the libraries of privileged structures can be used to identify new ligands for a variety of biological targets using high throughput screening (HTS) technique. Therefore, there is a great demand for the synthesis of new privileged scaffolds. One approach to their synthesis involves gold-catalysed cascade cyclizations – a technique which provides useful means of generating multiply substituted heterocyclic scaffolds from easily accessible starting materials with high atom economy. Clearly, such reactions can provide efficient means of reducing time, labour, energy and waste as the multiple reactions take place in one-pot without the isolation of each and every intermediate.

This article gives a brief overview on the research in our laboratory on developing new and elegant Au-catalysed one-pot cascade processes[8] for the efficient synthesis of privileged scaffolds[9]. The mechanism of these novel reactions has also been discussed.

## Gold catalysis

One of the earlier examples of gold-catalysed cascade reaction developed in our laboratory utilizes alkynols and symmetric bis-anilines as starting materials. For instance, the reaction of symmetrical diamines **1a**, **1b** and **1c** with 4-pentyn-1-ol **2**, under $Ph_3PAuOTf$ catalysis, gave corresponding indolo[3,2-*c*]quinolines **3a**, **3b** and **3c** in 60, 59 and 51% yields respectively (Scheme 1)[10]. The catalyst $Ph_3PAuOTf$ could conveniently be generated *in situ* by mixing equimolar amounts of $Ph_3PAuCl$ and AgOTf.

A plausible mechanism for the reaction is described in Scheme 2. In essence, a total of four catalytic cycles A (hydroalkoxylation), B (hydroamination), C (coupling) and D (dehydrative cyclization) were proposed. As shown in catalytic cycle A, the complexation of metal catalyst to the alkyne function in **2** would lead to intermediate **7**. The cyclization step may then occur directly by the attack of proximal hydroxyl group leading to vinylmetal intermediate **8**, which on protonation and regeneration of catalyst would afford 2-methylenetetrahydrofuran **9**. At the same time, 2-aminophenylindole **6** would be generated by intramolecular hydroamination of alkynyl amine **1a** via intermediates **4** and **5** (cycle B). As described in cycle C, the gold complex catalyses the formation of oxonium ion **10** from 2-methylenetetrahydrofuran **9**. Intermolecular



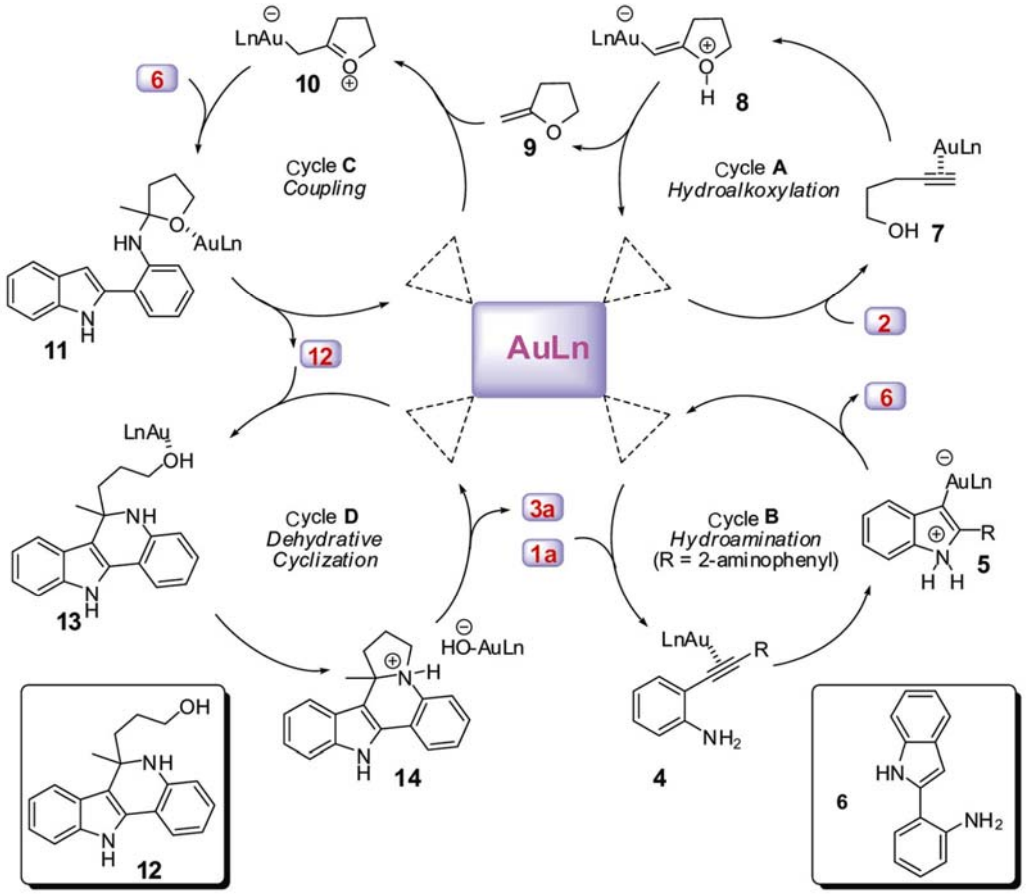

**Scheme 1.**

nucleophilic addition of the indole **6** to **10** might result in the formation of metal coordinated N,O-ketal **11** from which formal hydroamination-hydroarylation product **12** was obtained with regeneration of catalyst. The compound **12** thus obtained would undergo dehydrative cyclization, under the catalysis of Au(I) (cf. **13** and **14**), to afford fused indolo[3,2-*c*]quinolines **3a** (cycle D). Overall mechanism reflects the involvement of multiple catalytic cycles such as hydroalkoxylation (cycle A), hydroamination (cycle B), coupling (cycle C) and dehydrative cyclization (cycle D) assisted by a single catalyst.

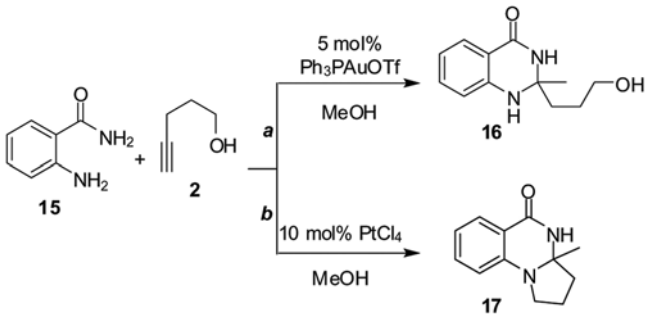
As further extension of the above studies, we conducted the reaction of 4-pentyn-1-ol **2** with 2-aminobenzamide **15** as bis-nucleophiles in the presence of 5 mol% of $Ph_3P$AuCl/AgOTf catalysts in methanol (Scheme 3, path a)[11]. This led to development of a process involving efficient Markownikoff's double hydroamination of alkynes to deliver the tetrahydroquinazolinone **16** in 91% yield. Interestingly, when the reaction was conducted in the presence of $PtCl_4$ catalyst, cyclic, angularly fused tetrahydroquinazolinone, i.e. hexahydropyrrolo[1,2-a]quinazolin-5-one **17** was obtained (Scheme 3, path b). This type of catalyst-dependent reactivity is important because it allows chemists to synthesize structurally diverse products utilizing the same starting materials. The mechanism of reaction has been proposed which is found to be similar to that reported in Scheme 2.

As can be judged from the chemistry described in Schemes 1–3, the proximal hydroxyl group is necessary. In this context, we assumed that the carboxylic group might also prove capable of catalysing similar transformation with bis-nucleophiles. Indeed, a process involving gold(I)-catalysed formal double hydroamination of alkynes, bearing a tethered carboxylic group, has been realized[12]. It is evident from Scheme 4 that alkynoic acids under the catalysis of gold could be made to react with various bis-nucleophiles such as 1,2-diaminobenzenes **19**, 2-aminobenzylamines **21**, 2-aminobenzohydrazides **23** and 2-amino-*N*′-arylbenzohydrazides **25**, leading to the formation of dihydrobenzimidazoles **20** (path A), tetrahydroquinazolines **22** (path B), linearly fused tetrahydroquinazolinone **24** (path C) and angularly fused tetrahydroquinazolinone **26** (path D). The reaction turned out to be general and with this model reaction we developed relay catalytic branching cascade – a new technique for accessing scaffold diversity in diversity-oriented synthesis[13].

The mechanism of the reaction turned out to be principally different compared to the one described in Scheme 2 (compare to Scheme 5). The first step would be the complexation of Au(I) catalyst to the alkyne function in **18**, which led to an intermediate **27** (cycle A). The cyclization may then occur directly by the attack of proximal hydroxyl group to form the vinylgold intermediate **28**. The next step would be the protodeauration to generate exocyclic enol lactone **29** with the release of catalyst.

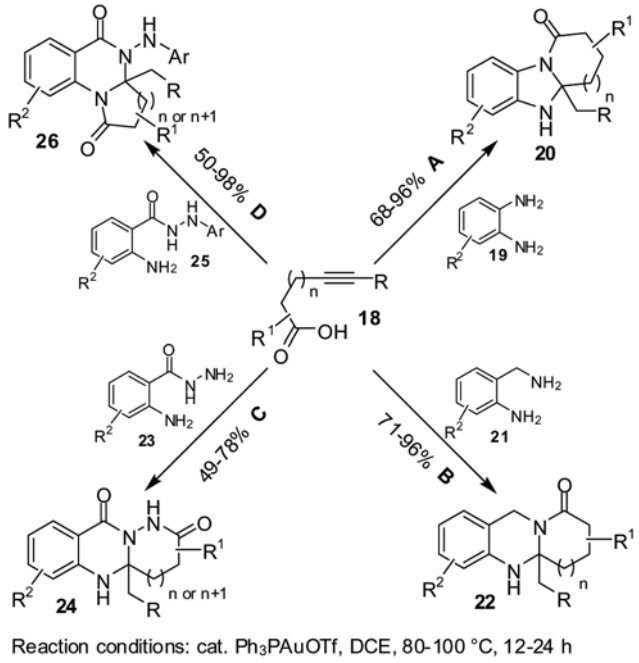



**Scheme 2.**



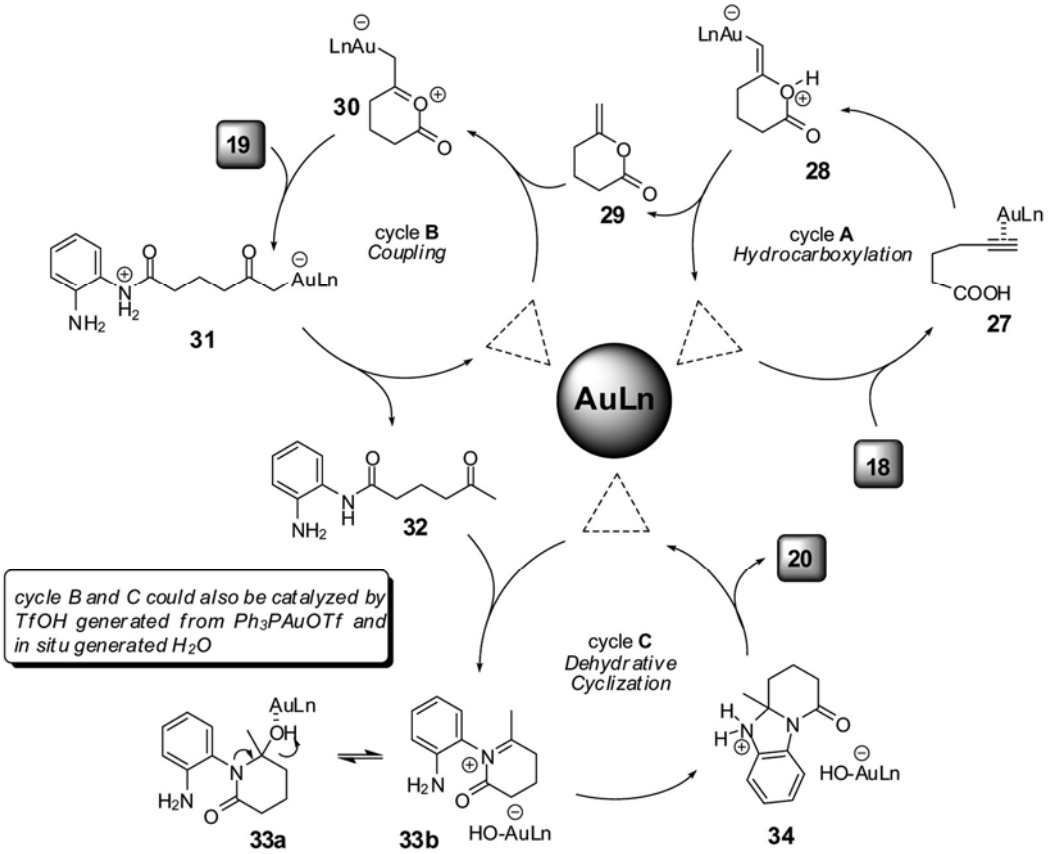

**Scheme 3.**

Once **29** is formed, it enters another catalytic cycle B where $Ph_3PAuOTf$ is supposed to act as a Lewis acid. Thus, the Lewis acidic Au(I)-complex catalyses the formation of oxonium ion **30** from **29**. Intermolecular nucleophilic addition of the benzene-1,2-diamine **19** to **30** (cf. **31**) followed by protodeauration would lead to the keto amide **32**, with the liberation of the catalyst. The keto amide **32** is poised to undergo *N*-acyl iminium ion formation **33b**, which could be derived from **33a** in the presence of Au(I) catalyst. The intramolecular trapping of *N*-acyl iminium ion in **33b** by tethered amine would produce the final product **20** (cf. **34**) with the regeneration of catalyst.

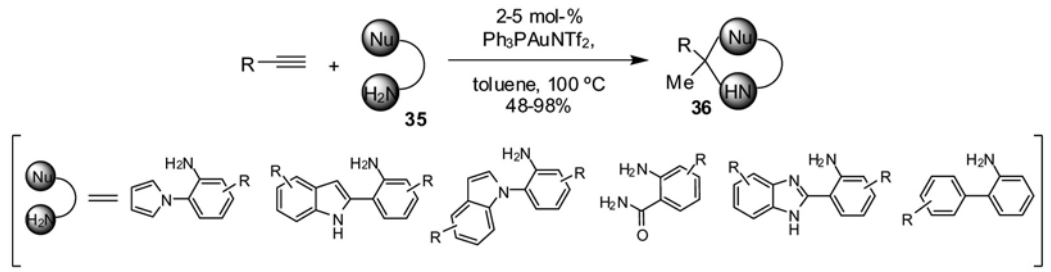



**Scheme 4.**

Clearly, the above examples reveal that the presence of either –OH or –COOH group is necessary in the alkyne




**Scheme 5.**

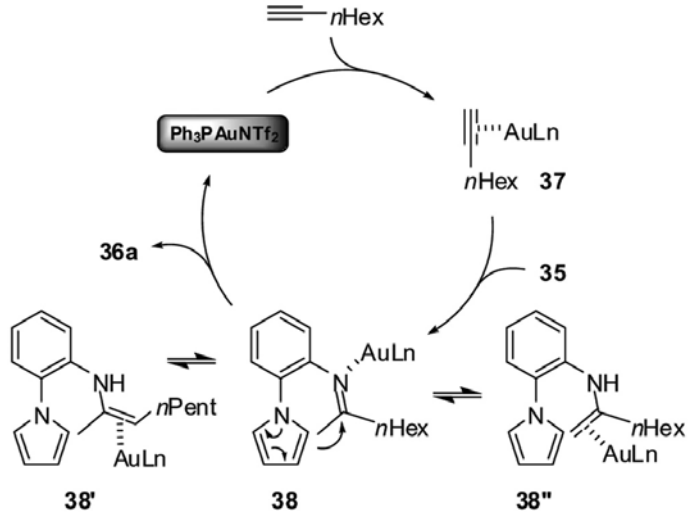



**Scheme 6.**

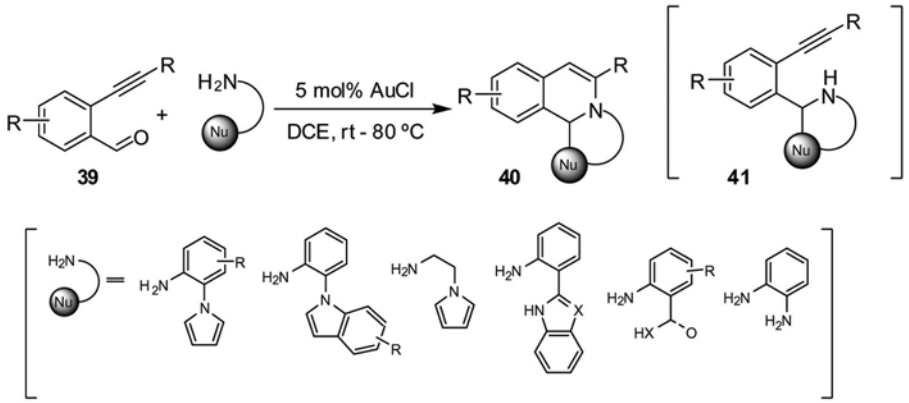
tether; alkynes not having hydroxyl groups in the tether (e.g. 1-octyne) failed to react. We surmised that the appropriate screening of various gold catalysts would allow us to realize this transformation. Indeed, after several attempts, we found that catalytic amounts of Gagosz catalyst ($Ph_3PAuNTf_2$) worked exceedingly well. For example, treatment of terminal alkynes with various bis-nucleophiles **35** in the presence of 2–5 mol% of $Ph_3PAuNTf_2$ in toluene at 100°C gave corresponding products **36** with excellent yields (Scheme 6)[14].

A mechanistic hypothesis based on hydroamination–hydroarylation cascade catalysed by $Ph_3PAuNTf_2$ is shown in Scheme 7, using 1-octyne and 2-aminophenyl pyrrole (**35**) as example. At first, coordination of alkyne to Au(I) might take place to generate Au-coordinated alkyne **37**. The formed intermediate **37** would react with 2-aminophenyl pyrrole to form Au-coordinated imine **38**, which might be in equilibrium with enamine **38′** or **38″**. A series of events such as Fridel–Crafts type reaction, protonation and regeneration of Au catalyst might then occur to afford product **36**.

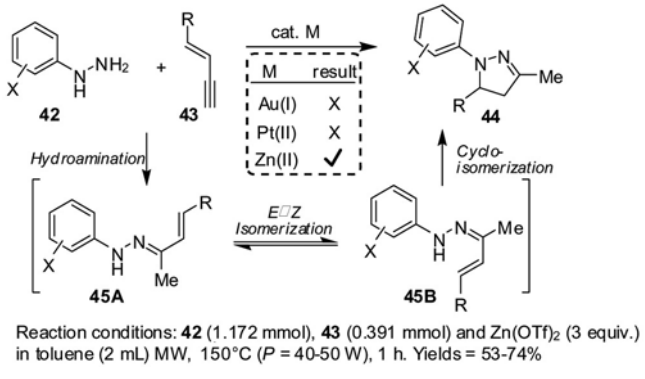
In continuation of our work, we recently reported a new coupling–cyclization technique for the synthesis of isoquinoline-fused polycyclic compounds **40** (Scheme 8)[15]. The reaction makes use of two coupling partners such as *o*-alkynylbenzaldehydes **39** and aromatic amines having tethered nucleophiles. The reaction is easy to perform, broad in scope and allows for the generation of a




**Scheme 7.**




**Scheme 8.**




Reaction conditions: **42** (1.172 mmol), **43** (0.391 mmol) and $Zn(OTf)_2$ (3 equiv.) in toluene (2 mL) MW, 150°C (*P* = 40-50 W), 1 h. Yields = 53-74%

**Scheme 9.**

number of biologically important heterocyclic motifs from readily accessible starting materials. Mechanistically, it was found that AuCl acts as a dual role catalyst and performs two jobs: (1) intermolecular condensation of **39** with bis-nucleophiles to generate **41** and (2) intramolecular hydroamination in **41** to produce the final product **40**.

Next, we become interested in whether enynes **43** could be used as a partner to react with aryl hydrazines **42** in Au-catalysed intermolecular hydroamination to afford the (*E*)-hydrazones **45A** which, in part, would be in equilibrium with (*Z*)-isomer **45B** (Scheme 9). The (*Z*)-hydrazones **45B** would then readily undergo an intramolecular cyclization[9] providing a strategically novel, atom-economical route to pyrazolines **44**. To explore our hypothesis, initial efforts were directed towards finding an appropriate Au-catalyst for the proposed reaction using phenyl hydrazine (**42a**, X = H) with (*E*)-1-(but-1-en-3-ynyl)benzene (**43a**, R = Ph) as model substrates. However, the reaction did not occur when AuCl, $Ph_3PAuOTf$ and $Ph_3PAuNTf_2$ were used as catalysts, even though these are commonly used in intermolecular hydroamination of alkynes[16]. After several attempts, we found that Zn(II) salts efficiently catalyse double hydroamination of enynes with aryl hydrazines to produce 1,3,5-trisubstituted pyrazolines under microwave conditions[17].

We assumed that the failure in case of gold catalysis could be probably due to the inhibition of Au catalyst

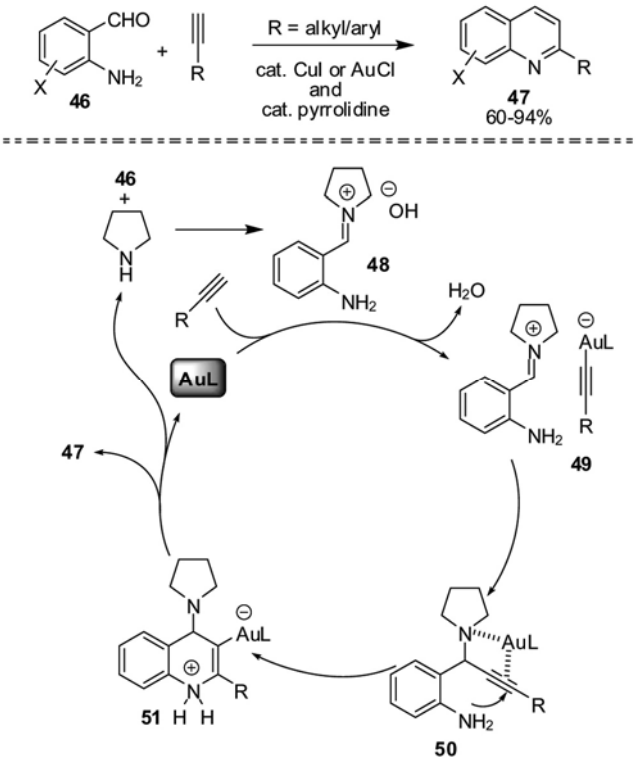
and/or reduction of Au salts to Au(0) particles[18]. This result showed that Zn(II) salts are a better alternative to gold catalyst when more basic amines such as hydrazines are employed.

## Merging gold catalysis with organocatalysis

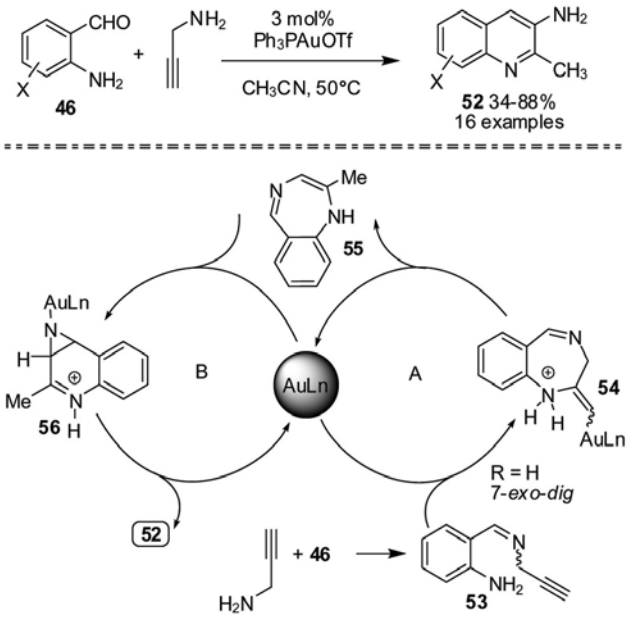
In recent years, the concept of combining transition metal catalysis with organo-catalysis has emerged as a promising strategy for developing unique transformations[19]. These types of reaction are important because a reaction catalysed by two different catalysts at the same time can provide access to both reactivity and selectivity, which is not possible by a single catalyst. The reaction catalysed by gold- and chiral organocatalysts, i.e. 'merged organo/gold catalysis' is supposed to be especially interesting for Au(I) catalysis, given the aforementioned difficulty of transferring chiral information from a ligand disposed 180° from the substrate. Thus, the horizon for enantioselective gold catalysis is expected to be expanded as there exists a possibility of using either of the catalyst chiral and/or both catalysts chiral in a synergistic fashion.

A cooperative catalytic system consisting of metal and pyrrolidine has been developed for the efficient synthesis of 2-substituted quinolines **47** from 2-amino benzaldehydes **46** and terminal alkynes (Scheme 10)[20]. The metal catalysts such as Au salts and Cu salts are effective in catalysing this transformation; however, we preferred the latter because of its inexpensiveness. A mechanistic hypothesis based on the dual activation concept, in which an organocatalyst is combined with Au-catalyst, is proposed. At first, aldehyde **46** would condense *in situ* with the pyrrolidine to give an iminium ion **48**. The iminium ion **48** on reaction with AuCl and terminal alkynes would produce intermediate **49** with expulsion of water. A union of gold acetylide and iminium ion in **49** would then lead to the formation of gold coordinated propargylamine derivative **50**. The intermediate **50** would then undergo 6-*endo-dig* cyclization to form **51**. A protonation and aromatization would then occur to give **47** with the liberation of AuCl and pyrrolidine. Later, DFT computational study in the cyclization of aminoalkynes of type **50** was made, which revealed that the mode of cyclization (*exo* vs *endo*) depends on the protecting group on nitrogen, oxidation state of the metal and substitution on alkyne[21].

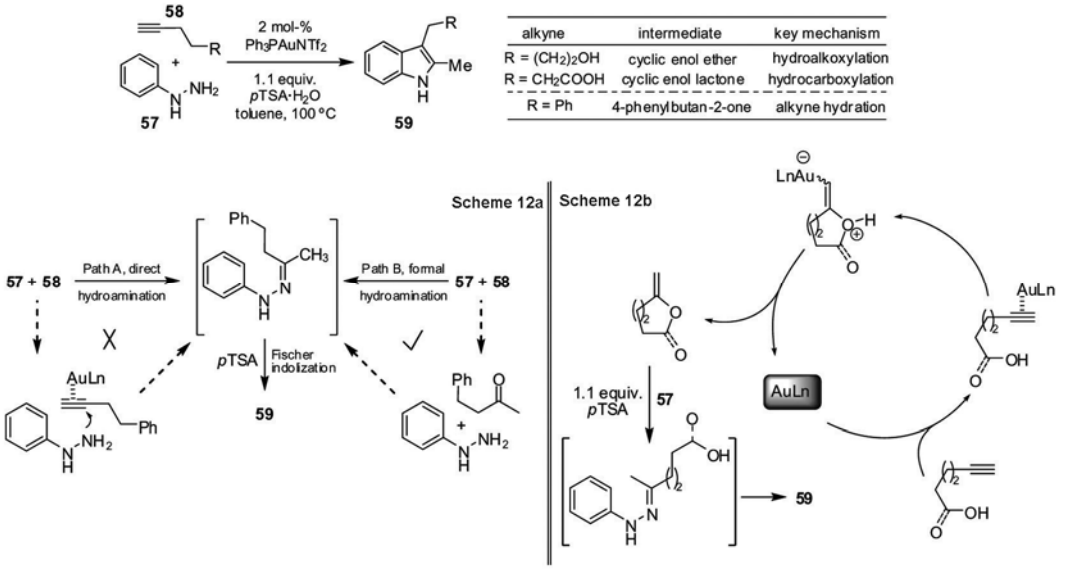
As a further extension, we postulated that this rudimentary mechanism could be adopted for the synthesis of synthetically valuable 2-aminomethylquinolines by replacing simple terminal alkynes with propargyl amine. Interestingly, work in this direction led to the development of Au(I)-catalysed cascade reaction to give 2-substituted 3-amino quinolines **52** from 2-amino benzaldehydes **46** with propargyl amine (Scheme 11). This is the first report on the synthesis of 3-amino quinolines in one step starting from readily available starting materials[22]. Mechanistically, the reaction turned out to be interesting. At first, condensation between **46** and propargyl amine would occur to provide imine **53**, which would be interconvertible as *E* and *Z* isomer under the influence of catalyst. The *Z* isomer would undergo gold-catalysed *exo-dig* cyclization (cf. **54**) and subsequent isomerization to form benzo-



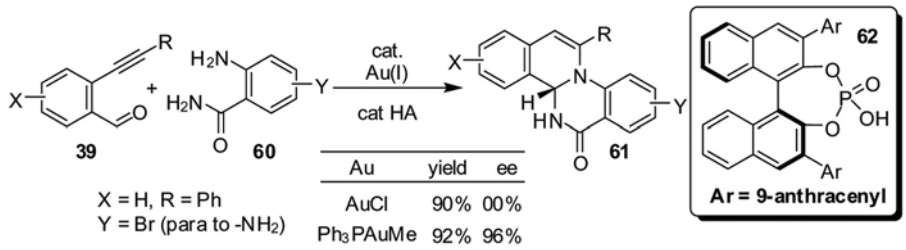

**Scheme 10.**




**Scheme 11.**




**Scheme 12.**




**Scheme 13.**

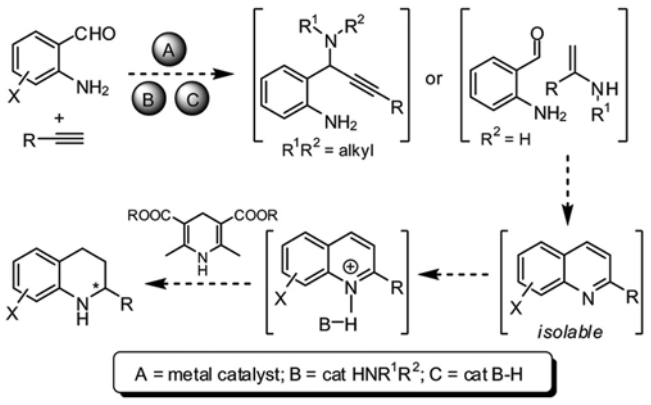
diazepine **55** (cycle A). The putative intermediate **55** would then rearrange to Au-cordinated azirinoquinoline **56**, which after subsequent skeletal rearrangement affords **52** (cycle B). Elegantly designed experiments were employed to unravel the mechanism of this unprecedented rearrangement, which was corroborated by DFT calculations.

A formal hydrohydrazination/Fischer indolization tandem reaction to synthesize 2,3-di-substituted indoles from alkynes and aryl hydrazines, has been developed by employing $Ph_3PAuNTf_2$/*p*TSA·$H_2O$ as a binary catalytic system. For instance, the reaction between alkynes **58** with substituted aryl hydrazines **57** afforded the corresponding indoles **59** in moderate to good yields (Scheme 12)[23]. The mechanism of these studies has been investigated, which led us to propose an interesting mechanistic dichotomy. When alkynes having –OH/–COOH group in the tether were used, hydroalkoxylation/hydrocarboxylation occurred to generate exocyclic enol ethers/lactones, which reacted with hydrazines to produce indoles (Scheme 12b). While in the case of alkynes which lack –OH/–COOH group, hydration occurred to generate ketones which reacted with aryl hydrazines to give the desired indoles (Scheme 12a).

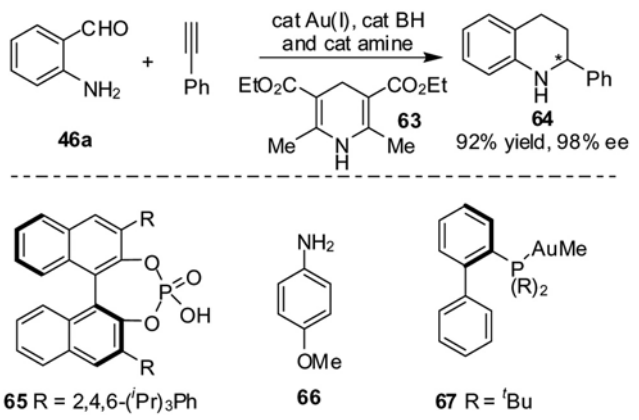
In continuation of our work depicted in Scheme 8, we postulated that the reaction can be made enantioselective under a cooperative catalysis utilizing achiral Au(I) complexes and chiral Brønsted acids to give optically active products. To test this idea, we proposed using the readily available 2-phenylalkynylbenzaldehydes and 2-aminobenzamides as the coupling partners utilizing a catalyst combination of Au(I) salts and chiral phosphoric acids. A major concern was that the Au(I)X salts would racemize the relatively labile optically pure aminals generated *in situ* by the enantioselective condensation of **39** with **60**, leading to the racemic products **61**. The challenge, therefore, was to search for a suitable achiral gold(I) catalyst which should only catalyse hydroamination and not take part in the condensation process. We surmised that the crucial tuning of Lewis acidity of gold(I) complexes can be achieved by varying the counter-anions[24]. Indeed, an enantioselective cooperative catalysis protocol utilizing achiral Au(I)-complexes and chiral Brønsted acids, has been realized for the synthesis of optically pure fused 1,2-dihydroisoquinolines **61** (Scheme 13). A key for obtaining the high ee is the tuning of reactivity of Au(I) complexes using the counter ions, which does not generate residual Brønsted acids. Careful mechanistic study

revealed that gold phosphate generated from $Ph_3PAuMe$ and phosphoric acid is responsible for the hydroamination reaction. The existence of gold phosphate was further confirmed by $^{31}P$ NMR analysis.

In continuation of the work described in Scheme 10, we postulated that *in situ* generated quinolines can be hydrogenated in the presence of Hantzch ester and chiral phosphoric acid to afford optically pure 2-substituted tetrahydroquinolines[25] – a class of compounds known to be found in several natural products (Scheme 14)[26]. Overall, the process can be considered as enantioselective cooperative triple catalysis because all catalysts are expected to be present at the onset and performing their unique roles. However, the major concern was that all the catalysts should remain friendly with each other, without deteriorating their functions. After several attempts, we found a mutually compatible catalytic system involving the concerted/simultaneous action of three different catalysts, i.e. Au(I)/amine/chiral Brønsted acid catalysts have been realized for the synthesis of 2-substituted tetrahydroquinolines from 2-aminobenzaldehydes and terminal alkynes[27]. For instance, a mixture of 2-aminobenzaldehyde (**46a**) and 1.2 equiv. phenyl acetylene in the presence of chiral phosphoric acid **65** (4 mol%), *p*-anisidine




**Scheme 14.**




**Scheme 15.**

**66** (20 mol%) and Au(I) catalyst **67** (2 mol%) was heated in $CH_3CN$ at 60°C for 16 h. After ensuring the formation of quinolines by TLC and $^1H$ NMR, Hantzsch ester (**63**) was introduced into the reaction mixture and stirring was continued for an additional 16 h at 35°C to afford 2-phenyl tetrahydroquinoline **64** in 92% yield and 98% ee (Scheme 15). Careful mechanistic study indicates the concerted/simultaneous action of Au(I), *p*-anisidine and chiral Brønsted acid catalysts; the absence of either of them does not give satisfactory results, indicating their essential presence.

## Perspectives

According to some, gold catalysts are expensive and the common drawback associated with homogeneous gold catalysis is the difficulty in catalyst recovery. While the statement above may be true, the issue is not about the cost of catalysts but how new libraries of privileged scaffolds could be generated in an efficient manner. Once the potent compounds have been identified, it is the responsibility of organic chemists to come up with the scalable and economically viable processes to generate the compound on a large scale. Next, the obvious question one would ask is why only gold and not other metals. The answer is that gold complexes often show unique reactivity, allowing transformations which are not possible with other transition metals. In the case where several transition metals can catalyse the same transformation, gold usually gives faster and/or more selective transformation. This superior activity of gold complexes could be due to maximum relativistic effects[28] exhibited by Au compared to other transition metals.

## Conclusion

Gold-catalysed cascade reactions are clearly becoming a powerful synthetic tool to generate a variety of privileged scaffolds from easily available starting materials under mild conditions. This article has outlined the progress in this area, focusing on the research done in our laboratory. Although homogeneous gold-catalysis is still in its infancy, it likely seems that many more applications expanding the horizon of this gold-alkyne chemistry will appear in the future. A few trends can easily be identified leading to new studies in this area: (1) Use of Au nanoparticles for reactions which were previously known to occur only with homogeneous catalysis[29]; (2) Enantioselective gold-catalysis[30]; (3) Application in total synthesis of natural products[31], and (4) Cooperative/relay catalysis using Au-salts and organocatalysts[32]. Though all the above aspects are important, the most significant would be point (4), because the binary-catalyst system consisting of Au and organocatalyst would give the products which are not accessible using either of the catalysts alone[33]. As there

exists a possibility of using several Au-salts and numerous organocatalysts (such as primary and secondary amines, NHCs, guanidines, Brønsted acids, thio-urea, etc.), a number of permutations and combinations can be envisioned which would generate several new reactivities. The feasibility of such auro-organocatalysis, with emphasis on enantioselective catalysis is being currently explored in the our laboratory.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